

UC Berkeley

UC Berkeley Electronic Theses and Dissertations

Title

Strained Intermediates in Total Synthesis: Total Synthesis of 14- and 15-Hydroxypatchoulol and Synthetic Studies Toward Plumisclerin A

Permalink

<https://escholarship.org/uc/item/58q7s6j9>

ISBN

9798189279706

Author

Kang, Suh Hyun

Publication Date

2026-05-01

Peer reviewed|Thesis/dissertation

Strained Intermediates in Total Synthesis: Total Synthesis of 14- and 15-Hydroxypatchoulol and
Synthetic Studies Toward Plumisclerin A

by

Suh Hyun Kang

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Chemistry

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

Professor Richmond Sarpong, Chair

Professor Thomas Maimone

Professor Gregory Aponte

Spring 2026

Strained Intermediates in Total Synthesis: Total Synthesis of 14- and 15-Hydroxypatchoulol and
Synthetic Studies Toward Plumisclerin A

Copyright 2026

by Suh Hyun Kang

All rights reserved

Abstract

Strained Intermediates in Total Synthesis: Total Synthesis of 14- and 15-Hydroxypatchoulol and Synthetic Studies Toward Plumisclerin A

By Suh Hyun Kang

Doctor of Philosophy of Chemistry

University of California, Berkeley

Professor Richmond Sarpong, Chair

Herein, I describe the development of a Pd-catalyzed C–C bond cleavage/vinylation/Mizoroki–Heck cyclization cascade reaction and its application to total syntheses of 14- and 15-hydroxypatchoulol, alongside our synthetic studies toward plumisclerin A.

Chapter 1 reviews Pd-catalyzed Mizoroki–Heck reactions in total synthesis. In addition, it highlights recent contributions from the Sarpong group on Pd-catalyzed C–C bond cleavage/C–C bond forming strategies in synthetic methods development and total synthesis of natural products.

Chapter 2 details our work on employing *gem*-dichloroalkene electrophiles as cross-coupling partners in palladium catalysis. Through the use of various phosphine-based ligands and careful substrate design, we achieved high selectivity among four possible products of the envisioned Pd-catalyzed cascade reaction: the vinylation product, bicyclo[2.2.2]octane, bicyclo[3.2.1]octane, and tricyclo[3.2.1.0]octane. Our mechanistic proposals regarding the observed product selectivity are supported by data science and computational studies conducted in collaboration with the Sigman group and the Coley group.

Chapter 3 reviews the isolation, biosynthesis, biological activity, and previous syntheses of patchouli alcohol, as well as our proposal to synthesize the newly isolated natural products, 14- and 15-hydroxypatchoulol, using the developed Pd-catalyzed cascade reaction.

Chapter 4 describes the total syntheses of 14- and 15-hydroxypatchoulol. It features two completed syntheses of 14-hydroxypatchoulol, each employing different *gem*-dichloroalkene electrophiles, completed in 9 and 12 overall steps, respectively. In addition to the completed syntheses, we report structural misassignment of 15-hydroxypatchoulol from the original isolation report.

Chapter 5 reviews the isolation, biosynthesis, biological activity, and previous syntheses of plumisclerin A, along with other structurally related xenicane marine terpenoid natural products.

Chapter 6 describes our synthetic studies toward plumisclerin A, in which we employ a titanocene-mediated reductive cyclization approach to construct the bicyclo[3.1.1]heptane moiety and introduce the side chain of the dihydropyran moiety through a Claisen rearrangement.

Meiner Mutter

CONTENTS

Acknowledgements

Chapter 1. Background on Pd-Catalyzed C–C Bond Cleavage/C–C Bond Forming Reactions.....	1
1.1 An Introduction to Natural Product Synthesis and Synthetic Methods Development.....	1
1.2 Selected Studies on Pd-Catalyzed Cascade Reactions in Natural Product Synthesis.....	2
1.2.1 Total Synthesis of (–)-Kumausallene (Tang, 2011)	2
1.2.2 Total Synthesis of (–)-Spinosyn A (Dai, 2016)	3
1.2.3 Total Synthesis of (–)-Galanthamine and (–)-Lycoramine (Jia, 2015)	5
1.3 Selected Studies on Pd-Catalyzed Mizoroki–Heck Cascade Carbocyclizations	6
1.3.1 Mizoroki–Heck Reaction	6
1.3.2 Biomimetic Polyene Cyclization	7
1.3.3 Total Synthesis of (±)-Tazettine and (±)-6a-Epipretazettine (Overman, 1990)	10
1.3.4 Total Synthesis of Scapadulcic acid A and B (Overman, 1993, 1999)	11
1.4 Selected Studies on Pd-Catalyzed Synthetic Methods from the Sarpong Group	13
1.4.1 Pd-Catalyzed Skeletal Rearrangement Methods Development for Terpenoid Natural Product Synthesis.....	13
1.4.2 Proposed Catalytic Cycle of the Pd-Catalyzed C–C Bond Cleavage/C–C Bond Formation Sequence.....	15
1.4.3 Total Synthesis of (–)-Xishacorene B	16
1.4.4 Pd-Catalyzed C–C Bond Cleavage/Arylation to Natural Product-Like Scaffolds ..	17
1.4.5 Synthetic Studies Toward the Taxagifine Core	18
1.5 Our Proposal	19
1.6 References.....	21
Chapter 2. Development of a Pd-Catalyzed C–C Bond Cleavage/Vinylation/Mizoroki–Heck Cyclization Cascade	24
2.1 Proposed Mechanism	24
2.2 Formation of the C–C Bond Cleavage/Vinylation Product With Trisubstituted <i>gem</i> -Dichloroalkene Electrophiles.....	27
2.3 Formation of the C–C Bond Cleavage/Vinylation Product With Tetrasubstituted <i>gem</i> -Dichloroalkene Electrophiles.....	36
2.4 Formation of the Bicyclo[2.2.2]octanone Product With Trisubstituted <i>gem</i> -Dichloroalkene Electrophiles	38
2.5 Extended Cascade Reactivity.....	46
2.6 Mizoroki–Heck Cyclization Selectivity With Trisubstituted <i>gem</i> -Dichloroalkene Electrophiles	47
2.7 Mizoroki–Heck Cyclization Selectivity With Tetrasubstituted <i>gem</i> -Dichloroalkene Electrophiles	53

2.8 Summary and Outlook	57
2.9 Contributions	58
2.10 Experimental Details.....	59
2.10.1 General Procedures	59
2.10.2 Synthetic Procedures and Product Characterization	60
2.11 References.....	86
Appendix 2A. NMR Spectra for Chapter 2	90
Chapter 3. Background on Patchoulol Natural Products	130
3.1 Introduction.....	130
3.2 Isolation.....	133
3.3 Biosynthesis	135
3.4 Biological Activity	136
3.5 Previous Syntheses of Patchouli Alcohol	137
3.5.1 Büchi (1961, 1962, 1964)	137
3.5.2 Danishefsky (1968).....	137
3.5.3 Mirrington (1972)	138
3.5.4 Ohloff (1974)	139
3.5.5 Yamada (1979)	140
3.5.6 Bertrand (1980).....	141
3.5.7 Ohloff (1981)	142
3.5.8 Cory (formal synthesis, 1990).....	143
3.5.9 Wu (formal synthesis, 1991).....	144
3.5.10 Magee (1995).....	144
3.5.11 Srikrishna (2005).....	145
3.5.12 Sun (2017).....	146
3.5.13 Summary	147
3.6 Selected Total Syntheses of Natural Products With Bicyclo[2.2.2]octane Scaffold.....	149
3.6.1 Seychellene	149
3.6.2 Maoecrystal V	150
3.6.3 Platencin.....	152
3.6.4 Crotogoudin	154
3.6.5 Lucidumone	155
3.6.6 Summary	157
3.7 Our Proposal	158

3.8	References.....	159
Chapter 4. Total Synthesis of 14- and 15-Hydroxypatchoulol		162
4.1	Initial Synthesis Strategy	162
4.2	Initial Attempts with Acyclic Tetrasubstituted <i>gem</i> -Dichloroalkene Electrophile.....	162
4.3	Retrosynthesis (1st generation).....	163
4.4	Total Synthesis of 14- and 15-Hydroxypatchoulol (1st generation)	164
4.5	Retrosynthesis (2nd generation)	166
4.6	Total Synthesis of 14-Hydroxypatchoulol (2nd generation).....	167
4.7	Attempted Total Synthesis of 15-Hydroxypatchoulol.....	171
4.8	Summary and Outlook	173
4.9	Contributions	173
4.10	Experimental Details.....	174
4.10.1	General Procedures	174
4.10.2	Synthetic Procedures and Product Characterization	174
4.11	References.....	200
Appendix 4A. NMR Spectra for Chapter 4		203
Chapter 5. Background on Xenicane Diterpenoid Natural Product Family		227
5.1	Introduction.....	227
5.2	Isolation.....	229
5.3	Biosynthesis	230
5.4	Biological Activity	231
5.5	Previous Synthetic Studies on Cristaxenicin A.....	232
5.5.1	Hosokawa's Synthesis of Cristaxenicin A's core (2016).....	232
5.5.2	Tanino's Total Synthesis of Cristaxenicin A (2025)	233
5.6	Previous Synthetic Studies on Plumisclerin A.....	235
5.6.1	Yao's Synthetic Studies Toward Plumisclerin A (2015).....	235
5.6.2	Yao's Total Synthesis of Plumisclerin A (2018).....	236
5.6.3	Ma's Synthetic Studies Toward Plumisclerin A (2019).....	239
5.7	Our Proposal	240
5.8	References.....	242
Chapter 6. Synthetic Studies Toward Plumisclerin A.....		245
6.1	Hetero-Diels–Alder Approach	245
6.1.1	Background and Retrosynthesis.....	245
6.1.2	Synthesis of the Dioxine Fragment.....	247

6.1.3 Synthesis of the Bicyclo[3.1.1]heptane Fragment	247
6.1.4 Intermolecular Hetero-Diels–Alder	253
6.1.5 Nitrogen Deletion-Intramolecular Hetero-Diels–Alder Approach	254
6.1.6 Esterification-Intramolecular Hetero-Diels–Alder Approach.....	261
6.1.7 Matteson Coupling-Intramolecular Hetero-Diels–Alder Approach.....	263
6.2 Chan–Lam Coupling–Claisen Rearrangement Approach	264
6.2.1 Retrosynthesis	264
6.2.2 Chan–Lam Coupling.....	264
6.2.3 Claisen Rearrangement	266
6.3 Intramolecular Michael Addition.....	267
6.3.1 Retrosynthesis	267
6.3.2 Preparation of Bicyclo[3.1.1]heptanoic acid	268
6.4 Summary and Outlook	269
6.5 Contributions	270
6.6 Experimental Details.....	271
6.6.1 General Procedures	271
6.6.2 Synthetic Procedures and Product Characterization	271
6.7 References.....	287
Appendix 6A. NMR Spectra for Chapter 6	290

Acknowledgements

First and foremost, I would like to thank my *Doktorvater*, Professor Richmond Sarpong for his mentorship and guidance throughout my graduate studies. Since my time as a visiting scholar in his group, the insights and advice he shared have profoundly shaped my perspective on chemistry and inspired me to pursue a Ph.D. in the United States. His continuous support has kept me both creative and motivated throughout my studies, for which I am truly grateful. I thank him for trusting me with my research and giving me the freedom to explore my ideas. I would also like to express my sincerest gratitude to my qualifying examination committee and dissertation committee for their valuable insights and feedback: Professors Thomas Maimone, Felix Fischer, Evan Miller, Peter Vollhardt, and Gregory Aponte. Especially I would like to thank Professor Maimone whose conversations and guidance on both chemistry and career matters have been especially meaningful.

I would like to thank my undergraduate advisors, Professors Bill Morandi and Jeffrey Bode, for introducing me to academic research and sparking my interest in pursuing a Ph.D. in synthetic organic chemistry. I deeply appreciate their continued support from overseas over the years, even after my graduation. I also want to thank all my mentors and supervisors who guided me during my undergraduate research: Professor Matthew Aronoff, Dr. Yi-Chung Dzen, Dr. Szabolcs Makai, Dr. Chalapat Jindakun, Dr. Moritz Jackl, Dr. Goh Sennari, and Dr. Robert Lusi. Their patience and willingness to walk me through the fundamentals of synthetic organic chemistry – both in theory and practice – laid the foundation for my graduate studies. I am especially indebted to Dr. Christina Na, my graduate school mentor. The techniques I learned under her guidance and the scientific discussions we shared have shaped me into the scientist I am today.

I would like to thank all the past and present members of the Sarpong lab for the stimulating scientific discussions and the camaraderie they provided during my time in the lab. A special thanks goes to my fellow cohort in the chemistry graduate program – including the Maimone, Hartwig, and Toste group – for their friendship and support over the years. I have benefited greatly from countless scientific discussions with lab mates and former colleagues. In this regard, I would particularly like to thank: Dr. Stefan Wiesler, Dr. Remi Lavernhe, Dr. Jack Hayward Cook, Dr. Lukas Spessert, and Tanner Myers. I would like to thank Dr. Luca McDermott, Katerina Gorou, and Matthew Su for their help in preparation of the manuscript.

I have also had the pleasure of working with many collaborators, all of whom I feel very fortunate to have met: Professor Matthew Sigman, Sierra Hart, Professor Connor Coley, Nicholas Casetti, and Professor Michael Marletta. I gratefully acknowledge University of California, Berkeley analytical facilities staff who have supported this work: Dr. Hasan Celik, Dr. Raynald Giovine, Dr. Nicholas Settineri, and Dr. Zhongrui Zhou.

Last but not least, I thank my parents for their unwavering support from afar over the past decade. Their unconditional love, constant encouragement, and trust in my potential have given me the courage to pursue my passions and dreams in different parts of the world, and I am eternally grateful to them.

Chapter 1. Background on Pd-Catalyzed C–C Bond Cleavage/ C–C Bond Forming Reactions

1.1 An Introduction to Natural Product Synthesis and Synthetic Methods Development

The synthesis of complex molecules and natural products remains an important pursuit in chemical synthesis. Owing to their sophisticated architecture, natural products have long been considered a key source of inspiration for the synthetic and medicinal chemistry communities.¹ Historically, total synthesis gained prominence because it provided suitable quantities of natural products with desirable biological activity and pharmaceutical potential, as such compounds were often only available from natural sources in trace amounts.² In addition, limitations in spectroscopic techniques in the past led to challenges in structure elucidation, for which scientists relied on the chemical synthesis of natural products in the laboratory to validate their proposed structures.³ Beyond their desirable biological activity and potential medicinal applications, the structural complexity of natural products has served as a major motivator for their total syntheses. Early practitioners in the field sought to demonstrate that the scope of human synthetic capability could match that of nature's machinery. Consequently, early natural product syntheses often placed less emphasis on reaction yield and selectivity and primarily focused on the completion of the first total synthesis.³ However, the role of total synthesis has evolved significantly since then.²

With the advancement of structure determination methods and the expansion of the synthetic toolbox, the strategies by which total syntheses are achieved have become increasingly relevant.⁴ The motivation for synthesizing natural products has shifted from merely accomplishing the first synthesis to emphasizing the efficiency and elegance with which the target compound is prepared. As such, recent total synthesis campaigns have increasingly embraced new paradigms for molecular construction. New strategies and approaches provide unprecedented ways for complex molecule assembly, potentially enabling more efficient access to related targets. In pursuing these approaches, the synthetic chemist needs to integrate a full breadth of attendant skills of organic chemistry: recall and invention of reactions, navigation through the physical-organic chemistry landscape to understand the intrinsic molecular properties of intermediates, and the careful orchestration of transformations while simultaneously addressing multivariable challenges such as competing reactivity and reaction yield optimization.³

During the pursuit of total syntheses of natural products, limitations in current strategies and synthetic methods are often encountered, which demands the development of new ones. Consequently, both the complexity of synthetically tractable targets and the efficiency with which they can be prepared scale with the capabilities of these methods, thereby driving innovation. In this context, targeting a structure for synthesis that has already been the subject of previous work can constitute a significant scientific contribution by showcasing recently discovered synthetic methods and evaluating new reactivity within complex molecular settings.³

The science of organic synthesis attracts chemists through the problem-solving challenges it poses as well as through the inspiration that comes with discovery. The pursuit of complex molecules inevitably leads to unexpected insights, the development of new methods, and innovative strategies. Achieving a balance of these elements is essential. Chemical synthesis offers a platform to explore new areas and to address previously unanswered synthetic questions. Unlike a conventional puzzle, solutions to synthetic problems are often open-ended and shaped by the creativity of the practitioner. This defining characteristic reflects the evolution of the discipline.³

Accordingly, synthetic chemists must adapt to the evolving demands of the field, which bring new priorities and interdisciplinary challenges to its science. These developments do not diminish the value of fundamental synthetic chemistry; rather, they enhance it and open new avenues for exploration.³ For instance, the recent emergence of data science and computational methods in organic chemistry exemplifies such opportunities, and organic chemistry is poised to play a central role at the interface of these disciplines. While each of the factors discussed above provides motivation for embarking on a total synthesis campaign, the most compelling targets and strategies are those that integrate aspects of all of them.

1.2 Selected Studies on Pd-Catalyzed Cascade Reactions in Natural Product Synthesis

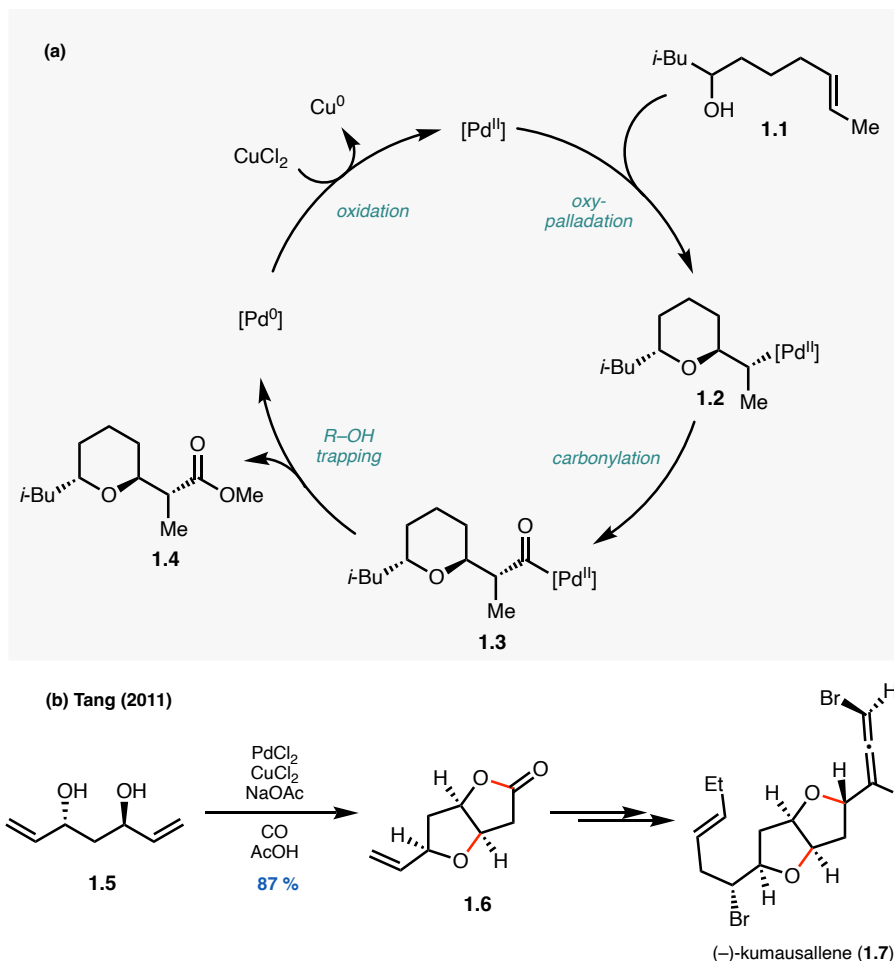
Among the popular strategies for rapid and efficient synthesis of natural products, cascade reactions are particularly attractive to synthetic chemists, as they involve multiple bond-forming and bond-breaking transformations that occur sequentially under a single set of conditions.⁵ The use of palladium as a transition metal catalyst to mediate cascade reactions is especially appealing due to its broad tolerance of phosphine ligands, which yields highly modular catalysts for organic synthesis. Palladium-catalyzed cascade cyclizations can expedite natural product synthesis by enabling the formation of multiple rings, as well as both carbon-carbon and carbon-heteroatom bonds in a single synthetic operation.⁵ Owing to their mild reaction conditions and high selectivity, palladium-catalyzed cascade cyclizations can be employed early in a synthesis to rapidly access polycyclic natural product frameworks, or at the end of a synthesis to selectively introduce functionality into a complex system. Selected examples of total syntheses that feature palladium-catalyzed bond-forming cascade reactions as a key step are shown below.

1.2.1 Total Synthesis of (–)-Kumausallene (Tang, 2011)

In 2011, Tang and co-workers published their (–)-kumausallene synthesis, featuring a Semmelhack palladium-catalyzed cascade cyclization as the key step (Scheme 1).⁶ The proposed catalytic cycle is initiated by oxypalladation of the alcohol to a Pd(II) species, which is a migratory insertion of the Pd–O bond into the pendant olefin group. Subsequent carbonylation and trapping with an exogenous alcohol source liberate a Pd(0) species, which can be converted back to the active Pd(II) catalyst through oxidation with a Cu(II) additive. When an internal nucleophile is

employed, such as an embedded alcohol within the substrate, this method enables the formation of two rings in a single transformation.

Tang and co-workers applied the Semmelhack reaction to construct the pseudosymmetric lactone **1.6** to rapidly access the polycyclic framework by exploiting the symmetry present in the natural product (Scheme 1b). Using the known C₂-symmetric diol **1.5**, they obtained the desired cyclization product in 87 % yield on gram scale in a single step. With this intermediate in hand, the synthesis was advanced to the desired natural product in 12 steps.

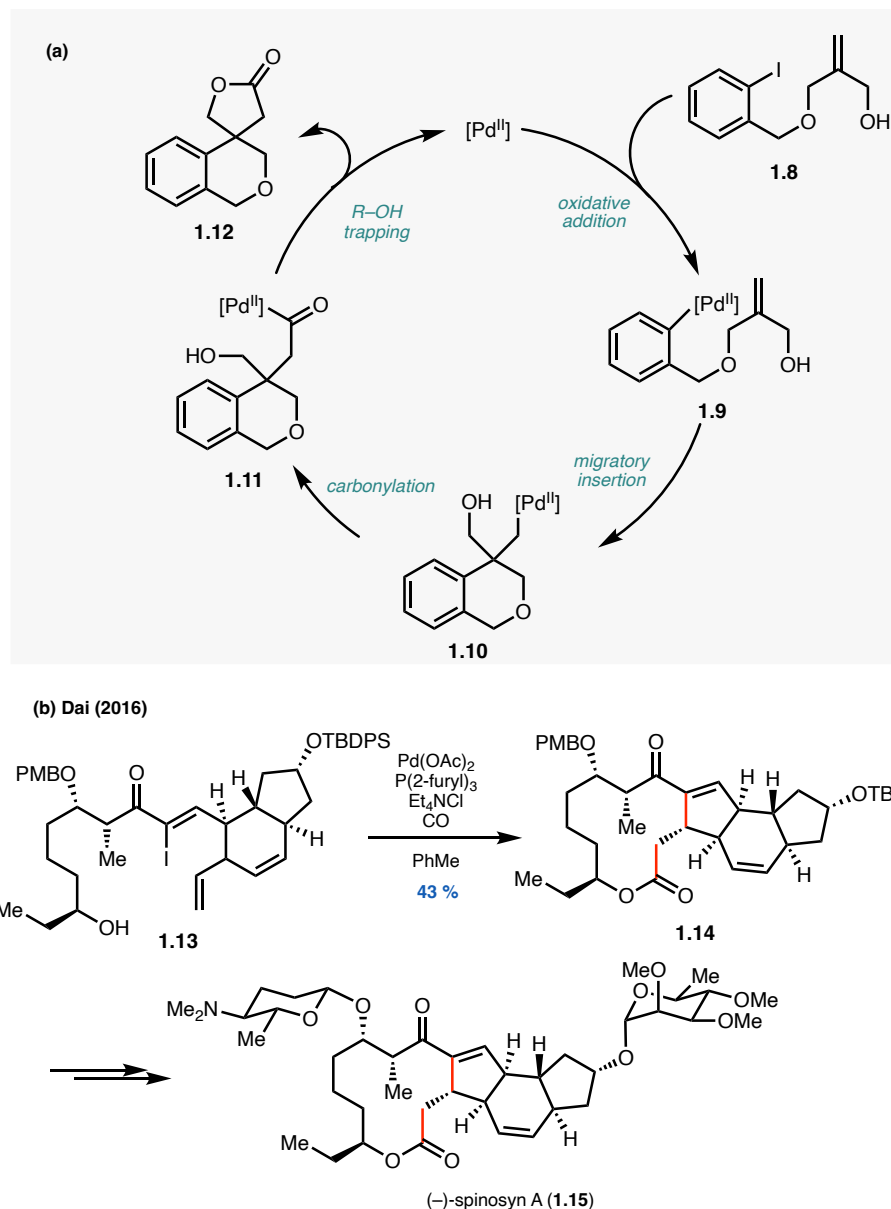


Scheme 1. (a) Proposed catalytic cycle of the Semmelhack reaction.(b) Pd-catalyzed cascade reaction of (–)-kumausallene (**1.7**) synthesis.⁶

1.2.2 Total Synthesis of (–)-Spinosyn A (Dai, 2016)

Similar to the previously described Semmelhack palladium-catalyzed cascade cyclization, Dai and co-workers first applied a carbopalladation/carbonylative lactonization cascade to the synthesis of (–)-spinosyn A in 2016.⁷ Unlike the olefin oxypalladation mechanism, the carbopalladation/carbonylative lactonization catalytic cycle is initiated by oxidative addition of an aryl or vinyl halide/pseudohalide to a Pd(0) species (Scheme 2a). Subsequent migratory insertion

into a pendant olefin group, followed by carbonylation, leads to a Pd(II) intermediate and effects the first cyclization. Intramolecular attack by an alcohol nucleophile forges the second ring and releases Pd(0). Overall, this cascade reaction forms one C–O and two C–C bonds. Despite the mechanistic similarities with the aforementioned Semmelhack reaction, this cascade offers access to a broader range of polycyclic systems through the formation of multiple C–C bonds. In addition, no exogenous oxidant to regenerate an active Pd(II) species is required.



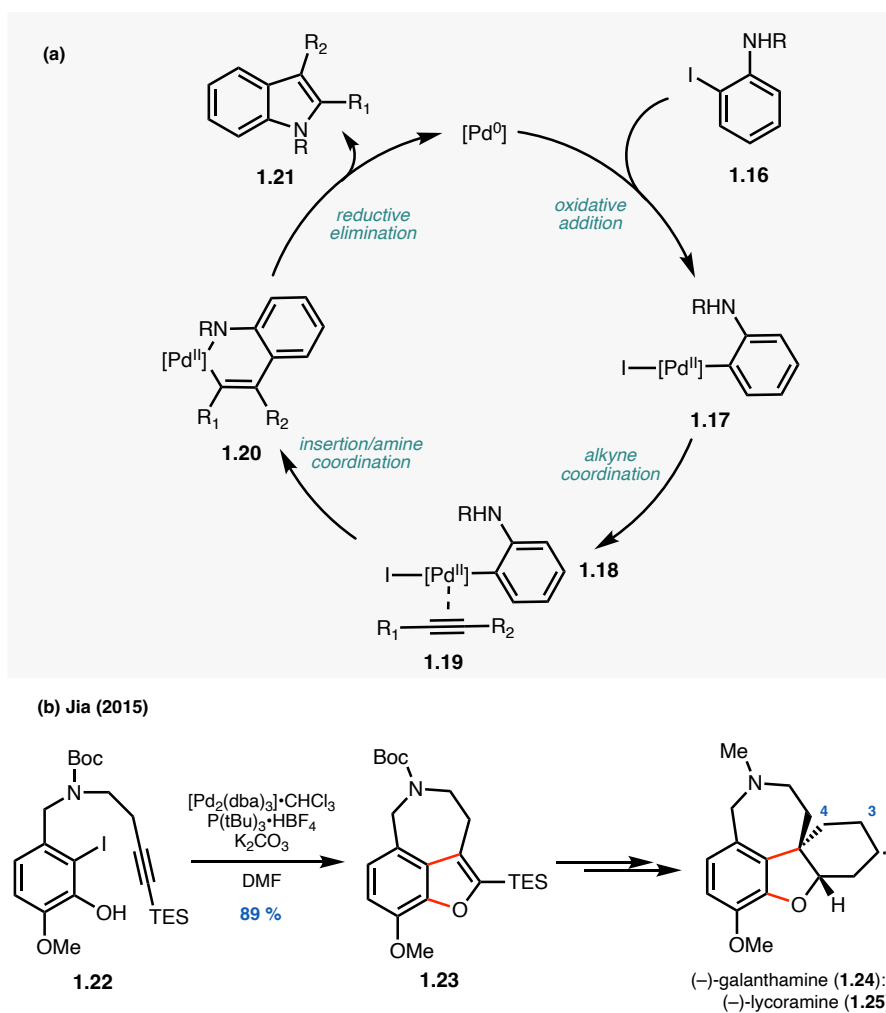
Scheme 2. (a) Proposed catalytic cycle of Pd-catalyzed carbopalladation/carbonylative lactonization. (b) Pd-catalyzed cascade reaction in (–)-spinosyn A (**1.15**) synthesis.⁷

To accomplish the total synthesis of (–)-spinosyn A (**1.15**), the envisioned macrocyclization presented several possible challenges: a competing 5-exo-trig cyclization onto the cyclohexene

olefin group that could interfere with the desired cyclization, uncertainty regarding the diastereoselectivity of the cyclization, and the unprecedented nature of such a macrocyclization in a complex system. They obtained the key macrocycle **1.14** in 43 % yield as a single diastereomer (Scheme 2b), which was then advanced to (–)-spinosyn A (**1.15**) in four additional steps, leading to an overall 23 step total synthesis.

1.2.3 Total Synthesis of (–)-Galanthamine and (–)-Lycoramine (Jia, 2015)

Distinct from the previously discussed cyclization methods, Larock heteroannulation enables the one-step synthesis of 2,3-disubstituted indoles, benzofurans, and related heterocycles.⁵ The proposed mechanism involves initial oxidative addition of Pd(0) to an aryl halide/pseudohalide, followed by alkyne coordination and migratory insertion (Scheme 3a). Coordination of the pendant polar functional group to the palladium catalyst precedes reductive elimination, which releases the annulated product and regenerates the Pd(0) species.



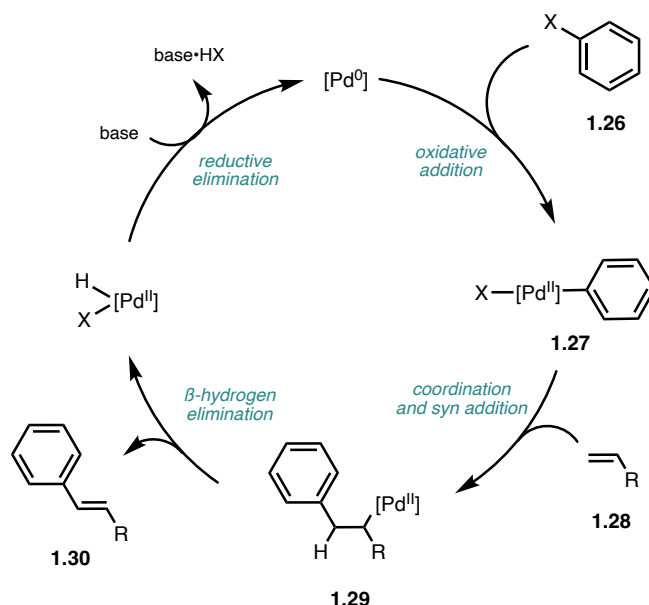
Scheme 3. (a) Proposed catalytic cycle of Larock heteroannulation. (b) Pd-catalyzed cascade reaction in (–)-galanthamine (**1.24**) and (–)-lycoramine (**1.25**) syntheses.⁸

Jia and co-workers have explored the Larock heteroannulation strategy for accessing various alkaloid natural products, including several ergot alkaloids.⁸ In pursuit of the total synthesis of the *Amaryllidacea* alkaloids (–)-galanthamine (**1.24**) and (–)-lycoramine (**1.25**) (Scheme 3b), they sought to expand the substrate scope of the intramolecular Larock heteroannulation methodology. Their studies demonstrated tolerance for the construction of 6–9-membered rings containing O and N heteroatoms, as well as various substitutions on the benzofuran. Notably, this work broadened the scope of the reaction, illustrating that strategic methodological development can have impacts beyond natural product synthesis alone. Building on these findings, the optimized reaction conditions translated well to the fully elaborated system, enabling the asymmetric total syntheses of (–)-galanthamine (**1.24**) and (–)-lycoramine (**1.25**) in 14 and 10 steps, respectively.

1.3 Selected Studies on Pd-Catalyzed Mizoroki–Heck Cascade Carbocyclizations

1.3.1 Mizoroki–Heck Reaction

The Pd(0)-catalyzed functionalization of alkenes with aryl halides was first reported independently in 1972 by Tsutomu Mizoroki and Richard F. Heck.^{9,10} This transformation, now known as the Mizoroki–Heck reaction, is defined as the Pd(0)-mediated coupling of an aryl or vinyl halide or triflate with an alkene.¹¹ The first intramolecular Mizoroki–Heck reaction was reported by Mori and Ban in 1977, who prepared a functionalized indole from a bromoaniline substrate.¹²



Scheme 4. Proposed catalytic cycle of a general Pd-catalyzed Mizoroki–Heck reaction.

The general proposed mechanism of a Mizoroki–Heck reaction is depicted in Scheme 4.¹¹ Oxidative addition of aryl or vinyl halides to Pd(0) generates a Pd(II) species, which subsequently

coordinates to the alkene and undergoes migratory insertion. The resulting alkylpalladium species then undergoes β -hydrogen elimination to afford the functionalized alkene, followed by reductive elimination of a Pd–H species to regenerate Pd(0). Over the years, extensive mechanistic investigations have revealed both cationic and neutral reaction manifolds, providing significant insight into the mechanism of the reaction.¹¹ In addition, the development of asymmetric, oxidative, and reductive variants has transformed this reaction into a powerful C–C bond-forming strategy, which is particularly useful for the construction of tertiary and quaternary stereocenters.¹¹

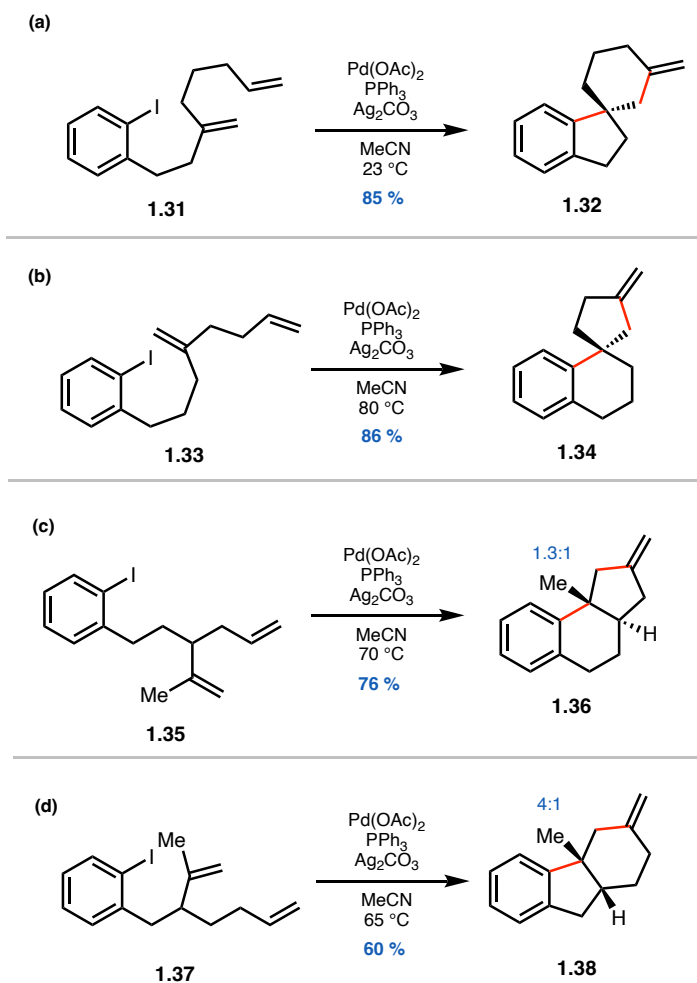
In contrast to intermolecular Mizoroki–Heck reactions, the intramolecular variant offers enhanced regiocontrol during the migratory insertion step. Moreover, through strategic placement of olefin groups in the substrate, tandem Mizoroki–Heck cyclizations can be achieved. Owing to the mild reaction conditions and high chemoselectivity of palladium catalysts, intramolecular Mizoroki–Heck reactions have become the subject of intensive investigation in the context of total synthesis.¹¹ Selected representative examples focusing on carbocycle formation are discussed below.

1.3.2 Biomimetic Polyene Cyclization

A pioneer in the development of annulative Mizoroki–Heck cascade reactions for natural product synthesis is Larry Overman, who has published several seminal contributions in this area.¹¹ Other leaders in this area of research include Grigg, Larock, Trost, and Negishi. In 1992, Overman and co-workers reported biomimetic polyene cyclization reactions employing organotransition-metal intermediates.¹³ This strategy was particularly appealing as it enabled access to polycyclic skeletons that would be difficult to access through traditional cationic or radical cyclization pathways.

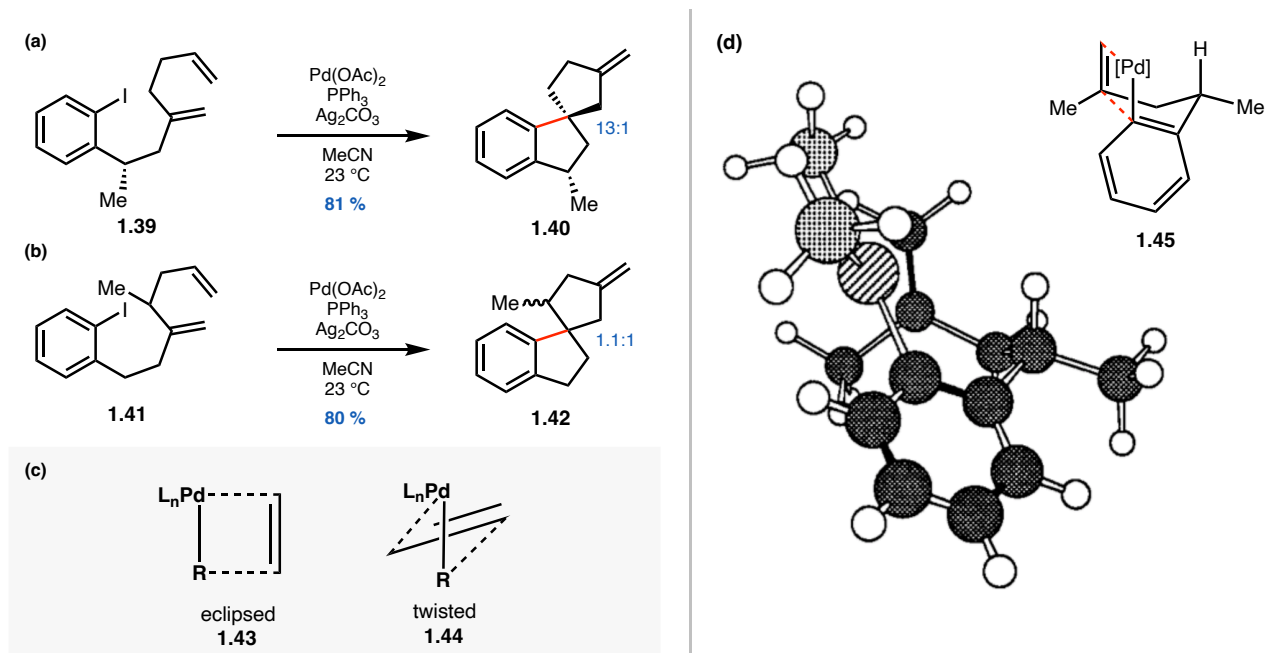
For exploratory studies, Overman and co-workers investigated polycyclizations on several dienyl and trienyl aryl iodides to access spirocyclic compounds. They observed that cyclizations forming 5-membered rings generally proceeded faster than the competing formation of the corresponding 6-membered rings. However, in the instances where the 6-membered ring is formed first, higher reaction temperatures were required to enable the subsequent cyclization of the 5 membered ring (Scheme 5b and c). The formation of fused linear polycyclic systems is less well developed than spirocyclizations. A few examples are described in Scheme 5.

Overman and co-workers further investigated asymmetric induction at the newly formed quaternary center in spirocyclizations of dienyl aryl iodides bearing stereocenters at different positions along the diene segment. When the stereocenter is located on the tether connecting the aromatic ring to the proximal double bond, good diastereoselectivity is observed (Scheme 6a). As expected, low selectivity is obtained when the stereogenic center is positioned distal to the exomethylene group of the cyclization precursor (Scheme 6b).



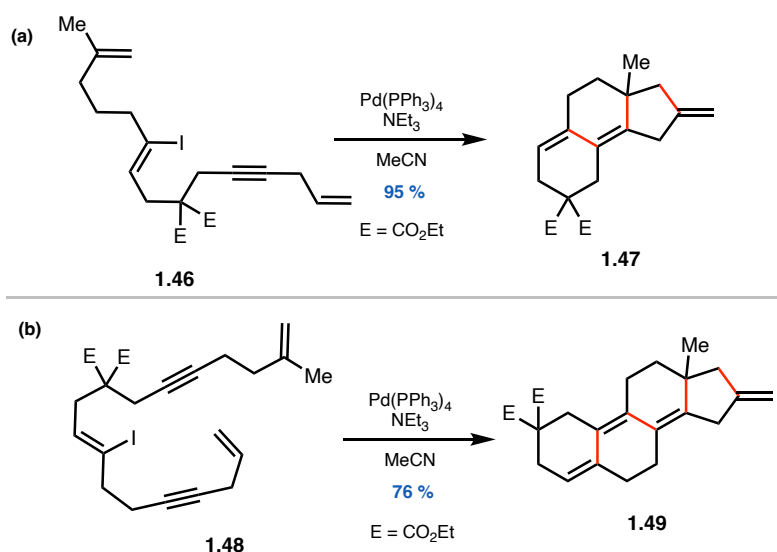
Scheme 5. Cyclization of spirocyclic and fused linear polycyclic systems reported by Overman.¹³

To rationalize this observation, Overman and co-workers have examined the transition state conformation of the first cyclization step using a molecular mechanics model shown in Scheme 6d. The preferential formation of spirocycle **1.40** (Scheme 6a) is attributed to an eclipsed alignment of the Pd–C σ -bond and alkene π -bond during the initial migratory insertion (Scheme 6c). Owing to the steric bulk of the palladium catalyst and its phosphine ligands, the equatorial orientation of the methyl substituent on the tether chain is favored in **1.45**, minimizing steric interactions in the 5-membered ring transition state conformer. The implications of the twisted alignment between the Pd–C σ -bond and alkene π -bond will be discussed in Chapter 1.3.3.



Scheme 6. (a,b) Asymmetric Pd-catalyzed spirocyclization. (c) Simplified scheme illustrating different Pd–C σ -bond and alkene π -bond orientations in the migratory insertion step. (d) Molecular mechanics model of eclipsed transition state for investigating diastereoselectivity in Pd-catalyzed spirocyclization.¹³

In 1992, Negishi published an article highlighting the utility of Pd-catalyzed cascade polycyclizations.¹⁴ He noted that, by the end of 1988, several research groups had reported applications of the Mizoroki–Heck reaction primarily for monocyclizations. Seeking to expand the scope of carbocycle synthesis using this strategy, Negishi introduced examples of tri- and tetracyclizations using Pd-based catalysts and termed this mode of ring construction as a “zipper-mode” cascade carbopalladation. The alternating placement of the olefin groups along two chains – described as a “zigzag” backbone structure – enables migration of the reactive Pd–C bond between the chains. Negishi emphasized the advantage of palladium catalysis in enabling the formation of three or more rings in a single sequence, in contrast to cobalt- or zirconium-promoted cyclization reactions, which are generally limited to the formation of only two rings per step. Representative examples demonstrating this concept on elaborate substrates are shown in Scheme 7.



Scheme 7. Polyene cyclizations reported by Negishi.¹⁴

1.3.3 Total Synthesis of (±)-Tazettine and (±)-6a-Epipretazettine (Overman, 1990)

In 1990, Overman and co-workers reported the total synthesis of (±)-tazettine (**1.50**) and (±)-6a-epipretazettine (**1.52**), utilizing Pd-catalyzed Heck reactions for the stereocontrolled construction of sterically congested quaternary centers.¹⁵ A central focus of this work was the development of both relative and absolute stereocontrol in intramolecular migratory insertion reactions. Notably, prior to this work, studies on precise transition-state orientation of the Pd–C σ-bond and alkene π-bond in a suprafacial insertion process were sparse. The lack of precedent and investigation was one of the key motivations for examining this issue.

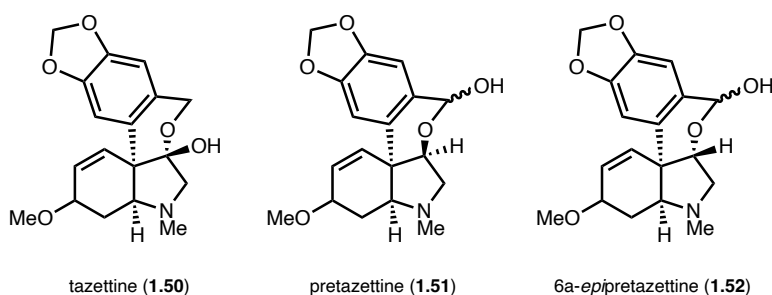
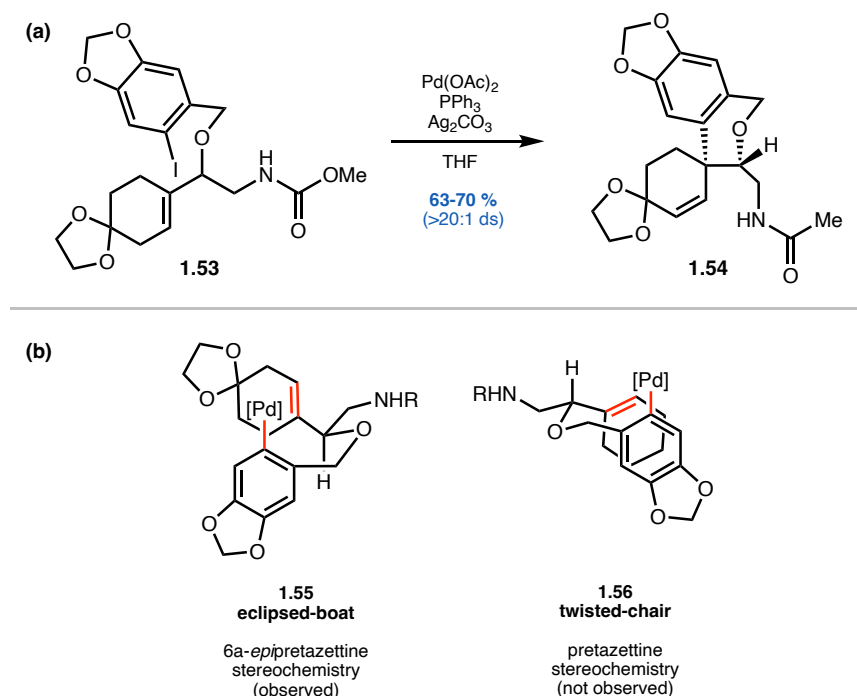


Figure 1. *Amaryllidaceae* alkaloids.

The family of *Amaryllidaceae* alkaloids include tazettine (**1.50**), pretazettine (**1.51**) and 6a-epipretazettine (**1.52**) (Figure 1). Among these, pretazettine (**1.51**) has been reported to exhibit significant anti-cancer activity, particularly against Rauscher leukemia, Lewis lung carcinoma, and spontaneous AKR leukemia.

At the outset of the investigation, two limiting conformations were considered for the key insertion step: placement of the aminomethyl side chain in a pseudo-equatorial orientation and minimizing steric interactions in the 6-membered transition state (Scheme 8a). These give rise to

two distinct conformations that differ in the relative orientation of the Pd–C σ -bond and the alkene π -bond (Scheme 8b). Insertion via an eclipsed-boat conformation (**1.55**) leads to the 6a-*epipretazettine* (**1.52**) relative configuration at the quaternary carbon center, whereas a similar disposition of the side chain in a twisted-chair conformation **1.56** results in the stereochemistry of *pretazettine* (**1.50**).



Scheme 8. (a) Pd-catalyzed spirocyclization in ($\pm$)-*tazettine* (**1.50**) and ($\pm$)-6a-*epipretazettine* (**1.52**) syntheses. (b) Transition state conformer analysis.

The precursor (**1.53**) for the key Pd-catalyzed cyclization step was prepared in 7 steps from commercially available 4-methoxybenzyl alcohol. The intramolecular insertion occurred preferentially to furnish the 6a-*epipretazettine* stereochemistry, consistent with cyclization proceeding through an eclipsed-boat transition state in which the aminomethyl side chain adopts an equatorial orientation. Although the corresponding boat ground-state conformer is disfavored, it possesses a lower barrier to insertion in the eclipsed orientation than the alternative conformation, enabling the reaction to proceed with excellent diastereoselectivity (Curtin-Hammett scenario).

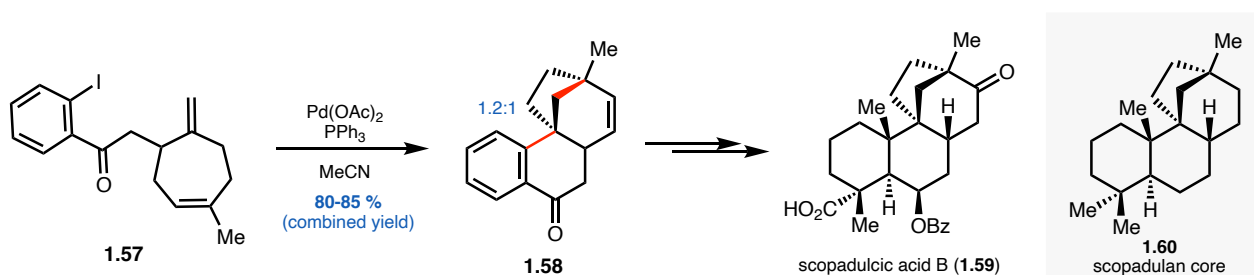
With **1.54** in hand, further elaboration completed the syntheses of ($\pm$)-*tazettine* (**1.50**) and ($\pm$)-6a-*epipretazettine* (**1.52**) in 11 steps overall.

1.3.4 Total Synthesis of Scopadulcic acid A and B (Overman, 1993, 1999)

Building on the insights discussed above regarding asymmetric Pd-catalyzed cascade cyclizations, Overman and co-workers applied this strategy to the total synthesis of scopadulcic acid A and B. These compounds were first isolated in 1987 from *Scoparia dulcis* L. as novel tetracyclic diterpene acids.¹⁶ Scopadulcic acid A and B have been reported to exhibit both *in vitro*

and *in vivo* antiviral and antitumor activities, as well as potent inhibitory activity against H⁺- and K⁺-adenosine triphosphatase.¹⁷

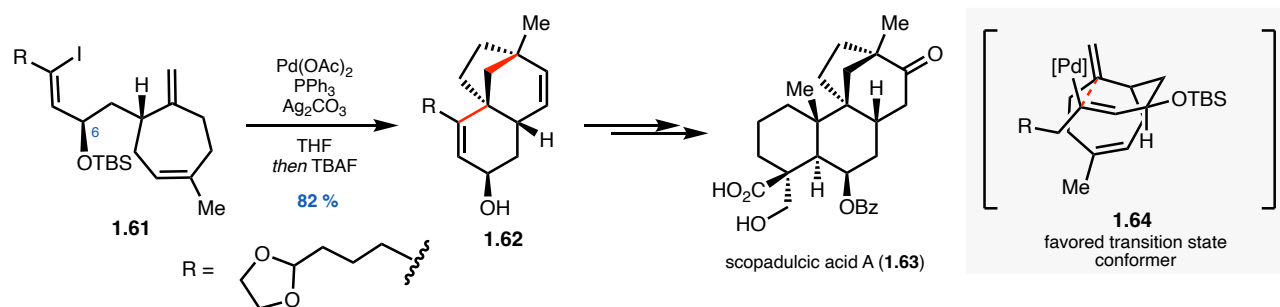
In 1993, Overman and co-workers reported the first racemic total synthesis of scopadulcic acid B (**1.59**).¹⁸ Their key step was a cascade Mizoroki–Heck cyclization of a methylene cycloheptenyl aryl ketone **1.57**. This designed cascade reaction furnished the tetracyclic core in 80–85 % yield, albeit with low facial selectivity, providing a 1.2:1 mixture of stereoisomers of **1.58**. As discussed above, the lack of stereochemical information imparted by a substituent at the benzylic position of the tether in **1.57** accounts for the observed low diastereoselectivity.



Scheme 9. Pd-catalyzed spirocyclization in scopadulcic acid B (**1.59**) synthesis.¹⁸

In the same year, this work was followed by the first total synthesis of scopadulcic acid A (**1.63**), featuring improved diastereoselectivity in the palladium-catalyzed key step.¹⁹ Beyond achieving the first total synthesis of scopadulcic acid A (**1.63**), the authors aimed to enhance diastereoselectivity in the initial cyclization step by incorporating a β-alkoxy substituent at C6 position of the precursor **1.61**. Guided by transition-state conformational analysis (depicted in **1.64**), desired tricyclic product **1.62** was obtained as a single diastereomer in 82 % yield, remarkably setting two quaternary centers of the scopadulan A core in one single transformation. This intermediate was subsequently elaborated to complete the first synthesis scopadulcic acid A (**1.63**) in 21 steps.

