

EXPLORATIONS IN MEDIUM-RING ETHER SYNTHESIS VIA
UMPOLUNG HETEROATOM ACTIVATION: TOTAL
SYNTHESIS, METHODS DEVELOPMENT,
AND REAGENT SYNTHESIS

A Dissertation
Submitted to
the Temple University Graduate Board

In Partial Fulfillment
of the Requirements for the Degree
DOCTOR OF PHILOSOPHY

by
Bilal Hoblos
August 2021

Examining Committee Members:

Sarah E. Wengryniuk, Advisory Chair, Department of Chemistry
Rongsheng Wang, Department of Chemistry
Daniel Kim, Department of Chemistry
Seth Herzon, External Member, Yale University

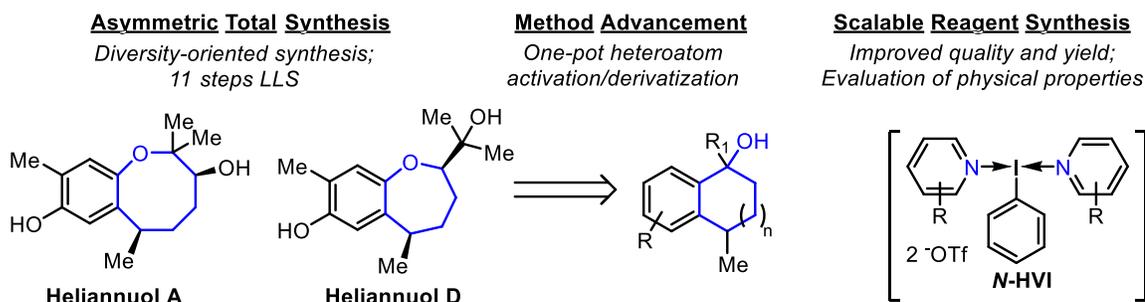
©
Copyright
2021

by

Bilal Hoblos
All Rights Reserved

ABSTRACT

The Heliannuols are a family of structurally diverse allelochemicals produced by the common sunflower which hold potential as environmentally benign herbicides; however, their further study and development has been hampered by lack of efficient and divergent synthetic strategies. Key challenges include 7- and 8-membered medium-ring ethers and isolated stereogenic centers. A novel (bis)cationic nitrogen-ligated HVI (*N*-HVI)-mediated oxidative rearrangement represents an innovative approach to the Heliannuols by providing expedient access to the challenging cyclic ether scaffold via umpolung reactivity of cyclic alcohols.



This dissertation provides the unified synthesis and isolation of various electronically and sterically distinct *N*-HVIs to promote their continued investigation in the Wengryniuk group as well as synthetic groups across the globe (Chapter 1). Additionally, synthetic efforts toward natural product targets led to new discoveries regarding the key electrophilic heteroatom rearrangement step which prompted a full study, resulting in improved yields, one-pot derivatization protocols, expanded scope, and a better understanding of substrate effects on reactivity (Chapter 2). Finally, armed with improved access to medium-sized cyclic ethers, the 11-step total syntheses of

Heliannuols D and A was accomplished in the most concise and highest yielding asymmetric syntheses to date (Chapters 3 and 4). The divergent synthetic strategy has also enabled access to a library of unnatural analogues which are being screened for bioactivity in collaboration with agrochemical industry (Chapter 5).

To my Family and colleagues.

ACKNOWLEDGMENTS

It is difficult to put into words the support offered by Professor Sarah Wengryniuk, but for the purposes of this acknowledgment I will try my hardest. From my earliest days in her group, Sarah was encouraging and overwhelmingly supportive. Her abundance of chemical knowledge was obvious from the first lesson she delivered in first-year organic chemistry. Her encouragement and leadership within the group helped not only me, but every person who stepped foot in the lab. She provided numerous opportunities to demonstrate leadership and independence through conferences, mentorship, and lab management which has helped me become who I am as a chemist today. When faced with adversity, Sarah finds a way to rise above and raise everybody around her. It is not hyperbolic to say I would not be where I am today without her guidance and support. I am eternally grateful; thank you.

I would also like to acknowledge the various professors at Temple University I have had the pleasure of working closely with over the past several years. First, my two committee members: Professor Ross Wang, who provided invaluable guidance in life after graduate school and Professor Daniel Kim, who I only had the pleasure of working with for a limited time, but who helped me put some aspects of chemistry and life after graduate school into perspective and never turned me away. Professor Graham Dobereiner, who gave me some extremely helpful organometallic lessons inside and out of the classroom, and did so while bringing a grin to my face. Professor Carol Manhart, who along with Professor Sarah Wengryniuk, provided me the opportunity to head a

recruitment committee during COVID-19 restrictions. Professor Charles Debrosse, who provided valuable skills in spectroscopy and did so with enthusiasm.

Finally, Professor Rodrigo Andrade. We stand on the shoulders of giants, and I expect your shoulders to be heavy with the weight of future generations. Thank you for everything.

Temple Chemistry staff, both in the front office and the store room, thank you all. Your management made things run smoothly and makes our jobs far easier.

I would like to thank Prof. Seth Herzon for serving as my external committee member and providing invaluable advice and feedback.

My colleagues in the W-lab. It's often said that your lab members are your family, and that rings true. We developed a bond which can only be forged in difficulty and triumph. Your endless support of me has been motivating beyond words. Thank you.

Dr. Anthony Tierno, from the first day in the group you helped me find my footing. You are one of the greatest chemists I've ever seen and learned from, but beyond that I am proud to call you one of my dearest friends. When life beat me down you were in my corner with the words and actions that helped me carry on. I love you, brother.

Dr. Felipe Silva, you helped me gain perspective on graduate school. You helped me see which battles are worth fighting and which are not. Your guidance helped me become a better leader, and your friendship helped me become a better man. Outside the lab, you introduced me to Brazilian steakhouses, and for that there is simply no way to repay you.

Andres Vazquez-Lopez, my friend. Process of elimination brought us together, and brotherhood kept us together. Our chemistry conversations were always informative

and truly fun to have. I will forever remember the steak nights with you, Felipe, and myself. Also, I can never forget our endless hours playing Rocket League with you and reminding you that we live in glass houses. I am happy to call you one of my closest friends.

Myriam Mikhael, we joined this fight together and we kept fighting side by side. Thank you for all of our conversations and for putting up with me as your hood mate.

Bill Motsch, you helped me become a leader. So much of what I see in myself as a chemist, I see in you. I guess I can call you my little big brother.

Andrew Mellinger, I am glad to call you my friend. I hope I offered you as much help as you offered me.

Brandon Bloomer, Maria Velopolcek, Nate Greenwood. Though you were undergrads in the group when we met, I learned so much chemistry from you all. Our conversations were incredibly insightful, and I am glad to call you all my friends today.

My friends outside the lab. Where to start?

Dr. Zakey Buuh. You were probably the first person I talked to at Temple. I was a wide-eyed first year and somehow it felt like you already had grad school figured out. You helped me through the hardest times in my life, and made the happiest times even happier.

Dr. Willy Sabbers, one of the smartest and driven people I know. You helped me analyze everything from natural products to sand. I learned more from you than you can ever know, and I valued every conversation we've ever had.

My Family: Rabih Hoblos, Prof. Jalaa Hoblos, Lina Hoblos, and Ashraf Hoblos, I simply can't put into words how much you mean to me, and how much you helped me

get through this. Your overwhelming support was a constant beacon of hope. Mom, you gave me some of the best advice having gone through this yourself. Both you and Dad were such an inspiration for me to get my PhD and to always keep trying. No matter how many times I failed, you told me to carry on. Dad, you put things in perspective. You helped me with everything, both in terms of chemistry and in terms of being an adult. Your success, along with Mom's, inspired me beyond comprehension. I love you both dearly.

Lina, your constant support especially in my hardest moments is a huge reason why I was able to reach the finish line. Your understanding is also valuable beyond words. You and Ashraf helped me so much when I first moved out and all I wanted to do was go back home. All of the inside jokes we have, all of the jokes we send to each other, it all helped make the days great. I love you, my sister

Ashraf, you don't know how much I relied on you. Just our day to day conversations helped pull me out of my own thoughts sometimes. I appreciated all of the texts we exchanged, our heart-to-heart conversations, our golf outings, our fight nights, every single thing. I love you, my brother.

To everyone else who has been part of this special journey, thank you.

TABLE OF CONTENTS

ABSTRACT.....	III
ACKNOWLEDGMENTS	VI
LIST OF TABLES	XIV
LIST OF FIGURES	XVII
LIST OF SCHEMES.....	XIX
CHAPTER 1: HYPERVALENT IODINE REAGENTS	1
1.1: Background and Significance	1
1.2: Properties and general reactivity of I(III) reagents.....	3
1.3: Oxygen ligated I(III) Reagents and their synthesis	5
1.4: Synthesis and reactivity of Nitrogen-ligated I(III) reagents	8
1.4i: Pseudocyclic (mono)cationic <i>N</i> -Ligated I(III)-HVIs.....	10
1.5: (Bis)Cationic Nitrogen-Ligated I(III) Reagents	12
1.5i: Background and Motivation	12
1.5ii: Synthesis and Structure	13
1.5iii: Early Reported Transformations Utilizing <i>N</i> -HVIs	15
1.5iv: <i>N</i> -HVI-Mediated Umpolung Heteroatom Activation (Wengryniuk).....	19
1.5v: <i>N</i> -HVI-Mediated Heteroatom Group Transfer (HGT)	22
1.6: Scalable Preparation of I(III) <i>N</i> -HVIs and investigation of Moisture and Thermal Stability	24
1.6i: Improvements to Synthesis.....	25
1.6ii: Investigation of Physical Properties	29
1.7: Conclusions.....	33
1.8: References.....	34
CHAPTER 2: IMPROVEMENTS TO UMPOLUNG RING EXPANSION OF BENZYLIC ALCOHOLS	44
2.1: Background and Significance	44
2.2: HVI-Mediated Electrophilic Heteroatom Rearrangement	46
2.2i: Reaction Optimization	46

2.2iii: Substrate Scope of Tertiary Benzyl Alcohols	48
2.2iv: <i>N</i> -HVI Umpolung Ring Expansion of Secondary Alcohols	50
2.3: Derivatization of HFIP Acetals.....	52
2.4: Improvements to Synthesis of Cyclic Ethers.....	54
2.4i: Initial Discovery	55
2.4ii: Development of One-Pot Method.....	57
2.4iii: Failed or Unoptimized Substrates	59
2.4iv: Future Directions	60
2.5: Conclusions.....	61
2.6: References.....	62
CHAPTER 3: DIVERGENT TOTAL SYNTHESIS OF HELIANNUOL D VIA I(III) UMPOLUNG ALCOHOL RING EXPANSION	66
3.1: Background and Significance	66
3.2: Prior Racemic Total Syntheses of Heliannuol D	67
3.3: Prior Enantioselective Syntheses of Heliannuol D	72
3.4: First Generation Retrosynthetic analysis; Benzyne Approach	76
3.5: Approaches via Asymmetric Ni(0) sp ³ -sp ³ Cross-Couplings	79
3.6: Asymmetric Relay Heck Coupling	84
3.7: Traditional Heck Coupling Approach.....	89
3.8: <i>N</i> -HVI Mediated Oxidative Rearrangement	94
3.9: Completion of Racemic Synthesis	98
3.10: Racemic Synthesis Optimization	101
3.10i: Diastereoselectivity and Epimerization	101
3.10ii: Optimization of Rearrangement/Reduction Sequence	102
3.10iii: Improvement of Alkyne Hydration	103
3.10iv: Alternative Late-Stage Arene Oxidation	104
3.11: Asymmetric Synthesis of (+)-Heliannuol D	105
3.12: Conclusions.....	108
3.13: References.....	109
CHAPTER 4: DIVERGENT SYNTHESIS OF (-) – HELIANNUOL A VIA I(III) UMPOLUNG RING EXPANSION	118

4.1: Heliannuol A Background	118
4.2: Racemic Synthesis of Heliannuol A	118
4.3: Enantioselective Synthesis of Heliannuol A.....	121
4.4: Attempts Towards Racemic Synthesis of Heliannuol A	125
4.5: Derivatization of HFIP Acetal	127
4.5ii: Oxidation of saturated Ether to Enol Ether	130
4.5iii: Installation of Eliminable Leaving Groups	131
4.5iv: Attempted Synthesis from Chlorohydrin.....	135
4.5v: Further Investigation of Acetal Electronics	135
4.6: Optimization of Oxidative Ring Expansion.....	139
4.6: Epoxidation and Methylative Opening	141
4.6i: Investigation of Epoxidation.....	144
4.6ii: Investigation of methylating agents.....	148
4.7: Completion of Heliannuol A.....	149
4.8: Conclusions.....	150
4.9: References.....	152
CHAPTER 5: SYNTHESIS OF UNNATURAL HELIANNUOLS ANALOGUES	158
5.1: Background and Motivation	158
5.2: Bioactivity of Heliannuols	159
5.3: Synthesis of Unnatural Analogues.....	160
5.3i: Synthesis of 7-Membered Heliannuol D Analogues	160
5.3ii. Synthesis of 8-Membered Heliannuol A Analogues	164
5.4: Biological Screening of Heliannuol Analogues.....	166
5.4i: Herbicidal Activity	167
5.4ii: Fungicidal Activity	168
5.4iii: Insecticidal Activity.....	169
5.5: Conclusions and Future Directions.....	170
5.6: References.....	171
APPENDIX A: (BIS)CATIONIC HYPERVALENT IODINE REAGENTS	175
APPENDIX B: ONE-POT REARRANGEMENT/REDUCTION PROTOCOL.....	200
APPENDIX C: TOTAL SYNTHESIS OF HELIANNUOL D	247

APPENDIX D: TOTAL SYNTHESIS OF HELIANNUOL A	383
APPENDIX E: SYNTHESIS OF HELIANNUOL ANALOGUES	471

LIST OF TABLES

Table 1.1. Summary of optimal conditions for <i>N</i> -HVI Synthesis.....	29
Table 3.1. Screening of aryl substituents in relay Heck coupling	86
Table 3.2. Screen of acids to enable cyclization of chiral aldehyde	87
Table 3.3. Screen of acids in Friedel-Crafts acylation.....	90
Table 3.4. Screen of bases in enolate formation of acetophenone 3.113.....	91
Table 3.5. Screen of Heck conditions	92
Table 3.6. Ullman conditions for hydroxylation of aryl halides.....	100
Table 3.7. Evaluation of epimerization conditions	101
Table 4.1. Screen of conditions to eliminate HFIP.....	127
Table 4.2. Screen of Lewis acids to promote HFIP elimination.....	130
Table 4.3. Alpha functionalizations of ketone 4.42	132
Table 4.4. Screen of methylation conditions on α -functionalized ketone	133
Table 4.5. Screening of olefin difunctionalizations	134
Table 4.6. Screen of elimination conditions from <i>para</i> -MeO HFIP acetal	138
Table 4.7. Optimization of ring expansion on electron-rich 8-membered ring system ..	140
Table 4.8. Modulation of temperature and water content in epoxidation.....	144
Table 4.9. Screen of Lewis acids and solvents to promote formation of 4.87.....	147
Table 4.10. Screen of nucleophilic methyl sources in various solvent.....	148
Table 5.1. Herbicidal activity for of 7- and 8-membered analogues	167
Table 5.2. Fungicidal activity data for 7- and 8-membered analogues.....	168

Table 5.3: Insecticidal activity data for 7- and 8-membered analogues	169
Table C1: Crystal data and structure refinement for 3.137.....	366
Table C2: Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 3.137.....	367
Table C3: Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 3.137.....	369
Table C4: Bond Lengths for 3.137	370
Table C5: Bond Angles for 3.137.....	371
Table C6: Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 3.137	372
Table C7: Crystal data and structure refinement for 3.2.....	376
Table C8: Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 3.2.....	378
Table C9: Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 3.2.....	379
Table C10: Bond Lengths for 3.2	380
Table C11: Bond Angles for 3.2.....	380
Table C12: Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 3.2.	381
Table D1: Crystal data and structure refinement for 4.82	463
Table D2: Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 4.82.....	464
Table D3: Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 4.82.....	466
Table D4: Bond Lengths for 4.82	467
Table D5: Bond Angles for 4.82.....	468

Table D6: Hydrogen Atom Coordinates ($\text{\AA}\times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2\times 10^3$) for 4.82	469
---	-----

LIST OF FIGURES

Figure 1.1. Geometries and examples of HVI species	2
Figure 1.2. Molecular orbitals of I(III) species	3
Figure 1.3. Examples of neutral and charged nitrogen-ligated I(III)-HVIs	8
Figure 1.4. Bond angle differences across various <i>N</i> -ligated I(III) species	9
Figure 1.5. Representative examples of (mono)cationic <i>N</i> -ligated i(III)-HVIs	10
Figure 1.6. Comparison of reactivity between <i>Py</i> -HVI and $\text{PhI}(\text{OAc})_2$	14
Figure 1.7. Stages of <i>N</i> -HVI Synthesis	25
Figure 1.8. Glovebox filtration of <i>N</i> -HVI	27
Figure 1.9. Inert benchtop filtration of <i>N</i> -HVIs	28
Figure 1.10. Crystal structure of moisture-degradation product	29
Figure 1.11. Visually observed degradation of <i>2-MeO-Py</i> -HVI	30
Figure 1.12. Degradation of <i>2-MeO-Py</i> -HVI tracked by ^1H NMR	31
Figure 1.13. TGA of <i>N</i> -HVI's with $\text{PhI}(\text{OAc})_2$ as a control	32
Figure 2.1. Unsuccessful or unoptimized substrates in one-pot procedure	60
Figure 3.1. Representative Heliannuols	66
Figure 4.1. Similarity in spectra between open chain products	143
Figure 5.1. Sites of derivatization of Heliannuol D	160
Figure 5.2. Sites of derivatization of 8-membered analogues	164
Figure 5.3. 7- and 8-membered analogues utilized in pesticidal assays	166
Figure 5.4. Promising analogues entering Level 2 insecticidal screening	170

Figure C1. Thermal Ellipsoid plot of 3.137 shown at 50% probability.....	366
Figure C2: Thermal ellipsoid plot for 3.2 shown at 50% probability	376
Figure D1. DMDO synthesis apparatus	413
Figure D2: Thermal Ellipsoid plot for 4.82 shown at 50% probability.....	463

LIST OF SCHEMES

Scheme 1.1. General reactivity of I(III) reagents	4
Scheme 1.2. I(III)-HVIs and general synthetic approach	5
Scheme 1.3. Examples of reactions utilizing oxygen-ligated I(III)-HVIs	6
Scheme 1.4. α -arylation of enones with I(III)-HVIs.....	7
Scheme 1.5. Synthesis of pseudo-cyclic (mono)cationic <i>N</i> -ligated I(III)-HVIs.....	10
Scheme 1.6. Unpublished work utilizing pseudo-cyclic HVIs	11
Scheme 1.7. Synthesis and structure of reported <i>N</i> -HVIs	13
Scheme 1.8. Initially reported reactivity of <i>N</i> -HVIs.....	15
Scheme 1.9. α -functionalization utilizing <i>Py</i> -HVI	16
Scheme 1.10. <i>Py</i> -HVI-mediated Achmatowicz rearrangement	16
Scheme 1.11. <i>Py</i> -HVI-mediated synthesis of diaryliodonium salts	17
Scheme 1.12. <i>DMAP</i> -HVI-mediated oxidative aminopyridine coupling	17
Scheme 1.13. <i>DMAP</i> -HVI-mediated formal C-H activation	17
Scheme 1.14. Oxidation of Pd(II) species utilizing various <i>N</i> -HVIs.....	18
Scheme 1.15. Example report of Umpolung reactivity (Seebach).....	19
Scheme 1.16. Heterocycle synthesis via oxidative rearrangement	20
Scheme 1.17. Conformationally-selective oxidation of secondary alcohols	21
Scheme 1.18. Aryl ether synthesis via C-H activation	22
Scheme 1.19. Umpolung activation of enol ethers	22
Scheme 1.20. Aminolactonization of olefins and incorporated heterocycle scope	23

Scheme 1.21. Synthesis of <i>N</i> -HVIs.....	26
Scheme 2.1. Prior approaches to medium-sized cyclic ethers	44
Scheme 2.2. Proposed approach to medium-sized cyclic ethers	45
Scheme 2.3. Initial screening of HVI-mediated oxidative rearrangement.....	46
Scheme 2.4. Optimized reaction conditions and <i>N</i> -HVI screen	47
Scheme 2.5. Substrate scope of tertiary alcohol rearrangement	49
Scheme 2.6. Oxidative rearrangement of secondary benzylic alcohols.....	50
Scheme 2.7. Scope of rearrangement on secondary aliphatic alcohols	51
Scheme 2.8. FMO analysis of iodate ester intermediates	52
Scheme 2.9. General reactivity of HFIP acetals	52
Scheme 2.10. Derivatization of tertiary benzylic HFIP acetals	53
Scheme 2.11. Derivatization of secondary aliphatic alcohols	53
Scheme 2.12. CTD manipulations of deoxycholic acid.....	54
Scheme 2.13. Undesired decomposition of HFIP acetal 2.91 in HFIP.....	55
Scheme 2.14. Improved acetal reduction and one-pot sequence	56
Scheme 2.15. Determination of yield-limiting step by ¹ HNMR.....	57
Scheme 2.16. Substrate scope of one-pot rearrangement/reduction protocol.....	58
Scheme 2.17. Preliminary advancements to one-pot procedure	61
Scheme 3.1. Proposed biosynthesis of Heliannuols A and D	67
Scheme 3.2. First racemic synthesis of Heliannuol D (Vyvyan, 2000).....	68
Scheme 3.3. Concise racemic synthesis of Heliannuol D (Macias, 2003)	69
Scheme 3.4. Baeyer Villiger approach to Heliannuol D (Venkateswaran, 2003)	70
Scheme 3.5. RCM approach to Heliannuol D (Venkateswaran, 2002)	71

Scheme 3.6. Enantioselective synthesis of Heliannuol D (Shishido, 2003)	72
Scheme 3.7. Asymmetric dihydroxylation route to Heliannuol D (Shishido, 2010)	73
Scheme 3.8. Biomimetic asymmetric synthesis of Heliannuol D (Shishido, 2014)	74
Scheme 3.9. First-generation retrosynthesis of Heliannuol D	76
Scheme 3.10. Proposed aryne synthesis observed in prior investigations	77
Scheme 3.11. Aryne Diels-Alder approach to key ketone intermediate	78
Scheme 3.12. Investigations and pitfall of aryne approach	78
Scheme 3.13. Proposed asymmetric Ni(0)-catalyzed approach	79
Scheme 3.14. Evaluation of asymmetric Ni(0)-catalyzed approach	80
Scheme 3.15. Potential alternative Ni(0)-catalyzed approaches	82
Scheme 3.16. Unsuccessful alternative Ni(0)-mediated approaches	83
Scheme 3.17. Reported redox-relay Heck oxidation to deliver chiral aldehydes	84
Scheme 3.18. Performance of redox-relay Heck coupling	85
Scheme 3.19. Attempted acid-mediated cyclization from chiral aldehyde	86
Scheme 3.20 Synthesis of chiral alcohol via oxidation/cyclization sequence	88
Scheme 3.21. Proposed Heck pathways to desired chiral alcohol	89
Scheme 3.22. Unsuccessful Friedel-Crafts reaction en route to Heck precursor	89
Scheme 3.23. Efficient synthesis of Heck precursor	91
Scheme 3.24. Heck reaction and subsequent reductions	93
Scheme 3.25. Precedented and unsuccessful ring expansion	94
Scheme 3.26. Investigation of alternative <i>N</i> -HVIs in ring expansion	94
Scheme 3.27. Successful ring expansion and modified retrosynthesis	95
Scheme 3.28. Continued racemic synthesis HFIP acetal derivatization	96

Scheme 3.29. Failed nitrile derivatization and modified retrosynthesis	97
Scheme 3.30. Racemic synthesis of des-OH Heliannuol D.....	98
Scheme 3.31. <i>Para</i> -halogenation of cyclic aryl ethers	99
Scheme 3.32. Issues with rearrangement and telescoping with subsequent reduction...	102
Scheme 3.33. Improved method for alkyne hydration.....	104
Scheme 3.34. Evaluation of alternative late-stage aryl oxidations	105
Scheme 3.35. Deviation from Heck approach and alternative asymmetric strategy	106
Scheme 3.36. Completed asymmetric synthesis of Heliannuol D	107
Scheme 4.1. Synthesis of Heliannuol A via Julia coupling (Grimm, 1994).....	119
Scheme 4.2. Ring expansion strategy toward Heliannuol A (Venkateswaran, 2002)	120
Scheme 4.3 RCM approach to 8-membered ring (Venkateswaran, 2007)	121
Scheme 4.4. Biomimetic asymmetric synthesis of Heliannuol A (Shishido, 2000).....	122
Scheme 4.5. RCM-mediated asymmetric synthesis of Heliannuol A (Shishido, 2004). 124	
Scheme 4.6. First generation retrosynthesis of Heliannuol A	125
Scheme 4.7. Racemic efforts toward 8-membered cyclic enol ether.....	126
Scheme 4.8. Successful reduction and unsuccessful iodination of HFIP acetal.....	128
Scheme 4.9. Proposed Lewis acidic role of triethylsilane	129
Scheme 4.10. Unsuccessful oxidation of saturated cyclic ether	130
Scheme 4.11. Proposed installation of leaving groups	131
Scheme 4.12. Approach to tertiary alcohols via olefin difunctionalization.....	133
Scheme 4.13. Chlorohydrin synthesis from tertiary alcohol.....	134
Scheme 4.14. Unsuccessful access to enol ether via chloride elimination	135
Scheme 4.15. Precedented synthesis of IPA acetals in ring expansion	136

Scheme 4.16. Synthesis of <i>para</i> -MeO HFIP acetal	137
Scheme 4.17. Failed ring expansion to deliver IPA acetal	137
Scheme 4.18. Asymmetric synthesis of aryl-methoxy cyclic enol ether 4.83	139
Scheme 4.19. Precedented epoxidation sequence and proposed transformation	141
Scheme 4.20. Unsuccessful approach to 4.87 due to hydrolysis of epoxide	142
Scheme 4.21. Evidence for formation of desired epoxide	144
Scheme 4.22. Proposed telescoped sequence using “acetone-free” DMDO	145
Scheme 4.23. Formation of acetonide and mechanistic rationale	146
Scheme 4.24. Proposed and unsuccessful conversion of acetonide to 4.87	146
Scheme 4.25. Improved synthesis of MeO-Heliannuol A 4.87	149
Scheme 4.26. Completed asymmetric total synthesis of (-)-Heliannuol A	150
Scheme 5.1. Access to analogues from late-stage intermediates of Heliannuol D	161
Scheme 5.2. Synthesis of 7-membered C11 alkynyl analogue	161
Scheme 5.3. Synthesis of various 7-membered analogues varied at C11	162
Scheme 5.4. Synthesis of aniline and phenolic regioisomers	163
Scheme 5.5. Synthesis of mono α -methyl and des β -OH 8-membered analogues	164
Scheme 5.6. Access to 8-membered acetonide and ketone analogues	165

CHAPTER 1: HYPERVALENT IODINE REAGENTS

1.1: BACKGROUND AND SIGNIFICANCE

Out of sheer necessity, Nature has demonstrated a wide variety of oxidative processes to deliver densely oxidized bioactive molecules.¹⁻⁴ As such, it is paramount that synthetic chemists develop similar processes to access these privileged molecules.⁵⁻⁷ Research into selective oxidations has become an area of critical interest in the field of synthetic chemistry.⁸⁻¹⁰ Despite significant effort, existing strategies still commonly rely on scarce,¹¹⁻¹³ toxic,¹⁴⁻¹⁸ transition metals or harsh conditions, and often provide poor functional group compatibility and chemo- or regioselectivity.¹⁹ Furthermore, atom and step economy is often far from ideal rendering the process costly and impractical for large scale production.^{20,21} Despite the efforts of chemists all around the globe, generally applicable solutions remain elusive and a significant gap remains between our tools in the laboratory and the elegant transformations of Nature.

The use of main-group elements as opposed to transition metals has emerged as a possible alternative approach to the development of efficient, green, and selective oxidative transformations.²²⁻²⁷ One example is the Swern Oxidation, which utilizes the readily available dimethylsulfoxide (DMSO) as an oxidant in the absence of expensive or toxic metals.²⁴⁻²⁷ The Swern oxidation is not without issues, however, as it utilizes stoichiometric quantities of reagents and generates an unpleasant byproduct in dimethylsulfide.^{28,29} The combination of these factors hinders the use of this

transformation on scale. In addition to sulfur and other chalcogens (i.e. selenium), halogens possess the ability to perform general oxidations. For example, sodium chlorite (NaClO_2), hypochlorite (NaClO , household bleach), or hypobromite (NaBrO) are often used as powerful, non-selective oxidants. However, the halogen garnering the most attention for its utility as a synthetic oxidant in recent years is iodine.³⁰ Compared to other halogens and most main group elements, iodine boasts a larger atomic radius, which allows further extension of its normal ground-state valency to adopt multiple, highly reactive “hypervalent” states.³¹ These hypervalent states have been demonstrated as powerful non-toxic, environmentally benign, and mild alternative to prior oxidative strategies.³²

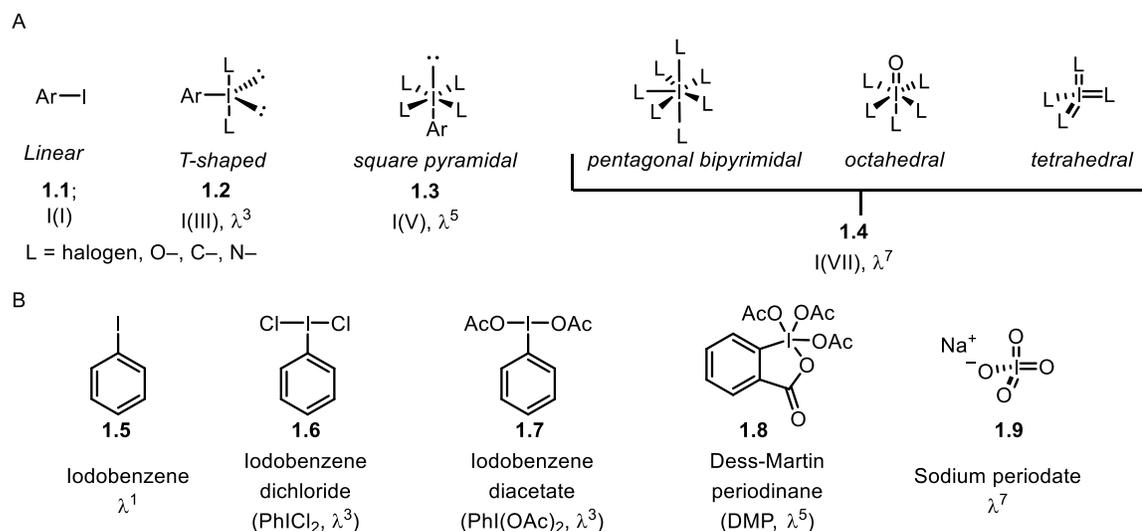


Figure 1.1. Geometries and examples of HVI species

Hypervalent iodine compounds (HVIs) can be distributed into three categories (Figure 1.1A): 1) Iodine (III), or I(III) HVIs (IUPAC) compounds, bearing a T-shaped geometry and one linear 3-center-4-electron bond (**1.2**), 2) iodine (V) or λ^5 -iodanes (IUPAC), possessing a square pyramidal geometry and two linear 3-center-4-electron bonds (**1.3**), and iodine (VII) which can adopt three different geometries (pentagonal

bipyramidal, octahedral, and tetrahedral; Figure.1.1A).³⁰ The λ nomenclature is rarely utilized of late and will not be included for the remainder of this thesis. A few representative examples of commonly utilized reagents of each class are provided in Figure 1.1B and this dissertation will focus on the reactivity and applications of I(III) HVIs.

1.2: PROPERTIES AND GENERAL REACTIVITY OF I(III) REAGENTS

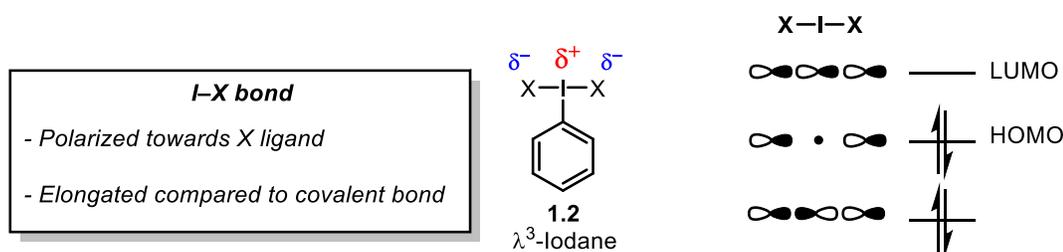
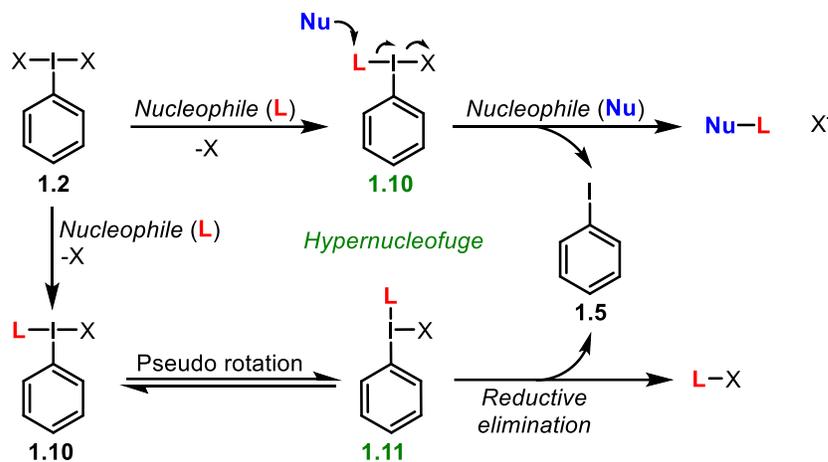


Figure 1.2. Molecular orbitals of I(III) species

I(III) HVIs possess 10 electrons on the iodine center and typically adopt a trigonal bipyramidal geometry. The X-ligands (e.g.- carbon, halogens, oxygen, nitrogen) typically orient 180° from each other, and for clarity purposes, the two electron pairs at the iodine center are usually omitted. Therefore, the I(III) HVIs are often represented with a T-shaped structure (**1.2**; Figure 1.1A, **1.7-1.9**; Figure 1.1B).³⁰ The bonding orbital in I(III) HVIs is composed of two electrons from the unhybridized 5p orbital of the iodine center and one electron from the 2p or 3p orbital from each of the X-ligands (Figure 1.2). This structure results in a net 3c-4e⁻ bond between the iodine center and the two X-ligands, and these bonds are (somewhat contentiously^{30,31}) termed “hypervalent” due to their unique properties. The 3c-4e⁻ bond is elongated when compared to traditional covalent bonds, which results in significant weakening and increased reactivity of the species. These bonds are also highly polarized which manifests in high electrophilicity of I(III)

HVIs at the iodine center (Figure 1.2). The electrophilicity at iodine can be further modulated by the sterics and electronics of the X-ligands, providing handles for tuning HVI reactivity (**1.4**). Excellent reviews on the general properties of HVIs and the phenomena leading to their reactivity have been reported^{30,33–35} and the reader is directed there for more detailed information.

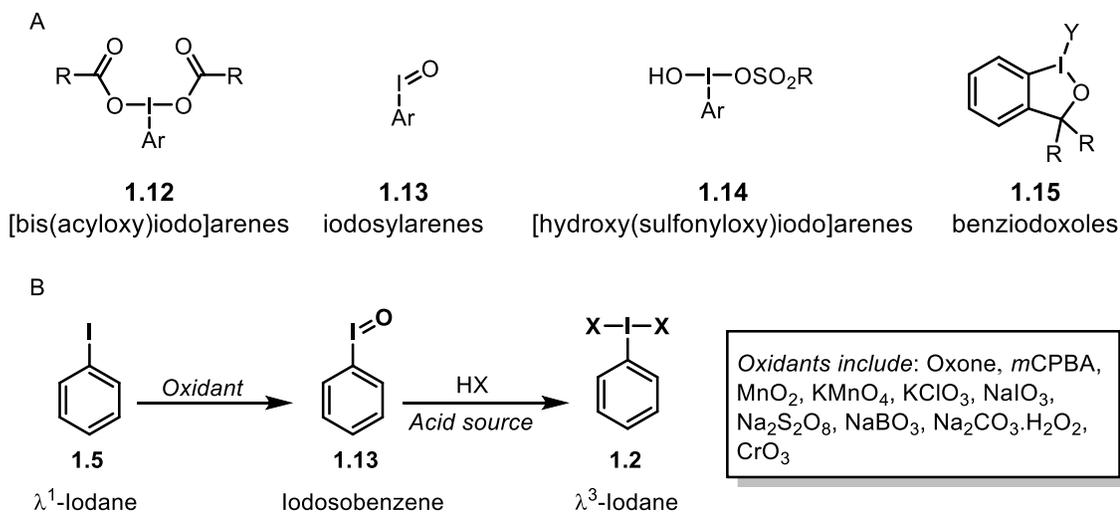


Scheme 1.1. General reactivity of I(III) reagents

Generally speaking, I(III) HVIs display reactivity and elementary steps analogous to transition metals, including ligand exchange, pseudo-rotations, and reductive eliminations (Scheme 1.1). Similar to transition metals, the driving force for subsequent reactivity is reduction to a more stable iodine center (+1 oxidation state) (**1.1**). In the case of I(III) reagents, reduction of the iodine center from the hypervalent I(III) to the native I(I) during reductive elimination demonstrates a leaving group ability one million times greater than that of a triflate anion; this property is termed “hypernucleofugality”.³⁶ By leveraging this principle, I(III) HVIs have been employed to affect a wide variety of synthetic transformations including oxidations, group transfer reactions, and pi-activation. While I(III) reagents exist with a broad scope of X-ligands, including those with carbon, halogen, oxygen, and nitrogen-based ligands, this chapter will only focus on

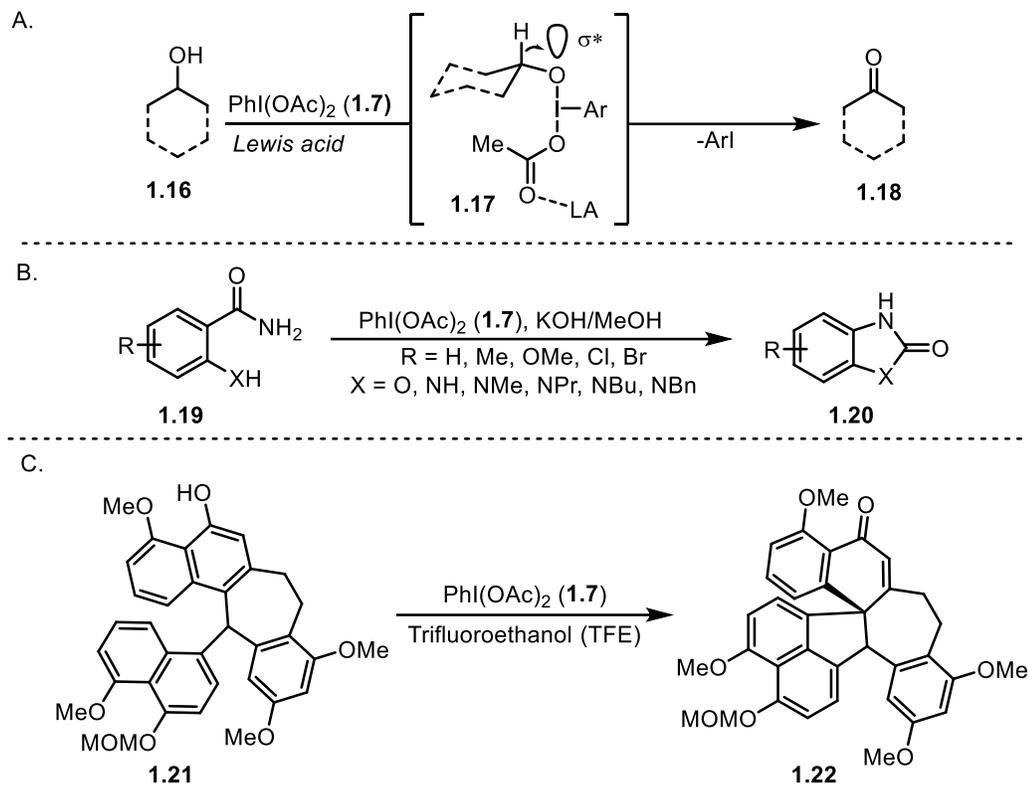
those reagents containing oxygen and nitrogen ligands as they pertain to the remainder of this thesis. Excellent reviews on the carbon-ligated^{37,38} and dihalogen^{39,40} I(III) reagents are cited and the reader is encouraged to read them for further information. The synthesis and examples displaying general reactivity will be discussed, organized by the heteroatomic ligand.

1.3: OXYGEN LIGATED I(III) REAGENTS AND THEIR SYNTHESIS



Scheme 1.2. I(III)-HVI's and general synthetic approach

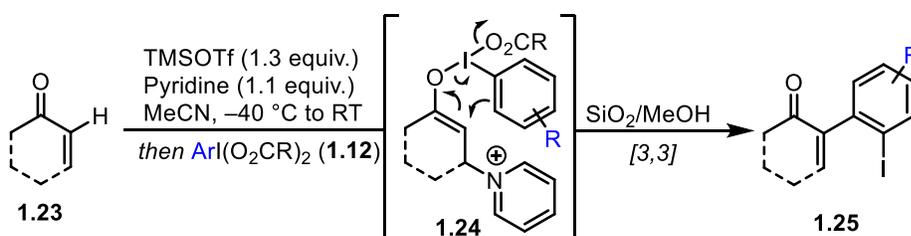
I(III) HVIs with oxygen-based ligands constitute the most commonly employed I(III) reagents, including cyclic and acyclic examples (Scheme 1.2A). Most commonly, the synthesis of these reagents relies on oxidation of an aryl iodide followed by ligand attack into the resulting iodosoarene species, with a variety of oxidants used to generate the reactive iodosoarene species (Scheme 1.2B).^{41,42}



Scheme 1.3. Examples of reactions utilizing oxygen-ligated I(III)-HVI

Many of these reagents have found broad synthetic utility, most commonly in oxidative transformations (Scheme 1.3). For example, diacetoxyiodobenzene ($\text{PhI}(\text{OAc})_2$; **1.7**; Scheme 1.3A) can be utilized to oxidize primary or secondary alcohols (**1.16**) to the respective aldehyde or ketone products (**1.18**). Importantly, $\text{PhI}(\text{OAc})_2$ requires activation in the presence of acid to sufficiently activate the alcohol for oxidation^{43,44} or acts as a co-oxidant for catalytic reagents such as TEMPO.⁴⁵ Oxygen-ligated I(III) reagents have also been found to promote Hoffman rearrangements of amides, providing a milder activation strategy to traditional Hoffman reactions, carried out in an alkaline solution of bromine or chlorine. The first example of a Hoffman rearrangement utilizing hypervalent iodine as the amide activator was reported in 1984, and since then a variety of hypervalent iodine species have been utilized. One such example is reported by Moriarty, wherein $\text{PhI}(\text{OAc})_2$ mediated the Hoffman rearrangement of anthranilamides or *o*-hydroxybenzamides (**1.19**; Scheme 1.3B) to deliver the corresponding 2-benzimidazolone

or 2-benzoxazolone products (**1.20**).³⁴ I(III) HVIs are also highly efficient reagents for oxidative dearomatization of phenols.^{46–48} Traditional methods to oxidize phenols or phenol-like derivatives typically employ stoichiometric quantities of toxic heavy metals. On the other hand, $\text{PhI}(\text{OAc})_2$ readily enables oxidative dearomatization as was demonstrated by Snyder in the total synthesis of Dalesconol A (Scheme 1.3C), where naphtholic substrate **1.21** was successfully activated which enabled the *para* functionalization by the electron-rich aryl moiety and delivered coupled **1.22**.⁴⁹



Scheme 1.4. α -arylation of enones with I(III)-HVIs

In our laboratory, oxygen-ligated HVIs have also found utility in C–C bond forming transformations. Felipe Silva found that either $\text{PhI}(\text{OCOCF}_3)_2$ or $\text{PhI}(\text{OAc})_2$ were able to successfully mediate the C–H α -arylation of enones (**1.23**; Scheme 1.4).⁴¹ This reaction was proposed to proceed via nucleophilic activation of the enone via a Morita-Baylis-Hillman reaction with pyridine and trapping with trimethylsilyl trifluoromethanesulfonate (TMSOTf) to generate the corresponding β -pyridinium silyl enol ether. Upon addition of the HVI, the silyl enol ether could undergo Si-I exchange to form the electrophilic enolonium species **1.24**. Following a reductive Iodonium-Claisen [3,3]-rearrangement and elimination of pyridine, α -iodoarylated cyclic enones were afforded in good yields with a variety of substitution patterns present on both the aryl iodide and cyclic enone **1.25**. Once again, the driving force for this reaction is the reduction of the iodine atom during the Iodonium-Claisen reaction from I(III) to the I(I). As the incorporated aryl group originates from the I(III) HVI, Felipe demonstrated the synthesis of a wide variety of $\text{ArI}(\text{OCOR})_2$ reagents via the aforementioned (Scheme

1.2B) oxidation of aryl iodides followed by treatment with acetic/trifluoroacetic acid, attesting to the versatility of this approach.

Outside of the aforementioned example of enone C–H α -arylation, the main focus of the Wengryniuk laboratory has been in utilizing (poly)cationic (bis)nitrogen-ligated I(III) HVIs to forge new paths in umpolung bond disconnections. The next section of this thesis will discuss the unique properties and reactivity of N-ligated I(III) compounds.

1.4: SYNTHESIS AND REACTIVITY OF NITROGEN-LIGATED I(III) REAGENTS

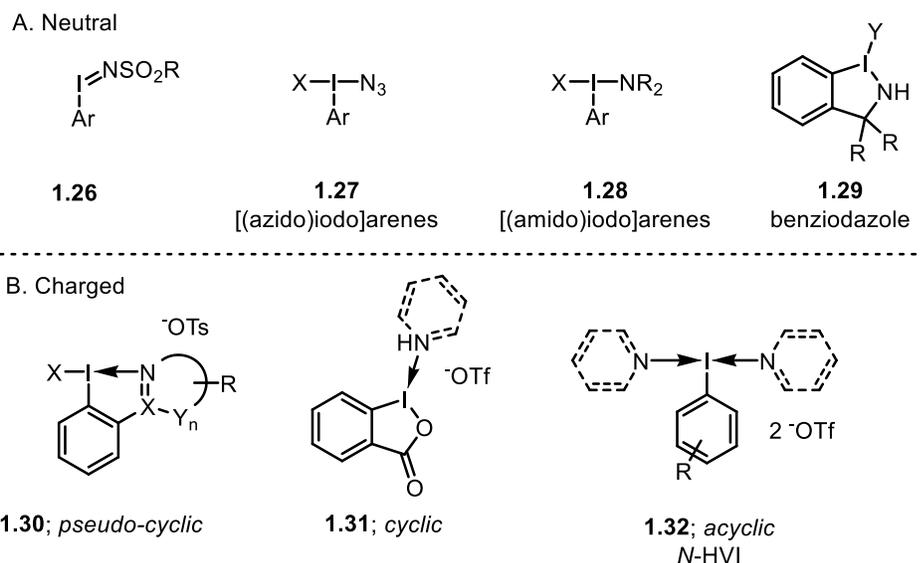


Figure 1.3. Examples of neutral and charged nitrogen-ligated I(III)-HVIs

The synthesis of I(III) HVIs bearing one or two nitrogen-based ligands has garnered recent attention from the synthetic community.³¹ There exist two classes of compounds: neutral (**1.26-1.29**; Figure 1.3A), containing azide and imido ligands, and charged (**1.30-1.32**; Figure 1.3B), containing aromatic heterocyclic ligands. This chapter will focus its discussion on the charged species, in particular a class of (bis)pyridinium HVIs, also termed *N*-HVIs (**1.32**) will constitute a majority of this thesis as it pertains to the chemistry developed herein.

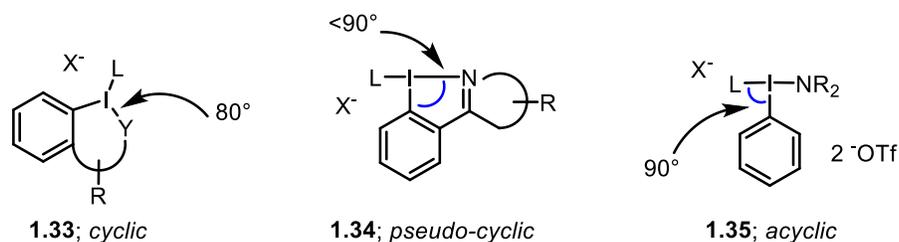


Figure 1.4. Bond angle differences across various *N*-ligated I(III) species

Within the charged species, an additional three distinct subclasses pertain to the coordination environment of the resultant HVI: acyclic, pseudocyclic, and cyclic species. Cyclic species possess an iodine center with a covalent bond to an X-ligand linked via *ortho*-position of the arene, forming either a 5- or 6-membered benziodoxole or benziodoxolone ring, and a datively-bound *N*-ligand in the form of an aromatic heterocycle.⁵⁰ Due to ring strain, the C–I–X angle of the benziodoxole is approximately 80° which is a distortion from the desired angle in a T-shaped geometry (90°) (**1.33**; Figure 1.4). Cyclic reagents, however, are the most structurally understood due to the ease of crystal growth and analysis by X-ray crystallography. Pseudocyclic reagents on the other hand possess a Lewis basic group in the *ortho* position of the aryl backbone which can participate in coordination or dative bonding to the iodine center (**1.34**). Despite the slightly distorted C–I–X bond angle due to strain, the coordinative interaction is stabilizing, leading to facile isolation and employment. Finally, acyclic compounds possess only dative bonds with respect to the ligands and the iodine center, and no covalency between the aryl backbone and the X-ligands (**1.35**). This allows for the molecule to adopt closer to a T-shaped geometry, however with only datively bound ligands, these reagents are quite thermally and hydrolytically unstable if proper care is not taken to exclude heat and moisture when handling or storing.

1.4i: Pseudocyclic (mono)cationic *N*-Ligated I(III)-HVI

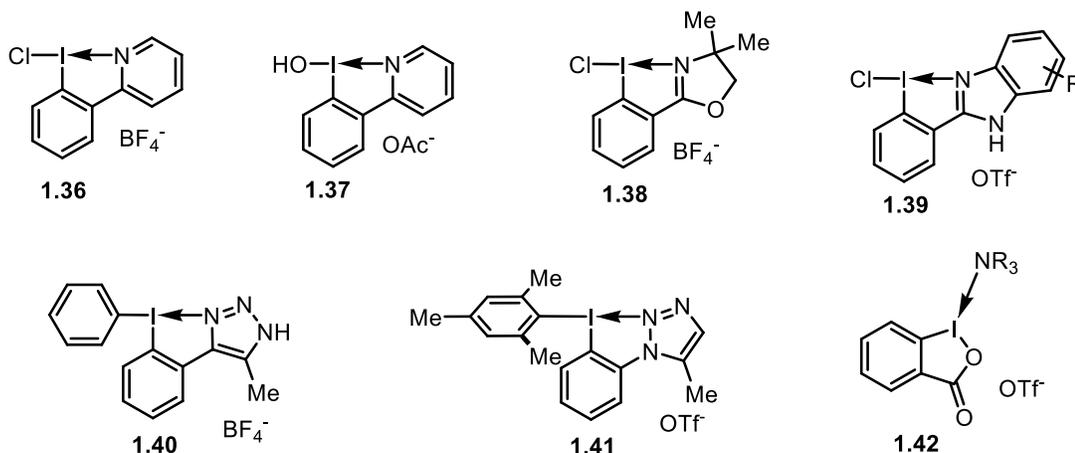
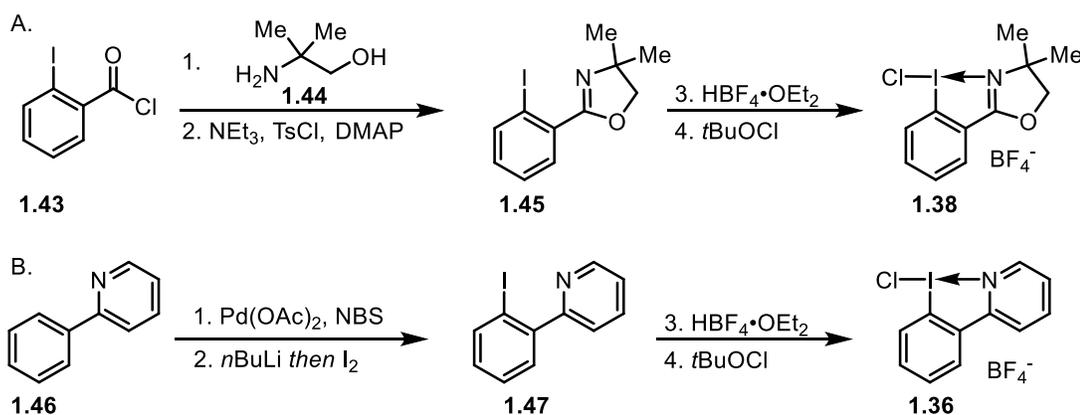


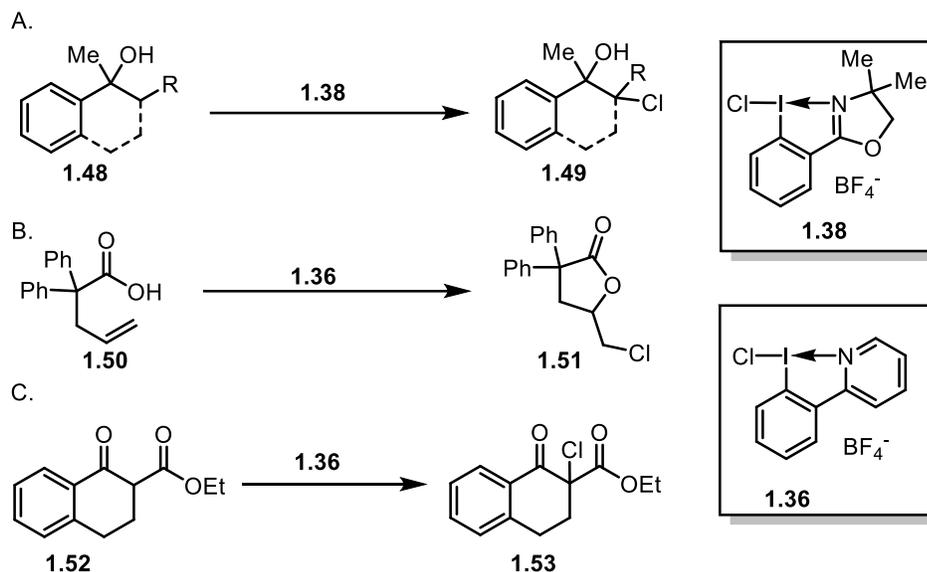
Figure 1.5. Representative examples of (mono)cationic *N*-ligated i(III)-HVIs

Pseudocyclic (mono)cationic nitrogen-ligated I(III) reagents possess increased reactivity due to weak dative coordination by the heterocyclic nitrogen-ligand leading to an increased (+)-charge at iodine, and therefore these reagents rarely require activation with Lewis or Bronsted acids. Figure 1.5 displays a variety of (mono)cationic nitrogen ligated trivalent iodane reagents which have been previously reported. Despite their potentially enhanced reactivity owing to the increased electrophilicity at iodine, examples demonstrating the utility of these reagents are scarce. This is likely due to the lengthy synthetic sequence required to access them.



Scheme 1.5. Synthesis of pseudo-cyclic (mono)cationic *N*-ligated I(III)-HVIs

The syntheses of **1.38** and **1.36** are shown in Scheme 1.5, both reported by Togni and coworkers.⁵¹ To access **1.38**, acyl chloride **1.43**, derived from the corresponding benzoic acid, is first treated with amino alcohol **1.44** followed by cyclization to afford oxazoline **1.45** (Scheme 1.5A). Acidification of the oxazoline nitrogen followed by oxidation of the iodine center provides **1.38** in 5 steps overall from commercial reagents. While at first glance **1.36** does not differ greatly from **1.38**, an entirely different synthetic sequence is required to synthesize it (Scheme 1.5B). Directed C–H bromination of 2-phenylpyridine (**1.46**) is followed by lithium/halogen exchange and quench with I₂ to deliver aryl iodide **1.47**. Once again, treatment with acid followed by oxidation provides the monocationic HVI in four steps from commercial. While these reagents did not find immediate utility following the initial report, our group set out to investigate their synthetic potential.



Scheme 1.6. Unpublished work utilizing pseudo-cyclic HVIs

Unpublished work in our group by former member Margaret Meade utilized oxazoline **1.38** as a mild chlorinating agent of tertiary benzylic alcohols resulting in the synthesis of chlorohydrins (**1.48** to **1.49**; Scheme 1.6A). Though the mechanism is uncertain at this time, the procedure showed moderate success in acyclic systems and

greater success in cyclic systems. Furthermore former postdoctoral researcher Prof. Anthony Tierno was able to demonstrate that pyridine substrate **1.36** shows moderate reactivity in halolactonization reactions of olefinic acids (**1.50**) to provide the primary alkyl halide product (**1.51** Scheme 1.6B). Furthermore, he demonstrated that these reagents to be competent in the chlorination of β -ketoesters under mild conditions (**1.52** to **1.53**; Scheme 1.6C); this work has expanded to include additional nucleophiles and halogens and is currently ongoing in our laboratory. Despite these successes, it was generally found that the pseudocyclic (mono)cationic *N*-ligated reagents possessed reactivity largely comparable to other known I(III) HVI reagents.

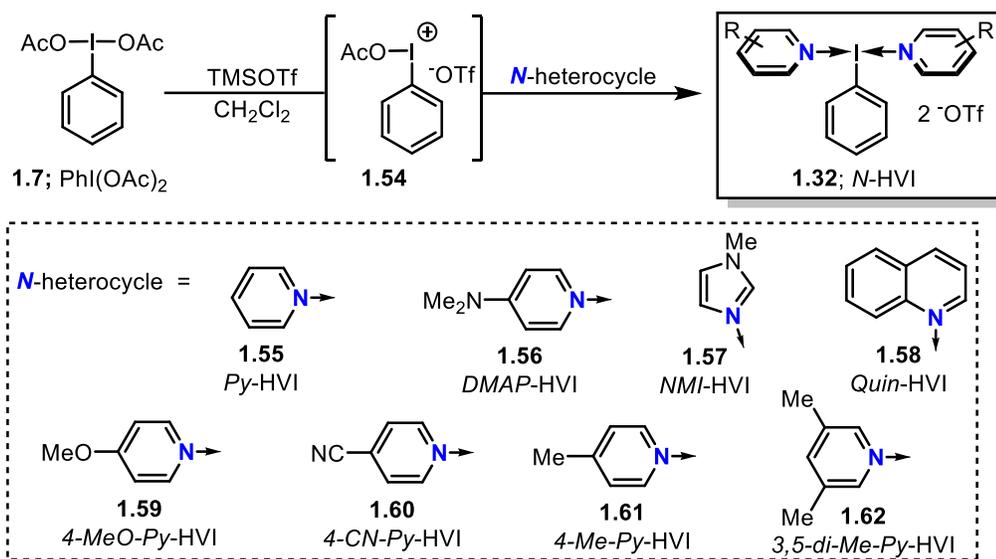
1.5: (BIS)CATIONIC NITROGEN-LIGATED I(III) REAGENTS

1.5i: Background and Motivation

(Bis)cationic nitrogen-ligated I(III) HVIs, colloquially termed *N*-HVIs, are an emerging class of hypervalent iodine reagent with utility in a wide variety of synthetic transformations. A beneficial property of these reagents is their tunable reactivity by modulation of the steric and/or electronic properties of the *N*-heterocyclic. A general, qualitative trend is observed which is as follows: heterocyclic ligands with *electron donating* groups *decrease* reactivity and ligands with *electron-withdrawing* or *sterically encumbering* groups *increase* reactivity. In recent years, the reported use of *N*-HVIs has increased, yet they are still underutilized and many questions remain regarding their synthesis, stability, and reactivity. A property of the majority of *N*-HVIs which has likely contributed to their scarce usage is their sensitivity to moisture, which often complicates synthesis and storage. Visually, this manifests as a yellowing of the white powdered product and loss of reactivity. However, despite their sensitivity and scarce reports in the synthetic community, our group has found great utility in these privileged reagents,

particularly in umpolung transformations of various functional groups. These reagents are central to our groups research, and in particular all of the research described in this thesis. As such, we have devoted multiple efforts to demystify these properties of *N*-HVIs in the hopes of improving their utility in the scientific community.

1.5ii: Synthesis and Structure



Scheme 1.7. Synthesis and structure of reported *N*-HVIs

Weiss first reported the synthesis of four reagents in 1994 (**1.55-1.58**; Scheme 1.7).⁵² In the original synthesis, $\text{PhI}(\text{OAc})_2$ was suspended in CH_2Cl_2 and treated with trimethylsilyl trifluoromethanesulfonate, which is thought to form the highly reactive mono-acetate iodonium salt with a triflate counterion.⁵³ The desired *N*-heterocyclic ligand was then added, and the product salt **1.32** precipitated out of solution and was isolated via vacuum filtration. In his original report, Weiss disclosed the synthesis of four distinct *N*-HVIs: *Py*-HVI (**1.55**), *DMAP*-HVI (**1.56**), *NMI*-HVI (**1.57**), and *Quin*-HVI (**1.58**). In recent years, four additional substrates have since been synthesized by Ritter and coworkers: 4-*MeO*-*Py*-HVI (**1.59**) and 4-*CN*-*Py*-HVI (**1.60**), 4-*Me*-*Py*-HVI (**1.61**), and 3,5-*di-Me*-*Py*-HVI (**1.62**).⁵⁴

Dutton and co-workers completed computation studies on Py-HVI (**1.55**; Figure 1.) which found hereroatom-iodine bond elongation when comparing $\text{PhI}(\text{OAc})_2$ (2.172 Å) to Py-HVI (2.220 Å) which results in a much weaker bond (BDE 590 kJ/mol and 244 kJ/mol, respectively).^{55,56} Additionally, the ligand bound to the iodine center in *N*-HVIs serves as a functional handle to modulate the reactivity (electrophilicity at iodine) by impacting the bond length and dissociation energy. However, it is worth noting that increased reactivity also results in increased sentivity and susceptibility to moisture-driven degradation. While these observations are currently qualitative, our group has ongoing efforts to quantify the described trend.

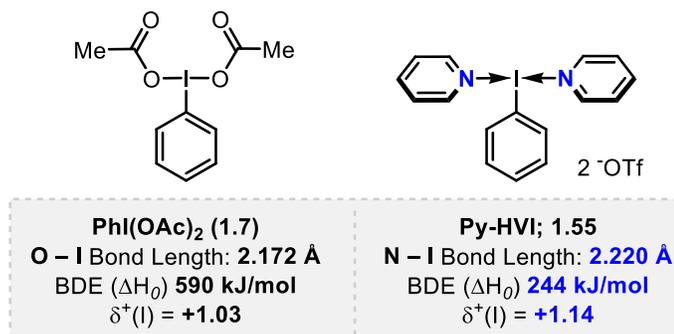
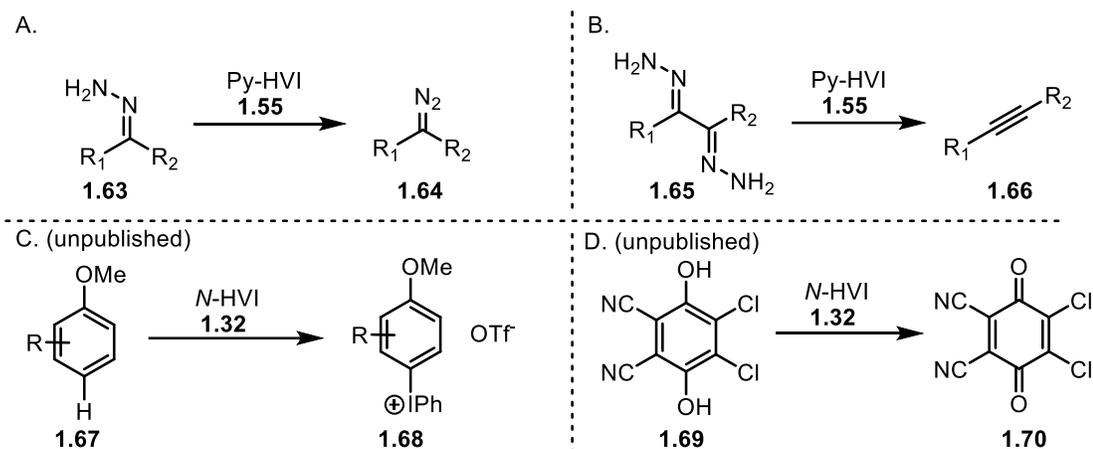


Figure 1.6. Comparison of reactivity between *Py*-HVI and $\text{PhI}(\text{OAc})_2$

For many years it was debated whether the most accurate way to represent the I-N bond is by dative bonds with delocalized charges or covalent bonds with formal charges on the nitrogen center. Calculations by Dutton and co-workers determined the partial charge on the iodine center to be +1.14, indicating the coordinative model to be a more appropriate representation of *N*-HVIs and will be used throughout this thesis. Despite their enhanced reactivity compared to traditional I(III) reagents, very little literature utilizing these privileged reagents exists.

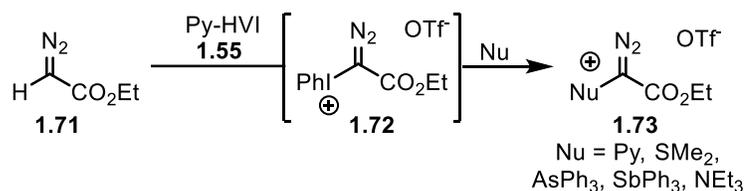
1.5iii: Early Reported Transformations Utilizing *N*-HVIs



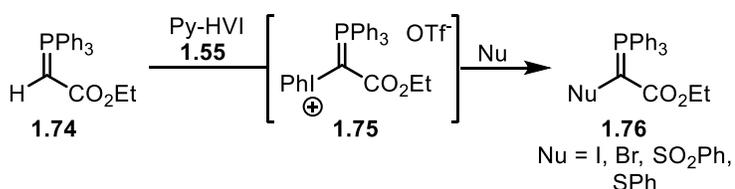
Scheme 1.8. Initially reported reactivity of *N*-HVIs

Early reports utilizing *N*-HVIs exclusively utilized *Py*-HVI **1.55**, and it wasn't until 2012 that alternative reagents were used. The first reported use of *Py*-HVI was by Weiss in the original synthetic report on the oxidative fragmentation of mono (**1.63**) and bishydrazones (**1.65**) to diazo compounds (**1.64**) and alkynes (**1.66**) respectively (Scheme 1.8A-B).⁵² Weiss notes that $\text{PhI}(\text{OAc})_2$ was not competent for this transformation which provided preliminary evidence of the enhanced reactivity of the *N*-HVI reagents. Additionally, a footnote in the seminal article mentioned preliminary investigations into the reaction of *N*-HVIs with electron-rich arenes to access diaryliodonium salts (**1.67** to **1.68**; Scheme 1.8C) and the oxidative dearomatization of electron-deficient hydroquinones (**1.69** to **1.70**; Scheme 1.8D)). It should be noted the two latter results were never published, and the aforementioned published experiments (Scheme 1.9A,B) were simply proof of principle, and no further experimentation or optimization was conducted.

A. Weiss (1994)

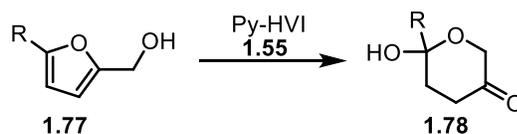


B. Zhdankin (2003)



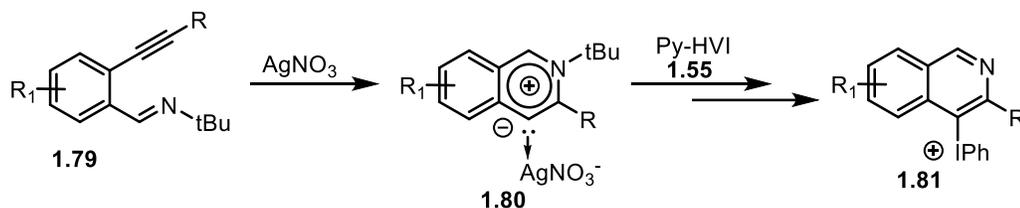
Scheme 1.9. α -functionalization utilizing *Py*-HVI

Weiss later reported the α -functionalization of diazo compounds using *Py*-HVI to install a variety of heteroatomic nucleophiles (Scheme 1.9A).⁵⁷ While this reaction could be conducted with $\text{PhI}(\text{OAc})_2$, a Lewis-acid activator (TMSOTf) was required, which often resulted in diminished yields. Additionally, no loss of N_2 was observed in any case, thereby avoiding carbene formation. The resulting products are described by the author as the synthetic equivalent of carbene cations. This work was followed up by Zhdankin in 2003, where he reported the α -functionalization of various phosphonium ylides to access a variety of α -(heteroaryl)onium substituted products (Scheme 1.9B).⁵⁸



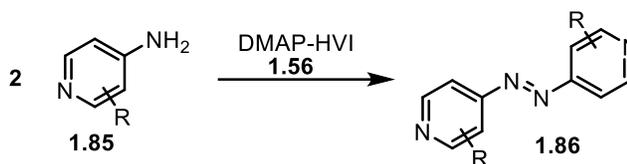
Scheme 1.10. *Py*-HVI-mediated Achmatowicz rearrangement

De Mico and coworkers reported the use of *Py*-HVI in the Achmatowicz reaction of furyl alcohols (**1.77**; Scheme 1.10) to deliver dihydropyran products (**1.78**).⁵⁹ The reaction proceeds by activation of the 2-position of the furan followed by ring cleavage and cyclization, analogous to activation with *m*-CPBA.



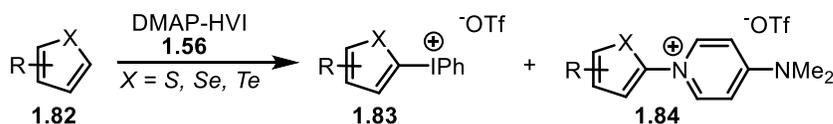
Scheme 1.11. Py-HVI-mediated synthesis of diaryliodonium salts

Py-HVI **1.55** was found to trap metal carbenes by Liu and Liang (Scheme 1.11).⁶⁰ In their procedure, a Lewis acid promoted cyclization occurs which in turn generates a mesoionic carbene complex (**1.80**). This complex acts as a nucleophile to displace the pyridine ligands on Py-HVI **1.55** and deliver the diaryliodonium salt **1.81**. The resulting salt could then be further functionalized by leveraging the hypernucleofugality of the I(III) species.



Scheme 1.12. DMAP-HVI-mediated oxidative aminopyridine coupling

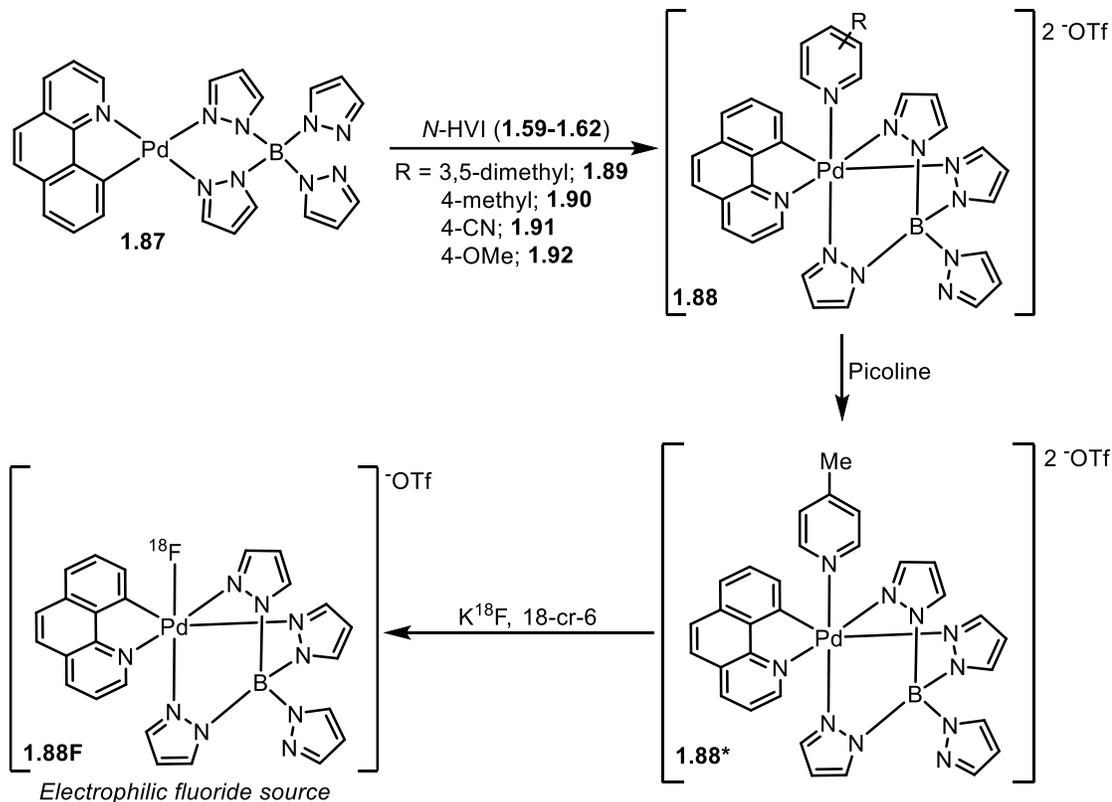
More recently, reports have emerged on the use of *N*-HVIs with different heterocyclic ligands. For example, Huber showcased the oxidative coupling of 4-aminopyridines to synthesize aryl diazo compounds using DMAP-HVI (**1.56**; Scheme 1.12).⁶¹



Scheme 1.13. DMAP-HVI-mediated formal C-H activation

Dutton was also able to utilize DMAP-HVI (**1.56**) to activate thio-, seleno-, and tellurophenes (**1.82**) (Scheme 1.13).⁵⁶ Following their activation, the corresponding diaryliodonium (**1.83**) or (heteroaryl)onium salt (**1.84**) was obtained. These example

reactions demonstrate that even the less reactive DMAP-HVI is a competent reagent in otherwise challenging oxidative transformations.



Scheme 1.14. Oxidation of Pd(II) species utilizing various N-HVIs

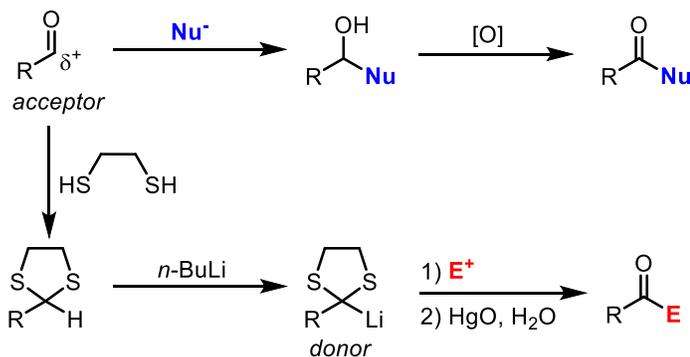
The first reported use of *N*-HVIs for transition metal oxidation was from Ritter and co-workers describing the synthesis of an isolable high valent Pd(IV) species **1.88** via the oxidation of **1.87** with various *N*-HVIs (**1.89–1.92**; Scheme 1.14).^{54,62,63} Through successive ligand exchange reactions, fluoride anion was then introduced access to the Pd(IV) fluoride (**1.88F**) which was subsequently utilized as an electrophilic source of fluorine for the generation a range of structurally diverse ¹⁸F labeled PET imaging molecules.

These early reports provided evidence that *N*-HVIs were highly reactive, versatile, and tunable reagents, however their scope of their application and study remained limited to the aforementioned 11 reports from 1994–2015. It was at this time that the

Wengryniuk laboratory began their in-depth investigations into the synthesis, stability, and reactivity of *N*-HVIs, greatly expanding the synthetic utility of this reagent class.

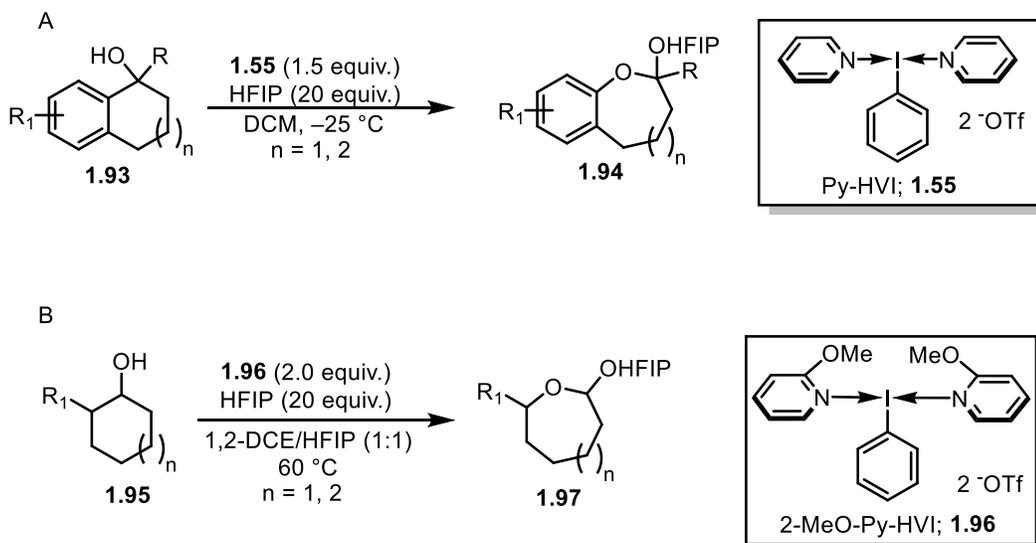
1.5iv: *N*-HVI-Mediated Umpolung Heteroatom Activation (Wengryniuk)

An attractive feature of *N*-HVIs and I(III) HVIs in general is their ability to activate heteroatoms induce a phenomenon known as umpolung activation.⁶⁴ Umpolung chemistry is particularly interesting in that innovative bond formations can be achieved by reversing typically observed polarity of various functional groups. The earliest example is the Corey-Seebach reaction, which allows a reversal of the normal reactivity of acyl carbon atoms. Typically, these carbon atoms combine only with nucleophiles, however by condensation with a dithiane the carbon atom can be deprotonated and act as a nucleophile to introduce various electrophiles (Scheme 1.15). The umpolung activation of heteroatoms became particularly interesting to our group, in particular the activation of oxygen to convert the once donor atom to an acceptor, enabling the formation of new carbon-oxygen bonds via incorporation of carbon nucleophiles.



Scheme 1.15. Example report of Umpolung reactivity (Seebach)

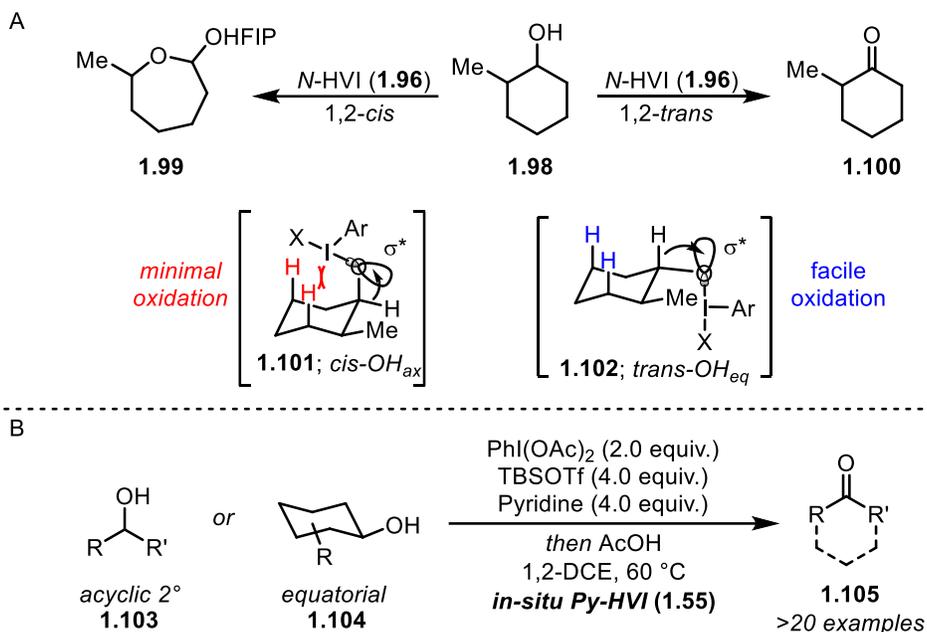
The Wengryniuk laboratory initially became interested in *N*-HVIs when screening for I(III) reagents to enable a novel polarity-inverted rearrangement of tertiary benzylic alcohols to access medium-ring ethers (**1.93**; Scheme 1.16A). The key umpoled oxygen



Scheme 1.16. Heterocycle synthesis via oxidative rearrangement

intermediate would be accessed upon initial ligand exchange between an I(III) reagent and the alcohol center (this likely needs a scheme or at least a structure in 1.16 where you have the N-HVIs currently) umpolung activation of the oxygen atom, followed by a carbon-carbon bond migration in a ring-expansion event to forge a new carbon-oxygen bond. It was found that while all traditional ArIX_2 reagents failed to give the desired rearrangement, *Py*-HVI (**1.55**) in the presence of hexafluoroisopropanol (HFIP) provided the desired medium-sized cyclic ether as the HFIP-acetal (**1.94**).⁶⁵ When looking to expand the scope to include secondary alcohols (**1.95**), it was found that *Py*-HVI was suitable for the benzylic systems and a novel, more reactive *N*-HVI was required (2-*MeO*-*Py*-HVI; **1.96**) for aliphatic alcohols (Scheme 1.16B).⁶⁶ These publications were the seminal works of the group and became a focal point for further research conducted in the group and more specifically in this thesis. This includes improvements made to the method to directly derivatize the HFIP-acetal products in one pot to deliver the cyclic ether products (Chapter 2). Additionally, with the improvements in hand the utility of the oxidative rearrangement was been demonstrated in the diversity-oriented total synthesis

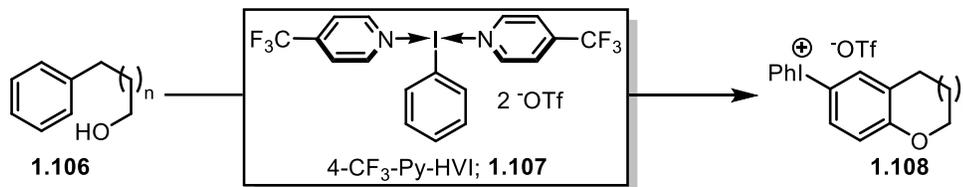
of natural products, allowing access to not only the natural members of the Heliannuol family, but also unnatural analogues (Chapters 3-5).



Scheme 1.17. Conformationally-selective oxidation of secondary alcohols

While investigating the aliphatic secondary alcohols in the rearrangement, it was observed that when *trans*-axial alcohols in a rigid system were subjected to the rearrangement conditions, oxidation was favored almost exclusively (**1.98** to **1.100**) Scheme 1.17A).⁶⁶ This experimental result can be explained by the conformation of the activated alcohol intermediate. When the alcohol is axial, in order to align the orbitals for oxidation there is significant 1,3-diaxial interactions with the iodonium component (**1.101**). Therefore, the highly reactive intermediate is unlikely to form. By contrast, when the alcohol is equatorial the diaxial interactions are alleviated which allows for facile oxidation (**1.102**). This serendipitous finding was leveraged into the first method for the selective oxidation of equatorial alcohols as well as acyclic alcohols, developed by graduate student Myriam Mikhael utilizing *Py*-HVI (Scheme 1.16B).⁴⁴ Additionally, this included the first *in situ* synthesis of an *N*-HVI. This preparation, which required use of

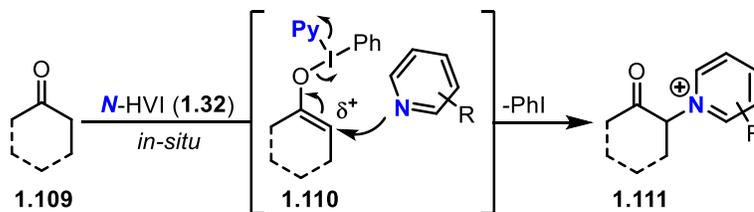
the bulkier TBSOTf activating agent, simplified the overall use of *N*-HVIs and avoided complications associated with isolation.



Scheme 1.18. Aryl ether synthesis via C-H activation

Pendant alcohols (**1.106**) can be activated such that they are prone to electrophilic aromatic substitution to deliver the corresponding cyclic ether products (Scheme 1.18). Following the cyclization, a second equivalent of *N*-HVI reacts with the now electron-rich aryl ring to produce diaryliodonium salts (**1.108**) which are easily isolated without the need for column chromatography. To enable this chemistry for most substrates, a highly reactive *N*-HVI is required in the form of 4-*CF*₃-*Py*-HVI (**1.107**). This work is being prepared for publication at the time of writing this thesis.

1.15v: *N*-HVI-Mediated Heteroatom Group Transfer (HGT)

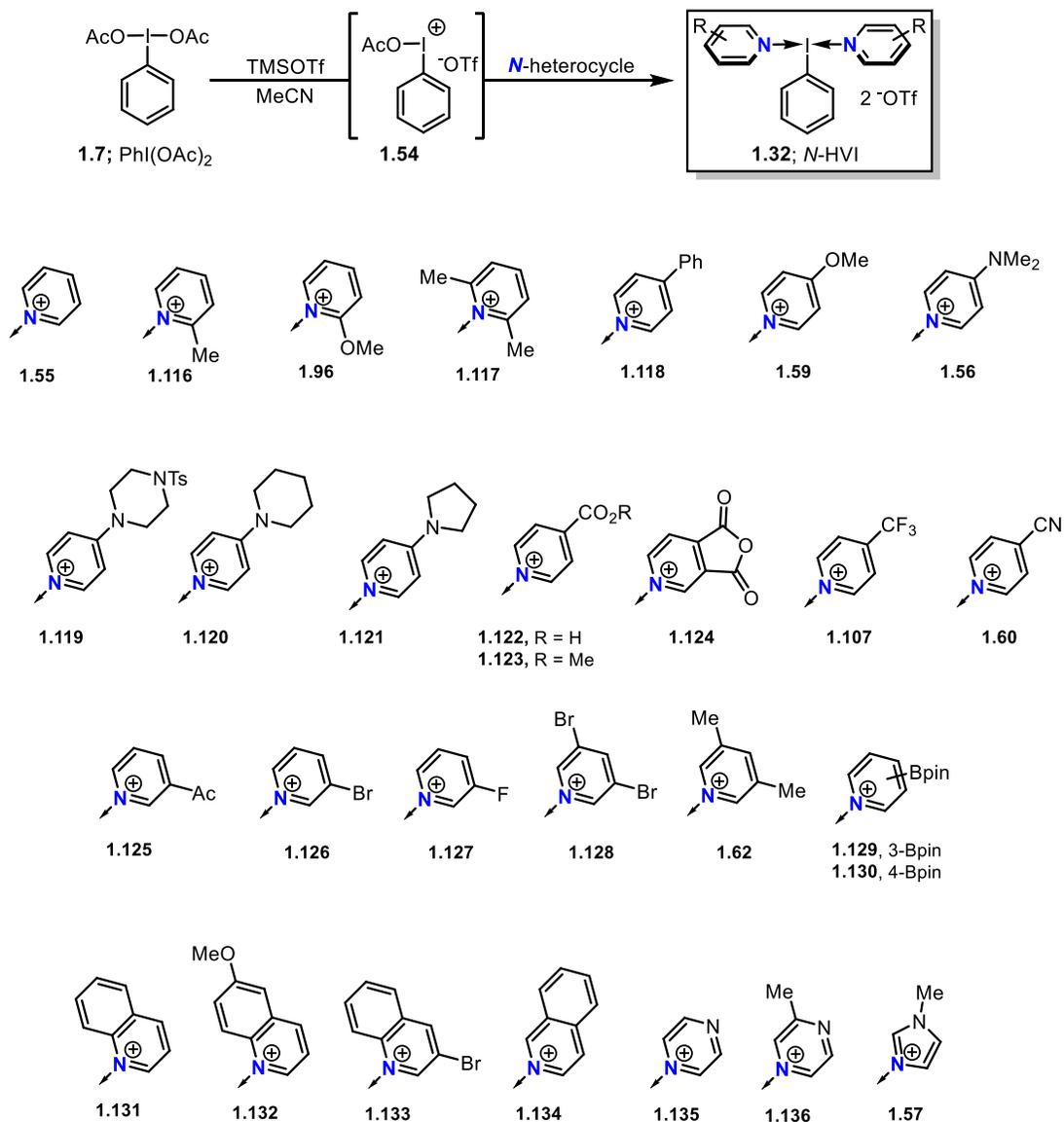


Scheme 1.19. Umpolung activation of enol ethers

Another form of umpolung transformations mediated by *N*-HVIs which our group became particularly interested in was in the activation of olefins. This would entail converting the typical Nu/E functionality of olefins to E/E to enable the sequential addition of two nucleophiles. One such example is the formation of enolonium species, rendering a traditionally nucleophilic enol species electrophilic and prone to nucleophilic attack (**1.110**; Scheme 1.19). This reactivity is currently being leveraged to synthesize a

variety of α -pyridyl ketones which are isolated as stable salts. Additionally, the *N*-HVI is synthesized *in-situ*, bypassing the need to synthesize it in a separate operation.

Preliminary investigations show that a variety of cyclic and acyclic ketones are tolerated, as well as variably substituted pyridyl moieties. As more modes of heteroatom activation is pursued in the laboratory program, alternative functional group activation is also under investigation.



Scheme 1.20. Aminolactonization of olefins and incorporated heterocycle scope

The aminolactonization of alkenoic acids was developed to deliver pyridinium lactones (**1.115**; Scheme 1.20); the first example of engaging an olefin to directly generate these salts.⁶⁷ Pyridinium and related *N* alkyl(heteroaryl)onium salts are versatile synthetic intermediates in organic chemistry, with applications ranging from ring functionalizations to provide diverse piperidine scaffolds to their recent emergence as radical precursors in deaminative cross couplings. The reactions proceed in excellent yields, under mild conditions, and are capable of incorporating a broad scope of sterically and electronically diverse aromatic heterocycles. Mechanistically, the reactions are thought to proceed via olefin activation and lactonization to deliver alkylidonium salt **1.14**. This extremely reactive intermediate then undergoes intermolecular S_N2 displacement by a the nitrogen heterocyclic ligand of the *N*-HVI to deliver the final aminolactone salt product (**1.115**). The *N*-HVI reagents can be generated *in situ*, the products isolated via simple trituration, and subsequent derivatizations demonstrate the power of this platform for diversity-oriented synthesis of 6-membered nitrogen heterocycles. In addition to the novelty of the transformation, this project opened the door for the *in situ* synthesis of an enormous variety of *N*-HVIs (Scheme 1.20). This represents a significant discovery, as synthesized *in-situ* would be extremely challenging to isolate with pre-existing synthetic procedures such as those bearing electron-withdrawing groups in mesomeric positions (**1.60**, **1.107**, **1.22**, **1.23**,) and those with sterically-demanding substituents occluding the nitrogen center (**1.96**, **1.116**, **1.117**).

1.6: SCALABLE PREPARATION OF I(III) *N*-HVIS AND INVESTIGATION OF MOISTURE AND THERMAL STABILITY

1.6i: Improvements to Synthesis

In light of ever-expanding suite of transformations enabled by *N*-HVIs, the disclosure of a detailed protocol for their synthesis and isolation that includes several useful updates to the original procedure seemed timely. As was previously mentioned, a key note in working with *N*-HVIs is their moisture sensitivity, which varies depending on the steric and electronic nature of the heterocyclic ligand. There are conflicting opinions regarding the stability of *N*-HVIs, however we have found that, with proper technique, a wide variety of *N*-HVIs can be reliably synthesized and handled either on the benchtop or using inert atmosphere conditions.

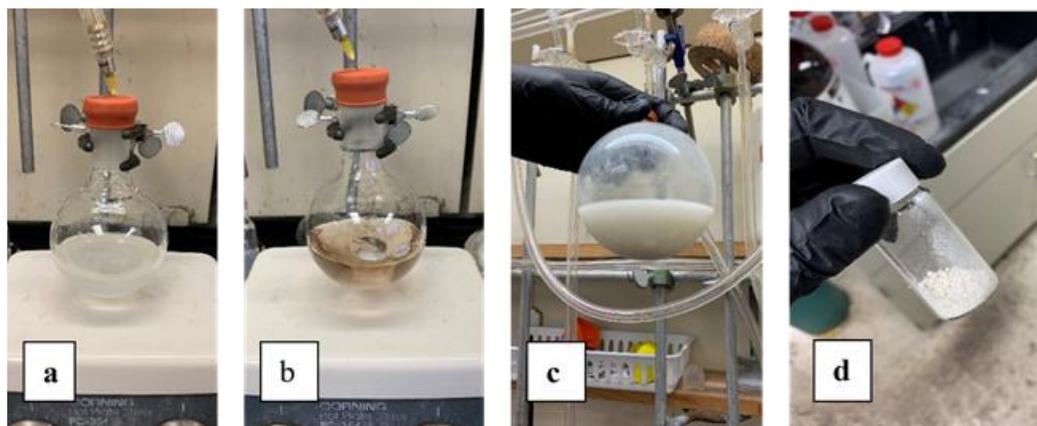
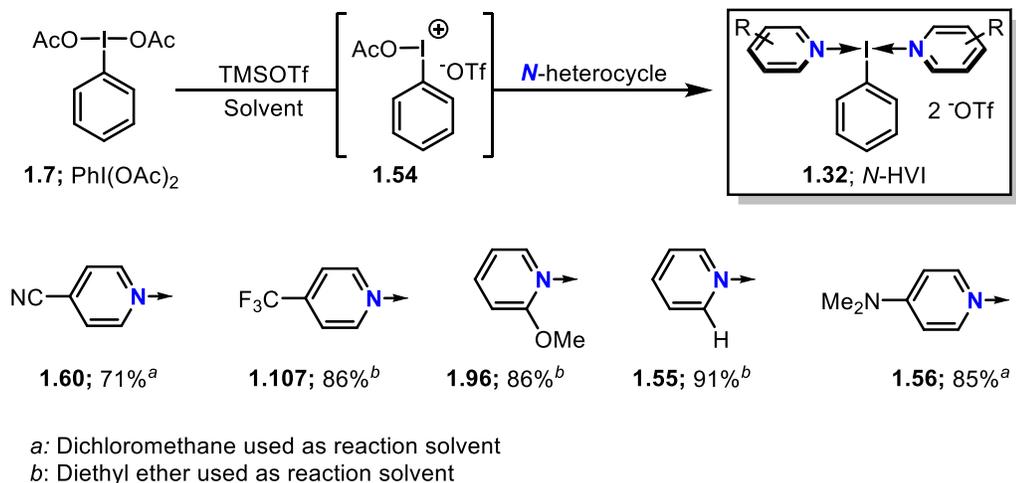


Figure 1.7. Stages of *N*-HVI Synthesis

The general synthesis proceeds as follows: *N*-HVIs can be readily accessed by following the activation protocol originally reported by Weiss⁵² wherein a suspension of commercially available $\text{PhI}(\text{OAc})_2$ in DCM (Figure 1.7a) is followed by addition of TMSOTf to form the activated monoacetate species (**1.54** Figure 1.7b). Following a short stirring period of 5 minutes, the *N*-heterocycle is added which results in the rapid precipitation of the desired *N*-HVI (Figure 1.7c). The product could then be quickly filtered and isolated and stored for future use. It was qualitatively known that *N*-HVI's are particularly moisture sensitive and this effect is seen mostly during filtration and isolation. To consistently deliver high yielding and high quality product, 3 modifications

were introduced: **A)** substitution of solvent, **B)** Glovebox filtration and **C)** Inert benchtop filtration; each will be discussed below. Five representative *N*-HVIs including electron rich (**1.56**), electron-deficient (**1.60**, **1.107**), and sterically demanding (**1.96**) heterocyclic ligands were selected to ensure development of a general protocol (Scheme 1.21).



Scheme 1.21. Synthesis of *N*-HVIs

Modification A: Substitution of Solvent

Oftentimes, the lengthy filtrations are due to the thick and gummy consistency of the *N*-HVI solution. It was hypothesized that by producing a more heterogenous solution and improving the crystal form of the product would facilitate an expedient filtration. To that end, diethyl ether (Et₂O) was used in place of DCM for each ligand. In the cases where solubility of the heterocycle is low, formation of undesired viscous oil was observed, complicating the filtration and lowering the yield. However, this solvent alteration was beneficial in cases where the heterocyclic ligand is soluble in Et₂O (**1.55**, **1.96**, **1.107**) and served the desired purpose to lower the solubility of the *N*-HVI and expedite filtration. This allowed for a simple benchtop filtration in the case of (**1.96**,

1.107) as compared to the synthesis of these reagents in CH_2Cl_2 where even brief exposure to atmospheric moisture led to rapid degradation.

Modification B: Glovebox Filtration

The simplest and most reliable procedural modification is to perform the filtration/isolation and store the material in a moisture- and oxygen-excluding glovebox. (Figure 1.8). Owing to the use of harshly acidic TMSOTf, synthesis of the *N*-HVI in a glovebox is difficult and requires several precautions to maintain the glovebox's integrity including the extreme care to prevent volatilization of harmful halogenated reagents. To avoid this onerous procedure, the *N*-HVI can be brought into the glovebox following its synthesis and prior to filtration (i.e.- after step shown in Figure 1.8a). The filtration (Figure 1.8b), drying, and storage (Figure 1.8c) are then all performed under an inert atmosphere.

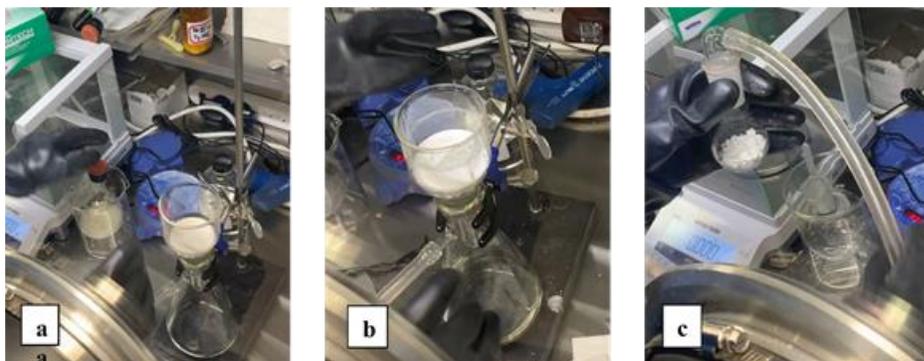


Figure 1.8. Glovebox filtration of *N*-HVI

Modification C: Inert Benchtop Filtration

Supplementing the use of a glovebox, our report disclosed the use of a filter stick for inert handling of sensitive reagents (Figure 1.9). To perform an inert filtration using the filter stick, two 3-neck (24/40) flasks are utilized. For each flask, the rightmost neck is connected to a glass adapter, which is connected via vacuum tubing to a Schlenk

apparatus. The two remaining necks are stoppered using the proper sized rubber septa (Figure 1.9a), and the same synthetic procedure to produce the *N*-HVI is carried out. Upon precipitation of the product, the septum on the leftmost neck of the reaction flask is removed and replaced with a dry filter stick. The septum on the central neck of the receiving flask is then replaced with the other, shallow end of the filter stick (Figure 1.9b). The entire apparatus is then flipped, and the suspension is allowed to fall into the filter stick. The receiving flask is then placed in a $-78\text{ }^{\circ}\text{C}$ dry ice/acetone bath (Figure 1.9c). After the solvent has fully passed through the material into the receiving flask, the vacuum line is closed, and the reaction flask is removed from the top of the filter stick to allow for the addition of rinsing solvent and agitation of the product cake. This rinsing process is performed twice and the product is allowed to dry on the filter for an additional few minutes before being placed into a dry flask for drying to completeness.

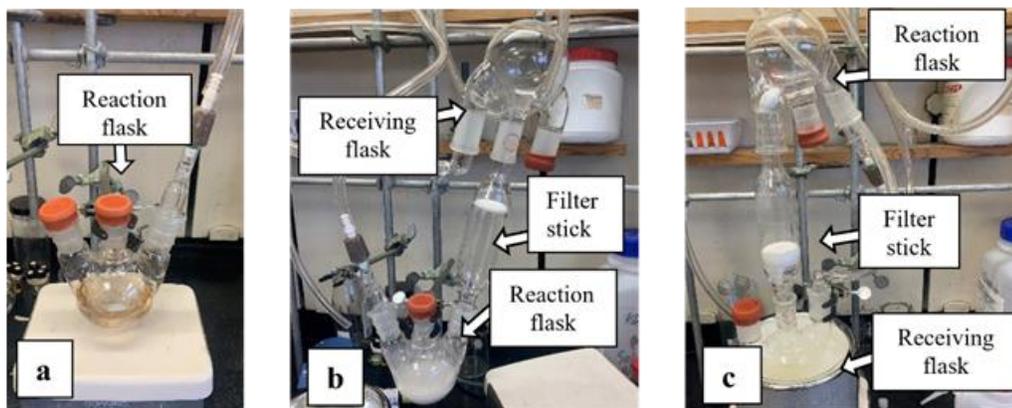


Figure 1.9. Inert benchtop filtration of *N*-HVIs

Regardless of the synthetic method, it is crucial to store the synthesized *N*-HVI in anhydrous conditions for optimal longevity and prolonged reactivity. In all cases, glovebox storage would be ideal, however storage in a dessicator is typically satisfactory if inert filtration was successfully carried out. In total, these modifications offer an alternative solvent to greatly expedite filtration, detailed and improved filtration protocols, and recommendations for storage. As a result, large batches (>40 grams) of

various *N*-HVIs are now regularly synthesized and stored indefinitely in our laboratory, further enabling investigations into their powerful and unique reactivity. A short reference summary of handling procedures for each distinct *N*-HVI is presented in Table 1.1.

<i>N</i> -HVI	Ligand Properties	Modification(s) for Best Results
<i>DMAP</i> -HVI (1.56)	Electron-rich	None; A not compatible
<i>Py</i> -HVI (1.55)	Electron-neutral	A ; (B or C optional)
<i>2-MeO-Py</i> -HVI (1.96)	Sterically-hindered	A ; (B or C optional)
<i>4-CF₃-Py</i> -HVI (1.107)	Electron-deficient	A ; B or C (B preferred)
<i>4-CN-Py</i> -HVI (1.60)	Electron-deficient	B or C (B preferred); A not compatible

Table 1.1. Summary of optimal conditions for *N*-HVI Synthesis

1.6ii: Investigation of Physical Properties

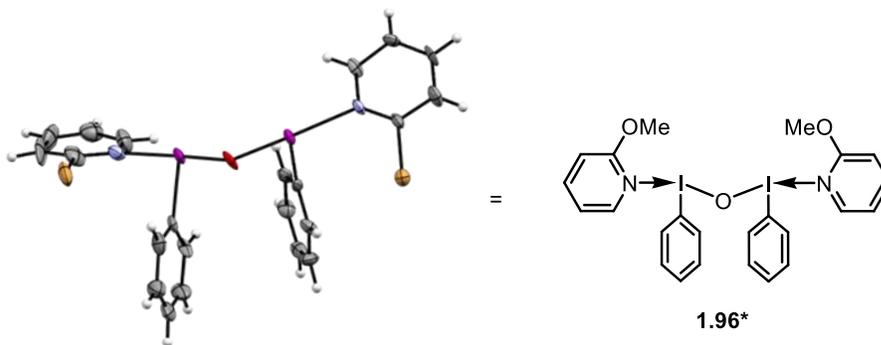


Figure 1.10. Crystal structure of moisture-degradation product

Our numerous efforts to avoid degradation due to moisture either during isolation or storage prompted a deeper investigation into the mechanism by which the *N*-HVIs are decomposing. Moisture instability was briefly mentioned in the seminal report, and it was known that degradation could be qualitatively observed by yellowing of the *N*-HVI.

Fortunately, during attempts to obtain a crystal structure of the desired *2-MeO-Py*-HVI, the degradation product also crystallized and was given unambiguous structure assignment (Figure 1.10). The species formed is an oxo-bridged dimer derived from incorporation of a water molecule and loss of a pyridine ligand (**1.96***). Qualitatively, the formation of this product can be tracked visually by yellowing of the *N*-HVI, as is demonstrated in Figure 1.11 with the degradation of *2-MeO-Py*-HVI (**1.96**)



Figure 1.11. Visually observed degradation of *2-MeO-Py*-HVI

To better understand and observe the time scale on which this degradation occurs, the time course of the reaction with atmospheric moisture was monitored by ^1H NMR (Figure 1.13). A sample of *2-MeO-Py*-HVI (**1.96**) was placed on a watch glass and samples taken at 5 minute intervals over the course of 15 minutes. The findings indicate that the *N*-HVI begins decomposing within 5 minutes and nearly fully converted to the far less reactive oxo-bridged dimer after 10 minutes show an upfield shift in the ortho- and para-hydrogen peaks of both the phenyl iodide moiety as well as the nitrogen ligand.

This is in line with the expected shift with the incorporation of oxygen and decrease of cationic character/increase of electron density at the iodine center.

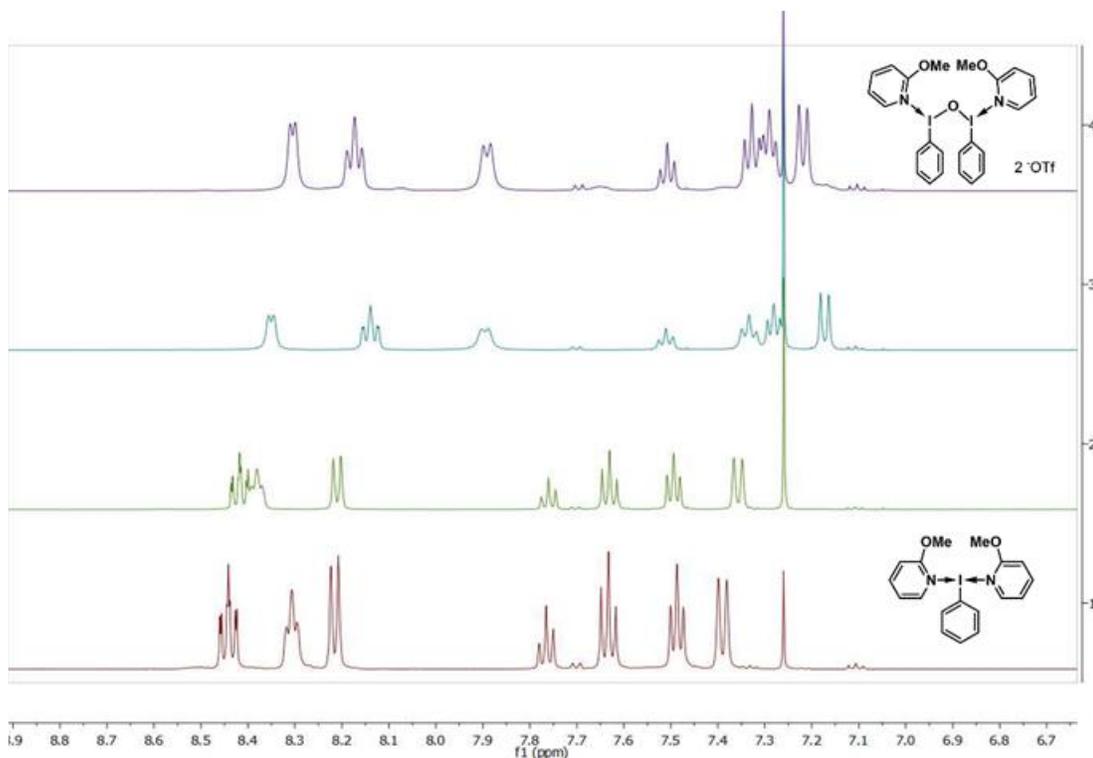


Figure 1.12. Degradation of 2-MeO-Py-HVI tracked by ^1H NMR

Finally, A well known property of HVIs (in particular I(V) reagents i.e. 2-iodoxybenzoic acid; IBX) is their thermal and shock sensitivity.⁶⁸ For reference, the shock sensitivity of IBX was evaluated by evaluating the impact of a steel ball onto a small sample.⁶⁹ The sample “exploded violently under impact.” The thermal stability of IBX as well as DMP were also evaluated by monitoring pressure with increasing temperature. IBX violently exploded at 194 °C and DMP at 130 °C, albeit in a less violent explosion. Explosivity is not limited to I(V) reagents, however, as I(III) reagents have also demonstrated concerning trends in thermal stability. Nachtsheim and co-workers evaluated various pseudocyclic *N*-ligated I(III) reagents by thermogravimetric analysis (TGA), which measures the mass of a sample with increasing temperature, and differential scanning calorimetry (DSC), which measures the energy released by a sample

as temperature increases. The results show increasing thermal sensitivity, or explosiveness, with increasing nitrogen content in the heterocycle as indicated by sharp slopes in both plots at around 200 °C. As such, triazole ligands were suggested to be handled with care. In light of the above results, TGA was performed on each reagent with $\text{PhI}(\text{OAc})_2$ as a control (Figure 1.12), beginning at ambient temperature and warming gradually to 800 °C. Unfortunately, DSC was not performed due to available instrument capabilities. The data shows gentle slopes for each sample, indicative of a gradual loss of mass beginning around 100 °C rather than an instantaneous, explosive event. Therefore, it can be concluded that each *N*-HVI is thermally stable. A rudimentary shock sensitivity test was performed by dropping a hammer from a constant height on each sample, and no detonation was observed in any case indicating satisfactory shock stability.

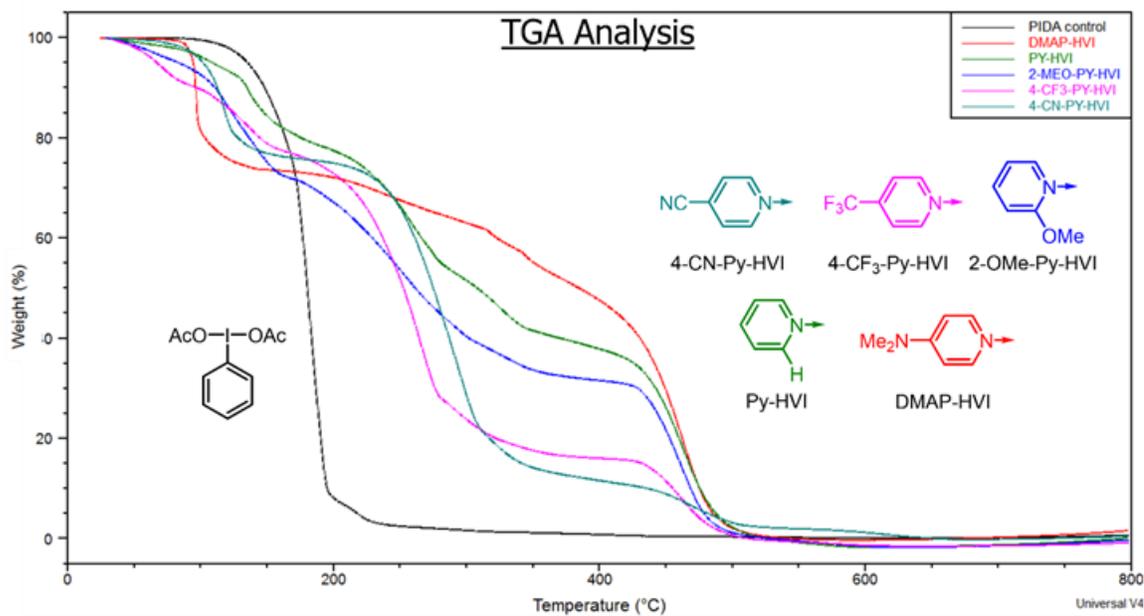


Figure 1.13. TGA of *N*-HVI's with $\text{PhI}(\text{OAc})_2$ as a control

1.7: CONCLUSIONS

There is a continued need for the development of safe, inexpensive, and tunable oxidants. Hypervalent iodine reagents, and in particular those in the I(III) oxidation state, represent an ever-expanding class of oxidants that fit these requirements. Within I(III) reagents, *N*-HVIs, which possess two *N*-heterocyclic ligands bound to a central iodine atom, represent a modular, tunable, and reactive class of reagents. These reagents have been shown to be effective oxidants for organic and organometallic species in the scope of C-H functionalization, oxidation of metal centers, and synthesis of diaryliodonium salts. The Wengryniuk laboratory has further demonstrated their utility in enabling a variety of umpolung transformations via heteroatom activation or olefin activation. These transformations include an oxidative rearrangement, electrophilic aromatic substitution, and di-functionalization of olefins, among others. This Chapter described our efforts in the improved synthesis, isolation, and storage of varied *N*-HVI analogues as well as insights into their moisture and thermal stability. A portion of these findings relating to the synthesis of **1.55** and **1.107** will be reported in *Organic Syntheses*, through which we aim to demystify and standardize the synthesis and handling of *N*-HVIs. With this information in hand, we believe that *N*-HVIs will be more broadly adopted by the synthetic community and their potential be fully realized as a new toolbox for I(III) reagent design and oxidative transformations.

Experimental data for this chapter can be found in Appendix A.

1.8: REFERENCES

- (1) Guengerich, F. P.; Macdonald, T. L. Mechanisms of Cytochrome P-450 Catalysis. *FASEB J.* **1990**, *4* (8), 2453–2459. <https://doi.org/10.1096/fasebj.4.8.2185971>.
- (2) Guengerich, F. P. Reactions and Significance of Cytochrome P-450 Enzymes. *Journal of Biological Chemistry*. Elsevier June 5, 1991, pp 10019–10022. [https://doi.org/10.1016/s0021-9258\(18\)99177-5](https://doi.org/10.1016/s0021-9258(18)99177-5).
- (3) Tyeklár, Z.; Karlin, K. D. Copper–Dioxygen Chemistry: A Bioinorganic Challenge. *Acc. Chem. Res.* **1989**, *22* (7), 241–248. <https://doi.org/10.1021/ar00163a003>.
- (4) Jang, H. G.; Cox, D. D.; Que, L. A Highly Reactive Functional Model for the Catechol Dioxygenases. Structure and Properties of [Fe(TPA)DBC]BPh₄. *J. Am. Chem. Soc.* **1991**, *113* (24), 9200–9204. <https://doi.org/10.1021/ja00024a028>.
- (5) Liu, J.; Bedell, T. A.; West, J. G.; Sorensen, E. J. Design and Synthesis of Molecular Scaffolds with Anti-Infective Activity. *Tetrahedron* **2016**, *72* (25), 3579–3592. <https://doi.org/10.1016/j.tet.2016.01.044>.
- (6) Abrams, D. J.; Provencher, P. A.; Sorensen, E. J. Recent Applications of C-H Functionalization in Complex Natural Product Synthesis. *Chemical Society Reviews*. **2018**, 8925–8967. <https://doi.org/10.1039/c8cs00716k>.
- (7) Nicolaou, K. C.; Rigol, S. The Role of Organic Synthesis in the Emergence and Development of Antibody–Drug Conjugates as Targeted Cancer Therapies. *Angew. Chem. Int. Ed.* **2019**, 11206–11241. <https://doi.org/10.1002/anie.201903498>.
- (8) Marui, K.; Nomoto, A.; Akashi, H.; Ogawa, A. Green Oxidation of Amines to

Imines Based on the Development of Novel Catalytic Systems Using Molecular Oxygen or Hydrogen Peroxide. *Synth.* **2016**, *48* (1), 31–42.

<https://doi.org/10.1055/s-0035-1560363>.

- (9) Thayer, A. M. Catalyst Suppliers Face Changing Industry. *Chemical and Engineering News*. **1992**, 27–49. <https://doi.org/10.1021/cen-v070n010.p027>.
- (10) Guo, Z.; Liu, B.; Zhang, Q.; Deng, W.; Wang, Y.; Yang, Y. Recent Advances in Heterogeneous Selective Oxidation Catalysis for Sustainable Chemistry. *Chemical Society Reviews*. **2014**, pp 3480–3524. <https://doi.org/10.1039/c3cs60282f>.
- (11) Gormisky, P. E.; White, M. C. Synthetic Versatility in C-H Oxidation: A Rapid Approach to Differentiated Diols and Pyrans from Simple Olefins. *J. Am. Chem. Soc.* **2011**, *133* (32), 12584–12589. <https://doi.org/10.1021/ja206013j>.
- (12) Murahashi, S. I.; Zhang, D. Ruthenium Catalyzed Biomimetic Oxidation in Organic Synthesis Inspired by Cytochrome P-450. *Chem. Soc. Rev.* **2008**, *37* (8), 1490–1501. <https://doi.org/10.1039/b706709g>.
- (13) Suzuki, T. Organic Synthesis Involving Iridium-Catalyzed Oxidation. *Chemical Reviews*. 2011, pp 1825–1845. <https://doi.org/10.1021/cr100378r>.
- (14) Henry, J. R.; Weinreb, S. M. A Convenient, Mild Method for Oxidative Cleavage of Alkenes with Jones Reagent/Osmium Tetraoxide. *Journal of Organic Chemistry*. **1993**, 4745. <https://doi.org/10.1021/jo00069a047>.
- (15) Harding, K. E.; May, L. M.; Dick, K. F. Selective Oxidation of Allylic Alcohols with Chromic Acid. *J. Org. Chem.* **1975**, *40* (11), 1664–1665. <https://doi.org/10.1021/jo00899a040>.
- (16) Li, J. J. *Name Reactions*; 2014. <https://doi.org/10.1007/978-3-319-03979-4>.

- (17) Corey, E. J.; Suggs, J. W. Pyridinium Chlorochromate. An Efficient Reagent for Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds. *Tetrahedron Lett.* **1975**, *16* (31), 2647–2650. [https://doi.org/10.1016/S0040-4039\(00\)75204-X](https://doi.org/10.1016/S0040-4039(00)75204-X).
- (18) Dauben, W. G.; Michno, D. M. Direct Oxidation of Tertiary Allylic Alcohols. A Simple and Effective Method for Alkylative Carbonyl Transposition. *J. Org. Chem.* **1977**, *42* (4), 682–685. <https://doi.org/10.1021/jo00424a023>.
- (19) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. Redox Economy in Organic Synthesis. *Angew. Chemie - Int. Ed.* **2009**, *48* (16), 2854–2867. <https://doi.org/10.1002/anie.200806086>.
- (20) Nicolaou, K. C.; Chen, P.; Zhu, S.; Cai, Q.; Erande, R. D.; Li, R.; Sun, H.; Pulukuri, K. K.; Rigol, S.; Aujay, M.; Sandoval, J.; Gavriluk, J. Streamlined Total Synthesis of Trioxacarcins and Its Application to the Design, Synthesis, and Biological Evaluation of Analogues Thereof. Discovery of Simpler Designed and Potent Trioxacarcin Analogues. *J. Am. Chem. Soc.* **2017**, *139* (43), 15467–15478. <https://doi.org/10.1021/jacs.7b08820>.
- (21) Siler, D. A.; Mighion, J. D.; Sorensen, E. J. An Enantiospecific Synthesis of Jiadifenolide. *Angew. Chemie - Int. Ed.* **2014**, *53* (21), 5332–5335. <https://doi.org/10.1002/anie.201402335>.
- (22) Zhang, S. L.; Xie, H. X.; Zhu, J.; Li, H.; Zhang, X. S.; Li, J.; Wang, W. Organocatalytic Enantioselective β -Functionalization of Aldehydes by Oxidation of Enamines and Their Application in Cascade Reactions. *Nat. Commun.* **2011**, *2* (1), 211. <https://doi.org/10.1038/ncomms1214>.

- (23) Toledo, H.; Pisarevsky, E.; Abramovich, A.; Szpilman, A. M. Organocatalytic Oxidation of Aldehydes to Mixed Anhydrides. *Chem. Commun.* **2013**, 49 (39), 4367–4369. <https://doi.org/10.1039/c2cc35220f>.
- (24) Mancuso, A. J.; Huang, S. L.; Swern, D. Oxidation of Long-Chain and Related Alcohols to Carbonyls by Dimethyl Sulfoxide “Activated” by Oxalyl Chloride. *J. Org. Chem.* **1978**, 43 (12), 2480–2482. <https://doi.org/10.1021/jo00406a041>.
- (25) Huang, S. L.; Omura, K.; Swern, D. Oxidation of Sterically Hindered Alcohols to Carbonyls with Dimethyl Sulfoxide-Trifluoroacetic Anhydride. *J. Org. Chem.* **1976**, 41 (20), 3329–3331. <https://doi.org/10.1021/jo00882a030>.
- (26) Huang, S. L.; Omura, K.; Swern, D. Further Studies on the Oxidation of Alcohols to Carbonyl Compounds by Dimethyl Sulfoxide/Trifluoroacetic Anhydride. *Synth.* **1978**, 1978 (4), 297–299. <https://doi.org/10.1055/s-1978-24729>.
- (27) Corey, E. J.; Kim, C. U. A New and Highly Effective Method for the Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds. *J. Am. Chem. Soc.* **1972**, 94 (21), 7586–7587. <https://doi.org/10.1021/ja00776a056>.
- (28) Tangerman, A.; Winkel, E. G. Extra-Oral Halitosis: An Overview. *Journal of Breath Research.* **2010**, 17003. <https://doi.org/10.1088/1752-7155/4/1/017003>.
- (29) Tangerman, A.; Winkel, E. G. Intra- and Extra-Oral Halitosis: Finding of a New Form of Extra-Oral Blood-Borne Halitosis Caused by Dimethyl Sulphide. *J. Clin. Periodontol.* **2007**, 34 (9), 748–755. <https://doi.org/10.1111/j.1600-051X.2007.01116.x>.
- (30) Gillespie, R. J.; Silvi, B. The Octet Rule and Hypervalence: Two Misunderstood Concepts. *Coordination Chemistry Reviews.* **2002**, 53–62.

[https://doi.org/10.1016/S0010-8545\(02\)00102-9](https://doi.org/10.1016/S0010-8545(02)00102-9).

- (31) Yoshimura, A.; Zhdankin, V. V. Advances in Synthetic Applications of Hypervalent Iodine Compounds. *Chemical Reviews*. **2016**, 3328–3435.
<https://doi.org/10.1021/acs.chemrev.5b00547>.
- (32) Yusubov, M. S.; Zhdankin, V. V. Iodine Catalysis: A Green Alternative to Transition Metals in Organic Chemistry and Technology. *Resour. Technol.* **2015**, *1* (1), 49–67. <https://doi.org/10.1016/j.reffit.2015.06.001>.
- (33) Moriarty, R. M.; Prakash, O. *Synthesis of Heterocyclic Compounds Using Organohypervalent Iodine Reagents*; **1998**.
- (34) Prakash, O.; Batra, H.; Kaur, H.; Sharma, P. K.; Sharma, V.; Singh, S. P.; Moriarty, R. M. Hypervalent Iodine Oxidative Rearrangement of Anthranilamides, Salicylamides and Some β -Substituted Amides: A New and Convenient Synthesis of 2-Benzimidazolones, 2-Benzoxazolones and Related Compounds. *Synthesis (Stuttg)*. **2001**, No. 4, 541–543. <https://doi.org/10.1055/s-2001-12346>.
- (35) Moriarty, R. M. Organohypervalent Iodine: Development, Applications, and Future Directions. *J. Org. Chem.* **2005**, 2893–2903.
<https://doi.org/10.1021/jo050117b>.
- (36) Okuyama, T.; Takino, T.; Sueda, T.; Ochiai, M. Solvolysis of Cyclohexenyliodonium Salt, a New Precursor for the Vinyl Cation: Remarkable Nucleofugality of the Phenyliodonio Group and Evidence for Internal Return from an Intimate Ion—Molecule Pair. *J. Am. Chem. Soc.* **1995**, *117* (12), 3360–3367.
<https://doi.org/10.1021/ja00117a006>.
- (37) Merritt, E. A.; Olofsson, B. Diaryliodonium Salts: A Journey from Obscurity to

Fame. *Angew. Chem. Int. Ed.* **2009**, 9052–9070.

<https://doi.org/10.1002/anie.200904689>.

- (38) Takenaga, N.; Kumar, R.; Dohi, T. Heteroarylodonium(III) Salts as Highly Reactive Electrophiles. *Frontiers in Chemistry*. **2020**, 599026.
<https://doi.org/10.3389/fchem.2020.599026>.
- (39) Zhdankin, V. V. *Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds*; Wiley, **2014**.
<https://doi.org/10.1002/9781118341155>.
- (40) Catalano, L.; Cavallo, G.; Mentrangolo, P.; Resnati, G.; Terraneo, G. Halogen Bonding in Hypervalent Iodine Compounds. *Top. Curr. Chem.* **2016**, 373, 289–310. https://doi.org/10.1007/128_2015_666.
- (41) Sousa E Silva, F. C.; Van, N. T.; Wengryniuk, S. E. Direct C-H α -Arylation of Enones with ArI(O₂CR)₂ Reagents. *J. Am. Chem. Soc.* **2020**, 142 (1), 64–69.
<https://doi.org/10.1021/jacs.9b11282>.
- (42) Alcock, N. W.; Harrison, W. D.; Howes, C. Secondary Bonding. Part 13. Aryl-Tellurium(IV) and -Iodine(III) Acetates and Trifluoroacetates. The Crystal and Molecular Structures of Bis-(p-Methoxyphenyl)Tellurium Diacetate, μ -Oxo-Bis[Diphenyltrifluoroacetoxytellurium] Hydrate, and [Bis(Trifluoroacet. *J. Chem. Soc. Dalt. Trans.* **1984**, No. 8, 1709–1716. <https://doi.org/10.1039/DT9840001709>.
- (43) Karade, N. N.; Budhewar, V. H.; Katkar, A. N.; Tiwari, G. B. Oxidative Methyl Esterification of Aldehydes Promoted by Molecular and Hypervalent (III) Iodine. *Arkivoc* **2006**, 2006 (11), 162–167. <https://doi.org/10.3998/ark.5550190.0007.b16>.
- (44) Mikhael, M.; Adler, S. A.; Wengryniuk, S. E. Chemoselective Oxidation of

- Equatorial Alcohols with N-Ligated Λ^3 -Iodanes. *Org. Lett.* **2019**, *21* (15), 5889–5893. <https://doi.org/10.1021/acs.orglett.9b02018>.
- (45) Vatèle, J. M. Yb(OTf)₃-Catalyzed Oxidation of Alcohols with Iodosylbenzene Mediated by TEMPO. *Synlett* **2006**, *2006* (13), 2055–2058. <https://doi.org/10.1055/s-2006-948181>.
- (46) Signo, K.; Mammasse, Z.; Canesi, S. Elaboration of Functionalized Organophosphates. *J. Org. Chem.* **2020**, *85* (4), 2832–2837. <https://doi.org/10.1021/acs.joc.9b03324>.
- (47) Deruer, E.; Coulibali, S.; Boukercha, S.; Canesi, S. Carbon-Phosphorus Bond Formation on Anilines Mediated by a Hypervalent Iodine Reagent. *J. Org. Chem.* **2017**, *82* (22), 11884–11890. <https://doi.org/10.1021/acs.joc.7b01595>.
- (48) Jacquemot, G.; Canesi, S. Oxidative Ipso -Rearrangement Performed by a Hypervalent Iodine Reagent and Its Application. *J. Org. Chem.* **2012**, *77* (17), 7588–7594. <https://doi.org/10.1021/jo301408j>.
- (49) Snyder, S. A.; Sherwood, T. C.; Ross, A. G. Total Syntheses of Dalesconol A and B. *Angew. Chemie - Int. Ed.* **2010**, *49* (30), 5146–5150. <https://doi.org/10.1002/anie.201002264>.
- (50) Yoshimura, A.; Yusubov, M. S.; Zhdankin, V. V. Synthetic Applications of Pseudocyclic Hypervalent Iodine Compounds. *Organic and Biomolecular Chemistry*. **2016**, 4771–4781. <https://doi.org/10.1039/c6ob00773b>.
- (51) Ibrahim, H.; Kleinbeck, F.; Togni, A. Catalytic Asymmetric Chlorination of β -Keto Esters with Hypervalent Iodine Compounds. *Helv. Chim. Acta.* **2004**, *87* (3), 605–610. <https://doi.org/10.1002/hlca.200490058>.

- (52) Weiss, R.; Seubert, J. Electrostatic Activation of Hypervalent Organo-Iodine Compounds: Bis(Onio)-Substituted Aryliodine(III) Salts. *Angew. Chemie Int. Ed. English* **1994**, *33* (8), 891–893. <https://doi.org/10.1002/anie.199408911>.
- (53) Izquierdo, S.; Essafi, S.; Del Rosal, I.; Vidossich, P.; Pleixats, R.; Vallribera, A.; Ujaque, G.; Lledós, A.; Shafir, A. Acid Activation in Phenyliodine Dicarboxylates: Direct Observation, Structures, and Implications. *J. Am. Chem. Soc.* **2016**, *138* (39), 12747–12750. <https://doi.org/10.1021/jacs.6b07999>.
- (54) Ritter, T.; Lee, E.; Kamlet, A. S.; Powers, D.; Furuya, T. HIGH-VALENT PALLADIUM FLUORIDE COMPLEXES AND USES THEREOF. WO2011US48451, February 23, 2012.
- (55) Corbo, R.; Dutton, J. L. Weiss' Reagents: A Synthetically Useful Class of Iodine(III) Coordination Compounds. *Coordination Chemistry Reviews*. Elsevier B.V. November 15, 2018, pp 69–79. <https://doi.org/10.1016/j.ccr.2017.10.018>.
- (56) Egalahewa, S.; Albayer, M.; Aprile, A.; Dutton, J. L. Diverse Reactions of Thiophenes, Selenophenes, and Tellurophenes with Strongly Oxidizing I(III) PhI(L)₂ Reagents. *Inorg. Chem.* **2017**, *56* (3), 1282–1288. <https://doi.org/10.1021/acs.inorgchem.6b02386>.
- (57) Weiss, R.; Seubert, J.; Hampel, F. A-Aryliodonio Diazo Compounds: SN Reactions at the A-C Atom as a Novel Reaction Type for Diazo Compounds. *Angew. Chemie Int. Ed. English* **1994**, *33* (19), 1952–1953. <https://doi.org/10.1002/anie.199419521>.
- (58) Zhdankin, V. V.; Maydanovych, O.; Herschbach, J.; Bruno, J.; Matveeva, E. D.; Zefirov, N. S. Preparation and Chemistry of Phosphoranyl-Derived Iodanes. *J.*

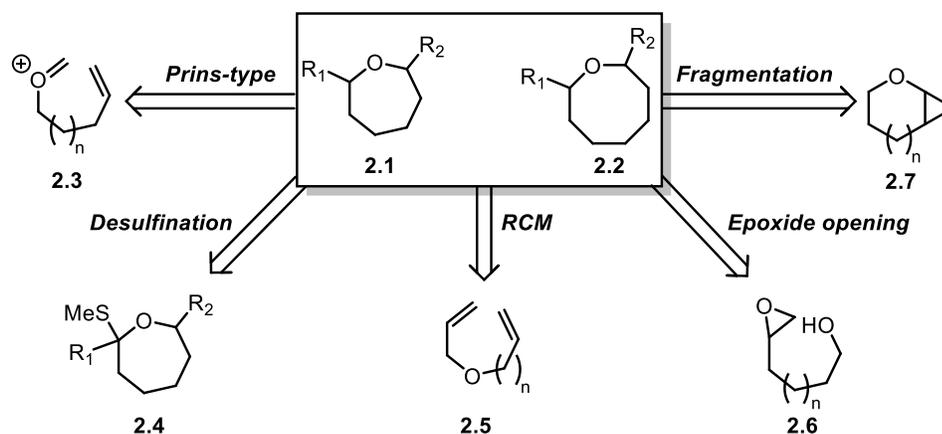
- Org. Chem.* **2003**, *68* (3), 1018–1023. <https://doi.org/10.1021/jo026604y>.
- (59) De Mico, A.; Margarita, R.; Piancatelli, G. Hypervalent Iodine-Induced Ring Enlargement of Furan-Derivatives into Pyran-3-(6H)-Ones. *Gazzetta Chim. Ital.* **1995**, *125* (7), 325–326.
- (60) Yuan, Z.; Cheng, R.; Chen, P.; Liu, G.; Liang, S. H. Efficient Pathway for the Preparation of Aryl(Isoquinoline)Iodonium(III) Salts and Synthesis of Radiofluorinated Isoquinolines. *Angew. Chemie - Int. Ed.* **2016**, *55* (39), 11882–11886. <https://doi.org/10.1002/anie.201606381>.
- (61) Kniep, F.; Walter, S. M.; Herdtweck, E.; Huber, S. M. 4,4'-Azobis(Halopyridinium) Derivatives: Strong Multidentate Halogen-Bond Donors with a Redox-Active Core. *Chem. - A Eur. J.* **2012**, *18* (5), 1306–1310. <https://doi.org/10.1002/chem.201103071>.
- (62) Lee, E.; Hooker, J. M.; Ritter, T. Nickel-Mediated Oxidative Fluorination for PET with Aqueous [¹⁸F] Fluoride. *J. Am. Chem. Soc.* **2012**, *134* (42), 17456–17458. <https://doi.org/10.1021/ja3084797>.
- (63) Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. A Fluoride-Derived Electrophilic Late-Stage Fluorination Reagent for PET Imaging. *Science.* **2011**, *334* (6056), 639–642. <https://doi.org/10.1126/science.1212625>.
- (64) Seebach, D. Methods of Reactivity Umpolung. *Angewandte Chemie International Edition in English*. John Wiley & Sons, Ltd April 1, 1979, pp 239–258. <https://doi.org/10.1002/anie.197902393>.
- (65) Kelley, B. T.; Walters, J. C.; Wengryniuk, S. E. Access to Diverse Oxygen

- Heterocycles via Oxidative Rearrangement of Benzylic Tertiary Alcohols. *Org. Lett.* **2016**, *18* (8), 1896–1899. <https://doi.org/10.1021/acs.orglett.6b00672>.
- (66) Walters, J. C.; Tierno, A. F.; Dubin, A. H.; Wengryniuk, S. E. (Poly)Cationic Λ^3 -Iodane-Mediated Oxidative Ring Expansion of Secondary Alcohols. *European J. Org. Chem.* **2018**, *2018* (12), 1460–1464. <https://doi.org/10.1002/ejoc.201800118>.
- (67) Tierno, A. F.; Walters, J. C.; Vazquez-Lopez, A.; Xiao, X.; Wengryniuk, S. E. Heterocyclic Group Transfer Reactions with I(III) N-HVI Reagents: Access to N-Alkyl(Heteroaryl)Onium Salts via Olefin Aminolactonization. *Chem. Sci.* **2021**, *12* (18), 6385–6392. <https://doi.org/10.1039/d1sc00187f>.
- (68) Frigerio, M.; Santagostino, M.; Sputore, S. A User-Friendly Entry to 2-Iodoxybenzoic Acid (IBX). *J. Org. Chem.* **1999**, *64* (12), 4537–4538. <https://doi.org/10.1021/jo9824596>.
- (69) Kiefer, D. M.; Krieger, J. H.; Long, J. R.; Sois-Son, D. J.; Storck, W. J.; Borman, S. A.; Brennan, M. B.; Menting, A. M.; Seltzer, R. J.; Baker, D. F.; Bodner, G. M.; Carpenter, W. D.; Ford, R. G.; Galloway, E. C.; Glunz, L. J.; Hertz, H. S.; Hill, C. T.; Houk, K. N.; Maryanoff, C. A.; McGown, L. B.; Moore, C. B.; Nakanishi, K.; Rathmann, G. B.; Shir-Ley, D. A.; Simon, R. M.; Spitz, P. H.; Trost, B. M.; Dixon, J. A.; Gassman, P. G.; Deming, R. L.; Jencks, W. P.; Long, G. J.; Quin, L. D. LETTERS. *Chem. Eng. News Arch.* **1990**, *68* (29), 2-3,45. <https://doi.org/10.1021/cen-v068n029.p002>.

CHAPTER 2: IMPROVEMENTS TO UMPOLUNG RING EXPANSION OF BENZYLIC ALCOHOLS

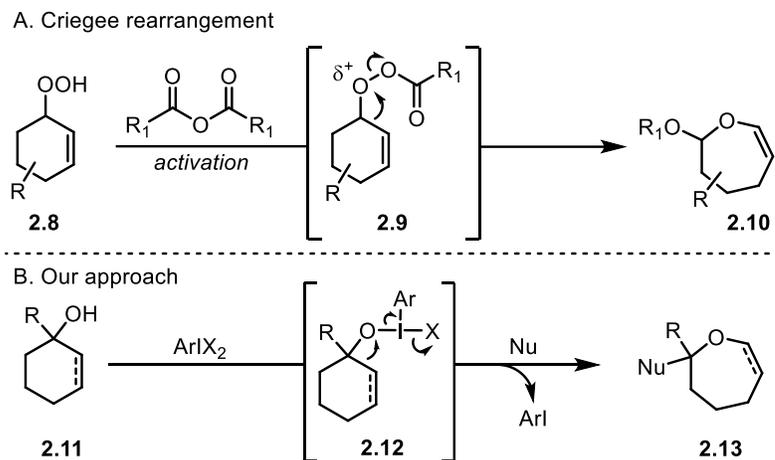
2.1: BACKGROUND AND SIGNIFICANCE

Medium-sized cyclic ethers are commonly encountered scaffolds present in a large variety of natural products. As such, methods for the synthesis of these structural motifs have garnered substantial interest.¹ Unlike the related furan and pyran rings, the synthesis of 7-9 membered rings is often difficult due to entropic penalties, unfavorable transannular interactions (Prelog strain), torsional (Pitzer) strain and angle (Baeyer) strain associated with their formation.^{2,3} Prior strategies have relied on approaches such as Prins-type cyclizations,^{4,5} sequential thiolactone synthesis and derivatization,⁶ ring closing metathesis,⁷⁻⁹ regioselective epoxide cleavage,¹⁰ and cyclopropane fragmentation¹¹ (Scheme 2.1). Despite their utility, these prior approaches often require complex pre-functionalized starting materials or undesired peripheral functionality, and poor functional group compatibility can require the use of protecting groups. Therefore, the development of new methods to directly access medium-sized cyclic ethers from simple and readily accessible precursors by implementing novel disconnections became a focal point of our research program. With such a method, the goal is move away from the



Scheme 2.1. Prior approaches to medium-sized cyclic ethers

current “flatland” of medicinal chemistry libraries and enable late-stage derivatization of complex molecules.



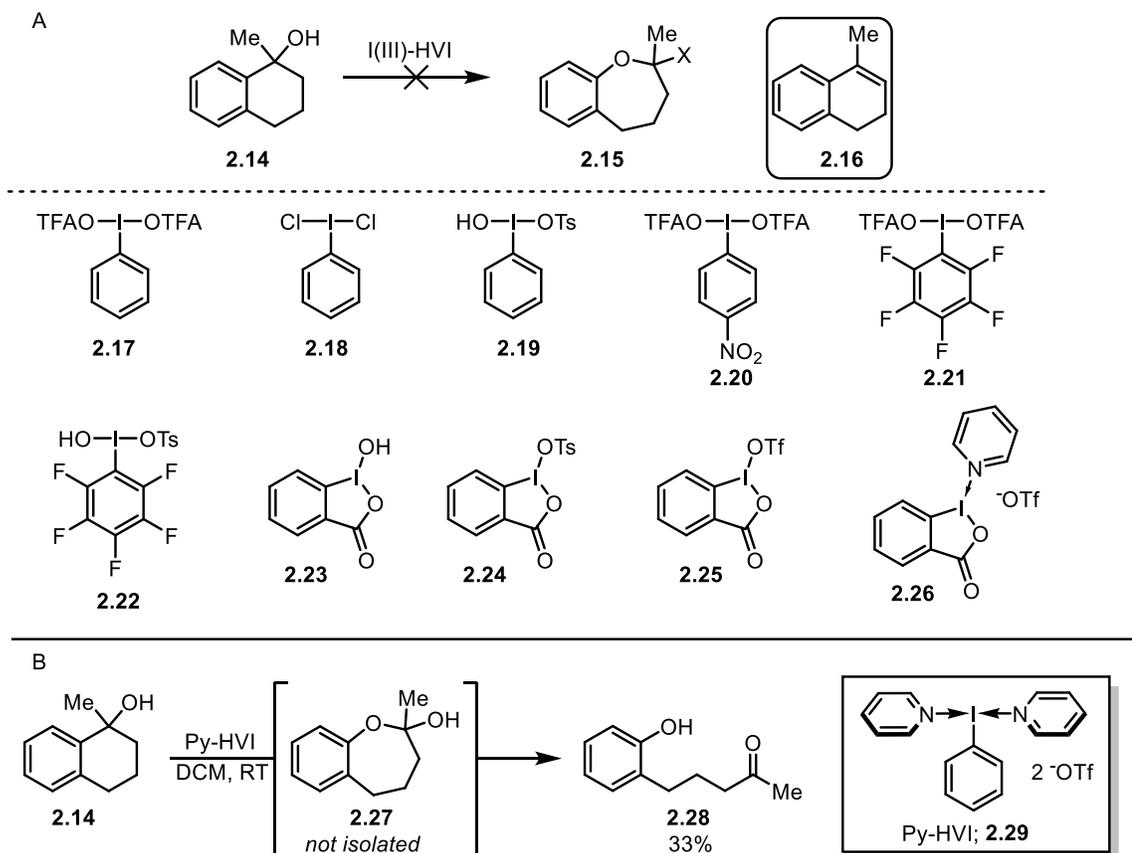
Scheme 2.2. Proposed approach to medium-sized cyclic ethers

In devising a method to access medium-sized cyclic ethers from readily available precursors, inspiration was drawn from the Criegee rearrangement of cyclic alkyl peroxides, in which activation of the terminal oxygen renders the carbon-bound oxygen atom suitably electrophilic to promote a carbon to oxygen bond migration, driven by with cleavage of the weak O–O bond (Scheme 2.2A).^{12,13} Unfortunately requirement of an alkyl peroxide has limited the synthetic utility of the Criegee Rearrangement^{14–17} and renders it ineffective for late-stage derivatizations. It was hypothesized that a peroxide could be replaced by a readily available alcohol, with a similar electrophilic intermediate intercepted through activation with an I(III) hypervalent iodine (HVI) reagent (Scheme 2.2B). Hypervalent iodine reagents are ideal for this transformation due to their low cost, low toxicity, ease of handling and availability, and excellent leaving group ability (see Chapter 1 for more information on HVI chemistry).¹⁸ As such, they have been utilized in a variety of other electrophilic rearrangements such as Hofmann rearrangements,^{19,20} and carbocyclic ring expansions;²¹ however there existed no reports employing an alcohol functionality in rearrangement chemistry. Their application in the context of alcohols was

effectively limited to oxidations to the corresponding carbonyls, via either one- or two-electron processes.^{22,23}

2.2: HVI-MEDIATED ELECTROPHILIC HETEROATOM REARRANGEMENT

2.2i: Reaction Optimization

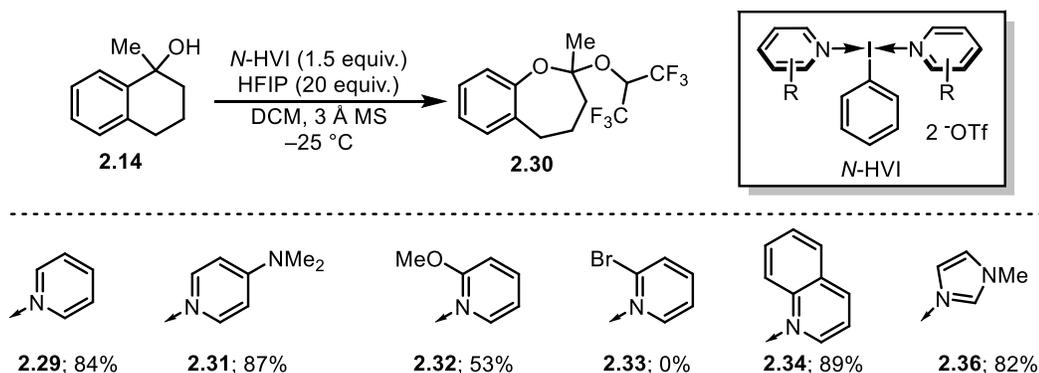


Scheme 2.3. Initial screening of HVI-mediated oxidative rearrangement

To begin method development, benzylic tertiary alcohols were first investigated in the desired transformation.²⁴ Following a screen of various I(III) HVIs on model substrate **2.14** it was quickly discovered that all oxygen-ligated reagents were incompetent in the desired transformation. Instead, the only product observed was styrene **2.16** resulting from the net elimination of the activated alcohol (Scheme 2.3A). It was hypothesized that the lack of desired rearrangement was due to the electronics of the iodine center, rendering them insufficiently electron-deficient to impart sufficient partial

positive charge on the alcohol oxygen. Based on this hypothesis, (poly)cationic nitrogen-ligated I(III) reagents²⁵ (*N*-HVIs) were screened as the presence of datively-bound heterocyclic ligands rendered the iodine center more electron-deficient. In fact, the use of *Py*-HVI provided phenol **2.28** in modest yield, arising from the desired rearrangement followed by the addition of water as the terminal nucleophile and subsequent ring opening of the resulting unstable hemi-acetal (**2.27**) (Scheme 2.3B).

While desired reactivity was observed, the reaction demonstrated low conversion of the starting alcohol and yielded an unstable product which could not be isolated. One possible solution commonly implemented in HVI-mediated transformations is the addition of fluoroalcohols such as hexafluoroisopropanol (HFIP) due to their unique physical properties, including their high polarity, low nucleophilicity, ionizing ability, and superior hydrogen bond donor abilities. Therefore, HFIP was added to the reaction mixture which necessitated the reactions to be performed at lower temperatures, however, the desired medium-sized cyclic ethers were isolated with incorporation of HFIP as the terminal nucleophile (Scheme 2.4). Subsequent screening of *N*-HVI ligands showed *Py*-HVI **2.29** to be the superior reagent for the transformation when considering factors such as ease of synthesis and functional group tolerability.



Scheme 2.4. Optimized reaction conditions and *N*-HVI screen

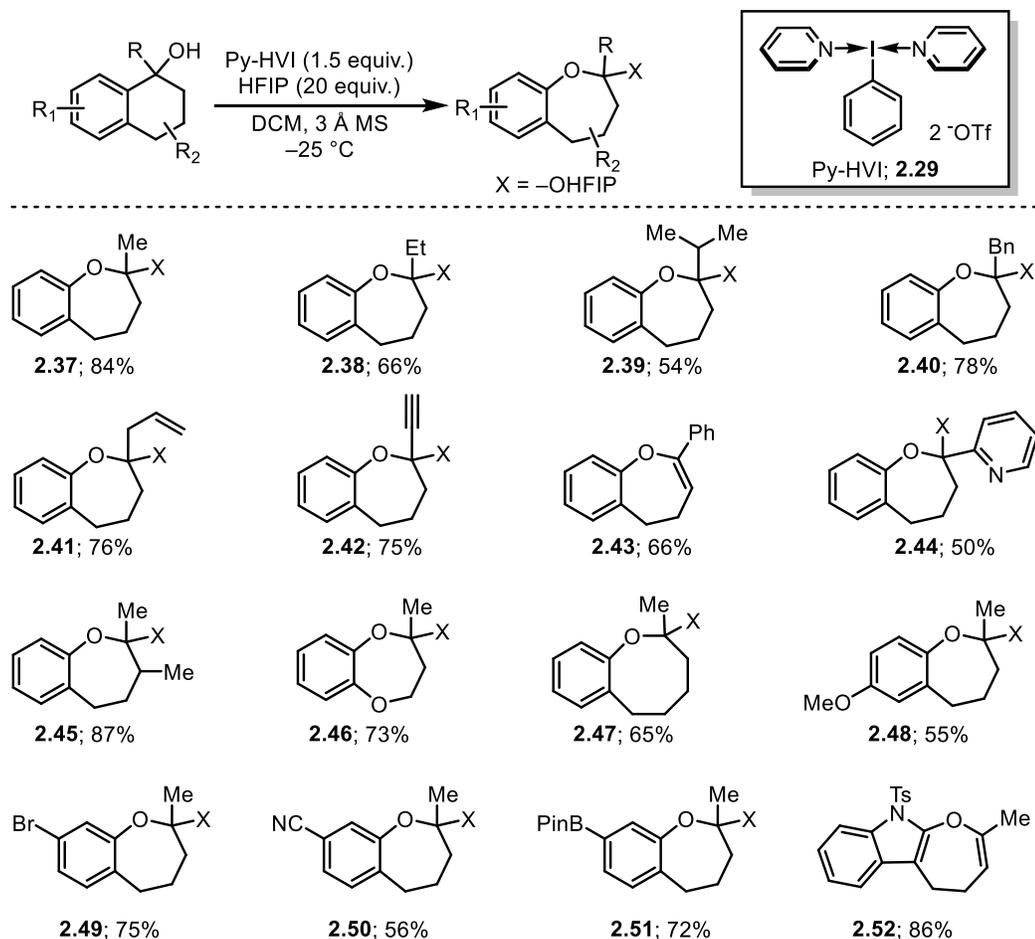
While the addition of HFIP facilitated the desired rearrangement, the resulting HFIP-acetals were hydrolytically unstable, and this was amplified in acidic media. Use of

aqueous workup resulted in complete decomposition of the desired product **2.30** to phenol **2.28**. Furthermore, reaction temperatures exceeding 0 °C even in the absence of water resulted in ring opening of the medium-ring ether. Re-cyclization was examined, however thermodynamically disfavored. It was found that isolation of the HFIP-acetals could be achieved via concentration at or below 0 °C, followed by rapid purification of the crude material to remove residual HFIP. Care must be taken to remove as much HFIP as possible prior to purification, as failure to do so results in the co-elution of desired product, phenyl iodide, and undesired open-chain byproduct. Once purified, the acetal products can be stored indefinitely at cold (−20 °C) temperatures in the absence of moisture. Despite finding a strategy for the isolation and handling of the HFIP-acetals, a long-term, more practical solution was sought and this will be addressed in Section 2.4.

2.2iii: Substrate Scope of Tertiary Benzyl Alcohols

To evaluate the versatility of the method a substrate scope was envisioned which includes substitution at the α -position of the tertiary alcohol, on the aromatic ring, and on the aliphatic ring. Substituents including alkyl groups, π -systems, and electron-neutral and deficient aryl groups were all included. (Scheme 2.5). Each of the rearrangements yielded the HFIP acetal with the exception of phenyl substituted **2.43** and indole substrate **2.52**, which underwent spontaneous elimination of HFIP to provide the enol ether. The tolerability of π -systems **2.41** and **2.42** is notable given the known reactivity of I(III) reagents as π -bond activators in various transformations.

The substitution on the aromatic and aliphatic rings was also evaluated. It was found that substitution on the aromatic ring was widely tolerated, including electron-rich

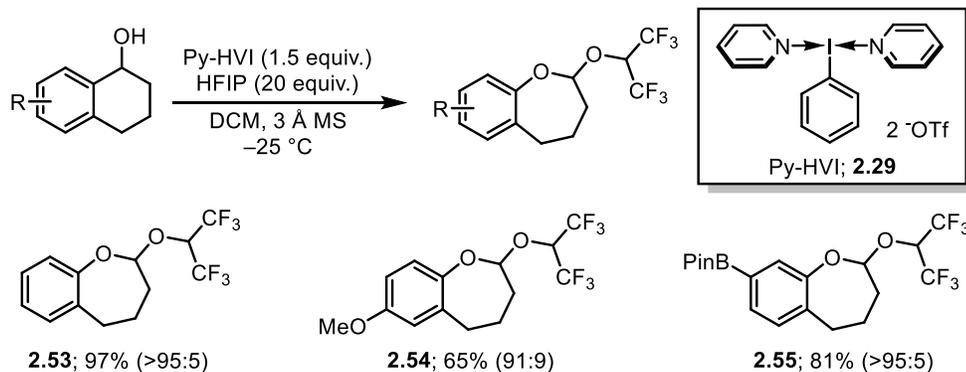


Scheme 2.5. Substrate scope of tertiary alcohol rearrangement

groups (**2.48**), halogens (**2.49**), electron-deficient groups (**2.50**) and boronic esters (**2.51**). Protected indole (**2.52**) was also tolerated under the reaction conditions, a gratifying result given the oxidative lability of indoles. Regarding the aliphatic substitution, a methyl group adjacent to the reaction center had very little impact on the yield, and reaction from dihydrobenzopyran provided the heterocyclic product (**2.46**) in good yield. Finally, the reaction from the benzosuberol provided 8-membered heterocycle **2.47** in good overall yield. This widely variable alcohol scope demonstrates the power and utility of this novel transformation, delivering a large library of heterocyclic products. For applications of this method in the diversity-oriented synthesis (DOS) of natural products, see Chapters 3 & 4.

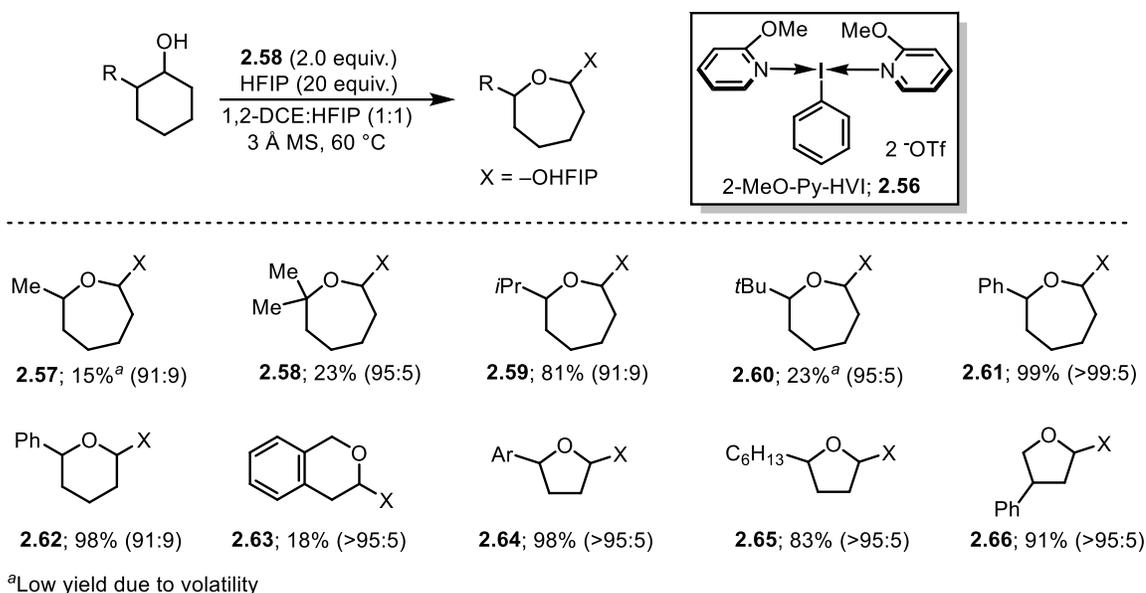
2.2iv: *N*-HVI Umpolung Ring Expansion of Secondary Alcohols

The ring umpolung ring expansion of secondary alcohols represents a more significant challenge, as secondary alcohols can undergo oxidation to the corresponding ketone via competitive α -elimination following activation by the I(III) *N*-HVI, chemistry that is well-established for HVI reagents. Despite this potential pathway, secondary benzylic alcohols proved to be extremely successful in the pre-existing conditions, providing the rearranged heterocyclic product (**2.53**) in a reported 97%, with only 3% oxidation to the tetralone product (Scheme 2.6). Additional secondary benzylic substrates were screened including the electron-rich 4-methoxy (**2.54**) and boronic ester (**2.55**) substituted arenes. In each case, rearrangement was overwhelmingly favored over oxidation to the corresponding ketone product (>90:10).



Scheme 2.6. Oxidative rearrangement of secondary benzylic alcohols

Next, a range of C2-substituted aliphatic *cis*-alcohols were targeted, where the migratory aptitude of the C–C bond is reduced when compared to the benzylic alcohols thereby increasing the potential for oxidation to the ketone. The trend is analogous to migratory aptitudes of the Baeyer-Villiger oxidation (phenyl > tertiary > secondary > primary). Additionally, a factor that must be considered is the selectivity of *cis* vs. *trans* alcohols pathway to undergo either the desired pathway or oxidation via α -elimination. Taking advantage of the modularity of *N*-HVI reagent synthesis, a screen of various *N*-ligands quickly revealed that a novel 2-*OMe*-Py-HVI (**2.56**) gave excellent levels of

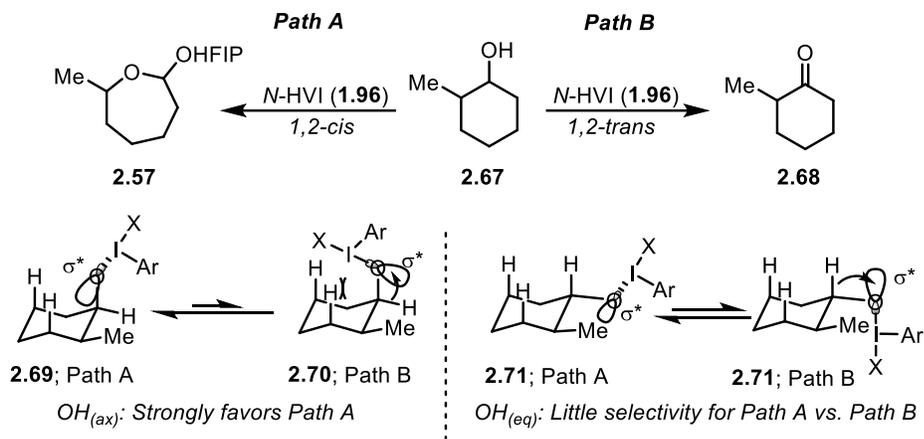


Scheme 2.7. Scope of rearrangement on secondary aliphatic alcohols

selectivity for rearrangement over oxidation. Further modification of solvent conditions and an increase in reaction temperature gave the HFIP acetal products in good yields (Scheme 2.7). While some HFIP acetals suffered from volatility, leading to decreased isolated yields (**2.57**, **2.60**), in all cases the selectivity for rearrangement over oxidation was overwhelmingly in favor of desired rearrangement (>90:10). The synthesis of 7-membered heterocycles was readily achieved with a variety of substituents at the resulting α -position. Additionally, it was demonstrated that pyrans were readily synthesized from the corresponding cyclopentanol, however it was limited to aryl-substituted alcohol starting materials. Finally, tetrahydrofurans were accessed in excellent yields from the corresponding cyclobutanols, with the high yield likely attributed to the release of ring strain.

Finally, it was discovered that the rearrangement was greatly favored over traditional oxidation in *cis* alcohols (Scheme 2.8). This phenomenon likely results from a conformational bias of the activated species, where in *cis* alcohols the equilibrium would greatly favor the alcohol existing in the axial conformation. When activated by *N*-HVI, significant 1,3-diaxial interactions would disfavor the transition state required for

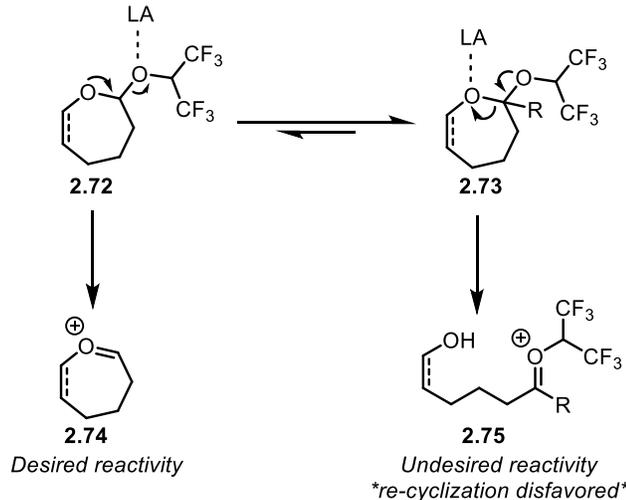
oxidation to the ketone (Path B), whereas the transition state for bond migration would be favored.



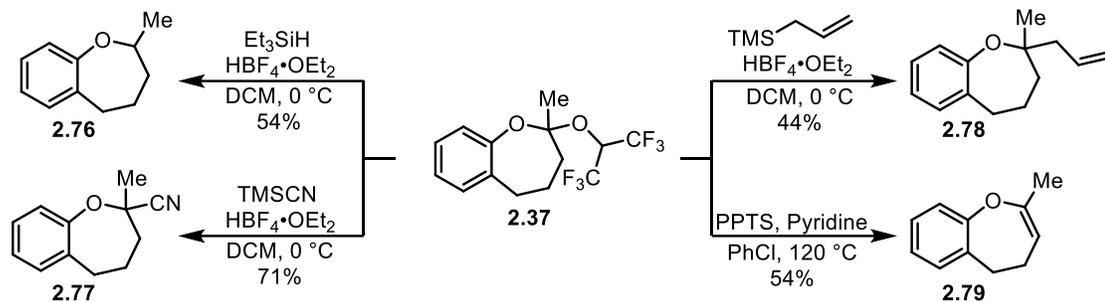
Scheme 2.8. FMO analysis of iodate ester intermediates

2.3: DERIVATIZATION OF HFIP ACETALS

The HFIP acetals were a challenging functional handle as a result of the decreased Lewis basicity of the exocyclic HFIP oxygen atom, rendering numerous Bronsted or Lewis acids ineffective for selective activation of the HFIP over the endocyclic ether oxygen. Activation of the endocyclic oxygen led to undesired open-chain products

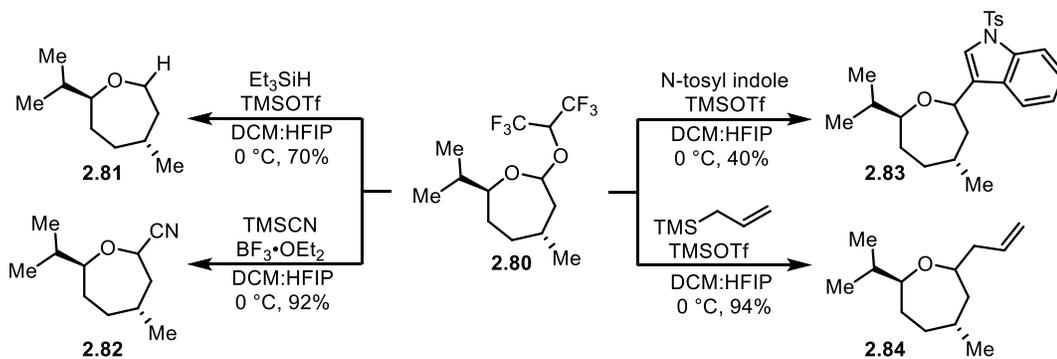


Scheme 2.9. General reactivity of HFIP acetals



Scheme 2.10. Derivatization of tertiary benzylic HFIP acetals

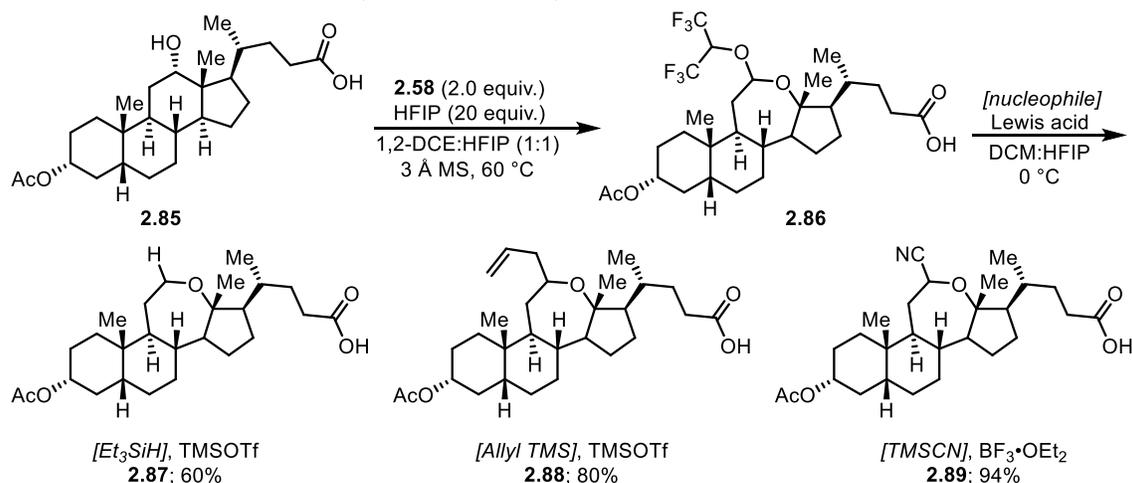
(Scheme 2.9). After extensive optimization, $\text{HBF}_4 \cdot \text{OEt}_2$ was found to be effective for activation of tertiary benzylic substrates (Scheme 2.10). For example, HFIP acetal **2.37** could be reduced to the corresponding cyclic ether (**2.76**) with the addition of triethylsilane and $\text{HBF}_4 \cdot \text{OEt}_2$ at low temperatures. Additionally, the hydride could be swapped for a nitrile or allyl nucleophile to provide the corresponding products in moderate yield. Elimination to provide the enol ether product required harsher conditions. In all of the derivatizations, the remaining mass balance consists of the corresponding open-chain phenol product following hydrolysis upon workup. It should be noted that in this original report, no additional tertiary benzylic substrates were evaluated for their competence under the derivatization conditions.