In 1999, Overman and co-workers further rendered the synthesis enantiodivergent, enabling the selective preparation of (+)- and (–)-scopadulcic acid A.²⁰



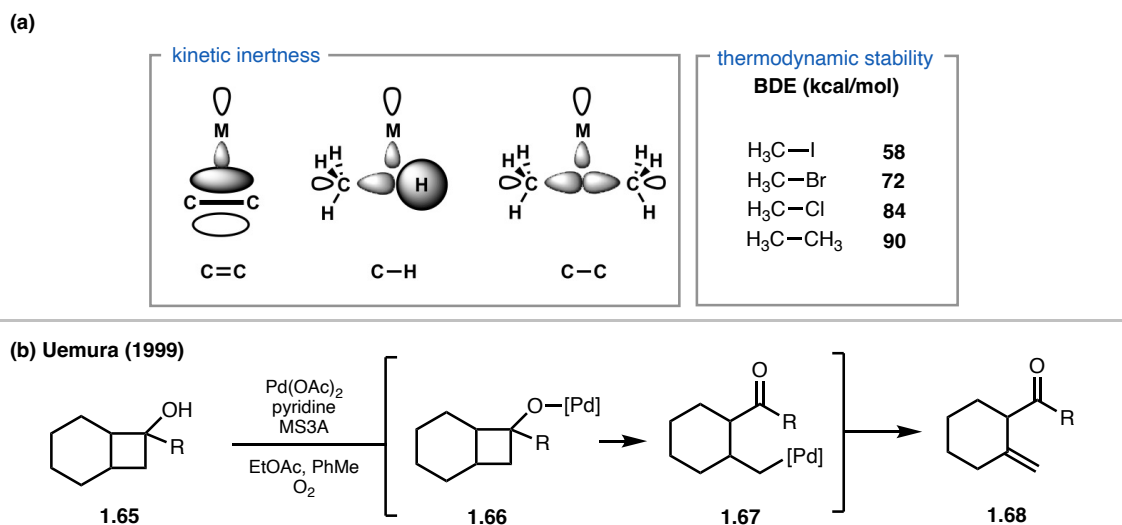
Scheme 10. Pd-catalyzed asymmetric spirocyclization in scopadulcic acid A (**1.63**) synthesis.¹⁹

1.4 Selected Studies on Pd-Catalyzed Synthetic Methods from the Sarpong Group

1.4.1 Pd-Catalyzed Skeletal Rearrangement Methods Development for Terpenoid Natural Product Syntheses

C–C bond forming reactions are central to synthetic organic chemistry because of their fundamental role in constructing the carbon frameworks of complex molecules, including natural products. Classic methods for C–C bond formation include the aldol reaction and 1,2-addition of organometallic nucleophiles to electrophilic carbonyl compounds. With the advent of cross-coupling reactions, strategic considerations for efficient C–C bond formation have changed profoundly, leading to significant advances in molecular synthesis.²¹

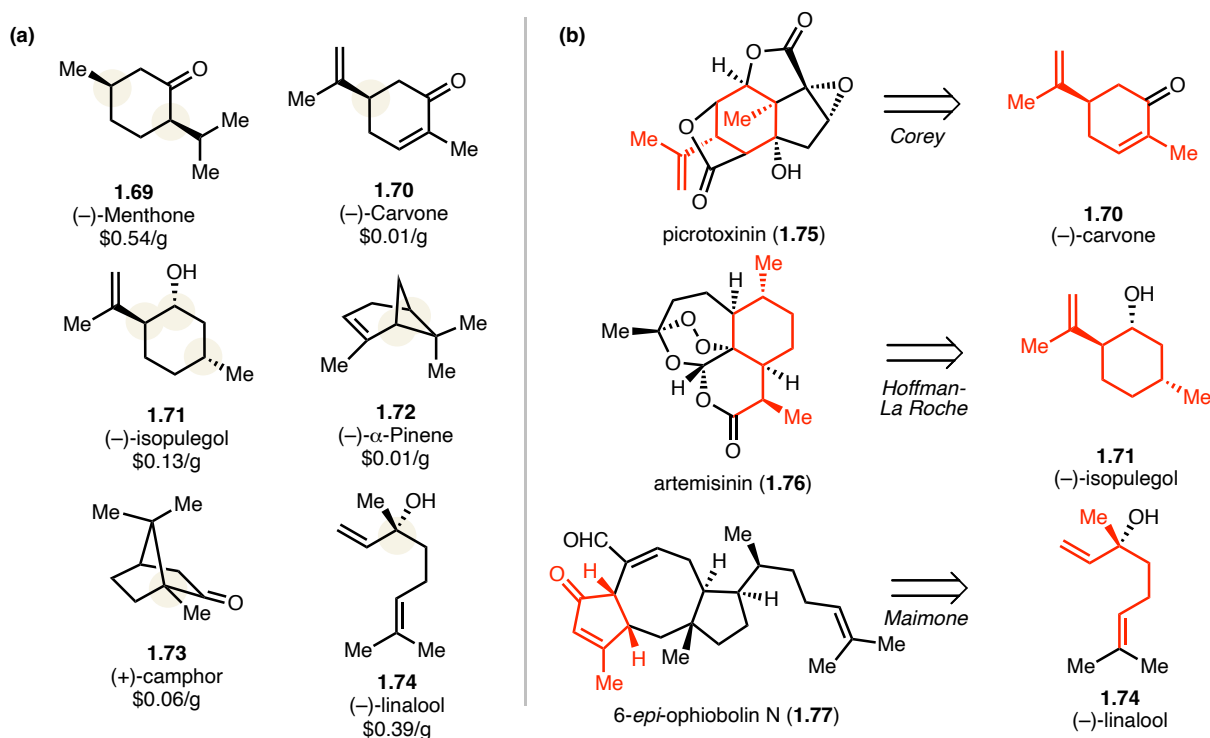
Alongside developments in bond-forming strategies, growing interest has emerged in methods for selective C–C bond cleavage or activation, enabling new retrosynthetic approaches to complex molecules. Despite their strategic promise, C–C bond activation reactions remain challenging. In contrast to C–H bonds, C–C single bonds are typically more sterically congested and are surrounded by kinetically accessible C–H bonds, which are often the first sites to react. As a result, C–C bonds exhibit low reactivity on both kinetic and thermodynamic bases (Scheme 11a).²¹ These challenges have been addressed through the use of transition-metal catalysts bearing pincer-type ligands, which enable access to sterically encumbered C–C bonds via intramolecular chelation, or by employing highly strained cyclic substrates in which bond cleavage is rendered thermodynamically favorable through ring strain release.²¹ Additionally, unstrained tertiary alcohols have been shown to undergo C–C bond cleavage due to the absence of competing β -hydrogen elimination pathways and the entropic gain associated with the formation of a second byproduct.



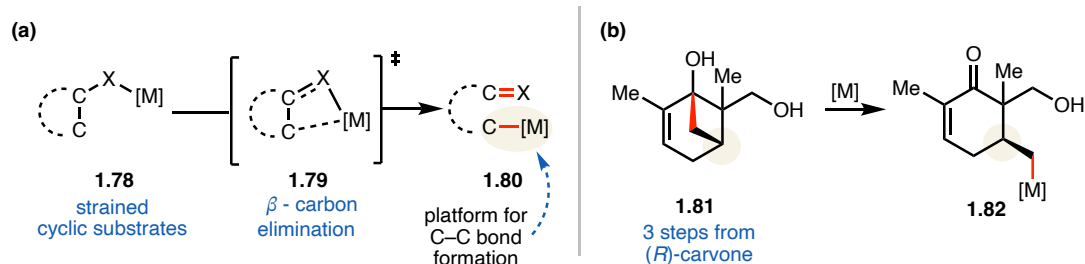
Scheme 11. (a) Kinetic and thermodynamic reactivity of C–C bonds. (b) Precedented work reported by Uemura.²²

Building on these insights, cyclobutanols present particularly attractive substrates for C–C bond activation, as they contain C–C bonds that are both highly strained and sterically accessible. Early examples of C–C bond activation in cyclobutanols were reported by Uemura and co-workers using simple tertiary cyclobutanol substrates (Scheme 11b).²² Exploiting the propensity of cyclobutanols to undergo facile ring opening, our group has been actively investigating Pd-catalyzed cyclobutanol openings coupled with C–C bond-forming cross-coupling reactions. Using this strategy, we sought to explore new reactivity patterns of these privileged substrates in the context of natural product synthesis, with the aim of establishing new paradigms for the construction of molecular complexity.

In parallel with these developments, growing interest has emerged in synthetic methodology centering on the use of naturally occurring “chiral pool terpenes” as starting materials for total synthesis (Scheme 12a).²³ Strategies that rapidly generate target-relevant molecular complexity from simple building blocks are particularly valuable in natural product synthesis. These inexpensive and readily available molecules offer an easily accessible source of enantioenriched material for the enantiospecific preparation of complex natural products. For example, many recent advances in terpenoid total synthesis can be traced to the strategic rearrangement of chiral feedstocks such as carvone **1.70**, isopulegol **1.71**, and linalool **1.74** (Scheme 12b).^{24–26}



Scheme 12. (a) Chiral pool monoterpenes. (b) Total syntheses employing chiral pool feedstock material as substrates.



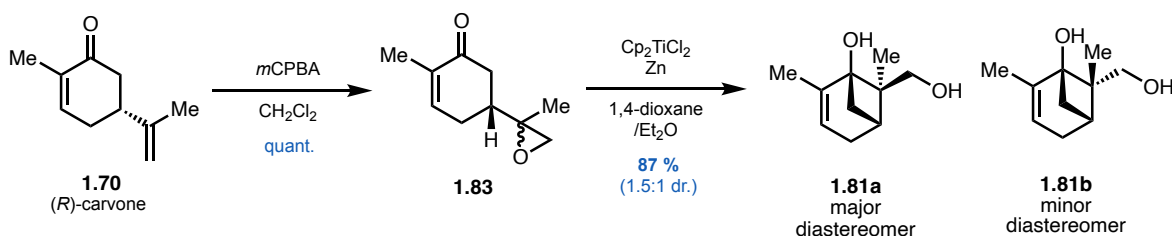
Scheme 13. (a) General reaction scheme. (b) Envisioned transformation on the cyclobutanol substrate with Pd-catalysis.

Unifying these interests, our group sought to employ tertiary cyclobutanol substrates derived from (*R*)- or (*S*)-carvone in a Pd-catalyzed C–C bond cleavage/C–C bond formation strategy (Scheme 13).²¹ Using this monoterpene-derived starting material, we aimed to exploit its enhanced reactivity arising from inherent ring strain to couple it with diverse fragments, enabling the synthesis of sesquiterpene and diterpene natural products. This skeletal remodeling approach reorganizes the carvone framework into synthetic intermediates bearing diverse carboskeletons, thereby providing non-intuitive routes to structurally disparate terpene natural products. Such transformations expand strategic possibilities and often enable significantly simplified syntheses through unconventional retrosynthetic disconnections.

Using this approach, we have reported the total syntheses of numerous natural products spanning multiple structural classes. Selected examples of completed syntheses employing the “break-it-to-make-it” strategy are described in the following sections. Other published work that utilizes fused cyclobutanol substrates that are not derived from chiral pool feedstock material are not covered in the following chapter.

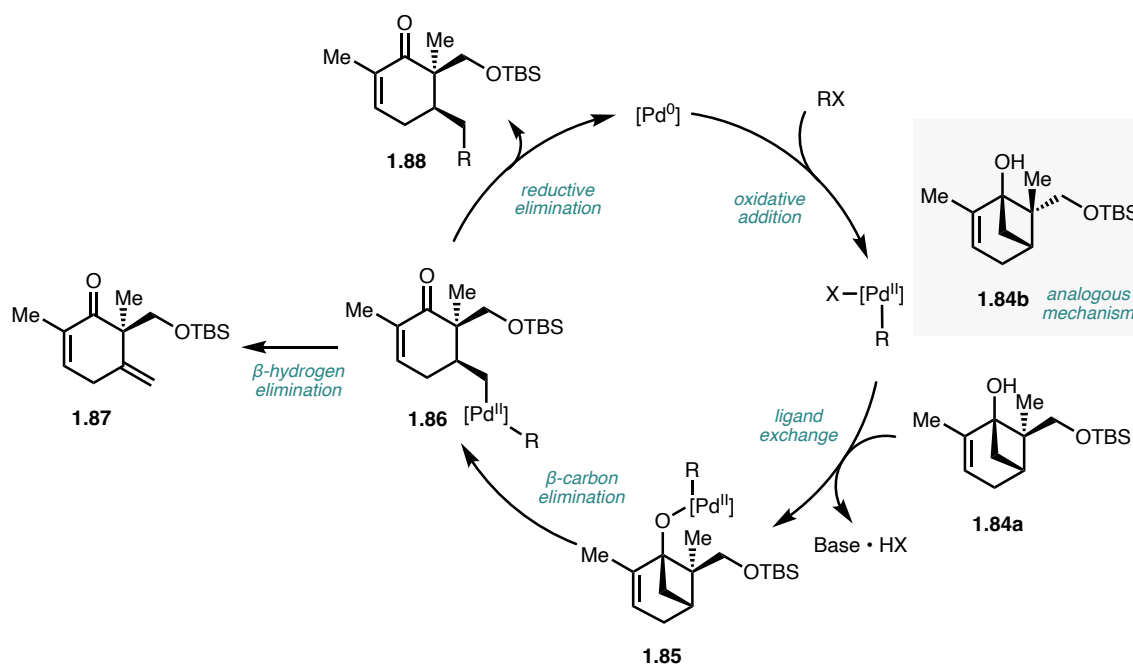
1.4.2 Proposed Catalytic Cycle of the Pd-Catalyzed C–C Bond Cleavage/C–C Bond Formation Sequence

The preparation of the cyclobutanol starting material derived from (*R*)-carvone **1.70** is based on seminal work reported by Bermejo and co-workers (Scheme 14).²⁷ Beginning from (*R*)-carvone **1.70**, electrophilic epoxidation affords epoxycarvone **1.83** in quantitative yield. Subsequent titanocene-mediated reductive cyclization furnishes the bishydroxylated α -pinene-derived cyclobutanol **1.81a** and **1.81b** with moderate diastereoselectivity.



Scheme 14. Preparation of the carvone-derived cyclobutanol substrate **1.81a** and **1.81b**.²⁷

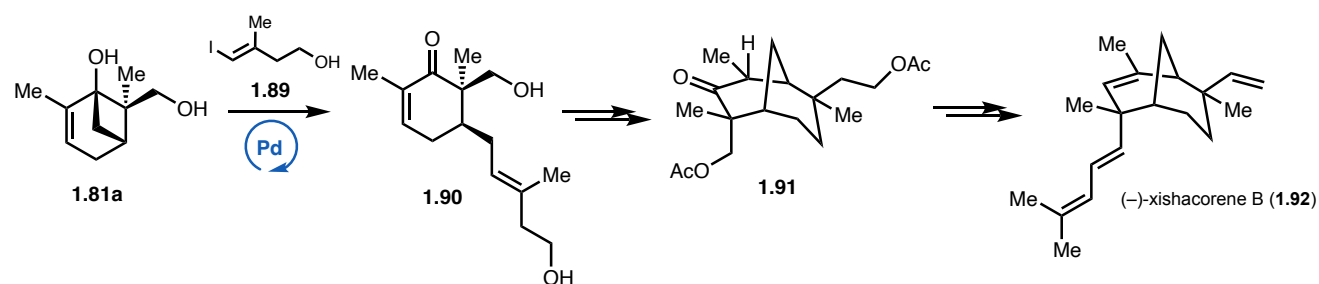
Using a protected version of this substrate, we propose initial oxidative addition of the palladium catalyst into the aryl or vinyl halide/pseudohalide electrophile generates a Pd(II) species (Scheme 15). Then, coordination of the cyclobutanol substrate **1.84a** via ligand exchange enables ring strain-driven β -carbon elimination to furnish ring-opened cyclohexyl-palladium species **1.85**. Owing to steric encumbrance at the adjacent quaternary carbon, β -carbon elimination occurs exclusively at the less substituted carbon. Also, the greater stability of the primary alkyl-Pd species contributes to the observed high selectivity in the β -carbon elimination step. Subsequent reductive elimination delivers cross-coupled product **1.88**. Notably, this pathway competes with undesired β -hydrogen elimination to give **1.87**, which can occur instead of the reductive elimination step. The diastereomer **1.84b** is proposed to undergo the same mechanism that is proposed with cyclobutanol **1.84a**. Completed total syntheses by the Sarpong group employing this strategy are discussed below.



Scheme 15. Proposed catalytic cycle for Pd-catalyzed C-C bond cleavage/C-C bond formation sequence.

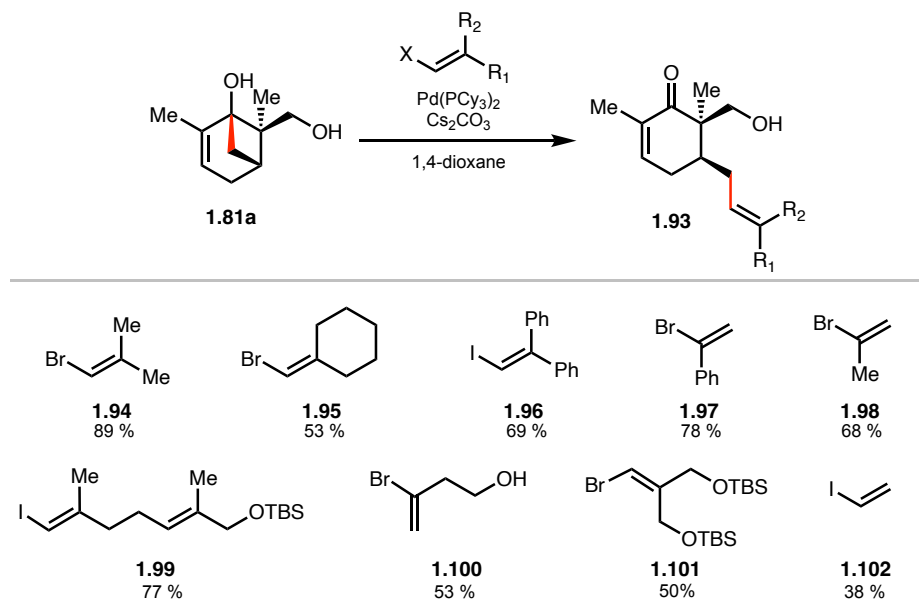
1.4.3 Total Synthesis of (–)-Xishacorene B

Xishacorene B (**1.92**) is a diterpene natural product isolated from the soft coral *Sinularia polydactyla* off the coast of the Xisha Islands in China. Biological studies have revealed its activity as a promoter of concanavalin A-induced T-lymphocyte proliferation, highlighting its utility in the development of small molecule immunopotentiators.²⁸ Retrosynthetically, construction of the bicyclo[3.3.1]nonane core **1.91** was envisioned to proceed via radical cyclization of a cyclohexanone precursor **1.90** (Scheme 16). This precursor could, in turn, be accessed from a Pd-catalyzed C-C bond cleavage/C-C bond formation sequence starting from carvone-derived cyclobutanol **1.81a**, as discussed above.



Scheme 16. Synthesis scheme of (-)-xishacorene B (**1.92**).

Initial work focused on identifying optimal reaction conditions for the palladium-catalyzed reaction sequence. A key requirement for the success of this transformation was suppressing the β -hydrogen elimination pathway. The highest yields (up to 85 %) of the cross-coupled product were obtained using PCy_3 as the ligand. The compatibility of the optimized catalytic system was subsequently evaluated across a range of vinyl bromide and vinyl iodide electrophiles, furnishing the corresponding cross-coupling products in moderate to excellent yields (Scheme 17).



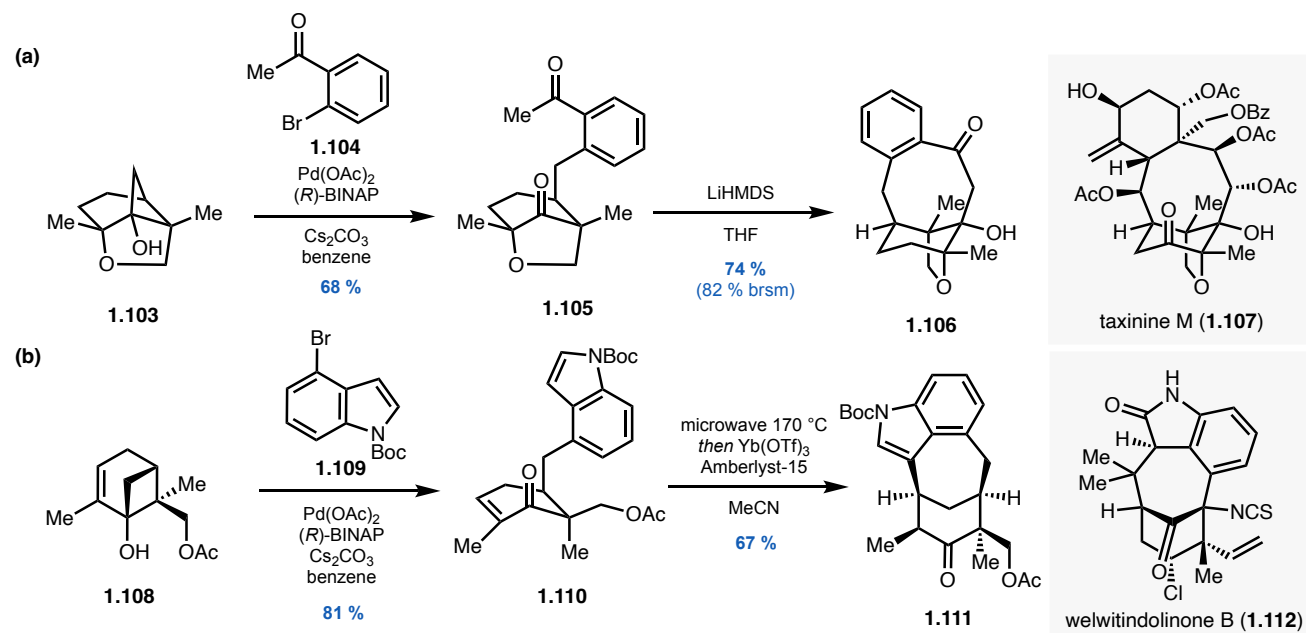
Scheme 17. Substrate scope of Pd-catalyzed C-C bond cleavage/C-C bond formation sequence with various vinyl halide electrophiles.

With the cross-coupled intermediate in hand, further elaboration under radical cyclization conditions furnished bicyclo[3.3.1]nonane core **1.91**, ultimately leading to the synthesis of (-)-xishacorene B (**1.92**) in 10 total steps.

1.4.4 Pd-Catalyzed C-C Bond Cleavage/Arylation to Natural Product-Like Scaffolds

Analogously, the palladium-catalyzed skeletal rearrangement strategy was found to tolerate aryl halide electrophiles as well. Initial work exploring this reactivity was reported in 2015.²⁹

Using two different cyclobutanol substrates (**1.103** and **1.108**), the core structures of taxinine M (**1.107**) and welwitindolinone B (**1.112**) were obtained, respectively (Scheme 18).

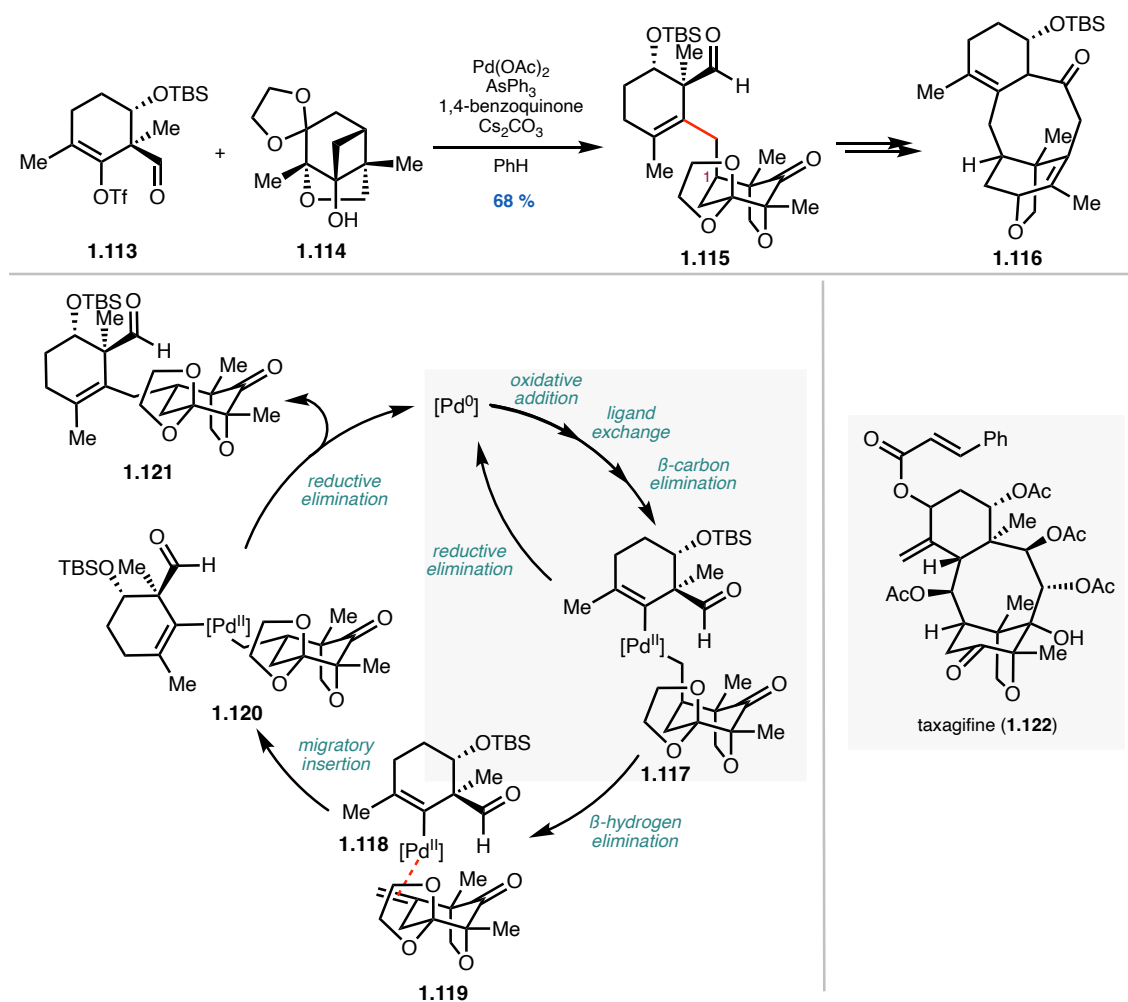


Scheme 18. Preparation of taxinine M (**1.107**) and welwitindolinone B (**1.112**) core structures using Pd-catalyzed reaction sequence, respectively.²⁹

1.4.5 Synthetic Studies Toward the Taxagifine Core

Building on the preliminary work, our group extended the reaction to a more elaborate system with the goal of targeting natural products belonging to the taxane diterpenoid class (Scheme 19).³⁰ Starting from the two diastereomers (**1.81a** and **1.81b**) obtained from the titanocene-mediated reductive cyclization of epoxycarvone **1.83**, each compound was independently advanced to the corresponding cross-coupling electrophile **1.113** and cyclobutanol substrate **1.114**, respectively.

Initial attempts at cross-coupling were outcompeted by the undesired premature β -hydrogen elimination, leading to scrambling of the stereochemistry at C1. The pathway is proposed to arise when, instead of undergoing the desired reductive elimination, complex **1.117** undergoes competing β -hydrogen elimination to generate a Pd(II)-hydride species (**1.118**) and cyclohexanone **1.119**. Re-addition of the Pd(II)-hydride across the exo-methylene group then furnishes the epimer of complex **1.120**, which upon reductive elimination delivers undesired C1 epimer **1.121**. Following extensive reaction optimization and ligand screening, an optimal catalytic system consisting of $\text{Pd}(\text{OAc})_2$ with AsPh_3 and 1,4-benzoquinone as an additive was identified which suppresses the undesired β -hydrogen elimination. With the desired cross-coupling adduct in hand, the intermediate was subsequently advanced to the taxagifine core (**1.116**).



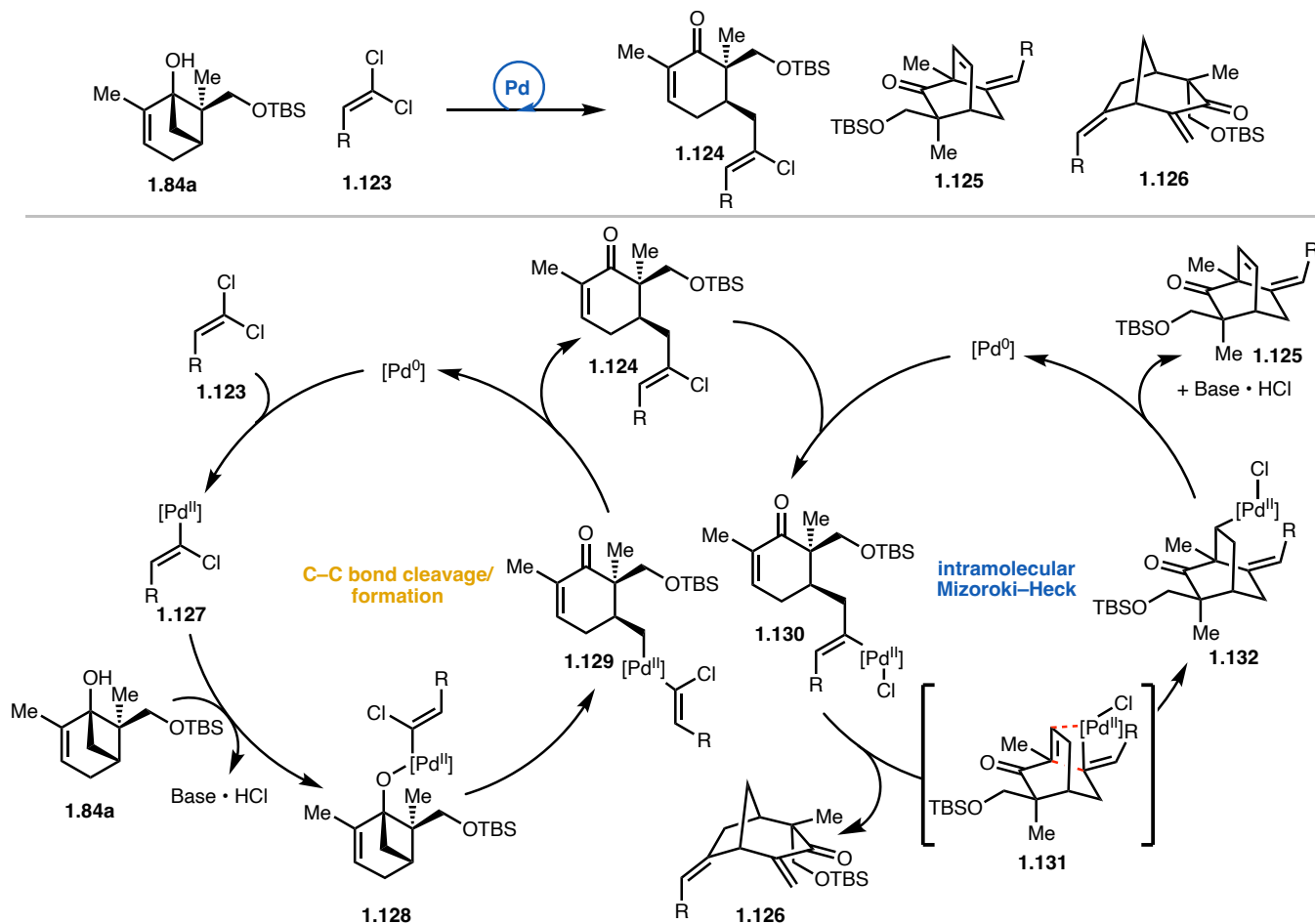
Scheme 19. Pd-catalyzed cross-coupling reaction to the taxagifine core **1.116** and proposed catalytic cycle.

1.5 Our Proposal

Building on these seminal reports, current research efforts in our group aim to expand this strategy to a broader scope of electrophiles. In this context, we became interested in employing *gem*-dihaloalkenes **1.122** which can function as “double-vinyl halides”. In an orchestrated Pd-catalyzed C–C bond cleavage/C–C bond formation sequence, such substrates would retain a second vinyl halide moiety in the product, thereby providing an additional reactive handle for downstream transformations, including transition metal catalyzed cross-coupling, elimination, and related reactions.

Although efficient methods for the preparation of *gem*-dihaloalkenes are well preceded in the literature,³¹ these substrates have been rarely exploited in the context of total synthesis to date. With respect to the generation of key intermediates for terpenoid natural product synthesis, we envisioned enabling an intramolecular Mizoroki–Heck cyclization following the established Pd-

catalyzed C–C bond cleavage/C–C bond formation sequence on chiral pool terpenes to access enantioenriched bicyclic structures (Scheme 20). This extended reaction sequence would, in effect, accomplish the formation of two new C–C bonds and the cleavage of one C–C bond in a single transformation. The products of the designed catalytic cascade reaction, bicyclo[2.2.2]octanone **1.124** and bicyclo[3.2.1]octanone **1.125**, are prevalent motifs in a variety of terpenoid natural product families, such as kaurene and trachylobane natural products.



Scheme 20. Proposed catalytic cycle of C–C bond cleavage/C–C bond formation/intramolecular Mizoroki–Heck cascade reaction.

Ultimately, our goal is to apply this newly developed reaction in the total synthesis of a terpenoid natural product, thereby demonstrating the utility and efficiency of this unprecedented cascade reaction. Through the work described herein, we aim to establish a novel paradigm for the construction of such bicyclic structures.

1.6 References

1. (a) Newman, D. J.; Cragg, G. M. Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. *J. Nat. Prod.* **2020**, *83*, 770–803. (b) Li, J. W.-H.; Vederas, J. C. Drug Discovery and Natural Products: End of an Era or an Endless Frontier? *Science* **2009**, *325*, 161–165. (c) Shen, B. A New Golden Age of Natural Products Drug Discovery. *Cell* **2015**, *163*, 1297–1300.
2. Shenvi, R. A. Natural Product Synthesis in the 21st Century: Beyond the Mountain Top. *ACS Cent. Sci.* **2024**, *10*, 519–528.
3. Carreira, E. M. Natural Product Synthesis: A Personal Retrospective and Outlook. *Isr. J. Chem.* **2018**, *58*, 114–121.
4. (a) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752–6756. (b) Lovering, F. Escape from Flatland 2: Complexity and Promiscuity. *Med. Chem. Commun.* **2013**, *4*, 515–519.
5. Holman, K. R.; Stanko, A. M.; Reisman, S. E. Palladium-Catalyzed Cascade Cyclizations Involving C–C and C–X Bond Formation: Strategic Applications in Natural Product Synthesis. *Chem. Soc. Rev.* **2021**, *50*, 7891–7908.
6. Werness, J. B.; Tang, W. Stereoselective Total Synthesis of (–)-Kumausallene. *Org. Lett.* **2011**, *13*, 3664–3666.
7. Bai, Y.; Shen, X.; Li, Y.; Dai, M. Total Synthesis of (–)-Spinosyn A via Carbonylative Macrolactonization. *J. Am. Chem. Soc.* **2016**, *138*, 10838–10841.
8. Li, L.; Yang, Q.; Wang, Y.; Jia, Y. Catalytic Asymmetric Total Synthesis of (–)-Galanthamine and (–)-Lycoramine. *Angew. Chem. Int. Ed.* **2015**, *54*, 6255–6259.
9. Mizoroki, T.; Mori, K.; Ozaki, A. Arylation of Olefin with Aryl Iodide Catalyzed by Palladium. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581–582.
10. Heck, R. F.; Nolley, J. P., Jr. Palladium-Catalyzed Vinylic Hydrogen Substitution Reactions with Aryl, Benzyl, and Styryl Halides. *J. Org. Chem.* **1972**, *37*, 2320–2322.
11. (a) Dounay, A. B.; Overman, L. E. The Asymmetric Intramolecular Heck Reaction in Natural Product Total Synthesis. *Chem. Rev.* **2003**, *103*, 2945–2963. (b) Le Bras, J.; Muzart, J. Intermolecular Dehydrogenative Heck Reactions. *Chem. Rev.* **2011**, *111*, 1170–1214.
12. Mori, M.; Chiba, K.; Ban, Y. The Reactions and Syntheses with Organometallic Compounds. V. A New Synthesis of Indoles and Isoquinolines by Intramolecular

- Palladium-Catalyzed Reactions of Aryl Halides with Olefinic Bonds. *Tetrahedron Lett.* **1977**, *18*, 1037–1040.
13. Overman, L. E.; Abelman, M. M.; Kuvera, D. J.; Tran, V. D.; Ricca, D. J. Palladium-Catalyzed Polyene Cyclizations. *Pure Appl. Chem.* **1992**, *64*, 1813–1818.
 14. Negishi, E. Zipper-Mode Cascade Carbometallation for Construction of Polycyclic Structures. *Pure Appl. Chem.* **1992**, *64*, 323–334.
 15. Abelman, M. M.; Overman, L. E.; Tran, V. D. Construction of Quaternary Carbon Centers by Palladium-Catalyzed Intramolecular Alkene Insertions: Total Synthesis of the Amaryllidaceae Alkaloids Tazettine and (±)-6a-Epipretazettine. *J. Am. Chem. Soc.* **1990**, *112*, 6959–6964.
 16. (a) Hayashi, T.; Kishi, M.; Kawasaki, M.; Arisawa, M.; Shimizu, M.; Suzuki, S.; Yoshizaki, M.; Morita, N.; Tezuka, Y.; Kikuchi, T.; Berganza, L. H.; Ferro, E.; Basualdo, I. Scopadulcic Acid A and B, New Diterpenoids with a Novel Skeleton, from a Paraguayan Crude Drug “Typychá Kuratũ” (*Scoparia dulcis* L.). *Tetrahedron Lett.* **1987**, *28*, 3693–3696. (b) Hayashi, T.; Kishi, M.; Kawasaki, M.; Arisawa, M.; Morita, N. The Crystal Structure of Scopadulcic Acid A from Paraguayan Crude Drug “Typychá Kuratũ” (*Scoparia dulcis*). *J. Nat. Prod.* **1988**, *51*, 360–364. (c) Hayashi, T.; Asano, S.; Mizutani, M.; Takeguchi, N.; Kojima, T.; Okamura, K.; Morita, N. Scopadulciol, an Inhibitor of Gastric H⁺,K⁺-ATPase from *Scoparia dulcis*, and Its Structure–Activity Relationships. *J. Nat. Prod.* **1991**, *54*, 802–809. (d) Ahmed, M.; Jakupovic, J. Diterpenoids from *Scoparia dulcis*. *Phytochemistry* **1990**, *29*, 3035–3040.
 17. (a) Asano, S.; Mizutani, M.; Hayashi, T.; Morita, N.; Takeguchi, N. Reversible Inhibitions of Gastric H⁺,K⁺-ATPase by Scopadulcic Acid B and Diacetyl Scopadol. *J. Biol. Chem.* **1990**, *265*, 22167–22173. (b) Hayashi, T.; Okamura, K.; Kakemi, M.; Asano, S.; Mizutani, M.; Takeguchi, N.; Kawasaki, M.; Tezuka, Y.; Kikuchi, T.; Morita, N. Scopadulcic Acid B, a New Tetracyclic Diterpenoid from *Scoparia dulcis* L.: Structure, H⁺,K⁺-ATPase Inhibitory Activity, and Pharmacokinetic Behavior in Rats. *Chem. Pharm. Bull.* **1990**, *38*, 2740–2745. (c) Hayashi, T.; Hayashi, K.; Uchida, K.; Niwayama, S.; Morita, N. Antiviral Agents of Plant Origin. II. Antiviral Activity of Scopadulcic Acid B Derivatives. *Chem. Pharm. Bull.* **1990**, *38*, 239–242. (d) Hayashi, K.; Hayashi, T.; Morita, N. Cytotoxic and Antitumor Activity of Scopadulcic Acid from *Scoparia dulcis* L. *Phytother. Res.* **1992**, *6*, 6–10.
 18. Overman, L. E.; Ricca, D. J.; Tran, V. D. First Total Synthesis of Scopadulcic Acid B. *J. Am. Chem. Soc.* **1993**, *115*, 2042–2044.
 19. Kucera, D. J.; O'Connor, S. J.; Overman, L. E. Total Synthesis of (±)-Scopadulcic Acid A: An Illustration of the Utility of Palladium-Catalyzed Polyene Cyclizations. *J. Org. Chem.* **1993**, *58*, 5304–5306.

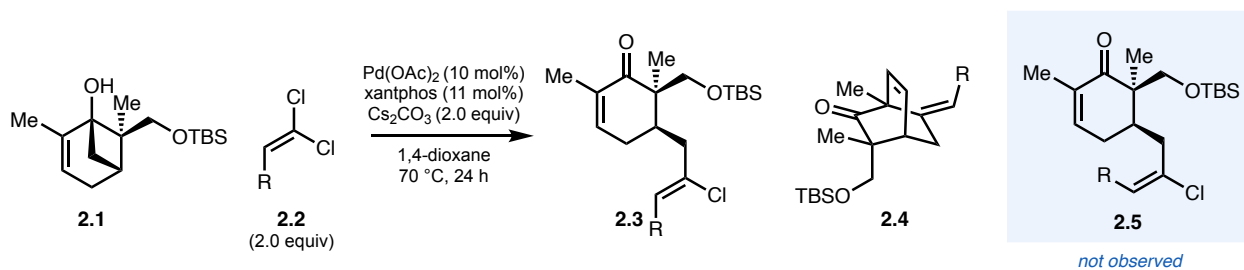
20. Fox, M. E.; Li, C.; Marino, J. P.; Overman, L. E. Enantiodivergent Total Synthesis of (+)- and (–)-Scopadulcic Acid A. *J. Am. Chem. Soc.* **1999**, *121*, 5467–5480.
21. Lusi, R. F.; Perea, M. A.; Sarpong, R. C–C Bond Cleavage of α -Pinene Derivatives Prepared from Carvone as a General Strategy for Complex Molecule Synthesis. *Acc. Chem. Res.* **2022**, *55*, 746–758.
22. Nishimura, T.; Uemura, S. Palladium-Catalyzed Arylation of *tert*-Cyclobutanols with Aryl Bromides via C–C Bond Cleavage: A New Approach to γ -Arylated Ketones. *J. Am. Chem. Soc.* **1999**, *121*, 11010–11011.
23. Brill, Z. G.; Condakes, M. L.; Ting, C. P.; Maimone, T. J. Navigating the Chiral Pool in the Total Synthesis of Complex Terpene Natural Products. *Chem. Rev.* **2017**, *117*, 11753–11795.
24. Corey, E. J.; Pearce, H. L. Total Synthesis of Picrotoxinin. *J. Am. Chem. Soc.* **1979**, *101*, 5841–5843.
25. Schmid, G.; Hofheinz, W. Total Synthesis of Qinghaosu. *J. Am. Chem. Soc.* **1983**, *105*, 624–625.
26. Brill, Z. G.; Grover, H. K.; Maimone, T. J. Enantioselective Synthesis of an Ophiobolin Sesterterpene via a Programmed Radical Cascade. *Science* **2016**, *352*, 1078–1082.
27. Bermejo, F. A.; Mateos, A. F.; Escribano, A. M.; Lago, R. M.; Burón, L. M.; López, M. R.; González, R. R. Ti(III)-Promoted Cyclizations: Application to the Synthesis of (E)-endo-Bergamoten-12-oic Acids, Moth Oviposition Stimulants Isolated from *Lycopersicon hirsutum*. *Tetrahedron* **2006**, *62*, 8933–8942.
28. Kerschgens, I.; Rovira, A. R.; Sarpong, R. Total Synthesis of (–)-Xishacorene B from (R)-Carvone Using a C–C Activation Strategy. *J. Am. Chem. Soc.* **2018**, *140*, 9810–9813.
29. Weber, M.; Owens, K.; Masarwa, A.; Sarpong, R. Construction of Enantiopure Taxoid and Natural Product-like Scaffolds Using a C–C Bond Cleavage/Arylation Reaction. *Org. Lett.* **2015**, *17*, 5432–5435.
30. Perea, M. A.; Wang, B.; Wyler, B. C.; Ham, J. S.; O'Connor, N. R.; Nagasawa, S.; Kimura, Y.; Manske, C.; Scherübl, M.; Nguyen, J. M.; Sarpong, R. General Synthetic Approach to Diverse Taxane Cores. *J. Am. Chem. Soc.* **2022**, *144*, 21398–21407.
31. Chelucci, G. Synthesis and Metal-Catalyzed Reactions of *gem*-Dihalovinyl Systems. *Chem. Rev.* **2012**, *112*, 1344–1462.

Chapter 2. Development of a Pd-catalyzed C–C Bond Cleavage/Vinylation/Mizoroki–Heck Cyclization Cascade

2.1 Proposed Mechanism

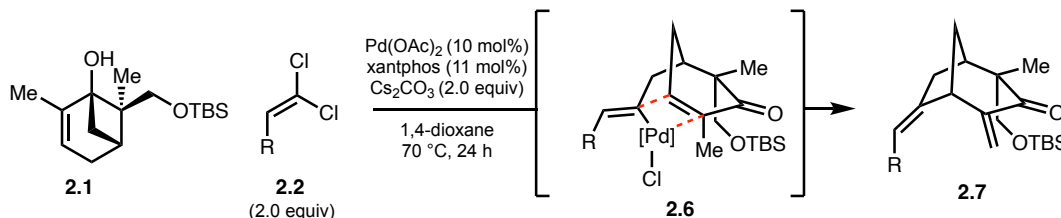
In the following initial optimization and mechanistic studies, 1-(2,2-dichlorovinyl)-4-methylbenzene **2.2** was used as a model electrophile with cyclobutanol **2.1** (Table 2.1). In our preliminary test reaction with xantphos, we obtained both vinyl chloride **2.3** and bicyclo[2.2.2]octanone **2.4**, albeit with low product selectivity (Table 2.1, entry 3). The reaction exclusively afforded the *trans*-alkene **2.3**, reflecting a selective oxidative addition of palladium to the sterically more accessible C–Cl bond of the *gem*-dichloroalkene electrophile **2.2**. Elongated reaction times afforded bicyclo[2.2.2]octane **2.4** in higher yield, validating the conversion of vinyl chloride **2.3** to the respective bicycle upon longer exposure to the reaction conditions (Table 2.1). Along with **2.4**, the alternative Mizoroki–Heck cyclization product, bicyclo[3.2.1] octanone **2.7** was observed throughout the optimization studies, albeit in low yields (Scheme 2.1). The factors governing the selectivity of migratory insertion leading instead to **2.7** will be discussed later in this chapter.

Table 2.1. Initial test reaction and reaction time screening.^a



entry	reaction time	2.1	2.3a	2.4a
1	6	49	23	5
2	12	0	26	39
3	24	0	12	38
4	48	0	18	46

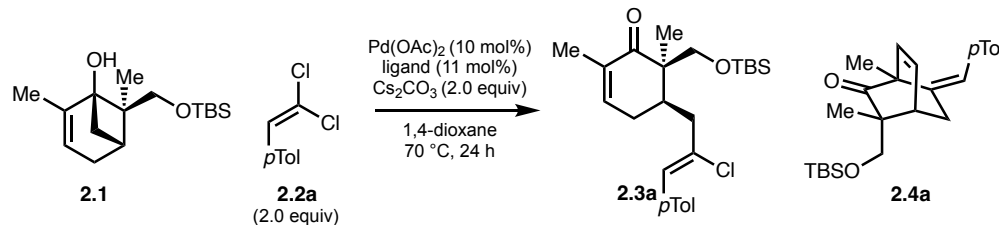
^a Reaction run with **2.1** (0.05 mmol), R = *p*-tolyl, all NMR yields with 1,3,5-trimethoxybenzene as internal standard.



Scheme 2.1. Formation of bicyclo[3.2.1]octanone **2.7** as minor cyclization product.

Overall, cyclization product **2.4** was favored in 1,4-dioxane, while toluene favored the formation of **2.3** (Table 2.2). In addition, switching from the rigid xantphos to the more flexible DPEPhos led primarily to formation of **2.3**.

Table 2.2. Solvent screening.

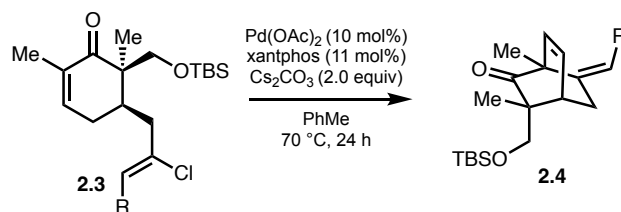


entry	ligand	solvent	2.3a	2.4a
1		1,4-dioxane	18	46
2	xantphos	THF	42	28
3		toluene	49	12
4		1,4-dioxane	65	2
5	DPEPhos	THF	63	3
6		toluene	72	3

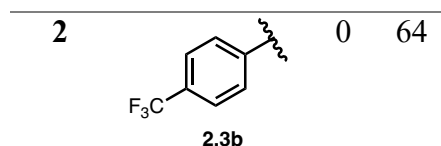
^a Reaction run with **2.1** (0.05 mmol), all NMR yields with 1,3,5-trimethoxybenzene as internal standard.

More direct support for the proposed mechanism was gained when a separate Mizoroki–Heck cyclization reaction starting from vinyl chloride **2.3** was conducted and afforded bicyclo[2.2.2]octanone **2.4** as the product, albeit in incomplete conversion (Table 2.3). Surprisingly, increasing the reaction time and temperature did not lead to full consumption of **2.3**. Comparison of vinyl chloride **2.3a** to its analog **2.3b**, which bears a more electron-deficient aryl substituent, showed faster and higher yielding conversion to bicyclo[2.2.2]octanone **2.4** (Table 2.3, entry 2). This is consistent with the expectation that electron-deficient vinyl halides would undergo oxidative additions more rapidly.

Table 2.3. Conversion of vinyl chloride **2.3** to bicyclo[2.2.2]octanone **2.4**.^a



entry	Ar-	2.3	2.4
1		37	24
	2.3a		



^a Reaction run with **2.3** (0.05 mmol), all NMR yields with 1,3,5-trimethoxybenzene as internal standard.

Mechanistic intricacies of the cascade reaction were revealed when *gem*-dichloroalkene electrophiles bearing varied aryl substituents (Figure 2.1) were employed. Starting from cyclobutanol **2.1**, aryl-substituted alkene electrophiles **2.2** bearing electron-withdrawing groups predominantly afforded vinyl chloride **2.3**, whereas those with electron-donating groups favored formation of bicyclo[2.2.2]octanone **2.4**.

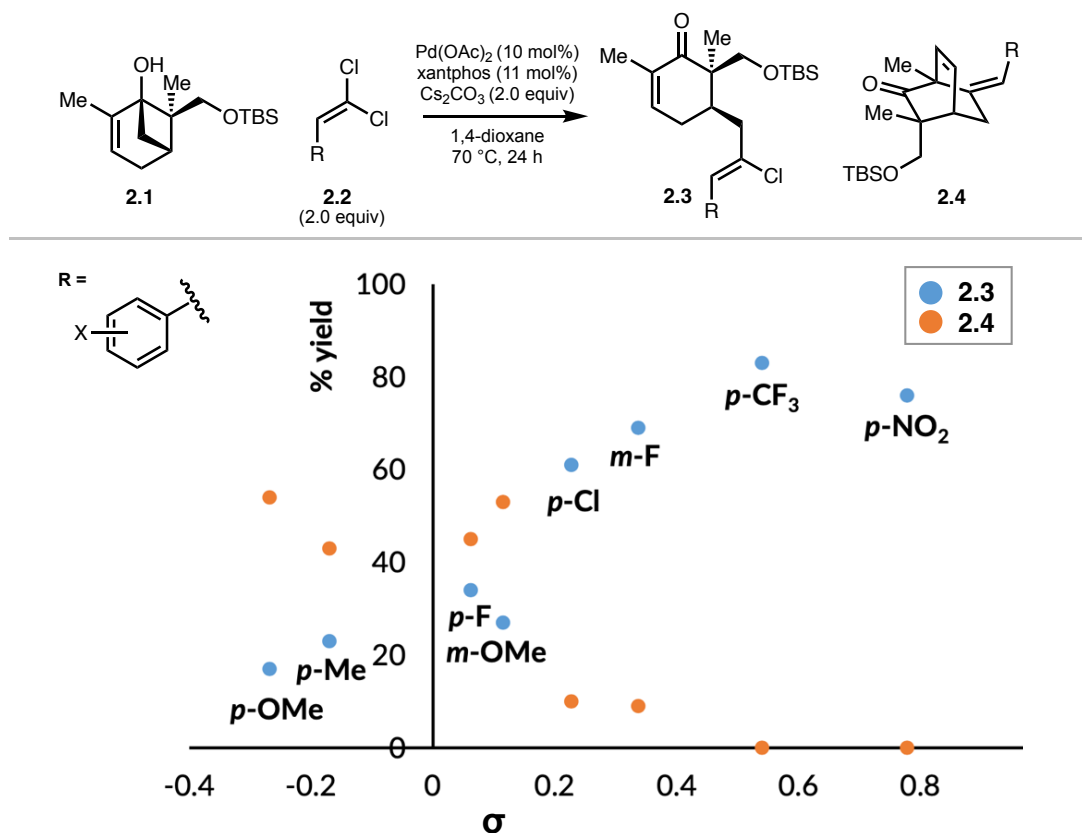


Figure 2.1. Cascade efficiency depending on electronic features of aryl substituents on *gem*-dichloroalkene electrophile **2.2**.

On the basis of these observations, we propose that the concept of “kinetics matching” applies to our system, in which the rates of oxidative addition in the first and second catalytic cycles depend on the electronic properties of the cross-coupling electrophile (Figure 2.2).¹ Given the observed trends, we hypothesize that the difference in oxidative addition rates between *gem*-dichloroalkenes **2.2** and vinyl chloride **2.3** increases with more electron-withdrawing aryl substituents. Because the two catalytic cycles share the same catalyst, rapid oxidative addition of electron deficient *gem*-dichloroalkene **2.2** diverts the palladium catalyst away from the second catalytic cycle, ultimately leading to a higher overall yield of **2.3**.