Scheme 2.11. Derivatization of secondary aliphatic alcohols

Derivatization of the HFIP acetals derived from secondary alcohols was found to be more difficult, and required re-optimization of conditions since the addition of $\text{HBF}_4 \cdot \text{OEt}_2$ resulted in a complex mixture of products. It was hypothesized that dual

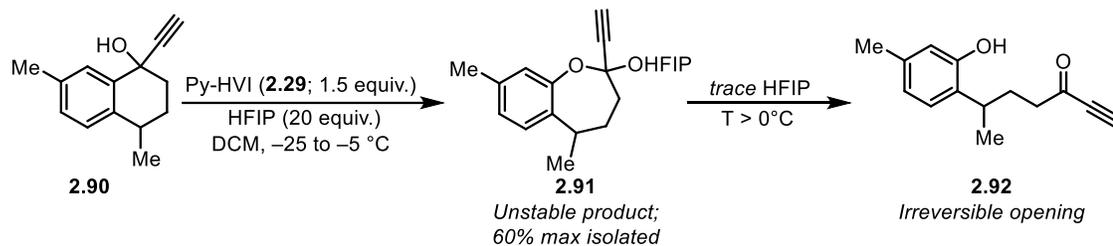
activation would be necessary, where the more Lewis basic endocyclic oxygen weakly first coordinates to an acidic group thereby allowing the less Lewis-basic exocyclic HFIP oxygen to be activated upon addition of Lewis acid. Indeed, screening of conditions found that the addition of HFIP prior to TMSOTf was beneficial, likely proceeding through a hydrogen bonding interaction with the endocyclic oxygen atom. This strategy proved quite successful, providing cyclic ethers derived from neomenthol with a variety of substitution patterns adjacent to the oxygen atom. These conditions proved to be a dramatic improvement to what was previously employed and allowed for greater demonstration of the CTD avenues possible with these procedures. More specifically, deoxycholic acid was subjected to the secondary aliphatic rearrangement conditions to provide HFIP acetal **2.86**. The acetal was then subjected to substitution of the HFIP moiety for a hydride, nitrile, and allyl group thereby adding diversity to the already complex molecule (Scheme 2.12). These results demonstrate the potential role of the *N*-HVI mediated umpolung alcohol rearrangement in late-stage natural product or complex molecule derivatization (i.e. DOS, CTD).



Scheme 2.12. CTD manipulations of deoxycholic acid

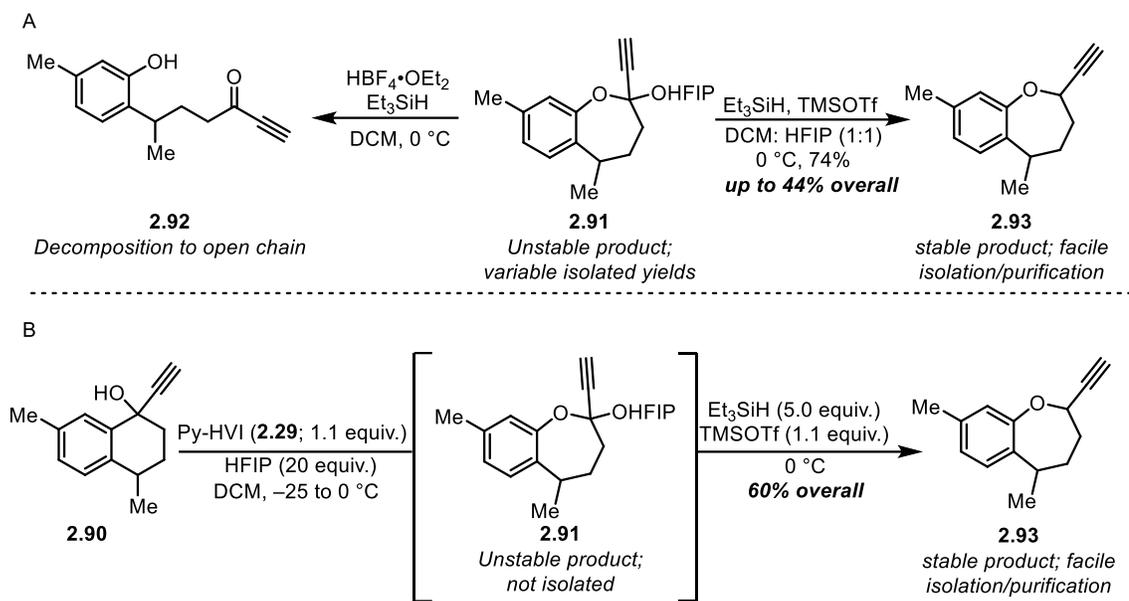
2.4: IMPROVEMENTS TO SYNTHESIS OF CYCLIC ETHERS

2.4i: Initial Discovery



Scheme 2.13. Undesired decomposition of HFIP acetal 2.91 in HFIP

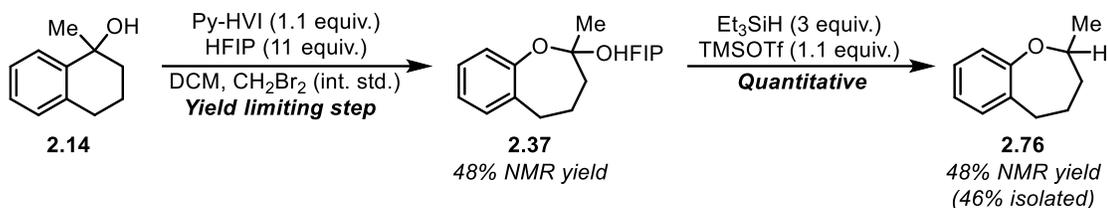
As is discussed in Chapter 3 during the synthesis of Heliannuol D, the main pitfall of the oxidative rearrangement, especially in complex molecules, is the propensity of the HFIP acetal products to undergo irreversible ring opening to deliver the phenol products, either as the ketone (tertiary starting materials) or aldehyde (secondary starting materials). In the case of the tertiary alkynyl alcohol **2.90** with a benzylic methyl group on the aliphatic ring, concentration of the product following the rearrangement resulted in dramatic changes to the desired product:open-chain ratio leading to inconsistent yields (Scheme 2.13). Despite the variability in yields, HFIP acetal **2.91** could be obtained and subjected to the subsequent hydride reduction as was necessary for the continuation of the synthesis of heliannuol D. Despite the reported success of $\text{HBF}_4 \cdot \text{OEt}_2$ on similar scaffolds (54%; **2.76**, Scheme 2.10), it proved ineffective in this more complex substrate; as was previously mentioned, only a single substrate (**2.37**) was examined in the initial study. Conversely, when second generation conditions (HFIP, TMSOTf, Et_3SiH) were implemented, the reduced cyclic ether product could be isolated in 74% yield, a 20% increase from the reported yield on a similar scaffold (Scheme 2.14A).



Scheme 2.14. Improved acetal reduction and one-pot sequence

When comparing the conditions of the rearrangement and and hydride reduction, similarities can be found in the reaction conditions wherein both implement HFIP as a co-solvent and both are performed at $0\text{ }^\circ\text{C}$. This led to the hypothesis that the two steps could be amenable to a telescoped, one-pot protocol. Telescoping reactions is advantageous in various transformations when reaction conditions are compatible due to the inherent benefits such as avoiding intermediate isolations and purifications, use of less solvent making the process greener, and oftentimes improvement in overall yield. Therefore a one-pot rearrangement and subsequent reduction was attempted from alcohol **2.90** using standard equivalents of *N*-HVI (1.2 equiv.) and HFIP (20 equiv.) in CH_2Cl_2 (Scheme 2.14B). Upon complete consumption of **2.90** and formation of HFIP acetal **2.91** by TLC, the temperature of the reaction was adjusted to $0\text{ }^\circ\text{C}$ and Et_3SiH was added, followed by the TMSOTf after five minutes. This resulted in complete conversion of **2.91** to reduced ether **2.93**. The reaction was then worked up according to the typical derivatization procedure: quench with aqueous sodium bicarbonate and extraction into CH_2Cl_2 . The yield was found to consistently be around 60%, which represents a 15% to almost two-fold greater yield over the 2-step protocol, as well as proving much more

consistent. Additionally a sequence which could take up to 8 hours to complete from start to finish previously was now reduced to 2 hours on average.



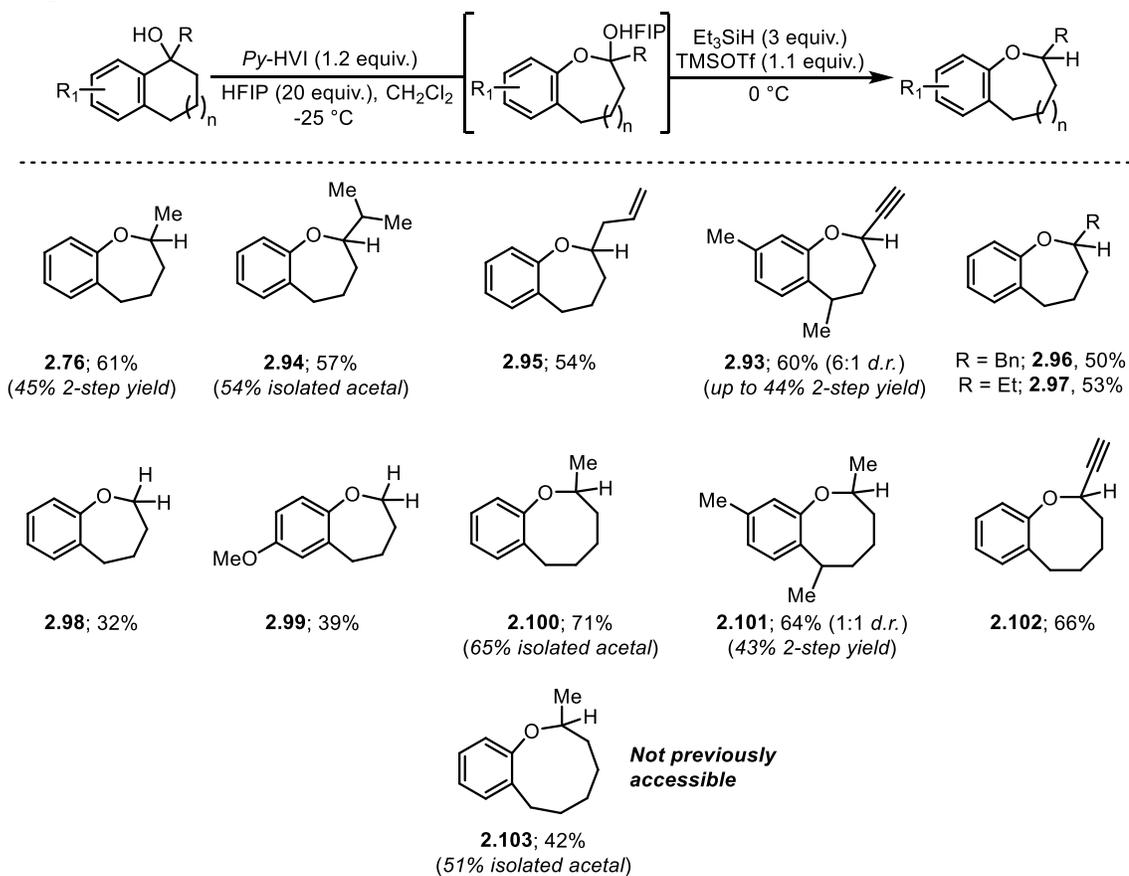
Scheme 2.15. Determination of yield-limiting step by ¹HNMR

Based on qualitative observation of distinct reaction, it was proposed that the one-pot reduction occurs quantitatively from the intermediate HFIP acetal (**2.37**), and any limitation in yield was due to open-chain byproduct (**2.28**) formation in rearrangement step. To probe this, an NMR experiment was performed on model substrate **2.14** in the presence of an internal standard (CH₂Br₂) to monitor the yield of HFIP acetal **2.78** and subsequent reduced ether **2.76**. It is worth noting that the quantity of HFIP (10 equiv. rather than 20 equiv.) and triethylsilane (3 equiv. rather than 5 equiv.) were altered to obtain more reliable integration quantities. Our hypothesis was confirmed by NMR, which showed the calculated yield of the HFIP acetal prior to reduction (48%) was equal to the yield of reduced cyclic ether (48% (46% isolated); Scheme 2.15). While the decreased quantity of HFIP led to poorer conversion to HFIP acetal **2.37**, the decrease in triethylsilane proved inconsequential.

2.4ii: Development of One-Pot Method

Identifying the value in this transformation to provide expedient access to otherwise challenging medium-sized cyclic ethers, this modification was expanded to a full method to include a variety of tertiary alcohol substrates. It was determined that only hydride reduction would be demonstrated for two reasons. Of the potential nucleophiles (organometallic reagents, cyanide, allyl silane, etc.) studies had shown that the silane reductant was most compatible with the conditions of the rearrangement. Additionally,

structural diversity could be readily introduced as a large variety of alkyl and aryl substituents could be installed at the base of the tertiary alcohol to quickly assemble a large library of cyclic ether products. Optimization revealed that the equivalents of HFIP had an impact on both the rate and conversion of the rearrangement with 20 equivalents being optimal. Lastly, the quantity of Et₃SiH could be decreased to 3 equivalents with no change in yield.



Scheme 2.16. Substrate scope of one-pot rearrangement/reduction protocol

A variety of tertiary alcohols were then synthesized and subjected to the transformation (Scheme 2.16). A range of alkyl substituents were tolerated to synthesize benzo-fused oxepanes (**2.76**, **2.94-2.97**), including the sterically encumbered isopropyl group, where previous isolated yields of the HFIP acetal was among the lowest reported (54%). Furthermore, the incorporation of methyl groups both on the aromatic ring and at the benzylic position on the aliphatic ring was found to have very little effect on reaction

yields (**2.76** vs **2.93**). Secondary benzylic alcohols (**2.98**, **2.99**) were also examined in the one-pot protocol, however this gave diminished yields. The reason for this is still unknown, however is the subject on ongoing investigation.

We then turned our attention to larger ring sizes, including 8-membered and even 9-membered rings, the latter of which had proven too labile to be accessed under the prior two-step procedure. Gratifyingly, the synthesis of benzo-fused oxocanes was readily achieved in excellent yields (**2.100-2.102**). Once again, incorporation of a benzylic methyl group on the aliphatic ring had little effect on the yield of the sequence (**2.100** vs **2.101**). Interestingly, no diastereoselectivity was observed which is contrary to what was observed in the 7-membered ring system (**2.93**). Finally, the synthesis of 9-membered rings was proved successful under the reaction conditions (**2.103**). In the two prior reports there was no success in synthesizing the 9-membered cyclic ethers, therefore this demonstrates a vast improvement to the method and access to otherwise challenging structures. Overall, The improvements made to the synthesis of medium-sized cyclic ethers via this one-pot procedure are reflected in yield (>15% yield over two steps) and overall reaction time and handling.

2.4iii: Failed or Unoptimized Substrates

Several substrates proved incompatible in the reaction conditions, due to either incomplete consumption of starting alcohol or formation of a variety of byproducts (Figure 2.1). In the case of allyl substrate **2.104**, the rearrangement step was quite sluggish and increases in time or temperature led to decomposition of the HFIP acetal. This result was rationalized by the propensity of *N*-HVI to activate olefins²⁶ leading to competitive complexation of the reagents. In the case of electron-rich substrate **2.105**, the desired cyclic ether product could be isolated in 49% calculated yield, however co-elution with the product resulting from ionization of the alcohol from the starting material followed by

hydride incorporation was observed. Separation via column chromatography could not be achieved despite extensive efforts. Finally, propargyl cyclooctanol **2.106** underwent successful rearrangement, however the reduction led to undesired reductive cleavage of the cyclic ether and isolation of the open-chain alcohol.

2.4iv: Future Directions

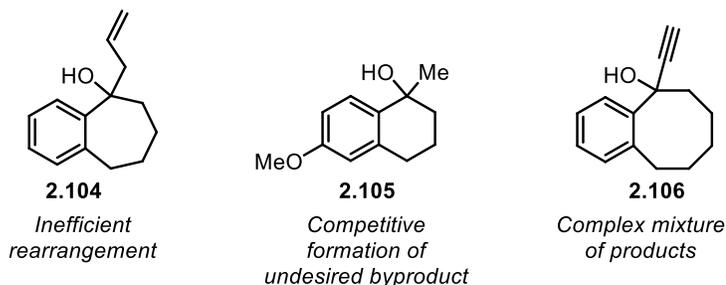
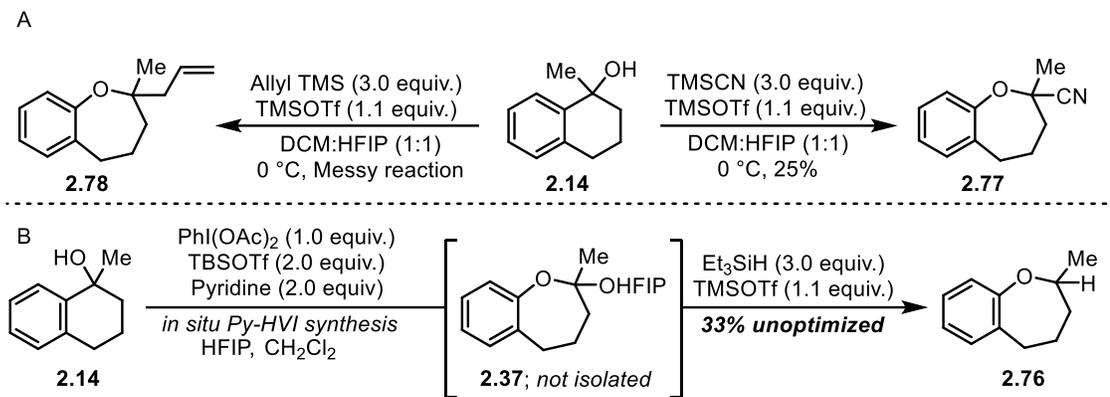


Figure 2.1. Unsuccessful or unoptimized substrates in one-pot procedure

In addition to the aforementioned reduction, which saw broad development, initial attempts were made at adding other nucleophiles including a nitrile and allyl, and those results are shown in Scheme 2.17A. The nitrile incorporation has demonstrated initial success, albeit with low yield. On the other hand, attempts to incorporate the allyl moiety have resulted in a complex mixture of products with no clean isolation of desired product to date. Optimization for these two transformations is currently the subject of additional investigation. Additionally, a one-pot *N*-HVI synthesis/rearrangement/reduction has been performed (Scheme 2.17B). The reaction requires the use of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) instead of TMSOTf to activate the *N*-HVI precursor to prevent TMS protection of the tertiary alcohol. The overall transformation has demonstrated some initial success and ultimately represents the performance of 3 distinct

reactions in one flask without any concentrations or isolations. Once again, the optimization of this reaction is underway and will be continued in the future.



Scheme 2.17. Preliminary advancements to one-pot procedure

2.5: CONCLUSIONS

The seminal work on the *N*-HVI mediated umpolung rearrangement of cyclic alcohols to deliver medium-ring ethers was a landmark methodology, providing facile access to challenging scaffolds from simple starting materials. However a limitation of the method was in handling the products, which are prone to irreversible degradation in the reaction solvent conditions. The implementation of a one-pot derivatization nullifies the pitfall and greatly simplifies reaction performance while improving overall yield. With this method, access to a broad range of cyclic ether products is made readily available from one diversity point. The value of the procedure in terms of diversity-oriented synthesis (DOS) is best exemplified in the total synthesis of Heliannuol D (See Chapter 3).

Experimental data for this chapter can be found in Appendix B.

2.6: REFERENCES

- (1) Kleinke, A. S.; Webb, D.; Jamison, T. F. Recent Progress in the Synthesis of Oxepanes and Medium Ring Ethers. *Tetrahedron* **2012**, *68* (35), 6999–7018. <https://doi.org/10.1016/j.tet.2012.05.081>.
- (2) Winnik, M. A. Cyclization and the Conformation of Hydrocarbon Chains. *Chem. Rev.* **1981**, *81* (5), 491–524. <https://doi.org/10.1021/cr00045a004>.
- (3) Illuminati, G.; Mandolini, L. Ring Closure Reactions of Bifunctional Chain Molecules. *Acc. Chem. Res.* **1981**, *14* (4), 95–102. <https://doi.org/10.1021/ar00064a001>.
- (4) Blumenkopf, T. A.; Bratz, M.; Castañeda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. Preparation of Eight-Membered Cyclic Ethers by Lewis Acid Promoted Acetal-Alkene Cyclizations. *J. Am. Chem. Soc.* **1990**, *112* (11), 4386–4399. <https://doi.org/10.1021/ja00167a041>.
- (5) Ghosh, A. K.; Tomaine, A. J.; Cantwell, K. E. Stereoselective Synthesis of Substituted Oxocene Cores by Lewis Acid Promoted Cyclization. *Org. Lett.* **2016**, *18* (3), 396–399. <https://doi.org/10.1021/acs.orglett.5b03411>.
- (6) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Veale, C. A.; Furst, G. T. Nucleophilic Additions to Thionolactones. New Synthetic Technology for the Construction of Medium-and Large-Ring Ethers. *J. Am. Chem. Soc.* **1987**, *109* (8), 2504–2506. <https://doi.org/10.1021/ja00242a041>.
- (7) Kishuku, H.; Shindo, M.; Shishido, K. Enantioselective Total Synthesis of (2)-Heliannuol A Iannuol A Has Been Accomplished by Employing Ring Closing Metathesis and Sequential Diastereoselective Epoxidation and Regioselective

Reductive Cleavage of the Epoxide Ring . *Chem. Commun.* **2003**, No. November 2002, 2002–2003.

- (8) Kamei, T.; Shindo, M.; Shishido, K. First Enantioselective Total Synthesis of (-)-Heliannuol C. *Tetrahedron Lett.* **2003**, *44* (46), 8505–8507.
<https://doi.org/10.1016/j.tetlet.2003.09.086>.
- (9) Biswas, B.; Sen, P. K.; Venkateswaran, R. V. The Synthesis of Heliannuol C, an Allelochemical from Helianthus Annuus. *Tetrahedron Lett.* **2006**, *47* (24), 4019–4021. <https://doi.org/10.1016/j.tetlet.2006.04.011>.
- (10) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. Activation of 7-Endo over 6-Exo Epoxide Openings. Synthesis of Oxepane and Tetrahydropyran Systems. *J. Am. Chem. Soc.* **1989**, *111* (14), 5335–5340.
<https://doi.org/10.1021/ja00196a044>.
- (11) Hoberg, J. O. Formation of Seven-Membered Oxacycles through Ring Expansion of Cyclopropanated Carbohydrates. *J. Org. Chem.* **1997**, *62* (19), 6615–6618.
<https://doi.org/10.1021/jo970649v>.
- (12) Goodman, R. M.; Kishi, Y. Extension of the Criegee Rearrangement: Synthesis of Enol Ethers from Secondary Allylic Hydroperoxides. *J. Org. Chem.* **1994**, *59* (18), 5125–5127. <https://doi.org/10.1021/jo00097a006>.
- (13) Criegee, R. Die Umlagerung Der Dekalin-peroxydester Als Folge von Kationischem Sauerstoff. *Justus Liebigs Ann. Chem.* **1948**, *560* (1), 127–135.
<https://doi.org/10.1002/jlac.19485600106>.
- (14) Beaulieu, M. A.; Guérard, K. C.; Maertens, G.; Sabot, C.; Canesi, S. Oxidative Prins-Pinacol Tandem Process Mediated by a Hypervalent Iodine Reagent: Scope,

- Limitations, and Applications. *J. Org. Chem.* **2011**, *76* (22), 9460–9471.
<https://doi.org/10.1021/jo2019027>.
- (15) Chanu, A.; Safir, I.; Basak, R.; Chiaroni, A.; Arseniyadis, S. Synthesis of a Norsesquiterpene Spirolactone/Steroid Hybrid by Using an Environmentally Friendly Domino Reaction as a Key Step. *European J. Org. Chem.* **2007**, *2007* (26), 4305–4312. <https://doi.org/10.1002/ejoc.200700446>.
- (16) Abo, T.; Sawaguchi, M.; Senboku, H.; Hara, S. Stereoselective Synthesis of 5-7 Membered Cyclic Ethers by Deiodonative Ring-Enlargement Using Hypervalent Iodine Reagents. *Molecules* **2005**, *10* (1), 183–189.
<https://doi.org/10.3390/10010183>.
- (17) Ohno, M.; Oguri, I.; Eguchi, S. PhI(OAc)₂-Promoted Rearrangement of the Hydroxyl Group: Ring Expansion of 4-Hydroxy-2-Cyclobutenone to 2(5H)-Furanone in Comparison with Ring Cleavage of the α -Hydroxycycloalkanone to the ω -Formyl Ester. *J. Org. Chem.* **1999**, *64* (25), 8995–9000.
<https://doi.org/10.1021/jo990704v>.
- (18) Zhdankin, V. V.; Stang, P. J. Chemistry of Polyvalent Iodine. *Chem. Rev.* **2008**, *108* (12), 5299–5358. <https://doi.org/10.1021/cr800332c>.
- (19) Zagulyaeva, A. A.; Banek, C. T.; Yusubov, M. S.; Zhdankin, V. V. Hofmann Rearrangement of Carboxamides Mediated by Hypervalent Iodine Species Generated in Situ from Iodobenzene and Oxone: Reaction Scope and Limitations. *Org. Lett.* **2010**, *12* (20), 4644–4647. <https://doi.org/10.1021/ol101993q>.
- (20) Zhang, B.; Li, X.; Guo, B.; Du, Y. Hypervalent Iodine Reagent-Mediated Reactions Involving Rearrangement Processes. *Chem. Commun.* **2020**, *56* (91),

14119–14136. <https://doi.org/10.1039/d0cc05354f>.

- (21) Ting, C. P.; Maimone, T. J. Total Synthesis of Hyperforin. *J. Am. Chem. Soc.* **2015**, *137* (33), 10516–10519. <https://doi.org/10.1021/jacs.5b06939>.
- (22) Togo, H.; Katohgi, M. Synthetic Uses of Organohypervalent Iodine Compounds through Radical Pathways. *Synlett* **2001**, *2001* (5), 565–581. <https://doi.org/10.1055/s-2001-13349>.
- (23) Uyanik, M.; Fukatsu, R.; Ishihara, K. IBS-Catalyzed Oxidative Rearrangement of Tertiary Allylic Alcohols to Enones with Oxone. *Org. Lett.* **2009**, *11* (15), 3470–3473. <https://doi.org/10.1021/ol9013188>.
- (24) Kelley, B. T.; Walters, J. C.; Wengryniuk, S. E. Access to Diverse Oxygen Heterocycles via Oxidative Rearrangement of Benzylic Tertiary Alcohols. *Org. Lett.* **2016**, *18* (8), 1896–1899. <https://doi.org/10.1021/acs.orglett.6b00672>.
- (25) Weiss, R.; Seubert, J. Electrostatic Activation of Hypervalent Organo-Iodine Compounds: Bis(Onio)-Substituted Aryliodine(III) Salts. *Angew. Chemie Int. Ed. English* **1994**, *33* (8), 891–893. <https://doi.org/10.1002/anie.199408911>.
- (26) Tierno, A. F.; Walters, J. C.; Vazquez-Lopez, A.; Xiao, X.; Wengryniuk, S. E. Heterocyclic Group Transfer Reactions with I(III)-N-HVI Reagents: Access to N-Alkyl(Heteroaryl)Onium Salts via Olefin Aminolactonization. *Chem. Sci.* **2021**, *12* (18), 6385–6392. <https://doi.org/10.1039/d1sc00187f>.

CHAPTER 3: DIVERGENT TOTAL SYNTHESIS OF HELIANNUOL D VIA

I(III) UMPOLUNG ALCOHOL RING EXPANSION

3.1: BACKGROUND AND SIGNIFICANCE

Allelochemicals have garnered much attention in the agrochemical field due to their innate ability to provide targeted modes of attack against specific invasive species. One example of a class of molecule which displays these characteristics is the Heliannuols are a class of environmentally benign molecules isolated from *Helianthus annuus*, or the common sunflower which were first isolated in 1993 by Macias et. al. Members of the Heliannuol family display activity against undesired weed species such as morning glory, velvetleaf, pigweed, jimson weed and wild mustard, among others.¹ Structurally, all members of the Heliannuol family exhibit a similar core scaffold of a benzofused cyclic ether ring. The ether ring in each molecule is between 5- to 8-members with the oxygen directly bound to the benzene ring, and a benzylic stereocenter is also always present (Figure 3.1).² The inherent challenges involved with forming the ring has

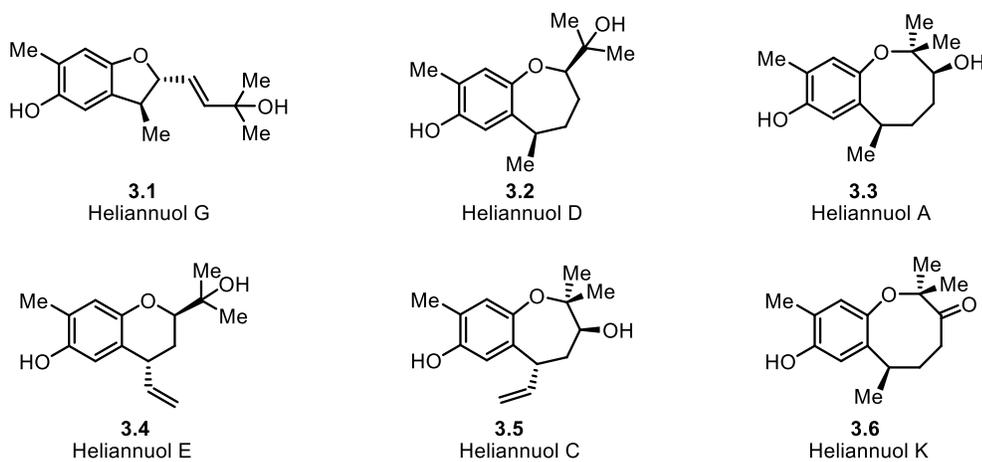
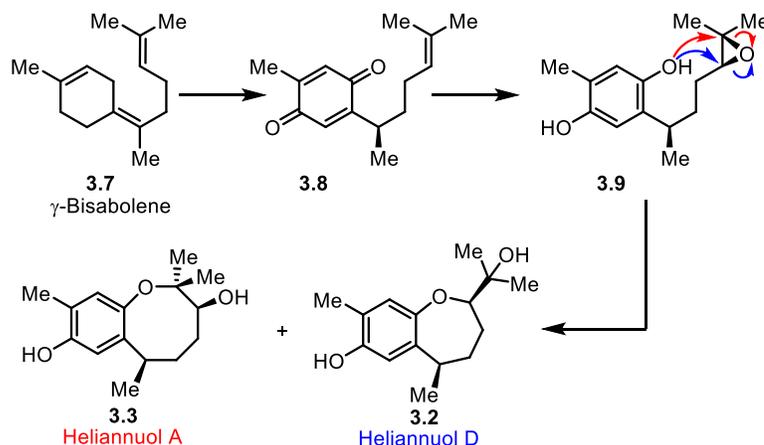


Figure 3.1. Representative Heliannuols

attracted the attention of many synthetic organic groups around the world. The Wengryniuk lab became interested in their synthesis based on an I(III) *N*-HVI-mediated umpolung heteroatom rearrangement developed in our group which provides the characteristic medium sized cyclic ether ring present in all Heliannuols (Chapter 2). Specifically, we focused our efforts on Heliannuols A, C, and D.

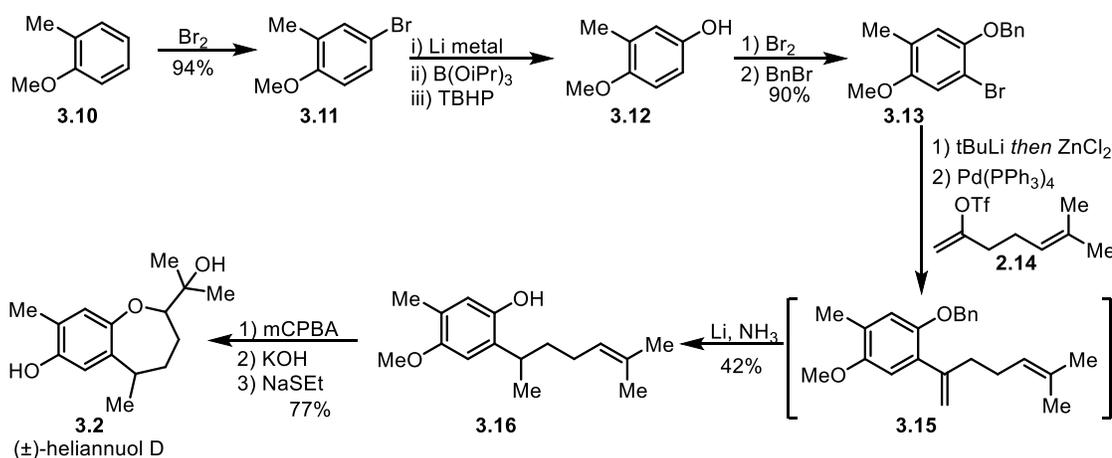


Scheme 3.1. Proposed biosynthesis of Heliannuols A and D

The proposed biosynthesis of Heliannuol D and A are predictably quite similar (Scheme 3.1).¹ Both natural products **3.1** and **3.2** are believed to arise from γ -bisabolene (**3.7**) via an oxidation to the corresponding quinone (**3.8**). Reduction to the hydroquinone and epoxidation of the remaining trisubstituted olefin provides the direct precursor to the natural product (**3.9**). The medium-ring ethers are then formed via two divergent epoxide openings; attack of the *ortho* phenolic oxygen on the epoxide via an acid-mediated 8-endo-tet cyclization affords Heliannuol A (**3.3**), whereas 7-exo-tet cyclization affords Heliannuol D (**3.2**).

3.2: PRIOR RACEMIC TOTAL SYNTHESSES OF HELIANNUOL D

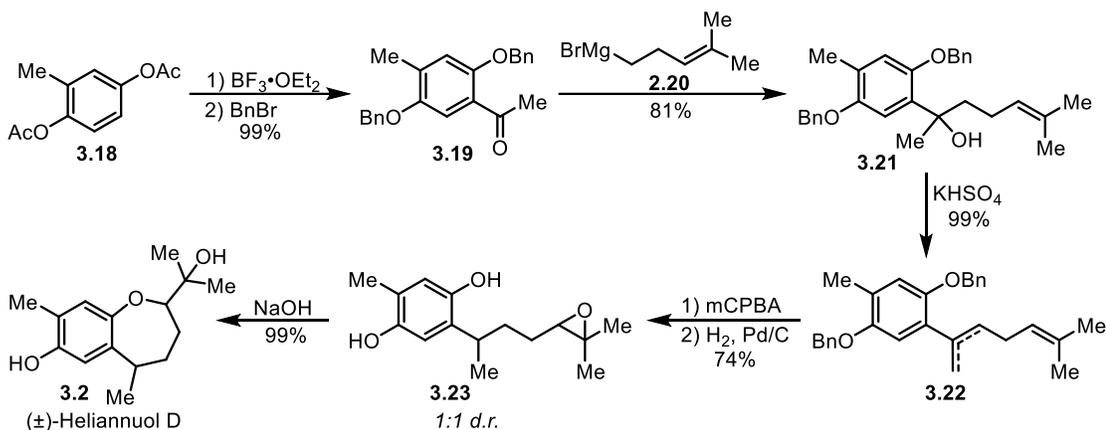
Since its discovery in 1994, many groups have devoted significant efforts toward the synthesis of Heliannuol D with 14 reported syntheses as of 2017.³⁻⁹ The most employed tactic to access the medium-ring ether is the biomimetic attack of the phenolic oxygen into an epoxide via a 7-exo-tet cyclization.¹⁰ Ring-closing metathesis (RCM)¹¹ is another common strategy, however less traditional approaches to access the 7-membered ring have been described including a pinacol/pinacolone rearrangement and acid-induced tertiary alcohol ionization.^{3,9,12}



Scheme 3.2. First racemic synthesis of Heliannuol D (Vyvyan, 2000)

The first synthesis of Heliannuol D was reported in 2000, six years after its isolation and characterization. The synthesis, disclosed by Vyvyan and Looper¹³, commences with the site-selective bromination of *o*-methylanisol (**3.10**, Scheme 3.2). Bromide **3.11** was then subjected to lithium/halogen exchange and subsequent addition of B(OiPr)_3 afforded the corresponding boronic ester which was oxidized with *tert*-butyl hydrogen peroxide (TBHP) deliver phenol **3.13**. Treatment with bromine enabled a regioselective bromination ortho to the free phenol, which was subsequently protected as the benzyl ether. Aryl bromide **3.13** was then treated with *t*BuLi followed by zinc chloride to provide corresponding arylzinc species and subsequent Negishi coupling with

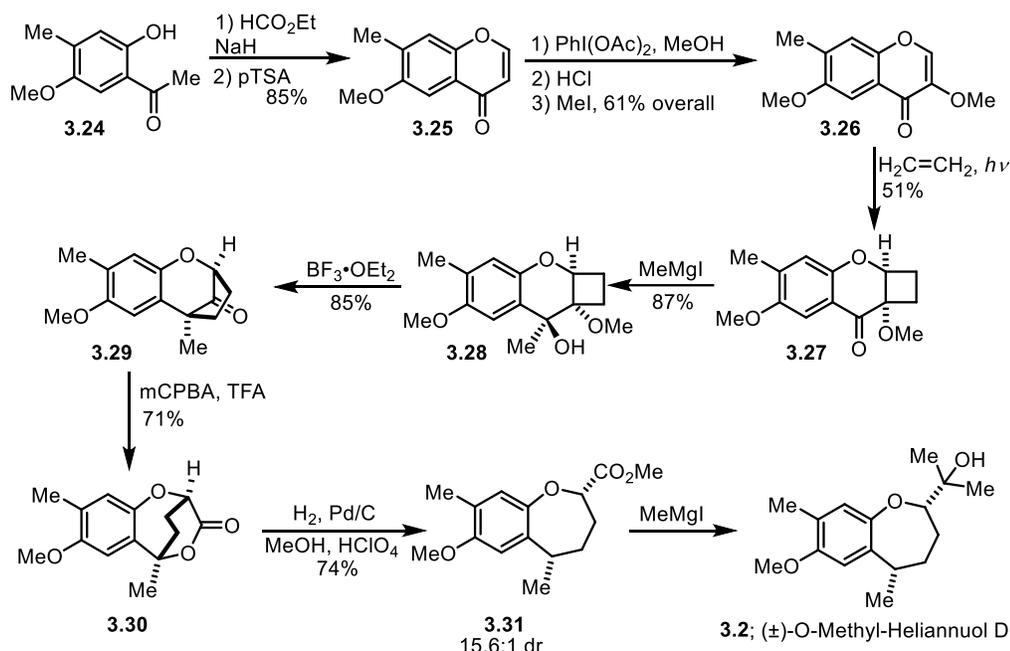
vinyl triflate **3.14** to afford styrenyl olefin **3.15**. was reduced with Birch reduction of the conjugated alkene installed the benzylic methyl stereocenter in racemic fashion and also deprotected the benzyl ether to reveal phenol **3.16**. The remaining trisubstituted olefin was then epoxidized using *m*CPBA, which provided a 1:1 mixture of diastereomers. The biomimetic ring formation was then performed with the addition of KOH and following demethylation (\pm) – Heliannuol D was isolated in 12% overall yield. While this synthesis is rather efficient (9 steps), the use of lithium metal, *tert*-butyllithium, and Birch conditions pose significant safety risks.



Scheme 3.3. Concise racemic synthesis of Heliannuol D (Macias, 2003)

In 2003 Macias⁴ disclosed a high yielding synthesis of (\pm) – Heliannuol D relying on a biomimetic ring formation (Scheme 8). Beginning with bis acetylated hydroquinone **3.18**, a Lewis acid-catalyzed Fries rearrangement delivered ortho acetylated **3.19**. Addition of Grignard **3.20** provided the corresponding tertiary alcohol, which upon treatment with potassium bisulfate afforded isomeric styrene **3.22**. Reaction with *m*CPBA furnished the epoxide and hydrogenation conditions simultaneously unmasked the diphenol via benzyl ether deprotection and reduced the remaining styrene to afford a 1:1 diastereomeric ratio of epoxide **3.23**. The biomimetic ring closure upon treatment with

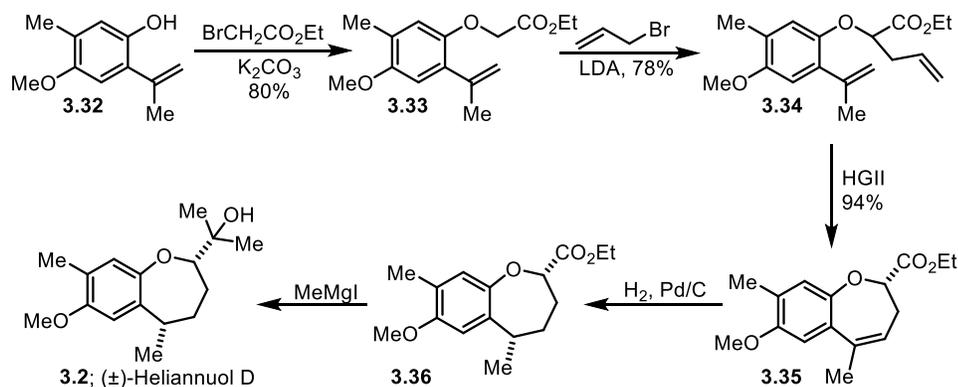
NaOH delivered both epimers of Heliannuol D in 60.7% overall yield. This synthesis by Macias, as well as the previous synthesis by Vyvyan, both display the enormous utility of the biomimetic ring formation in the synthesis of Heliannuol D.



Scheme 3.4. Baeyer Villiger approach to Heliannuol D (Venkateswaran,

An alternative approach to Heliannuol D was reported by Venkateswaran in 2003 which is a pinacol/pinacolone rearrangement to access the medium-ring ether.⁶ The synthesis commences with the condensation of ethyl formate with acetophenone **3.24** followed by dehydration to afford chromone **3.25**. Alpha hydroxylation was then carried out in the presence of $\text{PhI}(\text{OAc})_2$, followed by methylation of the resulting alcohol to afford chromone **3.26**. Irradiation with constant ethylene flow afforded the [6.6.4] fused ring system as the major product, which upon treatment with methyl Grignard afforded tertiary alcohol **3.28**. To forge the key 7-membered ring, **3.28** was exposed to Lewis acid to facilitate a pinacol-pinacolone rearrangement and furnish bridged ketone **3.29**. Addition of *m*CPBA formed the desired Baeyer-Villiger product **3.30** which upon hydrogenation in the presence of an oxidant and methanol provided the ring-opened

methyl ester **3.31**. With the desired 7-membered ring still intact, treatment with excess methyl Grignard afforded the expected tertiary alcohol group and concluded the formal synthesis of (\pm) – Heliannuol D. At the time of our initial investigation, this synthesis served as the only example which utilized a ring expansion as the key ring-forming step in the formal synthesis of Heliannuol D.

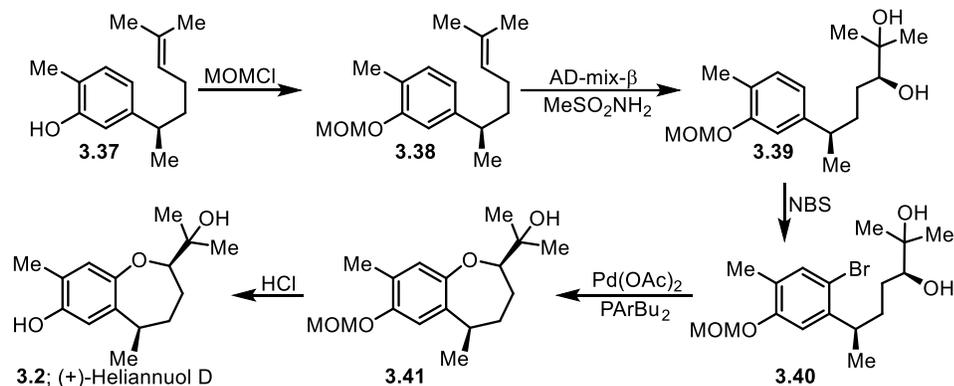


Scheme 3.5. RCM approach to Heliannuol D (Venkateswaran, 2002)

Another common method for constructing the medium-sized benzylic ether ring scaffold is by ring-closing metathesis (RCM) of the corresponding diol. While RCM is effective at delivering medium-sized rings, the precursors often require lengthy sequences to synthesize and leave little room for divergence. Venkateswaran and coworkers⁹ displayed the utility of this method in their expedient follow-up synthesis of Heliannuol D. Styrenol **3.32** was O-alkylated with ethyl bromoacetate to afford ether **3.33**. Upon treatment with LDA and allyl bromide, the α -allylated product di-olefin **3.34** was obtained. The key RCM was accomplished using HGII; alternative RCM catalysts resulted in low-yielding intermolecular reactions. The resulting olefin of **3.35** was hydrogenated to deliver almost the cis isomer almost exclusively (>95%), and upon treatment with excess methyl Grignard the ethyl ester was converted to the tertiary alcohol thus completing the formal synthesis of (\pm) – Heliannuol D.

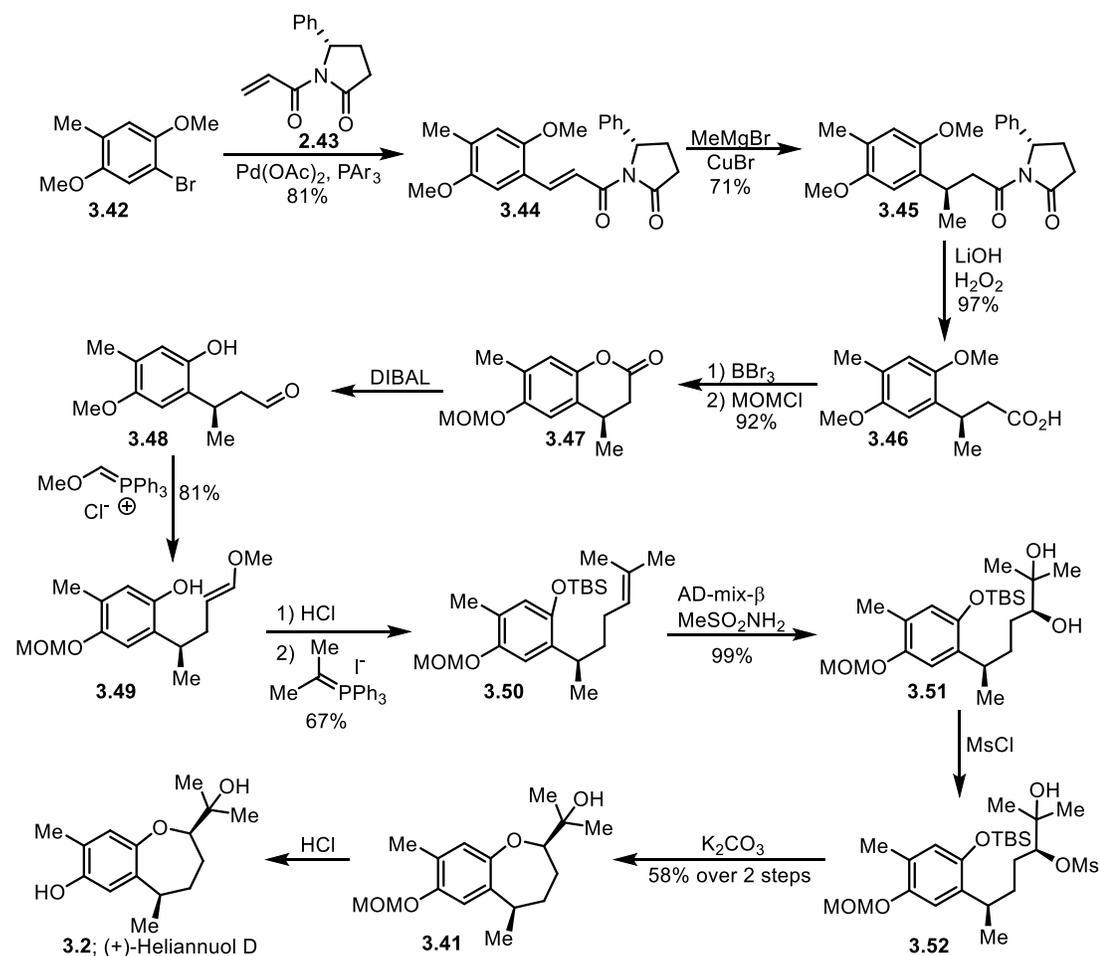
3.3: PRIOR ENANTIOSELECTIVE SYNTHESIS OF HELIANNUOL D

Accessing the chiral benzylic stereocenter has posed a significant challenge in prior Heliannuol D syntheses. Two commonly employed strategies to deliver a single stereoisomer are kinetic resolution and drawing from the chiral pool. Kinetic resolution often provides high levels of enantioselectivity, however requires the use of expensive reagents and limits throughput since at least half of the starting material is lost. Drawing from the chiral pool prohibits access to stereoisomers and therefore diversity in synthesis.



Scheme 3.6. Enantioselective synthesis of Heliannuol D (Shishido, 2003)

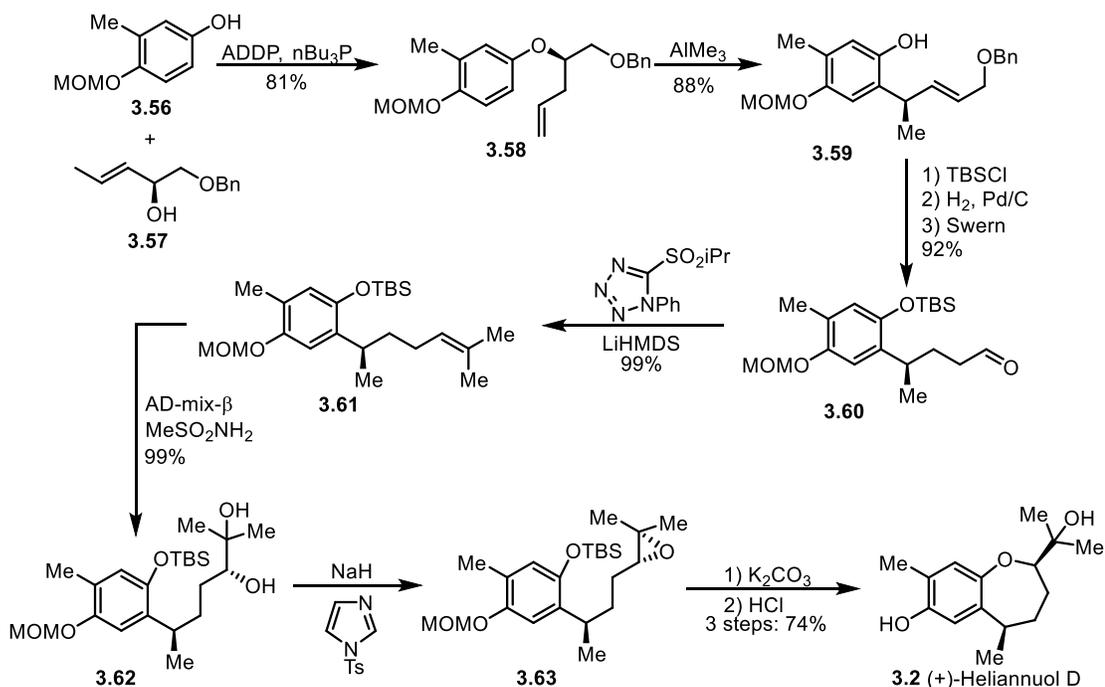
The first asymmetric synthesis of (+) – Heliannuol D was disclosed by Shishido in 2000.¹⁴ Drawing from the chiral pool, the synthesis commences with the phenol protection of **3.37** to the MOM ether. Sharpless asymmetric dihydroxylation afforded diol **3.39**, which was subjected to NBS to facilitate the para bromination of the aryl ring and provide cross-coupling precursor **3.40**. In the presence of Pd(0), cyclization was enabled to forge the desired 7-membered ring with the cis isomer **3.41** as the major product. Finally, acid-mediated MOM ether deprotection of the phenolic oxygen delivered (+) – Heliannuol D. This cyclization method offers a unique metal-mediated approach to the bicyclic ring scaffold.



Scheme 3.7. Asymmetric dihydroxylation route to Heliannuol D (Shishido, 2010)

Shishido disclosed a subsequent asymmetric synthesis of (+)-Heliannuol D by employing a chiral directing group in his 2010 synthesis.⁷ Beginning with dimethoxy bromoarene **3.42**, an intramolecular Heck reaction was carried out to install chiral imide **3.43** (Scheme 3.7). The chiral auxiliary was then used to direct the subsequent cuprate addition of a methyl group into the β -position of the imide, delivering the desired product (**3.45**) in a 12:1 ratio of diastereomers; following recrystallization the diastereotopically pure **3.45** was obtained in 71% yield. A subsequent hydrolysis of the imide provided enabled cleavage of the chiral auxiliary to provide carboxylic acid **3.46**. Demethylation was carried out using boron tribromide, which also facilitated attack of the resulting

phenolic oxygen into the pendant carboxylic acid moiety, and following MOM protection of the remaining phenolic oxygen, lactone **3.47** was obtained in excellent yield over 2 steps. Reductive cleavage of the lactone ring afforded aldehyde **3.48**, which was subjected to Wittig conditions to deliver enol ether **3.49**. Hydrolysis of the enol ether followed by a subsequent Wittig reaction and phenol protection delivered trisubstituted olefin **3.50**. In an identical fashion to his previous synthesis, Shishido performs the Sharpless asymmetric dihydroxylation to afford chiral alcohol **3.51**, which was mesylated to afford cyclization precursor **3.53**. Upon treatment with basic methanol, the sequential silyl deprotection and S_N2 reaction provided cyclized product **3.41**, which following MOM ether deprotection was transformed to (+) – Heliannuol D. Shishido’s cyclization method in this report is highly reminiscent of the biosynthesis, however he bypasses the formation of the epoxide entirely and instead opts for mesylation of the secondary alcohol.



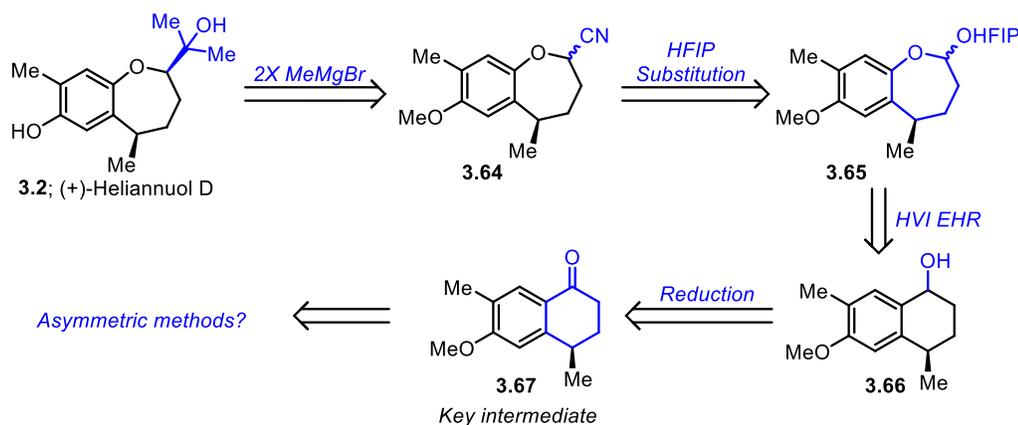
Scheme 3.8. Biomimetic asymmetric synthesis of Heliannuol D (Shishido, 2014)

In 2014, Shishido completed another total synthesis of (+) – Heliannuol D, this time successfully incorporating the biomimetic ring closure step in the process⁵. The synthesis commences with a Mitsunobu reaction to couple phenol **3.56** and chiral alcohol **3.57** with complete inversion of stereochemistry. A Lewis acid-mediated Claisen rearrangement was performed, which led to enantiomerically pure phenol **3.59** via chirality transfer. Following protection of the phenolic oxygen, hydrogenation was performed which facilitated the reduction of the olefin as well as hydrogenolysis of the benzyl ether to afford the alcohol, which was subsequently oxidized to the corresponding aldehyde **3.60**. A Julia-Kociensky reaction was then carried out using an isopropyl sulfone to install the trisubstituted *E* olefin **3.61**. Asymmetric dihydroxylation followed by epoxide ring formation afforded enantiopure epoxide **3.63**, which could be opened following silyl deprotection of the phenolic oxygen in a biomimetic pathway. After hydrolysis of the MOM ether, (+) – Heliannuol D was isolated after a lengthy sequence.

As was demonstrated by the numerous racemic and asymmetric syntheses of Heliannuol D, the key challenges to address throughout the synthesis are nearly consistent. The asymmetry, especially at the benzylic position, always results from either dipping into the chiral pool, use of directing groups, or by kinetic resolution strategies. Each method has their drawbacks, and therefore there is plenty of room for improvement. Additionally, while ring formation is shown to be far more facile in the 7-membered ring system than in the 8-, the diversity of methods used is limited, likewise with the diversity of products that can be obtained from the method.

3.4: FIRST GENERATION RETROSYNTHETIC ANALYSIS; BENZYNE APPROACH

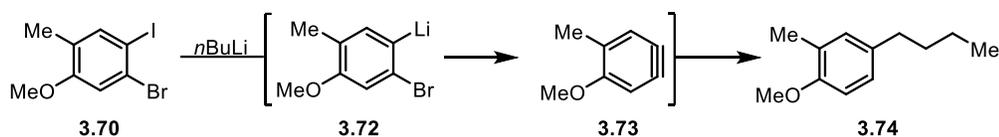
Central to each strategy to access Heliannuol D, whether racemically or asymmetrically, is the ring forming step as it is often challenging due to the inherent properties of medium-sized cyclic ethers. Our group recently disclosed an I(III) *N*-HVI-mediated umpolung alcohol rearrangement method which utilizes readily-available starting materials to access variably substituted medium sized cyclic ethers analogous to those found in Heliannuols (Chapter 2).^{15,16} This ring-expansion strategy would serve as the key step in the synthesis and provide expedient access to the most challenging structural component of Heliannuol D (**3.66** to **3.65**; Scheme 3.9).



Scheme 3.9. First-generation retrosynthesis of Heliannuol D

Having addressed the synthesis of the 7-membered cyclic aryl ether, the focus shifted to determining the ideal late stage functionalization and incorporation of asymmetry. Access to the alpha tertiary alcohol substituent was envisioned to proceed via sequential Grignard additions into the corresponding nitrile **3.64**, which could be installed by derivatization of the HFIP acetal (**3.65**) following the rearrangement from the

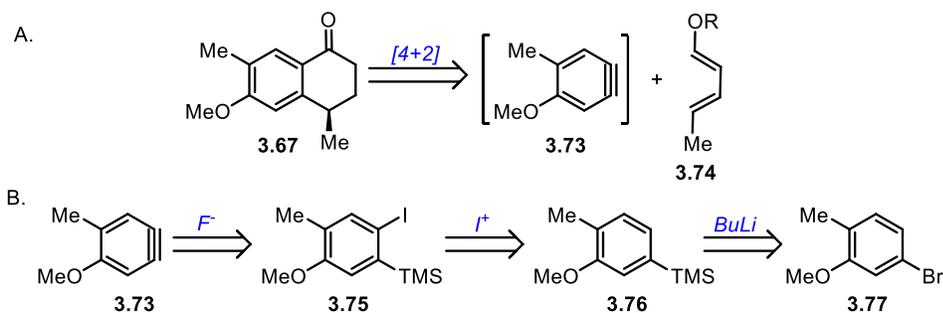
corresponding alcohol (**3.66**). Having surmised a reasonable approach to accessing the natural product following the key step, our attention shifted to approach chiral key ketone **3.67**. This ketone would be crucial on two fronts, as it serves as the point of divergence to access various analogues and serves as the once-removed precursor to the key rearrangement step. Various routes to access the **3.67** were investigated including an aryne [4+2] cycloaddition, asymmetric Ni(0)-mediated couplings, asymmetric Heck reactions, and stereoretentive homologations.



Scheme 3.10. Proposed aryne synthesis observed in prior investigations

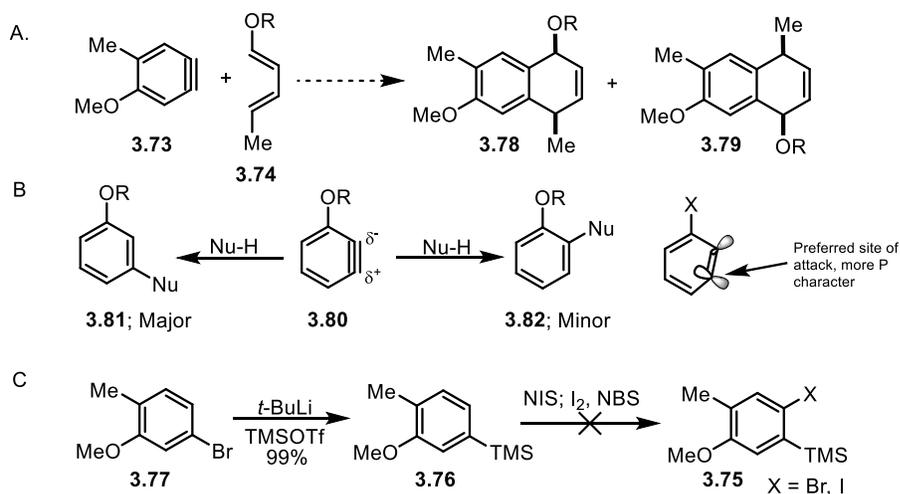
Our initial route to ketone **3.67** arose from preliminary studies performed by Dr. Brandon Kelly, a former member in our group who briefly investigated the synthesis of Heliannuol C. Brandon found that treatment of iodoarene **3.70** with *n*BuLi resulted in isolation of butylated product **3.74** (Scheme 3.10). Mechanistically, this product is thought to arise from lithium-halogen exchange of the iodide, followed by rapid elimination of the ortho-bromide and conversion to the electrophilic aryne species. The aryne can then undergo subsequent attack by an additional equivalent of butyllithium and deliver **3.74** following a quench. While this reactivity was undersired in the prior approach, we proposed that the aryne intermediate could be leveraged to rapidly assemble the desired ketone via a formal [4+2] benzyne Diels-Alder reaction with a suitable diene (Scheme 3.11A). Furthermore, this transformation could be made asymmetric at the desired benzylic position with the employment of a chiral Lewis acid. Therefore, our early efforts focused on the synthesis of aryne precursors which could

generate the reactive intermediate under mild conditions. Based off the Kobayashi protocol for the mild generation of benzyne, we proposed the synthesis of ortho-silyl haloarenes as precursors (Scheme 3.11B).



Scheme 3.11. Aryne Diels-Alder approach to key ketone intermediate

As is the case with all Diels-Alder reactions, two regioisomers are possible (**3.78**, **3.79**; Scheme 3.12A) and selectivity is typically dictated by electronics of each component or a significant steric effect. Recent investigations regarding the regioselectivity of nucleophilic incorporation into aryne intermediates, however, raised concern for the regioselectivity of the proposed cycloaddition. The report states that rather than the electronic effect of a substituent having the greatest impact on regioselectivity, aryne reactivity depends on the presence of a substituent ortho to the formed triple

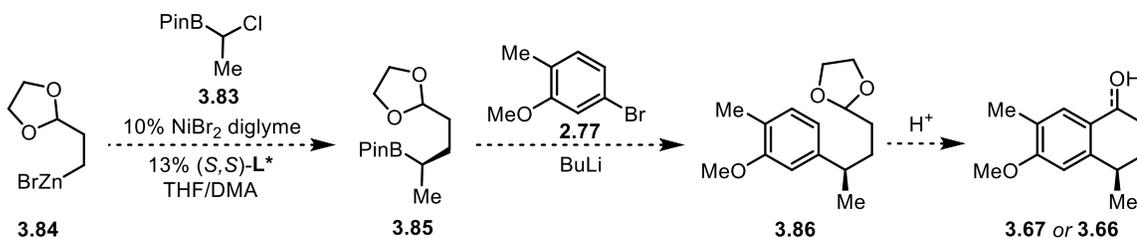


Scheme 3.12. Investigations and pitfall of aryne approach

bond.¹⁷ This phenomenon is due to a slight distortion that gives the meta position a more linear bond angle, and therefore more p character leading to nucleophilic incorporation meta to the existing substituent (Scheme 3.12B). While the desired aryne intermediate **3.73** lacked *ortho*-substitution, the electronic bias may have been sufficient to favor a single regioisomer

The synthesis toward a suitable aryne precursor commenced with the silylation of haloarene **3.77** via lithium-halogen exchange with *n*-butyllithium and subsequent silylation with TMSCl. It was found that *tert*-butyllithium as the lithiating agent and TMSOTf as the nucleophilic TMS source were optimal, delivering the desired silylated arene **3.76** in near quantitative yield. Unfortunately, subsequent bromination *ortho* to the TMS group did not proceed in any appreciable yield despite the electron-rich aryl system (Scheme 3.12C). Multiple electrophilic halogen sources (NIS, I₂, NBS) were screened, however each set of conditions resulted in full recovery of starting material. Lack of success in synthesizing aryne precursors and the potential lack of regiocontrol in the cycloaddition, efforts shifted to alternative approaches to **3.67**

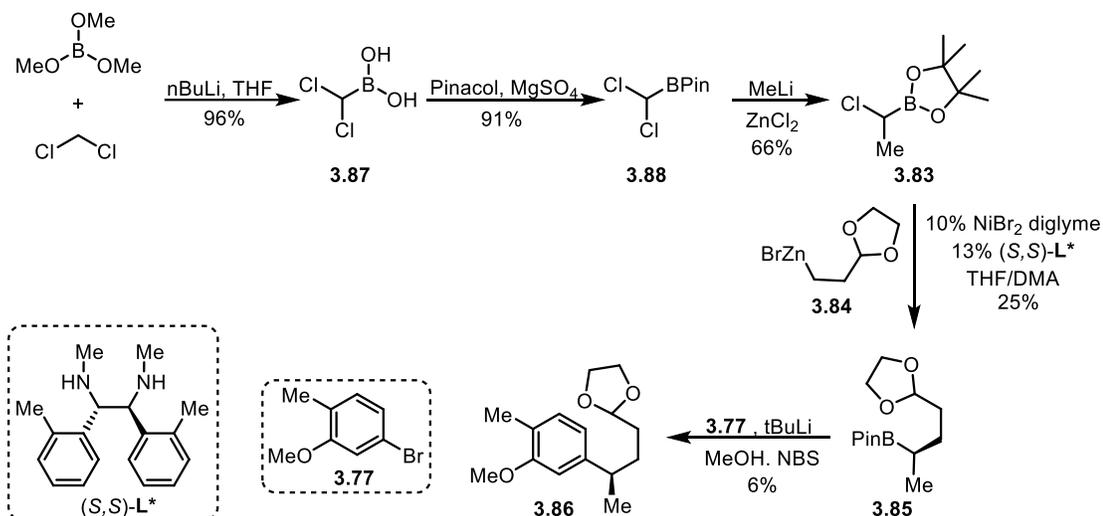
3.5: APPROACHES VIA ASYMMETRIC Ni(0) SP³-SP³ CROSS-COUPPLINGS



Scheme 3.13. Proposed asymmetric Ni(0)-catalyzed approach

One unique sequence to deliver chirality at the benzylic position of various arenes was disclosed by Fu and co-workers which detailed the synthesis of chiral boronic esters from easily synthesized zincates (Scheme 3.13) using Ni(0) catalysis¹⁸. The chiral

boronic esters (**3.85**) were then demonstrated as coupling partners in a subsequent stereoretentive homologation to aryl halides via a protocol disclosed by Aggarwal and coworkers.¹⁹ This sequence provides expedient access to acetal **3.86**, which upon deprotection and cyclization would provide either ketone **3.67** or **3.66** directly desired alcohol precursor to the key oxidative rearrangement. The substrates required for Heliannul D closely resemble substrates found in the seminal work which prompted investigation of the route.

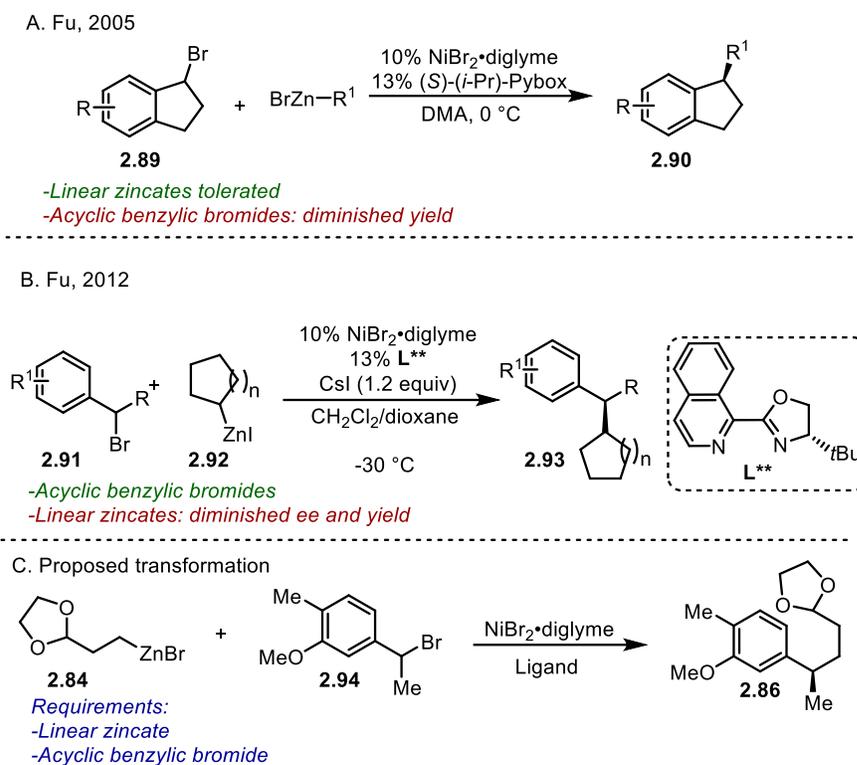


Scheme 3.14. Evaluation of asymmetric Ni(0)-catalyzed approach

First, the synthesis of the racemic α -chloro boronic ester was performed by deprotonation of dichloromethane using *n*BuLi followed by a quench with trimethylborate and acidic workup to cleanly provide boronic acid **3.87** (Scheme 3.14). Treatment of **3.87** with pinacol under anhydrous conditions to afford boronic ester **3.88**, which smoothly underwent methylation with methyl lithium in the presence of zinc chloride to provide product **3.83** in 58% yield overall. To prepare the organozinc coupling partner, the corresponding alkyl bromide was stirred with fine zinc dust in dimethylacetamide (DMA) at elevated temperatures. The subsequent enantioselective coupling of **3.83** and **3.84** provided the desired acetal (**3.85**) after filtration through silica,

however in quite low yield, and the enantiomeric ratio was not determined at this stage. Multiple attempts were made to improve the yield of the Ni coupling, including aqueous workup, de-activated silica, and alumina. Unfortunately, each modification to the workup proved futile, and a maximum of 25% yield was obtained. Regardless, the lithiation/borylation sequence was attempted with the obtained material. Following lithium/halogen exchange on aryl bromide **3.77**, chiral boronic ester **3.85** was added. Following a solvent swap from THF to methanol and addition of NBS, the reaction mixture was heated to reflux. Following standard workup and purification by prep TLC, merely 6% of the desired arene acetal **3.86** was isolated. Efforts were made to improve the yield of the transformation; however, the biggest hurdle was para substitution relative to the bond forming. Typically, the unoccupied para position is bromine-substituted by NBS to aid in bond formation, however with the present system, ortho substitution or sustained dearomatization was required which directly impacted the yield. Due to low

yields over the two key steps toward the synthesis of acetal **3.86**, alternative Ni-catalyzed approaches were investigated.

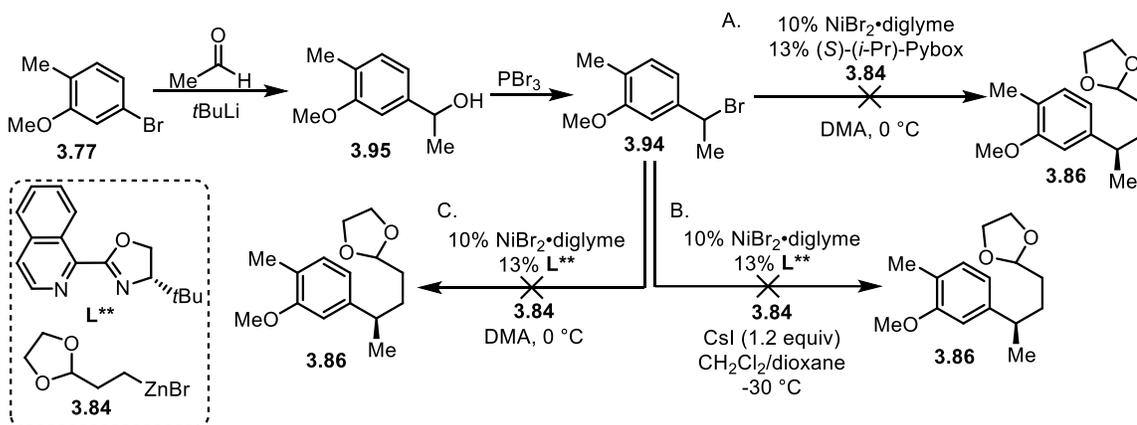


Scheme 3.15. Potential alternative Ni(0)-catalyzed approaches

Two additional Ni-catalyzed approaches were discovered, both describing the asymmetric coupling of benzylic bromides with zincates (Scheme 3.15A,B). The first approach (Scheme 3.15A), disclosed in 2005 by Fu and coworkers describes the asymmetric coupling of linear zincates with cyclic benzylic bromides (**3.89**) using (*S*)-(*i*Pr)-Pybox as the chiral ligand²⁰. Worth noting is that acyclic benzylic bromides were not tolerated in these conditions and resulted in diminished yield. The other approach (Scheme 3.15B), also published by Fu in 2012 describes the asymmetric coupling of branched or cyclic zincates (**3.92**) with acyclic benzylic bromides (**3.91**) using the chiral isoquinoline oxazoline ligand (**L****) shown in Scheme 3.16B²¹. This method is largely intolerant of linear zincates, as migrations tend to occur leading to undesired branched

products with diminished enantioselectivity. Our proposal, seen in Scheme 3.16C, stems from a combination of the two works shown above, wherein we would need to utilize an acyclic benzylic bromide (**3.94**) and a linear zincate (**3.84**); both of which are not traditionally tolerated by each standalone method.

To begin our investigations, the racemic benzylic bromide **3.94** was first synthesized by lithium-halogen exchange with aryl bromide **3.77** and addition into acetaldehyde, followed by treatment with PBr_3 (Scheme 3.16). Next, the two distinct conditions to perform the coupling of benzylic bromide **3.94** with the required zincate were screened (Scheme 3.16A,B). Unfortunately, each time the reactions were attempted using standard conditions for either transformation, no desired product was formed and the only discernable product obtained from each reaction was the benzylic bromide starting material and the quenched zincate product. Other products were formed during the course of each reaction, however they were never characterized.

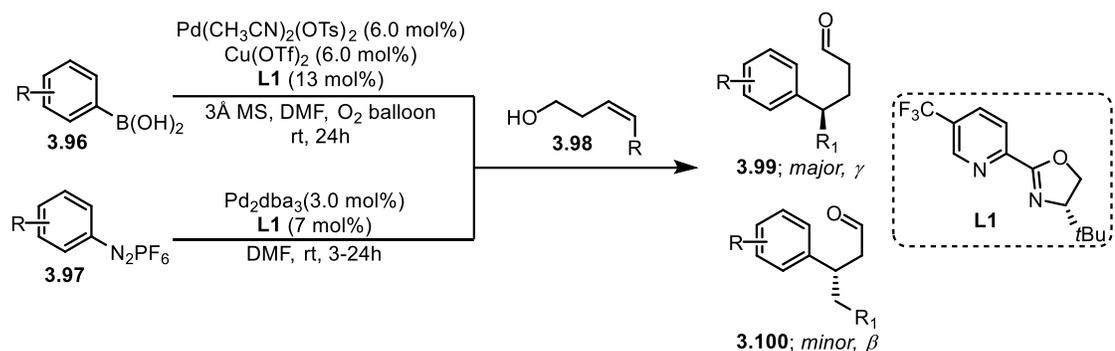


Scheme 3.16. Unsuccessful alternative Ni(0)-mediated approaches

Attempts were made to combine the two reported reaction conditions to enable the desired cross-coupling reaction. As was mentioned previously, neither standalone method is tolerant of both the acyclic benzylic bromide **3.94** and linear zincate **3.84**, only one or the other. One representative combination of conditions can be seen in Scheme

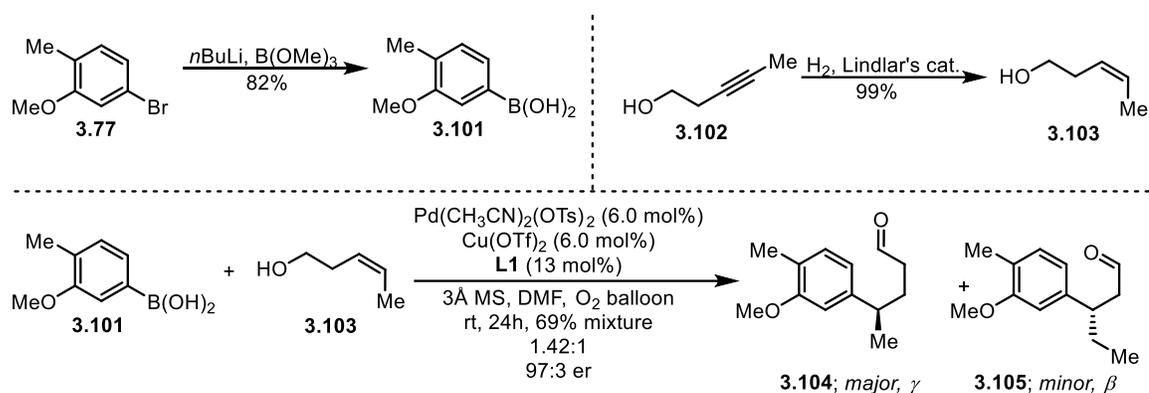
3.16C, where the reaction conditions from A were combined with the ligand from B. Unfortunately, however, each variation attempted resulted in complete recovery of starting material, and no reaction was ever observed, which prompted a continued search for alternatives.

3.6: ASYMMETRIC RELAY HECK COUPLING



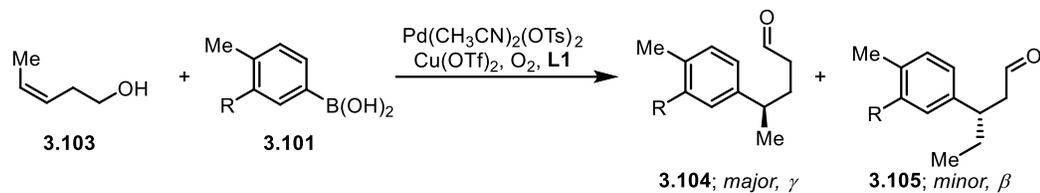
Scheme 3.17. Reported redox-relay Heck oxidation to deliver chiral aldehydes

In 2012 and 2013 the Sigman group reported an enantioselective redox relay Heck coupling in which alkenyl alcohols are coupled to aryl diazonium or arylboronic acids salts using Pd(0) or Pd(II) catalysts, respectively (Scheme 3.17).^{22,23} In each reaction, there are two regiochemically isomeric products possible arising from aryl insertion into either end of the olefin with the β product typically favored as a result of ligand and aryl electronics, wherein electron-rich aryl substrates typically suffer from poorer regioselectivity.^{24,25} This transformation would provide expedient access to the benzylic stereocenter with reportedly high enantioselectivity. Subsequently the major product (**3.99**) could undergo acid-mediated cyclization into the resulting aldehyde which would provide cyclic alcohol **3.66** or ketone **3.67** depending on the cyclization method.



Scheme 3.18. Performance of redox-relay Heck coupling

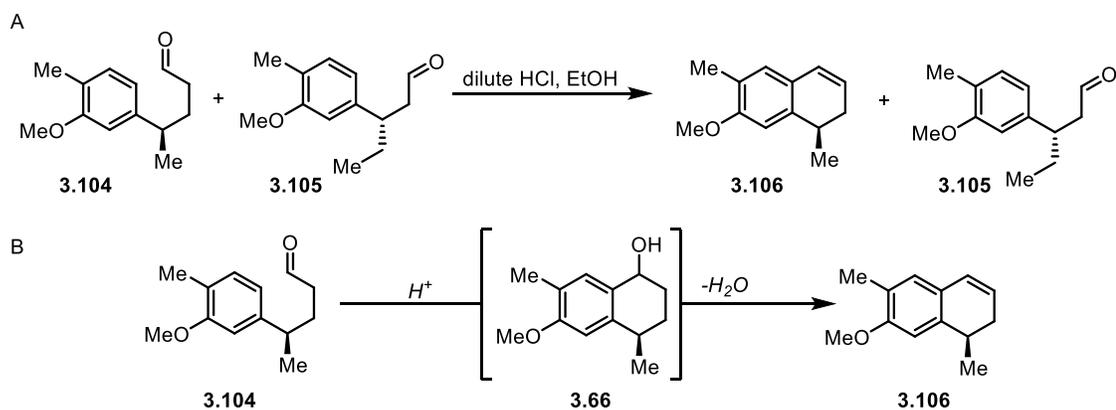
Early investigations began with the syntheses of arylboronic acid **3.101** from the corresponding aryl bromide **3.77** via lithium/halogen exchange followed by borylation and hydrolysis to the desired boronic ester (Scheme 3.18). Cis-alkenyl alcohol **3.103** was delivered from the hydrogenation of alkyne **3.102** using Lindlar's catalyst. With both starting materials in hand and the ligand synthesized, the Heck reaction was performed using standard conditions delivering the desired product with high enantioselectivity and moderate yield. Unfortunately, the regioselectivity of the transformation was quite low as the desired **3.104** was only favored by less than 3:2 over the undesired **3.105** and the mixture of regioisomers was inseparable via column chromatography. This regioselectivity was also observed with the related aryldiazonium salt coupling, with the added disadvantage of co-elution of dba ligand upon column chromatography purification. While the magnitude of lack of selectivity observed was surprising, it had



R =	Boronic acid yield	Heck coupling yield	Ratio (γ : β)
-OMe	82%	69%	1.0 : 0.69
-OTFAA	16%	21%	1.0 : 0.11
-OPiv	NA	NA	NA
-COCH ₃	80%	23%	1.0 : 0.40
NO ₂	NA	NA	NA
-F	99%	23%	1.0 : 0.40
-H	83%	70%	1.0 : 0.40

Table 3.1. Screening of aryl substituents in relay Heck coupling

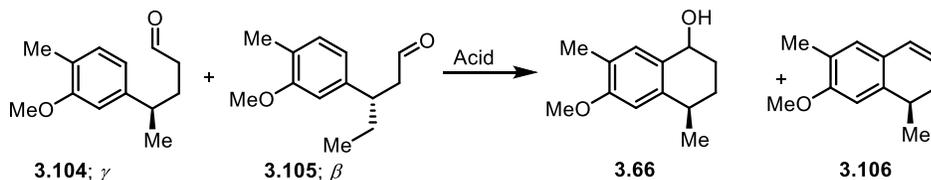
been reported that electron-rich arenes suffer relatively poorer selectivity. We therefore attempted to tune the electronics of the arene either by varying substitutions on the oxygen atom substitution for electron-neutral or withdrawing precursors which could later be converted to the required alcohol (Table 3.1). Each of the boronic acids was synthesized either by lithium/halogen exchange or via a cross coupling, with exception to



Scheme 3.19. Attempted acid-mediated cyclization from chiral aldehyde

the -OPiv and nitro substituted rings which were not successfully synthesized. From these results we concluded that the electron-withdrawn oxygen protecting group -TFAA

provided the best regiochemical outcome, however both the yield of the Heck coupling as well as the synthesis of the boronic acid, which combined provide the desired product in 3.4% over two steps.

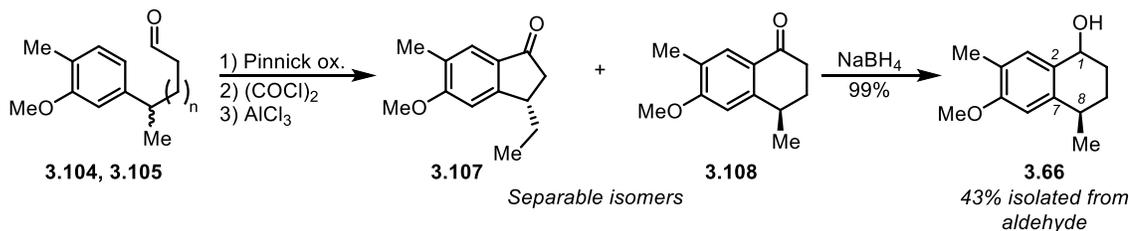


Acid	Conditions	Result
3M HCl	Added @ 0°C in THF, warmed until SM consumed	3.106, 3.105
TiCl₄	Added @ 0°C in THF, warmed until SM consumed	3.106, 3.105
AlCl₃	Added @ 0°C in THF, warmed until SM consumed	3.106, 3.105
PTSA	Added @ 0°C in THF, warmed until SM consumed	3.106, 3.105
Et₃SiH	Added @ 0°C in THF, raised to reflux	No reaction
BF₃•OEt₂	Added @ 0°C in THF, warmed until SM consumed	Complex mixture
HPF₆	Added @ 0°C in THF, warmed until SM consumed	3.106, 3.105
SiO₂ + HCl	Added @ 0°C in EtOH, warmed until SM consumed	3.106, 3.105

Table 3.2. Screen of acids to enable cyclization of chiral aldehyde

Despite the relatively low regiochemical outcome, -OMe substrate was utilized in subsequent transformations due to its ease of synthesis and similarity to the phenol substitution found in Heliannuol D. To access the alcohol required for the rearrangement to occur, an acid-mediated Friedel-Crafts type alkylation was envisioned wherein the activated para position of the electron-rich aryl ring would attack into the aldehyde resulting from the Heck coupling. An initial reaction was tested with aqueous hydrochloric acid in ethanol, however no desired product was obtained, instead delivering a mixture of starting material **3.105** and styrenyl product **3.106** (Scheme

3.19A). This elimination product was also used to determine the enantiomeric excess of the reaction, since the racemate could be easily synthesized rather easily. While the desired alcohol **3.66** was not isolated, the conditions were selective for 6-membered ring formation and did likely proceed via the desired alcohol which underwent subsequent elimination to **3.106** (Scheme 3.19B). In an effort to enable to isolation of **3.66**, a panel of acids were screened for their competence in the desired transformation (Table 3.2). Unfortunately, each acid screened led to the formation of **3.106** without any observation of desired alcohol **3.66** or failed to react at all.

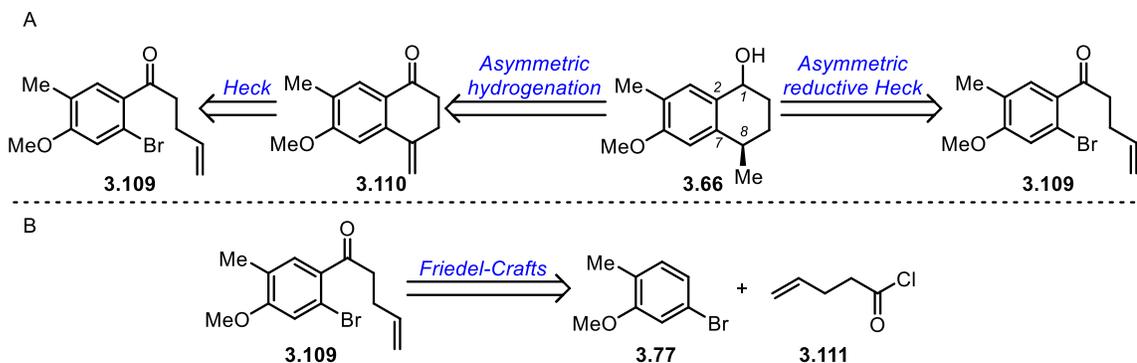


Scheme 3.20 Synthesis of chiral alcohol via oxidation/cyclization sequence

While acid-mediated cyclization represents the most straightforward approach to alcohol **3.66** from **3.104**, a lengthier sequence of oxidation and cyclization could also be carried out. As such, a mixture of **3.104** and **3.105** were subjected to Pinnick oxidation to the corresponding carboxylic acids then conversion to the corresponding acyl chlorides with oxalyl chloride (Scheme 3.20). At the stage of the acyl chloride, a Friedel-Crafts acylation was carried out in the presence of aluminum trichloride to forge the desired ketone product (**3.108**) and the 5-membered ring isomer (**3.107**). At this stage the regioisomers became separable by column chromatography and the desired **3.108** was cleanly isolated. Following a quantitative sodium borohydride reduction, the alcohol required for the key oxidative rearrangement (**3.66**) was delivered in 43% overall yield. While this sequence delivers provides excellent enantioselectivity (97:3 er), the issues

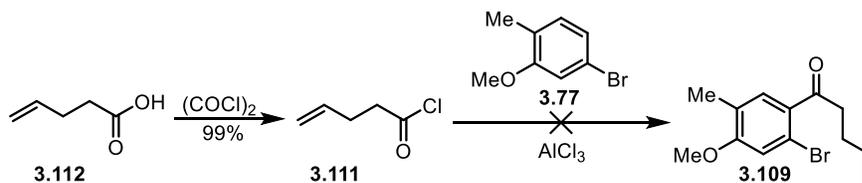
regarding of increased step count and large amount of regioisomeric waste product generated prompted investigations to improve the synthetic approach.

3.7: TRADITIONAL HECK COUPLING APPROACH



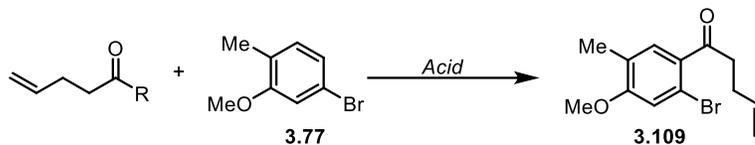
Scheme 3.21. Proposed Heck pathways to desired chiral alcohol

In order to address the issues which arose during the prior methods, a new general approach was devised which would utilize a Heck coupling to join C7 and C8 with the bond between C1 and C2 would already formed. The asymmetry could be introduced from an asymmetric reductive Heck coupling^{26–28} or an asymmetric hydrogenation following a traditional Heck reaction to afford the same product (Scheme 3.21A).^{29–31} Each of these pathways requires the use of olefin precursor **3.109**, derived from a Friedel-Crafts reaction between bromoarene **3.77** and acyl chloride **3.111** (Scheme 3.21B). Acyl chloride **3.111** was easily synthesized from 4-pentenoic acid in quantitative yield, and the subsequent Friedel-Crafts acylation reaction with **3.77** under standard conditions did not



Scheme 3.22. Unsuccessful Friedel-Crafts reaction en route to Heck precursor

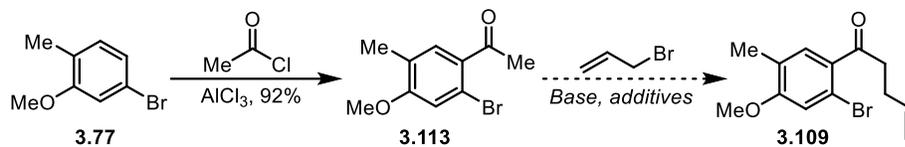
deliver any desired product, instead resulting in the recovery of aryl bromide **3.77** and formation a solid mass in the reaction flask likely due to polymerization (Scheme 3.22). Various Bronsted and Lewis acids were screened in the reaction both from the **3.111** and the 4-pentenoic acid, with the best conditions providing the **3.109** in 6% yield. (Table 3.3).



R =	Acid	Outcome
-Cl	AlCl ₃	Polymerization, recovery of 3.77
-Cl	TfOH (cat.)	Polymerization, recovery of 3.77
-Cl	TfOH	Polymerization, recovery of 3.77
-Cl	HFIP	No reaction, recovery of 3.77
-Cl	ZnCl ₂	Polymerization, recovery of 3.77
-Cl	FeCl ₃	Polymerization, recovery of 3.77
-OH	TFA+TFAA	6% 3.109 , recovery of 3.77

Table 3.3. Screen of acids in Friedel-Crafts acylation

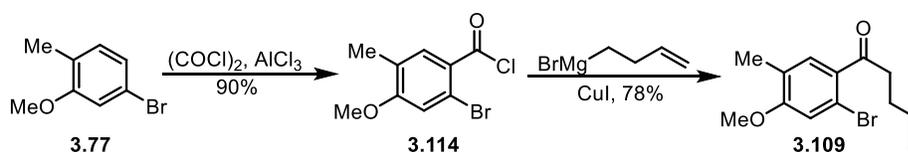
Efforts toward the synthesis of **3.109** evolved to target formation the C-C bond at the alpha position of the corresponding acetophenone **3.113**, which is easily synthesized from the reaction of arene **3.77** and acetyl chloride in the presence of AlCl₃. In the proposed transformation, the enolate of **3.113** could react with allyl bromide to deliver the desired product either via a S_N2 or S_N2' reaction pathway. Therefore, acetophenone **3.113** was synthesized in high yield, and a screen of conditions to enable the desired transformation was performed (Table 3.4). A search of prior work on similar scaffolds aided in the selection of three commonly used bases and conditions including the use additives such as triethylborane to suppress formation of dialkylation.³²⁻³⁴ Screening revealed that potassium and sodium hydride delivered an inseparable mixture of mono-



Base	Additive	Result
LDA	None	Trace 3.109 , recovered SM
	Pd(PPh ₃) ₄ (cat.)	Trace 3.109 , recovered SM
NaH	None	Mix; mono- and dialkylation
	Triethylborane	Complex mixture of products
KH	None	Mix; mono- and dialkylation
	Triethylborane	22% 3.109

Table 3.4. Screen of bases in enolate formation of acetophenone 3.113

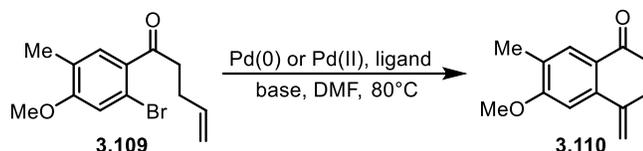
and dialkylation products and LDA was ineffective in this transformation. The addition of triethylborane with KH produced the most promising results, delivering olefin **3.109** in 22% yield with no dialkylation product. The transformation, however, still suffered from low and inconsistent yields due to discrepancies in purity/handling of KH. Therefore, we turned our attention to facilitating the Grignard addition into either an ester or acyl halide. Therefore, bromoarene **3.77** was converted to acyl chloride **3.114** by treatment with (COCl)₂ and AlCl₃ in good yield. **3.114** was then subjected to nucleophilic addition of the required Grignard in the presence of catalytic copper iodide to prevent di-alkylation which provided **3.109** in 78% yield (Scheme 3.23).³⁵



Scheme 3.23. Efficient synthesis of Heck precursor

With improved access to **3.109** in hand, investigations began on optimizing a reductive Heck cyclization using various literature precedented conditions on related substrates. Unfortunately, while cyclization was observed, no reductive Heck products were ever formed using relatively standard conditions. Two ubiquitous palladium

sources, Pd(OAc)₂ and Pd₂dba₃, were used in conjunction with triphenylphosphine as the racemic ligand. Common reductants were screened including proton sponge, triethylamine, and DIPEA as well as various silver salts such as silver carbonate and silver nitrate to no avail^{26,28}. Therefore, attention shifted to optimization of the traditional Heck reaction to produce olefin **3.110**, which we envisioned could be hydrogenated



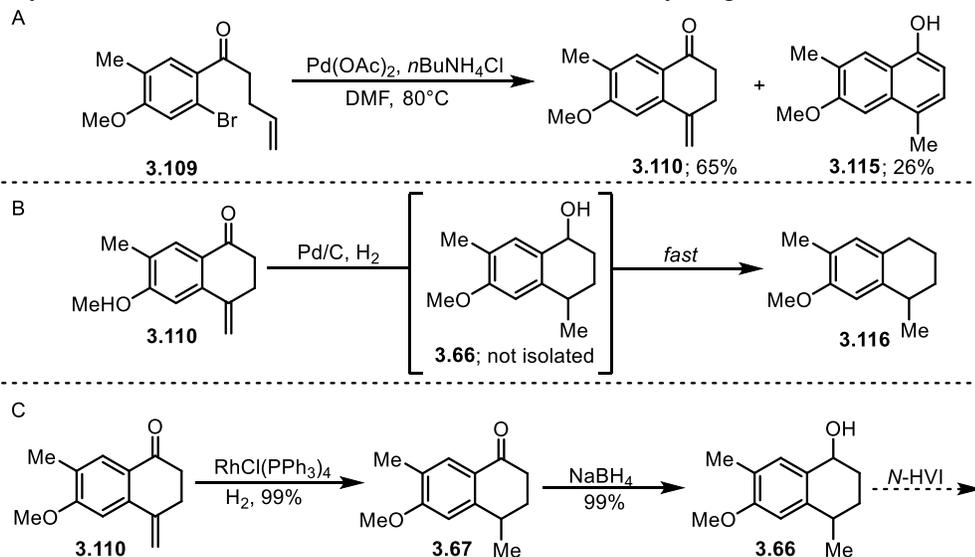
Catalyst	Ligand/Reductant	Base	Ratio (A:B)
Pd(OAc) ₂	PPh ₃	AgCO ₃	1.00 : 0.44
Pd(OAc) ₂	PPh ₃	TEA	1.00 : 0.59
Pd(OAc) ₂	PPh ₃	K ₂ CO ₃	1.00 : 0.41
Pd ₂ (dba) ₃	PPh ₃	AgCO ₃	1.00 : 0.24
Pd ₂ (dba) ₃	PPh ₃	TEA	1.00 : 0.12
Pd(OAc) ₂	Bu ₄ NBr	K ₂ CO ₃	1.00 : 6.67
Pd(OAc) ₂	Bu ₄ NCl	K ₂ CO ₃	Only Product

Table 3.5. Screen of Heck conditions

asymmetrically to provide the desired stereocenter. Multiple conditions were screened (Table 3.5) including the use of Pd(II) or Pd(0) sources in the presence of triphenylphosphine ligand. A base screen was also performed however no set of conditions was providing the product with full completion of starting material. Ligandless Heck conditions^{36,37} provided the best results, wherein tetrabutylammonium bromide provided the desired product in a greater than 6:1 ratio of product to starting material and tetrabutylammonium chloride provided the desired product exclusively with no remaining starting material by crude NMR. With optimized conditions in hand, the Heck reaction was carried out on large scale and **3.110** was isolated in modest yield (Scheme 3.24A). A pitfall of the reaction is the undesired and irreversible conversion of ketone

3.110 to naphthol **3.115** with prolonged exposure to palladium. Once isolated, however, **3.110** was stable to storage and handling.

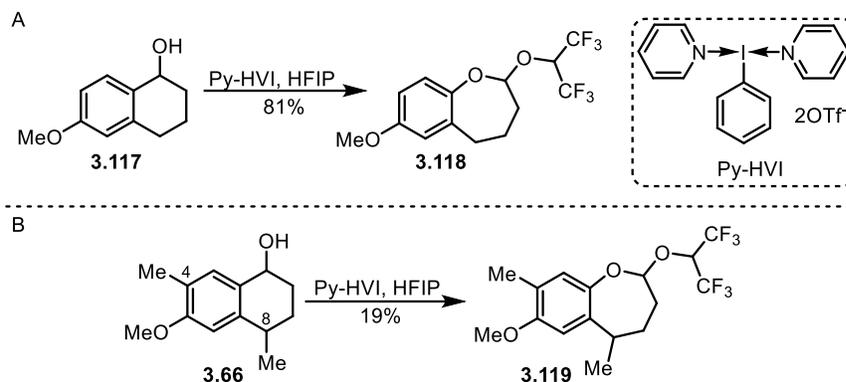
Synthetic efforts became focused on the selective hydrogenation of the exocyclic



Scheme 3.24. Heck reaction and subsequent reductions

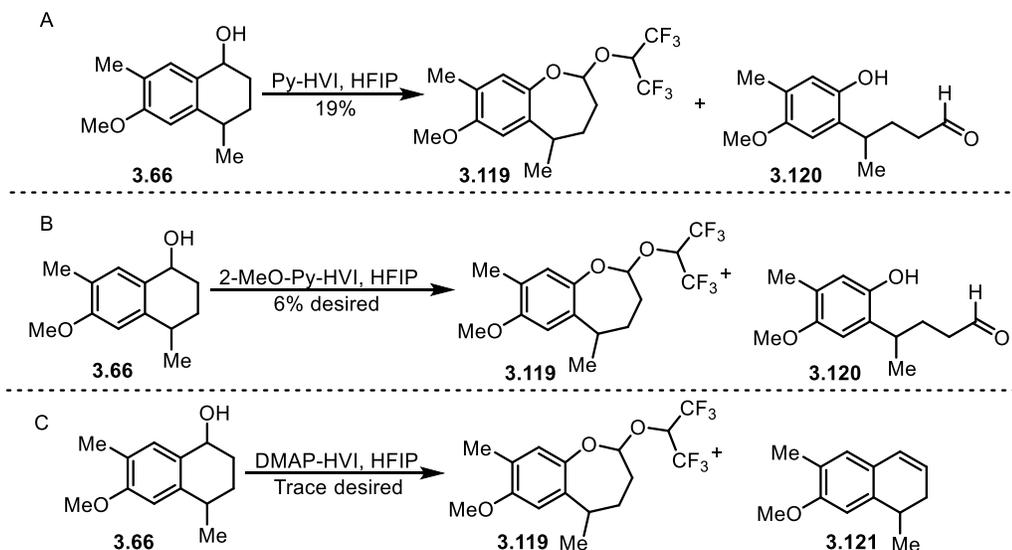
olefin in the presence of the acetophenone moiety. When **3.110** was subjected to hydrogenation conditions using palladium on carbon under a hydrogen atmosphere, global reduction was observed followed by benzylic alcohol cleavage to afford tetralin **3.116** (Scheme 3.24B). Conversely, treatment of **3.110** with Wilkinson's catalyst afforded the selective hydrogenation of the olefin with full conversion, leaving the ketone untouched (Scheme 3.24C). Despite the overall goal of asymmetric hydrogenation, the synthesis was carried forward with racemic material to optimize the late stage synthesis prior to a potentially costly and time-consuming catalyst/ligand screen. Thus, the subsequent sodium borohydride reduction provided the racemic alcohol required for the key *N*-HVI mediated oxidative rearrangement.

3.8: N-HVI MEDIATED OXIDATIVE REARRANGEMENT



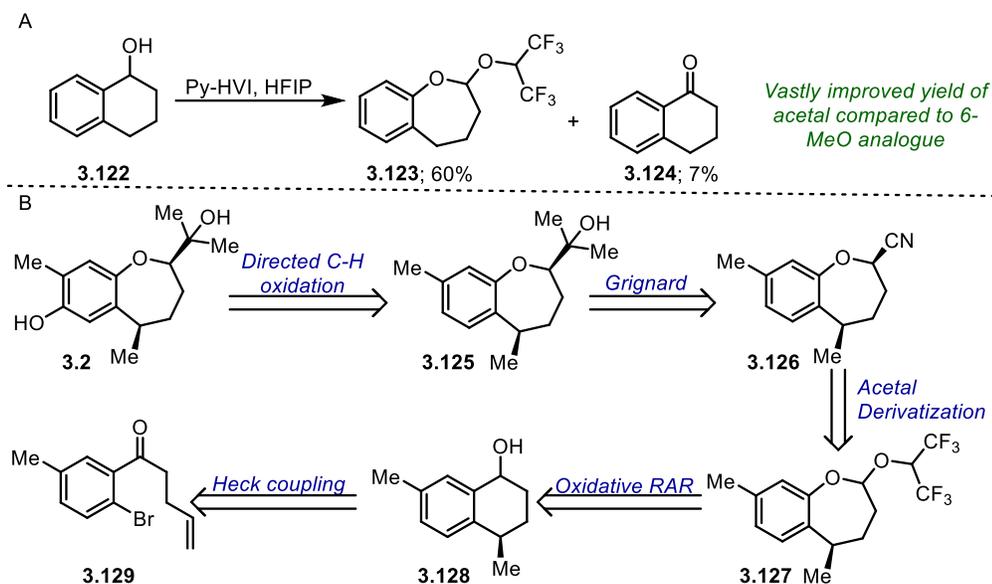
Scheme 3.25. Precedented and unsuccessful ring expansion

The novelty of our total synthesis of Heliannuol D stems from innovative approach to the medium-sized heterocycle which the *N*-HVI mediated oxidative rearrangement strategy^{15,16}. The method had also been performed and optimized with good yield on a similar molecular scaffold in the seminal publication (Scheme 3.25A). Therefore, standard conditions were applied to tetralin **3.66** using pyridinium hypervalent iodine reagent which provided HFIP acetal **3.119** in low yield (Scheme 3.25B). In



Scheme 3.26. Investigation of alternative *N*-HVIs in ring expansion

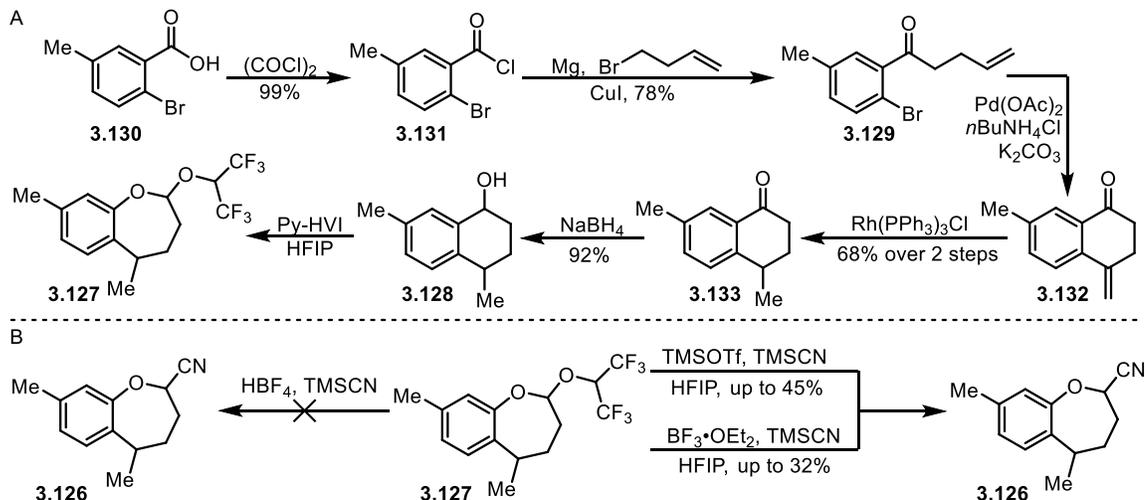
secondary alcohol systems oxidation to the corresponding ketone is plausible especially in complex systems, however no ketone products were observed.



Scheme 3.27. Successful ring expansion and modified retrosynthesis

Instead, product degradation seemed likely since aldehydic protons were observed in crude NMR samples arising from ring-opening acetal decomposition (Scheme 3.26A). 2-MeO-Py-HVI and DMAP-HVI were screened in an effort to alter reactivity and favor the desired transformation, however both resulted in further diminished yields (Scheme 3.26B,C). Due to the nature of the byproducts obtained and based on prior knowledge, it was hypothesized that the electronics of the ring was negatively affecting the reaction as has been observed previously. Therefore, tetralol **3.122** was subjected to standard rearrangement conditions resulting in a drastic improvement in isolated yield to 60% (Scheme 3.27A). This result prompted revision to the overall synthesis to exclude the oxygen on the aryl ring until the performance of the oxidative rearrangement and synthesis of the aryl cyclic ether. A similar retrosynthesis was assembled, however a late-stage directed C-H activation step would be incorporated to install the oxygen atom

required at C8 following the heterocycle synthesis. Outside of this minor modification, each step would be identical but performed on the corresponding des-MeO aryl substrate (Scheme 3.27B).

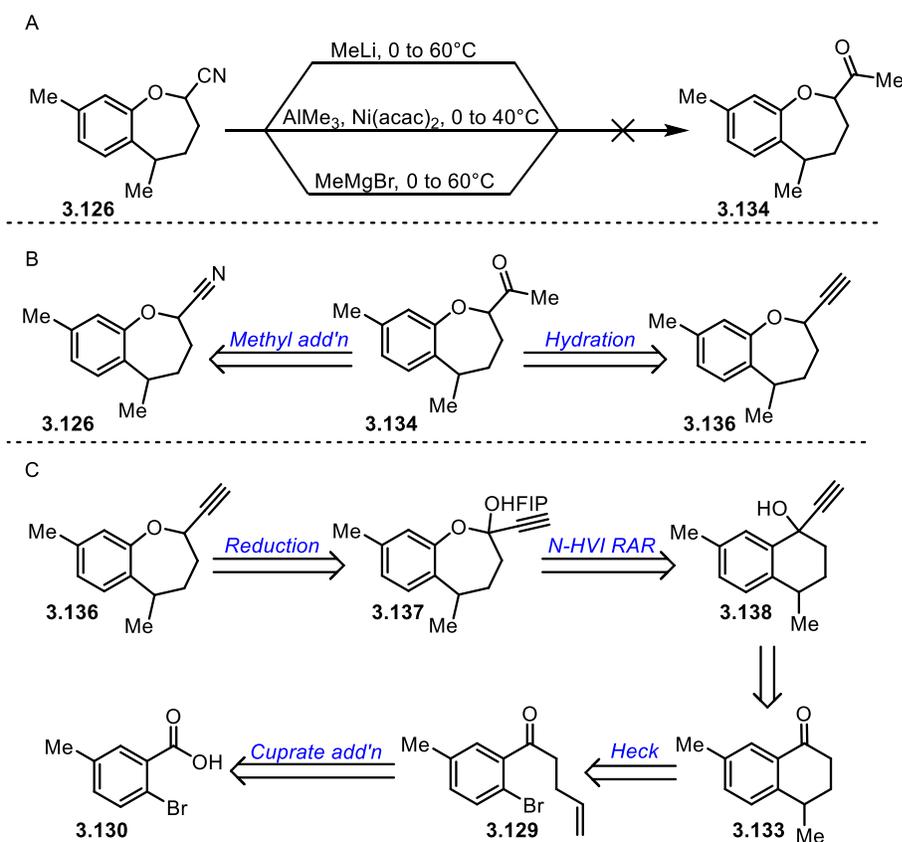


Scheme 3.28. Continued racemic synthesis HFIP acetal derivatization

Therefore, the modified synthesis commenced with the quantitative conversion of acid **3.130** to acyl chloride **3.131** using oxalyl chloride (Scheme 3.28A). Following a cuprate addition to afford **3.129** and subsequent Heck coupling, hydrogenation of the exocyclic olefin was **3.133** performed with Wilkinson's catalyst. Sodium borohydride reduction provided alcohol **3.128** which was poised for the key oxidative rearrangement, which proceeded in a 60% yield to deliver the heterocyclic core of Heliannuol D. The ensuing transformation entailed the derivatization of HFIP acetal **3.127** to the corresponding nitrile, which has been previously reported and utilized HBF₄, TMSOTf and BF₃•OEt₂.^{15,16} In this substrate HBF₄ was unsuccessful, resulting in decomposition to the open chain product, however BF₃•OEt₂ and TMSOTf both provided the desired product. Typical yields using boron trifluoride hovered in the teens with the best result

providing desired product in 32% yield. Conversely, TMSOTf provided the desired nitrile product (**3.126**) in roughly 45% yield consistently (Scheme 3.28B).

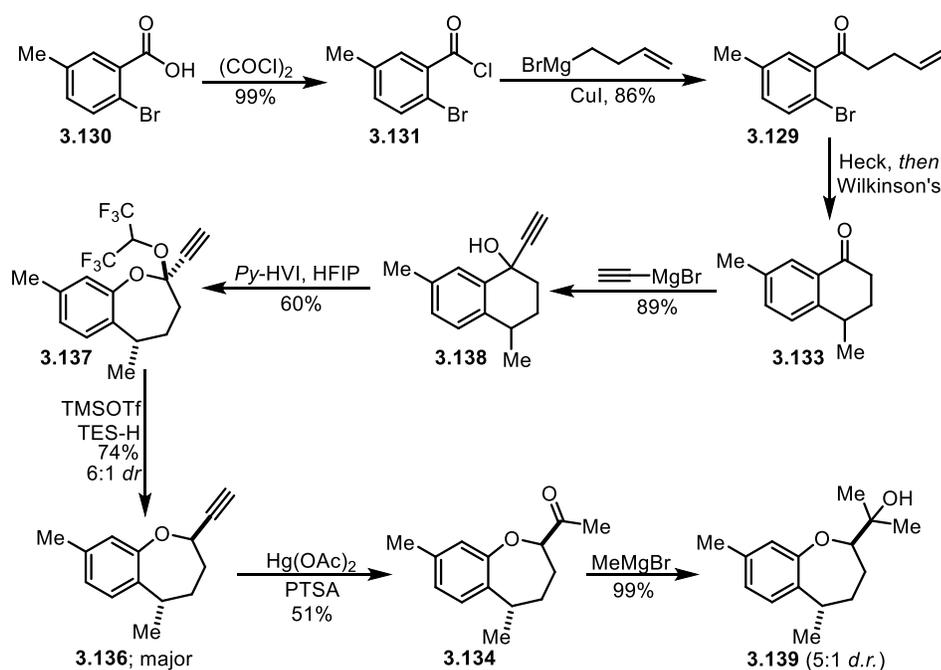
Next, efforts were made to methylate the nitrile and deliver the corresponding methyl ketone following hydrolysis which is typically performed using organometallic reagents such as methyllithium or methylmagnesium halides,^{38,39} and less commonly trimethylaluminum.⁴⁰ As can be seen in Scheme 3.29A, various attempts were made to methylate nitrile **3.126** using traditional organometallics, and all were unsuccessful resulting in no observed reaction and only recovery of starting material. Modulation of temperatures and conditions was futile, which prompted re-evaluation of the synthetic route.



Scheme 3.29. Failed nitrile derivatization and modified retrosynthesis

Ultimately methyl ketone (**3.134**) was desired, and aside from nitrile **3.126**, the desired methyl ketone **3.134** can also be delivered via hydration of the corresponding alkyne (**3.136**, Scheme 3.29B) by transition metal catalysis.^{41,42} Alkyne **3.135** is readily accessible from HFIP acetal **3.317** via reductive cleavage of the HFIP moiety. The only modification from the prior synthetic sequence up to the key rearrangement step is a Grignard addition from ketone **3.133** to deliver tertiary alcohol **3.138** rather than a hydride reduction. (Scheme 3.29C).

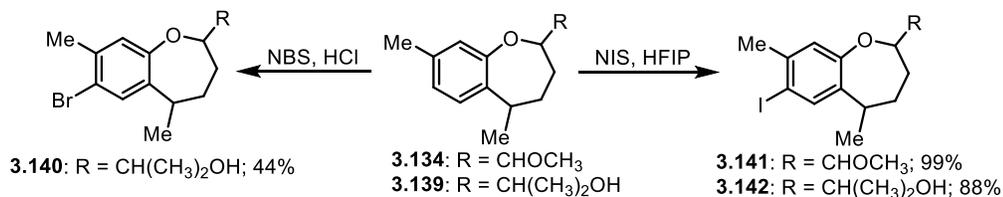
3.9: COMPLETION OF RACEMIC SYNTHESIS



Scheme 3.30. Racemic synthesis of des-OH Heliannuol D

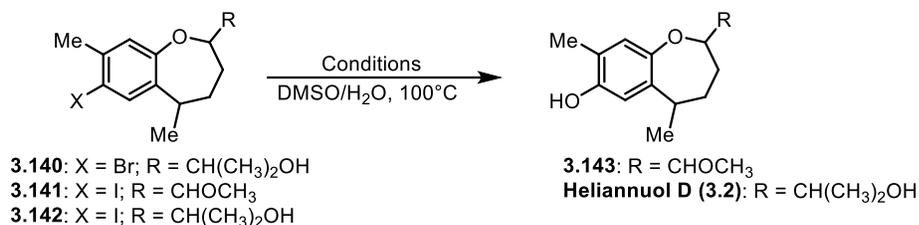
Analogous to the prior sequence, the modified synthetic procedure began with cuprate addition into acyl chloride **3.131** followed by a Heck coupling and hydrogenation of the resulting olefin to deliver ketone **3.133** (Scheme 3.30). Rather than reduction of the ketone in molecule **3.133**, alkynylmagnesium bromide was added to deliver the alkynyl

tertiary alcohol **3.138** in good yield as an inconsequential mixture of diastereomers (~3:2). The rearrangement reaction on alcohol **3.138** proceeded smoothly to deliver a single diastereomer of HFIP acetal **3.137** in modest yield as a single diastereomer. Single crystal X-ray analysis of HFIP acetal **3.137** revealed the cis diastereomer (with respect to the benzylic methyl group and the alkynyl functionality) to be the exclusive product formed, however this stereochemical result was ultimately inconsequential to the stereochemistry of the subsequent product. HFIP acetal **3.137** was reduced using TMSOTf and triethylsilane which resulted in clean conversion to the reduced product **3.136** with varying diastereomeric ratios, however each time the major diastereomer out of the reduction favors a trans relationship (epimeric to natural product) relative to the alkyne and benzylic methyl. This selectivity would later be addressed, and the synthesis was continued with the oxymercuration of alkyne **3.136** to deliver ketone **3.134** with unchanged diastereoselectivity. The addition of methyl Grignard provided tertiary alcohol **3.139** in quantitative yield, providing the des-hydroxylated natural product. Various methods for the regioselective hydroxylation of aryl ethers were investigated to complete the total synthesis of Heliannuol D.



Scheme 3.31. Para-halogenation of cyclic aryl ethers

To install the phenol functionality on the ring, para-bromination and iodination was carried out from ketone **3.134** and tertiary alcohol **3.139**.^{43,44} (Scheme 3.31). To transform the various haloarenes to their corresponding phenols, Ullman-type conditions



Substrate	Conditions	Target	Outcome
3.140	CuI, KOH, PEG400, No solvent	3.143	SM only
3.140	CuI, KOH	3.143	SM only
3.141	CuI, KOH, 1,10-phenanthroline	3.143	Complex mixture
3.141	CuI, KOH, tBuOH	3.143	Complex mixture
3.142	CuI, KOH, 8-OH-quinoline, tBuOH	3.2	55%
3.142	CuI, KOH, 1,10-phenanthroline	3.2	99%

Table 3.6. Ullman conditions for hydroxylation of aryl halides

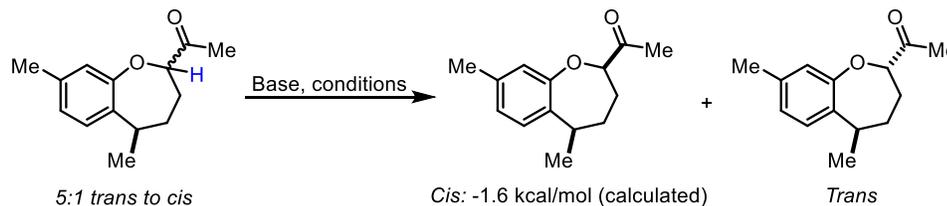
were applied wherein a copper catalyst in the presence of water and potassium hydroxide promotes the desired transformation according to literature precedent (Table 6).

Screening commenced with the screening of bromide substrate **3.140** using previous literature procedures⁴⁵, however no desired product was obtained from these efforts and only starting material was recovered. The analogous transformation from the corresponding iodoarenes was then evaluated,^{45,46} which revealed complete decomposition in ketone **3.141**, likely due to the acidic protons present in the ketone substrate and the highly basic conditions. Evaluation of **3.142** revealed a 55% yield of desired product when 8-hydroxyquinoline was employed as the ligand along with *tert*-butanol as a solvent, and full conversion was observed with 1,10-phenanthroline as the ligand in a 1:1 DMSO:water solvent system. With the successful installation of the phenol moiety, the racemic synthesis of (±)-Heliannuol D (**3.2**) was complete resulting in a 5:1 diastereomeric ratio of *trans* (*epi*) to *cis* isomers. Prior to continuing to the asymmetric synthesis, optimization was performed on select transformations or substrates requiring further attention.

3.10: RACEMIC SYNTHESIS OPTIMIZATION

3.10i: Diastereoselectivity and Epimerization

As was previously mentioned, the major observed diastereomer from the racemic synthesis is the trans, epimeric diastereomer. The favorability first emerges upon the hydride reduction of the HFIP acetal and remains unchanged throughout, however epimerization is plausible at the stage of the methyl ketone with an acidic alpha proton at the key stereocenter. To determine whether either isomer is thermodynamically favored over the other, a minimized energy calculation was performed which revealed that the desired cis isomer was favored by 1.6 kcal/mol. With this information in hand, epimerization was attempted using various basic conditions summarized in Table 3.7.



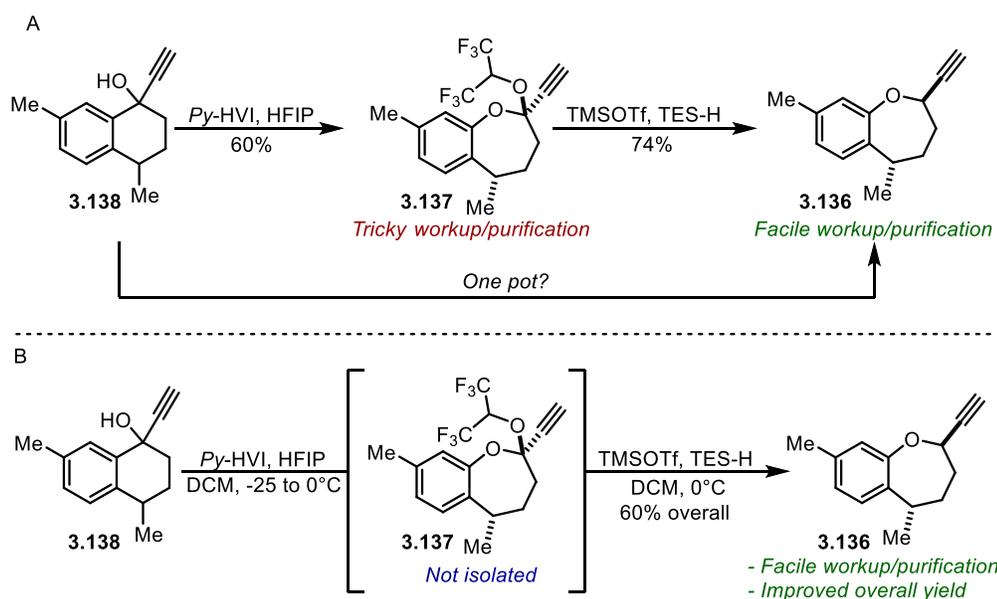
Base	Conditions	cis:trans
Cat. tBuOK	tBuOH, 10 mins	3:2
Cat. EtOK	EtOH, 5 hours	3:2
Cat. MeONa	MeOH, 12 hours	3:2
LDA (1.0 equiv.)	5 hours @ RT then quench @ RT	1:5
LDA (1.0 equiv.)	5 hours @ RT then quench @ 0°C	1:5
LDA (1.0 equiv.)	5 hours @ RT then quench @ -78°C	1:5
LDA (0.95 equiv.)	5 hours @ RT then quench @ RT	1:5

Table 3.7. Evaluation of epimerization conditions

Thermodynamic deprotonation conditions were first investigated using catalytic alkoxide bases with their corresponding alcoholic solvents. Inversion of selectivity favoring the *cis* isomer using *tert*-butoxide and *tert*-butanol within 10 minutes, however, the epimerization stalled at a ratio of 3:2 *cis* to *trans*. This ratio was not improved with

the use of methoxide or ethoxide bases or with heating in any case. Stoichiometric deprotonation was then screened using LDA and quenching at various temperatures in an effort to trap the thermodynamically favored isomer which resulted in no epimerization, likely due to the presence of the additional acidic protons of the adjacent methyl group. Additionally, thermodynamic deprotonation using sub-stoichiometric LDA was attempted, however no epimerization was observed. Therefore, epimerization efforts culminated in the inversion of the observed ratio to 3:2 favoring the desired *cis* isomer using catalytic amounts of alkoxide salts in alcoholic solvents.

3.10ii: Optimization of Rearrangement/Reduction Sequence



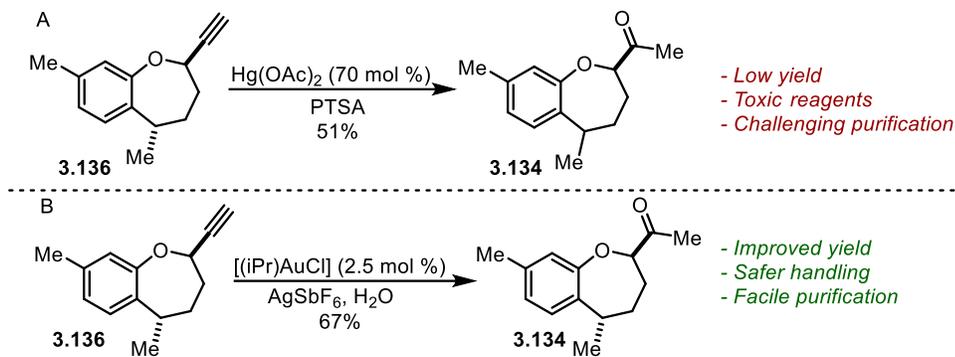
Scheme 3.32. Issues with rearrangement and telescoping with subsequent reduction

The isolation and purification of the HFIP acetals is a non-trivial operation often resulting in desired product decomposition with minor fluctuations in temperature in the presence of HFIP (Scheme 3.32A). This propensity to decompose necessitates special

handling of the reaction until the HFIP acetal product is fully purified. The subsequent hydride reduction, however, yields a stable product which does not require special handling and is performed under conditions similar to the rearrangement in terms of solvent (HFIP as a co-solvent) and temperature (roughly 0 °C). Therefore, the possibility of telescoping the rearrangement into the reduction and performing the two reactions in one-pot was investigated. Telescoping reactions is generally preferred as it reduces isolation and purification times, and from a green perspective utilizes less solvent. Therefore, a rearrangement reaction was performed, and upon complete consumption of starting alcohol **3.138** triethylsilane and TMSOTf were added (Scheme 3.32B). Following aqueous work-up and purification on column chromatography, the alkynyl ether product **3.136** was obtained in 60% yield which is a >15% improvement over the two iterative steps. Additionally, this telescoped procedure significantly decreased the amount of time required to deliver the reduced ether product and completely avoided handling of the unstable HFIP acetal (**3.137**). Identifying the utility of the synthetic modification, the one-pot procedure was leveraged into a standalone method to provide value in a broader context to the synthetic community. Refer to Chapter 2 for more information.

3.10iii: Improvement of Alkyne Hydration

The alkyne hydration of alkyne **3.136** to methyl ketone **3.134** was initially performed using oxymercuration conditions,⁴¹ however, the low yield, use of toxic mercury reagents, and challenging purification obviated the need for an alternative method (Scheme 3.35A). A potential alternative commonly reported in the literature is a

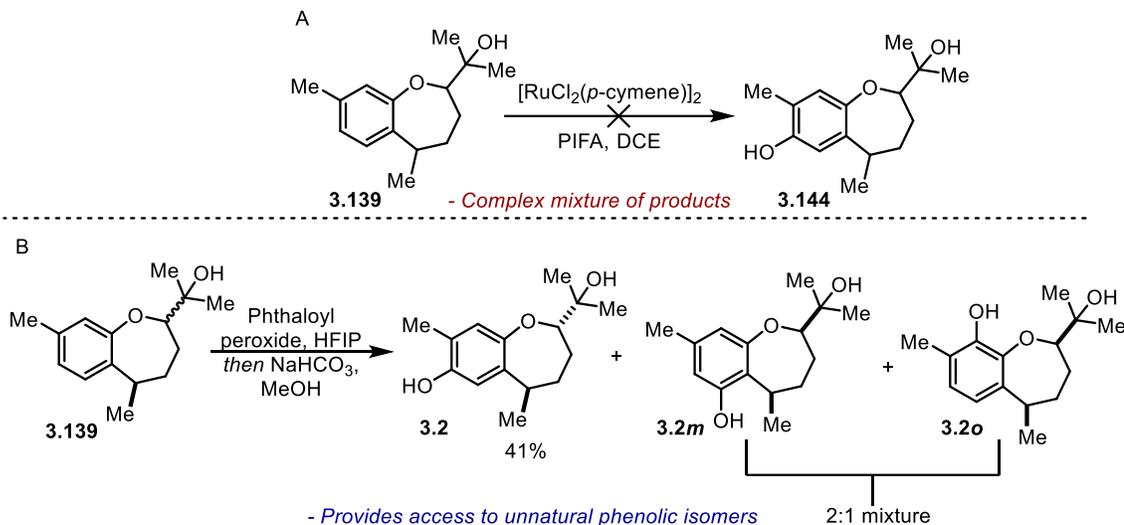


Scheme 3.33. Improved method for alkyne hydration

gold-catalyzed hydration⁴². While the catalyst is quite costly, the catalyst loading is a fraction of the amount required for the oxymercuration, and isolation and purification are often facile (Scheme 3.35B). Following literature protocol, a hydration reaction was performed with [(iPr)AuCl], which was synthesized and provided by William Sabbers, with the addition of AgSbF₆ and water. Following heating to 100 °C overnight, the starting material was fully consumed. Purification was vastly improved, affording 67% of **3.134** following column chromatography. This represents a dramatic improvement in yield, safety, and ease workup/purification compared to the oxymercuration.

3.10iv: Alternative Late-Stage Arene Oxidation

Despite the success and overall high yield of the sequential arene iodination/oxidation approach, the method requires the isolation and purification of the iodoarene intermediate. Therefore, two one-pot oxidation protocols were evaluated. First, a ruthenium-catalyzed method which had been reported to hydroxylate activated arenes was attempted,⁴⁷ however no desired product was obtained and instead a complex mixture of products was observed (Scheme 3.34A). The second method investigated is the

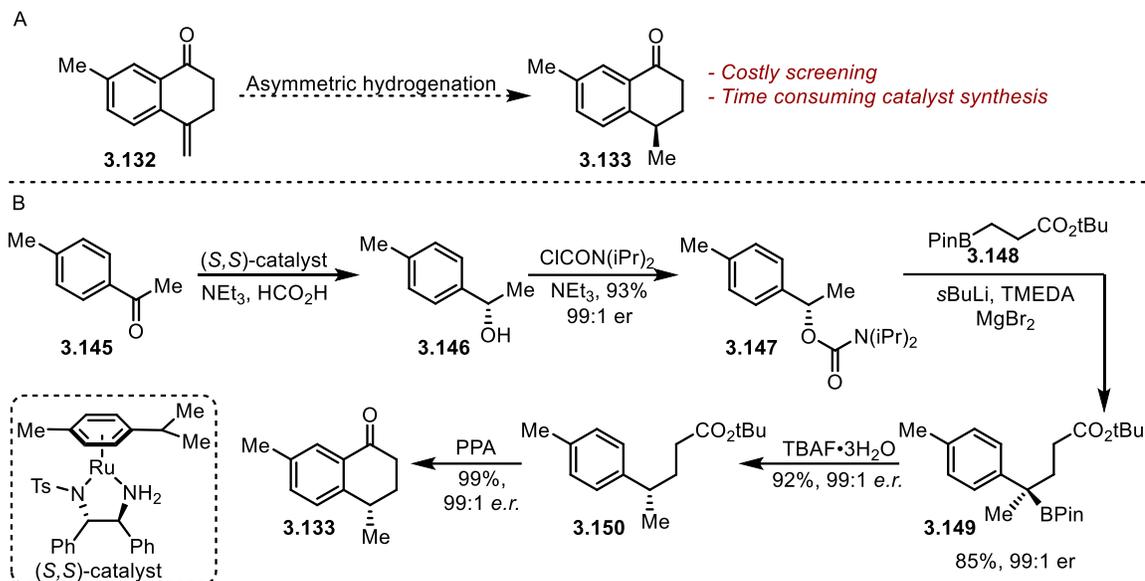


Scheme 3.34. Evaluation of alternative late-stage aryl oxidations

aryl oxidation using phthaloyl peroxide (PPO) followed by hydrolysis of the resulting ester to provide the desired phenol^{48,49}. The phthaloyl peroxide method provided a mixture of products including the desired phenol as the undesired trans diastereomer exclusively (Scheme 3.34B). The remaining products in the mixture were regioisomeric phenolic products of the desired diastereomer as well as recovered starting material. While this reaction does not provide the desired diastereomeric product, it does provide expedient access to unnatural phenolic analogues which would later be assayed for biological activity (see Chapter 5). With the conclusion of optimization of the each sequence in need, the racemic synthesis of Heliannuol D was complete and our efforts turned to the asymmetric synthesis.

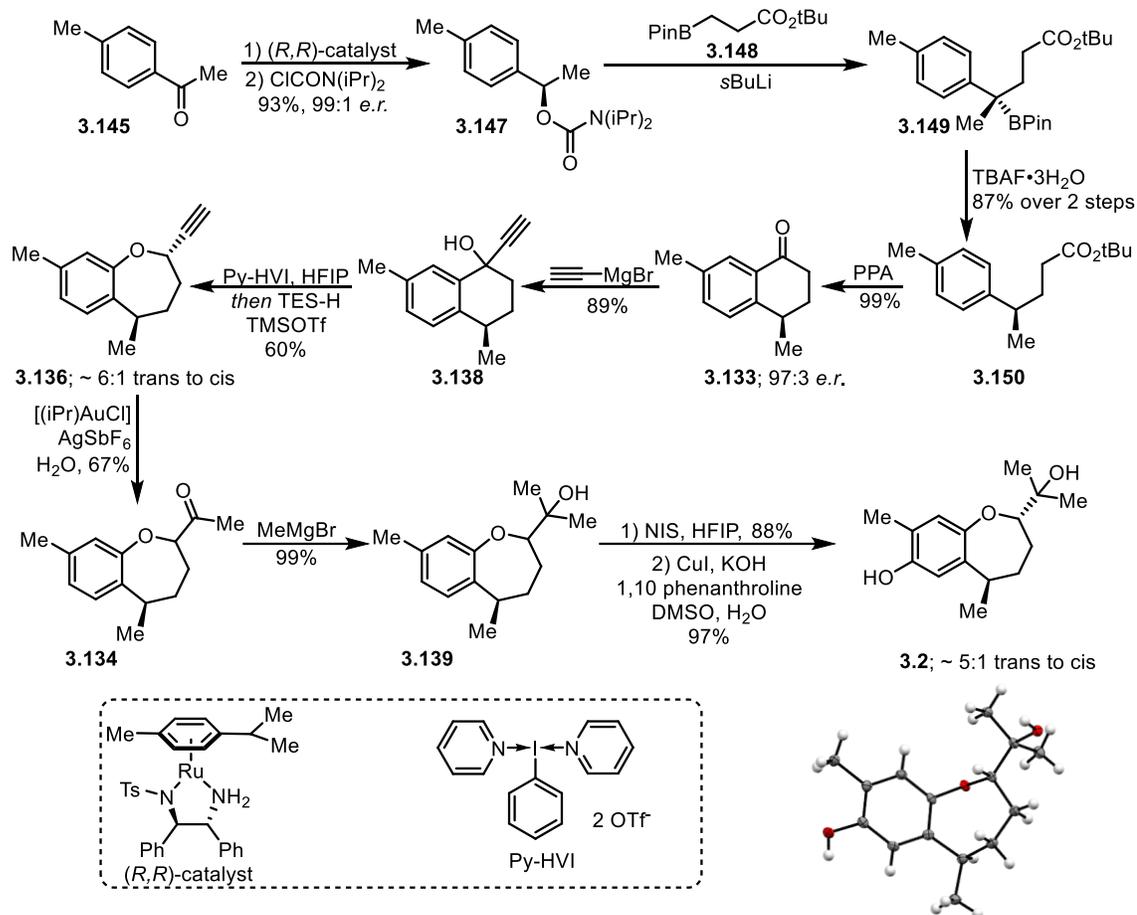
3.11: ASYMMETRIC SYNTHESIS OF (+)-HELIANNUOL D

As discussed previously, the envisioned transformation to deliver the chiral benzylic stereocenter in a selective fashion would be performed using an asymmetric hydrogenation following the standard Heck coupling. While a plethora of asymmetric



hydrogenating catalysts and conditions exist, they are often quite expensive or require multiple steps to synthesize (Scheme 3.35A). An alternative approach to the necessary chiral ketone emerged in the synthesis of Erogorgiaene reported by Aggarwal and co-workers.^{50,51} The synthesis commenced with the stereoselective Noyori reduction of acetophenone **3.145**⁵² (Scheme 3.35B). The chiral alcohol was then converted to the corresponding carbamate, then a stereoretentive lithiation/borylation sequence was carried out to deliver chiral boronic ester **3.149**. TBAF-induced de-borylation⁵³ provided ester **3.150** which was subjected to polyphosphoric acid to deliver the ring-closed product **3.133**. This ketone was the enantiomer of the identical substrate required for our synthesis and would only require the use of the opposite enantiomer of the chiral catalyst during the reduction.

The synthesis commenced with the asymmetric reduction of acetophenone **3.145** using the (*R,R*)-catalyst to provide the opposite enantiomer from the previous report with excellent enantioselectivity (Scheme 3.38). Following conversion to carbamate **3.147**, the



Scheme 3.36. Completed asymmetric synthesis of Heliannuol D

lithiation/borylation procedure was performed followed by TBAF-mediated deborylation to deliver ester **3.150**. It was found that addition of TMEDA was detrimental to the reaction resulting in incomplete conversion (ca 40% yield after deborylation) and recovered carbamate starting material. Exclusion of TMEDA improved the two-step yield to 87% with an unchanged enantiomeric ratio. The ensuing Friedel-Crafts type reaction of ester **3.150** proceeded smoothly to provide chiral ketone **3.133** in high enantioselectivity (97:3). Each step following the enantioselectivity sequence was identical to the optimized racemic synthesis, beginning with addition of alkynyl Grignard to **3.133** to deliver **3.138**, and the subsequent one-pot rearrangement/reduction sequence

to arrive at alkynyl ether **3.136**. Alkyne hydration and subsequent methyl Grignard addition provided tertiary alcohol **3.139** and the two-step aryl iodination/oxidation sequence provided (+)-Heliannuol D (**3.2**) as a ~5:1 mixture of the trans (*epi*) to cis diastereomers. Kinetic epimerization at the stage of the ketone could also be carried out to obtain a 3:2 diastereomeric ratio of cis to trans diastereomers. Thus, the asymmetric synthesis of (+)-Heliannuol D was complete.

3.12: CONCLUSIONS

The asymmetric total synthesis of Heliannuol D was achieved with the most expedient and highest-yielding route to date (11 steps, 24%). The synthesis was also completed with extremely high enantioselectivity at the important benzylic position (97:3 *e.r.*). Central to the success and uniqueness of this route was the employment of a novel oxidative rearrangement to umpole cyclic alcohols at the oxygen atom and deliver medium-sized cyclic ethers (See Chapter 2). This oxidative rearrangement was also improved upon during the synthesis to include a one-pot derivatization of the often unstable HFIP acetal products which greatly improves yield and handling. Additionally, various intermediates were intercepted and derivatized to provide a small library of unnatural analogues which were evaluated for their biological activity (Chapter 5).

Experimental data for this chapter can be found in Appendix C.

3.13: REFERENCES

- (1) Macías, F. A.; Molinillo, J. M. G.; Varela, R. M.; Torres, A.; Fronczek, F. R. Structural Elucidation and Chemistry of a Novel Family of Bioactive Sesquiterpenes: Heliannuols. *J. Org. Chem.* **1994**, *59* (26), 8261–8266. <https://doi.org/10.1021/jo00105a052>.
- (2) Shishido, K. Stereocontrolled Total Synthesis of Natural Products. *Chem. Pharm. Bulletin* **2013**, *61* (August), 781–798.
- (3) Biswas, B.; Sen, P. K.; Venkateswaran, R. V. Bargellini Condensation of Coumarins. Expedient Route to o-Carboxyvinylphenoxyisobutyric Acids and Application to the Synthesis of Sesquiterpenes Helianane, Heliannuol A and Heliannuol C. *Tetrahedron* **2007**, *63* (48), 12026–12036. <https://doi.org/10.1016/j.tet.2007.09.006>.
- (4) Macías, F. A.; Chinchilla, D.; Molinillo, J. M. G.; Marín, D.; Varela, R. M.; Torres, A. Synthesis of Heliannane Skeletons. Facile Preparation of (±)-Heliannuol D. *Tetrahedron* **2003**, *59* (10), 1679–1683. [https://doi.org/10.1016/S0040-4020\(03\)00134-0](https://doi.org/10.1016/S0040-4020(03)00134-0).
- (5) Manabe, Y.; Kanematsu, M.; Osaka, M.; Yoshida, M.; Shishido, K. Highly Efficient, Enantiocontrolled Total Syntheses of (+)-Heliannuol D and (-)-Helibisabonol A. *Heterocycles* **2014**, *88* (1), 441–452. [https://doi.org/10.3987/COM-13-S\(S\)50](https://doi.org/10.3987/COM-13-S(S)50).
- (6) Sabui, S. K.; Venkateswaran, R. V. Synthesis of Heliannuol D, an Allelochemical from *Helianthus Annus*. *Tetrahedron Lett.* **2004**, *45* (5), 983–985.

- <https://doi.org/10.1016/j.tetlet.2003.11.098>.
- (7) Osaka, M.; Kanematsu, M.; Yoshida, M.; Shishido, K. An Efficient Total Synthesis of (+)-Heliannuol D. *Tetrahedron Asymmetry* **2010**, *21* (19), 2319–2320. <https://doi.org/10.1016/j.tetasy.2010.08.018>.
- (8) Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. Enantioselective Total Synthesis of Heliannuols D and A. *J. Chem. Soc. Perkin Trans. I* **2000**, No. 12, 1807–1808. <https://doi.org/10.1039/b003553j>.
- (9) Tuhina, K.; Bhowmik, D. R.; Venkateswaran, R. V. Formal Syntheses of Heliannuols A and D, Allelochemicals from Helianthus Annus. *Chem. Commun.* **2002**, *2* (6), 634–635. <https://doi.org/10.1039/b200103a>.
- (10) Chen, K.; Li, Y.; Du, Z.; Tao, Z. Total Syntheses of Heliannuols: An Overview. *Synth. Commun.* **2015**, *45* (6), 663–691. <https://doi.org/10.1080/00397911.2014.979948>.
- (11) Kishuku, H.; Shindo, M.; Shishido, K. Enantioselective Total Synthesis of (2)-Heliannuol A. Iannuol A Has Been Accomplished by Employing Ring Closing Metathesis and Sequential Diastereoselective Epoxidation and Regioselective Reductive Cleavage of the Epoxide Ring. *Chem. Commun.* **2003**, No. November 2002, 2002–2003.
- (12) Grimm, E. L.; Levac, S.; Trimble, L. A. Total Synthesis of (±)-Heliannuol A. *Tetrahedron Lett.* **1994**, *35*, 6847–6850.
- (13) Vyvyan, J. R.; Looper, R. E. Total Synthesis of (±)-Heliannuol D, an Allelochemical from Helianthus Annus. *Tetrahedron Lett.* **2000**, *41*, 1151–1154.
- (14) Kishuku, H.; Yoshimura, T.; Kakehashi, T.; Shindo, M.; Shishido, K.

- Enantiocontrolled Total Synthesis of (+)-Heliannuol D via Palladium-Mediated Heterocyclization. *Heterocycles* **2003**, *61*, 125–131.
- (15) Walters, J. C.; Tierno, A. F.; Dubin, A. H.; Wengryniuk, S. E. (Poly)Cationic Λ^3 -Iodane-Mediated Oxidative Ring Expansion of Secondary Alcohols. *European J. Org. Chem.* **2018**, *2018* (12), 1460–1464. <https://doi.org/10.1002/ejoc.201800118>.
- (16) Kelley, B. T.; Walters, J. C.; Wengryniuk, S. E. Access to Diverse Oxygen Heterocycles via Oxidative Rearrangement of Benzylic Tertiary Alcohols. *Org. Lett.* **2016**, *18* (8), 1896–1899. <https://doi.org/10.1021/acs.orglett.6b00672>.
- (17) Medina, J. M.; MacKey, J. L.; Garg, N. K.; Houk, K. N. The Role of Aryne Distortions, Steric Effects, and Charges in Regioselectivities of Aryne Reactions. *J. Am. Chem. Soc.* **2014**, *136* (44), 15798–15805. <https://doi.org/10.1021/ja5099935>.
- (18) Schmidt, J.; Choi, J.; Liu, A. T.; Slusarczyk, M.; Fu, G. C. A General, Modular Method for the Catalytic Asymmetric Synthesis of Alkylboronate Esters. *Science* (80-.). **2016**, *354* (6317), 1265–1270.
- (19) Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. Enantiospecific Sp^2 - Sp^3 Coupling of Secondary and Tertiary Boronic Esters. *Nat. Chem.* **2014**, *6* (7), 584–589. <https://doi.org/10.1038/nchem.1971>.
- (20) Fischer, C.; Fu, G. C. Asymmetric Nickel-Catalyzed Negishi Cross-Couplings of Secondary α -Bromo Amides with Organozinc Reagents. *J. Am. Chem. Soc.* **2005**, *127* (13), 4594–4595. <https://doi.org/10.1021/ja0506509>.
- (21) Binder, J. T.; Cordier, C. J.; Fu, G. C. Catalytic Enantioselective Cross-Couplings of Secondary Alkyl Electrophiles with Secondary Alkylmetal Nucleophiles:

Negishi Reactions of Racemic Benzylic Bromides with Achiral Alkylzinc Reagents. *J. Am. Chem. Soc.* **2012**, *134* (41), 17003–17006.

<https://doi.org/10.1021/ja308460z>.

- (22) Werner, E. W.; Mei, T.; Burckle, A. J.; Sigman, M. S. Enantioselective Heck Arylations of Acyclic Alkenyl Alcohols Using a Redox-Relay Strategy. **2012**, No. December, 1455–1459.
- (23) Mei, T. S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. Enantioselective Redox-Relay Oxidative Heck Arylations of Acyclic Alkenyl Alcohols Using Boronic Acids. *J. Am. Chem. Soc.* **2013**, *135* (18), 6830–6833.
<https://doi.org/10.1021/ja402916z>.
- (24) Xu, L.; Hilton, M. J.; Zhang, X.; Norrby, P. O.; Wu, Y. D.; Sigman, M. S.; Wiest, O. Mechanism, Reactivity, and Selectivity in Palladium-Catalyzed Redox-Relay Heck Arylations of Alkenyl Alcohols. *J. Am. Chem. Soc.* **2014**, *136* (5), 1960–1967. <https://doi.org/10.1021/ja4109616>.
- (25) Hilton, M. J.; Xu, L. P.; Norrby, P. O.; Wu, Y. D.; Wiest, O.; Sigman, M. S. Investigating the Nature of Palladium Chain-Walking in the Enantioselective Redox-Relay Heck Reaction of Alkenyl Alcohols. *J. Org. Chem.* **2014**, *79* (24), 11841–11850. <https://doi.org/10.1021/jo501813d>.
- (26) Ghosh, T. Reductive Heck Reaction: An Emerging Alternative in Natural Product Synthesis. *ChemistrySelect*. Wiley-Blackwell April 29, 2019, pp 4747–4755.
<https://doi.org/10.1002/slct.201804029>.
- (27) Yue, G.; Lei, K.; Hirao, H.; Zhou, J. Palladium-Catalyzed Asymmetric Reductive Heck Reaction of Aryl Halides. *Angew. Chemie - Int. Ed.* **2015**, *54* (22), 6531–

6535. <https://doi.org/10.1002/anie.201501712>.

- (28) Minatti, A.; Zheng, X.; Buchwald, S. L. Synthesis of Chiral 3-Substituted Indanones via an Enantioselective Reductive-Heck Reaction. *J. Org. Chem.* **2007**, *72* (24), 9253–9258. <https://doi.org/10.1021/jo701741y>.
- (29) Yang, Q.; Sane, N.; Klosowski, D.; Lee, M.; Rosenthal, T.; X. Wang, N.; Wiensch, E. Mizoroki–Heck Cross-Coupling of Bromobenzenes with Styrenes: Another Example of Pd-Catalyzed Cross-Coupling with Potential Safety Hazards. *Org. Process Res. & Dev.* **2019**, *23* (10), 2148–2156. <https://doi.org/10.1021/acs.oprd.9b00126>.
- (30) Adak, A. K.; Mandal, A.; Manna, S. K.; Mondal, S. K.; Jana, A.; Ghosh, D.; Kundu, D.; Samanta, S.; Ray, J. K. Pd(0)-Catalyzed Intramolecular Heck Reaction: A General Route for Fused Oxepine Derivatives. *Synth. Commun.* **2016**, *46* (5), 452–459. <https://doi.org/10.1080/00397911.2016.1142566>.
- (31) Dounay, A. B.; Overman, L. E. The Asymmetric Intramolecular Heck Reaction in Natural Product Total Synthesis. *Chem. Rev.* **2003**, *103* (8), 2945–2963. <https://doi.org/10.1021/cr020039h>.
- (32) Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M.; Napolitano, E. Regio- and Stereoselectivity in the Cyclization of Enolates Derived from 4,5-, 5,6-, and 6,7-Epoxy-1-Phenyl-1-Alkanones. Competition between C- and O-Alkylation. *Tetrahedron* **1999**, *55* (18), 5853–5866. [https://doi.org/10.1016/S0040-4020\(99\)00226-4](https://doi.org/10.1016/S0040-4020(99)00226-4).
- (33) Waser, J.; Nambu, H.; Carreira, E. M. Cobalt-Catalyzed Hydroazidation of Olefins: Convenient Access to Alkyl Azides. *J. Am. Chem. Soc.* **2005**, *127* (23),

- 8294–8295. <https://doi.org/10.1021/ja052164r>.
- (34) Tu, J. L.; Liu, J. L.; Tang, W.; Su, M.; Liu, F. Radical Aza-Cyclization of α -Imino-Oxy Acids for Synthesis of Alkene-Containing N-Heterocycles via Dual Cobaloxime and Photoredox Catalysis. *Org. Lett.* **2020**, *22* (3), 1222–1226. <https://doi.org/10.1021/acs.orglett.0c00224>.
- (35) Nicolai, S.; Waser, J. Pd(0)-Catalyzed Oxy- and Aminoalkynylation of Olefins for the Synthesis of Tetrahydrofurans and Pyrrolidines. *Org. Lett.* **2011**, *13* (23), 6324–6327. <https://doi.org/10.1021/ol2029383>.
- (36) Jeffery, T. Palladium-Catalysed Vinylation of Organic Halides under Solid-Liquid Phase Transfer Conditions. *J. Chem. Soc. Chem. Commun.* **1984**, No. 19, 1287–1289. <https://doi.org/10.1039/C39840001287>.
- (37) Carrow, B. P.; Hartwig, J. F. Ligandless, Anionic, Arylpalladium Halide Intermediates in the Heck Reaction. *J. Am. Chem. Soc.* **2010**, *132* (1), 79–81. <https://doi.org/10.1021/ja909306f>.
- (38) Shelton, P. M. M.; Grosslight, S. M.; Mulligan, B. J.; Spargo, H. V.; Saad, S. S.; Vyvyan, J. R. Synthesis of Guaipyridine Alkaloids (\pm)-Cananodine and (\pm)-Rupestines D and G Using an Intramolecular Mizoroki-Heck Reaction. *Tetrahedron* **2020**, *76* (41), 131500. <https://doi.org/10.1016/j.tet.2020.131500>.
- (39) Lucas, B. S.; Luther, L. M.; Burke, S. D. A Catalytic Enantioselective Hetero Diels-Alder Approach to the C20-C32 Segment of the Phorboxazoles. *J. Org. Chem.* **2005**, *70* (9), 3757–3760. <https://doi.org/10.1021/jo050034v>.
- (40) Kolocouris, A.; Koch, A.; Kleinpeter, E.; Stylianakis, I. 2-Substituted and 2,2-Disubstituted Adamantane Derivatives as Models for Studying Substituent

Chemical Shifts and C-Hax···Yax Cyclohexane Contacts - Results from Experimental and Theoretical NMR Spectroscopic Chemical Shifts and DFT Structures. *Tetrahedron* **2015**, *71* (16), 2463–2481.

<https://doi.org/10.1016/j.tet.2015.01.044>.

- (41) Mott, B. T.; Tripathi, A.; Siegler, M. A.; Moore, C. D.; Sullivan, D. J.; Posner, G. H. Synthesis and Antimalarial Efficacy of Two-Carbon-Linked, Artemisinin-Derived Trioxane Dimers in Combination with Known Antimalarial Drugs. *J. Med. Chem.* **2013**, *56* (6), 2630–2641. <https://doi.org/10.1021/jm400058j>.
- (42) Li, F.; Wang, N.; Lu, L.; Zhu, G. Regioselective Hydration of Terminal Alkynes Catalyzed by a Neutral Gold(I) Complex [(IPr)AuCl] and One-Pot Synthesis of Optically Active Secondary Alcohols from Terminal Alkynes by the Combination of [(IPr)AuCl] and Cp*RhCl[(R, R)-TsDPEN]. *J. Org. Chem.* **2015**, *80* (7), 3538–3546. <https://doi.org/10.1021/acs.joc.5b00164>.
- (43) Lin, S. zheng; You, T. pa. Synthesis of 9,9'-Biphenanthryl-10,10'-Bis(Oxazoline)s and Their Preliminary Evaluations in the Friedel-Crafts Alkylations of Indoles with Nitroalkenes. *Tetrahedron* **2009**, *65* (5), 1010–1016. <https://doi.org/10.1016/j.tet.2008.11.083>.
- (44) Tang, R. J.; Milcent, T.; Crousse, B. Regioselective Halogenation of Arenes and Heterocycles in Hexafluoroisopropanol. *J. Org. Chem.* **2018**, *83* (2), 930–938. <https://doi.org/10.1021/acs.joc.7b02920>.
- (45) Xia, S.; Gan, L.; Wang, K.; Li, Z.; Ma, D. Copper-Catalyzed Hydroxylation of (Hetero)Aryl Halides under Mild Conditions. *J. Am. Chem. Soc.* **2016**, *138* (41), 13493–13496. <https://doi.org/10.1021/jacs.6b08114>.

- (46) Zhao, D.; Wu, N.; Zhang, S.; Xi, P.; Su, X.; Lan, J.; You, J. Synthesis of Phenol, Aromatic Ether, and Benzofuran Derivatives by Copper-Catalyzed Hydroxylation of Aryl Halides. *Angew. Chemie - Int. Ed.* **2009**, *48* (46), 8729–8732.
<https://doi.org/10.1002/anie.200903923>.
- (47) Liu, W.; Ackermann, L. Ortho- and Para-Selective Ruthenium-Catalyzed C(Sp²)-H Oxygenations of Phenol Derivatives. *Org. Lett.* **2013**, *15* (13), 3484–3486.
<https://doi.org/10.1021/ol401535k>.
- (48) Yuan, C.; Eliassen, A. M.; Camelio, A. M.; Siegel, D. Preparation of Phenols by Phthaloyl Peroxide-Mediated Oxidation of Arenes. *Nat. Protoc.* **2014**, *9* (11), 2624–2629. <https://doi.org/10.1038/nprot.2014.175>.
- (49) Yuan, C.; Liang, Y.; Hernandez, T.; Berriochoa, A.; Houk, K. N.; Siegel, D. Metal-Free Oxidation of Aromatic Carbon-Hydrogen Bonds through a Reverse-Rebound Mechanism. *Nature* **2013**, *499* (7457), 192–196.
<https://doi.org/10.1038/nature12284>.
- (50) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. Enantiodivergent Conversion of Chiral Secondary Alcohols into Tertiary Alcohols.
<https://doi.org/10.1038/nature07592>.
- (51) Elford, T. G.; Nave, S.; Sonawane, R. P.; Aggarwal, V. K. Total Synthesis of (+)-Erogorgiaene Using Lithiation–Borylation Methodology, and Stereoselective Synthesis of Each of Its Diastereoisomers. *J. Am. Chem. Soc.* **2011**, *133* (42), 16798–16801. <https://doi.org/10.1021/ja207869f>.
- (52) Genêt, J.-P.; Ratovelomanana-Vidal, V.; Pinel, C.; Synlett, D.; Gamez, P.; Fache, F.; Mangeney, P.; Lemaire, M.; Gamez, P.; Dunjic, B.; Krasik, P.; Alper, H.;

Yang, H.; Alvarez, M.; Lugan, N.; Mathieu, R. *Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation of Ketones Using a Formic Acid-Triethylamine Mixture*; 1991; Vol. 34.

- (53) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. Protodeboronation of Tertiary Boronic Esters: Asymmetric Synthesis of Tertiary Alkyl Stereogenic Centers. <https://doi.org/10.1021/ja1084207>.

CHAPTER 4: DIVERGENT SYNTHESIS OF (-) – HELIANNUOL A VIA I(III)

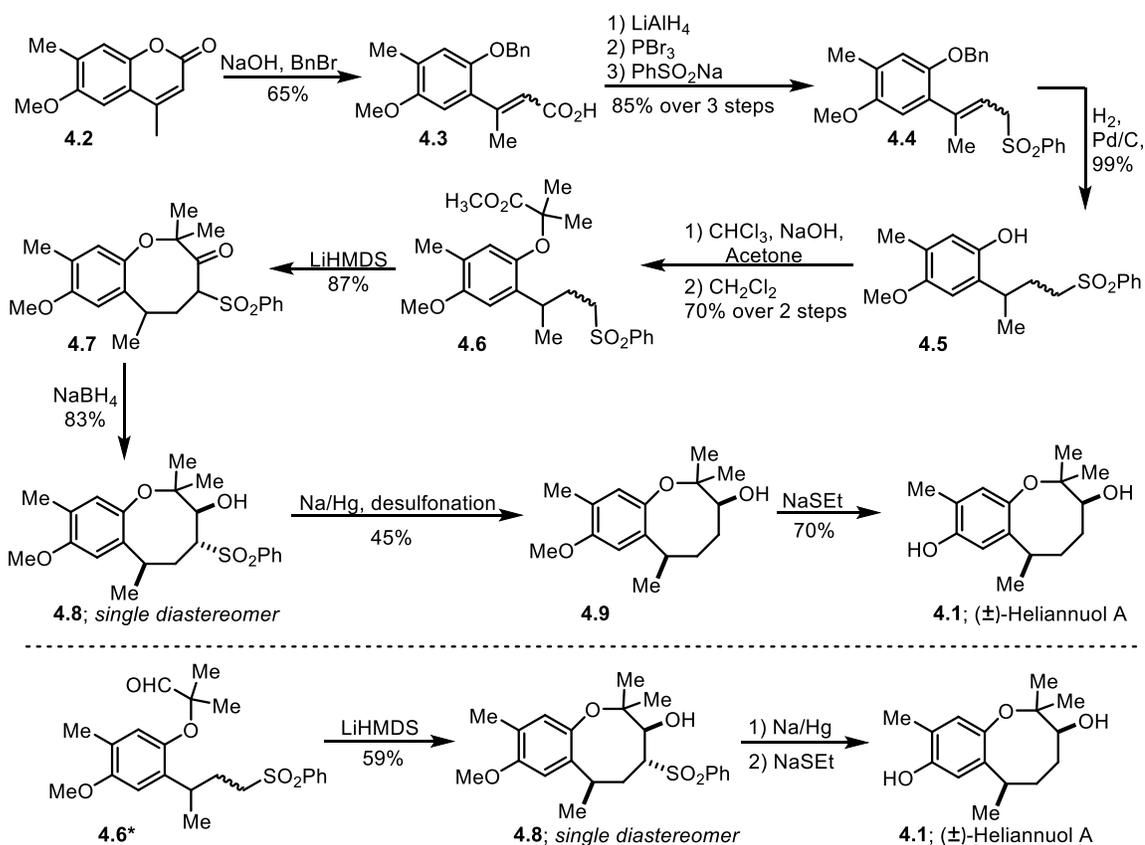
UMPOLUNG RING EXPANSION

4.1: HELIANNUOL A BACKGROUND

Heliannuol A was first isolated and characterized in 1993 by Macias¹, which was the first report on any members of the Heliannuol family. The following year, the first racemic synthesis was performed which highlighted the synthesis of the 8-membered cyclic aryl ether as the most challenging aspect of the molecular scaffold. The most commonly employed strategy to deliver the cyclic aryl ether is ring-closing metathesis (RCM), which necessitates the use of specialized starting materials and limits divergence. Additionally, most asymmetric approaches utilize kinetic resolution to establish chirality at the benzylic stereocenter which hinders throughput.

4.2: RACEMIC SYNTHESIS OF HELIANNUOL A

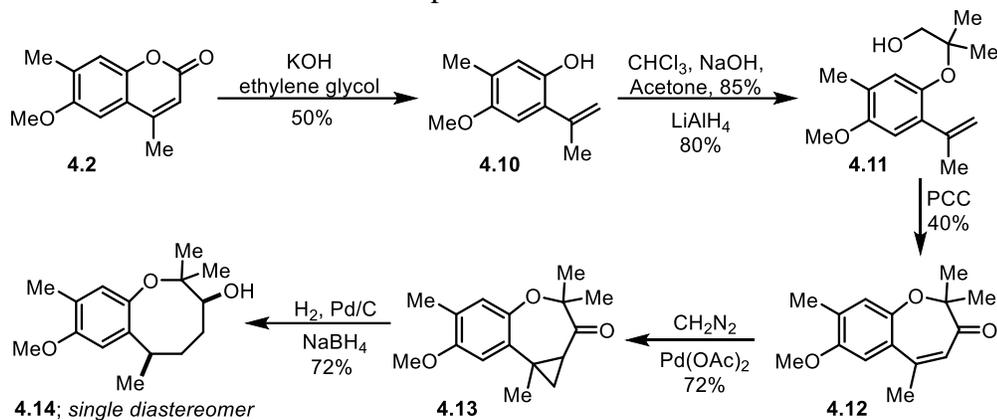
The first racemic synthesis of Heliannuol A completed in 1994 by Grimm and coworkers.² The synthesis of the 8-membered cyclic ether is achieved via intramolecular Julia cyclization which proceeds in good yield, however requires sodium/mercury amalgam to cleave the remaining sulfone. As demonstrated in Scheme 4.1, the synthesis begins with lactone cleavage of coumarin **4.2** followed by *in-situ* benzylation of the resulting phenol to deliver acid **4.3**. Treatment of **4.3** with lithium



Scheme 4.1. Synthesis of Heliannuol A via Julia coupling (Grimm, 1994)

aluminum hydride afforded the corresponding allylic alcohol and subsequent reaction with PBr_3 and PhSO_2Na provided unsaturated sulfone **4.4**. Hydrogenation conditions reduced the unsaturated sulfone and benzyl deprotected the phenol to reveal **4.5**, which was treated with chloroform, sodium hydroxide, and acetone in a Bargellini reaction to afford an α – dimethyl carboxylic acid which then subjected to diazomethane to deliver ester **4.6** in 70% over two steps. Cyclization was performed with LiHMDS provide ketone **4.7**, which underwent reduction by sodium borohydride to afford a single diastereomer of alcohol **4.8**, determined by extensive NOE experiments. An intramolecular Julia coupling (the first example to synthesize an 8-membered ring) was also performed from aldehyde **4.6*** to obtain the same alcohol, however in only 59% yield. Following desulfonation

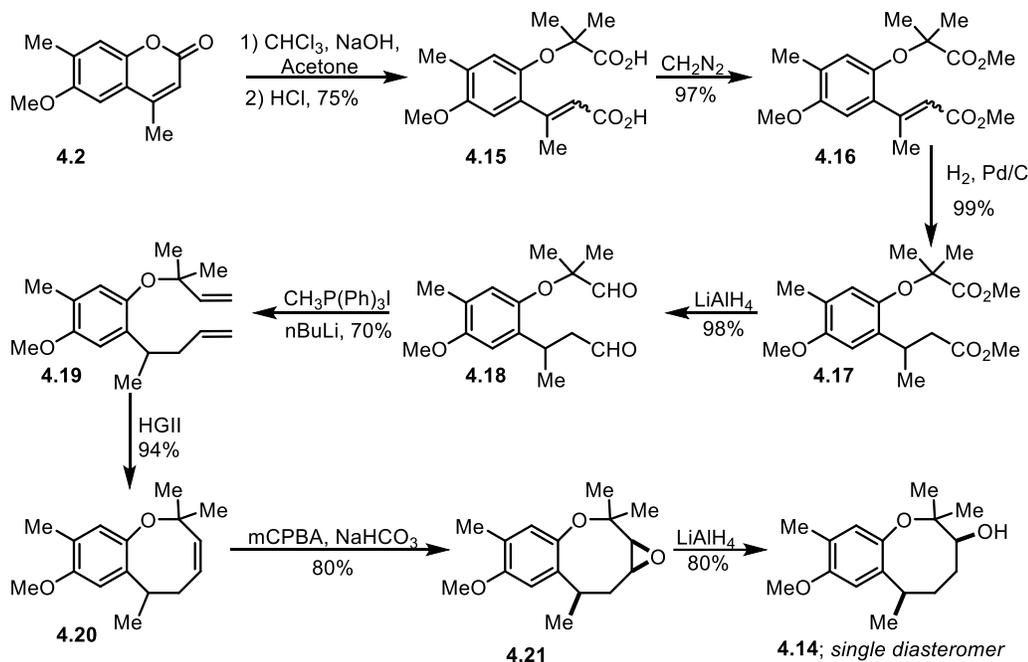
with sodium/mercury amalgam and demethylation with sodium ethanethiolate, (\pm) – Heliannuol A was afforded in an 11 steps and 8.7%.



Scheme 4.2. Ring expansion strategy toward Heliannuol A (Venkateswaran, 2002)

In 2002, Venkateswaran and coworkers demonstrated the synthesis of the 8-membered cyclic ether scaffold via ring expansion of a cyclopropane moiety (Scheme 4.2).³ The 7-membered ring precursor was accessed via a Prins cyclization from an aldehyde synthesized *in-situ*. Lactone cleavage and subsequent decarboxylation with KOH and refluxing ethylene glycol from coumarin **4.2** provided phenol **4.10**. The subsequent Bargellini reaction provides the corresponding carboxylic acid which was reduced to primary alcohol **4.11**. Treatment of **4.11** with PCC resulted in oxidation to the aldehyde and a subsequent Prins cyclization provided enone **4.12**, which was cyclopropanated with diazomethane in the presence of Pd(II). Hydrogenation of cyclopropane **4.13** resulted in C-C bond cleavage in a ring expansion to deliver the required 8-membered ring, and reduction of the remaining ketone provided the methoxy derivative of Heliannuol A and concluded the formal synthesis, providing **4.14** as a single diastereomer in 7 steps and 8% yield from coumarin **4.2**. While this ring expansion strategy represents an innovative approach to the challenging 8-membered cyclic ether,

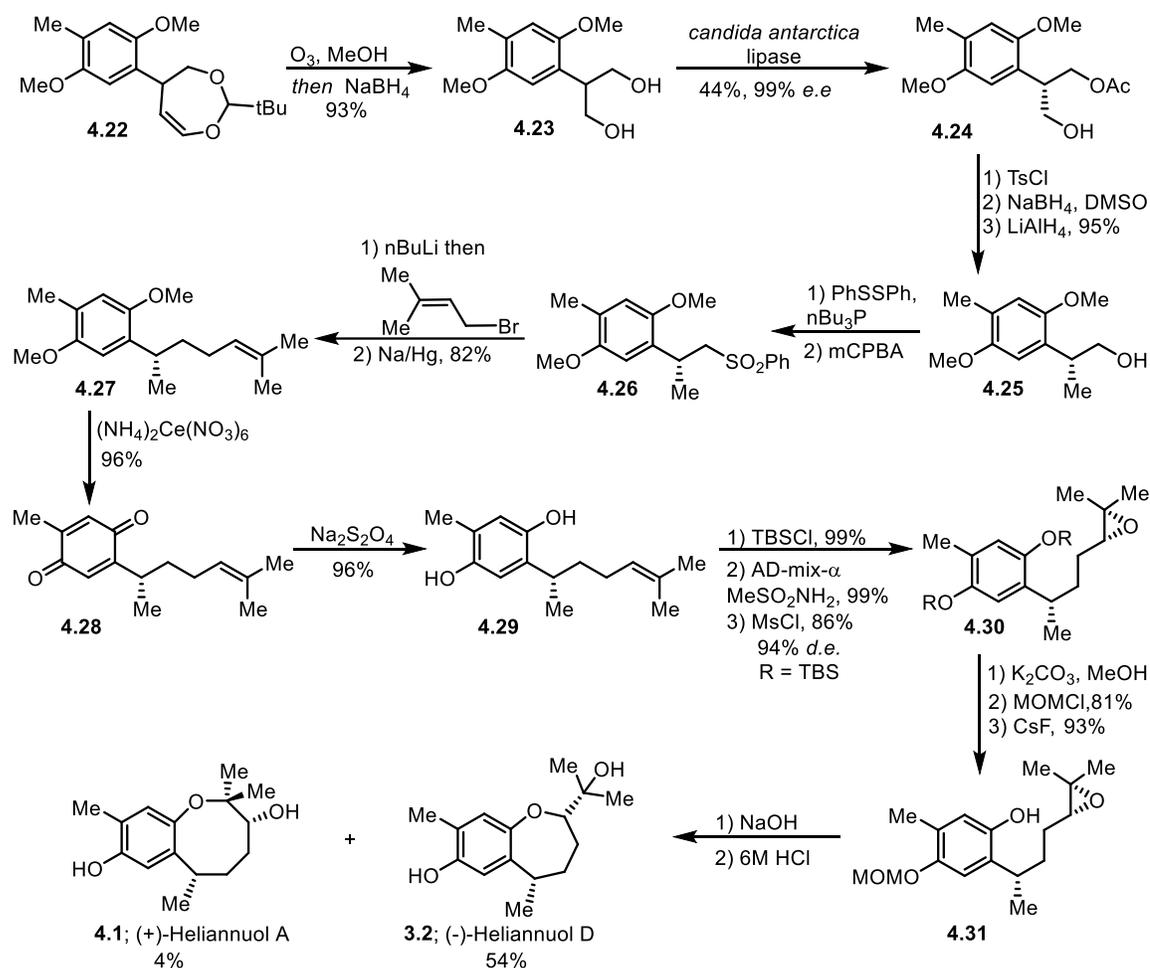
the approach to access cyclopropane **4.13** suffers from poor yield and limited avenues for diversity.



Scheme 4.3 RCM approach to 8-membered ring (Venkateswaran, 2007)

The first synthesis utilizing RCM as the key cyclization step was reported in the second formal synthesis of Heliannuol A by Venkateswaran in 2007 (Scheme 4.3).⁴ Once again proceeding via cleavage of coumarin **4.2** and a Bargellini reaction of the resulting phenol, di-acid **4.15** was revealed and converted to di-ester **4.16**. Hydrogenation of the conjugated olefin provided **4.17** and subsequent hydride reduction provided di-aldehyde **4.18**. Wittig olefination of both aldehydes in **4.18** provided RCM precursor **4.19**. The di-olefin was then treated with Hoveyda-Grubbs second generation catalyst (HGII) which accomplished the desired RCM providing allylic ether **4.20**. Epoxidation with *m*CPBA and subsequent reductive cleavage concluded the formal synthesis and provided MeO-Heliannuol A **4.14** as a single diastereomer in 9 steps and 29% overall yield.

4.3: ENANTIOSELECTIVE SYNTHESIS OF HELIANNUOL A

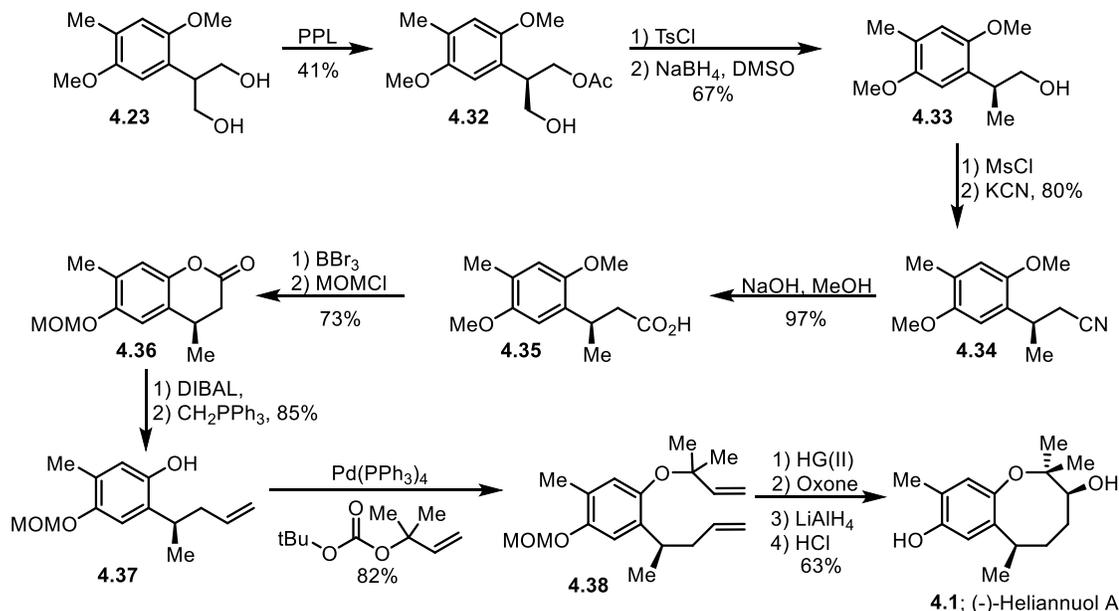


Scheme 4.4. Biomimetic asymmetric synthesis of Heliannuol A (Shishido, 2000)

Shishido disclosed the first enantioselective total synthesis of (+) – Heliannuol A by utilizing kinetic resolution to access a single benzylic stereoisomer and invoking the proposed biomimetic cyclization to access the 8-membered heterocycle (Scheme 4.4).⁵ This strategy reflected the inherent favorability of the epoxide precursor to undergo 7-exo-tet cyclization instead of the required 8-endo-tet. Beginning with dioxepine **4.22**, oxidative cleavage followed by borohydride reduction provided diol **4.23**. A deracemizing transesterification catalyzed by *Candida Antarctica* lipase (CAL) in the presence of vinyl acetate provided chiral monoacetate **4.24**. The resulting hydroxyl group was removed by a sequence of tosylation and subsequent sodium borohydride reduction, and acetyl deprotection with lithium aluminum hydride provided alcohol **4.25**. The

alcohol moiety was transformed to a sulfide, and subsequent oxidation with *m*CPBA provided sulfone **4.26**, which was alkylated with prenyl bromide followed by desulfonation to deliver olefin **4.27**. Oxidation of the di-methoxy arene with ceric ammonium nitrate (CAN) provided quinone **4.28** in 87% (based on consumed **4.27**), which was reduced with sodium dithionate to afford curcuhydroquinone **4.29** which was subsequently protected. Sharpless asymmetric dihydroxylation followed by epoxidation provided desired epoxide **4.30** as a 97:3 mixture of diastereomers, and subsequent treatment with basic methanol provided an inseparable mixture of TBS-protected monophenolic epoxide. Protection of the free phenol was followed by CsF-mediated desilylation of the remaining TBS-protected phenolic oxygen to deliver **4.31** which set the stage for the key biomimetic ring formation step. Treatment of monophenolic epoxide **4.31** with 5% aqueous NaOH afforded two distinct products, the minor product arising from the desired 8-endo-tet cyclization and the major product stemming from a 7-exo-tet cyclization. The desired 8-membered ring was formed in only 4% yield, and a

quantitative MOM deprotection provided Heliannuol A in 19 steps and 0.7% overall yield.



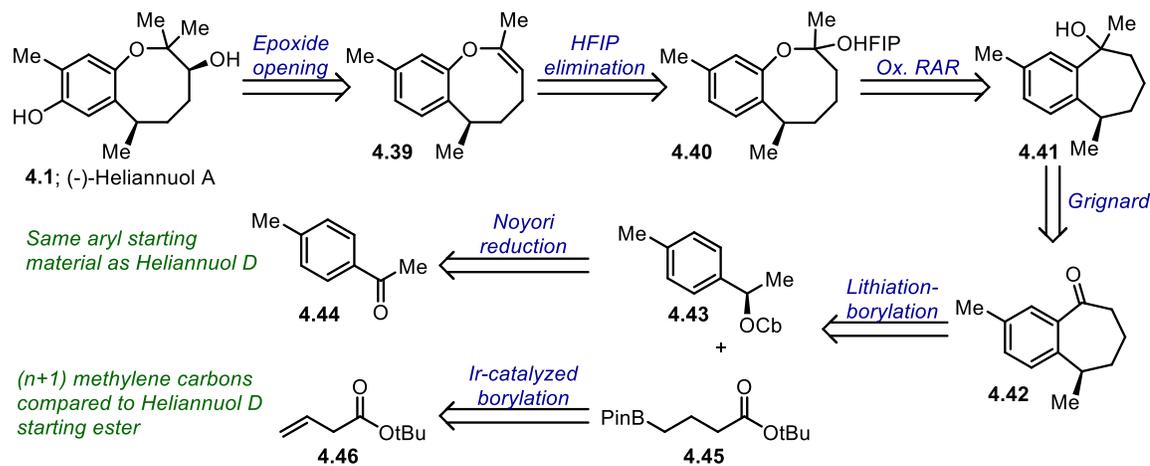
Scheme 4.5. RCM-mediated asymmetric synthesis of Heliannuol A (Shishido, 2004)

Ring closing metathesis (RCM) was utilized in Shishido's 2004 synthesis of (-) – Heliannuol A, and chirality at the benzylic position was established with kinetic resolution (Scheme 4.5).⁶ Beginning with the prochiral diol **4.23**, chiral resolution via *porcin pancreatic lipase* (PPL)-mediated transesterification provided chiral monoacetate **4.32** and subsequent deoxygenation afforded the desired chiral methyl group. Alkaline hydrolysis of the remaining acetate group delivered alcohol **4.33** which was converted to nitrile **4.34** via a two-step mesylation/substitution. The nitrile was then hydrolyzed to afford carboxylic acid **4.35**, and subsequent BBr₃-mediated de-methylation of the two aromatic methoxy groups enabled lactonization to form the 6-membered heterocycle which was MOM protected to afford chiral lactone **4.36**. The lactone was then cleaved and underwent a Wittig reaction to afford olefin **4.37**. A Tsuji-Trost reaction of the phenol moiety and a mixed carbonate provided diol **4.38** which was poised for the ring closing step via RCM using HGII catalyst. The resulting olefin was then epoxidized,

which provided a single diastereomer due to the conformation of the ring which allows for approach only on the bottom face of the olefin. Hydride reduction of the epoxide followed by acid-mediated MOM deprotection of the phenol provided the desired product (-) – Heliannuol A (**4.1**) as a single diastereomer in 15 steps and 6% overall.

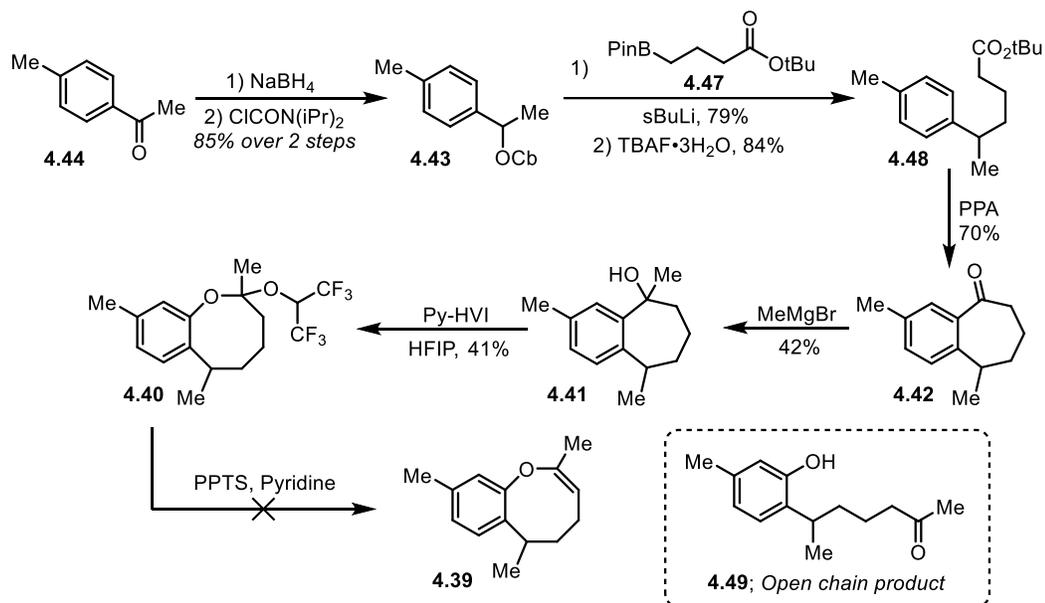
Each racemic and asymmetric sequence shown demonstrates the low modularity and highly specific synthesis invoked in the synthesis of Heliannuol A. Each approach requires a highly specific substrate to undergo the cyclization which leaves little room for diversification. Additionally, the reliance on kinetic resolution to deliver a single stereoisomer results in poor throughput and additional steps (de-acylation, deoxygenation) to deliver the desired benzylic methyl group.

4.4: ATTEMPTS TOWARDS RACEMIC SYNTHESIS OF HELIANNUOL A



Scheme 4.6. First generation retrosynthesis of Heliannuol A

The proposed approach to Heliannuol A centers around the key I(III) *N*-HVI-mediated umpolung ring expansion which provides expedient access to the otherwise challenging synthetic scaffold (**4.41** to **4.40**; Scheme 4.6). This strategy offers multiple avenues for diversification including the ring expansion strategy, which provides a versatile intermediate (**4.40**) that can be derivatized in various fashions (i.e. reduction, elimination, alkylation) to quickly access a library of analogues from the late-stage intermediate. Additionally, derivatives could quickly be accessed via modulation of the group added in to ketone intermediate **4.42**. Chiral intermediate **4.42** can be quickly accessed with high enantioselectivity from the stereoretentive homologation of carbamate **4.43** and boronic ester **4.45**.⁷⁻⁹ Following the ring expansion, elimination of hexafluoroisopropanol (HFIP) followed by epoxidation and methylative cleavage was envisioned to deliver Heliannuol A.

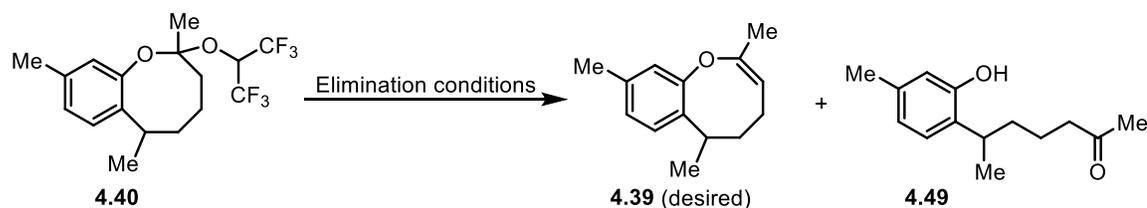


Scheme 4.7. Racemic efforts toward 8-membered cyclic enol ether

Synthetic efforts commenced on racemic substrate for throughput and screening efforts with the conversion of acetophenone **4.44** to carbamate **4.43** via sodium borohydride reduction and carbamylation of the resulting alcohol (Scheme 4.7). Coupling partner **4.47** was freshly synthesized and smoothly underwent stereoretentive

homologation and subsequent TBAF-mediated de-borylation to deliver *tert*-butyl ester **4.48**. The polyphosphoric acid-mediated cyclization proceeded to afford ketone **4.42** which was treated with methyl Grignard addition to deliver alcohol **4.41** in 41% yield with recovered starting material constituting the remainder of the material. With tertiary alcohol in hand, the rearrangement was performed using pyridinium HVI to provide HFIP acetal **4.40** in moderate yield.^{10,11} This reaction exhibited much slower reactivity and required higher temperatures to occur which is not surprising given the ring strain on 8-membered rings. The following literature precedented¹⁰ elimination of HFIP from the acetal to deliver enol ether **4.39** was attempted using pyridinium *para*-toluenesulfonate (PPTS) and pyridine while heating to reflux in toluene. Unfortunately, these conditions did not provide the desired cyclic enol ether product **4.39** and instead provided the open-chain product **4.49** exclusively. It is worth noting that in the seminal publication, all derivatizations were performed on 7-membered cyclic ethers exclusively.

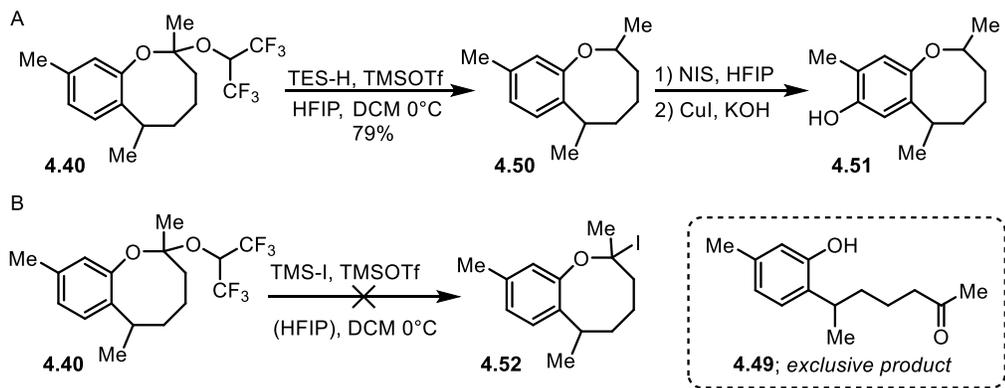
4.5: DERIVATIZATION OF HFIP ACETAL



Conditions	Exclusive Product
PPTS, pyridine, PhMe, 110°C	4.49
PPTS, pyridine, PhMe, 3Å MS, 110°C	4.49
PTSA, PhMe, 110°C	4.49
TMSOTf, 2,6-lutidine, HFIP, DCM, 0°C	4.49
TMSOTf, 2,6-lutidine, HFIP, 3Å MS DCM, 0°C	4.49
PhMe, 110°C	4.40
DBU, PhMe, 110°C	4.40
<i>t</i> BuLi, THF, -78°C to 65°C	4.40

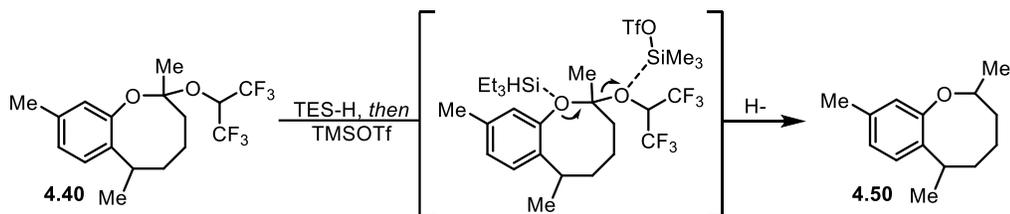
Table 4.1. Screen of conditions to eliminate HFIP

The failed HFIP elimination from acetal **4.40** to deliver **4.39** prompted a screening of conditions including variation of base, acid, and temperature (Table 4.1). The overall desired transformation was the elimination of HFIP from **4.40** to provide enol ether **4.39** while simultaneously suppressing formation of open-chain product **4.49**. The inclusion of 3 Å molecular sieves with PPTS and pyridine proved ineffective for the transformation, delivering the open-chain product each time. Switching to conditions for the elimination of more conventional acetals (PTSA, toluene, reflux) also proved fruitless, once again providing the open chain product exclusively. Employment of traditional derivatization conditions (i.e. TMSOTf, HFIP) with the addition of a sterically encumbered organic base (2,6-lutidine) provided the undesired ring-opened product exclusively. Suspension of acetal **4.40** in toluene and simply heating to reflux led to full recovery of starting material, and the addition of DBU did not enable any reactivity. Moving to more harshly basic conditions by using *tert*-butyllithium at various temperatures led to exclusive recovery of starting material. To determine the ability of the 8-membered cyclic ether to undergo any derivatization, the reduction using TES-H and TMSOTf in HFIP and DCM were applied as this transformation is the most traditionally successful HFIP acetal derivatization (Scheme 4.8A) which resulted in the desired reduced product (**4.50**) in 79% isolated yield from acetal **4.40**. As a proof of concept and to provide an unnatural analogue, the reduced product was then para hydroxylated to deliver Heliannuol A analogue **4.51**.



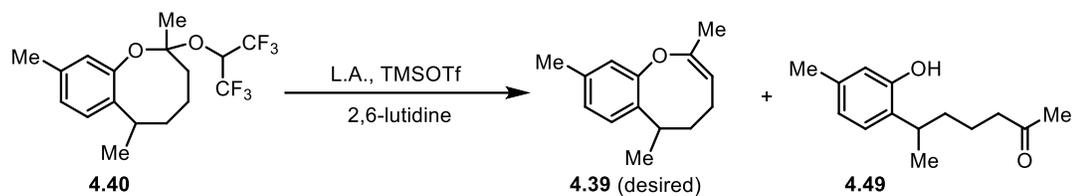
Scheme 4.8. Successful reduction and unsuccessful iodination of HFIP acetal

Provided the success of the reduction via hydride addition into the desired cyclic oxonium, α -iodination by addition of trimethylsilyl iodide (analogous to hydride addition) was attempted in the presence and absence of HFIP. Unfortunately, no iodinated (or eliminated) product was observed (Scheme 4.8B). Instead, the undesired open chain product was obtained exclusively. The success of the reduction and failure of all other derivatizations was peculiar as it indicates that under these specific conditions the desired oxonium can readily form and react (Scheme 4.9).



Scheme 4.9. Proposed Lewis acidic role of triethylsilane

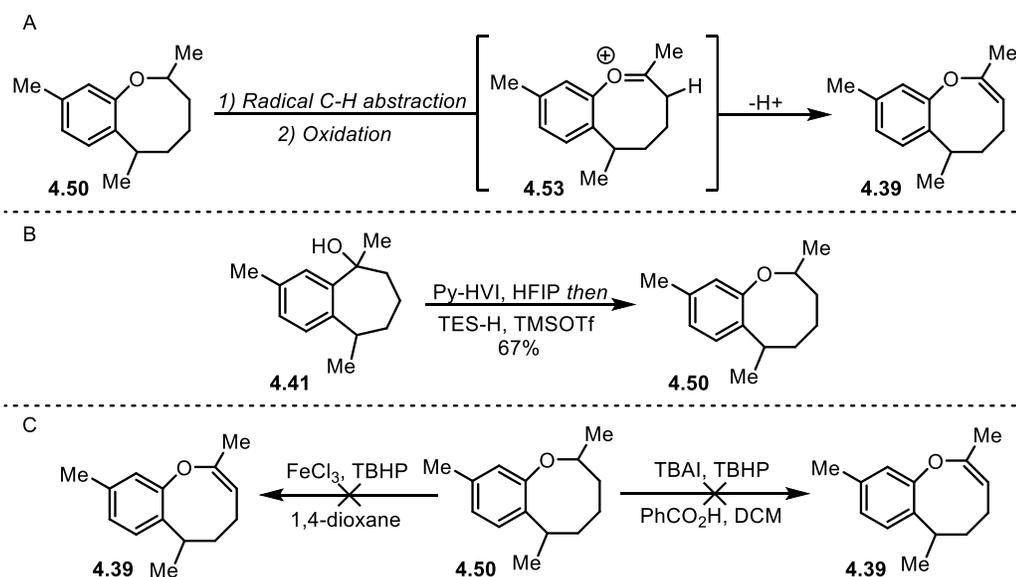
It was hypothesized that beyond just a hydride source, triethylsilane may be serving as a weak Lewis acid to occupy the more Lewis basic endocyclic oxygen atom prior to the addition of the more strongly acidic TMSOTf. Upon addition of TMSOTf, the remaining HFIP oxygen would then be activated to form the desired oxonium species for further reactivity. This hypothesis prompted a screen of Lewis acid additives which would be mildly oxophilic and weakly coordinating in conjunction with TMSOTf and mildly basic 2,6-lutidine to perform the formal elimination of HFIP from the acetal. Each acid was selected based on availability and was added, and unfortunately none of the acids screened enabled the desired reactivity, and the undesired open chain product was obtained each time (Table 4.2).



Lewis Acid (Y)	Conditions	Result
B(OMe) ₃	TMSOTf, 1:1 HFIP:DCM, 0°C to RT	Open chain
Al(OiPr) ₃	TMSOTf, 1:1 HFIP:DCM, 0°C to RT	Open chain
Et ₃ PO	TMSOTf, 1:1 HFIP:DCM, 0°C to RT	Open chain
Ti(OiPr) ₄	TMSOTf, 1:1 HFIP:DCM, 0°C to RT	Open chain
HMDSO	TMSOTf, 1:1 HFIP:DCM, 0°C to RT	Open chain
Bi(OTf) ₃	TMSOTf, DCM, 0°C to RT	Open chain

Table 4.2. Screen of Lewis acids to promote HFIP elimination

4.5ii: Oxidation of saturated Ether to Enol Ether

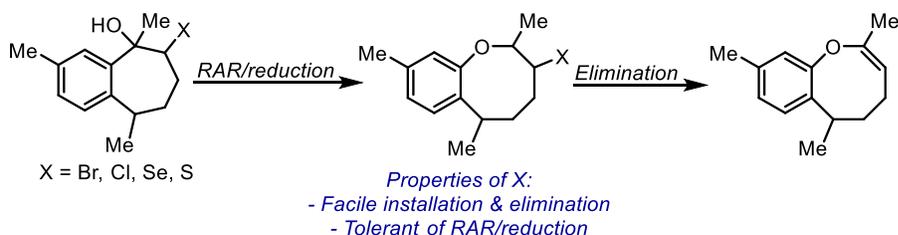


Scheme 4.10. Unsuccessful oxidation of saturated cyclic ether

Given the success of the reduction reaction an oxidation of the ether to the corresponding enol ether via C-H activation was proposed (Scheme 4.10A).

Mechanistically, the reaction would proceed via radical hydrogen abstraction of the activated alpha C-H bond in ether **4.50** followed by oxidation to the carbocation/oxocarbenium species **4.53** according to literature precedent¹²⁻¹⁹. In the absence of a nucleophile elimination was proposed to occur to furnish the desired enol ether **4.39**. To that end, cyclic ether **4.50** was synthesized by the one-pot rearrangement/reduction sequence in a satisfying 67% yield (Scheme 4.10B). Disappointingly, when ether **4.50** was subjected to two different sets of conditions only starting material was recovered and no reactivity was observed (Scheme 4.10C).

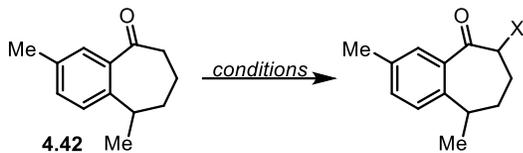
4.5iii: Installation of Eliminable Leaving Groups



Scheme 4.11. Proposed installation of leaving groups

Installation of a labile leaving group prior to the rearrangement and reduction sequence emerged as a promising route, wherein following the one-pot ring expansion and reduction, treatment of the product with base would provide the desired enol ether (Scheme 4.11). Two classes of leaving groups were selected: halogens (Cl, Br) and chalcogens (S, Se) were selected for their ease of attachment and elimination as well as their tolerability with the prior rearrangement and reduction sequence. Incorporations of halogens was first attempted with NCS²⁰ and NBS²¹ for chlorination and bromination respectively, however these reagents each provided the desired product in low yield. (Table 4.3). Improved yields were offered when bromination was performed with molecular bromine²² and chlorination was performed with FeCl₃ in the presence of an oxidant.²³ The sulfide was easily accessed from the corresponding bromide via treatment

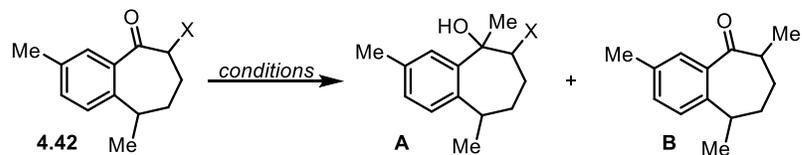
with sodium thiophenoxide. Finally, treatment of **4.42** with diphenyl diselenide selenation²⁴ seemed to deliver the desired product according to crude NMR, separation from the starting material proved to be challenging and was not accomplished.



X =	Conditions	Yield
-Br	NBS, NH ₄ OAc	NA
-Br	Br ₂	99%
-Cl	NCS, thiourea	41%
-Cl	FeCl ₃ , PhI(OAc) ₂ , AcOH	88%
-SPh	NaSPh (from alpha bromo)	99%
-SePh	(PhSe) ₂ , KF-alumina	51% (not isolated)

Table 4.3. Alpha functionalizations of ketone 4.42

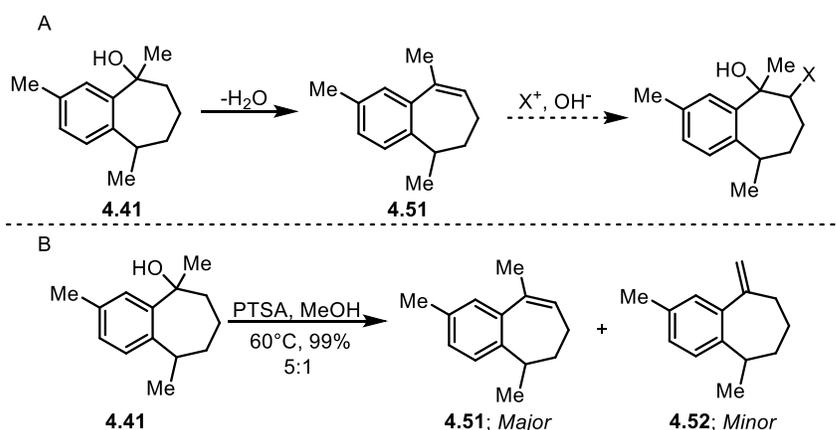
With three of the key functionalized starting materials in hand, methylation of each was attempted with a variety of methyl sources on the bromo, chloro, and sulfide functionalities present on the molecule. (Table 4.4)²⁵. Unfortunately, the alpha-brominated ketone yielded a complex mixture of products likely arising from undesired displacement of bromine or over-reactivity after addition of the resulting alkoxide to form epoxide products. The addition of lithium chloride had no effect on the efficacy, the desired product was not obtained. With the alpha chlorination, addition of lithium chloride in conjunction with methyl Grignard provided the desired product in 42% yield following optimization with 58% starting material. The sulfide was cleanly displaced under these conditions to provide the corresponding alpha-methyl ketone and the substrate was deemed incompatible for the transformation.



X =	Conditions	Result
-Br	MeLi	Complex mixture
-Br	MeMgBr	Complex mixture
-Br	MeMgBr, LiCl	Complex mixture
-Br	AlMe ₃ , TMSCH ₂ N ₂	No reaction
-Cl	MeLi	Complex mixture
-Cl	MeMgBr	Complex mixture
-Cl	MeMgBr, LiCl	42% A ; 52% 4.42
-SPh	MeMgBr	B exclusively

Table 4.4. Screen of methylation conditions on α -functionalized ketone

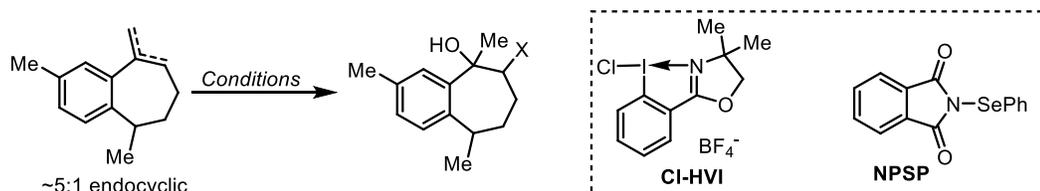
An alternative strategy to access the desired functionalized ring expansion precursors is via olefin di-functionalization to install both the hydroxyl moiety as well as the X group (Scheme 4.12A). Endocyclic olefin **4.51** was accessed by dehydration of alcohol **4.41** using PTSA,²⁶ however, a mixture of regioisomers (**4.51**, **4.52**) was often obtained in variable ratios and further isomerization to the endocyclic olefin proved unsuccessful (Scheme 4.12B).²⁷



Scheme 4.12. Approach to tertiary alcohols via olefin difunctionalization

Subsequent hydrobromination and hydrochlorination using NBS and NCS respectively were unsuccessful, providing a complex mixture of products each time

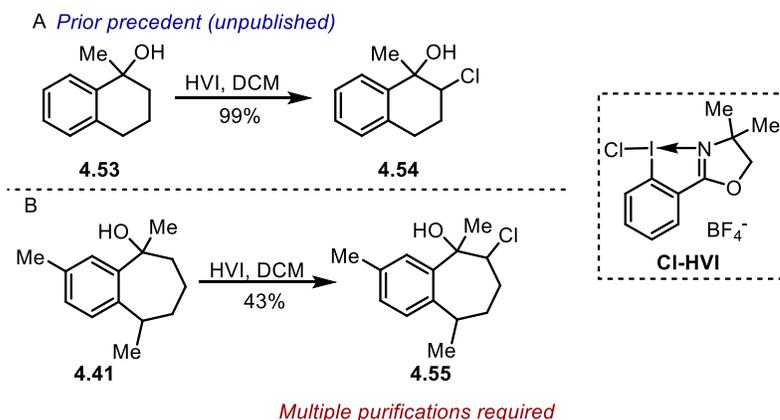
(Table 4.5). Hydrochlorination using the electrophilic chloride source **Cl-HVI** shown above provided the desired product in 13% yield along with a mixture of uncharacterized byproducts. Finally, selenohydrin synthesis using easily synthesized NPSP²⁸ yielded only a mixture endocyclic starting material as well as exocyclic selenohydrins.



X =	Conditions	Result
-Br	NBS, H ₂ O, dark	Complex mixture
-Cl	NCS, H ₂ O, dark	Complex mixture
-Cl	HVI, H ₂ O	13%
-SePh	NPSP, PTSA, H ₂ O	No desired product

Table 4.5. Screening of olefin difunctionalizations

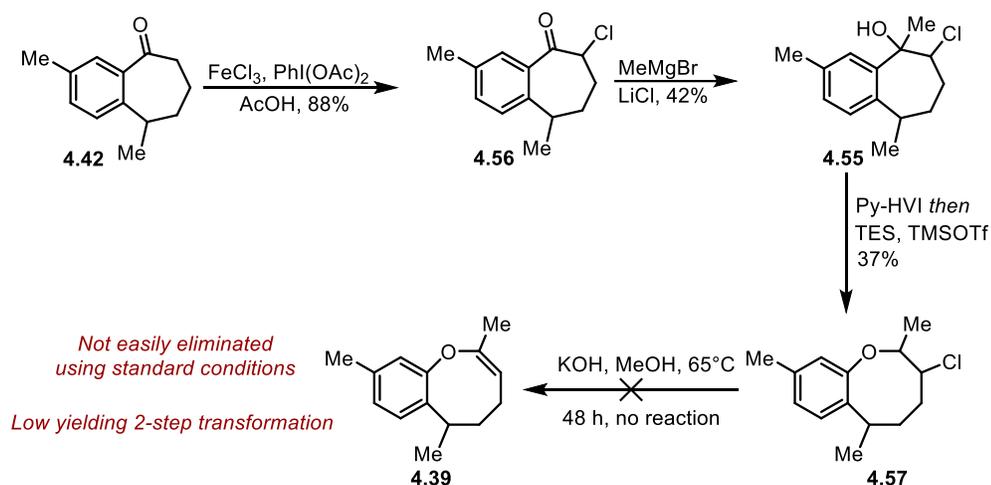
Chlorination was also attempted from the corresponding alcohol according to unpublished results obtained in our laboratory (Scheme 4.13A) delivering the chlorohydrin in roughly 43% yield (Scheme 4.13B) following multiple purifications.



Scheme 4.13. Chlorohydrin synthesis from tertiary alcohol

4.5iv: Attempted Synthesis from Chlorohydrin

With ample access to chlorohydrin **4.55** through α -chlorination of **4.42** and subsequent methyllithium addition, the one-pot rearrangement/reduction sequence was carried out which delivered **4.57** in 37% yield (Scheme 4.14). The low yield of the one-pot procedure can be attributed to increased steric bulk surround the reaction center. Attempted elimination of chloroether **4.57** using strongly alkaline conditions resulted in no reaction and complete recovery of starting material. These two factors combined forced us to reconsider our route. The additional steps required by this sequence as well as its overall low yield were deterring, and alternative methods were investigated.

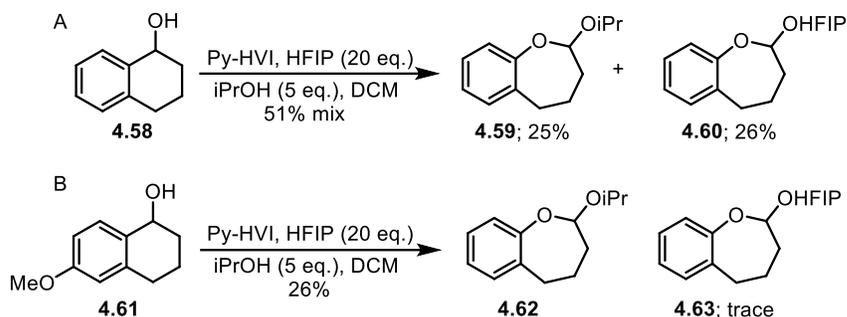


Scheme 4.14. Unsuccessful access to enol ether via chloride elimination

4.5v: Further Investigation of Acetal Electronics

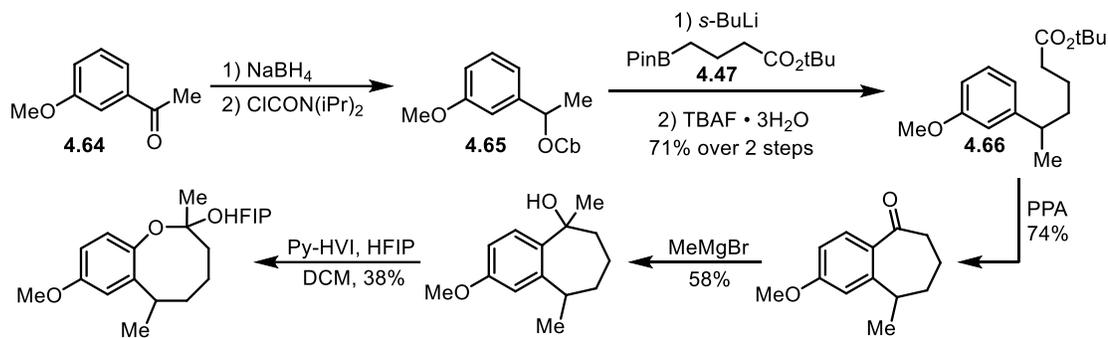
The inherent difficulty posed by HFIP acetals is their derivatizations due to the unique electronics of the two oxygen atoms in the system. In an effort to facilitate acetal functionalization, the synthesis of a more traditional isopropanol (IPA) acetal was investigated via the same ring expansion strategy. This has been demonstrated under modified reaction conditions, wherein rearrangement of electron-neutral secondary **4.58** in the presence of super-stoichiometric quantities (5 equiv.) of isopropyl alcohol

produced a mixture the corresponding IPA acetal (**4.59**) with roughly 1:1 selectivity to the HFIP acetal in 51% overall (Scheme 4.15A). When a methoxy group was placed in the *para* position relative to the migrating bond (**4.61**), the selectivity was vastly improved, producing IPA acetal **4.62** almost exclusively in 26% yield (Scheme 4.15B).



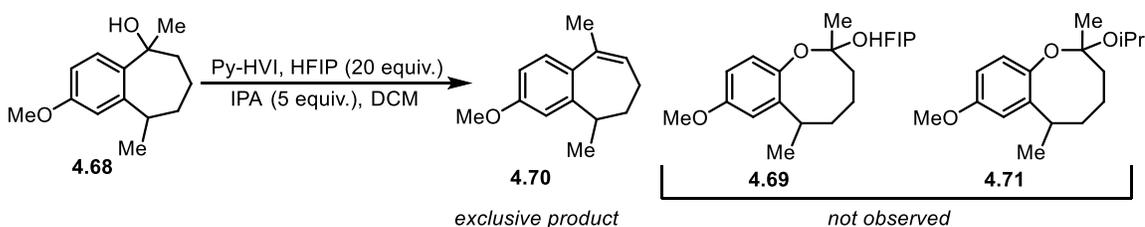
Scheme 4.15. Precedented synthesis of IPA acetals in ring expansion

With the greatest success demonstrated on electron-rich aryl groups, an analogous racemic model substrate lacking the aromatic methyl group (**4.69**) was synthesized via the identical sequence to the des-MeO substrate. As can be seen in Scheme 4.16, acetophenone **4.64** was reduced and carbamoylated to provide carbamate **4.65**. The subsequent homologation and deborylation were performed to deliver ester **4.66** in good yield over two steps. Polyphosphoric acid-mediated cyclization proceeded to forge cyclic ketone **4.67**, which was transformed to tertiary alcohol **4.68** via addition of methyl Grignard. At this stage, the traditional rearrangement to deliver HFIP acetal **4.69** was performed as a proof of concept, which proceeded in a modest 38% yield. The drop in yield from the electron-neutral system was to be expected based on prior experiments on electron-rich scaffolds.



Scheme 4.16. Synthesis of *para*-MeO HFIP acetal

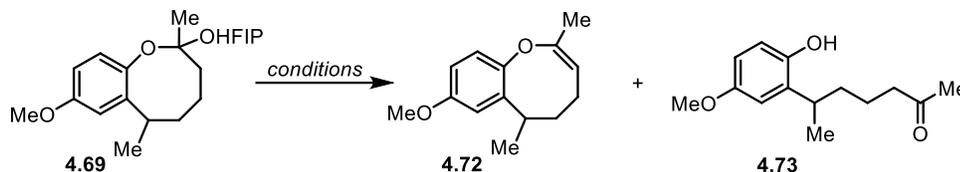
Unfortunately, the inclusion of isopropanol to the reaction inhibited all productive reactivity, and no HFIP (**4.69**) or IPA acetal (**4.71**) products were observed. Instead, the sole product isolated from the reaction was elimination of the tertiary alcohol to product endocyclic styrenyl olefin **4.70** (Scheme 4.17).



Scheme 4.17. Failed ring expansion to deliver IPA acetal

Having synthesized HFIP acetal **4.69** (Scheme 4.16) elimination conditions were screened to determine whether increased electron density on the cyclic ethereal oxygen would promote the formation of the desired oxocarbenium species, resulting in elimination to produce the desired cyclic enol ether. Gratifyingly, the desired cyclic enol ether product **4.72** was produced in 17% yield using standard literature protocol (PPTS, Pyridine, chlorobenzene as solvent, 80 °C) along with undesired open-chain product **4.73** and an unidentified byproduct. (Table 4.6). When toluene was used instead of chlorobenzene in the same reaction conditions, a nearly 2-fold increase in yield was observed (27%), and increasing the temperature to 110°C from 80 °C further improved the yield to 57%. Finally, starting and performing the entire reaction at 110°C provided

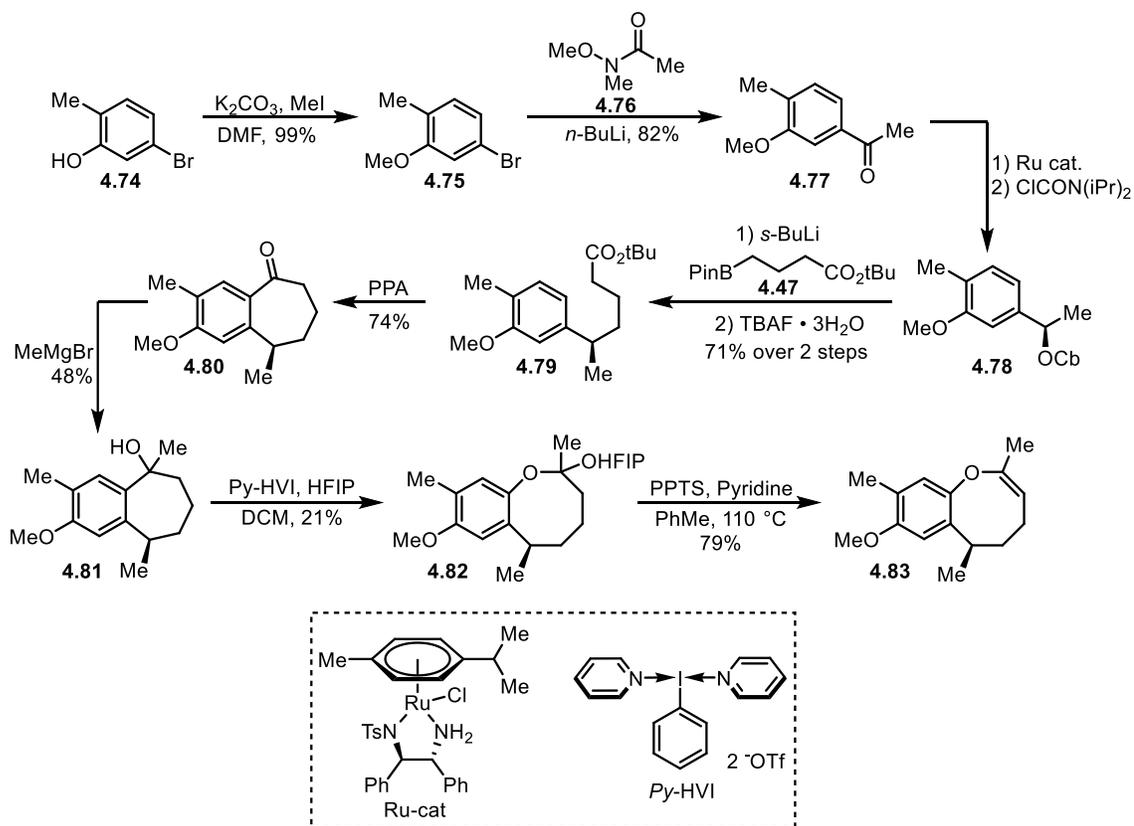
enol ether **4.72** in an optimized 79% yield with the remainder of the material being open chain **4.73**.



Conditions	Solvent	Yield 4.72	Yield 4.73
PPTS, Pyridine, 80 °C	Chlorobenzene	17%	36%
PPTS, Pyridine, 80 °C	Toluene	27%	73%
PPTS, Pyridine, 80° to 110 °C	Toluene	57%	43%
PPTS, Pyridine, 110 °C	Toluene	79%	21%

Table 4.6. Screen of elimination conditions from *para*-MeO HFIP acetal

Having demonstrated the elimination and accessed analogous enol ether, the substrate necessary for Heliannuol A (bearing a methyl group on the aryl ring) was synthesized (Scheme 4.18). While the acetophenone (**4.77**) necessary for the sequence is commercially available, cost restraints necessitated its synthesis from the corresponding aryl bromide via methylation of phenol **4.74** and acetylation via lithium halogen exchange of aryl bromide **4.75** and quench with Weinreb amide **4.76** on multi-gram scale. The asymmetric Noyori reduction was performed, followed by carbamoylation to provide carbamate **4.78**. The subsequent homologation and deborylation once again proceeded in excellent yield over two steps, providing ester **4.79** which was cyclized with PPA to deliver ketone **4.80**. A Grignard addition set the stage for the key rearrangement, which proceeded in a low 21% yield, which would require optimization. Despite the low yield, HFIP acetal **4.82** was obtained and smoothly underwent elimination to provide enol ether **4.83**, allowing us to investigate the next key transformation necessary. However, prior to investigating the epoxidation and methylative ring opening, our efforts focused on improving the yield of the rearrangement to provide greater yield and quantities of the enol ether for downstream investigations.

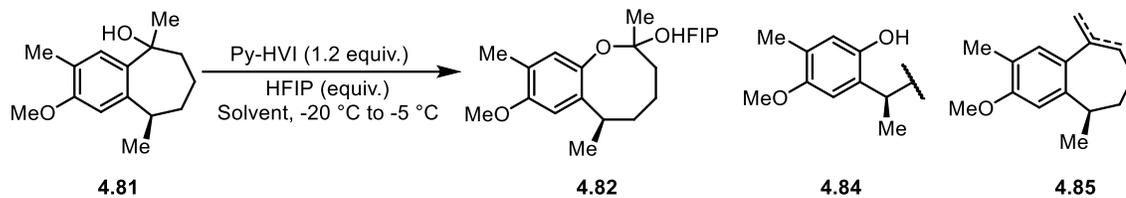


Scheme 4.18. Asymmetric synthesis of aryl-methoxy cyclic enol ether 4.83

4.6: OPTIMIZATION OF OXIDATIVE RING EXPANSION

Central to this synthetic sequence is the successful execution of the oxidative ring expansion of the 7-membered alcohol (**4.81**, Scheme 4.18) to produce the 8-membered cyclic ether (**4.82**) in the form of an HFIP acetal, which would be derivatized in the next step. With the reaction initially providing less than 25% yield under standard conditions, optimization was necessary. The major undesirable pathway for this and all electron-rich HFIP acetals is ring cleavage with slightly elevated temperatures under acidic conditions (Scheme 4.19), and is amplified in 8-membered systems. In the synthesis of Heliannuol D, HFIP acetal isolation and purification was bypassed and the subsequent reduction was performed in one-pot. Elimination, however, is not amenable to a one-pot derivatization

protocol, therefore optimization of the ring expansion and isolation of the HFIP acetal products was necessary (Table 4.7).



Entry	mmol 4.81	Solvent	Equiv. HFIP	Yield 4.82	Yield 4.84	Yield 4.85
1	0.430	CH ₂ Cl ₂	10	5% ^c	trace	16% ^c
2	0.138	CDCl₃	10	59%	trace	trace
3	0.157	CDCl ₃	1.2 ^a	trace	12%	50%
4	0.780	CDCl₃	10	71%* (46%)	trace	trace
5	0.086	CCl ₄	10	39%	trace	40%
6	0.075	1,2-DCE	10	56%	23%	trace
7	1.880	CHCl₃	10	(49%)	--	--
8	0.089	CDCl ₃	10 ^b	trace	4.5%	35%
9	0.079	CDCl ₃	5 ^b	61%	30%	trace
10	0.100	CDCl ₃	1 ^b	trace	trace	53%

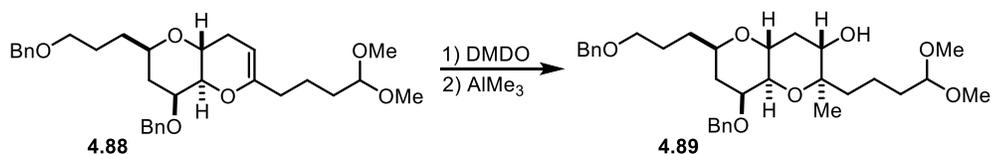
Table 4.7. Optimization of ring expansion on electron-rich 8-membered ring system

Initially, the quantity of acidic HFIP in the reaction was decreased (20 equivalents to 10 equivalents; Entry 1) which slowed reactivity and favored elimination of the benzylic alcohol to provide (**4.85**). Next, a solvent switch to deuterated chloroform (for facile NMR monitoring) was implemented with the same quantity (10 equivalents) of HFIP, providing an *in-situ* yield of 59% (Entry 2). Further decreasing the quantity of HFIP necessitated a reverse addition (substrate added to HFIP+HVI) to what is normally performed and was detrimental to the reaction, providing **4.85** as the major product (Entry 3). Scaling up the reaction from Entry 2 using deuterated chloroform (Entry 4) provided an improved *in-situ* yield (71%) and isolated yield (50%) from the initial reaction (21%). Additional chlorinated solvents were evaluated in this reaction including carbon tetrachloride and 1,2-dichloroethane, however no notable improvement was observed in either case, eliciting the continued screening of chloroform due to factors of

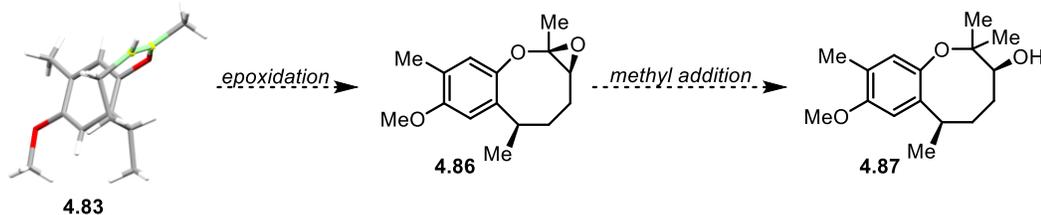
availability, safety, and volatility. Reverse additions with decreasing quantities of HFIP (Entries 8-10) were typically detrimental with exception to Entry 9, however with an increased quantity of open chain product **4.84** observed (30% compared to trace). Utilization of non-deuterated chloroform on a nearly 2 mmol scale (Entry 7) provided the HFIP acetal product (**4.83**) in a satisfactory 49% yield. In total, optimization of the ring expansion to access electron-rich aryl ether **4.82** resulted in a greater than two-fold increase in yield, permitting late-stage sequence optimization.

4.6: EPOXIDATION AND METHYLATIVE OPENING

A. Precedent for epoxidation and subsequent methylative opening



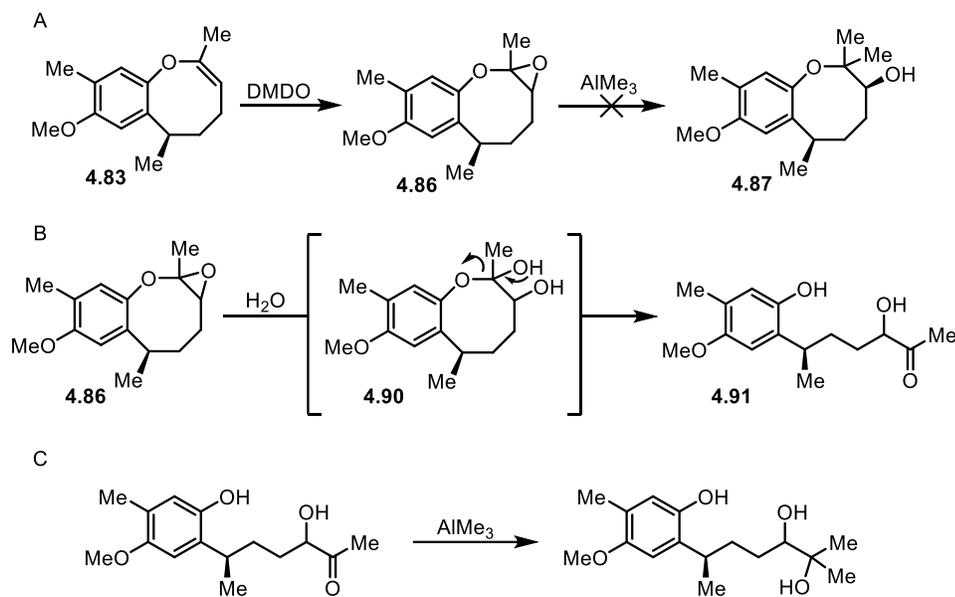
B. Proposed transformation



Scheme 4.19. Precedented epoxidation sequence and proposed transformation

Investigations into the epoxidation and methylative opening were approached with the hypothesis that the enol ether would undergo oxidation fairly rapidly and be prone to facile cleavage by nucleophiles including water due to the electronics of the system. Based on existing literature precedent in similar systems, the ideal epoxidizing agent for the epoxidation of cyclic enol ethers is dimethyldioxirane (DMDO) it can be utilized at cryogenic temperatures to slow reactivity, produces a relatively non-nucleophilic byproduct in acetone, and requires only concentration to remove reagent-based byproducts or starting material.^{29,30} The standard methylating agent used in the

opening of epoxides stemming from enol ethers is trimethylaluminum, likely due to its ability to deliver the methyl group regioselectively via coordination to the ethereal oxygen.³¹ Various examples exist to perform the desired transformation on different natural product scaffolds. One of which is displayed in scheme 4.19A, with Rainier's work on the synthesis of Hemibrevetoxin B. The 6-membered cyclic enol ether was epoxidized with DMDO, and following concentration and re-suspension in hexanes, trimethylaluminum was added to open the epoxide and deliver the beta-methyl alcohol functionality. In order to predict the stereochemical outcome of the sequence and resulting hydroxyl group, a crystal structure of enol ether **4.83** was obtained which was used to hypothesize that the desired stereochemistry would be favored (while a structure could be elucidated, the R factor and flak parameter of the resulting data was not suitable for publication). As can be seen in Scheme 4.19B, the most stable conformation orients the benzylic methyl group equatorial the 8-membered ring puckers in such a way to block the bottom face of the enol ether (green) on the ring likely resulting in favorable facial delivery of oxygen.



Scheme 4.20. Unsuccessful approach to 4.87 due to hydrolysis of epoxide

Enol ether **4.83** was subjected to freshly synthesized DMDO (typically 0.05-0.07 M in acetone) at $-30\text{ }^{\circ}\text{C}$ and allowed to warm to $0\text{ }^{\circ}\text{C}$, and following complete conversion of the starting material the reaction was concentrated to deliver a single product. The material was used without purification, and was suspended in DCM and cooled to $-30\text{ }^{\circ}\text{C}$, followed by the addition of trimethylaluminum (Scheme 4.20A). The temperature was increased to $25\text{ }^{\circ}\text{C}$ to partially consume the starting material, yet material from the epoxidation remained. Following purification, it was determined that 8-membered ring cleavage occurred by comparison of the crude ^1H NMR spectrum to open chain products obtained from the HFIP elimination reactions (Figure 4.1).

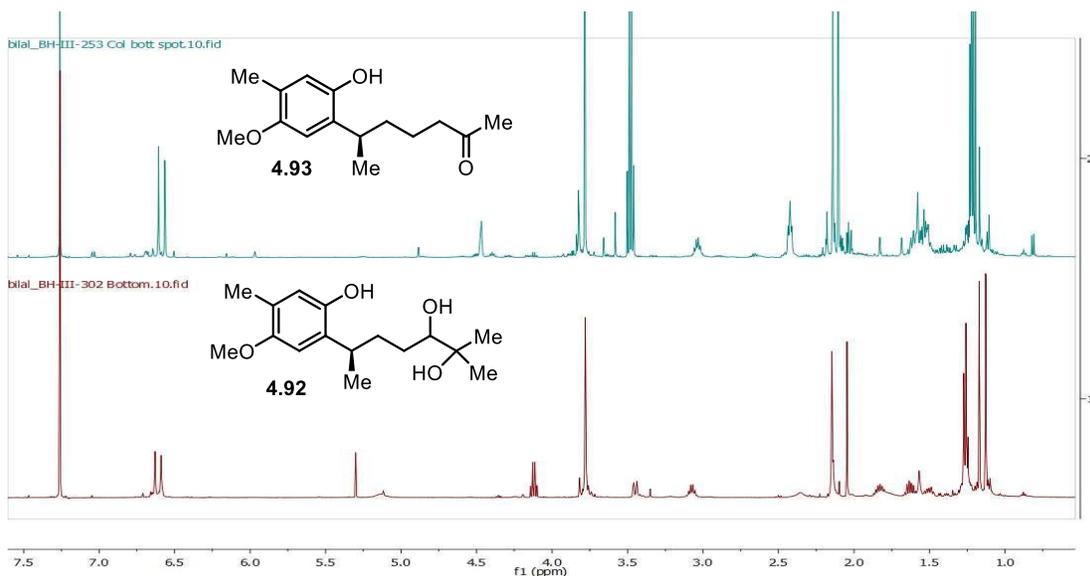
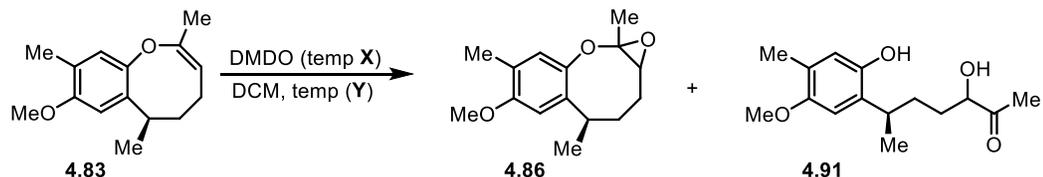


Figure 4.1. Similarity in spectra between open chain products

Ring cleavage was likely proceeding via incorporation of water (from the solution of DMDO) into desired epoxide **4.86**, which delivers unstable ketal **4.90** followed by a rapid and thermodynamically-favorable ring opening to provide **4.91** as a single diastereomer (Scheme 4.20B). The subsequent reactivity Following addition of AlMe_3 , the methyl ketone in **4.91** undergoes partial methyl incorporation to provide **4.92**. This result demonstrates the detrimental effect of water in the epoxidation which is introduced

from the solution of DMDO, and therefore efforts shifted to the exclusion of water and improvement of the epoxidation.

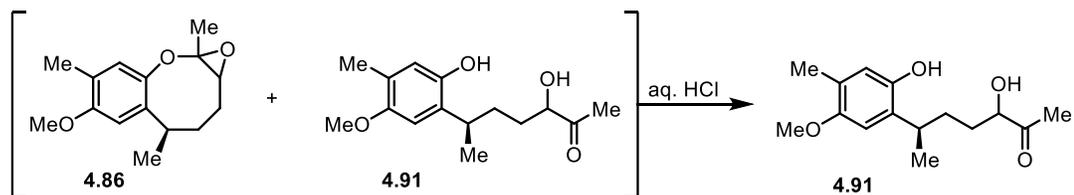
4.6i: Investigation of Epoxidation



Entry	Temperature X (°C)	Temperature Y (°C)	Result
1	-20	-30	4.91 only
2	-78	-30	4.86 & 4.91 (~3:1)
3	-78	-78	4.86 major (trace 4.91)

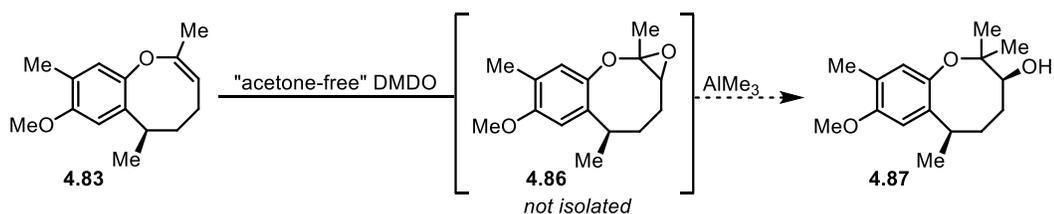
Table 4.8. Modulation of temperature and water content in epoxidation

In order to probe the epoxidation and formation of the undesired diol/open chain product, water exclusion by temperature decrease was performed and monitored by ¹HNMR (Table 4.8). A crude method to exclude water from DMDO during its addition is to pre-cool the DMDO solution to -78 °C which precipitates water out of solution. This modification was applied while keeping the reaction solution temperature at -30 °C with no change in reaction rate, and a mixture of two products by proton NMR favoring a new product (Entry 2), which when treated with dilute aqueous HCl resulted in full conversion to the open chain product, indicating that the newly observed species was indeed the desired epoxide (Scheme 4.21). Additionally cooling of reaction solution to -78 °C prior to addition of DMDO provided the desired epoxide almost exclusively, again leaving the rate of the reaction essentially unchanged. These results prompted further investigation into more effective exclusion of water from the DMDO solution.



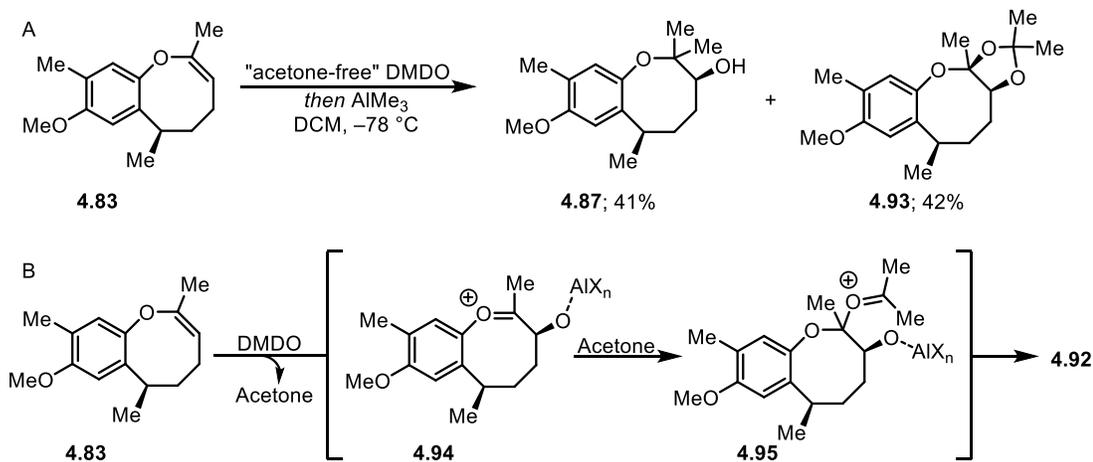
Scheme 4.21. Evidence for formation of desired epoxide

The complete drying of an acetone solution of DMDO is challenging and often results in evaporative loss of DMDO. An alternative approach is to make the DMDO “acetone-free” by extracting it into chlorinated solvents such as DCM or chloroform, and removing the remaining acetone with iterative phosphate buffer washes.³² This process results in a more DMDO solution (~0.1-.02 M) which can be efficiently dried by stirring in magnesium sulfate and filtering. Additionally, with the use of “acetone-free” DMDO no concentration or drying is required prior to the addition of AlMe₃ since water has been fully excluded and acetone in solution is limited to that which is produced from the consumption of DMDO (Scheme 4.22).



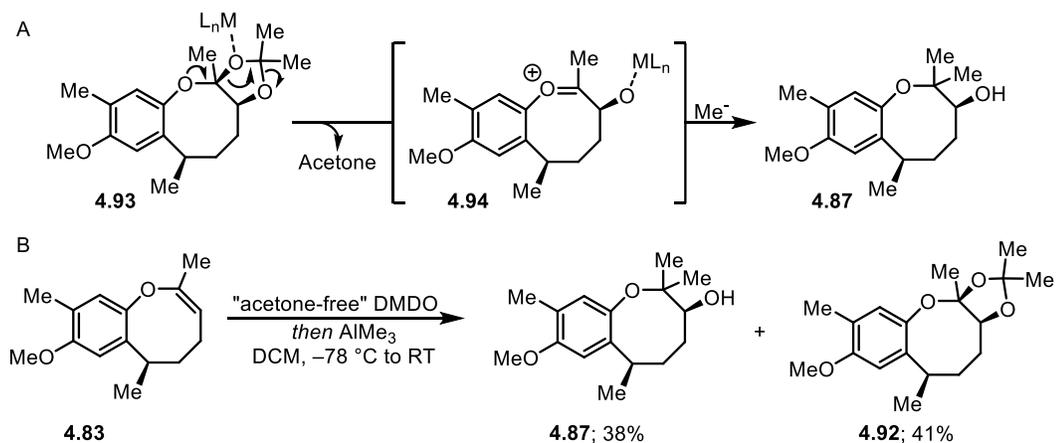
Scheme 4.22. Proposed telescoped sequence using “acetone-free” DMDO

Epoxidation of **4.83** was performed using “acetone-free” DMDO was performed, and following its complete consumption, trimethylaluminum was added to provide a single diastereomer of alcohol **4.87** in low yield owing to the formation of byproduct **4.93** (Scheme 4.23A). The structure of acetonide **4.93** was unambiguously determined via characterization by NMR and X-Ray crystallography. Unfortunately, an unwanted pause in data collection during X-Ray analysis resulted in incomplete data not suitable for a full crystal report. The synthesis of acetonides from epoxides has been reported using various Lewis acids,^{33–35} and a plausible mechanism is presented in Scheme 4.23B wherein Lewis acidic AlMe₃ promotes epoxide opening to form oxocarbenium **4.94**. An equivalent of acetone (liberated from DMDO) can undergo nucleophilic addition, resulting in exocyclic oxocarbenium **4.95**, which can subsequently undergo nucleophilic attack by the adjacent hydroxyl group and deliver acetonide **4.93**.



Scheme 4.23. Formation of acetone and mechanistic rationale

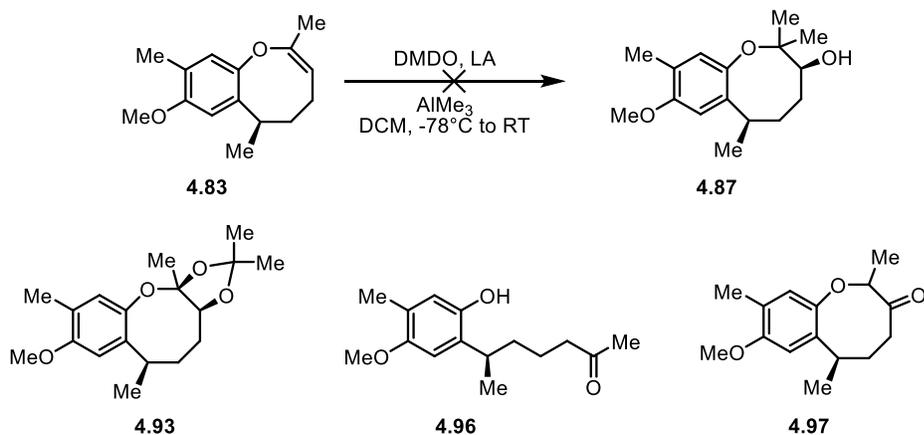
The conversion of **4.93** to desired alcohol **4.87** can still be envisioned via reversible acetone cleavage to **4.94** and quench of the resulting oxocarbenium species with a nucleophilic methyl source to provide the desired product (Scheme 4.24A). Allowing the reaction to warm to ambient temperature following the addition of trimethylaluminum resulted in essentially no change in product distribution (Scheme 4.24B).



Scheme 4.24. Proposed and unsuccessful conversion of acetone to 4.87

The incorporation of additional Lewis acids was screened in order to promote desired reactivity of the acetone using acids previously invoked in the synthesis of acetones from epoxides (Table 4.9).^{33–35} The additions of zinc chloride or $\text{BF}_3 \cdot \text{OEt}_2$ in DCM inhibited acetone **4.93** formation, but resulted in non-specific degradation with

small quantities of open-chain product **4.96** (Entries 1,2). Addition of TiCl_4 resulted in the formation of ketone **4.97** via hydride transfer, with small quantities of open-chain product **4.96** (Entry 3). Titanium tetrachloride addition was also examined with Et_2O as the solvent which provided the acetonide as the major product with no **4.96** present (Entry 4). Finally, Diethyl ether and toluene were screened as reaction solvents in the absence of external Lewis acids for their proficiency resulting in the formation of **4.93** as the major product.

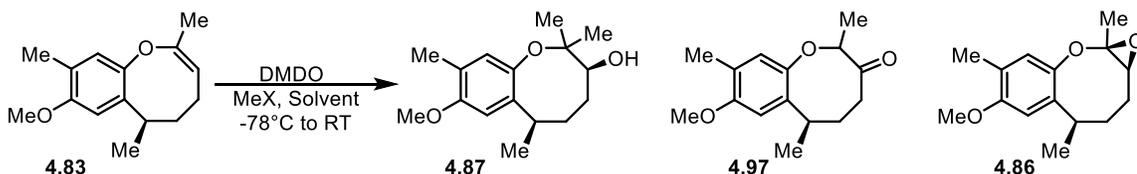


Entry	Acid	Solvent	Result	Comments
1	ZnCl_2	DCM	Decomposition	4.96 present, no 4.93
2	$\text{BF}_3 \cdot \text{OEt}_2$	DCM	Decomposition	4.96 present, no 4.93
3	TiCl_4	DCM	4.97	4.96 present, no 4.93
4	TiCl_4	Et_2O	4.93 major	No 4.96
5	None	Et_2O	4.93 major	No 4.96
6	None	Toluene	4.93 major	No 4.96

Table 4.9. Screen of Lewis acids and solvents to promote formation of **4.87**

4.6ii: Investigation of methylating agents

A feasible approach to inhibit acetonide formation is the use of alternative methyl sources lacking significant Lewis acidic properties such as methyl Grignard or methyllithium. While regioselectivity concerns are conceivable, it was proposed that the oxocarbenium species (Scheme 4.23; **4.94**) is a dominant resting species and regioselectivity would likely not be a concern. Therefore, a screen of methyl sources was conducted in 4 separate solvents (Table 4.10). As can be seen in Entries 1 and 2, diethyl ether did not provide desired alcohol **4.87** in any case, instead providing ketone **4.97** or resulting in recovery of the epoxide. The intact epoxide was isolated in a variety of conditions (Entries 1, 3, 5, 7, 8), and desired alcohol was only provided using methyl Grignard in toluene or DCM. In each case, however, the reaction proved to be quite messy and resulted in limited recovery of desired product.

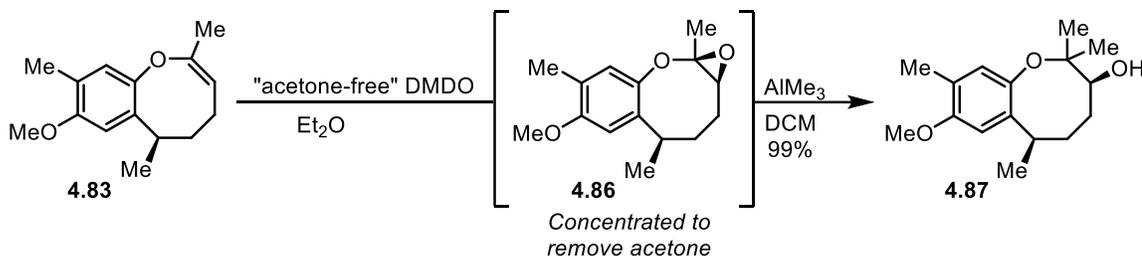


Solvent	Entry	Methyl Source	Major product
Et ₂ O	1	MeLi	4.86
	2	MeMgBr	4.97
Toluene	3	MeLi	4.86
	4	MeMgBr	Messy, 4.87
DCM	5	MeLi	4.86
	6	MeMgBr	Messy, 4.87
THF	7	MeLi	4.86
	8	MeMgBr	4.86

Table 4.10. Screen of nucleophilic methyl sources in various solvent

The recovery of intact epoxide in various solvents prompted a return to original reaction protocol involving the concentration of the reaction following epoxidation to remove all acetone, then re-suspension of the epoxide in solvent and addition of AlMe₃.

Diethyl ether was selected as the solvent during epoxidation due to its volatility and success in delivering the epoxide in during screening. Therefore, enol ether **4.83** was suspended in Et₂O and subjected to epoxidation with “acetone-free” DMDO, and the formed epoxide was concentrated. The subsequent methylation proceeded smoothly to deliver alcohol **4.87** (MeO-Heliannuol A) in quantitative yield (Scheme 4.25).

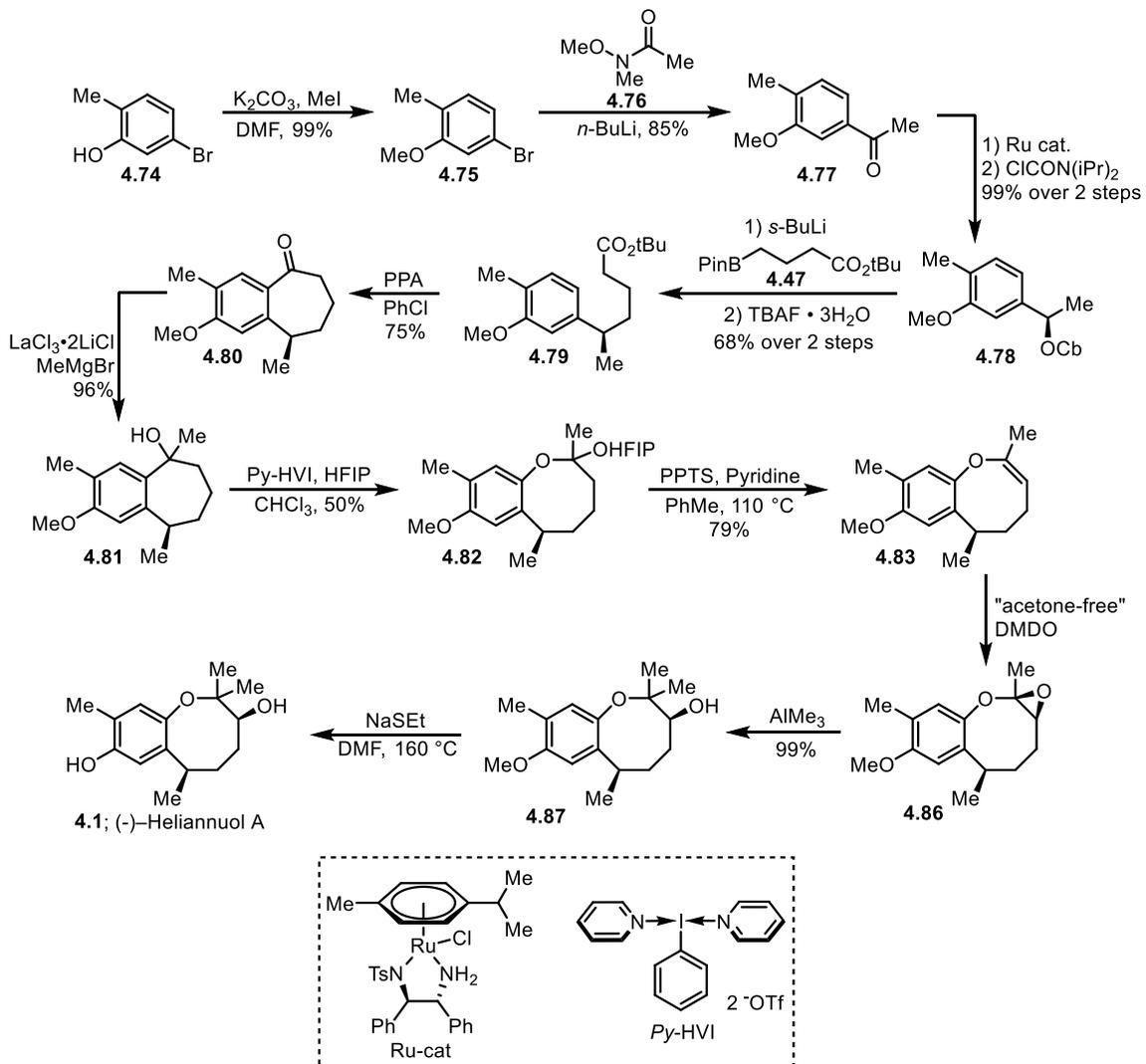


Scheme 4.25. Improved synthesis of MeO-Heliannuol A 4.87

4.7: COMPLETION OF HELIANNUOL A

The complete asymmetric synthesis of Heliannuol A is presented in Scheme 4.26 beginning with the synthesis of acetophenone **4.77** via phenol methylation and lithium/halogen exchange followed by addition of Weinreb amide **4.76**. Asymmetric transfer hydrogenation of **4.77** and subsequent carbamoylation provided carbamate **4.78** in quantitative yield over two steps. Homologation of the carbamate with boronic ester **4.47** and de-borylation afforded ester **4.79**, which was cyclized using polyphosphoric acid to afford ketone **4.80**. The methylation of ketone **4.80** was improved from roughly 50% to 96% by the addition of LaCl₃·2LiCl according to literature procedure³⁶ to provide alcohol **4.81**. The improved *N*-HVI mediated umpolung ring expansion proceeded smoothly to deliver HFIP acetal **4.82** in 50% isolated yield, followed by elimination of HFIP to afford enol ether **4.83**. The aforementioned epoxidation/methylative cleavage conditions were implemented to provide a single diastereomer of **4.87**, which was

subjected to aryl ether demethylation using sodium ethanethiolate which proceeded in 84% yield to provide (-)-Heliannuol A.



Scheme 4.26. Completed asymmetric total synthesis of (-)-Heliannuol A

4.8: CONCLUSIONS

Our sequence to arrive at Heliannuol A represents a modular approach to the 8-membered cyclic ether in the shortest sequence to date. High enantioselectivity is achieved by performing a stereoretentive homologation following an asymmetric transfer

hydrogenation from commercially available acetophenones (97:3 *e.r.*). Once again implementing the novel oxidative rearrangement seen in Chapters 2 and 3, our route quickly accesses the most challenging aspect of the Heliannuols: the medium-sized cyclic ether. Derivatization is easily achieved to install the necessary components of the aliphatic ring. With the completion of two natural members of the Heliannuol family, our efforts shifted to the synthesis of unnatural analogues, as seen in Chapter 5.

Experimental data for this chapter can be found in Appendix D.

4.9: REFERENCES

- (1) Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. Potential Allelopathic Guaianolides from Cultivar Sunflower Leaves, Var. SH-222. *Phytochemistry* **1993**, *34* (3), 669–674. [https://doi.org/10.1016/0031-9422\(93\)85337-Q](https://doi.org/10.1016/0031-9422(93)85337-Q).
- (2) Grimm, E. L.; Levac, S.; Trimble, L. A. Total Synthesis of (±)-Heliannuol A. *Tetrahedron Lett.* **1994**, *35*, 6847–6850.
- (3) Tuhina, K.; Bhowmik, D. R.; Venkateswaran, R. V. Formal Syntheses of Heliannuols A and D, Allelochemicals from Helianthus Annus. *Chem. Commun.* **2002**, *2* (6), 634–635. <https://doi.org/10.1039/b200103a>.
- (4) Biswas, B.; Sen, P. K.; Venkateswaran, R. V. Bargellini Condensation of Coumarins. Expeditious Route to o-Carboxyvinylphenoxyisobutyric Acids and Application to the Synthesis of Sesquiterpenes Helianane, Heliannuol A and Heliannuol C. *Tetrahedron* **2007**, *63* (48), 12026–12036. <https://doi.org/10.1016/j.tet.2007.09.006>.
- (5) Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. Enantioselective Total Synthesis of Heliannuols D and A. *J. Chem. Soc. Perkin Trans. 1* **2000**, No. 12, 1807–1808. <https://doi.org/10.1039/b003553j>.
- (6) Kishuku, H.; Shindo, M.; Shishido, K. Enantioselective Total Synthesis of (2)-Heliannuol A. Heliannuol A Has Been Accomplished by Employing Ring Closing Metathesis and Sequential Diastereoselective Epoxidation and Regioselective Reductive Cleavage of the Epoxide Ring. *Chem. Commun.* **2003**, No. November 2002, 2002–2003.
- (7) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. Protodeboronation of

- Tertiary Boronic Esters: Asymmetric Synthesis of Tertiary Alkyl Stereogenic Centers. <https://doi.org/10.1021/ja1084207>.
- (8) Elford, T. G.; Nave, S.; Sonawane, R. P.; Aggarwal, V. K. Total Synthesis of (+)-Erogorgiaene Using Lithiation–Borylation Methodology, and Stereoselective Synthesis of Each of Its Diastereoisomers. *J. Am. Chem. Soc.* **2011**, *133* (42), 16798–16801. <https://doi.org/10.1021/ja207869f>.
- (9) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. Enantiodivergent Conversion of Chiral Secondary Alcohols into Tertiary Alcohols. *Nature* **2008**, *456* (7223), 778–783. <https://doi.org/10.1038/nature07592>.
- (10) Kelley, B. T.; Walters, J. C.; Wengryniuk, S. E. Access to Diverse Oxygen Heterocycles via Oxidative Rearrangement of Benzylic Tertiary Alcohols. *Org. Lett.* **2016**, *18* (8), 1896–1899. <https://doi.org/10.1021/acs.orglett.6b00672>.
- (11) Walters, J. C.; Tierno, A. F.; Dubin, A. H.; Wengryniuk, S. E. (Poly)Cationic Λ^3 -Iodane-Mediated Oxidative Ring Expansion of Secondary Alcohols. *European J. Org. Chem.* **2018**, *2018* (12), 1460–1464. <https://doi.org/10.1002/ejoc.201800118>.
- (12) Malatesta, V.; Ingold, K. U. Kinetic Applications of Electron Paramagnetic Resonance Spectroscopy. 36. Stereoelectronic Effects in Hydrogen Atom Abstraction from Ethers. *J. Am. Chem. Soc.* **1981**, *103* (3), 609–614. <https://doi.org/10.1021/ja00393a018>.
- (13) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. Bu₄Ni-Catalyzed C–O Bond Formation by Using a Cross-Dehydrogenative Coupling (CDC) Reaction. *Chem. - A Eur. J.* **2011**, *17* (15), 4085–4089. <https://doi.org/10.1002/chem.201100192>.

- (14) Lyons, T. W.; Bézier, D.; Brookhart, M. Iridium Pincer-Catalyzed Dehydrogenation of Ethers Featuring Ethylene as the Hydrogen Acceptor. *Organometallics* **2015**, *34* (16), 4058–4062.
<https://doi.org/10.1021/acs.organomet.5b00501>.
- (15) Bézier, D.; Brookhart, M. Applications of PC(Sp³)P Iridium Complexes in Transfer Dehydrogenation of Alkanes. *ACS Catal.* **2014**, *4* (10), 3411–3420.
<https://doi.org/10.1021/cs500892p>.
- (16) Wang, L.; Zhu, K. Q.; Wu, W. T.; Chen, Q.; He, M. Y. N-Bu₄NI-Catalyzed Direct Amination of Ethers with Aryl Tetrazoles and Triazoles via Cross-Dehydrogenative Coupling Reaction. *Catal. Sci. Technol.* **2015**, *5* (5), 2891–2896.
<https://doi.org/10.1039/c5cy00229j>.
- (17) Grossman, O.; Azerraf, C.; Gelman, D. Palladium Complexes Bearing Novel Strongly Bent Trans-Spanning Diphosphine Ligands: Synthesis, Characterization, and Catalytic Activity. *Organometallics* **2006**, *25* (2), 375–381.
<https://doi.org/10.1021/om050906j>.
- (18) Jin, J.; MacMillan, D. W. C. Direct α -Arylation of Ethers through the Combination of Photoredox-Mediated C-H Functionalization and the Minisci Reaction. *Angew. Chemie - Int. Ed.* **2015**, *54* (5), 1565–1569.
<https://doi.org/10.1002/anie.201410432>.
- (19) Pan, S.; Liu, J.; Li, H.; Wang, Z.; Guo, X.; Li, Z. Iron-Catalyzed N-Alkylation of Azoles via Oxidation of C-H Bond Adjacent to an Oxygen Atom. *Org. Lett.* **2010**, *12* (9), 1932–1935. <https://doi.org/10.1021/ol100670m>.
- (20) Mei, Y.; Bentley, P. A.; Du, J. Thiourea Catalysis of NCS in the Synthesis of α -

Chloroketones. *Tetrahedron Lett.* **2008**, *49* (23), 3802–3804.

<https://doi.org/10.1016/j.tetlet.2008.03.154>.

- (21) Tanemura, K.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. A Mild and Efficient Procedure for α -Bromination of Ketones Using N-Bromosuccinimide Catalysed by Ammonium Acetate. *Chem. Commun.* **2004**, *4* (4), 470–471.
<https://doi.org/10.1039/b315340a>.
- (22) Prokopowicz, M.; Młynarz, P.; Kafarski, P. Synthesis of Phosphonate Derivatives of 2,3-Dihydroindene. *Tetrahedron Lett.* **2009**, *50* (52), 7314–7317.
<https://doi.org/10.1016/j.tetlet.2009.10.042>.
- (23) Tang, S. Z.; Zhao, W.; Chen, T.; Liu, Y.; Zhang, X. M.; Zhang, F. M. A Simple and Efficient Method for the Preparation of α -Halogenated Ketones Using Iron(III) Chloride and Iron(III) Bromide as Halogen Sources with Phenyliodonium Diacetate as Oxidant. *Adv. Synth. Catal.* **2017**, *359* (23), 4177–4183.
<https://doi.org/10.1002/adsc.201700833>.
- (24) Nazari, M.; Movassagh, B. α -Phenylselenenylation of Aldehydes and Ketones with Diphenyl Diselenide Mediated by $\text{KF}/\text{Al}_2\text{O}_3$. *Tetrahedron Lett.* **2009**, *50* (13), 1453–1455. <https://doi.org/10.1016/j.tetlet.2009.01.068>.
- (25) Carreira, E. M.; Hönig, M. Total Synthesis and Structural Revision of a Harziane Diterpenoid. *Angew. Chemie Int. Ed.* **2019**, 1–6.
<https://doi.org/10.1002/anie.201912982>.
- (26) Hartung, J.; Greb, M. A New Synthesis of the 2,2,3,5,6,6-Substituted Tetrahydropyran Aplysiapyranoid A and Its 5-Epimer. *Tetrahedron Lett.* **2003**, *44* (32), 6091–6093. [https://doi.org/10.1016/S0040-4039\(03\)01468-0](https://doi.org/10.1016/S0040-4039(03)01468-0).

- (27) Crotti, P.; Di Bussolo, V.; Favero, L.; Pineschi, M.; Sergiampietri, D.; Renzi, G.; Ricciutelli, M.; Roselli, G. Aromatic Substituent Effect on the Stereoselectivity of the Condensed- and Gas-Phase Acid-Induced Methanolysis in 2-Aryloxiranes Derived from 3,4-Dihydronaphthalene and Trans-1,2,3,4,4a,10a-Hexahydrophenanthrene Bearing a Tertiary Benzylic Oxirane Nucleop. *Tetrahedron* **1997**, *53* (15), 5515–5536. [https://doi.org/10.1016/S0040-4020\(97\)00209-3](https://doi.org/10.1016/S0040-4020(97)00209-3).
- (28) Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A. N-Phenylselenophthalimide (NPSP). A Valuable Selenenylating Agent. *Tetrahedron* **1985**, *41* (21), 4835–4841. [https://doi.org/10.1016/S0040-4020\(01\)96722-5](https://doi.org/10.1016/S0040-4020(01)96722-5).
- (29) Zhang, Y.; Rohanna, J.; Zhou, J.; Iyer, K.; Rainier, J. D. Total Synthesis of Brevenal. *J. Am. Chem. Soc.* **2011**, *133* (9), 3208–3216. <https://doi.org/10.1021/ja200089f>.
- (30) Majumder, U.; Cox, J. M.; Johnson, H. W. B.; Rainier, J. D. Total Synthesis of Gambierol: The Generation of the A-C and F-H Subunits by Using a C-Glycoside Centered Strategy. *Chem. - A Eur. J.* **2006**, *12* (6), 1736–1746. <https://doi.org/10.1002/chem.200500993>.
- (31) Rainier, J. D.; Allwein, S. P.; Cox, J. M. C-Glycosides to Fused Polycyclic Ethers. A Formal Synthesis of (±)-Hemibrevetoxin B. *J. Org. Chem.* **2001**, *66* (4), 1380–1386. <https://doi.org/10.1021/jo001514j>.
- (32) Gibert, M.; Ferrer, M.; Sánchez-Baeza, F.; Messeguer, A. Availability and Reactivity of Concentrated Dimethyldioxirane Solutions in Solvents Other than Acetone. *Tetrahedron* **1997**, *53* (25), 8643–8650. <https://doi.org/10.1016/S0040->

4020(97)00533-4.

- (33) Lohman, G. J. S.; Seeberger, P. H. One-Pot Conversion of Glycals to Cis-1,2-Isopropylidene- α -Glycosides. *J. Org. Chem.* **2003**, *68* (19), 7541–7543.
<https://doi.org/10.1021/jo034386i>.
- (34) Golinski, M.; Vasudevan, S.; Floresca, R.; Brock, C. P.; Watt, D. S. An Enantioselective Approach to Ring a of Taxol Using the Wieland-Miescher Ketone. *Tetrahedron Lett.* **1993**, *34* (1), 55–58. [https://doi.org/10.1016/S0040-4039\(00\)60056-4](https://doi.org/10.1016/S0040-4039(00)60056-4).
- (35) Wershofen, S.; Scharf, H. D. Synthesis of Side-Chain Unsaturated Endo- A Nd Exo-Brevicominsrepresentatives of Pheromone Analogs in the Dioxabicyclo[3.2.1]Octane Series. *Synth.* **1988**, *1988* (11), 854–858.
<https://doi.org/10.1055/s-1988-27729>.
- (36) Krasovskiy, A.; Kopp, F.; Knochel, P. Soluble Lanthanide Salts (LnCl₃·2 LiCl) for the Improved Addition of Organomagnesium Reagents to Carbonyl Compounds. *Angew. Chemie - Int. Ed.* **2006**, *45* (3), 497–500.
<https://doi.org/10.1002/anie.200502485>.

CHAPTER 5: SYNTHESIS OF UNNATURAL HELIANNUOLS ANALOGUES

5.1: BACKGROUND AND MOTIVATION

Global population is on the rise and is expected to increase by over 40% to more than 11 billion by 2100.¹ Consequently, food supply and demand will be directly impacted. With the expansion of urban landscapes and ever-shrinking farmlands², it becomes crucial to modulate crop growth to increase yields. As such, the ability to effectively control invasive and harmful species is necessary, as is the necessity to do so in as specific and benign a fashion as possible. This has been a challenge for environmental chemists evidenced by the deregistration of over ten pesticides by the EPA over a period of four years from 2005 to 2009³ due to their lack of specificity, which led to decreasing population numbers of pollinators such as bees and wasps. Therefore, there has been renewed interest in the exploration of natural sources of pesticides to limit the detriment on non-invasive plant and insect life, as well as human health.

Allelochemicals are defined as any chemical produced by a living organism which exerts a detrimental physiological effect on another species.^{4,5} These compounds have potential as environmentally-benign agents for the management of weeds (herbicidal), insects (insecticidal) and fungi (fungicidal). Additionally, they offer opportunity for the discovery of novel molecular targets. Despite this potential, few natural products possess the correct combination of traits desirable in general pesticides, namely...[insert traits].⁶ Fortunately, such properties can be incorporated via chemical modification of the natural compound through either late-stage modification or divergent synthesis. Upon the synthesis of analogues or installation of additional functional groups,

the new molecules can be screened for their bioactivity against invasive species which pose a threat to the growth and proliferation of desirable plant species.

The divergent approach utilized in the synthesis of Heliannuols D and A described in the two prior chapters was amendable to expedient analogue synthesis and provided access to 10 structural and stereochemical analogues. This chapter will describe the synthesis of analogues of both Heliannuol D and A, either via divergence from the route at key intermediates or by capitalizing on undesired byproducts. Preliminary bioactivity has been established in collaboration with Corteva Agrichemical including the evaluation of herbicidal, insecticidal and fungicidal activity, the latter two of which have not been previously evaluated or reported.

5.2: BIOACTIVITY OF HELIANNUOLS

The biological activity of Heliannuols^{7,8} is understudied despite the numerous forays into their total synthesis.⁹⁻¹⁸ To that end, a single publication has been reported which investigated solely the herbicidal properties of the family of natural products.¹⁹ Based on the report Heliannuols A, C, and D were among the most active members with inhibition of root growth and germination of dicotyledonous lettuce at concentrations as low as 10^{-9} nM. Interestingly, heliannuols tend to show no inhibition against and actually promote monocotyledonous plant growth.¹⁹ Other key findings include enhanced inhibitory properties with increasing heterocycle size and hydroxyl moieties on the heterocyclic ring. While these findings provide initial insight into key structural properties necessary for bioactivity, they are not comprehensive due to a lack of access to synthetic analogues. Therefore, further studies are needed in order to understand the structure-activity relationships and full scope of heliannuols potential as novel

agricultural agents, including insecticidal and fungicidal activity which has not yet been studied.

5.3: SYNTHESIS OF UNNATURAL ANALOGUES

5.3i: Synthesis of 7-Membered Heliannuol D Analogues

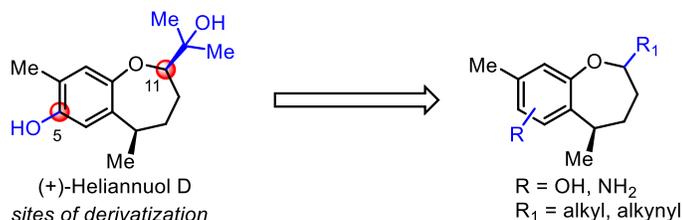
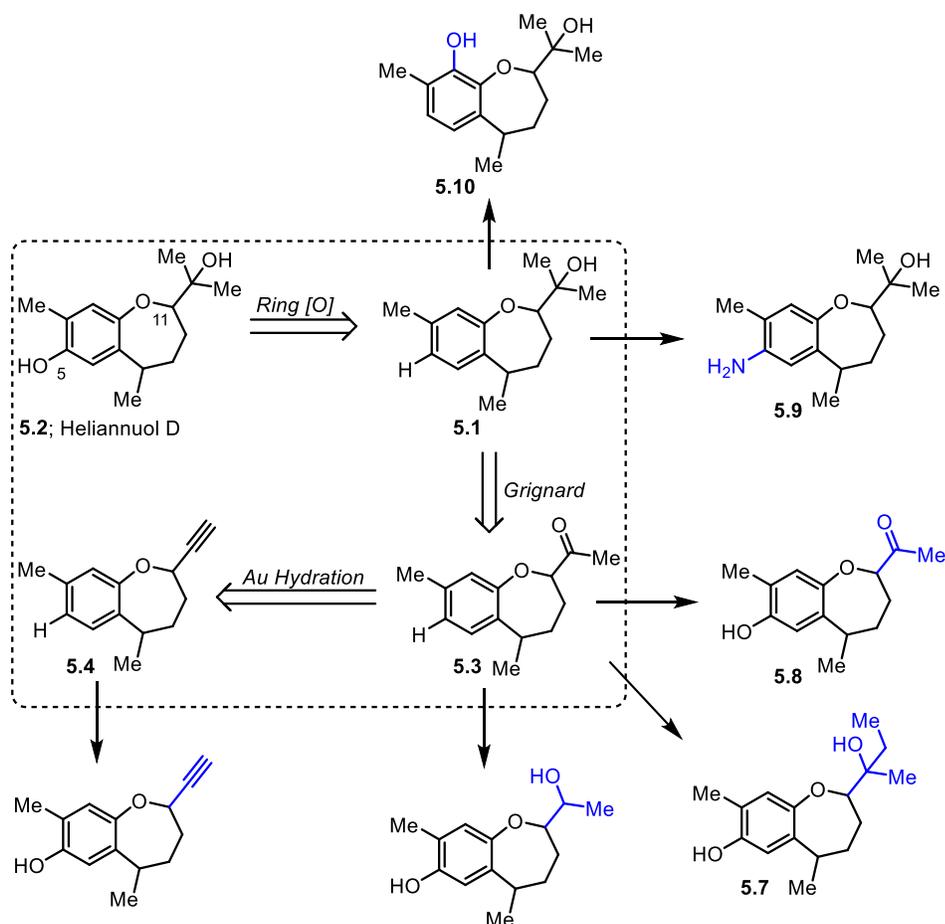


Figure 5.1. Sites of derivatization of Heliannuol D

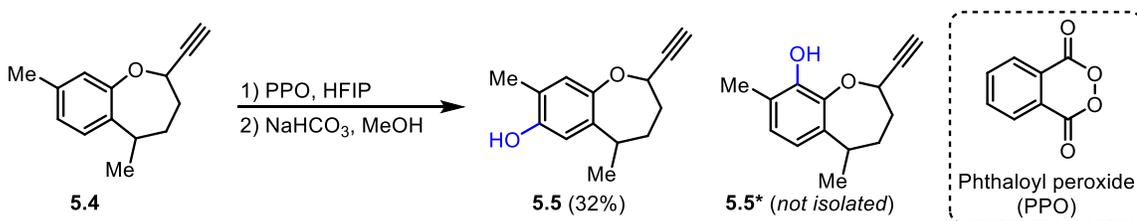
Without computational data or mode of action studies to predict probable binding or interactions leading to observed inhibitory effects of Heliannuols, a common theme with agricultural agents, analogue synthesis was driven by ease of access. Based on our synthetic route, it was envisioned that several sites of potential biological significance could be readily derivatized: The hydroxyl moiety at C5 and the alkyl substituent on C11. Regarding the phenolic moiety, while it is reported that the phenol is required for herbicidal activity,¹⁹ regioisomeric phenols and aniline derivatives have not yet been investigated. Additionally, the sterics and electronics of the C11 substituent will be probed by modulation of the geminal dimethyl group and replacement of the alcohol for a less Lewis-basic ketone.

Regarding the substituent at C11, alkyne **5.4** was identified as a point of divergence through which a variety of analogues could be evaluated (Scheme 5.1). These included the effect of alkyl chain length (**5.7**), the geminal dimethyl functionality (**5.6**), and the role of the sidechain heteroatom, either its hybridization (**5.8**) or deletion (**5.5**).



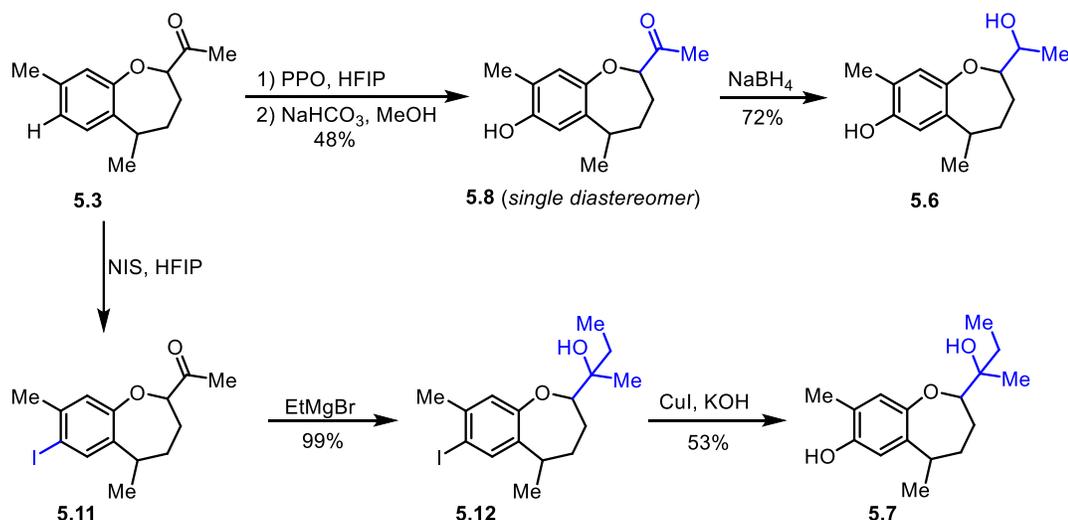
Scheme 5.1. Access to analogues from late-stage intermediates of Heliannuol D

The effect of the C5-phenol could be investigated by the synthesis of regioisomeric phenols (**5.10**) or via replacement with other heteroatoms such as in aniline (**5.9**). All of these analogues could be evaluated by interception of just three intermediates from the late-stage sequence to the natural analogue heliannuol D. Due to availability and cost, as well as access to analogues of each enantiomer for screening, derivatizations would be performed on racemic substrate.



Scheme 5.2. Synthesis of 7-membered C11 alkynyl analogue

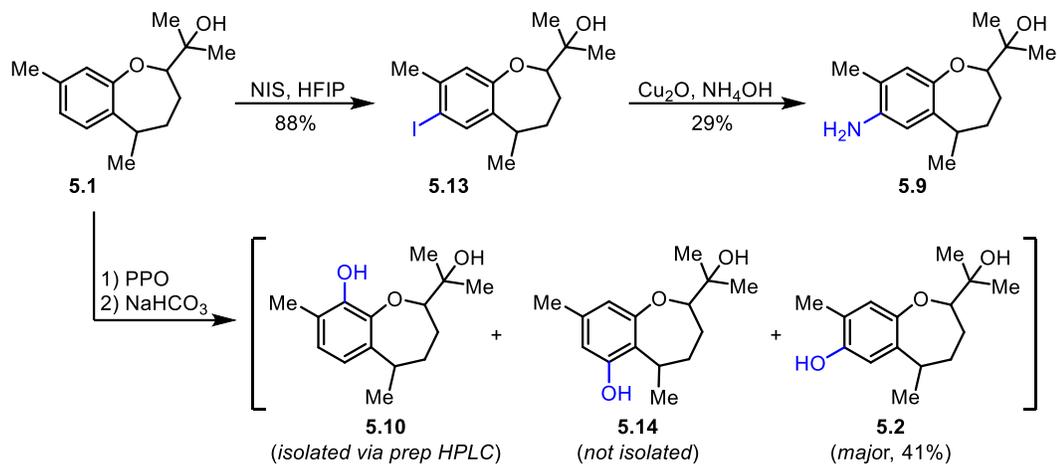
The synthesis of each analogue was performed beginning with racemic alkyne **5.5**. In order to install the phenolic functionality at C5 while retaining the alkyne moiety, the two-step iodination/hydroxylation utilized in the synthesis of Heliannuol D was not amenable due to the likelihood of competitive alkyne iodination, which had been previously reported under similar mildly acidic conditions.²⁰ Alkyne **5.4** was treated with freshly-synthesized^{21,22} phthaloyl peroxide (PPO) in the presence of HFIP, and the resulting ester was hydrolyzed to provide phenol **5.5** in 32% yield along with a complex mixture of byproducts containing the C3 phenol (not isolated; Scheme 5.2).



Scheme 5.3. Synthesis of various 7-membered analogues varied at C11

The C11-analogues were accessed from ketone **5.3**, which was prepared via gold-mediated hydration of alkyne **5.4**. During the course of the synthesis of Heliannuol D, it was demonstrated that the two-step iodination/hydroxylation sequence fails on substrate **5.3**, likely due to the presence of an acidic α -proton. Therefore, a PPO oxidation could be performed from **5.3**, which swiftly delivered analogue **5.8** as a single regioisomer in 48% yield. A portion of **5.8** was then reduced with sodium borohydride to deliver secondary alcohol **5.6**. To synthesize ethyl analogue **5.7**, previously prepared aryl iodide **5.11** was

treated with ethylmagnesium bromide, which provided **5.12**. The subsequent Ullman hydroxylation provided analogue **5.7** in 53% yield.



Scheme 5.4. Synthesis of aniline and phenolic regioisomers

To access aniline **5.9**, aryl iodide **5.13** was subjected to an Ullman coupling with aqueous ammonia as the nucleophile (Scheme 5.4).²³ This provided aniline **5.9** as the major product in 29% yield, along with minor amounts (9%) of Heliannuol D **5.1** due to the presence of water as a competitive nucleophile. Access to phenolic regioisomers was afforded when aryl ether **5.1** was subjected to PPO oxidation/hydrolysis which provided Heliannuol D (**5.2**) as the major product along with a complex mixture of unreacted **5.1**, C3-phenol **5.10**, and a minor quantity of presumed C6-phenol **5.14**. The regioisomeric phenols were inseparable via column chromatography and instead required preparatory HPLC, and **5.14** was not obtained in any appreciable quantity. Nonetheless, C3 phenol was obtained, and each synthesized sample was sent for biological screening at Corteva Agriscience (see Section 5.4).

5.3ii. Synthesis of 8-Membered Heliannuol A Analogues

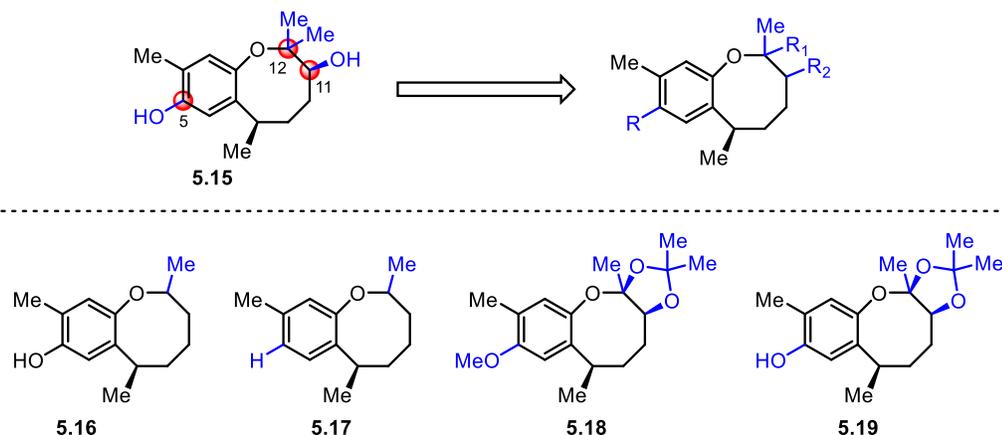
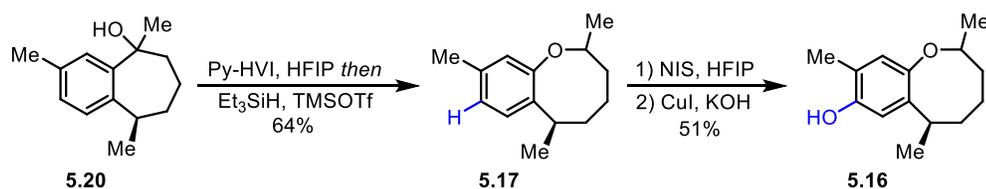


Figure 5.2. Sites of derivatization of 8-membered analogues

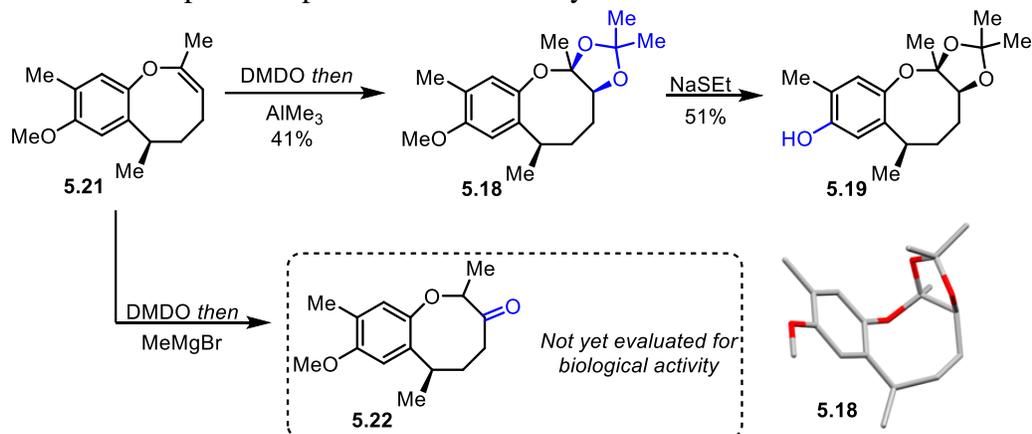
Similar to the synthesis of 7-membered analogues, structural derivatizations at C5 and the α -ethereal position C12 were targeted (Figure 5.2). Additionally, the effect of the aliphatic hydroxyl group at C11 was to be evaluated. Differing slightly from the Heliannuol D analogues, the Heliannuol A analogues were accessed from byproducts formed throughout the synthesis of the natural product. Due to time constraints, no more than the natural product **5.15** and 4 unnatural analogues (**5.16-5.19**) were submitted for analysis, however additional analogue synthesis is underway at the time of writing this thesis.



Scheme 5.5. Synthesis of mono α -methyl and des β -OH 8-membered analogues

To determine the importance of not only the alkyl hydroxyl group at C11, but also the geminal dimethyl functionality at C12, analogues **5.16** and **5.17** were first targeted. Their synthesis proceeds from from tertiary alcohol **5.20**, where the *N*-HVI-mediated umpolung ring expansion and hydride reduction of the resultant HFIP acetal could be performed in one-pot according to the procedure outlined in Chapter 2 to deliver

analogue **5.17** in 64% yield. A subsequent two-step iodination/hydroxylation was then carried out to deliver phenolic product **5.16** in 51% yield.



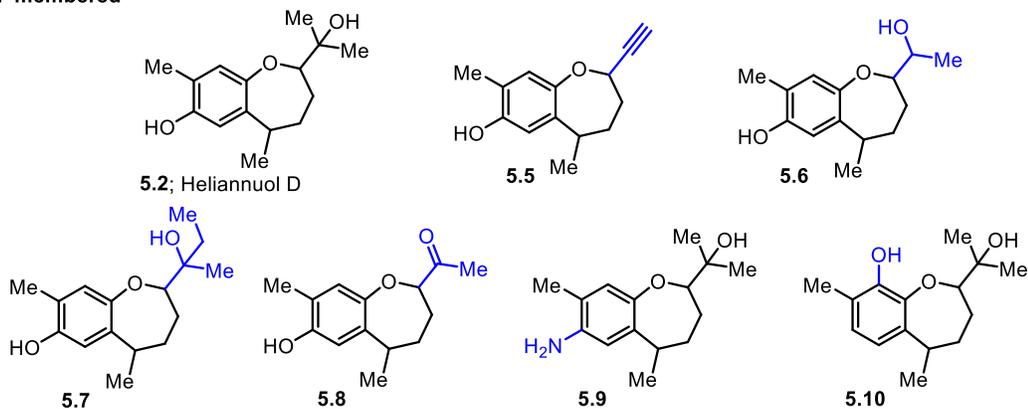
Scheme 5.6. Access to 8-membered acetonide and ketone analogues

Access to analogues **5.18** and **5.19** was the result of byproduct formation during the course of the epoxidation and methylative ring opening sequence to deliver the penultimate precursor to Heliannuol A. It was found that acetonide **5.18** forms readily from enol ether **5.21** in 41% yield following the formation of the corresponding epoxide by DMDO and addition of trimethylaluminum in the presence of acetone (see Chapter 4 for more details on reaction conditions and mechanistic hypotheses). While the acetonide formation was eventually suppressed through modification of the synthetic sequence, access to **5.18** provided a unique opportunity to assay the importance of the geminal dimethyl substitution at C12 as opposed to on the acetonide one atom removed. Furthermore, the oxygen atom at C11 is intact but as an ether allowing the evaluation of the importance of the alcohol moiety of the natural product. Access to the phenolic analogue was afforded via sodium ethanethiolate-mediated anisole demethylation to afford **5.19** in 51% yield. An additional 8-membered analogue was synthesized as a byproduct from the epoxidation and subsequent methylataion. When methylmagnesium bromide was utilized at the methyl source a hydride migration occurred which resulted in the formation of ketone **5.22**. This analogue bears striking resemblance to Heliannuol K,

which possesses a geminal dimethyl functionality at C12. **5.22** has not yet been evaluated for biological activity but will be included in future assays.

5.4: BIOLOGICAL SCREENING OF HELIANNUOL ANALOGUES

7-membered



8-membered

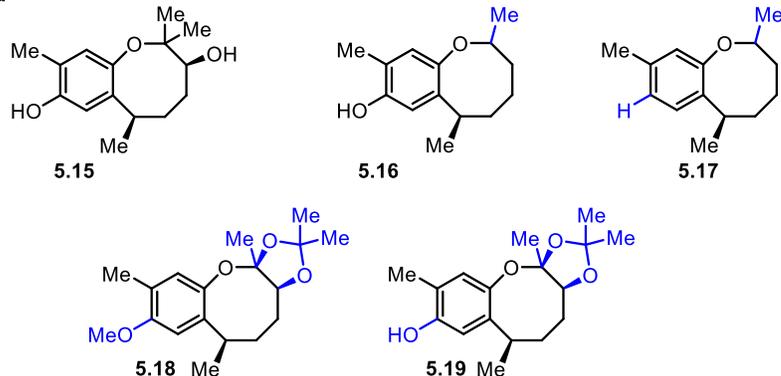


Figure 5.3. 7- and 8-membered analogues utilized in pesticidal assays

As was previously mentioned, Heliannuols have only been evaluated for their performance as herbicides. In order to gain a better understanding of their competence as general pesticides, each unnatural analogue and the natural Heliannuol D were screened against various invasive pests including weeds, fungi, and insects. This data was collected in collaboration with Corteva Agriscience, and in particular with the guidance of Dr. Jessica Herrick who organized each experiment. The data presented is from Level 1 testing, which screens activity against the most general species of each pest. For

continuation to Level 2 screening, values greater than 50% inhibition are generally required. Additionally, a desirable pesticidal compound exhibits specific toxicity and not widespread control, as such a compound would likely pose a threat to the health of the farmed crop or desired pollinating insects.

5.4i: Herbicidal Activity

Analogue	Control (%)	
	Giant Foxtail (monocot)	Sunflower (dicot)
5.2	0	0
5.5	0	0
5.6	0	0
5.7	0	0
5.8	0	0
5.9	0	0
5.10	0	0
5.15	0	0
5.16	0	0
5.17	0	0
5.18	0	0
5.19	0	0

Table 5.1. Herbicidal activity for of 7- and 8-membered analogues

Level 1 herbicidal screening at Corteva consists of each analogue being applied as a 1000 ppm solution in dimethylsulfoxide (DMSO) to Giant Foxtail (*Setaria faberi*; monocotyledon, thin leaf) and Sunflower (*Helianthus annuus*; dicotyledon, broad leaf). Growth inhibition was visually measured by expert plant biologists against control species based on the appearance of general health. The herbicidal data is summarized in Table 5.1, where no inhibition was observed against either the monocot or dicot test species in the 7-membered (5.2, 5.5-5.10) or 8-membered ring analogues (5.15-5.19). While the use of *Helianthus annuus* as a representative dicotyledon was part of the standard panel, in the case of the Heliannuols this is also their natural source and thus no inhibitory activity would be predicted or desired. To gain better understanding of the activity against alternative dicots, each sample is being subjected to Level 2 testing against six additional dicot species which is underway at the time of writing this thesis.

5.4ii: Fungicidal Activity

Level 1 fungicidal screening consisted of each analogue added as a 5 ppm solution in DMSO to a dish containing invasive strains of wheat leaf blotch (*Septoria tritici*) and corn smut (*Ustilago maydis*), common crop fungi. As the name indicates, wheat leaf blotch is among the most frequently occurring leaf blotch disease of wheat plants which causes browning and death of leaves.²⁴ Corn smut is a fungus which forms galls on all above-ground portions of corn species and is interestingly ingested as a delicacy in parts of Mexico.²⁵

Analogue	Control (%)	
	Wheat Leaf Blotch	Corn Smut
5.2	10	40
5.5	0	30
5.6	0	40
5.7	0	40
5.8	0	40
5.9	10	20
5.10	10	40
5.15	0	30
5.16	20	40
5.17	0	0
5.18	0	40
5.19	0	20

Table 5.2. Fungicidal activity data for 7- and 8-membered analogues

Inhibition was measured by spore death and growth inhibition in a controlled growth medium. It is reported by Corteva that significant amounts of error are present in this screen as quantification is challenging. Therefore, a successful inhibition would be considered that above 50% control in either species; any values below 50% can be considered “within error” of zero inhibition and can be disregarded. As can be seen in Table 5.2, no sample of either 7- or 8-membered ring analogues demonstrated more than 50% inhibition and each sample was deemed “within error” of zero inhibition. At this time, no analogues were identified as potential fungicidal from the Level 1 screening and none have been advanced to Level 2 evaluation.

5.4iii: Insecticidal Activity

Each 7-membered (**5.2, 5.5-5.10**) and 8-membered analogue (**5.15-5.19**) was screened against five common invasive insect species: Mosquito (4000 ppm solution in DMSO), Beet Armyworm (4000 ppm solution in DMSO), Green Peach Aphid (20 ppm solution in DMSO), Corn Rootworm (3.6 µg/well), Brown Stink Bug (12 µg/cm²). Quantification of control was determined by death count of insects per well plate relative to the start of the experiment; successful inhibition warranting advancement to Level 2 testing was considered >50% control. The results are summarized in Table 5.3.

Analogue	Control (%)				
	Mosquito	Beet Armyworm	Green Peach Aphid	Corn Rootworm	Brown Stink Bug
5.2	0	0	100	0	0
5.5	0	0	0	0	0
5.6	0	0	0	0	0
5.7	0	0	100	0	0
5.8	0	0	0	0	0
5.9	0	0	0	0	0
5.10	0	0	0	0	0
5.15	0	0	33	0	0
5.16	0	100	0	0	0
5.17	0	0	0	0	0
5.18	0	0	0	0	0
5.19	0	0	0	0	0

Table 5.3. Insecticidal activity data for 7- and 8-membered analogues

Seven-membered analogues Heliannuol D (**5.2**) and the C11 ethyl analogue **5.7** demonstrated excellent activity against Green Peach Aphid with 100% control of pesticidal activity with selectivity against only this species. 8-membered analogue Heliannuol A (**5.15**) demonstrated slight control (33%) against Green Peach Aphid, and **5.16** displayed complete control against Beet Armyworm with selectivity against only this species. It is worth noting that the similar non-phenolic **5.17** had no effect on the same species which confirms the importance of the phenolic functionality. This data represents the first demonstration of the insecticidal activity of Heliannuol analogues and

these results have prompted the elevation of **5.2**, **5.7** and **5.16** to Level 2 assays where they will undergo screening against a greater array of insect species to gain a better understanding of the mode of action. Level 2 screening is underway at the time of writing this thesis.

5.5: CONCLUSIONS AND FUTURE DIRECTIONS

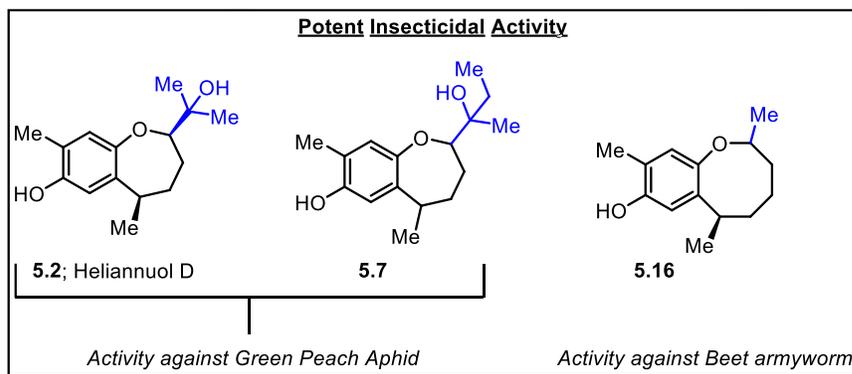


Figure 5.4. Promising analogues entering Level 2 insecticidal screening

Various structural analogues of the 7-membered Heliannuol D and 8-membered Heliannuol A were synthesized either by derivatization of late-stage intermediates or capitalization of byproduct formation. Each analogue was screened for pesticidal activity including herbicidal, fungicidal and insecticidal which revealed three promising analogues with potent activity against Green Peach Aphid (**5.2**, **5.7**) and Beet Armyworm (**5.16**; Figure 5.3); this is the first demonstration of Heliannuol analogues as insecticides. As additional analogues are synthesized and more comprehensive herbicidal activity assays are conducted, the three aforementioned analogues will be elevated to Level 2 testing against a greater variety of insect pests. In total, this data will serve to expand the knowledge behind the activity of Heliannuols as pesticides and demonstrate the potential of this unique class of natural product and related analogues as potent insecticides.

Experimental data for this chapter can be found in Appendix E.

5.6: REFERENCES

- (1) Kang, S.; Blair, J.; Geiser, D.; Khang, C.; Park, S.; Gehegan, M.; Luster, D.-D.; Ivors, K.; Kim, S.; Lee, Y.; Lee, Y.; Grunwald, N.; Veeraraghavan, N.; Makalowska, I. Publication : USDA ARS. *Phytopathology* **2006**, *96*, 920–925.
- (2) Bozhinova, K. U.S. Farmland Is Rapidly Decreasing
<https://givingcompass.org/article/u-s-farmland-is-rapidly-decreasing/>.
- (3) *Pesticide Reregistration Status | Pesticides | US EPA*; 2008.
- (4) Putnam, A. R. Allelopathic Chemicals. *Chem. Eng. News* **1983**, *61* (14), 34–45.
<https://doi.org/10.1021/cen-v061n014.p034>.
- (5) Allelochemicals - an overview | ScienceDirect Topics
<https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/allelochemicals> (accessed Jun 17, 2021).
- (6) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. Diversity-Oriented Synthesis as a Tool for the Discovery of Novel Biologically Active Small Molecules. *Nature Communications*. 2010. <https://doi.org/10.1038/ncomms1081>.
- (7) Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. Potential Allelopathic Guaianolides from Cultivar Sunflower Leaves, Var. SH-222. *Phytochemistry* **1993**, *34* (3), 669–674. [https://doi.org/10.1016/0031-9422\(93\)85337-Q](https://doi.org/10.1016/0031-9422(93)85337-Q).
- (8) Macías, F. A.; Molinillo, J. M. G.; Varela, R. M.; Torres, A.; Fronczek, F. R. Structural Elucidation and Chemistry of a Novel Family of Bioactive Sesquiterpenes: Heliannuols. *J. Org. Chem.* **1994**, *59* (26), 8261–8266.
<https://doi.org/10.1021/jo00105a052>.
- (9) Osaka, M.; Kanematsu, M.; Yoshida, M.; Shishido, K. An Efficient Total

- Synthesis of (+)-Heliannuol D. *Tetrahedron Asymmetry* **2010**, *21* (19), 2319–2320.
<https://doi.org/10.1016/j.tetasy.2010.08.018>.
- (10) Sabui, S. K.; Venkateswaran, R. V. Synthesis of Heliannuol D, an Allelochemical from *Helianthus Annus*. *Tetrahedron Lett.* **2004**, *45* (5), 983–985.
<https://doi.org/10.1016/j.tetlet.2003.11.098>.
- (11) Kamei, T.; Shindo, M.; Shishido, K. First Enantioselective Total Synthesis of (-)-Heliannuol C. *Tetrahedron Lett.* **2003**, *44* (46), 8505–8507.
<https://doi.org/10.1016/j.tetlet.2003.09.086>.
- (12) Biswas, B.; Sen, P. K.; Venkateswaran, R. V. Bargellini Condensation of Coumarins. Expeditious Route to o-Carboxyvinylphenoxyisobutyric Acids and Application to the Synthesis of Sesquiterpenes Helianane, Heliannuol A and Heliannuol C. *Tetrahedron* **2007**, *63* (48), 12026–12036.
<https://doi.org/10.1016/j.tet.2007.09.006>.
- (13) Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. Enantioselective Total Synthesis of Heliannuols D and A. *J. Chem. Soc. Perkin Trans. 1* **2000**, No. 12, 1807–1808. <https://doi.org/10.1039/b003553j>.
- (14) Grimm, E. L.; Levac, S.; Trimble, L. A. Total Synthesis of (±)-Heliannuol A. *Tetrahedron Lett.* **1994**, *35*, 6847–6850.
- (15) Vyvyan, J. R.; Looper, R. E. Total Synthesis of (±)-Heliannuol D, an Allelochemical from *Helianthus Annus*. *Tetrahedron Lett.* **2000**, *41*, 1151–1154.
- (16) Chen, K.; Li, Y.; Du, Z.; Tao, Z. Total Syntheses of Heliannuols: An Overview. *Synth. Commun.* **2015**, *45* (6), 663–691.
<https://doi.org/10.1080/00397911.2014.979948>.

- (17) Vyvyan, J. R.; Oaksmith, J. M.; Parks, B. W.; Peterson, E. M. Total Synthesis of (\pm)-Heliannuol C and E via Aromatic Claisen Rearrangement. *Tetrahedron Lett.* **2005**, *46* (14), 2457–2460. <https://doi.org/10.1016/j.tetlet.2005.02.053>.
- (18) Tuhina, K.; Bhowmik, D. R.; Venkateswaran, R. V. Formal Syntheses of Heliannuols A and D, Allelochemicals from Helianthus Annus. *Chem. Commun.* **2002**, *2* (6), 634–635. <https://doi.org/10.1039/b200103a>.
- (19) Galindo, J.; Molinillo, J.; Macías, F.; Chinchilla, D. Heliannanes - a Structure-Activity Relationship (SAR) Study. *Allelopathy* **2003**, No. May 2014, 103–124. <https://doi.org/10.1201/9780203492789.ch5>.
- (20) Yao, M.; Zhang, J.; Yang, S.; Liu, L. E.; Xiong, H. Acetic Acid Promoted Direct Iodination of Terminal Alkynes with N -Iodosuccinimide: Efficient Preparation of 1-Iodoalkynes. *Synlett* **2020**, *31* (11), 1102–1106. <https://doi.org/10.1055/s-0040-1708002>.
- (21) Yuan, C.; Liang, Y.; Hernandez, T.; Berriochoa, A.; Houk, K. N.; Siegel, D. Metal-Free Oxidation of Aromatic Carbon-Hydrogen Bonds through a Reverse-Rebound Mechanism. *Nature* **2013**, *499* (7457), 192–196. <https://doi.org/10.1038/nature12284>.
- (22) Yuan, C.; Eliassen, A. M.; Camelio, A. M.; Siegel, D. Preparation of Phenols by Phthaloyl Peroxide-Mediated Oxidation of Arenes. *Nat. Protoc.* **2014**, *9* (11), 2624–2629. <https://doi.org/10.1038/nprot.2014.175>.
- (23) Xu, H.; Wolf, C. Efficient Copper-Catalyzed Coupling of Aryl Chlorides, Bromides and Iodides with Aqueous Ammonia. *Chem. Commun.* **2009**, No. 21, 3035–3037. <https://doi.org/10.1039/b904188e>.

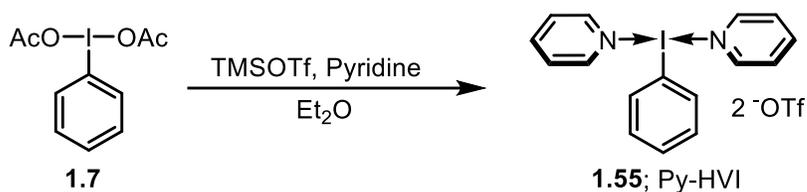
- (24) Brennan, C. J.; Benbow, H. R.; Mullins, E.; Doohan, F. M. A Review of the Known Unknowns in the Early Stages of Septoria Tritici Blotch Disease of Wheat. *Plant Pathology*. Blackwell Publishing Ltd October 1, 2019, pp 1427–1438. <https://doi.org/10.1111/ppa.13077>.
- (25) Pataky, J. K.; Snetselaar, K. M. Common Smut of Corn. *Plant Heal. Instr.* **2006**. <https://doi.org/10.1094/phi-i-2006-0927-01>.

APPENDIX A: (BIS)CATIONIC HYPERVALENT IODINE REAGENTS

A1: PROCEDURE A

This procedure is generally applied to the synthesis of N-HVI reagents with heterocyclic ligands that are (1) non-sterically hindered (2) electron neutral or (3) electron-rich.

Py-HVI (1.55)¹



A single neck (24/40) round-bottomed flask containing an egg-shaped Teflon-coated stir bar (12.5mm x 25mm) (Note 2) is evacuated (Note 3) and flame-dried (Note 4). After cooling to room temperature, the flask is then backfilled with argon and charged with diacetoxyiodobenzene ($\text{PhI}(\text{OAc})_2$; **1.7**; 2.00 g, 6.21 mmol, 1.0 equiv.) (Note 5), and fitted with a rubber septum. Diethyl ether (62 mL) (Note 6) was then added via syringe to generate a white, cloudy solution (Figure A1a). Stirring is initiated (Note 7), and, at room temperature, trimethylsilyl trifluoromethanesulfonate (2.25 mL, 12.4 mmol, 2.0 equiv.) (Note 8) is then added via syringe over a period of 10 seconds. The resulting mauve-colored, slightly cloudy mixture is stirred for 10 minutes, over which time the solution becomes homogenous and more yellow in appearance (Figure A1b). Pyridine (1.0 mL, 12.42 mmol, 2.0 equiv.) (Note 9) is added via syringe over a period of 20 seconds. Immediately upon addition of pyridine, the desired product precipitates as an off-white

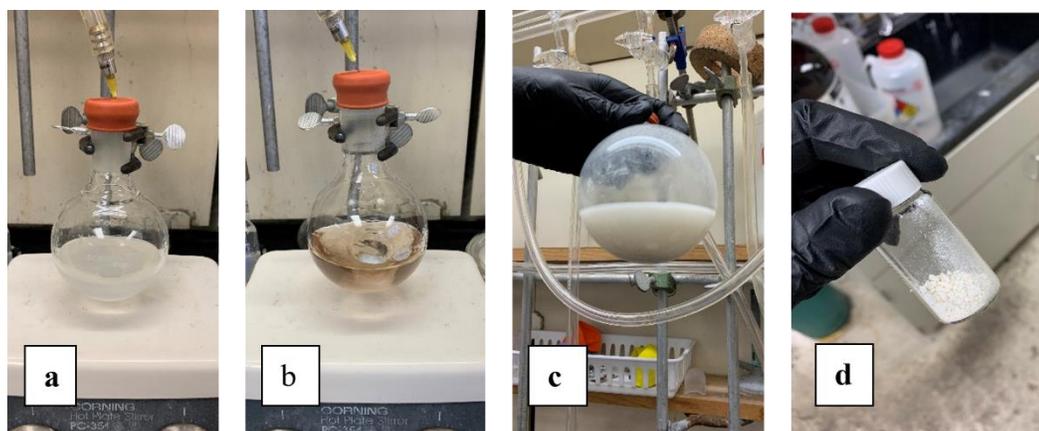
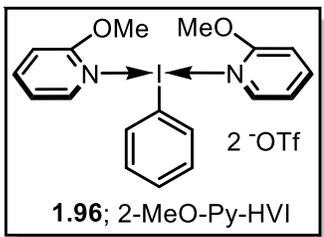


Figure A1. Stages of synthesis of *N*-HVI

solid along with a brown residue. Stirring is continued for 15 minutes, until any precipitate or residue that is stuck to the side of the flask is liberated (Figure A1c) (Note 10). The contents of the flask are then poured into a Buchner funnel with filter paper (Note 11) and the solids collected via vacuum filtration (Note 17). The flask is rinsed with 25 mL of diethyl ether to remove any residual solids (Note 6) and these are collected on the filter. The solids are washed with 35 mL of additional diethyl ether, and the product is quickly transferred to a pre-weighed, flame-dried, single-neck (24/40) 100 mL round bottom flask for drying. The flask is evacuated and left under constant vacuum for one hour (Note 3; Note 18), then backfilled with argon to reveal the product as a free-flowing, off-white powder. The product can be transferred to a flame-dried product vial (20 mL) for long term storage in a desiccator (Figure A1d) (Note 12). 3.71 g, 91%. **¹H-NMR** (500 MHz, 1:20 TFA:Chloroform-*d*) δ 8.85 (t, $J = 6.7, 1.6$ Hz, 4H), 8.62 (t, $J = 7.9, 1.6$ Hz, 2H), 8.24 – 8.21 (m, 2H), 8.09 (t, $J = 8.1, 6.4, 1.5$ Hz, 4H), 7.77 (t, 1H), 7.64 (t, 2H). **¹³C-NMR** (126 MHz, 1:20 TFA:Chloroform-*d*) δ 161.5 (q, TFA), 148.1, 141.8, 135.8, 134.6, 132.6, 128.2, 122.9, 120.9, 118.4, 114.6 (q, TFA). **IR (ATR)**: 3084, 2360, 1605, 1242, 1155, 1025, 753, 681, 630. **Elemental Analysis**: calc'd; C: 32.74, H: 2.29, N: 4.24, Found; C: 31.95, H: 2.38, N: 4.06. Due to inherent instability, melting point was not determined.

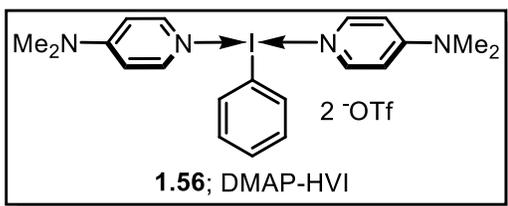
2-MeO-Py-HVI (1.96)



A single neck (24/40) round-bottomed flask containing an egg-shaped Teflon-coated stir bar (12.5mm x 25mm) (Note 2) is evacuated (Note 3) and flame-dried (Note 4). After cooling to room temperature, the flask is then backfilled with argon and charged with diacetoxyiodobenzene ($\text{PhI}(\text{OAc})_2$; **1.7**; 2.00 g, 6.21 mmol, 1.0 equiv.) (Note 5), and fitted with a rubber septum. Diethyl ether (62 mL) (Note 6) was then added via syringe to generate a white, cloudy solution (Figure A1a). Stirring is initiated (Note 7), and, at room temperature, trimethylsilyl trifluoromethanesulfonate (2.25 mL, 12.4 mmol, 2.0 equiv.) (Note 8) is then added via syringe over a period of 10 seconds. The resulting mauve-colored, slightly cloudy mixture is stirred for 10 minutes, over which time the solution becomes homogenous and more yellow in appearance (Figure A1b). 2-methoxypyridine (1.31 mL, 12.42 mmol, 2.0 equiv.) (Note 9) is added via syringe over a period of 20 seconds. Immediately upon addition of 2-methoxypyridine, the desired product precipitates as an off-white solid along with a brown residue. Stirring is continued for 15 minutes, until any precipitate or residue that is stuck to the side of the flask is liberated (Figure A1c) (Note 10). The contents of the flask are then poured into a Buchner funnel with filter paper (Note 11) and the solids collected via vacuum filtration (Note 17). The flask is rinsed with 25 mL of diethyl ether to remove any residual solids (Note 6) and these are collected on the filter. The solids are washed with 35 mL of additional diethyl ether, and the product is quickly transferred to a pre-weighed, flame-dried, single-neck (24/40) 100 mL round bottom flask for drying. The flask is evacuated and left under constant vacuum for one hour (Note 3; Note 18), then backfilled with argon to reveal the product as a free-flowing, off-white powder. The product was then transferred to a flame-dried product vial (20 mL) for long term storage in a desiccator (Figure A1d) (Note 12). **Yield:** 3.85 g, 86%. $^1\text{H NMR}$

(500 MHz, 1:20 TFA:Chloroform-*d*) δ 8.44 (t, $J = 9.1, 7.4, 1.9$ Hz, 2H), 8.30 (t, $J = 6.5, 4.6, 3.2$ Hz, 2H), 8.22 (d, 2H), 7.76 (t, 1H), 7.64 (t, 2H), 7.49 (t, $J = 6.8$ Hz, 2H), 7.39 (d, $J = 8.9$ Hz, 2H), 4.23 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.5 (q, TFA), 149.8, 138.8, 137.6, 135.5, 134.2, 132.4, 130.4, 123.3, 122.8, 120.8, 118.9, 118.3, 114.6 (q, TFA), 111.0, 58.6. **IR (ATR):** 3102, 3036, 2965, 2540, 1637, 1491, 1429, 1263, 1155, 1022, 199, 632. **Elemental Analysis:** calc'd; C: 33.35, H: 2.66, N: 3.89, Found; C: 33.74, H: 2.70, N: 3.85. Due to inherent instability, melting point was not determined.

DMAP-HVI (**1.56**)^{1,2}



A single neck (24/40) round-bottomed flask containing an egg-shaped Teflon-coated stir bar (12.5mm x 25mm) (Note 2) is evacuated (Note 3) and flame-dried (Note 4). After

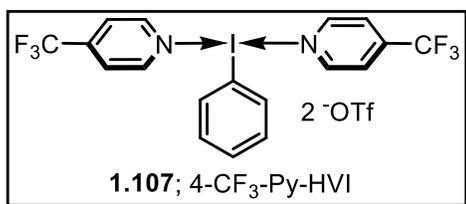
cooling to room temperature, the flask is then backfilled with argon and charged with diacetoxyiodobenzene ($\text{PhI}(\text{OAc})_2$; **1.7**; 2.00 g, 6.21 mmol, 1.0 equiv.) (Note 5), and fitted with a rubber septum. Dichloromethane (62 mL) (Note 6) was then added via syringe to generate a white, cloudy solution (Figure A1a). Stirring is initiated (Note 7), and, at room temperature, trimethylsilyl trifluoromethanesulfonate (2.25 mL, 12.4 mmol, 2.0 equiv.) (Note 8) is then added via syringe over a period of 10 seconds. The resulting mauve-colored, slightly cloudy mixture is stirred for 10 minutes, over which time the solution becomes homogenous and more yellow in appearance (Figure A1b). 4-dimethylaminopyridine (DMAP; 1.52 g, 12.42 mmol, 2.0 equiv.) (Note 9) is added via syringe over a period of 20 seconds. Immediately upon addition of DMAP, the desired product precipitates as an off-white solid along with a brown residue. Stirring is continued for 15 minutes, until any precipitate or residue that is stuck to the side of the flask is liberated (Note 10). The contents of the flask are then poured into a Buchner funnel with filter paper (Note 11) and the solids collected via vacuum filtration (Note 17).

The flask is rinsed with 25 mL of dichloromethane to remove any residual solids (Note 6) and these are collected on the filter. The solids are washed with 35 mL of additional dichloromethane, and the product is quickly transferred to a pre-weighed, flame-dried, single-neck (24/40) 100 mL round bottom flask for drying. The flask is evacuated and left under constant vacuum for one hour (Note 3; Note 18), then backfilled with argon to reveal the product as a free-flowing, yellow powder. The product was then transferred to a flame-dried product vial (20 mL) for long term storage in a desiccator (Note 12). **Yield:** 3.94g, 85%. **¹H NMR** (500 MHz, 1:20 TFA:Chloroform-*d*) δ 8.22 (d, *J* = 8.5, 1.1 Hz, 2H), 8.03 (t, *J* = 1.8 Hz, 4H), 7.77 (t, 1H), 7.64 (t, 2H), 6.78 (d, *J* = 6.6, 1.3 Hz, 4H), 3.26 (s, 12H). **¹³C NMR** (126 MHz, CDCl₃) δ 161.5 (q, TFA), 157.82, 139.08, 135.55, 134.29, 132.42, 123.33, 122.84, 120.81, 118.29, 115.77, 114.6 (q, TFA), 107.13, 40.20. **IR (ATR):** 3123, 3068, 2927, 1615, 1559, 1399, 1248, 1154, 1006, 820, 633. **Elemental Analysis:** calc'd; C: 35.40, H: 3.38, N: 7.51, Found; C: 35.49, H: 3.31, N: 7.41. Due to inherent instability, melting point was not determined.

A2: PROCEDURE B

This procedure is generally applied to the synthesis of N-HVI reagents with heterocyclic ligands that are (1) sterically hindered and (2) electron deficient.

4-CF₃-Py-HVI (1.107)



A single neck (24/40) round-bottomed flask containing an egg-shaped Teflon-coated stir bar (12.5mm x 25mm) (Note 2) is evacuated (Note 3) and flame-dried (Note 4). After cooling to room

temperature, the flask is then backfilled with argon and charged with diacetoxyiodobenzene (PhI(OAc)₂; **1.7**; 2.00 g, 6.21 mmol, 1 equiv.) (Note 5), and fitted

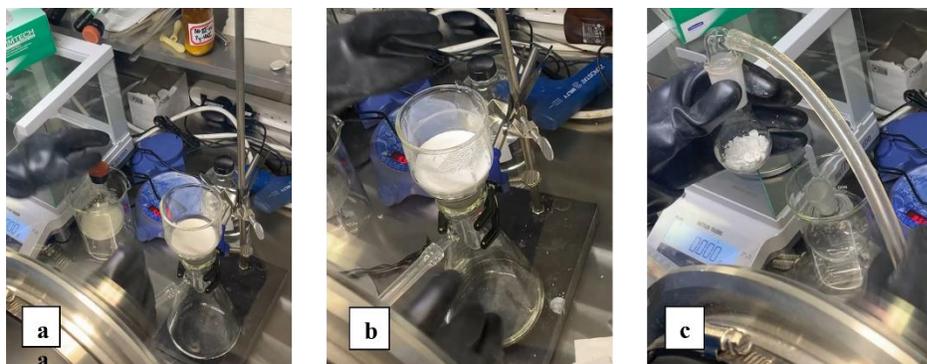
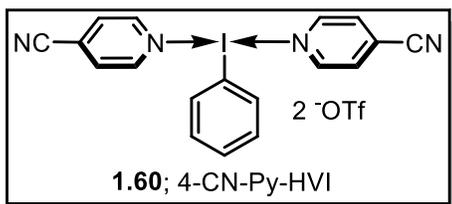


Figure A2. Glovebox filtration of sensitive *N*-HVIs

with a rubber septum. Diethyl ether (62 mL, Note 6) is then added via syringe to generate a white, cloudy solution (Figure A1a). Stirring is initiated (Note 7), then, at room temperature, trimethylsilyl trifluoromethanesulfonate (2.25 mL, 12.4 mmol, 2 equiv.) (Note 8) is added via syringe over a period of 10 seconds. The resulting mauve colored, slightly cloudy mixture is stirred for 10 minutes, over which time the solution becomes homogenous and yellow in appearance (Figure A1b). 4-(trifluoromethyl)pyridine (1.44 mL, 12.4 mmol, 2 equiv.) (Note 9) is added over a period of 20 seconds. Immediately upon addition of the heterocycle, the off-white product precipitates. Stirring is continued for 15 minutes, until any precipitate or residue that is stuck to the side of the flask is liberated (Figure A1c) (Note 10). The flask is evacuated and purged with dry argon 5 times, and the rubber septum is securely fixed to the neck with a liberal amount of electrical tape. The flask and its contents are then transferred to a glovebox for inert filtration under a nitrogen atmosphere (Figure A2a) (Note 13). Contents of the flask are poured onto a 4-5M glass fritted filter (Note 16) placed on a 250 mL filter flask, and suction is applied via vacuum (Figure A2b) (Note 14). The reaction flask is rinsed with 25 mL of diethyl ether (Note 6) to remove any residual solids and these are collected on the filter. The combined solids are then rinsed with 35 mL additional diethyl ether. Following filtration, the damp product is transferred via spatula to a pre-weighed, single-neck (24/40) 100 mL round bottom flask for drying (Figure A2c) (Note 18). The flask is

evacuated and left under constant vacuum for one hour to reveal the product as a free-flowing, off-white powder. The product can then be transferred to a flame-dried product vial (20 mL) for long term storage in reasonably moisture-free conditions such as a glovebox or desiccator. **Yield:** 4.25 g, 86%. **¹H NMR** (500 MHz, 1:20 TFA:Chloroform-*d*) δ 9.20 (d, *J* = 6.2 Hz, 4H), 8.30 (d, *J* = 6.4 Hz, 4H), 8.20 (d, *J* = 8.4, 1.2 Hz, 2H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.62 (t, *J* = 7.9 Hz, 2H). **¹³C NMR** (126 MHz, 1:20 TFA:Chloroform-*d*) δ 161.98 (q, TFA) 148.84 (q, *J* = 37.1), 144.1, 135.8, 134.6, 132.6, 124.8 (q, *J* = 3.3 Hz), 122.9, 121.9, 120.9, 119.7, 118.3, 114.5 (q, TFA). **IR (ATR):** 3100, 3060, 3032, 1433, 1320, 1250, 1145, 1024, 840, 632. **Elemental Analysis:** calc'd; C: 30.17, H: 1.65, N: 3.52. Found; C: 29.65, H: 1.66, N: 3.21. Due to inherent instability, melting point was not determined.

4-CN-Py-HVI (1.60)³



A single neck (24/40) round-bottomed flask containing an egg-shaped Teflon-coated stir bar (12.5mm x 25mm) (Note 2) is evacuated (Note 3) and flame-dried (Note 4). After cooling to room

temperature, the flask is then backfilled with argon and charged with diacetoxyiodobenzene (PhI(OAc)₂; **1.7**; 2.00 g, 6.21 mmol, 1 equiv.) (Note 5), and fitted with a rubber septum. Dichloromethane (62 mL, Note 6) is then added via syringe to generate a white, cloudy solution (Figure 1a). Stirring is initiated (Note 7), then, at room temperature, trimethylsilyl trifluoromethanesulfonate (2.25 mL, 12.4 mmol, 2 equiv.) (Note 8) is added via syringe over a period of 10 seconds. The resulting mauve colored, slightly cloudy mixture is stirred for 10 minutes, over which time the solution becomes homogenous and yellow in appearance. 4-cyanopyridine (1.29 g, 12.4 mmol, 2 equiv.) (Note 9) is added over a period of 20 seconds. Immediately upon addition of the heterocycle, the off-white product precipitates. Stirring is continued for 15 minutes, until any precipitate or residue that is stuck to the side of the flask is liberated (Figure 2c)

(Note 10). The flask is evacuated and purged with dry argon 5 times, and the rubber septum is securely fixed to the neck with a liberal amount of electrical tape. The flask and its contents are then transferred to a glovebox for inert filtration under a nitrogen atmosphere (Figure A2a) (Note 13). Contents of the flask are poured onto a 4-5M glass fritted filter (Note 16) placed on a 250 mL filter flask, and suction is applied via vacuum (Figure A2b) (Note 14). The reaction flask is rinsed with 25 mL of dichloromethane (Note 6) to remove any residual solids and these are collected on the filter. The combined solids are then rinsed with 35 mL additional dichloromethane. Following filtration, the damp product is transferred via spatula to a pre-weighed, single-neck (24/40) 100 mL round bottom flask for drying (Figure A2c) (Note 18). The flask is evacuated and left under constant vacuum for one hour to reveal the product as a free-flowing, off-white powder. The product can then be transferred to a flame-dried product vial (20 mL) for long term storage in reasonably moisture-free conditions such as a glovebox or desiccator. **Yield:** 3.46g, 71%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 8.88 (td, *J* = 6.6, 1.6 Hz, 4H), 8.60 (tt, *J* = 7.9, 1.5 Hz, 2H), 8.24 – 8.18 (m, 2H), 8.09 (t, *J* = 7.0 Hz, 4H), 7.79 – 7.72 (m, 1H), 7.63 (t, *J* = 7.9 Hz, 2H). **¹³C NMR** (126 MHz, CDCl₃) δ 161.5 (q, TFA), 143.9, 143.3, 137.6, 135.4, 134.0, 132.3, 130.8, 130.7, 130.4, 130.3, 122.9, 115.5, 114.5 (q, TFA), 113.3. **IR (ATR):** 3095, 3047, 3013, 1613, 1427, 1272, 1223, 1159, 1022, 635. **Elemental Analysis:** calc'd; C: 33.82, H: 1.84, N: 7.89, Found; C: 33.68, H: 1.81, N: 7.81. Due to inherent instability, melting point was not determined.

A3: NOTES

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for

analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at <https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical>. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at <https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html>. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with (enter list of chemicals here), as well as the proper procedures for (list any unusual experimental operations here). (Provide additional cautions with regard to exceptional hazards here).

2. The shape of the stir bar is important as a thick slurry forms after the addition of the heterocycle, which can stick to the inner walls of the flask. The shape of the stir bar allows for greater surface contact with the flask and more uniform stirring of the slurry
3. An Edwards RV12 direct-drive pump was used as the vacuum to evacuate the glassware as well as remove residual solvent from products (2-6 mmHg). High vacuum is necessary to swiftly remove excess solvent (See Note 18)
4. To flame dry, the flask (under vacuum via a needle through rubber the septum) is subjected to a torch flame from a benzomatic brand butane torch for around 20 seconds, making sure all surfaces of the glass receive nearly equal heat. The flask is allowed to cool under vacuum, then is backfilled with dry argon (Note 3).
5. Diacetoxyiodobenzene, $\text{PhI}(\text{OAc})_2$, was purchased from Oakwood Chemical (98% purity) and used without further purification

6. Solvents including diethyl ether were purchased from Fisher Scientific (HPLC grade passed through an activated alumina column). Diethyl ether is the preferred solvent for the examples provided herein. However, if the heterocycle used is found to be poorly soluble in diethyl ether, dichloromethane should be substituted as low yields and byproduct formation are observed if the heterocycle is not completely solubilized.
7. The stir plate used was a Corning PC351 and stir rate was around 600 RPM throughout the experiment
8. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was purchased from Oakwood Chemical (99% reagent grade). The reagent was distilled over calcium hydride and stored over activated 3Å molecular sieves (Sigma Aldrich)
9. Pyridine was purchased from Fisher Scientific (>99% ACS grade) and distilled over calcium hydride and stored over activated 3Å molecular sieves. 4-CF₃-pyridine: (99%, Oakwood) was purified and stored in the same fashion.
10. In some cases, the stir bar was unable to reach the solids that were stuck to the walls of the flask. In this case, the flask was removed from the clamp and manually agitated (swirled and lightly shaken) until the walls of the flask were sufficiently cleared of all residue.
11. The Buchner funnel (70mm diameter) was placed in the oven for one hour before use and allowed to cool to room temperature in a desiccator containing calcium sulfate (Drierite) dessicant. Filter paper was purchased from Whitman (qualitative, 70mm diameter).
12. The product should be stored in a cool, dry desiccator to avoid degradation into an undesired μ 2-oxo-species. Degradation from exposure to moisture is accelerated for N-HVIs possessing more sterically hindered or electron-deficient heterocyclic ligands. This degradation is pictured below for the 2-OMe-Py-HI, in which a small sample was placed on a watch glass and degradation was monitored both qualitatively, by color change and by ¹HNMR spectroscopy at 5-minute intervals.

- Partial degradation was observed after just 5 minutes, and complete disappearance of desired product was observed within 10 minutes of exposure to air inside a fume hood. See Chapter 1.6 for further information.
- The glovebox used is a Vacuum Atmospheres NexGen system with a maximum humidity of 0.05% (500 ppm). A glovebox is required to obtain high yields of chemically pure N-HVIs containing more sterically hindered or electron deficient heterocyclic ligands. The presence of trace water is known to cause rapid degradation, and therefore any exposure to atmospheric moisture during filtration or transfer for storage leads to depreciation of yield and reagent quality.
 - The vacuum used for glovebox filtration is a Welch Systems belt drive vacuum pump (8-11 mmHg; see Note 18).
 - Complex glassware was dried by placement in an oven (150 °C) and was cooled in a glass desiccator filled with calcium sulfate (Drierite) dessicant.
 - Due to the fine nature of the powder product, a fritted filter (150 or 250 mL) with small pore size (4-5M) is required to capture all solids.

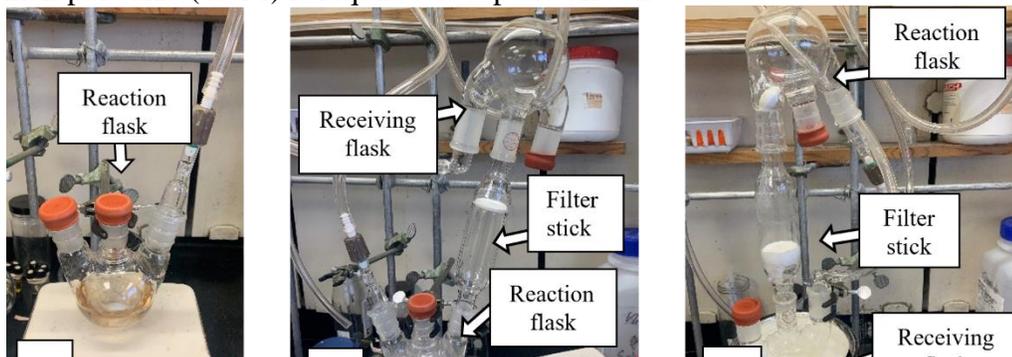


Figure A3. Inert filter stick apparatus

- Filtration of desired product may become problematic if atmospheric moisture levels are especially high. Rapid yellowing of the powder may be visually observed, which indicates degradation. An inert filtration may be carried out to limit exposure to atmospheric moisture without the use of a glovebox. To perform an inert filtration,

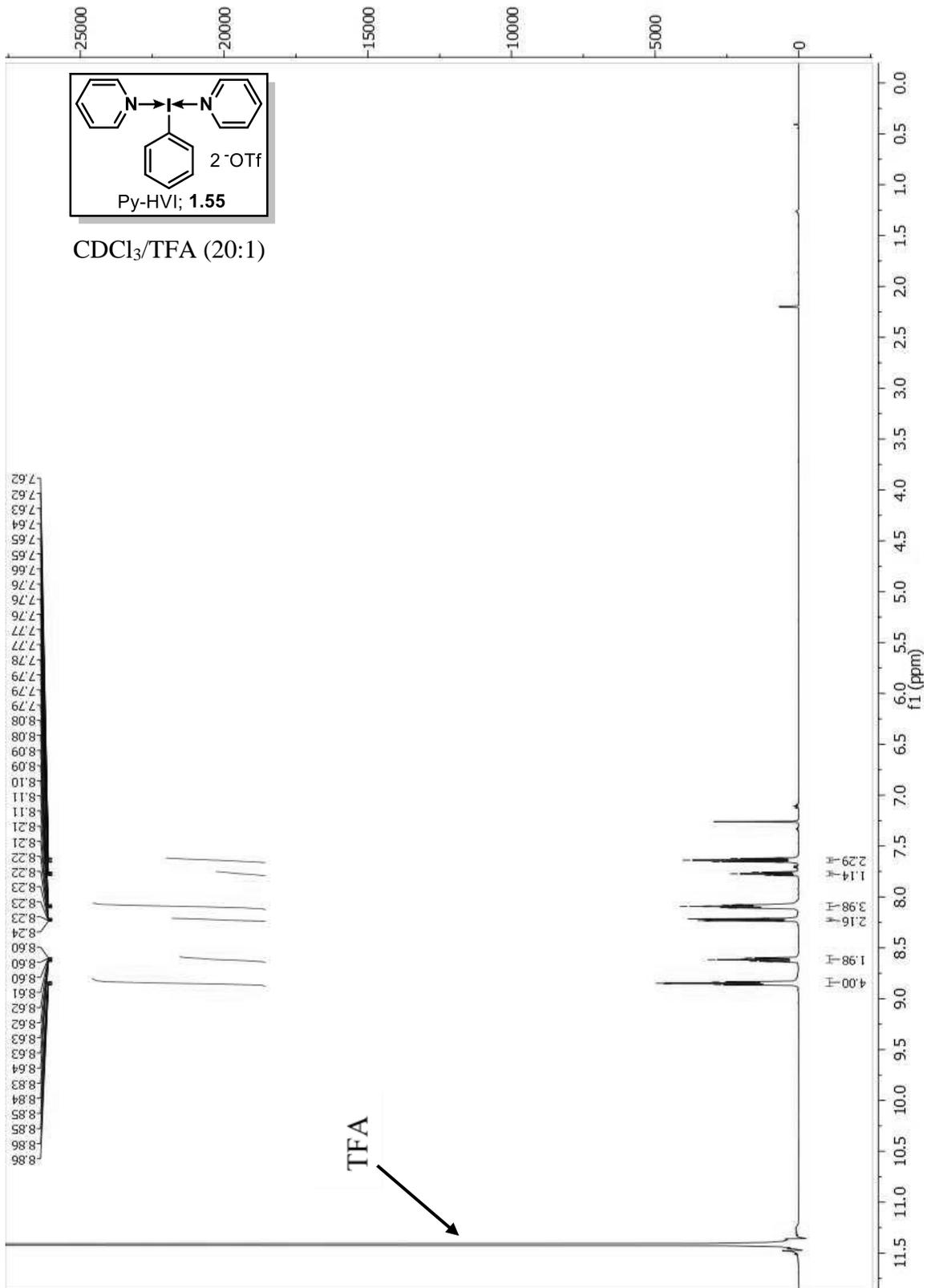
two 250 mL 3-neck (24/40) flasks are utilized. For each flask, the rightmost neck is connected to a glass 24/40 adapter neck, which is connected via vacuum tubing to a Schlenk apparatus. The two remaining necks are stoppered using the proper sized rubber septa (Figure A3a), and the same synthetic procedure (Procedure A or B) is carried out. Upon precipitation of the product, the septum on the leftmost neck of the reaction flask is removed and replaced by a sufficiently dry (Note 15) 24/40 adapter filter stick (Figure A3b). The septum on the central neck of the receiving flask is then replaced with the other, shallow end of the filter stick. The entire apparatus is then flipped, and the argon flow into the reaction flask is increased and a vacuum is applied to the receiving flask via the corresponding glass adapters connected to the Schlenk line (Figure A3c). After the solvent has fully passed through the material into the receiving flask, the vacuum line is closed, and the reaction flask is removed from the top of the filter stick to allow for the addition of rinsing solvent and agitation of the product cake. Between rinses, the flask is replaced, and argon flow is re-established. The vacuum line is then opened, and the solvent allowed to pass through the filter. This process is performed twice (25 mL each), and the product is allowed to dry on the filter for an additional 2 minutes.