In contrast, electron-rich *gem*-dichloroalkenes exhibit more comparable addition rates across both catalytic cycles, resulting in improved kinetic matching and a higher yield of bicyclo[2.2.2]octanone **2.4**. Accordingly, the relative rates of oxidative addition for *gem*-dichloroalkene **2.2** and vinyl chloride **2.3** are governed by the electronic nature of their aryl substituents. This result indicates that optimal yields of bicyclo[2.2.2]octanone **2.4** are achieved when the reactivities of the separate cycles are tuned to work in unison. Similar kinetic matching and mismatching effects in cascade reactions have been reported in recent literature.¹

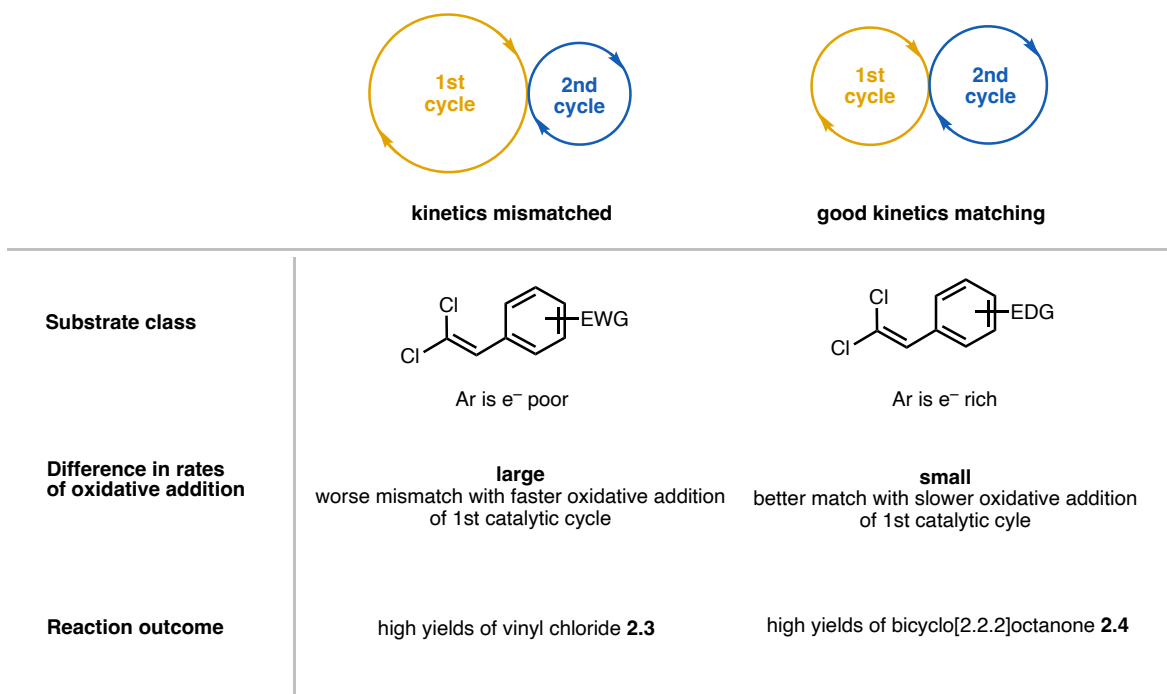


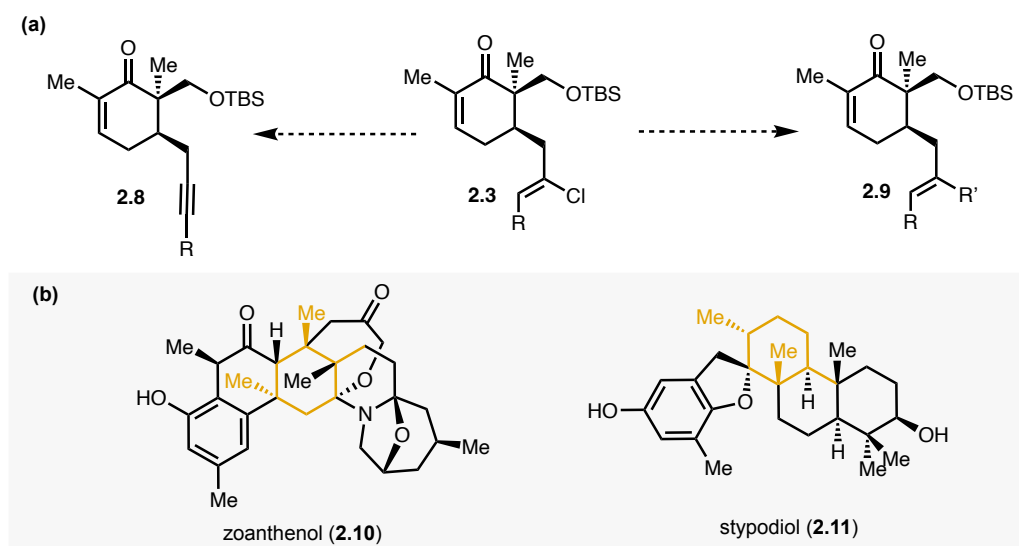
Figure 2.2. Kinetics matching depending on electronic features of substituents on *gem*-dichloroalkene electrophiles **2.2**.

A key feature of such cascade reactions is that the individual cycles do not operate independently, and hence overall reaction efficiency must account for the interplay between the two catalytic cycles. The concept of “kinetics matching” therefore guides the selection of reaction conditions and substrate features that are mutually compatible with the requirements of each catalytic cycle.¹ We aim to control the efficiency of the cascade reaction through the choice of appropriate phosphine ligands, as discussed in the following chapters.

2.2 Formation of the C–C Bond Cleavage/Vinylation Product With Trisubstituted *gem*-Dichloroalkene Electrophiles

We recognize that the product of the first catalytic cycle (i.e., vinyl chloride **2.3**), may serve as a valuable intermediate for the synthesis of various terpenoid natural products (Scheme 2.2).^{2,3} The vinyl chloride moiety in **2.3** offers considerable synthetic versatility, as it can undergo further

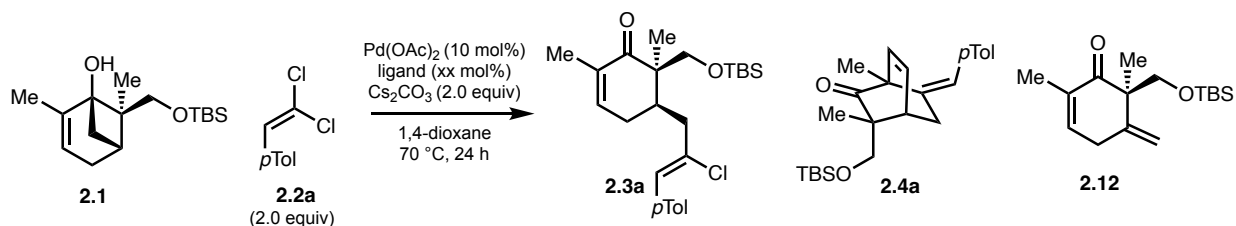
cross-coupling (i.e., **2.9**) to enable diverse functionalization, or be converted into alkynes (i.e., **2.8**), which can subsequently participate in a range of transformations, including cycloadditions and rearrangements.



Scheme 2.2. (a) Possible derivatives of vinyl chloride **2.3**. (b) Structural motifs of vinyl chloride **2.3** found in select natural products.

We sought to achieve control over product selectivity in the cascade reaction leading to vinyl chloride **2.3** through ligand selection. Representative results obtained with various phosphine ligands are summarized in Table 2.4. A commonly observed side product during the initial optimization studies was **2.12**, which we propose to arise from premature β -H elimination prior to reductive elimination to form vinyl chloride **2.3** (Scheme 2.4).

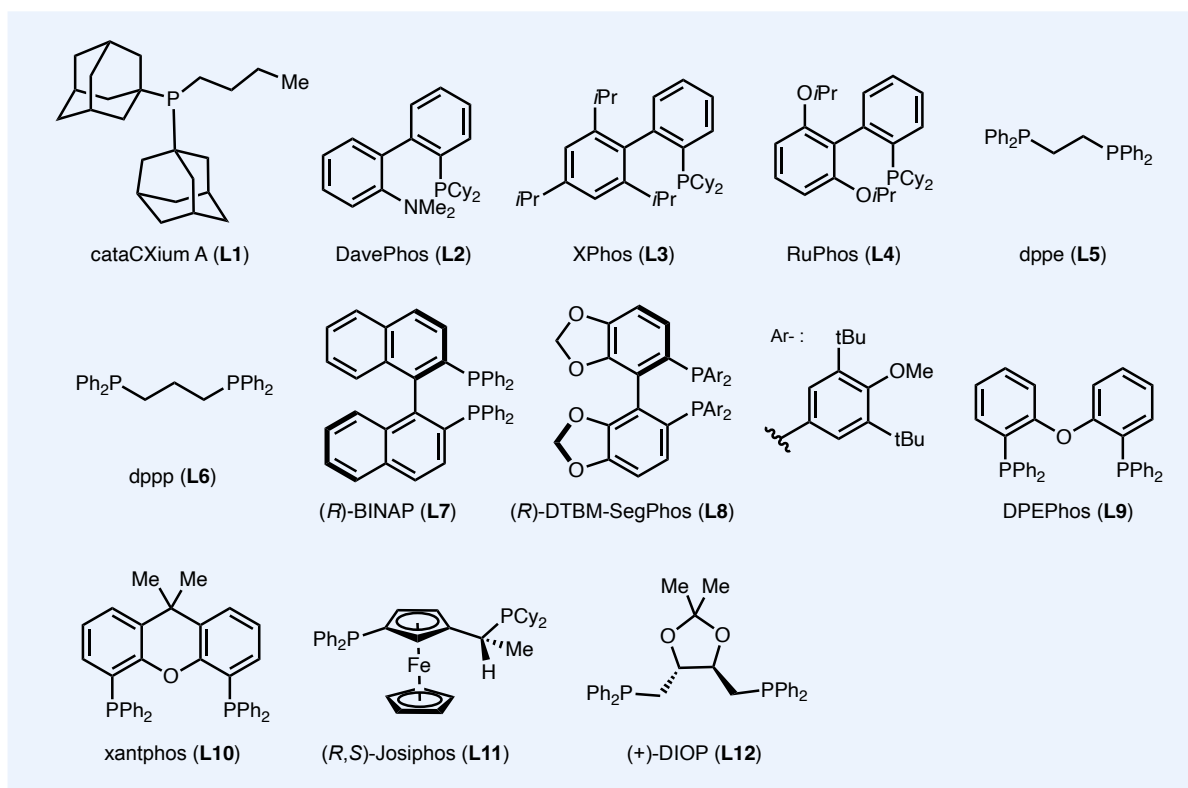
Table 2.4. Initial ligand screening results for C–C bond cleavage/vinylation to vinyl chloride **2.3a**.^a



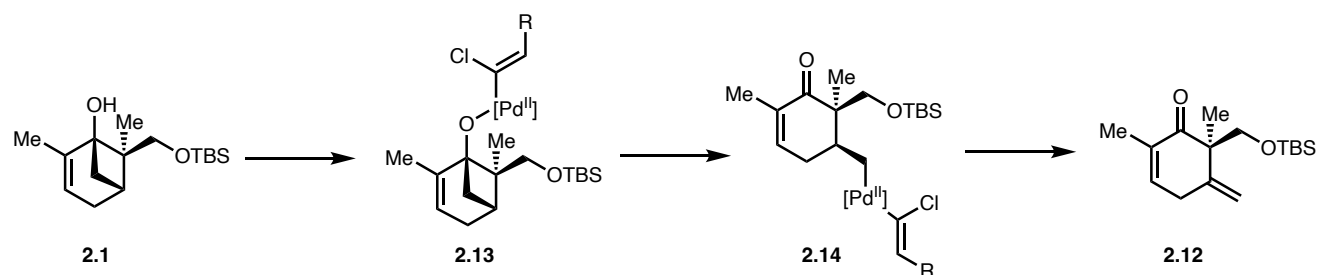
entry	ligand	2.1	2.3a [%]	2.4a [%]	2.12 [%]	Cone angle/ Bite angle ⁴
1	PPh ₃	0	10	30	2	145
2	P(<i>t</i> Bu) ₃	0	18	0	0	182
3	cataCXium [®]	0	24	0	1	180
4	AsPh ₃	0	30	27	3	141
5	DavePhos	0	0	23	0	175
6	XPhos	0	25	13	3	238-256
7	RuPhos	0	29	33	0	201

8	dppe	77	0	5	0	86
9	dppp	96	0	0	0	91
10	(<i>R</i>)-BINAP	0	32	19	0	93
11	(<i>R</i>)-DTBM-SegPhos	0	28	21	4	90-94
12	DPEPhos	0	65	2	1	103
13	xantphos	0	16	46	0	110
14	(<i>R,S</i>)-Josiphos	0	50	18	2	99
15	(+)-DIOP	74	24	2	0	100

^a Reaction run with **2.1** (0.05 mmol), ligand (11 mol% for bidentate; 20 mol% for monodentate), ¹H NMR yields obtained with 1,3,5-trimethoxybenzene as internal standard.



Scheme 2.3. Ligand structures.



Scheme 2.4. Proposed mechanism for the observed side product **2.12**.

Our attempts to rationalize the observed product distribution on the basis of literature-reported cone and bite angles as well as the electronic properties of the ligands were unsuccessful (Table

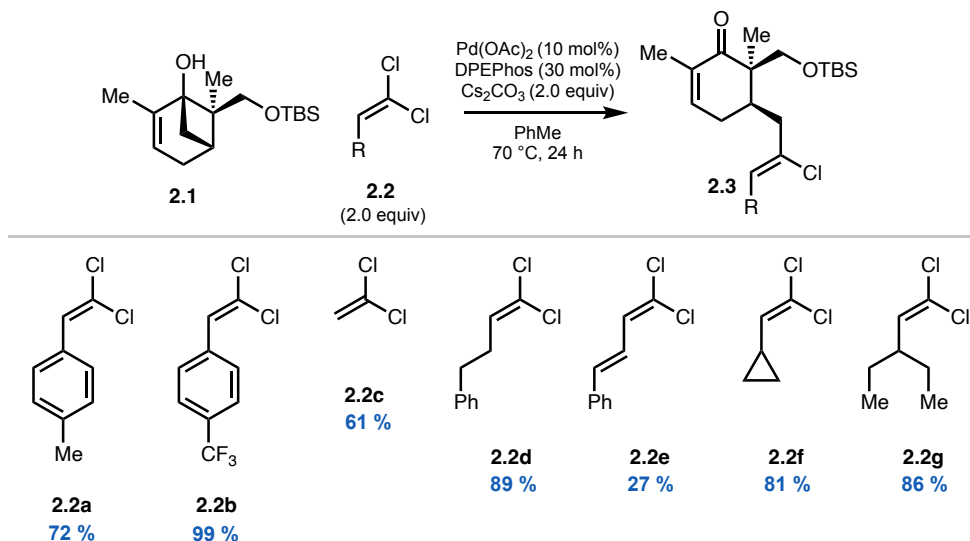
2.4).⁴ Notably, further screening of ligand loading revealed a significant increase in the conversion of **2.1** to vinyl chloride **2.3**, accompanied by high selectivity and minimal side reactions, when 30 mol% of DPEPhos (**L9**) and 10 mol% of Pd(OAc)₂ (Table 2.5) were employed. Interestingly, analogous effects of adding a large amount of ligand on product selectivity and reaction conversion were not observed with other monodentate or bidentate phosphine ligands, including xantphos (**L10**), despite its close structural similarity to DPEPhos. Instead, xantphos was found to predominantly yield Mizoroki–Heck cyclization product **2.3** under conditions with lower ligand:Pd ratios (Table 2.5, entry 1).

Table 2.5. Ligand loadings of xantphos and DPEPhos.

entry	Ligand	Ligand loading	solvent	2.1	2.3a [%]	2.4a [%]
1	xantphos	11 mol%	toluene	0	27	45
2	xantphos	20 mol%	toluene	2	51	37
3	DPEPhos	20 mol%	THF	0	63	3
4	DPEPhos	11 mol%	toluene	41	7	11
5	DPEPhos	22 mol%	toluene	5	61	4
6	DPEPhos	30 mol%	toluene	0	72	3

^a Reaction run with **2.1** (0.05 mmol), solvent (0.2 M), ¹H NMR yields obtained with 1,3,5-trimethoxybenzene as internal standard.

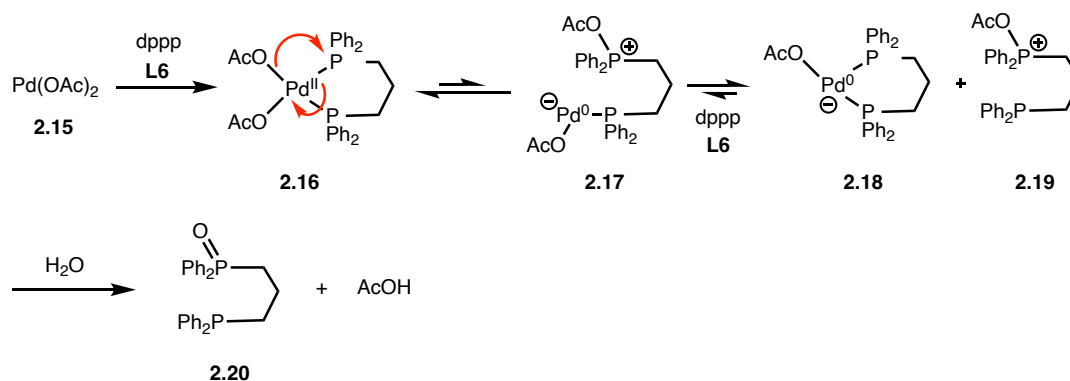
This product selectivity using DPEPhos was consistently observed across a range of trisubstituted *gem*-dichloroalkene electrophiles, as summarized in Scheme 2.5.



Scheme 2.5. Substrate scope for selective C–C bond cleavage/vinylation reaction.

On the basis of these observations, we sought to understand the unique properties of DPEPhos that give rise to the observed product selectivity. Inspired by literature reports on the role of DPEPhos in transition metal-catalyzed reactions, we investigated the possible involvement of differently oxidized DPEPhos species, as well as the ligand's dynamic denticity in the active catalyst arising from its flexibility.⁵

With respect to our studies on oxidized DPEPhos species, this line of inquiry was motivated by two considerations. First, it is well documented in the literature that when Pd(II) precatalysts are employed, an equimolar amount of ligand is consumed in the reduction of Pd(II) to Pd(0), leading to the formation of phosphine oxides as by-products (Scheme 2.6).⁶ Second, recent studies by Blackmond and co-workers on the influence of oxidized bisphosphine ligands on palladium-catalyzed C–H functionalization reactions, particularly mono-oxidized DPEPhos species, prompted us to investigate whether the corresponding phosphine mono-oxide serves as the active ligand in our system, thereby enabling the selective formation of vinyl chloride **2.3**.⁷



Scheme 2.6. Proposed mechanism of bisphosphine ligand oxidation in Pd(II) reduction with dppp.⁶

To test the hypothesis, we evaluated reaction performance using Pd₂dba₃ as a Pd(0) precatalyst while varying DPEPhos loadings (Figure 2.3). For this study, 1-(2,2-dichlorovinyl)-4-(trifluoromethyl)benzene **2.2b** was employed as the model electrophile. Notably, even with Pd₂dba₃, excess DPEPhos was required to achieve significant conversion. Comparable conversion and yields were observed only when using at least a 2:1 ligand: Pd ratio, relative to the original conditions employing Pd(OAc)₂ at the 3:1 ligand: Pd ratio (Figure 2.3).

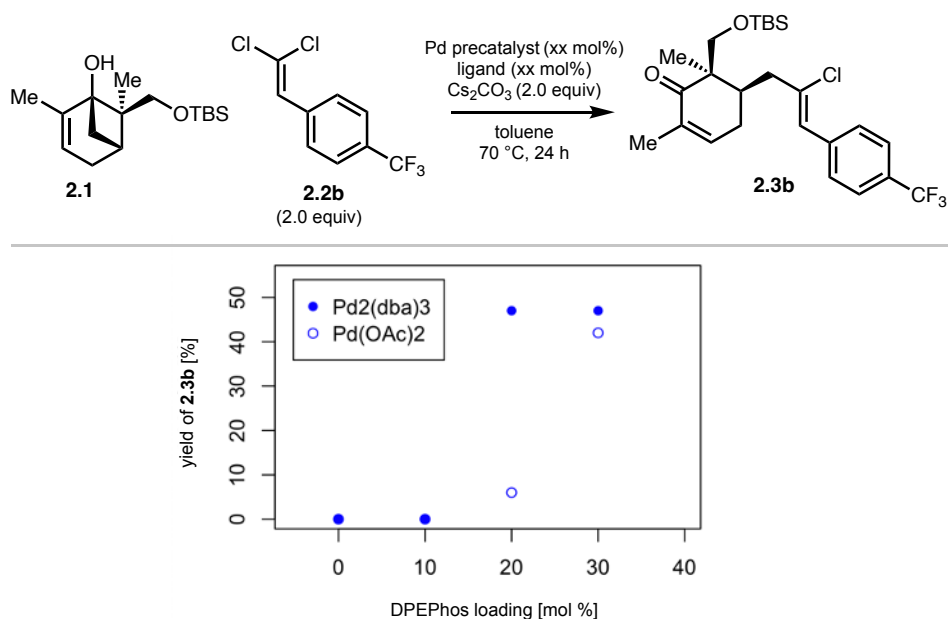
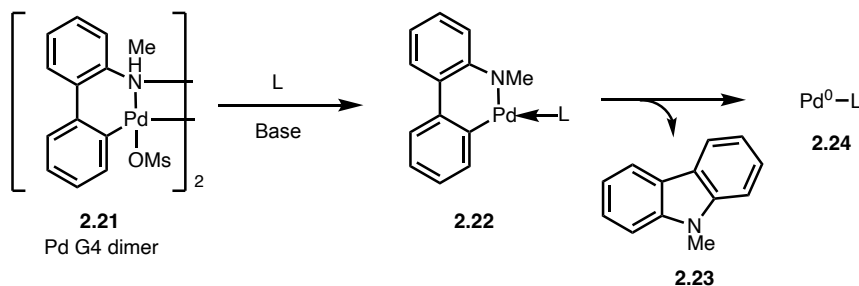


Figure 2.3. Reaction conversion comparison with Pd(0) and Pd(II) precatalysts.

As an additional control, we employed the Pd G4 dimer **2.21** as a Pd(0) precatalyst.⁸ This precatalyst is known to coordinate only one equivalent of phosphine ligand without inducing oxidation of phosphine ligands present in the reaction mixture (Scheme 2.7). Although adventitious water in the reaction medium may contribute to phosphine oxidation, the use of the Pd G4 dimer ensures that no oxidized phosphine ligand is coordinated to the palladium center.

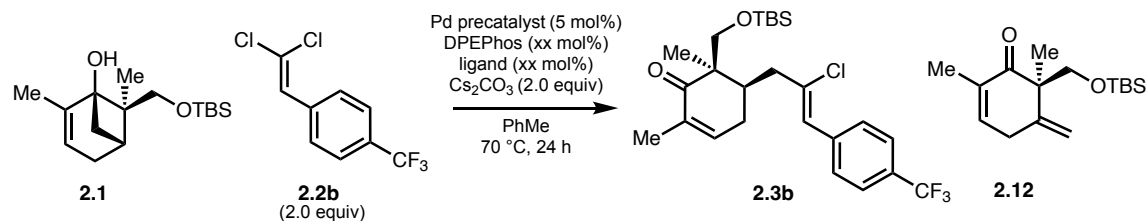


Scheme 2.7. Formation of Pd G4 DPEPhos.

When the Pd G4 dimer was employed with 1:1 ligand: Pd ratio, no conversion was observed, unless additional DPEPhos was introduced into the reaction mixture (Table 2.6, entry 1-3). Improved reaction performance at higher DPEPhos loading is consistent with the trends observed for Pd₂dba₃ (Figure 2.3). These findings suggest that a minimum of two equivalents of unoxidized DPEPhos relative to the Pd(0) catalyst are necessary to achieve efficient catalytic turnover. Notably, maintaining a 1:1 DPEPhos: Pd ratio while increasing the overall catalyst loading resulted in no conversion (Table 2.7). Taken together, in contrast to the report by Blackmond and co-workers on the effects of DPEPhos(O) (**L13**) in palladium catalysis, our results suggest that oxidized DPEPhos species are not required for catalytic turnover in our system.⁷

To verify this hypothesis, we introduced DPEPhos(O) (**L13**) and DPEPhos (O)(O) (**L14**) in varying ratios relative to the Pd(0) catalyst, which were prepared separately (Table 2.6, entries 4-13).⁹ The addition of these oxidized ligands did not have a discernible effect on reaction turnover when using Pd G4 dimer (Table 2.6, entries 4-5). Notably, significant conversion was observed only at an overall ligand:Pd ratio of 2:1 or higher with Pd₂dba₃ (Table 2.6, entries 6–13).

Table 2.6. Reaction performed with different Pd precatalyst and oxidized DPEPhos species.^a



entry	Pd precatalyst	L6	L13	L14	2.1 [%]	2.3b [%]	2.12 [%]
1	Pd G4	10 mol%	-	-	0	0	16
2	Pd G4	20 mol%	-	-	0	44	9
3	Pd G4	30 mol%	-	-	0	75	3
4	Pd G4	10 mol%	10 mol%	-	7	0	21
5	Pd G4	10 mol%	20 mol%	-	2	0	18
6	Pd ₂ dba ₃	-	10 mol%	-	27	0	0
7	Pd ₂ dba ₃	10 mol%	10 mol%	-	5	40	2
8	Pd ₂ dba ₃	20 mol%	10 mol%	-	0	41	2
9	Pd ₂ dba ₃	30 mol%	10 mol%	-	2	50	2
10	Pd ₂ dba ₃	-	20 mol%	-	0	0	24
11	Pd ₂ dba ₃	-	30 mol%	-	4	0	6
12	Pd ₂ dba ₃	-	-	10 mol%	27	0	4
13	Pd ₂ dba ₃	-	-	20 mol%	22	0	5

^a Reaction run with **2.1** (0.05 mmol), ¹H NMR yields obtained with 1,3,5-trimethoxybenzene as internal standard.

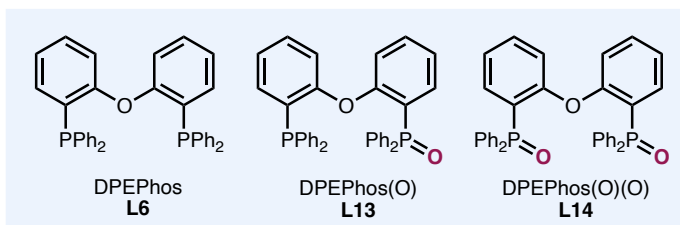
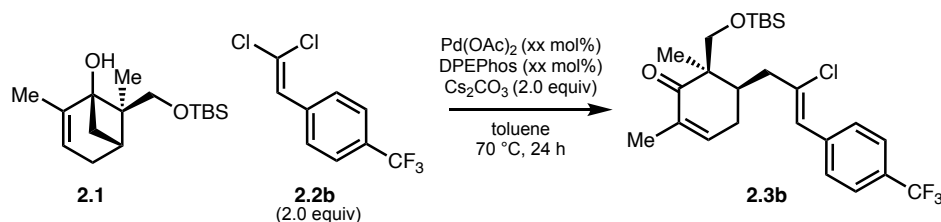


Table 2.7. Reaction performed with constant ligand:Pd ratio.^a



entry	Pd loading	L6 loading	2.1 [%]	2.3b [%]	2.11 [%]
1	10 mol%	10 mol%	no reaction	0	0
2	30 mol%	30 mol%	no reaction	0	0
3	50 mol%	50 mol%	no reaction	0	0

^a Reaction run with **2.1** (0.05 mmol), ¹H NMR yields obtained with 1,3,5-trimethoxybenzene as internal standard.

Another characteristic feature of DPEPhos that warrants attention is its flexibility. It is well-established in the literature that POP-type ligands of this class are dynamic in their coordination behavior and can adopt different binding modes to the metal catalyst during a reaction (Figure 2.4).⁵ In particular, DPEPhos has been suggested to be more flexible than its xantphos-type counterparts due to the absence of the CMe₂ linker in its backbone. Furthermore, reports have shown that DPEPhos can behave as both a κ^2 -P,P and κ^1 -P-ligand within the same molecule.⁵ This fluxional behavior in solution has been attributed to reversible coordination and decooordination of each phosphine arm.

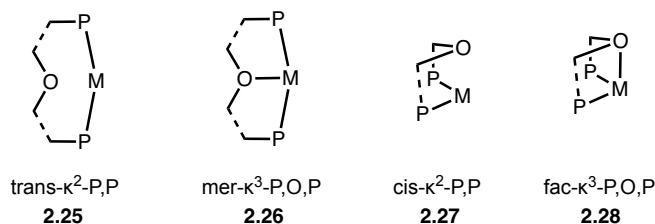


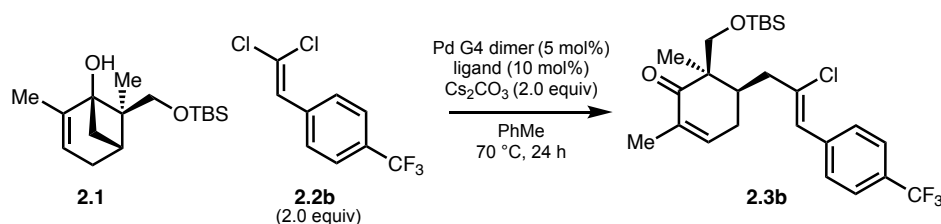
Figure 2.4. Ligand flexibility and hemilability in POP-type ligands.

A study conducted by Ohshima and co-workers in 2009 on Pt-catalyzed amination of allylic alcohols employed an *in situ*-formed catalyst from Pt(COD)Cl₂/DPEPhos.¹⁰ In this system, a 1:1 ligand:Pt ratio led to the formation of a black precipitate, attributed to decomposition of the active Pt(0) species. To suppress this decomposition pathway, two equivalents of DPEPhos relative to the metal were used, enabling stabilization of the active species through formation of Pt(κ^2 -P,P-DPEPhos)₂. The coordinatively saturated complex served as an active precatalyst, and it was proposed that either complete dissociation of one ligand, or partial decooordination of a single phosphine arm to form a κ^1 -P-DPEPhos species generates a coordinatively unsaturated, catalytically active Pt(0) center. An analogous stabilization strategy was also examined using xantphos, but the corresponding complex exhibited limited solubility in toluene and was therefore less effective.

A notable similarity in ligand-loading effects on overall conversion, as reported by Ohshima and co-workers, can be observed in our system. To probe the potential binding of two DPEPhos ligands to the palladium center, in analogy to the earlier report, we sought to perform kinetic time-course experiments to determine the rate law of the cross-coupling reaction. However, these experiments were unsuccessful due to the poor solubility of Cs₂CO₃ under the standard reaction conditions. This insolubility likely contributes to the observed induction period, which complicates the determination of initial rates. Efforts to replace Cs₂CO₃ with an organic base were unsuccessful, as comparable conversions could not be achieved with bases other than Cs₂CO₃.

As an alternative approach, we conducted control reactions using DPEPhos mimicking ligands to probe the denticity of DPEPhos in our cross-coupling reaction (Table 2.8). Among the ligands tested, which exhibit varying degrees of hemilability and coordination modes (i.e., **L15** and **L16**), only the rigid bidentate ligand **L17** led to significant conversion of the starting material **2.1** to the vinyl chloride **2.3b**. This observation suggests that a κ^2 -P,P-DPEPhos species may be the active catalytic form.

Table 2.8. Reaction with DPEPhos mimicking ligands.^a



entry	ligand	2.1 [%]	2.3b [%]	2.12 [%]
1		no reaction	0	0
2		no reaction	0	0
3		0	48	6

^a Reaction run with **2.1** (0.05 mmol), ¹H NMR yields obtained with 1,3,5-trimethoxybenzene as internal standard.

On the basis of these results, we hypothesize that the observed product selectivity at high DPEPhos loading arises from kinetic inhibition of the Mizoroki–Heck cyclization pathway (as in **2.3** → **2.4**). The experimental data suggest that the palladium catalyst is stabilized under conditions of excess DPEPhos, thereby reducing its propensity to decompose, in agreement with the report by Ohshima and co-workers.¹⁰ The high flexibility of DPEPhos, attributable to the absence of the

CMe₂ linker in its backbone, enables rapid and dynamic dissociation of the phosphine arms from the palladium center, thereby facilitating access to a coordinatively unsaturated catalytic species capable of promising cross-coupling. It is further proposed that such catalyst stabilization under increased phosphine loading may be general to other ligand systems, however, the higher barrier to dissociation in less flexible ligands likely limits formation of the active unsaturated species, resulting in reduced overall conversion.

In addition to catalyst stabilization, the high ligand concentration appears to promote rapid dissociation of vinyl chloride **2.3** from the palladium center, thereby disfavoring its re-coordination to the alkene and subsequent oxidative addition required for the Mizoroki–Heck cyclization. This kinetic inhibition is likely responsible for the observed product selectivity. Importantly, no involvement of oxidized forms of DPEPhos was detected, indicating that oxidized ligand species do not play a role in controlling product distribution.

2.3 Formation of the C–C Bond Cleavage/Vinylation Product With Tetrasubstituted *gem*-Dichloroalkene Electrophiles

In contrast to trisubstituted *gem*-dichloroalkene electrophiles, the optimized reaction conditions employing DPEPhos for the selective formation of vinyl chloride **2.3** were not transferable to tetrasubstituted alkene substrates. In a subsequent ligand screening for the cross-coupling reaction of (dichloromethylene)cyclohexane **2.2h** as the model tetrasubstituted *gem*-dichloroalkene electrophile for the study, generally low conversions were observed, accompanied by increased formation of side product **2.12** (Table 2.9). These results suggest that the initial oxidative addition of **2.2h** is challenging under the reaction conditions. Notably, low conversion and yield were also observed with *gem*-dibromoalkene analogues, which are known to undergo oxidative additions more readily than vinyl chlorides. Taken together, these findings indicate that the diminished reactivity is unlikely to arise from electronic differences between trisubstituted and tetrasubstituted *gem*-dichloroalkenes but is instead primarily attributed to steric effects.

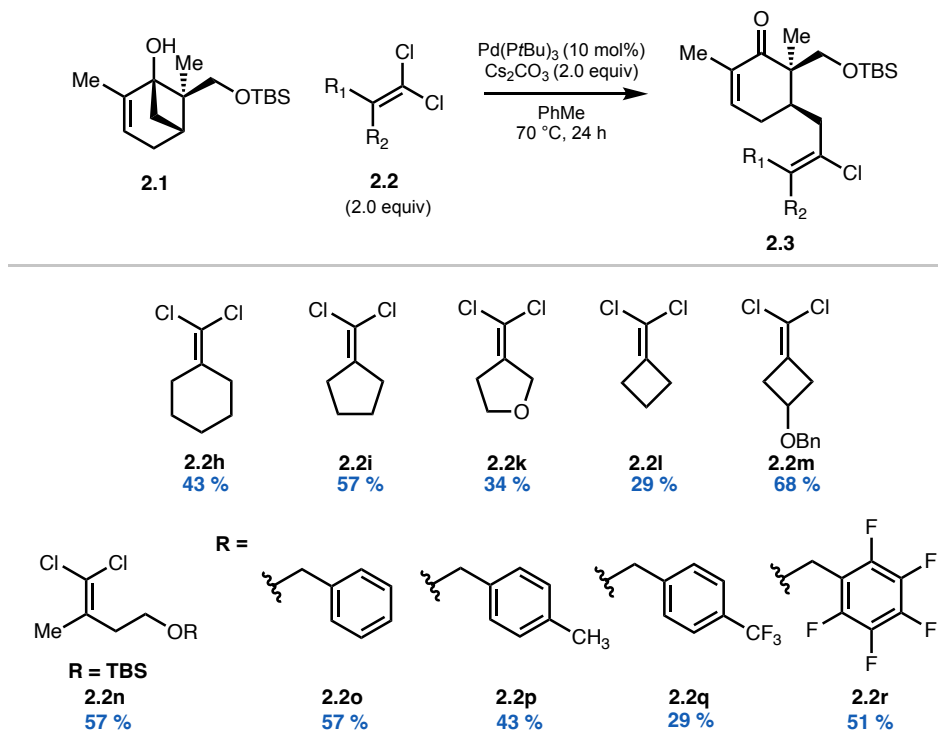
Hence, ligands with varying cone and bite angles were explored.⁴ In particular, monophosphine ligands were considered promising candidates, as sterically bulky phosphine ligands are expected to facilitate ligand dissociation.¹¹ Rapid ligand dissociation is thought to promote oxidative addition of sterically demanding electrophiles. Upon screening, P(*t*Bu)₃ was identified as an effective ligand for the selective formation of **2.3h** as the major product (Table 2.9, entry 7), with only trace amounts of Mizoroki–Heck cyclization products observed. The bulkiness of the ligand is thought to contribute to the selectivity as it makes it challenging to adopt Mizoroki–Heck cyclization transition state conformation. In contrast, other monophosphine ligands with comparable electron-donating properties to P(*t*Bu)₃, such as PCy₃ or Xphos, afforded vinyl chloride **2.2h** in low yields, supporting the proposed steric hypothesis (Table 2.9, entries 4 and 8). With these ligands, it is proposed that the product undergoes further decomposition pathways that

do not occur in the case of $P(tBu)_3$. A substrate scope encompassing various cyclic and acyclic alkene electrophiles is presented in Scheme 2.8.

Table 2.9. Ligand screening for vinyl chloride **2.3h**.^a

entry	ligand	Cone angle/ Bite angle ⁴	TEP [cm ⁻¹]	2.1 [%]	2.3h[%]	2.12 [%]
1	DPEPhos ^d	103	2055-2075	0	0	16 %
2	xantphos ^b	110	2058-2059	25 %	0	11 %
3	PPh ₃ ^c	145	2069.1	91 %	0	0
4	Xphos ^c	238	2053	38 %	0	27 %
5	(<i>R</i>)-BINAP ^b	93	1936-1997	48 %	0	22 %
6	(<i>R</i>)-SegPhos ^b	94	2067.5	9 %	0	34 %
7	PtBu ₃ ^c	182	2056.1	0	43 %	8 %
8	PCy ₃ ^c	148	2056.4	0	0	7 %

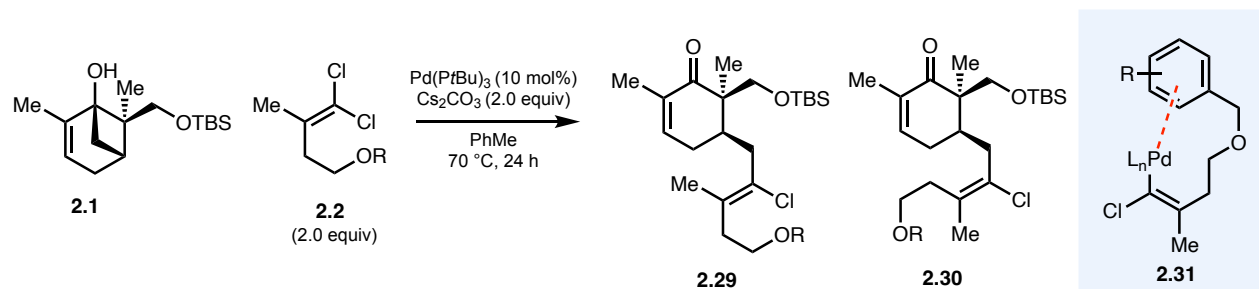
^a Reaction run with **2.1** (0.05 mmol), ¹H NMR yields obtained with 1,3,5-trimethoxybenzene as internal standard. ^b 11 mol% loading. ^c 20 mol% loading. ^d 30 mol% loading.

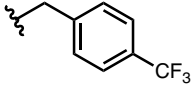
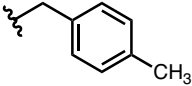
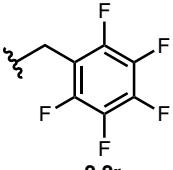


Scheme 2.8. Substrate scope on C–C bond cleavage/vinylation with tetrasubstituted alkene electrophiles.

Asymmetrically substituted alkenes (**2.2n–2.2r**) exhibited low selectivity for the C–Cl bond that underwent oxidative addition, leading to the formation of both alkene isomers (Table 2.10). Attempts to control the site of first oxidative addition by leveraging adjacent functional groups showed promising results in initial test reactions, however, due to difficulties in isolating both alkene isomers, the major alkene isomer could not be unambiguously assigned for each cross-coupling electrophile.

Table 2.10. Vinyl chloride alkene isomer ratio with asymmetric alkene electrophiles.^a



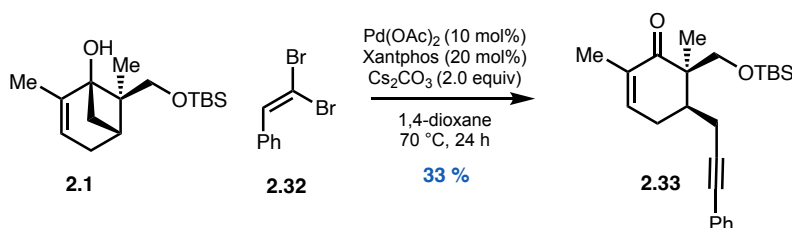
entry	electrophile	2.29 + 2.30 [%]	Alkene isomer ratio
1	 2.2q	29	3.5:1
2	 2.2p	43	2:1
3	 2.2r	51	1.6:1

^a Reaction run with **2.1** (0.05 mmol), ¹H NMR yields obtained with 1,3,5-trimethoxybenzene as internal standard.

2.4 Formation of the Bicyclo[2.2.2]octanone Product With Trisubstituted *gem*-Dichloroalkene Electrophiles

For our initial studies toward obtaining bicyclo[2.2.2]octanone **2.4**, we began with a generic *gem*-dichloroalkene electrophile (**2.2a**) and cyclobutanone substrate **2.1**. Preliminary ligand screening identified xantphos as the optimal ligand for formation of bicycle **2.4** in 45 % yield (Table 2.4, entry 13). As we consistently observed intermediate **2.3** in the reaction mixture without full conversion to **2.4**, we sought to improve conversion by facilitating the oxidative addition step in the second catalytic cycle.

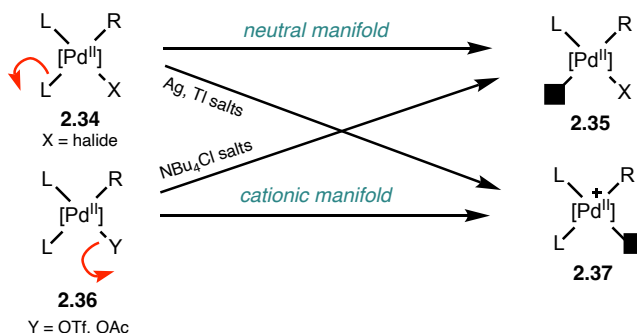
One strategy was to employ *gem*-dibromoalkenes (i.e. **2.32**), given their increased propensity for oxidative addition (Scheme 2.9). However, reactions using *gem*-dibromoalkenes exhibited messier reaction profiles and lower yields overall. These electrophiles were prone to decomposition at room temperature prior to reaction setup, despite careful handling, which likely contributes to the diminished performance and challenges in optimization. Overall, *gem*-dibromoalkene electrophiles predominantly produced β -H elimination side product **2.12**, along with additional side products such as **2.33** (Scheme 2.9).



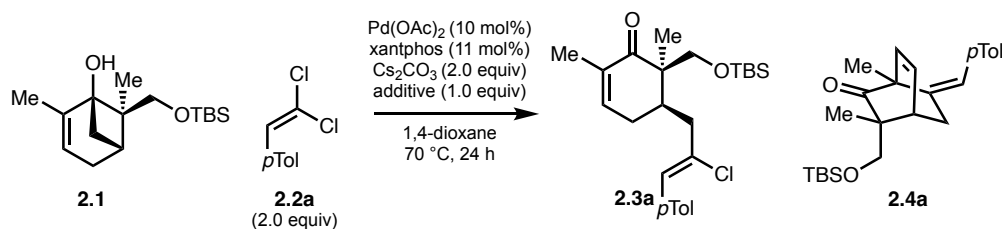
Scheme 2.9. Side reaction forming alkyne **2.33** with *gem*-dibromoalkene **2.32**.

It is well-documented in the literature that Ag(I) additives can enhance reaction rates of intramolecular Mizoroki–Heck reactions.¹² Ag(I) cations act as effective halide scavengers, shifting the reaction from a neutral to a cationic reaction manifold (Scheme 2.10). By promoting dissociation of the strongly coordinating halide ligand from the metal center, Ag(I) generates a vacant coordination site thereby facilitating subsequent migratory insertion and accelerating the reaction.

Consistent with this rationale, addition of an Ag(I) source led to significant increase in the yield for **2.4** (Table 2.11). Screening a selection of silver salts identified AgOAc as the most effective additive by increasing the yield from 45 % to 78 % (Table 2.11, entry 4). Interestingly, silver salts bearing more weakly coordinating counteranions (Table 2.11, entry 10–12) afforded comparable or even lower yields than those with more strongly coordinating anions. Thallium salts, which have been reported to exhibit reactivity similar to that of Ag(I) salts, were likewise as effective as AgOAc but did not demonstrate superior performance (Table 2.11, entries 13–15).



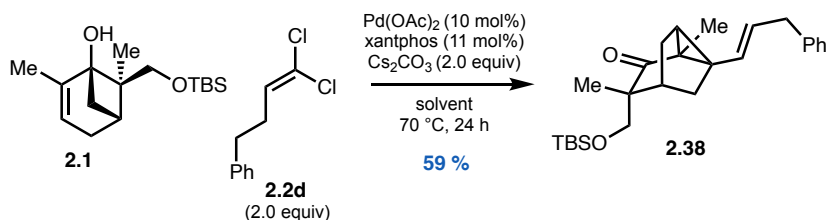
Scheme 2.10. Proposed Mechanism of Ag-cation engagement in the Mizoroki–Heck reaction.

Table 2.11. Additive screening.^a

entry	Additive	2.3a [%]	2.4a [%]
1	NBu ₄ Cl, PhMe	0	0
2	Ag ₃ PO ₄ , 6 h	7	12
3	Ag ₃ PO ₄	18	77
4	AgOAc	10	78
5	AgOAc (2.0 equiv)	17	70
6	Ag ₂ CO ₃	11	73
7	AgOTf	0	0
8	AgBF ₄	0	0
9	AgClO ₄	0	0
10	AgSbF ₆	0	25
11	AgNTf ₂	0	0
12	AgPF ₆	0	11
13	Tl ₂ CO ₃	19	75
14	Tl(OAc) ₃	14	8
15	TlOAc	20	62

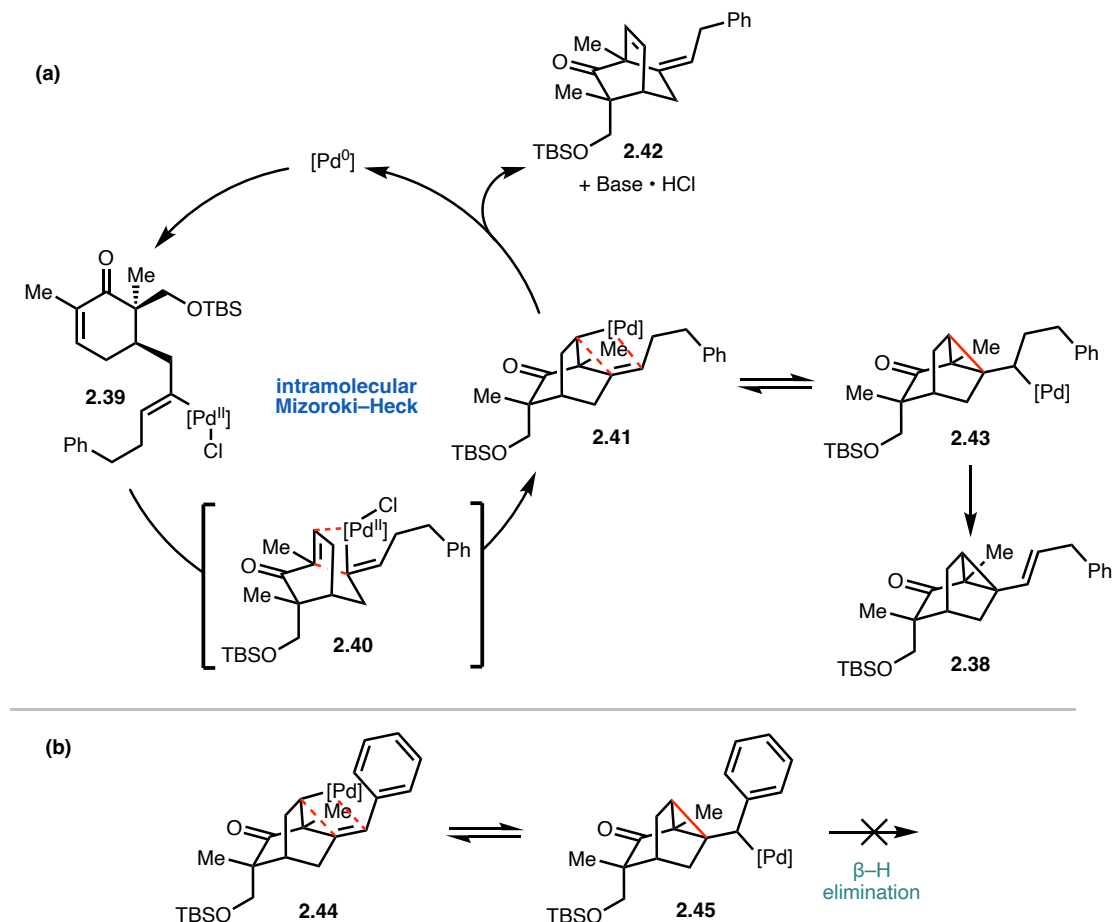
^a Reaction run with SM (0.05 mmol), all NMR yields with 1,3,5-trimethoxybenzene as internal standard.

After optimizing the reaction conditions for the formation of bicycle **2.4** with aryl substituted alkene electrophiles, we turned our attention to expanding the substrate scope to include alkene electrophiles bearing aliphatic substituents. Surprisingly, within this new subclass of electrophiles, we observed the formation of a previously unanticipated polycyclic product, tricyclo[3.2.1.0]octane **2.38** (Scheme 2.11).

Scheme 2.11. Formation of tricyclo[3.2.1.0]octanone **2.38**.

Mechanistically, we propose that this product arises from a second migratory insertion onto the pendant olefin of **2.41**, followed by an irreversible β -H elimination within the intramolecular Mizoroki–Heck sequence (Scheme 2.12a). In contrast, for the aryl-substituted *gem*-dichloroalkene

electrophiles discussed earlier, β -H elimination after the second carbopalladation event is not feasible (Scheme 2.12b). Instead, corresponding intermediate **2.45** undergoes reversible β -C elimination, which accounts for the absence of the tricyclic product in the earlier optimization studies with alkene electrophile **2.2a**.



Scheme 2.12. (a) Proposed mechanism for the formation of tricyclo[3.2.1.0]octanone **2.60**. (b) Proposed mechanism for no formation of tricyclo[3.2.1.0]octanone with styrenyl electrophiles.

Consistent with this hypothesis, we observed formation of the tricyclic core motif across a range of *gem*-dichloroalkenes bearing aliphatic chains that contain allylic hydrogens, a prerequisite for cyclopropanation in our proposed mechanism. A substrate scope encompassing various cyclic and acyclic alkene electrophiles is presented in Figure 2.5.

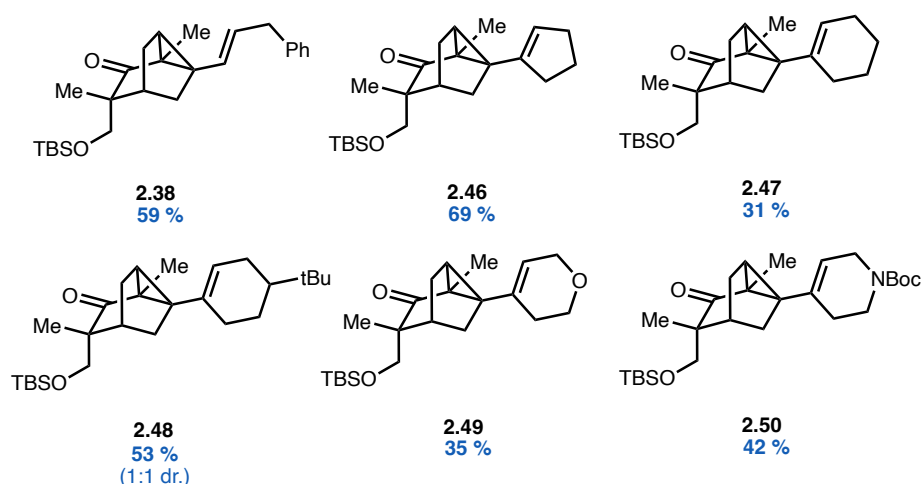
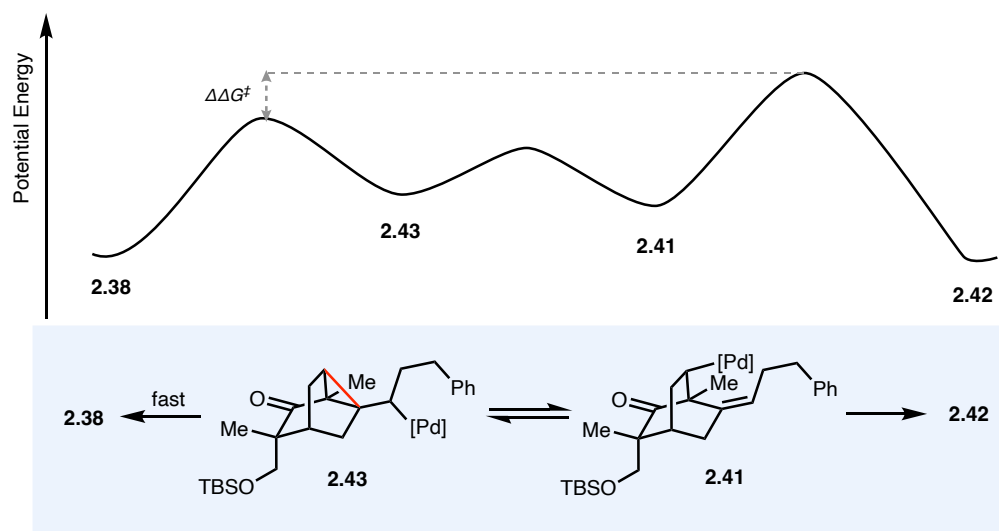


Figure 2.5. Substrate scope of tricyclo[3.2.1.0]octanone.

Given the reversibility of the migratory insertion step, we propose that this reaction operates under Curtin–Hammett control (Scheme 2.12). The rigid conformation of **2.41** is thought to conformationally set the system for rapid migratory insertion, furnishing the cyclopropane despite the increased ring strain of the product. The subsequent irreversible β -H elimination then kinetically traps the strained tricyclic product.



Scheme 2.12. Proposed Curtin–Hammett kinetics in formation of tricyclo[3.2.1.0]octanone **2.38**.