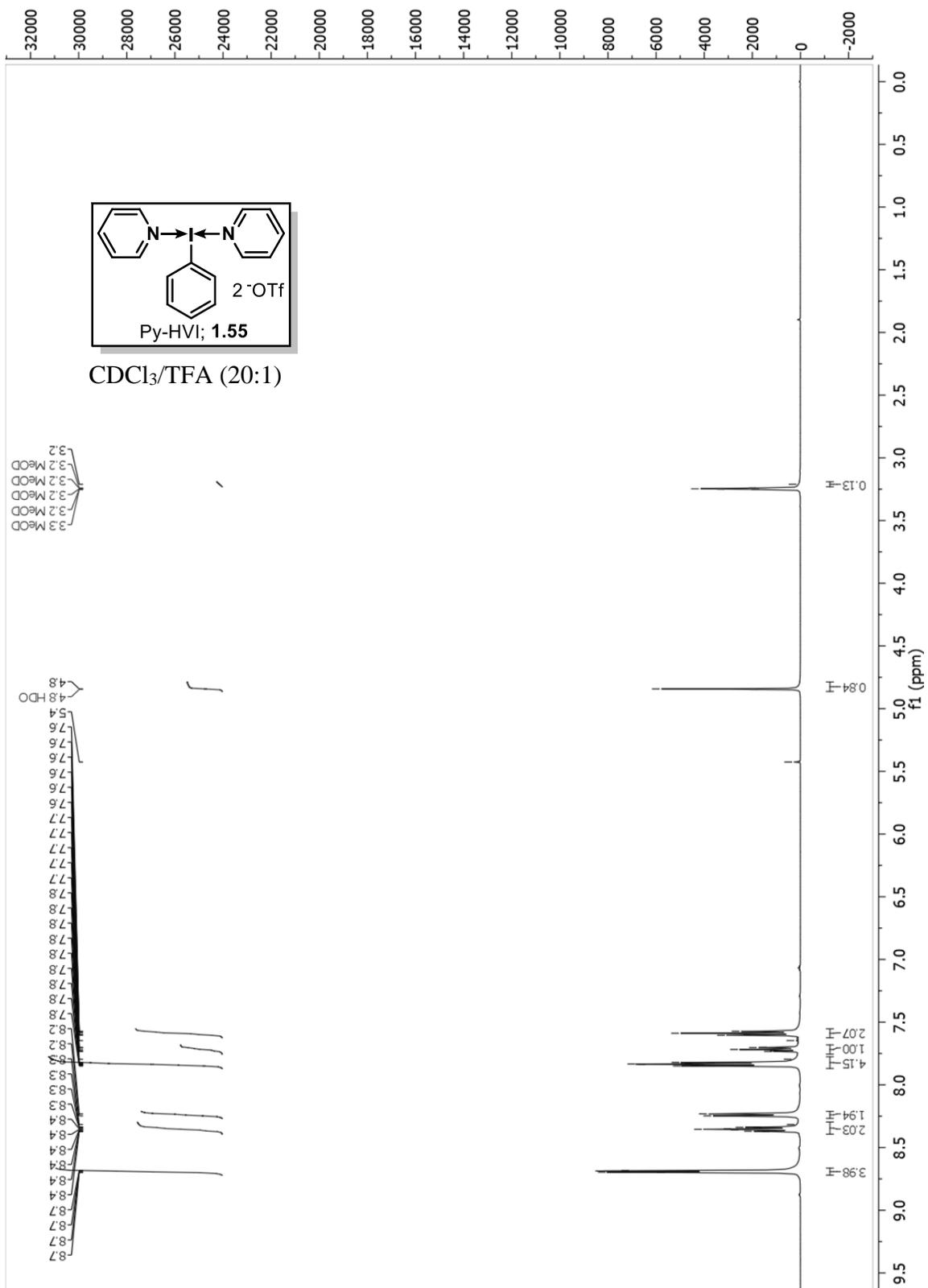
18. Undesired decomposition is accelerated when the product is damp with solvent. To limit decomposition, the product should be scooped from the filter and transferred to a flame-dried round-bottomed flask (24/40) to dry to completeness in vacuo. Delays in this process or incomplete drying will likely result in rapid decomposition upon exposure to atmospheric moisture.

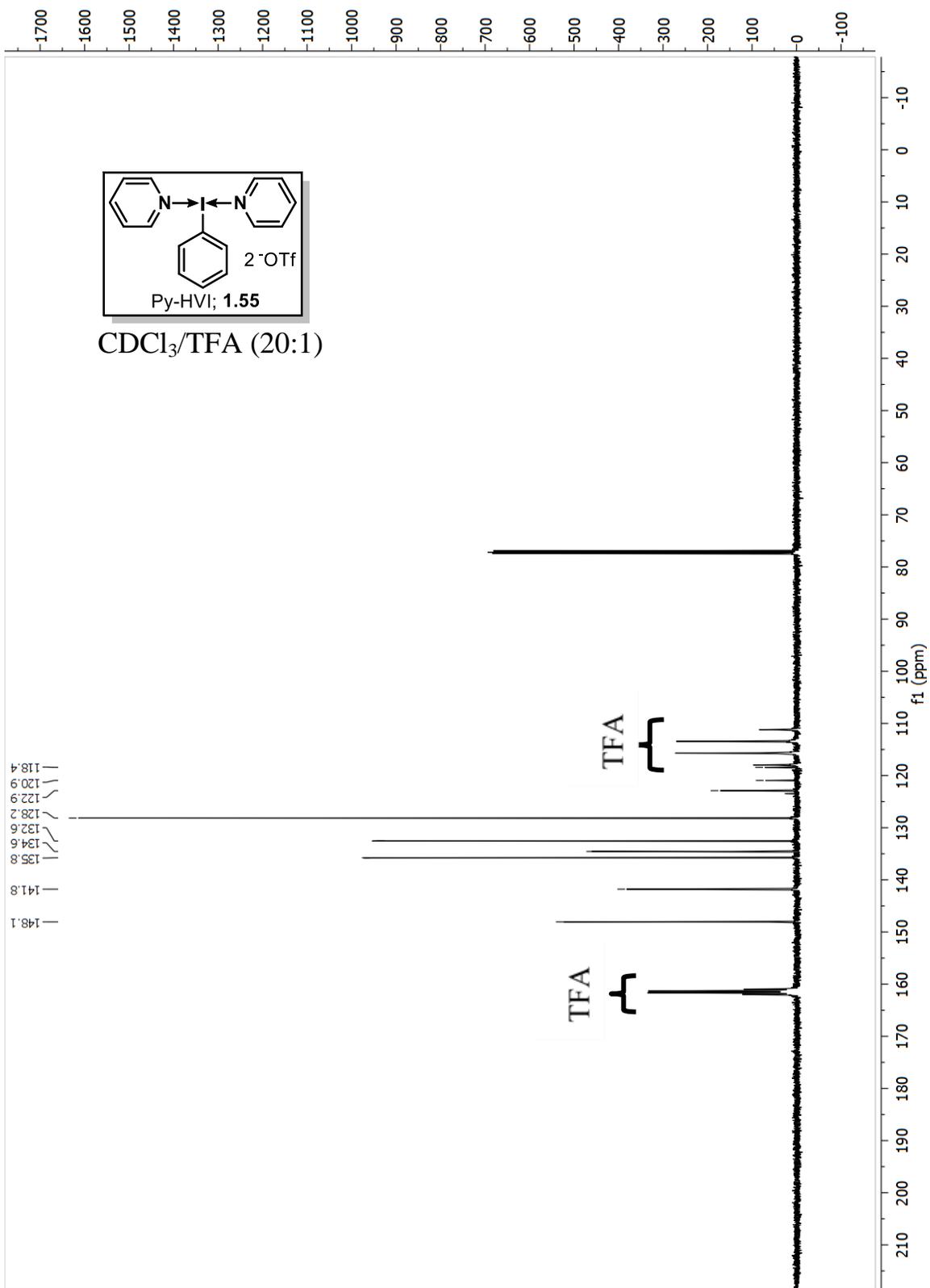
A4: REFERENCES

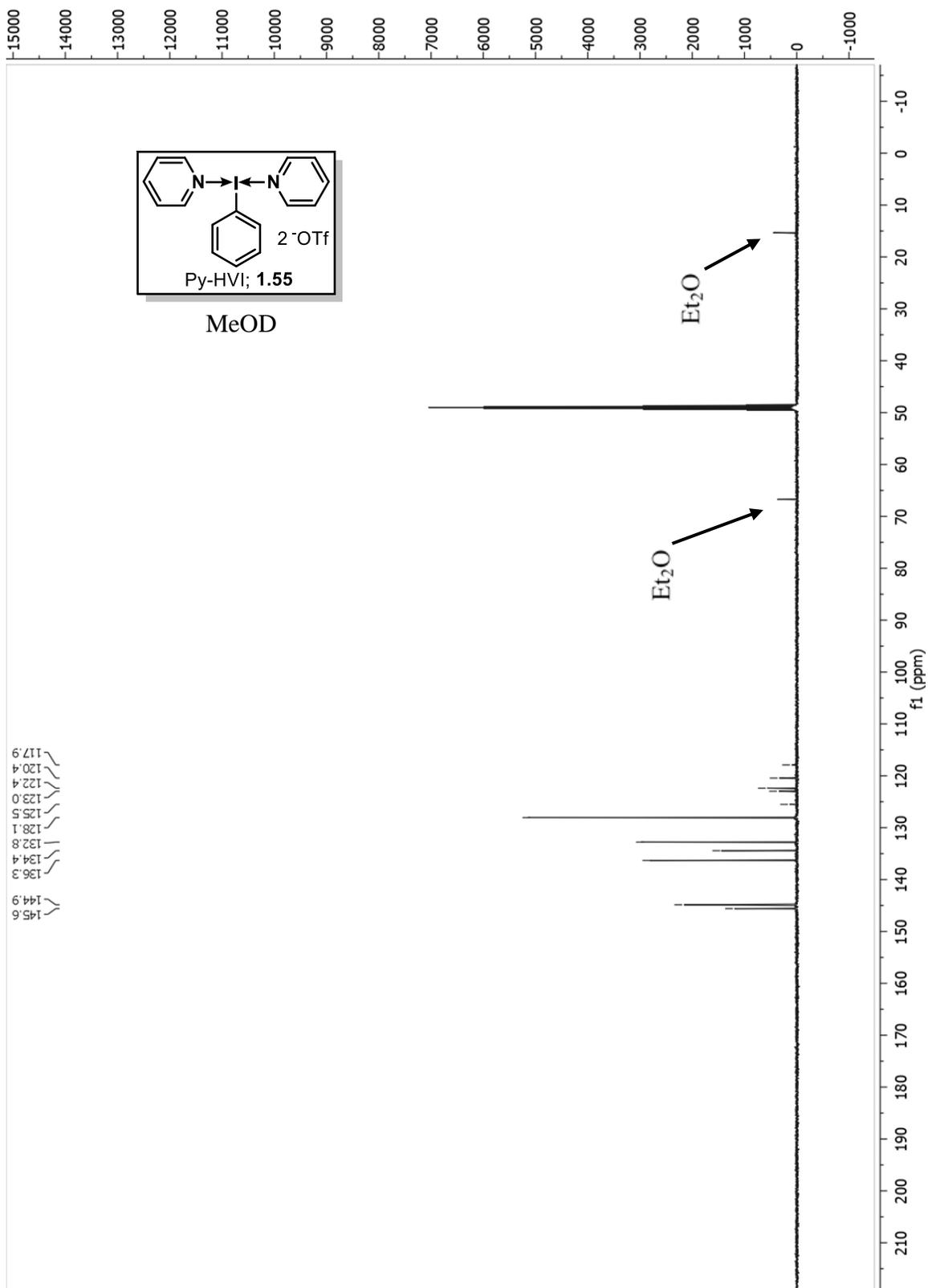
- (1) Weiss, R.; Seubert, J. Electrostatic Activation of Hypervalent Organo-Iodine Compounds: Bis(Onio)-Substituted Aryliodine(III) Salts. *Angew. Chemie Int. Ed. English* **1994**, *33* (8), 891–893. <https://doi.org/10.1002/anie.199408911>.
- (2) Weiss, R.; Seubert, J.; Hampel, F. A-Aryliodonio Diazo Compounds: SN Reactions at the A-C Atom as a Novel Reaction Type for Diazo Compounds. *Angew. Chemie Int. Ed. English* **1994**, *33* (19), 1952–1953. <https://doi.org/10.1002/anie.199419521>.
- (3) Ritter, T.; Lee, E.; Kamlet, A. S.; Powers, D.; Furuya, T. HIGH-VALENT PALLADIUM FLUORIDE COMPLEXES AND USES THEREOF. WO2011US48451, February 23, 2012.

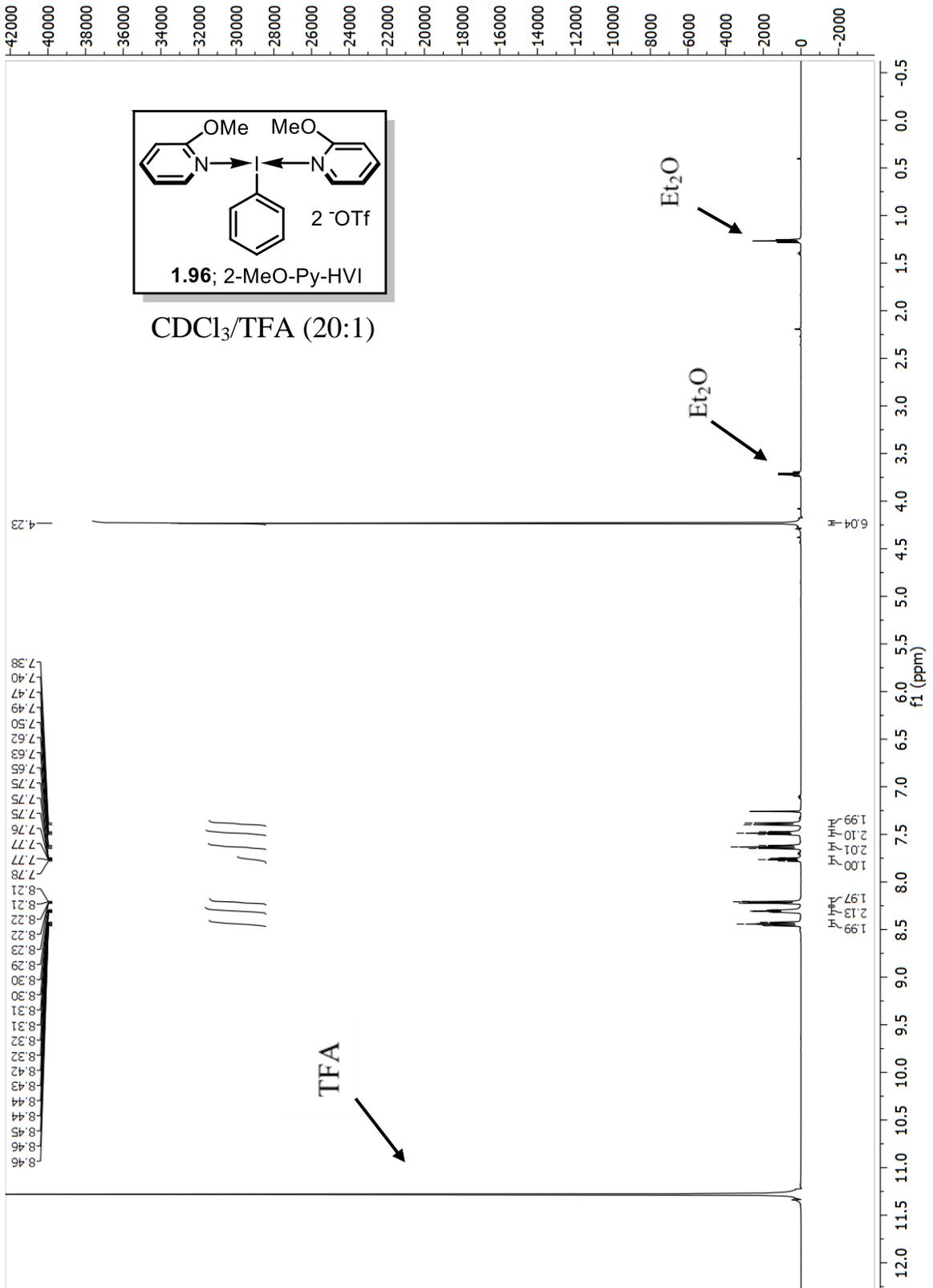
A5: SPECTRA

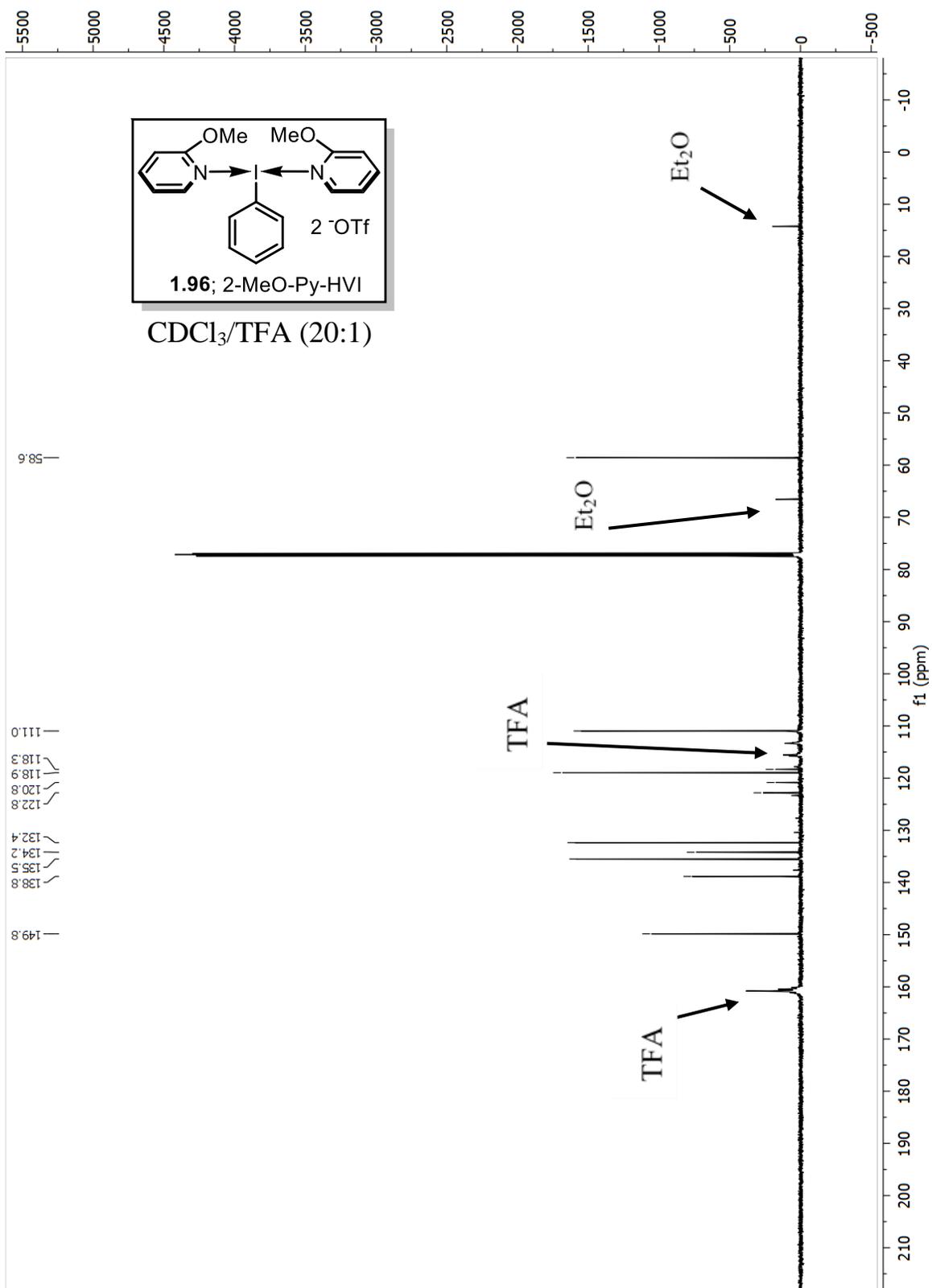


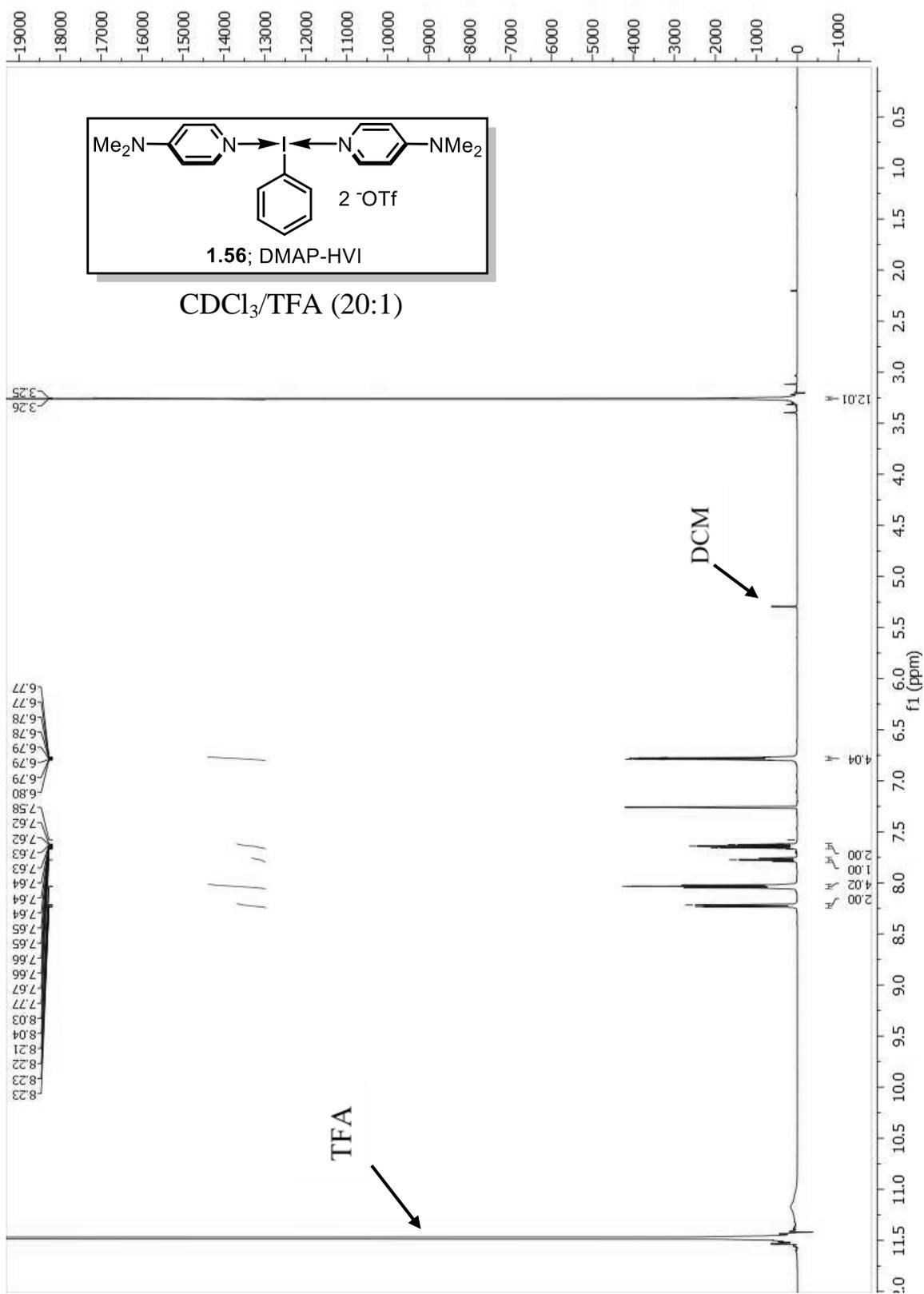


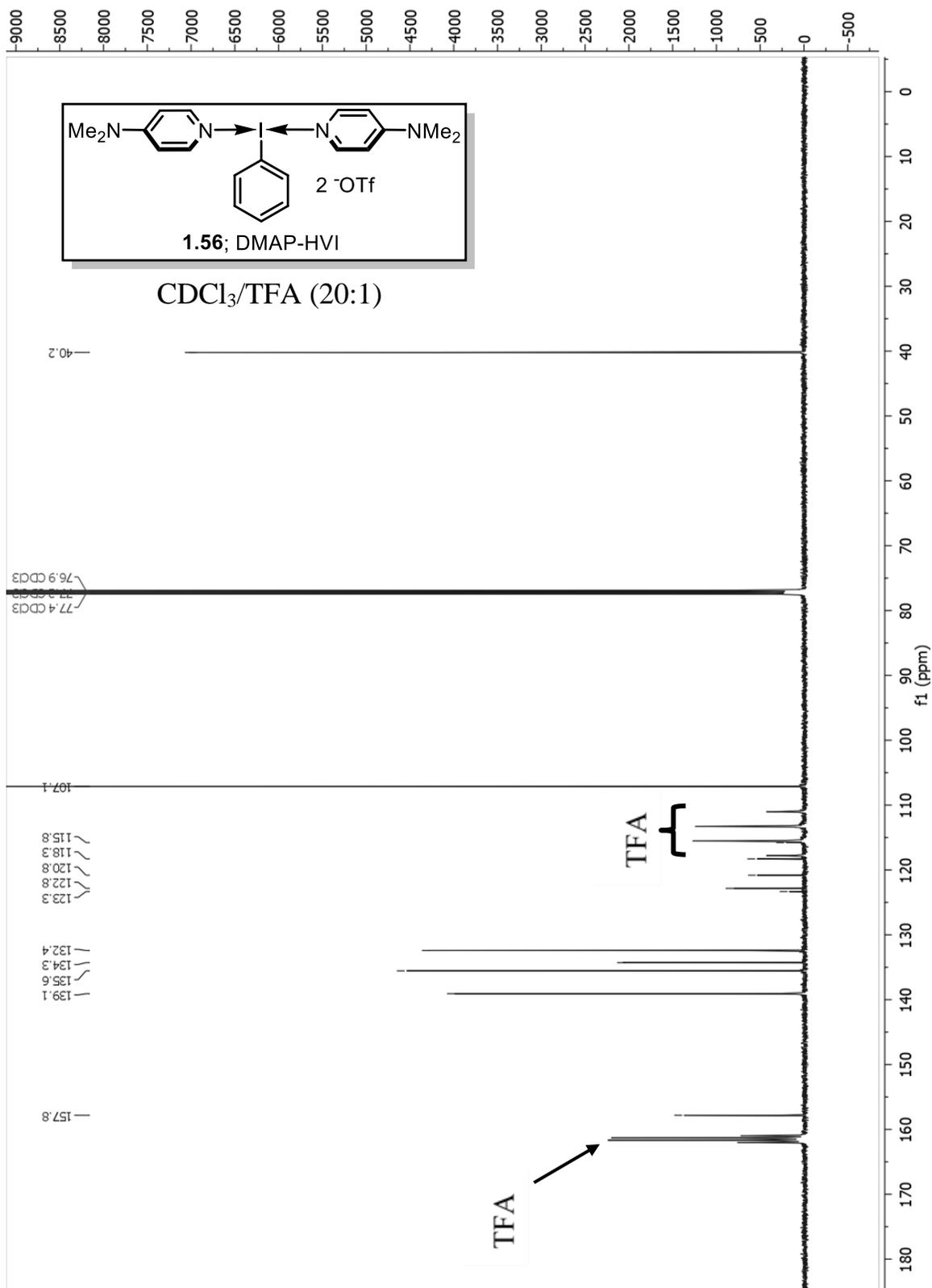


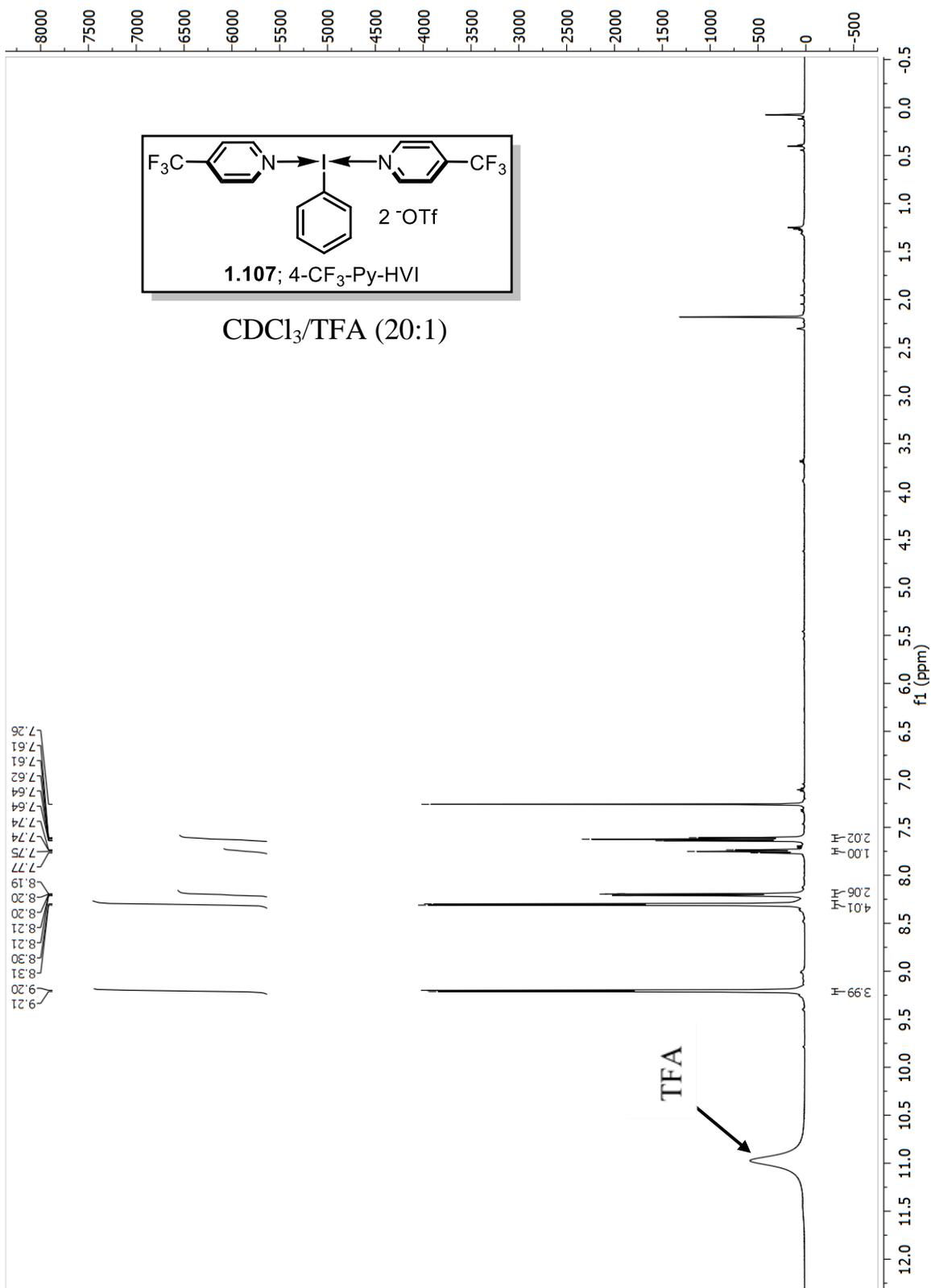


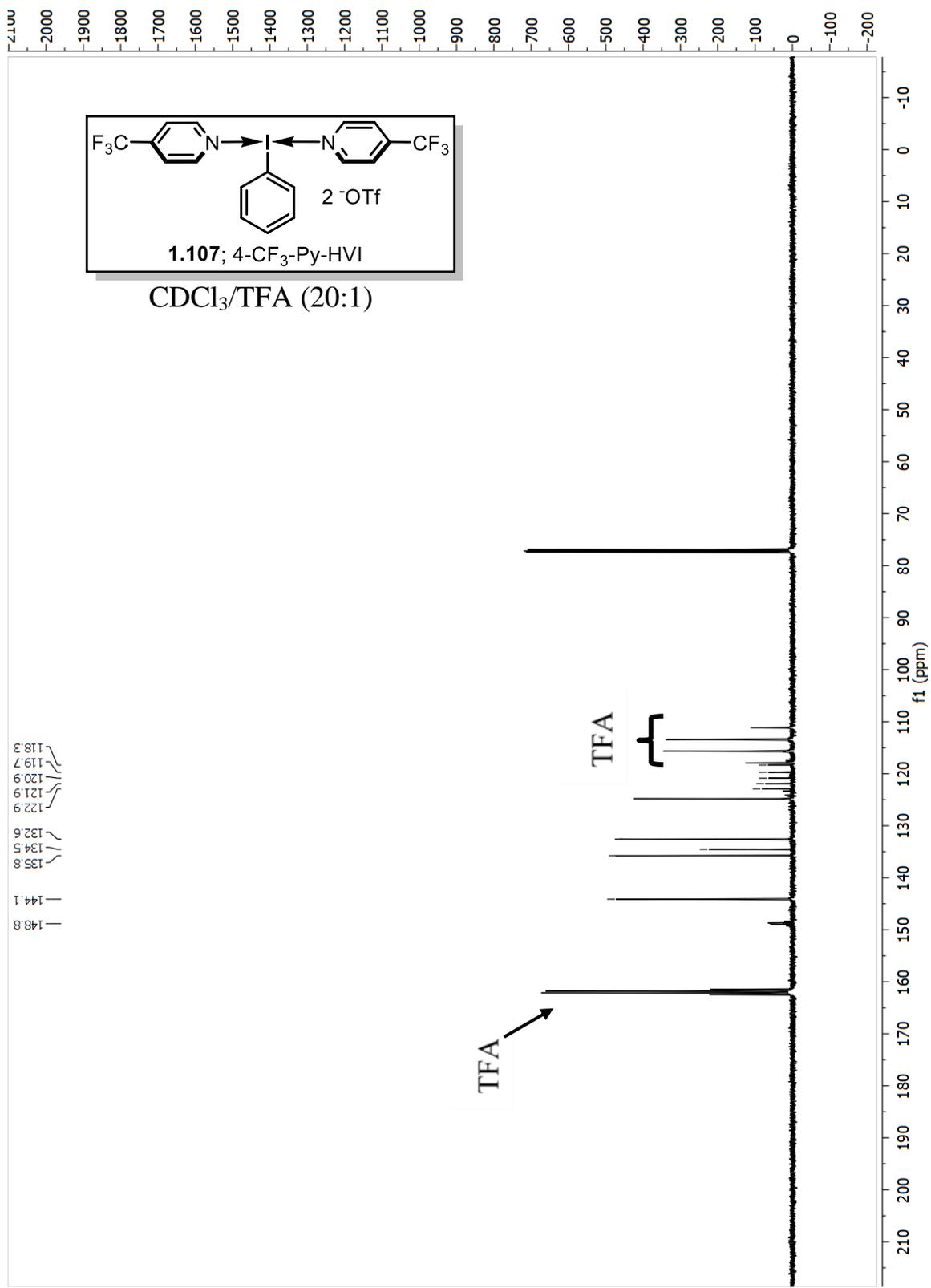


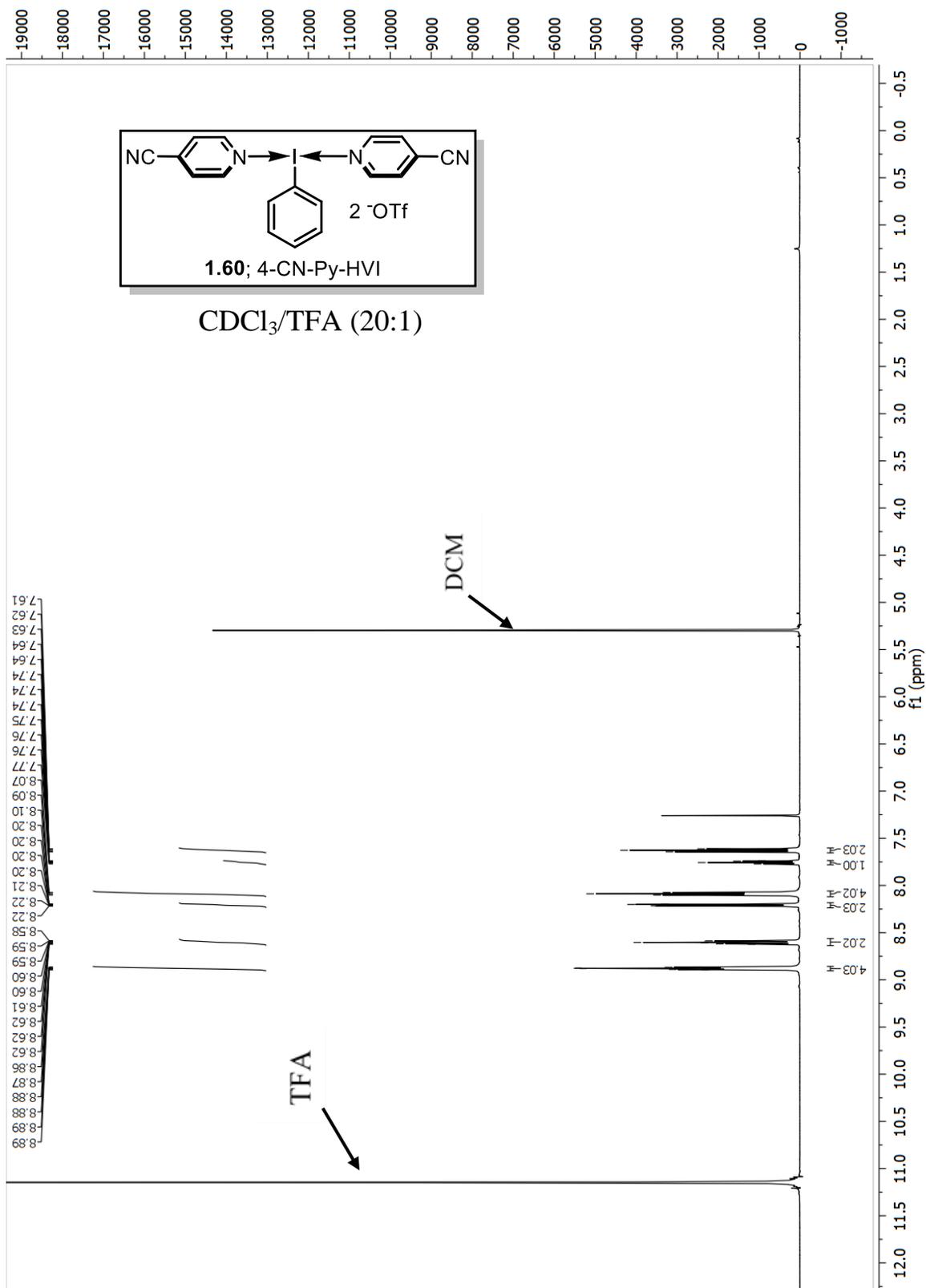


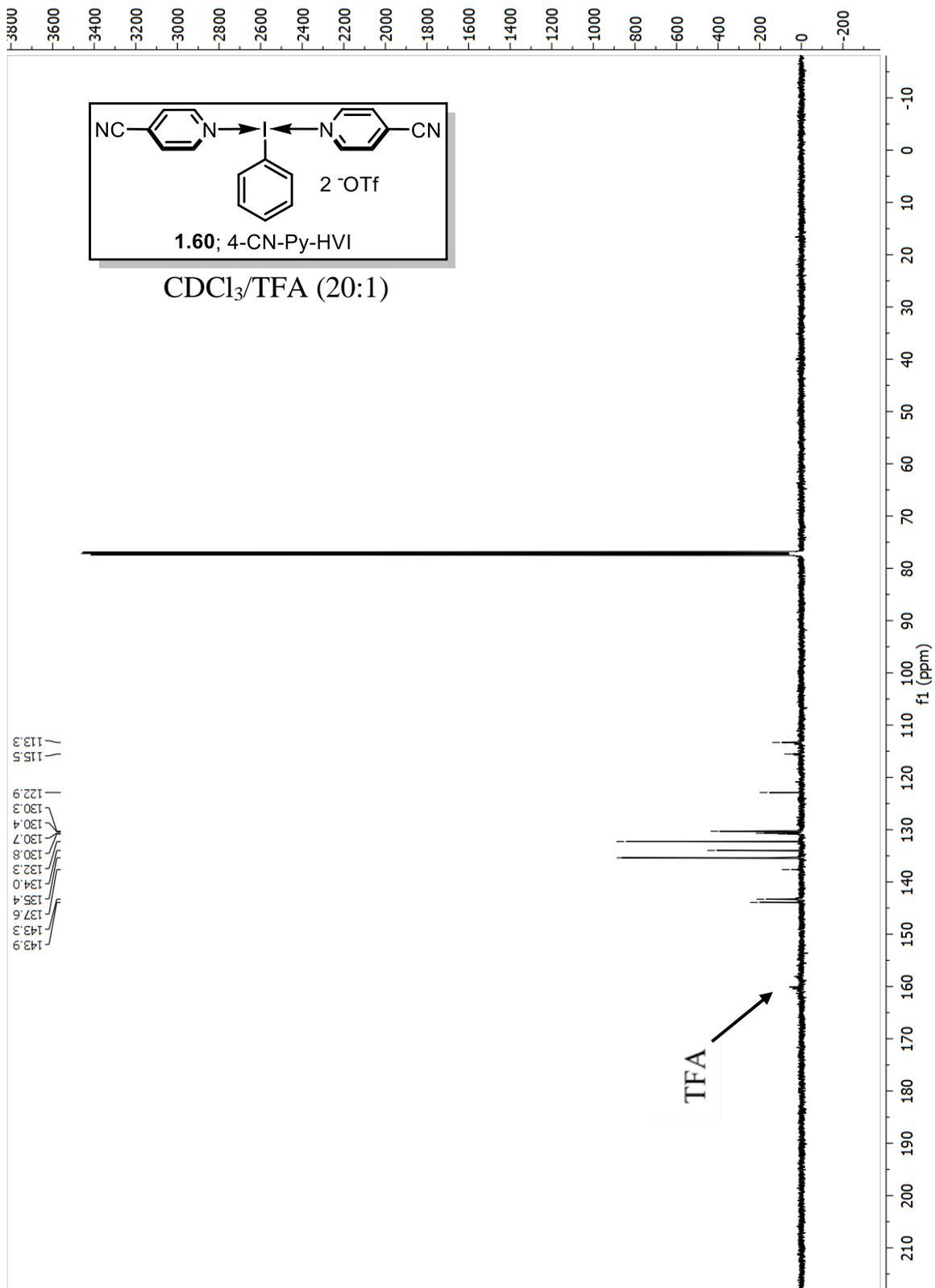












APPENDIX B: ONE-POT REARRANGEMENT/REDUCTION PROTOCOL

B1: GENERAL INFORMATION

^1H and ^{13}C NMR spectra were recorded at 500 MHz and 126 MHz on a Bruker Advance 500, 500 MHz and 126 MHz on a Bruker Advance III HD, or 400 MHz and 101 MHz on a Bruker Advance 400. ^1H NMR chemical shifts were reported in part per million (ppm) from the solvent resonance (CDCl_3 7.26 ppm or $\text{DMSO}-d_6$). The data was reported as follows: chemical shift number, multiplicity (s = singlet, d = doublet, t = triplet, s = septet, dd = doublet of doublets, td = triplet of doublets, m = multiplet, br = broad signal). Proton decoupled attached proton test (APT) ^{13}C NMR shifts were reported in ppm from the solvent resonance (CDCl_3 77.16 ppm). The glovebox used is a Vacuum Atmospheres NexGen system with a maximum humidity of 0.05% (500 ppm). The reaction solvents used were anhydrous (HPLC-grade solvent passed through an activated-alumina column) unless otherwise noted. 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) was purchased from Oakwood Chemical, distilled over CaH_2 and stored over activated 3 Å molecular sieves under an atmosphere of argon.

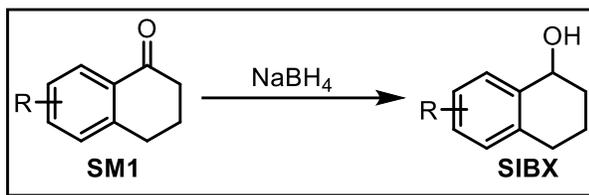
Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was purchased from Oakwood Chemical, distilled over CaH_2 and stored over activated 3 Å molecular sieves under an atmosphere of argon. Pyridine was purchased from Sigma Alrich (now Millipore Sigma), distilled over CaH_2 , and stored over activated 3 Å molecular sieves under an atmosphere of argon anhydrous organometallic reagents were purchased from Sigma Aldrich and used without further purification. All deuterated solvents were purchased from Cambridge Isotope Laboratories (CIL) and stored over activated 5 Å

molecular sieves. All other reagents were purchased from Sigma-Aldrich (now Millipore Sigma), Fisher Chemical, and Oakwood Chemical, and used without further purification. [(pyridine)₂IPh] 2OTf⁻, [(2-methoxypyridine)₂IPh] 2OTf⁻, and [(4-dimethylaminopyridine)₂IPh] 2OTf⁻ were synthesized (See Appendix A) and used without further purification.

Flash chromatography was carried out using Sorbent Technologies silica gel 60 Å (40–63 μm) in the solvent system listed in the individual experiments. Reactions were monitored using analytical thin-layer chromatography (TLC) on Merck silica gel (60 F254) plates. Accurate masses for derivatized products were conducted on an Agilent 6520. Accurate-Mass Q-TOF LC/MS. Samples were taken up in a suitable solvent for analysis. The signals were mass measured against an internal lock mass reference of perfluorotributylamine (PFTBA) for EI-GCMS, and leucine enkephalin for ESI-LCMS. Waters software calibrates the instruments, and reports measurements, by use of neutral atomic masses. The mass of the electron is not included. Melting points were obtained on a Stanford Research Systems MPA100 OptiMelt Automated Melting Point System and are uncorrected.

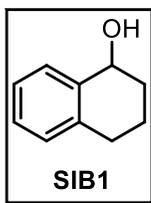
B2: SUBSTRATE SYNTHESIS

General Procedure 1 (GP1): Synthesis of Secondary Alcohols



A round-bottomed flask was charged with tetralol **SM1** (1.0 equiv.) followed by methanol to form a 0.3 M solution. To the solution was added sodium borohydride (1.1 equiv.) which resulted in vigorous bubbling and continued for several minutes. Once bubbling ceased, the reaction was checked for completeness by TLC. If the reaction was incomplete, a further 0.5 equivalents of sodium borohydride was added. Once complete, the reaction was quenched with saturated aqueous ammonium chloride and diethyl ether (Et₂O) was added. The organic layer was collected, and the aqueous layer was further extracted with Et₂O (3x). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The crude residue was used in the subsequent transformation without further purification.

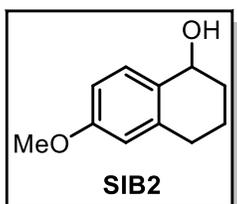
1,2,3,4-tetrahydronaphthalen-1-ol (**SIB1**)



SIB1 was prepared according to GP1 using 500 mg (3.4 mmol) of the corresponding tetralone. Spectral data matches prior reports.¹ **Yield:** 500 mg, 99%. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.45 – 7.42 (m, 1H), 7.23

– 7.18 (m, 2H), 7.13 – 7.09 (m, 1H), 4.79 (br s, 1H), 2.88 – 2.78 (m, 1H), 2.78 – 2.67 (m, 1H), 2.04 – 1.95 (m, 2H), 1.95 – 1.86 (m, 1H), 1.85 – 1.74 (m, 1H), 1.68 (s, 1H).

6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (SIB2)

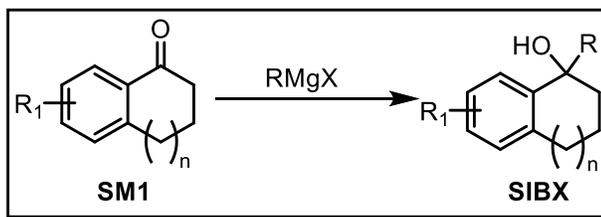


SIB2 was prepared according to GP1 using 2.0 g (11.3 mmol) of the corresponding tetralone. Spectral data matches prior reports.¹

Yield: 1.92 g, 95%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 8.5 Hz, 1H), 6.77 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.63 (d, *J* = 2.6 Hz,

1H), 4.75 (q, *J* = 4.9, 4.3 Hz, 1H), 3.79 (s, 3H), 2.80 (dt, *J* = 17.3, 4.2 Hz, 1H), 2.75 – 2.65 (m, 1H), 2.01 – 1.86 (m, 3H), 1.81 – 1.73 (m, 1H), 1.58 (d, *J* = 6.2 Hz, 1H).

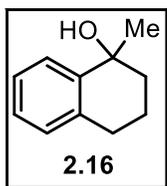
General Procedure 2 (GP2): Synthesis of Tertiary Alcohols



To a flame-dried round-bottomed flask was added ketone **SM1** (1.0 equiv.) followed by Et₂O to afford a 0.2 M solution. The solution was cooled to 0 °C and stirred for 5 minutes before a solution of RMgX (1.1 equiv.) was added dropwise over 2 minutes. The resulting reaction stirred overnight while gradually warming to ambient temperature. The following day, the solution was quenched with saturated aqueous ammonium chloride and diluted with Et₂O. The organic layer was collected, and the aqueous layer was further extracted with Et₂O (3x). The combined organic extracts were washed with brine then

dried over sodium sulfate and concentrated. The crude residue was purified via column chromatography to afford the desired tertiary alcohol.

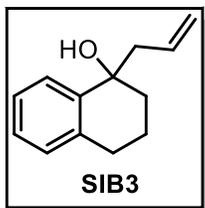
1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (2.14)



2.14 was prepared according to GP2 using 2.0 g (13.7 mmol) of the corresponding starting material. Spectral data matches prior reports.²

Yield: 1.83 g, 82%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.60 (d, $J = 7.7$, 1.4 Hz, 1H), 7.22 (t, $J = 7.5$, 1.5 Hz, 1H), 7.17 (td, $J = 7.4$, 1.5 Hz, 1H), 7.08 (d, $J = 7.5$, 1.3 Hz, 1H), 2.86 – 2.73 (m, 2H), 1.98 – 1.90 (m, 3H), 1.87 – 1.77 (m, 1H), 1.74 (s, 1H), 1.57 (s, 3H).

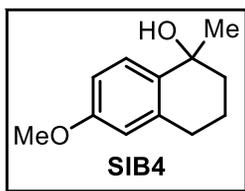
1-allyl-1,2,3,4-tetrahydronaphthalen-1-ol (SIB3)



SIB3 was prepared according to GP2 using 500 mg (3.4 mmol) of the corresponding starting material. Spectral data matches prior reports.²

Yield: 633 mg, 98%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.56 (dd, $J = 7.7$, 1.6 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.18 (td, $J = 7.4$, 1.5 Hz, 1H), 7.08 (dd, $J = 8.3$, 1.3 Hz, 1H), 5.87 – 5.76 (m, 1H), 5.18 – 5.10 (m, 2H), 2.86 – 2.70 (m, 2H), 2.61 (dt, $J = 7.3$, 1.2 Hz, 2H), 2.07 – 2.01 (m, 1H), 1.93 – 1.76 (m, 4H).

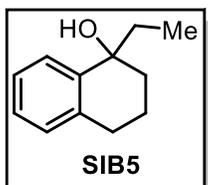
6-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (SIB4)



SIB4 was prepared according to GP2 using 1.0 g (5.7 mmol) of the corresponding starting material. Spectral data matches prior reports.² **Yield:** 1.0 g, 92%. **¹H NMR** (500 MHz, Chloroform-*d*) δ

7.51 (d, $J = 8.7$ Hz, 1H), 6.78 (dd, $J = 8.7, 2.7, 0.8$ Hz, 1H), 6.59 (d, $J = 2.4, 1.3$ Hz, 1H), 3.78 (s, 3H), 2.84 – 2.68 (m, 2H), 2.05 (s, 1H), 1.95 – 1.88 (m, 3H), 1.85 – 1.76 (m, 1H), 1.69 (s, 1H), 1.55 (s, 3H).

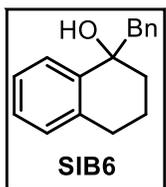
1-ethyl-1,2,3,4-tetrahydronaphthalen-1-ol (SIB5)



SIB5 was prepared according to GP2 using 500 mg (3.4 mmol) of the corresponding starting material. Spectral data matches prior reports.²

Yield: 363 mg, 61%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.53 (dd, $J = 7.7, 1.5$ Hz, 1H), 7.23 – 7.19 (m, 1H), 7.17 (td, $J = 7.4, 1.5$ Hz, 1H), 7.08 (d, 1H), 2.87 – 2.69 (m, 2H), 2.06 – 1.99 (m, 1H), 1.92 – 1.85 (m, 3H), 1.85 – 1.78 (m, 2H), 0.89 (t, $J = 7.5$ Hz, 3H).

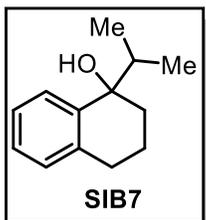
1-benzyl-1,2,3,4-tetrahydronaphthalen-1-ol (SIB6)



SIB6 was prepared according to GP2 using 500 mg (3.4 mmol) of the corresponding starting material. Spectral data matches prior reports.²

Yield: 390 mg, 48%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.62 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.33 – 7.28 (m, 2H), 7.26 – 7.22 (m, 3H), 7.20 (td, $J = 7.4, 1.6$ Hz, 1H), 7.10 (d, 1H), 3.17 (d, $J = 13.7$ Hz, 1H), 3.05 (d, $J = 13.7$ Hz, 1H), 2.88 – 2.71 (m, 2H), 1.97 – 1.91 (m, 1H), 1.91 – 1.84 (m, 2H), 1.81 (s, 1H), 1.68 – 1.60 (m, 1H).

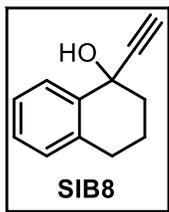
1-isopropyl-1,2,3,4-tetrahydronaphthalen-1-ol (SIB7)



A modified version of GP2 was utilized. In a glovebox void of oxygen and moisture, anhydrous CeCl_3 (1.49 g, 6.04 mmol, 1.76 equiv.) was suspended in THF (10 mL) and stirred for 1 hour at ambient temperature. The reaction flask was then removed from the glovebox and transferred to a fumehood, where it was subsequently cooled to 0 °C. After stirring for 5 minutes at this temperature, $i\text{PrMgCl}\cdot\text{LiCl}$ (1.3 M in THF, 4.72 mL, 6.04 mmol, 1.76 equiv.) was slowly added and the mixture was stirred for an additional hour at the same temperature. Next, α -tetralone (500 mg, 3.4 mmol, 1.0 equiv.) was added and the reaction was allowed to stir overnight while gradually warming to room temperature. The following day, the reaction was quenched with saturated aqueous ammonium chloride and diluted with Et_2O . The organic layer was collected, and the aqueous layer was further extracted with Et_2O (3x). The combined organic extracts were then dried over sodium sulfate and concentrated. The crude residue was purified via column chromatography to afford the desired product as a colorless oil. Spectral data corresponds with prior reports.²

Yield: 173 mg, 27%. **$^1\text{H NMR}$** (500 MHz, Chloroform-*d*) δ 7.52 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.21 (tt, $J = 7.7, 1.3$ Hz, 1H), 7.16 (td, $J = 7.4, 1.4$ Hz, 1H), 7.09 – 7.06 (m, 1H), 2.79 – 2.71 (m, 1H), 2.69 – 2.64 (m, 1H), 2.40 (h, $J = 6.8$ Hz, 1H), 1.91 – 1.77 (m, 5H), 1.09 (d, $J = 6.8$ Hz, 3H), 0.65 (d, $J = 6.9$ Hz, 3H).

1-ethynyl-1,2,3,4-tetrahydronaphthalen-1-ol (SIB8)

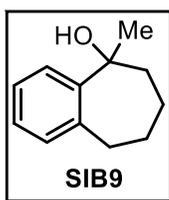


SIB8 was synthesized according to GP2 using 500 mg (3.4 mmol) of the corresponding starting material. Spectral data matches prior reports.²

Yield: 488 mg, 83%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.78 – 7.75 (m, 1H), 7.25 – 7.20 (m, 2H), 7.13 – 7.06 (m, 1H), 2.86 – 2.77 (m, 2H),

2.60 (s, 1H), 2.28 (s, 1H), 2.27 – 2.19 (m, 2H), 2.07 – 1.97 (m, 1H), 1.98 – 1.90 (m, 1H).

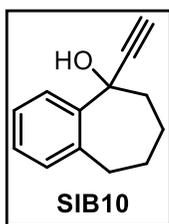
5-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ol (SIB9)



SIB9 was synthesized according to GP2 using 500 mg (3.1 mmol) of the corresponding starting material. Spectral data matches prior reports.²

Yield: 376 mg, 69%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.68 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.21 (td, $J = 7.5, 1.6$ Hz, 1H), 7.14 (td, $J = 7.3, 1.5$ Hz, 1H), 7.09 – 7.05 (m, 1H), 3.00 – 2.84 (m, 2H), 1.99 – 1.77 (m, 5H), 1.71 (s, 1H), 1.60 (s, 4H).

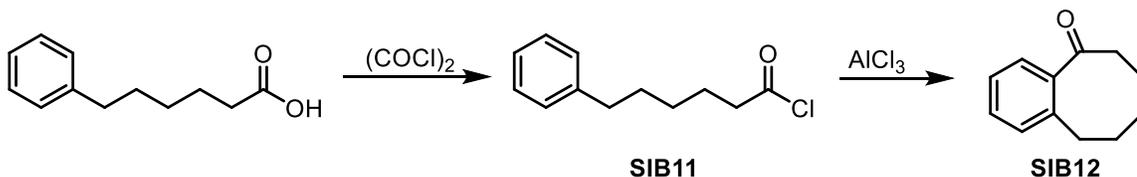
5-ethynyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ol (SIB10)



SIB10 was synthesized according to GP2 using 500 mg (3.1 mmol) of the corresponding starting material. Spectral data matches prior reports.

Yield: 353 mg, 61%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.80 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.25 – 7.17 (m, 2H), 7.11 (dd, $J = 7.2, 1.6$ Hz, 1H), 3.28 – 3.14 (m, 1H), 2.86 (dd, $J = 14.3, 7.9$ Hz, 1H), 2.71 (s, 1H), 2.38 (s, 1H), 2.20 – 2.07 (m, 2H), 2.07 – 1.98 (m, 2H), 1.89 – 1.80 (m, 1H), 1.52 – 1.39 (m, 1H).

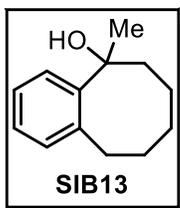
7,8,9,10-tetrahydrobenzo[8]annulen-5(6H)-one (SIB12)



In a flame-dried round-bottomed flask, a solution of 6-phenylhexanoic acid (5 g, 26 mmol, 1.0 equiv.) in DCM (100 mL) was cooled to 0 °C, then oxalyl chloride (3.34 mL, 39 mmol, 1.5 equiv) was added. A drop of DMF was also added to the reaction which resulted in vigorous bubbling. The reaction was allowed to stir for 90 minutes, at which point full conversion was observed by NMR. The reaction was fully concentrated and used in the subsequent step without further purification or yield analysis. **^1H NMR SIB11** (500 MHz, Chloroform-*d*) δ 7.28 (dd, $J = 8.3, 6.8$ Hz, 2H), 7.21 – 7.15 (m, 3H), 2.88 (t, $J = 7.3$ Hz, 2H), 2.62 (t, $J = 7.7$ Hz, 2H), 1.79 – 1.70 (m, 2H), 1.69 – 1.59 (m, 2H), 1.45 – 1.35 (m, 2H). Substrate **SIB11** was then dissolved in DCM (100 mL) and added to an addition funnel fitted to a separate round-bottomed flask containing a solution of AlCl_3 (13.9 g, 104 mmol, 4.0 equiv.) in DCM (500 mL). The substrate solution was slowly added over a period of roughly 45 minutes, and the resulting mixture was allowed to stir overnight. The following day, the reaction was quenched with saturated aqueous ammonium chloride, and the organic layer was collected. The aqueous layer was further extracted with DCM (2x), and the combined organic extracts were dried over sodium sulfate and concentrated. The crude residue was purified via flash column chromatography to afford the desired compound as a pale yellow oil. Spectral data matches prior reports.³ **Yield:** 2.0 g, 44%. **^1H NMR** (500 MHz, Chloroform-*d*) δ 7.65 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.39 (td, $J = 7.4, 1.5$ Hz, 1H), 7.28 (dd, $J = 7.6, 1.3$ Hz, 1H),

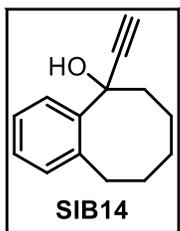
7.18 (dd, $J = 7.6, 1.2$ Hz, 1H), 3.08 – 3.01 (m, 2H), 2.91 (t, $J = 6.8$ Hz, 2H), 1.88 – 1.78 (m, 4H), 1.57 – 1.49 (m, 2H).

5-methyl-5,6,7,8,9,10-hexahydrobenzo[8]annulen-5-ol (SIB13)



SIB13 was prepared according to GP2 using 500 mg (2.87 mmol) of the corresponding ketone starting material. **Yield:** 383 mg, 70%. **$^1\text{H NMR}$** (500 MHz, Chloroform-*d*) δ 7.70 – 7.62 (m, 1H), 7.23 – 7.15 (m, 2H), 7.06 – 7.01 (m, 1H), 3.22 (br s, 1H), 3.01 – 2.89 (m, 1H), 2.33 (s, 1H), 2.27 (br s, 1H), 2.07 – 1.97 (m, 1H), 1.83 (s, 1H), 1.81 – 1.67 (m, 3H), 1.63 – 1.53 (m, 4H), 1.26 (br s, 1H), 1.15 (br s, 1H). **HRMS** (ESI) m/z calculated for $\text{C}_{13}\text{H}_{18}\text{O}$: 190.1358; found: 190.1375

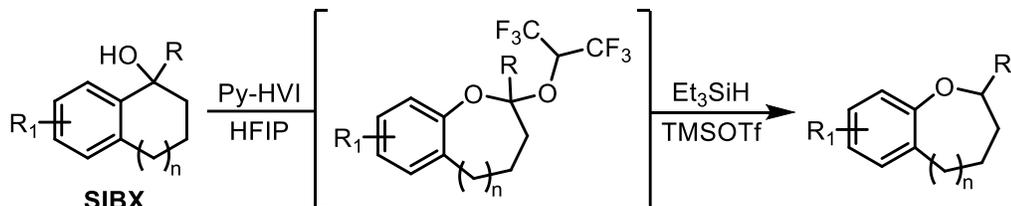
5-ethynyl-5,6,7,8,9,10-hexahydrobenzo[8]annulen-5-ol (SIB14)



SIB14 was prepared according to GP2 using 671 mg (3.85 mmol) of the corresponding ketone starting material. **Yield:** 415 mg, 54%. **$^1\text{H NMR}$** (500 MHz, Chloroform-*d*) δ 7.88 – 7.81 (m, 1H), 7.28 – 7.17 (m, 2H), 7.11 (dd, $J = 7.1, 2.0$ Hz, 1H), 3.63 – 3.50 (m, 1H), 3.04 – 2.90 (m, 1H), 2.70 (s, 1H), 2.64 (s, 1H), 2.30 – 2.21 (m, 1H), 1.98 (d, $J = 11.8$ Hz, 1H), 1.86 – 1.76 (m, 1H), 1.73 – 1.58 (m, 4H), 1.46 – 1.35 (m, 1H), 1.00 – 0.85 (m, 1H). **$^{13}\text{C NMR}$** (126 MHz, CDCl_3) δ 141.8, 139.5, 130.9, 128.0, 126.0, 125.3, 88.0, 73.8, 47.6, 31.6, 30.1, 23.8, 22.5. **HRMS** (ESI) m/z calculated for $\text{C}_{14}\text{H}_{16}\text{O}$: 200.1201; found: 200.1221

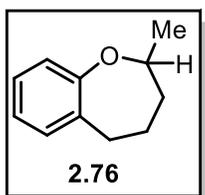
B3: SYNTHESIS OF CYCLIC ETHERS

General Procedure 3 (GP3): One-Pot Rearrangement/Reduction



In a flame dried test tube containing activated 3 Å molecular sieves, alcohol **SIBX** (100 mg, 1.0 equiv.) was dissolved in DCM to afford a 0.2 M solution. The flask was then submerged in a $-20\text{ }^{\circ}\text{C}$ dry ice/acetone bath and stirred for 5 minutes. At which point, a solution of Py-HVI (1.2 equiv.; see Appendix A for synthesis) in HFIP (20 equiv.) was added. The reaction was closely monitored by TLC for consumption of starting material while gradually warming (never above $0\text{ }^{\circ}\text{C}$). Once complete, the reaction temperature was adjusted to $0\text{ }^{\circ}\text{C}$, followed by the addition of Et_3SiH (3.0 equiv.). The resulting solution was stirred for 5 minutes, then TMSOTf (1.1 equiv.) was added. The reaction was allowed to stir to room temperature for 20 minutes. The reaction was then filtered over celite, and the filtrate was quenched with saturated aqueous sodium bicarbonate. The organic layer was collected, and the aqueous layer was further extracted with DCM (3x). The combined organic extracts were washed with brine (3x), dried over sodium sulfate, and concentrated. The crude residue was purified via flash column chromatography ($0\rightarrow 5\%$ Et_2O /pentane) to afford the desired product.

2-methyl-2,3,4,5-tetrahydrobenzo[*b*]oxepine (**2.76**)



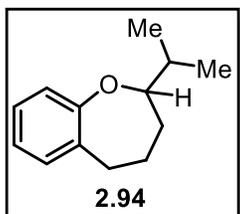
Ether **2.76** was prepared according to GP3 to afford a colorless oil.

Yield: 61 mg, 61%. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 7.12 (dd, $J = 8.9, 6.6$ Hz, 2H), 7.00 – 6.94 (m, 2H), 3.82 – 3.72 (m, 1H), 2.89 (ddd, $J = 14.0, 11.8, 2.1$ Hz, 1H), 2.75 – 2.65 (m, 1H), 2.00 – 1.89 (m,

2H), 1.86 – 1.73 (m, 1H), 1.54 – 1.42 (m, 1H), 1.38 (d, $J = 6.3$ Hz, 3H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 159.3, 136.1, 130.2, 127.4, 123.5, 121.7, 79.6, 39.2, 34.0, 26.0, 23.2.

HRMS (ESI) m/z calculated for $\text{C}_{11}\text{H}_{14}\text{O}$: 162.1045; found: 162.1044

2-isopropyl-2,3,4,5-tetrahydrobenzo[*b*]oxepine (2.94)

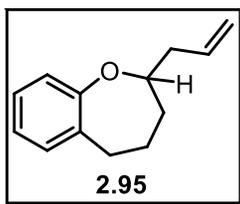


Ether **2.94** was prepared according to GP3 to afford a colorless oil.

Yield: 57 mg, 57%. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 7.16 – 7.10 (m, 2H), 7.00 (dd, $J = 7.8, 1.3$ Hz, 1H), 6.97 (td, $J = 7.3, 1.3$ Hz, 1H), 3.34 – 3.28 (m, 1H), 2.94 – 2.87 (m, 1H), 2.75 – 2.68 (m,

1H), 2.08 – 1.99 (m, 1H), 1.99 – 1.91 (m, 1H), 1.90 – 1.76 (m, 2H), 1.55 – 1.43 (m, 1H), 1.11 (d, $J = 6.7$ Hz, 3H), 1.05 (d, $J = 6.8$ Hz, 3H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 160.2, 136.0, 130.2, 127.3, 123.2, 121.2, 88.7, 34.5, 34.2, 34.0, 26.2, 19.6, 18.2. **HRMS** (ESI) m/z calculated for $\text{C}_{13}\text{H}_{18}\text{O}$: 190.1358; found: 190.1361

2-allyl-2,3,4,5-tetrahydrobenzo[*b*]oxepine (2.95)

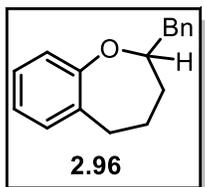


Ether **2.95** was prepared according to GP3 to afford a colorless oil.

Yield: 54 mg, 54%. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 7.12 (dd, $J = 8.8, 6.6$ Hz, 2H), 7.00 – 6.95 (m, 2H), 6.03 – 5.93 (m, 1H), 5.18 – 5.08 (m, 2H), 3.66 – 3.58 (m, 1H), 2.94 – 2.85 (m, 1H), 2.75

– 2.66 (m, 1H), 2.57 – 2.48 (m, 1H), 2.34 – 2.29 (m, 1H), 2.01 – 1.92 (m, 2H), 1.84 – 1.76 (m, 1H), 1.54 – 1.44 (m, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 159.4, 136.0, 135.4, 130.2, 127.4, 123.5, 121.6, 117.0, 83.1, 41.6, 37.1, 34.0, 26.0. **LRMS** was found due to issues with isomerization in HRMS. m/z calculated for $\text{C}_{13}\text{H}_{16}\text{O}$: 188.1201; found: 188.0.

2-benzyl-2,3,4,5-tetrahydrobenzo[*b*]oxepine (2.96)



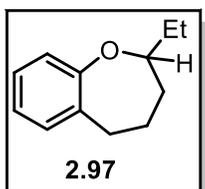
Ether **2.96** was prepared according to GP3 to afford a colorless oil.

Yield: 50 mg, 50%. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 7.33 – 7.25 (m, 4H), 7.22 (dd, $J = 7.1, 2.1$ Hz, 1H), 7.04 (dd, $J = 7.4, 1.7$ Hz, 1H), 6.98 (td, $J = 7.6, 1.8$ Hz, 1H), 6.89 (td, $J = 7.4, 1.4$ Hz, 1H), 6.56 (dd,

$J = 7.9, 1.3$ Hz, 1H), 3.78 – 3.69 (m, 1H), 3.03 (dd, $J = 13.8, 8.4$ Hz, 1H), 2.92 – 2.78 (m, 3H), 2.68 – 2.61 (m, 1H), 2.00 – 1.92 (m, 2H), 1.87 – 1.75 (m, 1H), 1.50 – 1.38 (m, 1H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 159.5, 139.2, 136.1, 130.1, 129.7, 128.3, 127.4, 126.3, 123.5, 121.5, 84.5, 43.7, 37.3, 33.9, 26.1. **HRMS** (ESI) m/z calculated for $\text{C}_{17}\text{H}_{18}\text{O}$: 238.1358; found: 238.1358

2-ethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepine (2.97)



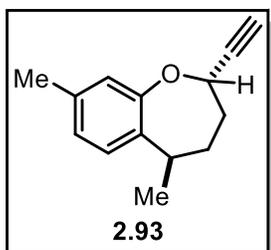
Ether **2.97** was prepared according to GP3 to afford a colorless oil.

Yield: 53 mg, 53%. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 7.16 – 7.11 (m, 2H), 7.03 – 6.96 (m, 2H), 3.51 – 3.43 (m, 1H), 2.96 – 2.87 (m, 1H), 2.76 – 2.67 (m, 1H), 2.04 – 1.90 (m, 2H), 1.84 – 1.73 (m, 2H),

1.63 – 1.53 (m, 1H), 1.53 – 1.46 (m, 1H), 1.11 (t, $J = 7.4$ Hz, 3H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 159.6, 136.0, 130.1, 127.3, 123.3, 121.3, 85.2, 37.3, 33.9, 30.1, 26.0, 10.8.

HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{16}\text{O}$: 176.1201; found: 176.1219

2-ethynyl-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepine (2.93)



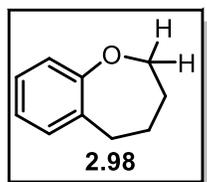
Ether **2.93** was synthesized according to GP3 using 165 mg of starting material to afford a ~6:1 mixture of diastereomers.

Yield: 99 mg, 60%. $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.61 – 7.57 (m, 1.73H), 7.16 (d, $J = 8.0$ Hz, 1H, Major), 7.10 (td, $J = 4.1, 3.3, 1.6$ Hz, 2.51H), 2.92 (dq, $J = 24.5, 6.6$ Hz, 2H), 2.60 (s,

0.69H), 2.59 (s, 1H Major), 2.36 (d, $J = 0.9$ Hz, 6H), 2.33 – 2.24 (m, 1.41H), 2.17 (dddd,

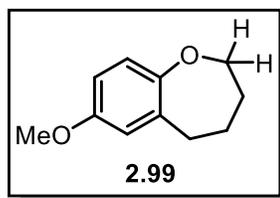
$J = 15.3, 9.6, 4.2, 2.6$ Hz, 1.88H), 2.15 – 1.97 (m, 1.88H), 1.81 – 1.73 (m, 1H, Major), 1.73 – 1.63 (m, 0.88H, Minor (1H)), 1.33 (d, $J = 7.0$ Hz, 3.38H, Major), 1.29 (d, $J = 7.1$ Hz, 2.17H, Minor (3H)). ^{13}C NMR (126 MHz, CDCl_3) δ 156.9, 137.2, 136.6, 128.3, 127.2, 126.2, 125.2, 124.2, 123.6, 123.4, 122.2, 84.8, 82.3, 74.5, 74.1, 72.1, 71.4, 37.3, 36.4, 35.8, 35.1, 34.3, 34.1, 31.7, 30.0, 20.9, 20.6, 20.0, 19.2. **HRMS:** (ESI) m/z calculated for $\text{C}_{14}\text{H}_{16}\text{O}^+$ 200.1201; found 201.1280 ($\text{M}+\text{H}^+$)

2,3,4,5-tetrahydrobenzo[*b*]oxepine (2.98)



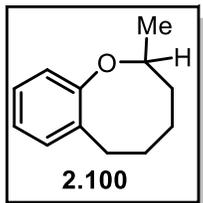
Ether **2.98** was synthesized according to GP3 to deliver the desired product as a colorless oil. **Yield:** 32 mg, 32%. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.16 – 7.08 (m, 2H), 7.02 – 6.93 (m, 2H), 4.02 – 3.97 (m, 2H), 2.85 – 2.78 (m, 2H), 2.00 – 1.93 (m, 2H), 1.76 – 1.69 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 160.6, 135.8, 130.5, 127.4, 123.5, 121.4, 73.7, 34.6, 32.7, 26.4. **HRMS** (ESI) m/z calculated for $\text{C}_{10}\text{H}_{12}\text{O}$: 148.0888; found: 148.0893

7-methoxy-2,3,4,5-tetrahydrobenzo[*b*]oxepine (2.99)



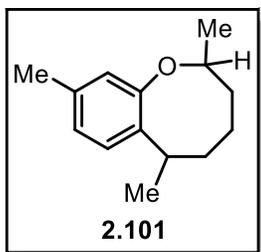
Ether **2.99** was synthesized according to GP3 to deliver the desired product as a colorless oil. **Yield:** 39 mg, 39%. ^1H NMR (500 MHz, Chloroform-*d*) δ 6.92 (d, $J = 8.6$ Hz, 1H), 6.68 (d, $J = 3.1$ Hz, 1H), 6.64 (dd, $J = 8.6, 3.1$ Hz, 1H), 3.96 – 3.92 (m, 2H), 3.76 (s, 3H), 2.80 – 2.73 (m, 2H), 1.97 – 1.91 (m, 2H), 1.73 – 1.66 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 155.5, 154.4, 137.0, 121.9, 115.8, 111.6, 73.9, 55.7, 34.8, 32.8, 26.6. **HRMS** (ESI) m/z calculated for $\text{C}_{11}\text{H}_{14}\text{O}_2$: 178.0994; found: 178.0998

2-methyl-3,4,5,6-tetrahydro-2H-benzo[b]oxocine (2.100)



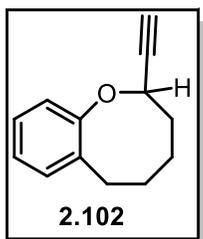
Ether **2.100** was synthesized according to GP3 to deliver the desired product as a colorless oil. **Yield:** 71 mg, 71%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.23 – 7.10 (m, 2H), 7.04 (dt, $J = 18.3, 5.5$ Hz, 2H), 4.18 – 4.09 (m, 1H), 2.99 (td, $J = 12.4, 3.6$ Hz, 1H), 2.62 – 2.52 (m, 1H), 1.97 – 1.82 (m, 1H), 1.80 – 1.67 (m, 1H), 1.63 – 1.50 (m, 2H), 1.49 – 1.41 (m, 5H). **¹³C NMR** (126 MHz, CDCl₃) δ 157.0, 137.2, 129.9, 127.4, 124.3, 122.4, 81.8, 33.8, 31.6, 30.4, 23.5, 21.5. **HRMS** (ESI) m/z calculated for C₁₂H₁₆O: 176.1201; found: 176.1212

2,6,9-trimethyl-3,4,5,6-tetrahydro-2H-benzo[b]oxocine (2.101)



Ether **2.101** was synthesized according to GP3 using 222 mg of the corresponding starting material to deliver a 1:1 mixture of diastereomers as a yellow oil. **Yield:** 141 mg, 64%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.05 (d, $J = 7.7$ Hz, 2H), 6.94 – 6.85 (m, 2H), 6.83 (s, 1H), 6.78 (s, 1H), 4.33 – 4.23 (m, 1H), 3.97 – 3.87 (m, 1H), 3.47 – 3.35 (m, 1H), 3.09 – 2.98 (m, 1H), 2.29 (d, $J = 5.3$ Hz, 6H), 1.89 – 1.46 (m, 9H), 1.41 (d, $J = 6.3$ Hz, 3H), 1.36 (d, $J = 6.6$ Hz, 3H), 1.30 (d, $J = 7.2$ Hz, 3H), 1.27 (d, $J = 7.1$ Hz, 3H).

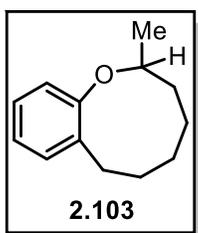
2-ethynyl-3,4,5,6-tetrahydro-2H-benzo[b]oxocine (2.102)



Ether **2.102** was synthesized according to GP3 to deliver the desired product as a yellow oil. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.19 (s, 2H), 7.14 (d, $J = 6.9$ Hz, 1H), 7.10 (dt, $J = 7.7, 4.1$ Hz, 1H), 4.83 – 4.78 (m, 1H), 2.89 – 2.81 (m, 1H), 2.72 – 2.65 (m, 1H), 2.56 (s, 1H), 1.97 – 1.88 (m, 2H), 1.81 – 1.71 (m, 3H), 1.71 – 1.55 (m, 5H). **¹³C NMR** (126 MHz, CDCl₃) δ 154.3, 137.8, 130.1, 127.4, 125.2, 123.0, 83.1, 74.5, 74.0,

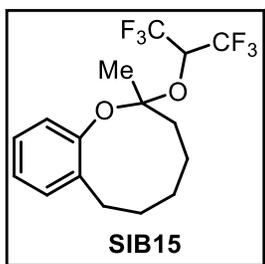
32.9, 31.4, 30.9, 25.1. **HRMS** (ESI) m/z calculated for $C_{13}H_{14}O$: 186.1045; found: 186.1029

2-methyl-2,3,4,5,6,7-hexahydrobenzo[*b*]oxonine (2.103)



Ether **2.103** was synthesized according to GP3 with slightly altered conditions. Following the addition of TMSOTf, the reaction was immediately quenched at low temperatures to prevent degradation of the desired product under reductive conditions. The desired product was isolated as a yellow oil. **Yield:** 42 mg, 42%. **1H NMR** (500 MHz, Chloroform-*d*) δ 7.16 (td, $J = 7.7, 1.8$ Hz, 1H), 7.10 (dd, $J = 7.5, 1.8$ Hz, 1H), 7.04 (dd, $J = 8.0, 1.2$ Hz, 1H), 6.98 (td, $J = 7.4, 1.2$ Hz, 1H), 4.31 – 4.23 (m, 1H), 3.21 – 3.10 (m, 1H), 2.50 – 2.40 (m, 1H), 1.91 – 1.75 (m, 2H), 1.73 – 1.64 (m, 2H), 1.64 – 1.57 (m, 2H), 1.51 (d, $J = 6.2$ Hz, 3H), 1.48 – 1.39 (m, 2H), 1.26 – 1.18 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.4, 135.0, 130.6, 127.3, 122.9, 119.4, 79.8, 34.5, 29.4, 28.7, 24.2, 22.6, 21.4. **HRMS** (ESI) m/z calculated for $C_{13}H_{18}O$: 190.1358; found: 190.1369

2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methyl-2,3,4,5,6,7-hexahydrobenzo[*b*]oxonine (SIB15)



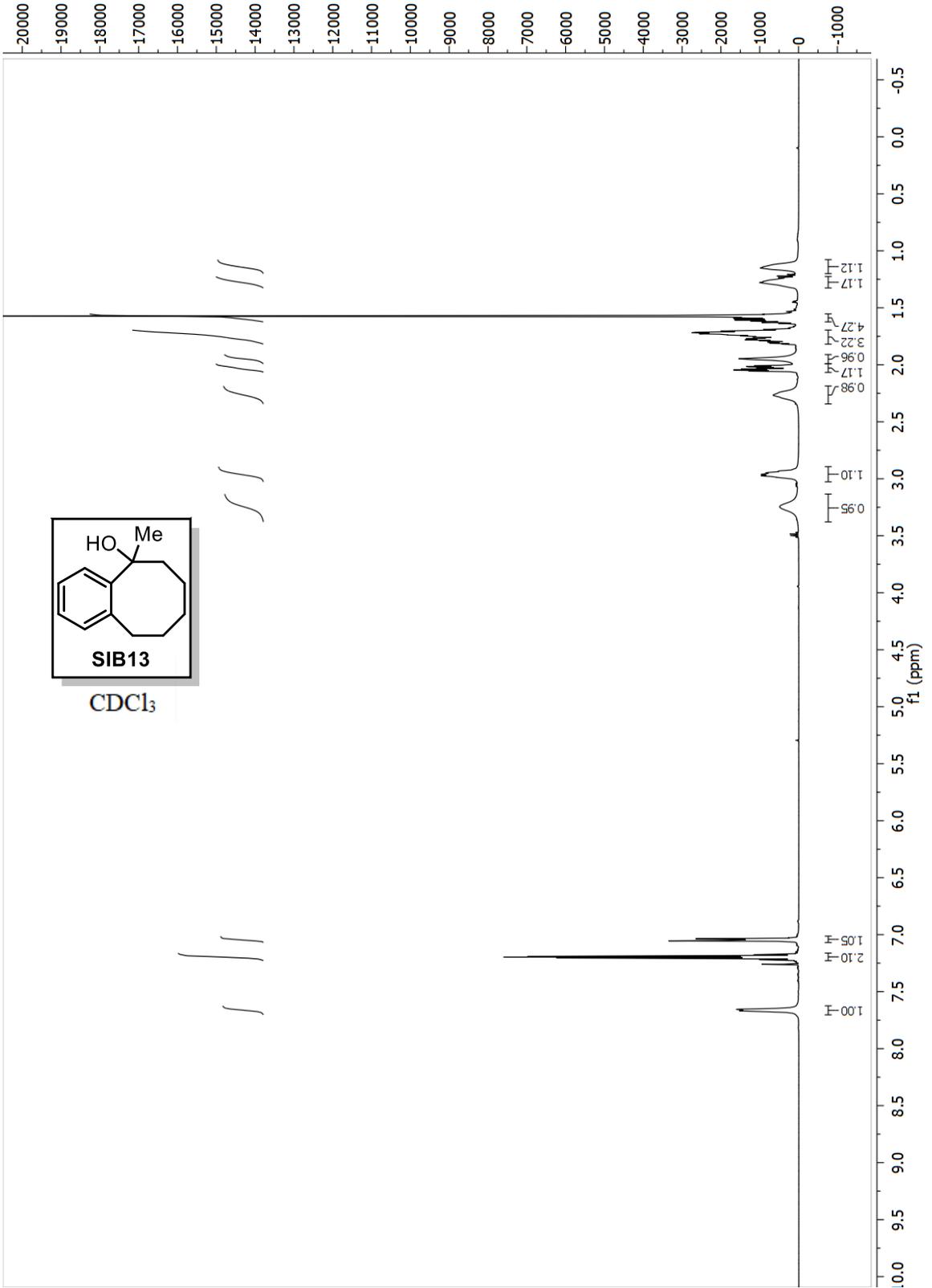
To a flame-dried test tube containing activated 3 Å molecular sieves was added alcohol **SIB13** (100 mg, 0.53 mmol, 1.0 equiv.) along with DCM (3 mL). The reaction was cooled to -20 °C, followed by the addition of a solution of Py-HVI (417 mg, 0.63 mmol, 1.2 equiv.) in HFIP (1.1 mL, 10.5 mmol, 20 equiv.). The reaction was stirred to completion by TLC while gradually warming to 0 °C. Once complete, the reaction was concentrated at 0 °C, and the crude residue was azeotroped with DCM (3x) to remove residual HFIP. The crude oil was then diluted with Et_2O which resulted in the precipitation of undesired byproduct salts. The suspension was filtered and

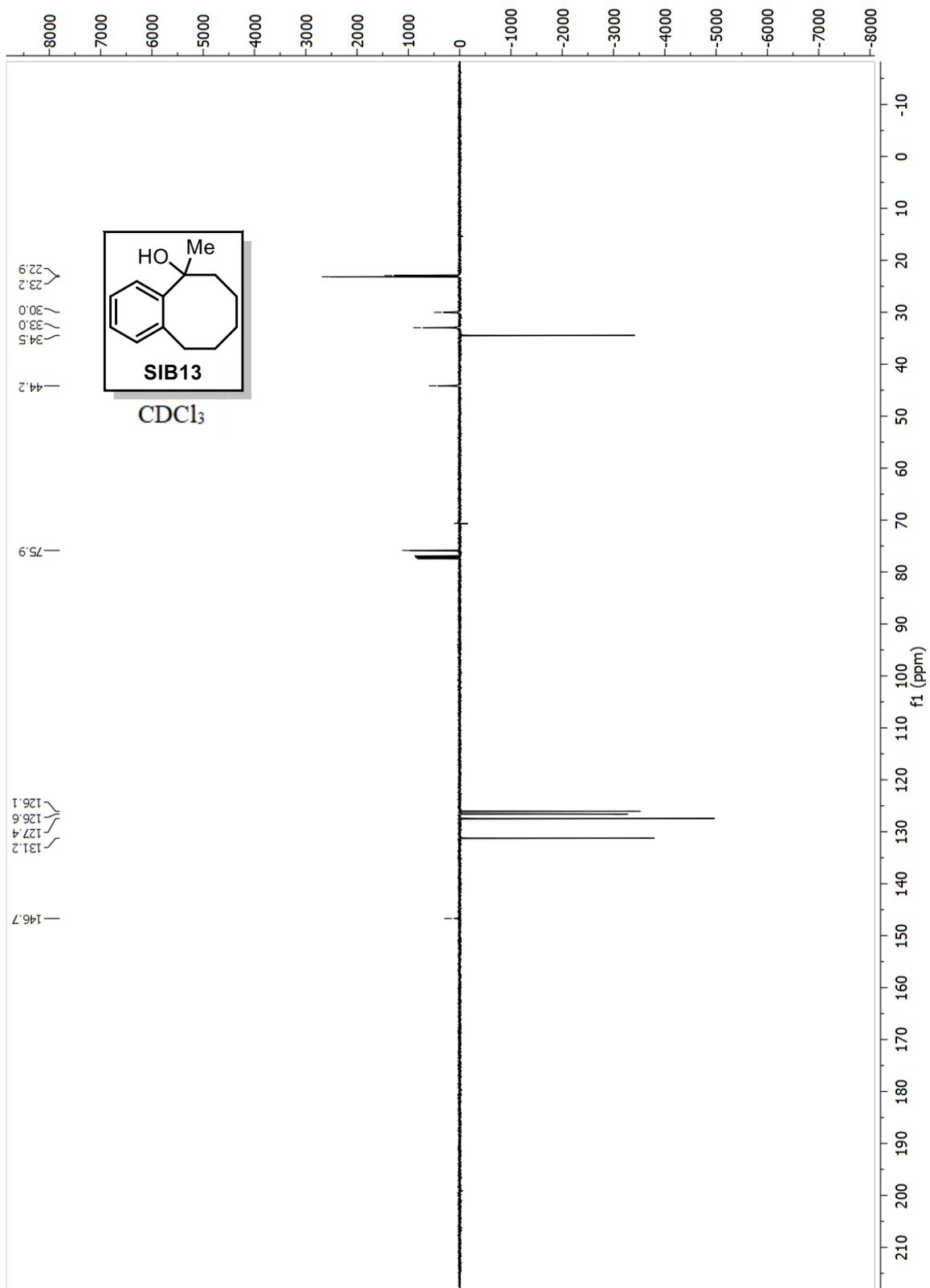
the filtrate was concentrated at 0 °C. The crude oil was purified via flash column chromatography (0→5% Et₂O/pentane) to afford the desired product as a pale yellow oil. **Yield:** 95 mg, 51%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.18 – 7.08 (m, 4H), 4.92 (hept, *J* = 6.1 Hz, 1H), 2.95 (ddd, *J* = 13.8, 8.7, 5.0 Hz, 1H), 2.68 (ddd, *J* = 13.8, 7.3, 5.2 Hz, 1H), 2.08 – 1.99 (m, 1H), 1.93 – 1.83 (m, 1H), 1.82 – 1.71 (m, 2H), 1.68 – 1.57 (m, 4H), 1.51 – 1.41 (m, 1H), 1.36 – 1.23 (m, 2H). **¹³C NMR** (126 MHz, CDCl₃) δ 152.4, 136.4, 130.4, 126.5, 124.8, 123.0, 109.5, 69.3 (p, *J* = 32.7 Hz), 39.3, 29.1, 27.6, 26.6, 23.9, 20.6. **HRMS** (ESI) *m/z* calculated for C₁₆H₁₈F₆O₂: 356.1211; found: 356.1208

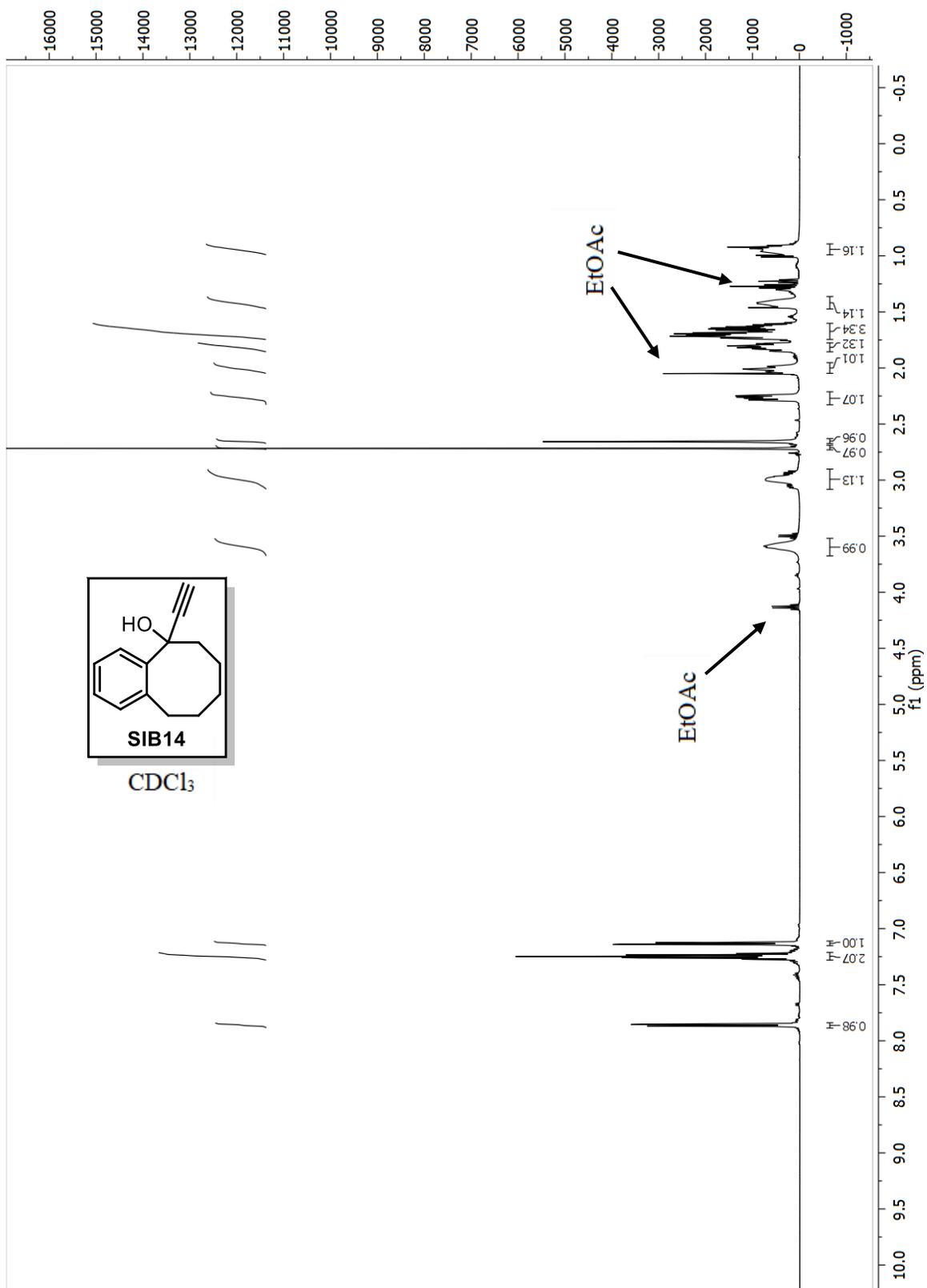
B4: REFERENCES

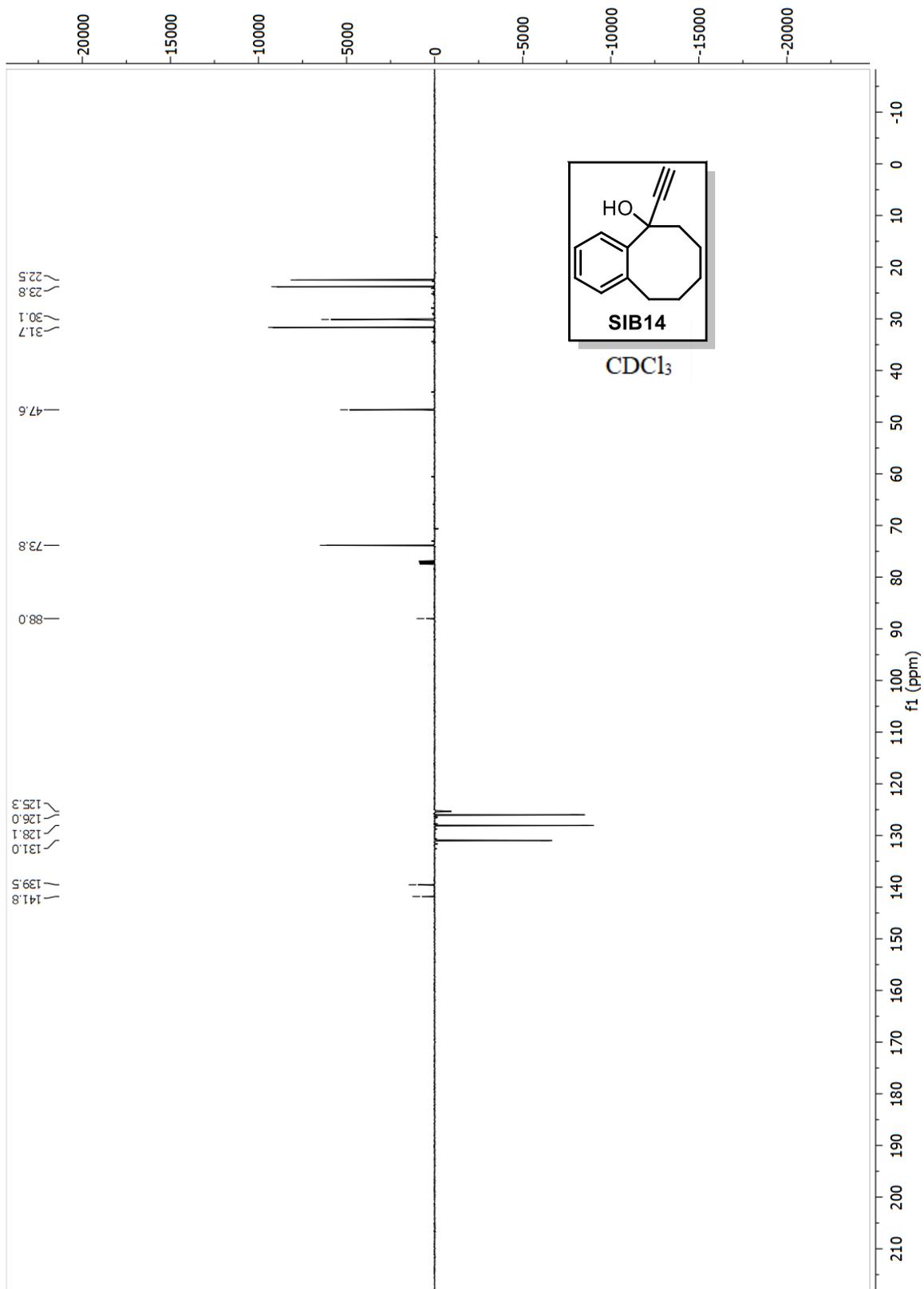
- (1) Walters, J. C.; Tierno, A. F.; Dubin, A. H.; Wengryniuk, S. E. (Poly)Cationic Λ^3 -Iodane-Mediated Oxidative Ring Expansion of Secondary Alcohols. *European J. Org. Chem.* **2018**, *2018* (12), 1460–1464. <https://doi.org/10.1002/ejoc.201800118>.
- (2) Kelley, B. T.; Walters, J. C.; Wengryniuk, S. E. Access to Diverse Oxygen Heterocycles via Oxidative Rearrangement of Benzylic Tertiary Alcohols. *Org. Lett.* **2016**, *18* (8), 1896–1899. <https://doi.org/10.1021/acs.orglett.6b00672>.
- (3) Metternich, J. B.; Artiukhin, D. G.; Holland, M. C.; Von Bremen-Kuhne, M.; Neugebauer, J.; Gilmour, R. Photocatalytic E \rightarrow Z Isomerization of Polarized Alkenes Inspired by the Visual Cycle: Mechanistic Dichotomy and Origin of Selectivity. *J. Org. Chem.* **2017**, *82* (19), 9955–9977. <https://doi.org/10.1021/acs.joc.7b01281>.

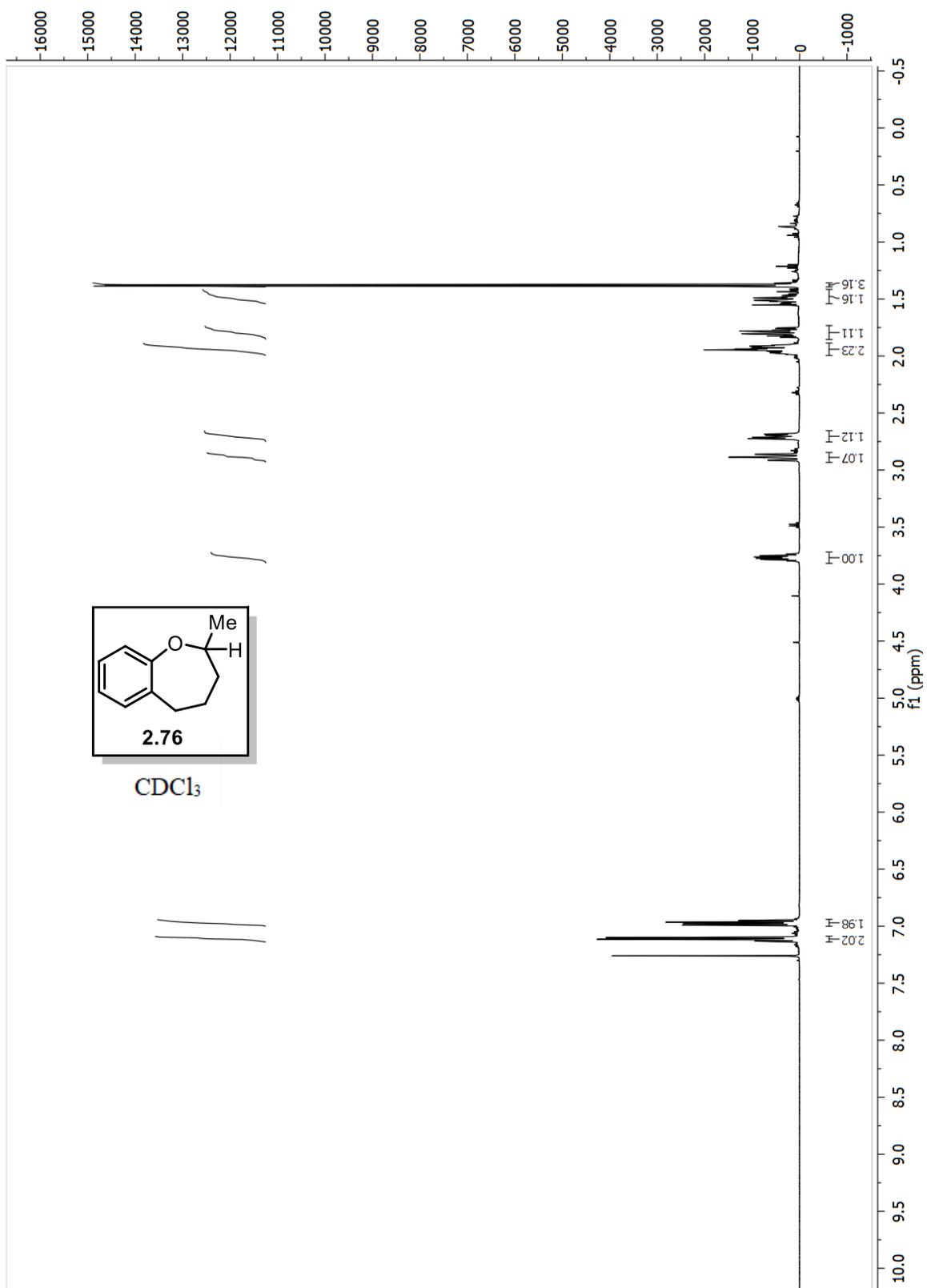
B5: SPECTRA

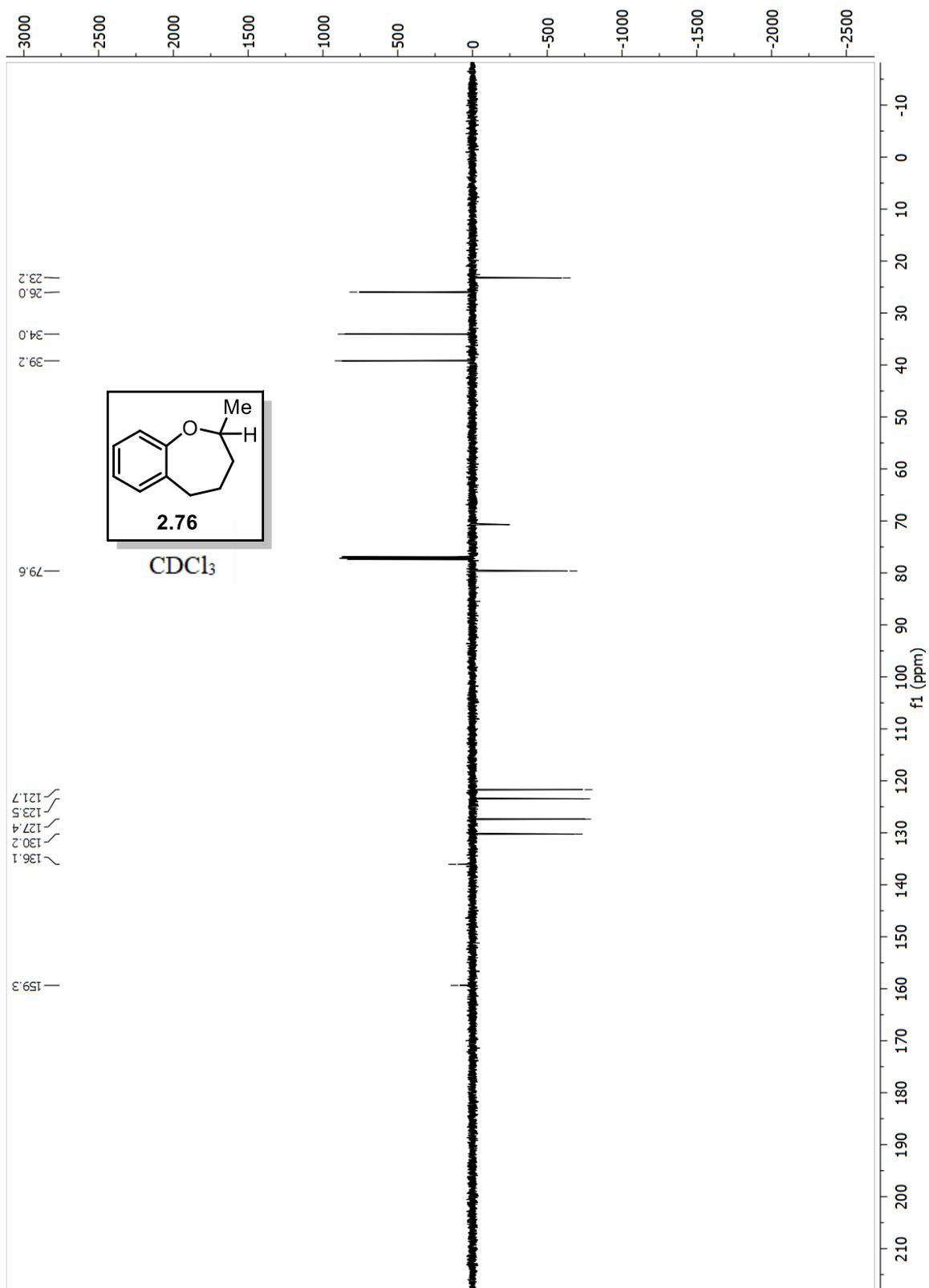


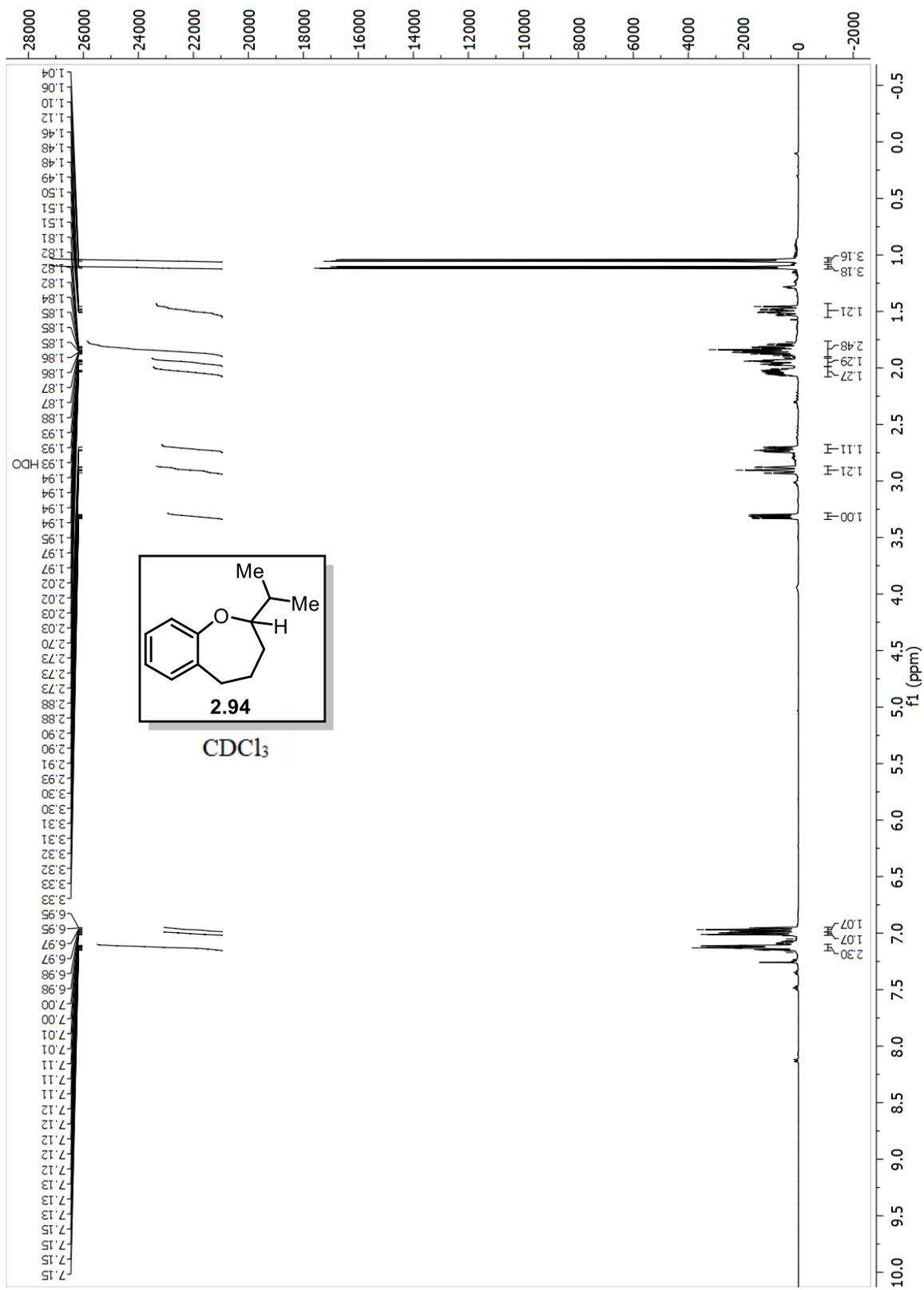


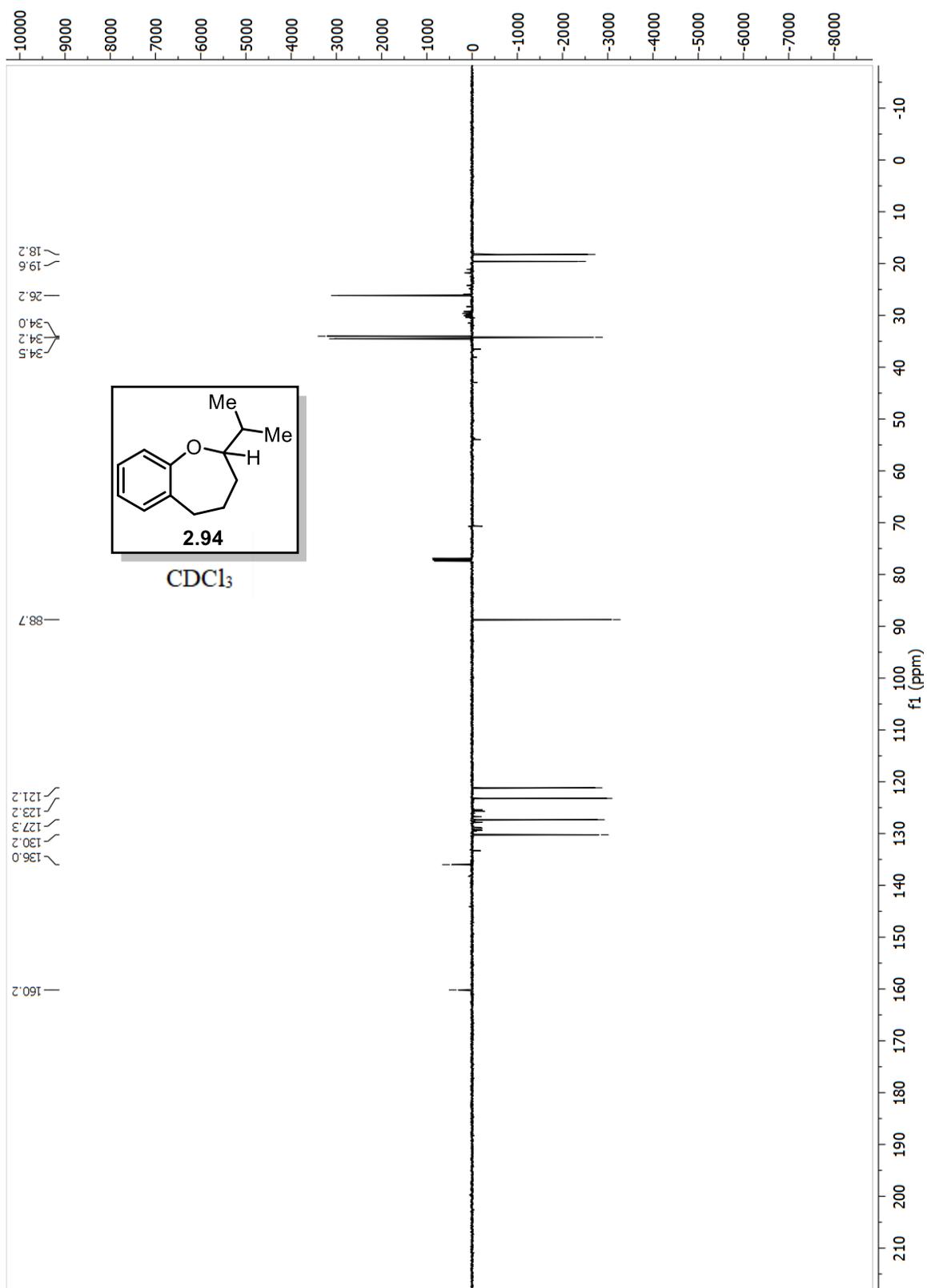


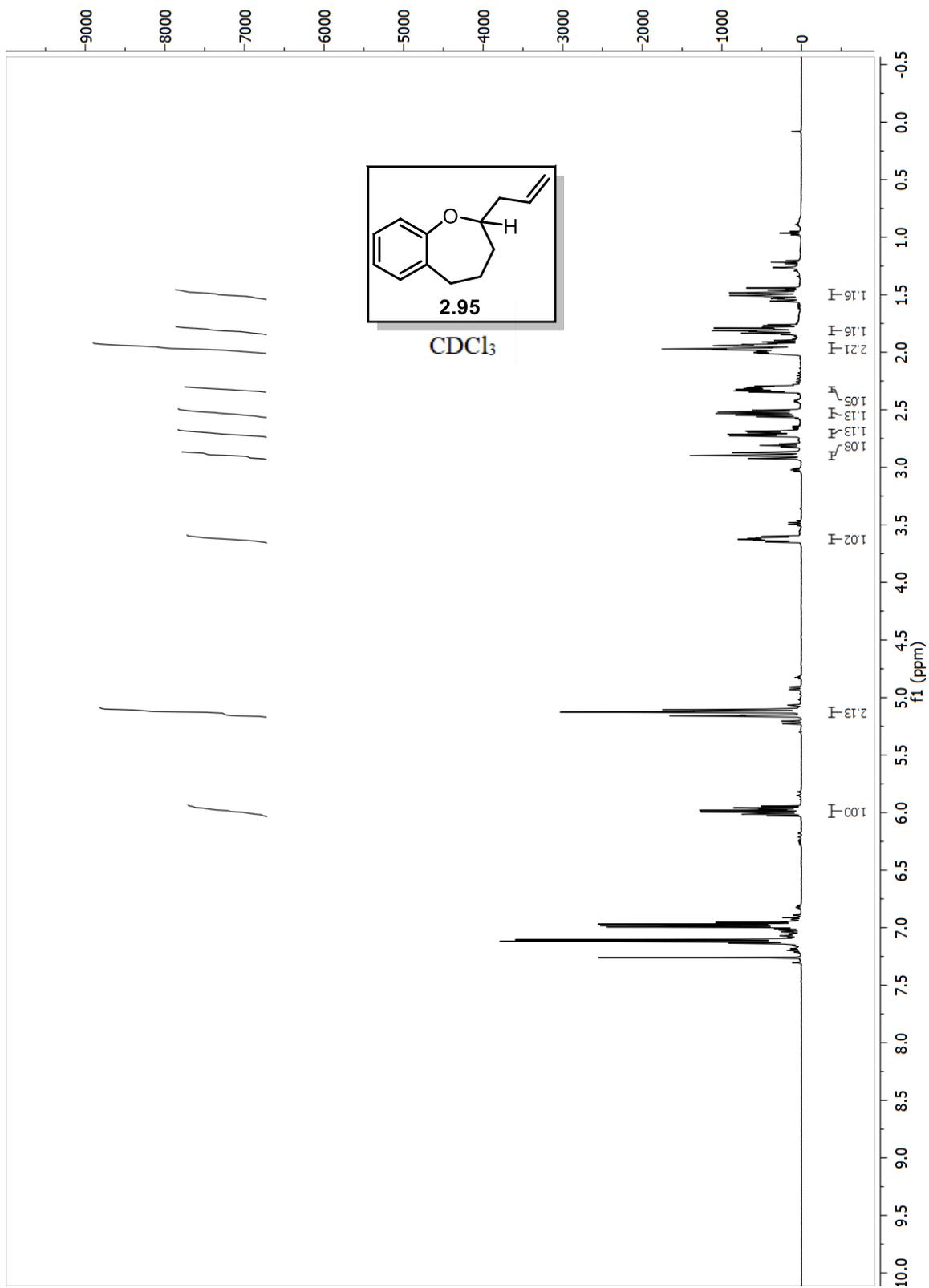


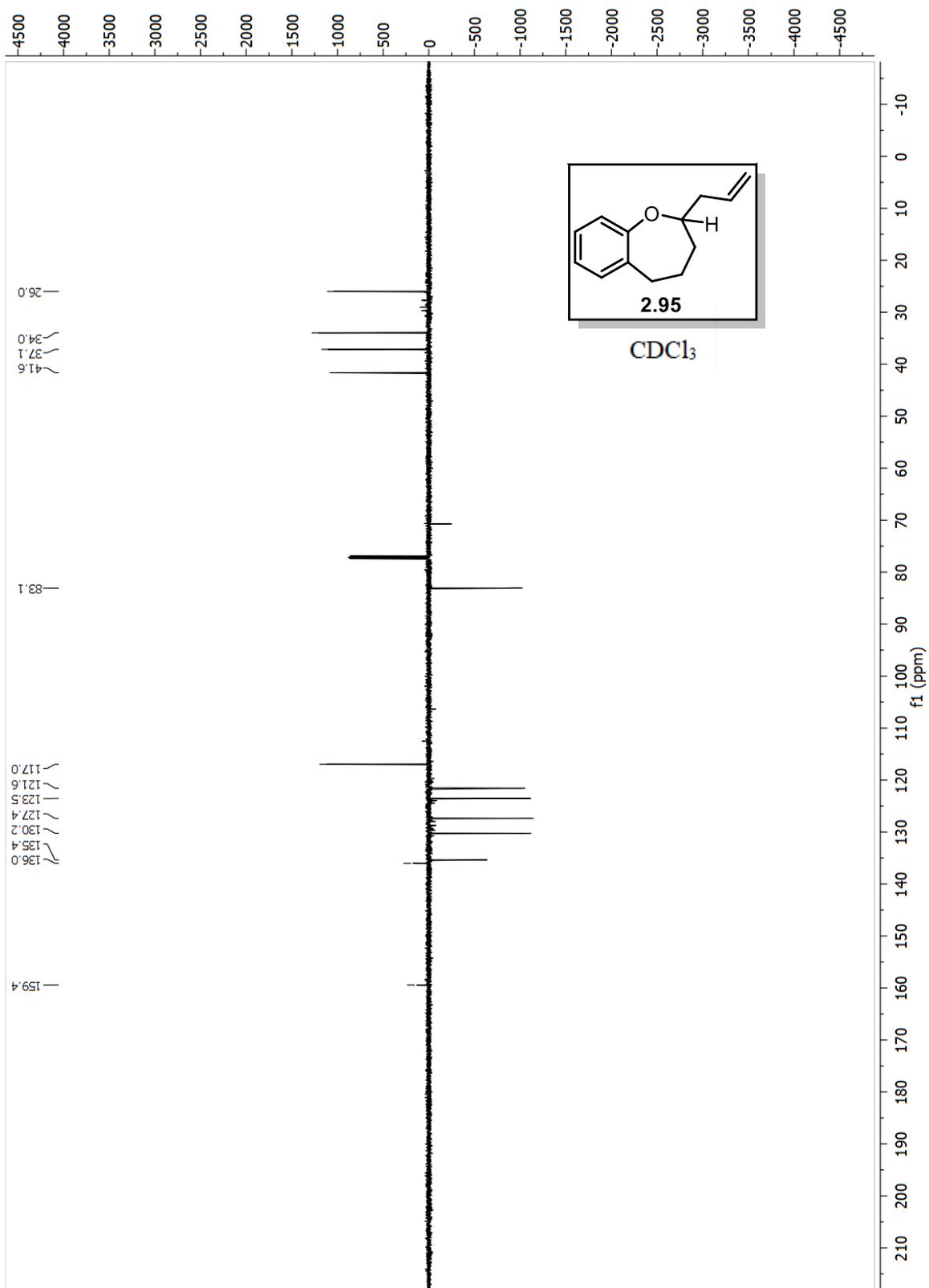


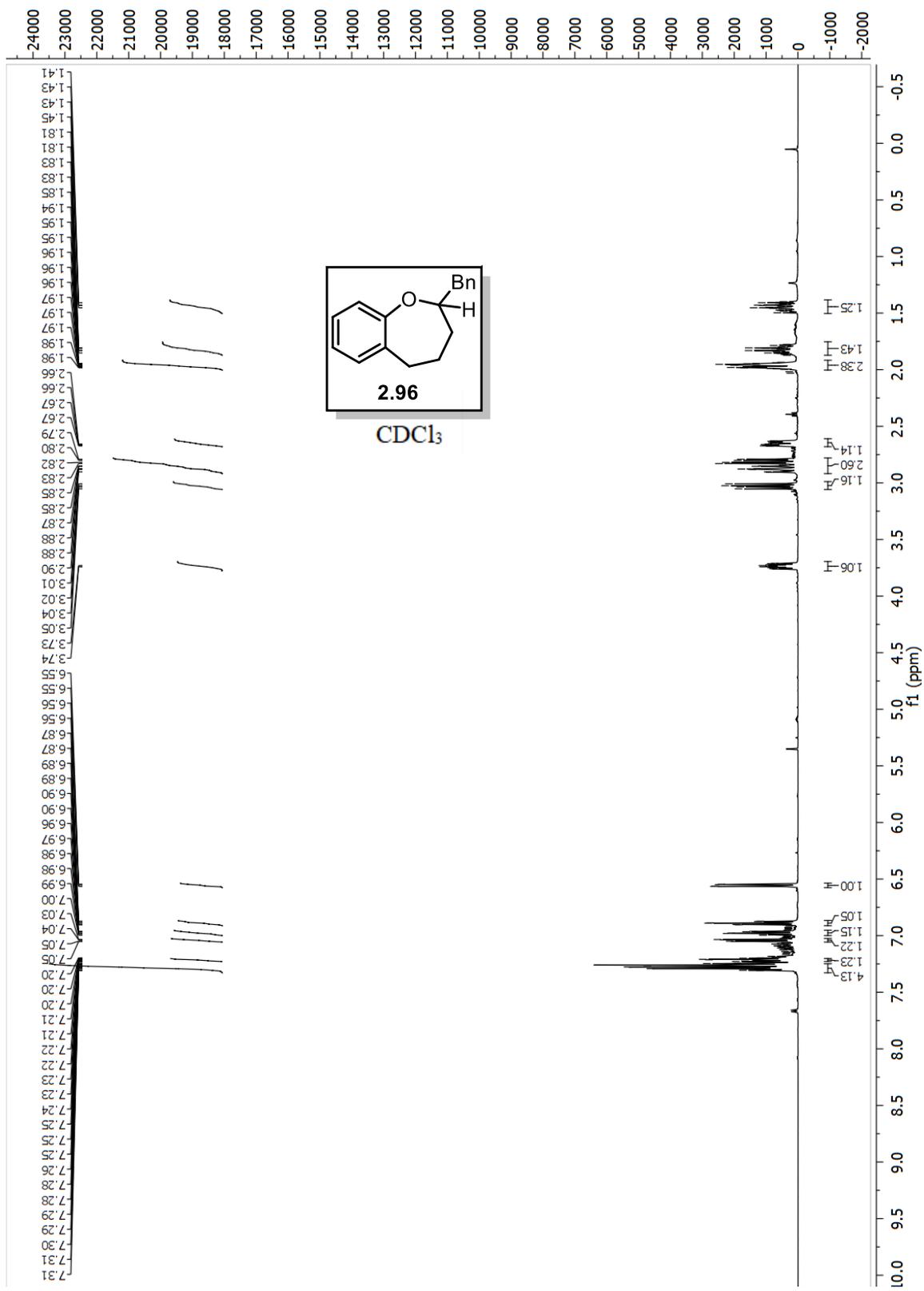


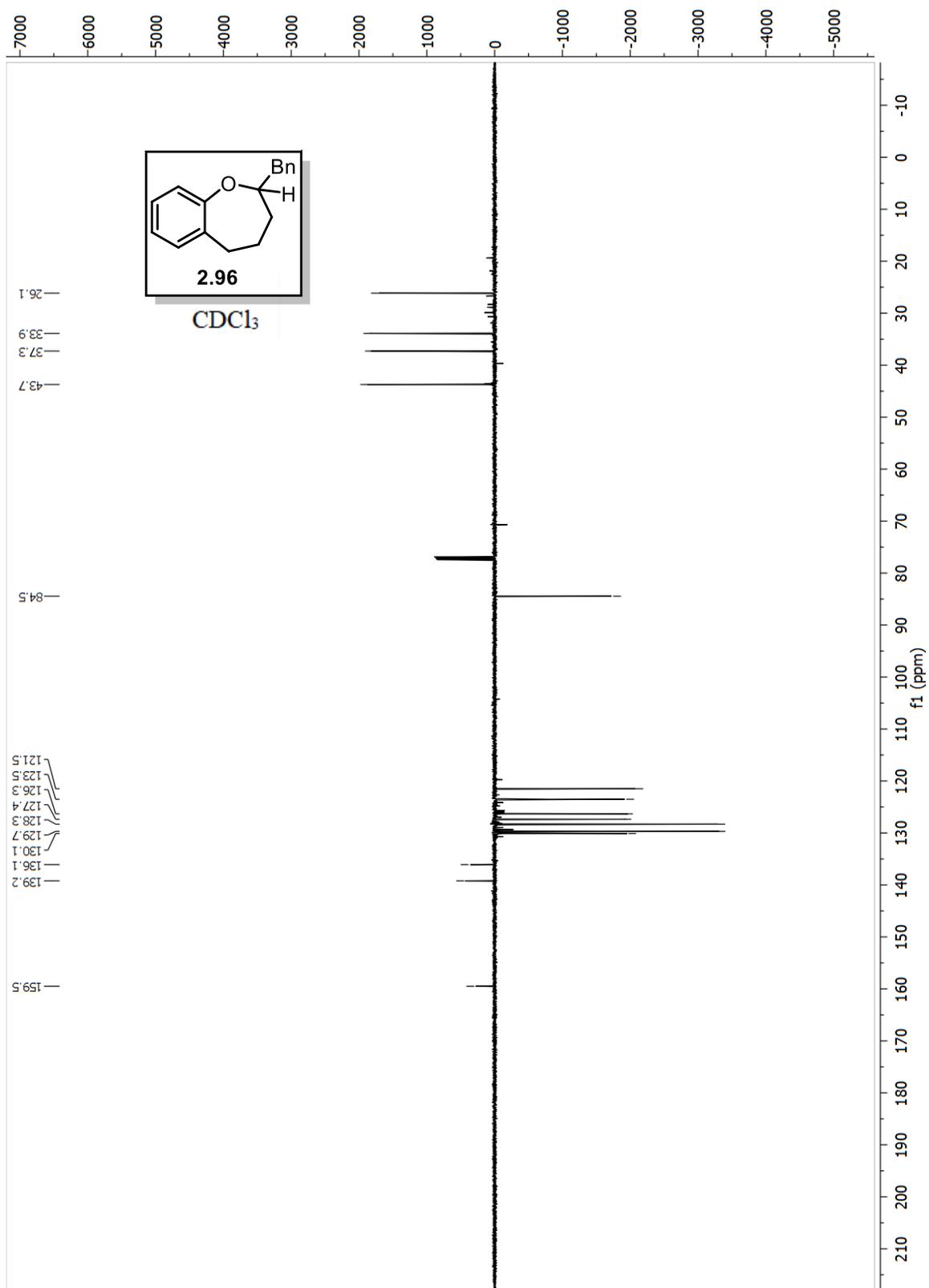


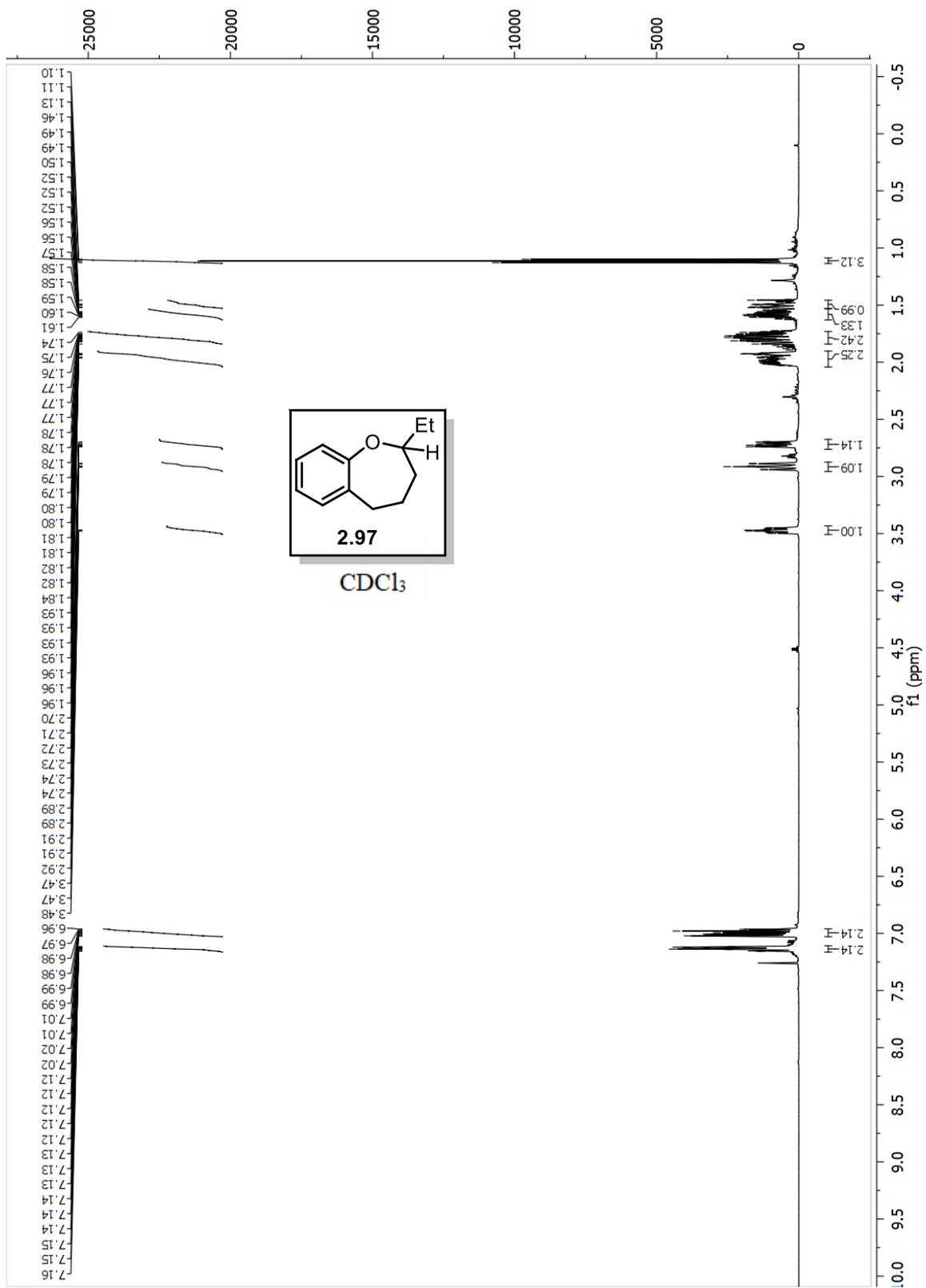


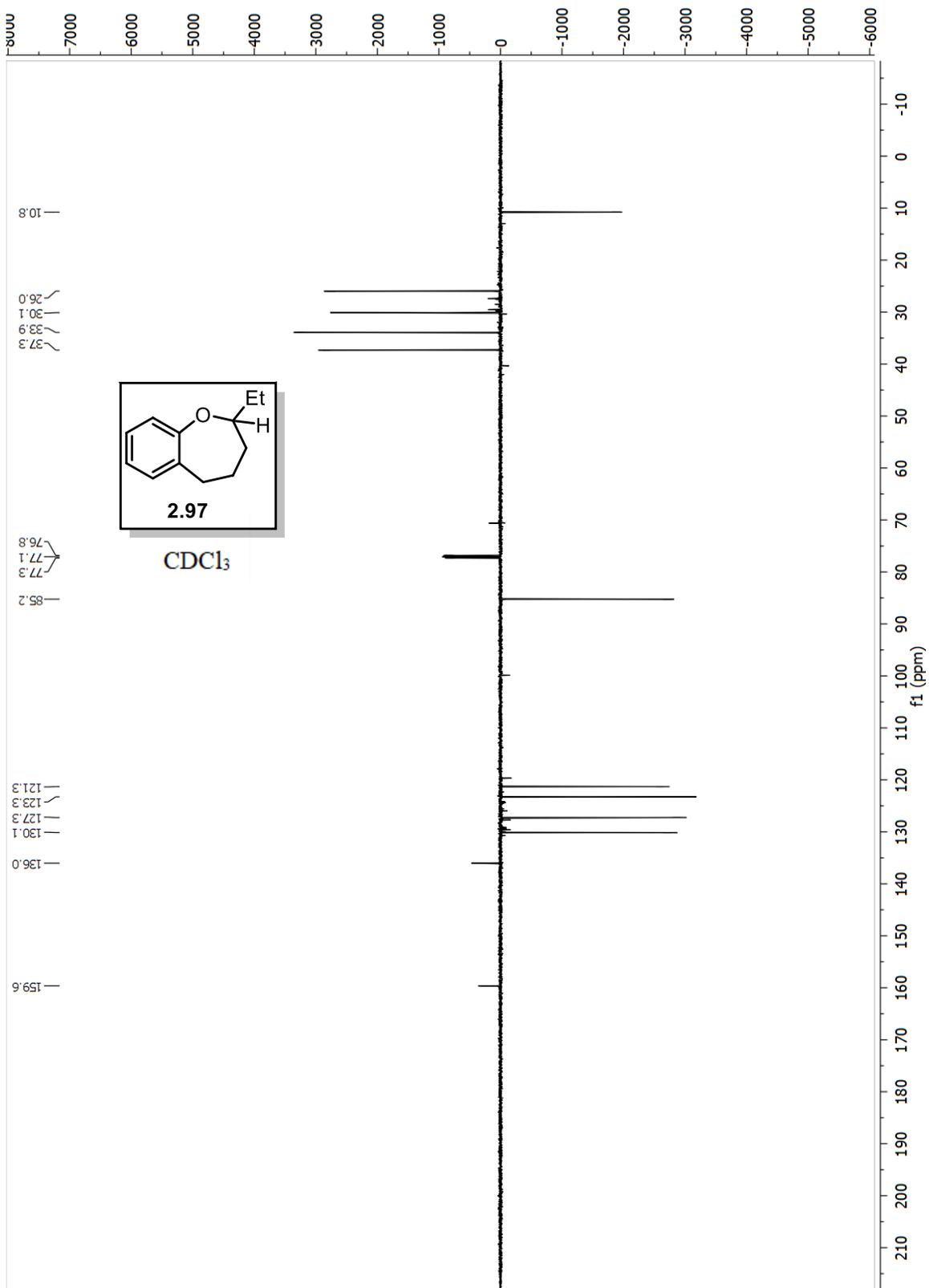


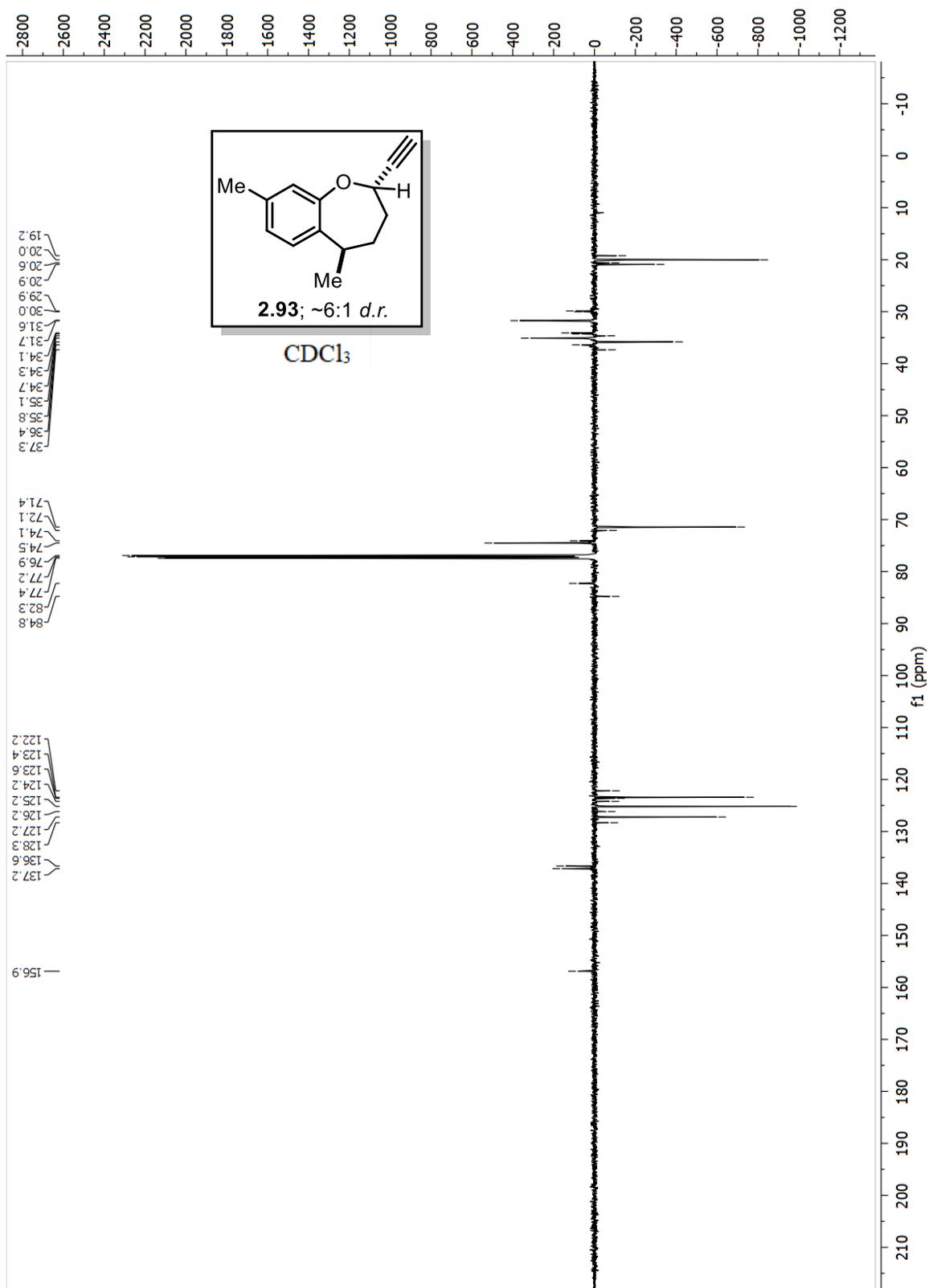


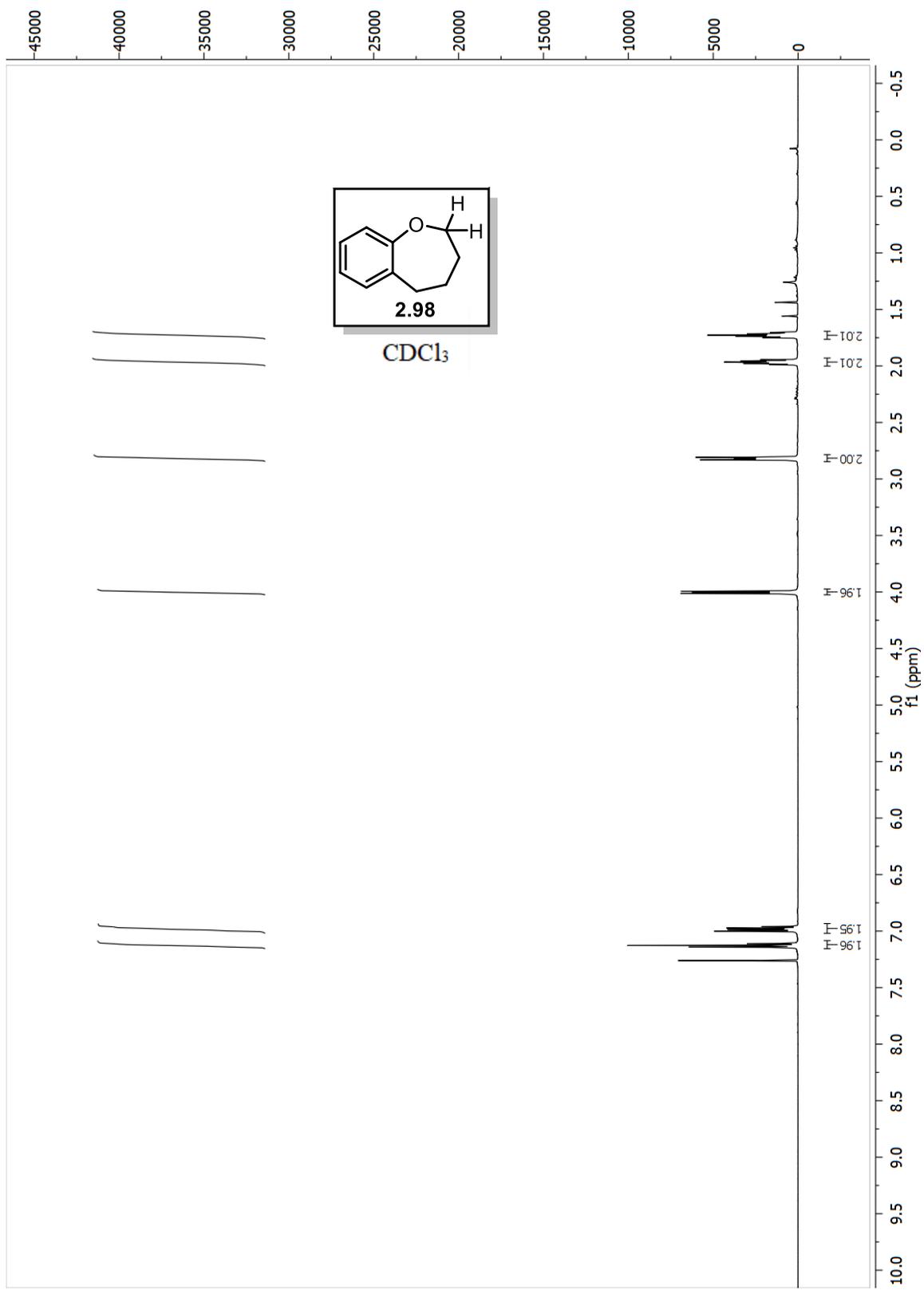


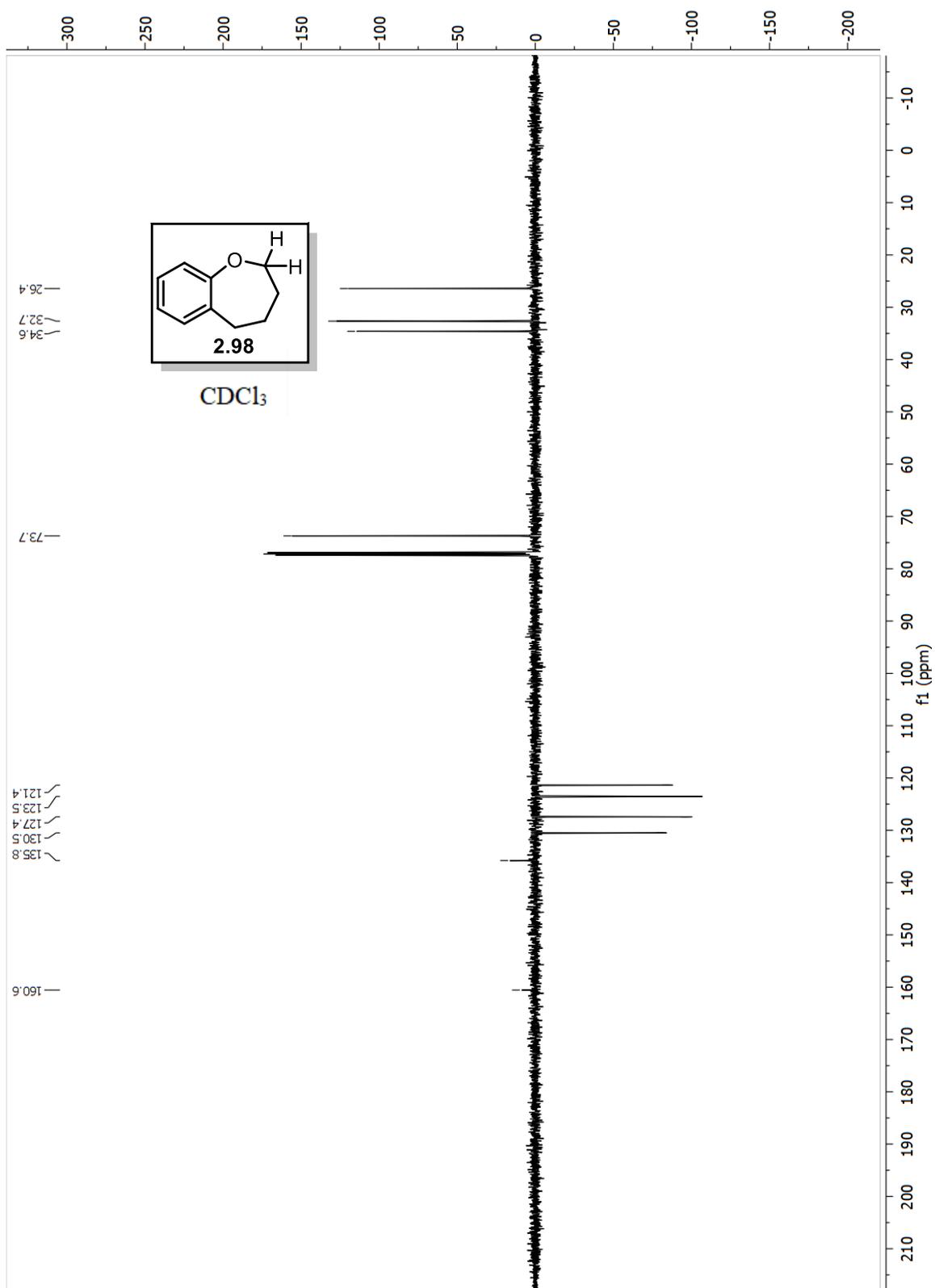


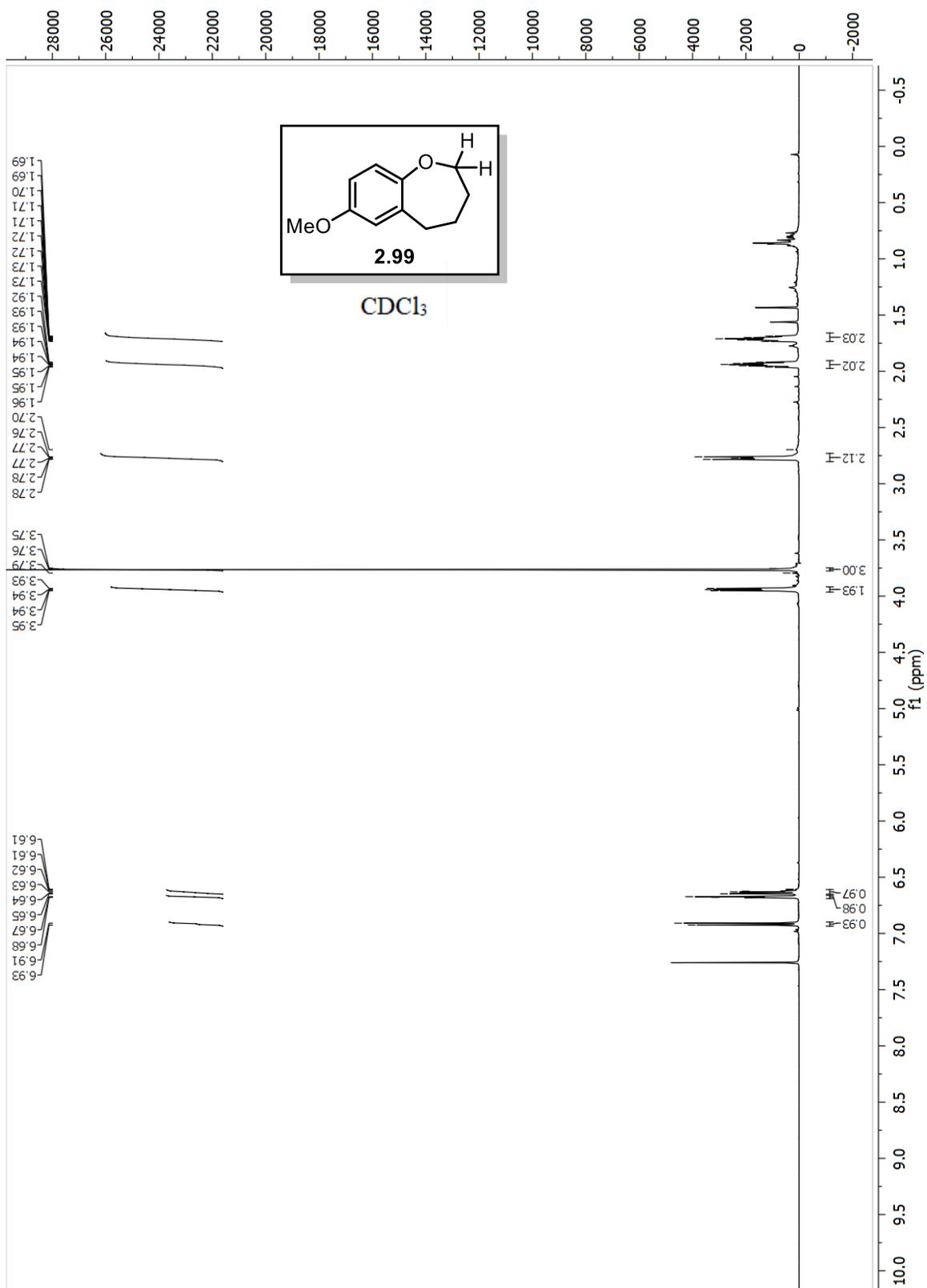


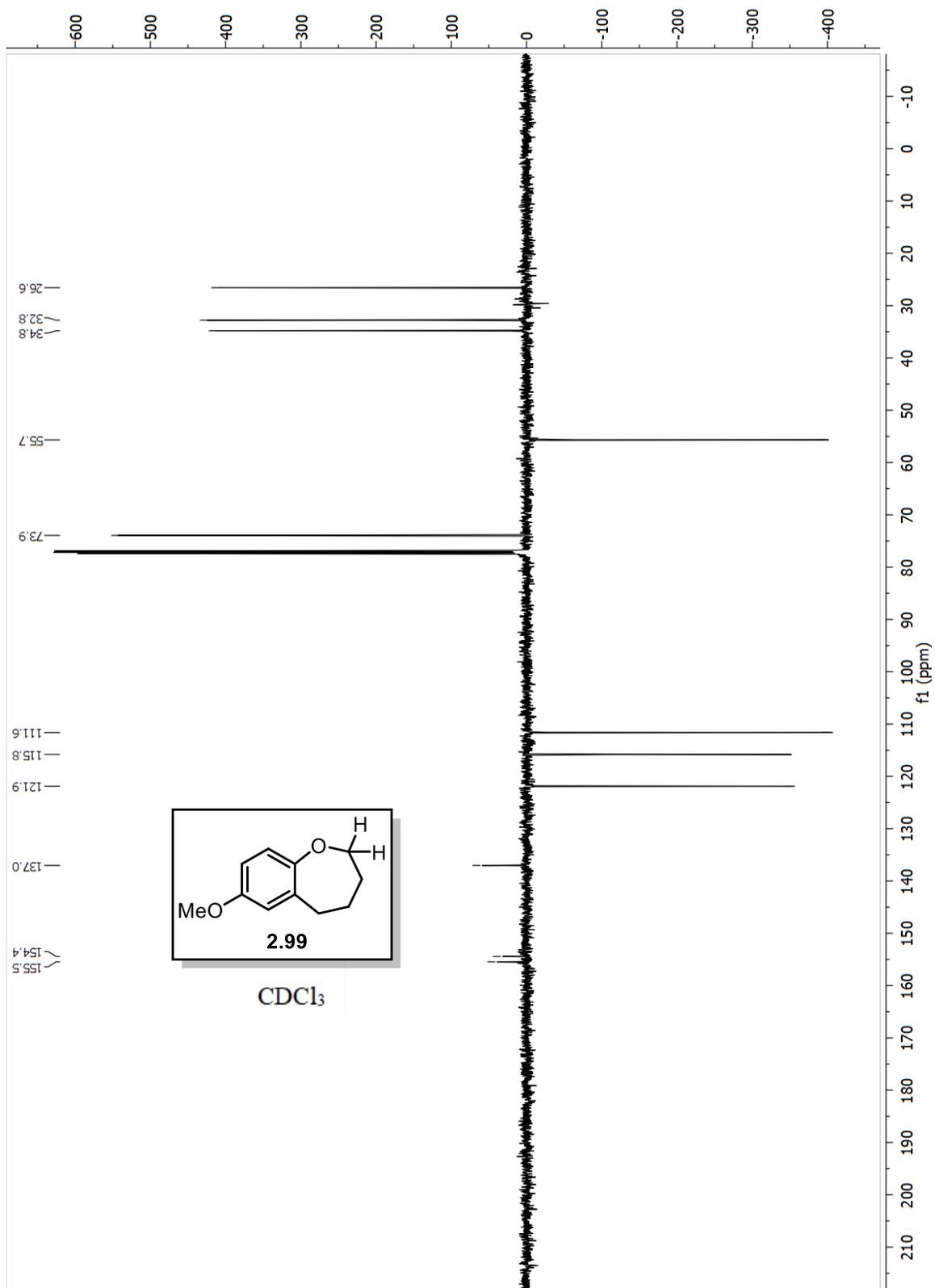


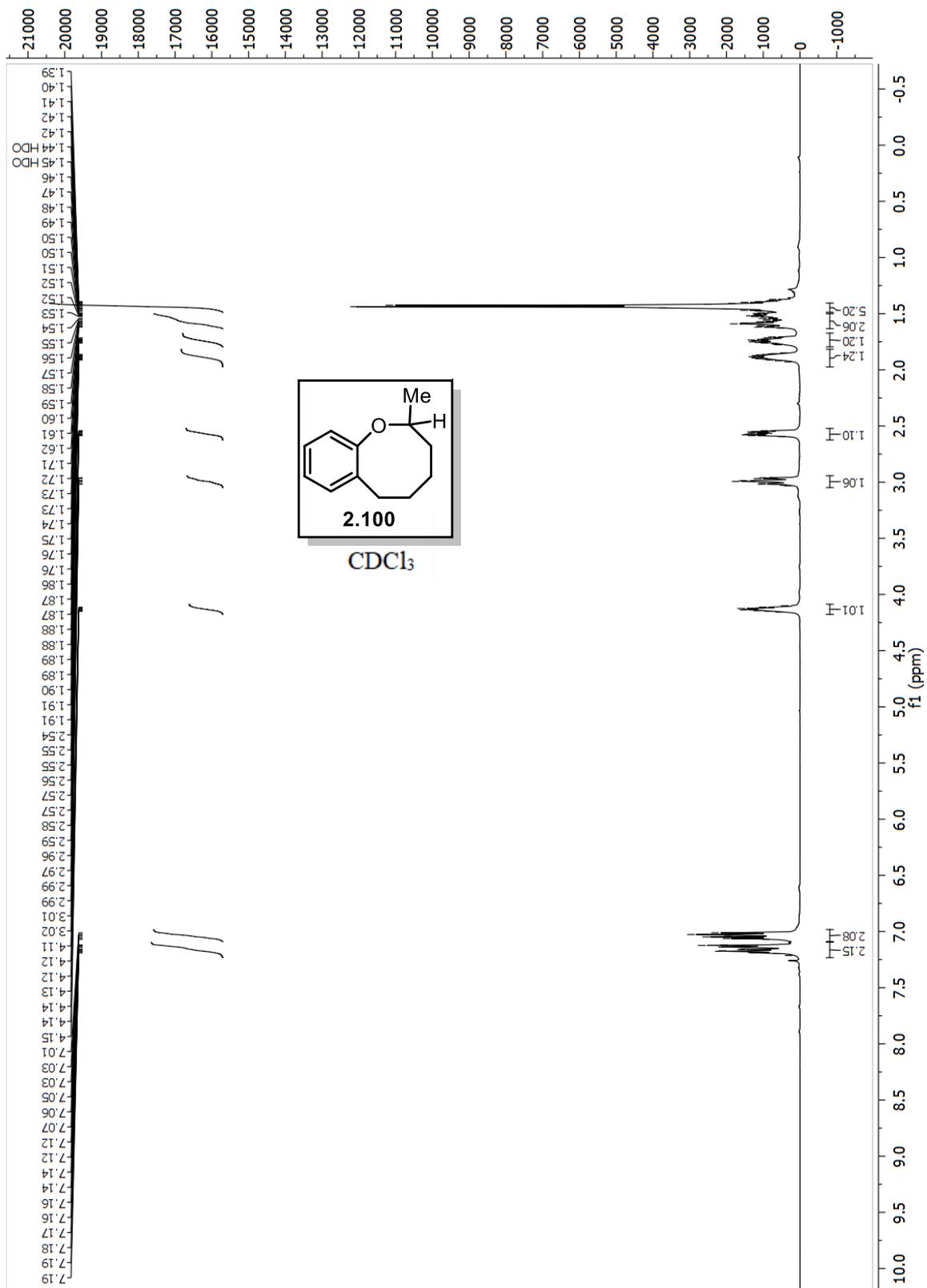


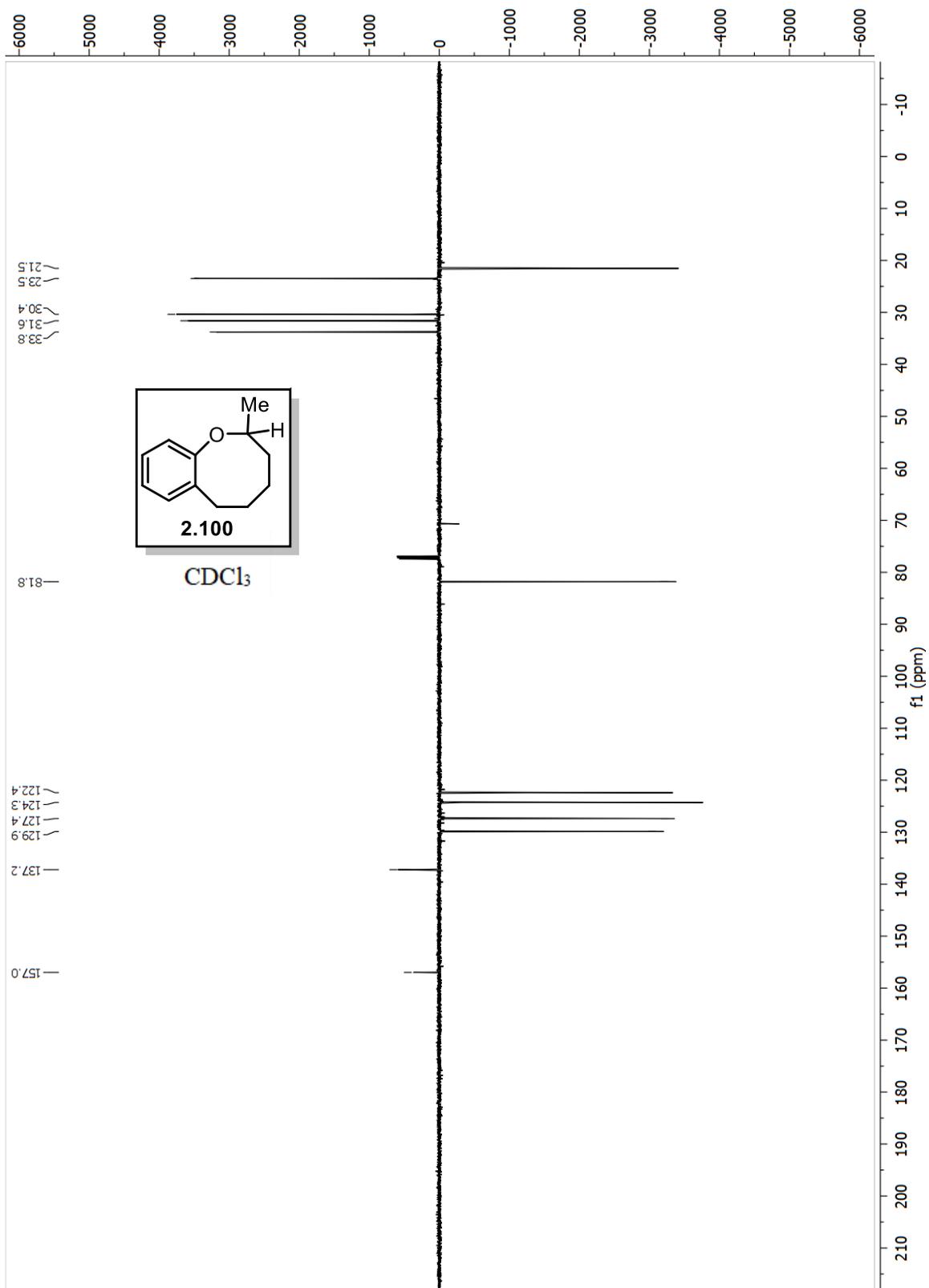


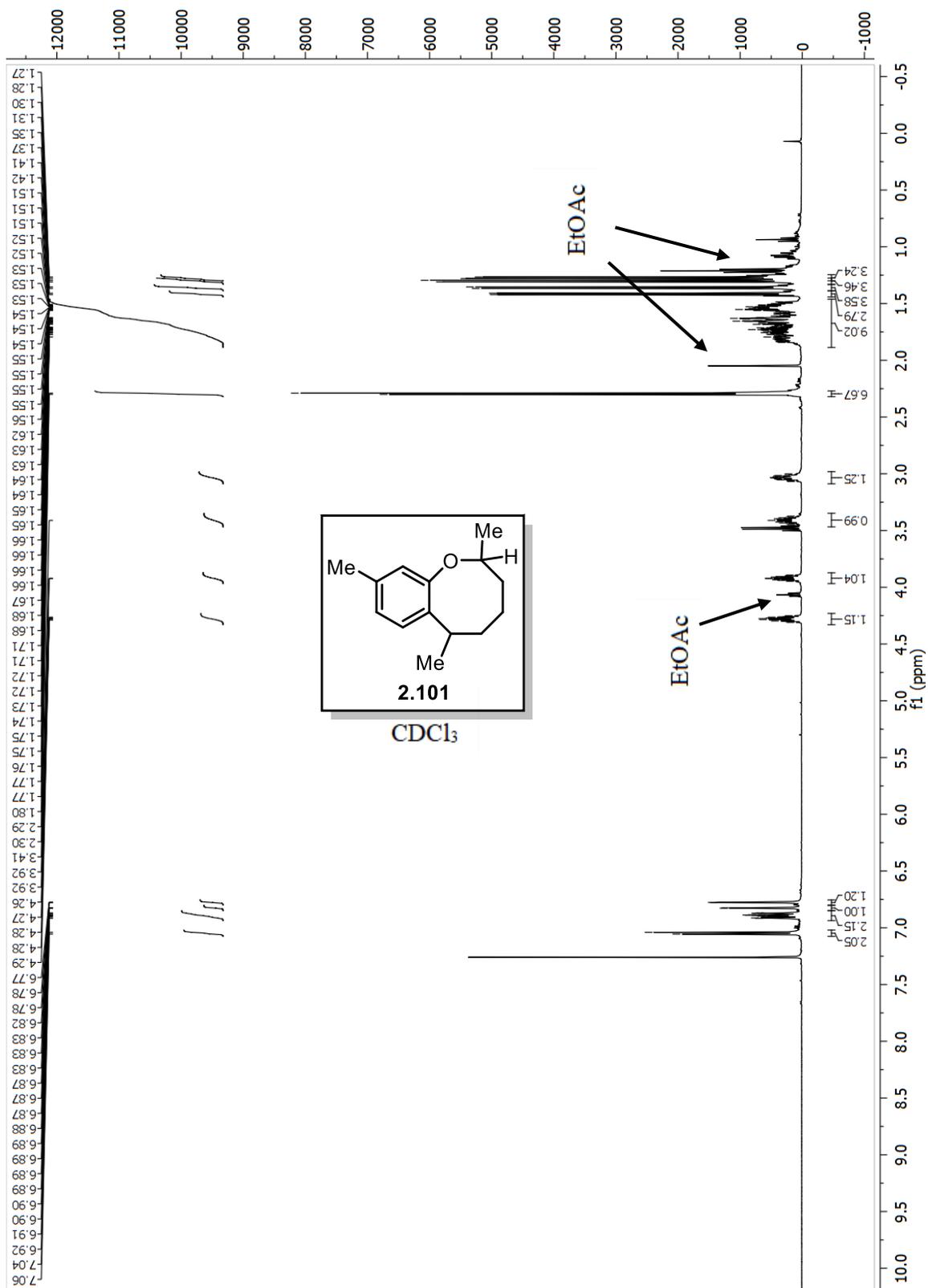


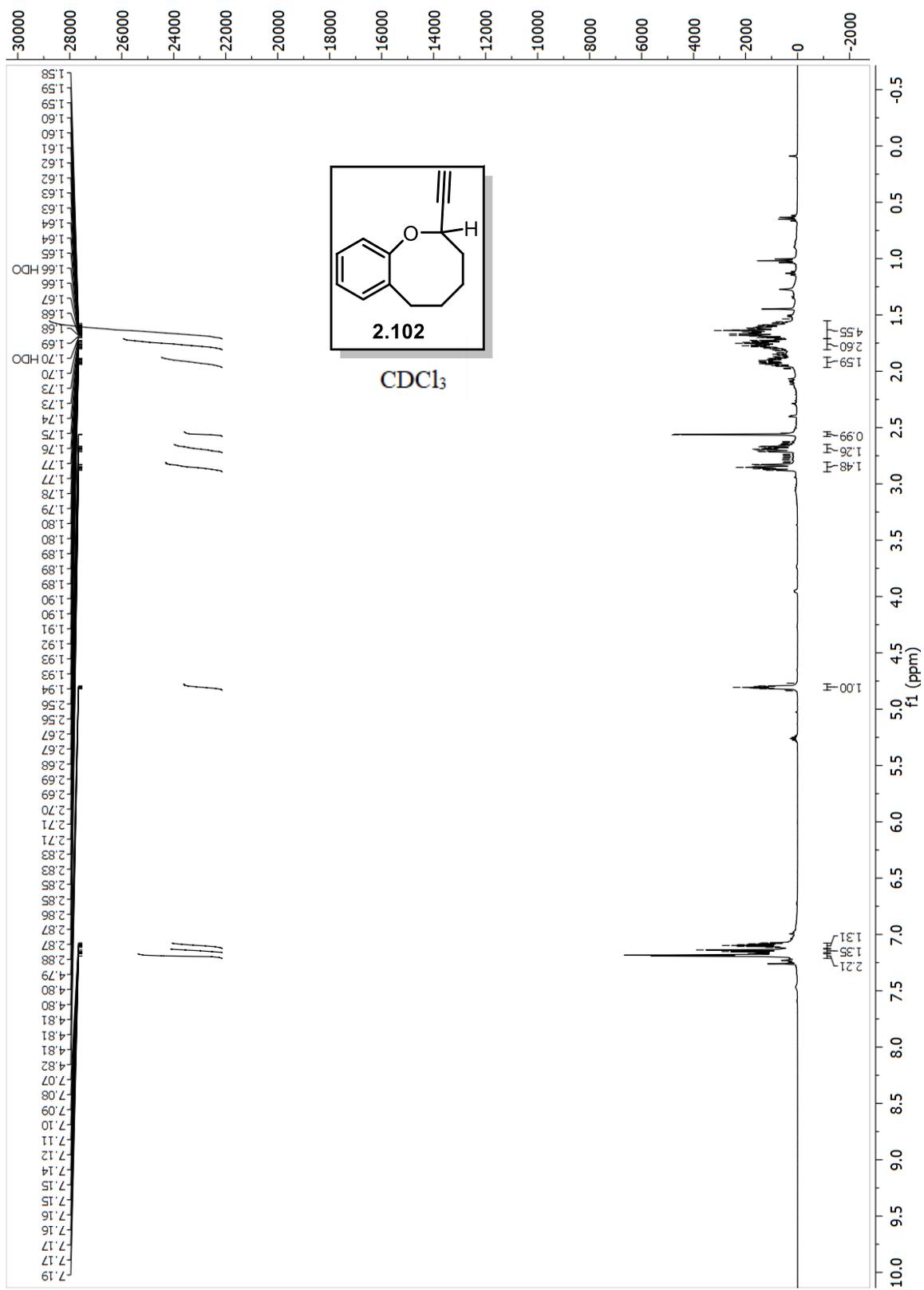


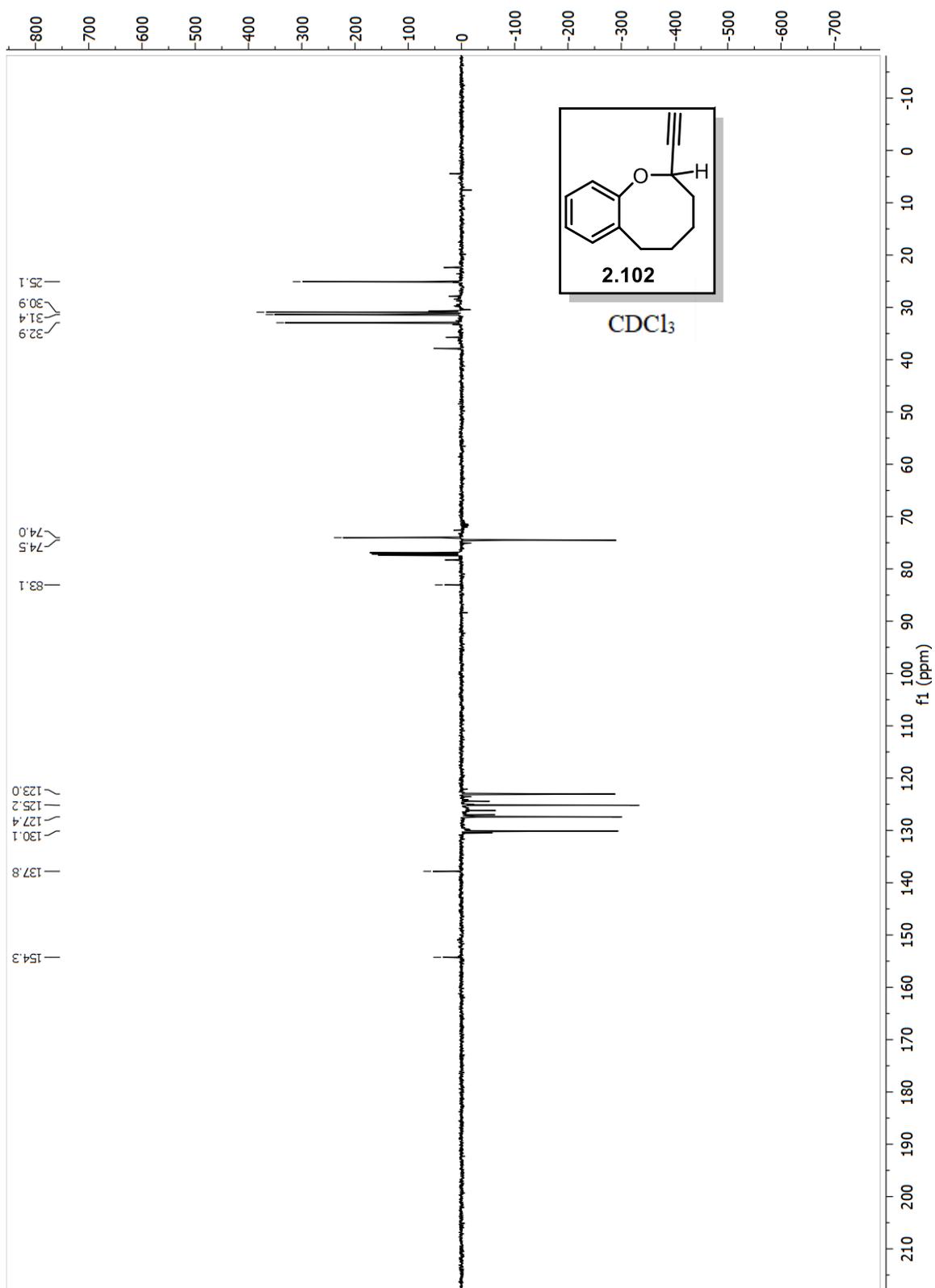


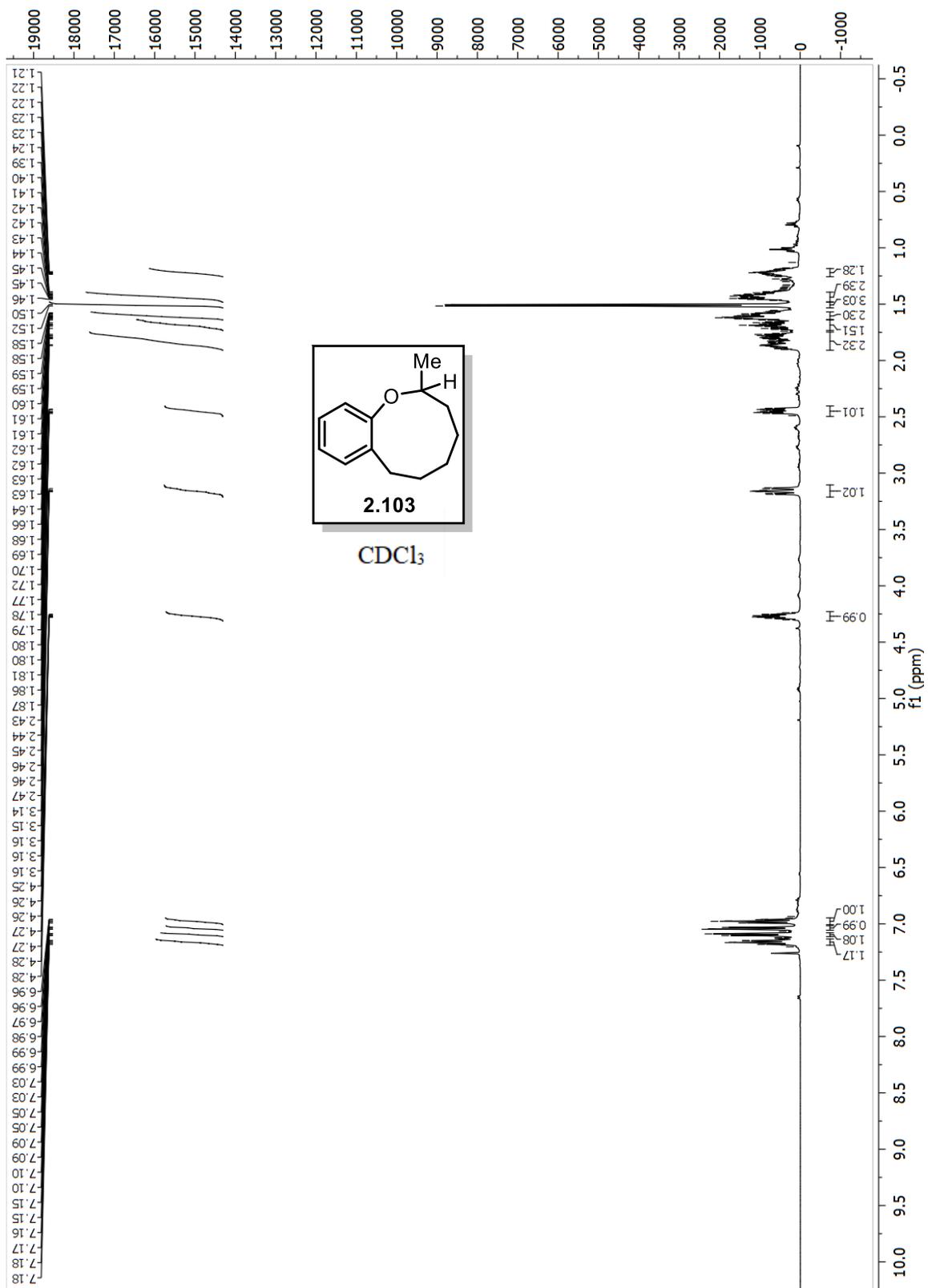


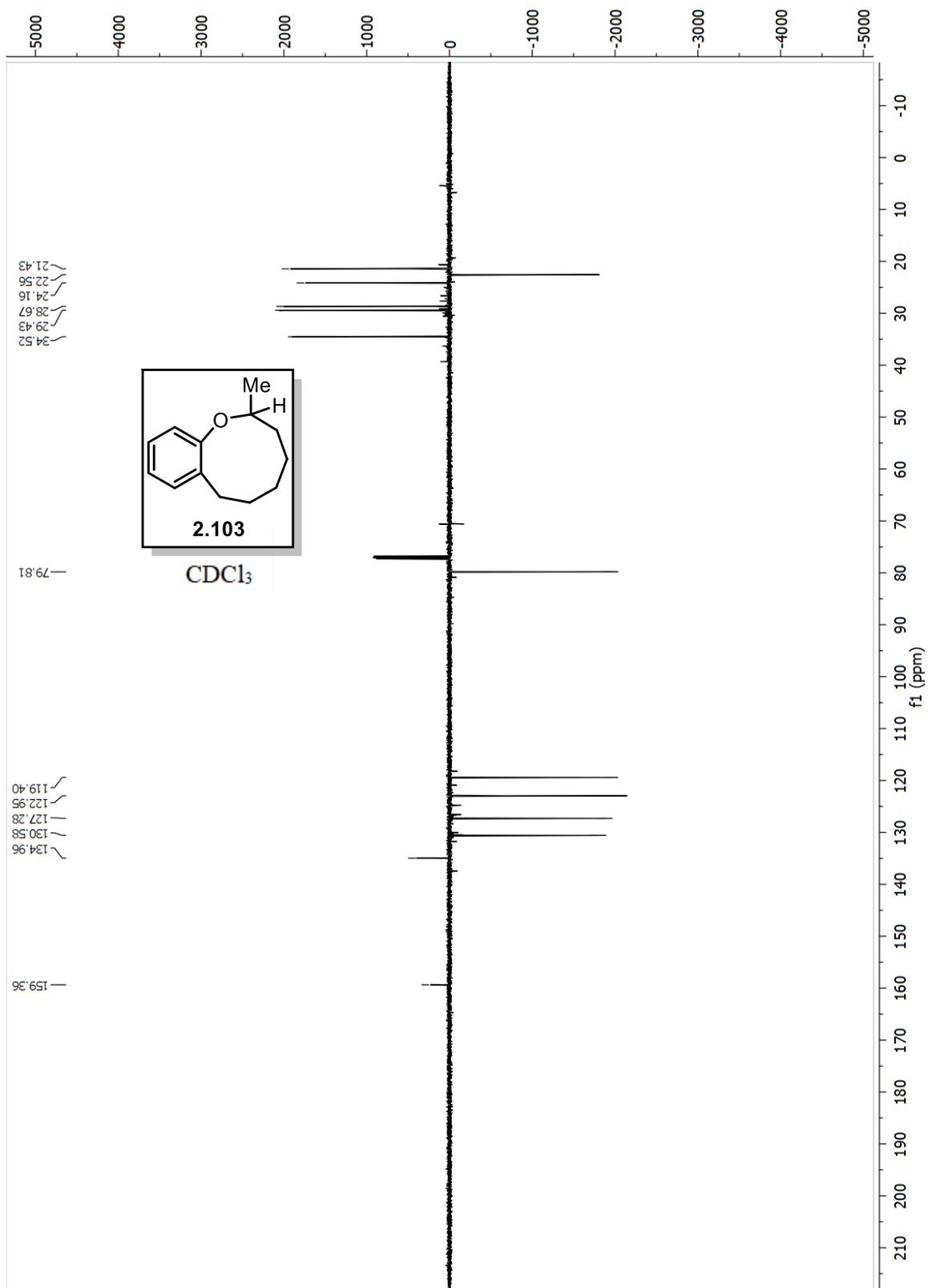


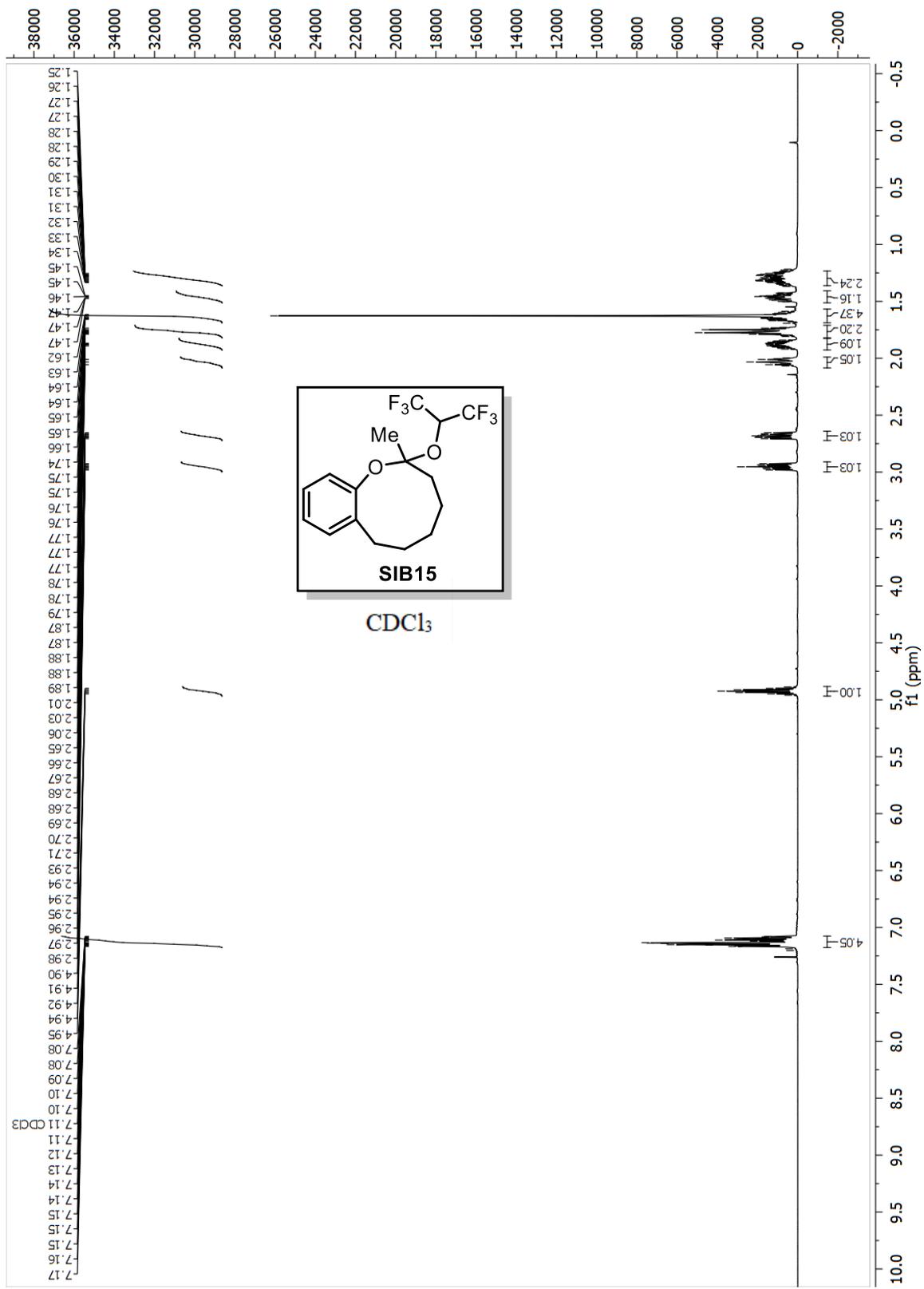


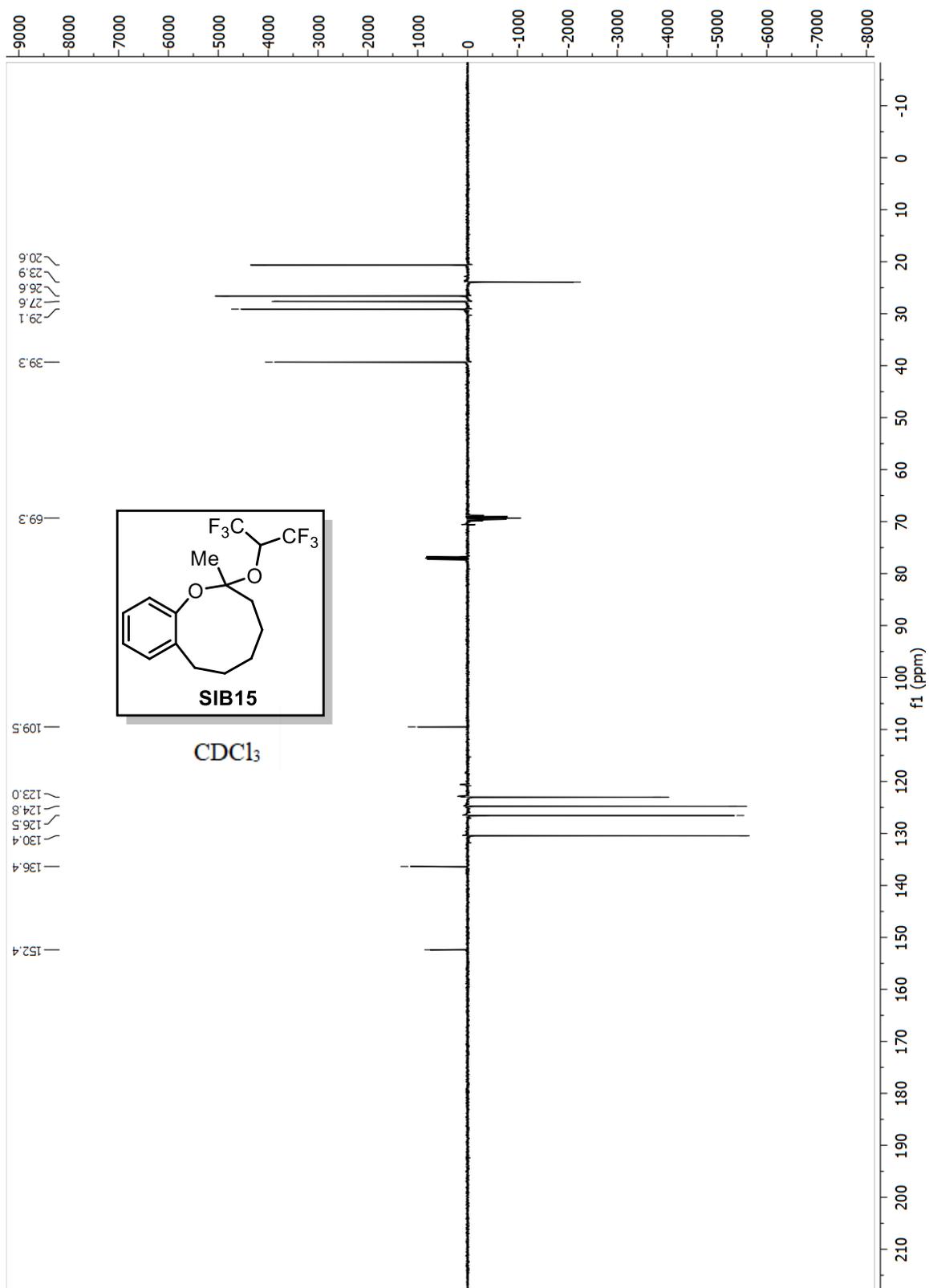












APPENDIX C: TOTAL SYNTHESIS OF HELIANNUOL D

C1: GENERAL INFORMATION

^1H and ^{13}C NMR spectra were recorded at 500 MHz and 126 MHz on a Bruker Advance 500, 500 MHz and 126 MHz on a Bruker Advance III HD, or 400 MHz and 101 MHz on a Bruker Advance 400. ^1H NMR chemical shifts were reported in part per million (ppm) from the solvent resonance (CDCl_3 7.26 ppm or $\text{DMSO-}d_6$). The data was reported as follows: chemical shift number, multiplicity (s = singlet, d = doublet, t = triplet, s = septet, dd = doublet of doublets, td = triplet of doublets, m = multiplet, br = broad signal). Proton decoupled attached proton test (APT) ^{13}C NMR shifts were reported in ppm from the solvent resonance (CDCl_3 77.16 ppm). The glovebox used is a Vacuum Atmospheres NexGen system with a maximum humidity of 0.05% (500 ppm). The reaction solvents used were anhydrous (HPLC-grade solvent passed through an activated-alumina column) unless otherwise noted. Hexafluoroisopropanol (HFIP) was purchased from Oakwood Chemical, distilled over CaH_2 and stored over activated 3 Å molecular sieves under an atmosphere of argon.

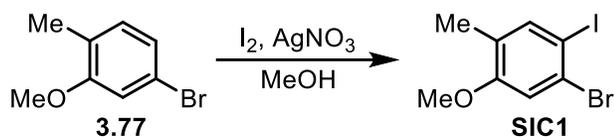
Trimethylsilyl trifluoromethanesulfonate (TMSOTf) and trimethylsilyl cyanide (TMSCN) were purchased from Oakwood Chemical, distilled over CaH_2 and stored over activated 3 Å molecular sieves under an atmosphere of argon. Diisopropylamine [(iPr) $_2\text{NH}$] was purchased from Oakwood Chemical and freshly distilled over CaH_2 prior to use. *N*-bromosuccinimide (NBS) was purchased from Oakwood Chemical and recrystallized from water prior to use. Septum sealed bottles of anhydrous butyllithium reagents were purchased from Sigma Aldrich and used without further purification. All

deuterated solvents were purchased from Cambridge Isotope Laboratories (CIL) and stored over activated 5 Å molecular sieves. All other reagents were purchased from Sigma-Aldrich (now Millipore Sigma), Fisher Chemical, and Oakwood Chemical, and used without further purification. [(pyridine)₂I⁺Ph] 2OTf⁻, [(2-methoxypyridine)₂I⁺Ph] 2OTf⁻, and [(4-dimethylaminopyridine)₂I⁺Ph] 2OTf⁻ were synthesized (See Appendix A) and used without further purification.

Flash chromatography was carried out using Sorbent Technologies silica gel 60 Å (40–63 μm) in the solvent system listed in the individual experiments. Reactions were monitored using analytical thin-layer chromatography (TLC) on Merck silica gel (60 F254) plates. GCMS analysis was performed using an Agilent 7980B GC/5977A MS. The products were separated using a J&W CycloSil-B GC Column (30% Heptakis (2,3-di-O-methyl-6-O-t-butyl dimethylsilyl)-β-cyclodextrin in DB-1701; 30 m length, 25 mm ID, 0.25 μm Film Thickness). Experiment parameters are listed for each individual separation. Accurate masses for derivatized products were conducted on an Agilent 6520 Accurate-Mass Q-TOF LC/MS. Samples were taken up in a suitable solvent for analysis. The signals were mass measured against an internal lock mass reference of perfluorotributylamine (PFTBA) for EI-GCMS, and leucine enkephalin for ESI-LCMS. Waters software calibrates the instruments, and reports measurements, by use of neutral atomic masses. The mass of the electron is not included. Melting points were obtained on a Stanford Research Systems MPA100 OptiMelt Automated Melting Point System and are uncorrected.

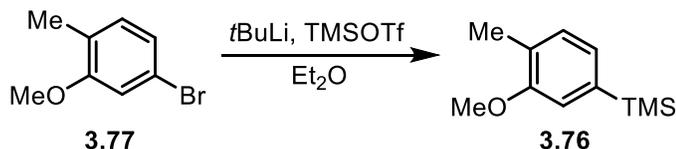
C2: ARYNE APPROACH

1-bromo-2-iodo-5-methoxy-4-methylbenzene (SIC1)



To a stirred solution of bromoarene **3.77** (1.00 g, 5.0 mmol, 1.0 equiv.) in methanol (25 mL) was added AgNO₃ (840 mg, 5.0 mmol, 1.0 equiv.) and I₂ (1.26 g, 5.0 mmol, 1.0 equiv.). The reaction was stirred for 2 hours under an argon atmosphere, then filtered over celite. The filtrate was quenched with saturated sodium thiosulfate and the following mixture was extracted with ethyl acetate (3x). The combined organics were washed with brine (3x) then dried over sodium sulfate and concentrated. Upon concentration, a yellow solid insoluble in Et₂O remained and was filtered away. The filtrate was concentrated to reveal **SIC1** as a yellow oil. **Yield:** 1.36 g, 83%. **¹H NMR:** (500 MHz, Chloroform-*d*) δ 7.55 (s, 1H), 7.05 (s, 1H), 3.80 (s, 3H), 2.11 (s, 3H).

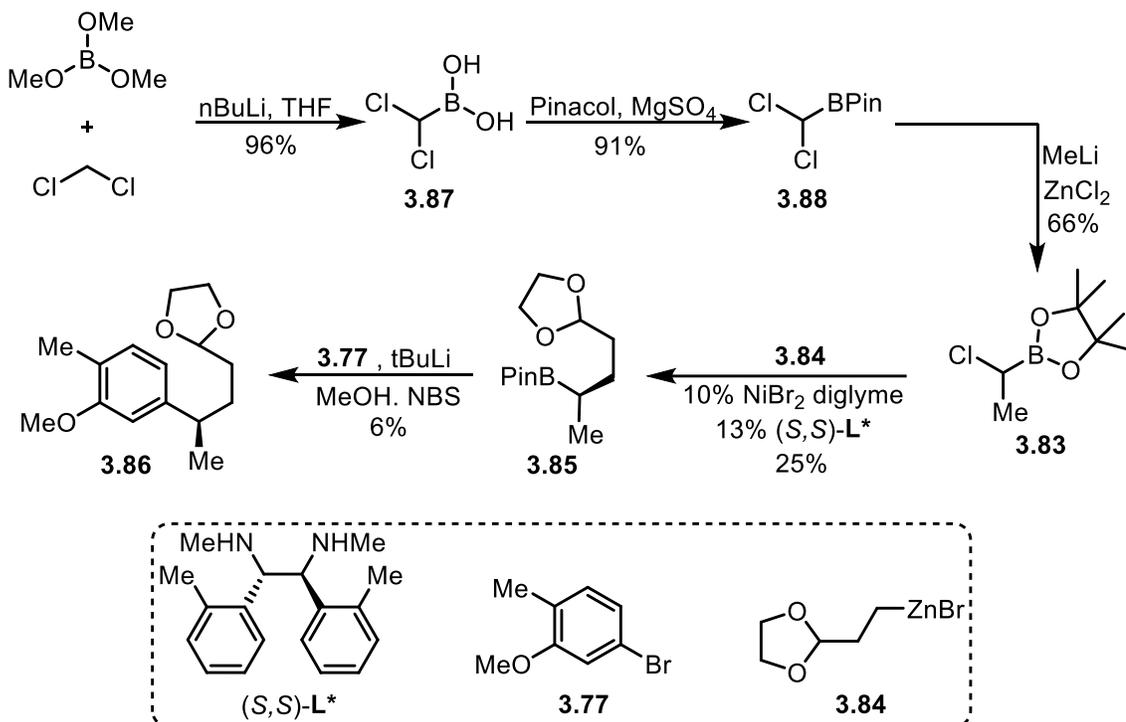
(3-methoxy-4-methylphenyl)trimethylsilane (3.76)



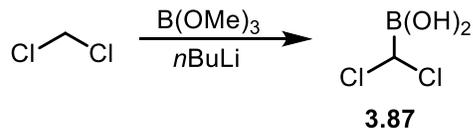
Bromoarene **3.77** (1.00 g, 5.0 mmol, 1.0 equiv.) was added to a flame-dried round-bottomed flask along with Et₂O (20 mL). The solution was cooled to -78 °C and stirred for 5 minutes, then *t*BuLi was added (5.88 mL, 10 mmol, 2.0 equiv.). The resulting lithiate was stirred for 30 minutes, followed by the addition of dry TMSOTf. The solutions was allowed to stir overnight while warming to ambient temperature. A

saturated solution of sodium bicarbonate was added, and the mixture was extracted with Et₂O (3x). The combined organic extracts were washed with water (3x) and brine (1x), then dried over sodium sulfate and concentrated to afford **3.76** as a yellow oil. **Yield:** 430 mg, 44%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.15 (dd, *J* = 7.2, 0.9 Hz, 1H), 7.03 (d, *J* = 7.1, 1.0 Hz, 1H), 6.95 (s, 1H), 3.86 (s, 3H), 2.22 (s, 3H), 0.27 (s, 9H).

C3: NICKEL-MEDIATED APPROACHES



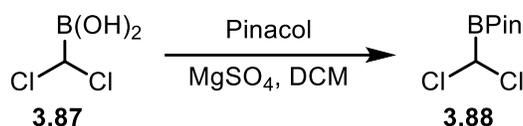
(dichloromethyl)boronic acid (**3.87**)¹



To a flame-dried round-bottomed flask was added THF (40 mL) and DCM (1.57 mL, 24.6 mmol, 1.23 equiv.). The solution was cooled to -78 °C, then *n*BuLi (8 mL, 20.0 mmol, 1.00 equiv.) was added dropwise over 5 minutes. The resulting lithiate was allowed to stir for 30 mins, followed by the addition of trimethylborate (2.34 mL, 21.0

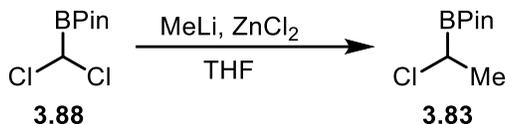
mmol, 1.05 equiv.). The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for a further 40 minutes, then warmed to ambient temperature. At which point, a solution of HCl (10 mL, 5 M) was added and the mixture was stirred for 1 hour. The mixture was transferred to a separatory funnel and the organics extracted with EtOAc (3x). The combined extracts were washed once with brine, then dried over sodium sulfate and concentrated to reveal the product as a pale-yellow oil. **Yield:** 2.51 g, 97%. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 5.33 (s, 1H).

2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.87)¹



To a flame-dried round-bottomed flask was added borate **3.87** (2.51 g, 19.52 mmol, 1.00 equiv.) in DCM (25 mL). Pinacol (2.54 g, 21.47 mmol, 1.1 equiv.) and MgSO₄ (spatula scoop) were quickly added and the resulting mixture was allowed to stir for 18 hours. The heterogeneous solution was then diluted with DCM and filtered, and the filtrate was concentrated and distilled under reduced pressure to reveal the product as a colorless oil. **Yield:** 3.75 g, 91%. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 5.35 (s, 1H), 1.33 (s, 12H).

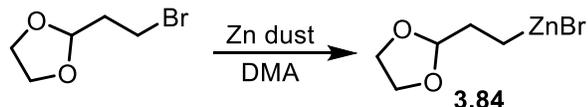
2-(1-chloroethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.83)²



Boronic ester **3.88** (2.00 g, 9.48 mmol, 1.0 equiv.) was dissolved in THF (20 mL) in a flame-dried round-bottomed flask, and the solution was cooled to $-78\text{ }^{\circ}\text{C}$. After stirring for 5 minutes, a solution of methyllithium (1.6 M Et₂O; 5.92 mL, 9.48 mmol, 1.0 equiv.) was added slowly and the reaction was stirred for 30 mins at $-78\text{ }^{\circ}\text{C}$. A solution of zinc chloride (ZnCl₂, 1 M Et₂O; 8.1 mL, 8.06 mmol, 0.85 equiv.) was added and stirring

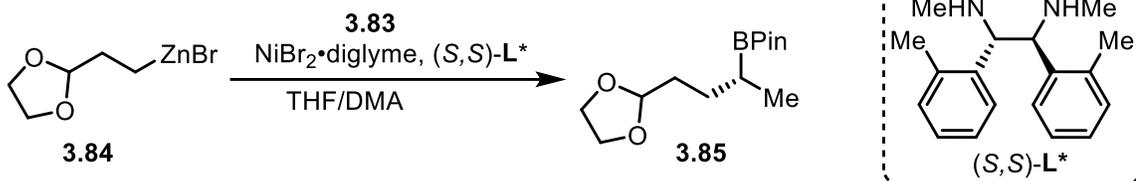
continued for 90 mins before allowing to warm to ambient temperature and stir overnight. The following morning, the solution was quenched with saturated ammonium chloride and extracted with DCM (3x). The combined organic extracts were then dried over sodium sulfate and concentrated to reveal the desired product as a colorless oil. **Yield:** 1.20 g, 66%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 3.51 (q, $J = 7.6, 1.0$ Hz, 1H), 1.54 (d, $J = 7.5, 1.0$ Hz, 3H), 1.28 (s, 12H).

(2-(1,3-dioxolan-2-yl)ethyl)zinc(II) bromide (3.84)³



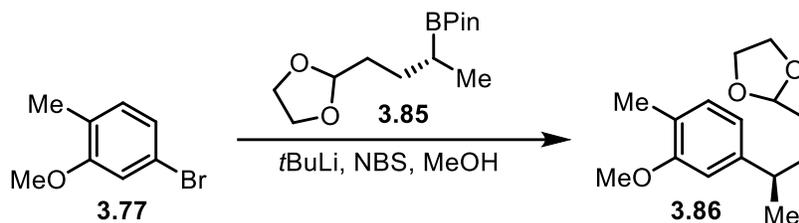
Following literature protocol³ Zinc dust (1.00 g, 15.28 mmol, 1.0 equiv.) was placed in a flame-dried round-bottomed flask and gently heated with a heat gun under vacuum to remove excess water. Catalytic iodine (129 mg, 0.06 mmol, 0.05 equiv.) was added, followed by distilled dimethylacetamide (DMA, 1.0 mL). The solution was stirred until colorless, then a solution of the bromoacetal (1.22 mL, 10.19 mmol, 1.0 equiv.) in DMA (2.4 mL) was added. The flask was sealed the suspension was stirred at 80 °C for 13 hours. The yellowish-grey suspension was pulled into a syringe, which was then fitted with a syringe filter. The solution was then dispensed into a flame-dried Schlenk flask. The solution was titrated by dissolving 0.25 mmol I₂ in 1.5 mL of a saturated solution of LiCl in dry THF. When an equimolar quantity of zincate (to I₂) is added the solution becomes colorless. Thus, a zincate solution of 0.45–1.50 M is obtained and can be stored under Ar for at least one month. The compound was not analyzed beyond titration.

2-(4-(1,3-dioxolan-2-yl)butan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.85)



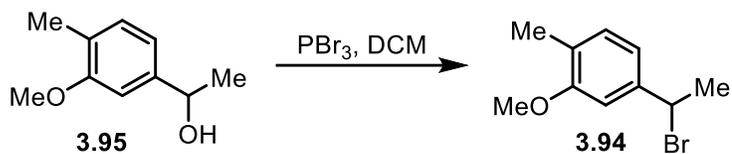
Following literature procedure³ the chiral diamine ligand (24.4 mg, 0.09 mmol, 0.13 equiv.) and $\text{NiBr}_2 \cdot \text{diglyme}$ (24.7 mg, 0.07 mmol, 0.10 equiv.) were placed in a flame-dried flask and pump-purged with argon (3x). THF (3 mL) and DMA (100 μL) were added, and the bluish-green solution was stirred for ~1 hour. At which point, the solution became yellow/green. In a separate flame-dried round-bottomed flask, boronic ester **3.83** (133 mg, 0.70 mmol, 1.0 equiv.) was added and pump-purged with argon (3x). The pre-formed catalyst solution was then transferred to the flask containing ester **3.83**. The catalyst flask was rinsed with 2 mL THF (2x), and the washings were added to the reaction flask. The reaction mixture was then cooled to 0 $^\circ\text{C}$, and a solution of zincate **3.84** (0.45 M, 2.82 mL, 1.26 mmol, 1.80 equiv.) was added. The reaction was stirred at 0 $^\circ\text{C}$ for 16 hours, over which period it became dark grey/black. A 20% solution of methanol in Et_2O (1 mL) was added and the reaction was loaded onto a silica plug. The plug was flushed 3x with 50 mL portions of Et_2O , and the flushes were concentrated. Purification on silica (10 \rightarrow 30% $\text{EtOAc}/\text{Hexanes}$) was performed to afford the desired product as a colorless oil. **Yield:** 44 mg, 25%. **$^1\text{H NMR}$** (500 MHz, $\text{Chloroform-}d$) δ 4.84 (t, $J = 4.9$ Hz, 1H), 3.98 – 3.93 (m, 2H), 3.87 – 3.79 (m, 2H), 1.70 – 1.64 (m, 2H), 1.61 – 1.52 (m, 1H), 1.45 – 1.37 (m, 1H), 1.23 (s, 12H), 0.98 (d, $J = 6.8$ Hz, 3H).

(R)-2-(3-(3-methoxy-4-methylphenyl)butyl)-1,3-dioxolane (3.86)



To a flame-dried test tube fitted with a Teflon-coated septum cap was added a solution of bromoarene **3.77** (15.0 mg, 0.12 mmol, 1.0 equiv.) in THF (400 μ L). The solution was cooled to -78 $^{\circ}$ C, followed by the addition of *t*BuLi (1.7 M pentane; 164 μ L, 0.28 mmol, 2.4 equiv.). The lithiate was allowed to continue stirring at -78 $^{\circ}$ C for 30 mins, then a solution of acetal **3.85** (27.9 mg, 0.14 mmol, 1.2 equiv.) in THF (300 μ L) was added. The resulting solution was stirred for 1 hour, then allowed to warm to ambient temperature.⁴ Upon reaching ambient temperature, the reaction was concentrated to remove THF and 300 μ L of MeOH was added. With stirring, N-bromosuccinimide (NBS, recrystallized from H₂O; 41.0 mg, 0.23 mmol, 2.0 equiv.) in 700 μ L MeOH was added, along with 100 μ L THF. The reaction was warmed to 60 $^{\circ}$ C and stirred for 8 hours, then quenched with a saturated solution of sodium thiosulfate. The quenched reaction was stirred for an additional 20 minutes, extracted with EtOAc (3x). The combined organic extracts were then washed once with water and brine each, then dried over sodium sulfate and concentrated. Purification was performed via preparatory thin layer chromatography (10% Et₂O/pentane) to deliver the product as a yellow oil. **Yield:** 2 mg, 6%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.03 (d, *J* = 7.5, 0.9 Hz, 1H), 6.69 (d, *J* = 7.5, 1.7 Hz, 1H), 6.65 (s, 1H), 4.82 (t, *J* = 4.6 Hz, 1H), 3.99 – 3.88 (m, 2H), 3.82 (d, *J* = 1.9 Hz, 5H), 2.67 (h, *J* = 7.1 Hz, 1H), 2.17 (d, *J* = 0.7 Hz, 3H), 1.78 – 1.45 (m, 5H), 1.25 (d, *J* = 6.9 Hz, 3H).

4-(1-bromoethyl)-2-methoxy-1-methylbenzene (**3.94**)



Benzylic alcohol **3.95** (2.03 g, 12.24 mmol, 1.0 equiv.) was transferred with DCM (1 mL) to a flame-dried round-bottomed flask under argon. (For the optimized synthesis and characterization of **3.95**, see Appendix D). The solution was cooled to 0 °C, then PBr₃ (0.84 mL, 8.82 mmol, 0.72 equiv.) in DCM (1 mL) was added dropwise. The resulting solution was stirred at 0 °C for 2 hours, then quenched with water (2 mL) and stirred for an additional 5 minutes. The mixture was extracted with DCM (3x), and the combined organic extracts were washed with saturated aqueous sodium bicarbonate (1x) and brine (1x). The crude material was concentrated, then reconstituted in Et₂O to precipitate insoluble byproducts. The suspension was filtered and the filtrate concentrated to deliver benzylic bromide **3.94** as a dark yellow oil. Spectral data was identical to prior reports.⁵

Yield: 2.0 g, 71%. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.09 (d, *J* = 7.6, 0.9 Hz, 1H), 6.93 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.90 (s, 1H), 5.21 (q, *J* = 6.9 Hz, 1H), 3.86 (s, 3H), 2.20 (d, *J* = 0.7 Hz, 3H), 2.05 (d, *J* = 6.9 Hz, 3H).

C4: RELAY HECK APPROACH

C4i: Catalyst Synthesis

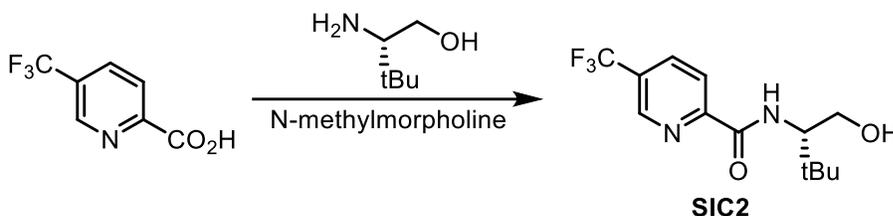


To a round-bottomed flask was added *para*-toluenesulfonate monohydrate (4.58 g, 24.1 mmol, 5.4 equiv) and MeCN (58 mL). In a separate flask, Pd(OAc)₂ (1.0 g, 4.45 mmol, 1.0 equiv.) was dissolved in 86 mL MeCN. The solution of *p*TSA was added to this palladium solution, and the reaction was cooled to 0 °C. An addition funnel was fitted to

the flask and filled with Et₂O (106 mL). The ether was added over a period of 30 minutes, during which the product crashed out of solution as a yellow powder. The product powder was collected via filtration and washed with additional ether, then transferred to a flame-dried vial and dried *in vacuo*. The flask was backfilled with argon and the powder stored indefinitely.^{6,7}

C4ii: Ligand Synthesis

(S)-N-(1-hydroxy-3,3-dimethylbutan-2-yl)-5-(trifluoromethyl)picolinamide (SIC2)⁷

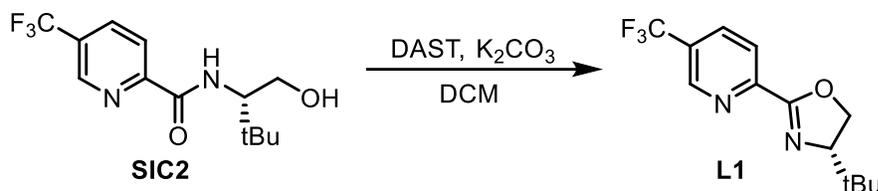


A flame-dried round-bottomed flask was charged with the picolinic acid (280 mg, 1.50 mmol, 1.0 equiv.), followed by the addition of DCM (20 mL). N-methylmorpholine (200 μ L, 1.73 mmol, 1.15 equiv.) was added, then the reaction was cooled to 0 °C.

Isobutylchloroformate (240 μ L, 1.80 mmol, 1.2 equiv) was then added, and the reaction was stirred at this temperature for 20 minutes. After which, a mixture of *tert*-leucinol (190 mg, 1.60 mmol, 1.1 equiv.) in DCM (15 mL) was added. The resulting solution was stirred overnight while warming to ambient temperature. The following day, the solution was transferred to a separatory funnel and diluted with water. The organic layer was removed, and the aqueous layer extracted with DCM (3x). The organic extracts were combined and washed once each with water and brine, then dried over sodium sulfate and concentrated. The material was used in the subsequent step without further purification.

Yield: 420 mg, 96%. ¹H NMR (500 MHz, Chloroform-*d*) δ 8.85 (dd, J = 2.0, 1.0 Hz, 1H), 8.40 – 8.30 (m, 1H), 8.26 (d, J = 8.9 Hz, 1H), 8.12 (ddd, J = 8.2, 2.1, 0.8 Hz, 1H), 4.06 – 3.96 (m, 2H), 3.71 (ddd, J = 11.1, 8.1, 5.0 Hz, 1H), 2.28 (t, J = 5.7 Hz, 1H), 1.05 (s, 9H).

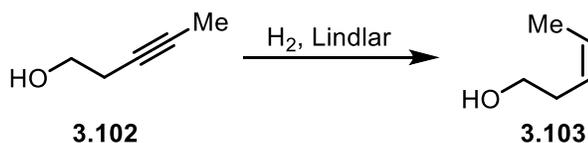
(S)-4-(tert-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (L1)



Peptide **SIC2** (420 mg, 1.44 mmol, 1.0 equiv.) was added to a flame-dried flask under argon and diluted with DCM (20 mL). The solution was cooled to $-78\text{ }^{\circ}\text{C}$, then diethylaminosulfur trifluoride (DAST, 250 μL , 1.88 mmol, 1.3 equiv) was added. The reaction was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for an additional hour, at which point potassium carbonate (398 mg, 2.88 mmol, 2.0 equiv.) and the heterogenous solution was warmed to ambient temperature. DCM was then added, followed by water, and the mixture was transferred to a separatory funnel and extracted with DCM (2x). The combined organic extracts were washed once each with saturated aqueous sodium bicarbonate and brine, then dried over sodium sulfate and concentrated. The crude residue was purified on deactivated silica (10% EtOAc/hexanes, 0.01% triethylamine) to reveal the product as an off-white solid. **Yield:** 215 mg, 55%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 8.96 (s, 1H), 8.22 (d, $J = 8.3, 0.9$ Hz, 1H), 8.02 (d, $J = 8.2, 2.3, 0.8$ Hz, 1H), 4.49 (dd, $J = 10.3, 8.8$ Hz, 1H), 4.35 (t, $J = 8.6$ Hz, 1H), 4.16 (dd, $J = 10.3, 8.5$ Hz, 1H), 0.98 (s, 9H).

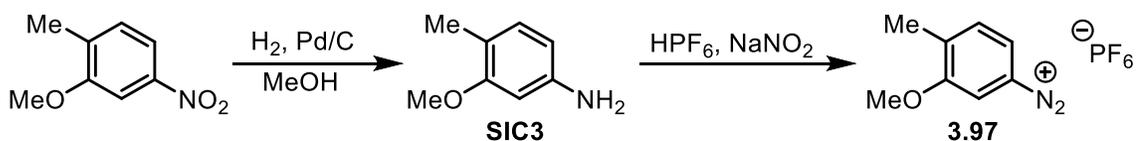
C4iii: Substrate Synthesis

(Z)-pent-3-en-1-ol (3.103)^{6,7}



To a flame-dried round-bottomed flask was added Lindlar catalyst (75 mg). The solid was pump purged with argon (3x), then Et₂O (98 mL) was added. Alkyne **3.102** (1.8 mL, 19.5 mmol, 1.0 equiv.) was added. The argon atmosphere was replaced with hydrogen and the reaction was allowed to stir at ambient temperature overnight. The following day the reaction was filtered over silica and concentrated to reveal *cis* olefin **3.103** which was used without further purification. **Yield:** 1.68, 99%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 5.64 (dddd, *J* = 10.8, 8.3, 6.8, 5.3 Hz, 1H), 5.40 (dddd, *J* = 10.9, 7.4, 4.6, 1.8 Hz, 1H), 3.65 (t, *J* = 6.5 Hz, 2H), 2.37 – 2.29 (m, 2H), 1.65 (ddd, *J* = 6.8, 1.8, 0.9 Hz, 3H).

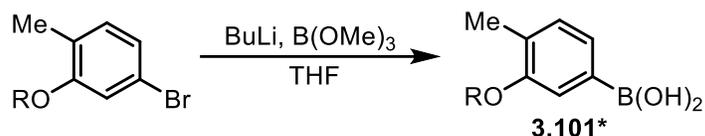
3-methoxy-4-methylbenzenediazonium hexafluorophosphate (**3.97**)



To a round-bottomed flask was added the nitroarene starting material (4.0 g, 24 mmol) along with methanol (120 mL) under argon. 800 mg of Pd/C powder was added, and the argon atmosphere was replaced with hydrogen. The resulting solution was stirred for 12 hours under positive argon pressure (balloon). Once the reaction was complete by TLC, the black solution was filtered over celite and concentrated to afford the intermediate amine as a red solid which was used in the subsequent step without purification. **Yield:** 3.15g, 96%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 6.92 (d, *J* = 7.9 Hz, 1H), 6.23 (d, *J* = 6.4 Hz, 2H), 3.79 (s, 3H), 3.59 (s, 2H), 2.14 (s, 3H). The aniline (2.46 g, 17.95 mmol, 1.0 equiv.) was added to a round-bottomed flask and suspended in water (35 mL). A 55% solution of HPF₆ (5.8 mL, 35.89 mmol, 2 equiv.) was then added, and the resulting solution was cooled to 0 °C. A solution of sodium nitrite (1.24 g) in water (6 mL) was

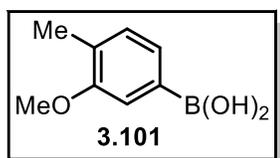
added dropwise, which caused the precipitation of the diazonium salt. The reaction was stirred for an additional 15 minutes at 0 °C, then filtered to afford the desired compound as a light purple powder **Yield:** 5.20 g, 98%. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.30 – 8.23 (m, 2H), 7.77 (d, *J* = 8.2, 0.9 Hz, 1H), 3.92 (s, 3H), 2.38 (s, 3H).

General Procedure 1 (GP1): Synthesis of boronic acids (3.101*)



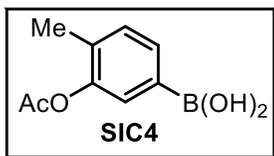
In a flame-dried round-bottomed flask, bromoarene (1.0 equiv) was suspended in THF (0.25 M) and cooled to –78 °C. A solution of *n*BuLi (1.2 equiv) was added and the resulting lithiate was allowed to stir at this temperature for 40 mins. Trimethylborate (2.4 equiv) was then added, and the reaction was allowed to slowly warm to –30 °C, at which point a solution of aqueous 3 M HCl was added. The resulting solution was stirred until it reached ambient temperature, at which point it was added to a separatory funnel and extracted with EtOAc (3x). The combined organic extracts were washed once with brine, then dried over sodium sulfate and concentrated. The resulting pasty solid was diluted with pentane and filtered to collect the solids, which were washed with additional pentane to reveal the desired.

(3-methoxy-4-methylphenyl)boronic acid (3.101)



The compound was synthesized according to GP1 from the corresponding aryl bromide (2.0 g, 10.0 mmol) to deliver the product as an off-white powder. **Yield:** 1.36 g, 82%. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.95 (s, 2H), 7.34 (s, 1H), 7.28 (d, *J* = 7.1, 1.0 Hz, 1H), 7.08 (d, *J* = 7.3, 0.9 Hz, 1H), 3.78 (s, 3H), 2.14 (s, 3H).

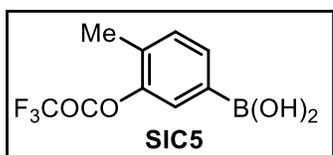
(3-acetoxy-4-methylphenyl)boronic acid (SIC4)



The compound was synthesized according to GP1 from the corresponding aryl bromide (2.0 g, 8.73 mmol) to deliver the product as an off-white powder. **Yield:** 1.35 g, 80%. **¹H NMR**

(400 MHz, Chloroform-*d*) δ 7.28 (dd, 1H), 7.19 (d, $J = 2.0$ Hz, 1H), 7.10 (d, $J = 8.1, 0.8$ Hz, 1H), 2.32 (s, 3H), 2.13 (s, 3H).

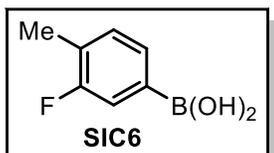
(4-methyl-3-(2,2,2-trifluoroacetoxy)phenyl)boronic acid (SIC5)



The compound was synthesized according to GP1 from the corresponding aryl bromide (2.83 g, 10.0 mmol) to deliver the product as a brown powder. **Yield.** 397 mg, 16%. **¹H**

NMR (500 MHz, DMSO-*d*₆) δ 9.00 (s, 1H), 7.80 (s, 2H), 7.16 (s, 1H), 7.13 (d, $J = 7.3, 1.1$ Hz, 1H), 7.00 (d, $J = 7.4$ Hz, 1H), 2.11 (s, 3H).

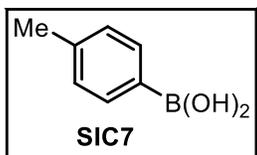
(3-fluoro-4-methylphenyl)boronic acid (SIC6)



The compound was synthesized according to GP1 from the corresponding aryl bromide (1.0 g, 5.29 mmol) to deliver the product as a yellow oil. **Yield:** 809 mg, 99%. **¹H NMR** (500

MHz, Chloroform-*d*) δ 7.87 (d, $J = 7.4, 1.1$ Hz, 1H), 7.79 (d, $J = 10.0, 1.1$ Hz, 1H), 7.33 (t, $J = 7.4$ Hz, 1H), 2.38 (d, $J = 1.8$ Hz, 3H).

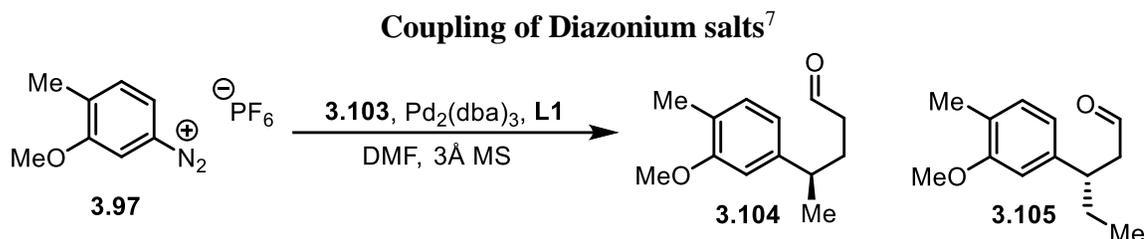
p-tolylboronic acid (SIC7)



The compound was synthesized according to GP1 from the corresponding aryl bromide (2.0 g, 11.7 mmol) to deliver the product as a fluffy white solid. **Yield:** 1.0 g, 62%. **¹H NMR** (500

MHz, Chloroform-*d*) δ 8.13 (d, $J = 7.9$ Hz, 2H), 7.32 (d, $J = 7.1$ Hz, 2H), 2.45 (s, 3H).

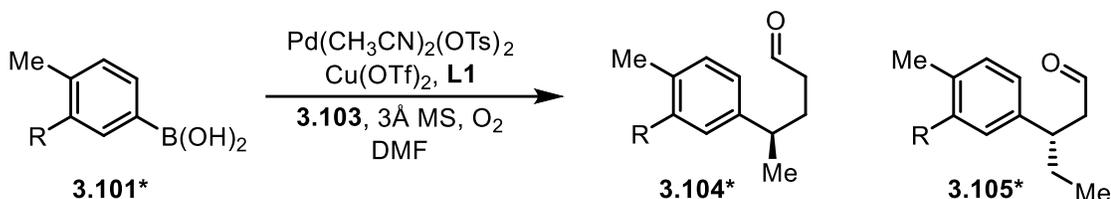
C4iv: Relay Heck Coupling Procedures



To a flame-dried round-bottomed flask was added ligand **L1** (10.0 mg, 0.04 mmol, 0.07 equiv.) along with 2 mL dry DMF. In a separate flame-dried flask was added tris(dibenzylideneacetone)dipalladium (14.0 mg, 0.02 mmol, 0.03 equiv.) and 2 mL dry DMF. The palladium catalyst solution was added to the ligand solution, and the mixture was allowed to stir for 15 mins. At which point, alcohol **3.103** (43 mg, 0.50 mmol, 1.0 equiv.) in 1 mL DMF was added. In a separate flame-dried flask, diazonium **3.97** was cooled to 0 °C, and the catalyst/alcohol mixture was added slowly. The resulting mixture was allowed to stir overnight while warming to ambient temperature. Upon completion, the reaction was diluted with Et₂O and water, and extracted with Et₂O (3x). The combined organic extracts were washed with water (3x) and brine (5x), then dried over sodium sulfate and concentrated. The mixture of regioisomeric products was purified by column chromatography (5% EtOAc/hexanes) to afford an inseparable mixture of regioisomers along with dibenzylideneacetone. No yield was obtained, however the ratio of products was determined via ¹H NMR to be ~3:2 favoring **3.104**. The NMR shifts are reported as a single compound due to rampant overlap of peaks, however the ratio was determined by the integrations of the aldehyde peaks (9.69 ppm for **3.104**; 9.67 for **3.105**), which was determined by the relative integration of the benzylic and homobenzylic methyl group respectively. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.69 (t, *J* = 1.6 Hz, 0.54H, Major (1H)), 9.67 (t, *J* = 2.2 Hz, 0.36H, Minor (1H)), 7.06 (d, *J* = 7.5,

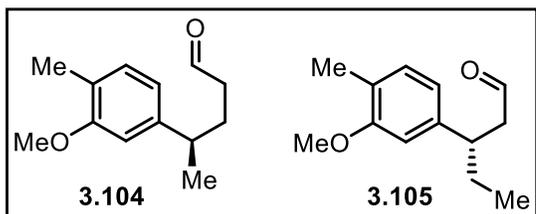
0.9 Hz, 1H), 6.68 (td, $J = 7.6, 4.8, 1.7$ Hz, 1H), 6.63 (s, 1H), 3.83 (s, 3H), 3.04 (dtd, $J = 8.9, 7.3, 5.6$ Hz, 0.42H, Minor, 1H), 2.74 – 2.56 (m, 1H), 2.39 – 2.27 (m, 1H), 2.31 – 2.19 (m, 1H), 2.23 – 2.10 (m, 4H), 2.10 – 1.79 (m, 1H), 1.76 – 1.55 (m, 1H), 1.29 (d, 2.04H Major (3H)), 0.83 (t, $J = 7.4$ Hz, 1H).

General Procedure 2 (GP2): Coupling of Boronic Acids⁶



A flame-dried three-necked round-bottomed flask was charged with activated 3Å molecular sieves, palladium pre-catalyst (0.06 equiv.), and $\text{Cu}(\text{OTf})_2$ (0.06 equiv.), followed by dry DMF (3.75 mM with respect to Pd catalyst). This mixture was stirred under positive oxygen pressure (balloon) for 10 mins. In a separate flame-dried dram vial, a mixture of alcohol **3.103** (1.0 equiv.) and arene **3.101*** (3.0 equiv.) was diluted with dry DMF (0.2 M with respect to **3.103**), then added to the catalyst mixture. The resulting solution was allowed to stir for 24 hours under an oxygen atmosphere. Once complete, the reaction was quenched with Et_2O and water (4:1), and the organic layer was removed. The aqueous layer was extracted with Et_2O (3x), then the combined organic layers were washed with water (3x) and brine (1x). The organic extracts were then dried over sodium sulfate and concentrated, then purified via column chromatography (5% EtOAc /hexanes) to reveal a mixture of regioisomeric products. The ratio regioisomers was determined in each case by comparison of integral values of the aldehyde protons (~9.5 – 10 ppm). Most proton peaks are reported as a single molecule due to overlap of the majority of peaks. Bolded values were used to determine regioselectivity.

R = -OMe



Following **GP2**, **3.101** (1.0 g, 6.02 mmol)

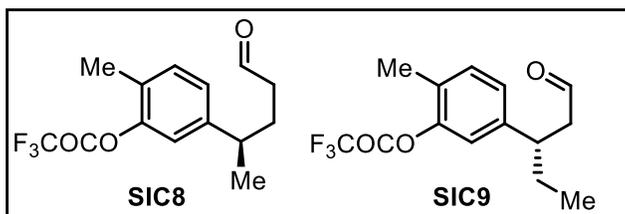
provided a ~3:2 mixture of regioisomers

favoring **3.104**. **Yield:** 258 mg, 63%. **¹H**

NMR (400 MHz, Chloroform-*d*) δ **9.69** (t, *J*

= 1.5 Hz, **0.60H** Major (1H)), **9.67** (t, *J* = 2.2 Hz, **0.40H** Minor (1H)), 7.05 (dt, *J* = 7.6, 0.9 Hz, 1H), 6.67 (ddd, *J* = 7.3, 4.9, 1.6 Hz, 1H), 6.62 (dd, *J* = 3.1, 1.7 Hz, 1H), 3.82 (s, 3H), 3.10 – 2.94 (m, 0.50H), 2.70 (dd, *J* = 7.3, 2.1 Hz, 1H), 2.34 (dddd, *J* = 7.9, 6.3, 4.7, 1.6 Hz, 1H), 2.22 – 2.15 (m, 4H), 2.01 – 1.79 (m, 1H), 1.74 – 1.58 (m, 1H), 1.56 (s, 3H), 1.27 (d, *J* = 6.9 Hz, 1.63H Major (3H)), 0.83 (t, *J* = 7.4 Hz, 1.52H Minor (3H)).

R = -OTFA



Following **GP2**, **SIC5** (45.0 mg,

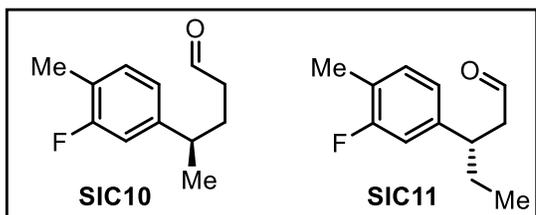
0.18 mmol) provided a ~10:1

mixture favoring **SIC9**. **Yield:** 11

mg, 21%. **¹H NMR** (500 MHz,

Chloroform-*d*) δ **9.68** (t, *J* = 1.6 Hz, **0.09H** Minor (1H)), **9.66** (t, *J* = 2.1 Hz, **0.86H** Major (1H)), 7.04 (dd, *J* = 7.6, 0.9 Hz, 1H), 6.67 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.61 (d, *J* = 1.8 Hz, 1H), 2.99 (dtd, *J* = 9.2, 7.3, 5.4 Hz, 1H), 2.67 (dd, *J* = 7.3, 2.1 Hz, 2H), 2.21 (s, 3H), 1.72 – 1.53 (m, 2H), 0.81 (t, *J* = 7.4 Hz, 3Hj).

R = -F



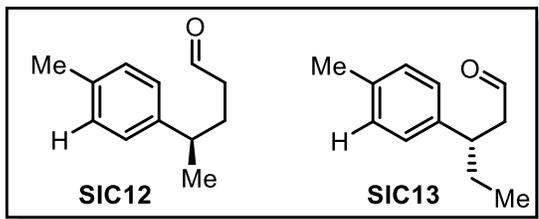
Following **GP2**, **SIC6** (309 mg, 2.01 mmol)

provided a ~2:1 mixture favoring **SIC10**.

Yield: 89 mg, 23%. **¹H NMR** (500 MHz,

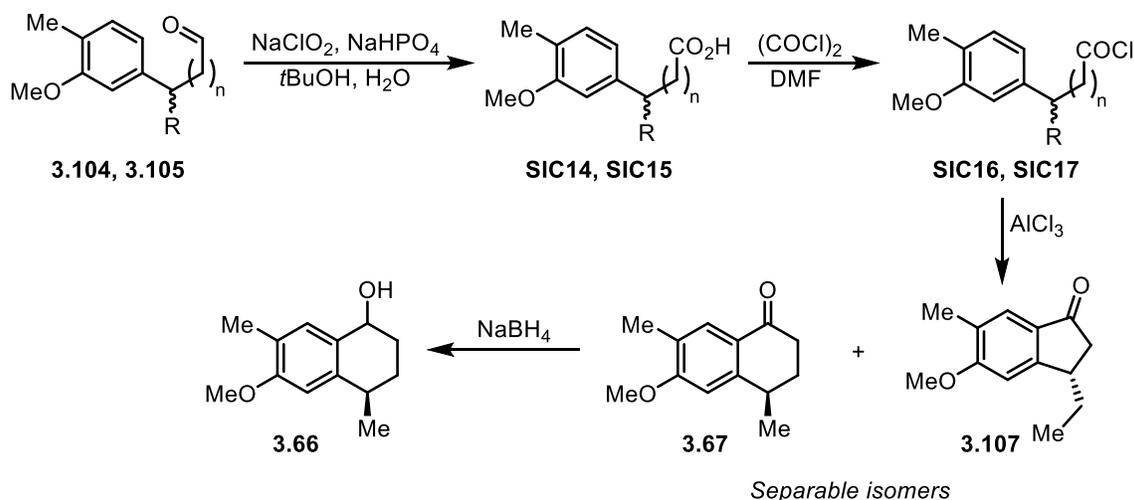
Chloroform-*d*) δ **9.62** (t, $J = 1.6$ Hz, **0.58** Major (1H)), **9.60** (t, $J = 2.0$ Hz, **0.29H** Minor (1H)), 7.07 – 6.97 (m, 1H), 6.84 – 6.68 (m, 2H), 2.98 (p, $J = 7.2$ Hz, 0.43H), 2.69 – 2.55 (m, 2H), 2.33 – 2.22 (m, 3H), 2.17 (d, $J = 1.9$ Hz, 4H), 1.92 – 1.70 (m, 2H), 1.67 – 1.49 (m, 0.47H), 1.48 (s, 1H), 1.18 (d, $J = 6.9$ Hz, 1H), 0.74 (t, $J = 7.4$ Hz, 1H).

R = -H



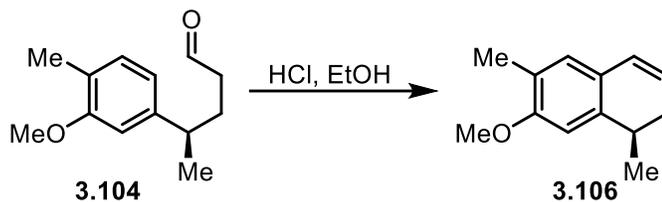
Following **GP2**, **SIC7** (275 mg, 2.02 mmol) provided a ~1.2:1 mixture favoring **SIC12**. The reaction was not purified due to such a low regioselectivity, however the aldehyde

protons are listed. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ **9.61** (t, $J = 1.6$ Hz, **1.23H**), **9.59** (t, $J = 2.2$ Hz, **1.0H**).



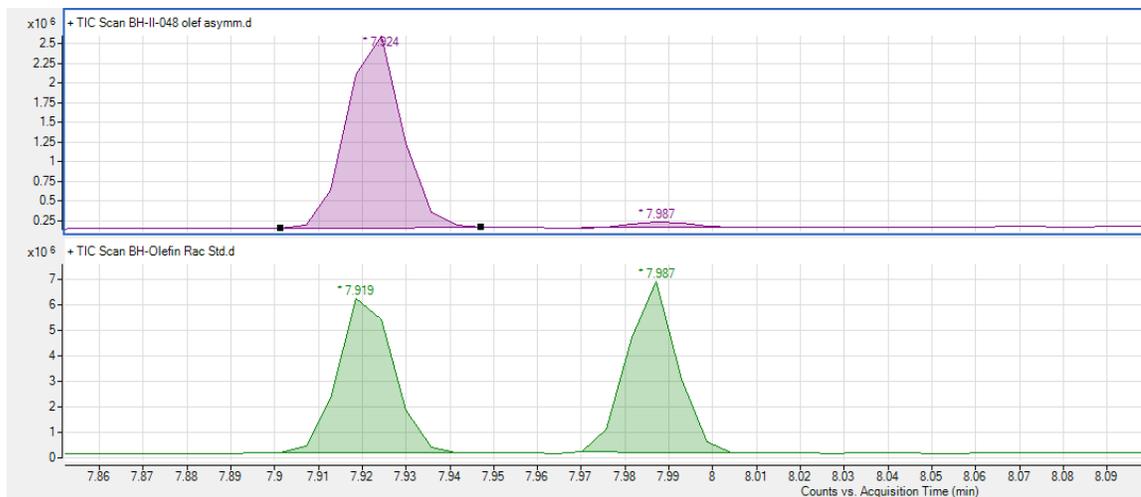
C4v: Derivatization of Aldehyde

7-methoxy-6-methyl-1,2-dihydronaphthalene (3.106)

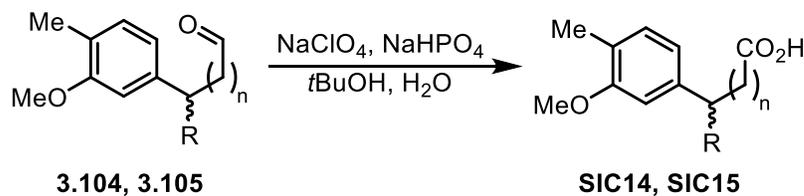


A mixture of **3.104** and **3.105** (~3:2) was dissolved in ethanol and cooled to $-10\text{ }^{\circ}\text{C}$ in an ice/brine bath. A few drops of 3 M HCl in H_2O was added to make the solution acidic. The reaction was allowed to warm to ambient temperature, at which point the reaction was complete. The solution was diluted with DCM and water, then the organics were extracted with DCM (3x). The combined organic extracts were dried over sodium sulfate, then concentrated. A column was performed (5% Et_2O /Pentane) to isolate the least polar spot, correlating to **3.106**, with quantitative conversion. **3.105** remains untouched in these conditions. Additionally, due to the ease of synthesis and excellent baseline resolution, **3.106** was used to determine enantioselectivity in the relay Heck coupling (~97:3). ^1H NMR (500 MHz, Chloroform-*d*) δ 6.84 (s, 1H), 6.67 (s, 1H), 6.37 (d, $J = 9.6$ Hz, 1H), 5.81 (ddd, $J = 9.3, 4.8, 4.0$ Hz, 1H), 3.85 (s, 3H), 2.89 (h, $J = 7.0$ Hz, 1H), 2.45 (dddd, $J = 17.0, 7.0, 4.0, 2.2$ Hz, 1H), 2.18 (s, 3H), 2.09 (dddd, $J = 16.9, 7.1, 4.8, 1.6$ Hz, 1H), 1.44 (s, 1H), 1.24 (d, $J = 7.0$ Hz, 3H).

E.R. determined by GCMS (cyclosilB chiral column, 40 °C start, 20 °C/min to 225 °C) retention times: 7.92 min (major) and 7.99 min (minor); 97:3



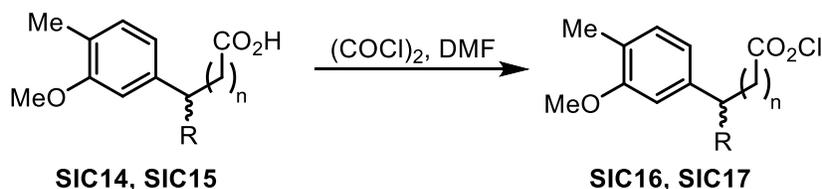
(R)-4-(3-methoxy-4-methylphenyl)pentanoic acid (SIC14 (R = Me), major)



A mixture of **3.104** and **3.105** (258 mg, 1.25 mmol, 1.0 equiv.) was dissolved in *t*BuOH (8 mL), and 2-methyl-2-butene (1 mL) was added. The solution was stirred, then a solution of $NaClO_2$ (226 mg, 2.50 mmol, 2.0 equiv.) and $NaHPO_4$ (450 mg, 3.75 mmol, 3.0 equiv.) in water (4 mL) was added. The reaction was monitored by TLC, and upon completion the reaction was washed with 1 M HCl and extracted with EtOAc (3x). The combined organic extracts were dried over sodium sulfate and concentrated to reveal a mixture of carboxylic acids **SIC14** & **SIC15**. The mixture was used in the next step without further purification. Due to a majority of overlapping peaks, the NMR data is reported as a single molecule except when peak separation is clear. **Yield:** 275 mg, 99%. 1H NMR (500 MHz, Chloroform-*d*) δ 7.05 (dd, $J = 7.6, 0.9$ Hz, 1H), 6.68 (ddd, $J = 7.6,$

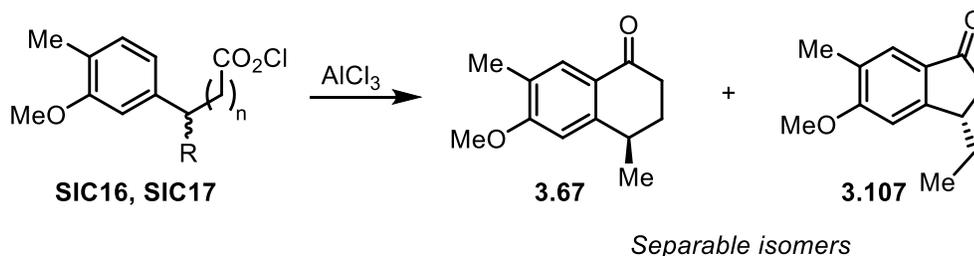
3.9, 1.7 Hz, 1H), 6.63 (dd, $J = 3.5, 1.6$ Hz, 1H), 3.82 (d, $J = 2.9$ Hz, 3H), 2.96 (dt, $J = 15.1, 7.5$ Hz, 0.41H), 2.75 – 2.56 (m, 1.35H), 2.24 (ddd, $J = 8.6, 7.0, 1.9$ Hz, 1H), 2.18 (s, 2.56H), 2.05 (s, 1.93H), 1.97 – 1.82 (m, 1H), 1.76 – 1.56 (m, 1H), 1.52 (d, $J = 6.8$ Hz, 1H), 1.27 (d, $J = 7.4$ Hz, 2.25H), 0.81 (t, $J = 7.3$ Hz, 1.21H).

(R)-4-(3-methoxy-4-methylphenyl)pentanoyl chloride (SIC16 (R = Me), major)



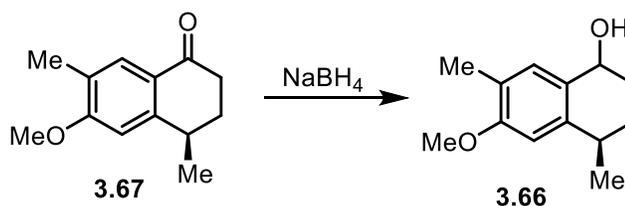
A mixture of **SIC14** & **SIC15** (275 mg, 1.25 mmol, 1.0 equiv.) was added to a flame-dried round-bottomed flask followed by DCM (6.25 mL). Oxalyl chloride (327 μ L, 3.75 mmol, 3.0 equiv.) was added and the reaction was stirred for 1 minute, at which point a few drops of dimethylformamide were added. Upon addition, the reaction began bubbling vigorously and continued for several minutes. The bubbling eventually ceased, and the reaction was stirred for a total of 1 hour, at which point it was deemed complete by NMR. The solution was concentrated revealing a mixture of **SIC16** & **SIC17** which was used in the subsequent step without further purification. Due to a majority of overlapping peaks, the NMR data is reported as a single molecule except when peak separation is clear. **Yield:** 300 mg, 99%. **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.06 (dt, $J = 7.6, 0.9$ Hz, 1H), 6.66 (ddd, $J = 7.5, 3.4, 1.6$ Hz, 1H), 6.61 (t, $J = 2.3$ Hz, 1H), 3.83 (d, $J = 1.0$ Hz, 2.87H), 3.77 (s, 1.21H), 3.23 (s, 1.19H), 3.16 (dd, $J = 7.3, 6.2$ Hz, 0.77H), 3.11 – 2.99 (m, 0.45H), 2.76 (t, $J = 7.5$ Hz, 1.10H), 2.70 (dt, $J = 9.6, 6.4$ Hz, 0.50H), 2.18 (dd, $J = 2.7, 0.7$ Hz, 3H), 2.07 – 1.90 (m, 1H), 1.90 (s, 1H), 1.79 (s, 1H), 1.77 – 1.59 (m, 1H), 1.58 (d, $J = 6.7$ Hz, 1H), 1.54 – 1.35 (m, 0.66H), 1.28 (d, $J = 6.9$ Hz, 1.65H), 0.82 (t, $J = 7.4$ Hz, 1.37H).

(R)-6-methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2H)-one (3.67)



A mixture of acyl chlorides **SIC16** & **SIC17** (300 mg, 1.25 mmol, 1.0 equiv.) was dissolved in DCM (11 mL), then AlCl_3 (250 mg, 1.87 mmol, 1.5 equiv.) was added. The resulting solution was stirred for 4 hours, at which point the reaction was quenched with saturated aqueous sodium bicarbonate (2 mL). A 10% solution of aqueous potassium sodium tartrate (Rochelle's salt) was added to the flask, and the resulting mixture was stirred for 2 hours. The mixture was then transferred to a separatory funnel and extracted with DCM (3x). The combined organic extracts were washed once each with water and brine, then dried over sodium sulfate and concentrated. The mixture of isomers was purified on silica (10% Et_2O /Pentane) to deliver the desired **3.67**. Multiple purifications are necessary to recover **3.67** cleanly due to co-elution of products, however the yield is representative of a single purification. **Yield:** 109 mg, 43%. **$^1\text{H NMR}$** (500 MHz, Chloroform-*d*) δ 7.83 (s, 1H), 6.67 (s, 1H), 3.90 (s, 3H), 3.04 (dt, $J = 13.6, 6.9$ Hz, 1H), 2.73 (ddd, $J = 17.4, 9.1, 4.6$ Hz, 1H), 2.54 (ddd, $J = 17.4, 8.2, 4.7$ Hz, 1H), 2.28 – 2.22 (m, 1H), 2.20 (s, 3H), 1.89 (dddd, $J = 13.0, 8.1, 6.9, 4.6$ Hz, 1H), 1.39 (d, $J = 7.0$ Hz, 3H).

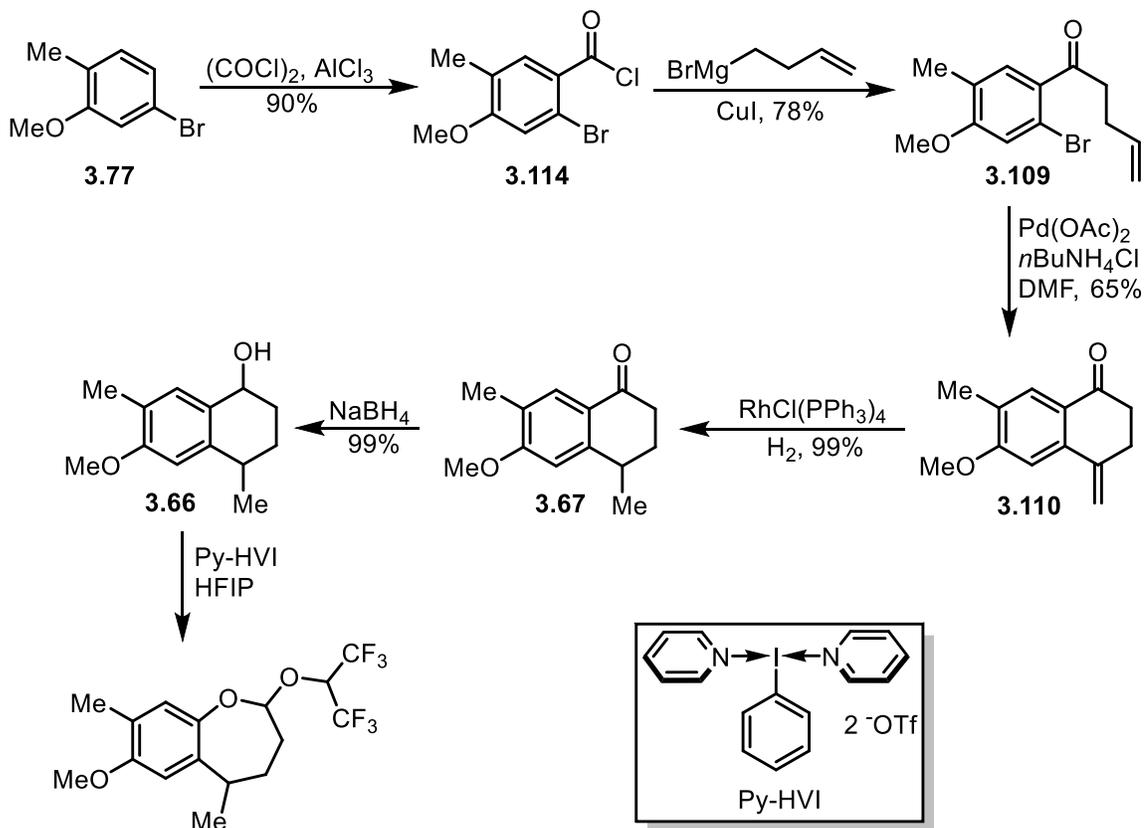
(4R)-6-methoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (3.66)



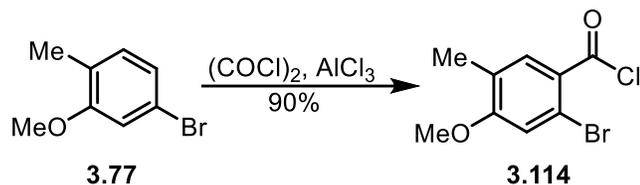
To a solution of ketone **3.67** (109 mg, 0.53 mmol, 1.0 equiv.) in methanol (5 mL) was added NaBH₄ (30 mg, 0.80 mmol, 1.5 equiv.). The solution began bubbling vigorously and continued for around 10 minutes. At which point, the reaction was deemed complete by TLC and was quenched with a solution of ammonium chloride. The mixture was extracted with EtOAc (3x), and the combined organic extracts were washed with brine and concentrated to afford a mixture of diastereomers which was not purified further.

Yield: 109 mg, 99%. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.17 (s, 1.67H), 6.69 (s, 1H), 6.62 (s, 0.65H), 4.69 (q, *J* = 4.0, 3.4 Hz, 1.61H), 3.82 (d, *J* = 1.6 Hz, 4.65H), 2.93 (t, *J* = 6.4 Hz, 0.87H), 2.79 (p, *J* = 7.0 Hz, 0.92H), 2.19 (d, *J* = 0.9 Hz, 4.86H), 2.14 – 2.05 (m, 1H), 2.02 – 1.65 (m, 4H), 1.57 – 1.44 (m, 0.84H), 1.35 (d, *J* = 7.0 Hz, 2.44H), 1.25 (d, *J* = 7.1 Hz, 2H).

C5: INTRAMOLECULAR HECK APPROACH

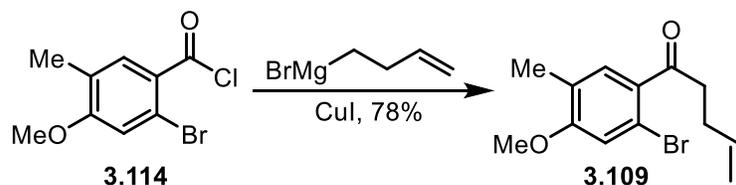


2-bromo-4-methoxy-5-methylbenzoyl chloride (3.114)⁸



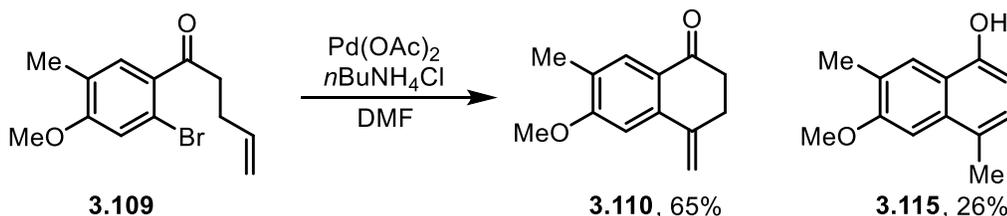
A solution of AlCl₃ (4.65 g, 34.9 mmol, 3.6 equiv.) in DCM (60 mL) was cooled to -15 °C in an ice/brine bath. Once cooled, oxalyl chloride (2.91 mL, 34.9 mmol, 3.6 equiv.) was added dropwise and the resulting solution was stirred for 30 mins. Still at -15 °C, bromoarene **3.77** (2.0 g, 9.69 mmol, 1.0 equiv.) in DCM (20 mL) was then added over a period of 30 minutes and stirred for 5 hours. Once the time elapsed, the reaction was poured over ice water and the bottom organic layer was extracted. The aqueous layer was extracted with a 50/50 mixture of DCM and Et₂O (2x), and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. On some occasions, hydrolysis of the acyl chloride to the carboxylic acid during workup was observed in considerable quantities. In order to rectify this, the rough amount of carboxylic acid was calculated by NMR, and further treatment with oxalyl chloride was performed. In this case, ~800 mg (3.26 mmol, 1.0 equiv.) of the carboxylic acid was present, so the mixture of products was dissolved in THF (8 mL) and (COCl)₂ (400 μL, 4.57 mmol, 1.4 equiv.) was added along with a drop of DMF. Once complete, the reaction was concentrated to reveal acyl chloride **3.114** as an orange solid. **Yield:** 2.30 g, 90%. ¹H NMR (500 MHz, Chloroform-*d*) δ 8.00 (s, 1H), 7.10 (s, 1H), 3.91 (s, 3H), 2.21 (s, 3H).

1-(2-bromo-4-methoxy-5-methylphenyl)pent-4-en-1-one (3.109)⁹ waser



In a flame-dried round-bottomed flask, magnesium powder (233 mg, 9.6 mmol, 1.1 equiv.) was suspended in THF (11.5 mL). 4-bromo-1-butene (890 μ L, 8.72 mmol, 1.0 equiv.) was added and the mixture was stirred for 1 hour to allow complete formation of the desired Grignard reagent. In a separate flame-dried round-bottomed flask, acyl chloride **3.114** (2.30 g, 8.72 mmol, 1.0 equiv.) was dissolved in THF (9.2 mL), and copper iodide (83 mg, 0.44 mmol, 0.05 equiv.) was added. The suspension was cooled to -15 $^{\circ}$ C in an ice/brine bath and allowed to cool thoroughly. At which point, the pre-formed Grignard solution was added over a period of 1 hour with the aid of a syringe pump. Following the complete addition of the Grignard reagent, the reaction was removed from the ice bath and allowed to warm to ambient temperature. After 30 minutes of stirring, the reaction was concentrated to remove all THF, then diluted with DCM (20 mL). The suspension was filtered to remove copper salts, and the filtrate was washed with 1 M HCl, and the aqueous layer was extracted with DCM (2x). The combined organic extracts were dried over sodium sulfate then purified via column chromatography (5 \rightarrow 10% Et₂O/Pentane) to reveal the product as a yellow oil. **Yield:** 1.94 g, 78%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.32 (s, 1H), 7.01 (s, 1H), 5.87 (ddt, $J = 16.9, 10.2, 6.5$ Hz, 1H), 5.07 (dq, $J = 17.1, 1.7$ Hz, 1H), 5.00 (dq, $J = 10.2, 1.4$ Hz, 1H), 3.86 (s, 3H), 3.03 (t, $J = 7.3$ Hz, 2H), 2.51 – 2.42 (m, 2H), 2.17 (s, 3H).

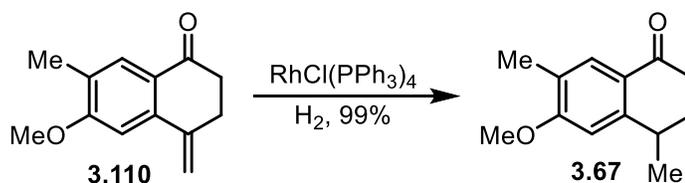
6-methoxy-7-methyl-4-methylene-3,4-dihydronaphthalen-1(2H)-one (3.110)^{10,11}



A solution of bromoarene **3.109** (360 mg, 1.27 mmol, 1.0 equiv.) in DMF (12.7 mL) was thoroughly degassed in a flame-dried round-bottomed flask. In a separate flame-dried flask, $\text{Pd}(\text{OAc})_2$ (28.5 mg, 0.127 mmol, 10 mol %), $n\text{BuNH}_4\text{Cl}$ (371 mg, 1.33 mmol, 1.05

equiv.) and K_2CO_3 (263 mg, 1.91 mmol, 1.5 equiv.) were mixed together and pump-purged with argon (3x). The solution of bromoarene **3.109** was then added to the catalyst mixture. The flask was sealed and warmed to 80 °C and stirred for 3 hours. Once complete, the reaction was cooled to ambient temperature. The mixture was quenched with water and Et_2O was added. The organic layer was extracted, the aqueous layer was further extracted with Et_2O (3x). The combined organic extracts were washed with brine (4x), then dried over sodium sulfate and concentrated. Two products were obtained from this reaction (**3.110** & **3.115**), and they were separated via column chromatography (5% EtOAc/hexanes). Characterization is presented for each. **3.110**; Yellow oil. **Yield:** 168 mg, 65%. 1H NMR (500 MHz, Chloroform-*d*) δ 7.83 (s, 1H), 6.96 (s, 1H), 5.53 (s, 1H), 5.23 (s, 1H), 3.93 (s, 3H), 2.82 (t, $J = 7.0$ Hz, 2H), 2.71 (dd, $J = 7.4, 5.9$ Hz, 2H), 2.23 (s, 3H). **3.115**; White solid. 1H NMR (500 MHz, Chloroform-*d*) δ 7.94 (s, 1H), 7.08 (s, 1H), 7.05 (d, $J = 7.8$ Hz, 1H), 6.58 (d, $J = 7.6$ Hz, 1H), 3.97 (s, 3H), 2.55 (s, 3H), 2.40 (s, 3H).

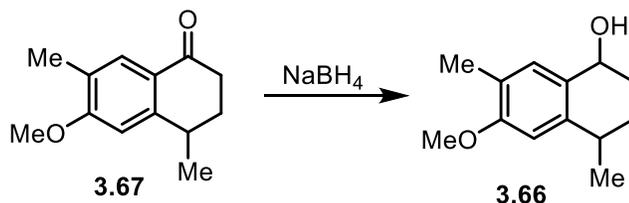
6-methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2H)-one (3.67)¹²



To a round-bottomed flask was added **3.110** (100 mg, 0.49 mmol, 1.0 equiv.) and Wilkinson's catalyst ($RhCl(PPh_3)_3$; 23 mg, 0.025 mmol, 5 mol %) under argon. Ethyl acetate (2 mL) was added, and the argon atmosphere was replaced with hydrogen. The reaction was allowed to stir for 12 hours at ambient temperature, at which point the solution was concentrated to remove EtOAc. The paste was diluted with Et_2O , filtered, and concentrated to afford a dark red oil. Purification was performed on silica (5% EtOAc/hexanes) to afford the desired molecule as a yellow oil. **Yield:** 100 mg, 99%. 1H

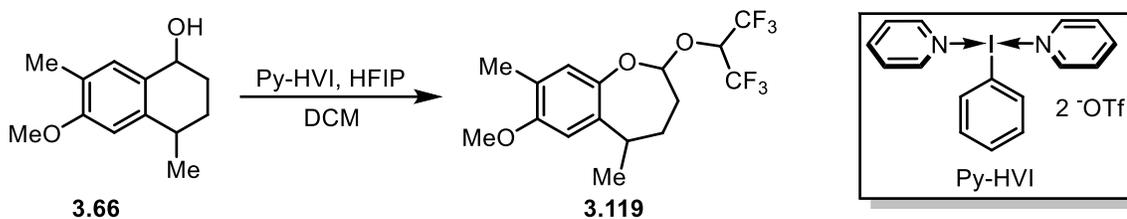
NMR: Spectrum identical to what was previously observed; (500 MHz, Chloroform-*d*) δ 7.83 (s, 1H), 6.67 (s, 1H), 3.90 (s, 3H), 3.05 (td, $J = 7.1, 4.6$ Hz, 1H), 2.73 (ddd, $J = 17.4, 9.1, 4.6$ Hz, 1H), 2.54 (ddd, $J = 17.4, 8.3, 4.8$ Hz, 1H), 2.23 (td, $J = 9.0, 4.6$ Hz, 1H), 2.20 (s, 3H), 1.89 (dddd, $J = 13.1, 8.2, 6.9, 4.6$ Hz, 1H), 1.39 (d, $J = 7.0$ Hz, 3H).

6-methoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (3.66)



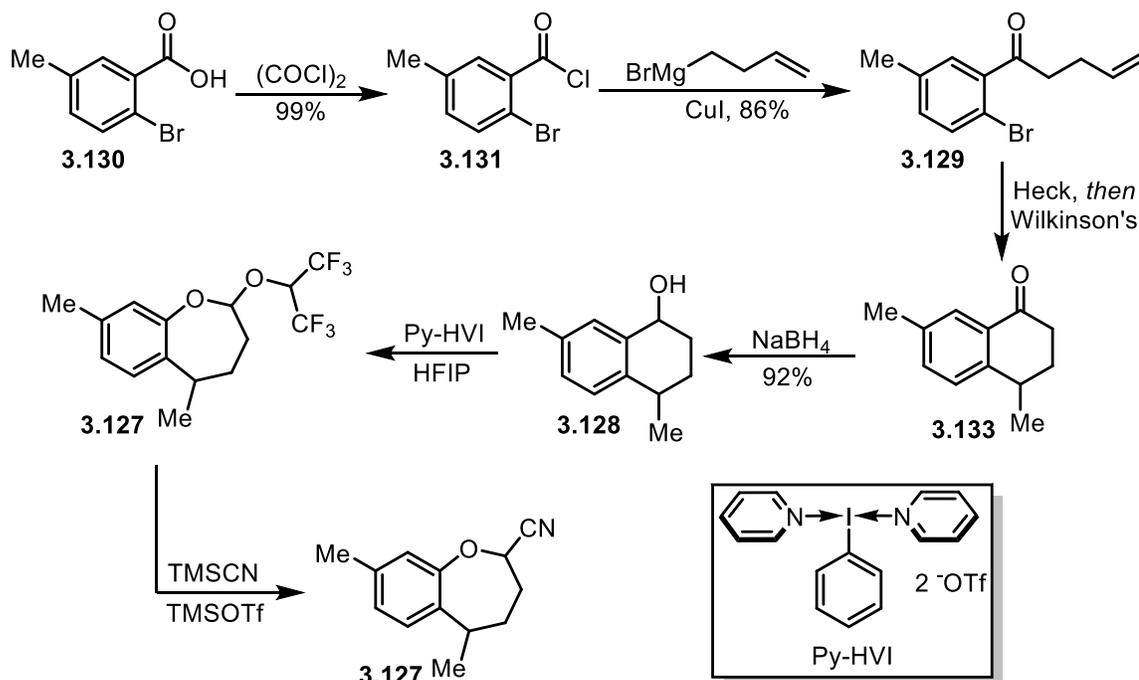
To a solution of ketone **3.67** (109 mg, 0.53 mmol, 1.0 equiv.) in methanol (5 mL) was added NaBH₄ (30 mg, 0.80 mmol, 1.5 equiv.). The solution began bubbling vigorously and continued for around 10 minutes. At which point, the reaction was deemed complete by TLC and was quenched with a solution of ammonium chloride. The mixture was extracted with EtOAc (3x), and the combined organic extracts were washed with brine and concentrated to afford a mixture of diastereomers which used in the subsequent step without further purification. **Yield:** 101 mg, 99%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.17 (s, 1.66H), 6.69 (s, 1H), 6.62 (s, 0.70H), 4.69 (p, $J = 5.3$ Hz, 2H), 3.82 (d, $J = 1.5$ Hz, 5.25H), 2.93 (p, $J = 6.7, 5.9$ Hz, 0.71H), 2.80 (h, $J = 7.0$ Hz, 1H), 2.20 – 2.17 (d, 5.93H), 2.11 (ddt, $J = 10.8, 6.0, 2.4$ Hz, 1.33H), 1.93 (dddd, $J = 13.1, 10.0, 4.8, 3.2$ Hz, 1.85H), 1.89 – 1.83 (m, 1.32H), 1.81 – 1.75 (m, 0.74H), 1.70 (dddd, $J = 13.5, 10.2, 8.3, 3.5$ Hz, 1H), 1.57 (d, $J = 6.2$ Hz, 1H), 1.55 – 1.52 (m, 0.85H), 1.50 (ddd, $J = 10.4, 5.5, 3.4$ Hz, 0.55H), 1.35 (d, $J = 7.0$ Hz, 3H), 1.25 (d, $J = 7.1$ Hz, 2.43H).

2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-7-methoxy-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[b]oxepine (3.119)^{13,14}

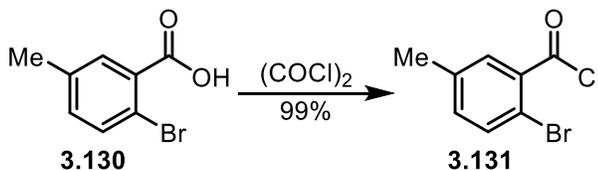


Alcohol **3.66** (62 mg, 0.30 mmol, 1.0 equiv.) in DCM (1.5 mL) was transferred to a flame-dried round-bottomed flask containing finely ground activated 3Å MS. The solution was cooled to $-25\text{ }^{\circ}\text{C}$ and stirred for 5 minutes. During which, Py-HVI (298 mg, 0.45 mmol, 1.0 equiv.; see appendix A for synthesis and characterization) was dissolved in hexafluoroisopropanol (HFIP; 632 μL , 6.0 mmol, 20 equiv.). The resulting solution was added to the flask containing alcohol **3.66**, and the reaction was stirred until the starting material was fully consumed as deemed by TLC. Once complete, the reaction was concentrated at $0\text{ }^{\circ}\text{C}$. The resulting thick oil was azeotroped with DCM (3x) to remove all residual HFIP, then the crude oil was diluted with Et₂O and filtered to remove pyridinium salts and powdered molecular sieves, then concentrated. The crude material was purified via column chromatography (0→5% Et₂O/Pentane) to afford a diastereomeric mixture (~2:1) of the desired molecule as a colorless oil. **Yield:** 16 mg, 15%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 6.78 (s, 0.40H), 6.77 (s, 1H), 6.62 (s, 0.46H), 6.57 (s, 1H), 4.95 (dd, $J = 8.7, 2.9\text{ Hz}$, 1H), 4.82 (dd, $J = 9.1, 2.3\text{ Hz}$, 0.53H), 4.76 (dp, $J = 15.1, 6.1\text{ Hz}$, 1.28H), 3.81 (d, $J = 2.4\text{ Hz}$, 3.97H), 3.04 (ddt, $J = 12.0, 7.2, 4.2\text{ Hz}$, 1.28H), 2.20 – 2.15 (m, 4H), 2.08 – 1.83 (m, 3.34H), 1.63 (ddt, $J = 14.0, 7.8, 4.0\text{ Hz}$, 1H), 1.47 – 1.37 (m, 0.49H), 1.34 (d, $J = 7.1\text{ Hz}$, 1.33H), 1.31 (d, $J = 7.1\text{ Hz}$, 3H).

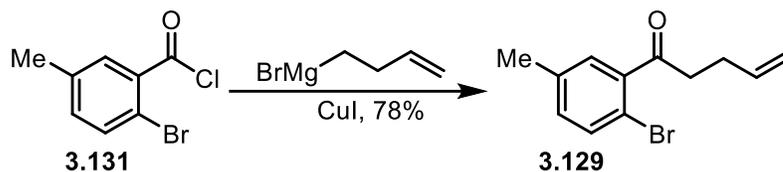
C5i: Racemic Synthesis of Heliannuol D via Intramolecular Heck



2-bromo-5-methylbenzoyl chloride (3.131)

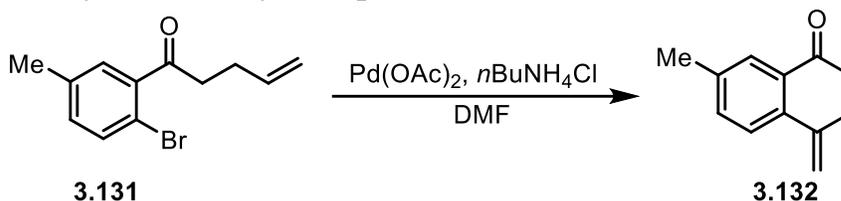


To a flame-dried round-bottomed flask was added acid **3.130** (7.0 g, 32.5 mmol, 1.0 equiv.) along with THF (32 mL). Oxalyl chloride (4.2 mL, 48.8 mmol, 1.5 equiv.) was added, followed by 50 μ L DMF. The reaction began bubbling vigorously and continued for several minutes. Once bubbling ceased and after 30 minutes of additional stirring, the reaction was checked by NMR, which showed complete conversion to desired product. The reaction was concentrated to afford acyl chloride **3.131** as an orange solid which was used without purification. **Yield:** 7.6 g, 99%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.86 (s, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.24 (dd, *J* = 8.3, 2.2 Hz, 1H), 2.39 (s, 3H).

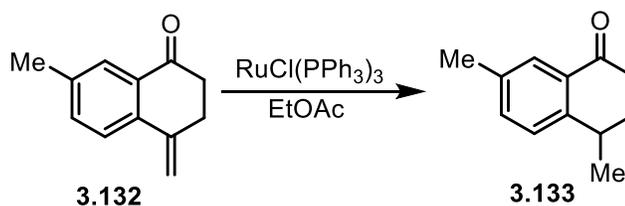
1-(2-bromo-5-methylphenyl)pent-4-en-1-one (3.129)

To a flame-dried round-bottomed flask was added magnesium powder (802 mg, 33.0 mmol, 1.1 equiv.), followed by THF (39 mL) and 4-bromo-1-butene (3.04 mL, 30.0 mmol, 1.0 equiv.). The mixture was allowed to stir for 30 minutes to allow the Grignard reagent to fully form. In a separate flame-dried flask, acyl chloride **3.131** (7.0 g, 30.0 mmol, 1.0 equiv.) was suspended in 32 mL THF, then copper iodide (286 mg, 1.5 mmol, 5 mol %) was added. The suspension was cooled to $-15\text{ }^{\circ}\text{C}$ in an ice/brine bath and stirred for 10 minutes. the Grignard solution was then added dropwise over a period of 1 hour with the assistance of a syringe pump. Following the complete addition, the reaction was allowed to warm to room temperature and stir for an additional hour, at which point the reaction was complete by TLC. The reaction was concentrated to remove all THF, then diluted with DCM and filtered to remove copper salts. The filtrate was then diluted with aqueous 1 M HCl and transferred to a separatory funnel where the organic layer was collected. The aqueous layer was back-extracted with DCM (2x), and the combined organic extracts were washed with saturated aqueous sodium bicarbonate, then dried over sodium sulfate and concentrated. The crude residue was purified via column chromatography (7% EtOAc/hexanes) to afford the desired compound as a yellow oil.

Yield: 6.6 g, 86%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.46 (d, $J = 8.1$ Hz, 1H), 7.16 (s, 1H), 7.09 (dd, $J = 8.2, 2.3, 0.8$ Hz, 1H), 5.87 (ddt, $J = 16.8, 10.2, 6.5$ Hz, 1H), 5.08 (dq, $J = 17.1, 1.7$ Hz, 1H), 5.01 (dq, $J = 10.2, 1.4$ Hz, 1H), 3.01 (t, $J = 37.6, 15.0, 7.8, 7.0$ Hz, 2H), 2.50 – 2.44 (m, 2H), 2.33 (s, 3H).

7-methyl-4-methylene-3,4-dihydronaphthalen-1(2H)-one (3.132)^{10,11}

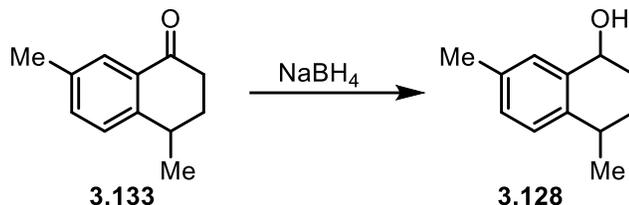
In a flame-dried round-bottomed flask, bromoarene **3.131** (3.02 g, 11.8 mmol, 1.0 equiv.) was dissolved in DMF (50 mL) and the solution was degassed thoroughly. In a separate flame-dried flask, Pd(OAc)₂ (266 mg, 1.18 mmol, 10 mol %), nBuNH₄Cl (3.46 g, 12.4 mmol, 1.05 equiv.), and K₂CO₃ (2.46 g, 17.8 mmol, 1.5 equiv.) were added along with activated 3Å MS and were pump-purged with argon (3x). The solution of **3.131** in DMF was added to the catalyst mixture and the resulting solution was warmed to 75 °C for 4 hours or until complete by TLC. The reaction was then cooled to ambient temperature and concentrated to remove as much DMF as possible. The solids were filtered through silica with Et₂O and the filtrate was purified via column chromatography (5% EtOAc/hexanes) to deliver the desired product (**3.132**) as a pale yellow solid. **Yield:** 1.41 g, 69%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 1.6 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.39 – 7.33 (m, 1H), 5.54 (s, 1H), 5.22 (s, 1H), 2.86 – 2.80 (m, 2H), 2.77 – 2.73 (m, 2H), 2.39 (s, 3H).

4,7-dimethyl-3,4-dihydronaphthalen-1(2H)-one (3.133)¹²

To a round-bottomed flask containing **3.132** (740 mg, 4.30 mmol, 1.0 equiv.) and EtOAc (23 mL) was added RuCl(PPh₃)₃ (Wilkinson's catalyst, 200 mg, 0.22 mmol, 5 mol %). The atmosphere was pumped away and replaced with hydrogen (balloon) and the reaction

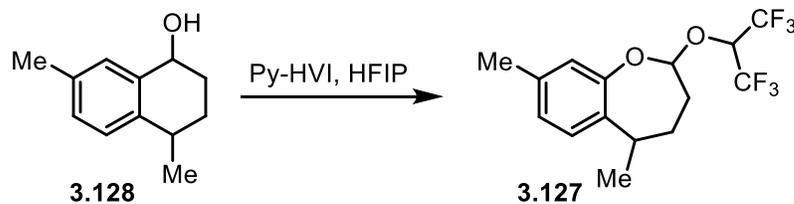
was allowed to stir for 2 hours, at which point the starting material was consumed by TLC. The reaction was then concentrated to remove ethyl acetate, and the crude material was suspended in Et₂O. The solids were filtered and the filtrate was concentrated and purified via column chromatography to afford a yellow oil. **Yield:** 650 mg, 88%. **For NMR Characterization See Asymmetric Synthesis of Heliannuol D**

4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (3.128)



To a solution of ketone **3.133** (376 mg, 2.16 mmol, 1.0 equiv.) in methanol (22 mL) was added NaBH₄ (122 mg, 3.24 mmol, 1.5 equiv.). As a result, the reaction began bubbling vigorously and continued for several minutes. Once bubbling ceased, the reaction was monitored by TLC and was determined to be complete. A saturated solution of aqueous ammonium chloride was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with brine (2x), dried over magnesium sulfate, and concentrated to afford a ~1.3:1 diastereomeric mixture of alcohol **3.128** which was used without purification. **Yield:** 380 mg, 99%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.25 (s, 1.31H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.11 (d, *J* = 7.9 Hz, 0.73H), 7.09 – 7.03 (m, 1.57H), 4.73 (q, *J* = 5.4 Hz, 1.93H), 2.99 – 2.88 (m, 0.8H), 2.81 (h, *J* = 7.0 Hz, 1.07H), 2.33 (s, 5.21H), 2.17 – 2.09 (m, 1.35H), 1.99 – 1.92 (m, 2H), 1.92 – 1.82 (m, 1H), 1.83 – 1.69 (m, 1.20H), 1.73 – 1.60 (m, 2.20H), 1.54 – 1.44 (m, 0.75H), 1.33 (d, *J* = 7.0 Hz, 3H), 1.24 (d, *J* = 7.1 Hz, 2.3H).

2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepine (3.127)^{13,14}



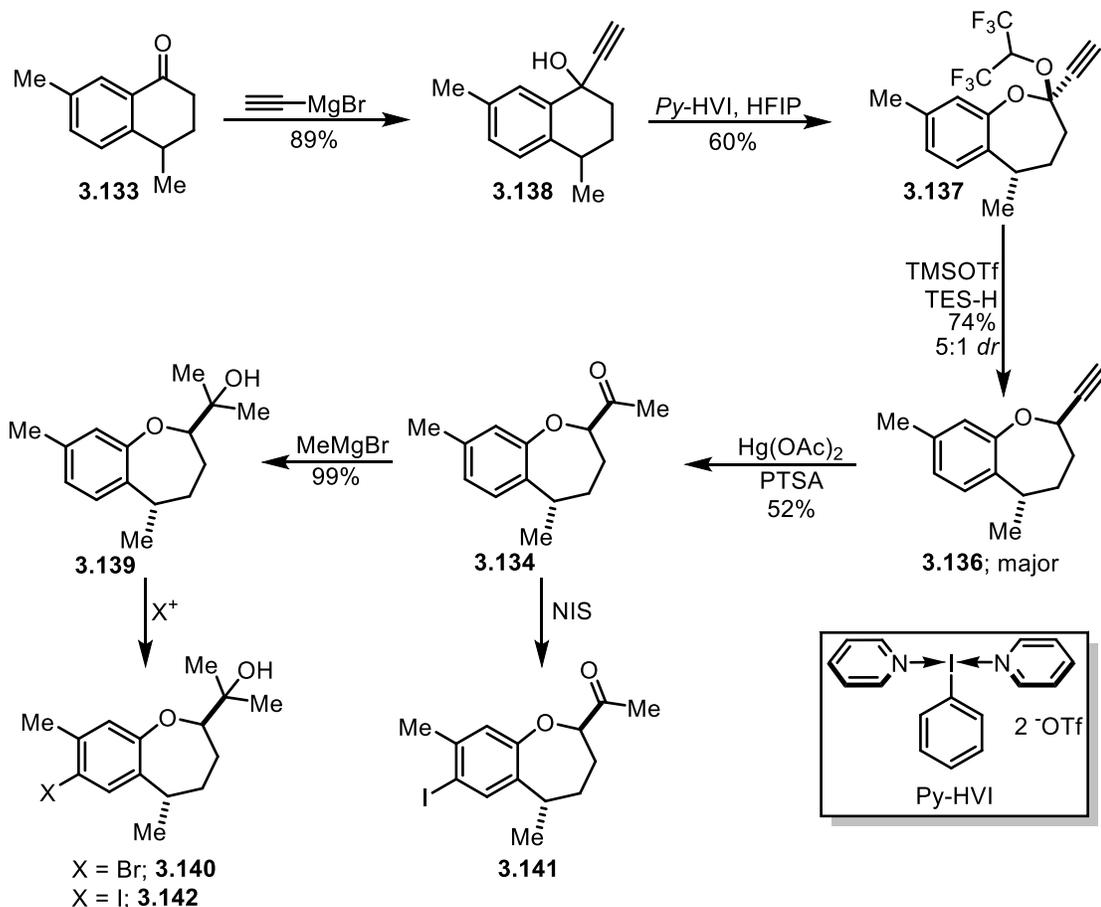
In a flame-dried round-bottomed flask, alcohol **3.128** (306 mg, 1.74 mmol, 1.0 equiv.) was dissolved in DCM (8.7 mL) with finely ground activated 3Å MS. The solution was cooled to $-25\text{ }^{\circ}\text{C}$ in a dry ice/acetone bath and stirred for 5 minutes. After which, a solution of Py-HVI (1.26 g, 1.91 mmol, 1.1 mmol) in HFIP (3.7 mL, 34.8 mmol, 20 equiv.) was added slowly. The reaction was then stirred while slowly warming and monitoring by TLC. When starting material was fully consumed ($-5\text{ }^{\circ}\text{C}$), the reaction was concentrated at ambient temperature and azeotroped with DCM (3x) to remove residual HFIP. The crude material was then diluted with Et₂O and filtered to remove the solids, and the filtrate was concentrated. Purification via column chromatography (0→5% Et₂O/pentane) delivered the desired product as a colorless oil (1.6:1 d.r.). **Yield:** 330 mg, 56%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.07 (d, $J = 7.9$ Hz, 0.53H), 7.02 (d, $J = 7.7$ Hz, 1H), 6.97 – 6.89 (m, 1.6H), 6.81 (dd, $J = 6.3, 1.7$ Hz, 1.42H), 5.04 (dd, $J = 6.7, 4.6$ Hz, 1H), 4.85 (dd, $J = 8.9, 2.2$ Hz, 0.58H), 4.77 (dp, $J = 21.9, 6.0$ Hz, 1.6H), 3.05 (ddd, $J = 11.9, 8.4, 6.2$ Hz, 1.59H), 2.32 (d, $J = 4.3$ Hz, 4.78H), 2.21 – 2.11 (m, 0.66H), 2.11 – 2.00 (m, 0.59H), 2.00 – 1.80 (m, 3.87H), 1.59 (ddt, $J = 13.4, 7.9, 3.7$ Hz, 1H), 1.44 – 1.36 (m, 0.75H), 1.33 (d, $J = 7.1$ Hz, 1.8H), 1.29 (d, $J = 7.1$ Hz, 3H).

5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepine-2-carbonitrile (3.126)¹⁴

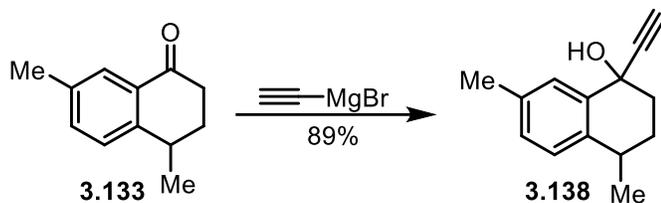


In a flame-dried round-bottomed flask was added HFIP acetal **3.127** (600 mg, 1.75 mmol, 1.0 equiv.) along with DCM (4.4 mL) and HFIP (4.4 mL). The solution was cooled to 0 °C, then freshly distilled TMSCN (1.1 mL, 8.75 mmol, 5.0 equiv.) was added. The reaction was stirred for 5 minutes, followed by the dropwise addition of a solution of freshly distilled TMSOTf (317 μ L, 1.75 mmol, 1.0 equiv.) in DCM (3.5 mL). The reaction was stirred for a further 15 mins, at which point it was deemed complete by TLC as indicated by complete consumption of starting material. The solution was quenched with methanol (5 mL) and concentrated, then purified by column chromatography (8% EtOAc/hexanes) to deliver the product (1:1 d.r.) as a yellow oil. **Yield:** 158 mg, 45%. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.19 – 7.12 (m, 2H), 7.16 – 7.05 (m, 1H), 3.93 (dt, *J* = 19.3, 6.3 Hz, 1H), 3.06 (d, *J* = 6.4 Hz, 1H), 2.93 (dq, *J* = 36.4, 6.7 Hz, 1H), 2.77 – 2.61 (m, 1H), 2.33 (t, *J* = 0.7 Hz, 3H), 2.23 – 2.02 (m, 2H), 1.88 – 1.64 (m, 2.45H), 1.31 (d, *J* = 7.0 Hz, 1.9H), 1.27 (d, *J* = 7.0 Hz, 1.6H).

**** Unless listed, characterization data for the following molecules can be found in the Asymmetric Synthesis of Heliannuol D ****



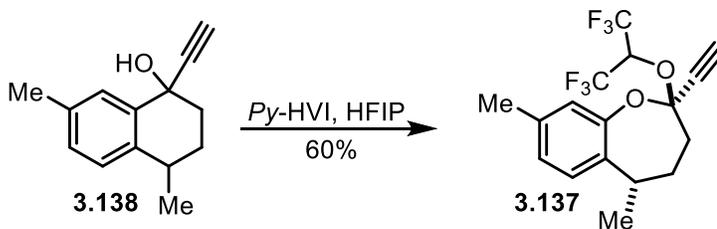
1-ethynyl-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (3.138)



To a 0 °C solution of ketone **3.133** (120 mg, 0.68 mmol, 1.0 equiv.) in THF (3.0 mL) in a flame-dried round-bottomed flask was added ethynylmagnesium chloride (0.5 M THF, 2.7 mL, 1.43 mmol, 2.5 equiv.) dropwise over 5 minutes. The resulting solution was stirred for 10 mins, then slowly warmed to 55 °C and stirred overnight. The following day, the reaction was once again cooled to 0 °C and quenched slowly with saturated aqueous ammonium chloride, then extracted with Et₂O (3x). The combined organic extracts were washed with brine, dried over sodium sulfate, then concentrated.

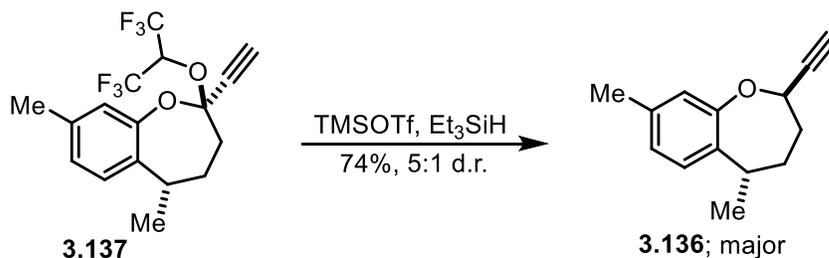
Purification was performed via column chromatography (5% EtOAc/hexanes) to afford the desired alcohol as a yellow oil (4:3 *d.r.*). **Yield:** 124 mg, 89%.

2-ethynyl-2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepine (3.137)¹³



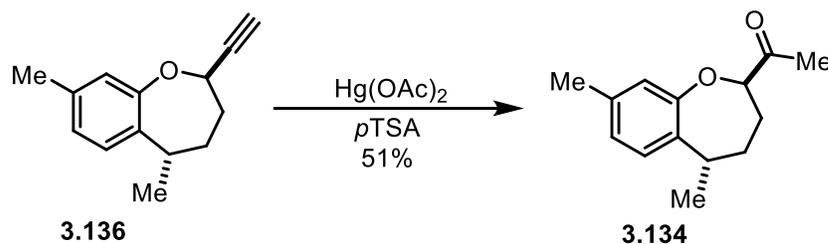
In a flame-dried round-bottomed flask, alcohol **3.138** (100 mg, 0.5 mmol, 1.0 equiv.) was dissolved in DCM (2.5 mL) with finely ground activated 3Å MS. The solution was cooled to $-25\text{ }^{\circ}\text{C}$ in a dry ice/acetone bath and stirred for 5 minutes. After which, a solution of Py-HVI (396 mg, 0.55 mmol, 1.1 mmol) in HFIP (1.05 mL, 10 mmol, 20 equiv.) was added slowly. The reaction was then stirred while slowly warming and monitoring by TLC. When starting material was fully consumed ($-5\text{ }^{\circ}\text{C}$), the reaction was concentrated at ambient temperature and azeotroped with DCM (3x) to remove residual HFIP. The crude material was then diluted with Et₂O and filtered to remove the solids, and the filtrate was concentrated. Purification via column chromatography (0→5% Et₂O/pentane) delivered the desired product as a colorless oil which crystallized overnight at $-20\text{ }^{\circ}\text{C}$ and remained crystalline. **Yield:** 109 mg, 60%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.01 (d, $J = 7.7\text{ Hz}$, 1H), 6.93 (d, $J = 7.6, 1.8, 0.8\text{ Hz}$, 1H), 6.79 (s, 1H), 5.18 (h, $J = 6.0\text{ Hz}$, 1H), 3.13 (td, $J = 8.0, 7.5, 4.8\text{ Hz}$, 1H), 2.78 (s, 1H), 2.31 (s, 3H), 2.27 – 2.10 (m, 2H), 2.13 – 2.03 (m, 1H), 1.56 – 1.47 (m, 1H), 1.30 (d, $J = 7.0\text{ Hz}$, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ 151.1, 137.5, 134.9, 126.9, 126.1, 123.1, 101.9, 78.6, 76.9, 72.3, 72.0, 71.7, 71.5, 70.7, 35.7, 33.3, 29.4, 21.1, 18.5. **MP:** 49–52 $^{\circ}\text{C}$

2-ethynyl-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepine (3.136)¹⁴



In a flame-dried round-bottomed flask, HFIP acetal **3.137** (616 mg, 1.68 mmol, 1.0 equiv.) was dissolved in DCM (8.4 mL) and cooled to 0 °C. Triethylsilane (1.34 mL, 8.41 mmol, 5.0 equiv.) was added and the resulting reaction was stirred for 5 minutes, then TMSOTf (0.46 mL, 2.52 mmol, 1.5 equiv.). The reaction was allowed to warm to room temperature and stir for 25 minutes, at which point saturated aqueous sodium bicarbonate was added. The organic layer was collected, and the aqueous layer was back extracted with DCM (3x), then the combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated. Purification was performed via column chromatography (5% Et₂O/pentane) to afford the product as a colorless oil (6:1 *d.r. trans* major). **Yield:** 249 mg, 74%.

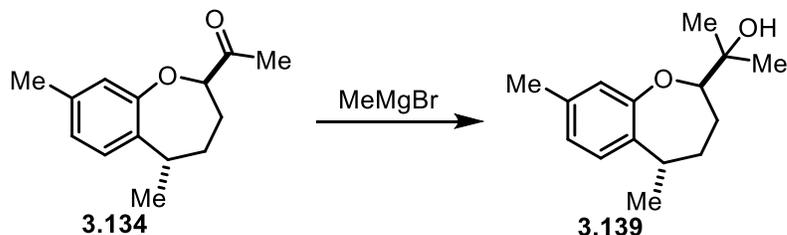
5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-2-yl)ethan-1-one (3.134)¹⁵



To a round-bottomed flask was added alkyne **3.136** (89 mg, 0.44 mmol, 1.0 equiv.) along with acetone (3 mL). Water (40 μL, 2.22 mmol, 5.0 equiv.) was added, followed by *p*TSA (77 mg, 0.44 mmol, 1.0 equiv.) and mercury(II) acetate (99 mg, 0.31 mmol, 0.70 equiv.). The resulting solution was allowed to stir for 12 hours overnight. The following morning, the slurry was diluted with acetone and filtered through celite and the filtrate

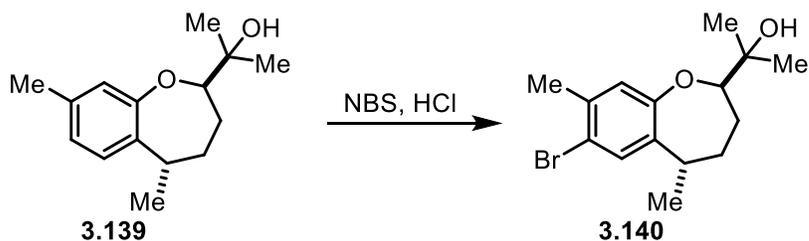
was concentrated, then loaded onto silica for purification via column chromatography (5% EtOAc/hexanes). Purification afforded the desired product as a yellow oil with an unchanged diastereomeric ratio (6:1 *d.r. trans*). **Yield:** 50 mg, 51%.

5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-2-yl)propan-2-ol (3.139)



In a flame-dried round-bottomed flask, ketone **3.134** (50 mg, 0.23 mmol, 1.0 equiv.) was dissolved in THF (3 mL) and cooled to $-78\text{ }^{\circ}\text{C}$. A solution of methylmagnesium bromide (3.0 M Et₂O, 0.47 mL, 1.38 mmol, 6.0 equiv.) was added dropwise and the resulting solution was stirred for 20 minutes. The reaction was removed from the dry ice/acetone bath and quenched with saturated aqueous ammonium chloride, then transferred to a separatory funnel. The solution was extracted with DCM (3x), then the combined organic extracts were dried over sodium sulfate and concentrated to afford the desired product as a pale yellow oil which was used without further purification. (6:1 *d.r. trans*). **Yield:** 53 mg, 99%.

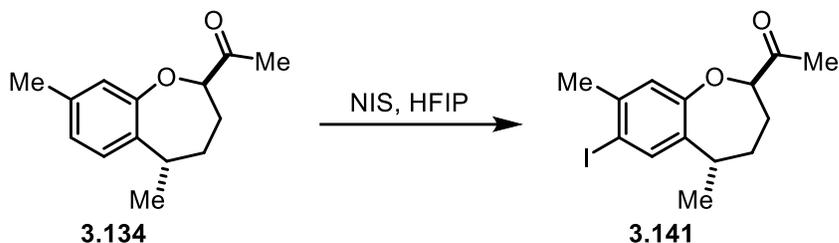
7-bromo-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-2-yl)propan-2-ol (3.140)¹⁶



In a round-bottomed flask, **3.139** (15 mg, 0.063 mmol, 1.0 equiv.) was dissolved in dry acetone (500 μL). To this solution was added a drop of aqueous 3 M HCl and the reaction

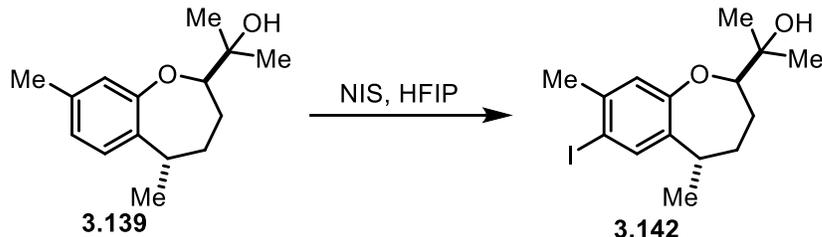
was closely monitored by TLC. Once the starting material was fully consumed, the reaction was quenched with saturated aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate (3x) and the combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated. Purification via column chromatography afforded the desired product as a reddish-yellow oil (single diastereomer). **Yield:** 9 mg, 44%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.30 (s, 1H), 6.87 (s, 1H), 3.28 (dd, $J = 10.2, 3.0$ Hz, 1H), 3.01 (dt, $J = 14.4, 7.1$ Hz, 1H), 2.32 (s, 3H), 1.99 – 1.86 (m, 4H), 1.33 (d, $J = 7.2$ Hz, 3H), 1.28 (d, $J = 6.5$ Hz, 6H).

7-iodo-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-2-yl)ethan-1-one (3.141)¹⁷



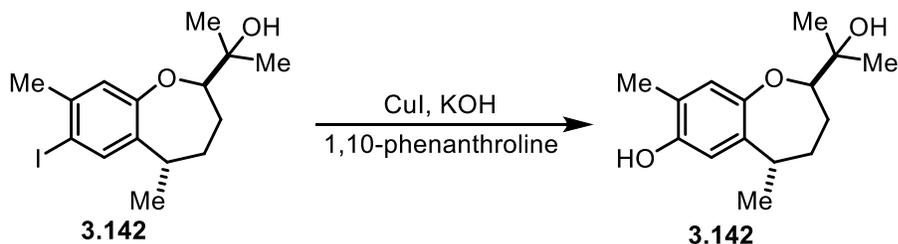
To a flask containing ketone **3.1334** (40 mg, 0.20 mmol, 1.1 equiv.) was added HFIP (1.2 mL). N-iodosuccinimide (60 mg, 0.24 mmol, 1.2 equiv.) was added to the reaction, and the mixture was allowed to stir for 5 hours. Upon completion as determined by ¹H NMR, the reaction was concentrated and purified via column chromatography. **Yield:** 68 mg, 99%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.57 (s, 1H), 6.95 (s, 1H), 3.87 (dd, $J = 11.2, 2.4$ Hz, 1H), 3.00 (q, $J = 8.0, 7.3$ Hz, 1H), 2.40 (s, 3H), 2.36 (s, 3H), 2.21 – 2.15 (m, 1H), 1.98 – 1.86 (m, 2H), 1.34 (d, $J = 7.1$ Hz, 4H).

7-iodo-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-2-yl)propan-2-ol (3.142)¹⁷



Tertiary alcohol **3.139** (273 mg, 1.16 mmol, 1.0 equiv.) was suspended in HFIP (7 mL) in a 20 mL scintillation vial. To the vial was added N-iodosuccinimide (315 mg, 1.40 mmol, 1.2 equiv.), and the resulting red solution was monitored for completion by ¹H NMR. After approximately 1 hour the reaction was complete, and the reaction was concentrated in vacuo. The crude material was purified by column chromatography (20% EtOAc/Hex) to afford the product as a viscous orange paste. **Yield:** 360 mg, 86%.

2-(2-hydroxypropan-2-yl)-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-7-ol; Heliannuol D (3.2)¹⁸

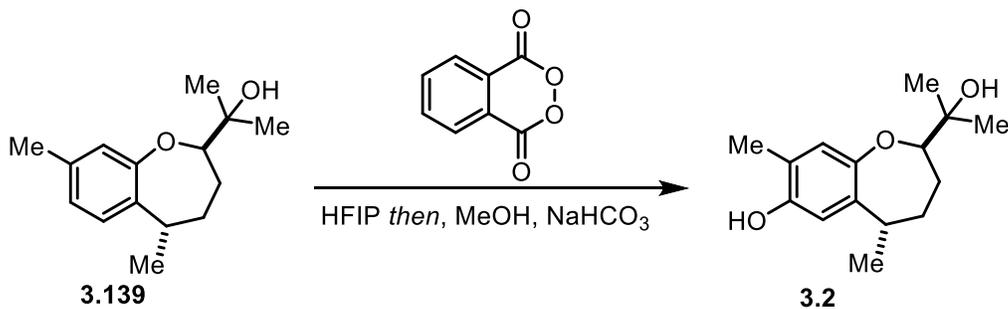


A 4mL scintillation vial was charged with iodoarene **3.142** (67 mg, 0.19 mmol, 1.0 equiv.), CuI (11 mg, 0.06 mmol, 0.3 equiv.), 1,10-phenanthroline (20 mg, 0.11 mmol, 0.6 equiv.) and KOH (63 mg, 1.12 mmol, 6 equiv.). The vial was evacuated and purged with argon 3 times. Vigorously degassed DMSO (0.31mL) and H₂O (0.31 mL) were added, and the vial was tightly capped and submerged in a 100°C oil bath. The reaction was stirred for 40 hours at this temperature, then cooled to room temperature and quenched with a few drops of 2M HCl. The mixture was passed through a silica plug to reveal the product as an off white solid. **Yield:** 45 mg, 99% 4:1 d.r.). ¹H NMR (500 MHz,

Chloroform-*d*) δ 6.76 (s, 1H), 6.73 (s, 0.24H), 6.61 (s, 1H), 6.54 (s, 0.25H), 4.58 – 4.46 (m, 1.22H), 3.30 (dd, $J = 11.2, 1.2$ Hz, 0.33H), 3.24 (dd, $J = 10.3, 2.8$ Hz, 1H), 3.07 – 2.97 (m, 1.22H), 2.93 – 2.85 (m, 0.36H), 2.66 (s, 1.25H), 2.37 – 2.30 (m, 0.33H), 2.18 (s, 3H), 2.16 (s, .078H), 1.96 – 1.84 (m, 3.75H), 1.80 – 1.68 (m, 0.85H), 1.32 – 1.24 (m, 15.46H).

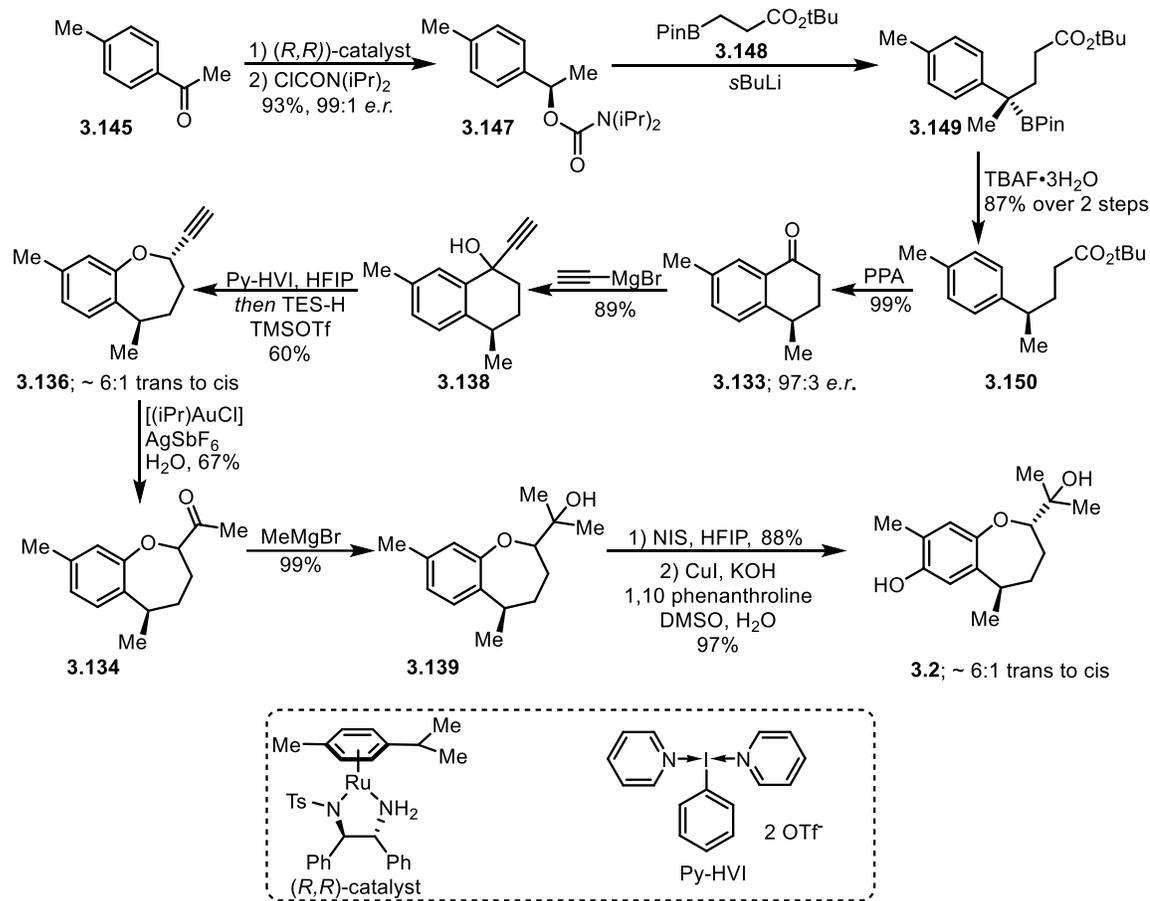
2-(2-hydroxypropan-2-yl)-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-7-ol;

Heliannuol D (3.2)¹⁹

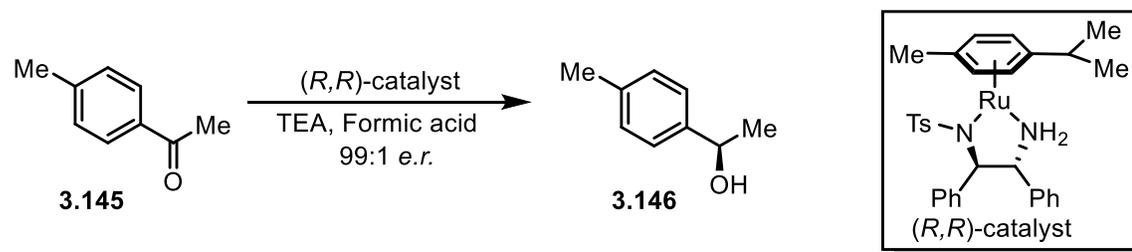


Aryl ether **3.139** (97 mg, 0.42 mmol, 1.0 equiv.) was added to a 20 mL scintillation vial, then diluted with HFIP (4.2 mL). With strong stirring, phthaloyl peroxide¹⁹ was added and the vial was capped. The reaction was then warmed to 40 °C allowed to stir for 12 hours overnight. The following morning, the reaction was concentrated to remove HFIP, then degassed methanol (3.8 mL) was added and stirring was initiated. Saturated aqueous sodium bicarbonate (400 μ L) was then added and the vial was sealed and once again warmed to 40 °C with stirring. After 6 hours, the mixture was quenched with pH 7 phosphate buffer (10 mL) and extracted with EtOAc (3x). The combined organic extracts were washed with brine then dried over sodium sulfate and concentrated. Column chromatography was performed to isolate *trans*-Heliannuol D as the major product along with a mixture of phenolic regioisomers (See Appendix E for characterization of C3 regioisomer) **Yield:** 43 mg, 41%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 6.76 (s, 1H), 6.61 (s, 1H), 4.62 (s, 1H), 3.24 (dd, $J = 10.3, 2.8$ Hz, 1H), 3.01 (dt, $J = 14.3, 7.1$ Hz, 1H), 2.67 (s, 1H), 2.18 (s, 3H), 1.99 – 1.83 (m, 3H), 1.29 (dd, $J = 11.8, 7.6$ Hz, 10H).

C6: ASYMMETRIC TOTAL SYNTHESIS OF HELIANNUOL D



(*R*)-1-(*p*-tolyl)ethan-1-ol (**3.146**)^{20,21}

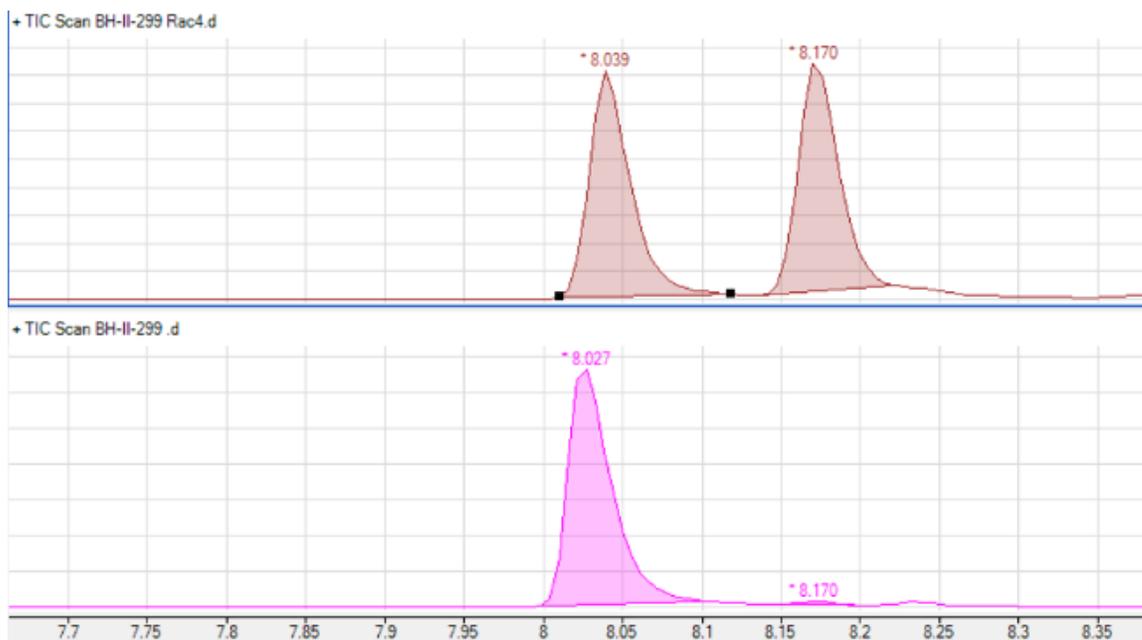


To a flask containing triethylamine (11 mL, 78.5 mmol, 2.5 equiv.) cooled to 0°C was slowly added formic acid (7.11 mL, 188.4 mmol, 6 equiv.). This solution was allowed to stir for 10 minutes before addition of 4-methylacetophenone (**3.145**; 4.2 mL, 31.4 mmol, 1.0 equiv.) and RuCl(*p*-cymene)[(*S,S*)-Ts-DPEN] (1 g, 1.57 mmol, 0.05 equiv.). The

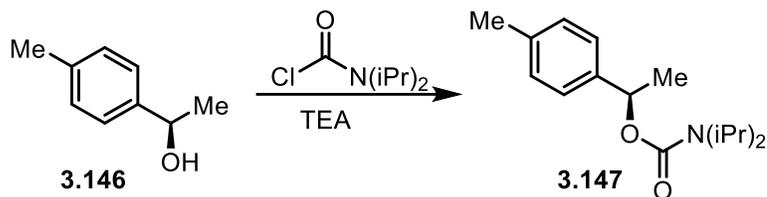
mixture was allowed warm to room temperature and stirred for 18 hours with occasional manual stirring. The mixture was slowly quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with saturated NaHCO₃, water, and brine, then dried over Na₂SO₄ and concentrated. Purification by flash chromatography (gradient 5% to 25% EtOAc/hexanes) provided alcohol (**3.146**) as a pale yellow oil.

Yield: 3.98 g, 93%. Spectral data matches literature reports²⁰ ¹HNMR (500 MHz, Chloroform-d) δ 7.27 (d, 2H), 7.17 (d, 2H), 4.87 (q, J = 6.5 Hz, 1H), 2.35 (s, 3H), 1.49 (d, J = 6.4 Hz, 3H).

E.R. determined by GCMS (cyclosilB chiral column, 40 °C start, 20 °C/min to 146 °C, 2 min hold, 0.1 °C/min to 148 °C, 20 °C/min to 225 °C) retention times: 8.03 min (major) and 8.17 min (minor); 99:1

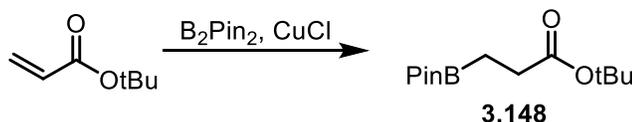


(R)-1-(p-tolyl)ethyl diisopropylcarbamate (3.147)²⁰



In a flame-dried flask under an atmosphere of argon, alcohol (3.151) (3.98 g, 32.5 mmol, 1.0 equiv.) was dissolved in 65 mL of Dichloromethane. Diisopropylcarbonyl chloride (6.39 g, 39.0 mmol, 1.2 equiv.) and triethylamine (5.44 mL, 39.0 mmol, 1.2 equiv.) were added sequentially, then the flask was sealed with electrical tape and stirred at 45°C for 48 h. After cooling to room temperature, 3M HCl (20 mL) was added and stirred for 10 minutes. The aqueous phase was extracted with dichloromethane (3x), and the combined organic phases were dried over Na₂SO₄ and concentrated. Flash column chromatography (7% EtOAc/hexanes) afforded pure carbamate (3.147) as a colorless oil. **Yield:** 7.11 g, 86%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 5.83 (q, *J* = 6.6 Hz, 1H), 2.35 (s, 3H), 1.55 (d, *J* = 6.6 Hz, 3H), 1.31 – 1.16 (m, 12H). **¹³C NMR** (126 MHz, CDCl₃) δ 155.2, 134.0, 137.1, 129.1, 126.1, 72.7, 22.9, 21.2. **HRMS** (ESI) *m/z* calculated for C₁₆H₂₅NO₂⁺ 263.1885; found 286.1795 (M+Na)⁺

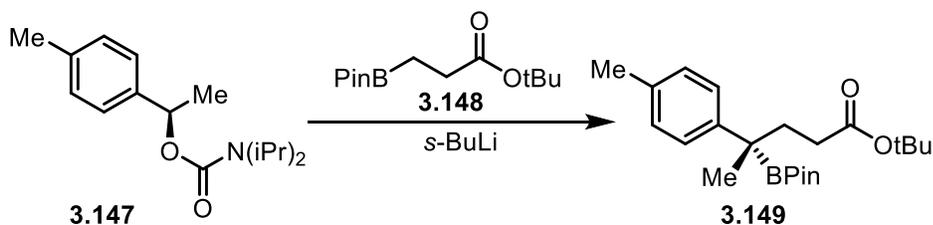
***tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (3.148)²⁰**



A dry flask was charged with CuCl (178 mg, 0.94 mmol, 0.03 equiv.), DPEPhos (504 mg, 0.94 mmol, 0.03 equiv.) and sodium *tert*-butoxide (270 mg, 2.81 mmol, 0.09 equiv.) and pump-purged with argon 3 times. Dry THF (25 mL) was added and the mixture was allowed to stir for 30 minutes at room temperature. Bis(pinacolato)diboron (8.32 g, 32.77 mmol, 1.05 equiv.) was dissolved in 25 mL THF and added dropwise via syringe, using an additional 5 mL of THF to rinse the flask. This mixture was allowed to stir for 30

minutes, followed by the sequential addition of *tert*-butyl acrylate (4.7 mL, 31.21 mmol, 1.0 equiv.) and MeOH (2.5 mL). After stirring for 3 h, the slurry was filtered through celite and concentrated. The crude oil was purified by flash chromatography (10% EtOAc/hexanes) to afford boronic ester (**3.148**) as a colorless oil. **Yield:** 7.3 g, 81%. Spectral data was identical to a prior report.²⁰ ¹H NMR (500 MHz, Chloroform-*d*) δ 2.35 (t, *J* = 7.5 Hz, 2H), 1.43 (s, 9H), 1.24 (s, 12H), 0.97 (t, *J* = 7.5 Hz, 2H).

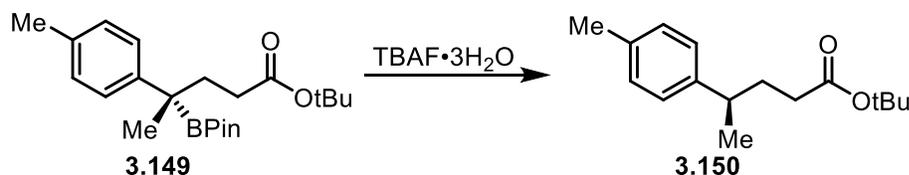
***tert*-butyl (*R*)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(*p*-tolyl)pentanoate (**3.149**)^{20,22}**



Carbamate **3.147** (6.01g, 22.8 mmol, 1.0 equiv.) was dissolved in 115 mL of diethyl ether, and the solution was cooled to -78 °C in a dry ice/acetone bath. After a few minutes at this temperature, *s*-BuLi (17.9 mL, 25.04 mmol, 1.1 equiv.) was added dropwise over a period of 5 minutes, and the resultant solution was stirred for 30 minutes. A solution of boronic ester **3.148** (7.00 g, 25.04 mmol, 1.2 equiv.) in 27 mL Et₂O was added dropwise over a period of 5 minutes and stirred for 30 minutes at -78 °C, then 6 hours at room temperature. The reaction was then cooled to 0°C and quenched by the addition of 1M KHSO₄ slowly. The mixture was allowed to warm to room temperature and stir for an additional 10 mins. Extraction with Et₂O (3x) and drying over Na₂SO₄ afforded the crude oil, which was subjected to flash chromatography (0→5% Et₂O/pentane) to afford a mixture of unreacted carbamate and desired product which is used in the next step without further purification. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.18 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 7.7 Hz, 2H), 2.30 (s, 3H), 2.16 – 1.95 (m, 4H), 1.41

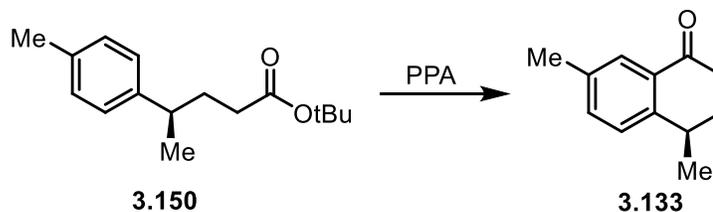
(s, 9H), 1.31 (s, 3H), 1.20 (s, 6H), 1.19 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 174.1, 143.3, 134.9, 129.3, 127.2, 83.7, 80.2, 34.6, 32.1, 28.5, 25.0, 21.6, 21.3. **HRMS:** (ESI) m/z calculated for $\text{C}_{22}\text{H}_{35}\text{BO}_4^+$ 374.2628; found 397.2530 ($\text{M}+\text{Na}$) $^+$

tert-butyl (R)-4-(p-tolyl)pentanoate (3.150)^{20,23}

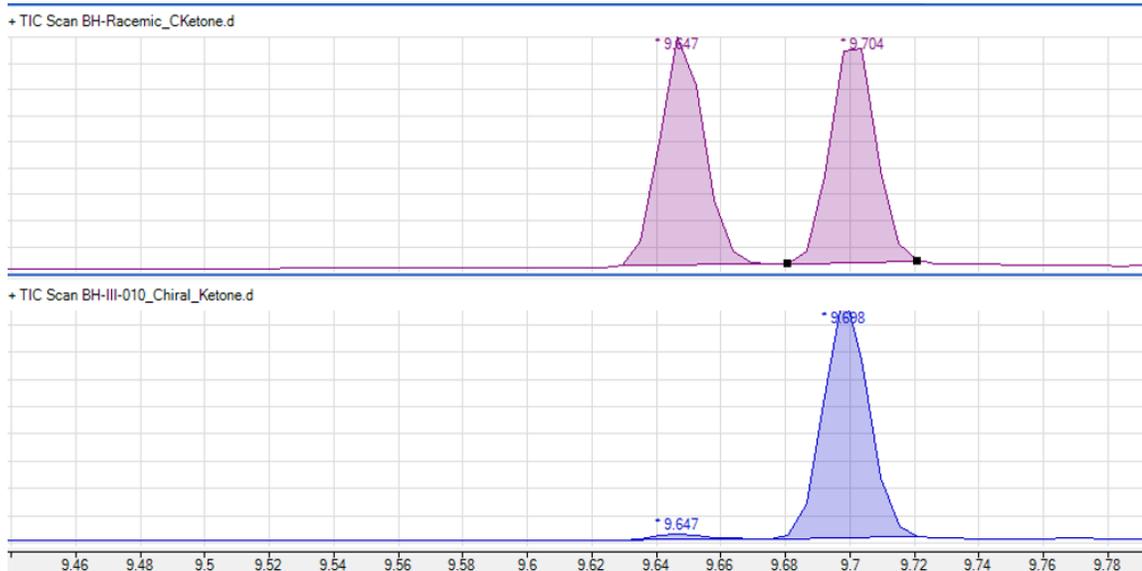


To a flame dried flask containing a mixture of boronic ester **3.149** and unreacted carbamate **3.147** was added toluene (122 mL), followed by TBAF·3H₂O (8.46 g, 26.79 mmol, 1.2 equiv. theoretical). The mixture was heated to 50°C and stirred overnight. The solution was then cooled to room temperature and quenched with water. The aqueous phase was extracted with Et₂O (3x) and the combined organic phases were dried over Na₂SO₄ and concentrated. The resulting oil was purified by flash chromatography (5% Et₂O/pentane) to afford the desired product as a colorless oil. **Yield:** 4.93 g, 87% over two steps. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.11 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 2.68 (dp, J = 8.9, 6.9 Hz, 1H), 2.33 (s, 3H), 2.11 (ddd, J = 8.3, 6.8, 2.8 Hz, 2H), 1.91 – 1.79 (m, 2H), 1.43 (s, 9H), 1.25 (d, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.3, 143.6, 135.6, 129.2, 127.0, 80.1, 39.1, 33.9, 33.6, 28.2, 22.4, 21.1. **HRMS:** (ESI) m/z calculated for $\text{C}_{16}\text{H}_{24}\text{O}_4^+$ 248.1776; found 271.1674 ($\text{m}+\text{Na}$) $^+$

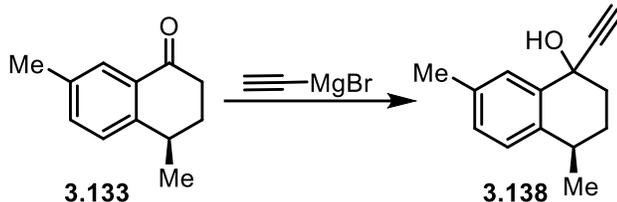
(R)-4,7-dimethyl-3,4-dihydronaphthalen-1(2H)-one (3.133)²⁰



To a vial containing ester **3.150** (89 mg, 0.36 mmol, 1.0 equiv.) was added polyphosphoric acid (~1 mL). The vial was capped and stirred at 80°C for 3 hours. The reaction was cooled to room temperature and quenched with water. The aqueous phase was extracted with EtOAc (3x) and the combined organic phases were washed with water, saturated aqueous sodium bicarbonate (3x), and brine, dried over Na₂SO₄ and concentrated. The crude oil was purified flash chromatography (5→20% EtOAc/hexanes) to afford the desired product as a yellow oil. **Yield:** 62 mg, 99% **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.84 (s, 1H), 7.33 (dd, *J* = 7.9, 2.1, 0.7 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 3.06 (td, *J* = 7.2, 4.6 Hz, 1H), 2.78 (ddd, *J* = 17.3, 8.5, 4.5 Hz, 1H), 2.59 (ddd, *J* = 17.4, 8.9, 4.8 Hz, 1H), 2.36 (s, 3H), 2.23 (ddt, *J* = 13.2, 8.6, 4.6 Hz, 1H), 1.88 (dddd, *J* = 13.4, 8.9, 7.4, 4.5 Hz, 1H), 1.38 (d, *J* = 7.0 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ 198.9, 146.2, 136.3, 134.7, 131.7, 127.5, 70.7, 36.6, 32.6, 30.9, 21.0, 20.9. **HRMS:** (ESI) *m/z* calculated for C₁₂H₁₄O⁺ 174.1045; found 175.1123 (M+H)⁺ E.R. determined by GCMS (cyclosilB chiral column, 40 °C start, 20 °C/min to 225 °C) retention times: 9.47 min (minor) and 9.70 min (minor); 97:3



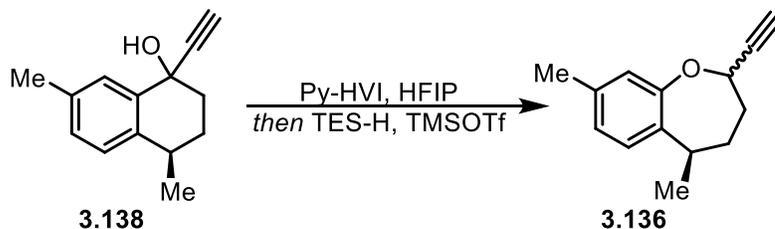
(4*R*)-1-ethynyl-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (3.138)



To a 0°C solution of ketone **3.133** (300 mg, 1.72 mmol, 1.0 equiv.) in 9 mL THF was added a 0.5M solution of ethynylmagnesium bromide in THF (5.16 mL, 2.58 mmol, 1.5 eq). The reaction was warmed to RT for 30 minutes then to 60°C overnight. After cooling to room temperature, saturated aqueous NH_4Cl was added slowly and the aqueous phase was extracted with Et_2O (x3). The combined organic phases were dried over Na_2SO_4 and concentrated. The crude oil was purified by flash chromatography (5→10%

EtOAc /hexanes) to afford the desired product as a yellow oil (3:2 *d.r.*). **Yield:** 306 mg, 89% *d.r* = 3:2 **$^1\text{H NMR}$** (400 MHz, CDCl_3) δ 7.61 – 7.57 (m, 1.73H), 7.16 (d, J = 8.0 Hz, 1H), 7.10 (td, J = 4.1, 3.3, 1.6 Hz, 2.51H), 2.92 (dq, J = 24.5, 6.6 Hz, 2H), 2.60 (s, 0.69H), 2.59 (s, 1H), 2.36 (d, J = 0.9 Hz, 6H), 2.33 – 2.24 (m, 1.41H), 2.17 (dddd, J = 15.3, 9.6, 4.2, 2.6 Hz, 1.88H), 2.15 – 1.97 (m, 1.88H), 1.85 – 1.62 (m, 1.86H), 1.33 (d, J = 7.0 Hz, 3H), 1.29 (d, J = 7.1 Hz, 2H). **$^{13}\text{C NMR}$** (101 MHz, CDCl_3) δ 138.0, 136.1, 129.5, 128.5, 128.0, 128.0, 127.8, 88.4, 72.5, 72.4, 68.2, 67.9, 36.9, 36.0, 32.1, 32.0, 27.5, 27.0, 22.6, 22.3, 21.1. **HRMS:** (ESI) m/z calculated for $\text{C}_{14}\text{H}_{16}\text{O}^+$ 200.1201; found 201.1277 ($\text{M}+\text{H}$)⁺

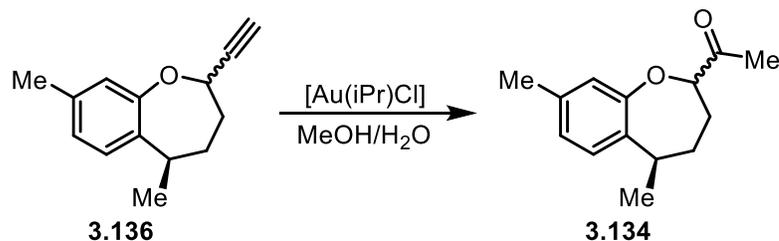
(5*R*)-2-ethynyl-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepine (3.136)^{13,14}



A solution of tertiary alcohol **3.138** (165 mg, 0.83 mmol, 1.0 equiv.) in 4.0 mL DCM was added to a flame-dried RBF containing powdered, activated 3Å MS. The flask was submerged in a -25°C bath and stirred for 5 minutes. A solution of Py-HVI (657 mg, 0.996 mmol, 1.2 equiv.) in HFIP (1.75 mL, 20 equiv.) was then slowly added, and the resulting solution was stirred while slowly warming to 0°C. Once all starting material had been consumed as judged by TLC (20% Et₂O/Pentane), the ice bath was maintained at 0°C and triethylsilane (0.398 mL, 2.18 mmol, 3.0 equiv.) was added. The solution was stirred for 5 minutes, at which point trimethylsilyl trifluoromethanesulfonate (0.165 mL, 0.913 mmol, 1.1 equiv) was added dropwise. The reaction was monitored by TLC (5% Et₂O/Pentane), and once the HFIP acetal was fully consumed the reaction was quenched with a saturated solution of sodium bicarbonate. The aqueous phase was extracted with DCM (x3), dried over Na₂SO₄, and concentrated in vacuo. The product was purified via column chromatography (0→5% Et₂O/Pentane) to afford the product as an orange oil.