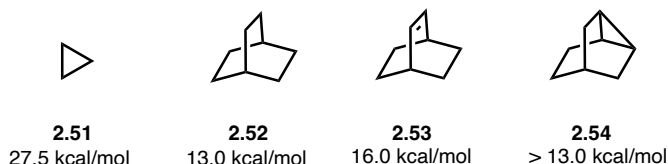


Figure 2.6. Molecules and their associated strain energies.

Notably, the core structure of this tricyclic product (**2.38**) is found in natural products belonging to the trachylobane diterpenoid family, which feature the tricyclo[3.2.1.0]octane motif.

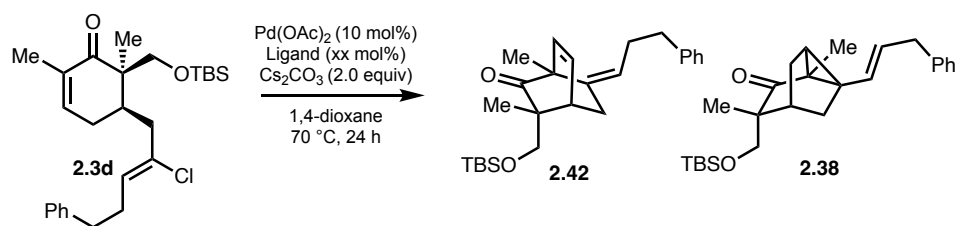
Accordingly, this extended C–C bond cleavage/vinylation/Mizoroki–Heck/ cyclopropanation cascade may provide a viable strategy for the total synthesis of these natural products.

Given the unexpected cyclopropanation observed with alkene electrophiles bearing aliphatic substituents, we sought to identify reaction conditions that would suppress the second migratory insertion and thereby selectively afford the desired bicycle **2.42**.

As such, we explored more sterically demanding and unconventional ligands with the aim of inhibiting coordination between the C–Pd bond and the adjacent alkene, thereby favoring the desired pathway to bicycle **2.42**.¹³ However, despite extensive ligand screening, selective formation of **2.42** via ligand control was not achieved. Given the complexity of the cascade, identifying a ligand that is both electronically and sterically compatible with the catalytic sequence, while also sufficiently bulky to disrupt the undesired interaction, proved challenging.

To gain further mechanistic insight into this cyclization, we conducted optimization studies starting from **2.3d**, thereby isolating the intramolecular Mizoroki–Heck step from the preceding cascade events. Among the ligands tested, Xphos provided the highest yield (78 %; Table 2.12, entry 8), along with trace amounts of **2.3d**. Surprisingly, the reaction of **2.3d** with xantphos did not lead to any significant conversion, which contrasts with the initial observation of tricycle formation when starting from **2.1**.

Table 2.12. Ligand screening.^a



entry	Ligand	2.3d [%]	2.42 [%]	2.38 [%]
1	PPh ₃ ^c	74	0	0
2	dppe ^b	70	0	0
3	(<i>R</i>)-BINAP ^b	80	0	0
4	(<i>R</i>)-SegPhos ^b	47	3	17
5	Brettphos ^c	n.r.	0	0
6	Davephos ^c	0	15	69
7	CyJohnPhos ^c	n.r.	0	0
8	Xphos ^c	0	5	76
9	Pd-G2-Xphos ^b	0	13	23
10	DPEPhos ^b	mostly	0	0
11	xantphos ^b	mostly	0	0

^a Reaction run with **2.3d** (0.05 mmol), all NMR yields with 1,3,5-trimethoxybenzene as internal standard. ^b 11 mol% loading. ^c 20 mol% loading.

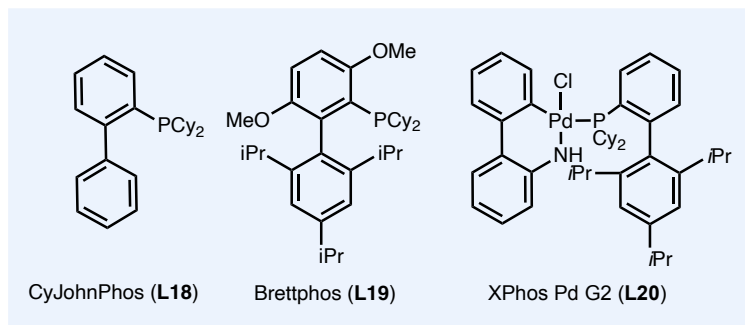
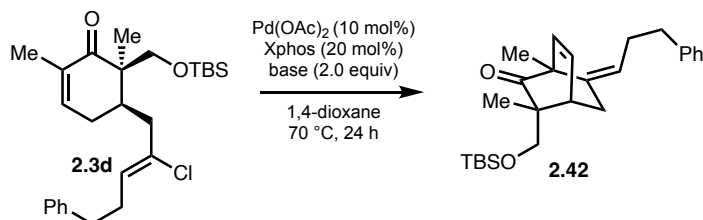


Figure 2.7. Ligand structures.

Serendipitously, switching the base from Cs_2CO_3 to LiOtBu enabled the formation of the desired bicyclo[2.2.2]octanone **2.42** from **2.3d** with high selectivity, for the first time (53 % yield, Table 2.13, entry 1).¹⁴ This product selectivity was observed only with Xphos as any other tested ligand showed no conversion (Table 2.12). A similar result was observed with LiOPh (63 % yield; Table 2.13, entry 5).

Table 2.13. Additive screening.^a



entry	base	2.3d [%]	2.42 [%]
1	LiOtBu	0	53
2	NaOtBu	mostly	0
3	KOtBu	decomposition	0
4	LiOMe	mostly	3
5	LiOPh	0	63
6	LiOAc	mostly	0
7	Li_2CO_3	mostly	0
8	KOH	63	8
9	DBU	42	0
10	NEt_3	mostly	0
11	LiHMDS	0	10
12	DIPEA	59	0

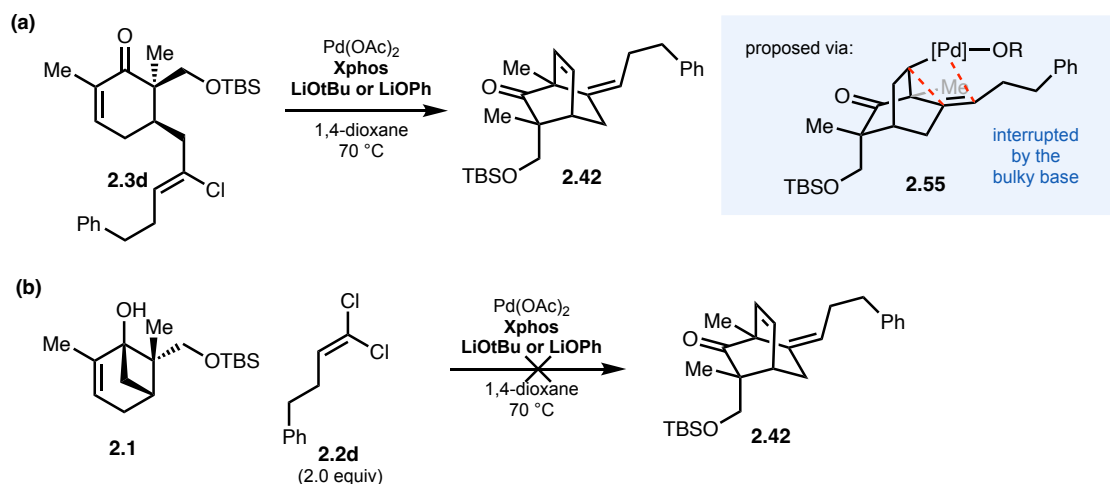
^a Reaction run with **2.3d** (0.05 mmol), all NMR yields with 1,3,5-trimethoxybenzene as internal standard.

Mechanistically, we propose that the alkoxide coordinates to the palladium center, sterically disrupting undesired C–Pd coordination with the adjacent alkene and thereby inhibiting cyclopropanation (Scheme 2.13a). LiOtBu and LiOPh likely provide optimal results due to their

high nucleophilicity, which promotes strong binding to the palladium, and their steric bulk, which effectively prevents the undesired interaction. Other lithium alkoxide bases, such as lithium acetate or lithium carbonates, were less effective, possibly due to weaker binding to palladium and a reduced ability to exert this inhibitory effect (Table 2.13, entry 6–7). In contrast, lithium methoxide, being less sterically demanding than LiOtBu and LiOPh, is also less effective in suppressing the undesired pathway (Table 2.13, entry 4).

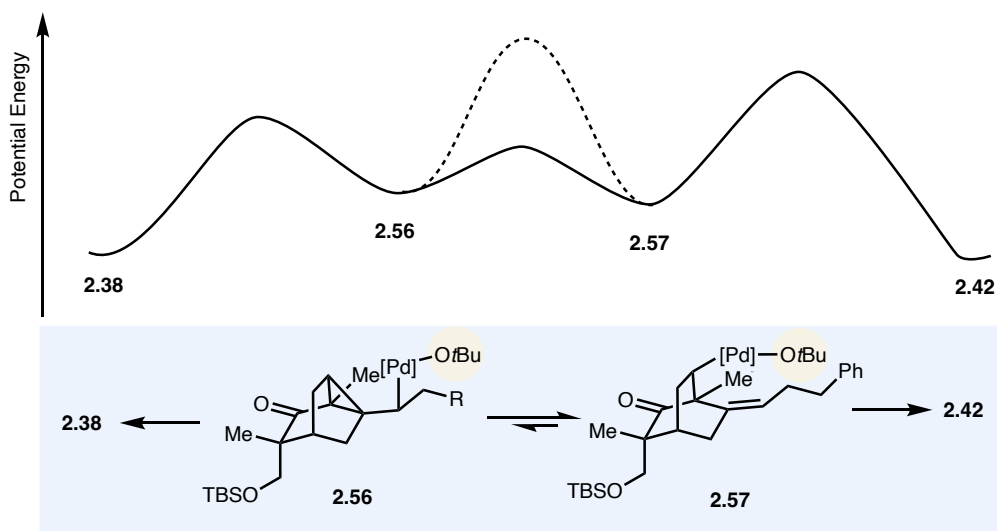
In addition to the alkoxide bases described above, we explored other classes of bases, including organic amines with varying nucleophilicity and basicity (Table 2.13, entry 8–12). As these bases did not produce beneficial effects on product formation comparable to those observed with LiOtBu and LiOPh, this result supports our proposed mechanism in which the base coordinates to the palladium catalyst rather than promoting an outer-sphere deprotonation pathway for the formation of **2.642**.

Consistent with the proposed mechanism, the reaction does not proceed when cyclobutanol substrate **2.1** is employed, likely because the comparable nucleophilicity of the alkoxide base competes with substrate coordination to the palladium catalyst (Scheme 2.13b). The addition of Ag-salts in reactions involving electrophilic alkenes bearing aliphatic substituents was not beneficial, resulting in a more complex reaction profile and low catalytic turnover.¹⁵ In contrast to aryl-substituted alkene electrophiles, alkenes with aliphatic substituents appear to undergo a greater number of side reactions in the presence of Ag(I) in the reaction mixture.



Scheme 2.13. Proposed mechanism for bicyclo[2.2.2]octanone **2.42** formation.

Returning to the previously proposed Curtin–Hammett kinetics in the cyclopropanation step, we suggest that the addition of a nucleophilic alkoxide base increases the energy barrier of the equilibrium between species **2.56** and **2.57**, thereby shifting the reaction pathway toward formation of bicyclic product **2.42** as the major product (Scheme 2.14).



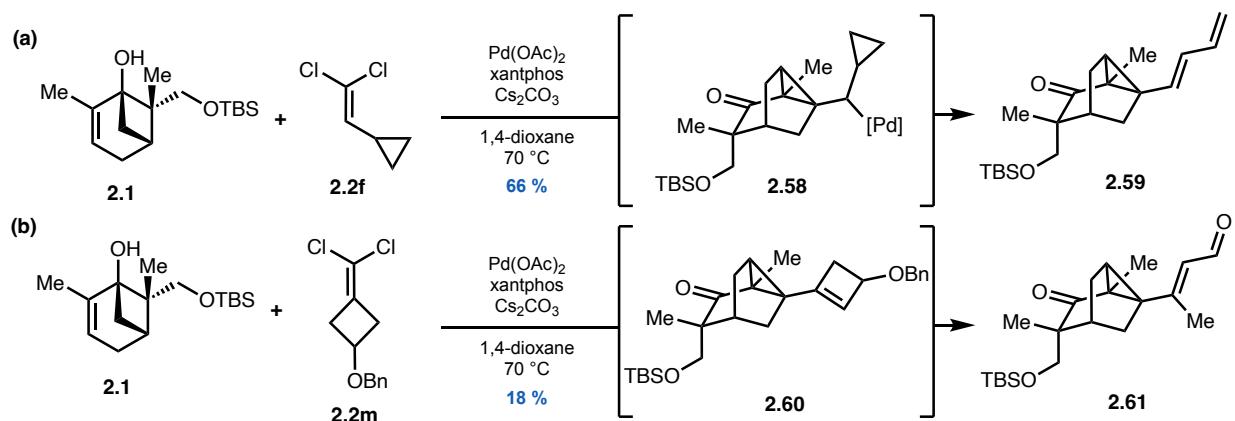
Scheme 2.14. Proposed Curtin-Hammett kinetics for formation of bicyclo[2.2.2]octanone **2.42**.

Overall, two distinct products were identified in the cascade reaction for different classes of *gem*-dichloroalkene electrophiles. Alkenes lacking allylic hydrogens undergo the Mizoroki–Heck cyclization cascade to afford bicycle **2.4**, whereas alkenes bearing allylic hydrogens are prone to an additional cyclopropanation, yielding a tricyclic product (i.e., **2.38**). This cyclopropanation pathway can be suppressed by using LiOtBu or LiOPh as additives. We propose that these alkoxide bases coordinate to the palladium catalyst, thereby sterically disrupting the C–Pd–alkene interaction required for the cyclopropanation.

2.5 Extended Cascade Reactivity

In addition to the observed cyclopropanation in the Mizoroki–Heck cyclization cascade, we found that certain electrophiles enable further bond-breaking steps within the reaction sequence (Scheme 2.15). For example, when cyclopropane-containing electrophile **2.2f** was employed, diene-appended tricyclo[3.2.1.0]octane **2.59**, was formed (Scheme 2.15a). We propose that this product arises from a second, strain-driven β -C elimination, accompanied by β -H elimination of the cyclopropyl group from intermediate **2.58**.

Similarly, coupling cyclobutanol **2.1** with electrophile **2.2m** yielded tricyclic product **2.61**, likely via cyclobutenyl tricyclo[3.2.1.0]octanone intermediate **2.60** (Scheme 2.15b). This intermediate is proposed to undergo an *in situ* electrocyclic ring opening, followed by concomitant benzyl enol ether hydrolysis to afford tricyclo[3.2.1.0]octanone enal **2.61**.



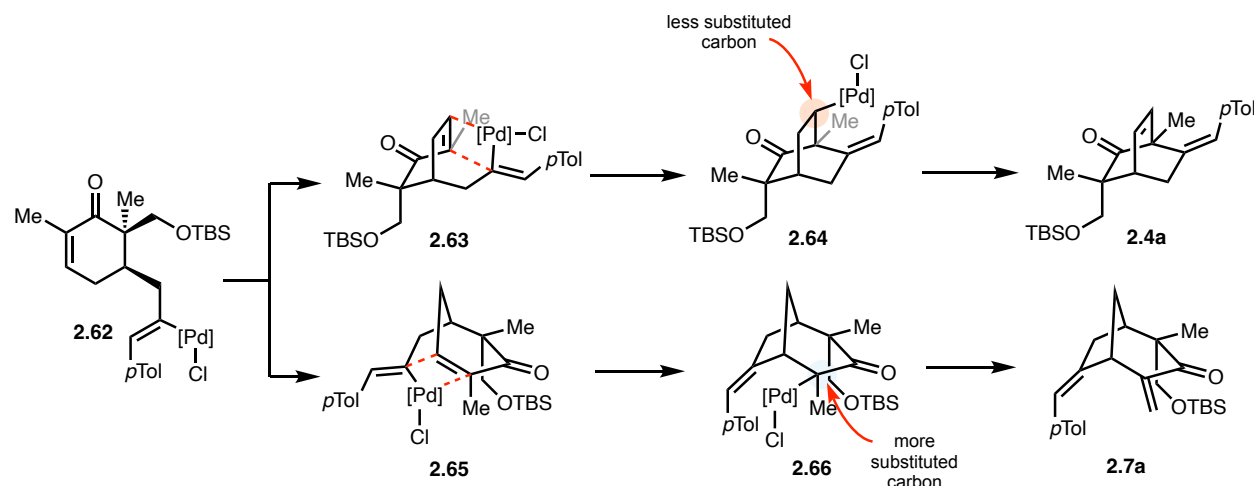
Scheme 2.15. Extended cascade reactivity with select electrophiles.

These examples illustrate that, with careful design of the electrophile, more elaborate substrates can be developed to install diverse side chains.

2.6 Mizoroki–Heck Cyclization Selectivity with Trisubstituted *gem*-Dichloroalkene Electrophiles

As briefly mentioned in Chapter 2.1, low amounts of the alternative Mizoroki–Heck cyclization product, bicyclo[3.2.1]octanone **2.7**, were observed throughout the optimization and mechanistic studies. We propose that this product stems from an alternative migratory insertion pathway on the cyclohexenone (Scheme 2.1).

Guidelines for the selection and tuning of ligand properties to optimize migratory insertion of palladium catalysts are relatively rare in the literature in contrast to relationships studied for oxidative addition and reductive elimination. Selectivity in migratory insertion is often guided by the substitution pattern of the alkene or, in the case of intramolecular insertions, by the size of the ring that is being formed.¹² Hence, our initial rationalization for the preferential formation of bicyclo[2.2.2]octanone **2.4** as the major product is based on differences in alkene substitution. Migratory insertion leading to bicyclo[2.2.2]octanone **2.4** forms the C–Pd bond at the less substituted carbon in **2.64**, which is both electronically and sterically favored (Scheme 2.16).¹⁶ This substitution-controlled selectivity likely accounts for the preferential formation of **2.4**, despite its higher overall ring strain compared to bicyclo[3.2.1]octanone **2.7** (Scheme 2.16 and Figure 2.8).



Scheme 2.16. Proposed mechanism for the formation of bicyclo[3.2.1]octanone **2.7** and preliminary rationalization in observed selectivity of migratory insertion.

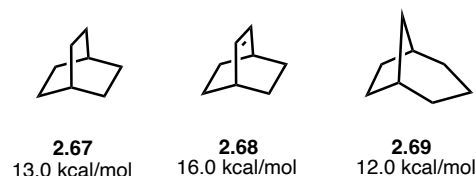


Figure 2.8. Molecules and their associated strain energies.

However, throughout our optimization studies, we observed varying ratios of **2.4** and **2.7** depending on the employed bisphosphine ligand, likely due to differences in their steric and electronic properties. In initial optimization campaigns with in-house catalysts, bisphosphine ligands proved most effective for trisubstituted alkene substrates. Early ligand screening identified SegPhos as providing the most favorable product ratio toward bicyclo[3.2.1]octanone **2.7**, prompting further exploration of SegPhos-derived ligands (Table 2.14 and 2.15). Subsequent screening revealed enhanced selectivity for bicyclo[3.2.1]octanone **2.7** when using more sterically demanding ligands, such as DTMSM-SegPhos (**L27**) and DTMGM-SegPhos (**L28**), which bear silyl and germanyl groups, respectively, albeit with low overall yields.¹⁷

Table 2.14. Formation of bicyclo[3.2.1]octanone **2.7a** from vinyl chloride **2.3a**.^a

entry	ligand	2.3a [%]	2.4a [%]	2.7a [%]	2.12 [%]
1	dppe	63	11	2	1
2	(<i>R,R</i>)-chiraphos	59	11	2	1
3	(+)-diop	56	9	0	0

4	dcypf	51	22	0	0
5	Josiphos	58	8	0	3
6	WalPhos	58	15	2	4
7	xantphos	0	64	5	0
8	(<i>R</i>)-SegPhos	0	64	22	0
9	(<i>S</i>)-SegPhos	30	34	11	3
10	(<i>R</i>)-Phanephos	53	15	2	2

^a Reaction run with **2.3a** (0.05 mmol), all NMR yields with 1,3,5-trimethoxybenzene as internal standard.

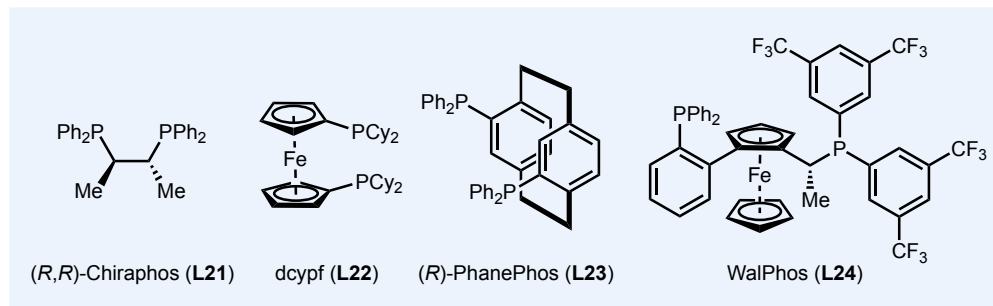
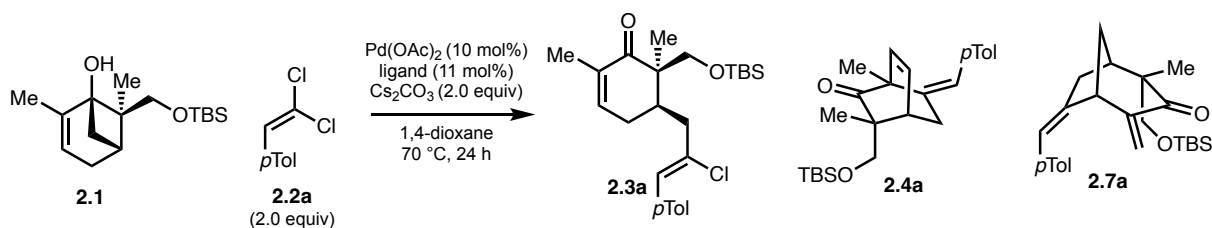


Figure 2.9 Ligand structures.

Table 2.15. Formation of bicyclo[3.2.1]octanone **2.7** with select SegPhos-derived ligands.



entry	ligand	2.3a [%]	2.4a [%]	2.7a [%]	2.12 [%]
1	SegPhos	30	12	3	17
2	DM-SegPhos	17	9	4	12
3	(<i>R</i>)-DTBM-SegPhos	28	21	4	5
4	(<i>S</i>)-DTBM-SegPhos	0	12	16	14
5	(<i>R</i>)-DTMSM-SegPhos	12	0	22	9
6	(<i>R</i>)-DTMGM-SegPhos	6	0	9	5
7	(<i>R</i>)-DTBM-synphos	22	3	1	14
8	(<i>R</i>)-DTBM-garphos	13	0	0	2
9	(<i>R</i>)-DTBM-MeOBIPHEP	4	0	1	7
10	(<i>R</i>)-DTBM-difluorophos	0	0	0	0

^a Reaction run with **2.1** (0.05 mmol), all NMR yields with 1,3,5-trimethoxybenzene as internal standard.

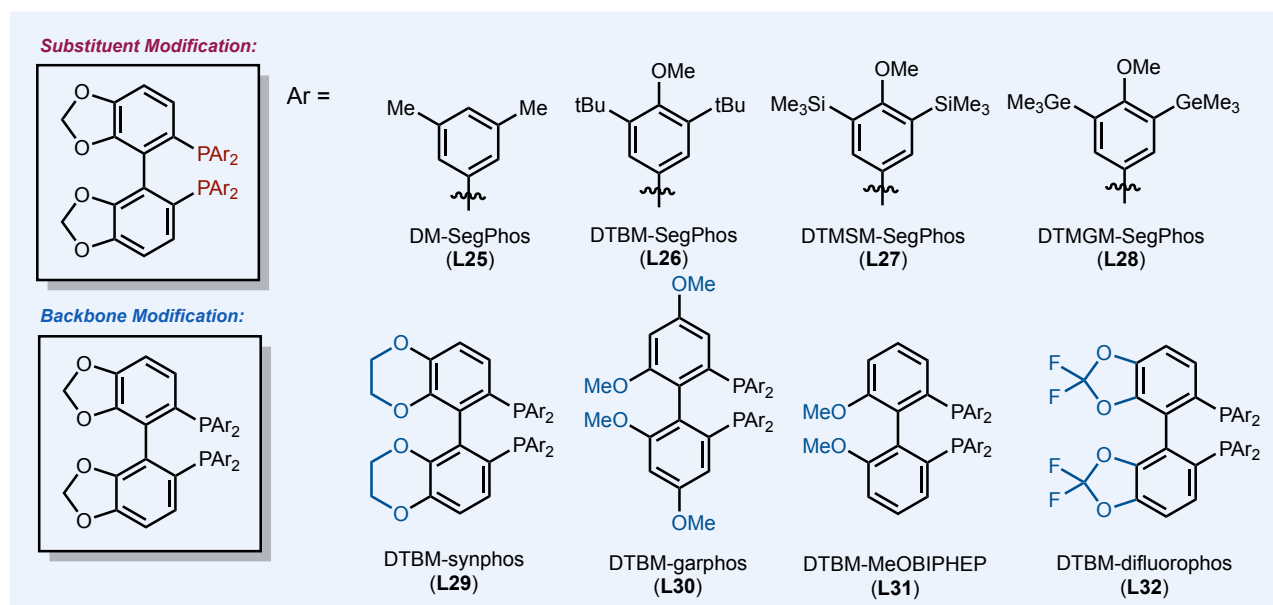


Figure 2.10 Ligand structures.

Although certain trends were observed, a definitive rationale could not be established (Table 2.15). To address this, we sought to rationalize the observed product distribution in our reaction system and further advance our understanding of migratory insertion aptitude using statistical modelling reaction performance with bisphosphine ligand descriptors.¹⁸

Computationally generated molecular descriptor libraries have become essential for integrating data science approaches into organic reaction development. These libraries often consist of “ground-state” computed structures from which various descriptors are derived. A central premise of this approach is that ground-state properties can be used to explain trends in reactivity or selectivity, similar to how Hammett correlations and other linear free-energy relationships are used in physical organic chemistry. When constructing such libraries, it is also important to consider descriptors derived from molecular conformations, as both steric and electronic properties can depend strongly on conformational dynamics. For instance, reaction energy barriers may differ by as much as 10 kcal/mol due to conformational variation, making it difficult to predict in advance which conformers are most relevant.¹⁸

To accomplish this statistical modeling, we used a recently reported workflow to extract conformationally sensitive descriptors.^{18,19} Virtual screening of catalysts includes examination of all commercial bisphosphine ligands, with preference given to scaffolds available in-house. To explore the relationship between the two regioisomeric Mizoroki-Heck products (expressed as $\Delta\Delta G^\ddagger$ (2.4/2.7)), multiple linear regression (MLR) was deployed (Figure 2.11).

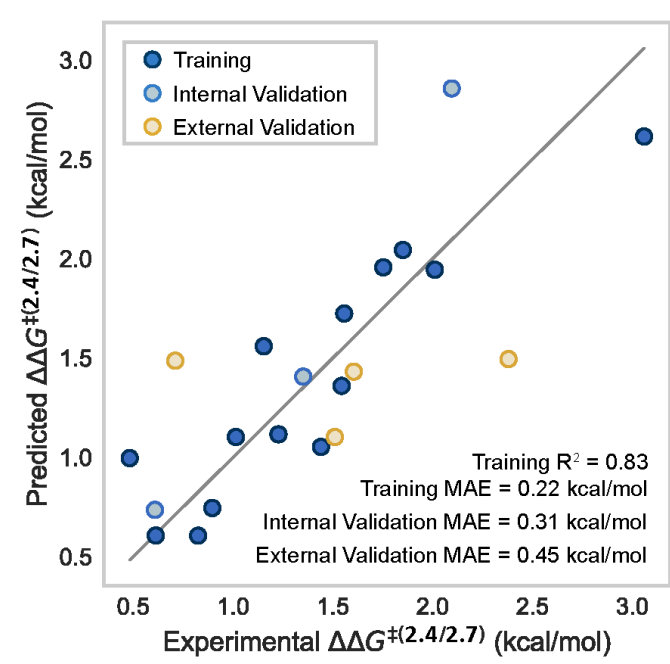


Figure 2.11. Multiple linear regression model for observed product selectivity between **2.4** and **2.7**.

A three-term statistical model was constructed with the first contributor being τ_4 , which describes the distortion from a square planar geometry for the bisphosphine- PdCl_2 complexes (Figure 2.12). This descriptor reports that a minimal deviation from a square plane is required for significant preference for bicyclo[2.2.2]octanone **2.4**. The second feature, $\text{Pd-P}_{\text{large}}$ bond distance, describes the minimum bonding distance for the larger of the two phosphine donors (differentiated using V_{bur} at 3.5 Å) across the ligand conformational ensemble. For this feature, a large minimum phosphorus–palladium bond length leads to preferential formation of bicyclo[2.2.2]octanone **2.4**. The last feature describes the accessible range from the conformational minimum bond distance of $\text{Pd-P}_{\text{large}}$ to the maximum conformational bond distance across both P–Pd bonds. This feature is included as a corrective term in this model, where a restriction is placed on the flexibility in the $\text{Pd-P}_{\text{large}}$ bonding distance. The minimum $\text{Pd-P}_{\text{large}}$ bond length is required to be within approximately 0.01 Å of the maximum accessible bond length, which may help to distinguish ligands with hemilabile properties.

We propose this combination of bond lengths and square planar distortion to read out the propensity of a bisphosphine ligand to undergo *in situ* oxidation to a bisphosphine mono-oxide (BPMP) ligand.²⁰ This suggests that a catalytically active BPMP species results in a higher preference towards migratory insertion product **2.4**.^{7,21}

bisphosphine counterpart. Additionally, ^{31}P NMR confirmed the *in situ* formation of mono-oxide ligands in several of the catalytic reactions utilizing unoxidized bisphosphine catalysts. In this optimization, interpretation of MLR features allowed identification of an unexplored but catalytically active ligand class.

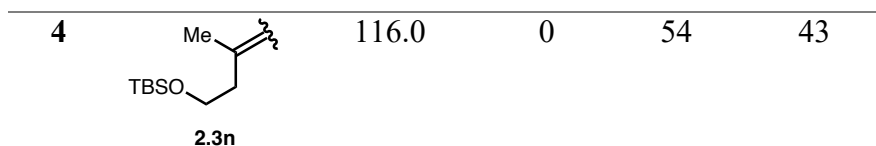
In conclusion, the Mizoroki–Heck cyclization appears to favor formation of bicyclo[2.2.2]octanone **2.4**. Consistent with our initial hypothesis, we propose that the alkene substitution pattern is the primary factor governing this selectivity. Additionally, statistical modelling reaction performance with bisphosphine ligand descriptors reveals that the interplay between Pd–P bond length and square planar geometry distortion influence the propensity for *in situ* ligand oxidation, which in turn affects the migratory insertion aptitude of the Mizoroki–Heck cyclization.

2.7 Mizoroki–Heck Cyclization Selectivity with Tetrasubstituted *gem*-Dichloroalkene Electrophiles

In contrast to the migratory insertion selectivity observed with trisubstituted *gem*-dichloroalkene electrophiles, reactions involving tetrasubstituted *gem*-dichloroalkenes appear to be governed primarily by substituent effects on the alkene rather than ligand control. In exploring a range of cyclic alkene electrophiles with varied ring sizes, we observed a trend toward formation of bicyclo[2.2.2]octanone **2.4** with smaller ring systems, whereas bicyclo[3.2.1]octanone **2.7** predominated with larger ring systems and acyclic tetrasubstituted alkenes (Table 2.16).

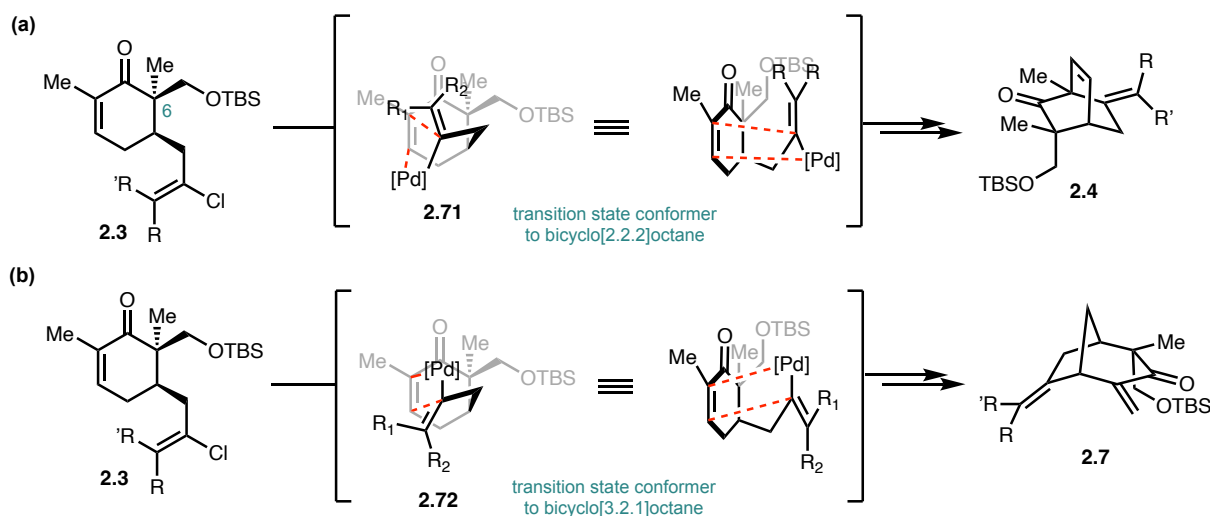
Table 2.16. Mizoroki–Heck cyclization selectivity with substituent dependency.^a

entry	R, R' =	Bond angle	2.4 [%]	2.7 [%]	2.70 [%]
1		-	63	0	0
2		90.9	22	20	0
3		102.3	< 5	66	0



^a all NMR yields with 1,3,5-trimethoxybenzene as internal standard. Bond angles calculated at OPLS4 FF level of theory.

On the basis of this observation, we propose that with tetrasubstituted *gem*-dichloroalkene electrophiles, the bulkiness of the substituents on the alkene affect relative energies of the transition-state conformers leading to bicyclo[2.2.2]octanone **2.4** and bicyclo[3.2.1]octanone **2.7** (Scheme 2.17).

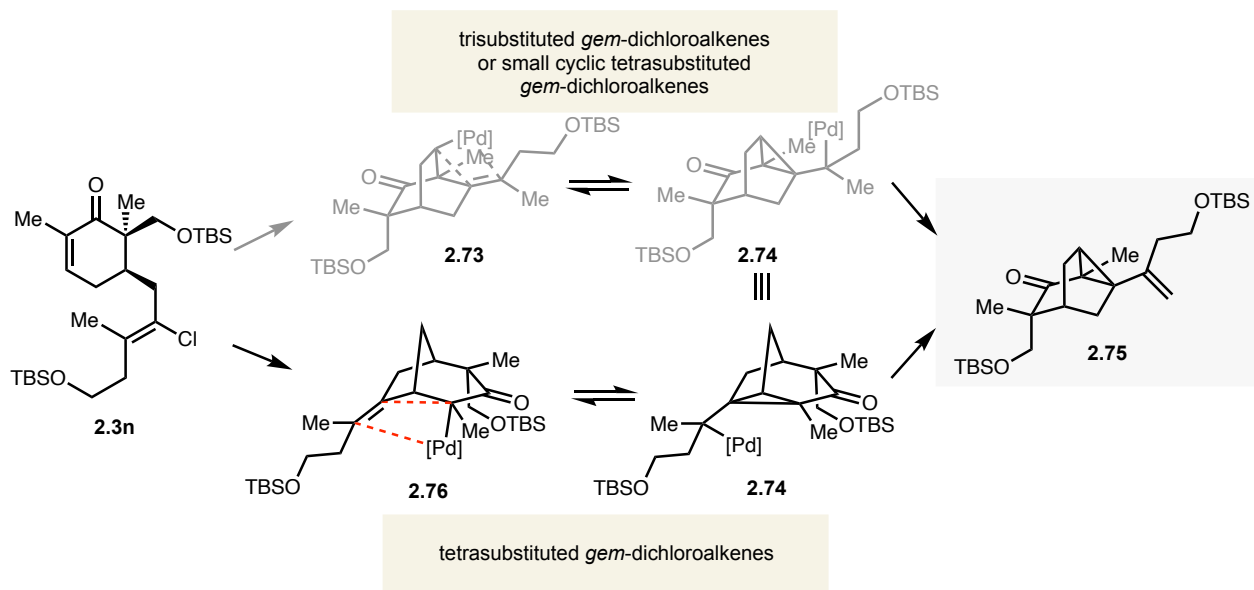


Scheme 2.17. Proposed transition state conformers with tetrasubstituted alkene electrophile.

Increased substitution leads to steric clash with the quaternary carbon C6 and its substituents, destabilizing the corresponding transition state (**2.71**). To alleviate this, the C–C bond rotates out of its original orientation to adopt transition state **2.72**, which minimizes steric strain. This conformer ultimately leads to formation of bicyclo[3.2.1]octanone **2.7**. In cyclic alkene electrophiles, where the substituents are constrained within a ring, this steric interaction is reduced, resulting in formation of bicyclo[2.2.2]octanone **2.4** as the major product, along with bicyclo[3.2.1]octanone **2.7**. Minimization of steric interactions is best achieved with smaller ring systems (Table 2.16, entry 2). In the case of a trisubstituted alkene electrophile, steric interactions between the quaternary carbon and hydrogen are negligible (Table 2.16, entry 1).

Notably, the formation of the tricyclo[3.2.1.0]octanone **2.75** in Table 2.16 (entry 4) can be explained by its origin from the bicyclo[3.2.1]octanone intermediate (Scheme 2.18). In contrast to the previously proposed mechanism for tricycle **2.75** formation from the bicyclo[2.2.2]octane intermediate **2.73** (Chapter 2.4), we propose that, with vinyl chloride **2.3n**, the conformation of bicyclo[3.2.1]octanone intermediate **2.76** still enables insertion of the C–Pd bond into the pendant alkene, again via Curtin–Hammett kinetics. The resulting intermediate (**2.74**) is identical to that obtained from bicyclo[2.2.2]octane intermediate **2.73**. We further hypothesize that increased steric

encumbrance around the palladium center promotes facile dissociation of the alkoxide base, thereby leading to significant formation of tricyclic product **2.75**.



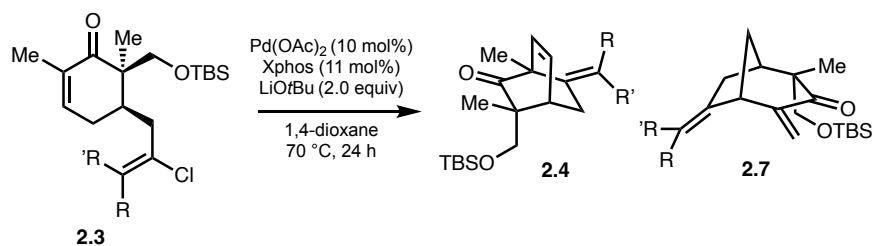
Scheme 2.18. Proposed mechanism for tricyclic **2.75** formation with acyclic tetrasubstituted *gem*-dichloroalkene.

Calculations of the relative energies of the proposed transition-state conformers support our substituent interaction-based hypothesis. Calculations were performed with AIMNet2-Pd,²² a neural network potential trained on ~925k Pd-containing molecular geometries (including ~20k reactive geometries) with a reference functional of B97-3c.²³ Transition states were found using climbing image nudged elastic band method²⁴ followed by transition state optimization with the Sella software package.²⁵ The conformational space of the transition states was explored using Multiple Minimum Monte Carlo.²⁶

A comparison of the experimental and calculated relative energetics is presented in Table 2.17. The energy differences for the globally optimized transition states preserves the rank order of selectivity across substrates; however, the calculated selectivity appears to overly favor the reaction to form bicyclo[2.2.2]octanone **2.4**

Consistent with the calculations, our sterics-based hypothesis regarding transition-state energy conformers, illustrated in Scheme 2.17, was also supported by the optimized structures of the corresponding transition states for each intermediate (Figures 2.14-2.16). In **2.3i**, the more constrained cyclobutane substituent minimizes steric interactions with substituents on C6 in the transition-state structure to bicyclo[2.2.2]octane **2.4** (Figure 2.14), whereas increased proximity between the acyclic substituents on the alkene and the OTBS group is observed in the transition state of **2.3n** (Figure 2.15). The transition-state structure to bicyclo[3.2.1]octane **2.7** with **2.3n** shows that both substituents are positioned farther apart from each other (Figure 2.16).

Table 2.17. Mizoroki–Heck cyclization selectivity with substituent dependency.



entry	R =	Experimental ratio (2.4:2.7)	$\Delta\Delta G^\ddagger(\text{exp})$	$\Delta\Delta G^\ddagger(\text{AIMNET})$
1	 2.3d	~1:0	> 5.0	10.5
2	 2.3l	0.52:0.48	0.05	1.20
3	 2.3i	0.3:0.7	−0.58	−2.6
4	 2.3n	~0:1	< −5.0	−5.2

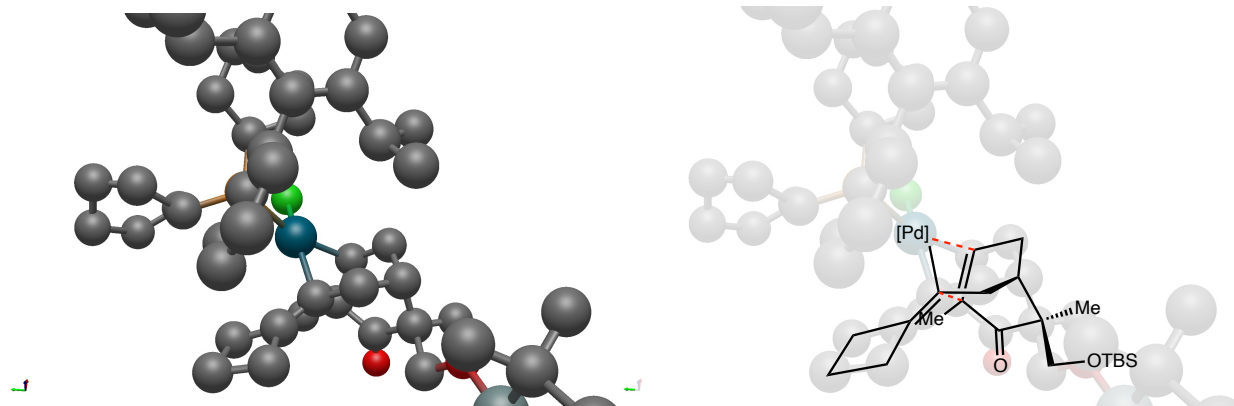


Figure 2.14. Calculated transition state conformer for bicyclo[2.2.2]octanone **2.4** with an enantiomer of **2.3l**.

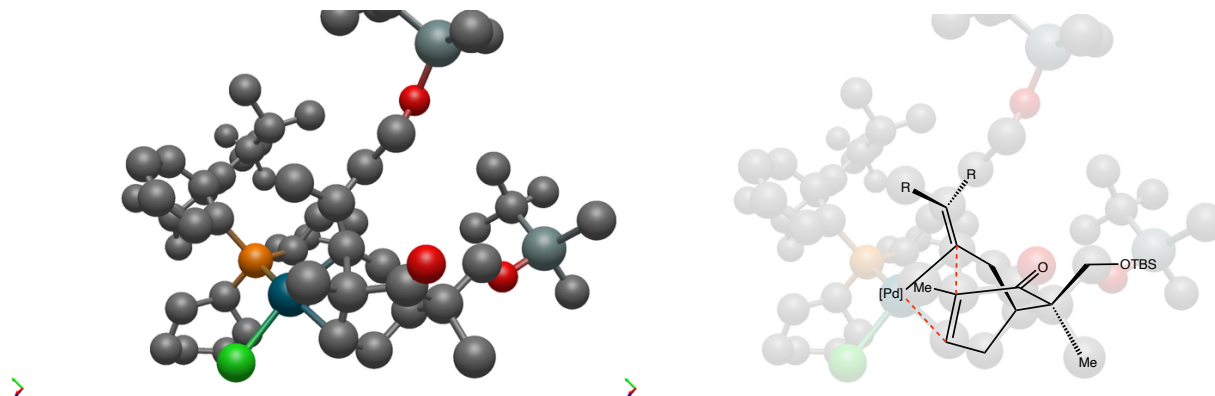


Figure 2.15. Calculated transition state conformer for bicyclo[2.2.2]octanone **2.4** with an enantiomer of **2.3n**.

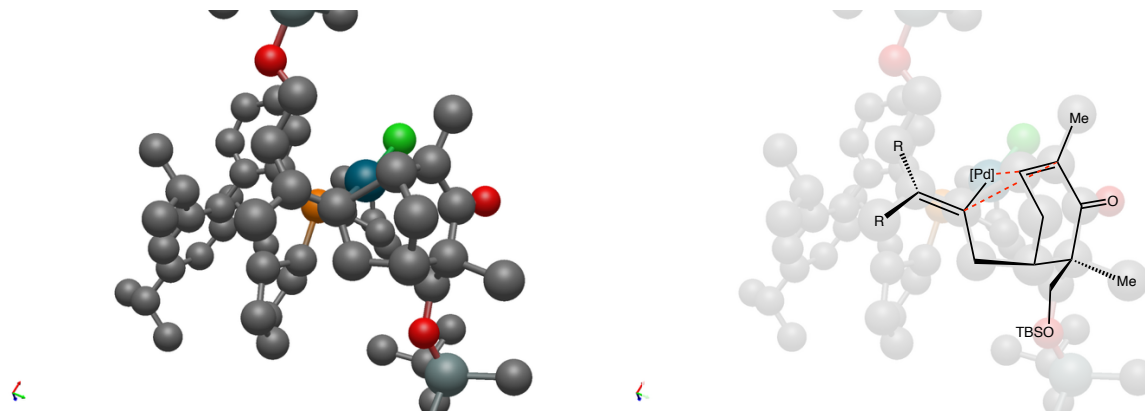


Figure 2.16. Calculated transition state conformer for bicyclo[3.2.1]octanone **2.7** with an enantiomer of **2.3n**.

Taken together, our hypothesis that substituent sterics govern migratory insertion selectivity with tetrasubstituted *gem*-dichloroalkene electrophiles is supported by transition state conformational analyses. Although the calculated energy differences are not fully consistent with the experimentally determined energy differences, they correctly reproduce the observed rank order of selectivity across substrates.

2.8 Summary and Outlook

Herein, we report advances in establishing a Pd-catalyzed C–C bond cleavage/cross-coupling/Mizoroki–Heck cyclization cascade for the synthesis of diverse cyclic compounds, including highly substituted bridged polycycles. This strategy is based on the coupling of an enantioenriched hydroxylated pinene (**2.1**) derived from carvone with *gem*-dichloroalkenes to access a range of cyclic intermediates. Notably, this work highlights the use of *gem*-dichloroalkenes, an underutilized class of building blocks in synthetic chemistry.

We identified key mechanistic intricacies governing product selectivity of the Mizoroki–Heck cyclization, which depend on the substituents of the *gem*-dichloroalkene electrophile, leading to the formation of bicyclo[2.2.2]octanone, bicyclo[3.2.1]octanone and tricyclo[3.2.1.0]octanone

products. Gratifyingly, the use of specific phosphine ligands and additives enabled these polycyclic frameworks to be obtained with excellent product selectivity. Computational studies, combined with data-driven bisphosphine ligand parametrization, provided insight into the origin of this selectivity, revealing energy differences between the relevant transition state conformers in the Mizoroki–Heck cyclization. Such in-depth mechanistic investigations on the cascade reaction revealed multiple unprecedented features of the reaction that controlled product formation.

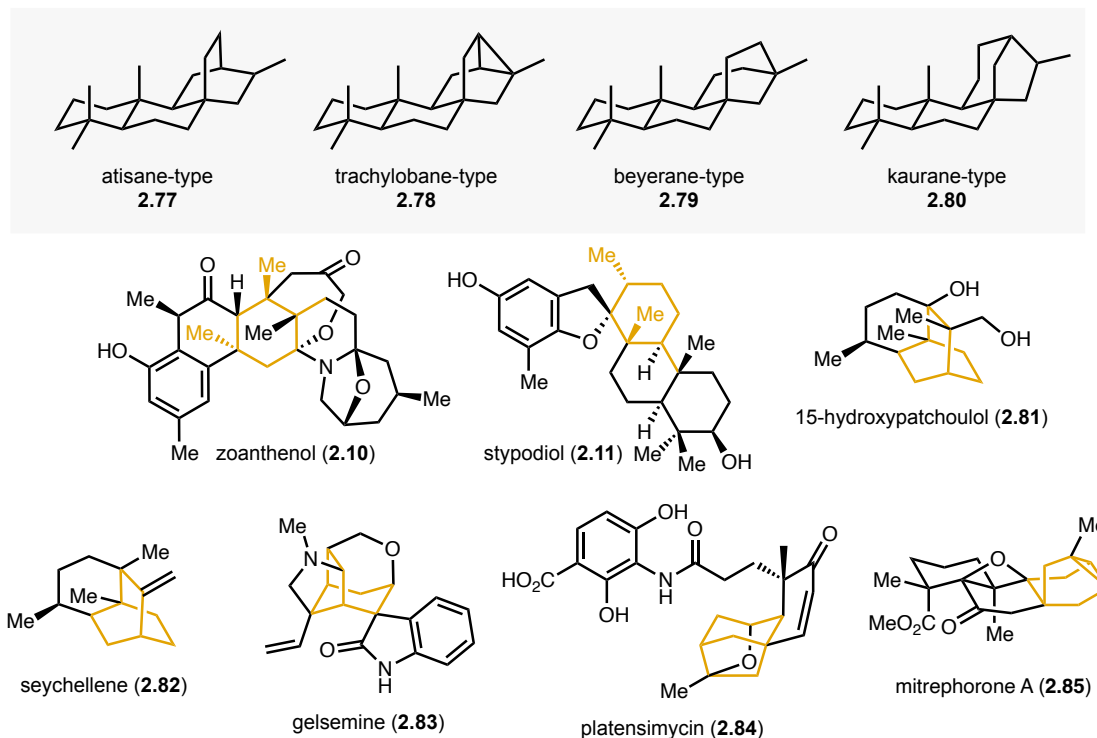


Figure 2.17. Summary of terpenoid natural products with various bridged bicyclic frameworks.

We anticipate that insights from this study will provide useful guidelines for future investigations of transition metal catalyzed cascade processes and Mizoroki–Heck cyclizations in related systems. Further, this protocol offers a viable and efficient route to a range of polycyclic frameworks and is expected to be applicable to the synthesis of terpene natural products, such as 15-hydroxypatchoulol (**2.81**), seychellene (**2.82**), and more (Figure 2.17).

2.9 Contributions

This chapter includes collaborative results from the Sigman lab at the University of Utah, and the Coley lab at the Massachusetts Institute of Technology. Bisphosphine parametrization studies were conducted and the corresponding paragraph was written by Sierra Hart (Sigman lab). The transition state energy calculations were conducted by Nicholas Casetti (Coley lab). This chapter includes their work with permission from both collaborators.

2.10 Experimental Details

2.10.1 General Procedures

Solvents and Reagents

Unless noted below, commercial reagents were purchased from Sigma Aldrich, Acros Organics, Ambeed, Fisher Scientific, Matrix Scientific, Chem-Impex, Combi-blocks, TCI, Oakwood Chemical, Strem Chemicals, Spectrum Chemical and/or Alfa Aesar, and used without additional purification. Solvents were purchased from Fisher Scientific, Acros Organics, Alfa Aesar, and Sigma Aldrich. THF, Et₂O, PhH, PhMe, MeOH, and Et₃N were sparged with argon and dried by passing through alumina columns using argon in a Glass Contour solvent purification system. DCM was freshly distilled over calcium hydride under a N₂ atmosphere prior to each use.

Experimental Procedures

Unless otherwise noted in the experimental procedures, reactions were carried out in flame- or oven- dried glassware under a positive pressure of N₂ in anhydrous solvents using standard Schlenk techniques. Reaction temperatures above room temperature (22–23 °C) were controlled by an IKA® temperature modulator and monitored using liquid-in-glass thermometers. Reaction progress was monitored by thin-layer chromatography (TLC) on Macherey-Nagel TLC plates (60 Å, F254 indicator). TLC plates were visualized by exposure to ultraviolet light (254 nm), and/or stained by submersion in aqueous potassium permanganate solution (KMnO₄), *p*-anisaldehyde or ceric ammonium molybdate (CAM) stains and heating with a heat gun. Organic solutions were concentrated under reduced pressure on an Heidolph temperature-controlled rotary evaporator equipped with a dry ice/isopropanol condenser. Flash column chromatography was performed with either glass columns using Silicycle SiliaFlash® P60 silica gel (40– 63 µm particle size) using ACS grade solvents. All yields refer to chromatographically and spectroscopically (¹H and ¹³C NMR) pure material.

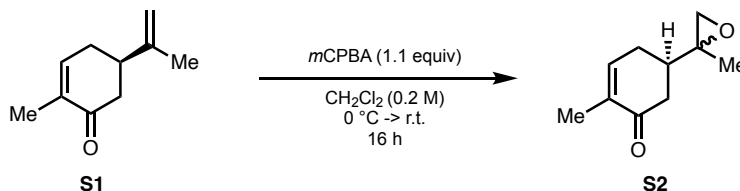
Analytical Instrumentation

NMR spectral data were obtained using deuterated solvents, obtained from Cambridge Isotope Laboratories, Inc. ¹H NMR and ¹³C NMR data were recorded on Bruker AVQ-400, AVB-400, NEO-401, NEO-500, AV-600 and AV-700 spectrometers using CDCl₃ as solvent at 20–23 °C. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ 7.26 for ¹H NMR & δ 77.16 for ¹³C NMR in CDCl₃, δ 7.15 for ¹H NMR & δ 128.62 for ¹³C NMR in C₆D₆). Data for ¹H and ¹³C spectroscopy are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), coupling constant (Hz), integration. All raw FID files were processed, and the spectra analyzed, using the program MestReNOVA 11.0 from Mestrelab Research S. L. Melting points were determined using a MEL-TEMPTM apparatus and are uncorrected. High-resolution mass spectra (HRMS) were obtained from the Mass Spectral Facility at the University of California, Berkeley, on a Finnigan/Thermo

LTQ-FT instrument (ESI). Data acquisition and processing were performed using the XcaliburTM software.

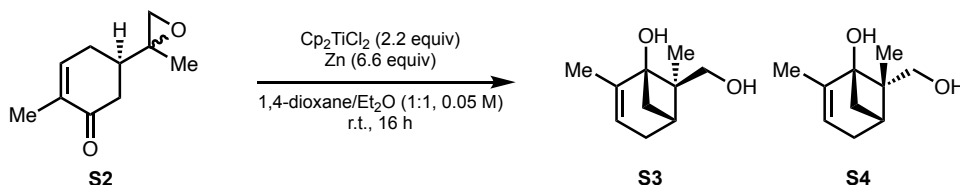
2.10.2 Synthetic Procedures and Product Characterization

Cyclobutanol Substrate Synthesis



(5R)-2-methyl-5-(2-methyloxiran-2-yl)cyclohex-2-en-1-one (S2): To a solution of (*R*)-carvone (**S1**, 5.0 g, 33.3 mmol, 1.0 equiv) in dichloromethane (165 mL, 0.2 M) was added 3-chloroperoxybenzoic acid (9.1 g, 37.0 mmol, 1.1. equiv) at 0 °C. After its complete dissolution, the reaction mixture was warmed up to room temperature and stirred overnight. The reaction mixture was quenched with a saturated aqueous solution of Na₂S₂O₃ (150 mL) and extracted with dichloromethane (1x 300 mL). The organic phase was washed with 1M NaOH (1x 300 mL) and brine (1x 300 mL). The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*, affording **S2** as pale yellow oil (5.49 g, 33.0 mmol, 99%). The crude product was used in the next step without further purification. The spectral data are consistent with those reported in the literature.²⁷

¹H NMR (400 MHz, CDCl₃) δ 6.75 (t, 1H), 2.72-2.71 (dd, 1H), 2.61-2.58 (m, 1H), 2.56-2.53 (m, 1H), 2.44-2.38 (m, 1H), 2.31-2.17 (m, 2H), 2.11-2.06 (m, 1H), 1.78-1.77 (s, 3H), 1.33-1.31 (d, 3H) ppm.



(1S,5R,6R)-6-(hydroxymethyl)-2,6-dimethylbicyclo[3.1.1]hept-2-en-1-ol (S3) and (1S,5R,6S)-6-(hydroxymethyl)-2,6-dimethylbicyclo[3.1.1]hept-2-en-1-ol (S4): To a 1000 mL three-necked flask, Cp₂TiCl₂ (17.5 g, 70.2 mmol, 2.2 equiv) and Zn powder (13.8 g, 210.5 mmol, 6.6 equiv) were added. To the mixture was added degassed dioxane/Et₂O solvent system (1:1, 319 mL, 0.22 M), which was prepared by sparging with N₂ for 30 min before use. The mixture was stirred for at least 3 h until the reaction color turned dark green. The prepared stock solution of **S2** (5.3 g, 31.6 mmol, 1.0 equiv) in degassed dioxane/Et₂O (1:1, 150 mL, 0.22 M) was then added dropwise to the mixture via a dropping funnel and stirred overnight at room temperature. The reaction was quenched with saturated aqueous solution of NaH₂PO₄ (400 mL) and the mixture was bubbled with air until the color turned orange. The crude mixture was filtered over celite, and the phases were separated. After extracting the aqueous phase with EtOAc (1x 400 mL), the organic layers

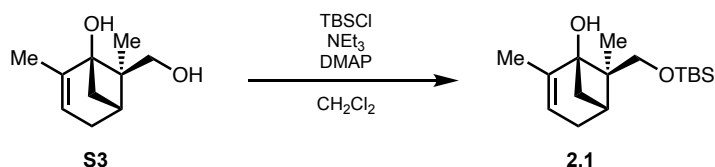
were combined, dried over Na₂SO₄, and concentrated *in vacuo*. The resulting residue was purified by column chromatography using hexane:EtOAc (2:1) to afford the product as a yellow solid (**S3**: 2.76 g, 16.4 mmol, 52%; **S4**: 1.65 g, 9.81 mmol, 35 %). The spectral data are consistent with those reported in the literature.²⁸

(1*S*,5*R*,6*R*)-6-(hydroxymethyl)-2,6-dimethylbicyclo[3.1.1]hept-2-en-1-ol (S3**):**

¹H NMR (400 MHz, CDCl₃) δ 5.24-5.23 (t, 1H), 4.32-4.29 (d, 1H), 3.72-3.70 (d, 1H), 2.42-2.39 (dd, 1H), 2.19-2.04 (m, 2H), 1.98-1.95 (m, 1H), 1.77-1.75 (q, 3H), 1.68-1.66 (d, 1H), 1.07 (s, 3H) ppm.

(1*S*,5*R*,6*S*)-6-(hydroxymethyl)-2,6-dimethylbicyclo[3.1.1]hept-2-en-1-ol (S4**):**

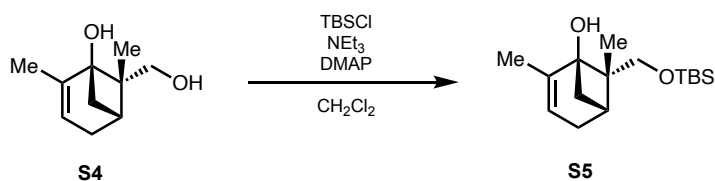
¹H NMR (700 MHz, CDCl₃) δ 5.33 – 5.24 (m, 1H), 3.75 (d, *J* = 10.3 Hz, 1H), 3.40 (d, *J* = 10.3 Hz, 1H), 2.27 (dd, *J* = 8.3, 6.8 Hz, 1H), 2.21 – 2.10 (m, 2H), 2.12 – 1.99 (m, 1H), 1.93 (s, 1H), 1.81 (app q, *J* = 2.1 Hz, 3H), 1.62 (d, *J* = 8.3 Hz, 1H), 1.59 (s, 2H), 1.34 (s, 3H).



(1*S*,5*R*,6*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethylbicyclo[3.1.1]hept-2-en-1-ol (2.1**)** was prepared using a procedure adapted from the literature:²⁹ To a 100 mL round-bottomed flask equipped with a stir bar was charged sequentially with cyclobutanol **S3** (1.00 g, 5.94 mmol, 1 equiv), DMAP (73 mg, 0.59 mmol, 0.1 equiv), TBSCl (1.08 g, 7.13 mmol, 1.2 equiv), and CH₂Cl₂ (30 mL, 0.2 M). Triethylamine (2.1 mL, 14.9 mmol, 2.5 equiv) was added dropwise, and the solution was stirred at 23 °C overnight. The reaction mixture was then diluted with CH₂Cl₂ (100 mL), and washed sequentially with 1 N HCl (100 mL) and brine (100 mL). The organic phase was dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by silica column chromatography (2.5% EtOAc/hexane) to give TBS ether **2.1** (1.58 g, 94% yield) as a colorless oil, which overtime solidified to a white crystalline solid.

¹H NMR (500 MHz, CDCl₃) δ 5.17 (s, 1H), 4.30 (s, 1H), 4.27 (d, *J* = 10.1 Hz, 1H), 3.72 (d, *J* = 10.1 Hz, 1H), 2.36 (dd, *J* = 8.6, 6.9 Hz, 1H), 2.17 – 2.01 (m, 2H), 1.91 (dd, *J* = 6.8, 2.8 Hz, 1H), 1.75 (d, *J* = 2.1 Hz, 3H), 1.67 (d, *J* = 8.6 Hz, 1H), 1.00 (s, 3H), 0.92 (s, 9H), 0.10 (d, *J* = 3.6 Hz, 6H).

The spectral data were consistent with those reported in the literature.²⁹



(1*S*,5*R*,6*S*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethylbicyclo[3.1.1]hept-2-en-1-ol (S5) was prepared using a procedure from the literature:²⁹ To a 100 mL round-bottomed flask equipped with a stir bar was charged sequentially with cyclobutanol **S4** (2.36 g, 15.6 mmol, 1 equiv), DMAP (191 mg, 1.56 mmol, 0.1 equiv), TBSCl (1.21 g, 18.9 mmol, 1.2 equiv), and CH₂Cl₂ (70 mL, 0.2 M). Triethylamine (6.54 mL, 46.9 mmol, 3.0 equiv) was added dropwise, and the solution was stirred at 23 °C for 14 h. The reaction mixture was then diluted with CH₂Cl₂ (200 mL), and washed sequentially with 1 N HCl (200 mL) and brine (200 mL). The organic phase was dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by silica column chromatography (2.5% EtOAc/hex) to give TBS ether **S5** (3.77 g, 85% yield) as a colorless oil.

R_f (10% EtOAc/hexanes, CAM) 0.48

[α]_D²⁵ = +28.27 (c = 0.008, CH₂Cl₂)

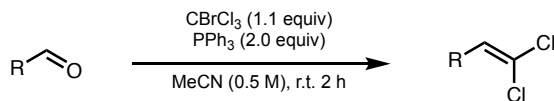
¹H NMR (400 MHz, CDCl₃) δ 5.23 (tt, *J* = 3.0, 1.5 Hz, 1H), 3.70 (dd, *J* = 9.0, 0.8 Hz, 1H), 3.25 (s, 1H), 2.27 (dd, *J* = 8.2, 6.8 Hz, 1H), 2.17 (s, 1H), 2.12 (ddd, *J* = 12.4, 5.8, 2.5 Hz, 2H), 2.08 – 1.99 (m, 1H), 1.78 (q, *J* = 2.1 Hz, 3H), 1.57 (d, *J* = 8.2 Hz, 1H), 1.29 (s, 3H), 0.87 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 146.36, 116.99, 65.98, 46.16, 43.22, 38.93, 34.69, 31.14, 26.08, 25.95, 25.99, 18.36, 17.61, 14.55, -5.44, -5.43.

HRMS (ESI) Exact mass calcd for C₁₆H₃₁O₂Si [M+H], 283.20. Found 283.21.

Synthetic Preparation of *gem*-Dichloroalkenyl Electrophiles

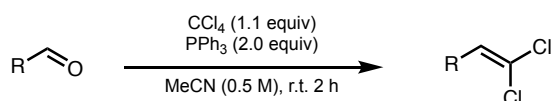
General Procedure A:



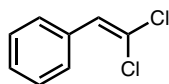
The reaction flask with triphenylphosphine (2.0 equiv) and anhydrous acetonitrile (0.5 M) is cooled down to 0 °C with an ice bath. Aldehyde (1.0 equiv) and bromotrichloromethane (1.1 equiv) are added with a syringe. After stirring the reaction mixture for 15 min at 0 °C the ice bath was removed and the reaction mixture was stirred for 2 h. Reaction conversion was monitored with TLC (9:1 Hexane:EtOAc). The reaction mixture was diluted with diethyl ether and extracted with H₂O. The aqueous phase was washed with diethyl ether and the combined organic phases were

dried over Na₂SO₄ and concentrated *in vacuo*. The pure compound was obtained with column chromatography (100% hexane).

General Procedure B:

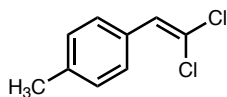


The reaction flask with triphenylphosphine (2.0 equiv) and anhydrous acetonitrile (0.5 M) is cooled down to 0 °C with an ice bath. Aldehyde (1.0 equiv) and perchloromethane (1.1 equiv) are added with a syringe. After stirring the reaction mixture for 15 min at 0 °C the ice bath was removed and the reaction mixture was stirred for 2 h. Reaction conversion was monitored with TLC (9:1 Hexane:EtOAc). The reaction mixture was diluted with diethyl ether and extracted with H₂O. The aqueous phase was washed with diethyl ether and the combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo*. The pure compound was obtained with column chromatography (100% hexane).



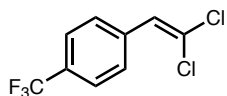
(2,2-dichlorovinyl)benzene (S6): Compound was prepared with general procedure A (85% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.54-7.52 (m, 2H), 7.39-7.30 (m, 3H) 6.86 (s, 1H) ppm. The spectral data are consistent with those reported in the literature.³⁰

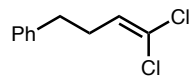


1-(2,2-dichlorovinyl)-4-methylbenzene (2.2a): Compound was prepared with general procedure A (65% yield).

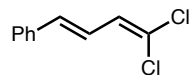
¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.82 (s, 1H), 2.35 (s, 3H) ppm. The spectral data are consistent with those reported in the literature.³¹



¹H NMR (400 MHz, CDCl₃) δ 7.63 (s, 4H), 6.90 (s, 1H) ppm. The spectral data are consistent with those reported in the literature.³⁰

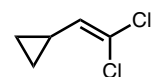


¹H NMR (400 MHz, CDCl₃) δ 7.32-7.29 (m, 2H), 7.23-7.18 (m, 3H), 5.89-5.85 (t, 1H), 2.75-2.71 (m, 2H), 2.52-2.46 (dt, 2H) ppm. The spectral data are consistent with those reported in the literature.³²



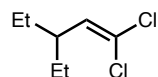
¹H NMR (600 MHz, CDCl₃) δ 7.46 – 7.44 (m, 2H), 7.37 – 7.33 (m, 2H), 7.31 – 7.27 (m, 1H), 6.93 – 6.87 (m, 1H), 6.65 (d, *J* = 15.7 Hz, 1H), 6.59 (dd, *J* = 10.5, 0.8 Hz, 1H).

HRMS (ESI) Exact mass calcd for C₁₀H₈Cl₂ [M], 198.0003. Found 198.002.



¹H NMR (600 MHz, CDCl₃) δ 5.26 (d, *J* = 9.5 Hz, 1H), 1.70 – 1.64 (m, 1H), 0.89 – 0.84 (m, 2H), 0.52 – 0.47 (m, 2H).

HRMS (ESI) Exact mass calcd for C₅H₆Cl₂ [M], 135.9847. Found 135.9849.

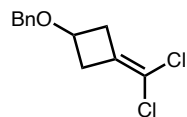


1,1-dichloro-3-ethylpent-1-ene (2.2g): Compound was prepared with general procedure **B** (74 % yield).

¹H NMR (600 MHz, CDCl₃) δ 5.60 (d, *J* = 10.0 Hz, 1H), 2.30 (dt, *J* = 10.1, 8.6, 5.1 Hz, 1H), 1.52 – 1.44 (m, 2H), 1.28 (ddq, *J* = 13.5, 8.7, 7.4 Hz, 2H), 0.88 (t, *J* = 7.5 Hz, 6H).

¹³C NMR (151 MHz, CDCl₃) δ 134.60, 119.88, 43.96, 27.43, 11.73.

HRMS (ESI) Exact mass calcd for C₇H₁₂Cl₂ [M], 166.0316. Found 166.0318.

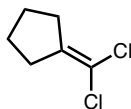


((3-(dichloromethylene)cyclobutoxy)methyl)benzene (2.2m): Compound was prepared with general procedure **B** (92 % yield).

¹H NMR (600 MHz, CDCl₃) δ 7.39 – 7.28 (m, 1H), 4.46 (s, 0H), 4.13 (td, *J* = 6.3, 1.2 Hz, 0H), 3.00 – 2.94 (m, 0H), 2.76 – 2.70 (m, 0H).

¹³C NMR (151 MHz, CDCl₃) δ 137.70, 132.13, 128.65, 128.05, 112.53, 70.80, 67.23, 39.01.

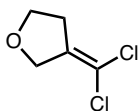
HRMS (ESI) Exact mass calcd for C₁₂H₁₂Cl₂O [M], 242.03. Found 242.03.



(Dichloromethylene)cyclopentane (2.2i): Compound was prepared with general procedure **A** (47% yield).

¹H NMR (500 MHz, CDCl₃) δ 2.43 – 2.33 (m, 4H), 1.81 – 1.71 (m, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 143.7, 109.8, 33.7, 27.1.

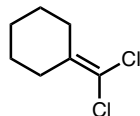


3-(dichloromethylene)tetrahydrofuran (2.2k): Compound was prepared with general procedure **B** (36 % yield).

¹H NMR (600 MHz, CDCl₃) δ 4.33 (t, *J* = 1.7 Hz, 2H), 3.99 (t, *J* = 6.9 Hz, 2H), 2.68 – 2.61 (m, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ 139.53, 110.11, 71.23, 69.34, 33.74.

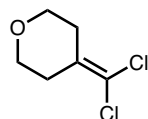
HRMS (ESI) Exact mass calcd for $\text{C}_5\text{H}_6\text{Cl}_2\text{O}$ [M], 151.9796. Found 151.9796.



(dichloromethylene)cyclohexane (2.2h): Compound was prepared with general procedure **B** (51 % yield).

^1H NMR (400 MHz, CDCl_3) δ 2.38 (m, 4H), 1.58 (m, 6H).

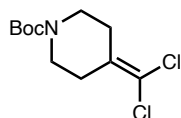
The spectral data are consistent with those reported in the literature.³³



4-(Dichloromethylene)tetrahydro-2H-pyran (S7): Compound was prepared with general procedure A (71 % yield)

^1H NMR (500 MHz, CDCl_3) δ 3.72 – 3.66 (m, 4H), 2.53 – 2.47 (m, 4H).

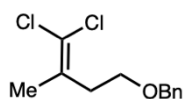
^{13}C NMR (126 MHz, CDCl_3) δ 133.1, 113.6, 67.5, 32.2.



Tert-butyl 4-(dichloromethylene)piperidine-1-carboxylate (S8): Compound was prepared with general procedure A (84 % yield)

^1H NMR (500 MHz, CDCl_3) δ 3.44 (t, J = 5.8 Hz, 4H), 2.46 (t, J = 5.9 Hz, 4H), 1.47 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 154.8, 133.9, 114.1, 80.1, 31.1, 28.6



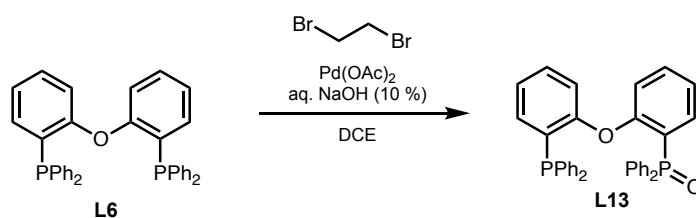
(((4,4-dichloro-3-methylbut-3-en-1-yl)oxy)methyl)benzene (2.2o): Compound was prepared with general procedure B (38 % yield)

¹H NMR (600 MHz, CDCl₃) δ 7.38 – 7.27 (m, 5H), 4.52 (s, 2H), 3.59 (t, *J* = 6.8 Hz, 2H), 2.59 (t, *J* = 6.8 Hz, 2H), 1.91 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 138.37, 132.72, 128.56, 127.77, 127.71, 115.88, 73.05, 67.53, 35.86, 20.60.

HRMS (ESI) Exact mass calcd for C₁₂H₁₄Cl₂O [M], 244.0422. Found 244.0422.

DPEPhos(O) (L13):



Aqueous NaOH (10%, 20 mL) was added to a solution of Pd(OAc)₂ (1.0 mg, 5.00 μmol), DPEPhos (539 mg, 1.0 mmol), and 1,2-dibromoethane (285 mg, 1.52 mmol) in 1,2-dichloroethane (3 mL). The biphasic system was vigorously stirred at room temperature for 12 h, until the originally yellow mixture turned light yellow. The solution was then heated to 50 °C for 5 hours, and 80 °C for 2 hours until it turned pale yellow. The reaction mixture was then diluted with water (50 mL) and extracted with CH₂Cl₂ (50 mL × 3). The combined organic phase was washed with brine, dried over MgSO₄, and concentrated to give a solid. The crude product was then further purified by flash column chromatography (dichloromethane/ethyl acetate = 3:1) on silica gel to yield **DPEPhos(O) (L13)** as a white powder (179 mg, 32% yield).

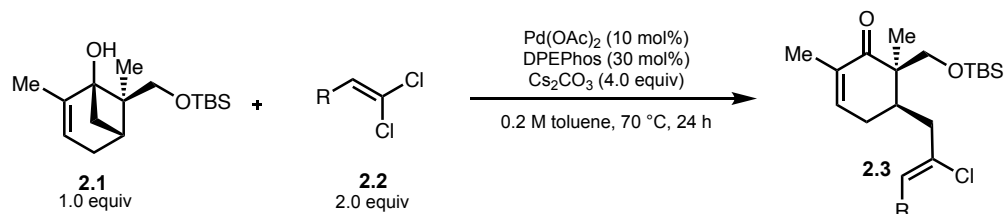
¹H NMR (400 MHz, CD₂Cl₂) δ 8.44 – 8.16 (m, 1H), 8.16 – 7.19 (m, 22H), 7.08 (dt, *J* = 34.2, 7.7 Hz, 2H), 6.85 (q, *J* = 7.6 Hz, 1H), 6.73 (dt, *J* = 13.7, 7.6 Hz, 1H), 6.29 – 6.04 (m, 1H).

³¹P NMR (202 MHz, CD₂Cl₂) δ 24.97 (s, 1P), -17.85 (s, 1P).

The spectral data are consistent with those reported in the literature.⁹

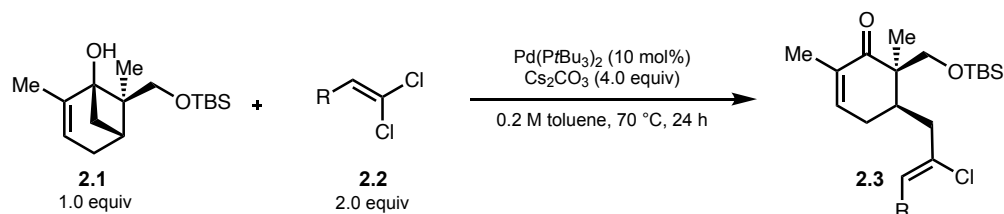
General Procedures for Vinyl Chloride Formation

General Procedure C:

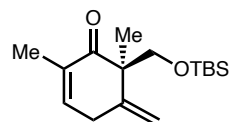


An oven-dried 4 mL vial is charged with the **2.1** (1.0 equiv), **2.2** (2.0 equiv), Pd(OAc)₂ (10 mol%), DPEPhos (30 mol%) and cesium carbonate (4.0 equiv) were added with anhydrous toluene in the glovebox and sealed with a teflon cap. The reaction mixture was stirred at 70 °C for 24 h. The reaction was filtered over celite with EtOAc and concentrated *in vacuo*. The product was isolated with column chromatography (2.5 % EtOAc in hexane).

General Procedure D:



An oven-dried 4 mL vial is charged with the **2.1** (1.0 equiv) and **2.2** (2.0 equiv). Pd(PtBu₃)₂ (10 mol%) and cesium carbonate (4.0 equiv) were added with anhydrous toluene in the glovebox and sealed with a teflon cap. The reaction mixture was stirred at 70 °C for 24 h. The reaction was filtered over celite with EtOAc and concentrated *in vacuo*. The product was isolated with column chromatography (2.5 % EtOAc in hexane).



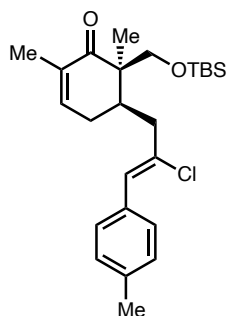
(*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethyl-5-methylenecyclohex-2-en-1-one (**2.12**):

¹H NMR (600 MHz, CDCl₃) δ 6.68 (ddt, *J* = 4.6, 2.9, 1.5 Hz, 1H), 4.95 (d, *J* = 2.0 Hz, 1H), 4.93 (dt, *J* = 2.0, 0.9 Hz, 1H), 3.75 (d, *J* = 9.3 Hz, 1H), 3.60 (d, *J* = 9.3 Hz, 1H), 3.33 – 3.25 (m, 1H), 3.03 (ddt, *J* = 20.6, 5.1, 1.5 Hz, 1H), 1.77 (dt, *J* = 2.5, 1.6 Hz, 3H), 1.25 (s, 3H), 0.84 (s, 8H), -0.01 (s, 3H), -0.02 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 201.40, 146.63, 142.28, 134.46, 111.12, 69.50, 55.57, 34.14, 25.87, 18.31, 17.34, 16.57, -5.52, -5.53.

HR-MS (m/z): ESI [M⁺] calculated for C₁₆H₂₈O₂Si: 280.19, found for C₁₆H₂₈O₂SiNa: 303.1751.

IR (neat): ν_{max} 2953, 2928, 2856, 1668, 1646, 1254, 1101, 1007, 836, 776, 668 cm^{-1} .



(5R,6R)-6-(((tert-butyldimethylsilyl)oxy)methyl)-5-((Z)-2-chloro-3-(p-tolyl)allyl)-2,6-dimethyl cyclohex-2-en-1-one (2.3a):

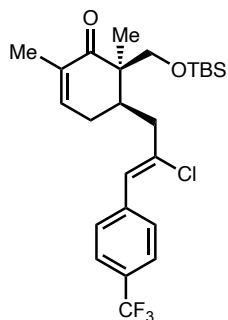
The title compound was prepared using General Procedure C (72 % yield).

^1H NMR (600 MHz, CDCl_3) δ 7.50 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 7.5 Hz, 2H), 6.60 (td, J = 4.3, 1.4 Hz, 1H), 6.40 (s, 1H), 3.75 (d, J = 10.3 Hz, 1H), 3.65 (d, J = 10.3 Hz, 1H), 2.73 (ddd, J = 13.3, 3.3, 1.3 Hz, 1H), 2.56 – 2.49 (m, 1H), 2.49 – 2.42 (m, 2H), 2.39 (ddd, J = 6.5, 4.1, 2.0 Hz, 1H), 2.35 (s, 3H), 1.78 (d, J = 1.6 Hz, 3H), 1.22 (s, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H) ppm.

^{13}C NMR (151 MHz, CDCl_3) 203.44, 142.73, 137.72, 134.71, 132.70, 132.19, 131.52, 129.12, 129.05, 126.27, 66.09, 49.74, 41.32, 38.95, 29.86, 27.46, 25.95, 25.94, 21.41, 20.10, 18.27, 16.44, 1.17, -5.50, -5.55 ppm.

HR-MS (m/z): ESI [M^+] calculated for $\text{C}_{25}\text{H}_{38}\text{O}_2\text{ClSi}$: 433.10, found: 433.2327.

IR (neat): ν_{max} 2953, 2926, 2856, 1665, 1612, 1511, 1463, 1255, 1007, 837, 777, 737 cm^{-1} .



(5R,6R)-6-(((tert-butyldimethylsilyl)oxy)methyl)-5-((Z)-2-chloro-3-(4-(trifluoromethyl)phenyl)allyl)-2,6-dimethylcyclohex-2-en-1-one (2.3b):

The title compound was prepared using General Procedure C (99% yield).

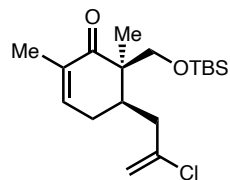
¹H NMR (500 MHz, CDCl₃) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 6.61 (q, *J* = 3.8 Hz, 1H), 6.47 (s, 1H), 3.76 (d, *J* = 10.4 Hz, 1H), 3.65 (d, *J* = 10.4 Hz, 1H), 2.77 (d, *J* = 12.3 Hz, 1H), 2.63 – 2.30 (m, 4H), 1.78 (q, *J* = 1.7 Hz, 3H), 1.23 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H) ppm.

¹³C NMR (151 MHz, CDCl₃) 203.39, 142.39, 138.55, 136.20, 134.84, 129.34, 125.29, 125.22, 66.03, 49.72, 41.39, 38.94, 27.42, 25.95, 20.14, 18.26, 16.44, 1.17, -5.49, -5.55 ppm.

¹⁹F NMR (470 MHz, CDCl₃) δ -62.64 (s, 1F).

HR-MS (m/z): ESI [M⁺] calculated for C₂₅H₃₄ClF₃O₂Si: 486.20, found: 486.1957.

IR (neat): ν_{max} 2954, 2928, 2856, 1325, 1126, 1049, 1033, 871, 838, 668 cm⁻¹.



(5*R*,6*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(2-chloroallyl)-2,6-dimethylcyclohex-2-en-1-one (2.3c):

The title compound was prepared using General Procedure C (61 % yield).

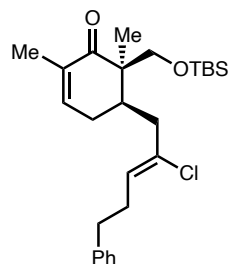
R_f (2.5 % EtOAc/hexanes, p-anisaldehyde) 0.65

[α]_D²⁵ = +8.72 (c = 0.07, CH₂Cl₂)

¹H NMR (600 MHz, CDCl₃) δ 6.62 – 6.58 (m, 1H), 5.21 (d, *J* = 1.1 Hz, 1H), 5.12 (t, *J* = 1.3 Hz, 1H), 3.70 (d, *J* = 10.3 Hz, 1H), 3.61 (d, *J* = 10.3 Hz, 1H), 2.57 (d, *J* = 13.0 Hz, 1H), 2.47 – 2.28 (m, 4H), 1.76 (q, *J* = 1.8 Hz, 3H), 1.19 (s, 3H), 0.87 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 203.31, 142.66, 141.82, 134.67, 114.17, 66.06, 49.66, 39.44, 38.55, 27.39, 25.91, 20.03, 18.23, 16.40, -5.54, -5.59.

HRMS (ESI) Exact mass calcd for C₁₈H₃₂ClO₂Si [M+H], 343.1855. Found 343.1852.



(5*R*,6*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-((*Z*)-2-chloro-5-phenylpent-2-en-1-yl)-2,6-dimethylcyclohex-2-en-1-one (2.3d):

The title compound was prepared using General Procedure C (89 % yield).

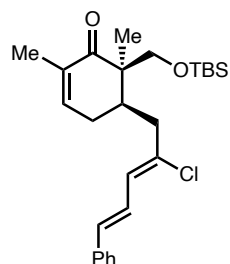
R_f (2.5 % EtOAc/hexanes, p-anisaldehyde) 0.57

[α]_D²⁵ = +0.97 (c = 0.01, CH₂Cl₂)

¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.30 (m, 3H), 7.26 (d, *J* = 12.4 Hz, 2H), 6.56 (d, *J* = 4.2 Hz, 1H), 5.49 (t, *J* = 6.9 Hz, 1H), 3.73 (d, *J* = 10.2 Hz, 1H), 3.64 (d, *J* = 10.1 Hz, 1H), 2.77 (dt, *J* = 11.6, 7.3 Hz, 2H), 2.58 (tq, *J* = 14.6, 7.3 Hz, 3H), 2.41 (q, *J* = 6.8, 5.9 Hz, 1H), 2.35 – 2.11 (m, 3H), 1.83 – 1.77 (m, 3H), 1.22 (d, *J* = 1.2 Hz, 3H), 0.92 (d, *J* = 1.2 Hz, 9H), 0.07 (d, *J* = 1.2 Hz, 3H), 0.05 (d, *J* = 1.3 Hz, 3H) ppm.

¹³C NMR (151 MHz, CDCl₃) 203.4, 142.9, 141.5, 134.5, 128.6, 128.5, 126.8, 126.1, 66.0, 49.6, 39.7, 38.5, 34.9, 30.2, 27.2, 25.9, 20.0, 18.2, 16.4, -5.5, -5.6 ppm.

HRMS (ESI) Exact mass calcd for C₂₆H₄₀ClO₂Si [M+H], 447.2481. Found 447.2484.



(5*R*,6*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-((2*Z*,4*E*)-2-chloro-5-phenylpenta-2,4-dien-1-yl)-2,6-dimethylcyclohex-2-en-1-one (2.3e)

The title compound was prepared using General Procedure C (27 % yield).

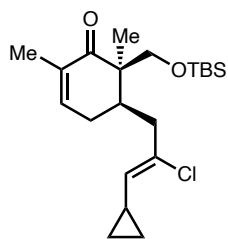
R_f (2.5 % EtOAc/hexanes, p-anisaldehyde) 0.50

[α]_D²⁵ = +9.69 (c = 0.12, CH₂Cl₂)

¹H NMR (600 MHz, CDCl₃) δ 7.46 – 7.40 (m, 2H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 1H), 7.10 (dd, *J* = 15.8, 10.3 Hz, 1H), 6.63 – 6.58 (m, 2H), 6.22 (dt, *J* = 10.2, 1.0 Hz, 1H), 3.74 (d, *J* = 10.3 Hz, 1H), 3.63 (d, *J* = 10.3 Hz, 1H), 2.69 (dd, *J* = 13.5, 3.1 Hz, 1H), 2.51 – 2.45 (m, 1H), 2.45 – 2.38 (m, 2H), 2.32 (dddt, *J* = 17.3, 6.4, 4.1, 2.0 Hz, 1H), 1.78 (q, *J* = 1.8 Hz, 3H), 1.21 (s, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 203.35, 142.70, 137.18, 135.13, 134.70, 133.82, 128.82, 128.09, 127.12, 126.72, 124.16, 66.08, 49.74, 40.09, 39.06, 27.56, 25.95, 20.08, 18.26, 16.42, -5.50, -5.56.

HRMS (ESI) Exact mass calcd for C₂₆H₃₈ClO₂Si [M+H], 444.2251. Found 445.2321.



(5R,6R)-6-(((tert-butyldimethylsilyl)oxy)methyl)-5-((Z)-2-chloro-3-cyclopropylallyl)-2,6-dimethyl cyclohex-2-en-1-one (2.3f)

The title compound was prepared using General Procedure C (81% yield).

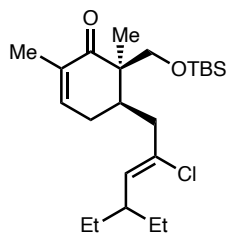
R_f (2.5 % EtOAc/hexanes, p-anisaldehyde) 0.65

[α]_D²⁵ = +0.13 (c = 0.081, CH₂Cl₂)

¹H NMR (700 MHz, CDCl₃) δ 6.60 – 6.50 (m, 1H), 4.83 (dd, *J* = 9.2, 1.3 Hz, 1H), 3.68 (d, *J* = 10.3 Hz, 1H), 3.59 (d, *J* = 10.2 Hz, 1H), 2.54 (ddd, *J* = 13.9, 3.3, 1.4 Hz, 1H), 2.39 (dtd, *J* = 18.0, 5.8, 3.2 Hz, 2H), 2.31 – 2.25 (m, 1H), 2.22 (dd, *J* = 13.8, 11.3 Hz, 1H), 1.77 (tt, *J* = 8.4, 4.0 Hz, 1H), 1.74 (q, *J* = 1.7 Hz, 3H), 1.17 (s, 3H), 0.86 (s, 9H), 0.81 – 0.78 (m, 2H), 0.39 (dd, *J* = 4.8, 2.0 Hz, 2H), 0.01 (s, 3H), -0.01 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 203.51, 142.80, 134.57, 131.65, 131.40, 66.02, 49.65, 39.42, 38.62, 27.41, 25.92, 20.05, 18.22, 16.41, 10.92, 6.92, 6.81, -5.54, -5.60.

HRMS (ESI) Exact mass calcd for C₂₁H₃₆ClO₂Si [M+H], 383.2168. Found 383.2165.



(5R,6R)-6-(((tert-butyldimethylsilyl)oxy)methyl)-5-((Z)-2-chloro-4-ethylhex-2-en-1-yl)-2,6-dimethyl cyclohex-2-en-1-one (2.3g)

The title compound was prepared using General Procedure C (86 % yield).

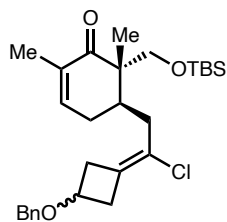
R_f (2.5 % EtOAc/hexanes, p-anisaldehyde) 0.75

[α]_D²⁵ = +6.21 (c = 0.07, CH₂Cl₂)

¹H NMR (600 MHz, CDCl₃) δ 6.58 (q, *J* = 4.0 Hz, 1H), 5.15 (dd, *J* = 9.5, 1.3 Hz, 1H), 3.70 (d, *J* = 10.2 Hz, 1H), 3.63 (d, *J* = 10.3 Hz, 1H), 2.59 (ddd, *J* = 13.6, 3.2, 1.4 Hz, 1H), 2.40 (dddd, *J* = 20.8, 9.5, 5.1, 2.3 Hz, 3H), 2.35 – 2.26 (m, 2H), 1.76 (t, *J* = 1.7 Hz, 3H), 1.50 – 1.40 (m, 4H), 1.19 (s, 3H), 0.87 (s, 9H), 0.87 – 0.85 (m, 6H), 0.02 (s, 3H), 0.00 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 203.47, 142.75, 134.64, 133.48, 132.53, 66.10, 49.68, 42.38, 39.79, 38.55, 28.16, 27.73, 27.71, 27.41, 20.07, 18.24, 16.43, 12.02, 11.80, -5.52, -5.58.

HRMS (ESI) Exact mass calcd for C₂₃H₄₂ClO₂Si [M+H], 413.2637. Found 413.2635.



(5*R*,6*S*)-5-(2-(3-(benzyloxy)cyclobutylidene)-2-chloroethyl)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethylcyclohex-2-en-1-one (2.3m):

The title compound was prepared according to General Procedure **D** (68 % yield). Product was isolated as a mixture of two diastereomers that were inseparable. Reported are the chemical shifts of the mixture of diastereomers.

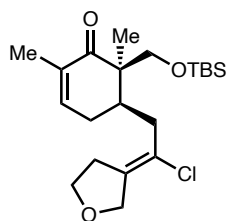
R_f (25 % EtOAc/hexanes, *p*-anisaldehyde) 0.45

[α]_D²⁵ = – 25.41 (*c* = 0.012, CH₂Cl₂)

¹H NMR (600 MHz, CDCl₃) δ 7.38 – 7.28 (m, 5H), 6.61 (ddt, *J* = 5.6, 2.8, 1.4 Hz, 1H), 4.49 – 4.43 (m, 2H), 4.15 – 4.08 (m, 2H), 3.36 (d, *J* = 9.8 Hz, 1H), 3.00 – 2.95 (m, 0H), 2.95 – 2.83 (m, 1H), 2.79 – 2.69 (m, 1H), 2.69 – 2.60 (m, 2H), 2.44 – 2.29 (m, 2H), 2.14 (ddd, *J* = 13.8, 11.4, 5.1 Hz, 1H), 1.98 (dddt, *J* = 19.2, 9.6, 7.0, 2.6 Hz, 1H), 1.76 (t, *J* = 2.0 Hz, 3H), 0.85 (s, 9H), 0.05 (d, *J* = 1.6 Hz, 3H), 0.03 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 202.19, 202.16, 142.83, 142.67, 137.95, 137.92, 134.86, 134.76, 129.28, 129.22, 128.63, 128.62, 128.05, 128.03, 127.99, 127.96, 125.35, 125.30, 70.72, 70.63, 68.18, 68.10, 64.85, 64.80, 50.36, 50.35, 38.74, 38.71, 37.91, 37.81, 34.97, 34.69, 34.45, 34.27, 27.00, 26.91, 25.97, 18.35, 16.60, 16.57, 14.50, 14.47, -5.41, -5.43, -5.47.

HRMS (ESI) Exact mass calcd for C₂₈H₄₂ClO₃Si [M+H], 489.25. Found 489.26.



(5R,6S)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-((*Z*)-2-chloro-2-(dihydrofuran-3(2H)-ylidene)ethyl)-2,6-dimethylcyclohex-2-en-1-one (2.3k):

The title compound was prepared using General Procedure **D**. Product was isolated as a mixture of two alkene isomers that were inseparable. Reported are the chemical shifts of the mixture of alkene isomers. (34 % yield).

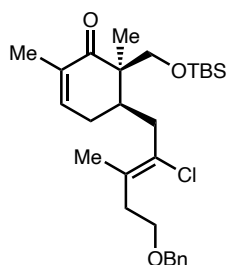
R_f (2.5 % EtOAc/hexanes, *p*-anisaldehyde) 0.55

[α]_D²⁵ = + 0.13 (*c* = 0.039, CH₂Cl₂)

¹H NMR (400 MHz, CDCl₃) δ 6.59 (s, 1H), 4.42 – 4.28 (m, 1H), 4.27 – 4.15 (m, 1H), 4.05 – 3.84 (m, 2H), 3.72 (dd, *J* = 10.3, 6.2 Hz, 1H), 3.65 – 3.54 (m, 1H), 2.65 (tt, *J* = 5.3, 2.0 Hz, 1H), 2.46 (q, *J* = 11.6 Hz, 5H), 2.27 (dd, *J* = 14.5, 11.9 Hz, 1H), 1.76 (p, *J* = 1.8 Hz, 3H), 1.19 (d, *J* = 3.4 Hz, 3H), 0.87 (s, 9H), 0.03 (d, *J* = 1.0 Hz, 3H), 0.00 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 203.47, 203.41, 142.58, 142.54, 137.70, 137.45, 134.71, 134.69, 123.51, 123.18, 71.40, 69.71, 69.56, 68.63, 66.07, 66.05, 49.71, 49.69, 38.81, 38.77, 36.65, 36.58, 33.19, 31.66, 27.39, 27.33, 25.92, 20.04, 20.03 – 20.00 (m), 18.23, 16.36, 16.34, -5.52, -5.57.

HRMS (ESI) Exact mass calcd for C₂₁H₃₆ClO₃Si [M+H], 399.2119. Found 399.2118.



(5R,6R)-5-((*Z*)-5-(benzyloxy)-2-chloro-3-methylpent-2-en-1-yl)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethylcyclohex-2-en-1-one (2.3o):

The title compound was prepared using General Procedure **D**. Product was isolated as a mixture of two alkene isomers that were inseparable. Reported are the chemical shifts of the mixture of alkene isomers (57 % yield).

R_f (2.5 % EtOAc/hexanes, *p*-anisaldehyde) 0.65

$[\alpha]_D^{25} = +1.25$ ($c = 0.034$, CH_2Cl_2)

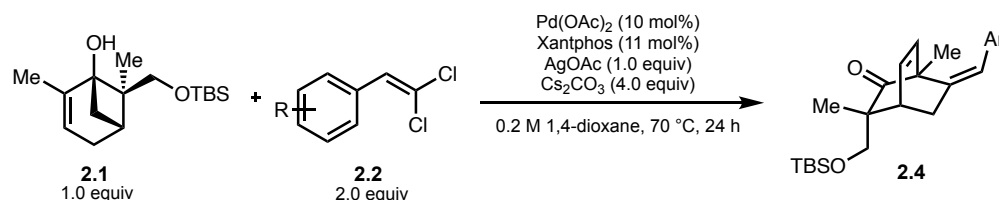
^1H NMR (700 MHz, CDCl_3) δ 7.36 – 7.27 (m, 5H), 6.54 – 6.49 (m, 1H), 4.53 (s, 2H), 4.48 (s, 2H), 3.72 (t, $J = 10.1$ Hz, 1H), 3.66 – 3.59 (m, 2H), 3.48 (td, $J = 6.7, 4.7$ Hz, 1H), 2.71 – 2.62 (m, 1H), 2.55 (dt, $J = 13.4, 6.9$ Hz, 1H), 2.49 – 2.23 (m, 5H), 1.86 (d, $J = 1.6$ Hz, 1H), 1.76 – 1.74 (m, 3H), 1.18 (s, 3H), 0.87 (s, 9H), 0.04 – 0.01 (m, 3H), 0.00 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 203.71, 143.11, 143.06, 138.65, 138.42, 134.43, 134.38, 130.52, 130.32, 129.68, 128.84, 128.52, 128.50, 127.74, 127.67, 73.15, 72.94, 68.16, 66.12, 65.99, 49.80, 49.76, 39.10, 36.11, 35.07, 34.84, 34.57, 27.13, 25.94, 20.33, 20.09, 20.04, 19.56, 18.25, 16.37, 16.35, -5.51, -5.58.

HRMS (ESI) Exact mass calcd for $\text{C}_{28}\text{H}_{44}\text{ClO}_3\text{Si}$ $[\text{M}+\text{H}]$, 491.2743. Found 491.2742.

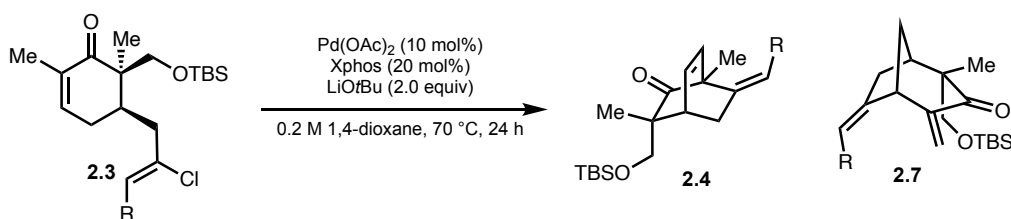
General Procedures for Bicyclo[2.2.2]octanone and Bicyclo[3.2.1]octanone Formation

General Procedure E:

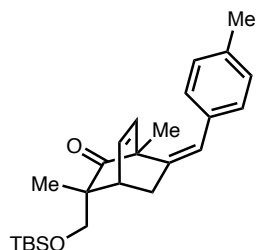


An oven-dried 4 mL vial is charged with **2.1** (1.0 equiv), **2.2** (2.0 equiv), $\text{Pd}(\text{OAc})_2$ (10 mol%) and Xantphos (11 mol%). Cesium carbonate (4.0 equiv) and silver acetate (1.0 equiv) were added with anhydrous 1,4-dioxane in the glovebox and the vial is sealed with a teflon cap. The reaction mixture is stirred at 70 °C for 24 h. The reaction mixture is filtered over celite with EtOAc and concentrated *in vacuo*. The product was isolated with column chromatography (2.5 % EtOAc in hexane).

General Procedure F:



An oven-dried 4 mL vial is charged with **2.3** (1.0 equiv) and $\text{Pd}(\text{OAc})_2$ (10 mol%). Xphos (20 mol%) and LiOtBu (2.0 equiv) were added with anhydrous 1,4-dioxane in the glovebox and the vial is sealed with a teflon cap. The reaction mixture is stirred at 70 °C for 24 h. The reaction mixture is filtered over celite with EtOAc and concentrated *in vacuo*. The product was isolated with column chromatography (2.5 % EtOAc in hexane).



(1*S*,3*R*,4*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,3-dimethyl-7-((*Z*)-4-methylbenzylidene)bicyclo[2.2.2]oct-5-en-2-one (2.4a):

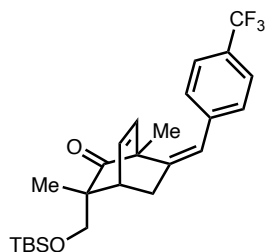
The title compound was prepared using General Procedure E (78 % yield).

¹H NMR (400 MHz, CDCl₃) δ 7.20 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 6.59 (dd, *J* = 7.8, 6.6 Hz, 1H), 6.31 (d, *J* = 2.5 Hz, 1H), 5.83 (dd, *J* = 7.8, 1.9 Hz, 1H), 3.38 (d, *J* = 10.1 Hz, 1H), 3.29 (d, *J* = 10.1 Hz, 1H), 3.04 (dd, *J* = 6.4, 2.7 Hz, 1H), 2.91 (dt, *J* = 16.9, 2.5 Hz, 1H), 2.50 – 2.35 (m, 1H), 2.33 (s, 3H), 1.44 (s, 3H), 1.17 (s, 3H), 0.84 (s, 9H), -0.05 (s, 3H), -0.11 (s, 3H) ppm.

¹³C NMR (126 MHz, CDCl₃) 212.22, 138.11, 137.09, 136.40, 132.01, 129.07, 128.56, 123.38, 66.75, 57.42, 49.22, 38.45, 31.29, 25.93, 21.29, 18.35, 15.12, 1.177, -5.51, -5.64 ppm.

HR-MS (m/z): ESI [*M*⁺] calculated for C₂₅H₃₆O₂Si: 396.25, found for C₂₅H₃₆O₂SiNa: 419.2377.

IR (neat): ν_{max} 2955, 2929, 2856, 1718, 1096, 819, 668 cm⁻¹.



(1*S*,3*R*,4*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,3-dimethyl-7-((*Z*)-4-(trifluoromethyl)benzylidene)bicyclo[2.2.2]oct-5-en-2-one (2.4b):

The title compound was prepared using General Procedure E (64 % yield).

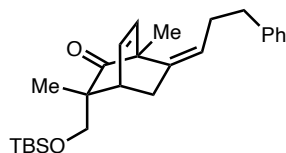
¹H NMR (500 MHz, CDCl₃) δ 7.57 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 6.62 (dd, *J* = 7.8, 6.6 Hz, 1H), 6.37 (d, *J* = 2.5 Hz, 1H), 5.84 (dd, *J* = 7.9, 1.9 Hz, 1H), 3.38 (d, *J* = 10.1 Hz, 1H), 3.25 (d, *J* = 10.1 Hz, 1H), 3.05 (dd, *J* = 6.5, 2.7 Hz, 1H), 2.90 (dt, *J* = 17.1, 2.6 Hz, 1H), 2.48 (dt, *J* = 16.9, 2.9 Hz, 1H), 1.46 (s, 3H), 1.17 (s, 3H), 0.81 (s, 9H), -0.07 (s, 3H), -0.15 (s, 3H) ppm.

¹³C NMR (126 MHz, CDCl₃) 211.57, 138.40, 131.75, 128.74, 125.30, 125.27, 122.21, 66.88, 57.76, 49.12, 38.50, 31.54, 25.86, 23.20, 18.34, 15.02, -5.55, -5.77 ppm.

¹⁹F NMR (500 MHz, CDCl₃) δ -62.47 ppm.

HR-MS (m/z): ESI [M^+] calculated for $C_{25}H_{33}F_3O_2Si$: 450.22, found: 450.2202.

IR (neat): $\nu_{\max}$ 2954, 2930, 2858, 1720, 1615, 1326, 1126, 836, 668 cm^{-1} .



(1S,3R,4S,Z)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,3-dimethyl-7-(3-phenylpropylidene)bicyclo[2.2.2]oct-5-en-2-one (2.42):

The title compound was prepared using General Procedure F (53 % yield).

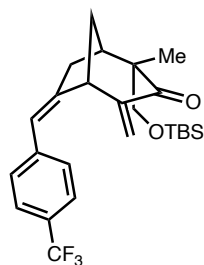
R_f (2.5 % EtOAc/hexanes, p-anisaldehyde) 0.75

[α]_D²⁵ = +6.85 (C = 0.02, CH_2Cl_2)

¹H NMR (600 MHz, $CDCl_3$) δ 7.28 (s, 2H), 7.17 (dd, J = 21.6, 7.4 Hz, 3H), 6.50 (t, J = 7.2 Hz, 1H), 5.77 – 5.70 (m, 1H), 5.36 (d, J = 7.1 Hz, 1H), 3.39 (d, J = 10.0 Hz, 1H), 3.29 (d, J = 10.1 Hz, 1H), 2.94 (d, J = 6.4 Hz, 1H), 2.64 (t, J = 7.2 Hz, 2H), 2.58 (d, J = 16.4 Hz, 1H), 2.28 (d, J = 8.3 Hz, 2H), 2.04 (d, J = 16.6 Hz, 1H), 1.28 (s, 3H), 1.15 (s, 3H), 0.91 – 0.85 (m, 9H), 0.03 (s, 3H), 0.02 (s, 3H) ppm.

¹³C NMR (151 MHz, $CDCl_3$) 212.9, 142.1, 137.9, 135.8, 132.0, 129.1, 128.6, 128.5, 128.5, 126.0, 122.7, 66.6, 56.6, 49.5, 38.0, 35.7, 31.5, 29.9, 28.7, 26.0, 25.9, 23.2, 18.4, 14.6, 1.2, -5.4 ppm.

HRMS (ESI) Exact mass calcd for $C_{26}H_{38}O_2SiNa$ [$M+Na$], 433.2539. Found 433.2532.



(1R,2S,5S)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methyl-4-methylene-6-((Z)-4-(trifluoromethyl)benzylidene)bicyclo[3.2.1]octan-3-one (2.7b):

The title compound was obtained as a minor product in reactions using General Procedure E.

¹H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 6.40 (s, 1H), 5.66 (d, J = 1.5 Hz, 1H), 5.02 (d, J = 1.5 Hz, 1H), 3.87 (d, J = 4.7 Hz, 1H), 3.79 (s, 2H), 2.84 – 2.76 (m, 1H), 2.62 (ddd, J = 17.8, 6.7, 2.7 Hz, 1H), 2.49 (ddd, J = 6.5, 4.7, 1.7 Hz, 1H), 2.18 (dd,

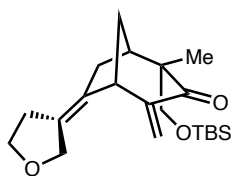
$J = 12.1, 2.9$ Hz, 1H), 1.94 (dt, $J = 12.1, 4.8$ Hz, 1H), 1.21 (s, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm.

^{13}C NMR (126 MHz, CDCl_3) 205.46, 147.72, 147.13, 141.57, 128.51, 125.25, 125.22, 125.19, 123.52, 117.96, 65.77, 53.45, 46.39, 39.77, 36.21, 35.51, 25.98, 23.29, 18.35, -5.39, -5.42 ppm.

^{19}F NMR (500 MHz, CDCl_3) δ -62.40 ppm.

HR-MS (m/z): ESI [M^+] calculated for $\text{C}_{25}\text{H}_{33}\text{F}_3\text{O}_2\text{Si}$: 450.22, found: 450.2197.

IR (neat): ν_{max} 2954, 2929, 2856, 1718, 1615, 1324, 1187, 1109, 1068, 1029, 836, 777 cm^{-1} .



(1*R*,2*S*,5*S*,*Z*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-(dihydrofuran-3(2*H*)-ylidene)-2-methyl-4-methylenebicyclo[3.2.1]octan-3-one (2.7k):

The title compound was prepared using General Procedure **F** (66 % yield).

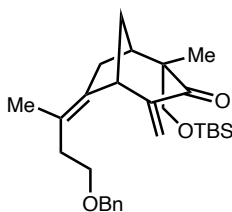
R_f (2.5 % EtOAc/hexanes, *p*-anisaldehyde) 0.60

$[\alpha]_D^{25}$ = -13.0 ($C = 0.002$, CH_2Cl_2)

^1H NMR (500 MHz, CDCl_3) δ 5.69 (d, $J = 1.8$ Hz, 1H), 5.00 (d, $J = 1.8$ Hz, 1H), 4.14 (q, $J = 13.0$ Hz, 2H), 3.88 (ddt, $J = 31.4, 8.5, 6.9$ Hz, 2H), 3.73 (d, $J = 10.2$ Hz, 1H), 3.64 (d, $J = 10.2$ Hz, 1H), 3.35 (d, $J = 4.9$ Hz, 1H), 2.49 – 2.44 (m, 1H), 2.40 – 2.33 (m, 3H), 2.21 (ddd, $J = 14.1, 6.5, 3.5$ Hz, 1H), 2.08 (dd, $J = 12.1, 2.6$ Hz, 1H), 1.87 (dt, $J = 12.2, 4.9$ Hz, 1H), 1.20 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 205.01, 132.24, 130.19, 116.47, 70.10, 68.83, 65.69, 53.14, 47.70, 41.34, 34.42, 32.50, 30.03, 25.83, 23.41, 18.21, -5.57.