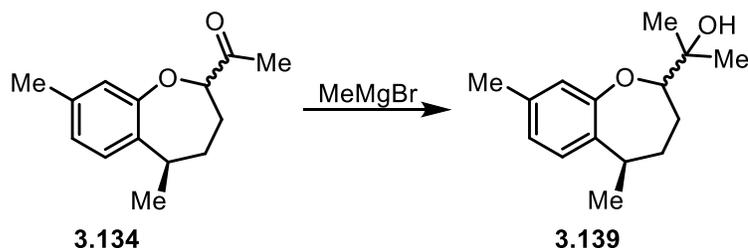
Yield: (99 mg, 60%, ~6:1 d.r.) **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.61 – 7.57 (m, 1.73H), 7.16 (d, *J* = 8.0 Hz, 1H, Major), 7.10 (td, *J* = 4.1, 3.3, 1.6 Hz, 2.51H), 2.92 (dq, *J* = 24.5, 6.6 Hz, 2H), 2.60 (s, 0.69H), 2.59 (s, 1H Major), 2.36 (d, *J* = 0.9 Hz, 6H), 2.33 – 2.24 (m, 1.41H), 2.17 (dddd, *J* = 15.3, 9.6, 4.2, 2.6 Hz, 1.88H), 2.15 – 1.97 (m, 1.88H), 1.81 – 1.73 (m, 1H, Major), 1.73 – 1.63 (m, 0.88H, Minor (1H)), 1.33 (d, *J* = 7.0 Hz, 3.38H, Major), 1.29 (d, *J* = 7.1 Hz, 2.17H, Minor (3H)). **¹³C NMR** (126 MHz, CDCl₃) δ 156.9, 137.2, 136.6, 128.3, 127.2, 126.2, 125.2, 124.2, 123.6, 123.4, 122.2, 84.8, 82.3, 74.5, 74.1, 72.1, 71.4, 37.3, 36.4, 35.8, 35.1, 34.3, 34.1, 31.7, 30.0, 20.9, 20.6, 20.0, 19.2. **HRMS:** (ESI) *m/z* calculated for C₁₄H₁₆O⁺ 200.1201; found 201.1280 (M+H)⁺

1-((5*R*)-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-2-yl)ethan-1-one (3.134)²⁴



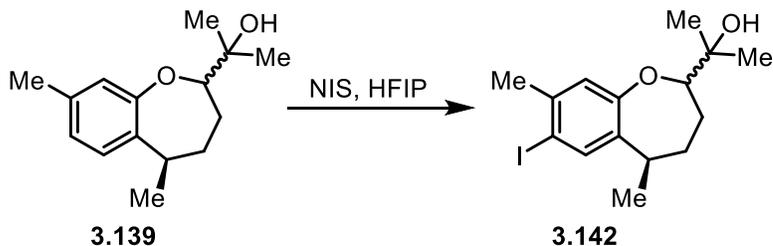
Alkyne **3.136** (362 mg, 1.81 mmol, 1.0 equiv.) was dissolved in a 2:1 mixture of MeOH and H₂O (6 ml total) in a 20 mL scintillation vial. [Au(*i*Pr)Cl] (28 mg, .045 mmol, 0.025 equiv.) was then added, followed by a small scoop of AgSbF₆. The vial was capped tightly, and the reaction was heated to 120 °C for 18 hours. Following stirring, the reaction was concentrated in vacuo then purified by column chromatography (20% Et₂O/Pentane), and the product was isolated as a pale yellow oil. **Yield:** 266 mg, 67% d.r. = 3:1. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.02 (dd, *J* = 7.9, 0.8 Hz, 1H, Major), 6.95 (d, *J* = 7.6 Hz, 0.32H, Minor (1H)), 6.87 – 6.73 (m, 3H), 3.88 – 3.84 (m, 0.31H, Minor (1H)), 3.81 (dd, *J* = 11.2, 2.4 Hz, 1H, Major), 2.98 (ddt, *J* = 9.8, 8.0, 6.2 Hz, 1.52H), 2.35 (s, 4H), 2.24 (s, 3H, Major), 2.22 (s, 1.52H, Minor (3H)), 2.15-2.09 (m, 1H, Major), 2.03 – 1.97 (m, 0.62H, Minor (2H)), 1.91 – 1.81 (m, 2H, Major), 1.28 (d, *J* = 7.1 Hz, 3H, Major), 1.22 (d, *J* = 7.2 Hz, 1H, Minor (3H)). **¹³C NMR** (126 MHz, CDCl₃) δ 209.3, 158.3, 137.7, 137.3, 136.3, 129.7, 126.3, 126.1, 125.2, 124.2, 122.5, 122.2, 121.8, 88.2, 87.2, 84.8, 38.4, 36.4, 34.6, 34.3, 33.6, 32.5, 31.6, 30.0, 27.8, 26.6, 20.9, 20.6, 20.4, 18.9, 10.9. **HRMS:** (ESI) *m/z* calculated for C₁₄H₁₈O₂⁺ 218.1307; found 241.1208 (M+Na)⁺

2-((5*R*)-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-2-yl)propan-2-ol (3.139)



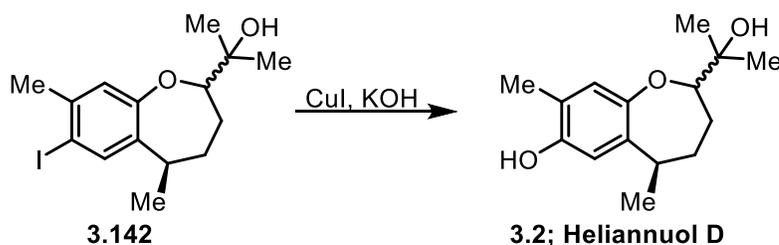
Ketone **3.134** (250 mg, 1.14 mmol, 1.0 equiv.) was dissolved in 11 mL dry THF in a flame-dried RBF. The solution was cooled to -78°C , and MeMgBr (3.0 M, 2.3 mL, 6.9 mmol, 6 eq.) was added dropwise and the reaction was monitored by TLC (20% Et₂O/Pentane). After 15 minutes, the starting material was fully consumed, and the reaction was removed from the ice bath and quenched with saturated ammonium chloride. The aqueous layer was extracted with Et₂O (x3) and dried with Na₂SO₄. After concentration in vacuo, the product was obtained as a pale yellow oil and directly used in the next step without further purification. 3:1 d.r. **Yield:** 268 mg, 99%. **¹H NMR MAJOR** ¹H NMR (500 MHz, Chloroform-*d*) δ 7.07 (dd, $J = 7.8, 0.8$ Hz, 1H), 6.88 (dd, $J = 7.9, 1.8$ Hz, 1H), 6.82 (s, 1H), 3.34 – 3.29 (m, 1H), 3.09 – 2.96 (m, 1H), 2.65 (s, 1H), 2.30 (s, 3H), 2.0 – 1.67 (m, 4H), 1.31 – 1.27 (m, 9H). **¹H NMR MINOR** (500 MHz, Chloroform-*d*) δ 7.01 (d, $J = 7.5$ Hz, 1H), 6.85 – 6.78 (m, 2H), 3.37 (dd, $J = 11.2, 1.3$ Hz, 1H), 3.01 (d, $J = 3.0$ Hz, 1H), 2.67 (s, 1H), 2.28 (s, 3H), 2.07 (dddd, $J = 14.2, 12.7, 11.2, 3.4$ Hz, 1H), 1.90 (t, $J = 1.9$ Hz, 1H), 1.84 – 1.70 (m, 2H), 1.35 (d, $J = 7.1$ Hz, 9H). **¹³C NMR** (126 MHz, CDCl₃) δ 159.2, 158.2, 137.5, 137.1, 136.7, 136.6, 129.6, 126.2, 124.6, 122.2, 121.6, 90.5, 89.6, 72.7, 72.6, 38.5, 34.6, 34.1, 32.0, 30.8, 26.4, 26.2, 25.7, 24.6, 24.6, 20.9, 20.5, 19.0. **HRMS:** (ESI) m/z calculated for C₁₅H₂₂O₂⁺ 234.162; found 234.1700 (M+H)⁺

2-((5*R*)-7-iodo-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-2-yl)propan-2-ol
(3.142)¹⁷



Tertiary alcohol **3.139** was suspended in HFIP in a 20 mL scintillation vial. To the vial was added N-iodosuccinimide, and the resulting red solution was monitored for completion by ^1H NMR. After approximately 1 hour the reaction was complete, and the reaction was concentrated in vacuo. The crude material was purified by column chromatography (20% EtOAc/Hex) to afford the product as a viscous orange paste. 5:1 d.r. **Yield:** 360 mg, 89%. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.55 (s, 1H), 6.88 (s, 1H), 3.28 (dd, $J = 10.3, 3.0$ Hz, 1H), 2.99 (tt, $J = 12.1, 6.1$ Hz, 1H), 2.52 (s, 1H), 2.35 (s, 3H), 2.00 – 1.85 (m, 3H), 1.32 (d, $J = 7.1$ Hz, 3H), 1.28 (d, $J = 6.9$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 159.2, 158.2, 137.5, 137.1, 136.7, 136.6, 129.6, 126.2, 124.6, 122.2, 121.6, 90.5, 89.6, 72.7, 72.6, 38.5, 34.6, 34.1, 32.0, 30.8, 26.4, 26.2, 25.7, 24.6, 24.6, 20.9, 20.5, 19.0. **HRMS:** (ESI) m/z calculated for $\text{C}_{15}\text{H}_{21}\text{IO}_2^+$ 360.0586; found 383.0465 ($\text{M}+\text{Na}$) $^+$ **MP:** 77–80 °C

(5*R*)-2-(2-hydroxypropan-2-yl)-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-7-ol (Heliannuol D; 3.2)¹⁸



A 4mL scintillation vial was charged with iodoarene **3.142** (67 mg, 0.19 mmol, 1.0 equiv.), CuI (11 mg, 0.06 mmol, 0.3 equiv.), 1,10-phenanthroline (20 mg, 0.11 mmol, 0.6 equiv.) and KOH (63 mg, 1.12 mmol, 6 equiv.). The vial was evacuated and purged with argon 3 times. Vigorously degassed DMSO (0.31mL) and H_2O (0.31 mL) were added, and the vial was tightly capped and submerged in a 100°C oil bath. The reaction was stirred for 40 hours at this temperature, then cooled to room temperature and quenched with a few drops of 2M HCl. The mixture was passed through a silica plug to reveal the

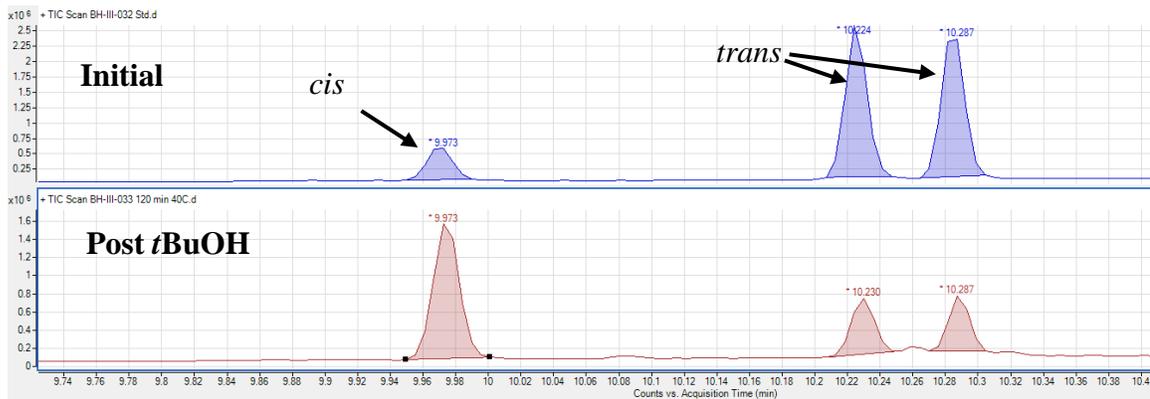
product as an off white solid. **Yield:** 45 mg, 98% 5:1 d.r.). Recrystallization (DCM layered with pentane) was performed to obtain a single crystal suitable for X-Ray crystallography. **¹H NMR MAJOR** (*trans*) (500 MHz, Chloroform-*d*) δ 6.76 (s, 1H), 6.61 (s, 1H), 4.62 (s, 1H), 3.24 (dd, $J = 10.3, 2.8$ Hz, 1H), 3.01 (dt, $J = 14.3, 7.1$ Hz, 1H), 2.67 (s, 1H), 2.18 (s, 3H), 1.99 – 1.83 (m, 3H), 1.29 (dd, $J = 11.8, 7.6$ Hz, 10H). **¹H NMR MINOR** (*cis*) (500 MHz, Chloroform-*d*) δ 6.73 (s, 1H), 6.54 (s, 1H), 3.30 (dd, $J = 11.2, 1.2$ Hz, 1H), 2.90 (ddd, $J = 7.5, 4.8, 2.8$ Hz, 1H), 2.16 (s, 3H), 1.97 – 1.68 (m, 4H), 1.32 – 1.24 (m, 10H). **¹³C NMR MAJOR** (126 MHz, CDCl₃) δ 152.6, 149.8, 138.5, 122.9, 121.5, 112.7, 89.7, 72.5, 34.3, 34.3, 30.9, 26.3, 24.4, 20.2, 15.3. **HRMS** (ESI) m/z calculated for C₁₅H₂₂O₃: 250.1569; found 250.1572. **MP:** 156–159 °C

C6i: Epimerization of Ketone 3.134



A known ratio of *trans* to *cis* isomers of **3.134** (9:1, 7 mg, 0.032 mmol, 1.0 equiv.) was dissolved in *tert*-butanol (500 μ L). To this solution was added potassium *tert*-butoxide (0.72 mg, 0.064 mmol, 2.0 equiv.). The reaction was closely monitored by chiral GCMS by pulling small aliquots at various time/temperature points. Within 10 minutes at ambient temperature, the ratio of *cis* to *trans* inverted from 9:1 to 4:6. Attempts to further epimerize with heating and longer reaction times were met with failure, and epimerization to 6:4 *cis* was the maximum observed.

D.R. determined by GCMS (cyclosilB chiral column, 40 °C start, 20 °C/min to 225 °C)



C7: REFERENCES

- (1) Murai, M.; Mizuta, C.; Taniguchi, R.; Takai, K. Synthesis of Borylcyclopropanes by Chromium-Promoted Cyclopropanation of Unactivated Alkenes. *Org. Lett.* **2017**, *19* (22), 6104–6107. <https://doi.org/10.1021/acs.orglett.7b02956>.
- (2) Matteson, D. S.; Sadhu, K. M.; Peterson, M. L. 99% Chirally Selective Syntheses via Pinanediol Boronic Esters: Insect Pheromones, Diols, and an Amino Alcohol. *J. Am. Chem. Soc.* **1986**, *108* (4), 810–819. <https://doi.org/10.1021/ja00264a039>.
- (3) Schmidt, J.; Choi, J.; Liu, A. T.; Slusarczyk, M.; Fu, G. C. A General, Modular Method for the Catalytic Asymmetric Synthesis of Alkylboronate Esters. *Science* (80-.). **2016**, *354* (6317), 1265–1270.
- (4) Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. Enantiospecific Sp²-Sp³ Coupling of Secondary and Tertiary Boronic Esters. *Nat. Chem.* **2014**, *6* (7), 584–589. <https://doi.org/10.1038/nchem.1971>.
- (5) Fischer, C.; Fu, G. C. Asymmetric Nickel-Catalyzed Negishi Cross-Couplings of Secondary α -Bromo Amides with Organozinc Reagents. *J. Am. Chem. Soc.* **2005**, *127* (13), 4594–4595. <https://doi.org/10.1021/ja0506509>.
- (6) Mei, T. S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. Enantioselective Redox-Relay Oxidative Heck Arylations of Acyclic Alkenyl Alcohols Using Boronic Acids. *J. Am. Chem. Soc.* **2013**, *135* (18), 6830–6833. <https://doi.org/10.1021/ja402916z>.
- (7) Werner, E. W.; Mei, T. S.; Burckle, A. J.; Sigman, M. S. Enantioselective Heck Arylations of Acyclic Alkenyl Alcohols Using a Redox-Relay Strategy. *Science* (80-.). **2012**, *338* (6113), 1455–1458. <https://doi.org/10.1126/science.1229208>.

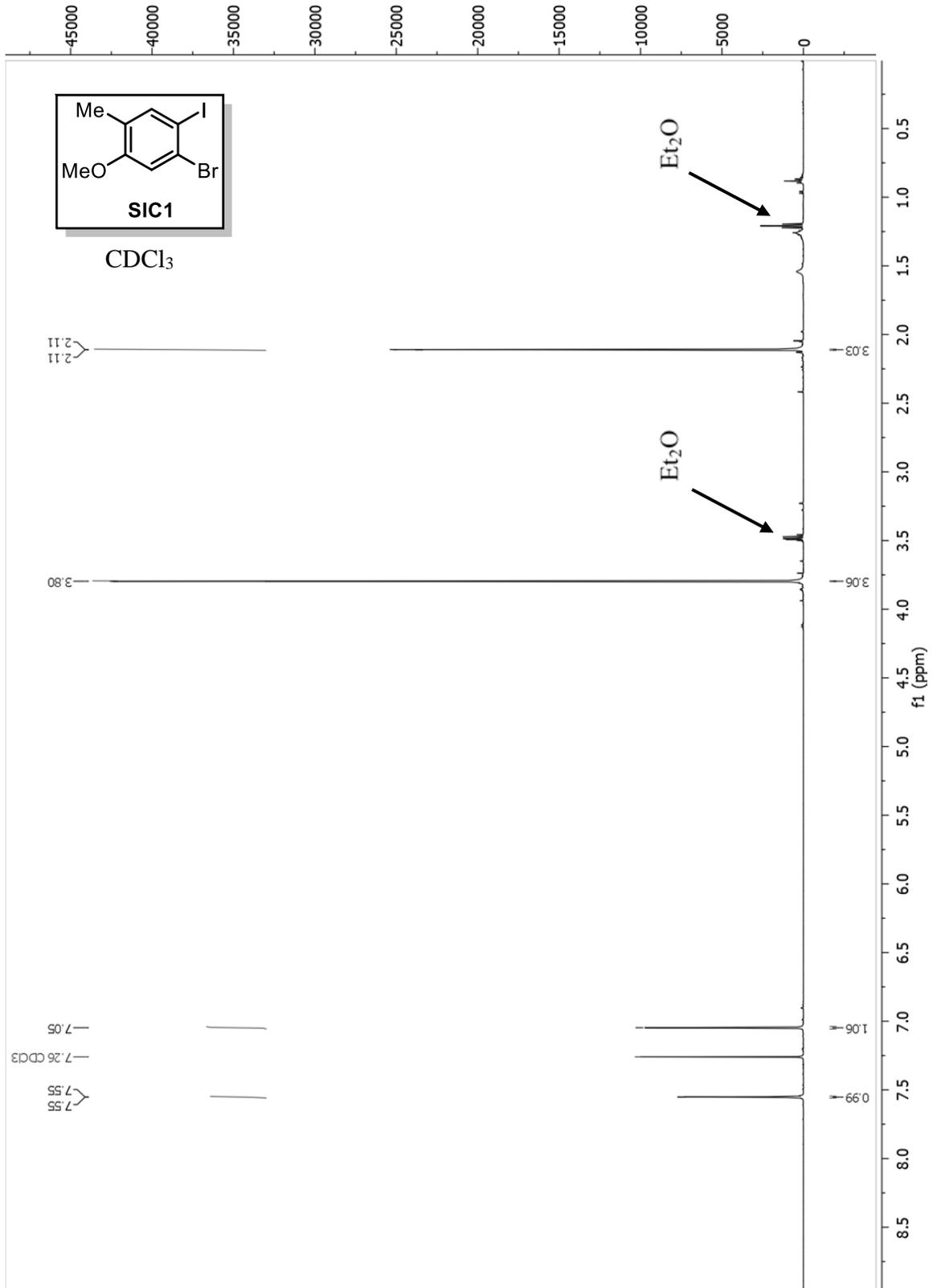
- (8) Qiao, J. X.; Pinto, D. J.; Orwat, M. J.; Friedrich, S. R.; Han, W. 1,1-Disubstituted Cycloalkyl Derivatives as Factor Xa Inhibitors. 0254158 A1, December 16, 2004.
- (9) Nicolai, S.; Waser, J. Pd(0)-Catalyzed Oxy- and Aminoalkynylation of Olefins for the Synthesis of Tetrahydrofurans and Pyrrolidines. *Org. Lett.* **2011**, *13* (23), 6324–6327. <https://doi.org/10.1021/ol2029383>.
- (10) Jeffery, T. Palladium-Catalysed Vinylation of Organic Halides under Solid-Liquid Phase Transfer Conditions. *J. Chem. Soc. Chem. Commun.* **1984**, No. 19, 1287–1289. <https://doi.org/10.1039/C39840001287>.
- (11) Carrow, B. P.; Hartwig, J. F. Ligandless, Anionic, Arylpalladium Halide Intermediates in the Heck Reaction. *J. Am. Chem. Soc.* **2010**, *132* (1), 79–81. <https://doi.org/10.1021/ja909306f>.
- (12) Kolodziej, I.; Green, J. R. Vinylogous Nicholas Reactions in the Synthesis of Bi- and Tricyclic Cycloheptynedicobalt Complexes. *Org. Biomol. Chem.* **2015**, *13* (44), 10852–10864. <https://doi.org/10.1039/c5ob01684c>.
- (13) Kelley, B. T.; Walters, J. C.; Wengryniuk, S. E. Access to Diverse Oxygen Heterocycles via Oxidative Rearrangement of Benzylic Tertiary Alcohols. *Org. Lett.* **2016**, *18* (8), 1896–1899. <https://doi.org/10.1021/acs.orglett.6b00672>.
- (14) Walters, J. C.; Tierno, A. F.; Dubin, A. H.; Wengryniuk, S. E. (Poly)Cationic Λ^3 -Iodane-Mediated Oxidative Ring Expansion of Secondary Alcohols. *European J. Org. Chem.* **2018**, *2018* (12), 1460–1464. <https://doi.org/10.1002/ejoc.201800118>.
- (15) Mott, B. T.; Tripathi, A.; Siegler, M. A.; Moore, C. D.; Sullivan, D. J.; Posner, G. H. Synthesis and Antimalarial Efficacy of Two-Carbon-Linked, Artemisinin-Derived Trioxane Dimers in Combination with Known Antimalarial Drugs. *J.*

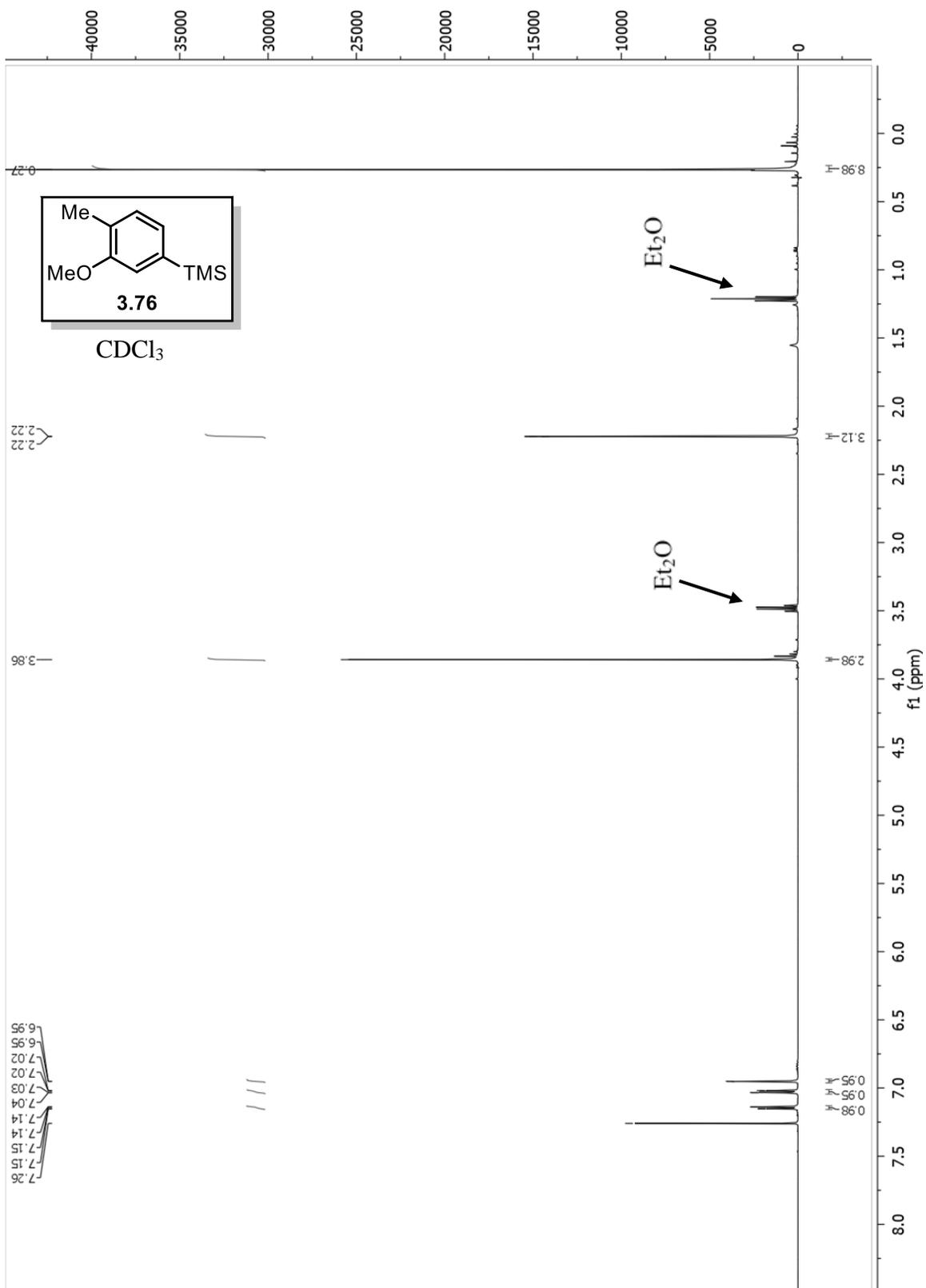
- Med. Chem.* **2013**, *56* (6), 2630–2641. <https://doi.org/10.1021/jm400058j>.
- (16) Das, B.; Venkateswarlu, K.; Krishnaiah, M.; Holla, H. An Efficient, Rapid and Regioselective Nuclear Bromination of Aromatics and Heteroaromatics with NBS Using Sulfonic-Acid-Functionalized Silica as a Heterogeneous Recyclable Catalyst. *Tetrahedron Lett.* **2006**, *47* (49), 8693–8697. <https://doi.org/10.1016/j.tetlet.2006.10.029>.
- (17) Tang, R. J.; Milcent, T.; Crousse, B. Regioselective Halogenation of Arenes and Heterocycles in Hexafluoroisopropanol. *J. Org. Chem.* **2018**, *83* (2), 930–938. <https://doi.org/10.1021/acs.joc.7b02920>.
- (18) Zhao, D.; Wu, N.; Zhang, S.; Xi, P.; Su, X.; Lan, J.; You, J. Synthesis of Phenol, Aromatic Ether, and Benzofuran Derivatives by Copper-Catalyzed Hydroxylation of Aryl Halides. *Angew. Chemie - Int. Ed.* **2009**, *48* (46), 8729–8732. <https://doi.org/10.1002/anie.200903923>.
- (19) Yuan, C.; Eliassen, A. M.; Camelio, A. M.; Siegel, D. Preparation of Phenols by Phthaloyl Peroxide-Mediated Oxidation of Arenes. *Nat. Protoc.* **2014**, *9* (11), 2624–2629. <https://doi.org/10.1038/nprot.2014.175>.
- (20) Elford, T. G.; Nave, S.; Sonawane, R. P.; Aggarwal, V. K. Total Synthesis of (+)-Erogorgiaene Using Lithiation–Borylation Methodology, and Stereoselective Synthesis of Each of Its Diastereoisomers. *J. Am. Chem. Soc.* **2011**, *133* (42), 16798–16801. <https://doi.org/10.1021/ja207869f>.
- (21) Genêt, J.-P.; Ratovelomanana-Vidal, V.; Pinel, C.; Synlett, D.; Gamez, P.; Fache, F.; Mangeney, P.; Lemaire, M.; Gamez, P.; Dunjic, B.; Krasik, P.; Alper, H.; Yang, H.; Alvarez, M.; Lugan, N.; Mathieu, R. *Ruthenium(II)-Catalyzed*

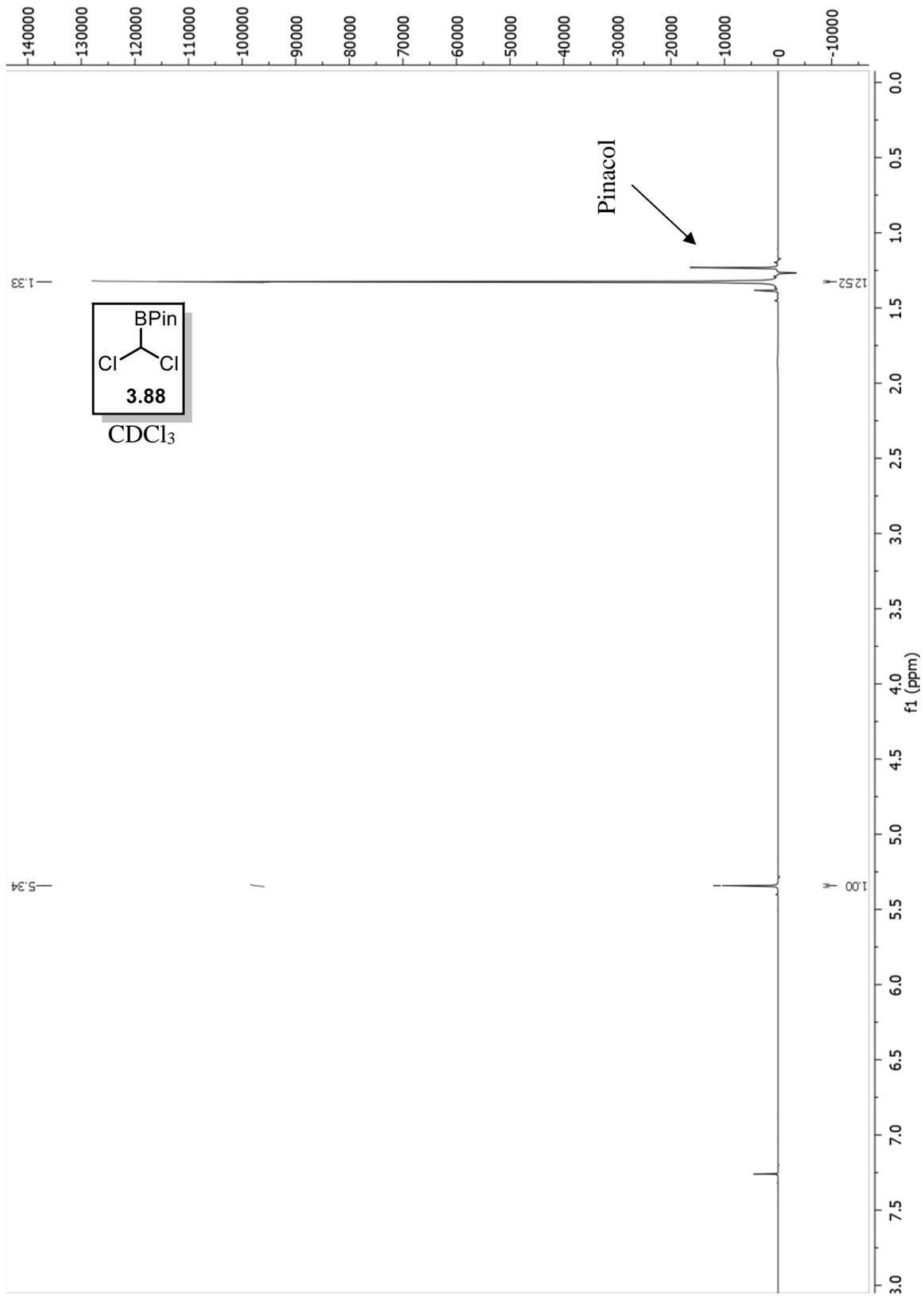
Asymmetric Transfer Hydrogenation of Ketones Using a Formic Acid-Triethylamine Mixture; 1991; Vol. 34.

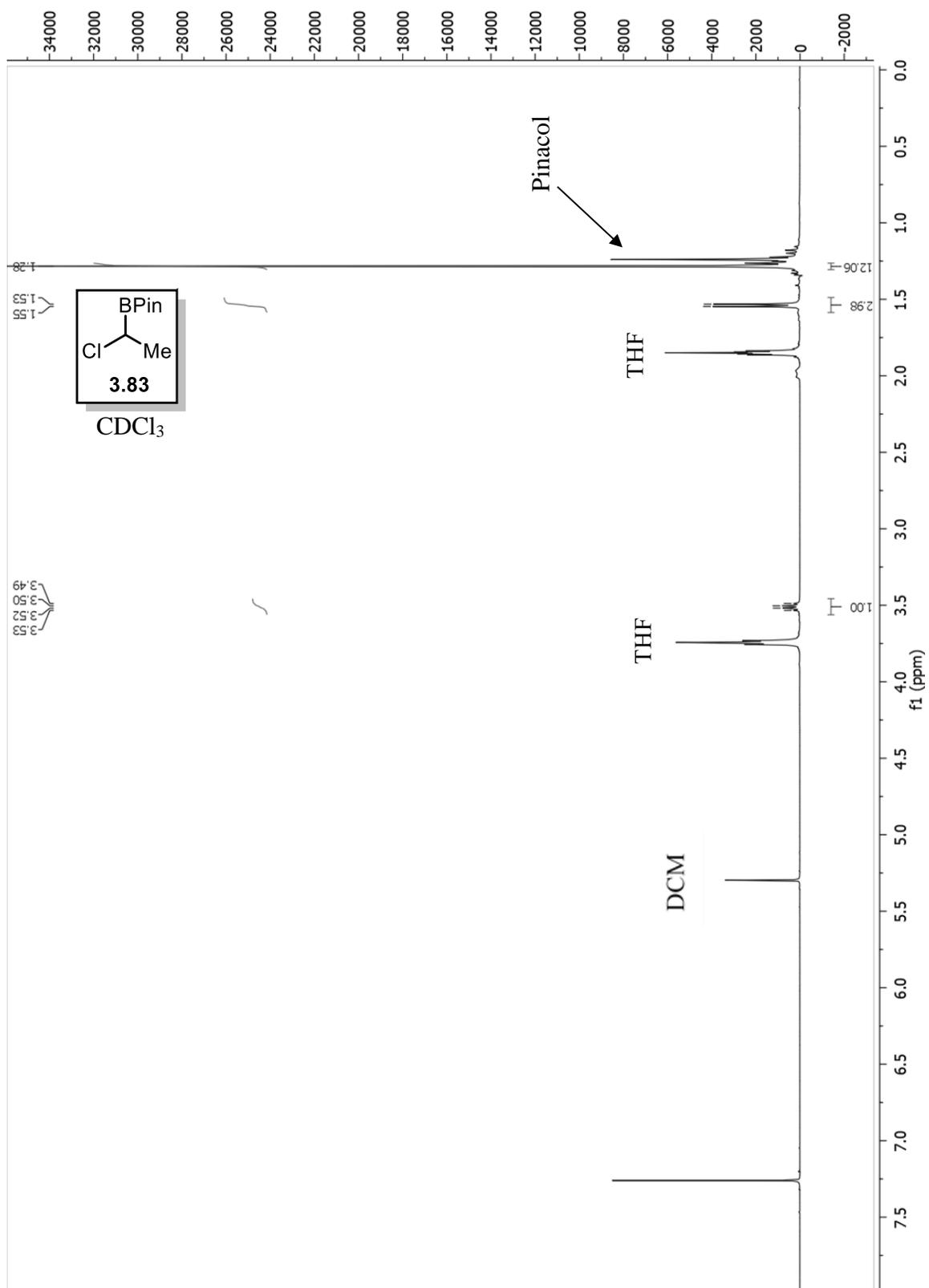
- (22) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. Enantiodivergent Conversion of Chiral Secondary Alcohols into Tertiary Alcohols. *Nature* **2008**, *456* (7223), 778–783. <https://doi.org/10.1038/nature07592>.
- (23) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. Protodeboronation of Tertiary Boronic Esters: Asymmetric Synthesis of Tertiary Alkyl Stereogenic Centers. *J. Am. Chem. Soc.* **2010**, *132* (48), 17096–17098. <https://doi.org/10.1021/ja1084207>.
- (24) Li, F.; Wang, N.; Lu, L.; Zhu, G. Regioselective Hydration of Terminal Alkynes Catalyzed by a Neutral Gold(I) Complex [(IPr)AuCl] and One-Pot Synthesis of Optically Active Secondary Alcohols from Terminal Alkynes by the Combination of [(IPr)AuCl] and Cp*RhCl[(R, R)-TsDPEN]. *J. Org. Chem.* **2015**, *80* (7), 3538–3546. <https://doi.org/10.1021/acs.joc.5b00164>.