HRMS (ESI) Exact mass calcd for $\text{C}_{21}\text{H}_{35}\text{O}_3\text{Si}$ [$\text{M}+\text{H}$], 363.2350. Found 363.2356.



(1*R*,2*S*,5*S*,*Z*)-6-(4-(benzyloxy)butan-2-ylidene)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methyl-4-methylenebicyclo[3.2.1]octan-3-one (2.7o):

The title compound was prepared using General Procedure F (54 % yield).

R_f (2.5 % EtOAc/hexanes, *p*-anisaldehyde) 0.60

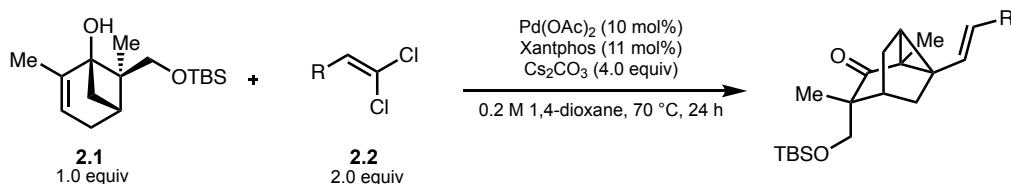
[α]_D²⁵ = −15.0 (*c* = 0.0012, CH₂Cl₂)

¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.29 (m, 5H), 5.58 (d, *J* = 1.7 Hz, 1H), 5.01 (d, *J* = 1.7 Hz, 1H), 4.49 (s, 2H), 3.74 (d, *J* = 10.2 Hz, 1H), 3.69 (d, *J* = 10.0 Hz, 1H), 3.50 – 3.43 (m, 2H), 2.49 (d, *J* = 17.4 Hz, 1H), 2.43 (t, *J* = 6.2 Hz, 1H), 2.28 (dd, *J* = 13.9, 6.5 Hz, 2H), 2.06 (dd, *J* = 12.0, 2.7 Hz, 1H), 1.85 – 1.80 (m, 1H), 1.74 (d, *J* = 3.5 Hz, 1H), 1.68 (dd, *J* = 15.2, 2.8 Hz, 1H), 1.59 (d, *J* = 1.5 Hz, 3H), 1.18 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

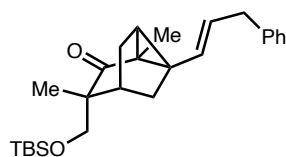
¹³C NMR (151 MHz, CDCl₃) δ 205.98, 148.54, 136.93, 128.51, 127.74, 127.67, 126.04, 116.30, 73.03, 68.57, 65.77, 53.36, 46.33, 40.75, 35.54, 34.79, 32.64, 25.99, 23.44, 19.35, 18.36, −5.40, −5.43.

HRMS (ESI) Exact mass calcd for C₂₈H₄₃O₃Si [M+H], 455.2976. Found 455.2974.

General Procedure for Tricyclo[3.2.1.0]octane Formation



An oven-dried, 4 mL vial equipped with a stir bar was charged sequentially with **2.1** (1 equiv), **2.2** (2.0 equiv), Pd(OAc)₂ (10 mol%), and xantphos (11 mol%), and then taken into an N₂-filled glovebox. Cs₂CO₃ (4 equiv) was added, followed by degassed and anhydrous 1,4-dioxane (0.2 M) to give an orange-yellow heterogeneous mixture. The vial was fitted with a PTFE lined screw cap, sealed with Teflon tape, removed from the glovebox, and placed on a block plate at 70 °C. After 24 h, the mixture was filtered over a plug of Celite®, flushed with EtOAc (10 mL), and concentrated *in vacuo*. The crude residue was purified by preparative TLC (pTLC) or flash column chromatography to afford the desired products.



(*E*)-4-(((*Tert*-butyldimethylsilyl)oxy)methyl)-2,4-dimethyl-1-(3-phenylprop-1-en-1-yl)tricyclo[3.2.1.0^{2,7}]octan-3-one (2.42):

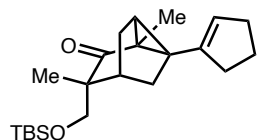
The title compound was prepared in 59 % yield.

$[\alpha]_D^{25} = +6.85$ ($c = 0.02$, CH_2Cl_2)

¹H NMR (600 MHz, CDCl_3) δ 7.30 (dd, $J = 8.2, 6.9$ Hz, 2H), 7.24 – 7.15 (m, 3H), 5.76 (dt, $J = 15.4, 6.8$ Hz, 1H), 5.67 – 5.60 (m, 1H), 3.60 (d, $J = 9.9$ Hz, 1H), 3.46 (d, $J = 9.9$ Hz, 1H), 3.42 – 3.39 (m, 2H), 2.17 (t, $J = 5.1$ Hz, 1H), 2.07 (d, $J = 12.6$ Hz, 1H), 1.97 (d, $J = 12.6$ Hz, 1H), 1.84 (ddd, $J = 12.6, 10.4, 5.2$ Hz, 2H), 1.69 (d, $J = 2.9$ Hz, 1H), 1.15 (s, 3H), 1.03 (s, 3H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H).

¹³C NMR (151 MHz, CDCl_3) δ 213.08, 140.53, 130.96, 129.57, 128.70, 128.60, 126.26, 65.54, 49.33, 40.38, 39.77, 39.43, 36.82, 34.79, 31.35, 28.42, 25.97, 19.76, 18.34, 13.83, -5.38 (d, $J = 2.1$ Hz).

HRMS (ESI) Exact mass calcd for $\text{C}_{26}\text{H}_{38}\text{O}_2\text{NaSi}$ $[\text{M}+\text{Na}]^+$, 433.2539. Found 433.2533.



4-(((*Tert*-butyldimethylsilyl)oxy)methyl)-1-(cyclopent-1-en-1-yl)-2,4-dimethyltricyclo[3.2.1.0^{2,7}]octan-3-one (2.46):

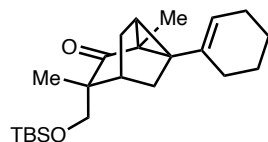
The title compound was prepared in 69 % yield.

$[\alpha]_D^{25} = +34.3$ ($c = 0.010$, CHCl_3)

¹H NMR (500 MHz, CDCl_3) δ 5.49 – 5.44 (m, 1H), 3.62 (d, $J = 9.9$ Hz, 1H), 3.47 (d, $J = 9.9$ Hz, 1H), 2.41 – 2.30 (m, 3H), 2.22 – 2.11 (m, 3H), 1.96 (t, $J = 11.0$ Hz, 1H), 1.90 – 1.81 (m, 3H), 1.78 – 1.74 (m, 1H), 1.70 (dd, $J = 12.6, 5.1$ Hz, 1H), 1.03 (s, 3H), 1.01 (s, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H).

¹³C NMR (126 MHz, CDCl_3) δ 213.66, 141.72, 127.74, 65.63, 49.47, 40.32, 38.73, 35.15, 35.12, 35.02, 32.74, 32.44, 28.38, 25.99, 23.67, 19.69, 18.39, 13.00, -5.38, -5.39.

HRMS (ESI) Exact mass calcd for $\text{C}_{22}\text{H}_{36}\text{O}_2\text{NaSi}$ $[\text{M}+\text{Na}]^+$, 383.2377. Found 383.2381.



4-(((*Tert*-butyldimethylsilyl)oxy)methyl)-1-(cyclohex-1-en-1-yl)-2,4-dimethyltricyclo[3.2.1.0^{2,7}]octan-3-one (2.47):

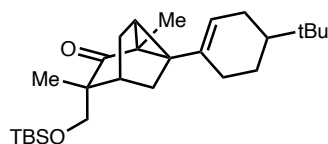
The title compound was prepared in 31 % yield.

$[\alpha]_D^{25} = +79.0$ ($c = 0.0060$, CHCl_3)

^1H NMR (500 MHz, CDCl_3) δ 5.56 (tt, $J = 3.6, 1.7$ Hz, 1H), 3.60 (d, $J = 9.9$ Hz, 1H), 3.46 (d, $J = 9.9$ Hz, 1H), 2.19 – 2.13 (m, 2H), 2.12 – 2.00 (m, 3H), 1.96 (d, $J = 12.5$ Hz, 1H), 1.85 – 1.76 (m, 2H), 1.76 – 1.73 (m, 1H), 1.68 – 1.62 (m, 2H), 1.56 (q, $J = 4.4, 2.4$ Hz, 3H), 1.03 (s, 3H), 1.01 (s, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 213.86, 135.18, 124.90, 65.61, 49.38, 46.13, 38.26, 35.17, 34.16, 32.94, 28.62, 28.37, 25.99, 25.31, 22.95, 22.58, 19.61, 18.39, 12.77, -5.37, -5.39.

HRMS (ESI) Exact mass calcd for $\text{C}_{23}\text{H}_{38}\text{O}_2\text{NaSi}$ $[\text{M}+\text{Na}]^+$, 397.2533. Found 397.2538.



1-(4-(*Tert*-butyl)cyclohex-1-en-1-yl)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,4-dimethyltricyclo[3.2.1.0^{2,7}]octan-3-one (2.48):

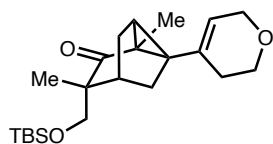
The title compound was prepared in 53 % yield (1:1 dr).

$[\alpha]_D^{25} = +26.0$ ($c = 0.0039$, CHCl_3)

^1H NMR (500 MHz, CDCl_3) δ 5.60 – 5.52 (m, 1H), 3.61 (d, $J = 10.0$ Hz, 1H), 3.46 (d, $J = 9.9$ Hz, 1H), 2.19 – 2.11 (m, 3H), 2.05 (dtd, $J = 17.8, 4.2, 3.4, 1.7$ Hz, 1H), 1.96 (dd, $J = 12.5, 2.5$ Hz, 1H), 1.91 – 1.75 (m, 6H), 1.75 – 1.72 (m, 1H), 1.64 (dd, $J = 12.6, 5.1$ Hz, 1H), 1.03 (s, 3H), 1.02 (s, 1.5H), 0.99 (s, 1.5H), 0.87 (s, 9H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 213.85, 135.16, 134.87, 125.35, 125.01, 65.64, 49.40, 49.37, 45.95, 45.32, 44.36, 44.21, 38.42, 38.14, 35.26, 35.17, 34.37, 34.23, 33.17, 32.88, 32.37, 32.35, 30.48, 29.49, 28.40, 28.38, 27.37, 27.35, 26.98, 26.89, 25.99, 24.33, 24.32, 19.62, 19.61, 18.40, 12.86, 12.82, -5.37, -5.40.

HRMS (ESI) Exact mass calcd for $\text{C}_{27}\text{H}_{46}\text{O}_2\text{NaSi}$ $[\text{M}+\text{Na}]^+$, 453.3159. Found 453.3161.



4-(((*Tert*-butyldimethylsilyl)oxy)methyl)-1-(3,6-dihydro-2H-pyran-4-yl)-2,4-dimethyltricyclo[3.2.1.0^{2,7}]octan-3-one (2.49):

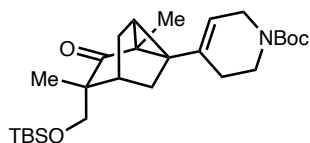
The title compound was prepared in 35 % yield.

$[\alpha]_D^{25} = +45.8$ ($c = 0.0078$, CHCl_3)

¹H NMR (500 MHz, CDCl_3) δ 5.55 (q, $J = 2.3$ Hz, 1H), 4.12 (q, $J = 2.7$ Hz, 2H), 3.79 (dt, $J = 10.6, 5.2$ Hz, 1H), 3.69 (ddd, $J = 11.4, 7.0, 4.5$ Hz, 1H), 3.57 (d, $J = 10.0$ Hz, 1H), 3.43 (d, $J = 10.0$ Hz, 1H), 2.26 – 2.12 (m, 3H), 1.99 – 1.85 (m, 2H), 1.81 (ddd, $J = 12.5, 5.3, 2.8$ Hz, 1H), 1.76 – 1.71 (m, 1H), 1.65 (dd, $J = 12.6, 5.1$ Hz, 1H), 1.00 (d, $J = 2.1$ Hz, 6H), 0.84 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H).

¹³C NMR (126 MHz, CDCl_3) δ 213.22, 133.26, 123.52, 65.58, 65.32, 64.24, 49.31, 44.71, 38.08, 35.13, 33.63, 32.47, 28.59, 28.21, 25.85, 19.50, 18.26, 12.80, -5.52.

HRMS (ESI) Exact mass calcd for $\text{C}_{22}\text{H}_{36}\text{O}_3\text{NaSi}$ $[\text{M}+\text{H}]^+$, 399.2326. Found 399.2330.



***Tert*-butyl 4-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,4-dimethyl-3-oxotricyclo[3.2.1.0^{2,7}]octan-1-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (2.50):**

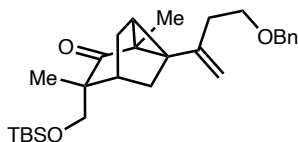
The title compound was prepared in 42 % yield.

$[\alpha]_D^{25} = +44.9$ ($c = 0.010$, CHCl_3)

¹H NMR (500 MHz, CDCl_3) δ 5.52 (s, 1H), 4.00 – 3.91 (m, 1H), 3.83 (dd, $J = 18.5, 3.2$ Hz, 1H), 3.68 – 3.63 (m, 1H), 3.60 (d, $J = 10.0$ Hz, 1H), 3.46 (d, $J = 10.0$ Hz, 1H), 3.32 (ddd, $J = 12.7, 7.6, 4.6$ Hz, 1H), 2.27 – 2.14 (m, 3H), 2.00 – 1.89 (m, 2H), 1.84 (ddd, $J = 12.5, 5.1, 2.8$ Hz, 1H), 1.78 – 1.74 (m, 1H), 1.66 (dd, $J = 12.6, 5.1$ Hz, 1H), 1.46 (s, 9H), 1.03 (s, 3H), 1.00 (s, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

¹³C NMR (126 MHz, CDCl_3) δ 213.21, 154.96, 79.67, 65.55, 49.30, 44.92, 38.05, 35.14, 33.95, 32.58, 28.47, 28.23, 25.84, 25.59, 19.47, 18.25, 12.84, -5.52.

HRMS (ESI) Exact mass calcd for $\text{C}_{27}\text{H}_{45}\text{O}_4\text{NNaSi}$ $[\text{M}+\text{Na}]^+$, 498.3010. Found 498.3018.



1-(4-(benzyloxy)but-1-en-2-yl)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,4-dimethyltricyclo[3.2.1.0^{2,7}]octan-3-one (2.70):

The title compound was prepared using General Procedure F (42 % yield).

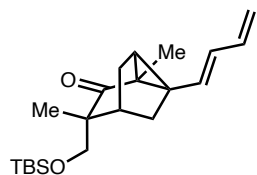
R_f (2.5 % EtOAc/hexanes, p-anisaldehyde) 0.55

[α]_D²⁵ = +1.5 (c = 0.002, CH₂Cl₂)

¹H NMR (600 MHz, CDCl₃) δ 7.36 – 7.27 (m, 5H), 5.02 (d, *J* = 1.5 Hz, 1H), 4.93 (dt, *J* = 1.5, 0.8 Hz, 1H), 4.50 (s, 2H), 3.60 (d, *J* = 10.0 Hz, 1H), 3.57 (ddd, *J* = 7.6, 6.5, 2.2 Hz, 2H), 3.46 (d, *J* = 10.0 Hz, 1H), 2.45 (dt, *J* = 14.7, 7.2 Hz, 1H), 2.40 – 2.30 (m, 1H), 2.20 – 2.14 (m, 2H), 1.97 (d, *J* = 12.6 Hz, 1H), 1.83 (ddd, *J* = 12.6, 5.3, 3.0 Hz, 1H), 1.77 – 1.74 (m, 1H), 1.71 (dd, *J* = 12.7, 5.2 Hz, 1H), 1.07 – 1.02 (m, 3H), 1.01 (s, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 213.20, 143.42, 138.43, 128.54, 127.89, 127.76, 114.15, 73.22, 68.73, 65.50, 49.50, 45.24, 38.42, 35.90, 35.14, 34.24, 33.43, 28.26, 25.99, 19.64, 18.40, 13.23, -5.36.

HRMS (ESI) Exact mass calcd for C₂₈H₄₃O₃Si [M+H], 455.2976. Found 455.2974.



(*E*)-1-(buta-1,3-dien-1-yl)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,4-dimethyltricyclo[3.2.1.0^{2,7}] octan-3-one (2.59):

The title compound was prepared in 66 % yield.

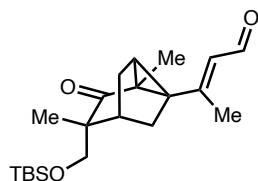
R_f (2.5 % EtOAc/hexanes, p-anisaldehyde) 0.55

[α]_D²⁵ = +21.3 (c = 0.0071, CH₂Cl₂)

¹H NMR (600 MHz, CDCl₃) δ 6.41 – 6.31 (m, 1H), 6.26 – 6.18 (m, 1H), 5.79 (d, *J* = 15.3 Hz, 1H), 5.17 (ddd, *J* = 16.9, 1.7, 0.8 Hz, 1H), 5.05 – 4.99 (m, 1H), 3.61 (d, *J* = 10.0 Hz, 1H), 3.48 (d, *J* = 10.0 Hz, 1H), 2.20 (t, *J* = 5.1 Hz, 1H), 2.11 (d, *J* = 12.6 Hz, 1H), 2.00 (s, 1H), 1.91 (dd, *J* = 12.6, 5.2 Hz, 1H), 1.86 – 1.80 (m, 1H), 1.75 (d, *J* = 3.0 Hz, 1H), 1.17 (s, 3H), 1.04 (s, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 212.60, 136.95, 132.70, 115.97, 65.53, 49.36, 40.59, 40.49, 37.49, 34.73, 30.84, 28.44, 25.98, 19.76, 18.35, 13.88, -5.37, -5.39.

HRMS (ESI) Exact mass calcd for C₂₁H₃₅O₂Si [M+H], 347.2401. Found 347.2399.



(E)-3-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,4-dimethyl-3-oxotricyclo[3.2.1.0^{2,7}]octan-1-yl)but-2-enal (2.61):

The title compound was prepared in 18 % yield.

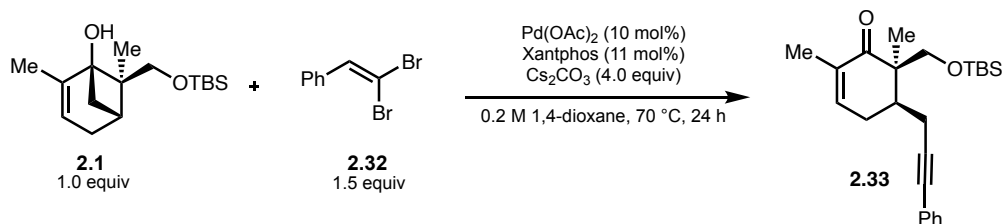
R_f (2.5 % EtOAc/hexanes, *p*-anisaldehyde) 0.55

[α]_D²⁵ = +7.00 (*c* = 0.1, CH₂Cl₂)

¹H NMR (600 MHz, CDCl₃) δ 10.06 (d, *J* = 7.9 Hz, 1H), 5.95 (dq, *J* = 8.0, 1.3 Hz, 1H), 3.66 (d, *J* = 10.0 Hz, 1H), 3.50 (d, *J* = 10.0 Hz, 1H), 2.34 (d, *J* = 12.5 Hz, 1H), 2.24 (t, *J* = 5.1 Hz, 1H), 2.21 (d, *J* = 1.3 Hz, 3H), 2.05 – 2.00 (m, 2H), 1.90 (ddd, *J* = 12.5, 5.1, 2.9 Hz, 1H), 1.76 (dd, *J* = 12.5, 5.1 Hz, 1H), 1.06 – 1.04 (m, 3H), 1.03 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 212.16, 191.26, 159.67, 129.29, 66.01, 49.69, 47.25, 38.44, 35.49, 34.32, 32.52, 28.40, 25.98, 19.64, 18.42, 17.84, 12.98, -5.39.

HRMS (ESI) Exact mass calcd for C₂₁H₃₅O₃Si [M+H], 363.2350. Found 363.2349.



(5*R*,6*R*)-6-(((*Tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethyl-5-(3-phenylprop-2-yn-1-yl)cyclohex-2-en-1-one (2.33):

An oven-dried, 1 dram vial equipped with a stir bar was charged sequentially with **11** (14 mg, 0.050 mmol, 1 equiv), **17** (20 mg, 0.015 mmol, 1.5 equiv), Pd(OAc)₂ (1.1 mg, 5 μmol, 10 mol%), and xantphos (3.2 mg, 5.5 μmol, 11 mol%), and then taken into an N₂-filled glovebox. Cs₂CO₃ (33 mg, 0.010 mmol, 2 equiv) was added, followed by solvent (0.25 mL, 0.2 M) to give an orange-yellow heterogeneous mixture. The vial was fitted with a PTFE lined screw cap, sealed with Teflon tape, removed from the glovebox, and placed on a block plate at 70 °C. After 24 h, the mixture was filtered over a plug of Celite®, flushed with EtOAc (10 mL), and concentrated *in vacuo*. The crude residue was purified by preparative TLC (pTLC) or flash column chromatography to afford **XX** as a yellow oil (6.4 mg, 33 % yield).

$[\alpha]_{\text{D}}^{25} = +23.8$ ($c = 0.0050$)

^1H NMR (500 MHz, CDCl_3) δ 7.42 – 7.35 (m, 2H), 7.30 – 7.27 (m, 3H), 6.69 – 6.63 (m, 1H), 3.75 (d, $J = 10.3$ Hz, 1H), 3.66 (d, $J = 10.3$ Hz, 1H), 2.74 – 2.57 (m, 3H), 2.47 (dd, $J = 10.8, 6.1$ Hz, 1H), 2.37 – 2.26 (m, 1H), 1.76 (d, $J = 1.7$ Hz, 3H), 1.21 (s, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 203.07, 142.83, 134.58, 131.65, 128.36, 127.82, 123.92, 89.16, 82.27, 65.90, 49.84, 41.14, 29.86, 28.71, 25.93, 20.70, 20.22, 18.26, 16.43, -5.53, -5.55.

HRMS (ESI) Exact mass calcd for $\text{C}_{24}\text{H}_{35}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$, 383.2401. Found 383.2399.

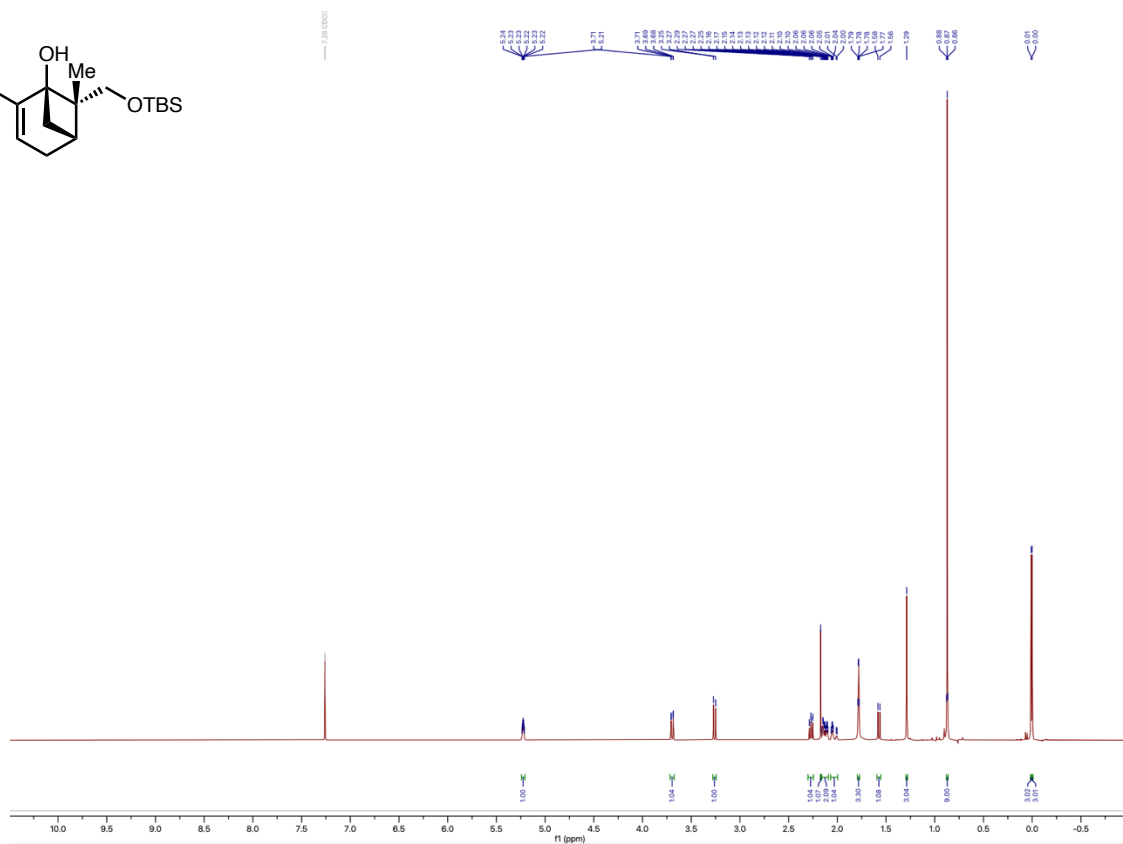
2.11 References

1. Cagan, D. A.; Péter, Á.; Vokits, B.; Chan, M.; Baran, P. S.; Blackmond, D. G. Decoding the Nested, Multicycle Mechanism of Ni-Catalyzed Redox-Neutral Cross-Coupling through Temperature Scanning Reaction Calorimetry. *J. Am. Chem. Soc.* **2026**, *148*, 677–691.
2. Takahashi, Y.; Yoshimura, F.; Tanino, K.; Miyashita, M. Total Synthesis of Zoanthanol. *Angew. Chem., Int. Ed.* **2009**, *48*, 8905–8908.
3. Abad, A.; Agulló, C.; Arnó, M.; Cunat, A. C.; Meseguer, B.; Zaragoza, R. J. An Efficient Stereoselective Synthesis of Stypodiol and Epistypodiol. *J. Org. Chem.* **1998**, *63*, 5100–5106.
4. (a) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. Ligand Bite Angle Effects in Metal-Catalyzed C–C Bond Formation. *Chem. Rev.* **2000**, *100*, 2741–2769. (b) Jover, J.; Cirera, J. Computational Assessment on the Tolman Cone Angles for P-Ligands. *Dalton Trans.* **2019**, *48*, 15036–15048. (c) Dierkes, P.; van Leeuwen, P. W. N. M. The Bite Angle Makes the Difference: A Practical Ligand Parameter for Diphosphine Ligands. *J. Chem. Soc., Dalton Trans.* **1999**, 1519–1530.
5. Adams, G. M.; Weller, A. S. POP-Type Ligands: Variable Coordination and Hemilabile Behaviour. *Coord. Chem. Rev.* **2018**, *355*, 150–172.
6. (a) Amatore, C.; Jutand, A.; M'Barki, M. Evidence of the Formation of Zerovalent Palladium from Pd(OAc)₂ and Triphenylphosphine. *Organometallics* **1992**, *11*, 3009–3013. (b) Amatore, C.; Jutand, A.; Thuilliez, A. Formation of Palladium(0) Complexes from Pd(OAc)₂ and a Bidentate Phosphine Ligand (dppp) and Their Reactivity in Oxidative Addition. *Organometallics* **2001**, *20*, 3241–3249.
7. (a) Ju, Y.; Plata, R. E.; Regens, C. S.; Hay, M.; Schmidt, M.; Razler, T.; Qiu, Y.; Geng, P.; Hsiao, Y.; Rosner, T.; Eastgate, M. D.; Blackmond, D. G. Mono-Oxidation of Bidentate Bis-phosphines in Catalyst Activation: Kinetic and Mechanistic Studies of a Pd/Xantphos-Catalyzed C–H Functionalization. *J. Am. Chem. Soc.* **2015**, *137*, 13272–13281. (b) Yang, S.; Deng, M.; Daley, R. A.; Darù, A.; Wolf, W. J.; George, D. T.; Ma, S.; Werley, B. K.; Samolova, E.; Bailey, J. B.; Gembicky, M.; Marshall, J.; Wisniewski, S. R.; Blackmond, D. G.; Engle, K. M. Palladium Bisphosphine Monoxide Complexes: Synthesis, Scope, Mechanism, and Catalytic Relevance. *J. Am. Chem. Soc.* **2025**, *147*, 409–425.
8. (a) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. Design and Preparation of New Palladium Precatalysts for C–C and C–N Cross-Coupling Reactions. *Chem. Sci.* **2013**, *4*, 916–920. (b) Ingoglia, B. T.; Buchwald, S. L. Oxidative Addition Complexes as Precatalysts for Cross-Coupling Reactions Requiring Extremely Bulky Biarylphosphine Ligands. *Org. Lett.* **2017**, *19*, 2853–2856. (c) Bruno, N. C.; Niljianskul, N.; Buchwald, S. L. N-Substituted 2-Aminobiphenylpalladium Methanesulfonate Precatalysts and Their Use in C–C and C–N Cross-Couplings. *J. Org. Chem.* **2014**, *79*, 4161–4166. (d) Kinzel, T.; Zhang, Y.; Buchwald, S. L. A New Palladium Precatalyst Allows for the Fast Suzuki–Miyaura

- Coupling Reactions of Unstable Polyfluorophenyl and 2-Heteroaryl Boronic Acids. *J. Am. Chem. Soc.* **2010**, *132*, 14073–14075. (e) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. A New Class of Easily Activated Palladium Precatalysts for Facile C–N Cross-Coupling Reactions and the Low Temperature Oxidative Addition of Aryl Chlorides. *J. Am. Chem. Soc.* **2008**, *130*, 6686–6687.
9. Dong, Y.; Lu, G.; Wang, J.; Liu, P.; Dong, G. Modular Ipso/Ortho Difunctionalization of Aryl Bromides via Palladium/Norbornene Cooperative Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 8551–8562.
 10. Ohshima, T.; Miyamoto, Y.; Ipposhi, J.; Nakahara, Y.; Utsunomiya, M.; Mashima, K. Platinum-Catalyzed Direct Amination of Allylic Alcohols under Mild Conditions: Ligand and Microwave Effects, Substrate Scope, and Mechanistic Study. *J. Am. Chem. Soc.* **2009**, *131*, 14317–14328.
 11. (a) Basolo, F.; Pearson, R. G. *Mechanism of Inorganic Reactions*; John Wiley: New York, 1967. (b) Wilkins, R. G. *Kinetics and Mechanism of Reactions of Transition Metal Complexes*, 2nd ed.; VCH: Weinheim, 1991.
 12. (a) Overman, L. E. *Organic Reactions*; Vol. 60; John Wiley & Sons: Hoboken, NJ, 2010. (b) Dounay, A. B.; Overman, L. E. The Asymmetric Intramolecular Heck Reaction in Natural Product Total Synthesis. *Chem. Rev.* **2003**, *103*, 2945–2963.
 13. Newman-Stonebreaker, S. H.; Smith, S. R.; Borowski, J. E.; Peters, E.; Gensch, T.; Johnson, H. C.; Sigman, M. S.; Doyle, A. G. Univariate Classification of Phosphine Ligation State and Reactivity in Cross-Coupling Catalysis. *Science* **2021**, *374*, 301–308.
 14. Ackermann, L.; Kornhaass, C.; Zhu, Y. Palladium-Catalyzed Direct C–H Bond Alkynylations of Heteroarenes Using gem-Dichloroalkenes. *Org. Lett.* **2012**, *14*, 1824–1826.
 15. Satavolum, N. S. R.; Peinetti, A. S.; Wang, Y.; Ali, A. S.; Lin, J. W.; Lu, Y. Silver-Assisted Synthesis of High-Indexed Palladium Tetrahedral Nanoparticles and Their Morphological Variants. *Chem. Mater.* **2019**, *31*, 2923–2929.
 16. (a) Friestad, G. K.; Branchaud, B. P. Intramolecular Pd-Catalyzed Aryl-Enone Conjugate Additions: Control of Reductive vs Non-Reductive Cyclization. *Tetrahedron Lett.* **1995**, *36*, 7047–7050. (b) Hirai, G.; Koizumi, Y.; Moharram, S. M.; Oguri, H.; Hirma, M. Construction of the Benzylic Quaternary Carbon Center of Zoanthanol by Intramolecular Mizoroki–Heck Reaction of Enone. *Org. Lett.* **2002**, *4*, 1627–1630. (c) Lautens, M.; Fang, Y.-Q. Synthesis of Novel Tetracycles via an Intramolecular Heck Reaction with anti-Hydride Elimination. *Org. Lett.* **2003**, *5*, 3679–3682. (d) Fürstner, A.; Ackerstaff, J. Formal Total Synthesis of (–)-Haouamine A. *Chem. Commun.* **2008**, 2870–2872.
 17. Xi, Y.; Su, B.; Qi, X.; Pedram, S.; Liu, P.; Hartwig, J. F. Application of Trimethylgermyl-Substituted Bisphosphine Ligands with Enhanced Dispersion Interactions to Copper-Catalyzed Hydroboration of Disubstituted Alkenes. *J. Am. Chem. Soc.* **2020**, *142*, 18213–18222.

18. Cadge, J. A.; Hart, S. D.; Walroth, R. C.; Mack, K. A.; Sigman, M. S. Bisphosphine Ligand Conformer Selection to Enhance Descriptor Database Representation: Improving Statistical Modelling Outcomes. *Chem. Sci.* **2025**, *16*, 20473–20485.
19. Dotson, J. J.; van Dijk, L.; Timmerman, J. C.; Grosslight, S.; Walroth, R. C.; Gosselin, F.; Püntener, K.; Mack, K. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2022**, *145*, 110–121.
20. (a) Grushin, V. V. Synthesis of Hemilabile Phosphine-Phosphine Oxide Ligands via the Highly Selective Pd-Catalyzed Mono-Oxidation of Bidentate Phosphines: Scope, Limitations, and Mechanism. *Organometallics* **2001**, *20*, 3950–3961. (b) Grushin, V. V. Mixed Phosphine-Phosphine Oxide Ligands. *Chem. Rev.* **2004**, *104*, 1629–1662. (c) Wöste, T. H.; Oestreich, M. BINAP versus BINAP(O) in Asymmetric Intermolecular Mizoroki–Heck Reactions: Substantial Effects on Selectivities. *Chem. Eur. J.* **2011**, *17*, 11914–11918.
21. (a) Ji, Y.; Li, H.; Hyde, K.; Chen, Q.; Belyk, K. M.; Lexa, K. W.; Yin, J.; Sherer, E. C.; Williamson, T. R.; Brunskill, A.; Ren, S.; Campeau, L.-C.; Davies, I. W.; Ruck, R. T. *Chem. Sci.* **2017**, *8*, 2841. (b) Doggett, A.; Hay, M.; McKenna, S.; Saurer, E. M.; Steinhardt, S.; Tan, Y.; Wilbert, C. R.; Wisniewski, S. R. *Org. Process Res. Dev.* **2023**, *27*, 1129. (c) Payard, P.-A.; Bohn, A.; Tocqueville, D.; Jaouadi, K.; Escoude, E.; Ajig, S.; et al. *Organometallics* **2021**, *40*, 1120.
22. Anstine, D.; Zubatyuk, R.; Gallegos, L.; Paton, R.; Wiest, O.; Nebgen, B.; Jones, T.; Gomes, G.; Tretiak, S.; Isayev, O. Transferable Machine Learning Interatomic Potential for Pd-Catalyzed Cross-Coupling Reactions. *ChemRxiv* **2025**. DOI: 10.26434/chemrxiv-2025-n36r6.
23. Brandenburg, J. G.; Bannwarth, C.; Hansen, A.; Grimme, S. B97-3C: A Revised Low-Cost Variant of the B97-D Density Functional Method. *J. Chem. Phys.* **2018**, *148*, 064104.
24. Henkelman, G.; Uberuaga, B. P.; Jónsson, H. A Climbing Image Nudged Elastic Band Method for Finding Saddle Points and Minimum Energy Paths. *J. Chem. Phys.* **2000**, *113*, 9901–9904.
25. Hermes, E. D.; Sargsyan, K.; Najm, H. N.; Zádor, J. Sella, an Open-Source Automation-Friendly Molecular Saddle Point Optimizer. *J. Chem. Theory Comput.* **2022**, *18*, 6974–6988.
26. Chang, G.; Guida, W. C.; Still, W. C. An Internal-Coordinate Monte Carlo Method for Searching Conformational Space. *J. Am. Chem. Soc.* **1989**, *111*, 4379–4386.
27. Masarwa, A.; Weber, M.; Sarpong, R. Selective C–C Bond Activation/Cleavage of Pinene Derivatives: Synthesis of Enantiopure Cyclohexanone Scaffolds and Mechanistic Insights. *J. Am. Chem. Soc.* **2015**, *137*, 6327–6334.
28. Bermejo, F. A.; Mateos, A. F.; Escribano, A. M.; Lago, R. M.; Burón, L. M.; López, M. R.; González, R. R. Ti(III)-Promoted Cyclizations: Application to the Synthesis of ϵ -Endo-Bergamoten-12-oic Acids, Moth Oviposition Stimulants Isolated from *Lycopersicon hirsutum*. *Tetrahedron* **2006**, *62*, 8933–8942.

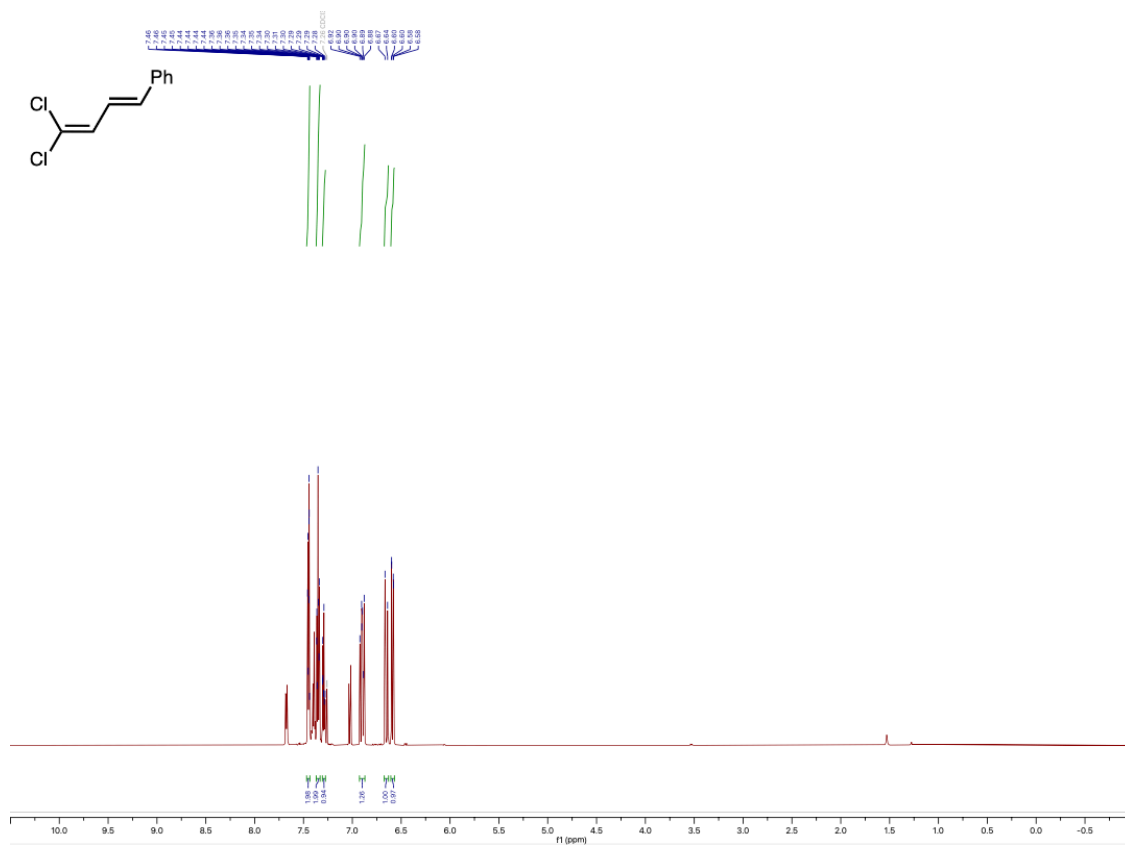
29. Leger, P. R.; Kuroda, Y.; Chang, S.; Jurczyk, J.; Sarpong, R. C–C Bond Cleavage Approach to Complex Terpenoids: Development of a Unified Total Synthesis of the Phomactins. *J. Am. Chem. Soc.* **2020**, *142*, 15536–15542.
30. Abdellaoui, M.; Millanvois, A.; Levernier, E.; Ollivier, C.; Fensterbank, L. Visible-Light-Mediated Z-Stereoselective Monoalkylation of β,β -Dichlorostyrenes by Photoredox/Nickel Dual Catalysis. *Synlett* **2021**, *32*, 1513–1518.
31. Maddali, L. N.; Meka, S. Cross-Coupling Reactivity of 1,1-Dichloroalkenes under Palladium Catalysis: Domino Synthesis of Diarylalkynes. *New J. Chem.* **2018**, *42*, 4412–4418.
32. Nitelet, A.; Evano, G. A General Copper-Catalyzed Vinylic Halogen Exchange Reaction. *Org. Lett.* **2016**, *18*, 1904–1907.
33. Kropp, P. J.; McNeely, S. A.; Davis, R. D. Photochemistry of Alkyl Halides. 10. Vinyl Halides and Vinylidene Dihalides. *J. Am. Chem. Soc.* **1983**, *105*, 6907.

¹H NMR (400 MHz, CDCl₃) (S5)

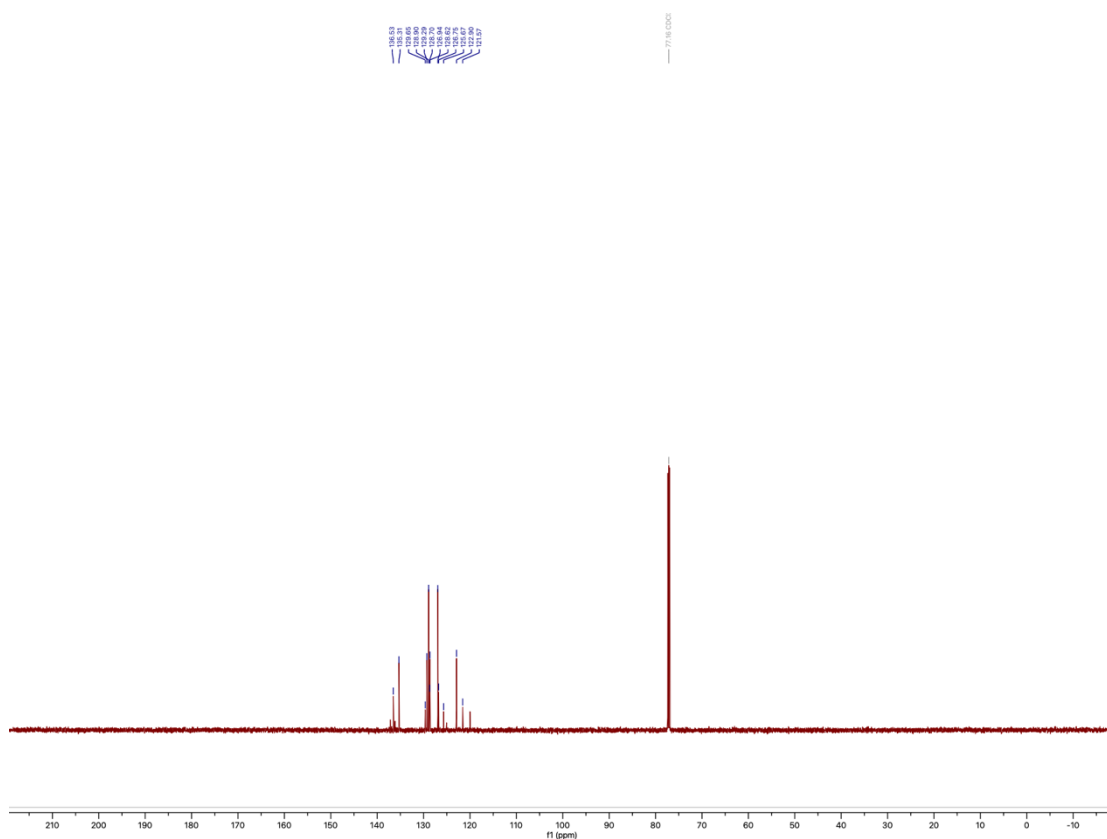
(126 MHz, CDCl₃) (SS)

148.36
118.89
77.00 (CDCl₃)
63.84
48.76
43.22
38.85
35.66
32.66
28.66
25.66
22.66
18.66
-2.66

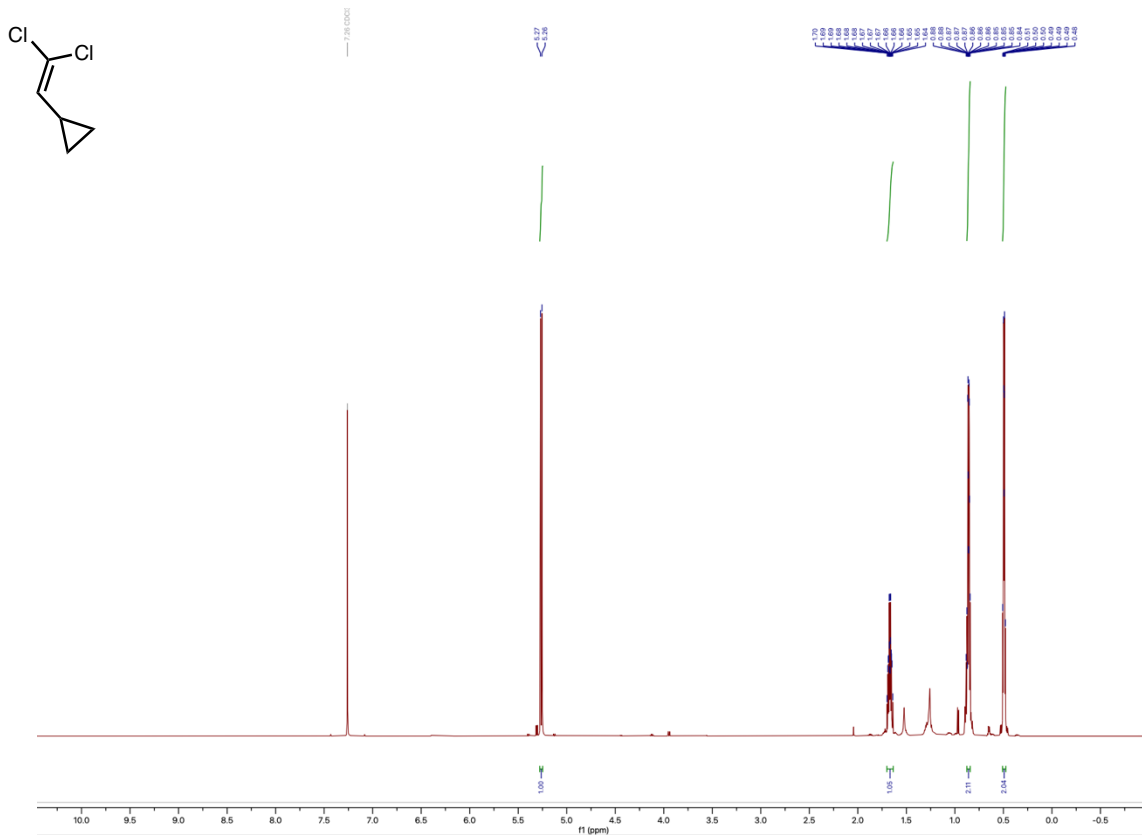
^1H NMR (600 MHz, CDCl_3) (**2.2e**)



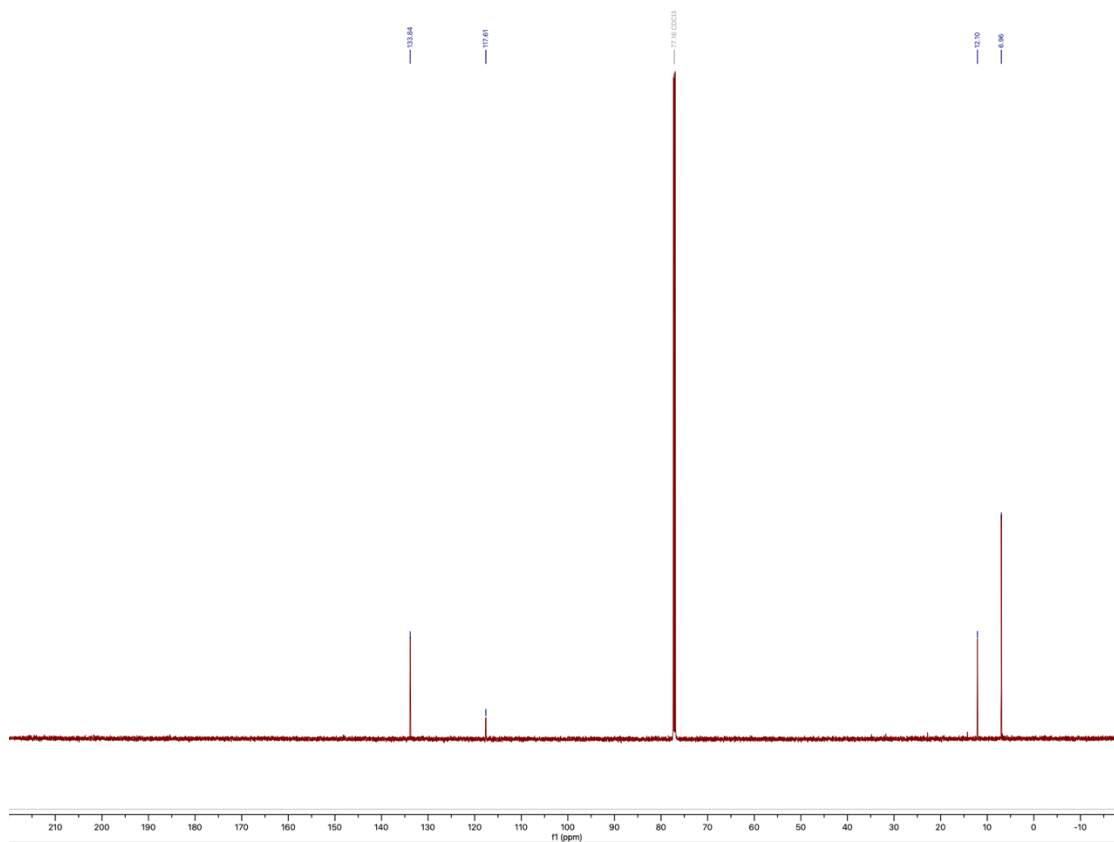
^{13}C NMR (151 MHz, CDCl_3) (**2.2e**)

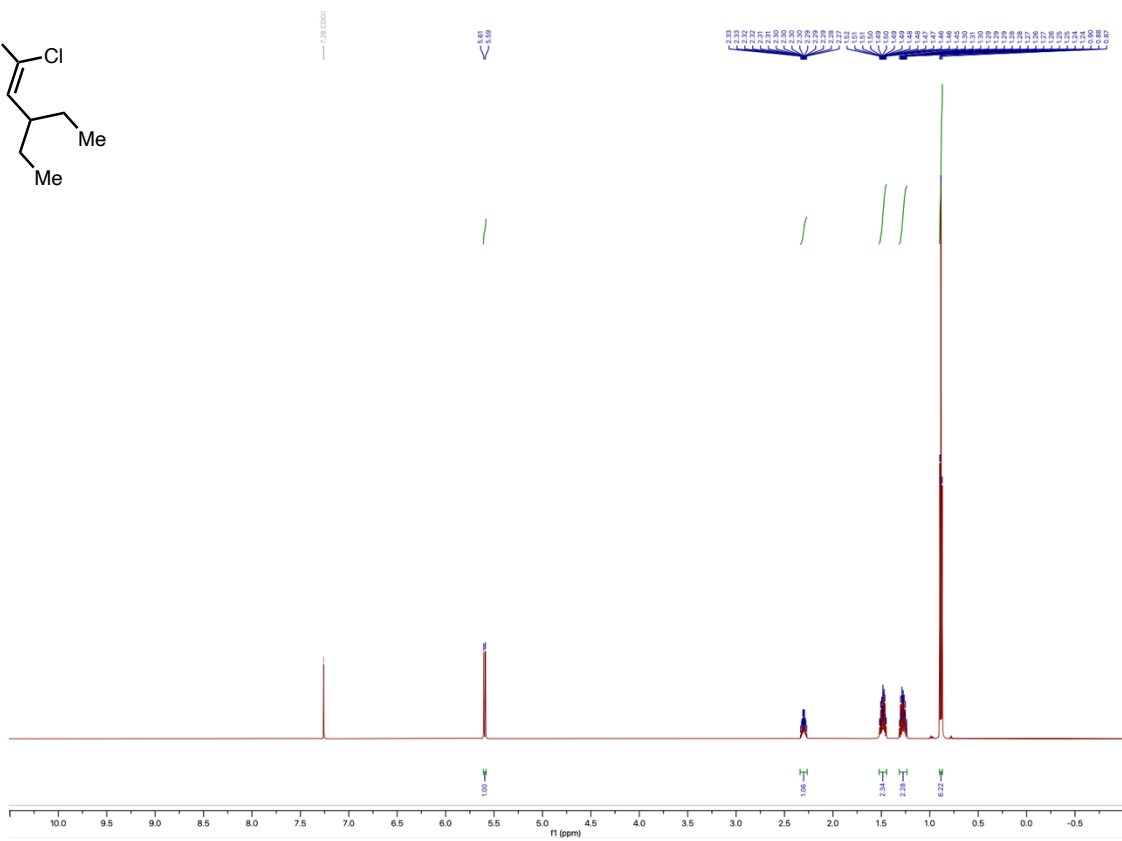
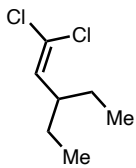
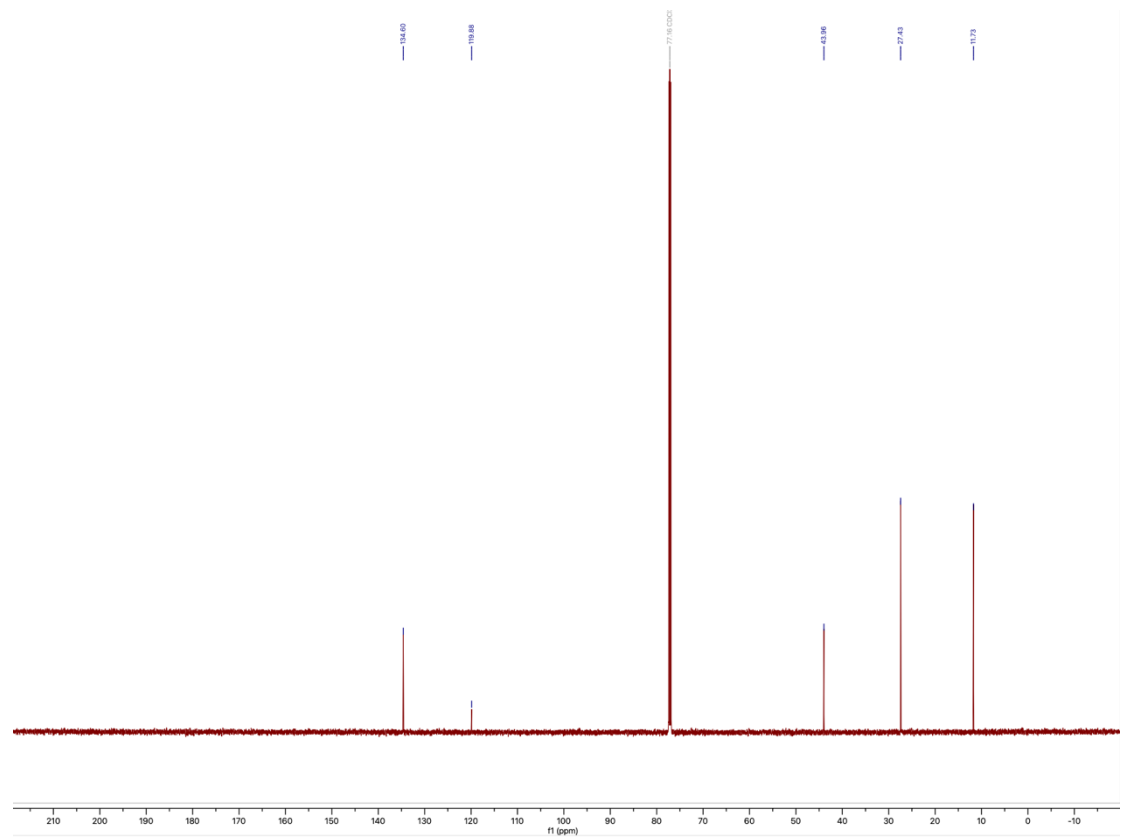


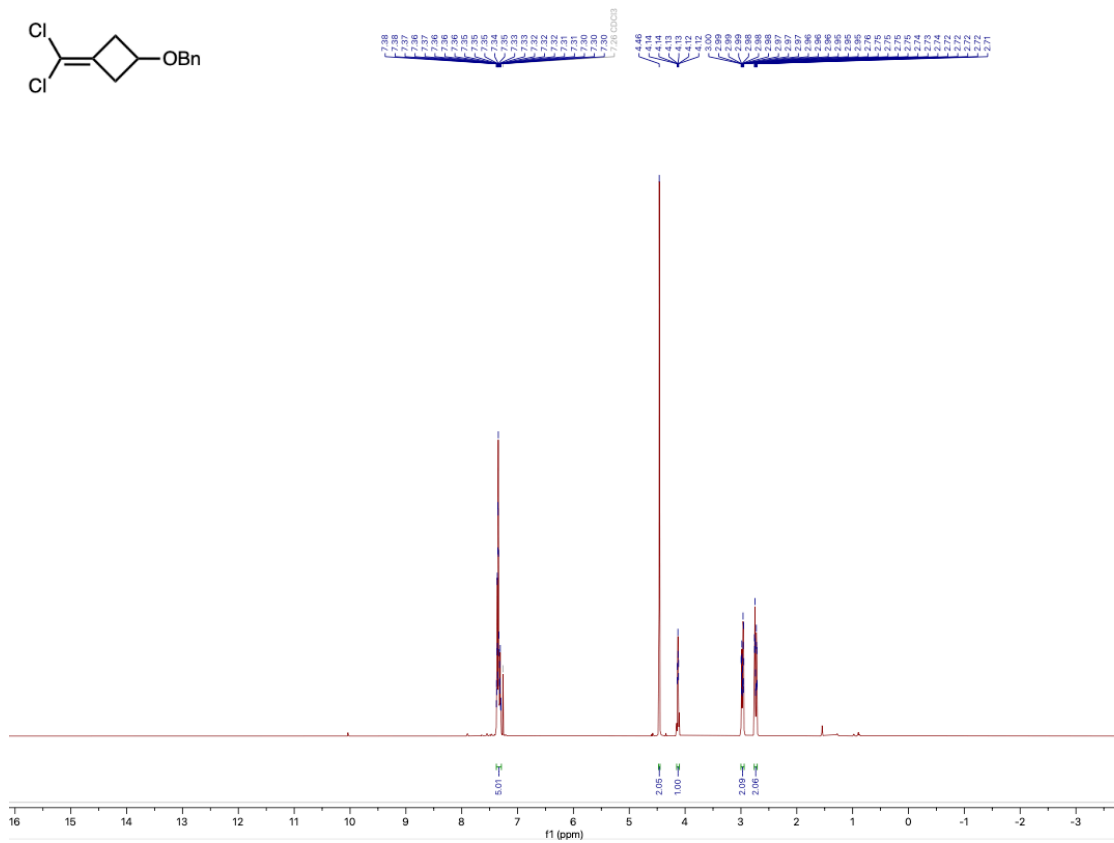
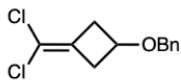
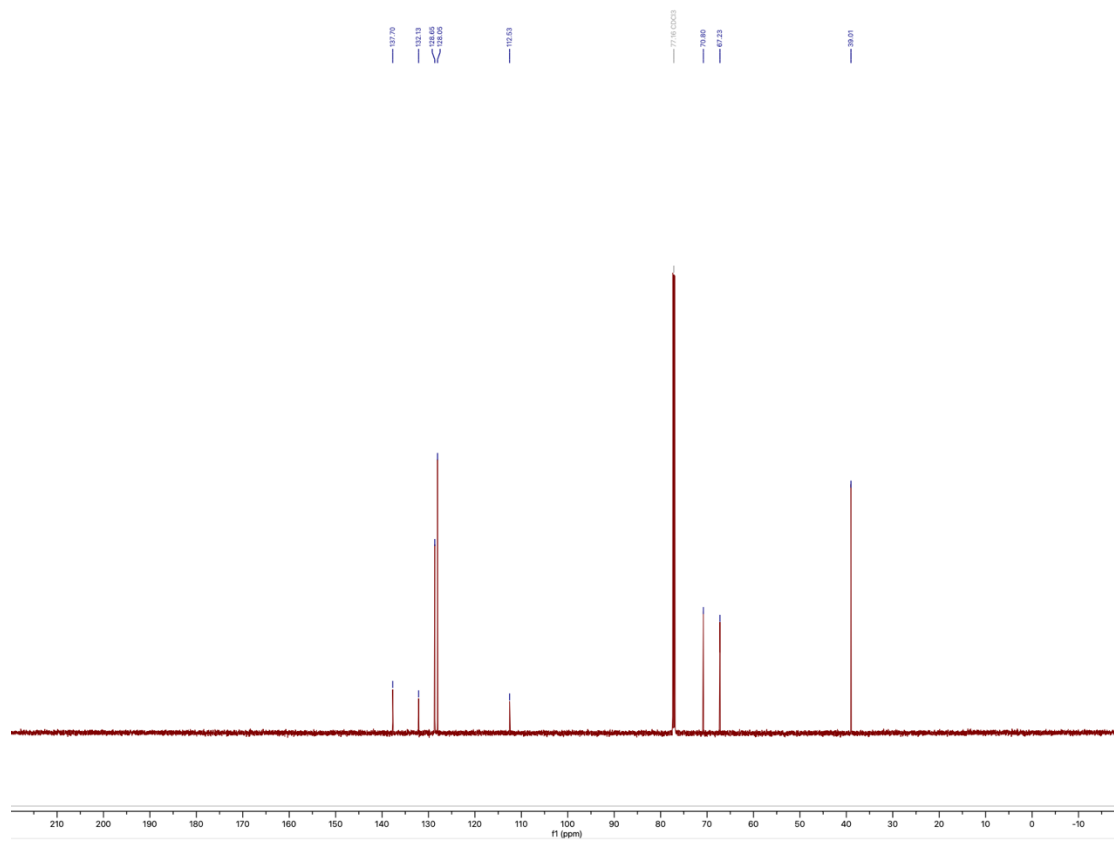
^1H NMR (600 MHz, CDCl_3) (**2.2f**)



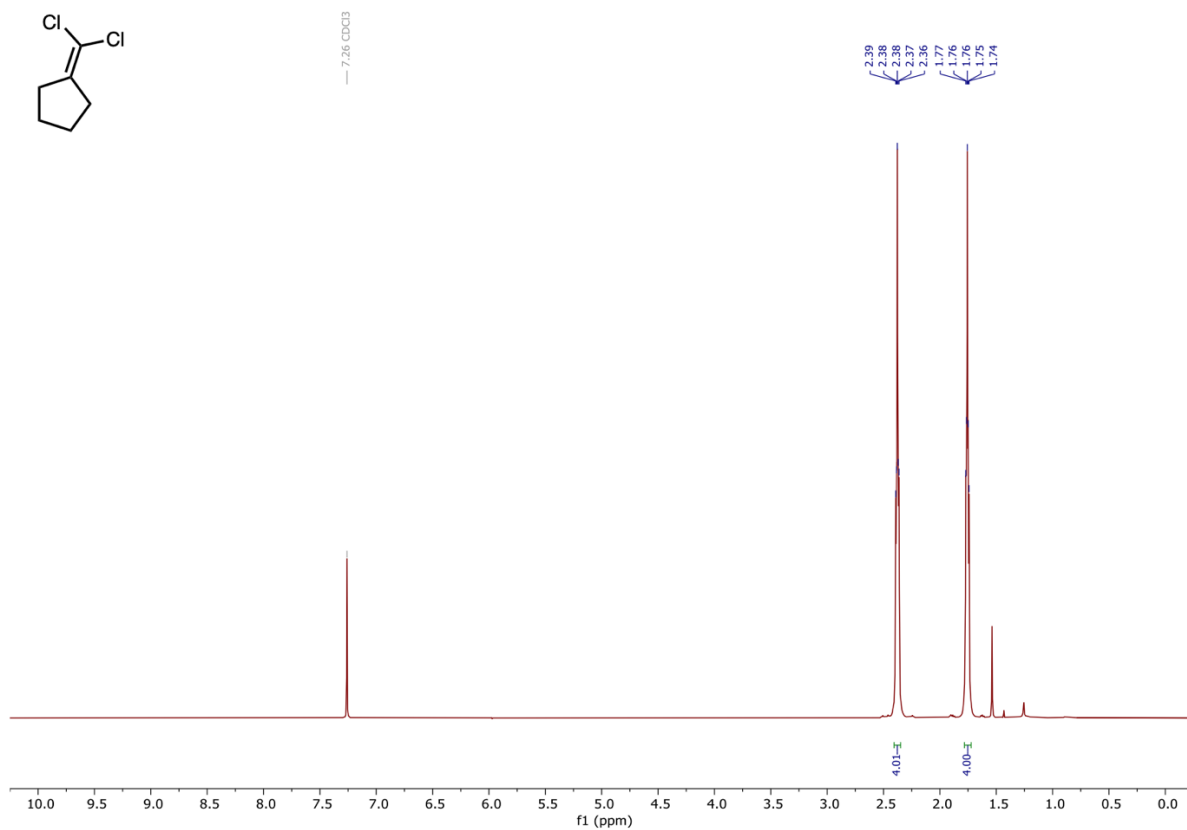
^{13}C NMR (151 MHz, CDCl_3) (**2.2f**)



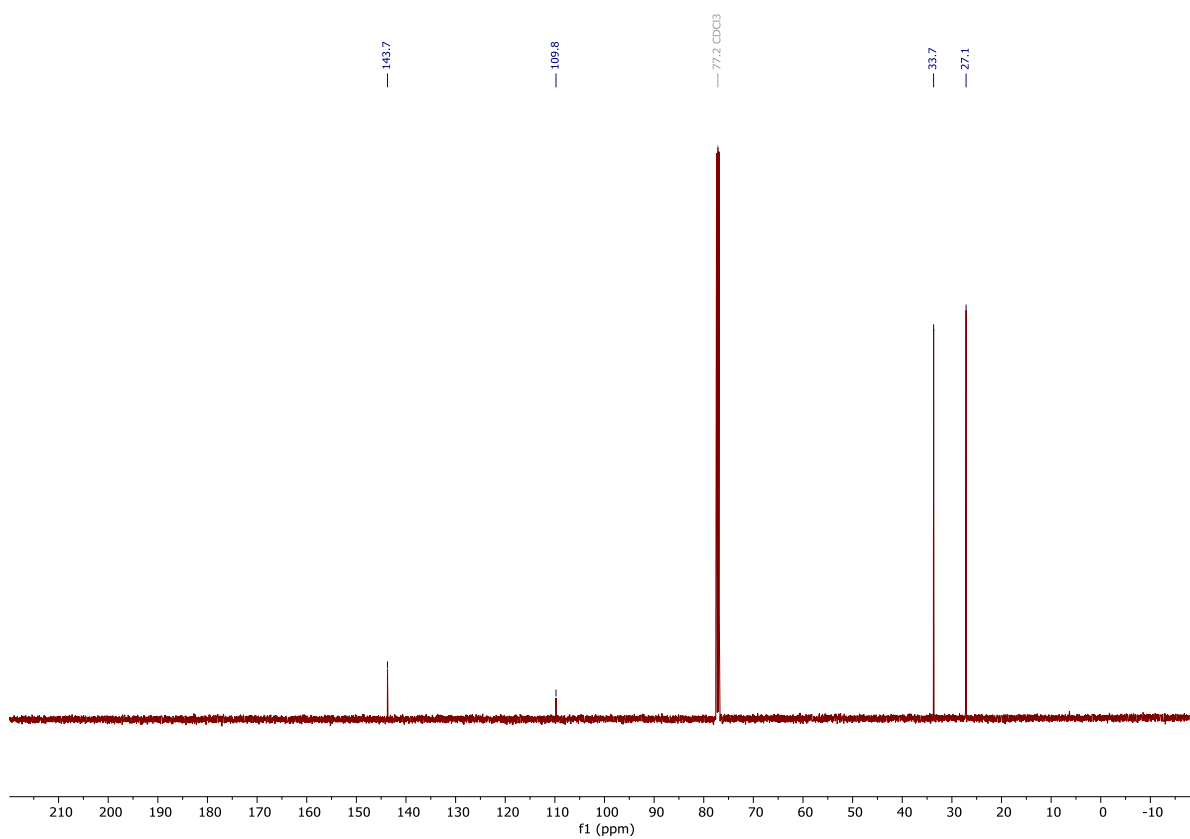
¹H NMR (600 MHz, CDCl₃) (2.2g) ^{13}C NMR (151 MHz, CDCl_3) (2.2g)

¹H NMR (600 MHz, CDCl₃) (2.2m) ^{13}C NMR (151 MHz, CDCl_3) (2.2m)

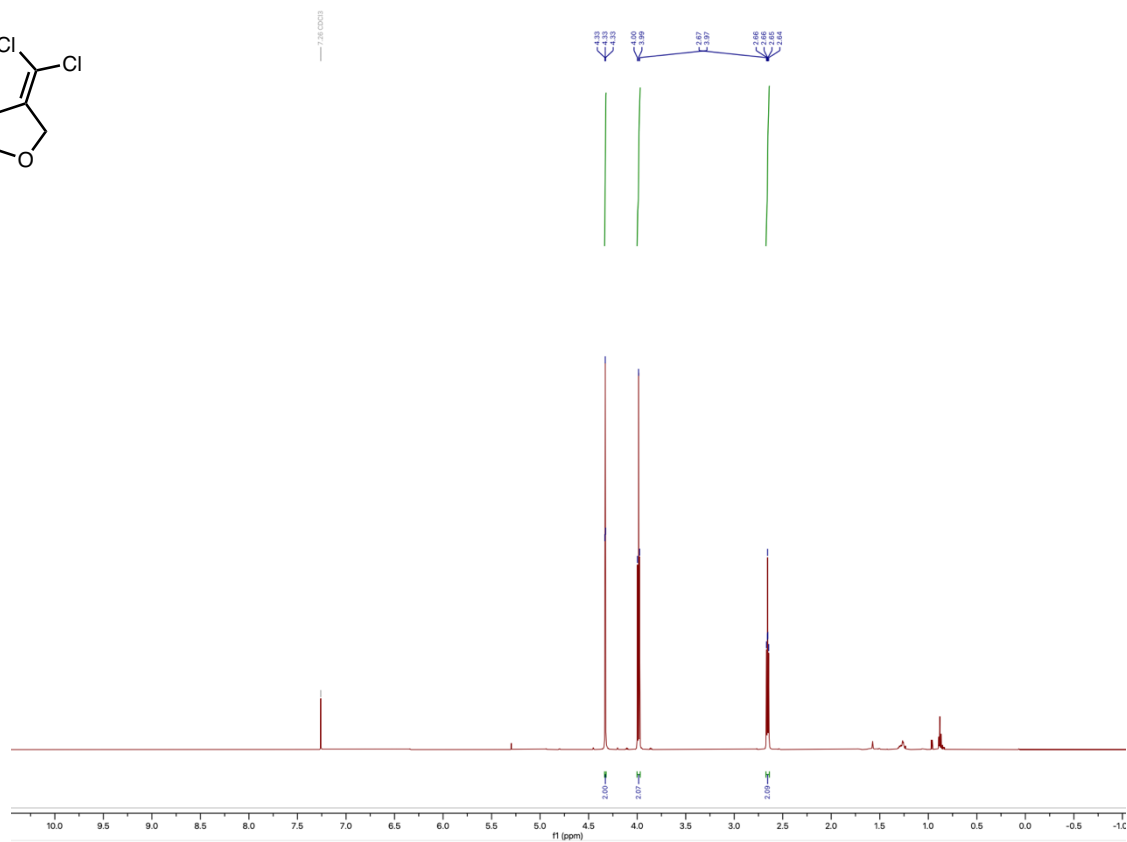
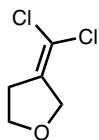
^1H NMR (600 MHz, CDCl_3) (**2.2i**)



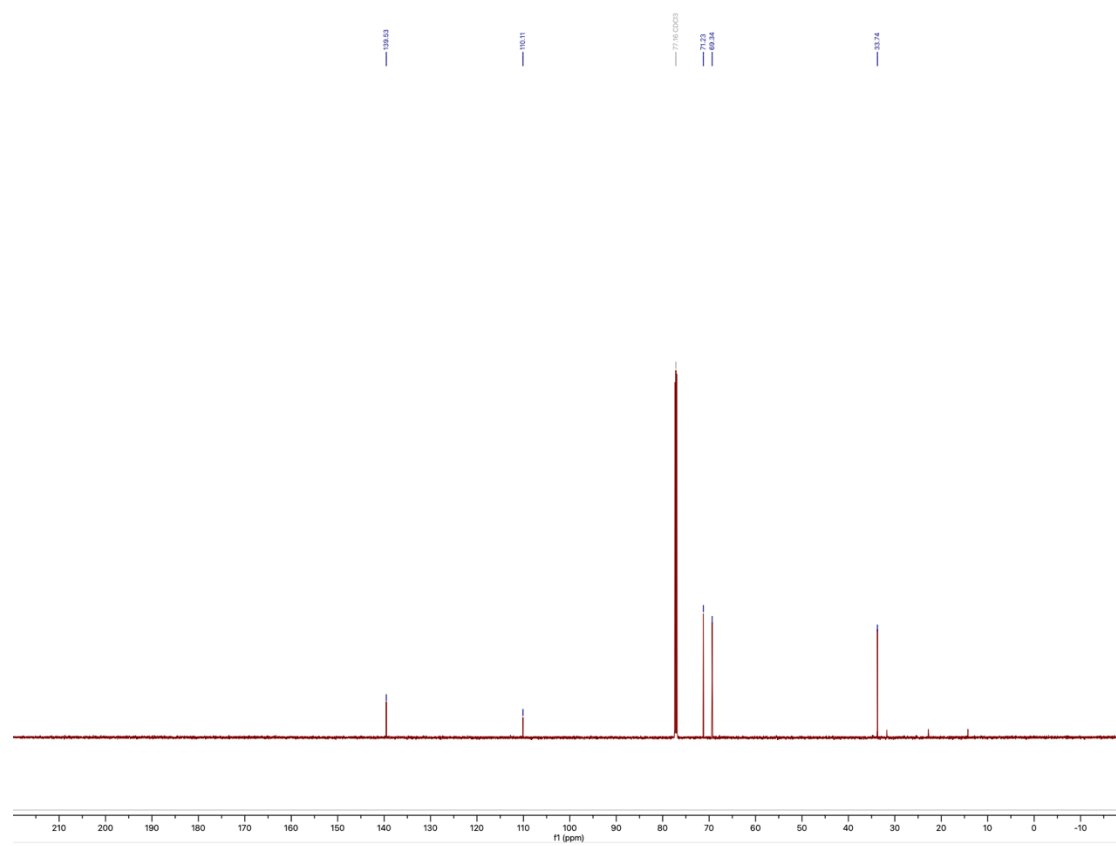
^{13}C NMR (151 MHz, CDCl_3) (**2.2i**)



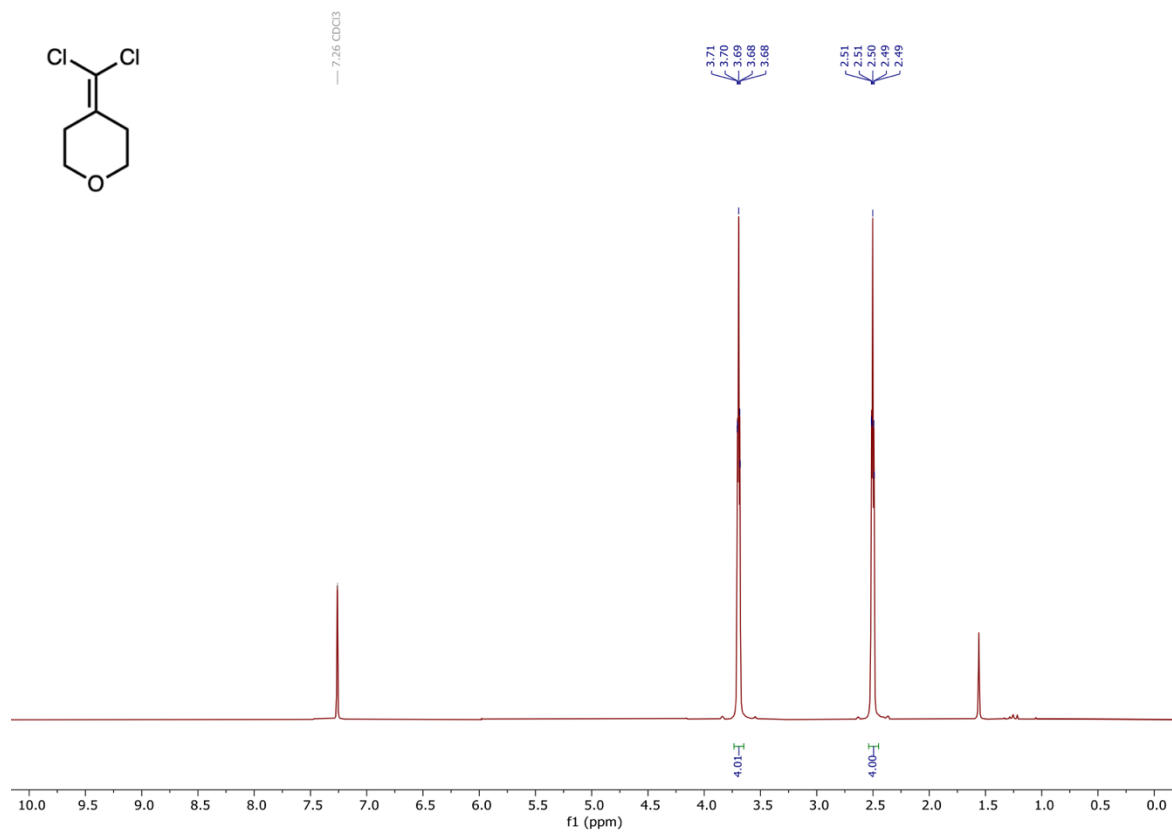
^1H NMR (600 MHz, CDCl_3) (**2.2k**)



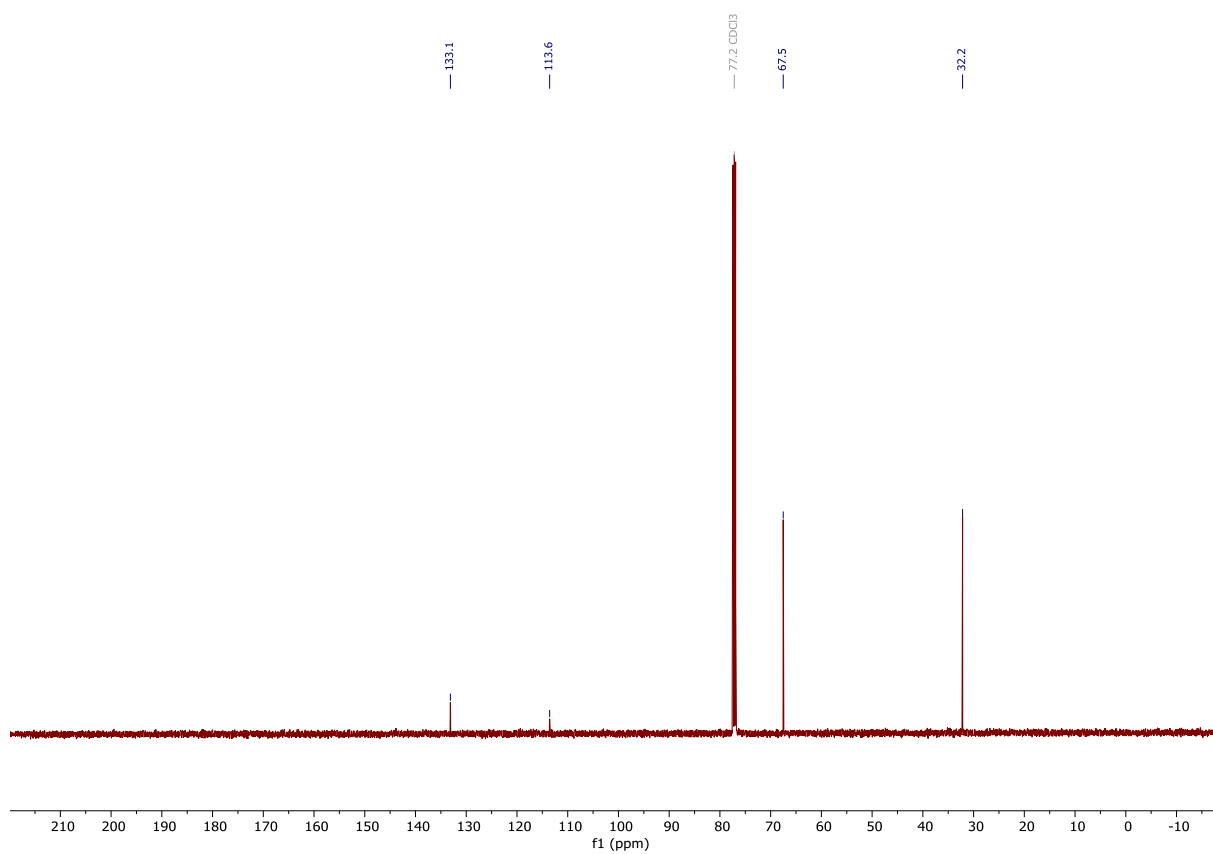
^{13}C NMR (151 MHz, CDCl_3) (**2.2k**)



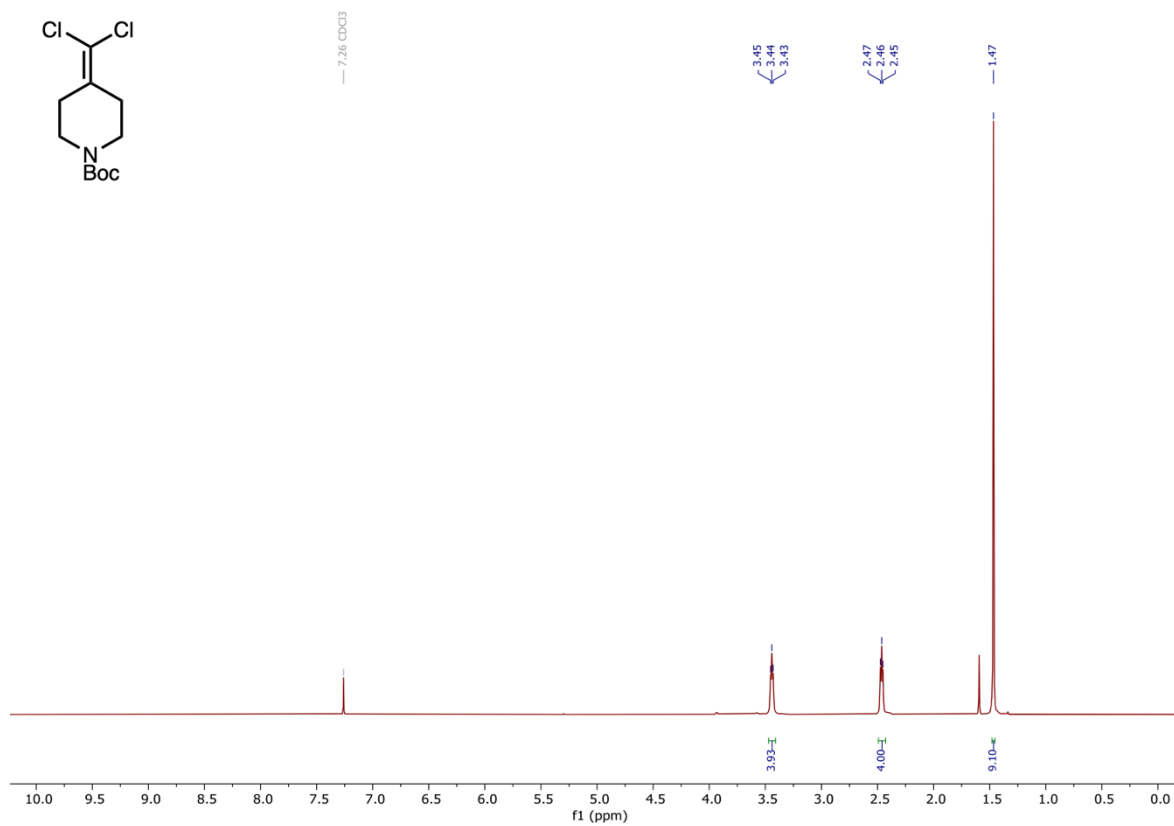
^1H NMR (600 MHz, CDCl_3) (**S7**)



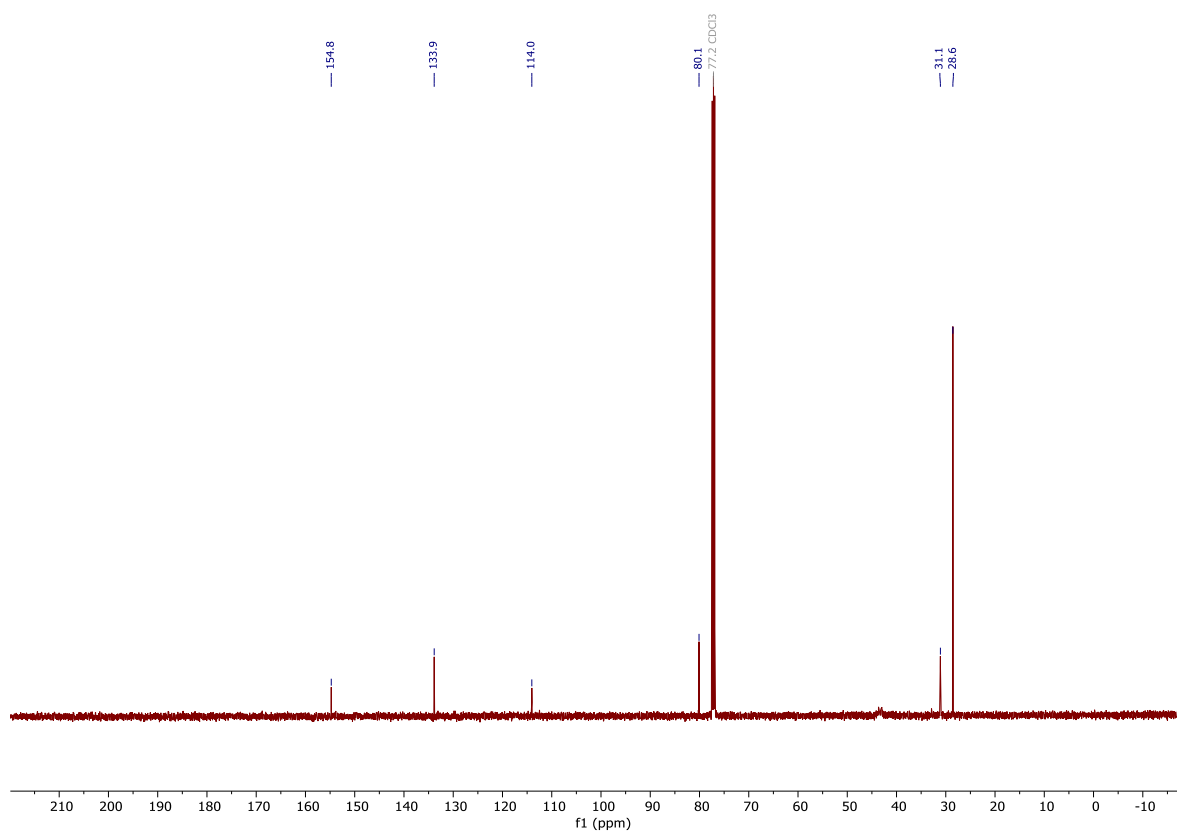
^{13}C NMR (151 MHz, CDCl_3) (**S7**)

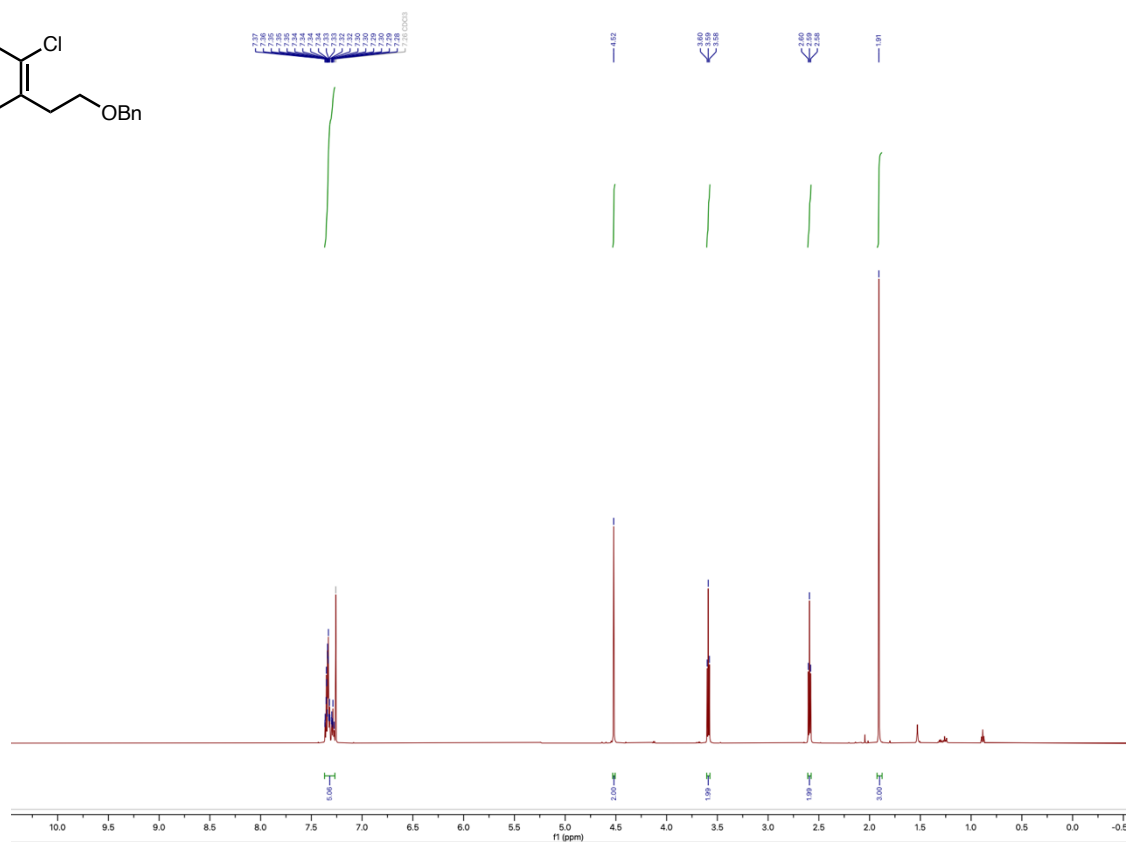
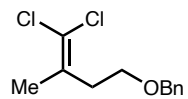
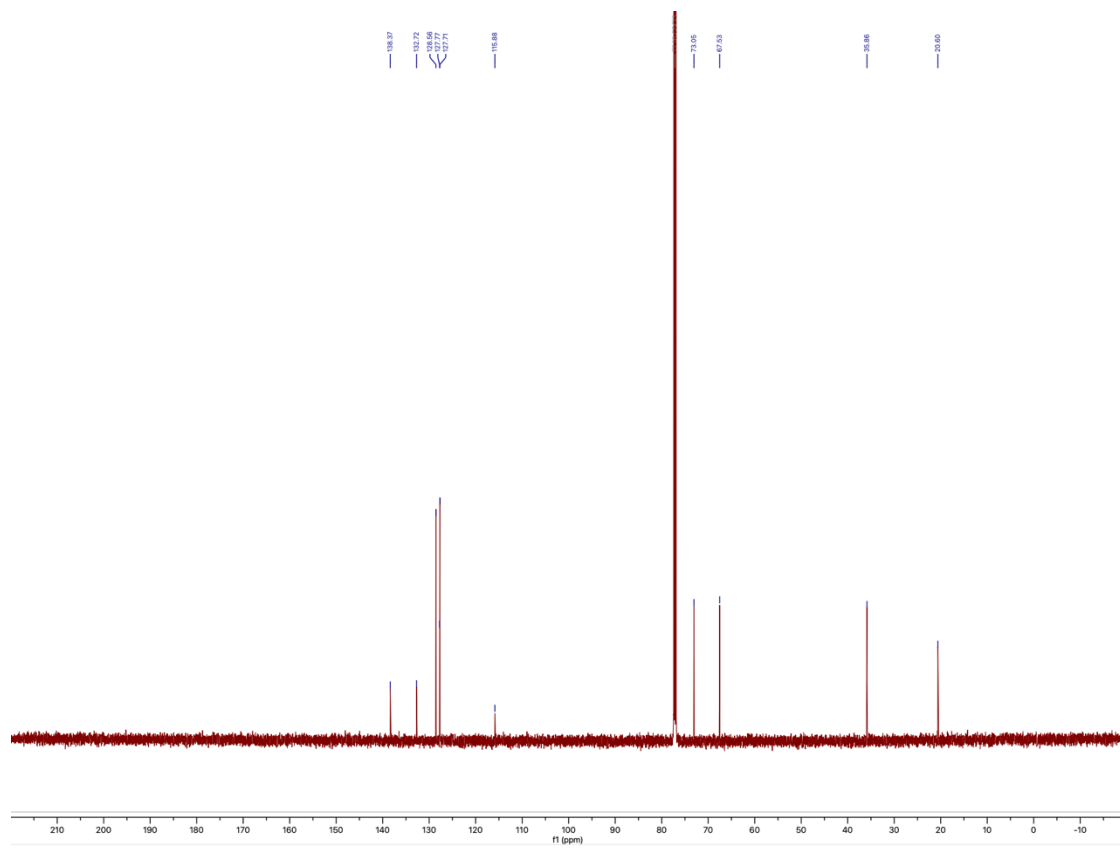


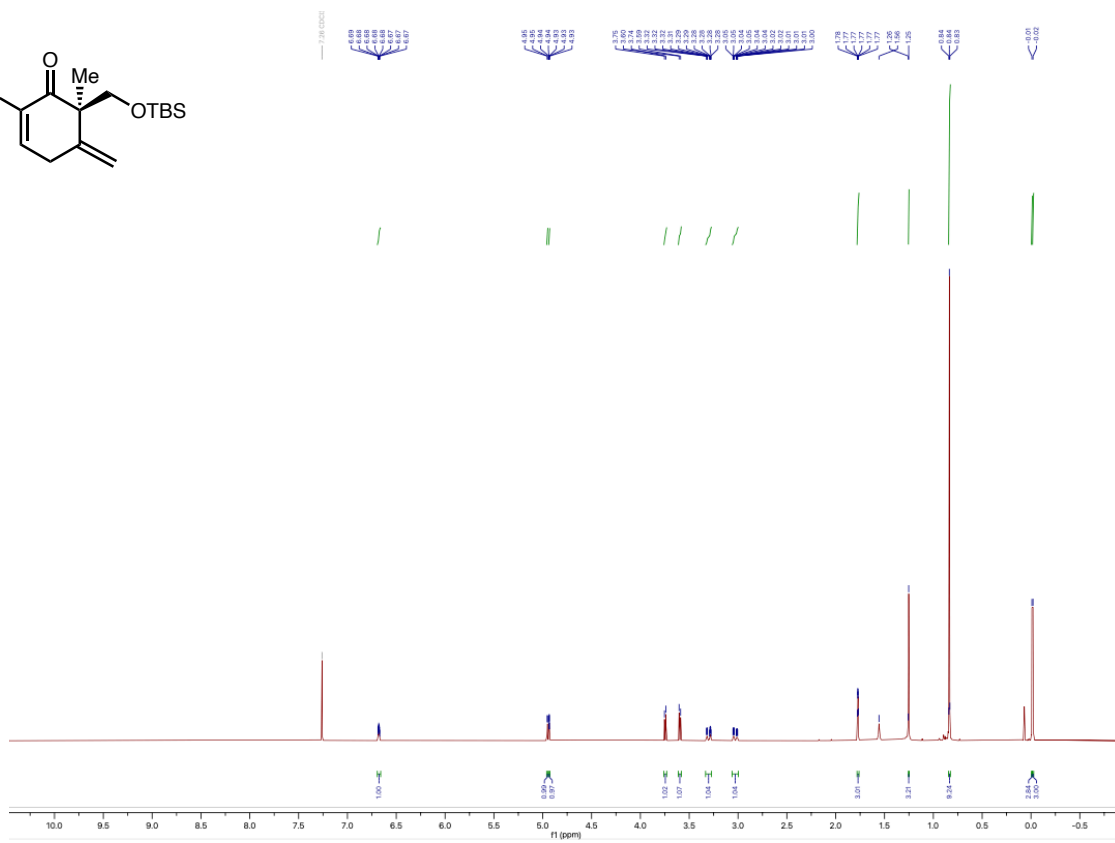
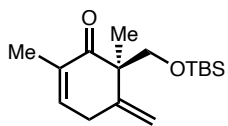
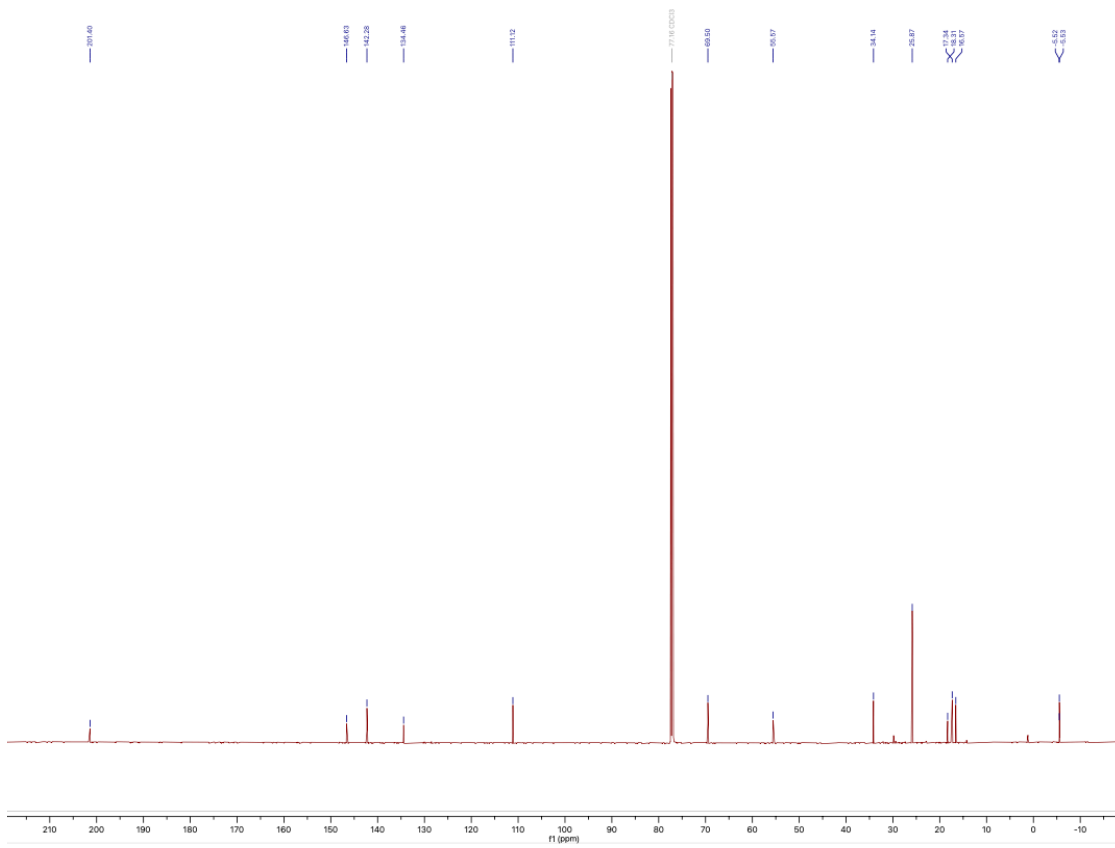
^1H NMR (500 MHz, CDCl_3) (**S8**)



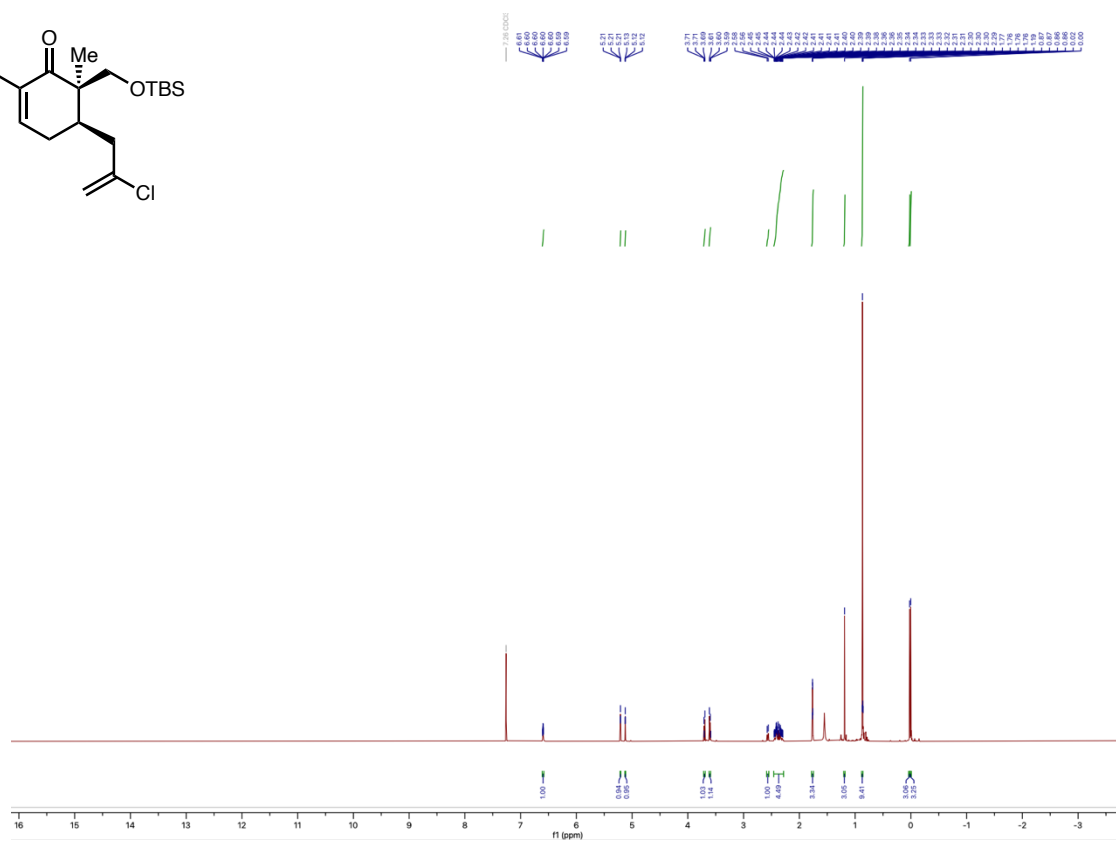
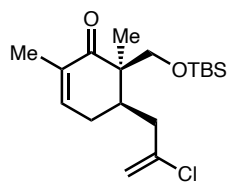
^{13}C NMR (126 MHz, CDCl_3) (**S8**)



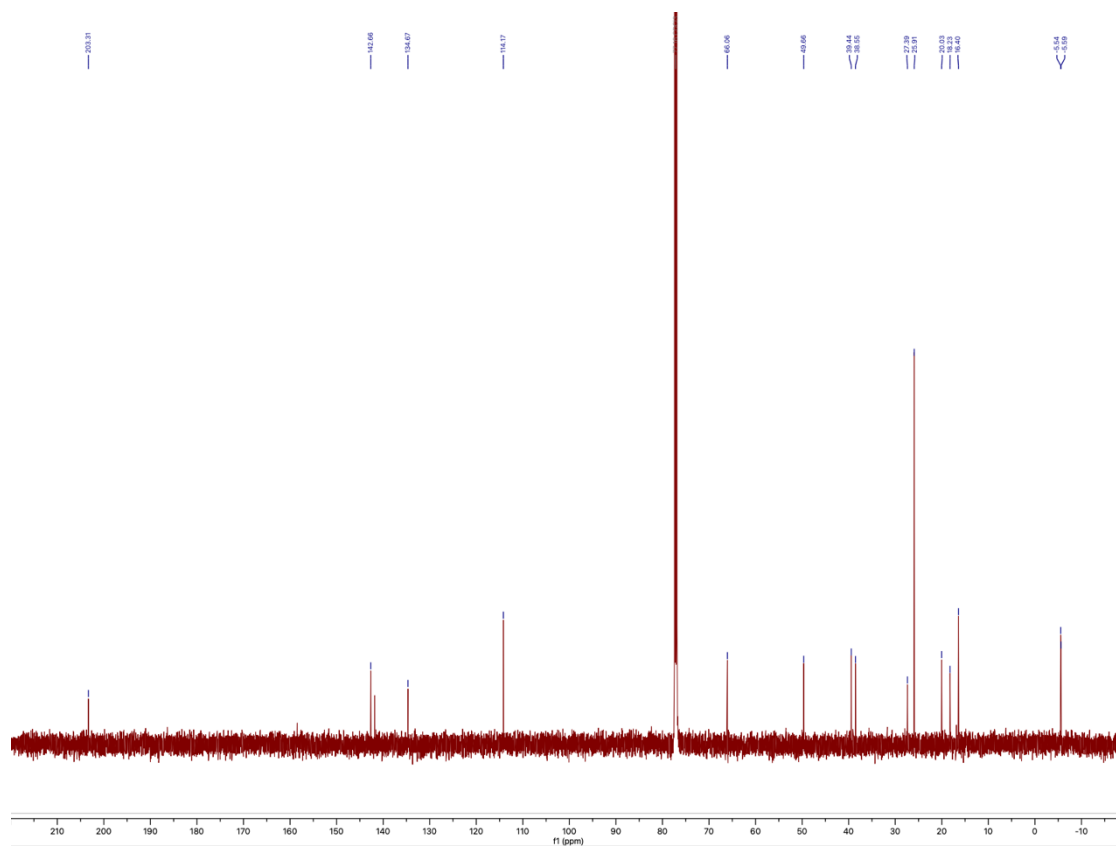
¹H NMR (600 MHz, CDCl₃) (**2.2o**) ^{13}C NMR (151 MHz, CDCl_3) (**2.20**)

¹H NMR (600 MHz, CDCl₃) (**2.12**) ^{13}C NMR (151 MHz, CDCl_3) (2.12)