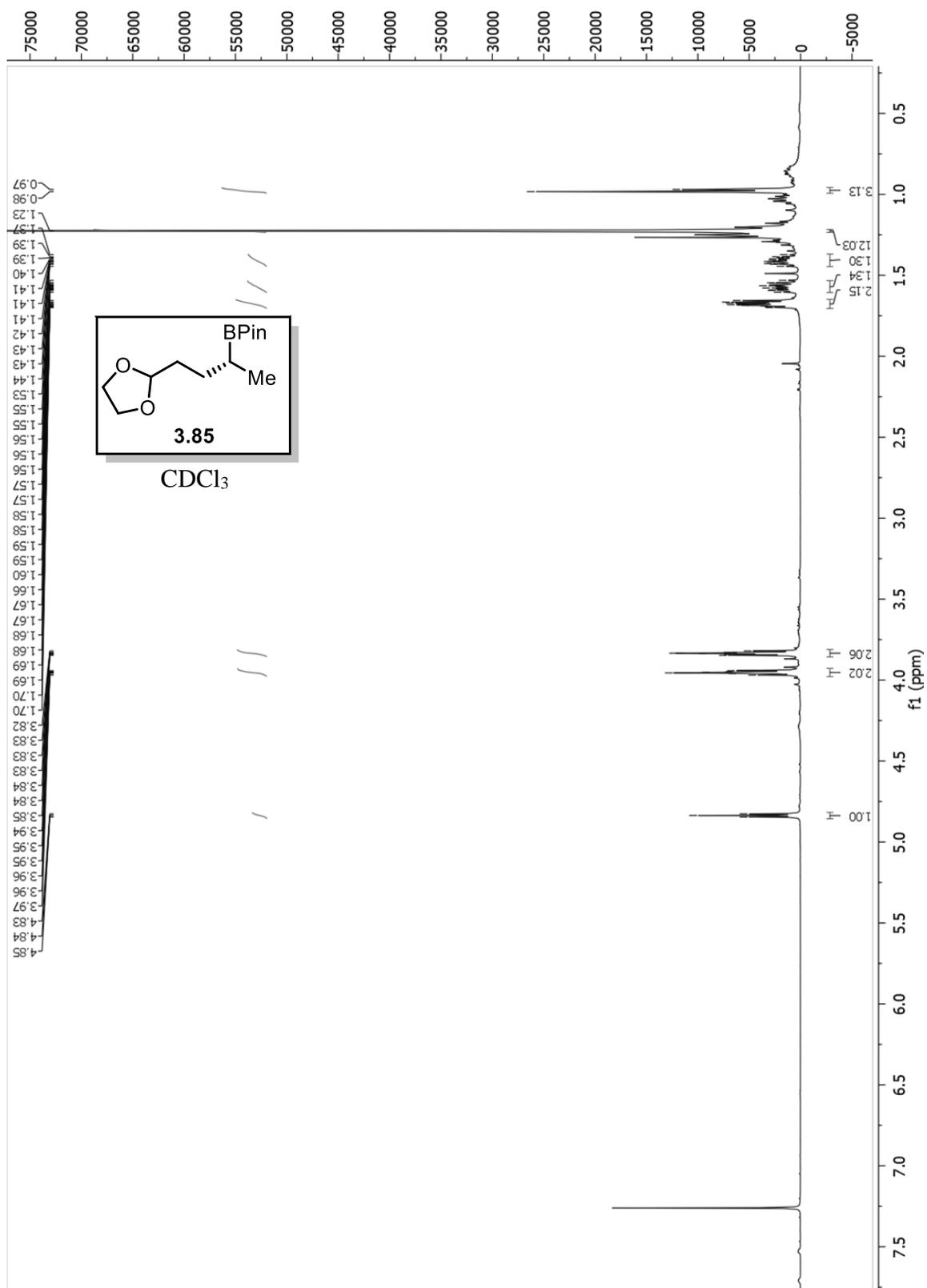
C8: SPECTRA

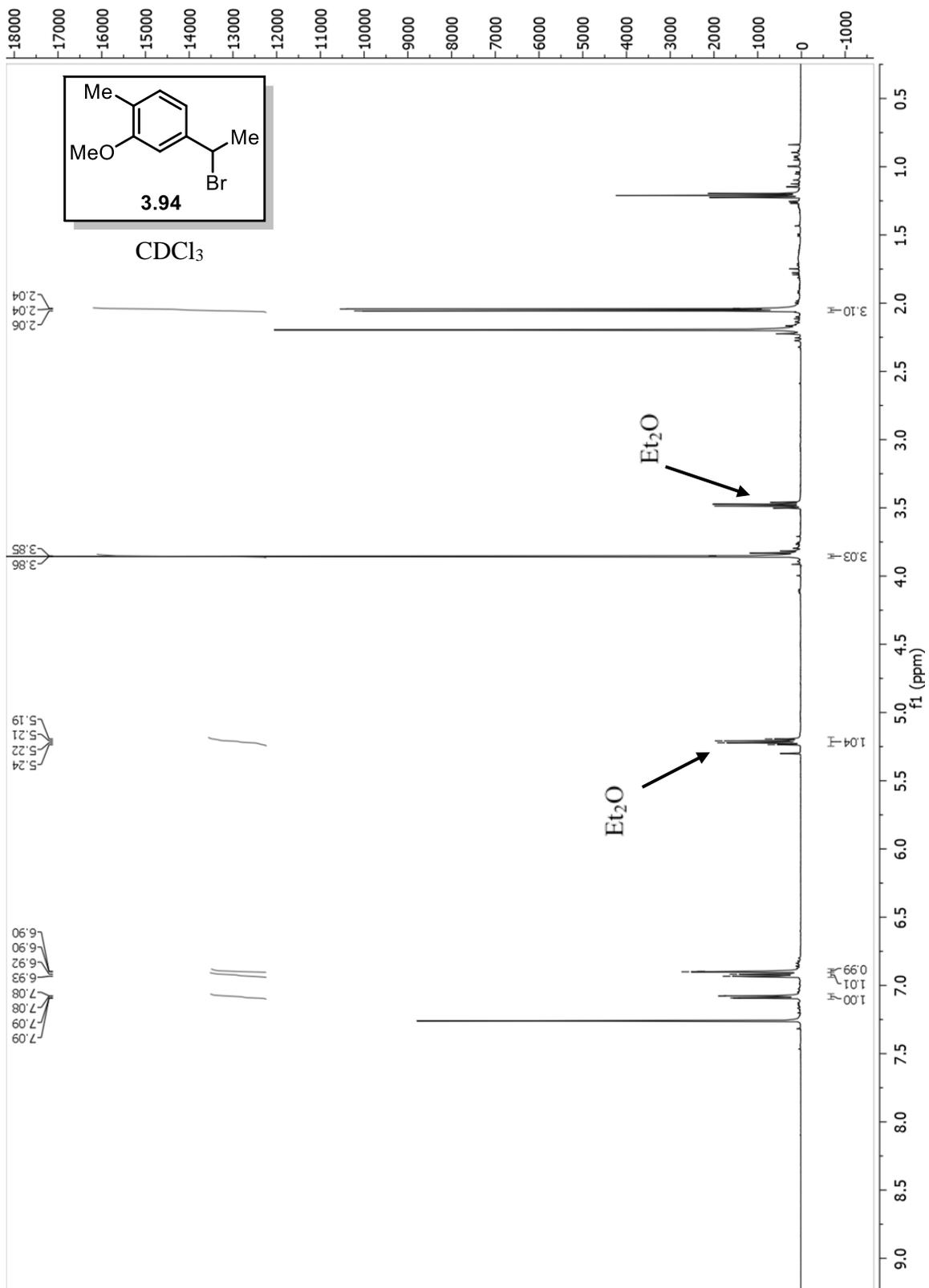


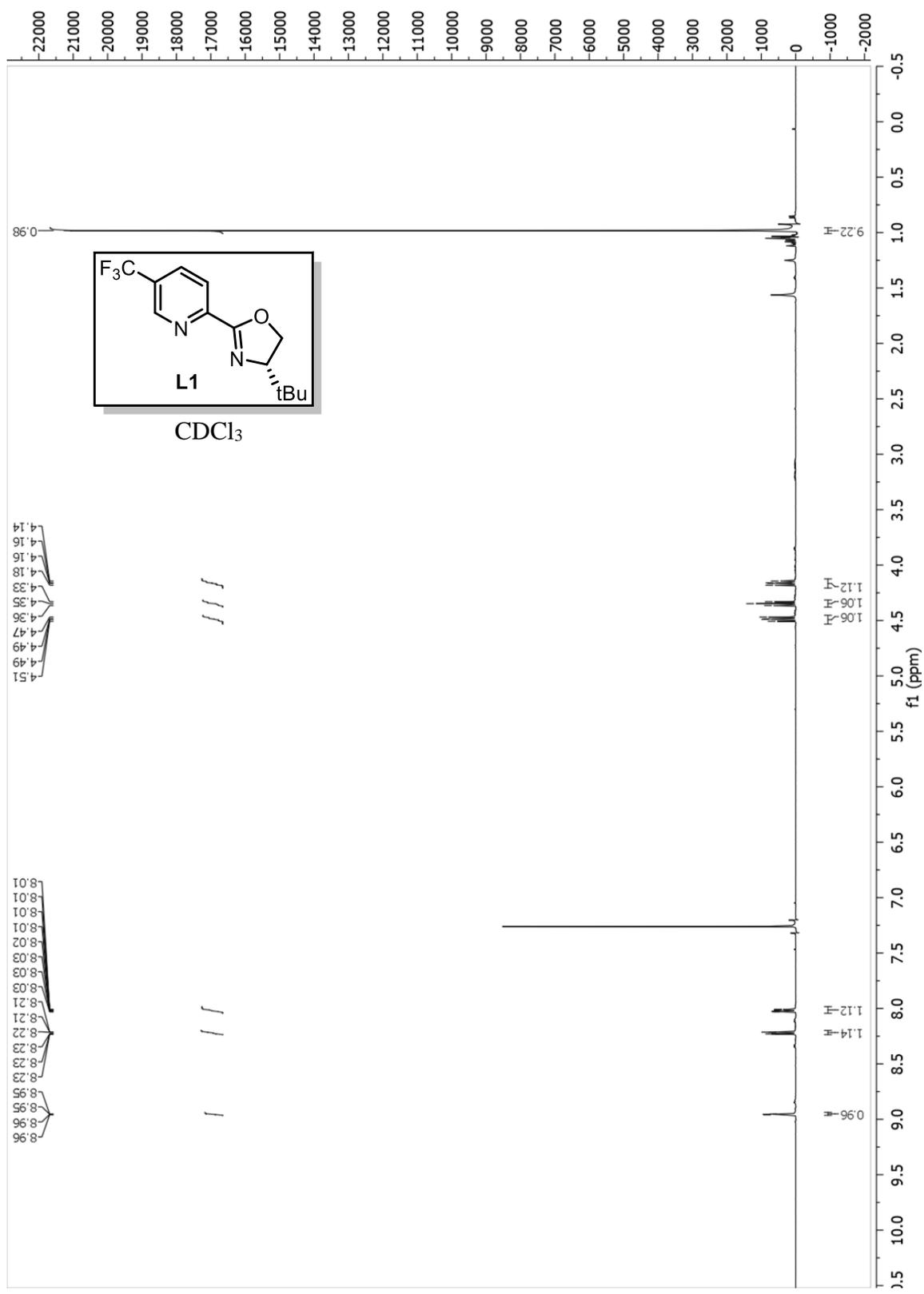


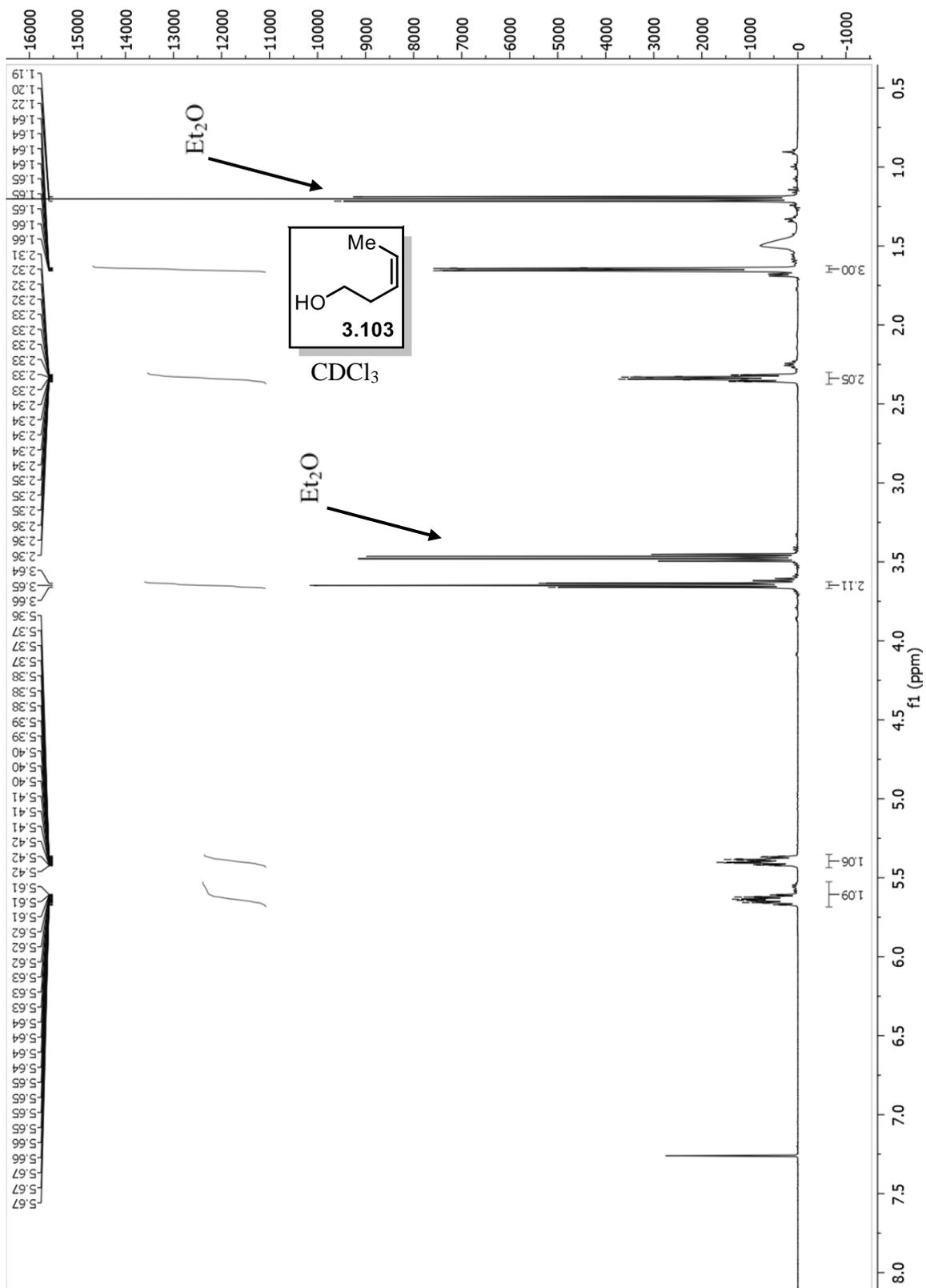


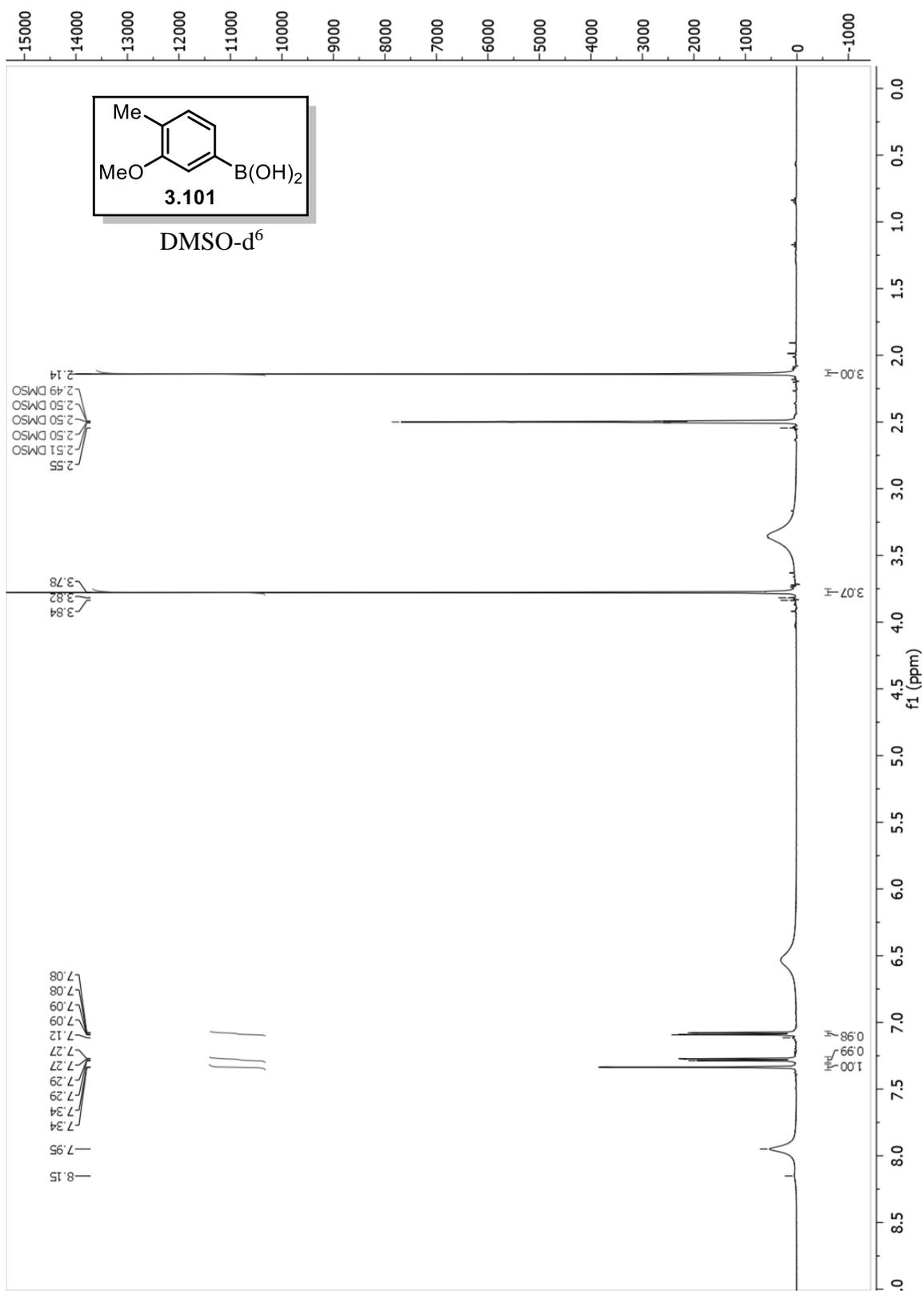


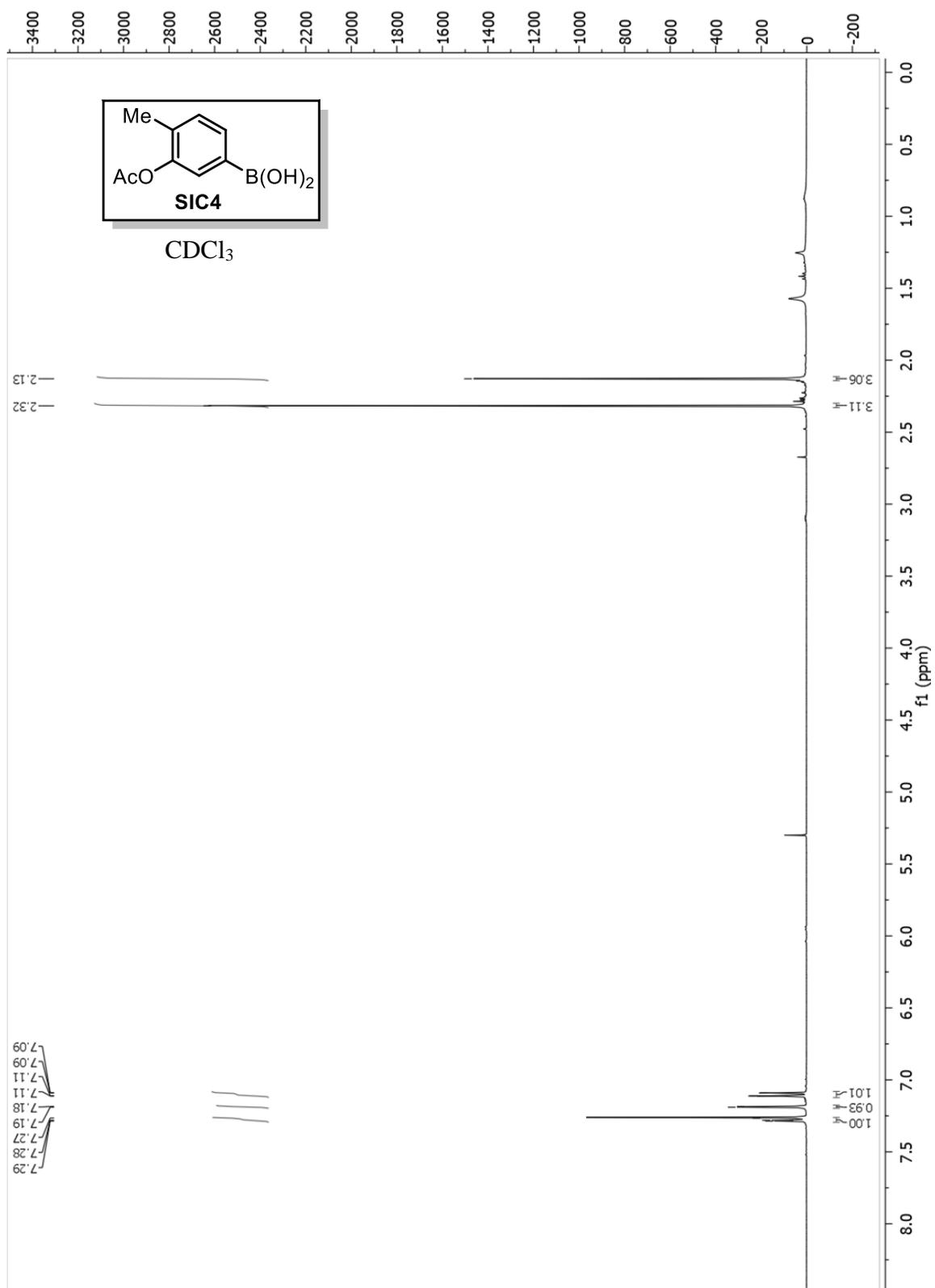


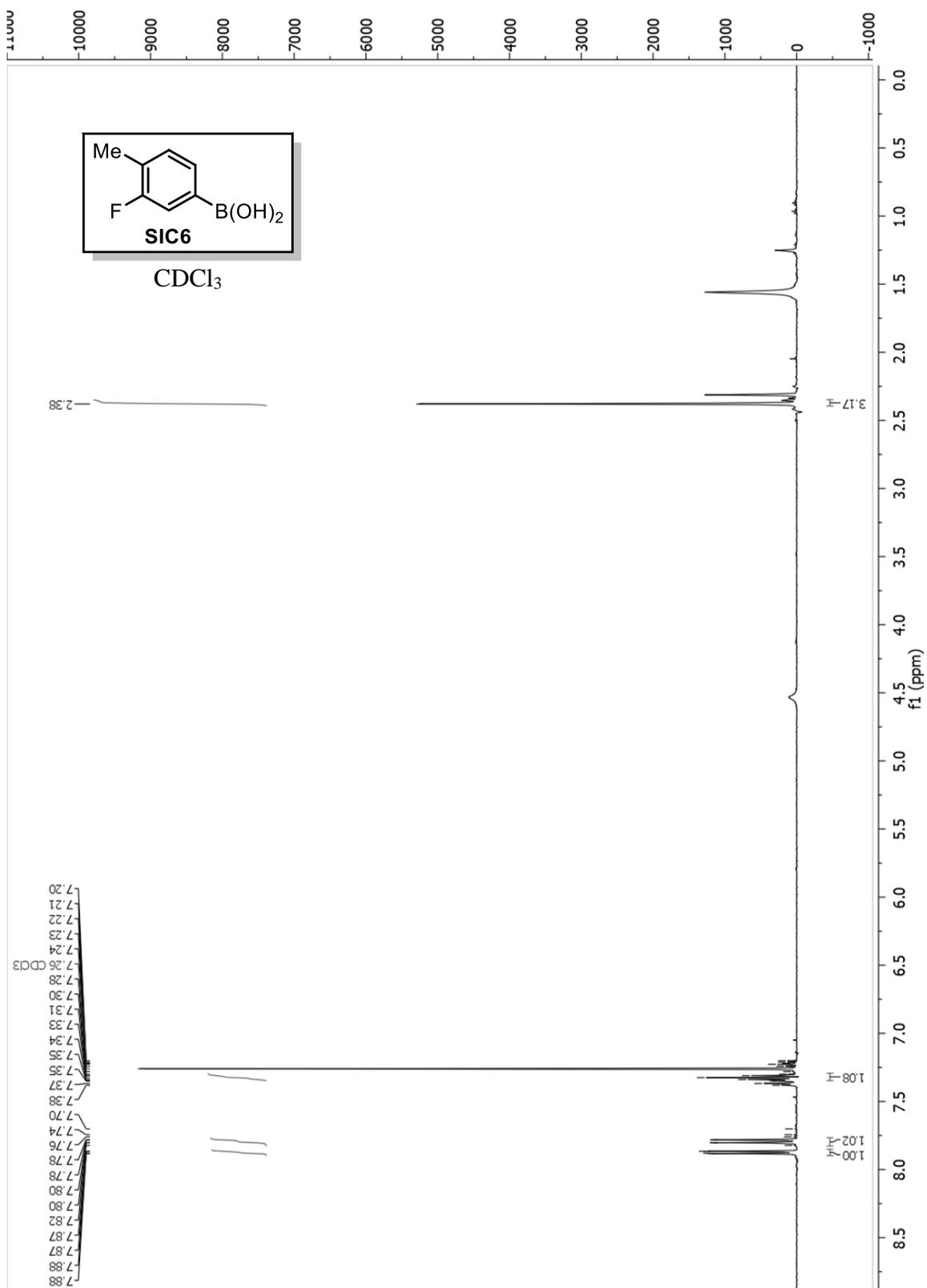


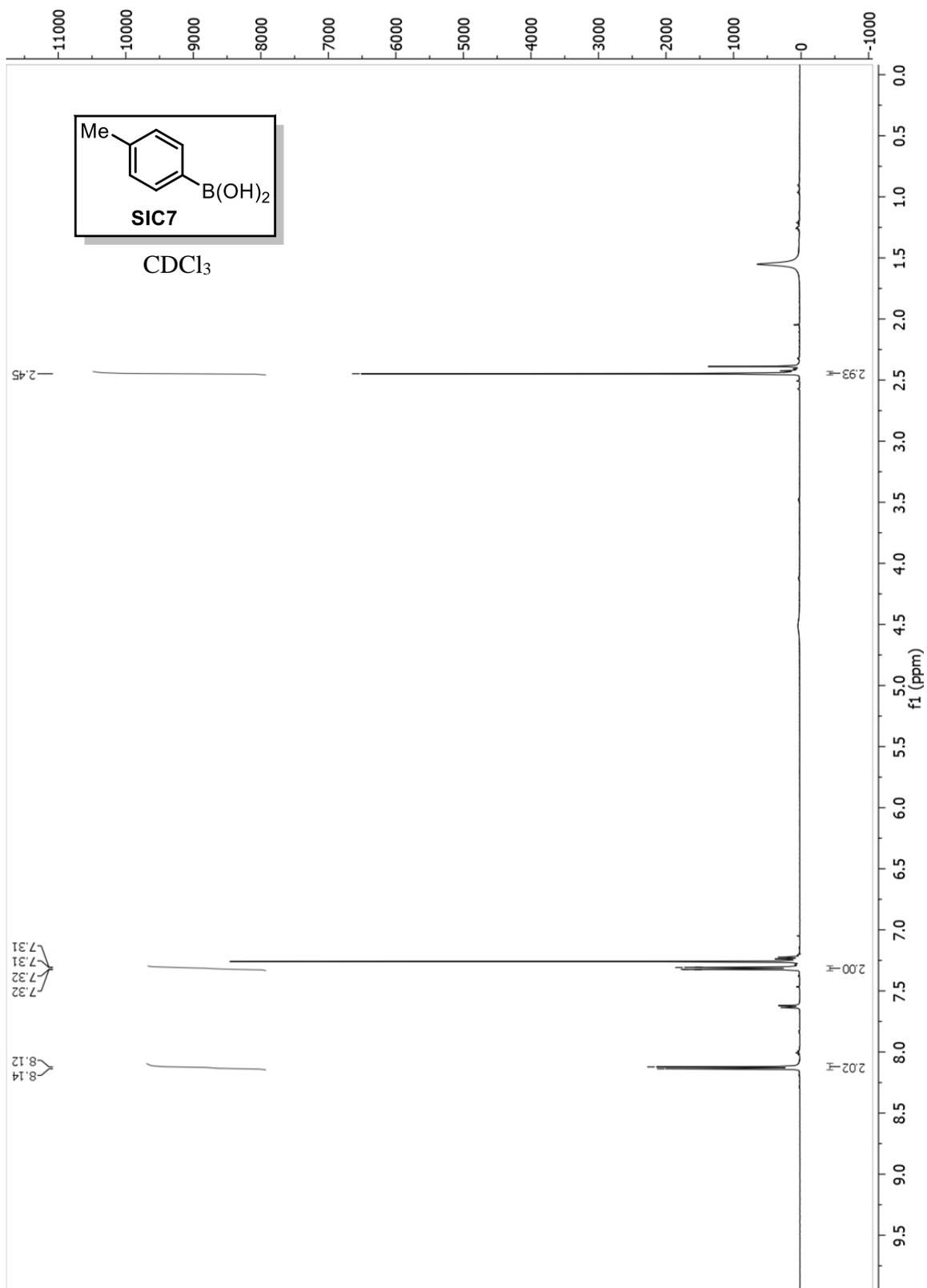


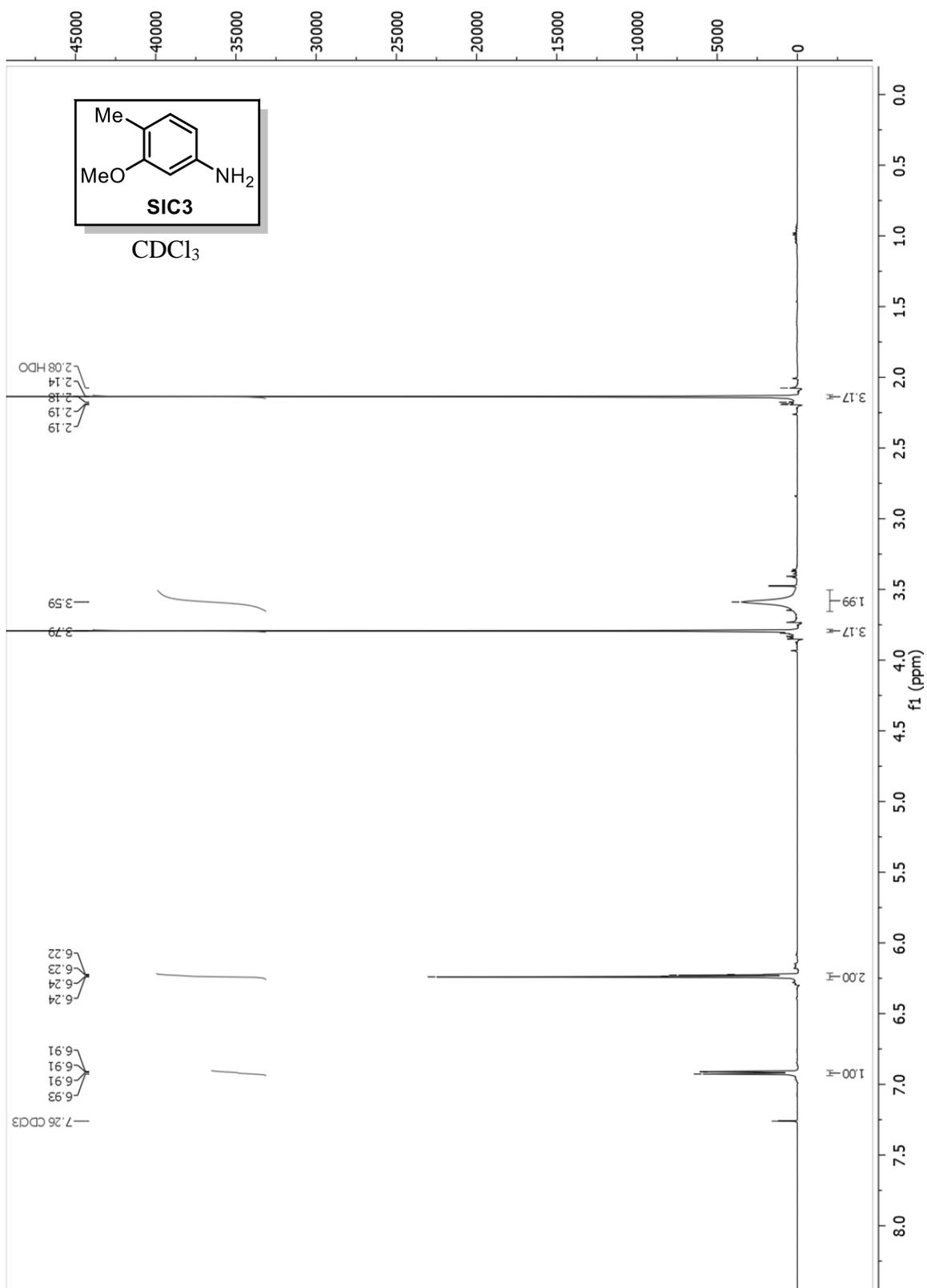


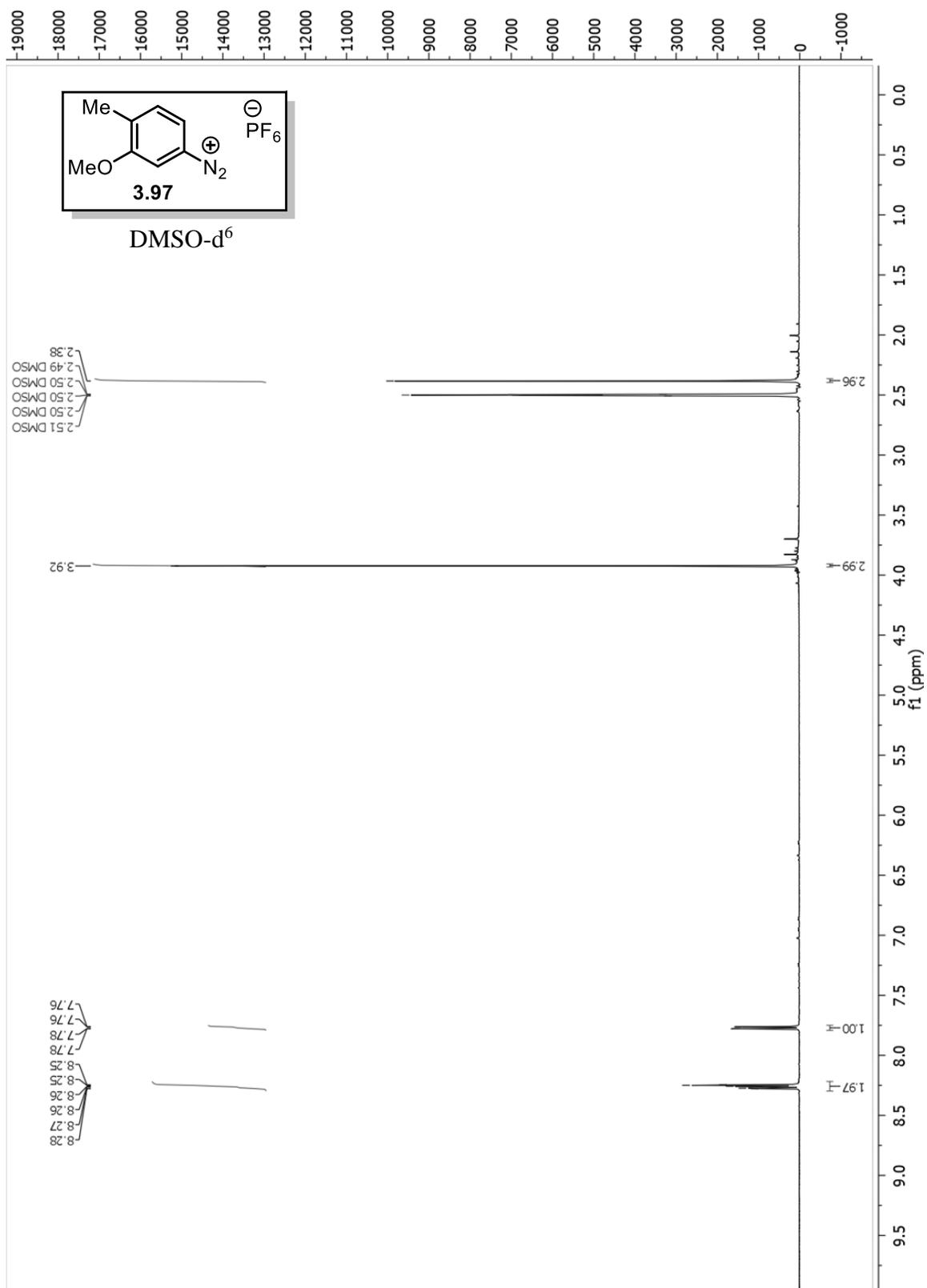


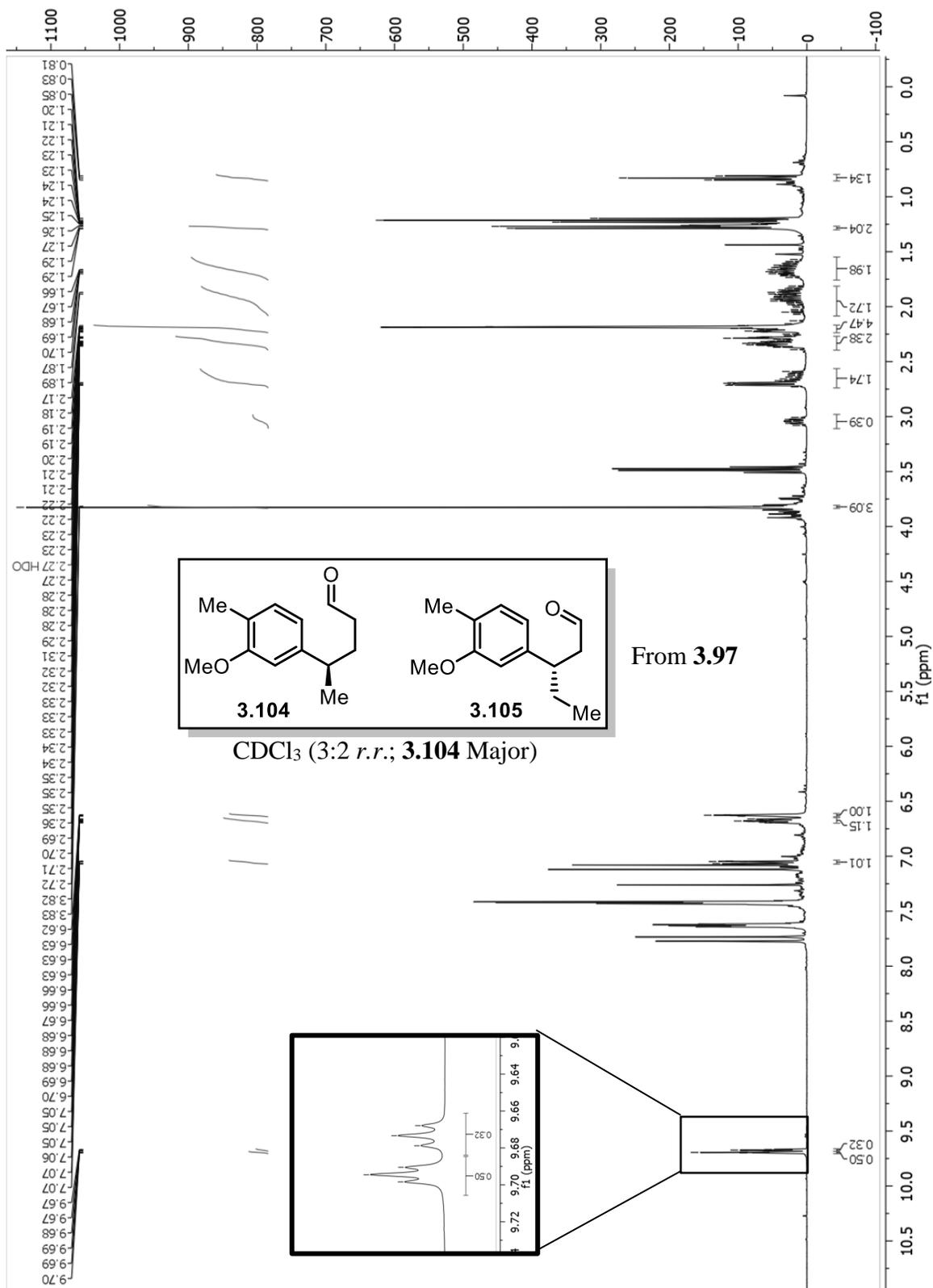


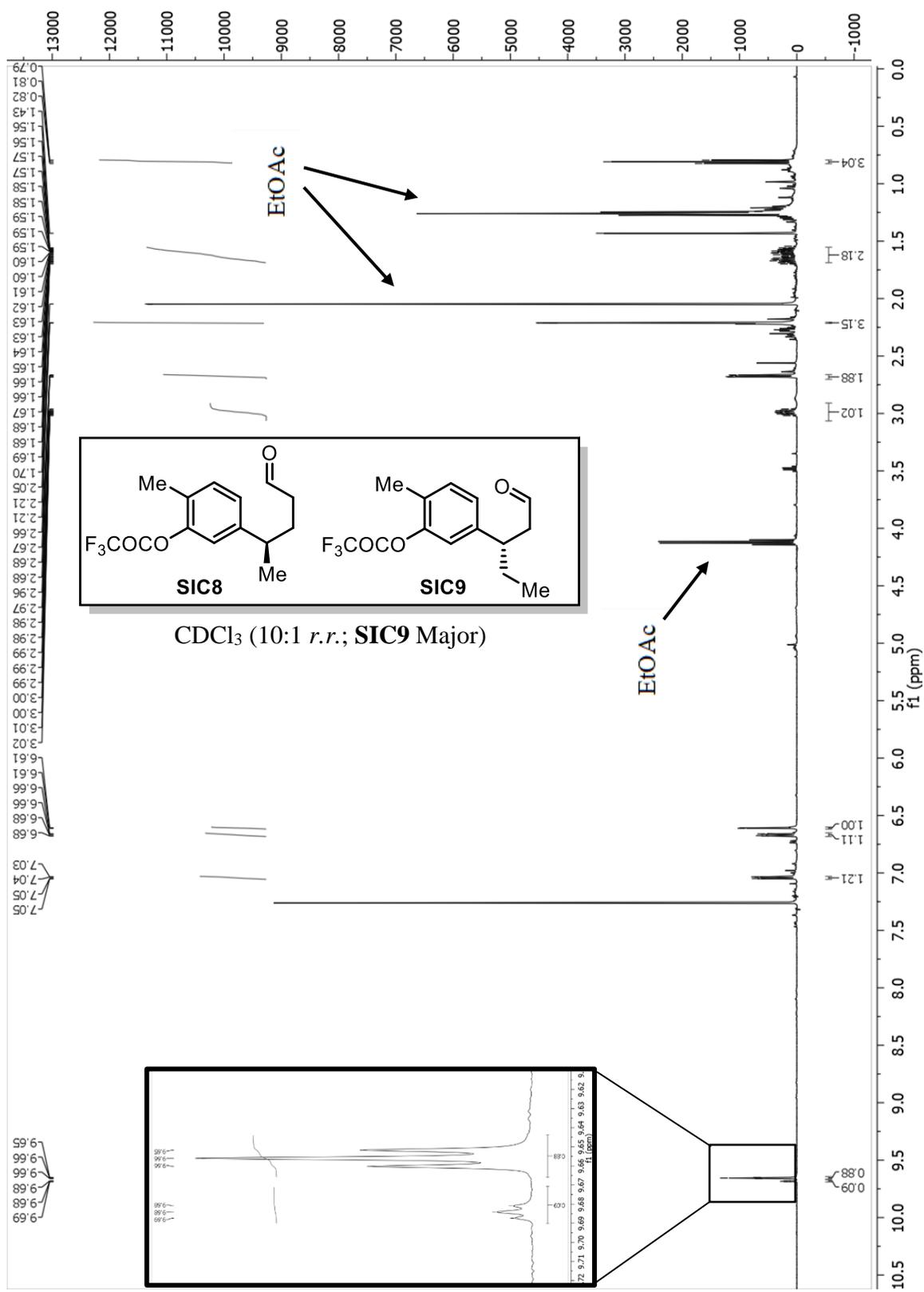


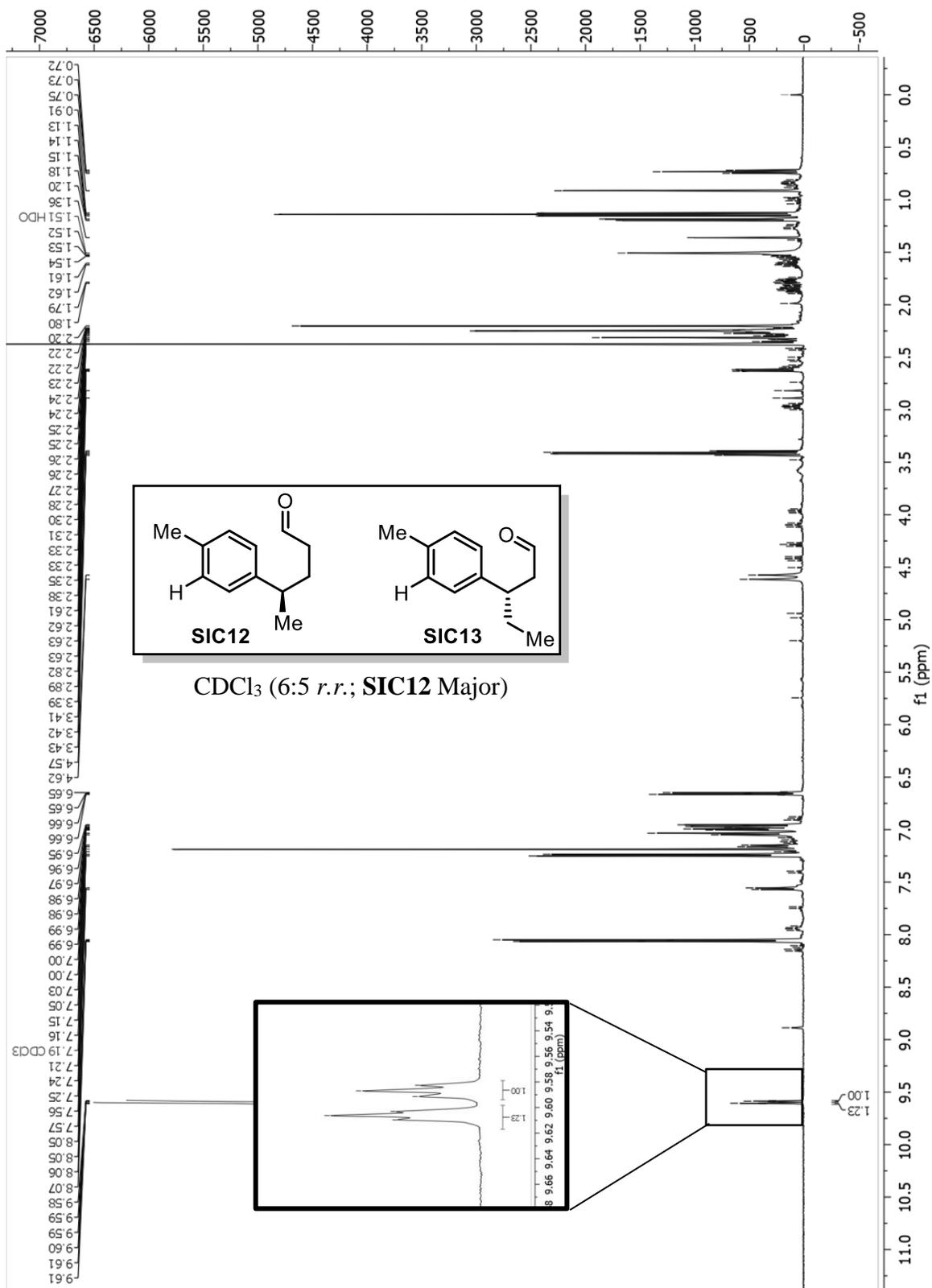


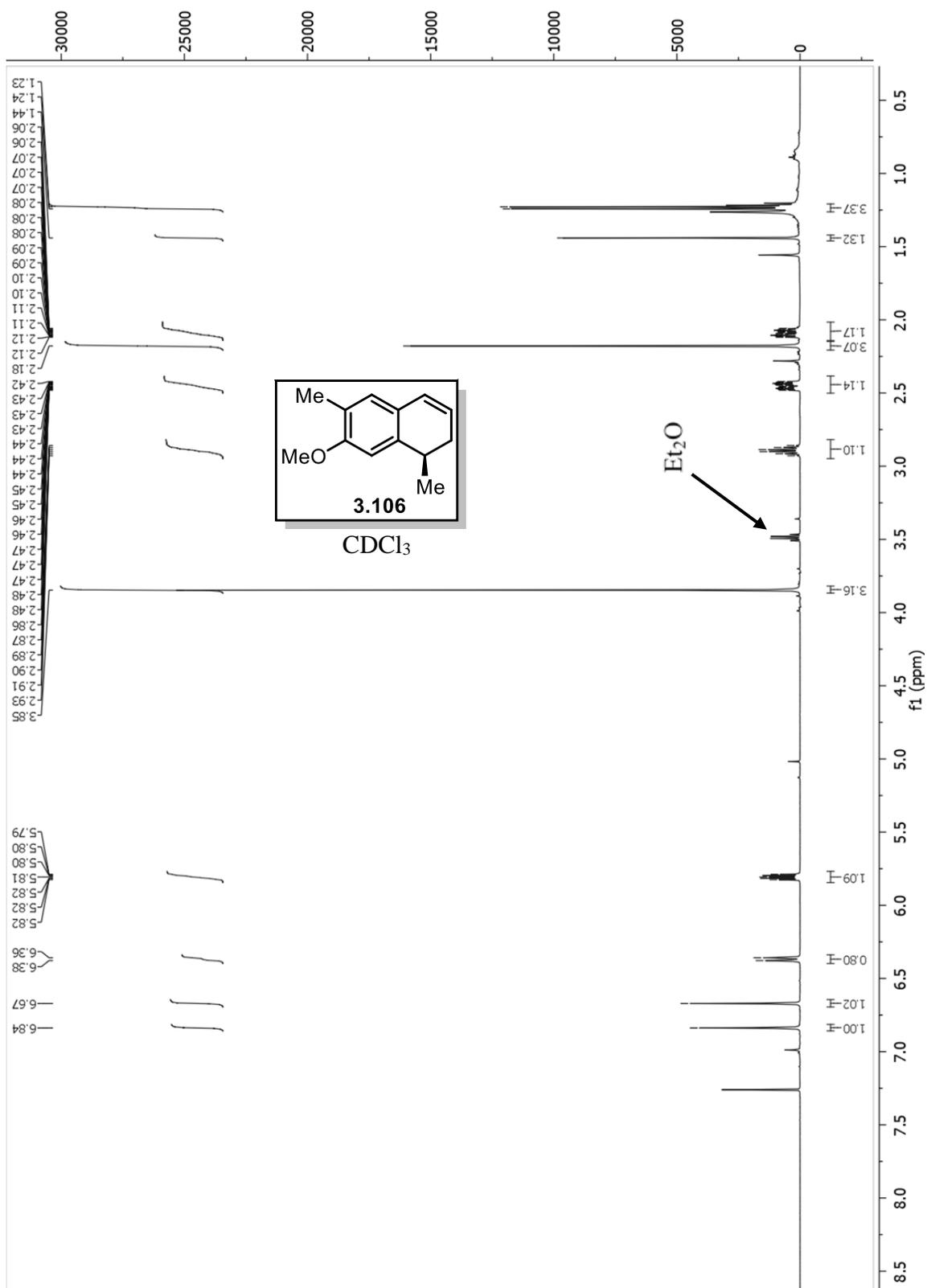


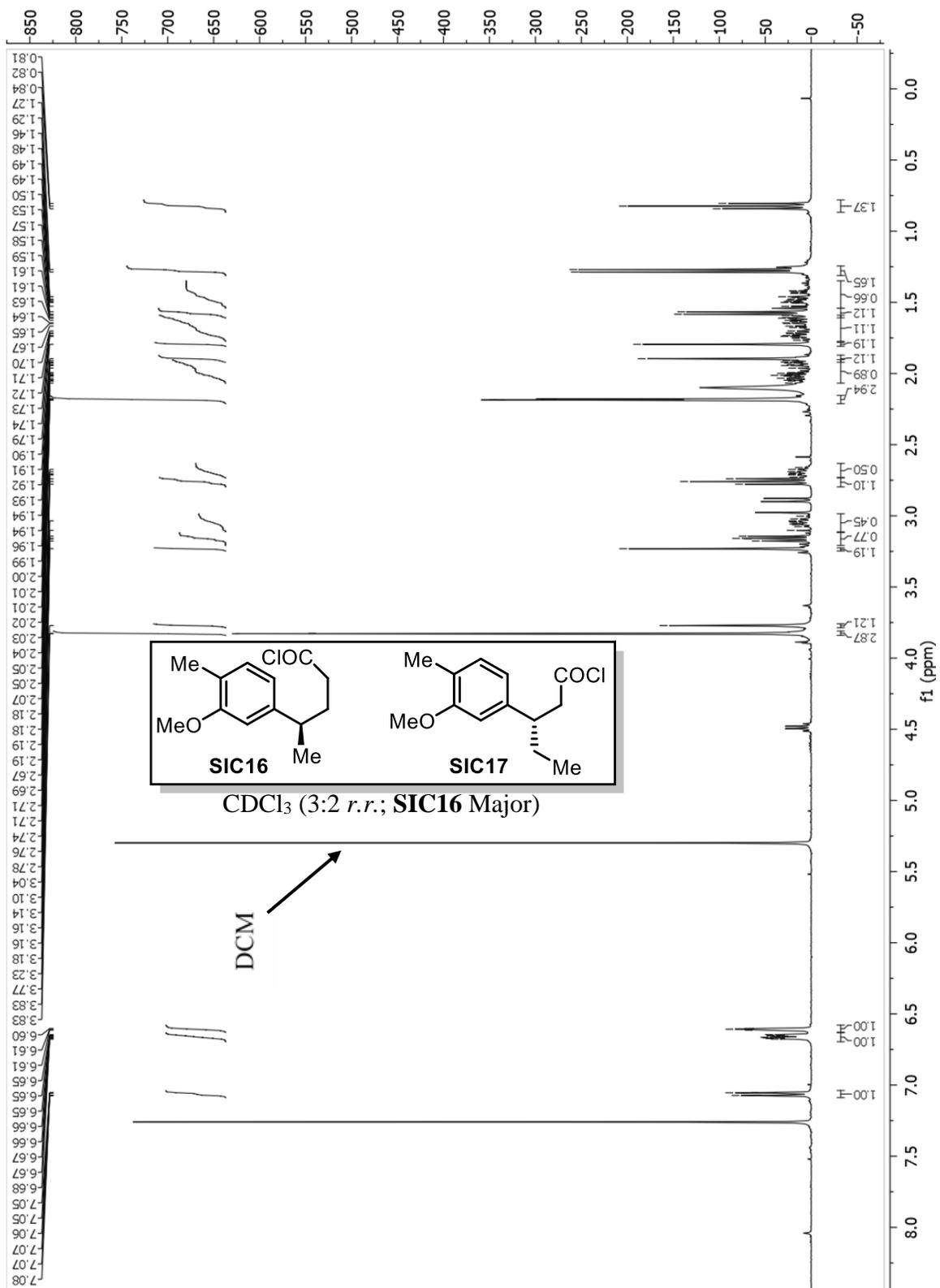


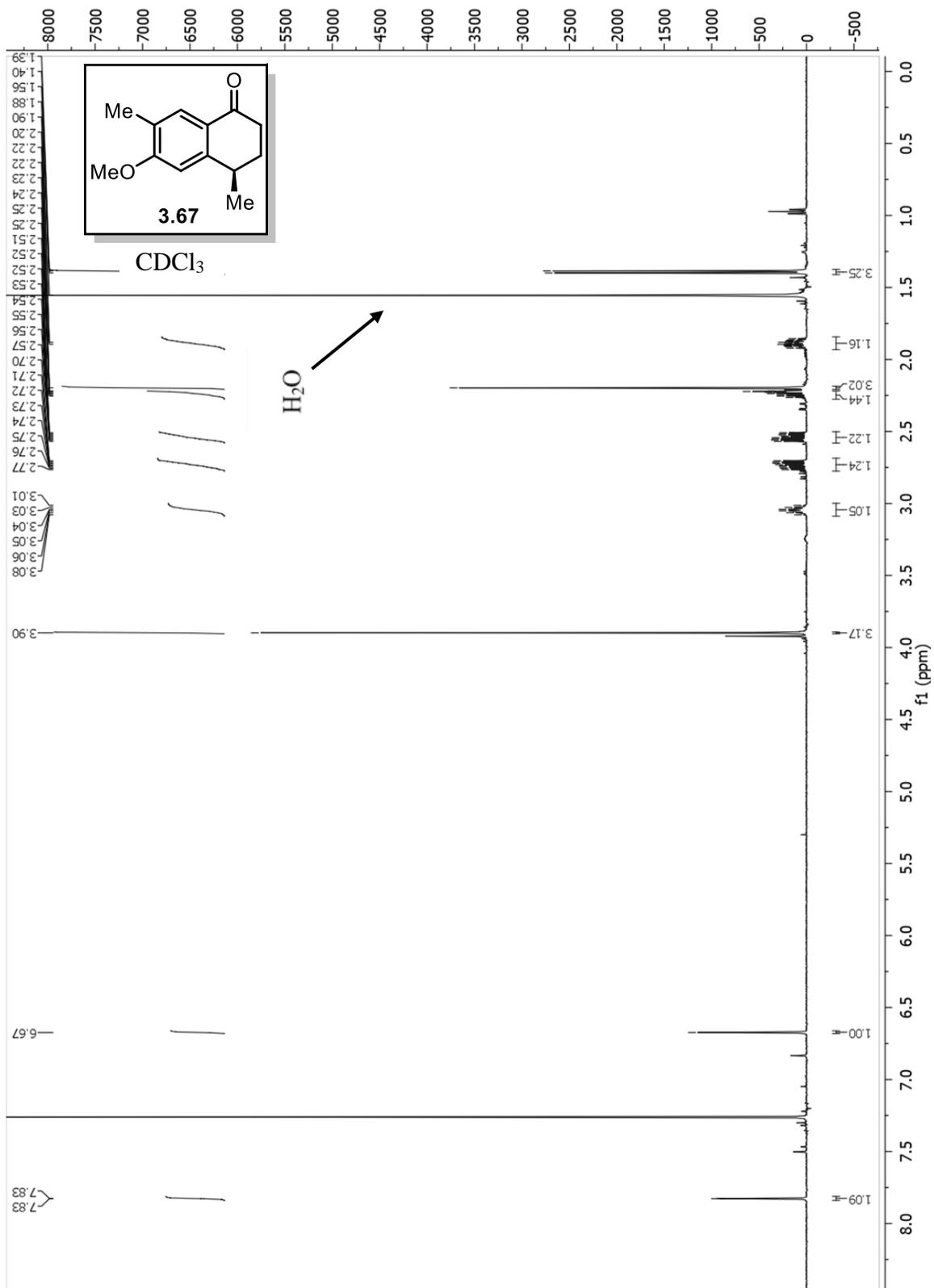


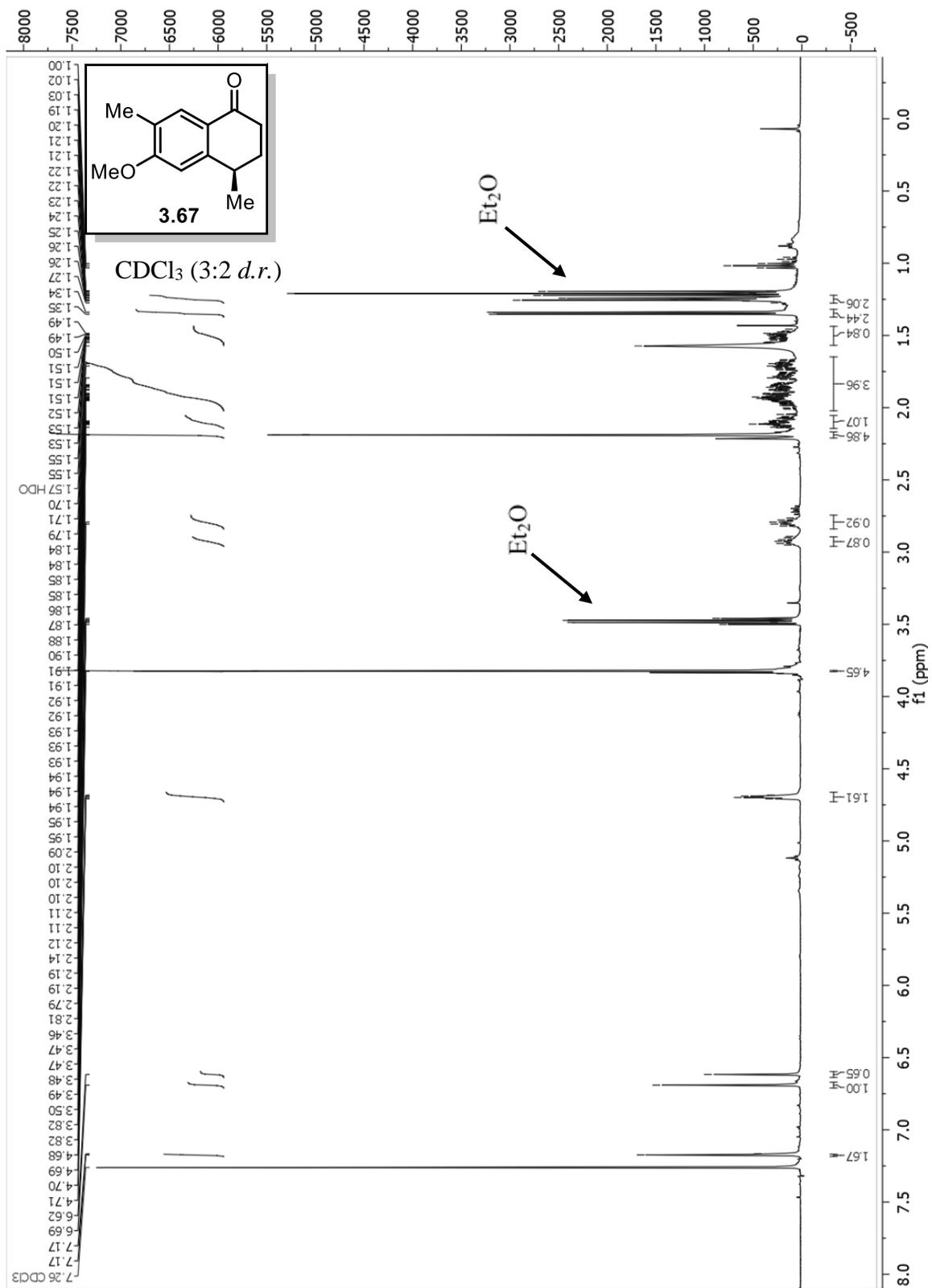


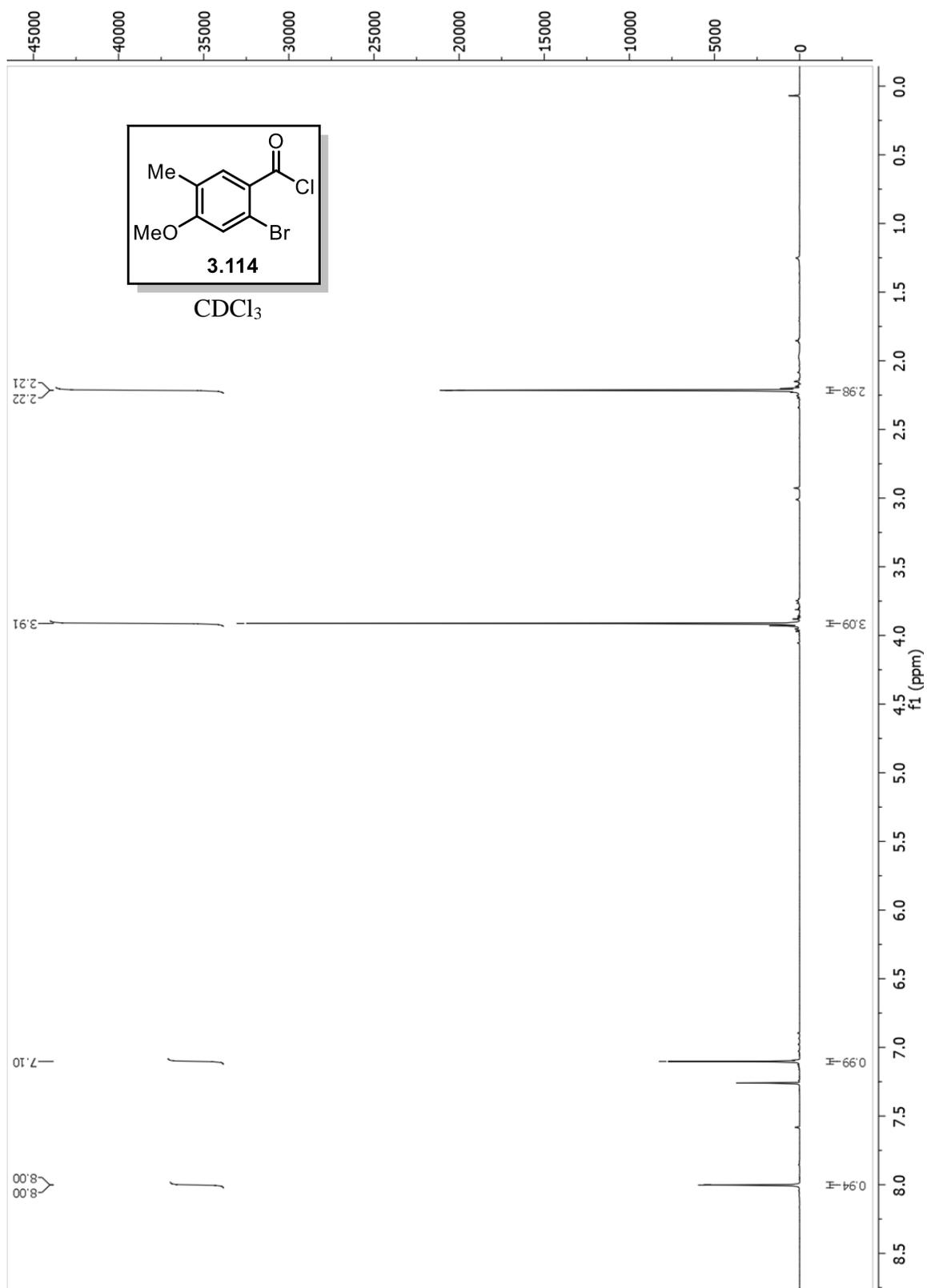


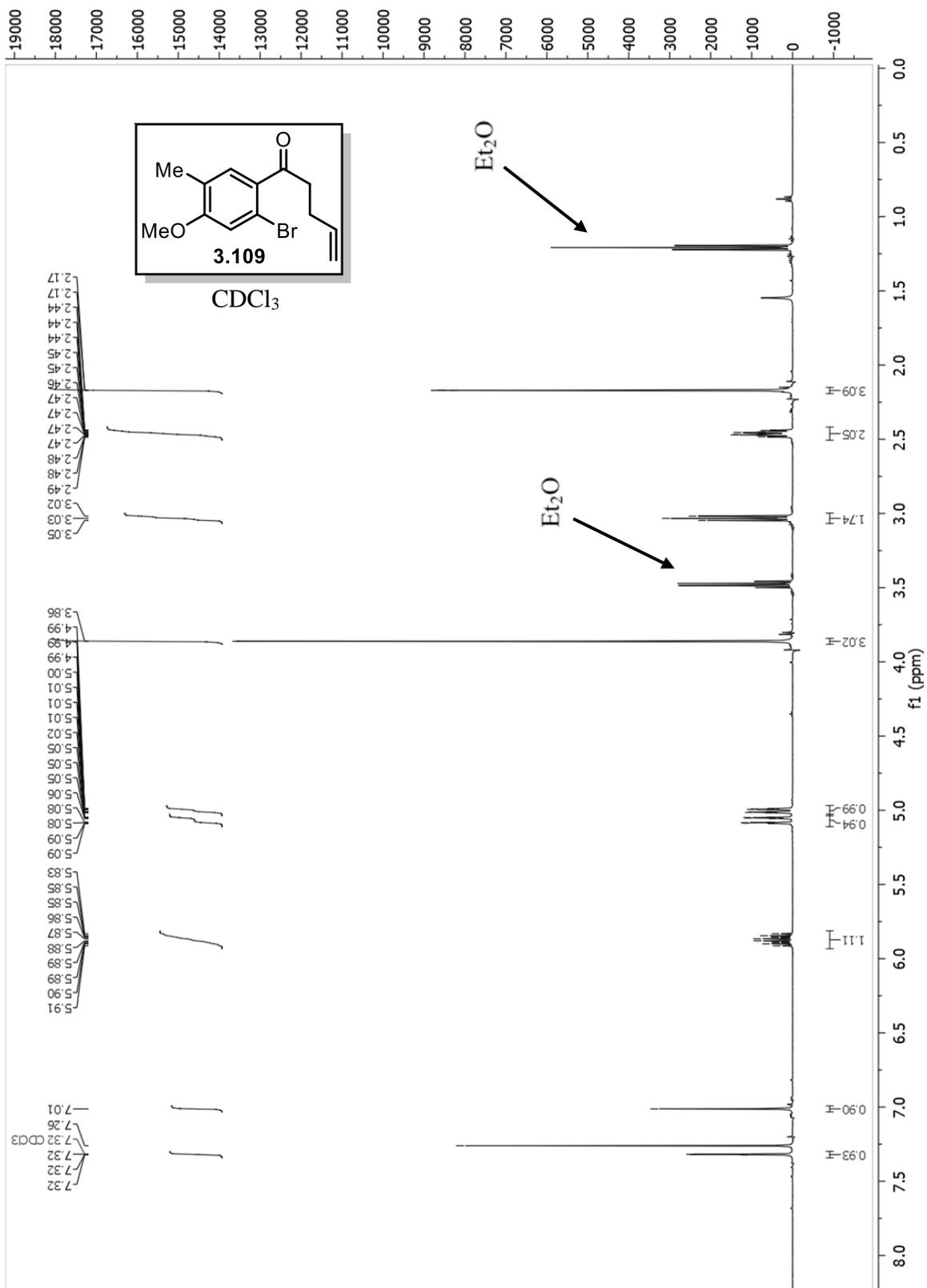


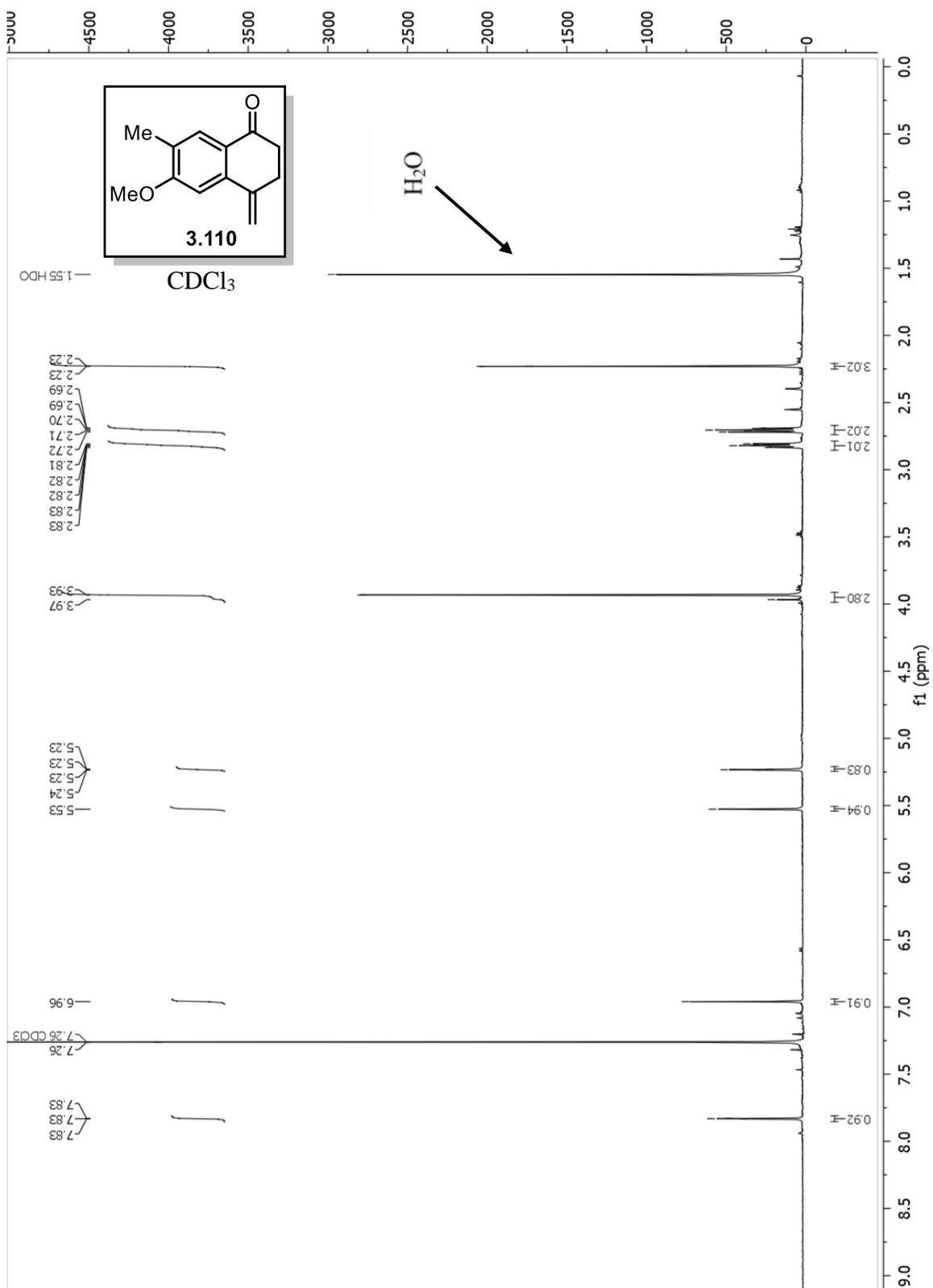


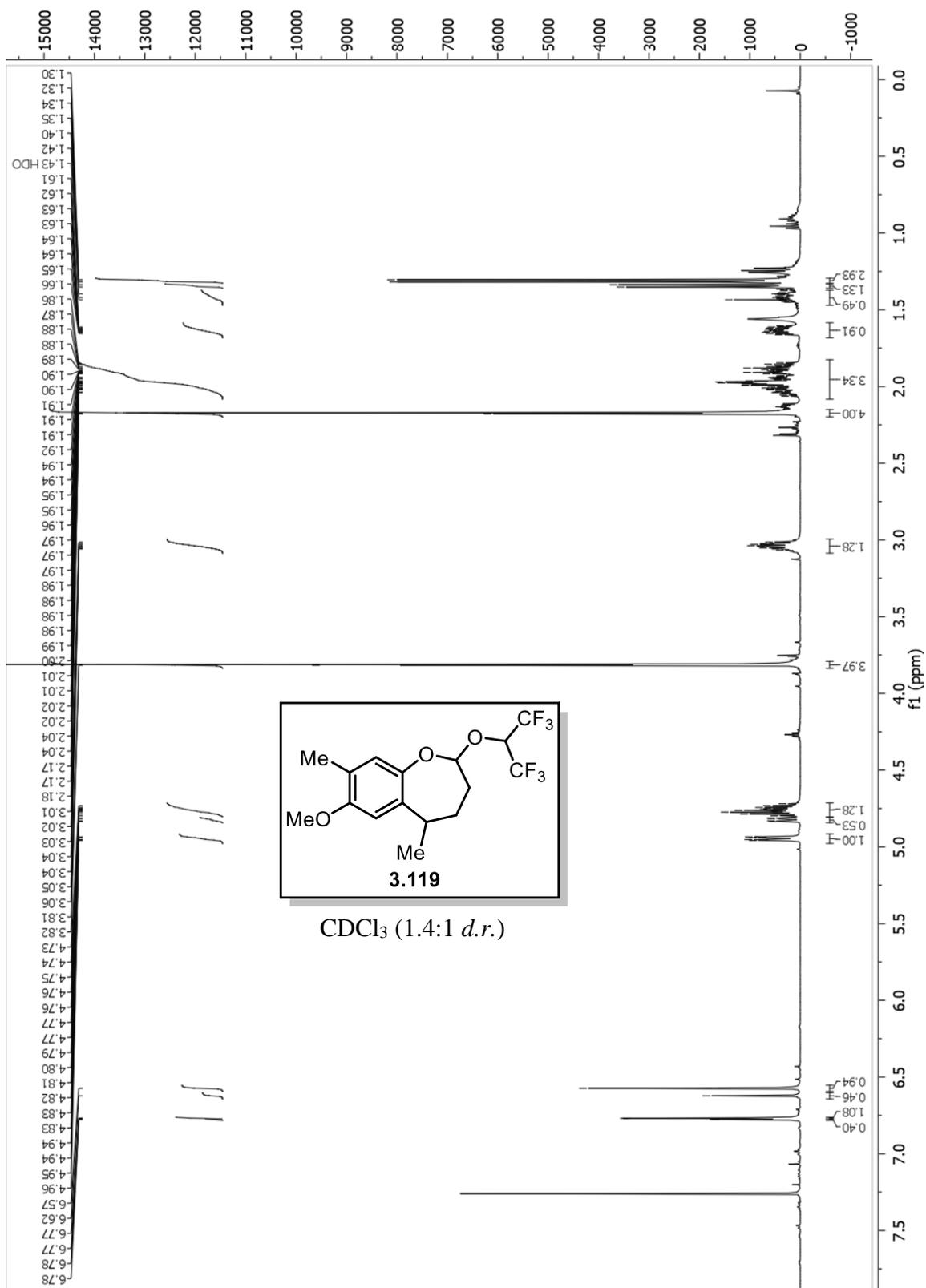


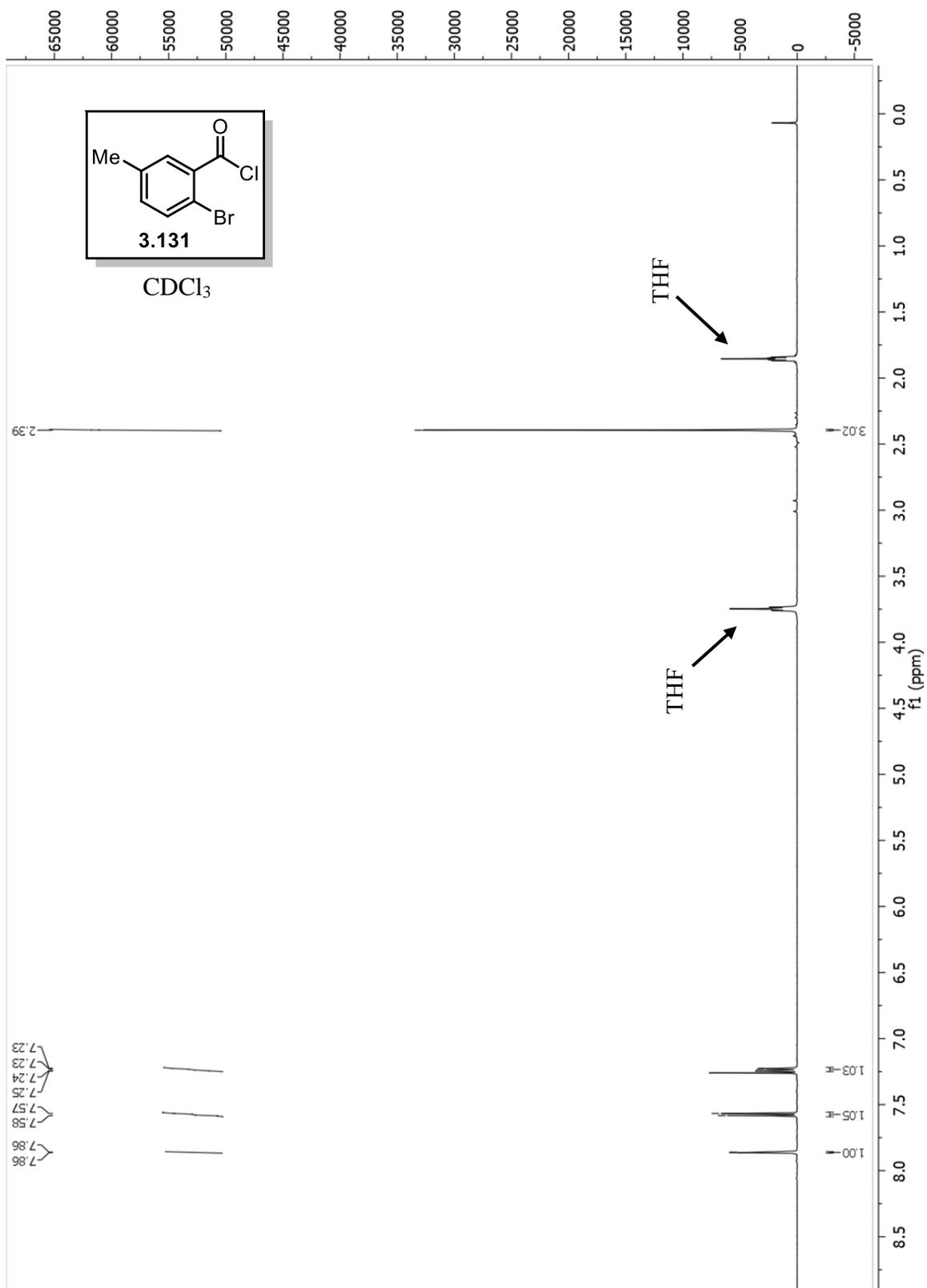


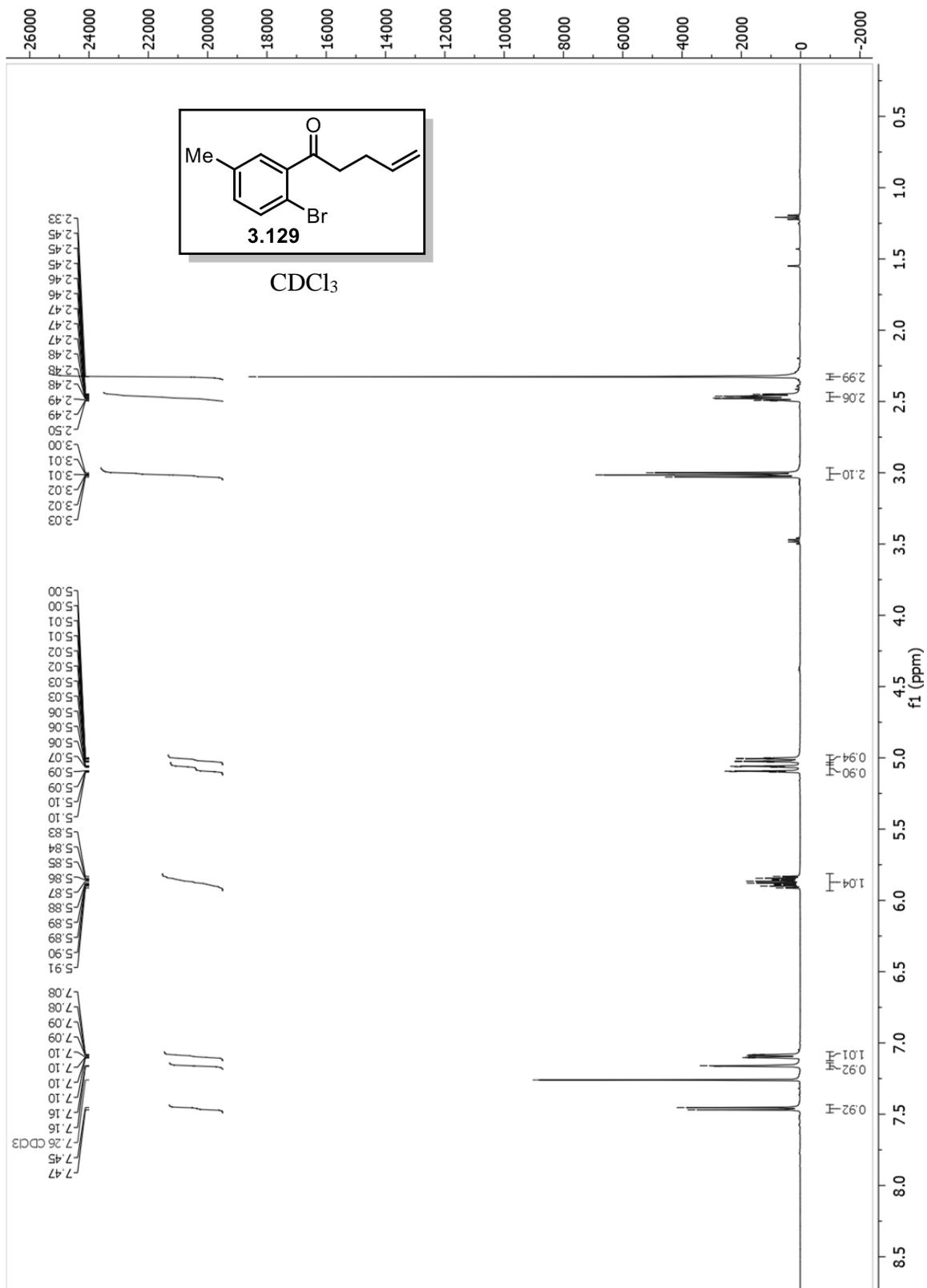


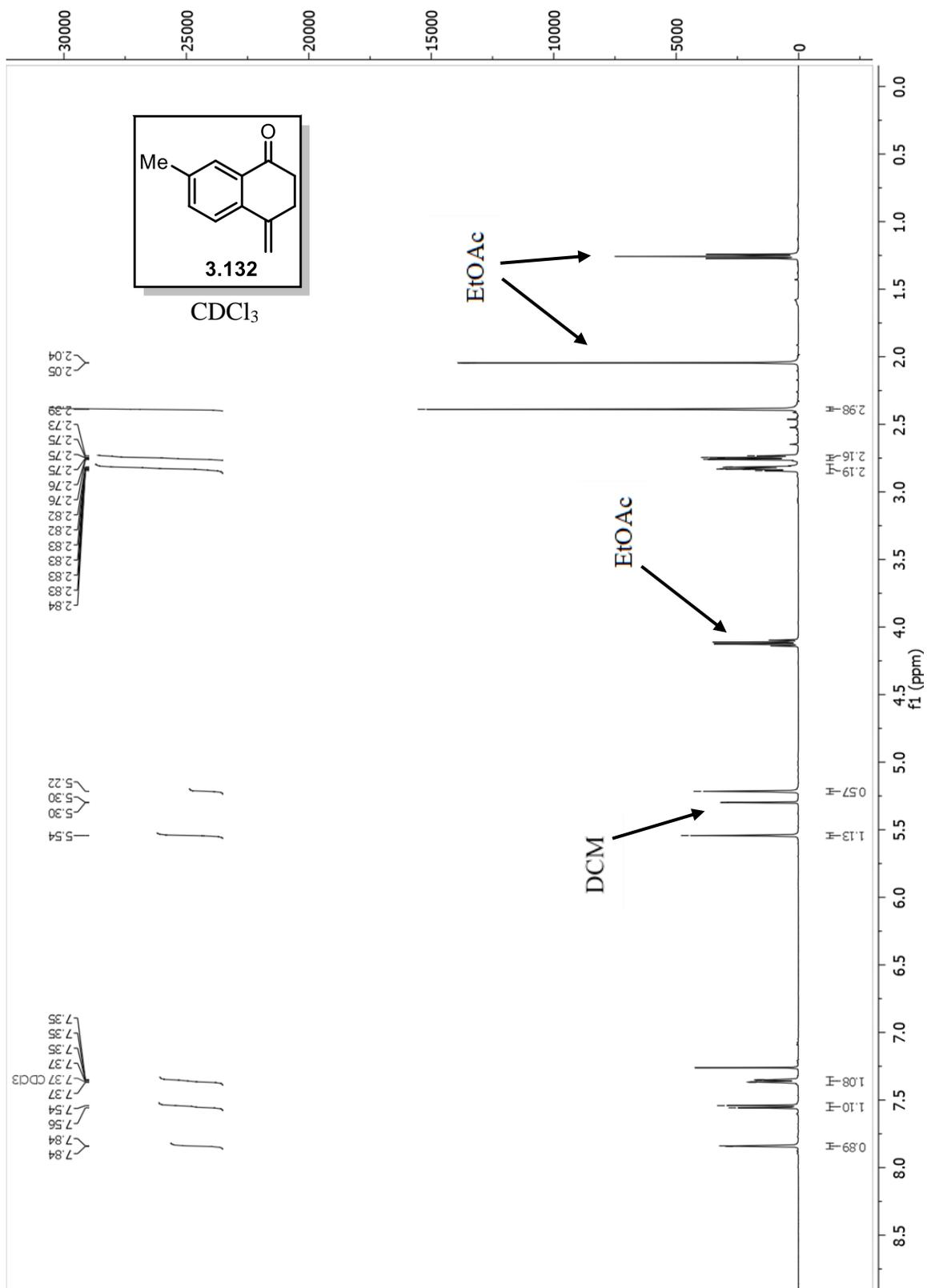


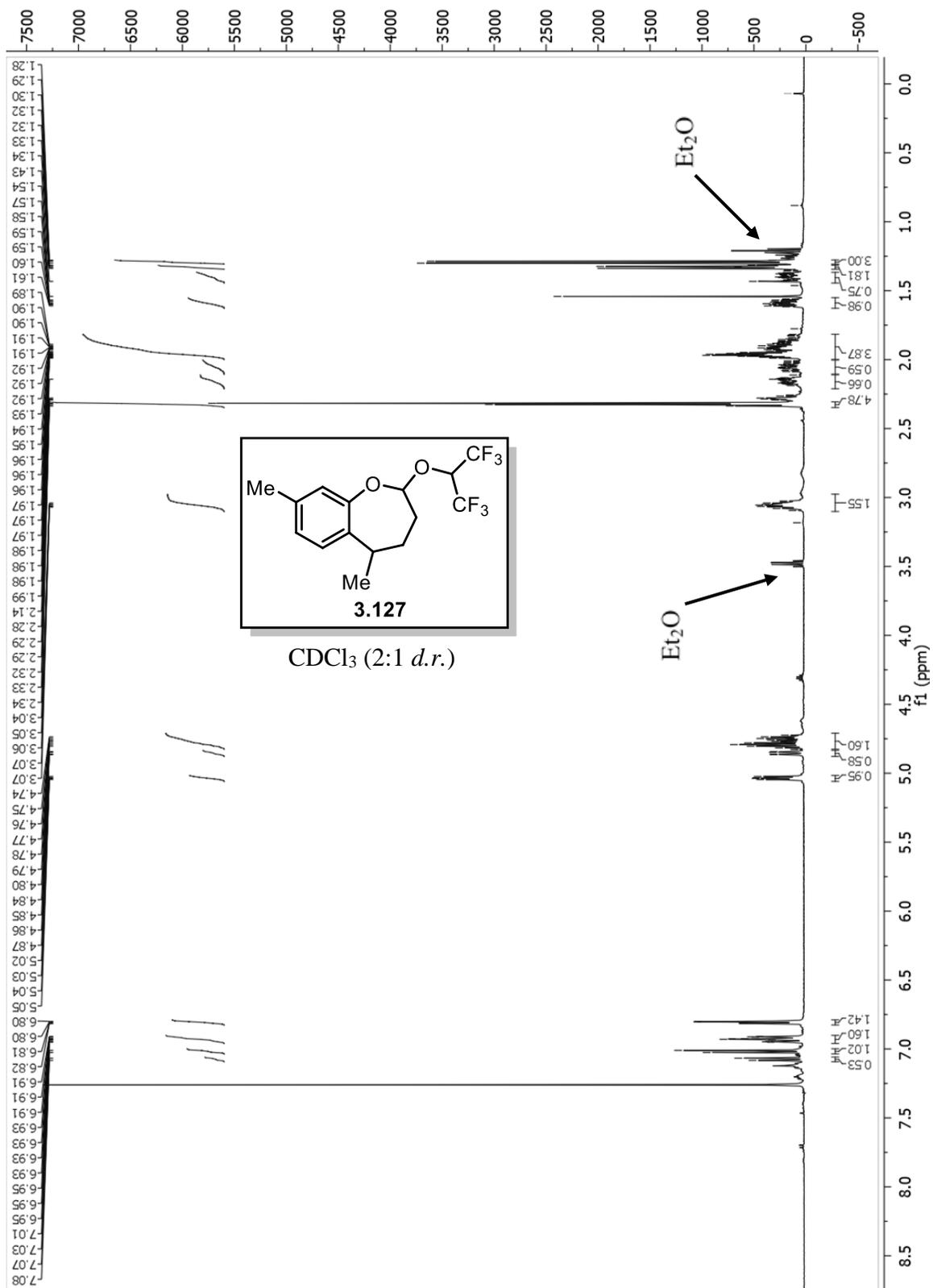


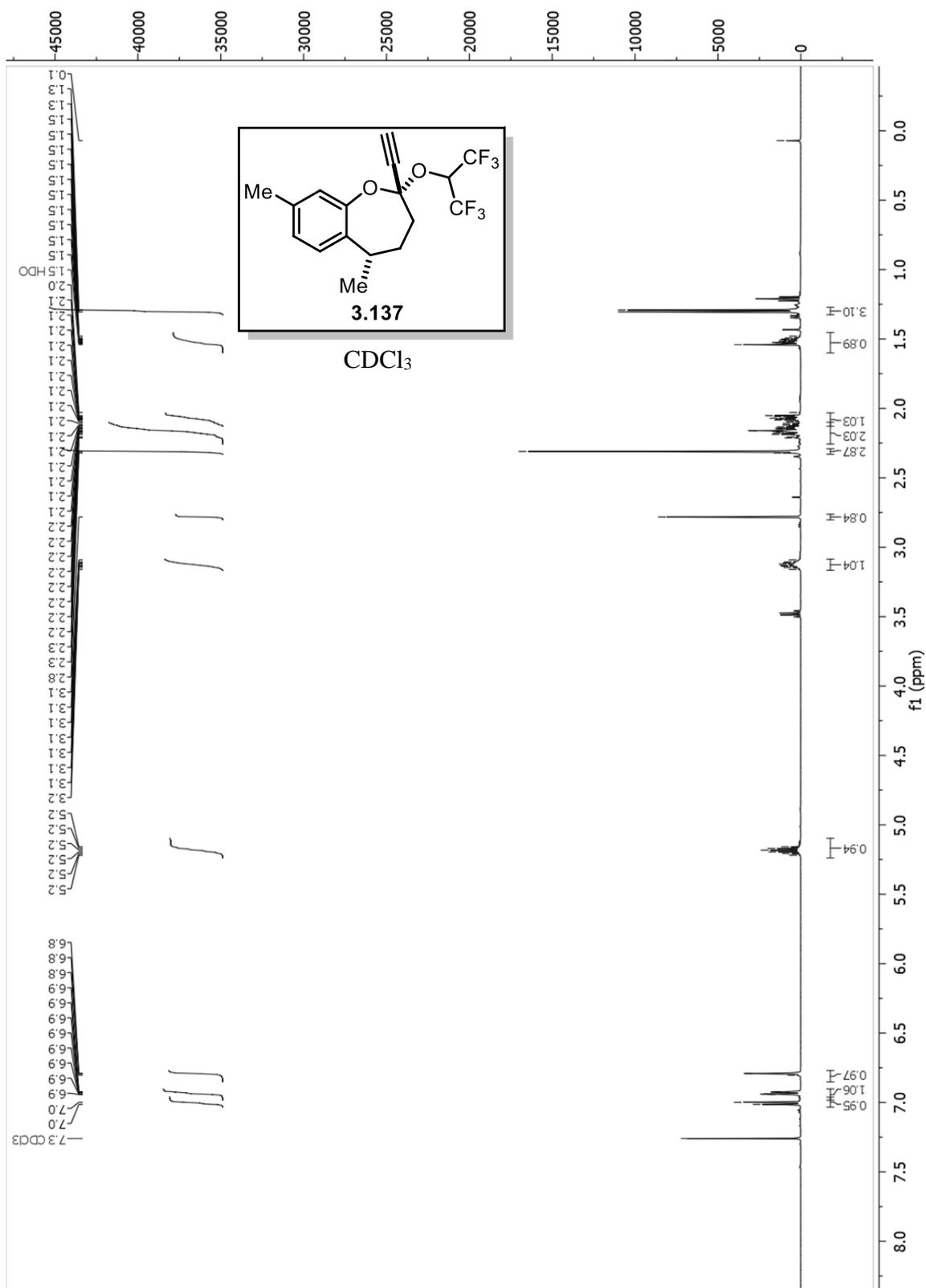


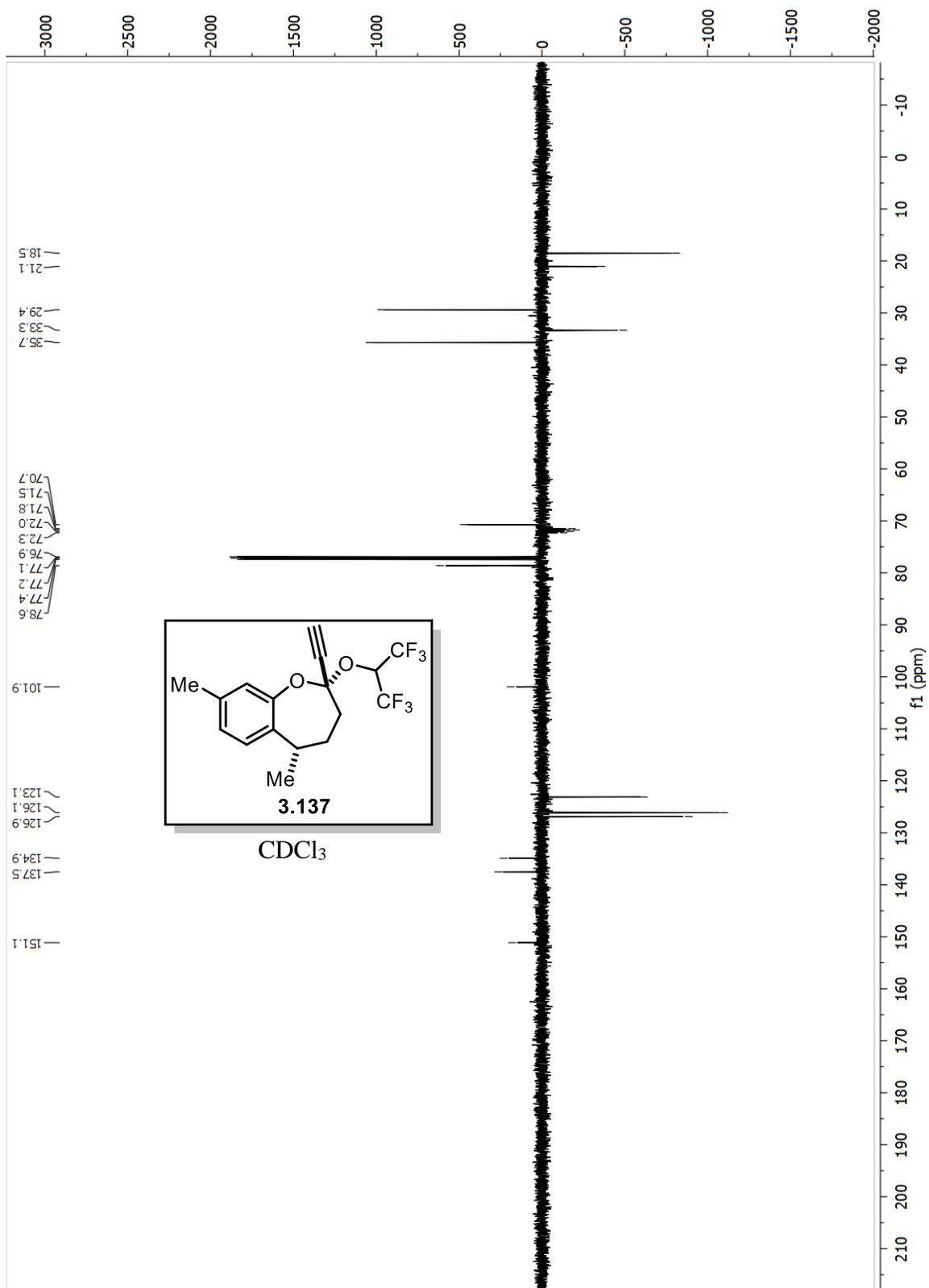


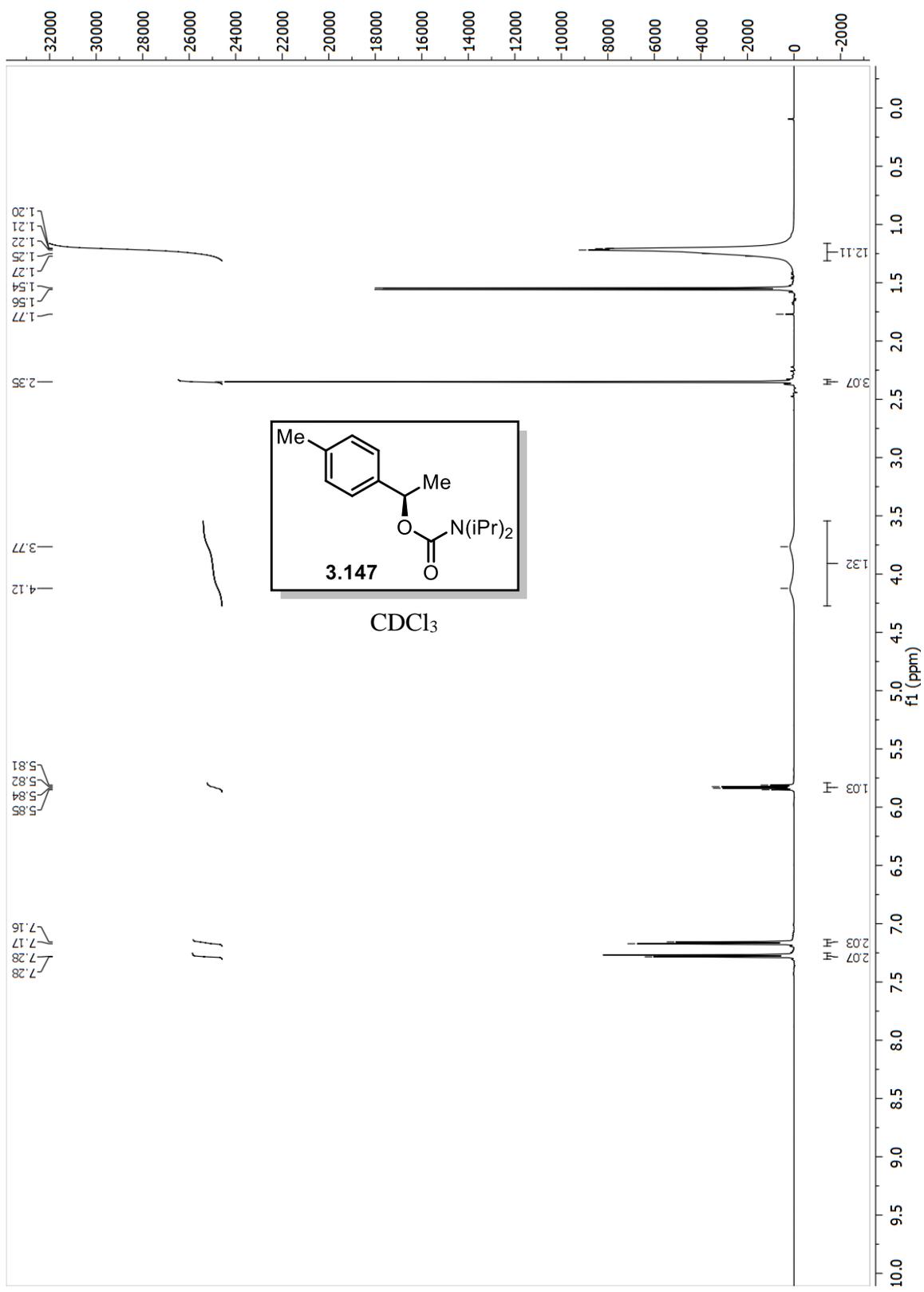


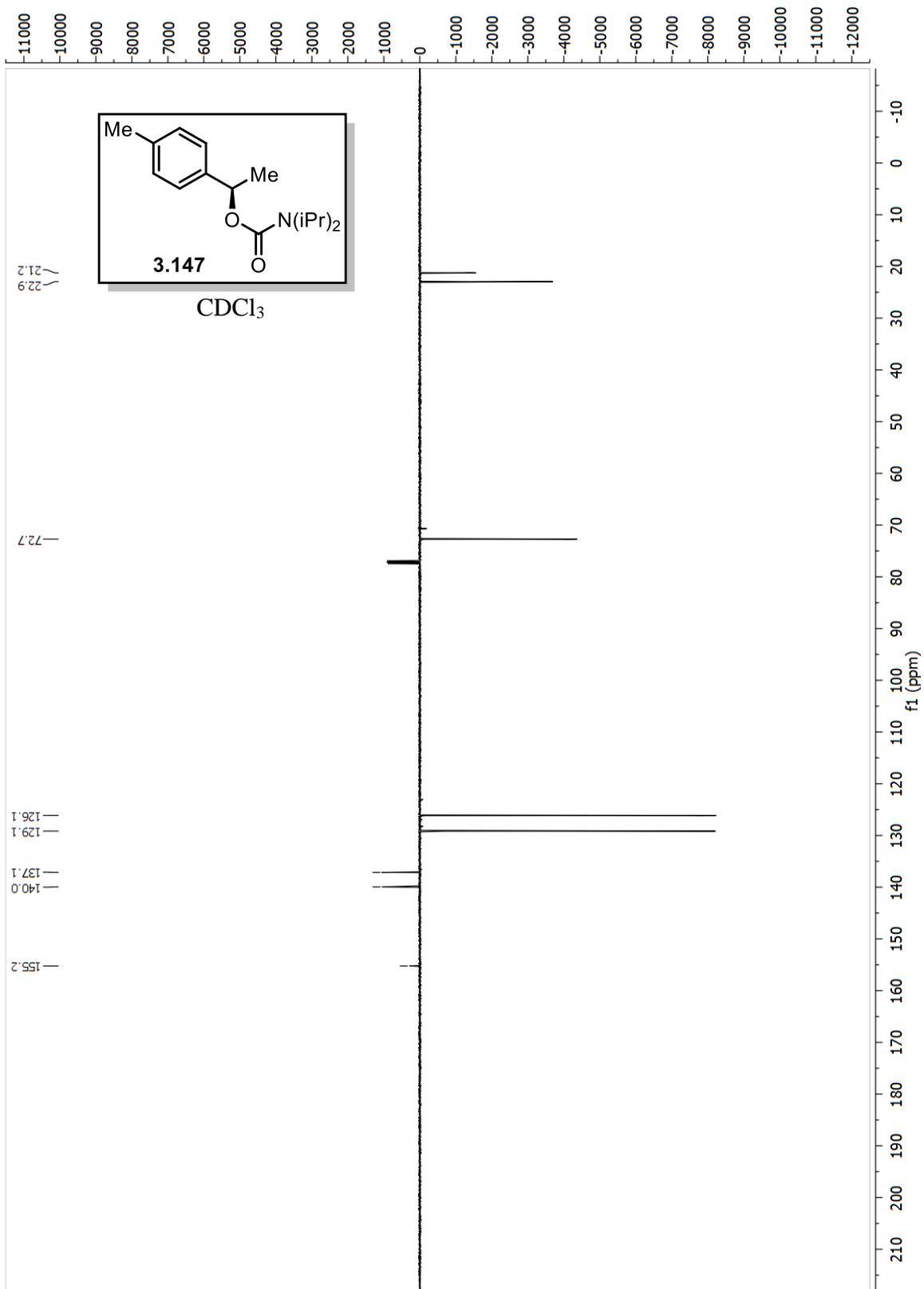


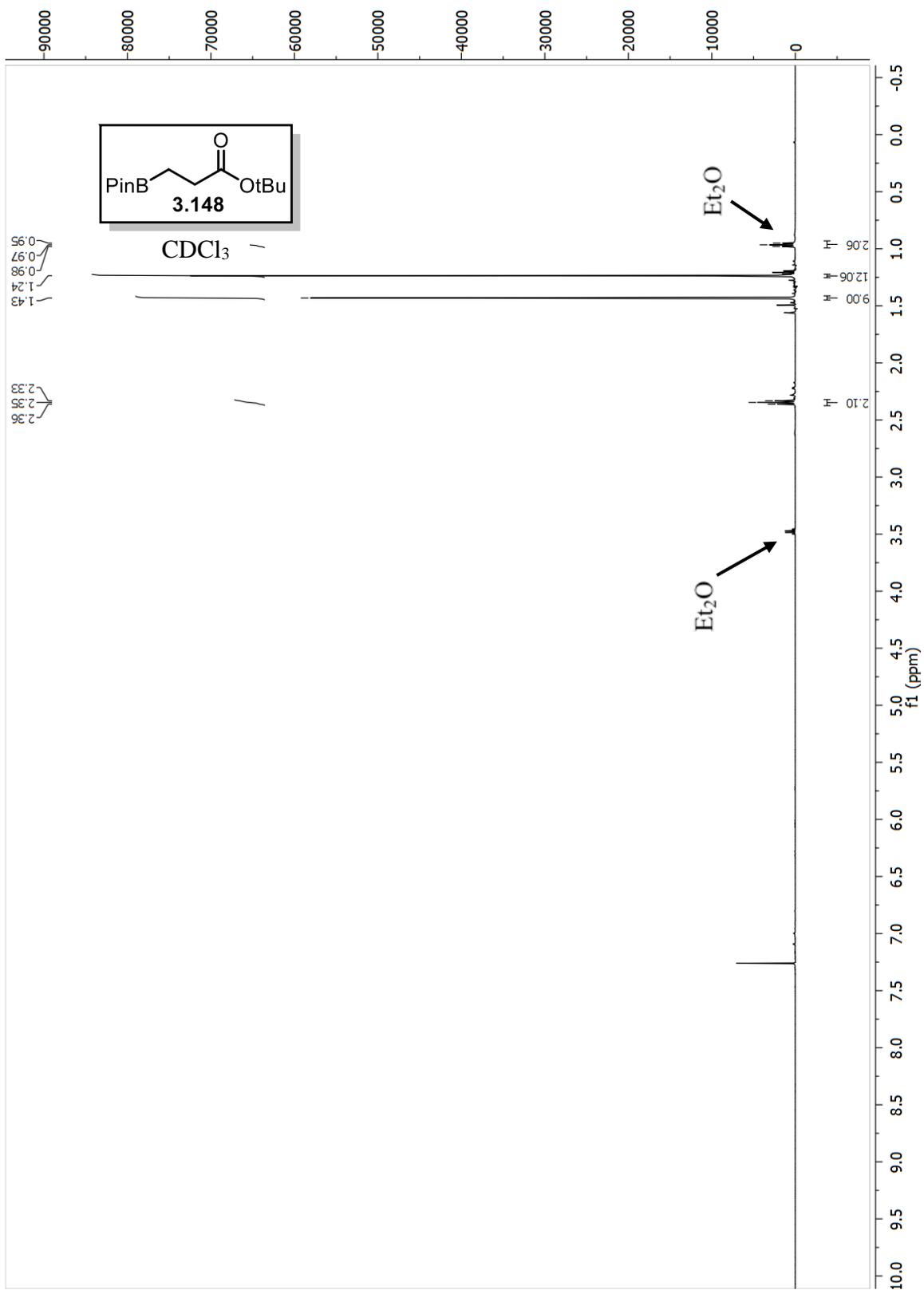


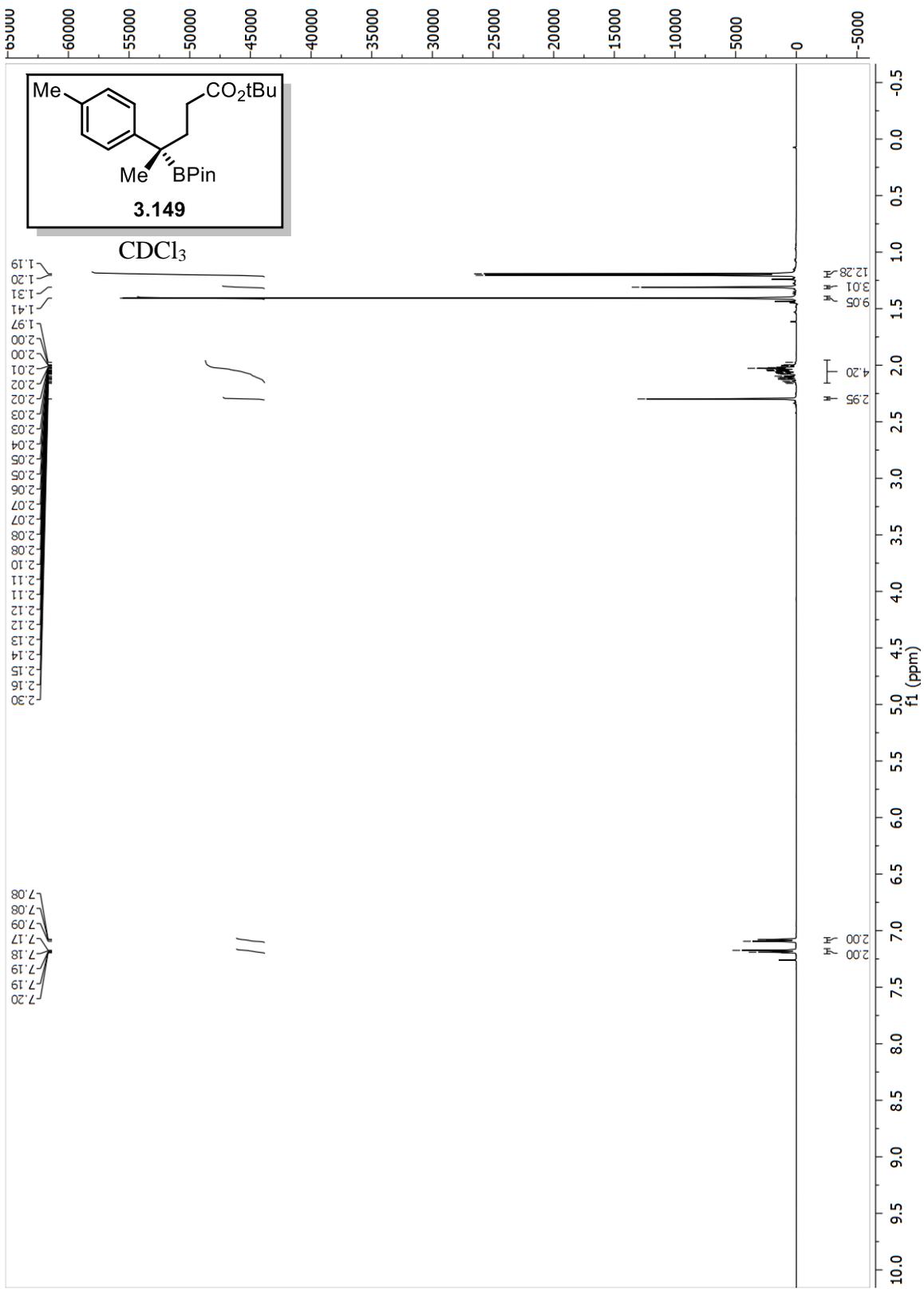


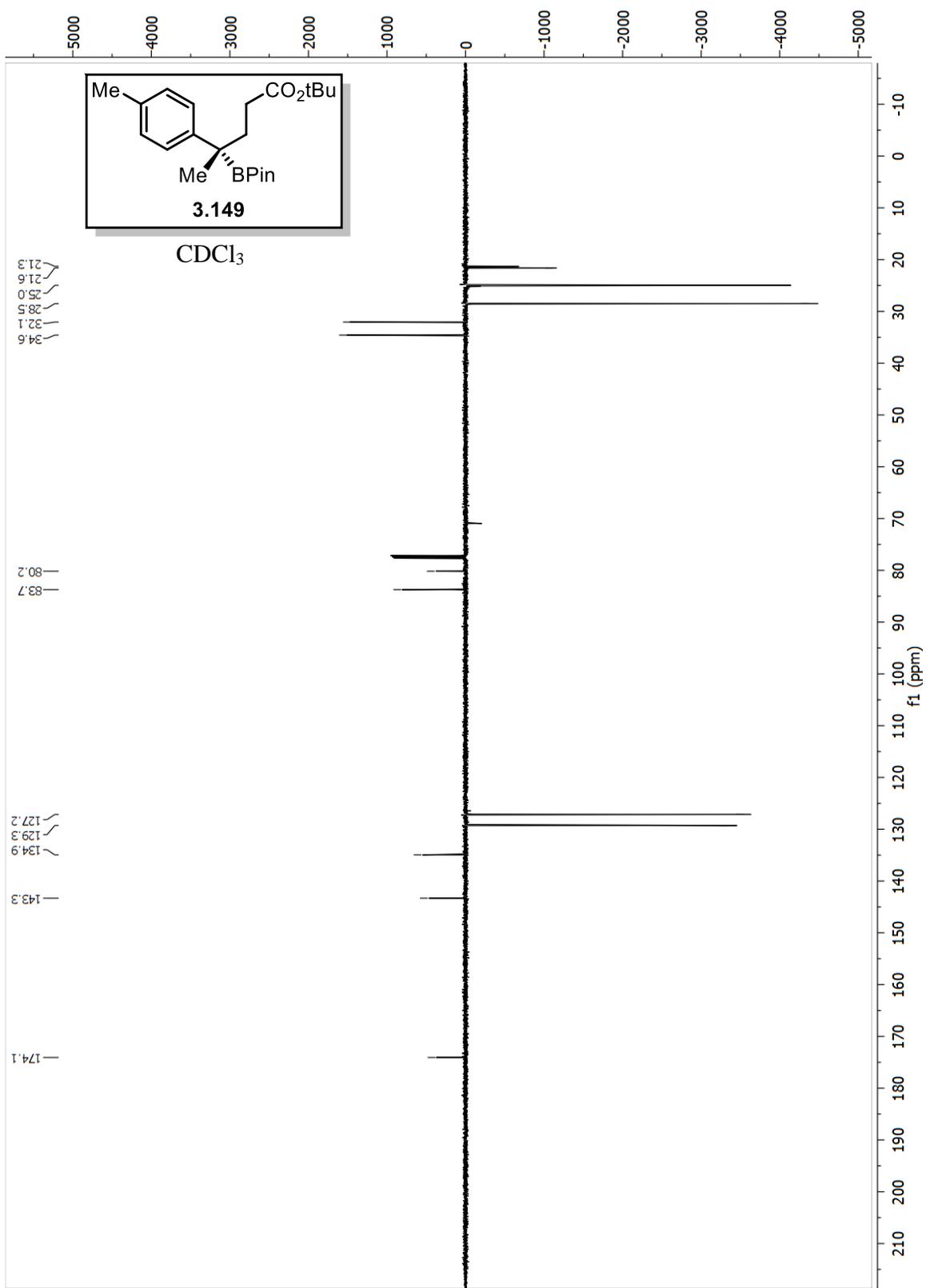


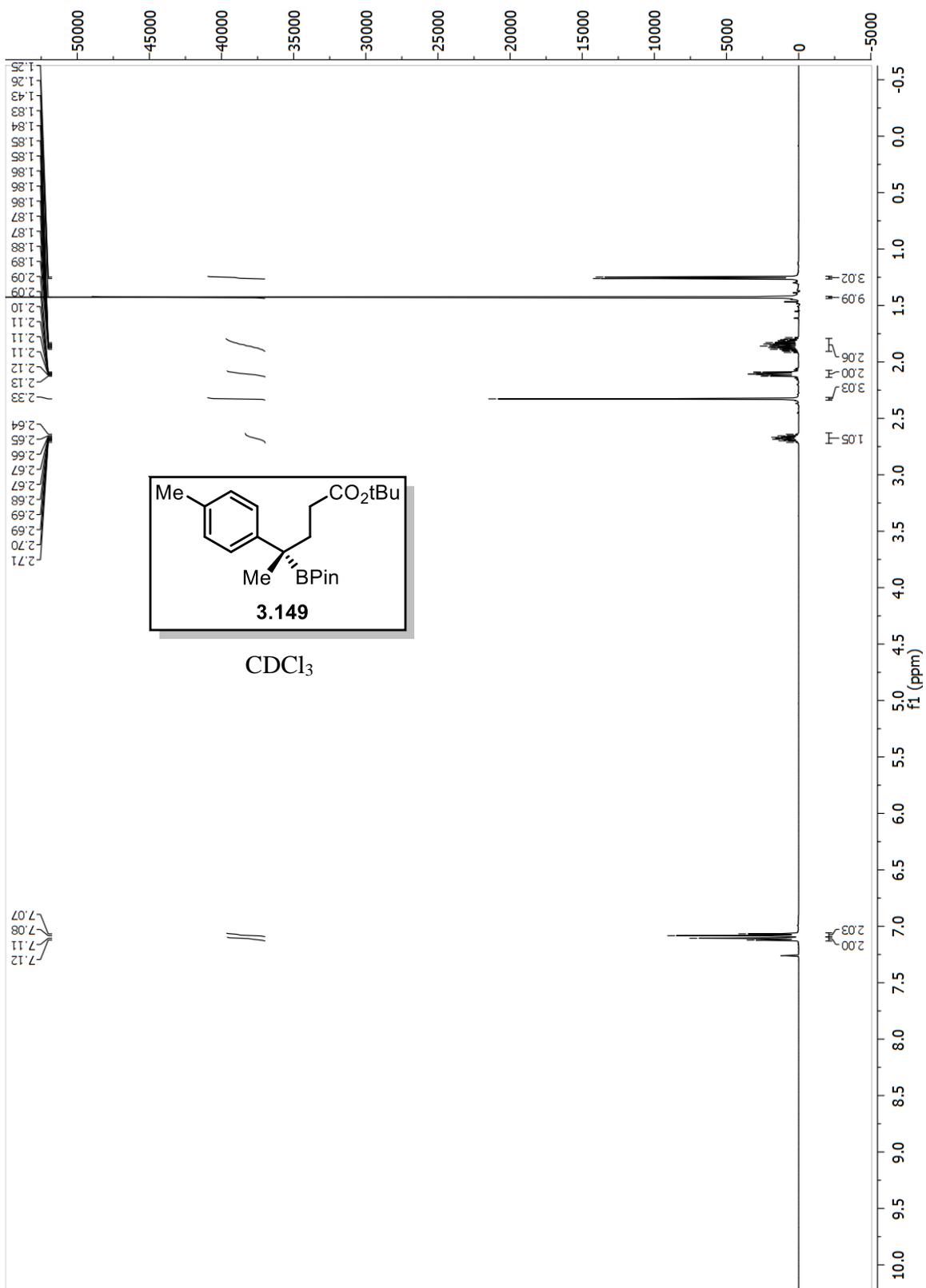


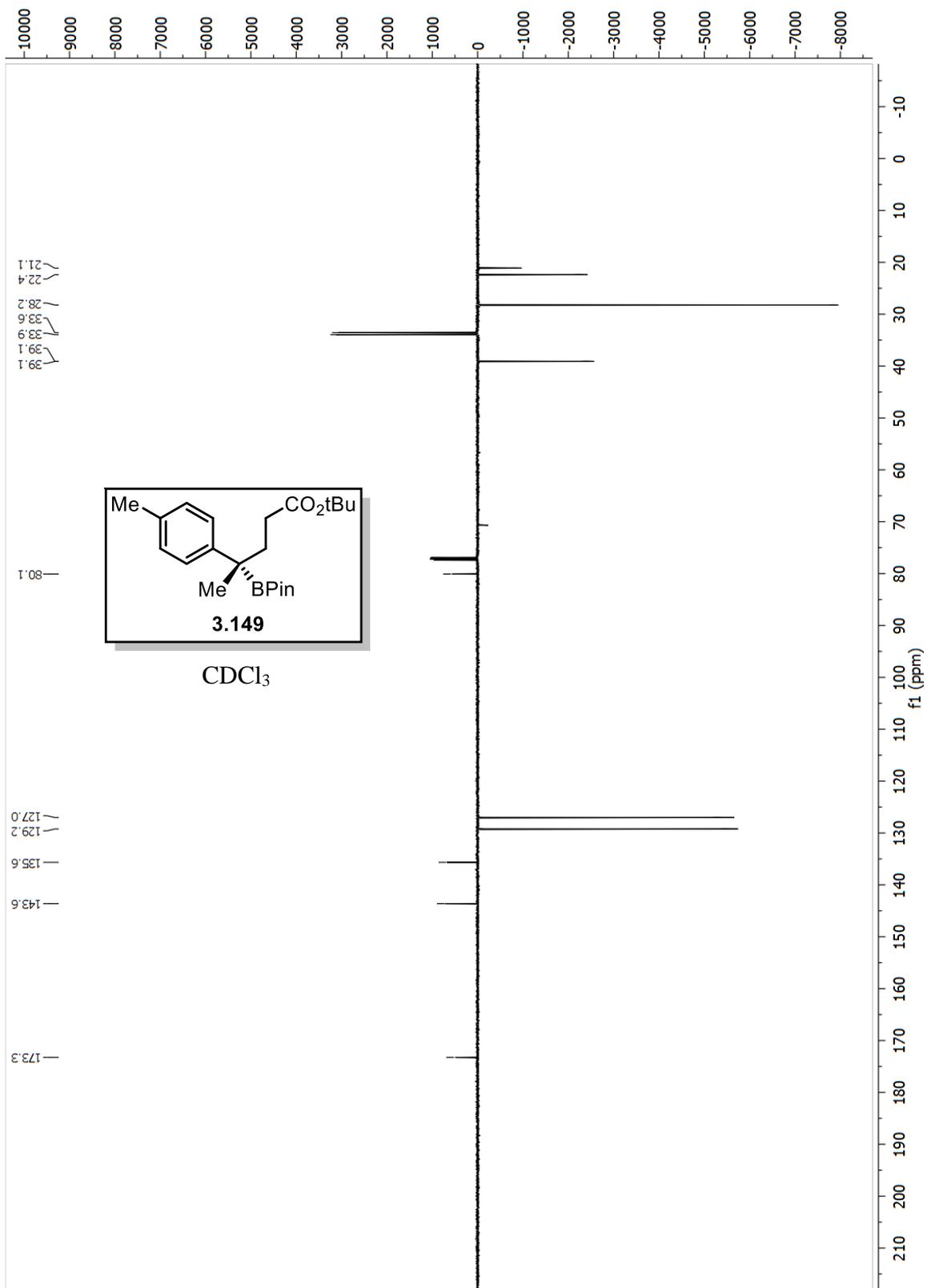


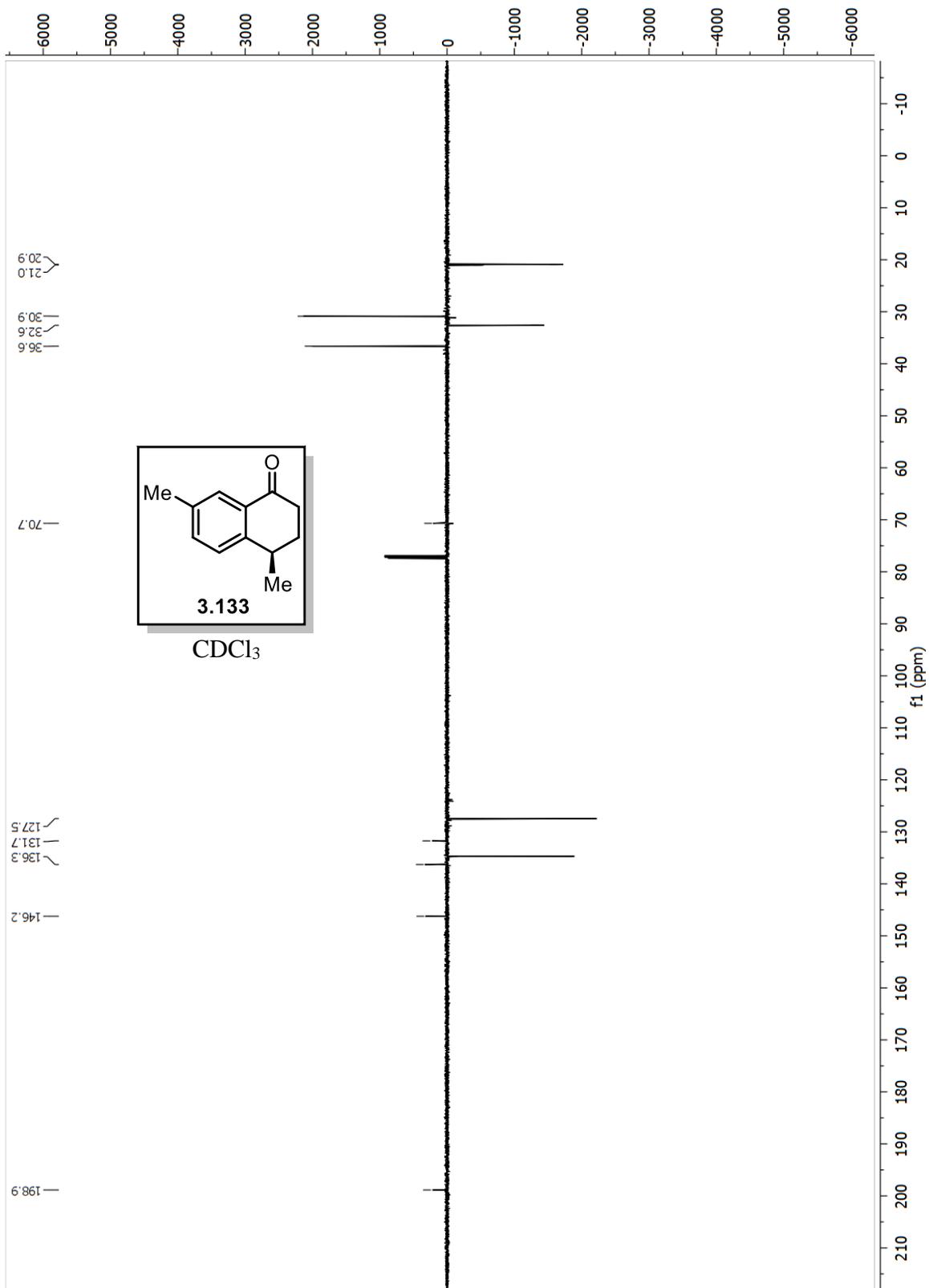


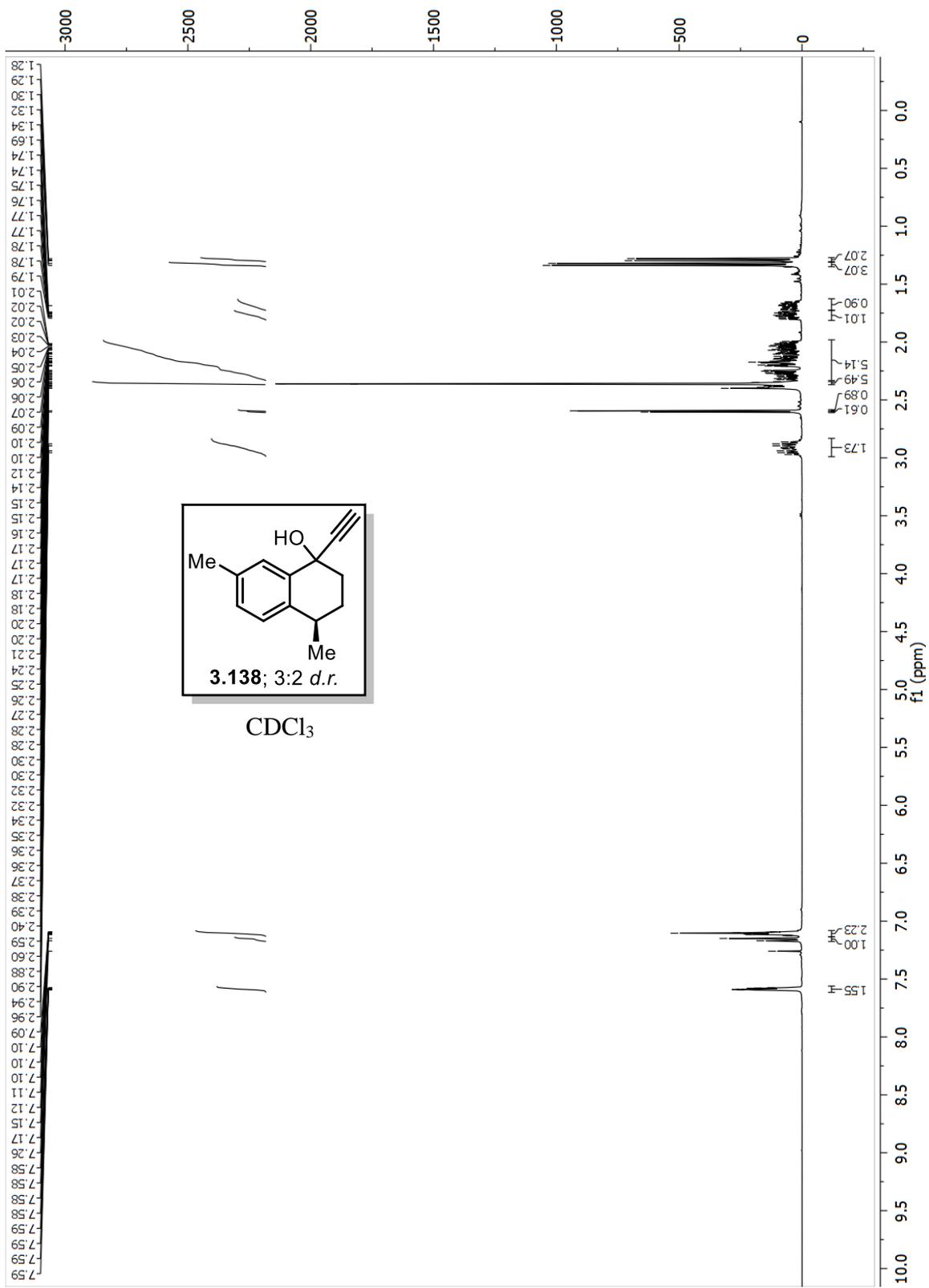


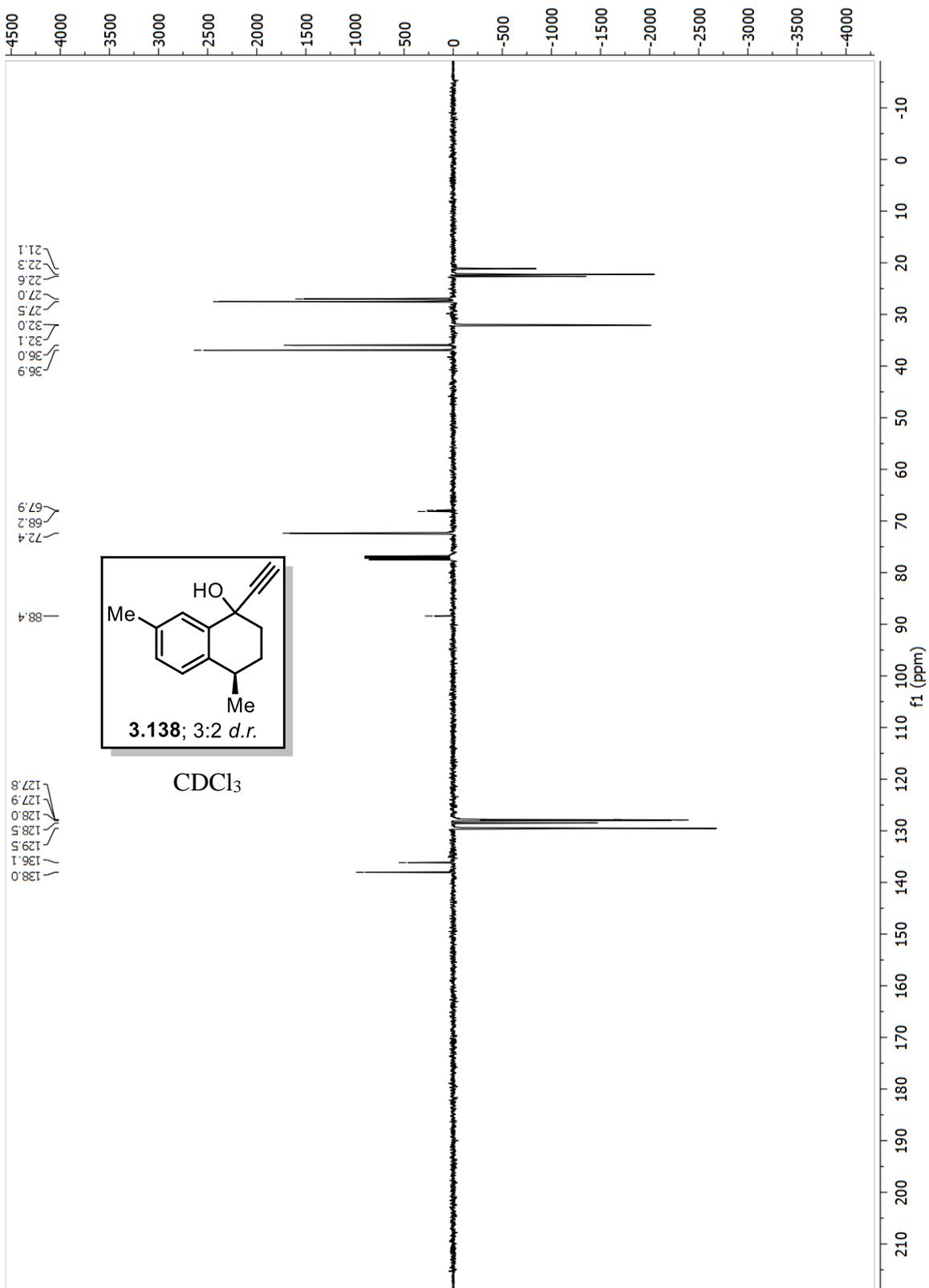


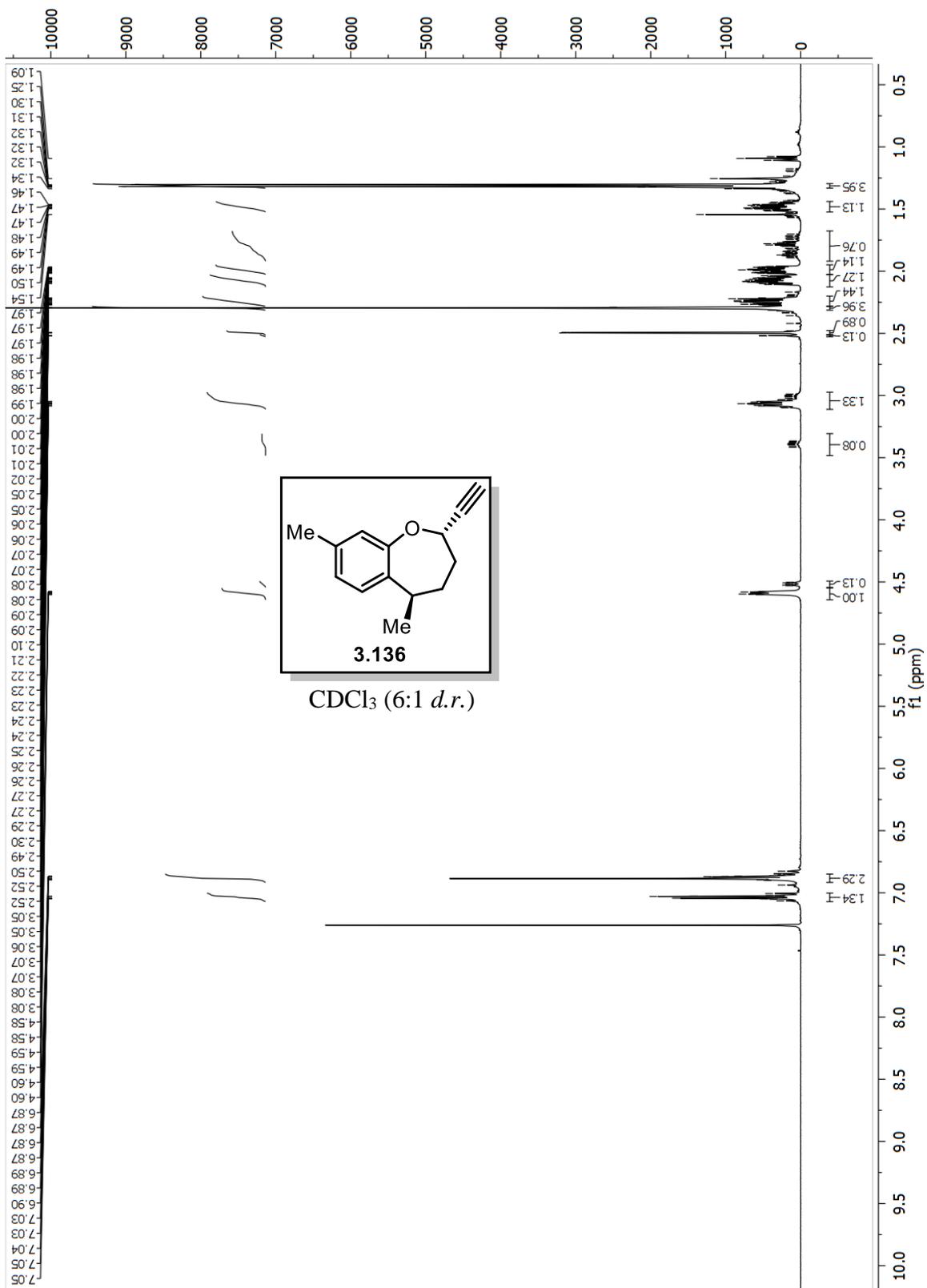


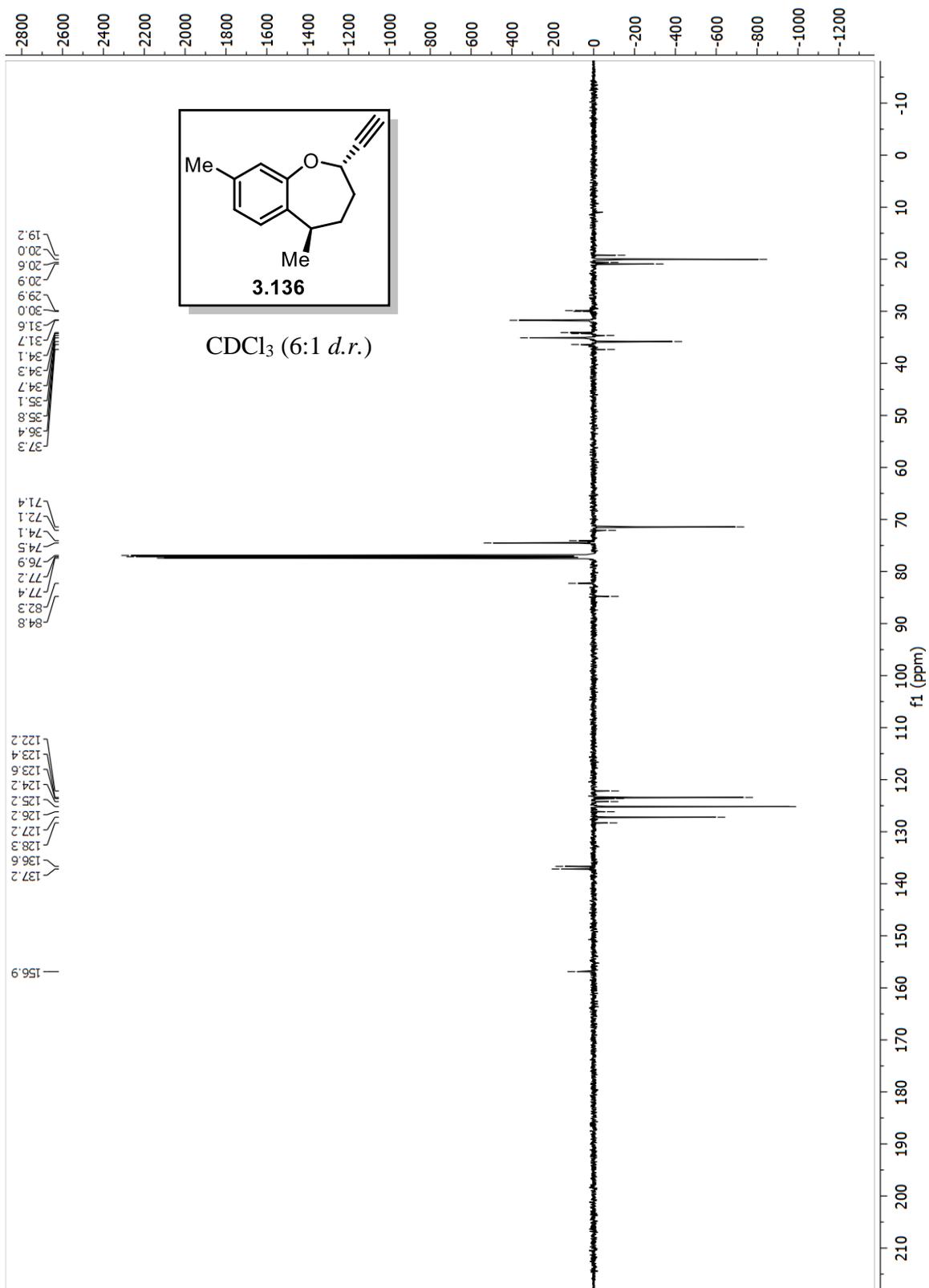


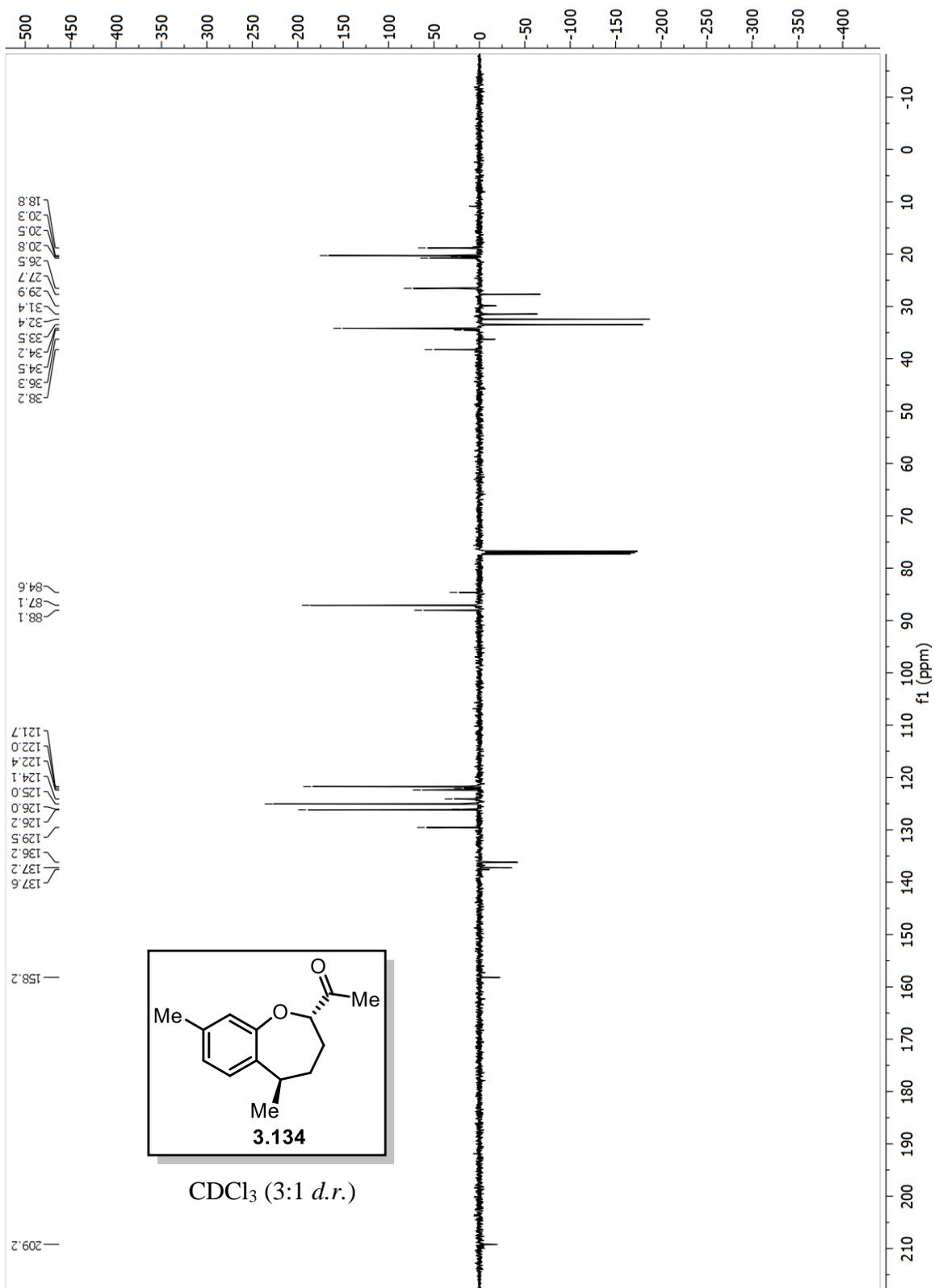


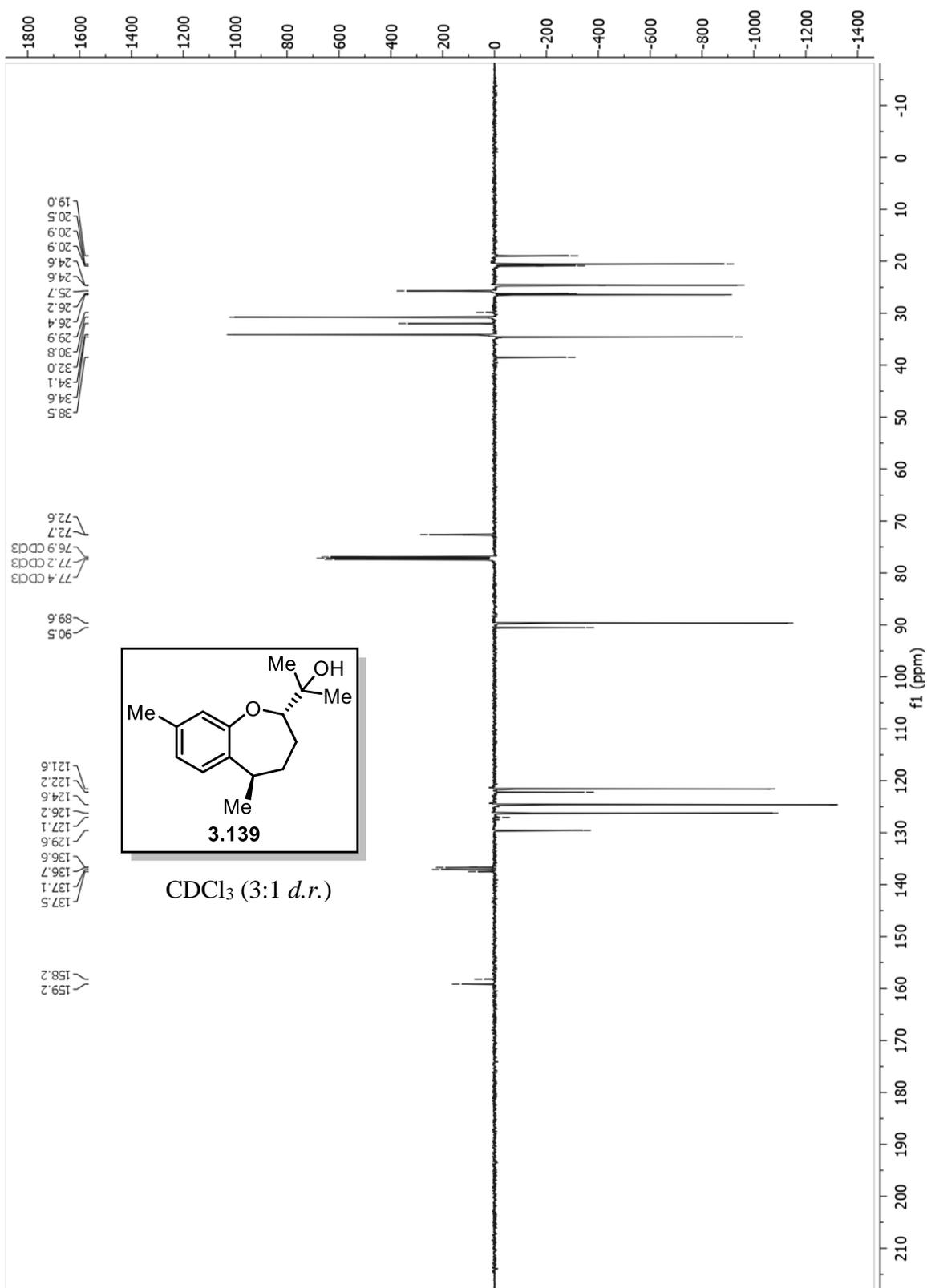


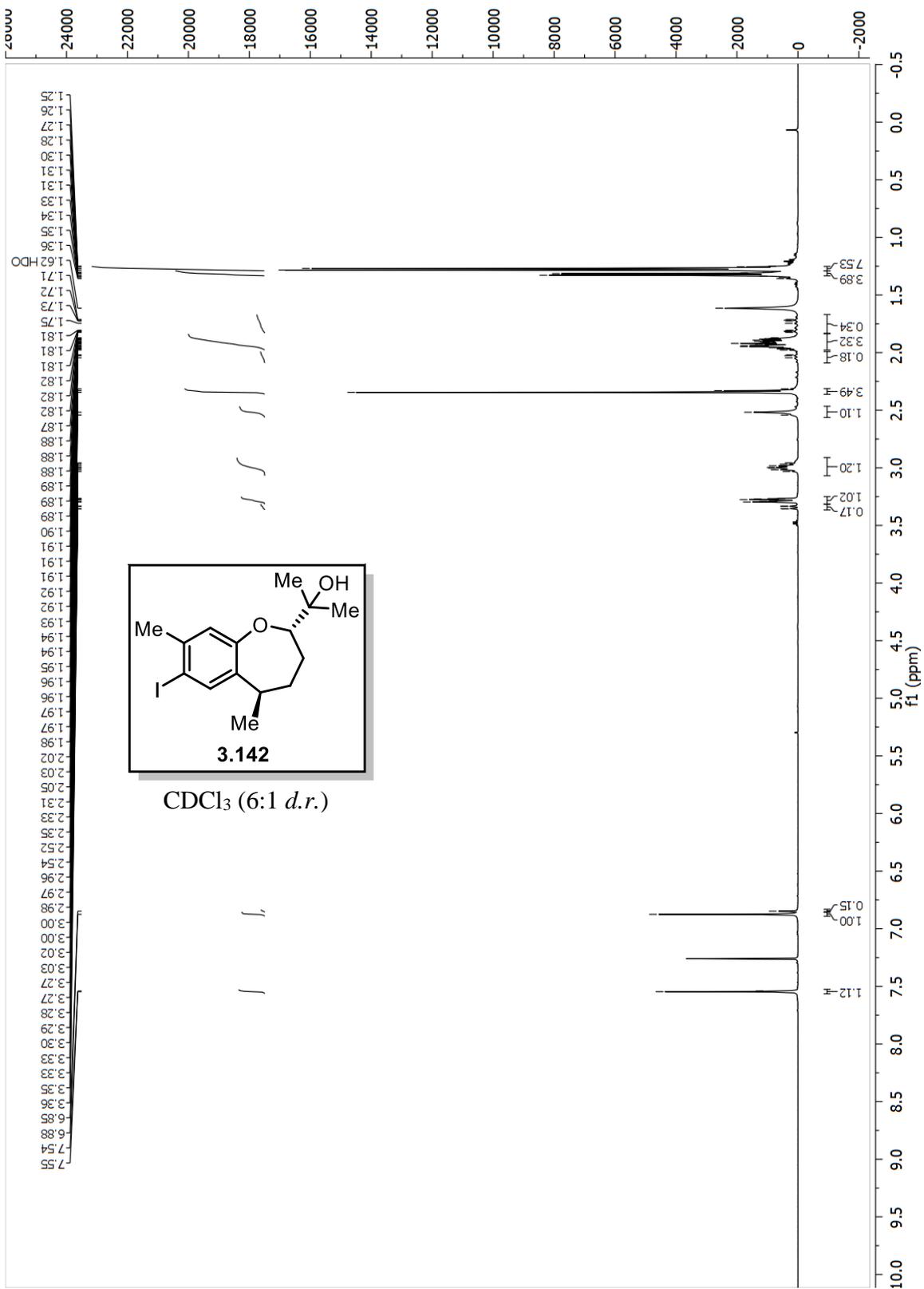


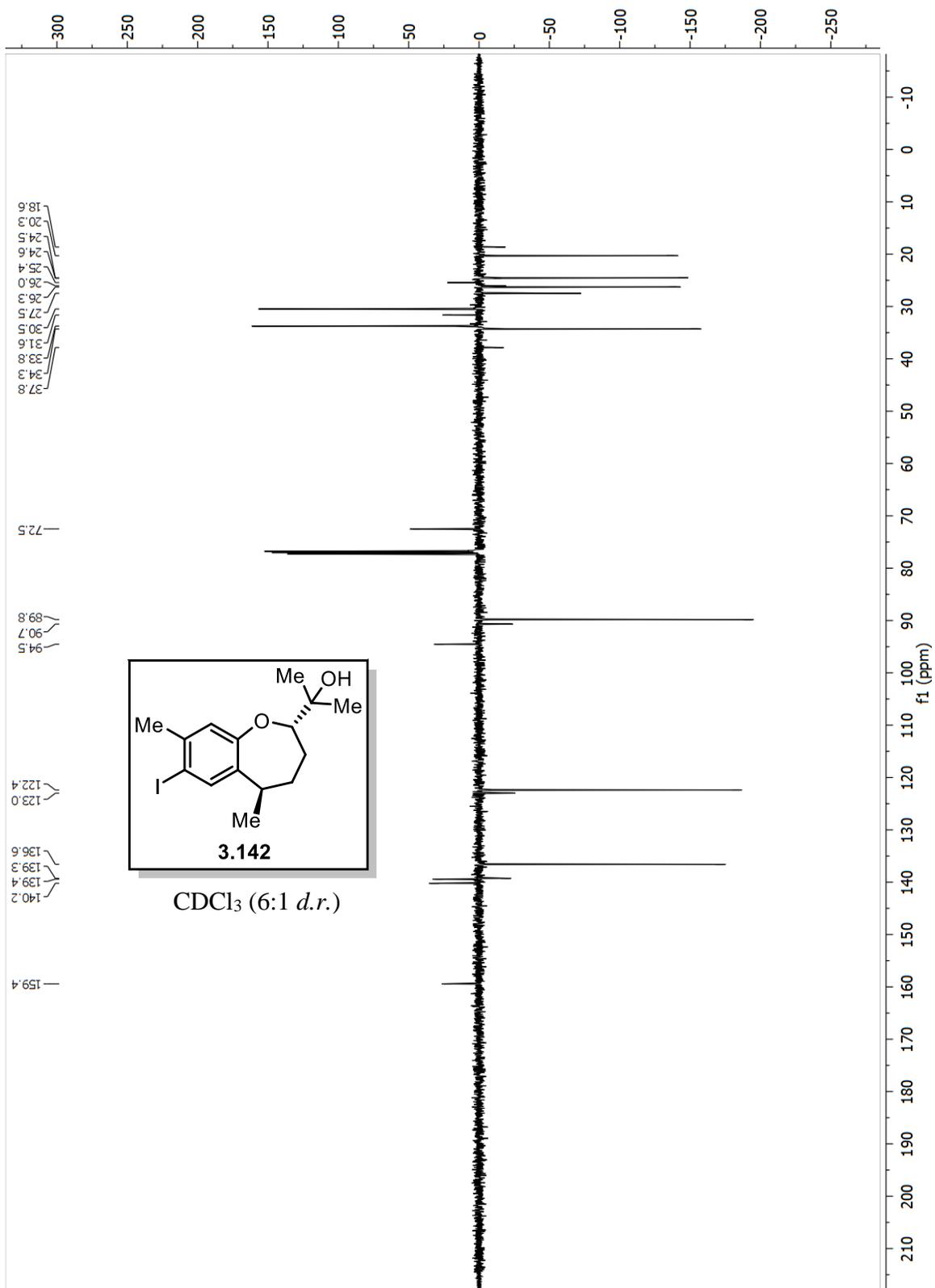


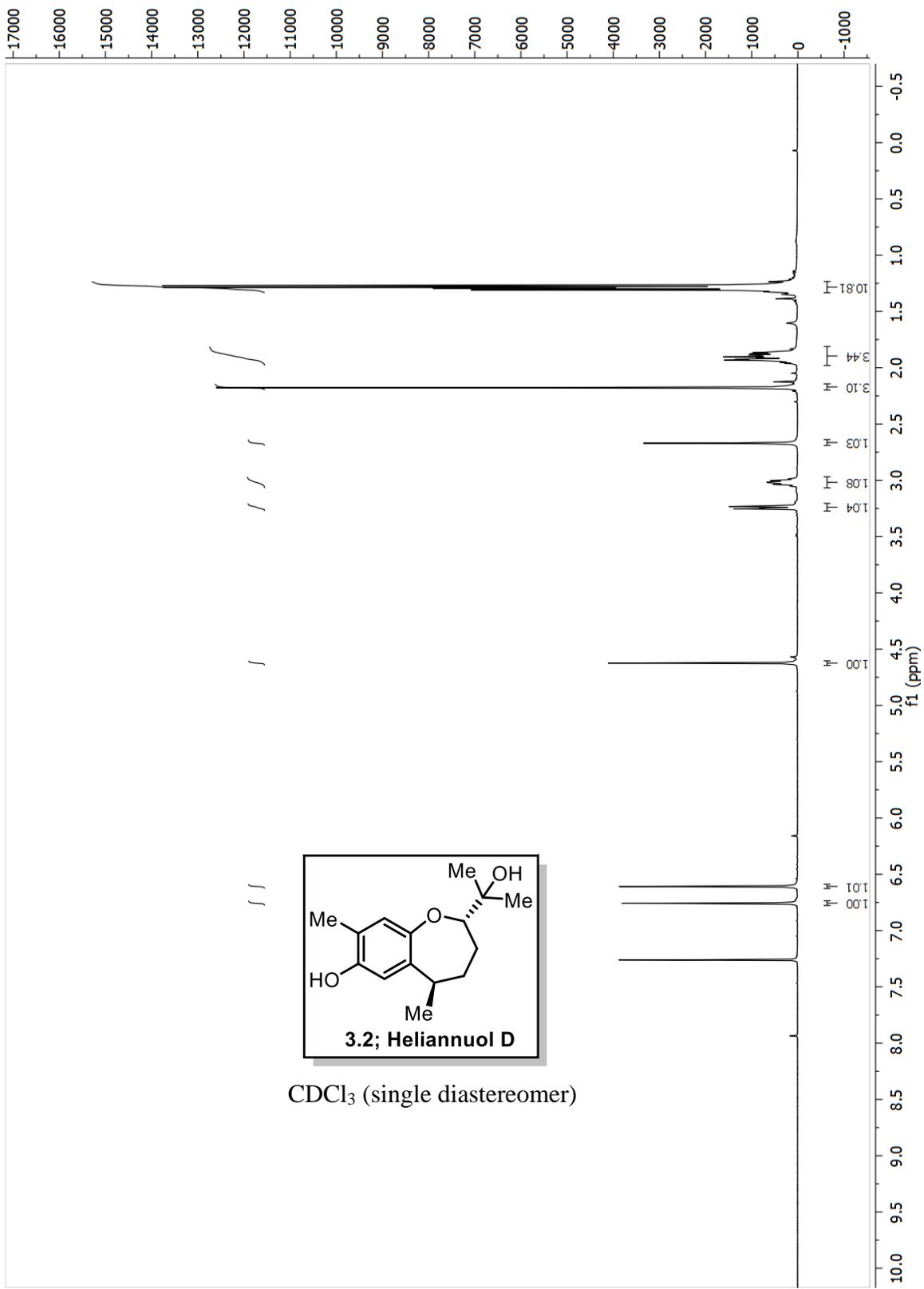


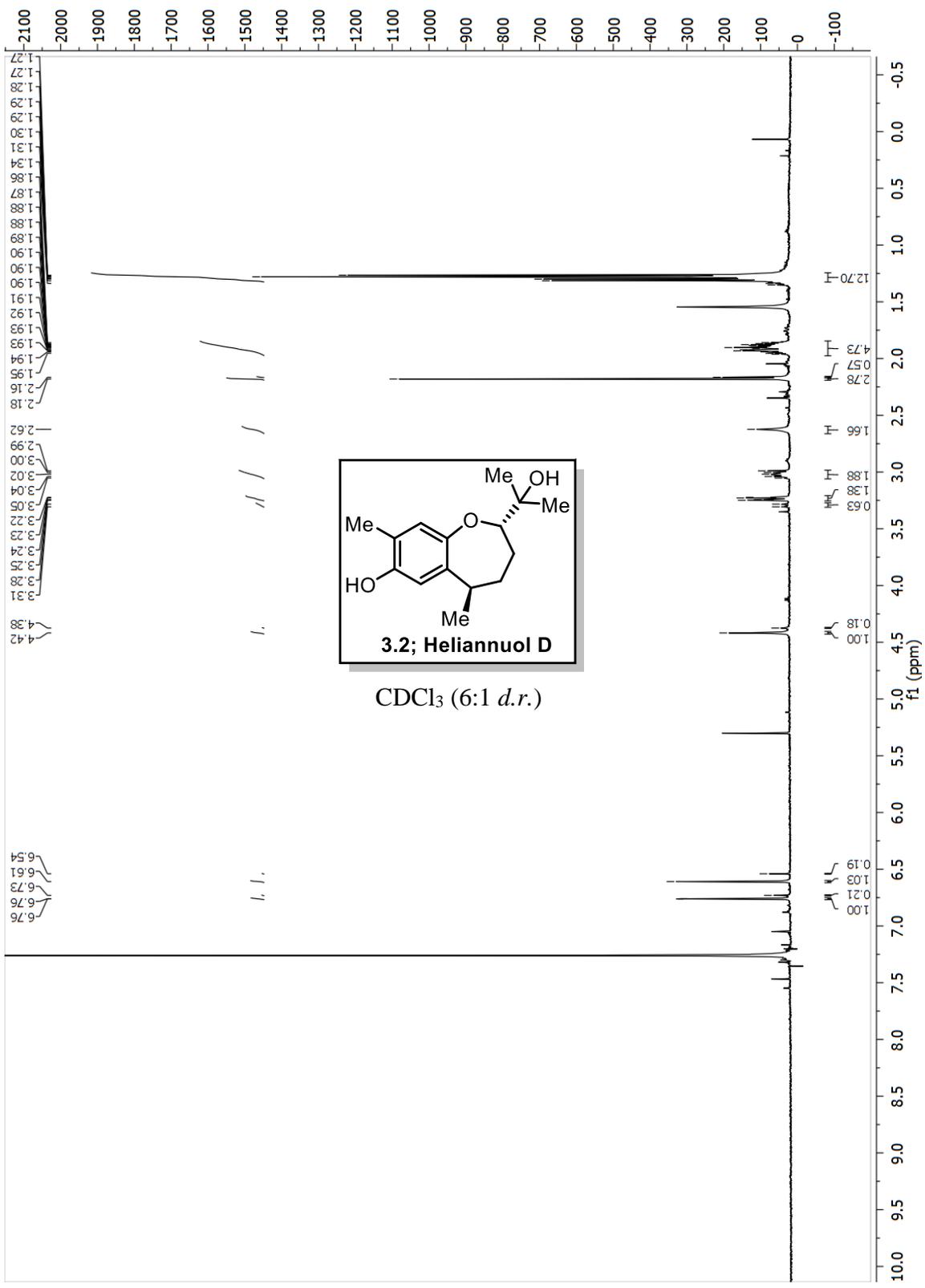


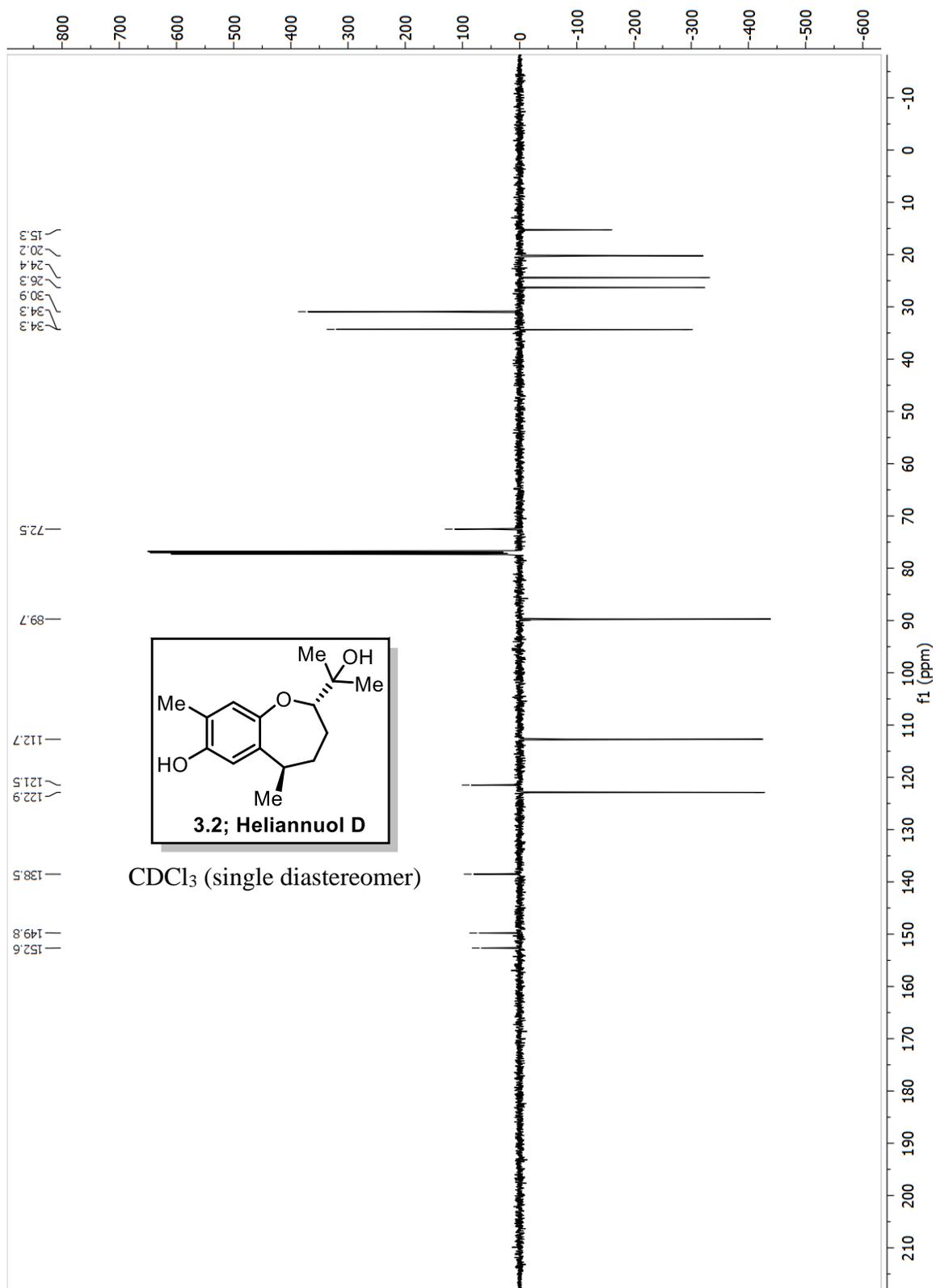












C8: CRYSTAL STRUCTURE DETERMINATION OF COMPOUND 3.137

Single crystals of $C_{17}H_{16}F_6O_2$ compound 3.137 were selected using a MiTeGen loop and was run on a 'Bruker APEX-II CCD' diffractometer. The crystal was kept at 99.95 K during data collection. Using Olex2¹, the structure was solved with the olex2.solve² structure solution program using Charge Flipping and refined with the XL³ refinement package using Least Squares minimisation.

Crystal Data for $C_{17}H_{16}F_6O_2$ ($M = 366.30$ g/mol): monoclinic, space group $P2_1/c$ (no. 14), $a = 10.4274(8)$ Å, $b = 16.3181(12)$ Å, $c = 9.8767(7)$ Å, $\beta = 93.221(2)^\circ$, $V = 1677.9(2)$ Å³, $Z = 4$, $T = 99.95$ K, $\mu(\text{MoK}\alpha) = 0.138$ mm⁻¹, $D_{\text{calc}} = 1.450$ g/cm³, 15788 reflections measured ($3.912^\circ \leq 2\theta \leq 55.726^\circ$), 3989 unique ($R_{\text{int}} = 0.0297$, $R_{\text{sigma}} = 0.0306$) which were used in all calculations. The final R_1 was 0.0467 ($I > 2\sigma(I)$) and wR_2 was 0.1086 (all data).

Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

1. Fixed Uiso at 1.2 times of: All C(H) groups, All C(H,H) groups; At 1.5 times of: All C(H,H,H) groups
- 2.a Ternary CH refined with riding coordinates: C15(H15), C8(H8)
- 2.b Secondary CH₂ refined with riding coordinates: C11(H11A,H11B), C10(H10A,H10B)
- 2.c Aromatic/amide H refined with riding coordinates: C3(H3), C7(H7), C6(H6)

2.d Idealised Me refined as rotating group: C1(H1A,H1B,H1C), C9(H9A,H9B,H9C)

2.e C14(H14)

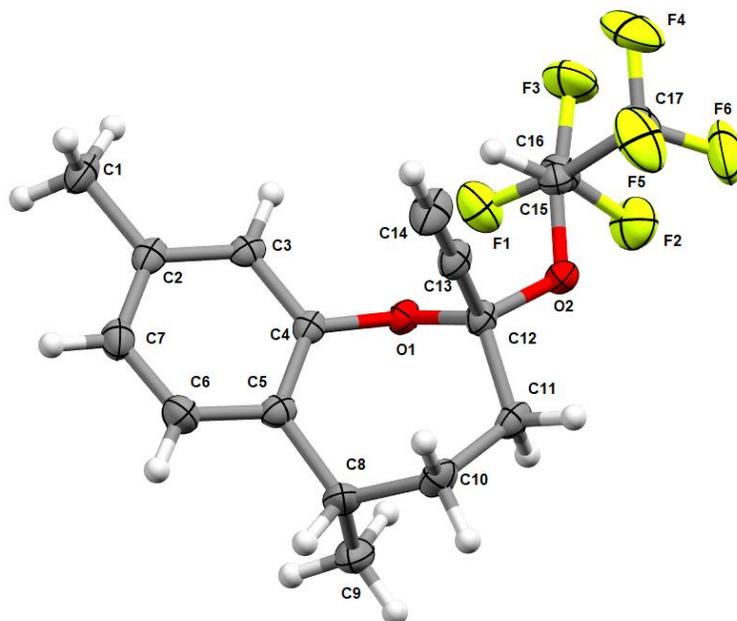


Figure C1. Thermal Ellipsoid plot of 3.137 shown at 50% probability.

Table C1: Crystal data and structure refinement for 3.137

Identification code	3.137
Empirical formula	C ₁₇ H ₁₆ F ₆ O ₂
Formula weight	366.3
Temperature/K	99.95
Crystal system	monoclinic
Space group	P2 ₁ /c
a/Å	10.4274(8)
b/Å	16.3181(12)
c/Å	9.8767(7)
α/°	90

$\beta/^\circ$	93.221(2)
$\gamma/^\circ$	90
Volume/ \AA^3	1677.9(2)
Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.45
μ/mm^{-1}	0.138
F(000)	752
Crystal size/ mm^3	$0.072 \times 0.066 \times 0.054$
Radiation	MoK α ($\lambda = 0.71073$)
2Θ range for data collection/ $^\circ$	3.912 to 55.726
Index ranges	$-13 \leq h \leq 13, -21 \leq k \leq 21, -12 \leq l \leq 12$
Reflections collected	15788
Independent reflections	3989 [$R_{\text{int}} = 0.0297, R_{\text{sigma}} = 0.0306$]
Data/restraints/parameters	3989/0/228
Goodness-of-fit on F^2	1.017
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0467, wR_2 = 0.0976$
Final R indexes [all data]	$R_1 = 0.0724, wR_2 = 0.1086$
Largest diff. peak/hole / $e \text{\AA}^{-3}$	0.37/-0.24

Table C2: Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 3.137

U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij} tensor

Atom	x	y	z	$U(\text{eq})$
------	---	---	---	----------------

O1	1945.4(10)	5504.1(7)	2278.1(11)	21.2(3)
O2	2958.4(12)	6469.5(7)	1081.3(11)	25.4(3)
F1	723.9(11)	7084.8(7)	2320.1(13)	43.1(3)
F2	1347.1(13)	7747.5(8)	600.5(12)	48.8(3)
F3	1682.0(14)	8239.9(7)	2609.5(14)	54.0(4)
F6	5171.1(13)	7270.8(9)	1763.2(17)	64.4(4)
F5	3909.5(15)	8072.3(9)	591.0(15)	66.9(4)
F4	4214.9(16)	8250.0(10)	2720.6(17)	76.0(5)
C3	1726.2(15)	5053.5(11)	4528.5(16)	22.1(4)
C4	1947.7(15)	4849.2(10)	3193.8(16)	20.5(3)
C12	3091.4(15)	5652.2(11)	1583.4(16)	22.3(4)
C2	1611.4(15)	4447.2(12)	5503.2(16)	25.0(4)
C5	2072.6(16)	4038.5(11)	2779.7(17)	24.7(4)
C13	4227.9(16)	5568.0(12)	2540.6(17)	27.2(4)
C11	3143.2(16)	5126.1(11)	322.0(16)	26.1(4)
C7	1737.3(18)	3635.3(12)	5104.1(18)	30.1(4)
C15	2956.4(18)	7109.4(11)	2037.6(17)	27.5(4)
C10	3311.4(18)	4215.5(11)	613.8(18)	29.5(4)
C1	1378.5(18)	4662.8(13)	6955.8(17)	32.5(4)
C6	1972.5(19)	3440.3(12)	3776.1(19)	31.5(4)
C8	2216.7(19)	3783.8(11)	1313.2(18)	30.7(4)
C16	1667(2)	7547.5(12)	1886(2)	34.5(4)

C14	5106.6(18)	5500.0(14)	3339(2)	37.5(5)
C17	4072(2)	7680.6(14)	1772(2)	43.1(5)
C9	931(2)	3844.4(13)	510.0(19)	40.7(5)

Table C3: Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 3.137

The Anisotropic displacement factor exponent takes the form: -

$$2\pi^2[h^2a^2U_{11}+2hka*b*U_{12}+...]$$

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
O1	17.8(6)	26.6(6)	19.4(6)	0.3(5)	2.9(4)	1.4(5)
O2	29.3(7)	27.8(7)	19.0(6)	0.5(5)	0.2(5)	-2.4(5)
F1	32.7(6)	34.9(6)	62.3(8)	2.2(6)	9.2(6)	1.1(5)
F2	54.9(8)	46.6(7)	43.6(7)	10.6(6)	-8.5(6)	9.3(6)
F3	69.0(9)	31.1(7)	62.7(8)	-14.5(6)	10.3(7)	0.4(6)
F6	34.6(7)	63.6(9)	95.3(11)	13.4(8)	6.4(7)	-19.3(7)
F5	70.0(10)	68.9(10)	61.6(9)	30.8(8)	2.2(7)	-30.7(8)
F4	80.3(11)	64.2(10)	82.9(11)	-25.6(9)	-1.2(9)	-42.8(9)
C3	16.1(8)	28.4(9)	21.7(8)	-2.8(7)	-1.3(6)	0.0(7)
C4	14.2(7)	27.7(9)	19.3(8)	1.1(7)	-0.6(6)	-0.4(6)
C12	18.2(8)	28.1(9)	20.9(8)	1.4(7)	2.0(6)	-1.1(7)
C2	16.6(8)	37.7(10)	20.4(8)	1.8(7)	-1.3(6)	-3.2(7)
C5	21.7(8)	29.4(9)	23.2(8)	-3.2(7)	1.5(7)	-1.1(7)
C13	20.6(9)	36.7(10)	24.6(8)	2.0(8)	3.9(7)	-2.4(7)

C11	21.4(8)	38.3(10)	18.8(8)	-0.9(7)	3.6(7)	1.2(7)
C7	30.5(10)	32.6(10)	27.0(9)	6.8(8)	0.6(7)	-4.0(8)
C15	33.1(10)	27.1(9)	22.1(8)	0.4(7)	-1.2(7)	-7.1(8)
C10	32.4(10)	33.1(10)	23.8(8)	-3.7(8)	6.5(7)	6.3(8)
C1	31.4(10)	46.5(12)	19.7(8)	2.0(8)	1.6(7)	-3.6(9)
C6	37.1(11)	25.4(9)	32.0(10)	0.1(8)	1.3(8)	-1.1(8)
C8	41.9(11)	25.6(9)	24.9(9)	-5.0(7)	5.6(8)	-2.2(8)
C16	42.3(11)	26.1(10)	35.0(10)	-1.1(8)	2.6(9)	-2.7(8)
C14	21.4(9)	59.0(13)	31.5(10)	5.3(10)	-2.8(8)	-3.1(9)
C17	43.8(13)	41.3(12)	43.8(12)	1.4(10)	-2.0(10)	-17.0(10)
C9	49.0(13)	47.7(13)	25.2(10)	-3.0(9)	-0.4(9)	-19.4(10)

Table C4: Bond Lengths for 3.3137

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C4	1.4000(19)	C12	C13	1.480(2)
O1	C12	1.4315(19)	C12	C11	1.516(2)
O2	C12	1.427(2)	C2	C7	1.391(3)
O2	C15	1.408(2)	C2	C1	1.510(2)
F1	C16	1.330(2)	C5	C6	1.394(3)
F2	C16	1.335(2)	C5	C8	1.522(2)
F3	C16	1.336(2)	C13	C14	1.180(3)
F6	C17	1.328(3)	C11	C10	1.522(3)
F5	C17	1.333(3)	C7	C6	1.385(3)

F4	C17	1.322(3)	C15	C16	1.523(3)
C3	C4	1.392(2)	C15	C17	1.525(3)
C3	C2	1.390(2)	C10	C8	1.538(3)
C4	C5	1.393(2)	C8	C9	1.522(3)

Table C5: Bond Angles for 3.137

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C4	O1	C12	117.86(12)	O2	C15	C16	108.47(14)
C15	O2	C12	117.63(12)	O2	C15	C17	107.96(15)
C2	C3	C4	120.71(16)	C16	C15	C17	111.96(16)
C3	C4	O1	115.77(14)	C11	C10	C8	116.86(15)
C3	C4	C5	121.94(15)	C7	C6	C5	122.13(17)
C5	C4	O1	122.14(14)	C5	C8	C10	114.68(15)
O1	C12	C13	109.76(13)	C5	C8	C9	110.30(16)
O1	C12	C11	111.55(13)	C9	C8	C10	112.99(15)
O2	C12	O1	104.89(13)	F1	C16	F2	107.20(16)
O2	C12	C13	111.56(14)	F1	C16	F3	107.12(16)
O2	C12	C11	104.53(13)	F1	C16	C15	111.51(15)
C13	C12	C11	114.08(15)	F2	C16	F3	107.26(16)
C3	C2	C7	117.95(16)	F2	C16	C15	112.35(16)
C3	C2	C1	121.11(17)	F3	C16	C15	111.13(16)
C7	C2	C1	120.94(16)	F6	C17	F5	107.62(19)

C4	C5	C6	116.47(16)	F6	C17	C15	111.13(18)
C4	C5	C8	123.68(16)	F5	C17	C15	112.52(17)
C6	C5	C8	119.71(16)	F4	C17	F6	107.21(18)
C14	C13	C12	177.77(19)	F4	C17	F5	106.67(19)
C12	C11	C10	113.97(14)	F4	C17	C15	111.40(18)
C6	C7	C2	120.79(17)				

Table C6: Hydrogen Atom Coordinates ($\text{\AA}\times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2\times 10^3$) for 3.137

Atom	<i>x</i>	<i>y</i>	<i>Z</i>	U(eq)
H3	1652.7	5613.39	4776.32	27
H11A	3864.75	5315.15	-208.52	31
H11B	2339.83	5206.6	-245.1	31
H7	1661.06	3209.24	5750.18	36
H15	3076.82	6876.77	2972.78	33
H10A	4111.82	4142.69	1188.97	35
H10B	3432.87	3932.36	-256.18	35
H1A	2165.87	4569.26	7523.89	49
H1B	687.61	4318.43	7276.02	49
H1C	1130.85	5240.71	7010.3	49
H6	2068.75	2880.73	3536.31	38
H8	2443.23	3188.3	1339.37	37

H14	5814.22	5445.31	3981.11	45
H9A	303.07	3490.06	924.58	61
H9B	1033.32	3669.29	-426.81	61
H9C	627.93	4412.87	515.35	61

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K. & Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339-341.
2. Bourhis, L.J., Dolomanov, O.V., Gildea, R.J., Howard, J.A.K., Puschmann, H. *Acta Cryst.* **2015**, *A71*, 59-75.
3. Sheldrick, G.M. *Acta Cryst.* **2008**, *A64*, 112-122.

This report has been created with Olex2, compiled on 2018.05.29 svn.r3508 for OlexSys.

C9: CRYSTAL REPORT FOR 3.2

Experimental:

Single crystals of $C_{15}H_{22}O_3$ [3.2] were selected using a MiTeGen loop and were run on a 'Bruker APEX-II CCD' diffractometer. The crystal was kept at 100.01 K during data collection. Using Olex2¹ the structure was solved with the olex2.solve² structure solution program using Charge Flipping and refined with the XL³ refinement package using Least Squares minimisation.

Crystal structure determination of [3.2]

Crystal Data for $C_{15}H_{22}O_3$ ($M = 250.32$ g/mol): orthorhombic, space group $Pna2_1$ (no. 33), $a = 9.6279(7)$ Å, $b = 16.0801(13)$ Å, $c = 8.7270(7)$ Å, $V = 1351.09(18)$ Å³, $Z = 4$, $T = 100.01$ K, $\mu(\text{MoK}\alpha) = 0.084$ mm⁻¹, $D_{\text{calc}} = 1.231$ g/cm³, 23618 reflections measured ($4.932^\circ \leq 2\Theta \leq 56.004^\circ$), 3260 unique ($R_{\text{int}} = 0.0366$, $R_{\text{sigma}} = 0.0228$) which were used in all calculations. The final R_1 was 0.0332 ($I > 2\sigma(I)$) and wR_2 was 0.0840 (all data).

Refinement model description

Number of restraints - 1, number of constraints - unknown.

Details:

1. Twinned data refinement: Scales: 1.3(11), -0.3(11)
2. Fixed Uiso at 1.2 times of: All C(H) groups, All C(H,H) groups; At 1.5 times of: All C(H,H,H) groups, All O(H) groups
- 3.a Ternary CH refined with riding coordinates: C8(H8), C11(H11)
- 3.b Secondary CH₂ refined with riding coordinates: C10(H10A,H10B), C9(H9A,H9B)
- 3.c Aromatic/amide H refined with riding coordinates: C1(H1A), C4(H4)

3.d Idealised Me refined as rotating group: C13(H13A,H13B,H13C),
C14(H14A,H14B,H14C), C7(H7A,H7B,H7C), C15(H15A,H15B,H15C)

3.e Idealised tetrahedral OH refined as rotating group: O3(H3), O1(H1)

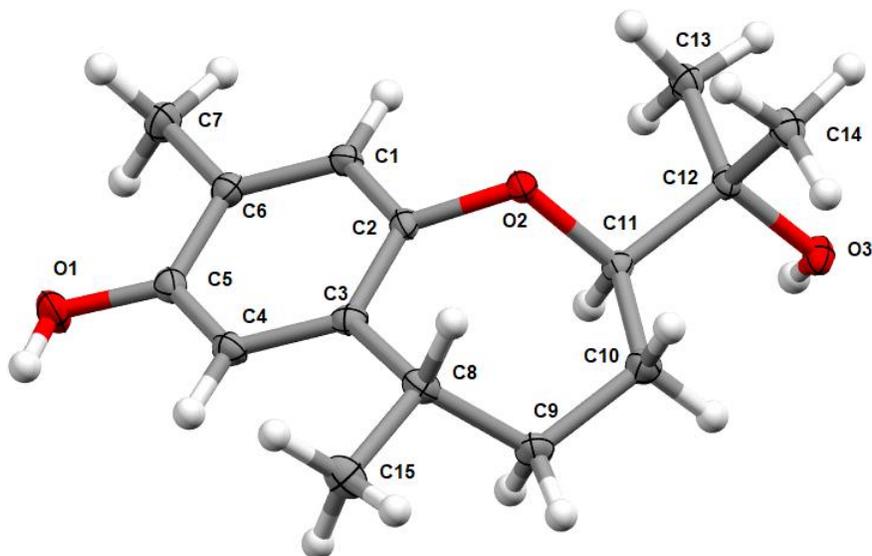


Figure C2: Thermal ellipsoid plot for 3.2 shown at 50% probability

Table C7: Crystal data and structure refinement for 3.2

Identification code	3.2
Empirical formula	C ₁₅ H ₂₂ O ₃
Formula weight	250.32
Temperature/K	100.01
Crystal system	orthorhombic
Space group	Pna2 ₁
a/Å	9.6279(7)
b/Å	16.0801(13)
c/Å	8.7270(7)

$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
Volume/ \AA^3	1351.09(18)
Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.231
μ/mm^{-1}	0.084
F(000)	544.0
Crystal size/ mm^3	$0.094 \times 0.05 \times 0.044$
Radiation	MoK α ($\lambda = 0.71073$)
2 Θ range for data collection/ $^\circ$	4.932 to 56.004
Index ranges	$-12 \leq h \leq 10, -21 \leq k \leq 21, -11 \leq l \leq 11$
Reflections collected	23618
Independent reflections	3260 [$R_{\text{int}} = 0.0366, R_{\text{sigma}} = 0.0228$]
Data/restraints/parameters	3260/1/170
Goodness-of-fit on F^2	1.054
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0332, wR_2 = 0.0816$
Final R indexes [all data]	$R_1 = 0.0376, wR_2 = 0.0840$
Largest diff. peak/hole / $e \text{\AA}^{-3}$	0.28/-0.19
Flack parameter	-0.3(11)

Table C8: Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 3.2

U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij} tensor

Atom	x	y	z	$U(\text{eq})$
O3	6889.0(13)	1687.8(8)	8145.9(16)	16.0(3)
O2	3712.1(13)	2408.4(8)	6260.6(15)	14.5(3)
O1	2796.7(16)	4051.1(8)	799.8(16)	22.0(3)
C5	3021(2)	3611.3(12)	2121(2)	16.0(4)
C2	3508.1(18)	2793.1(11)	4841(2)	13.7(4)
C3	3070.7(19)	2323.5(12)	3592(2)	14.3(4)
C8	2909(2)	1385.1(12)	3787(2)	15.9(4)
C11	5011.7(19)	1947.0(11)	6368(2)	13.6(3)
C1	3703.7(19)	3646.9(12)	4748(2)	15.6(4)
C12	5523.7(17)	2053.7(11)	8036(2)	13.7(4)
C4	2826.4(18)	2751.2(13)	2227(2)	15.9(4)
C6	3467.0(19)	4070.2(11)	3388(2)	16.4(4)
C13	5621(2)	2975.0(12)	8432(2)	17.6(4)
C14	4634.0(19)	1591.1(13)	9194(2)	18.2(4)
C10	4786(2)	1055.8(12)	5846(2)	17.7(4)
C9	4320(2)	971.5(11)	4171(2)	18.5(4)
C7	3683(2)	4995.4(12)	3269(2)	21.3(4)
C15	2231(2)	956.5(13)	2411(2)	21.6(4)

Table C9: Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 3.2

The Anisotropic displacement factor exponent takes the form: -

$$2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\dots]$$

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
O3	12.0(6)	20.2(7)	15.8(7)	4.6(5)	0.3(5)	1.6(5)
O2	14.0(6)	17.7(6)	11.8(6)	0.7(5)	-0.1(5)	2.4(5)
O1	33.0(8)	18.4(7)	14.6(7)	0.7(5)	-6.5(6)	-1.4(6)
C5	15.0(9)	19.3(10)	13.8(9)	0.7(7)	-0.8(6)	2.4(7)
C2	11.2(8)	18.7(9)	11.3(8)	1.5(7)	0.7(6)	3.1(7)
C3	11.4(8)	15.9(8)	15.7(9)	-2.2(7)	2.2(7)	0.1(7)
C8	18.0(9)	15.9(9)	13.8(9)	-0.7(7)	1.0(7)	-2.7(7)
C11	11.7(7)	16.1(8)	12.9(8)	0.7(7)	0.6(6)	2.0(7)
C1	16.0(8)	16.3(9)	14.4(9)	-3.8(7)	-1.2(7)	2.2(7)
C12	11.8(8)	16.5(9)	12.9(8)	1.7(7)	-0.9(7)	1.5(7)
C4	15.7(8)	18.3(9)	13.8(8)	-3.1(7)	-1.5(7)	-0.4(7)
C6	15.2(9)	16.1(9)	18.1(9)	-0.7(8)	-0.7(7)	3.2(7)
C13	18.7(9)	18.2(9)	15.8(10)	-1.0(8)	-4.2(7)	0.3(7)
C14	17.1(9)	22.0(10)	15.3(9)	2.8(8)	1.2(7)	-1.5(7)
C10	20.1(9)	16.2(9)	16.9(9)	-0.7(8)	-2.3(7)	1.5(7)
C9	23.4(9)	14.2(9)	18.0(9)	-2.3(8)	-1.5(7)	0.9(7)
C7	28.1(10)	15.9(9)	20.0(10)	0.2(8)	-4.3(8)	2.1(8)

C15	22.9(9)	22.4(10)	19.6(10)	-1.5(8)	-1.9(8)	-7.2(8)
-----	---------	----------	----------	---------	---------	---------

Table C10: Bond Lengths for 3.2

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O3	C12	1.443(2)	C8	C9	1.550(3)
O2	C2	1.399(2)	C8	C15	1.530(3)
O2	C11	1.458(2)	C11	C12	1.547(2)
O1	C5	1.370(2)	C11	C10	1.519(3)
C5	C4	1.399(3)	C1	C6	1.388(3)
C5	C6	1.397(3)	C12	C13	1.524(3)
C2	C3	1.391(2)	C12	C14	1.519(2)
C2	C1	1.388(3)	C6	C7	1.506(3)
C3	C8	1.527(3)	C10	C9	1.535(3)
C3	C4	1.396(3)			

Table C11: Bond Angles for 3.2

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C2	O2	C11	113.74(13)	C10	C11	C12	115.62(15)
O1	C5	C4	123.02(17)	C6	C1	C2	120.83(16)
O1	C5	C6	116.22(16)	O3	C12	C11	107.90(14)
C6	C5	C4	120.76(17)	O3	C12	C13	108.99(14)

C3	C2	O2	119.76(16)	O3	C12	C14	105.66(14)
C1	C2	O2	118.01(16)	C13	C12	C11	109.90(14)
C1	C2	C3	122.18(16)	C14	C12	C11	113.07(15)
C2	C3	C8	118.71(16)	C14	C12	C13	111.12(16)
C2	C3	C4	116.89(17)	C3	C4	C5	121.39(17)
C4	C3	C8	124.39(16)	C5	C6	C7	120.67(17)
C3	C8	C9	111.01(15)	C1	C6	C5	117.94(17)
C3	C8	C15	113.67(16)	C1	C6	C7	121.39(17)
C15	C8	C9	110.53(16)	C11	C10	C9	114.24(15)
O2	C11	C12	106.12(14)	C10	C9	C8	115.15(16)
O2	C11	C10	109.77(15)				

Table C12: Hydrogen Atom Coordinates ($\text{\AA}\times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2\times 10^3$) for 3.2.

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U(eq)
H3	7457	1976	7643	24
H1	2481	3732	123	33
H8	2284	1294	4687	19
H11	5704	2213	5668	16
H1A	4003	3945	5628	19
H4	2522	2452	1350	19
H13A	6083	3041	9425	26

H13B	4685	3213	8484	26
H13C	6158	3264	7640	26
H14A	4727	991	9029	27
H14B	3660	1754	9066	27
H14C	4941	1730	10233	27
H10A	4077	796	6513	21
H10B	5664	743	5984	21
H9A	4260	373	3916	22
H9B	5043	1219	3506	22
H7A	4213	5122	2339	32
H7B	4197	5192	4168	32
H7C	2779	5275	3223	32
H15A	1339	1224	2186	32
H15B	2077	368	2648	32
H15C	2842	1003	1517	32

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K. & Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339-341.
2. Bourhis, L.J., Dolomanov, O.V., Gildea, R.J., Howard, J.A.K., Puschmann, H. *Acta Cryst.* **2015**, *A71*, 59-75.
3. Sheldrick, G.M. *Acta Cryst.* **2008**, *A64*, 112-122.

APPENDIX D: TOTAL SYNTHESIS OF HELIANNUOL A

D1: GENERAL INFORMATION

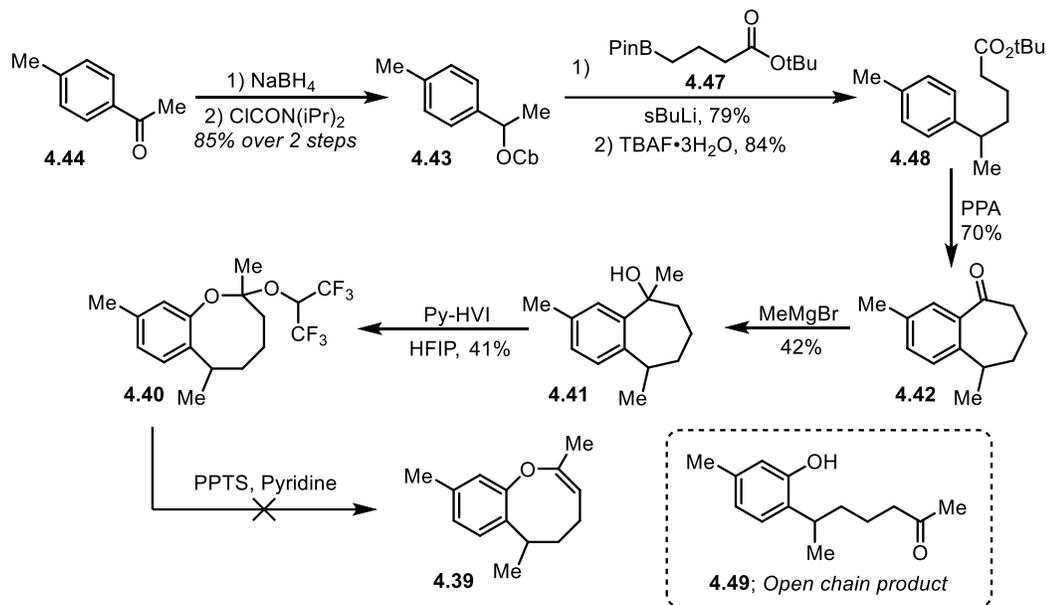
^1H and ^{13}C NMR spectra were recorded at 500 MHz and 126 MHz on a Bruker Advance 500, 500 MHz and 126 MHz on a Bruker Advance III HD, or 400 MHz and 101 MHz on a Bruker Advance 400. ^1H NMR chemical shifts were reported in part per million (ppm) from the solvent resonance (CDCl_3 7.26 ppm or $\text{DMSO-}d_6$). The data was reported as follows: chemical shift number, multiplicity (s = singlet, d = doublet, t = triplet, s = septet, dd = doublet of doublets, td = triplet of doublets, m = multiplet, br = broad signal). Proton decoupled attached proton test (APT) ^{13}C NMR shifts were reported in ppm from the solvent resonance (CDCl_3 77.16 ppm). The glovebox used is a Vacuum Atmospheres NexGen system with a maximum humidity of 0.05% (500 ppm). The reaction solvents used were anhydrous (HPLC-grade solvent passed through an activated-alumina column) unless otherwise noted. 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) was purchased from Oakwood Chemical, distilled over CaH_2 and stored over activated 3 Å molecular sieves under an atmosphere of argon.

Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was purchased from Oakwood Chemical, distilled over CaH_2 and stored over activated 3 Å molecular sieves under an atmosphere of argon. Pyridine was purchased from Sigma Alrich (now Millipore Sigma), distilled over CaH_2 , and stored over activated 3 Å molecular sieves under an atmosphere of argon. Diisopropylamine [(iPr) $_2$ NH] was purchased from Oakwood Chemical and freshly distilled over CaH_2 prior to use. *N*-bromosuccinimide

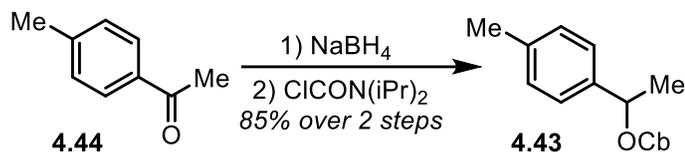
(NBS) was purchased from Oakwood Chemical and recrystallized from water prior to use. Septum sealed bottles of anhydrous butyllithium reagents were purchased from Sigma Aldrich and used without further purification. All deuterated solvents were purchased from Cambridge Isotope Laboratories (CIL) and stored over activated 5 Å molecular sieves. All other reagents were purchased from Sigma-Aldrich (now Millipore Sigma), Fisher Chemical, and Oakwood Chemical, and used without further purification. [(pyridine)₂I⁺Ph] 2OTf⁻, [(2-methoxypyridine)₂I⁺Ph] 2OTf⁻, and [(4-dimethylaminopyridine)₂I⁺Ph] 2OTf⁻ were synthesized (See Appendix A) and used without further purification.

Flash chromatography was carried out using Sorbent Technologies silica gel 60 Å (40–63 µm) in the solvent system listed in the individual experiments. Reactions were monitored using analytical thin-layer chromatography (TLC) on Merck silica gel (60 F254) plates. GCMS analysis was performed using an Agilent 7980B GC/5977A MS. The products were separated using a J&W CycloSil-B GC Column (30% Heptakis (2,3-di-O-methyl-6-O-t-butyl dimethylsilyl)-β-cyclodextrin in DB-1701; 30 m length, 25 mm ID, 0.25 µm Film Thickness). Experiment parameters are listed for each individual separation. Accurate masses for derivatized products were conducted on an Agilent 6520 Accurate-Mass Q-TOF LC/MS. Samples were taken up in a suitable solvent for analysis. The signals were mass measured against an internal lock mass reference of perfluorotributylamine (PFTBA) for EI-GCMS, and leucine enkephalin for ESI-LCMS. Waters software calibrates the instruments, and reports measurements, by use of neutral atomic masses. The mass of the electron is not included. Melting points were obtained on a Stanford Research Systems MPA100 OptiMelt Automated Melting Point System and are uncorrected.

D2: INITIAL RACEMIC EFFORTS ON DES-MEO SUBSTRATE



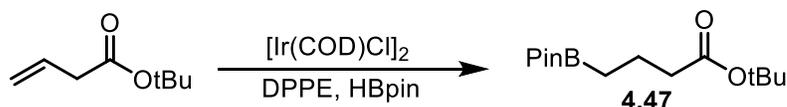
1-(p-tolyl)ethyl diisopropylcarbamate (4.43)



To a stirred solution of acetophenone **4.44** (8.0 g, 58.7 mmol, 1.0 equiv.) methanol (75 mL) was added sodium borohydride (2.48 g, 65.6 mmol, 1.1 equiv.). Following the addition of NaBH₄, the reaction began bubbling vigorously and continued for several minutes. Once bubbling ceased, the reaction was checked by TLC which showed complete consumption of starting material. Thus, the reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (3x). The combined organic extracts were washed with brine then dried over sodium sulfate and concentrated. The crude residue was then diluted with DCM in the same flask, and DCM (200 mL) was added. Diisopropylcarbamoyl chloride (11.5 g, 70.5 mmol, 1.2 equiv.) was added along with triethylamine (10 mL, 70.5 mmol, 1.2 equiv.). The flask was sealed with electrical tape and placed in a 50 °C bath to stir for 48 hours. After which, the

mixture was allowed to cool to ambient temperature before quenching with aqueous 1 M HCl. The mixture was transferred to a separatory funnel and extracted with DCM (3x). The combined organic extracts were dried over sodium sulfate and concentrated to reveal the product as a colorless oil. **Yield:** 13.1g, 85%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.28 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 7.8 Hz, 2H), 5.83 (q, J = 6.6 Hz, 1H), 2.35 (s, 3H), 1.55 (d, J = 6.6 Hz, 3H), 1.31 – 1.16 (m, 12H). **¹³C NMR** (126 MHz, CDCl₃) δ 155.2, 134.0, 137.1, 129.1, 126.1, 72.7, 22.9, 21.2. **HRMS** (ESI) m/z calculated for C₁₆H₂₅NO₂⁺ 263.1885; found 286.1795 (M+Na)⁺.

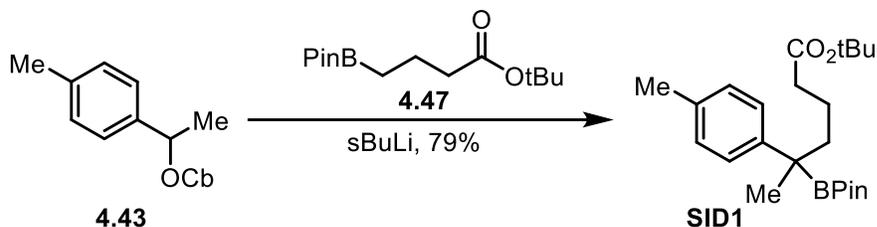
tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (4.47)



In a flame-dried round-bottomed flask, a mixture of [Ir(COD)Cl]₂ (189 mg, 0.28 mmol, 0.8 mol %) and 1,2-bis(diphenylphosphino)ethane (DPPE; 411 mg, 1.06 mmol, 3 mol %) was thoroughly degassed via iterative pump/purge cycles with argon. DCM (64 mL) was added and the resulting brightly-colored solution was cooled to 0 °C. *Tert*-butyl vinylacetate (5.7 mL, 35.2 mmol, 1.0 equiv.) was added and the mixture stirred for 5 minutes, followed by the dropwise addition of pinacolborane (7.66 mL, 52.8 mmol, 1.5 equiv.) over a period of 5 minutes. The reaction was then allowed to stir for 12 hours while warming to ambient temperature. Once complete, the reaction was diluted with water and stirred until bubbling ceased. After transferring to a separatory funnel, the solution was extracted with EtOAc (3x), and the combined organic extracts were washed with brine then dried over sodium sulfate. The crude material was purified via column chromatography (7% EtOAc/Hexanes) to afford the desired product as a colorless oil. **Yield:** 7.5 g, 78%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 2.18 (t, J = 7.6 Hz, 2H), 1.66

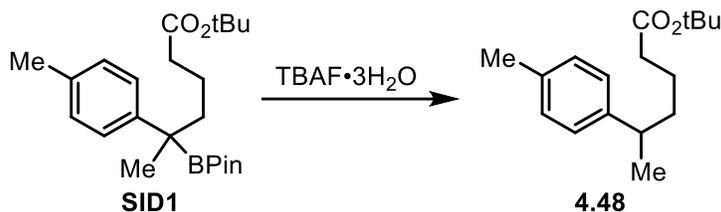
(p, $J = 7.7$ Hz, 2H), 1.40 (s, 9H), 1.21 (s, 12H), 0.76 (t, $J = 7.9$ Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.18, 83.07, 79.88, 37.95, 28.22, 27.68, 24.90, 19.87.

tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(p-tolyl)hexanoate (SID1)^{1,2}



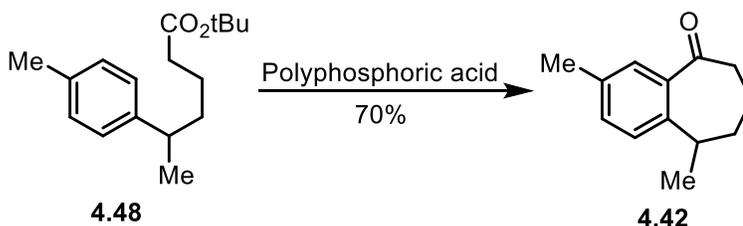
Carbamate **4.43** (2.8 g, 10.6 mmol, 1.0 equiv.) was dissolved in 43 mL of diethyl ether, and the solution was cooled to -78 °C in a dry ice/acetone bath. After a few minutes at this temperature, $s\text{-BuLi}$ (9.1 mL, 12.8 mmol, 1.2 equiv.) was added dropwise over a period of 5 minutes, and the resultant solution was stirred for 30 minutes. A solution of boronic ester **4.47** (3.3 g, 12.8 mmol, 1.2 equiv.) in 27 mL Et_2O was added dropwise over a period of 5 minutes and stirred for 30 minutes at -78 °C, then 6 hours at room temperature. The reaction was then cooled to 0 °C and quenched by the addition of 1M KHSO_4 slowly. The mixture was allowed to warm to room temperature and stir for an additional 10 mins. Extraction with Et_2O (3x) and drying over Na_2SO_4 afforded the crude oil, which was subjected to flash chromatography (0 \rightarrow 5% Et_2O /pentane) to afford the desired product as a colorless oil. **Yield:** 3.26 g, 79%. ^1H NMR (400 MHz, Chloroform- d) δ 7.22 – 7.11 (m, 2H), 7.07 (d, 2H), 2.29 (s, 3H), 2.26 – 2.10 (m, 2H), 1.78 (ddd, $J = 12.8, 11.9, 4.8$ Hz, 1H), 1.72 – 1.56 (m, 1H), 1.58 – 1.47 (m, 1H), 1.42 (s, 9H), 1.32 (s, 3H), 1.19 (d, $J = 4.3$ Hz, 12H).

tert-butyl 5-(p-tolyl)hexanoate (**4.48**)³



To a flame dried flask containing a mixture of boronic ester **SID1** (3.26 g, 8.39 mmol, 1.0 equiv.) was added toluene (56 mL), followed by TBAF·3H₂O (2.91 g, 9.23 mmol, 1.1 equiv.). The mixture was heated to 50°C and stirred overnight. The solution was then cooled to room temperature and quenched with water. The aqueous phase was extracted with Et₂O (3x) and the combined organic phases were dried over Na₂SO₄ and concentrated. The resulting oil was purified by flash chromatography (5% Et₂O/pentane) to afford the desired product as a colorless oil. **Yield:** 1.84 g, 84% (66% over two steps). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.13 – 7.04 (m, 4H), 2.66 (q, *J* = 6.8 Hz, 1H), 2.32 (d, *J* = 1.2 Hz, 3H), 2.21 – 2.14 (m, 2H), 1.45 – 1.40 (m, 9H), 1.22 (d, *J* = 6.9, 0.9 Hz, 3H).

3,9-dimethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (**4.42**)

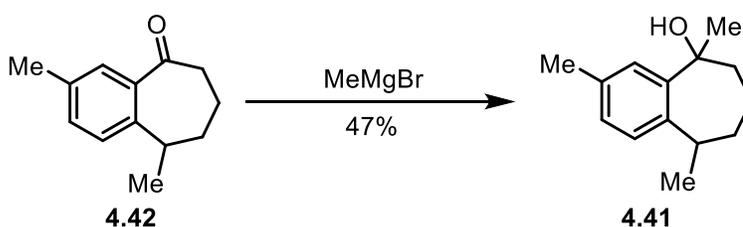


To a flask containing ester **4.48** (1.84 g, 7.1 mmol) was added approximately 8 mL of polyphosphoric acid. The flask was submerged in a pre-heated bath set to 80 °C, and the reaction was stirred slowly for 3 hours. The viscous mixture was then removed from heat and allowed to cool to ambient temperature before the addition of water (40 mL). The material was agitated with a spatula to a point where stirring was feasible, then the cloudy white solution was stirred for 5 minutes. The mixture was transferred to a separatory

funnel along with EtOAc. The organic layer was removed, and the aqueous layer was further extracted with EtOAc (2x). The combined organic extracts were then washed with saturated aqueous sodium bicarbonate (3x), water (1x), and finally brine (1x). The organic solution was dried over sodium sulfate and concentrated, and the crude material was purified via column chromatography to afford the desired product as a yellow oil.

Yield: 930 mg, 70%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.35 (s, 1H), 7.28 (d, *J* = 7.8, 2.1 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 3.13 – 3.03 (m, 1H), 2.76 – 2.67 (m, 1H), 2.65 – 2.51 (m, 1H), 2.34 (s, 3H), 2.02 – 1.89 (m, 1H), 1.92 – 1.81 (m, 1H), 1.68 – 1.46 (m, 2H), 1.36 (d, *J* = 6.9 Hz, 3H).

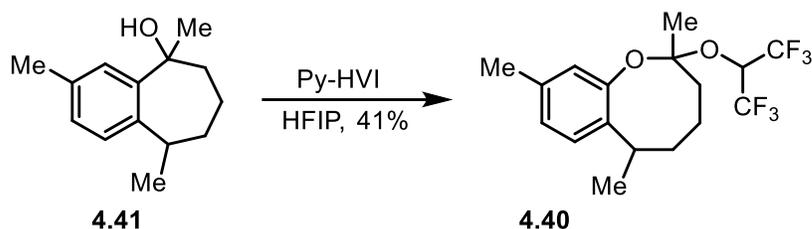
3,5,9-trimethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ol (4.41)



Ketone **4.42** (930 mg, 4.93 mmol, 1.0 equiv.) was added to a flame-dried round-bottomed flask followed by THF (25 mL). The resulting solution was cooled to 0 °C and stirred for 5 minutes, then a solution of methylmagnesium bromide (3.0 M, 9.9 mL, 29.61 mmol, 6.0 equiv.) was added. The resulting solution was allowed to warm to ambient temperature and stir overnight. The following morning, the reaction was cooled to 0 °C and quenched with saturated aqueous ammonium chloride. The mixture was transferred to a separatory funnel along with Et₂O, and the organic layer was removed. The aqueous layer was back-extracted with Et₂O (3x), and the combined organic extracts were dried over sodium sulfate then concentrated. The crude material was purified via column chromatography (10% EtOAc/Hexanes) to afford the desired product as a thick colorless oil. **Yield:** 481 mg, 47%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.61 (s, 1H), 7.12 (d, *J* =

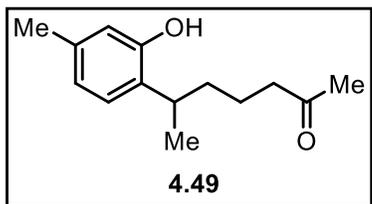
7.8 Hz, 1H), 7.04 (d, 1H), 3.12 – 3.01 (m, 1H), 2.34 (s, 3H), 2.11 – 2.02 (m, 1H), 1.94 – 1.85 (m, 1H), 1.85 – 1.76 (m, 2H), 1.73 – 1.59 (m, 1H), 1.57 (s, 3H), 1.35 (d, $J = 6.9$ Hz, 3H).

2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2,6,9-trimethyl-3,4,5,6-tetrahydro-2H-benzo[b]oxocine (4.40)⁴



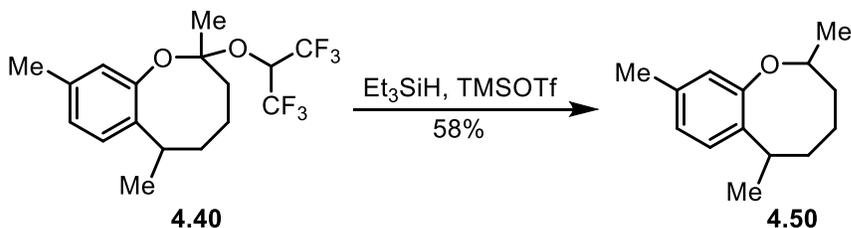
In a flame-dried round-bottomed flask, alcohol **4.41** (481 mg, 2.35 mmol, 1.0 equiv.) was dissolved in DCM (12 mL) in the presence of activated 3 Å MS. The suspension was cooled to -25 °C, then a solution of Py-HVI (1.71 g, 2.59 mmol, 1.1 equiv.; see Appendix A for synthesis) in hexafluoroisopropanol (HFIP; 5.00 mL, 47.0 mmol, 20 equiv.) was added. The reaction was closely monitored by TLC while slowly warming to 0 °C, at which point complete consumption of starting material was observed. The reaction was then concentrated at 0 °C, and the concentrated residue was azeotroped with DCM (3x) to remove residual HFIP. The crude oil was diluted with Et₂O which caused the precipitation of insoluble byproducts. Filtration over celite and concentration, followed by column chromatography (0→5% Et₂O/pentane) afforded HFIP acetal **4.40** (~5:1 *d.r.*) as a colorless oil. **Yield:** 354 mg, 41%. **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.12 (d, $J = 7.9$ Hz, 1.3H), 6.98 (d, $J = 8.1$ Hz, 1.22H), 6.80 (s, 1H, Major), 5.05 (p, $J = 6.1$ Hz, 1H), 4.78 – 4.68 (m, 0.12H, Minor (1H)), 3.25 – 3.17 (m, 1H), 3.00 – 2.95 (m, 0.26H, Minor, 1H), 2.30 (s, 3.28H), 1.95 – 1.78 (m, 2H), 1.75 – 1.68 (m, 0.40H, Minor (2H)), 1.66 – 1.57 (m, 2H), 1.50 (s, 3H), 1.46 – 1.33 (m, 0.44H, Minor (2H)), 1.27 (d, $J = 7.1$ Hz, 4H).

6-(2-hydroxy-4-methylphenyl)heptan-2-one (4.49)



Phenol **4.49** was isolated from a wide variety of elimination attempts (See Chapter 3) and is characterized by proton NMR here: $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.02 (d, $J = 7.7$ Hz, 1H), 6.72 (dd, $J = 7.9, 1.5$ Hz, 1H), 6.58 (dd, $J = 1.6, 0.8$ Hz, 1H), 4.49 – 4.02 (m, 2H), 3.12 – 3.00 (m, 1H), 2.44 (td, $J = 6.7, 2.8$ Hz, 2H), 2.26 (s, 3H), 2.12 (s, 2H), 2.09 – 1.98 (m, 0H), 1.71 – 1.36 (m, 2H), 1.22 (d, $J = 6.9$ Hz, 3H).

2,6,9-trimethyl-3,4,5,6-tetrahydro-2H-benzo[b]oxocine (4.50)⁵ (For one-pot synthesis, see Appendix B)

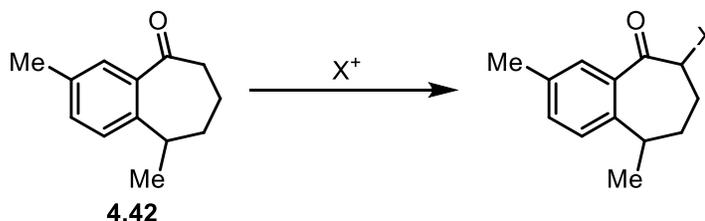


HFIP acetal **4.40** (196 mg, 0.53 mmol, 1.0 equiv.) was added to a flame-dried round-bottomed flask containing activated 3 Å MS in solution with DCM (1.4 mL). HFIP (1.4 mL) was added, and the resulting solution was cooled to 0 °C. Triethylsilane (0.42 mL, 2.65 mmol, 5.0 equiv.) was added, and the solution was stirred for 5 minutes. At which point, TMSOTf (106 μL , 0.58 mmol, 1.1 equiv.) was added. The reaction was stirred for a further 10 minutes then filtered and quenched with saturated aqueous sodium bicarbonate. The product was extracted with DCM (3x), and the combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated.

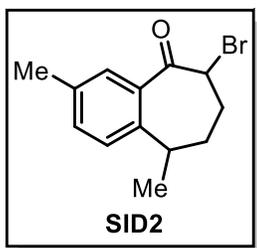
Purification via column chromatography afforded a ~1:1 diastereomeric mixture of ether **4.50**. **Yield:** 63 mg, 58%. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 7.05 (d, $J = 7.7$ Hz, 2H), 6.94 – 6.85 (m, 2H), 6.83 (s, 1H), 6.78 (s, 1H), 4.33 – 4.23 (m, 1H), 3.97 – 3.87 (m, 1H), 3.47 – 3.35 (m, 1H), 3.09 – 2.98 (m, 1H), 2.29 (d, $J = 5.3$ Hz, 6H), 1.89 – 1.46 (m, 9H),

1.41 (d, $J = 6.3$ Hz, 3H), 1.36 (d, $J = 6.6$ Hz, 3H), 1.30 (d, $J = 7.2$ Hz, 3H), 1.27 (d, $J = 7.1$ Hz, 3H).

D3: INSTALLATION OF LEAVING GROUPS ON SUBERONE 4.42



6-bromo-3,9-dimethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (SID2)⁶

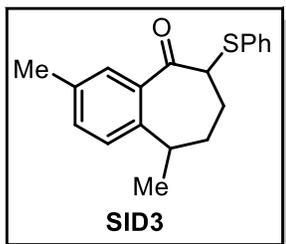


To a 0 °C solution of suberone **4.42** (69 mg, 0.37 mmol, 1.0 equiv.) in Et₂O (500 μL) was added bromine (19 μL). The solution was stirred for 15 minutes at this temperature, at which point TLC indicated complete consumption of starting material.

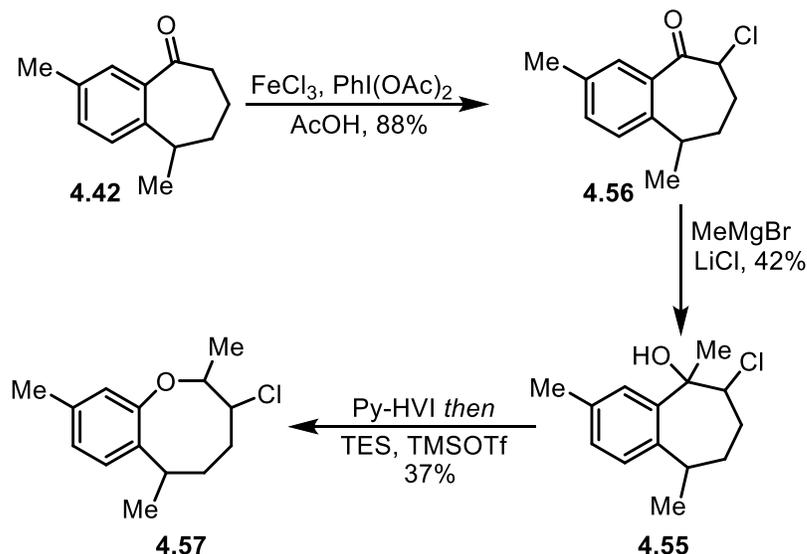
The reaction was quenched with water and extracted with Et₂O (3x), then the combined organic extracts were washed with saturated aqueous sodium thiosulfate (1x) and water (1x), and dried over sodium sulfate. Following concentration, the desired product was afforded as a mixture of diastereomers (~2:1) as a yellow oil.

Yield: 87 mg, 88%. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.22 (m, 3H), 7.20 – 7.08 (m, 2H), 4.81 – 4.78 (m, 0.78H, Major (1H)), 4.73 (dd, $J = 11.1, 3.7$ Hz, 0.35H, Minor (1H)), 3.26 – 3.15 (m, 1H), 3.00 – 2.87 (m, 1H), 2.80 (ddd, $J = 15.3, 4.9, 3.0$ Hz, 1H), 2.68 – 2.51 (m, 1H), 2.48 – 2.26 (m, 8H), 2.30 – 2.15 (m, 1H), 2.19 – 2.00 (m, 1H), 1.75 – 1.59 (m, 1H), 1.42 (d, $J = 9.0$ Hz, 1H), 1.33 (dd, $J = 6.9, 3.2$ Hz, 3H), 1.27 (d, $J = 7.1$ Hz, 2H).

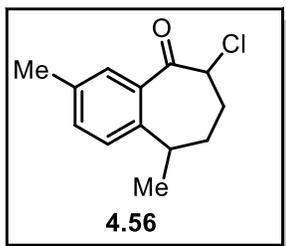
3,9-dimethyl-6-(phenylthio)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (SID3)⁷



In a flame-dried round-bottomed flask, THF (1.4 mL) was added to sodium thiophenoate (50 mg, 0.37 mmol, 1.1 equiv.) and the resulting solution was cooled to 0 °C. A solution of bromoketone **SID2** (90 mg, 0.34 mmol, 1.0 equiv.) in THF (0.5 mL) was added, and the reaction was allowed to stir for 30 minutes while warming to room temperature. Water was then added, followed by ammonium chloride, and the organics were extracted with Et₂O (3x). The combined organic extracts were washed with saturated aqueous ammonium chloride, then dried over sodium sulfate and concentrated. The crude residue was purified via column chromatography (5% EtOAc/Hexanes) to afford the product (5:4 *d.r.*) as a yellow oil. **Yield:** 99 mg, 99%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.47 – 7.34 (m, 4H), 7.36 – 7.18 (m, 7H), 7.12 (t, 3H), 7.06 (s, 1H), 4.25 (dd, *J* = 6.7, 4.6 Hz, 1H, Major), 4.14 (dd, *J* = 11.0, 3.7 Hz, 0.77H, Minor, (1H)), 3.26 – 3.15 (m, 1H), 3.05 – 2.94 (m, 0.80H, Minor (1H)), 2.39 (ddt, *J* = 14.2, 8.2, 4.2 Hz, 1H), 2.32 (s, 2H), 2.30 (s, 3H), 2.26 – 2.14 (m, 1H), 2.08 – 1.82 (m, 3H), 1.76 – 1.62 (m, 2H), 1.32 (d, *J* = 6.9 Hz, 2H), 1.27 (d, *J* = 7.2 Hz, 3H).

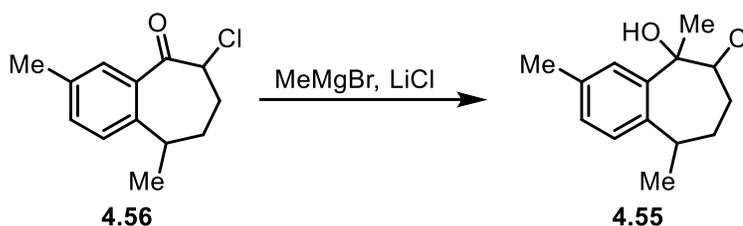


6-chloro-3,9-dimethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (4.56)⁸



A 20 mL vial containing suberone **4.42** (385 mg, 2.04 mmol, 1.0 equiv.) was charged with acetic acid (10.5 mL). $\text{PhI}(\text{OAc})_2$ (789 mg, 2.5 mmol, 1.2 equiv.) and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (1.11 g, 4.09 mmol, 2.0 equiv.) were then added, and the reaction vial was capped and stirred for 36 hours. The reaction mixture was then diluted with water and extracted with Et_2O (3x). The combined organic extracts were washed once each with saturated aqueous sodium bicarbonate, water, and brine, then dried over sodium sulfate and concentrated. The crude material was purified via column chromatography (5% $\text{EtOAc}/\text{Hexanes}$) to afford the product in a 3:1 *d.r.* as a yellow oil. **Yield:** 400 mg, 88%. **$^1\text{H NMR}$** (500 MHz, $\text{Chloroform-}d$) δ 7.29 (s, 0.87H, Major (1H)), 7.26 – 7.23 (m, 1.2H), 7.14 (dd, $J = 10.4, 8.1$ Hz, 1.2H), 4.73 – 4.65 (m, 1.2H), 3.24 – 3.13 (m, 0.32H, Minor (1H)), 3.05 – 2.93 (m, 0.92H, Major (1H)), 2.34 (d, $J = 3.7$ Hz, 3.53H), 2.27 – 2.03 (m, 2.34H), 1.85 – 1.74 (m, 0.90H), 1.72 – 1.62 (m, 0.35H), 1.31 (d, $J = 7.0$ Hz, 3H), 1.28 (d, $J = 7.2$ Hz, 1H).

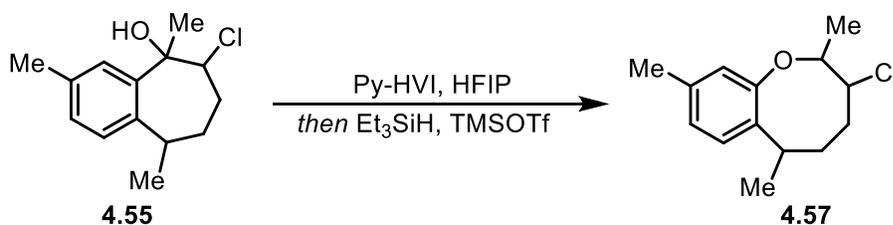
6-chloro-3,5,9-trimethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ol (4.55)



In a flame-dried test tube, α -chlorosuberone **4.56** (92 mg, 0.41 mmol, 1.0 equiv.) was dissolved in THF (2.2 mL) under an argon atmosphere. Anhydrous lithium chloride (53 mg, 1.24 mmol, 3.0 equiv.; dried under vacuum at 200 °C prior to use) was added and the mixture was stirred until homogenous. At which point, the solution was cooled to 0 °C, followed by the addition of methyl Grignard (3 M in Et_2O ; 145 μL , 0.43 mmol, 1.05 equiv.). The reaction was allowed to stir for 4 hours while gradually warming to room

temperature before being slowly quenched with saturated aqueous ammonium chloride. The mixture was then extracted with Et₂O (3x) and the combined organic extracts were dried over sodium sulfate, then concentrated. The crude residue was purified via column chromatography to afford a single diastereomer of chlorohydrin **4.55** as a pale yellow oil. **Yield:** 41 mg, 42%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.59 (s, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.08 (d, 1H), 4.52 (dd, *J* = 4.8, 2.6 Hz, 1H), 3.06 (dq, *J* = 13.5, 7.0 Hz, 1H), 2.93 (q, *J* = 1.3 Hz, 1H), 2.52 – 2.43 (m, 1H), 2.35 (s, 3H), 2.29 – 2.20 (m, 1H), 1.89 – 1.76 (m, 1H), 1.69 (s, 3H), 1.40 (d, *J* = 6.9 Hz, 3H), 1.33 – 1.22 (m, 1H).

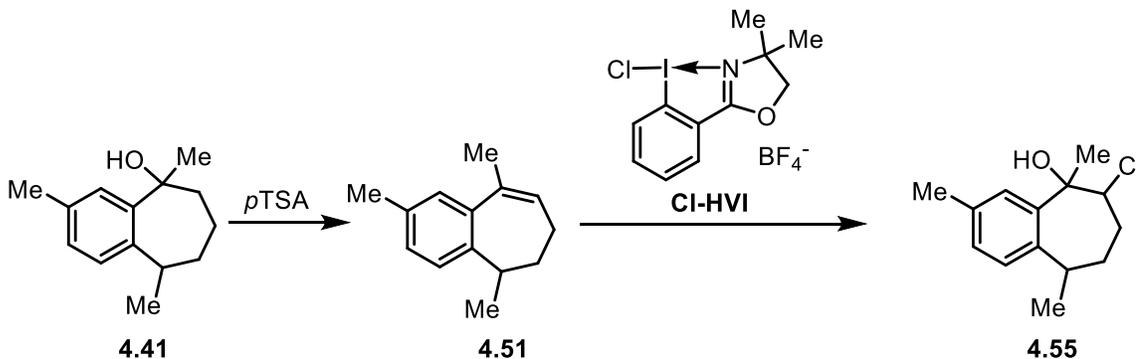
3-chloro-2,6,9-trimethyl-3,4,5,6-tetrahydro-2H-benzo[*b*]oxocine (**4.57**)



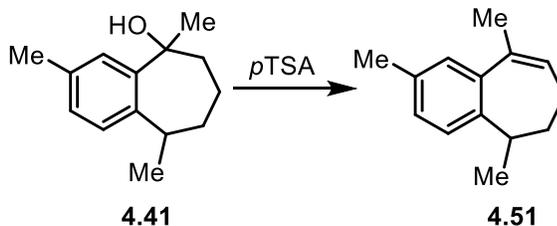
A solution of chlorohydrin **4.55** (35 mg, 0.15 mmol, 1.0 equiv.) in DCM (0.8 mL) was added to a small flame-dried vial containing activated 3 Å MS. The mixture was cooled to –20 °C, then a solution of Py-HVI (145 mg, 0.22 mmol, 1.5 equiv.) in HFIP (0.31 mL, 2.94 mmol, 20 equiv.) was added. The reaction was allowed to stir overnight while gradually warming to room temperature. The following morning, TLC indicated that chlorohydrin **4.55** was fully consumed, therefore the reaction was cooled to 0 °C before triethylsilane (60 μ L, 0.37 mmol, 2.5 equiv.) was added. The solution was stirred, followed by the addition of TMSOTf (27 μ L, 0.15 mmol, 1.0 equiv.). After 5 minutes, the reaction was filtered and quenched with saturated aqueous sodium bicarbonate, then extracted with DCM (3x). The organic extracts were washed with brine (3x) then concentrated and purified via column chromatography (0→5% Et₂O/pentane) to reveal the pale-yellow oily product as a mixture of diastereomers. **Yield:** 13 mg, 37%. **¹H NMR**

(500 MHz, Chloroform-*d*) δ 7.06 (d, $J = 7.8$ Hz, 0.11H), 7.00 (d, $J = 7.8$ Hz, 1H), 6.94 – 6.91 (m, 0.15H), 6.87 (d, $J = 7.9$, 1.7 Hz, 1H), 6.84 (d, $J = 1.6$ Hz, 0.20H), 6.81 (s, 1H), 4.27 – 4.21 (m, 0.88H), 4.17 – 4.11 (m, 1H), 3.98 (ddd, $J = 7.2$, 3.8, 1.9 Hz, 0.13H), 3.88 (dq, $J = 9.3$, 6.1 Hz, 0.13H), 3.76 (t, $J = 9.5$ Hz, 0.12H), 3.44 (tq, $J = 12.4$, 6.6 Hz, 0.16H), 2.97 – 2.87 (m, 1H), 2.83 (q, $J = 7.3$ Hz, 0.12H), 2.56 – 2.49 (m, 0.10H), 2.32 (s, 0.38H), 2.29 (s, 3H), 2.02 – 1.91 (m, 1H), 1.81 – 1.72 (m, 0.84H), 1.63 (d, $J = 6.1$ Hz, 0.40H), 1.52 (d, $J = 6.5$ Hz, 3H), 1.33 (d, $J = 7.1$ Hz, 0.31H), 1.29 (d, $J = 7.1$ Hz, 3H).

D4: INVESTIGATIONS WITH STYRENE 4.51



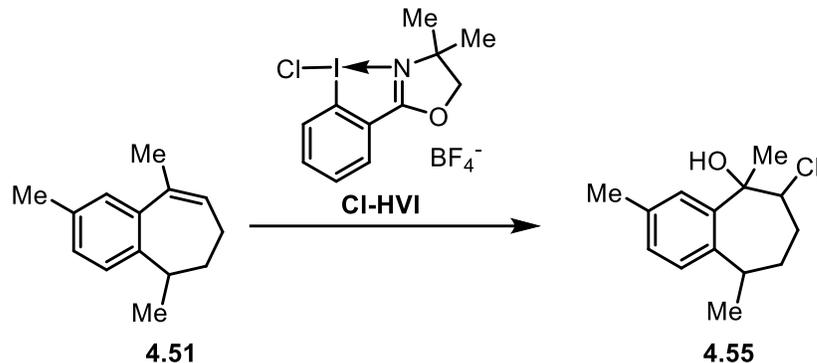
2,5,9-trimethyl-6,7-dihydro-5H-benzo[7]annulene (4.51)



Alcohol **4.41** (323 mg, 1.58 mmol, 1.0 equiv) was added to a 20 mL vial followed by methanol (4 mL). *Para*-toluenesulfonate (15 mg, 0.08 mmol, 5 mol %) was added, then the reaction vial was sealed and warmed to 65 °C with stirring for 3 hours. Once complete, the reaction was quenched with water, and the mixture was extracted with Et₂O

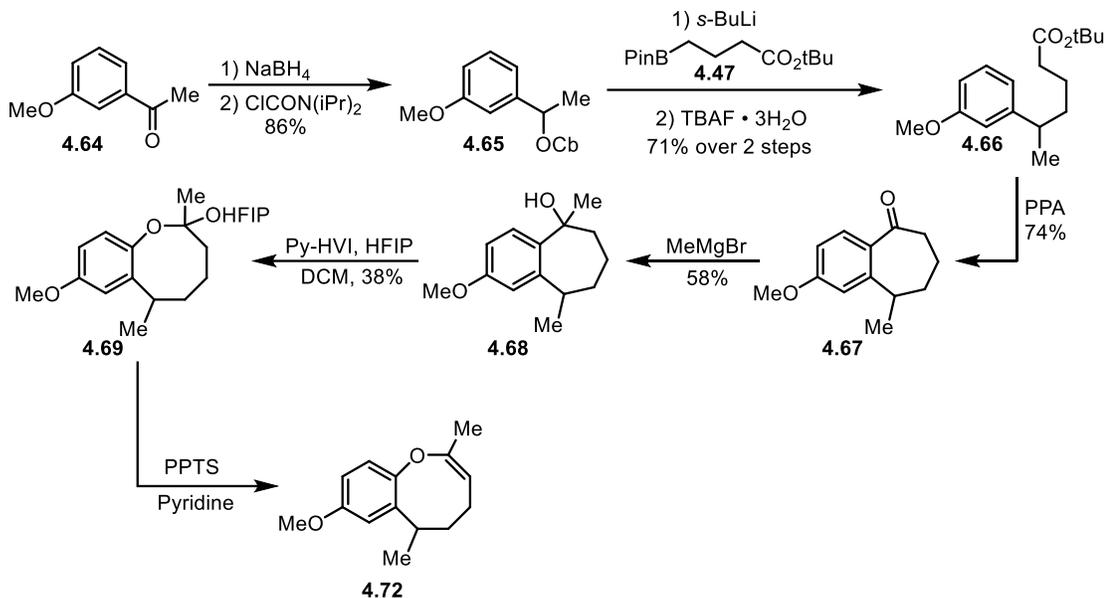
(3x). The combined organic extracts were dried over sodium sulfate and concentrated, then purified via column chromatography (5% Et₂O/pentane) to afford the product as a colorless oil. Varying ratios of endo/exocyclic olefin were observed with multiple runs, however, NMR data is representative of endocyclic olefin **4.51**. **Yield:** 269 mg, 91%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.19 (d, *J* = 7.8 Hz, 1H), 7.08 (s, 1H), 7.06 (d, *J* = 7.7, 1.9 Hz, 1H), 6.01 – 5.93 (m, 1H), 2.88 – 2.76 (m, 1H), 2.35 (s, 3H), 2.21 – 2.13 (m, 1H), 2.08 (s, 3H), 1.91 – 1.82 (m, 1H), 1.71 – 1.56 (m, 2H), 1.29 (d, *J* = 7.0 Hz, 3H).

6-chloro-3,5,9-trimethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ol (**4.55**)

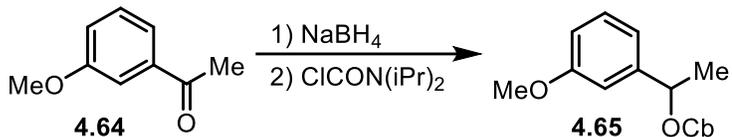


To a stirred solution of substrate **4.51** (30 mg, 0.16 mmol, 1.0 equiv.) in DCM (1.0 mL) was added deionized water (3.0 μ L, 0.193 mmol, 1.2 equiv.) and **Cl-HVI** (82 mg, 0.193 mmol, 1.2 equiv.). The cloudy reaction was allowed to stir for 2 hours, at which point it became colorless and TLC analysis displayed complete consumption of starting material. At which point, the reaction was concentrated and purified via column chromatography (5% EtOAc/Hexanes) to reveal the desired product as a yellow oil. **Yield:** 5 mg, 13%.
For characterization see above synthesis of 4.55.

D5: SYNTHESIS WITH ARYLMETHOXY MODEL SUBSTRATE



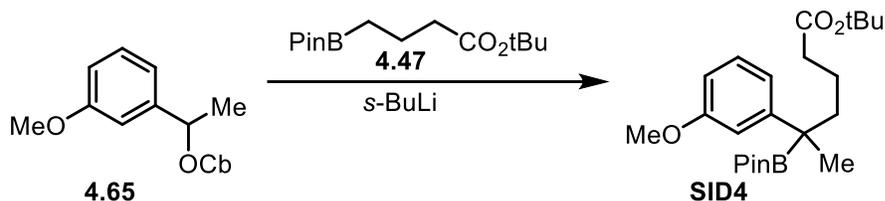
1-(3-methoxyphenyl)ethyl diisopropylcarbamate (**4.65**)



To a stirred solution of acetophenone **4.64** (7.50 g, 49.9 mmol, 1.0 equiv.) methanol (75 mL) was added sodium borohydride (2.08 g, 54.9 mmol, 1.1 equiv.). Following the addition of NaBH_4 , the reaction began bubbling vigorously and continued for several minutes. Once bubbling ceased, the reaction was checked by TLC which showed complete consumption of starting material. Thus, the reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (3x). The combined organic extracts were washed with brine then dried over sodium sulfate and concentrated. The crude residue was then diluted with DCM in the same flask, and DCM (100 mL) was added. Diisopropylcarbamoyl chloride (9.7 g, 59.9 mmol, 1.2 equiv.) was added along with triethylamine (8.25 mL, 59.9 mmol, 1.2 equiv.). The flask was sealed with electrical tape and placed in a 50 °C bath to stir for 24 hours. After which, the

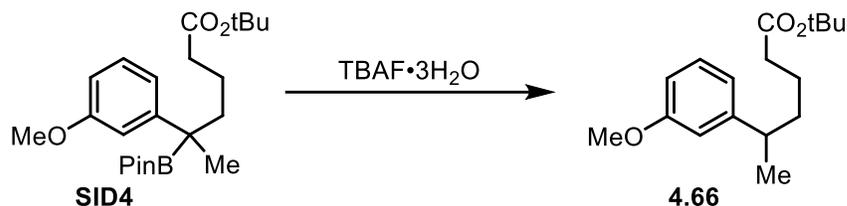
mixture was allowed to cool to ambient temperature before quenching with aqueous 1 M HCl. The mixture was transferred to a separatory funnel and extracted with DCM (3x). The combined organic extracts were dried over sodium sulfate and concentrated to reveal the product as a colorless oil. **Yield:** 8.21 g, 59% over two steps.

tert-butyl 5-(3-methoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanoate (SID4)



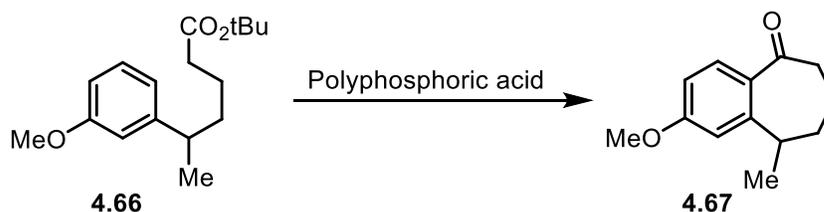
Carbamate **4.65** (3.65 g, 13.1 mmol, 1.0 equiv.) was dissolved in 52 mL of diethyl ether, and the solution was cooled to -78°C in a dry ice/acetone bath. After a few minutes at this temperature, *s*-BuLi (10.3 mL, 15.7 mmol, 1.2 equiv.) was added dropwise over a period of 5 minutes, and the resultant solution was stirred for 30 minutes. A solution of boronic ester **4.47** (4.23 g, 12.8 mmol, 1.2 equiv.) in 27 mL Et₂O was added dropwise over a period of 5 minutes and stirred for 30 minutes at -78°C , then 6 hours at room temperature. The reaction was then cooled to 0°C and quenched by the addition of 1 M KHSO₄ slowly. The mixture was allowed to warm to room temperature and stir for an additional 10 mins. Extraction with Et₂O (3x) and drying over Na₂SO₄ afforded the crude oil, which was subjected to flash chromatography (0→5% Et₂O/pentane) to afford the desired product as a colorless oil. **Yield:** 4.55 g, 86%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.19 (t, *J* = 8.0 Hz, 1H), 6.91 – 6.85 (m, 2H), 6.68 (dd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 3.79 (s, 3H), 2.24 – 2.13 (m, 3H), 1.82 – 1.62 (m, 2H), 1.56 – 1.44 (m, 2H), 1.42 (s, 9H), 1.33 (s, 3H), 1.32 – 1.27 (m, 2H), 1.20 (d, *J* = 5.7 Hz, 12H).

tert-butyl 5-(3-methoxyphenyl)hexanoate (**4.66**)



To a flame dried flask containing a mixture of boronic ester **SID4** (4.55 g, 11.3 mmol, 1.0 equiv.) was added toluene (55 mL), followed by TBAF·3H₂O (3.91 g, 12.4 mmol, 1.1 equiv.). The mixture was heated to 50°C and stirred overnight. The solution was then cooled to room temperature and quenched with water. The aqueous phase was extracted with Et₂O (3x) and the combined organic phases were dried over Na₂SO₄ and concentrated. The resulting oil was purified by flash chromatography (5% Et₂O/pentane) to afford the desired product as a colorless oil. **Yield:** 2.60 g, 83%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.20 (dd, *J* = 8.9, 7.6 Hz, 1H), 6.77 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.74 – 6.70 (m, 2H), 3.80 (s, 3H), 2.67 (h, *J* = 6.8 Hz, 1H), 2.17 (t, *J* = 7.1 Hz, 2H), 1.62 – 1.44 (m, 4H), 1.42 (s, 9H), 1.23 (d, *J* = 7.0 Hz, 3H).

2-methoxy-9-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (**4.67**)

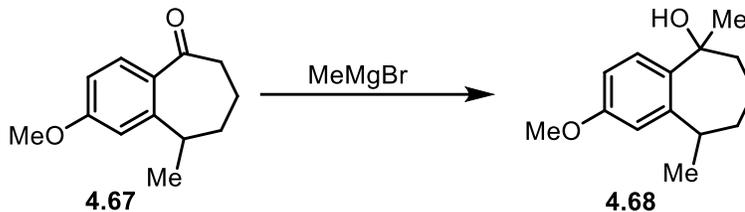


To a flask containing ester **4.66** (2.60 g, 9.3 mmol) was added approximately 5 mL of polyphosphoric acid. The flask was submerged in a pre-heated bath set to 80 °C, and the reaction was stirred slowly for 3 hours. The viscous mixture was then removed from heat and allowed to cool to ambient temperature before the addition of water (40 mL). The material was agitated with a spatula to a point where stirring was feasible, then the cloudy white solution was stirred for 5 minutes. The mixture was transferred to a separatory

funnel along with EtOAc. The organic layer was removed, and the aqueous layer was further extracted with EtOAc (2x). The combined organic extracts were then washed with saturated aqueous sodium bicarbonate (3x), water (1x), and finally brine (1x). The organic solution was dried over sodium sulfate and concentrated, and the crude material was purified via column chromatography to afford the desired product as a yellow oil.

Yield: 1.4 g, 74%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.63 – 7.59 (m, 1H), 6.82 – 6.76 (m, 2H), 3.86 (s, 3H), 3.15 – 3.07 (m, 1H), 2.76 – 2.68 (m, 1H), 2.63 – 2.54 (m, 1H), 2.00 – 1.91 (m, 1H), 1.91 – 1.83 (m, 1H), 1.65 – 1.56 (m, 1H), 1.56 – 1.48 (m, 1H), 1.38 (d, $J = 6.8$ Hz, 3H).

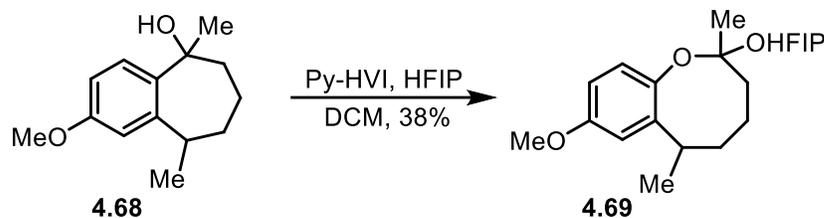
2-methoxy-5,9-dimethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ol (4.68)



Ketone **4.67** (500 mg, 2.45 mmol, 1.0 equiv.) was added to a flame-dried round-bottomed flask followed by THF (13 mL). The resulting solution was cooled to 0 °C and stirred for 5 minutes, then a solution of methylmagnesium bromide (3.0 M, 2.45 mL, 7.35 mmol, 3.0 equiv.) was added. The resulting solution was allowed to warm to ambient temperature and stir overnight. The following morning, the reaction was cooled to 0 °C and quenched with saturated aqueous ammonium chloride. The mixture was transferred to a separatory funnel along with Et₂O, and the organic layer was removed. The aqueous layer was back-extracted with Et₂O (3x), and the combined organic extracts were dried over sodium sulfate then concentrated. The crude material was purified via column chromatography (10% EtOAc/Hexanes) to afford the desired product as a thick colorless oil. **Yield:** 313 mg, 58%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.71 (d, $J = 8.7$ Hz, 1H), 6.79 (d, $J = 2.8$ Hz, 1H), 6.76 (dd, $J = 8.6, 2.8$ Hz, 1H), 3.81 (s, 3H), 3.12 – 3.03 (m, 1H),

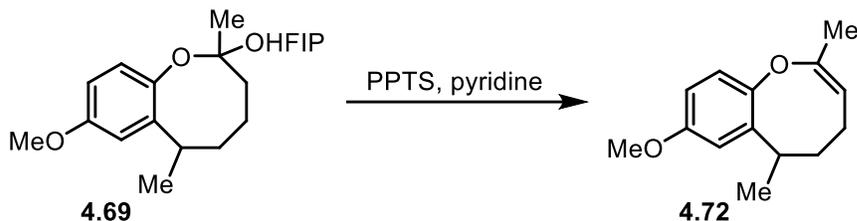
2.09 – 2.02 (m, 1H), 1.92 – 1.85 (m, 1H), 1.83 – 1.75 (m, 3H), 1.56 (s, 3H), 1.35 (d, $J = 7.0$ Hz, 3H).

2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-8-methoxy-2,6-dimethyl-3,4,5,6-tetrahydro-2H-benzo[b]oxocine (4.69)



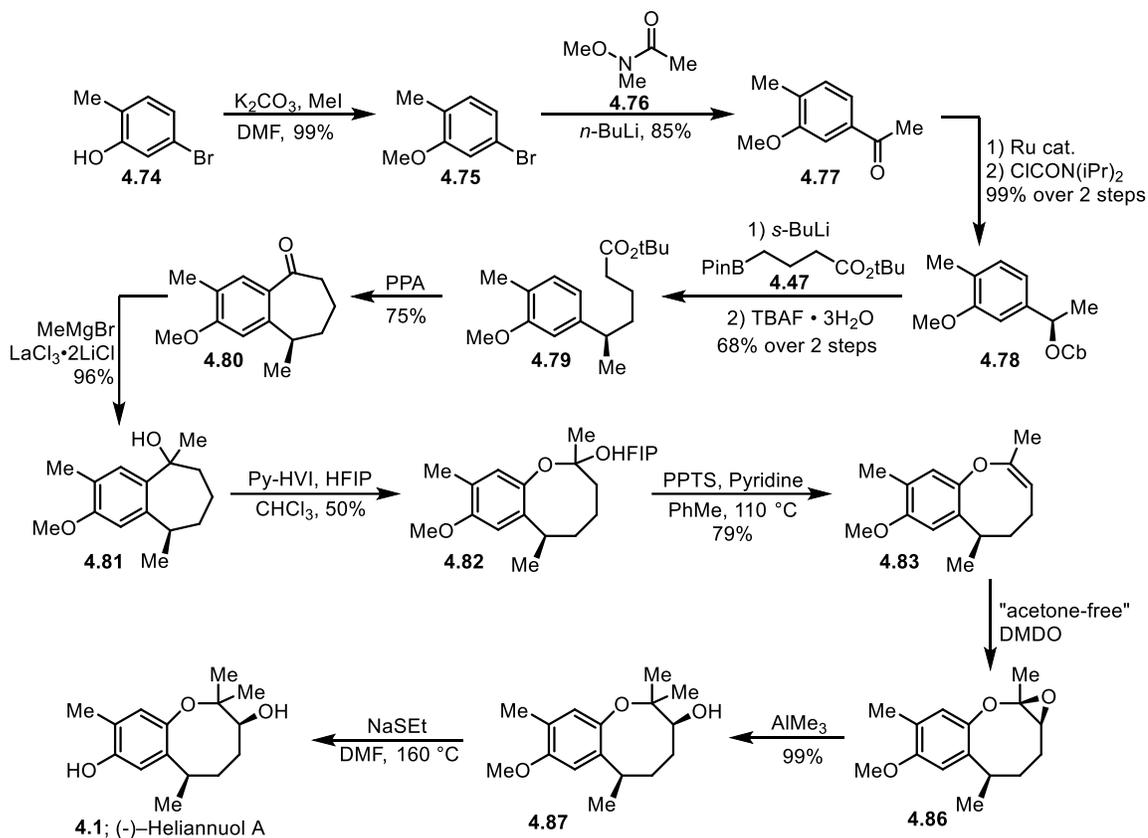
In a flame-dried round-bottomed flask, alcohol **4.68** (74 mg, 0.34 mmol, 1.0 equiv.) was dissolved in DCM (2.0 mL) in the presence of activated 3 Å MS. The suspension was cooled to -25 °C, then a solution of Py-HVI (332 mg, 2.59 mmol, 1.1 equiv.) in HFIP (0.71 mL, 6.72 mmol, 20 equiv.) was added.⁴ The reaction was closely monitored by TLC while slowly warming to 0 °C, at which point complete consumption of starting material was observed. The reaction was then concentrated at 0 °C, and the concentrated residue was azeotroped with DCM (3x) to remove residual HFIP. The crude oil was diluted with Et₂O which caused the precipitation of insoluble byproducts. Filtration over celite and concentration, followed by column chromatography (0→5% Et₂O/pentane) afforded a single diastereomer of HFIP acetal **4.69** as a colorless oil. **Yield:** 50 mg, 38%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 6.85 (d, $J = 8.7$ Hz, 1H), 6.77 (d, $J = 3.1$ Hz, 1H), 6.65 (dd, $J = 8.8, 3.1$ Hz, 1H), 5.05 (m, 1H), 3.79 (s, 3H), 3.22 (m, 1H), 1.95 – 1.77 (m, 2H), 1.62 – 1.53 (m, 1H), 1.47 (s, 3H), 1.27 (d, $J = 7.1$ Hz, 3H).

(Z)-8-methoxy-2,6-dimethyl-5,6-dihydro-4H-benzo[b]oxocine (4.72)

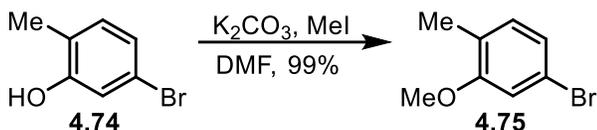


To a flame-dried test tube was added HFIP acetal **4.69** (50 mg, 0.13 mmol, 1.0 equiv.) along with toluene (2.0 mL). Pyridine (8.1 μ L, 0.10 mmol, 0.78 mmol) was then added, followed by pyridinium *para*-toluenesulfonate (36 mg, 0.14 mmol, 1.1 equiv.). The test tube was sealed and placed into a pre-heated 110 $^{\circ}$ C oil bath and allowed to stir for 3 hours. The reaction was then removed from heating and allowed to cool to room temperature, at which point the mixture became heterogenous. Et₂O (10 mL) was added, which resulted in precipitation of PPTS. The reaction was filtered over celite and concentrated, then the crude residue was purified via column chromatography (5% Et₂O/pentane) to afford the desired product as a colorless oil. **Yield:** 15 mg, 57%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 6.94 (d, *J* = 8.6 Hz, 1H), 6.68 (d, *J* = 3.0 Hz, 1H), 6.65 (dd, *J* = 8.6, 3.1 Hz, 1H), 4.44 – 4.36 (m, 1H), 3.79 (s, 3H), 3.46 – 3.35 (m, 1H), 1.92 (s, 3H), 1.79 – 1.62 (m, 1H), 1.58 – 1.49 (m, 1H), 1.34 (d, *J* = 6.9 Hz, 3H), 1.11 – 1.03 (m, 1H). **¹³C NMR** (126 MHz, CDCl₃) δ 157.14, 153.32, 148.40, 138.39, 121.16, 111.38, 110.86, 99.20, 70.71, 55.62, 37.39, 30.83, 22.60, 21.56, 18.51.

D6: ASYMMETRIC SYNTHESIS OF HELIANNUOL A



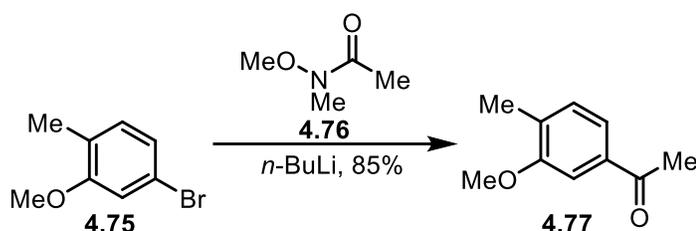
4-bromo-2-methoxy-1-methylbenzene (4.75)



Phenol **4.74** (20.0 g, 107 mmol, 1.0 equiv.) was added to round-bottomed flask followed by DMF (120 mL). Potassium carbonate (22.2 g, 160 mmol, 1.5 equiv.) was added, followed by methyl iodide (7.32 mL, 118 mmol, 1.1 equiv.). The resulting mixture was stirred at ambient temperature for 3 hours, by which point TLC indicated complete consumption of starting material. The reaction was diluted with water (250 mL) and Et₂O (120 mL). The organic layer was removed, and the aqueous layer was further extracted

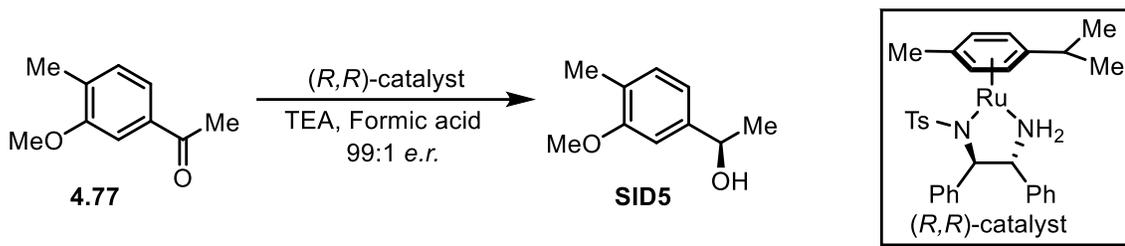
with Et₂O (3x). The combined organic extracts were then washed with brine (5x), dried over sodium sulfate, and then concentrated. The crude material was purified via column chromatography (5% Et₂O/pentane) to afford the desired product as a colorless oil. **Yield:** 21.4 g, 99%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 6.99 (d, *J* = 1.2 Hz, 2H), 6.94 (s, 1H), 3.82 (s, 3H), 2.16 (s, 3H).

1-(3-methoxy-4-methylphenyl)ethan-1-one (4.77)



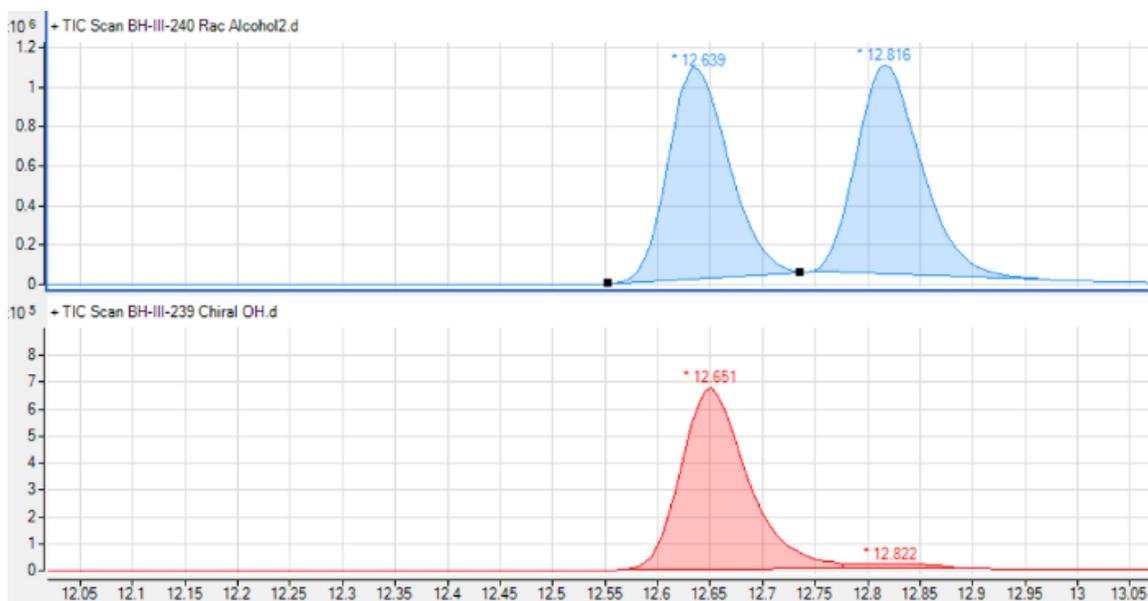
To a flame-dried round-bottomed flask was added aryl bromide **4.75** (12.4 g, 61.9 mmol, 1.0 equiv.) along with THF (310 mL). The solution was cooled to $-78\text{ }^{\circ}\text{C}$, then *n*BuLi (24.8 mL, 61.9 mmol, 1.0 equiv.) was added dropwise over 15 minutes. The resulting lithaite solution was stirred for 1 hour while maintaining the temperature, then Weinreb amide **4.76** (7.89 mL, 74.3 mmol, 1.2 equiv.) was added dropwise over 10 minutes. The reaction was stirred for an additional 30 minutes at $-78\text{ }^{\circ}\text{C}$, then was removed from the ice bath and stirred at ambient temperature for an hour. Once complete, the reaction was quenched with aqueous 2 M HCl and extracted with diethyl ether (3x). The combined organic extracts were washed with brine then dried over sodium sulfate and concentrated. The crude material was purified via column chromatography (5% EtOAc/Hexanes) to afford the product as colorless crystals. **Yield:** 8.7 g, 85%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.48 – 7.42 (m, 2H), 7.20 (d, *J* = 7.6, 0.9 Hz, 1H), 3.89 (s, 3H), 2.59 (s, 3H), 2.27 (s, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ 198.00, 158.04, 136.45, 133.16, 130.50, 121.60, 108.51, 55.55, 26.69, 16.70. **MP:** 30 °C

(R)-1-(3-methoxy-4-methylphenyl)ethan-1-ol

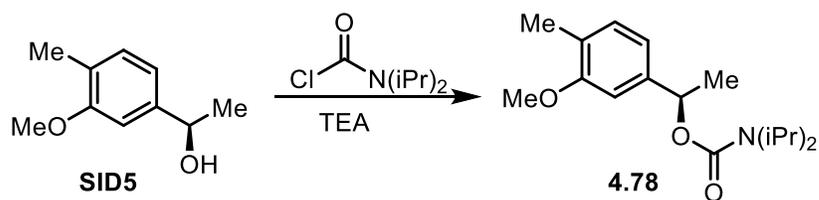


In a flame-dried round-bottomed flask, triethylamine (13.4 mL, 132 mmol, 2.5 equiv.) was cooled to 0 °C, then formic acid (12 mL, 318 mmol, 6.0 equiv.) was slowly added. The resulting mixture was stirred for 10 minutes, then acetophenone **4.77** was added. RuCl(p-cymene)[(S,S)-Ts-DPEN]⁹ ((R,R)-catalyst; 1.68 g, 2.65 mmol, 5 mol %) was then added to the reaction flask, and the reaction was allowed to stir overnight while warming to ambient temperature. The following day, the reaction was quenched with water and extracted with EtOAc (3x). The combined organic extracts were washed once each with saturated aqueous sodium bicarbonate, water, and brine. The organic layer was then dried over sodium sulfate and concentrated, then the crude material was purified via column chromatography (5→20% EtOAc/Hexanes) to afford the product as a pale yellow oil. **Yield:** 8.76 g, 99%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.10 (d, *J* = 7.5, 0.9 Hz, 1H), 6.88 (s, 1H), 6.83 (d, *J* = 7.4, 1.6 Hz, 1H), 4.83 (q, *J* = 6.5 Hz, 1H), 3.84 (s, 3H), 2.45 (s, 1H), 2.23 (s, 3H), 1.49 (d, *J* = 6.4 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ 157.85, 145.00, 130.50, 125.72, 117.16, 107.11, 70.59, 70.39, 55.29, 25.22, 16.00. **HRMS** (ESI) *m/z* calculated for C₁₀H₁₄O₂ 166.0994; found 166.0991.

E.R. determined by GCMS (cyclosilB chiral column, 40 °C start, 20 °C/min to 146 °C, 2 min hold, 0.1 °C/min to 148 °C, 20 °C/min to 225 °C) retention times: 12.6 min (major) and 12.8 min (minor); 99:1



(R)-1-(3-methoxy-4-methylphenyl)ethyl diisopropylcarbamate (4.78)

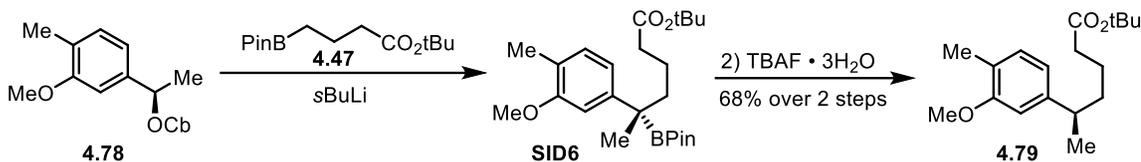


To a pre-dried high-pressure round-bottomed flask was added triethylamine (5.24 mL, 37.6 mmol, 1.2 equiv.), diisopropylcarbonyl chloride (6.16 g, 37.6 mmol, 1.2 equiv.) and DCM (75 mL). Chiral alcohol **SID5** (5.21g, 31.5 mmol, 1.0 equiv.) was then added, and the flask was tightly sealed, The reaction was then heated to 60 °C and stirred for 72 hours. Upon completion, the reaction was quenched with aqueous 1 M HCl. The organic layer was collected, then the aqueous layer was extracted with DCM (3x). The combined organic extracts were washed with brine then dried over sodium sulfate and concentrated. Column chromatography (5% EtOAc/Hexanes) afforded the desired carbamate as a thick colorless oil. **Yield:** 8.2 g, 99%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.09 (d, *J* = 7.6, 0.8 Hz, 1H), 6.86 (d, *J* = 7.6, 1.6 Hz, 1H), 6.83 (s, 1H), 5.81 (q, *J* = 6.6 Hz, 1H), 3.83 (s, 3H), 2.20 (s, 3H), 1.55 (d, *J* = 6.5 Hz, 3H), 1.31 – 1.14 (m, 12H). **¹³C NMR** (126 MHz,

CDCl₃) δ 157.7, 155.3, 141.9, 130.6, 125.8, 117.8, 108.0, 72.9, 70.7, 55.3, 23.1, 16.1.

HRMS (ESI) m/z calculated for C₁₇H₂₇NO₃: 293.1991 found 293.1979.

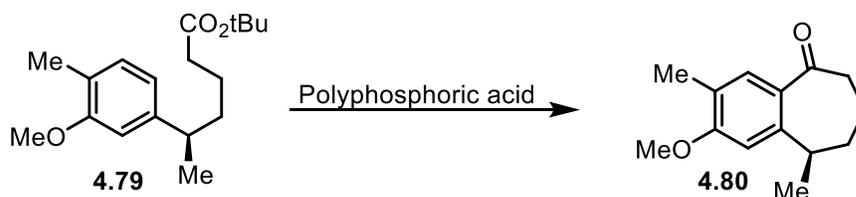
tert-butyl (R)-5-(3-methoxy-4-methylphenyl)hexanoate (4.79)



In a flame-dried round-bottomed flask, carbamate **4.78** (2.17 g, 7.40 mmol, 1.0 equiv.) was dissolved in diethyl ether (30 mL) and the resulting solution was cooled to -78 °C. *Sec*-butyllithium (1.4 M in Et₂O; 5.81 mL, 8.13 mmol, 1.1 equiv.) was then added, and the lithiate solution was stirred at this temperature for 1 hour. A solution of boronic ester **4.47** (2.40 g, 8.80 mmol, 1.2 equiv.) in Et₂O (8.8 mL) was slowly added, then the reaction stirred for an additional 30 minutes at -78 °C. The flask was then removed from the ice bath and stirred for 2 hours at ambient temperature, at which point an aqueous 1 M solution of KHSO₄ was added to quench. The mixture was extracted with Et₂O (3x) and the combined organic extracts were dried over sodium sulfate and concentrated. Purification via column chromatography (7% EtOAc/Hexanes) afforded the desired product, however co-elution with either or both starting materials was often observed. The mixtures were used in the subsequent step without further purification. Yield was calculated over 2 steps. **SID6**: ¹H NMR (500 MHz, Chloroform-*d*) δ 7.06 – 6.98 (m, 1H), 6.81 (d, J = 1.8 Hz, 1H), 6.79 (dd, J = 7.7, 1.8 Hz, 1H), 3.81 (s, 3H), 2.24 – 2.17 (m, 1H), 2.16 (s, 3H), 1.92 – 1.75 (m, 1H), 1.76 – 1.59 (m, 1H), 1.57 – 1.45 (m, 1H), 1.43 (s, 9H), 1.21 (d, J = 5.6 Hz, 12H). ¹³C NMR (126 MHz, CDCl₃) δ 173.1, 157.4, 146.0, 130.2, 123.2, 118.4, 109.1, 83.3, 79.8, 70.6, 55.1, 39.2, 36.4, 31.6, 28.1, 24.8, 24.7, 24.6, 22.7, 21.5, 21.4, 15.8, 14.1. **HRMS** (ESI) m/z calculated for C₂₄H₄₀BO₅⁺: 419.2969; found 362.2252 (C₂₀H₃₂BO₅⁺), 57.0709 (C₄H₉⁺). The mixture of **SID6** was then dissolved in

toluene, and TBAF•3H₂O (2.57 g, 8.14 mmol, 1.1 equiv.) was added. The reaction flask was sealed and submerged into a pre-heated 50 °C oil bath, then stirred overnight. The following day, the reaction was quenched with water and diluted with Et₂O. The organic layer was removed, and the aqueous layer was further extracted with Et₂O (3x). The combined organic extracts were washed with brine, dried over sodium sulfate, then concentrated. Column chromatography (5% Et₂O/Pentane) afforded the desired product as a colorless oil. **Yield:** 1.46 g, 68%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.04 (d, *J* = 7.6, 0.9 Hz, 1H), 6.69 (d, *J* = 7.6, 1.7 Hz, 1H), 6.65 (s, 1H), 3.83 (s, 3H), 2.69 – 2.62 (m, 1H), 2.18 (s, 3H), 1.62 – 1.47 (m, 4H), 1.43 (s, 9H), 1.24 (d, *J* = 6.9 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ 173.1, 157.7, 146.4, 130.4, 124.0, 118.6, 108.9, 80.0, 70.6, 55.2, 39.8, 37.8, 35.6, 28.1, 23.3, 22.3, 15.9. **HRMS** (ESI) *m/z* calculated for C₁₈H₂₈O₃: 292.2038; found 292.2042.

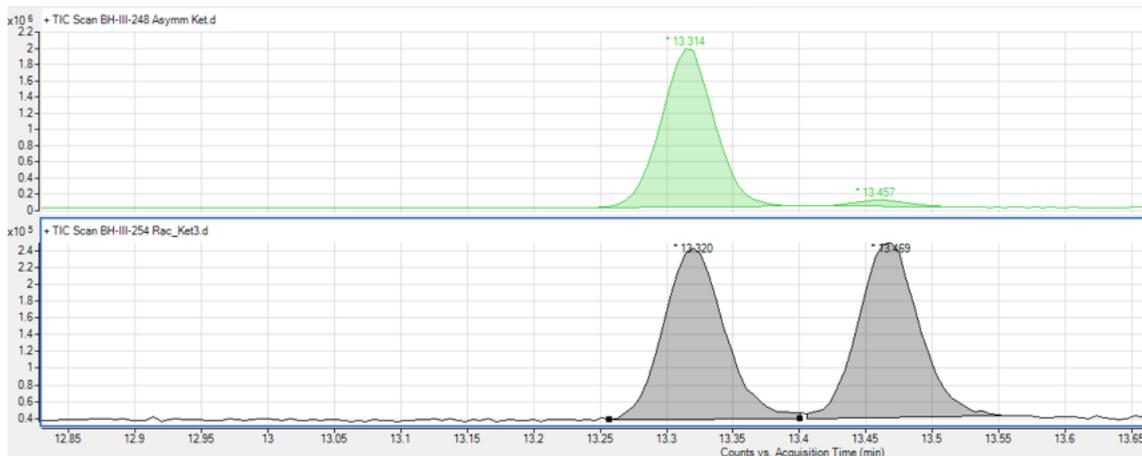
(*R*)-2-methoxy-3,9-dimethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (4.80)



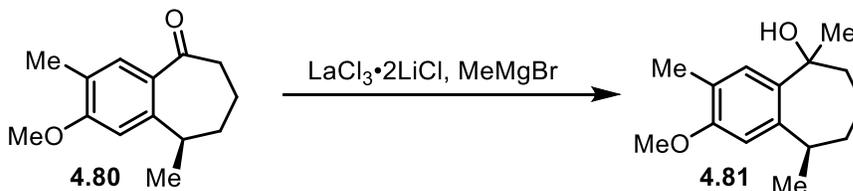
To a flame-dried round-bottomed flask containing ester **4.79** (2.10 g, 7.18 mmol) in chlorobenzene (6 mL) was added ~6 mL PPA. The reaction mixture was placed in a pre-heated 80 °C oil bath and stirred for 3 hours. Once complete, water (20 mL) was added and the mixture was manually agitated with a spatula to ensure full quenching of the PPA. Ethyl acetate was added (20 mL), and the organic layer was extracted. The aqueous layer was further extracted with EtOAc (3x). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (2x), water (1x), and finally brine (2x). The solution was dried over sodium sulfate and concentrated, then the crude residue was purified on silica (7% EtOAc/Hexanes) to afford the desired product as a pale yellow oil

which solidified after a few hours. 96:3 *e.r.* **Yield:** 1.18 g, 75%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.44 (s, 1H), 6.68 (s, 1H), 3.89 (s, 3H), 3.17 – 3.08 (m, 1H), 2.71 (ddd, *J* = 17.9, 6.1, 2.3 Hz, 1H), 2.57 (ddd, *J* = 17.9, 12.3, 2.6 Hz, 1H), 2.18 (s, 3H), 1.99 – 1.90 (m, 1H), 1.90 – 1.81 (m, 1H), 1.67 – 1.48 (m, 2H), 1.39 (d, *J* = 6.8 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ 207.0, 161.0, 144.0, 131.6, 131.2, 124.6, 106.8, 70.7, 55.5, 41.4, 34.5, 34.3, 20.5, 19.7, 15.7. **HRMS** (ESI) *m/z* calculated for C₁₄H₁₈O₂: 218.1307; found 218.1307. **MP:** 45–47 °C

E.R. determined by GCMS (cyclosilB chiral column, 40 °C start, 20 °C/min to 200 °C, 0.2 °C/min to 204 °C, 20 °C/min to 225 °C) retention times: 12.6 min (major) and 12.8 min (minor); 99:1



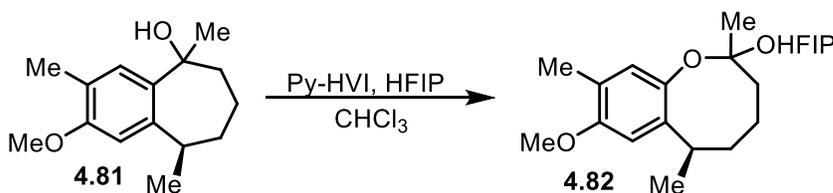
(9*R*)-2-methoxy-3,5,9-trimethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ol (4.81)



In a flame-dried round-bottomed flask, ketone **4.80** (641 mg, 2.93 mmol, 1.0 equiv.) was dissolved in THF (2 mL). A solution of LaCl₃•2LiCl¹⁰ (0.6 M THF; 4.89 mL, 2.93 mmol, 1.0 equiv.) was added and the solution was stirred for 1 hour at ambient temperature. The solution was then cooled to 0 °C, and a solution of methylmagnesium bromide (3 M

Et₂O; 1.07 mL, 3.22 mmol, 1.1 equiv.) was added slowly. The reaction was stirred for 15 minutes before quenching with saturated aqueous ammonium chloride and water. Diethyl ether was added, and the organic layer was removed. The aqueous layer was further extracted with Et₂O (3x), and the combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated. The crude residue was purified on silica (10% EtOAc/Hexanes) to afford the desired product as a colorless viscous oil. **Yield:** 661 mg, 96%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.56 (s, 1H), 6.72 (s, 1H), 3.85 (s, 3H), 3.15 – 3.06 (m, 1H), 2.23 (s, 3H), 2.06 (ddd, *J* = 14.3, 8.3, 2.4 Hz, 1H), 1.94 – 1.86 (m, 2H), 1.85 – 1.75 (m, 2H), 1.69 – 1.61 (m, 1H), 1.57 (s, 3H), 1.39 (d, *J* = 6.9 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ 156.5, 140.3, 138.7, 128.8, 123.7, 107.9, 76.2, 70.7, 55.4, 42.6, 35.2, 30.1, 23.0, 20.9, 15.9. **HRMS** (ESI) *m/z* calculated for C₁₅H₂₂O₂: 234.1620; found 234.1606.

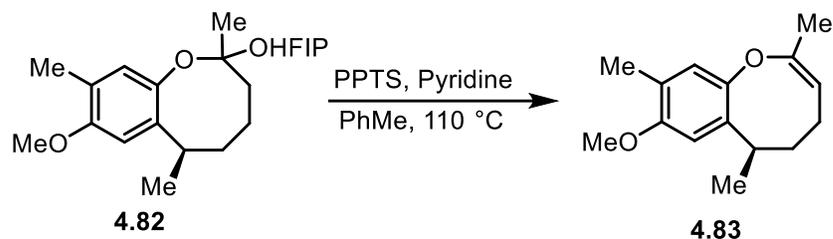
(6*R*)-2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-8-methoxy-2,6,9-trimethyl-3,4,5,6-tetrahydro-2H-benzo[*b*]oxocine (4.82)



A solution of tertiary alcohol **4.81** (460 mg, 1.96 mmol, 1.0 equiv.) in 9.8 mL of chloroform (stirred in potassium carbonate and magnesium sulfate, then filtered) was added to a flame-dried RBF containing powdered, activated 3Å MS. The flask was submerged in a –25 °C dry ice/acetone bath and stirred for 5 minutes. A solution of Py-HVI (1.43 g, 2.16 mmol, 1.1 equiv.) in HFIP (2.27 mL, 11 equiv.) was then slowly added, and the resulting solution was stirred while slowly warming to 0°C. Once all starting material had been consumed as judged by TLC (20% Et₂O/pentane), the reaction was directly concentrated in vacuo at room temperature. The crude residue was diluted

with DCM and concentrated (x3) to sufficiently remove HFIP. The remaining crude residue was diluted with diethyl ether and filtered over celite. The filtrate was concentrated and purified via column chromatography (0→5% Et₂O/pentane) to afford the desired product (~4:1 *d.r.*) as a colorless oil which became crystalline upon storage at -20 °C. **Yield:** 394 mg, 50% **¹H NMR** (500 MHz, Chloroform-*d*) δ 6.79 (s, 0.23H, Minor (1H)), 6.71 (s, 1H, Major), 6.66 (s, 1H), 6.61 (s, .21H, Minor (1H)), 5.09 – 5.00 (m, 1H), 4.79 – 4.70 (m, 0.23H, Minor (1H)), 3.82 (s, 3H), 3.81 (s, 0.57H, Major (3H)), 3.28 – 3.16 (m, 1H), 3.01 – 2.88 (m, 0.22H, Minor (1H)), 2.16 (s, 3H), 2.14 (s, 0.63H, Minor (3H)), 1.92 – 1.78 (m, 3H), 1.64 – 1.52 (m, 2.45H), 1.47 (s, 3H), 1.28 (d, *J* = 7.2, 1.0 Hz, 3.6H). **¹³C NMR** (126 MHz, CDCl₃) δ 155.4, 144.5, 144.0, 139.5, 139.4, 127.6, 124.6, 124.4, 123.0, 120.7, 108.4, 107.7, 70.7, 70.1, 68.8, 55.8, 55.7, 37.6, 35.5, 29.9, 24.5, 23.6, 21.5, 21.1, 15.9, 15.8. **HRMS** (ESI) *m/z* calculated for C₁₈H₂₂F₆O₃: 400.1473; found 400.1468. **MP:** 36 °C

(*R,Z*)-8-methoxy-2,6,9-trimethyl-5,6-dihydro-4H-benzo[*b*]oxocine (4.83)



To a flame-dried scintillation vial containing a stir bar was added a solution of HFIP acetal **4.82** (370 mg, 0.92 mmol, 1.0 equiv.) in toluene (4.6 mL). Pyridine (58 μL, 0.72 mmol, 0.78 equiv.) was added, followed by pyridinium *p*-toluenesulfonate (254 mg, 1.01 mmol, 1.1 equiv.). The vial was quickly capped and sealed with electrical tape, then placed in an oil bath pre-heated to 110 °C. The reaction was allowed to stir for 3 hours at this temperature, then was removed and allowed to cool to room temperature. The heterogeneous solution was then diluted with diethyl ether and filtered over celite. The

filtrate was then concentrated, and the crude material purified by column chromatography (0→5% Et₂O/pentane) to deliver the product as a pale-yellow oil which solidifies at low temperatures (<0 °C). **Yield:** 166 mg, 77%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 6.82 (s, 1H), 6.56 (s, 1H), 4.38 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.82 (s, 3H), 3.40 (h, *J* = 12.3, 7.2, 5.1 Hz, 1H), 2.17 (s, 3H), 1.77 – 1.65 (m, 2H), 1.60 – 1.48 (m, 1H), 1.35 (d, *J* = 6.9 Hz, 3H), 1.33 – 1.20 (m, 1H), 1.07 (dq, *J* = 11.1, 8.0, 2.9 Hz, 1H). **¹³C NMR** (126 MHz, CDCl₃) δ 155.29, 153.31, 147.67, 134.56, 124.77, 122.80, 106.93, 99.12, 70.70, 55.85, 37.13, 30.83, 22.63, 21.67, 18.69, 15.82. **HRMS** (ESI) *m/z* calculated for C₁₅H₂₀O₂: 232.1463; found 232.1455. **MP:** 35–37 °C

Synthesis of “Acetone-Free” DMDO



Figure D1. DMDO synthesis apparatus

To a 2 L three-neck round-bottomed flask was added distilled water (522 mL) followed by sodium bicarbonate (284 g). Acetone (378 mL) was added, then an elbow joint was attached to one neck. The other end of the elbow joint was fitted to a dry ice/acetone cooled condenser, which was placed on top of a 500 mL two-neck receiving

flask. The receiving flask was fitted with a vacuum line and was submerged in a $-78\text{ }^{\circ}\text{C}$ dry ice/acetone bath. The condenser and receiving flask were jacketed with aluminum foil to prevent loss of DMDO upon formation. With strong stirring, Oxone (513 g) was added in 6 portions, with 15 minutes of stirring between each addition. Directly following each addition, vacuum ($\sim 225\text{ mmHg}$) was carefully applied to the entire system. Upon the final addition, the mixture was allowed to stir for an additional hour. The apparatus was then carefully disassembled and the receiving flask was sealed to prevent evaporation of product prior to extraction. At this stage, the concentration of DMDO was found to be 0.05 M on average (See below for titration procedure).

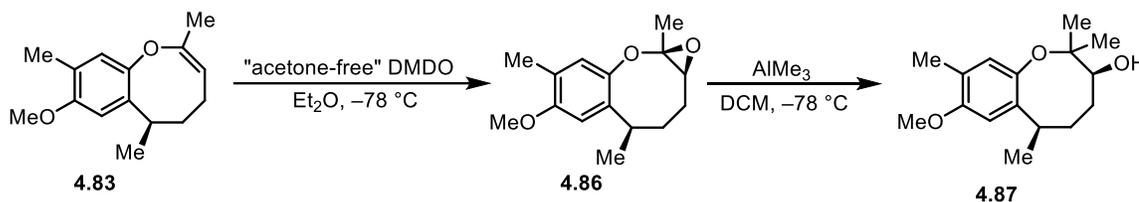
For each subsequent operation, all glassware used must be pre-cooled by placement in a refrigerator or freezer to prevent significant product loss

The DMDO solution in acetone and water was quickly transferred to a separatory funnel with an equivalent volume of pre-chilled distilled water. Dry DCM (5% of the DMDO solution volume) was added, and the mixture quickly shaken. Another portion of DCM was required for suitable phase separation. The lower DCM layer was extracted, and this operation was repeated 3 more times. To remove residual acetone, the combined DCM extracts were then added to a different separatory funnel, along with 0.05 M pH 7 phosphate buffer (1.5x volume of total DCM extracts). After shaking, the DCM was dispensed and the volume measured, and the entire phosphate buffer wash operation was repeated 4 additional times (Note: a new volume of DCM is obtained after the first several washes, so the new volume must be measured to add the proper quantity of phosphate buffer in subsequent washes). Once complete, the DCM extracts were placed in a small round-bottomed flask and cooled to $0\text{ }^{\circ}\text{C}$, then MgSO_4 was added. The solution was stirred for 2 minutes, then filtered to reveal the “acetone-free” DMDO as a solution in DCM. Typical concentrations obtained ranged between 0.15-0.30 M.

Titration was performed by dissolving thioanisole (50 μL , 0.38 mmol) in d^6 -acetone, and cooling the solution to $10\text{ }^{\circ}\text{C}$. 500 μL of DMDO was added and the resulting

solution was stirred for 5 minutes. An aliquot was removed and used for NMR analysis to determine the ratio of sulfide/sulfoxide. The ratio was then used to determine the quantity of DMDO added, and therefore the concentration of the solution.

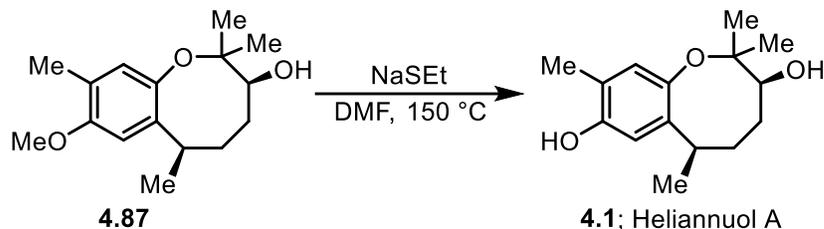
(3*S*,6*R*)-8-methoxy-2,2,6,9-tetramethyl-3,4,5,6-tetrahydro-2*H*-benzo[*b*]oxocin-3-ol (4.87)



To a stirred solution of enol ether **4.83** (50 mg, 0.21 mmol, 1.0 equiv.) in DCM (2.2 mL) in a flame-dried vial was added “acetone-free” DMDO (0.2 M, 1.2 mL, 1.1 equiv.) at -78 °C. The resulting reaction was allowed to stir for 5 minutes then concentrated to reveal epoxide **4.86**. The material was used in the subsequent step without further purification. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 6.81 (s, 1H), 6.52 (s, 1H), 3.79 (s, 3H), 3.23 – 3.14 (m, 1H), 2.79 (dd, $J = 8.4, 6.3$ Hz, 1H), 2.14 (s, 3H), 1.99 – 1.87 (m, 4H), 1.72 (s, 3H), 1.33 (d, $J = 6.9$ Hz, 3H). The crude residue was reconstituted in DCM (2.2 mL) and the solution was cooled to -78 °C. At which point, AlMe_3 (2 M in hexanes; 0.32 mL, 0.65 mmol, 3.0 equiv.) was added slowly. The resulting reaction was stirred for 30 minutes while monitoring by TLC, and once complete, saturated aqueous ammonium chloride was added and the mixture was stirred for 5 minutes. The mixture was transferred to a separatory funnel where it was extracted with EtOAc (3x), and the combined organic extracts were washed with brine (3x), dried over sodium sulfate, and concentrated. The crude residue was passed through a silica plug with EtOAc as the eluent to reveal the desired product as a pale-yellow oily foam. **Yield:** 55.8 mg, 98%. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 6.72 (s, 1H), 6.58 (s, 1H), 3.80 (s, 3H), 3.70 – 3.60 (m, 1H), 3.40 – 3.04 (m, 1H), 2.15 (s, 3H), 1.53 – 1.40 (m, 4H), 1.36 – 1.19 (m, 9H). **HRMS** (ESI) m/z

calculated for C₁₆H₂₄O₃: 264.1725; found 264.1709. ¹³CNMR data is pending at the time of writing this thesis and will be available in the corresponding publication.

Heliannuol A (4.1)



To a flame-dried vial was added a solution of methyl ether **4.87** (76 mg, 0.29 mmol, 1.0 equiv.) in DMF (1.5 mL). To the solution was added 80% by weight sodium ethanethiolate (194 mg, 2.3 mmol, 8 equiv.), and the vial was sealed tightly. The reaction was warmed to 150 °C in an oil bath and stirred at this temperature for 24 hours. Upon completion, the mixture was poured into a beaker containing 10 mL deionized H₂O and extracted with DCM (3x). The combined organic extracts were washed with brine (2x), dried over sodium sulfate, and concentrated. The crude residue was purified via flash column chromatography to afford the natural product as a crunchy orange foam. **Yield:** 63 mg, 86%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 6.69 (s, 1H), 6.54 (s, 1H), 3.72 – 3.59 (m, 1H), 3.33 – 3.15 (m, 1H), 2.17 (s, 3H), 1.31 – 1.20 (m, 14H). **HRMS** (ESI) *m/z* calculated for C₁₆H₂₄O₃: 250.1569; found 250.1562. ¹³CNMR data is pending at the time of writing this thesis and will be available in the corresponding publication.

D8: REFERENCES

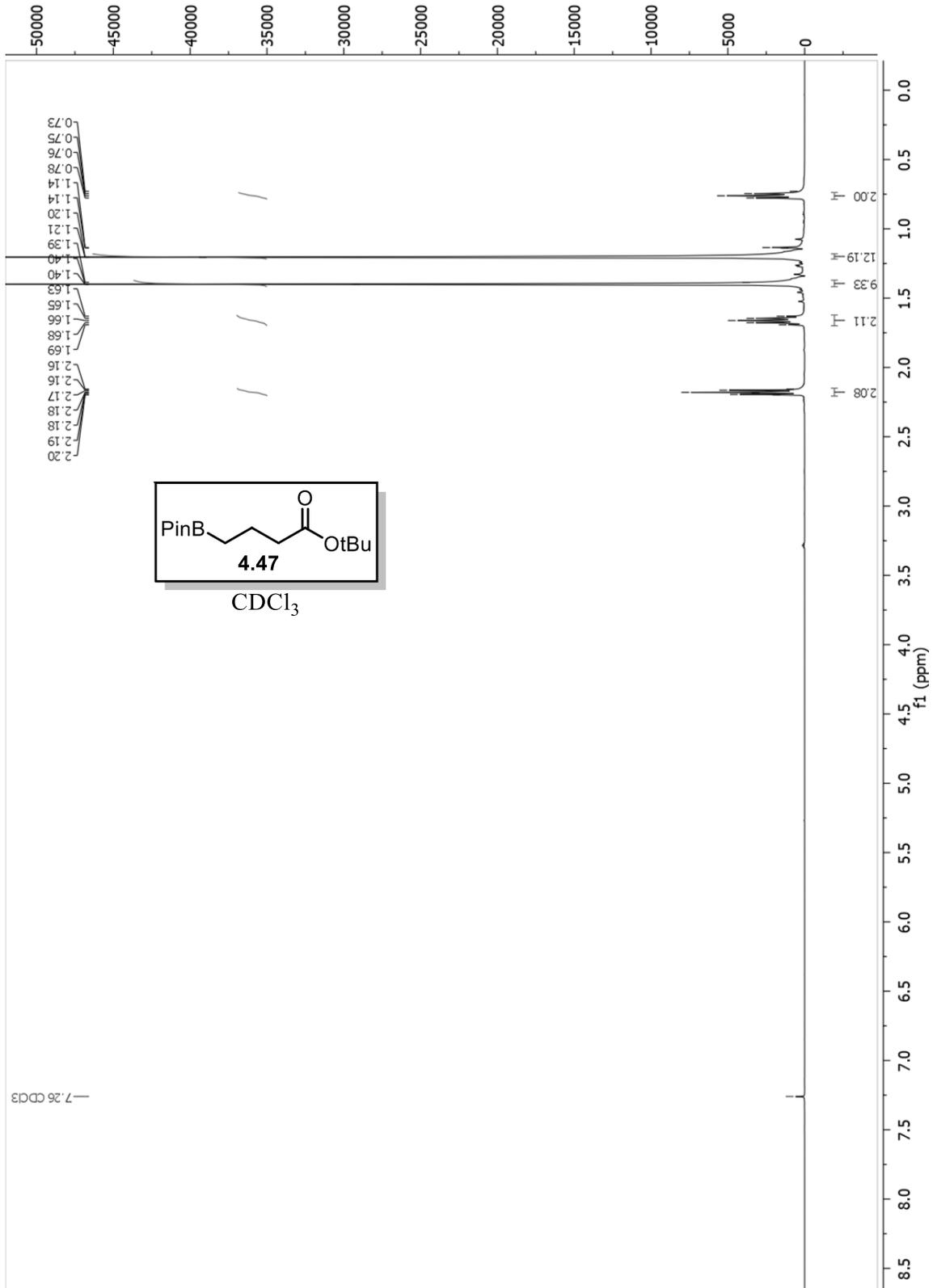
- (1) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. Enantiodivergent Conversion of Chiral Secondary Alcohols into Tertiary Alcohols. <https://doi.org/10.1038/nature07592>.
- (2) Elford, T. G.; Nave, S.; Sonawane, R. P.; Aggarwal, V. K. Total Synthesis of (+)-Erogorgiaene Using Lithiation–Borylation Methodology, and Stereoselective Synthesis of Each of Its Diastereoisomers. *J. Am. Chem. Soc.* **2011**, *133* (42), 16798–16801. <https://doi.org/10.1021/ja207869f>.
- (3) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. Protodeboronation of Tertiary Boronic Esters: Asymmetric Synthesis of Tertiary Alkyl Stereogenic Centers. *J. Am. Chem. Soc.* **2010**, *132* (48), 17096–17098. <https://doi.org/10.1021/ja1084207>.
- (4) Kelley, B. T.; Walters, J. C.; Wengryniuk, S. E. Access to Diverse Oxygen Heterocycles via Oxidative Rearrangement of Benzylic Tertiary Alcohols. *Org. Lett.* **2016**, *18* (8), 1896–1899. <https://doi.org/10.1021/acs.orglett.6b00672>.
- (5) Walters, J. C.; Tierno, A. F.; Dubin, A. H.; Wengryniuk, S. E. (Poly)Cationic Λ^3 -Iodane-Mediated Oxidative Ring Expansion of Secondary Alcohols. *European J. Org. Chem.* **2018**, *2018* (12), 1460–1464. <https://doi.org/10.1002/ejoc.201800118>.
- (6) Rueeger, H.; Gerspacher, M.; Buehlmayer, P.; Rigollier, P.; Yamaguchi, Y.; Schmidlin, T.; Whitebread, S.; Nuesslein-Hildesheim, B.; Nick, H.; Cricione, L. Discovery and SAR of Potent, Orally Available and Brain-Penetrable 5,6-Dihydro-4H-3-Thia-1-Aza-Benzo[e]Azulen- and 4,5-Dihydro-6-Oxa-3-Thia-1-Aza-Benzo[e]Azulen Derivatives as Neuropeptide Y Y5 Receptor Antagonists.

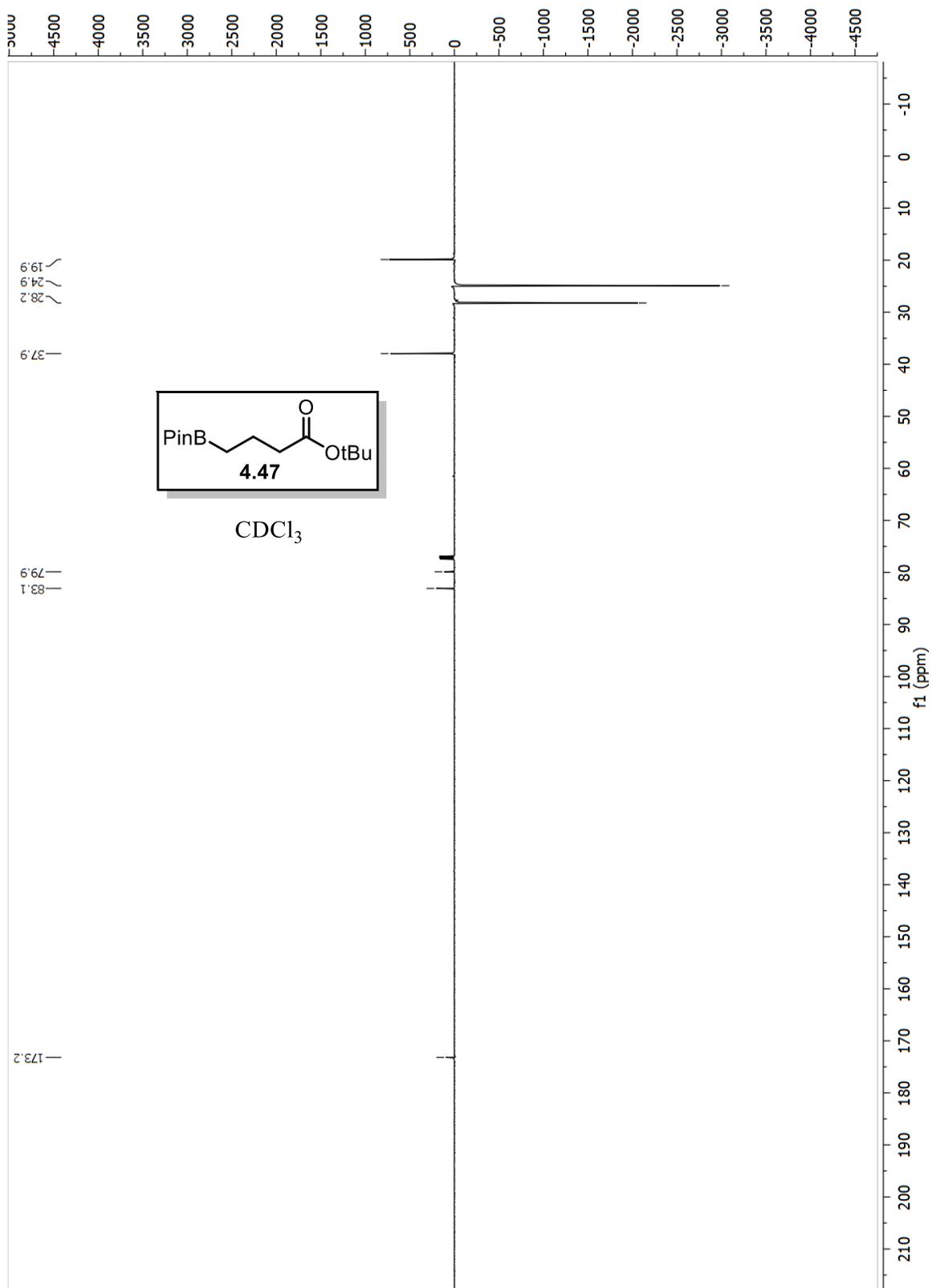
Bioorganic Med. Chem. Lett. **2004**, *14* (10), 2451–2457.

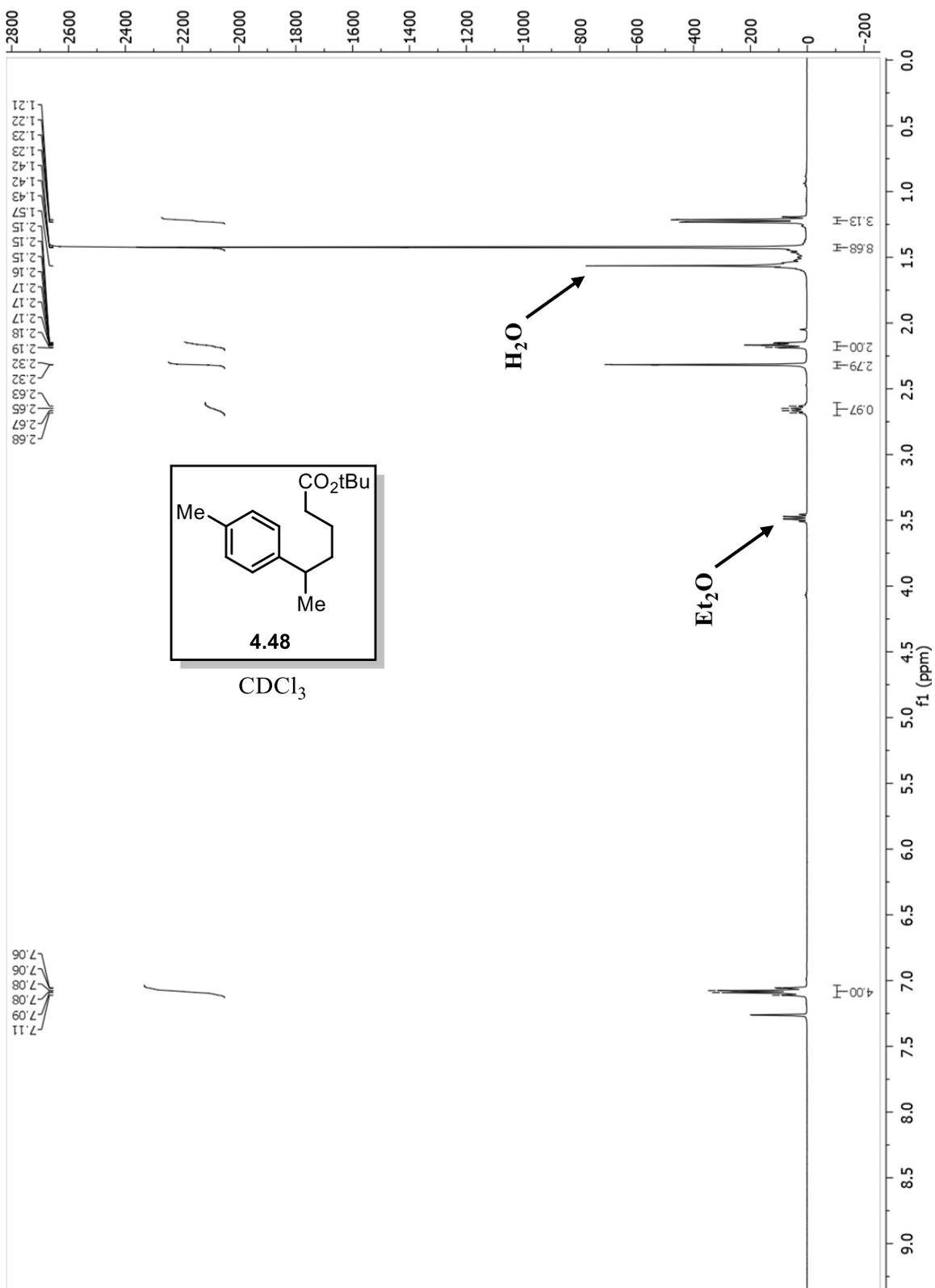
<https://doi.org/10.1016/j.bmcl.2004.03.014>.

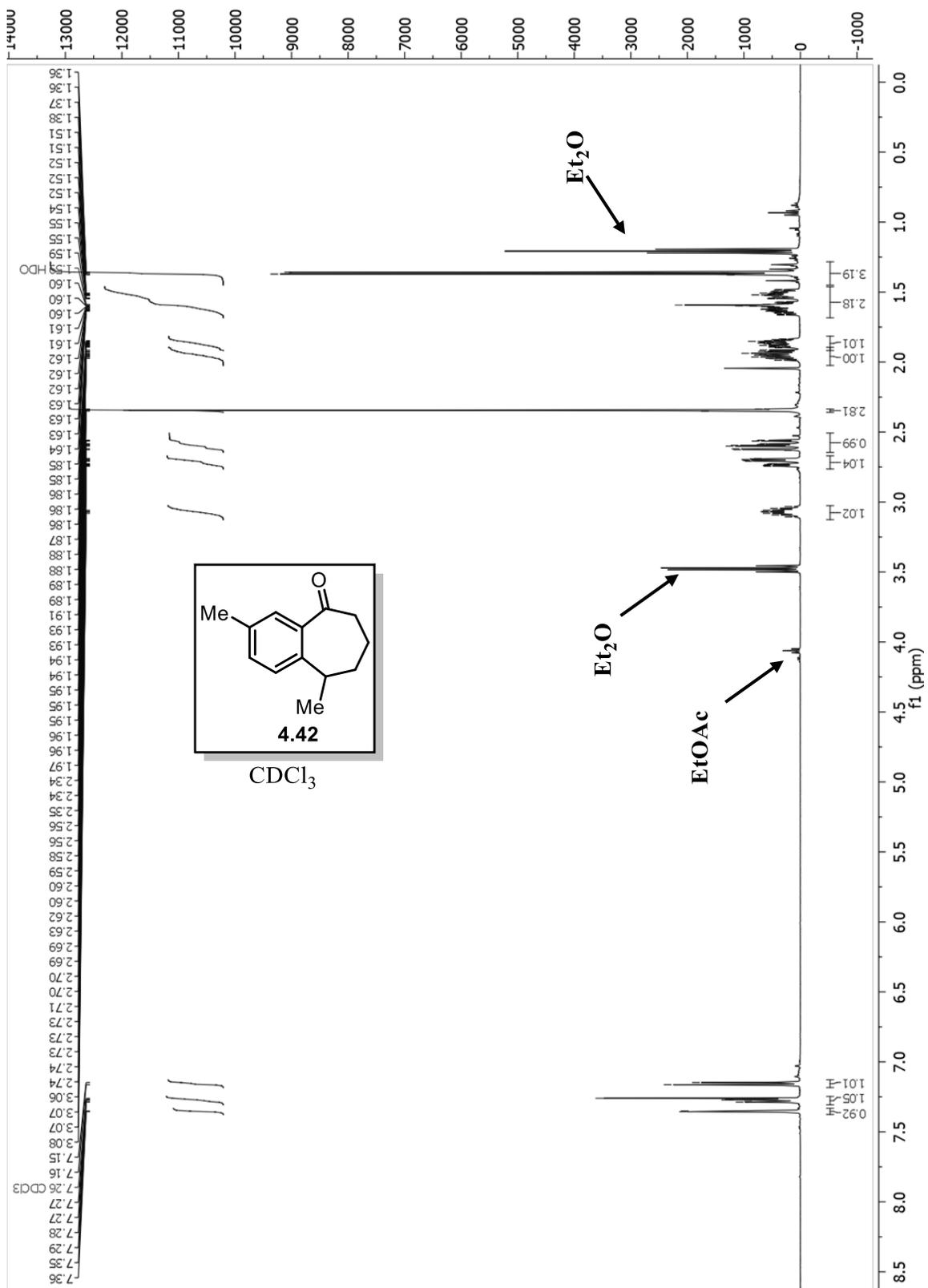
- (7) Nagai, M.; Urimoto, H.; Uetake, K.; Sakikawa, N.; Gonzalez, R. D. The Desulfurization of Polynuclear Aromatic Sulfur Compounds with a Raney Nickel. *Bull. Chem. Soc. Jpn.* **1989**, *62* (2), 557–562. <https://doi.org/10.1246/bcsj.62.557>.
- (8) Tang, S. Z.; Zhao, W.; Chen, T.; Liu, Y.; Zhang, X. M.; Zhang, F. M. A Simple and Efficient Method for the Preparation of α -Halogenated Ketones Using Iron(III) Chloride and Iron(III) Bromide as Halogen Sources with Phenyliodonium Diacetate as Oxidant. *Adv. Synth. Catal.* **2017**, *359* (23), 4177–4183. <https://doi.org/10.1002/adsc.201700833>.
- (9) Genêt, J.-P.; Ratovelomanana-Vidal, V.; Pinel, C.; Synlett ; D) Gamez, P.; Fache, F.; Mangeney, P.; Lemaire, M.; Gamez, P.; Dunjic, B.; Krasik, P.; Alper, H.; Yang, H.; Alvarez, M.; Lugan, N.; Mathieu, R. *Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation of Ketones Using a Formic Acid-Triethylamine Mixture*; 1991; Vol. 34.
- (10) Krasovskiy, A.; Kopp, F.; Knochel, P. Soluble Lanthanide Salts ($\text{LnCl}_3 \cdot 2 \text{LiCl}$) for the Improved Addition of Organomagnesium Reagents to Carbonyl Compounds. *Angew. Chemie - Int. Ed.* **2006**, *45* (3), 497–500. <https://doi.org/10.1002/anie.200502485>.

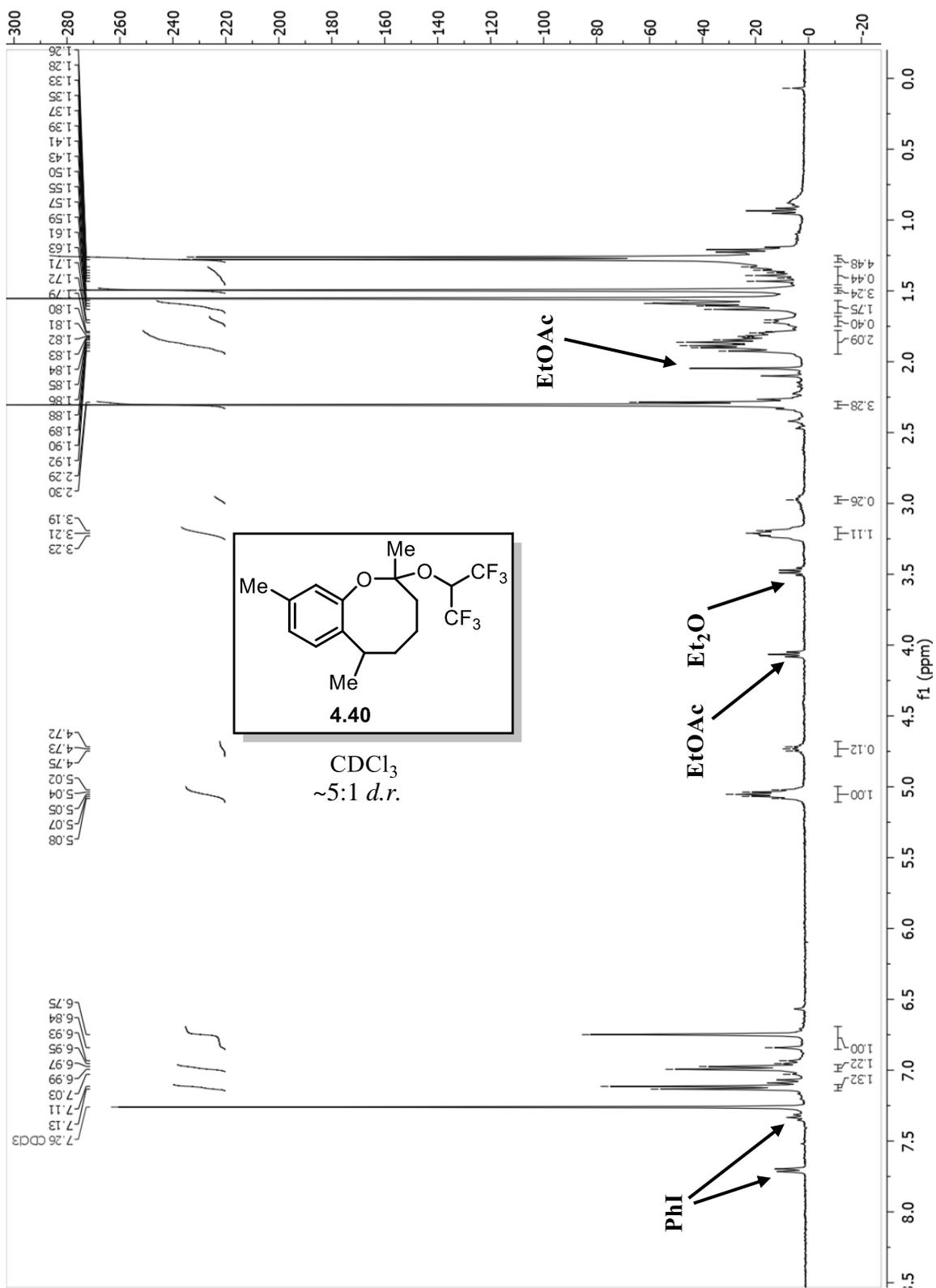
D9: SPECTRA

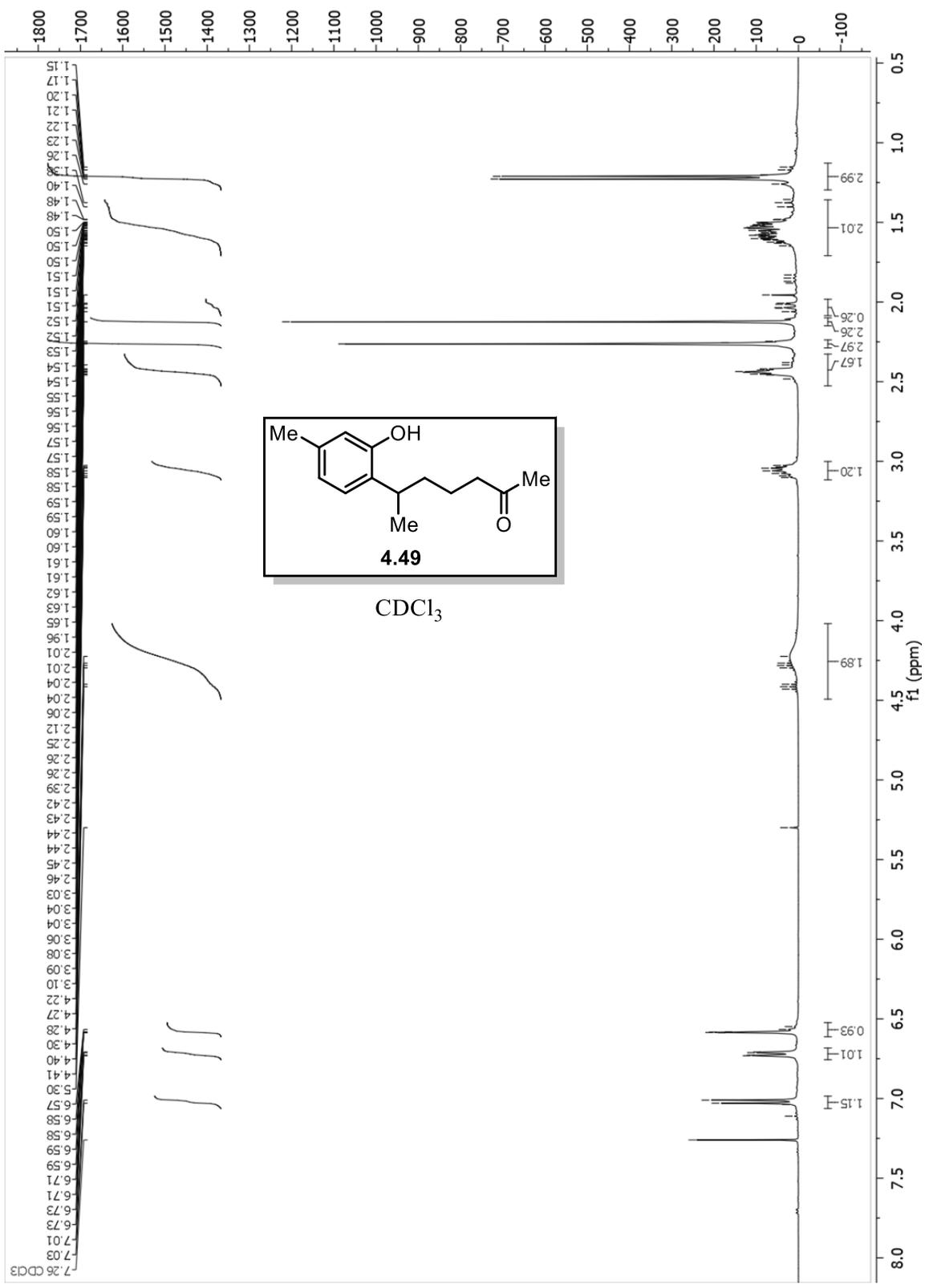


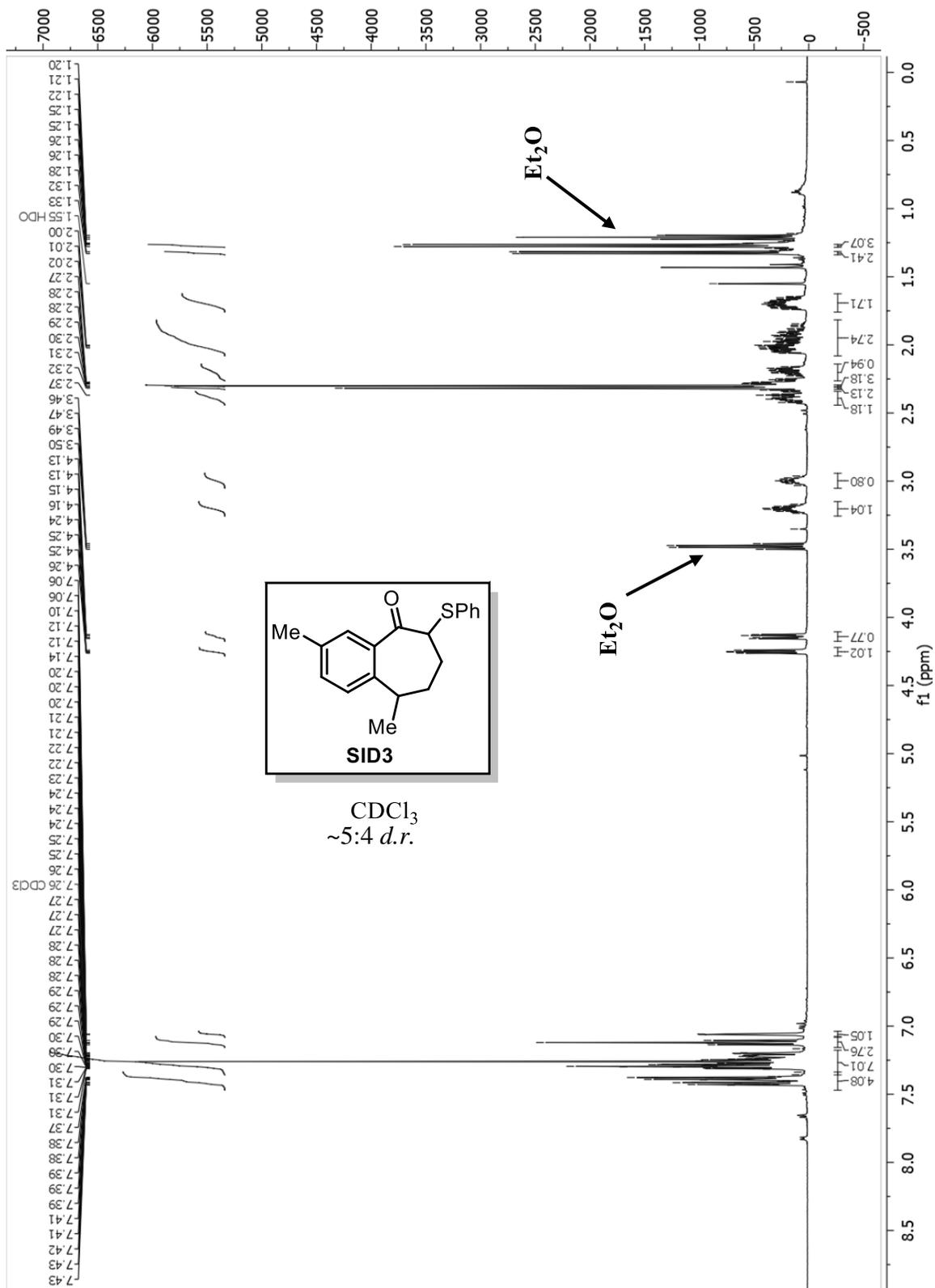


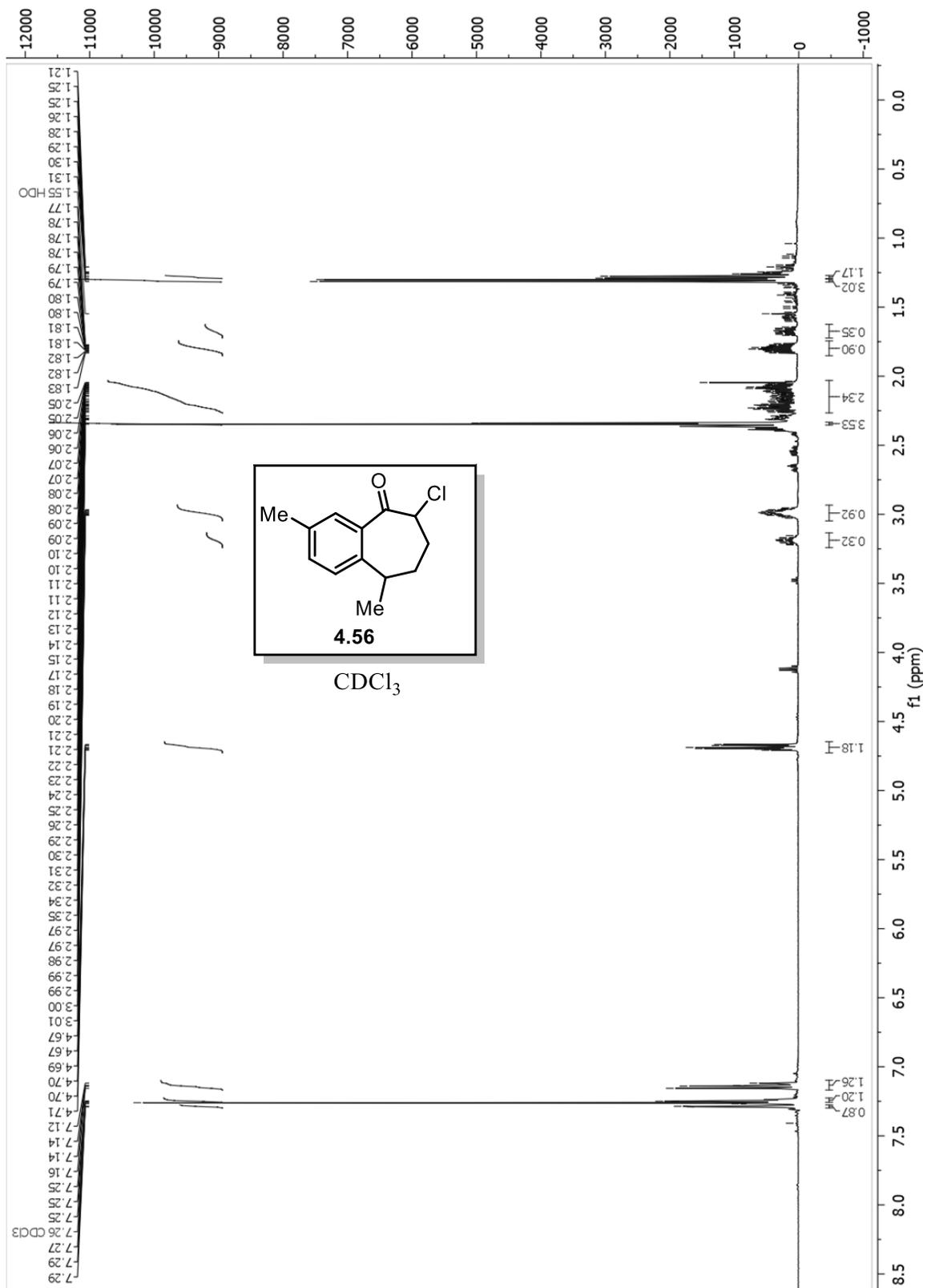


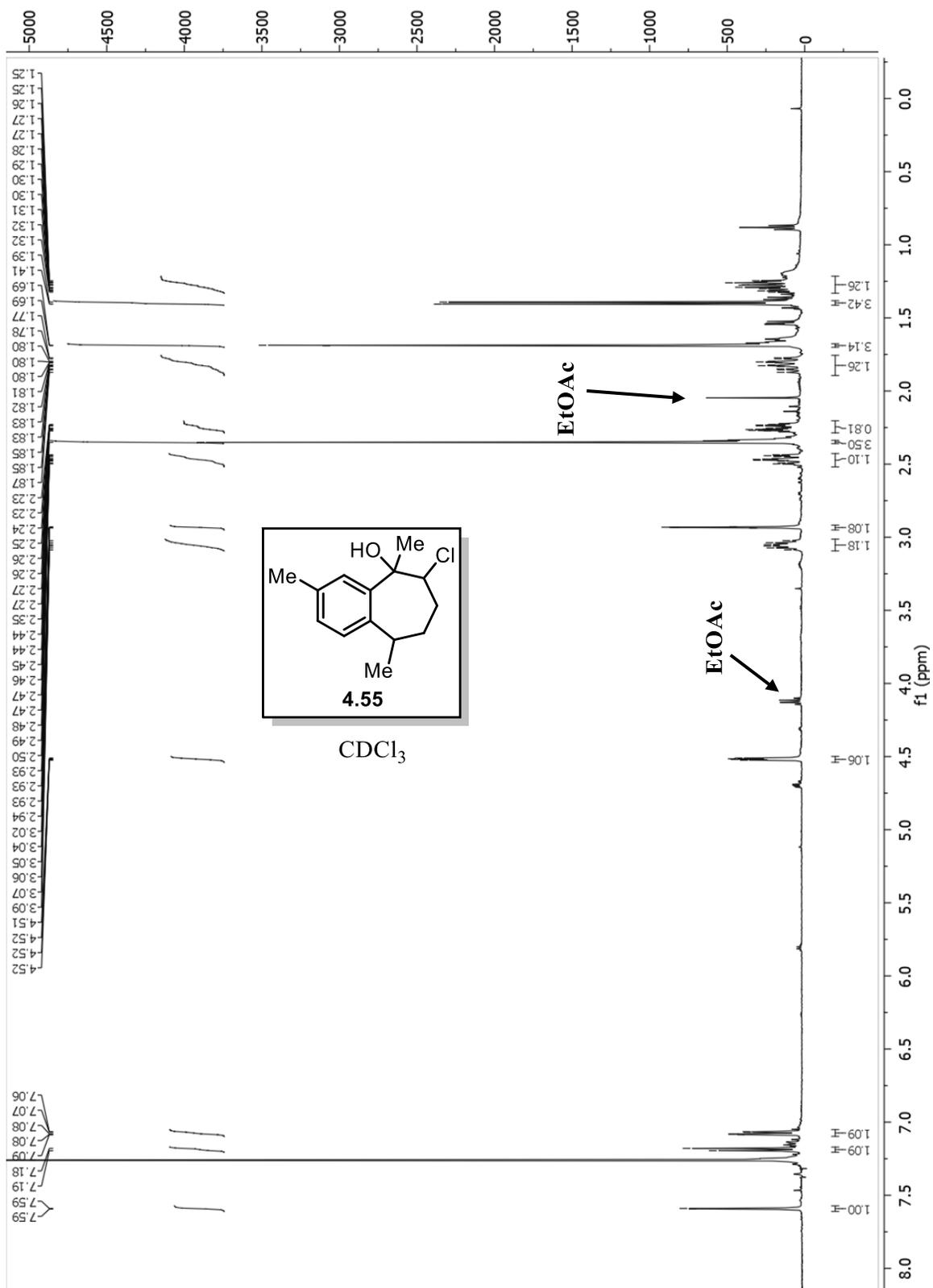


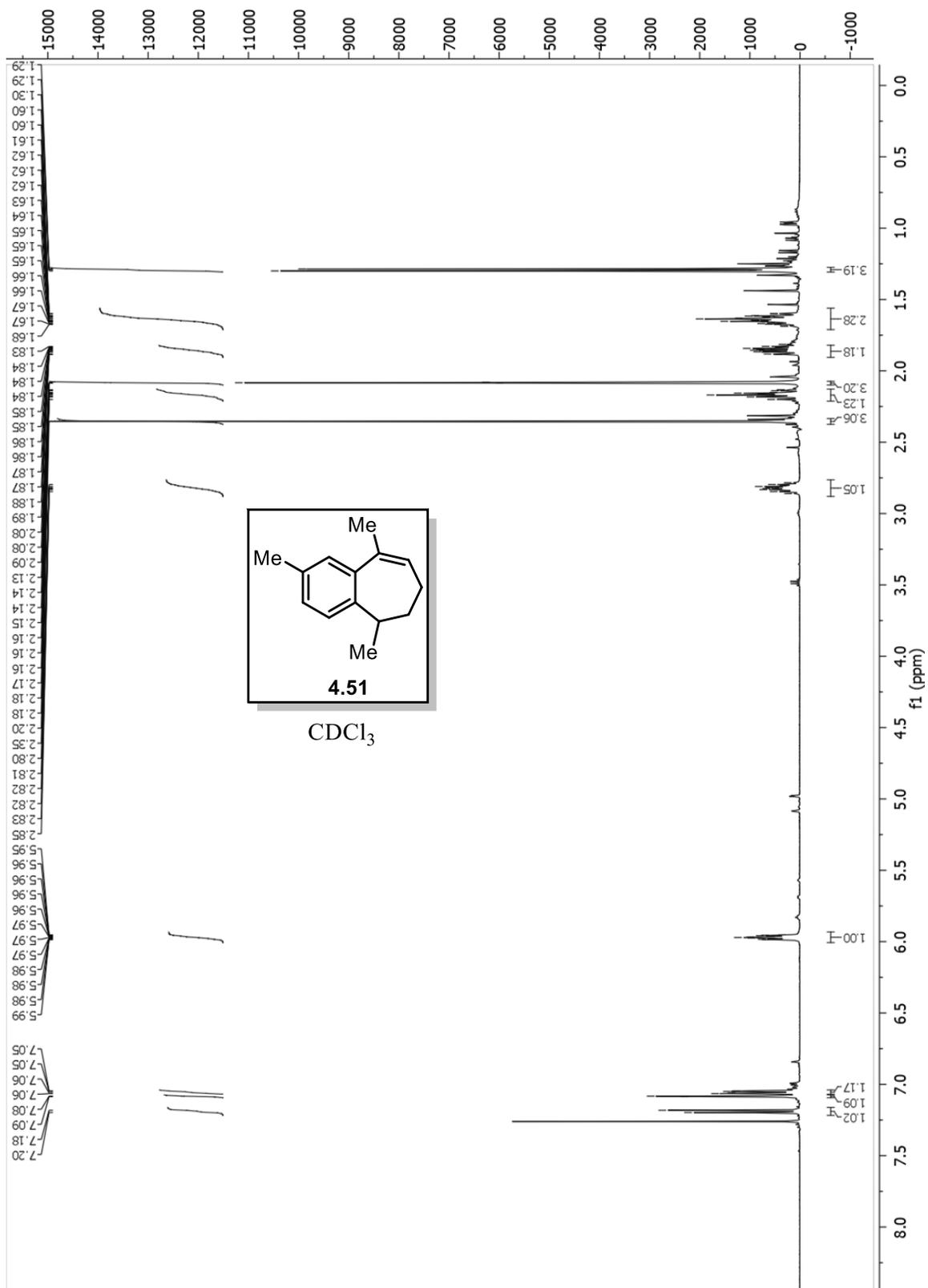


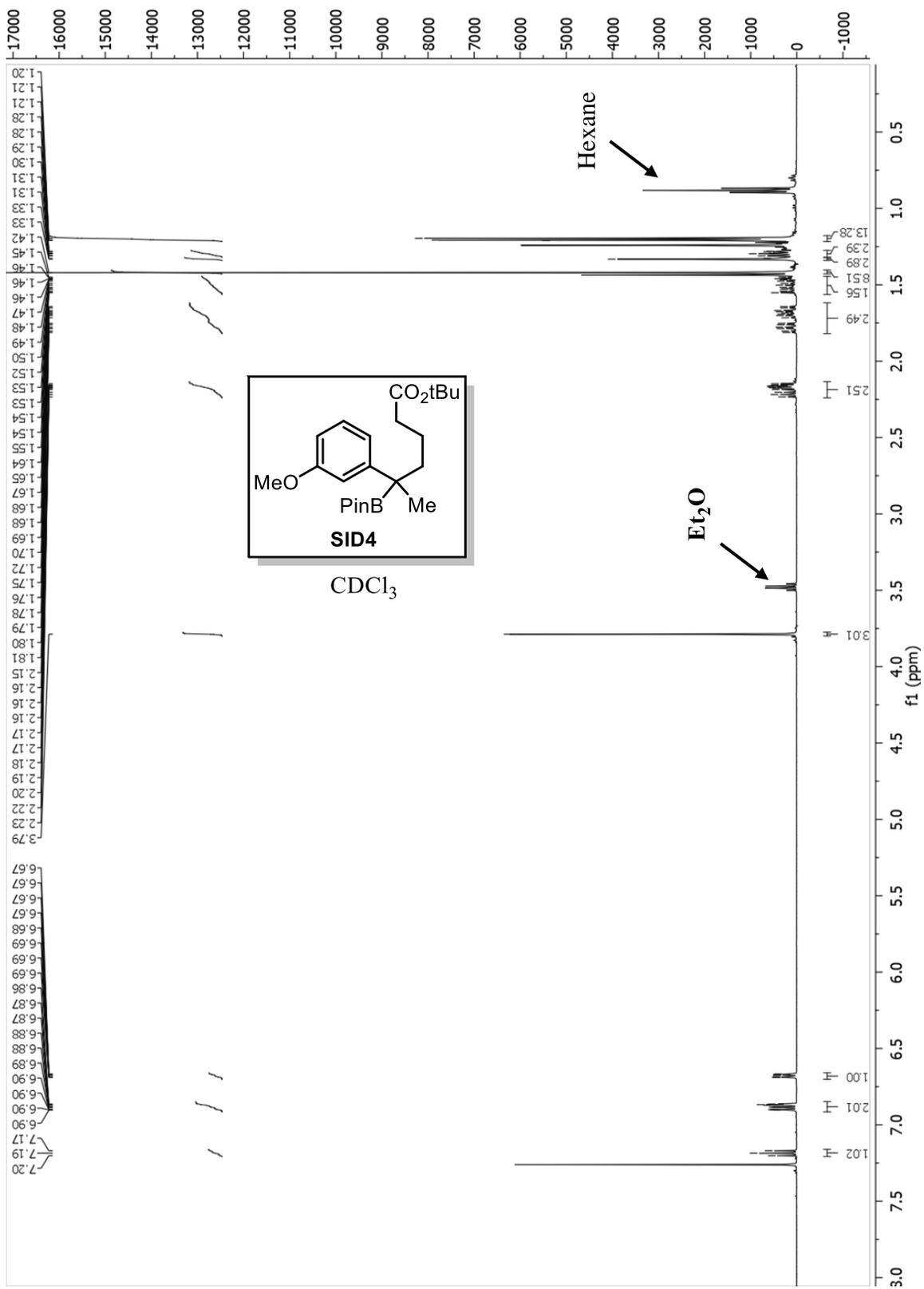


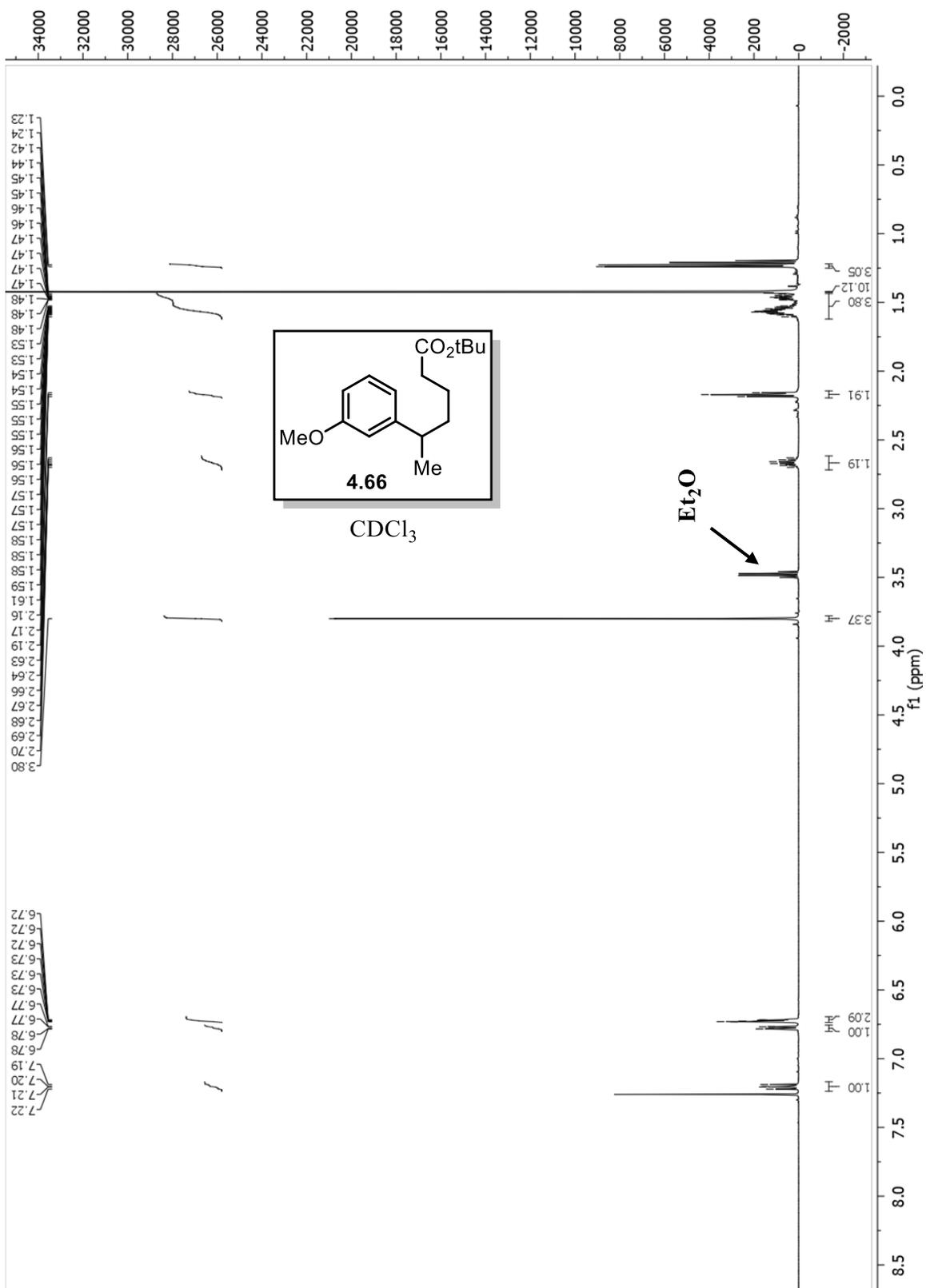


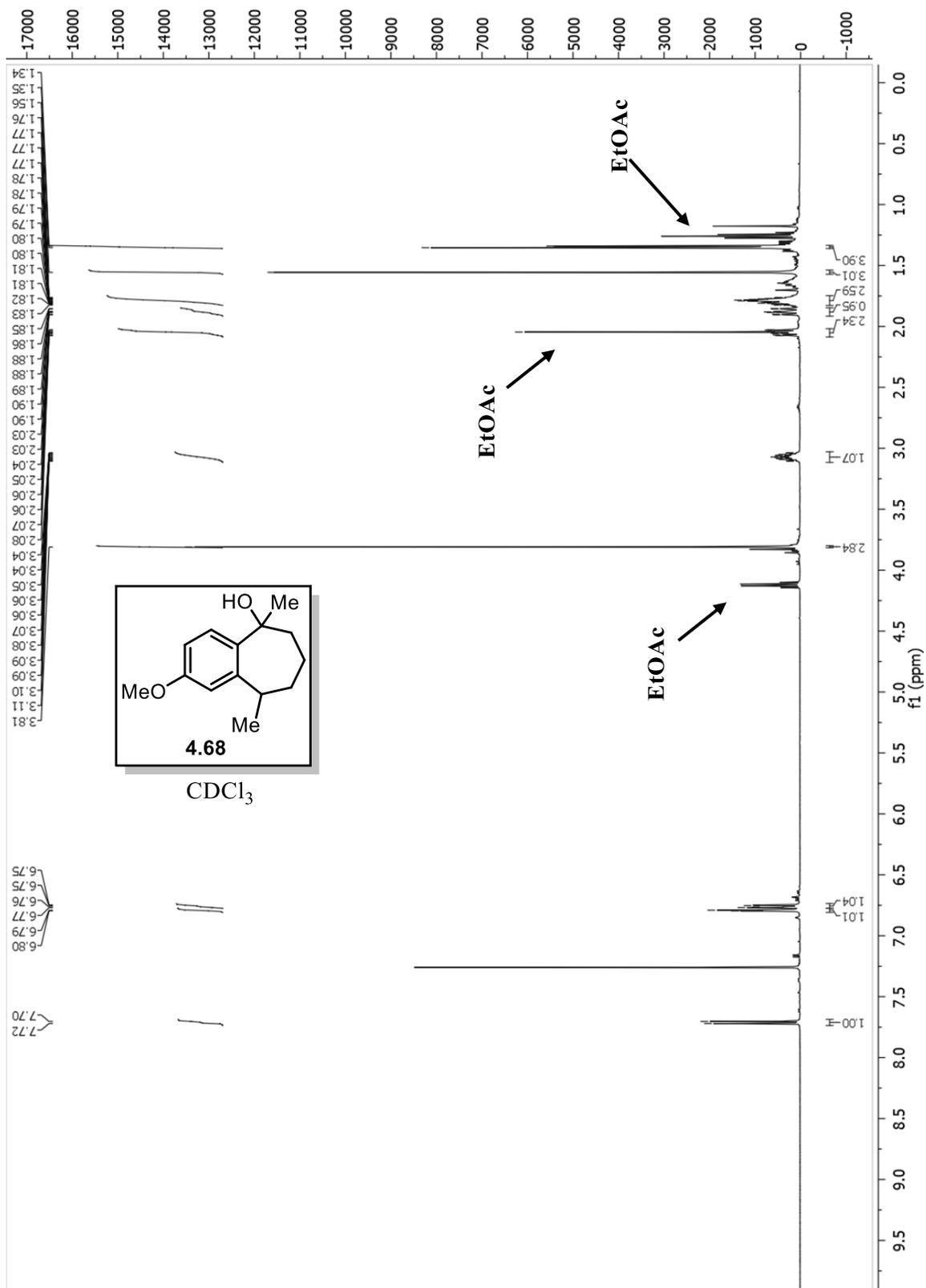


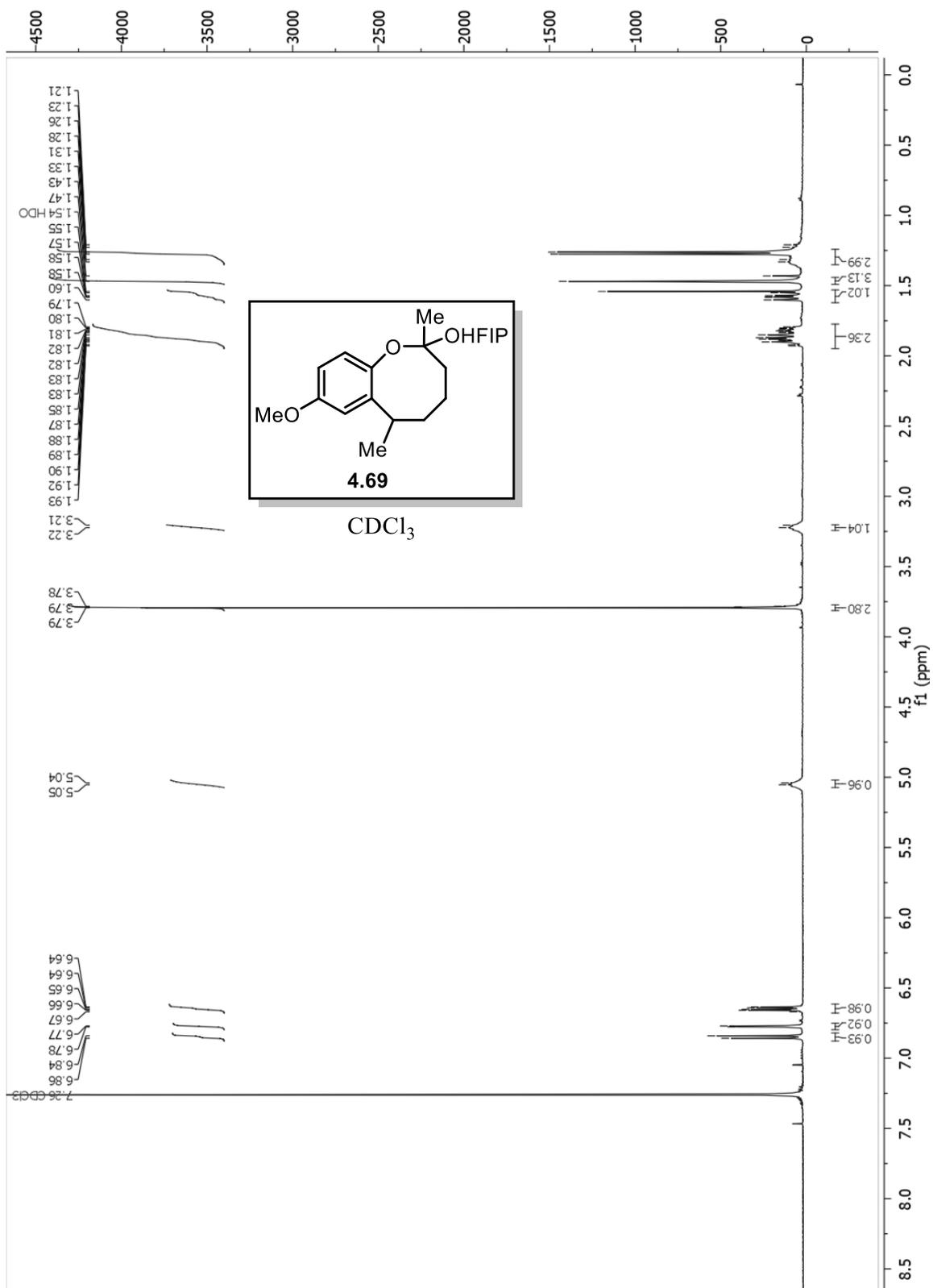


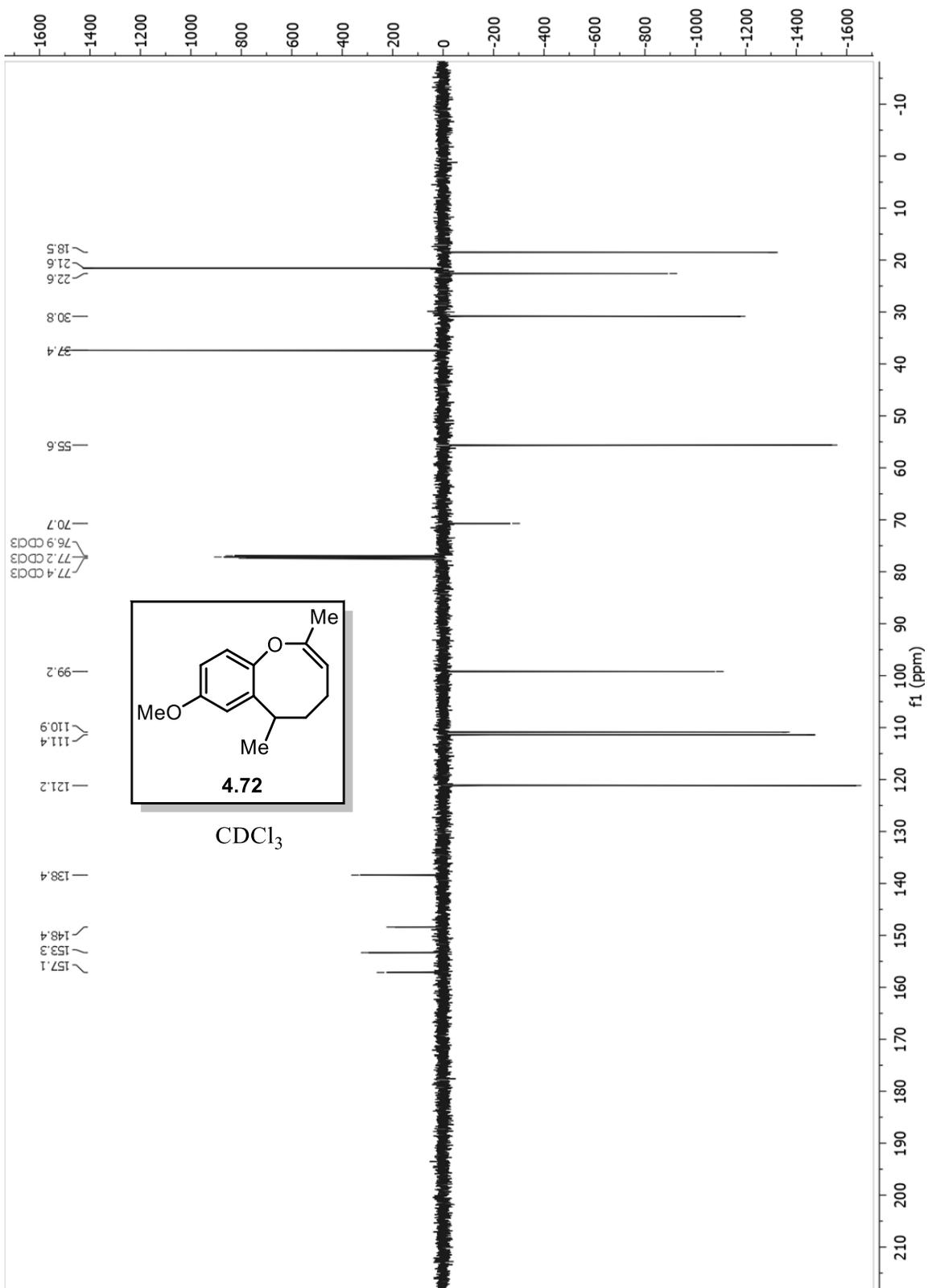


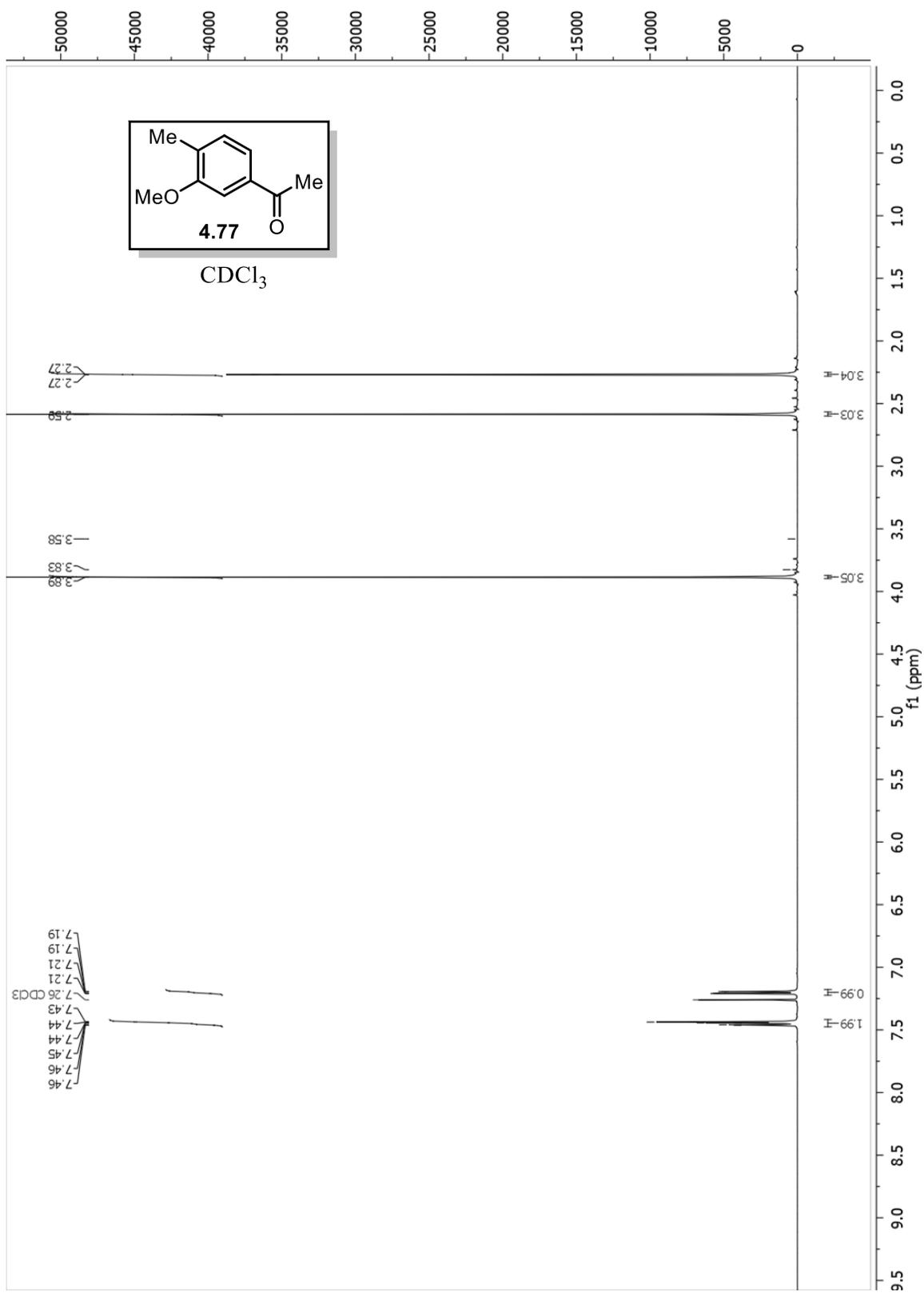


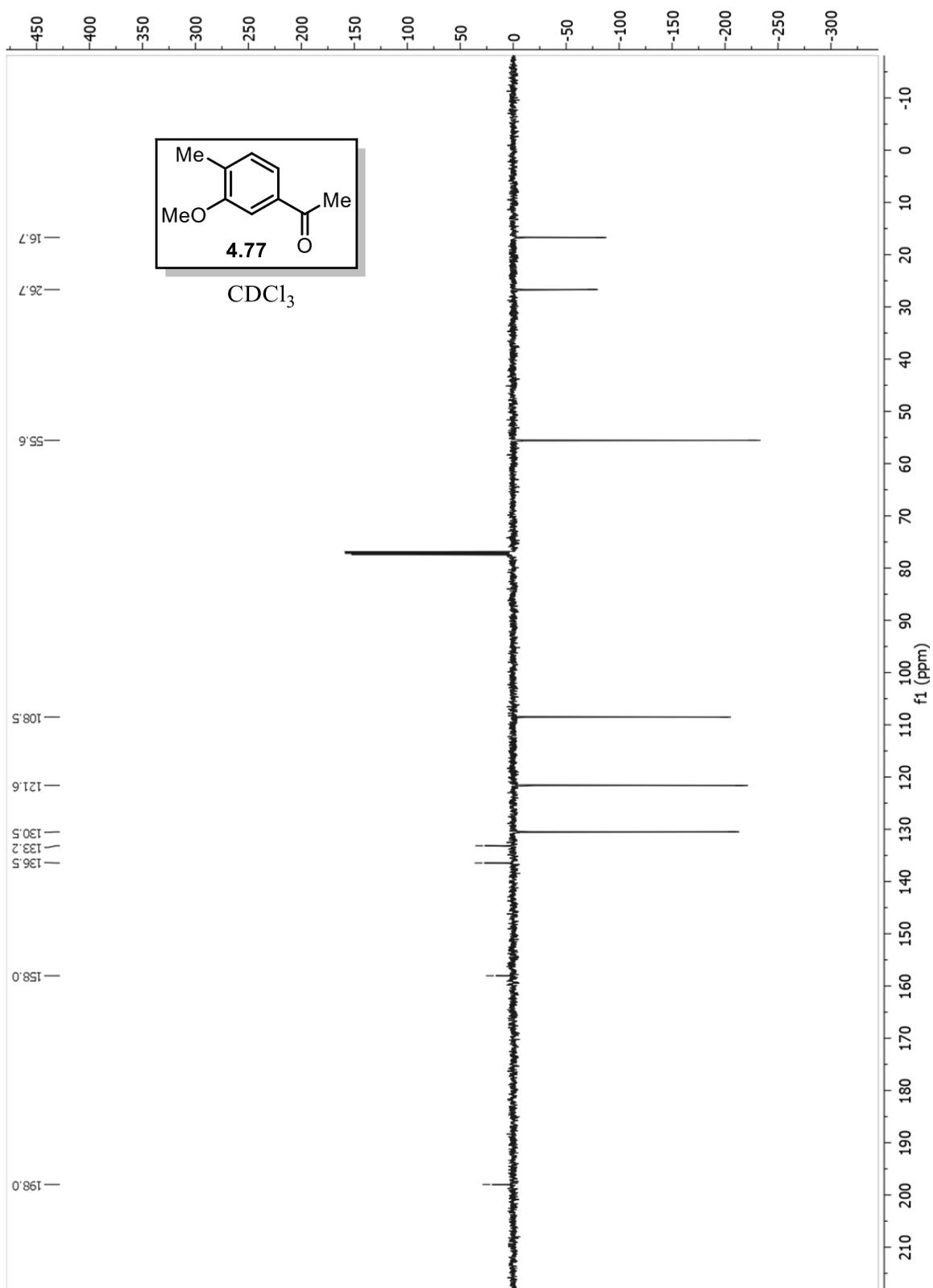


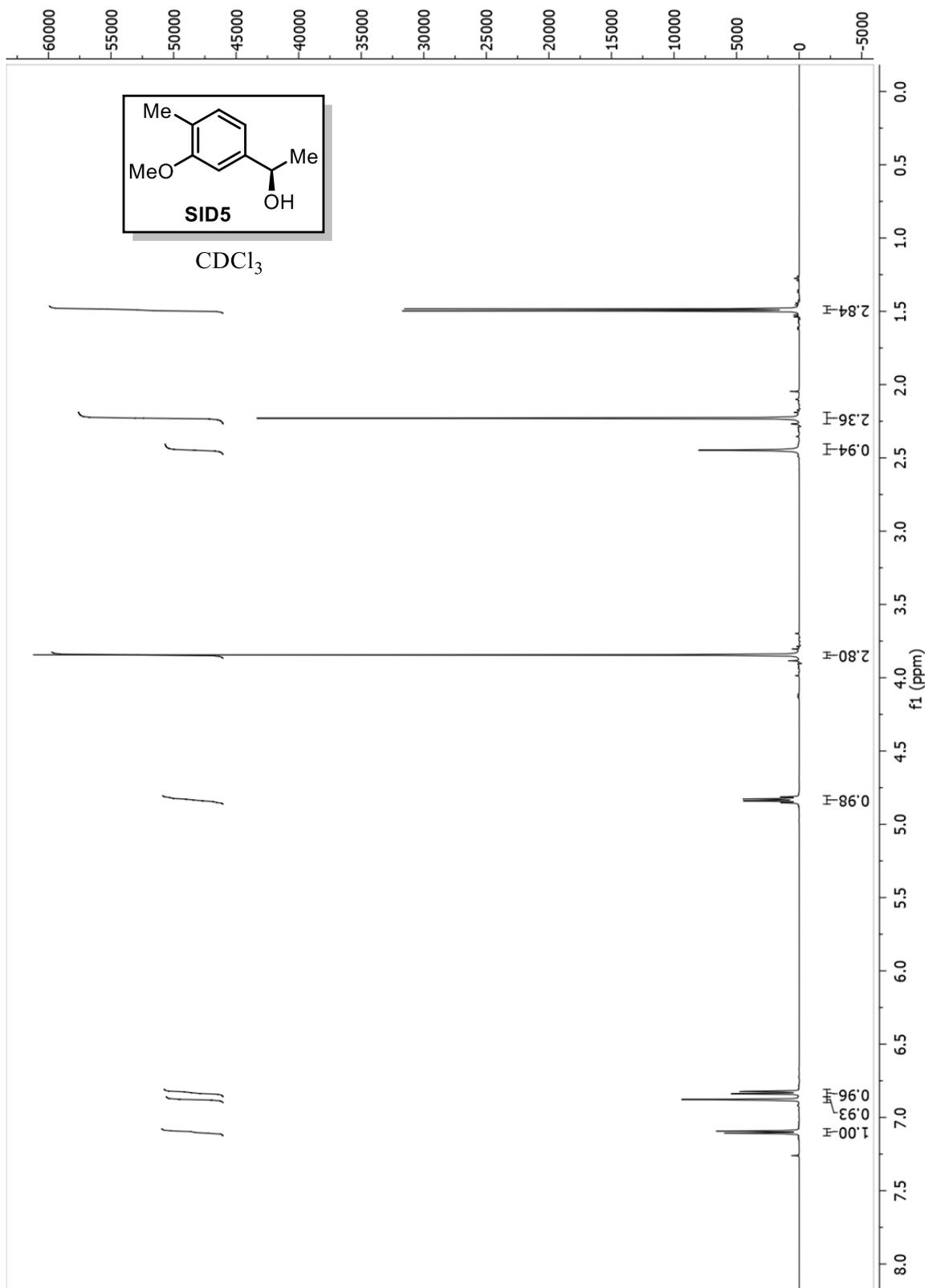


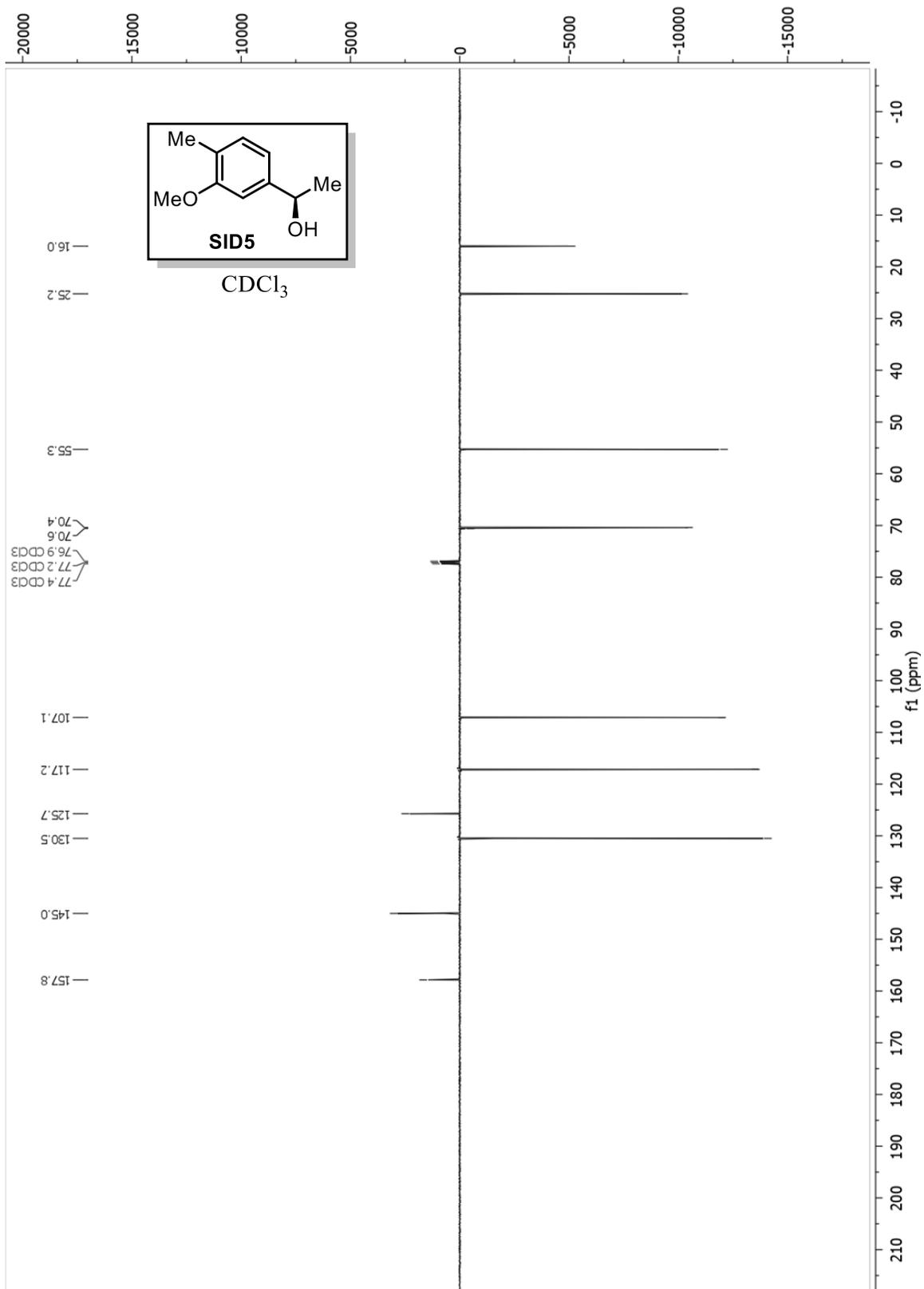


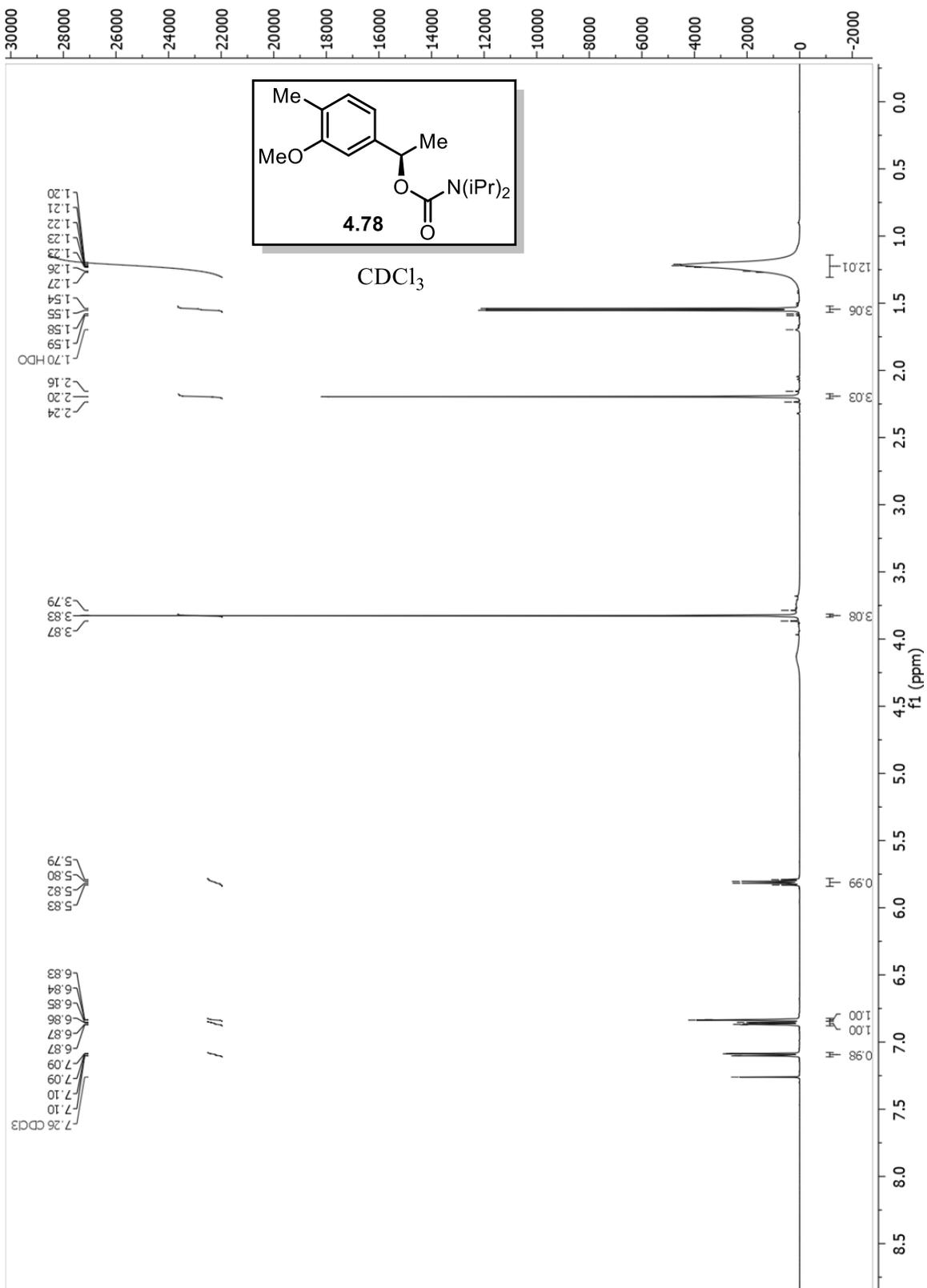


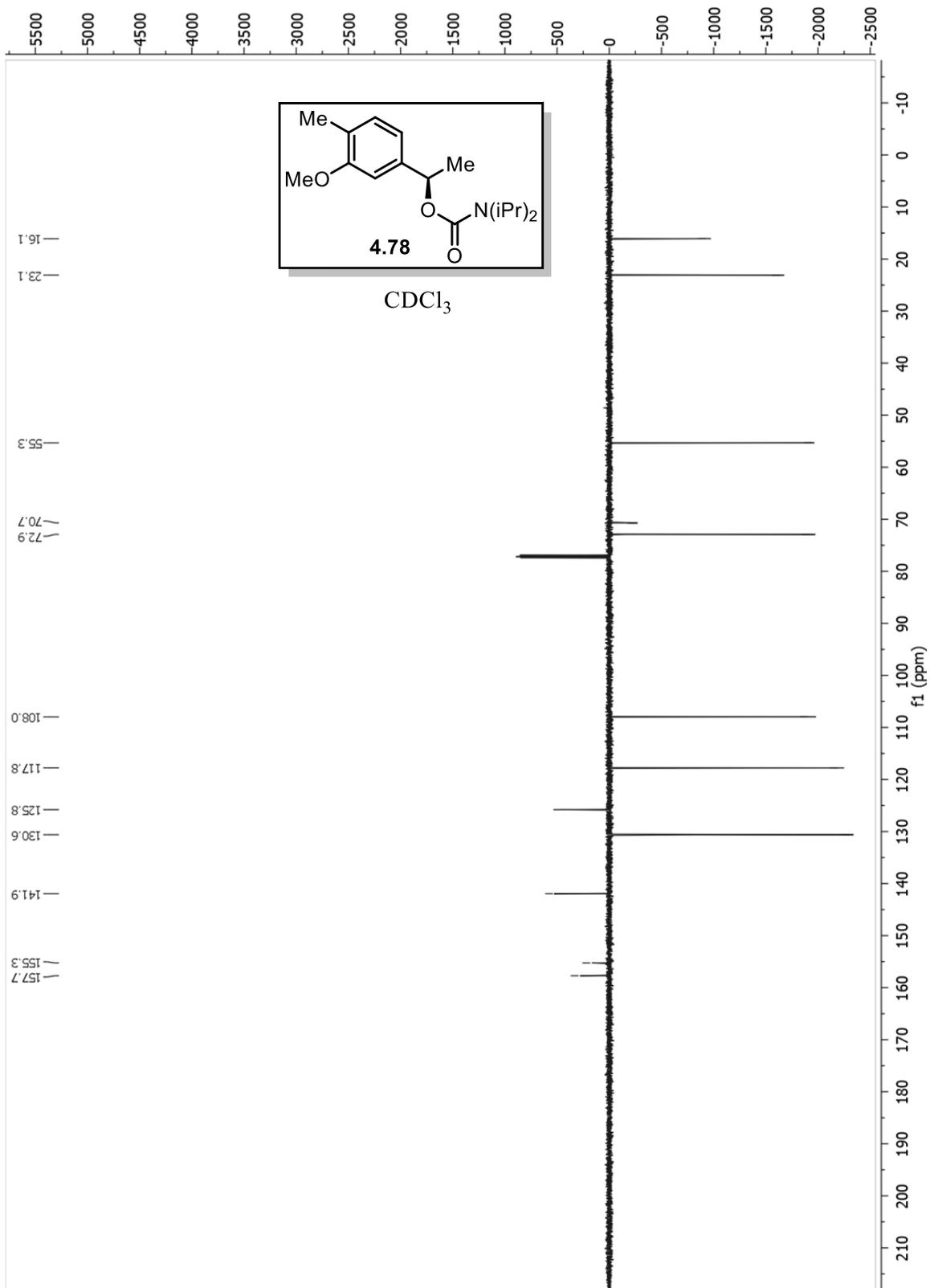


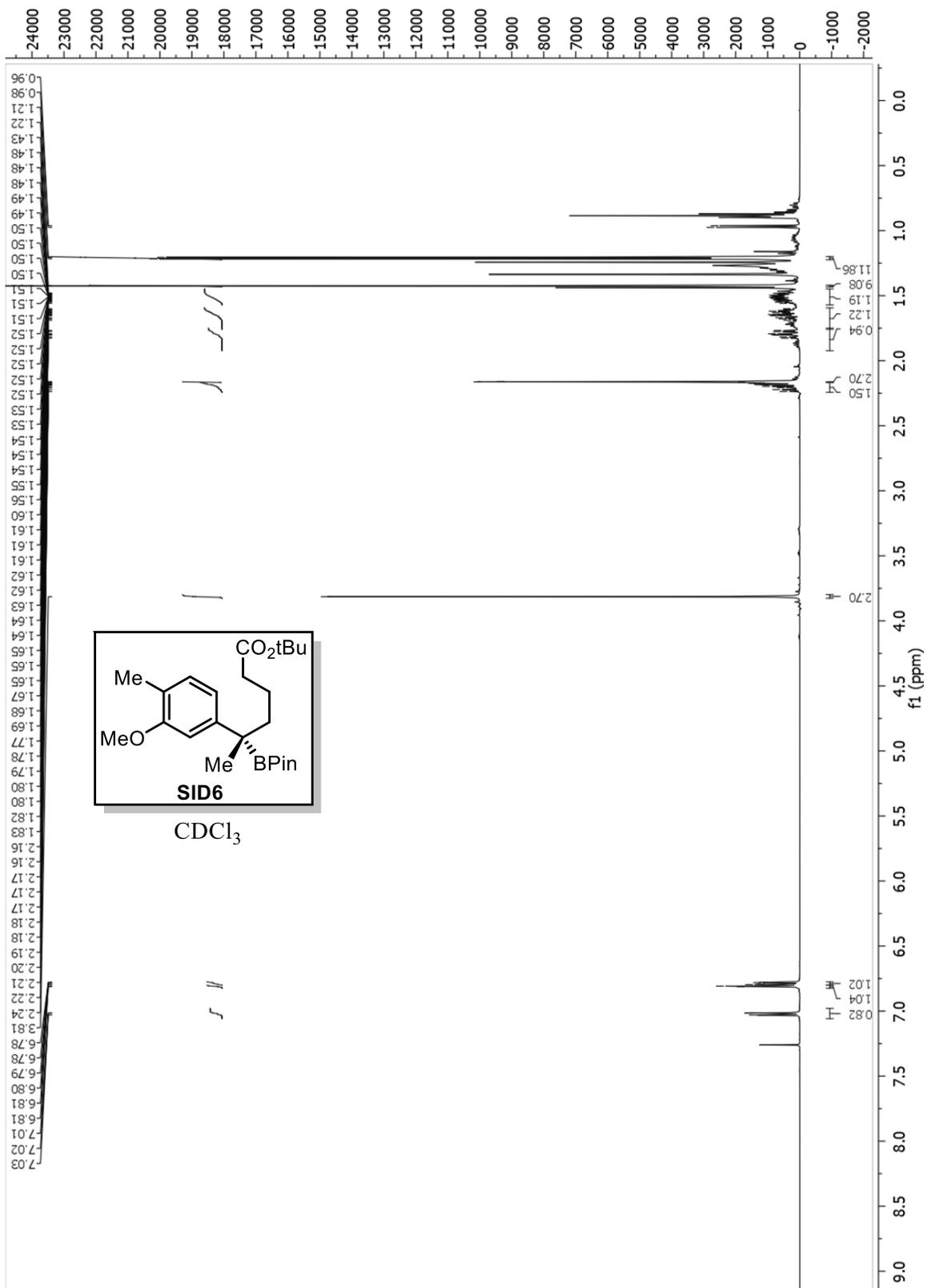


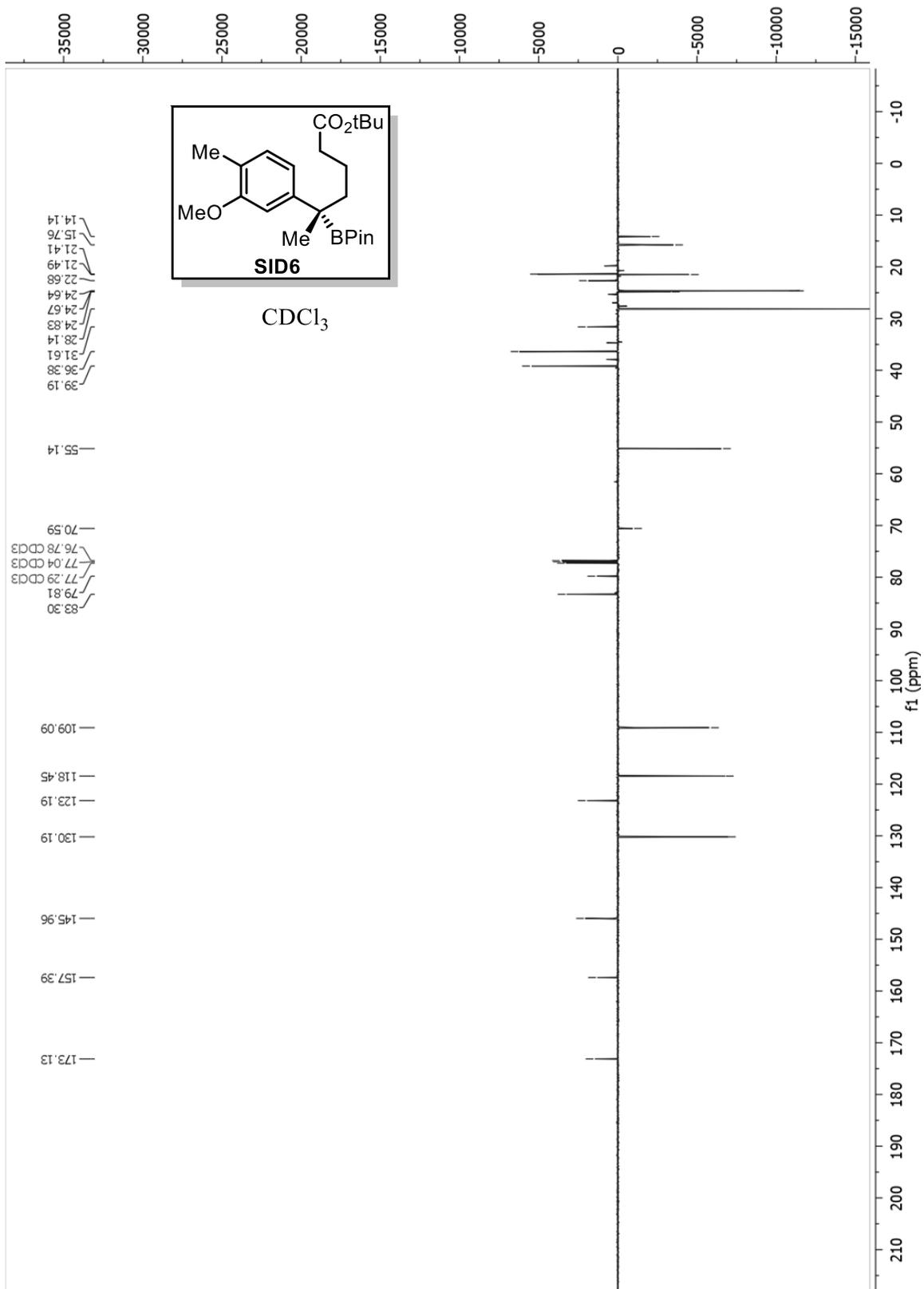


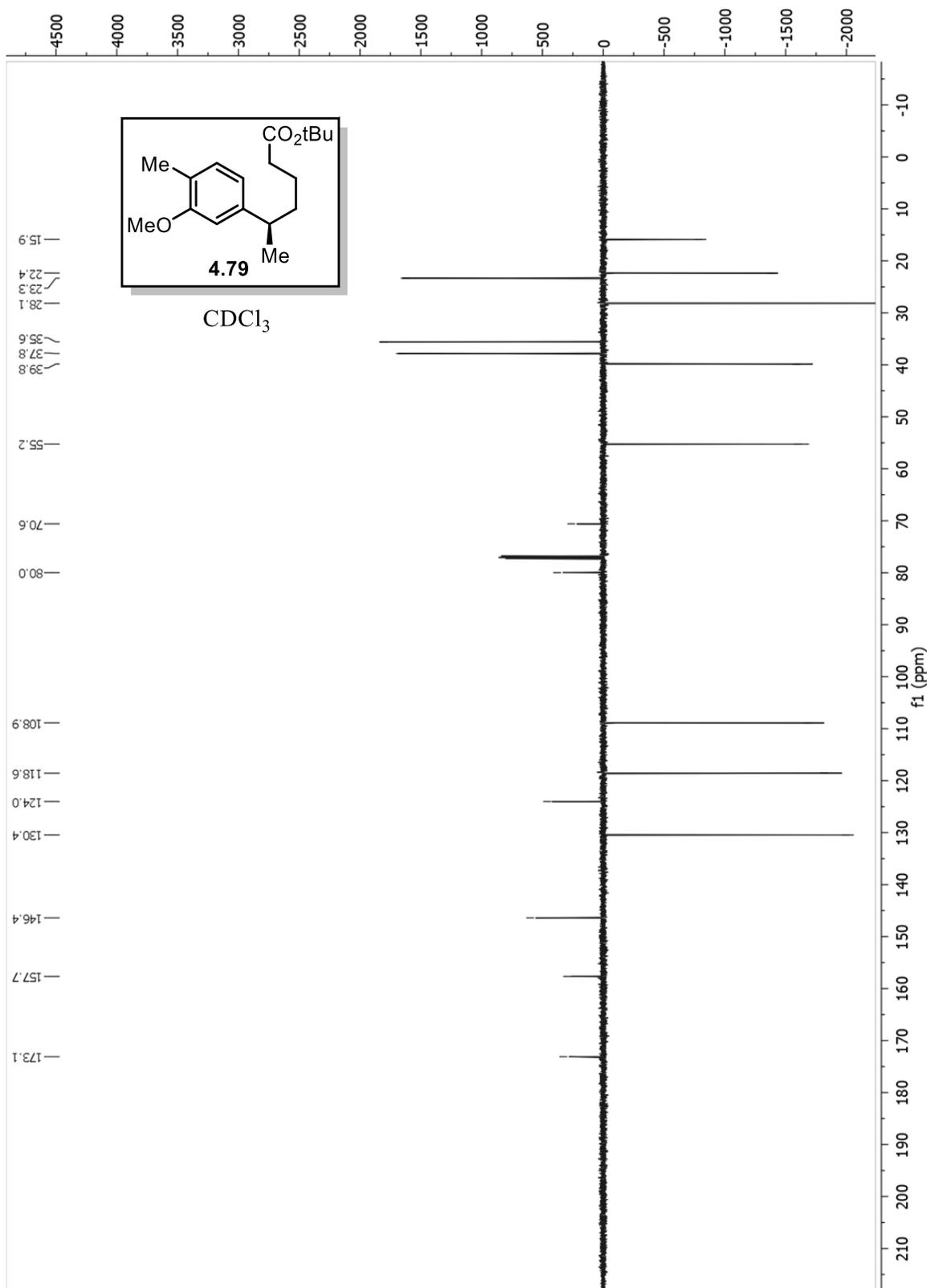


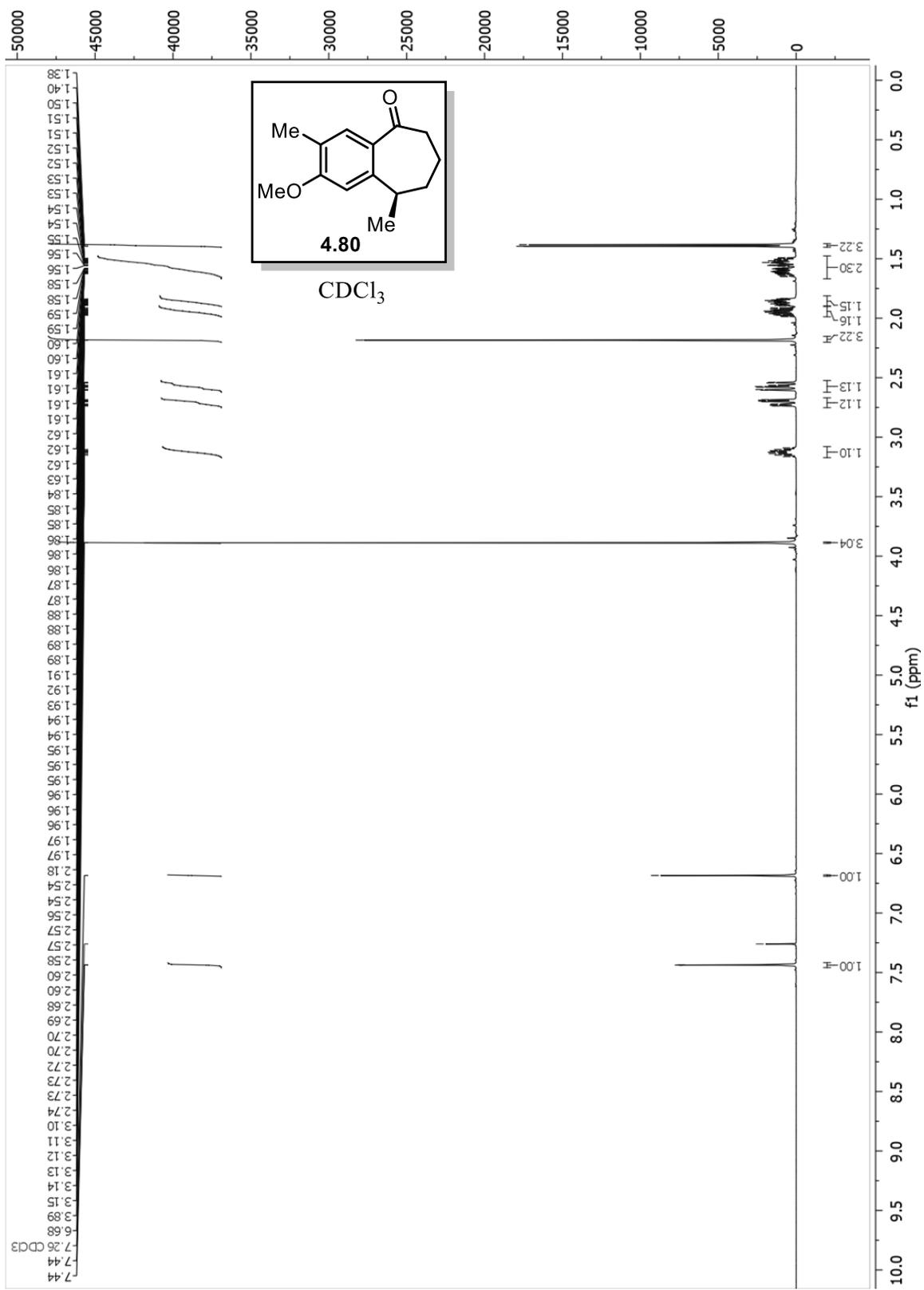


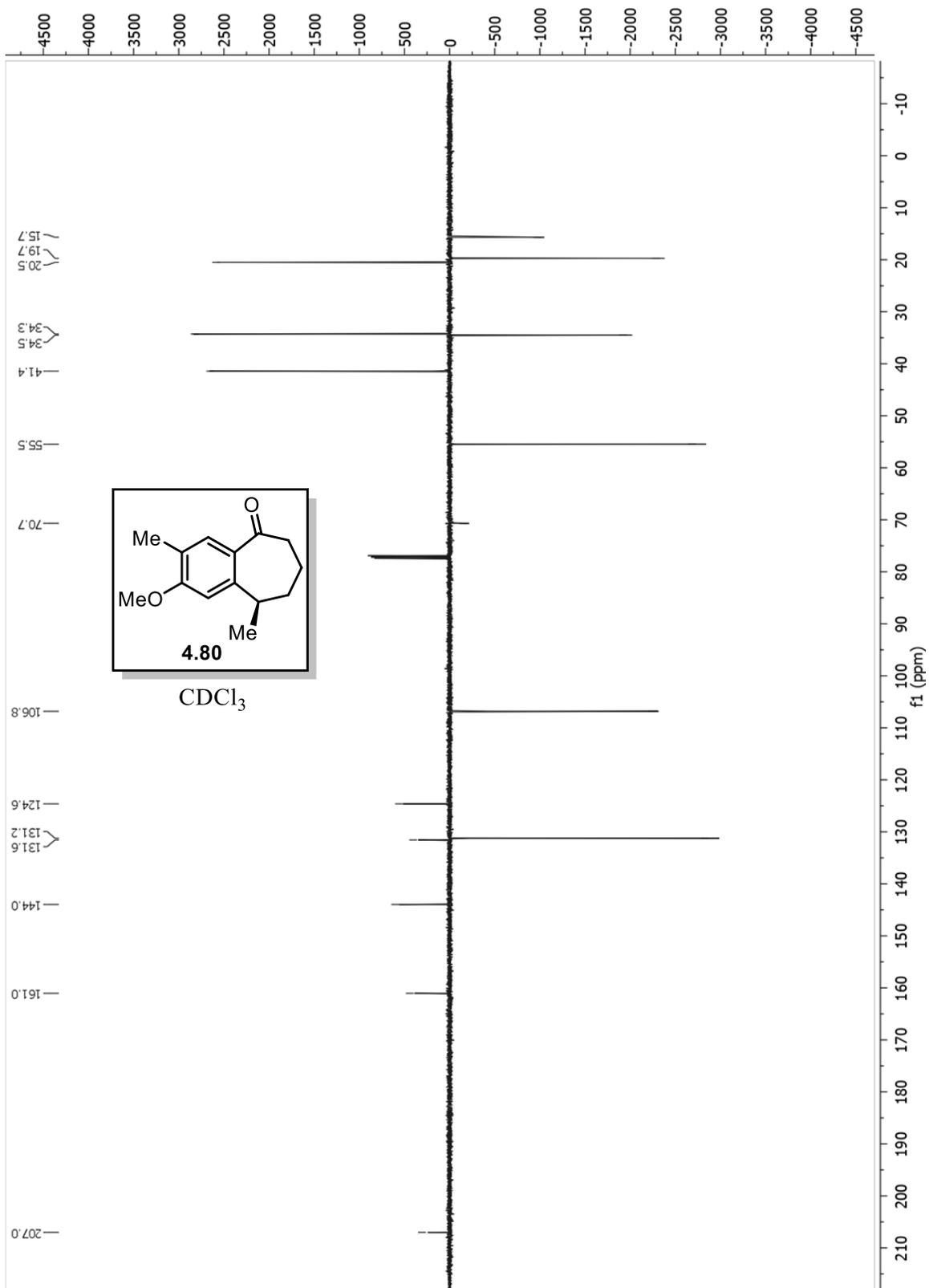


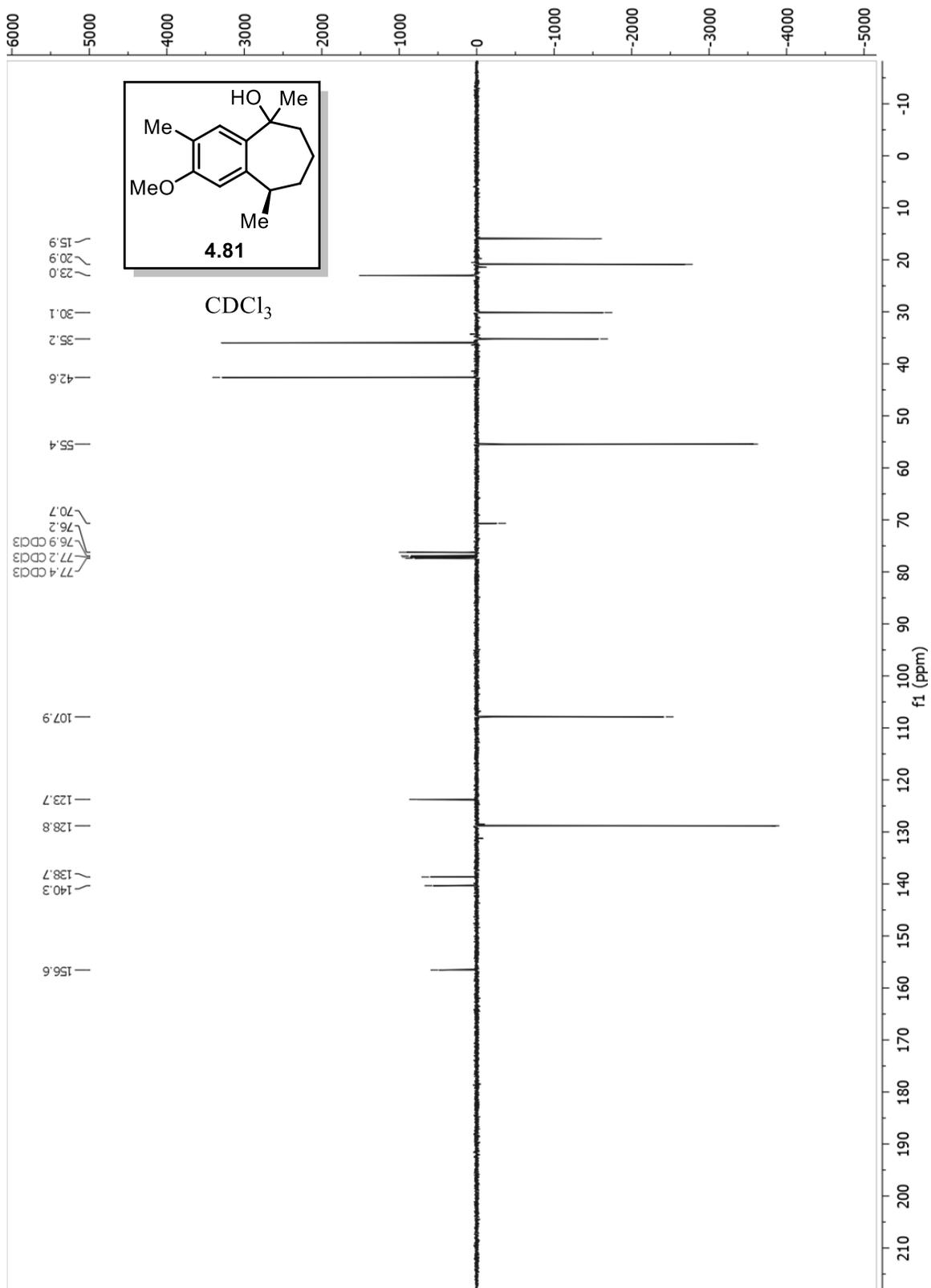


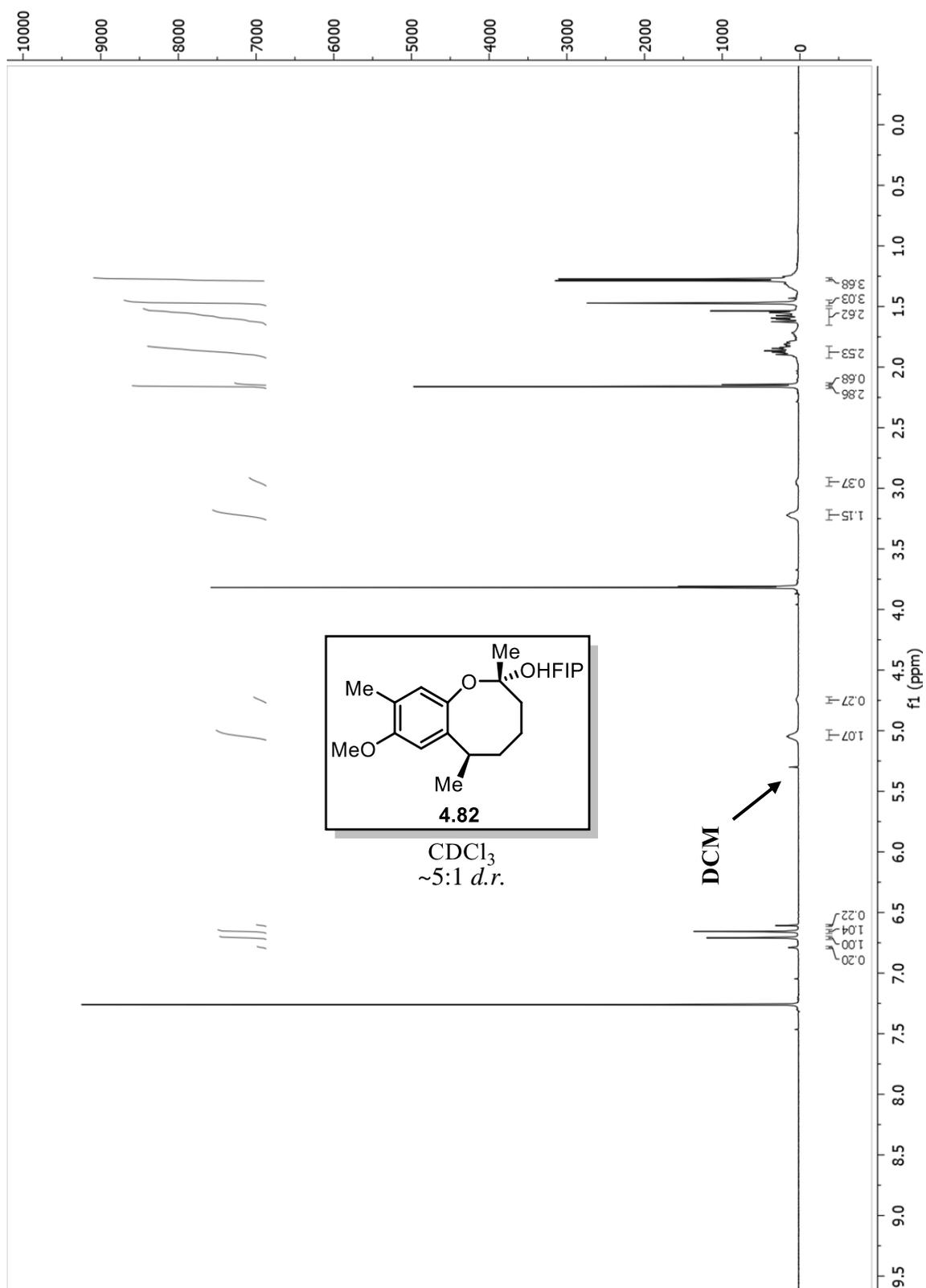


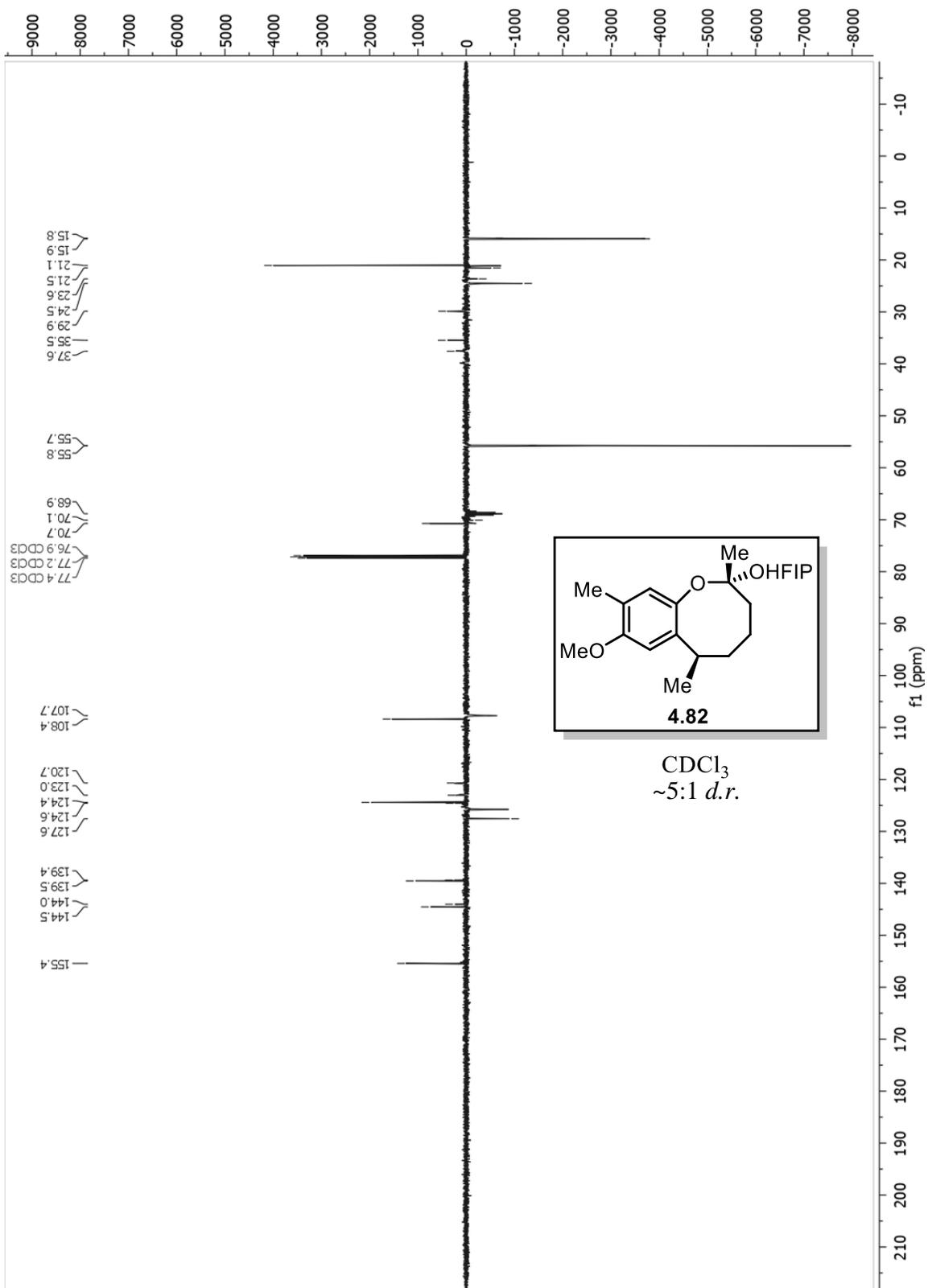


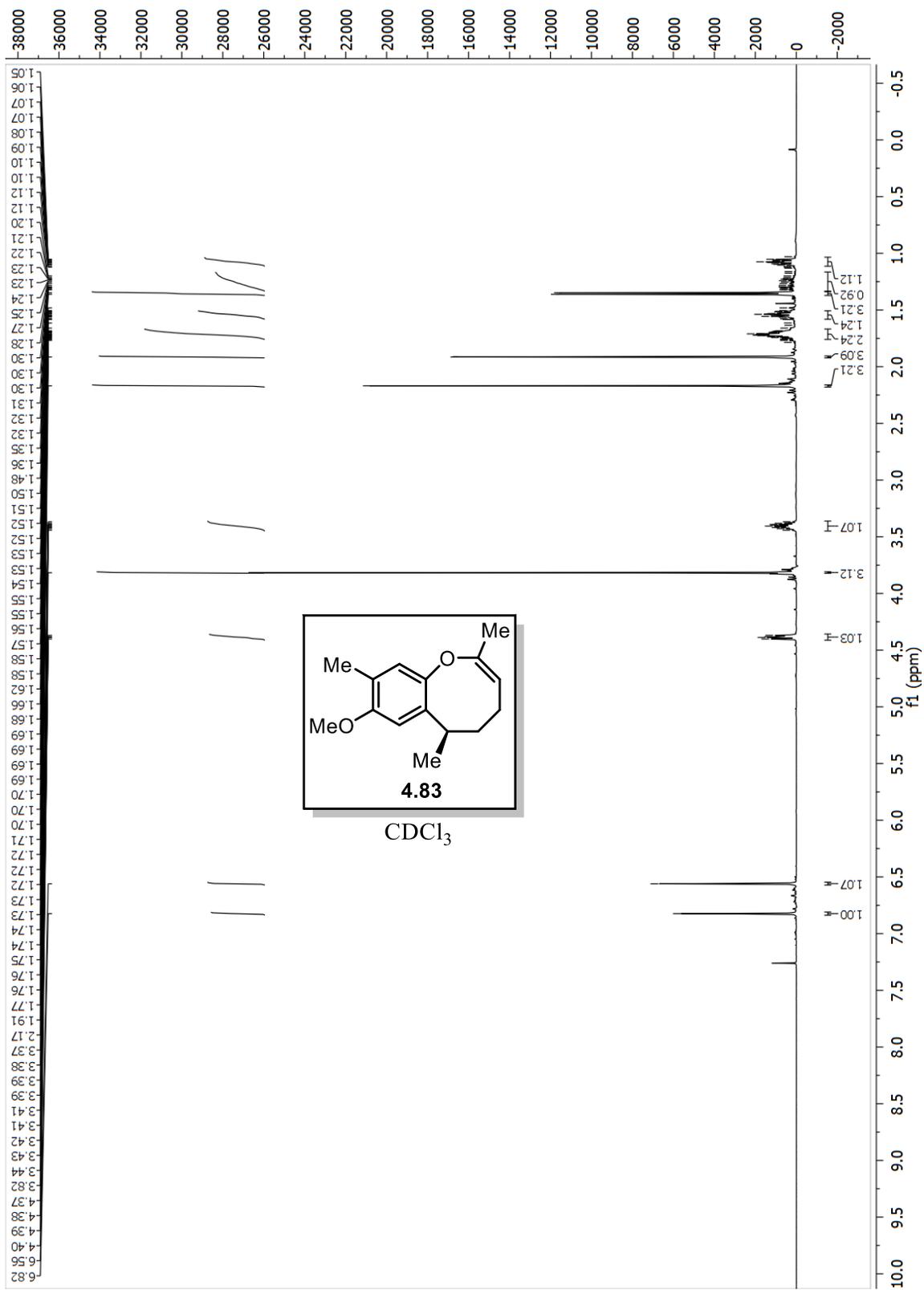


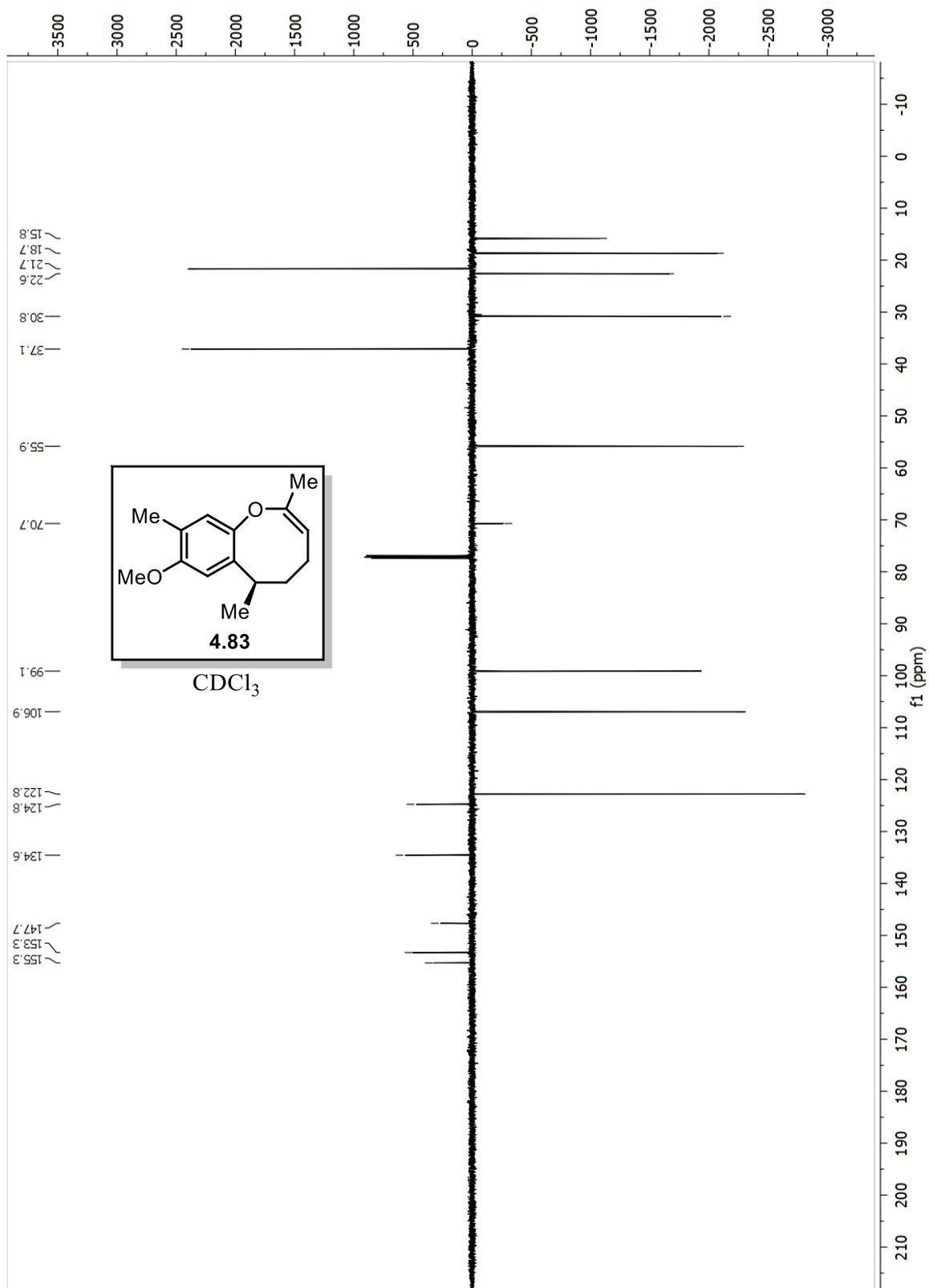


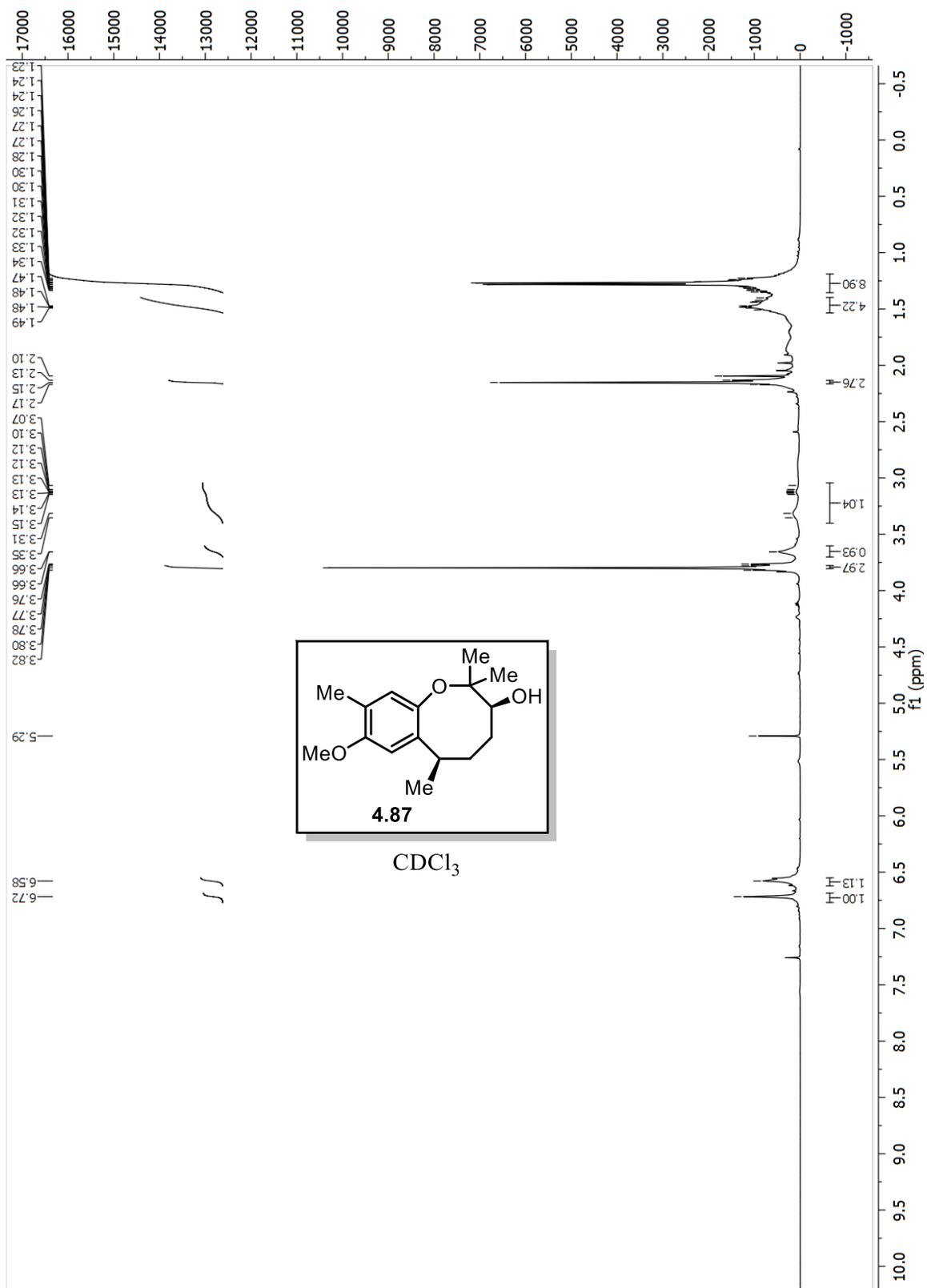


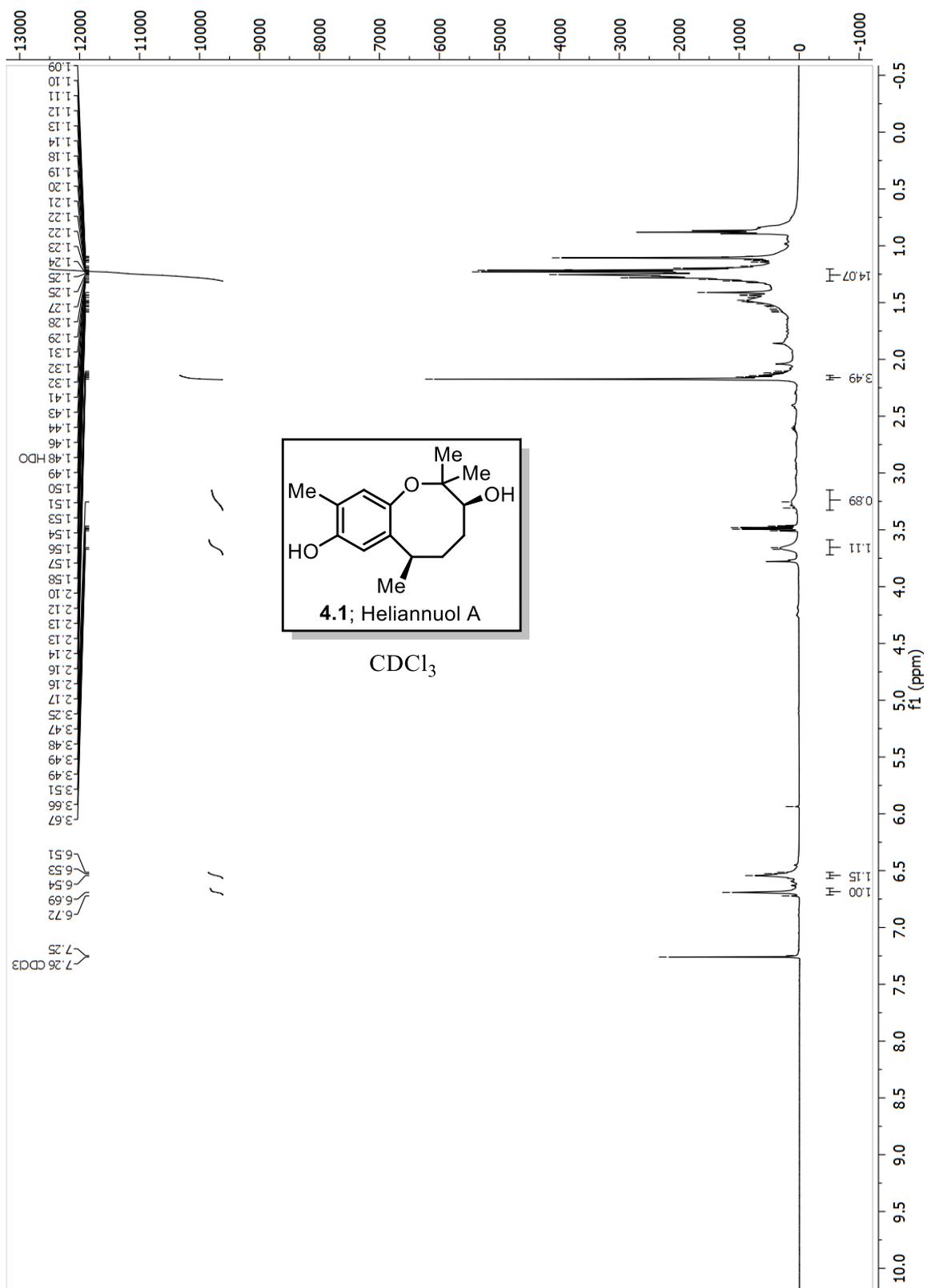












D10: CRYSTAL REPORT FOR 4.82

Single crystals of $C_{18}H_{22}F_6O_3$ [4.82] were selected using a MiTeGEN loop and paratone oil. A suitable crystal was selected and run on a 'Bruker APEX-II CCD' diffractometer. The crystal was kept at 99.98 K during data collection. Using Olex2, the structure was solved with the olex2.solve structure solution program using Charge Flipping and refined with the XL refinement package using Least Squares minimisation.

Crystal Data for $C_{18}H_{22}F_6O_3$ ($M = 400.35$ g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 8.2136(13)$ Å, $b = 9.9790(15)$ Å, $c = 22.872(3)$ Å, $V = 1874.6(5)$ Å³, $Z = 4$, $T = 99.98$ K, $\mu(\text{MoK}\alpha) = 0.134$ mm⁻¹, $D_{\text{calc}} = 1.419$ g/cm³, 30323 reflections measured ($3.562^\circ \leq 2\theta \leq 56.016^\circ$), 4526 unique ($R_{\text{int}} = 0.0281$, $R_{\text{sigma}} = 0.0210$) which were used in all calculations. The final R_1 was 0.0326 ($I > 2\sigma(I)$) and wR_2 was 0.0809 (all data).

Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

1. Twinned data refinement Scales: 1.1(6) -0.1(6)
2. Fixed Uiso At 1.2 times of: All C(H) groups, All C(H,H) groups; At 1.5 times of: All C(H,H,H) groups
- 3.a Ternary CH refined with riding coordinates: C9(H9), C16(H16)
- 3.b Secondary CH2 refined with riding coordinates: C10(H10A,H10B), C12(H12A,H12B), C11(H11A,H11B)
- 3.c Aromatic/amide H refined with riding coordinates: C6(H6), C3(H3)
- 3.d Idealised Me refined as rotating group: C14(H14A,H14B,H14C), C7(H7A,H7B,H7C), C15(H15A,H15B,H15C), C8(H8A,H8B,H8C)

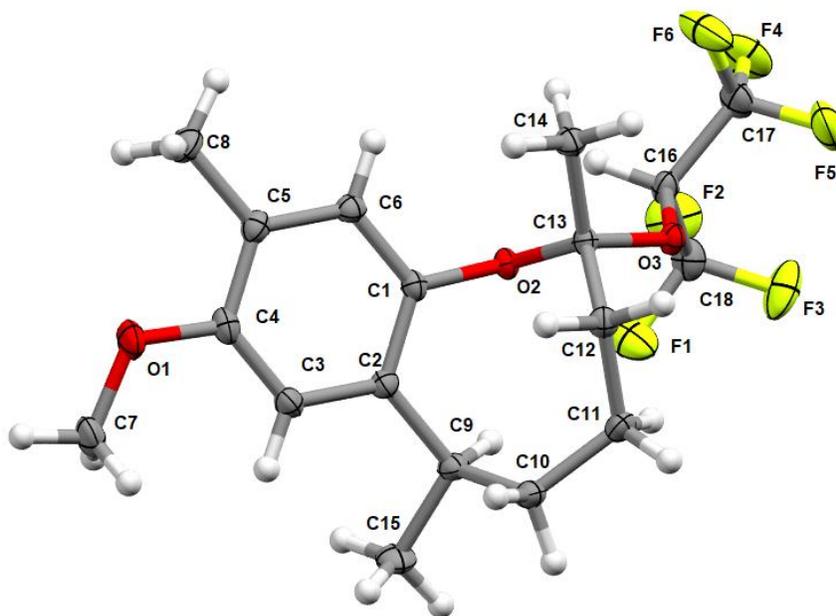


Figure D2: Thermal Ellipsoid plot for 4.82 shown at 50% probability.

Table D1: Crystal data and structure refinement for 4.82

Identification code	4.82
Empirical formula	$C_{18}H_{22}F_6O_3$
Formula weight	400.35
Temperature/K	99.98
Crystal system	orthorhombic
Space group	$P2_12_12_1$
$a/\text{\AA}$	8.2136(13)
$b/\text{\AA}$	9.9790(15)
$c/\text{\AA}$	22.872(3)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90

Volume/Å ³	1874.6(5)
Z	4
ρ _{calc} /cm ³	1.419
μ/mm ⁻¹	0.134
F(000)	832.0
Crystal size/mm ³	0.21 × 0.2 × 0.19
Radiation	MoKα (λ = 0.71073)
2θ range for data collection/°	3.562 to 56.016
Index ranges	-10 ≤ h ≤ 10, -13 ≤ k ≤ 13, -30 ≤ l ≤ 27
Reflections collected	30323
Independent reflections	4526 [R _{int} = 0.0281, R _{sigma} = 0.0210]
Data/restraints/parameters	4526/0/249
Goodness-of-fit on F ²	1.055
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0326, wR ₂ = 0.0779
Final R indexes [all data]	R ₁ = 0.0385, wR ₂ = 0.0809
Largest diff. peak/hole / e Å ⁻³	0.27/-0.20
Flack parameter	-0.1(6)

Table D2: Fractional Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Parameters (Å²×10³) for 4.82

U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij} tensor.

Atom	x	y	z	U(eq)
O3	1597.1(15)	4236.2(13)	7306.7(5)	16.1(3)

F1	3984.0(18)	3138.7(15)	6646.9(6)	39.5(3)
O2	2115.4(15)	5685.1(13)	6566.7(6)	15.4(3)
F2	5785.4(16)	3327.9(16)	7321.9(7)	43.1(4)
F3	3753.7(19)	2011.0(13)	7437.6(8)	44.5(4)
O1	790.1(18)	9433.4(14)	4848.6(6)	25.1(3)
F5	2456(2)	3346.5(17)	8389.0(7)	47.9(4)
F4	4809.4(17)	4277.3(17)	8355.2(6)	43.5(4)
F6	2658(2)	5474.5(16)	8372.8(6)	48.6(4)
C1	1670(2)	6608.1(18)	6131.2(8)	15.4(4)
C6	1774(2)	7975.4(19)	6249.2(8)	17.2(4)
C2	1310(2)	6130.2(18)	5574.9(8)	16.1(4)
C4	1073(2)	8450.7(19)	5258.9(8)	19.2(4)
C3	996(2)	7084.5(19)	5139.9(8)	18.7(4)
C13	892(2)	5343.8(18)	6988.4(8)	14.8(3)
C9	1313(2)	4628.0(18)	5446.3(8)	18.0(4)
C5	1471(2)	8923.0(18)	5818.0(8)	18.9(4)
C10	-280(2)	3942.8(19)	5637.2(8)	20.1(4)
C14	532(2)	6504.1(19)	7401.4(8)	19.5(4)
C17	3292(3)	4353(2)	8157.8(9)	25.4(4)
C16	3224(2)	4359.9(19)	7486.7(8)	18.0(4)
C18	4190(3)	3200(2)	7221.1(9)	25.4(4)
C12	-663(2)	4803.8(19)	6713.9(8)	17.7(4)

C11	-464(3)	3616.9(19)	6289.9(9)	20.9(4)
C7	702(3)	9016(2)	4252.0(9)	27.2(5)
C15	1650(3)	4326(2)	4800.9(9)	26.6(4)
C8	1579(3)	10404.0(19)	5937.5(10)	26.6(4)

Table D3: Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 4.82

*The Anisotropic displacement factor exponent takes the form:-
 $2\pi^2 [h^2 a^{*2} U_{11} + 2hka^* b^* U_{12} + \dots]$.*

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O3	14.8(6)	15.1(6)	18.6(6)	4.0(5)	-3.3(5)	0.0(5)
F1	46.6(8)	40.4(8)	31.6(7)	-6.4(6)	-0.8(6)	21.5(7)
O2	15.0(6)	16.1(6)	15.1(6)	2.7(5)	0.0(5)	1.3(5)
F2	16.5(6)	54.2(9)	58.7(10)	-3.3(7)	-1.4(6)	9.2(6)
F3	44.9(9)	19.5(6)	69.2(11)	11.4(7)	11.6(7)	8.5(6)
O1	32.7(8)	21.4(7)	21.4(7)	8.1(6)	0.4(6)	4.2(6)
F5	59.5(10)	58.0(10)	26.2(8)	18.9(7)	-6.7(7)	-21.5(8)
F4	29.3(7)	66.7(10)	34.6(8)	-0.2(7)	-17.3(6)	3.3(7)
F6	70.7(11)	52.4(9)	22.8(7)	-7.2(7)	-11.2(7)	29.0(9)
C1	15.1(8)	15.7(8)	15.2(9)	2.4(6)	1.0(6)	1.8(7)
C6	17.5(9)	17.2(9)	16.9(9)	-2.1(7)	1.4(7)	0.1(7)
C2	16.3(9)	15.6(8)	16.5(9)	0.0(6)	0.4(6)	1.6(7)
C4	19.1(9)	20.6(9)	18.0(9)	5.4(7)	2.3(7)	3.3(7)

C3	19.9(9)	21.1(9)	15.2(9)	1.5(7)	-1.2(7)	-0.3(7)
C13	15.1(8)	14.3(8)	15.1(9)	2.1(6)	-0.3(6)	1.2(7)
C9	22.2(10)	14.8(8)	17.0(9)	-2.4(7)	-1.2(7)	1.0(7)
C5	19.4(9)	15.3(8)	22.0(10)	0.4(7)	2.6(7)	0.7(7)
C10	24.5(10)	16.4(8)	19.4(9)	-2.7(7)	-3.8(7)	-0.7(7)
C14	22.8(9)	17.5(9)	18.1(9)	-1.8(7)	1.0(7)	2.5(7)
C17	25.5(10)	27.7(10)	23.0(10)	4.8(8)	-7.5(8)	0.7(9)
C16	16.3(9)	16.7(8)	21.1(9)	3.8(7)	-3.1(7)	-2.5(7)
C18	20.0(10)	25.9(10)	30.4(11)	5.7(8)	-0.6(8)	4.1(8)
C12	14.7(9)	19.2(9)	19.2(10)	1.6(7)	-1.3(7)	-0.6(7)
C11	23.7(10)	16.7(9)	22.3(10)	0.6(7)	-2.7(8)	-5.1(8)
C7	28.9(11)	32.3(11)	20.4(10)	10.0(8)	-3.3(8)	-2.1(9)
C15	34.4(11)	24.0(10)	21.4(10)	-8.5(8)	3.2(8)	3.8(9)
C8	35.6(11)	15.2(9)	28.9(11)	0.2(8)	2.8(9)	1.7(9)

Table D4: Bond Lengths for 4.82

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O3	C13	1.445(2)	C6	C5	1.389(3)
O3	C16	1.404(2)	C2	C3	1.401(3)
F1	C18	1.326(2)	C2	C9	1.528(2)
O2	C1	1.405(2)	C4	C3	1.392(3)

O2	C13	1.434(2)	C4	C5	1.402(3)
F2	C18	1.337(2)	C13	C14	1.523(3)
F3	C18	1.335(2)	C13	C12	1.521(2)
O1	C4	1.377(2)	C9	C10	1.539(3)
O1	C7	1.428(3)	C9	C15	1.532(3)
F5	C17	1.327(3)	C5	C8	1.506(3)
F4	C17	1.328(3)	C10	C11	1.535(3)
F6	C17	1.329(3)	C17	C16	1.536(3)
C1	C6	1.393(3)	C16	C18	1.529(3)
C1	C2	1.391(2)	C12	C11	1.539(3)

Table D5: Bond Angles for 4.82

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C16	O3	C13	117.53(14)	C15	C9	C10	109.86(16)
C1	O2	C13	116.75(13)	C6	C5	C4	117.44(17)
C4	O1	C7	116.87(15)	C6	C5	C8	121.93(18)
C6	C1	O2	119.26(16)	C4	C5	C8	120.63(17)
C2	C1	O2	118.62(15)	C11	C10	C9	116.98(16)
C2	C1	C6	121.73(16)	F5	C17	F4	107.87(18)
C5	C6	C1	121.22(17)	F5	C17	F6	106.69(19)
C1	C2	C3	117.11(16)	F5	C17	C16	112.51(17)

C1	C2	C9	120.83(16)	F4	C17	F6	106.87(18)
C3	C2	C9	122.04(16)	F4	C17	C16	111.99(18)
O1	C4	C3	123.83(18)	F6	C17	C16	110.61(16)
O1	C4	C5	114.94(17)	O3	C16	C17	109.12(15)
C3	C4	C5	121.23(17)	O3	C16	C18	108.11(16)
C4	C3	C2	121.24(17)	C18	C16	C17	112.01(16)
O3	C13	C14	110.29(15)	F1	C18	F2	107.49(18)
O3	C13	C12	105.88(14)	F1	C18	F3	107.00(18)
O2	C13	O3	103.86(14)	F1	C18	C16	111.25(16)
O2	C13	C14	111.87(15)	F2	C18	C16	111.58(18)
O2	C13	C12	113.25(15)	F3	C18	F2	106.49(18)
C12	C13	C14	111.25(15)	F3	C18	C16	112.71(17)
C2	C9	C10	112.35(16)	C13	C12	C11	116.32(16)
C2	C9	C15	112.25(16)	C10	C11	C12	117.39(16)

Table D6: Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 4.82

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U(eq)
H6	2056.79	8264.69	6631.66	21
H3	725.64	6793.45	4756.53	22
H9	2216.16	4219.46	5679	22
H10A	-1198.18	4527.61	5521.38	24

H10B	-388.03	3096.3	5414.85	24
H14A	-169.17	6191.59	7720.13	29
H14B	-20.96	7221.03	7186.26	29
H14C	1555.29	6846.24	7563.65	29
H16	3673.97	5227.01	7338.64	22
H12A	-1200.14	5545.55	6500.83	21
H12B	-1404.71	4524.61	7032.5	21
H11A	504.5	3098.11	6413.08	25
H11B	-1422.06	3024.32	6335.88	25
H7A	575.14	9804.01	4000.17	41
H7B	-232.96	8418.39	4199.87	41
H7C	1704.1	8540.89	4146.77	41
H15A	702.32	4583.36	4565.99	40
H15B	1859.68	3365.97	4752.3	40
H15C	2603.68	4836.56	4671.59	40
H8A	496.16	10806.94	5899.82	40
H8B	2322.05	10820.29	5655.7	40
H8C	1989.53	10548.69	6334.87	40

This report has been created with Olex2, compiled on 2018.05.29 svn.r3508 for OlexSys.

APPENDIX E: SYNTHESIS OF HELIANNUOL ANALOGUES

E1: GENERAL INFORMATION

^1H and ^{13}C NMR spectra were recorded at 500 MHz and 126 MHz on a Bruker Advance 500, 500 MHz and 126 MHz on a Bruker Advance III HD, or 400 MHz and 101 MHz on a Bruker Advance 400. ^1H NMR chemical shifts were reported in part per million (ppm) from the solvent resonance (CDCl_3 7.26 ppm or $\text{DMSO-}d_6$). The data was reported as follows: chemical shift number, multiplicity (s = singlet, d = doublet, t = triplet, s = septet, dd = doublet of doublets, td = triplet of doublets, m = multiplet, br = broad signal). Proton decoupled attached proton test (APT) ^{13}C NMR shifts were reported in ppm from the solvent resonance (CDCl_3 77.16 ppm). The glovebox used is a Vacuum Atmospheres NexGen system with a maximum humidity of 0.05% (500 ppm). The reaction solvents used were anhydrous (HPLC-grade solvent passed through an activated-alumina column) unless otherwise noted. Hexafluoroisopropanol (HFIP) was purchased from Oakwood Chemical, distilled over CaH_2 and stored over activated 3 Å molecular sieves under an atmosphere of argon. $[(\text{pyridine})_2\text{IPh}] \text{2OTf}^-$ was synthesized (See Appendix A) and used without further purification.

Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was purchased from Oakwood Chemical, distilled over CaH_2 and stored over activated 3 Å molecular sieves under an atmosphere of argon. Phthaloyl peroxide (PPO) was synthesized according to literature protocol¹ and stored for up to two weeks at $-25\text{ }^\circ\text{C}$. Septum sealed bottles of anhydrous butyllithium reagents were purchased from Sigma Aldrich and used without further purification. All deuterated solvents were purchased from Cambridge Isotope

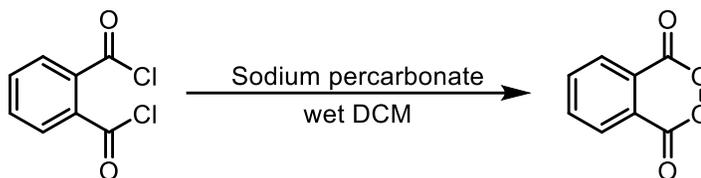
Laboratories (CIL) and stored over activated 5 Å molecular sieves. All other reagents were purchased from Sigma-Aldrich (now Millipore Sigma), Fisher Chemical, and Oakwood Chemical, and used without further purification.

Flash chromatography was carried out using Sorbent Technologies silica gel 60 Å (40–63 µm) in the solvent system listed in the individual experiments. Reactions were monitored using analytical thin-layer chromatography (TLC) on Merck silica gel (60 F254) plates. GCMS analysis was performed using an Agilent 7980B GC/5977A MS. The products were separated using a J&W CycloSil-B GC Column (30% Heptakis (2,3-di-O-methyl-6-O-t-butyl dimethylsilyl)-β-cyclodextrin in DB-1701; 30 m length, 25 mm ID, 0.25 µm Film Thickness). Experiment parameters are listed for each individual separation. Accurate masses for derivatized products were conducted on an Agilent 6520 Accurate-Mass Q-TOF LC/MS. Samples were taken up in a suitable solvent for analysis. The signals were mass measured against an internal lock mass reference of perfluorotributylamine (PFTBA) for EI-GCMS, and leucine enkephalin for ESI-LCMS. Waters software calibrates the instruments, and reports measurements, by use of neutral atomic masses. The mass of the electron is not included. Melting points were obtained on a Stanford Research Systems MPA100 OptiMelt Automated Melting Point System and are uncorrected.

E2: SYNTHESIS OF 7-MEMBERED ANALOGUES

For synthesis and characterization of precursors **5.1**, **5.3**, **5.4**, **5.11**, **5.13**, and Heliannuol D (**5.2**), please refer to Appendix C.

Phthaloyl peroxide (PPO)¹



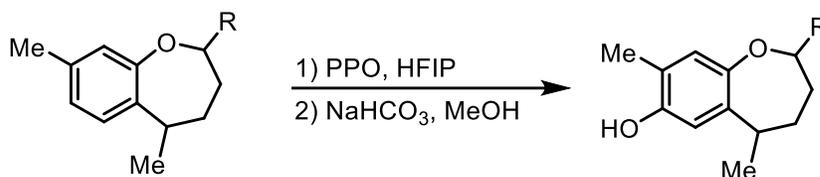
Note: Special precautions must be implemented to prevent detonation of the organoperoxide including handling at mild temperatures and avoiding shock or friction.

In a 100 mL round-bottomed flask was added wet DCM (49 mL; made wet by shaking with water (100 mL) in separatory funnel prior to use) and sodium percarbonate (2.32 g, 14.8 mmol, 1.5 equiv.). To this mixture was added neat phthaloyl peroxide (1.4 mL, 9.9 mmol, 1.0 equiv.) and the resulting reaction was stirred for 3 hours at ambient temperature. The suspension was then filtered over celite and the filtrate was concentrated at ambient temperature. (Note: DO NOT concentrate at elevated temperatures for risk of detonation. Additionally, make certain that all glass joints are clear of peroxide prior to fitting additional adapters as the friction may cause an explosion.)

To the crude residue was slowly added hot (70 °C) benzene (10 mL) to fully dissolve the product. The clear solution was then added to 25 mL of ambient temperature pentane resulting in the rapid precipitation of a fluffy white solid. The suspension was filtered to reveal the desired product as a fluffy white solid. Spectral data matches prior reports.¹

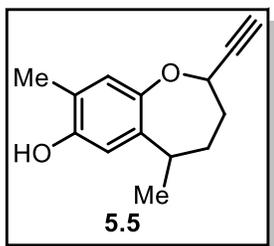
Yield: 790 mg, 49%. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 8.33 – 8.26 (m, 2H), 8.05 – 8.01 (m, 2H).

General Procedure 1 (GP1): PPO Oxidation



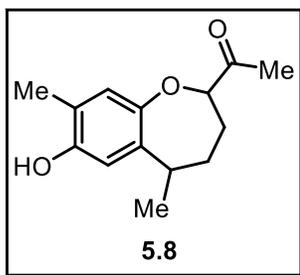
To a round-bottomed flask containing aryl ether (1.0 equiv.) was added HFIP (0.1 M solution) followed by PPO (1.3 equiv.). The resulting dark-colored solution was warmed to 45 °C and stirred for 18 hours. Once complete, the reaction was concentrated at 40 °C and azeotroped with DCM (3x) to remove trace HFIP. To the crude residue was added thoroughly degassed methanol (0.11 M solution) and aqueous saturated sodium bicarbonate (1.0 mL/mmol aryl ether). The resulting mixture was then warmed to 40 °C and stirred for 6 hours. Upon completion, the reaction was diluted with pH 7 phosphate buffer and extracted with ethyl acetate (3x). The combined organic extracts were then washed with brine, dried over sodium sulfate and concentrated. The crude residue was purified via flash column chromatography (15% EtOAc/Hexanes) to afford the desired product.

2-ethynyl-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-7-ol (**5.5**)



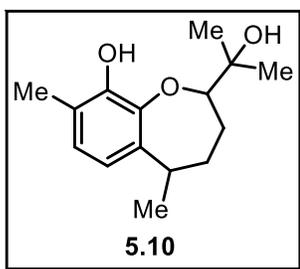
Alkynyl substrate **5.5** was synthesized according to **GP1** using 324 mg (1.62 mmol) of the corresponding starting material to afford a pale-yellow foam. **Yield:** 114 mg, 33%. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 6.84 (s, 1H), 6.57 (s, 1H), 4.50 (d, $J = 8.6$ Hz, 1H), 4.44 (s, 1H), 3.05 – 2.97 (m, 1H), 2.50 (d, $J = 2.3$ Hz, 1H), 2.25 – 2.20 (m, 1H), 2.18 (s, 3H), 2.11 – 2.01 (m, 1H), 1.99 – 1.92 (m, 1H), 1.50 – 1.41 (m, 1H), 1.30 – 1.27 (d, $J = 7.1$ Hz, 3H)

1-(7-hydroxy-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-2-yl)ethan-1-one (5.8)



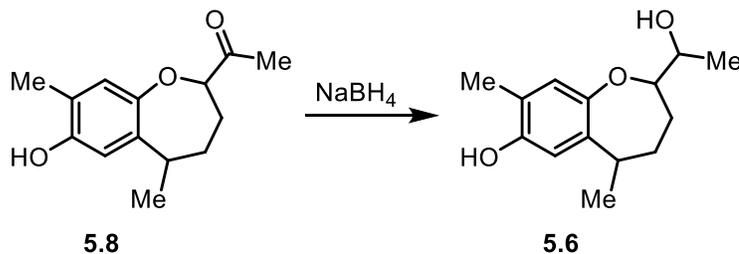
Methyl ketone substrate **5.8** was synthesized according to **GP1** using 114 mg (0.52 mmol) of a 3:1 diastereomeric mixture of starting material to afford the desired product as an off-white foam with an unchanged diastereomeric ratio. **Yield:** 59 mg, 48%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 6.83 (s, 1H (Major)), 6.81 (s, 0.33H (Minor, 1H)), 6.62 (s, 1H (Major)), 6.55 (s, 0.32H (Minor, 1H)), 4.49 (d, $J = 1.4$ Hz, 1H (Major)), 4.45 (d, $J = 1.5$ Hz, 0.36H (Minor, 1H)), 3.91 – 3.86 (m, 0.4H (Minor, 1H)), 3.82 (dd, $J = 11.2, 2.3$ Hz, 1H (Major)), 3.06 – 3.00 (m, 1H (Major)), 2.94 (ddd, $J = 7.6, 5.3, 3.2$ Hz, 0.26H (Minor, 1H)), 2.40 (s, 4H), 2.26 – 2.21 (m, 2H), 2.19 (s, 3H), 2.18 (s, 1.38H (Minor, 3H)), 1.95 – 1.87 (m, 3H), 1.37 – 1.33 (m, 1H), 1.32 (d, $J = 7.0$ Hz, 4H), 1.30 – 1.23 (m, 4H).

2-(2-hydroxypropan-2-yl)-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-9-ol (5.10)

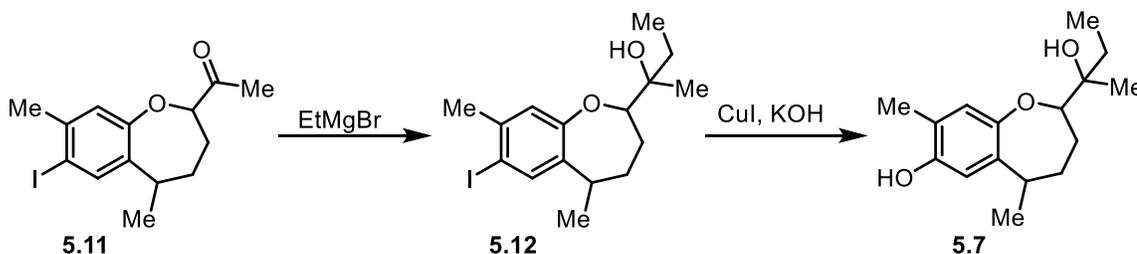


Ortho phenol **5.10** was synthesized according to **GP1** using 158 mg (0.68 mmol) of the corresponding starting material. Purification was performed via preparatory HPLC to afford 6 mg as a pale-yellow foam (3:1 *d.r.*) **¹H NMR** (500 MHz, Chloroform-*d*) δ 6.53 (d, $J = 1.6$ Hz, 0.31H (Minor, 1H)), 6.44 (q, $J = 1.5$ Hz, 1H (Major)), 5.95 (d, $J = 2.4$ Hz, 0.38H (Minor, 1H)), 5.92 (d, $J = 1.2$ Hz, 1H (Major)), 4.28 – 4.22 (m, 1.37H), 2.78 – 2.64 (m, 1.4H), 2.13 – 2.03 (m, 2.59H), 1.94 – 1.88 (m, 0.79H), 1.85 (d, $J = 1.5$ Hz, 4H), 1.83 – 1.77 (m, 1H), 1.64 – 1.55 (m, 1.71H), 1.43 (d, $J = 2.2$ Hz, 5.6H), 1.41 (s, 1.31H), 1.38 (s, 1H), 1.26 (d, $J = 7.3$ Hz, 4.5H), 1.20 (d, $J = 6.8$ Hz, 1.35H).

2-(1-hydroxyethyl)-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[b]oxepin-7-ol (**5.6**)



To a solution of ketone **5.8** (22 mg, 0.094 mmol, 1.0 equiv.) in methanol (2.0 mL) was added a small scoop of sodium borohydride. The reaction was stirred at ambient temperature until bubbling ceased, at which point it was checked by TLC which deemed starting material was consumed. The reaction was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (3x). The combined organic extracts were dried over sodium sulfate and concentrated. The crude material was then purified via preparatory thin-layer chromatography (20% EtOAc/Hexanes) to afford the desired product as a complex mixture of diastereomers. **Yield:** 16 mg, 72%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 6.77 (d, $J = 6.6$ Hz, 1H), 6.73 (d, $J = 6.0$ Hz, 0.40H), 6.61 (s, 1H), 6.54 (d, $J = 2.9$ Hz, 0.37H), 4.43 (d, $J = 8.6$ Hz, 1H), 4.39 (d, $J = 10.1$ Hz, 0.44H), 3.95 – 3.87 (m, 0.53H), 3.79 – 3.71 (m, 0.81H), 3.45 (dd, $J = 10.4, 4.0$ Hz, 0.18H), 3.40 – 3.34 (m, 0.41H), 3.27 (dd, $J = 10.7, 6.6$ Hz, 0.27H), 3.24 – 3.17 (m, 0.59H), 3.03 (p, $J = 9.7, 8.7$ Hz, 1H), 2.89 (d, $J = 3.3$ Hz, 0.75H), 2.85 (d, $J = 3.3$ Hz, 0.25H), 2.18 (s, 3H), 2.17 (d, $J = 1.8$ Hz, 1H), 2.14 (t, $J = 7.7$ Hz, 0.59H), 1.92 – 1.84 (m, 3H), 1.73 (t, $J = 14.8$ Hz, 0.66H), 1.35 – 1.20 (m, 11.5H).



2-(7-iodo-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-2-yl)butan-2-ol (5.12)

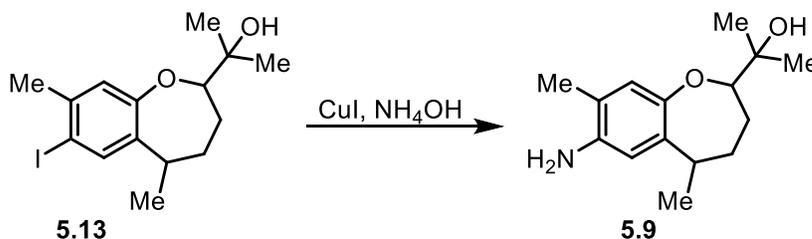
A solution of aryl iodide **5.11** (135 mg, 0.39 mmol, 1.0 equiv.) in THF (4.0 mL) was cooled to $-78\text{ }^{\circ}\text{C}$ in a dry ice/acetone bath. To the solution was added ethylmagnesium bromide (3.0 M in Et_2O ; 0.78 mL, 2.35 mmol, 6.0 equiv.) and the reaction was allowed to stir for 20 minutes. At which point, the reaction was removed from the ice bath and quenched with saturated aqueous ammonium chloride and extracted with Et_2O (3x). The combined organic extracts were dried over sodium sulfate and concentrated, and the crude residue was purified via column chromatography (20% EtOAc/Hexanes) to afford the desired product as a pale yellow oil. **Yield:** 149 mg, 99%. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 7.55 (s, 1H), 6.86 (s, 1H), 3.39 – 3.33 (m, 1H), 3.04 – 2.96 (m, 1H), 2.44 (s, 1H), 1.95 – 1.88 (m, 3H), 1.70 – 1.55 (m, 3H), 1.32 (d, $J = 7.1\text{ Hz}$, 3H), 1.19 (s, 3H), 0.93 (t, $J = 7.5\text{ Hz}$, 3H).

2-(2-hydroxybutan-2-yl)-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-7-ol (5.7)

To a 4 mL vial containing aryl iodide **5.12** (149 mg, 0.39 mmol, 1.0 equiv.) was added copper iodide (23 mg, 0.12 mmol, 0.30 equiv.), 1,10-phenanthroline (43 mg, 0.24 mmol, 0.60 equiv.) and potassium hydroxide (134 mg, 2.39 mmol, 6.0 equiv.).² The mixture of solids was pump/purged with argon (3x) to remove all oxygen. To the mixture was added a thoroughly degassed 1:1 mixture degassed DMSO (0.70 mL) and de-ionized H_2O (0.70 mL). The resulting black mixture was tightly sealed and heated to $110\text{ }^{\circ}\text{C}$ for 24 hours. At which point, the reaction was cooled to ambient temperature and quenched with aqueous 2 M HCl (0.50 mL) and the entire mixture was filtered through silica with EtOAc as the eluent. The filtrate was then concentrated, and the crude residue was purified via flash column chromatography (15 \rightarrow 40% EtOAc/Hexanes) to afford the desired product as a pale-yellow crunchy foam (10:1 *d.r.*). **Yield:** 56 mg, 53%. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 6.75 (s, 1H (Major)), 6.72 (s, 0.11H (Minor, 1H)), 6.61 (s, 1H (Major)), 6.54 (s, 0.1H (Minor, 1H)), 4.42 (s, 1H), 4.38 (s, 0.09H (Minor, 1H)), 3.36 (d, $J = 11.5$

Hz, 0H), 3.34 – 3.28 (m, 1H), 3.02 (dt, $J = 15.8, 7.3$ Hz, 1H), 2.59 (s, 0.11H (Minor, 1H)), 2.58 (s, 1H), 2.18 (d, $J = 3.3$ Hz, 3H (Major)), 2.16 (s, 0.30H (Minor, 3H)), 1.95 – 1.85 (m, 3H), 1.62 (ddt, $J = 36.3, 14.0, 7.2$ Hz, 2H), 1.54 (s, 2H), 1.33 – 1.23 (m, 4H), 1.26 – 1.18 (m, 1H), 1.19 (s, 3H), 0.93 (t, $J = 7.5$ Hz, 3.3H).

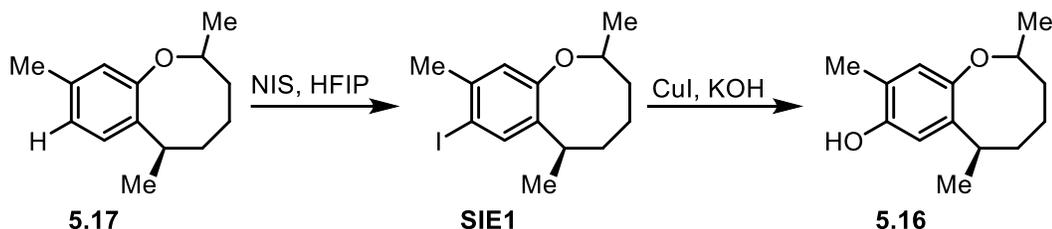
2-(7-amino-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-2-yl)propan-2-ol (5.9)



Following literature protocol,³ a 4 mL vial was charged with Cu₂O (1 mg, 0.007 mmol, 5 mol %) and aryl iodide **5.13** (50 mg, 0.14 mmol, 1.0 equiv.). *N*-methylpyrrolidone (NMP; 100 μ L) and ammonium hydroxide (28-30% NH₃ in H₂O; 100 μ L) were added, then the vial was sealed and stirred at 80 °C overnight. The following day, the reaction was cooled to ambient temperature and diluted with H₂O (2 mL), then extracted with Et₂O (3x). The combined organic extracts were dried over magnesium sulfate, then filtered and concentrated. The crude residue was purified via flash column chromatography (15→40% EtOAc/Hexanes) to afford the desired product as a yellow crunchy foam (6:1 *d.r.*) **Yield:** 10 mg, 29%. ¹H NMR (500 MHz, Chloroform-*d*) δ 6.71 (s, 1H (Major)), 6.68 (s, 0.16H (Minor, 1H)), 6.50 (s, 1H (Major)), 6.44 (s, 0.15H (Minor, 1H)), 3.27 (dd, $J = 11.3, 1.2$ Hz, 0.15H (Minor, 1H)), 3.22 (dd, $J = 10.5, 2.8$ Hz, 1H (Major)), 3.01 (dd, $J = 10.4, 6.9$ Hz, 1.20H), 2.11 (s, 3H), 2.09 (s, 0.52H (Minor, 3H)), 1.99 – 1.79 (m, 4H), 1.79 – 1.70 (m, 0.3H (Minor, 2H)), 1.28 (dd, $J = 17.8, 7.4$ Hz, 14H).

E3: SYNTHESIS OF 8-MEMBERED ANALOGUES

For synthesis and characterization of **5.17** please refer to either Appendix B (one-pot) or Appendix D (sequential). For the synthesis and characterization of **5.21** please refer to Appendix B.



(6R)-8-iodo-2,6,9-trimethyl-3,4,5,6-tetrahydro-2H-benzo[b]oxocine (SIE1)

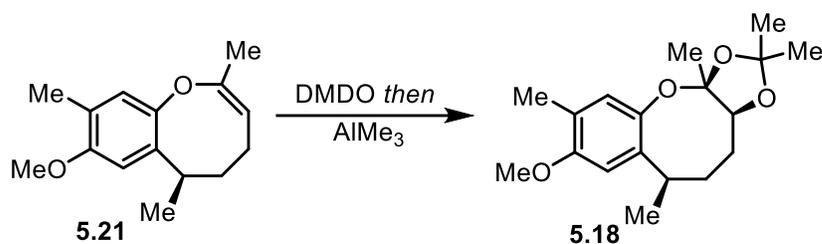
To a solution of aryl ether **5.17** (63 mg, 0.31 mmol, 1.0 equiv.) was added HFIP (2 mL). *N*-iodosuccinimide (84 mg, 0.37 mmol, 1.2 equiv.) was added and the resulting solution was stirred for 30 minutes.⁴ The reaction was checked for completion by ¹HNMR, and when complete was concentrated and purified via column chromatography (5% EtOAc/Hexanes) to afford the desired product as an oily orange foam (1:1 *d.r.*). **Yield:** 86 mg, 84%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.49 (s, 1H), 7.46 (s, 1H), 6.83 (s, 1H), 6.77 (d, *J* = 0.8 Hz, 1H), 4.23 – 4.16 (m, 1H), 3.86 – 3.79 (m, 1H), 3.32 – 3.23 (m, 1H), 2.95 – 2.87 (m, 1H), 2.28 (d, 6H), 1.78 – 1.62 (m, 4H), 1.61 – 1.53 (m, 3H), 1.53 – 1.38 (m, 4H), 1.33 (d, *J* = 6.4 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H), 1.24 – 1.15 (m, 9H).

(6R)-2,6,9-trimethyl-3,4,5,6-tetrahydro-2H-benzo[b]oxocin-8-ol (5.16)

To a 4 mL vial containing aryl iodide **SIE1** (86 mg, 0.26 mmol, 1.0 equiv.) was added copper iodide (15 mg, 0.78 mmol, 0.30 mmol), 1,190-phenanthroline (28 mg, 0.16 mmol, 0.60 equiv.) and potassium hydroxide (87 mg, 1.6 mmol, 6.0 equiv.). The entire mixture was pump-purged with argon (3x) to remove all oxygen, then a thoroughly degassed 1:1 mixture of DMSO and de-ionized water (0.9 mL total) was added. The reaction was then sealed and stirred at 110 °C for 24 hours. The following day, the reaction was quenched with aqueous 2 M HCl (1.5 mL) and the entire mixture was filtered over celite with

EtOAc as the eluent. The filtrate was then concentrated and the crude residue purified via column chromatography (20% EtOAc/Hexanes) to afford the desired product as an oily yellow foam (1:1 *d.r.*). **Yield:** 29 mg, 51%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 6.77 (s, 1H), 6.71 (s, 1H), 6.58 (s, 1H), 6.56 (s, 1H), 4.53 (d, *J* = 5.5 Hz, 2H), 4.27 – 4.19 (m, 1H), 3.85 (p, *J* = 10.3, 6.4, 3.1 Hz, 1H), 3.41 – 3.31 (m, 1H), 3.03 – 2.95 (m, 1H), 2.18 (d, *J* = 4.4 Hz, 6H), 1.83 – 1.69 (m, 3H), 1.67 – 1.43 (m, 7H), 1.39 (d, *J* = 6.3 Hz, 3H), 1.32 (d, *J* = 6.6 Hz, 4H), 1.27 – 1.24 (m, 5H), 1.22 (s, 2H), 1.13 – 1.04 (m, 1H).

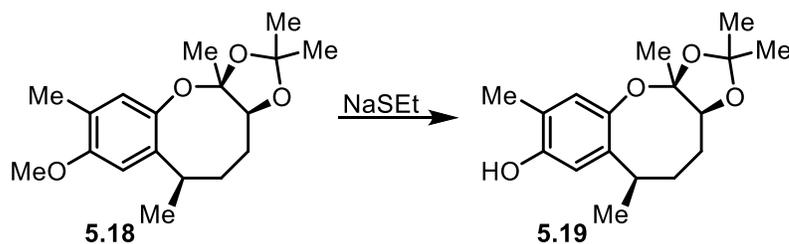
(3a*S*,6*R*,11a*S*)-8-methoxy-2,2,6,9,11a-pentamethyl-3a,5,6,11a-tetrahydro-4*H*-benzo[*b*][1,3]dioxolo[4,5-*g*]oxocine (5.18)



In a flame-dried round-bottomed flask, a solution of enol ether **5.21** (169 mg, 0.73 mmol, 1.0 equiv.) in DCM (3.6 mL) was cooled to -78 °C. A solution of “acetone-free” DMDO (0.2 M in DCM; 3.6 mL, 0.73 mmol, 1.0 equiv.; See Appendix D for synthesis). The mixture was stirred for 3 minutes, at which point a solution of AlMe₃ (2 M Hexanes; 0.44 mL, 0.873 mmol, 1.2 equiv.) was added. The reaction was allowed to warm to 0 °C, at which point a saturated aqueous solution of ammonium chloride was added slowly. The reaction was poured into a separatory funnel along with EtOAc, and the organic layer was collected. The aqueous layer was further extracted with EtOAc (2x), then the combined organic extracts were washed with brine (2x), dried over sodium sulfate, and concentrated. Purification via column chromatography (5% EtOAc/Hexanes) afforded the acetonide as the major product. The product was obtained as a pale yellow oil which crystallized overnight. **Yield:** 61 mg, 27%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 6.77 (d,

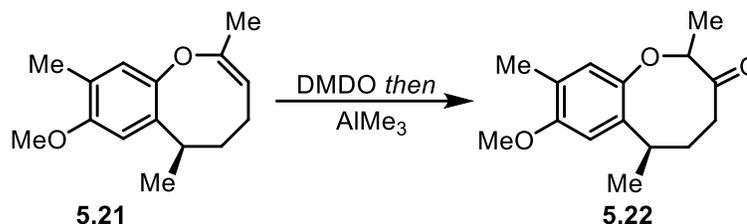
$J = 0.9$ Hz, 1H), 6.62 (s, 1H), 4.09 (d, $J = 7.8$ Hz, 1H), 3.80 (s, 3H), 3.04 (p, $J = 7.7$ Hz, 1H), 2.14 (s, 3H), 2.02 – 1.95 (m, 1H), 1.83 (q, $J = 12.1, 11.2$ Hz, 1H), 1.69 (dd, $J = 14.1, 7.0$ Hz, 2H), 1.30 (d, $J = 7.3$ Hz, 3H), 1.27 (s, 3H), 0.79 (s, 3H).

(3*a*S,6*R*,11*a*S)-2,2,6,9,11*a*-pentamethyl-3*a*,5,6,11*a*-tetrahydro-4*H*-benzo[*b*][1,3]dioxolo[4,5-*g*]oxocin-8-ol (5.19)



To a flame-dried 4 mL vial was added methyl ether **5.18** (8.8 mg, 0.027 mmol, 1.0 equiv.) in solution with 1 mL DMF.⁵ Sodium ethanethiolate (41 mg, 0.22 mmol, 8.0 equiv.) was added, then the vial was sealed and stirred at 150 °C for 12 hours. Upon completion, the reaction was quenched with water (5 mL) and diluted with EtOAc (5 mL). The organic layer was collected, and the aqueous layer was further extracted with EtOAc (3x). The combined organic extracts were washed with brine (3x), then dried over sodium sulfate and concentrated. The crude residue was purified via preparatory TLC (20% EtOAc/Hexanes) to afford the desired product as a yellow solid. **Yield:** 4 mg, 51%. **¹H NMR** (500 MHz, Chloroform-*d*) δ 6.75 (s, 1H), 6.58 (s, 1H), 4.46 (s, 1H), 4.10 (dd, $J = 7.7, 6.7$ Hz, 1H), 2.99 (q, $J = 7.8, 6.2$ Hz, 1H), 2.17 (s, 3H), 1.98 (dd, $J = 15.3, 11.5$ Hz, 1H), 1.83 – 1.73 (m, 1H), 1.69 – 1.63 (m, 1H), 1.62 (s, 3H), 1.27 (s, 3H), 1.25 (d, $J = 7.2$ Hz, 3H), 0.79 (s, 3H).

(6*R*)-8-methoxy-2,6,9-trimethyl-5,6-dihydro-2*H*-benzo[*b*]oxocin-3(4*H*)-one (5.22)



To a stirred solution of enol ether **5.22** (6.5 mg, 0.029 mmol, 1.0 equiv.) in Et₂O (300 μL) at -78 °C was added “acetone-free” DMDO (0.2 M in DCM; 144 μL, 0.029 mmol, 1.0 equiv.). The reaction was stirred for 5 minutes, then a solution of methylmagnesium bromide (3 M Et₂O; 60 μL, 0.17 mmol, 6.0 equiv.) was added. The reaction was warmed to room temperature, then quenched with saturated aqueous ammonium chloride. The mixture was extracted with Et₂O (3x), and the combined organic extracts were dried over sodium sulfate then concentrated. No purification was performed. ¹H NMR (500 MHz, Chloroform-*d*) δ 6.80 (s, 1H), 6.46 (s, 1H), 3.77 (s, 3H), 3.23 – 3.16 (m, 1H), 2.94 – 2.87 (m, 1H), 2.28 – 2.20 (m, 2H), 2.12 (s, 3H), 1.98 – 1.88 (m, 2H), 1.53 (d, *J* = 7.0 Hz, 3H), 1.47 (d, *J* = 7.2 Hz, 3H). **LRMS**: Calculated for C₁₅H₂₀O₃ 248.32; found 248.0

E4: REFERENCES

- (1) Yuan, C.; Eliassen, A. M.; Camelio, A. M.; Siegel, D. Preparation of Phenols by Phthaloyl Peroxide-Mediated Oxidation of Arenes. *Nat. Protoc.* **2014**, *9* (11), 2624–2629. <https://doi.org/10.1038/nprot.2014.175>.
- (2) Xia, S.; Gan, L.; Wang, K.; Li, Z.; Ma, D. Copper-Catalyzed Hydroxylation of (Hetero)Aryl Halides under Mild Conditions. *J. Am. Chem. Soc.* **2016**, *138* (41), 13493–13496. <https://doi.org/10.1021/jacs.6b08114>.
- (3) Xu, H.; Wolf, C. Efficient Copper-Catalyzed Coupling of Aryl Chlorides, Bromides and Iodides with Aqueous Ammonia. *Chem. Commun.* **2009**, No. 21, 3035–3037. <https://doi.org/10.1039/b904188e>.
- (4) Tang, R. J.; Milcent, T.; Crousse, B. Regioselective Halogenation of Arenes and Heterocycles in Hexafluoroisopropanol. *J. Org. Chem.* **2018**, *83* (2), 930–938. <https://doi.org/10.1021/acs.joc.7b02920>.
- (5) Galindo, J.; Molinillo, J.; Macías, F.; Chinchilla, D. Heliannanes - a Structure-Activity Relationship (SAR) Study. *Allelopathy* **2003**, No. May 2014, 103–124. <https://doi.org/10.1201/9780203492789.ch5>.

E5: SPECTRA