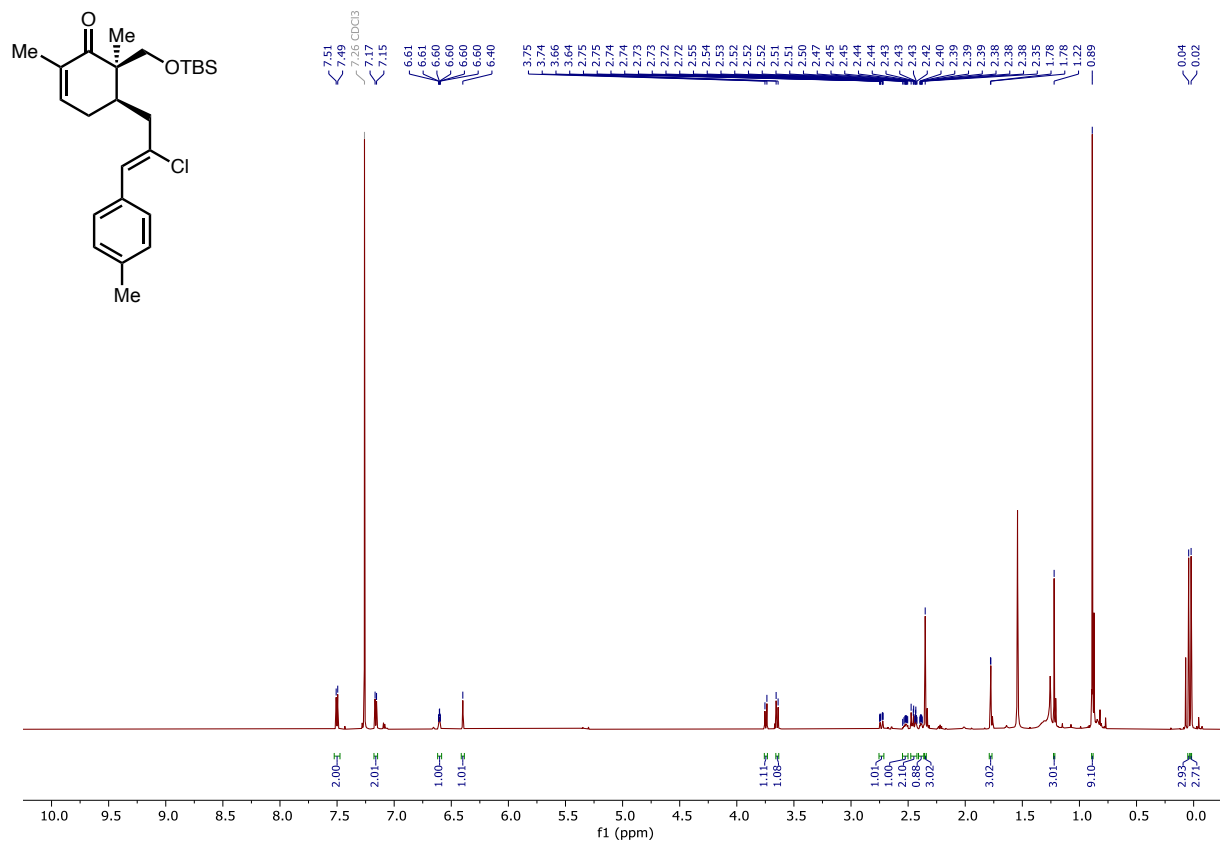
^1H NMR (600 MHz, CDCl_3) (**2.3c**)



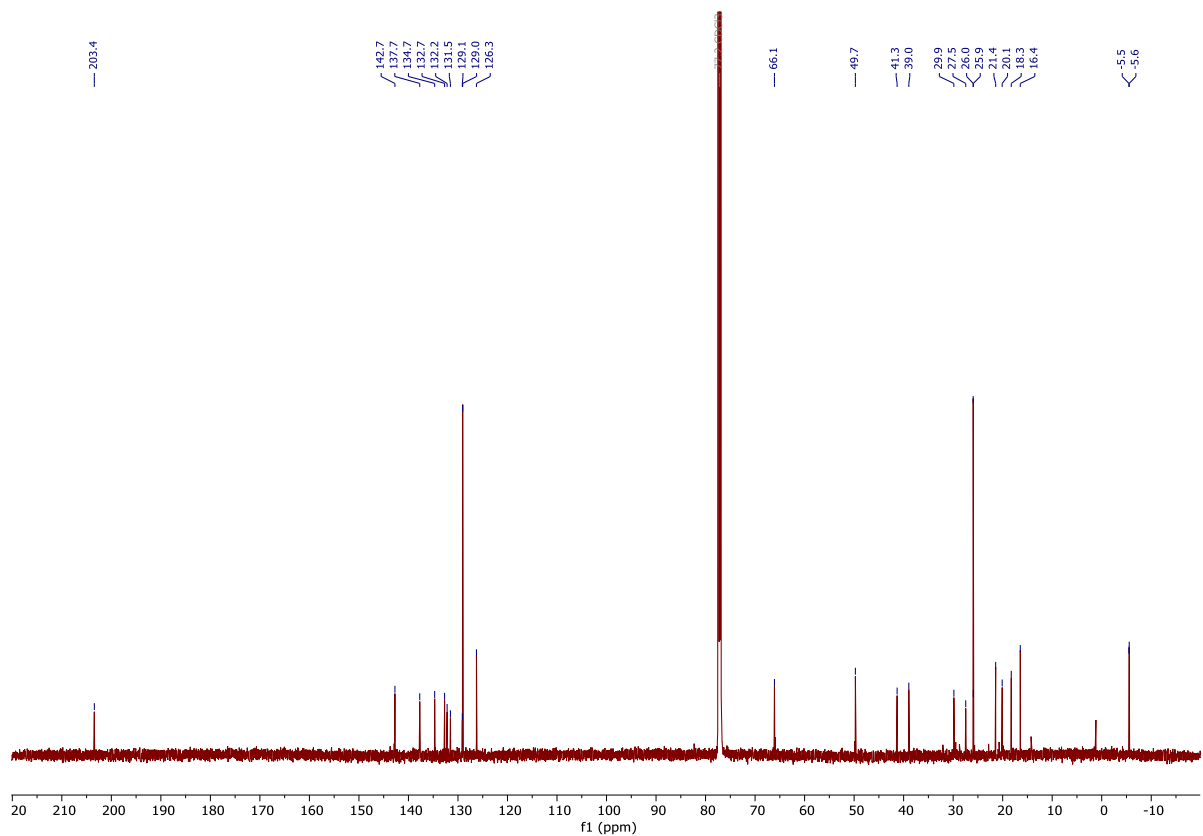
^{13}C NMR (151 MHz, CDCl_3) (**2.3c**)

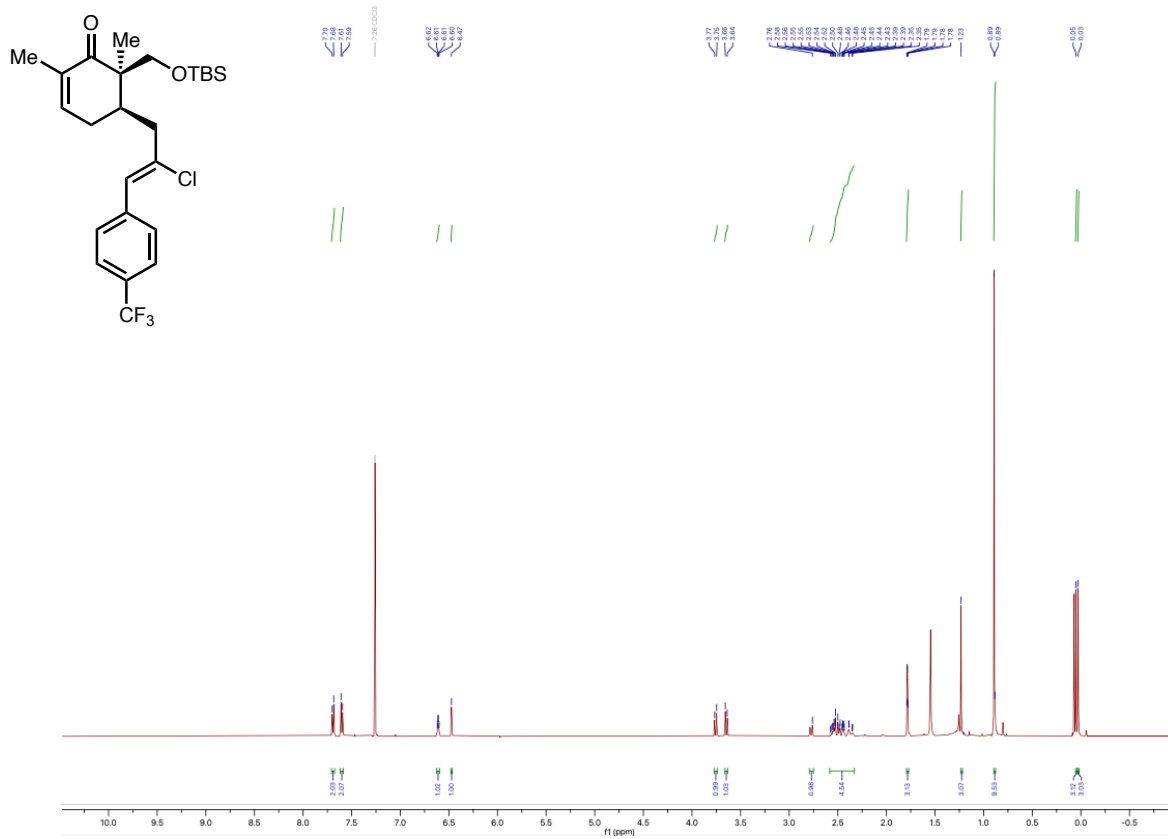
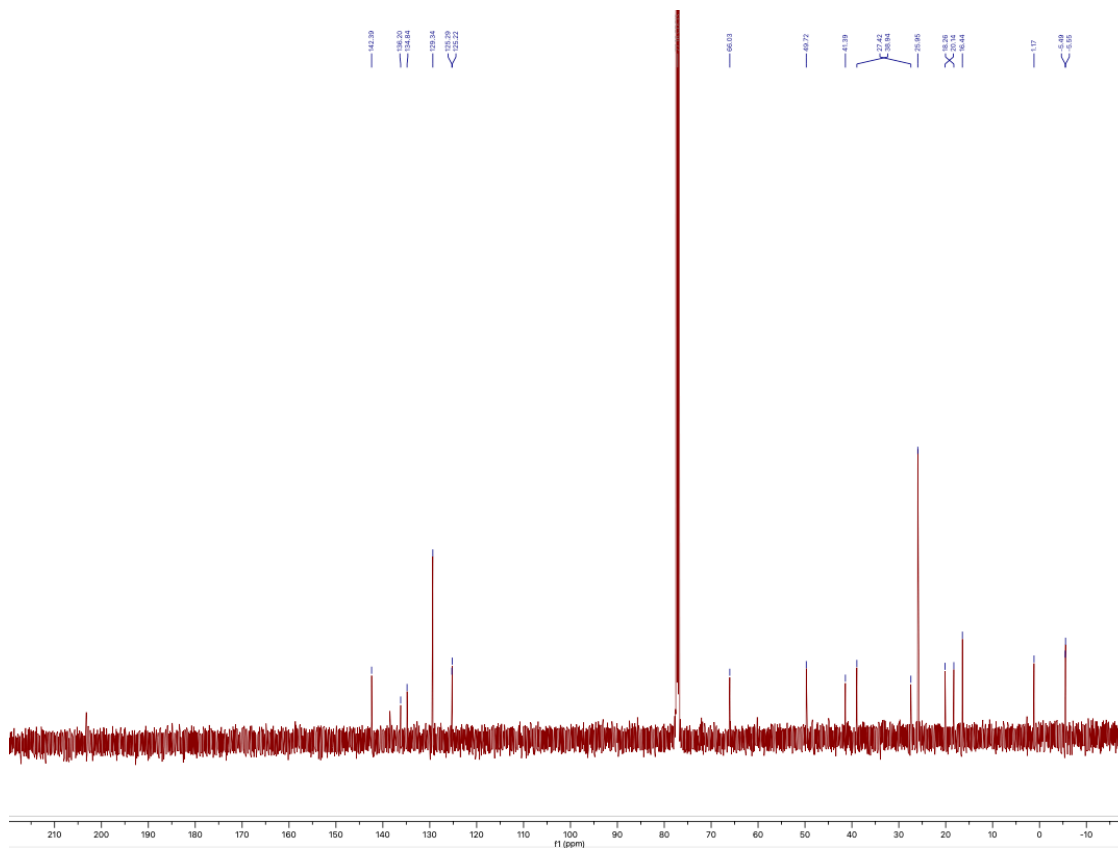


^1H NMR (600 MHz, CDCl_3) (**2.3a**)

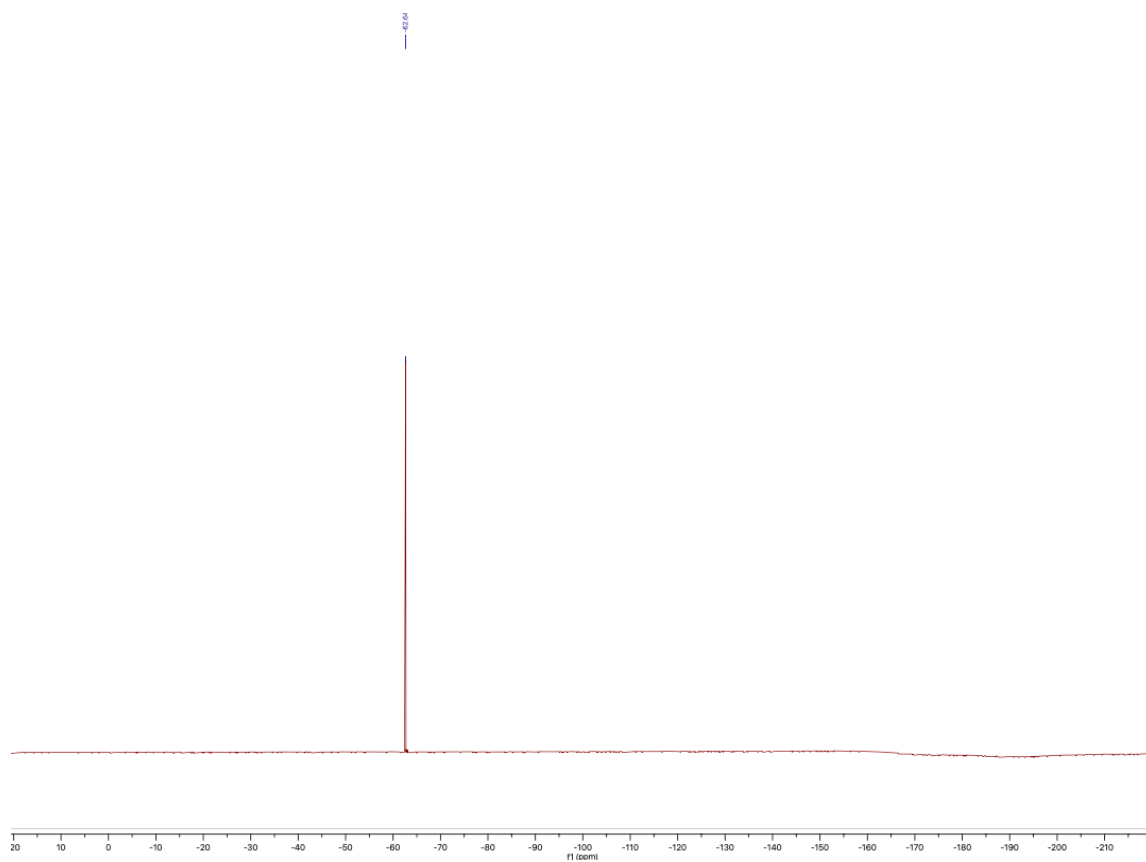


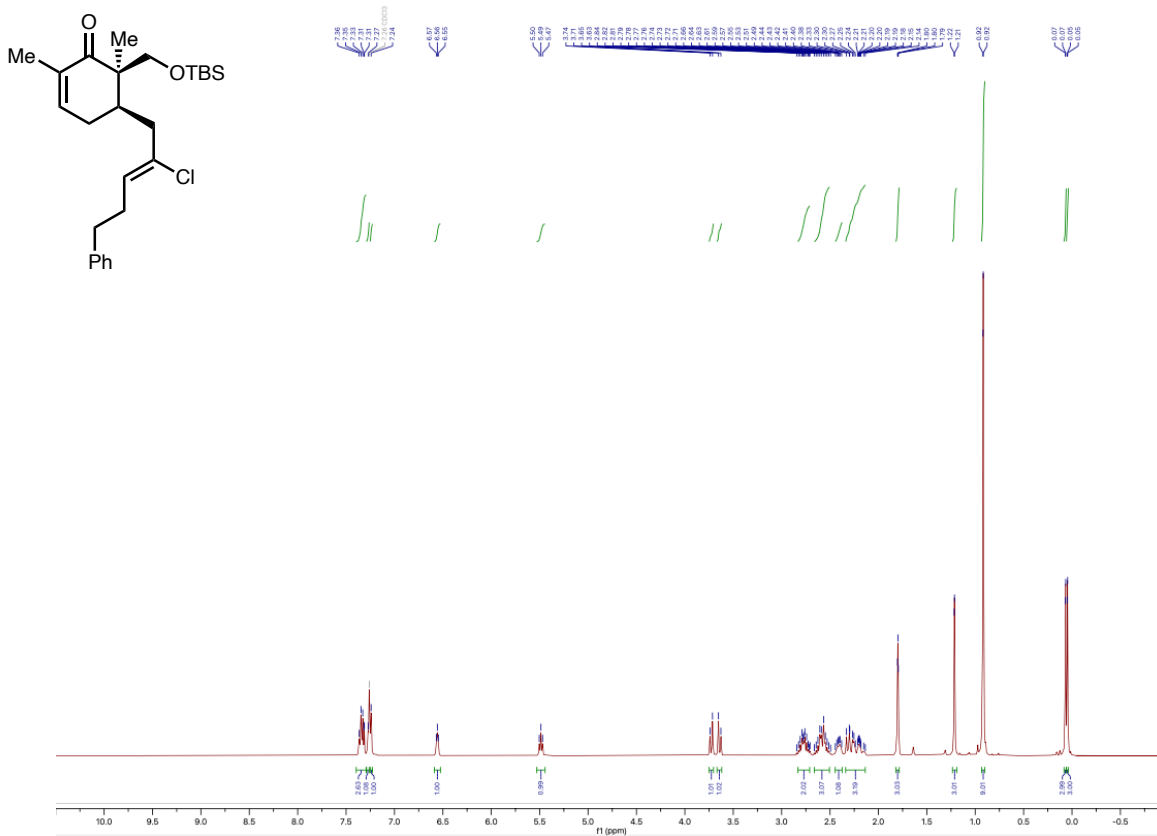
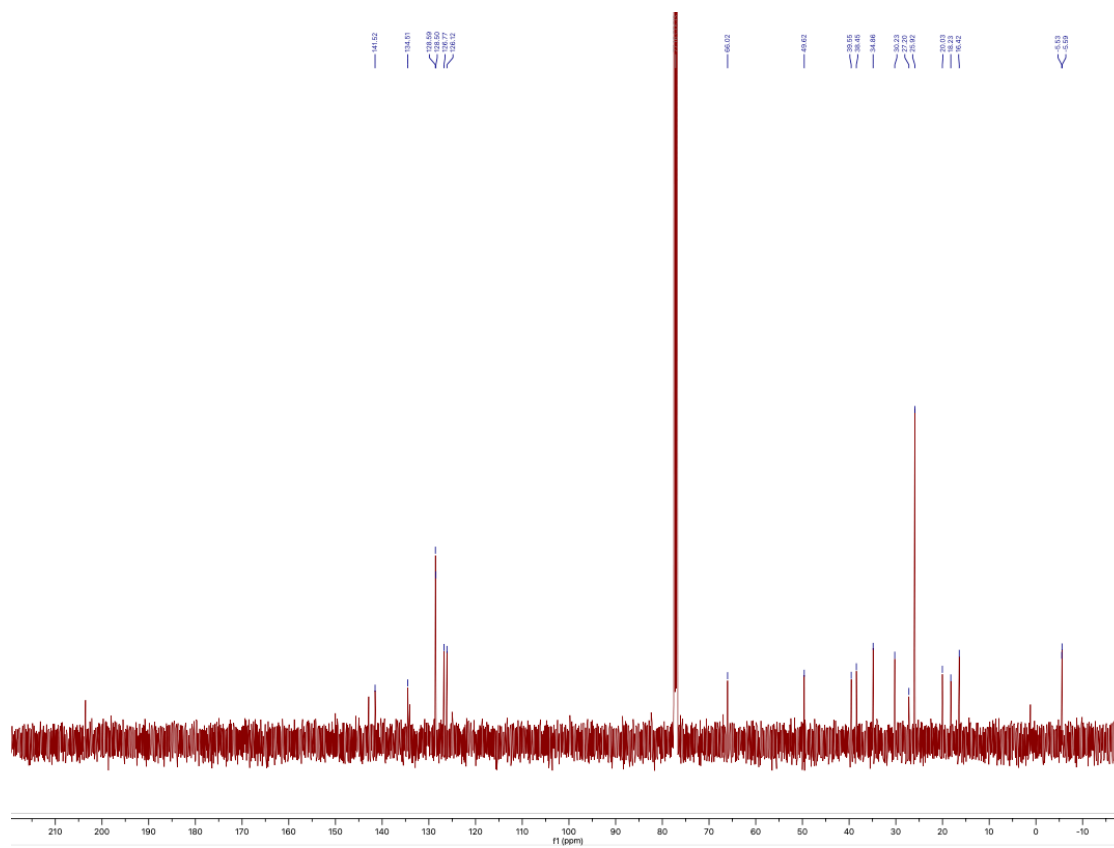
^{13}C NMR (151 MHz, CDCl_3) (**2.3a**)



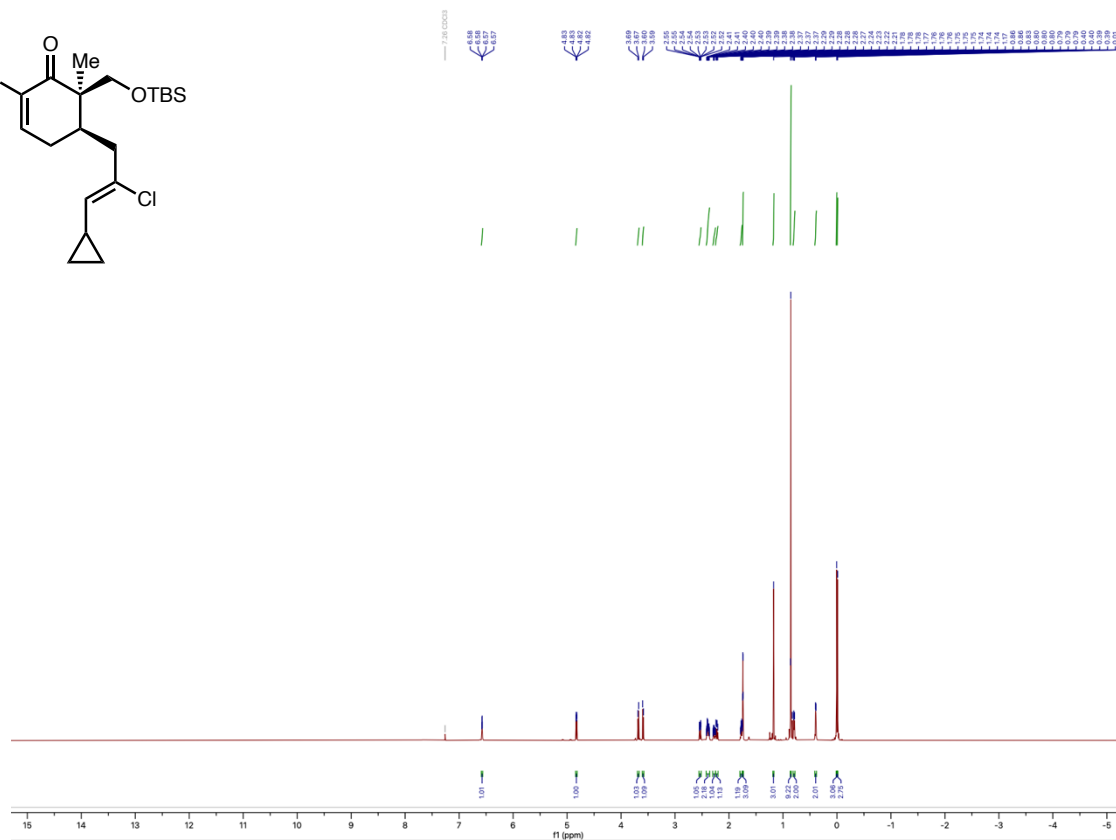
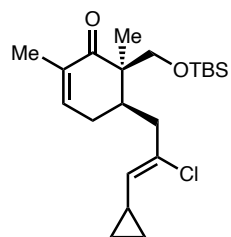
¹H NMR (500 MHz, CDCl₃) (**2.3b**)¹³C NMR (151 MHz, CDCl₃) (**2.3b**)

^{19}F NMR (470 MHz, CDCl_3) (**2.3b**)

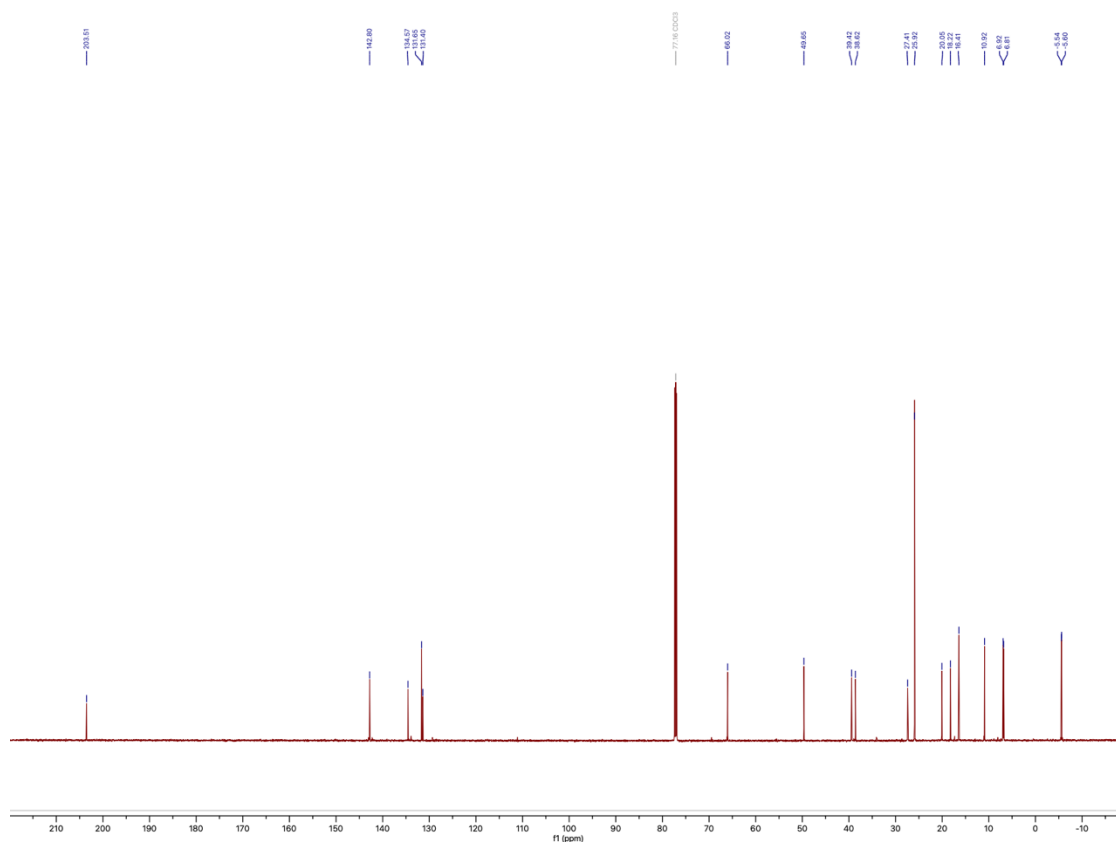


¹H NMR (400 MHz, CDCl₃) (**2.3d**) ^{13}C NMR (151 MHz, CDCl_3) (**2.3d**)

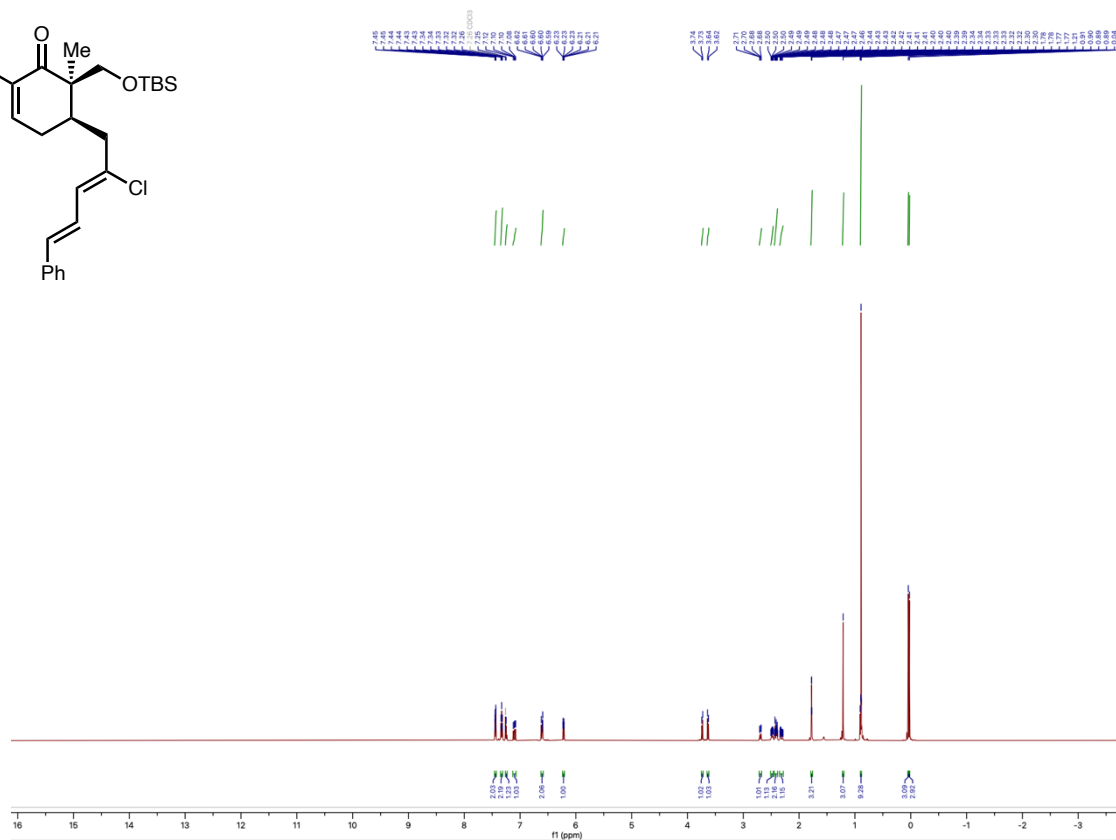
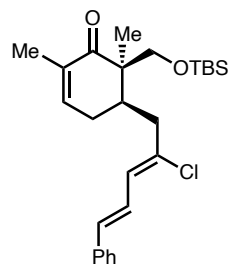
^1H NMR (700 MHz, CDCl_3) (**2.3f**)



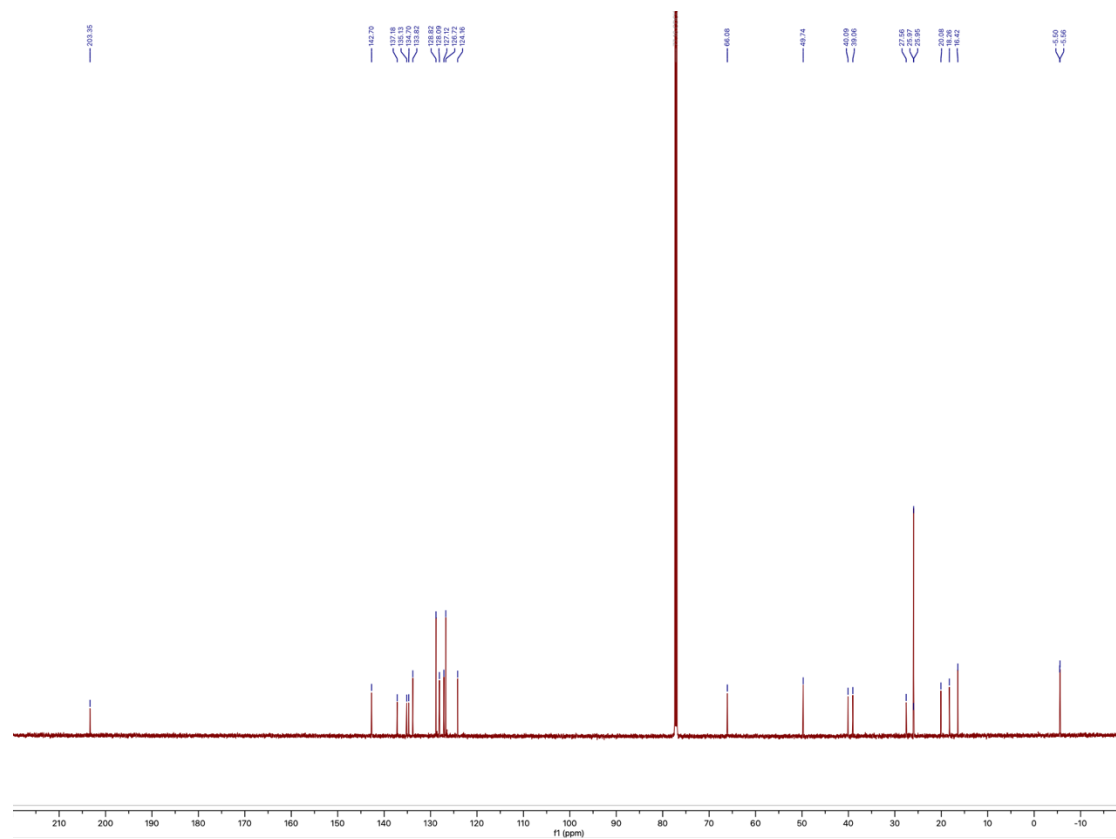
^{13}C NMR (151 MHz, CDCl_3) (**2.3f**)

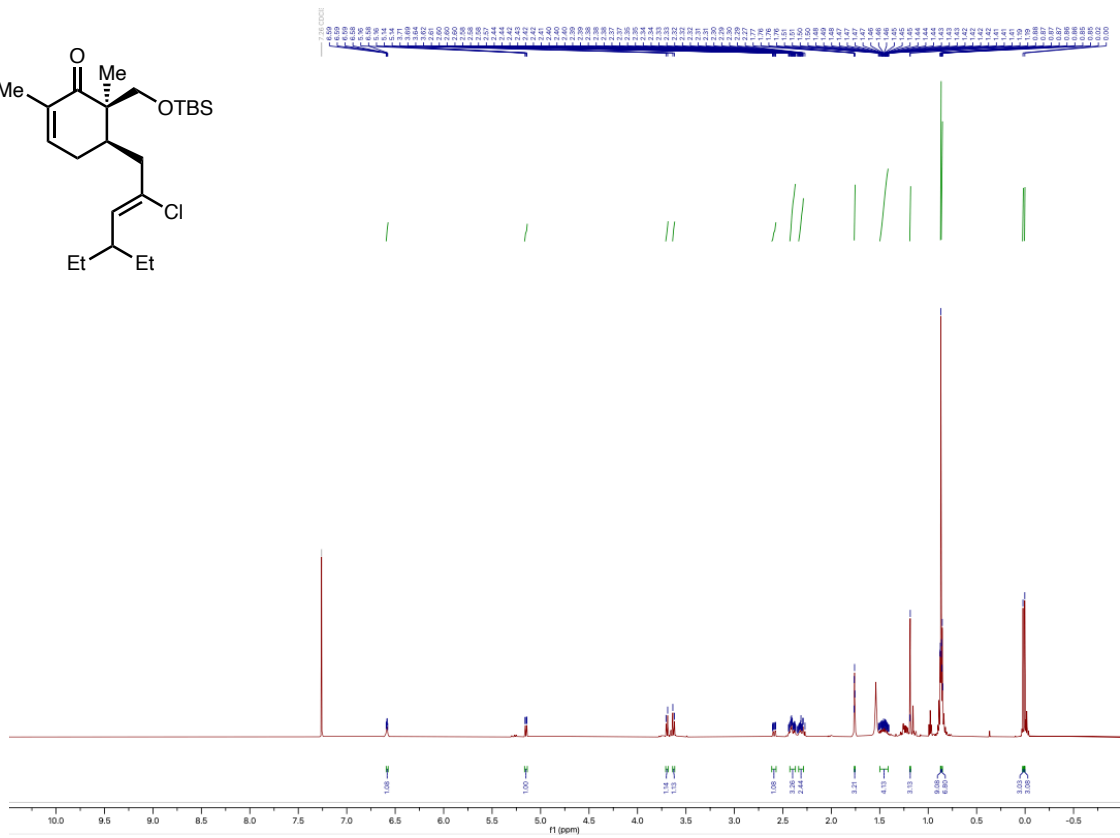
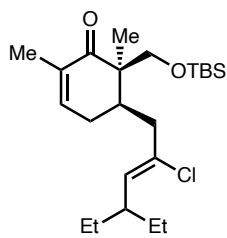
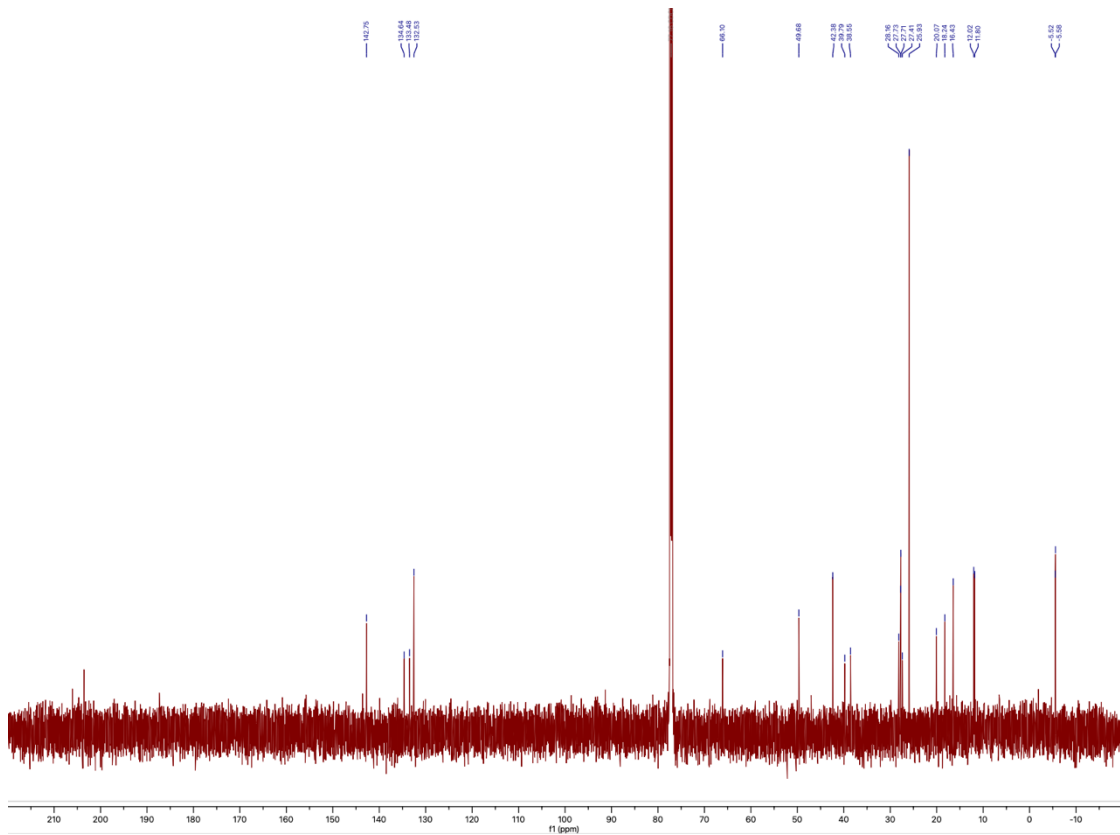


^1H NMR (600 MHz, CDCl_3) (**2.3e**)

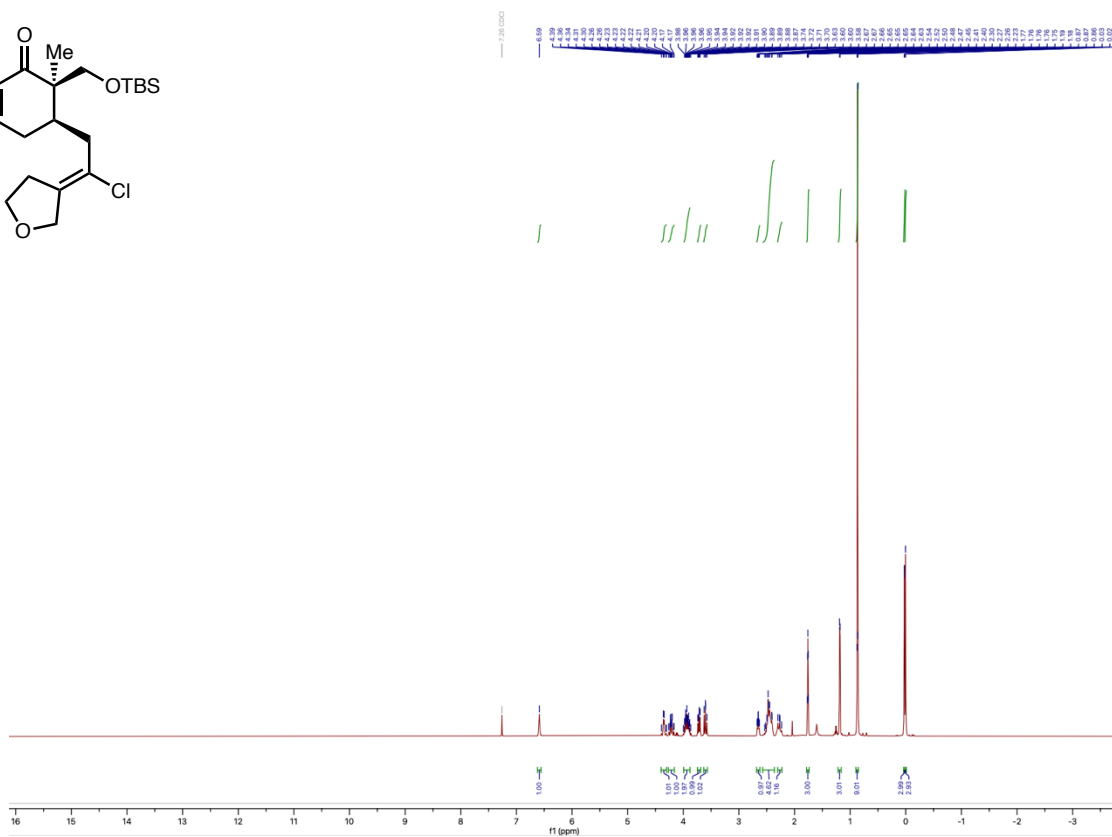
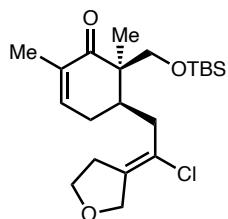


^{13}C NMR (151 MHz, CDCl_3) (**2.3e**)

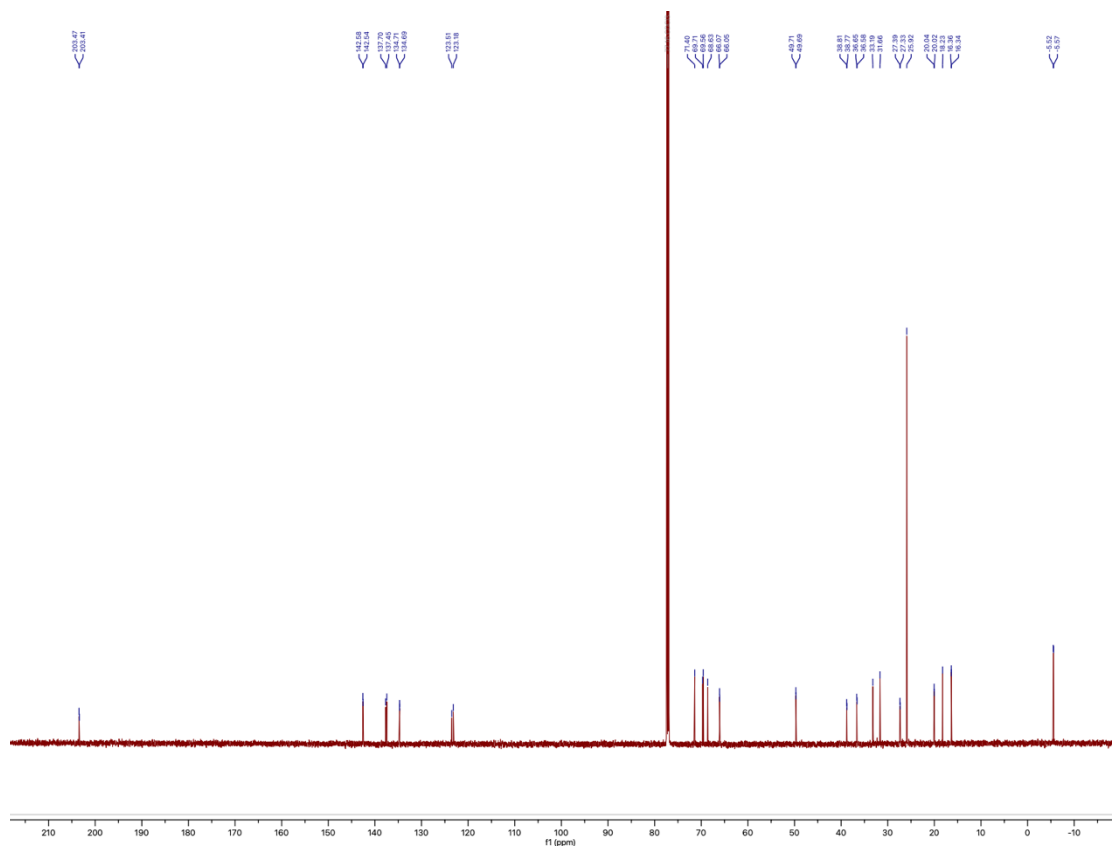


¹H NMR (600 MHz, CDCl₃) (2.3g) ^{13}C NMR (151 MHz, CDCl_3) (2.3g)

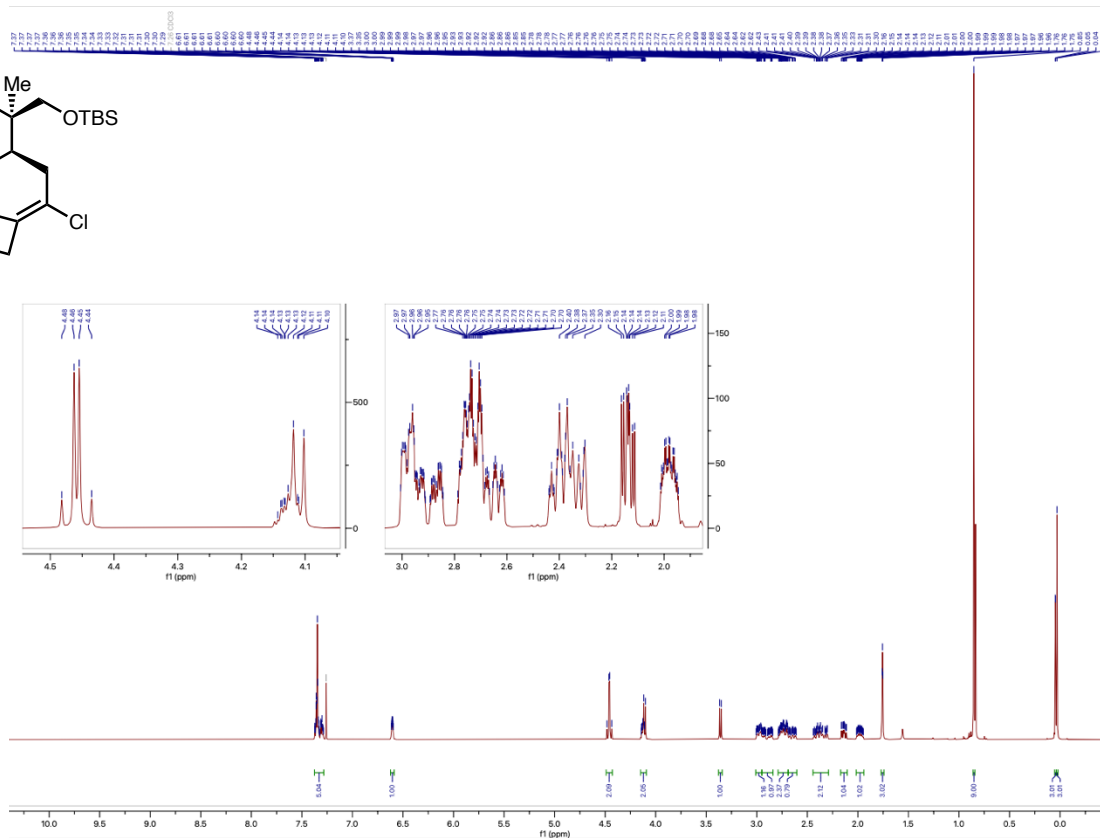
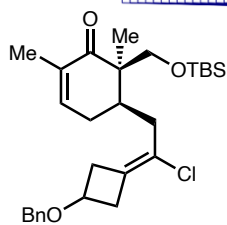
^1H NMR (600 MHz, CDCl_3) (**2.3k**)



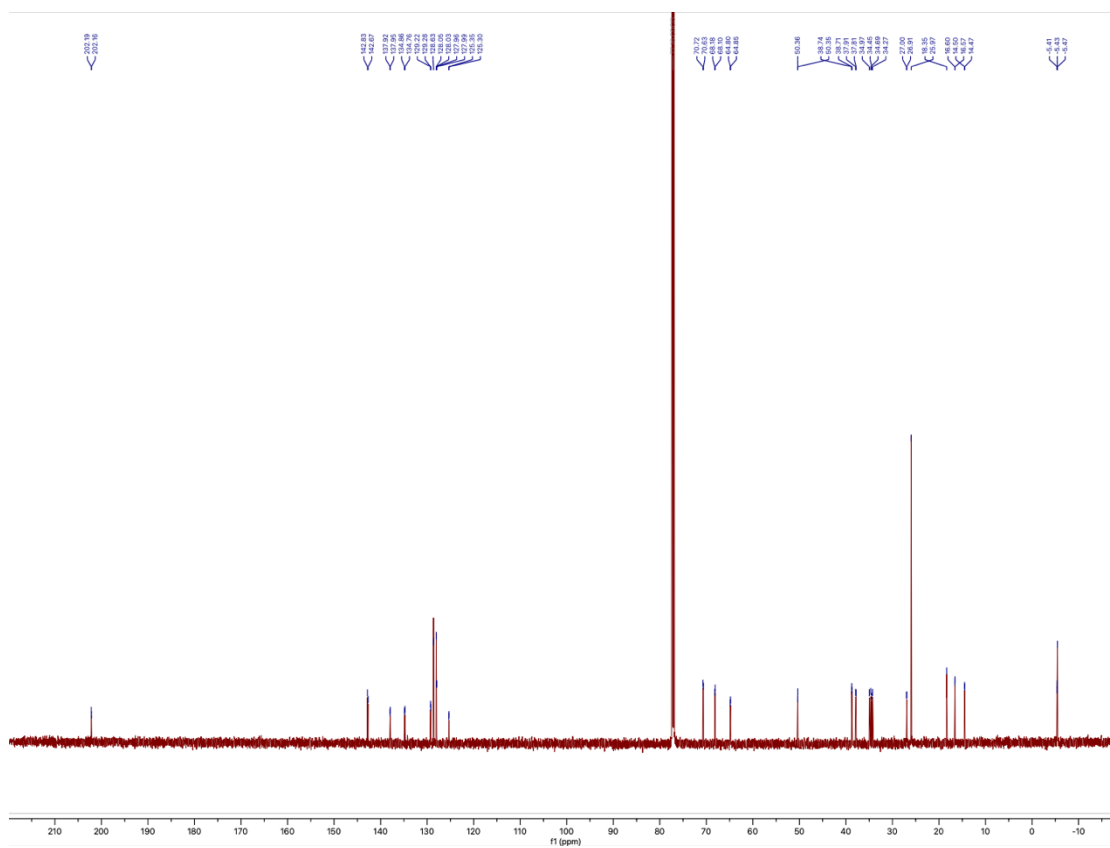
^{13}C NMR (151 MHz, CDCl_3) (**2.3k**)

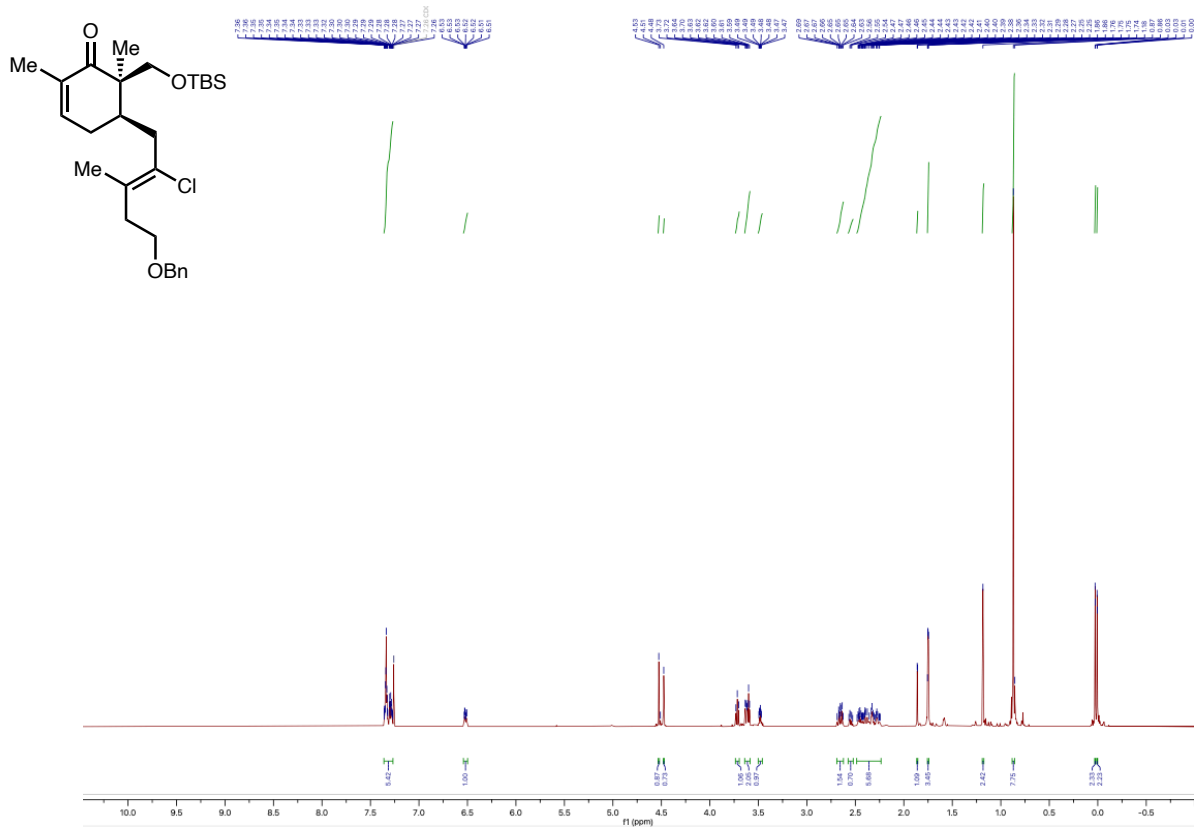
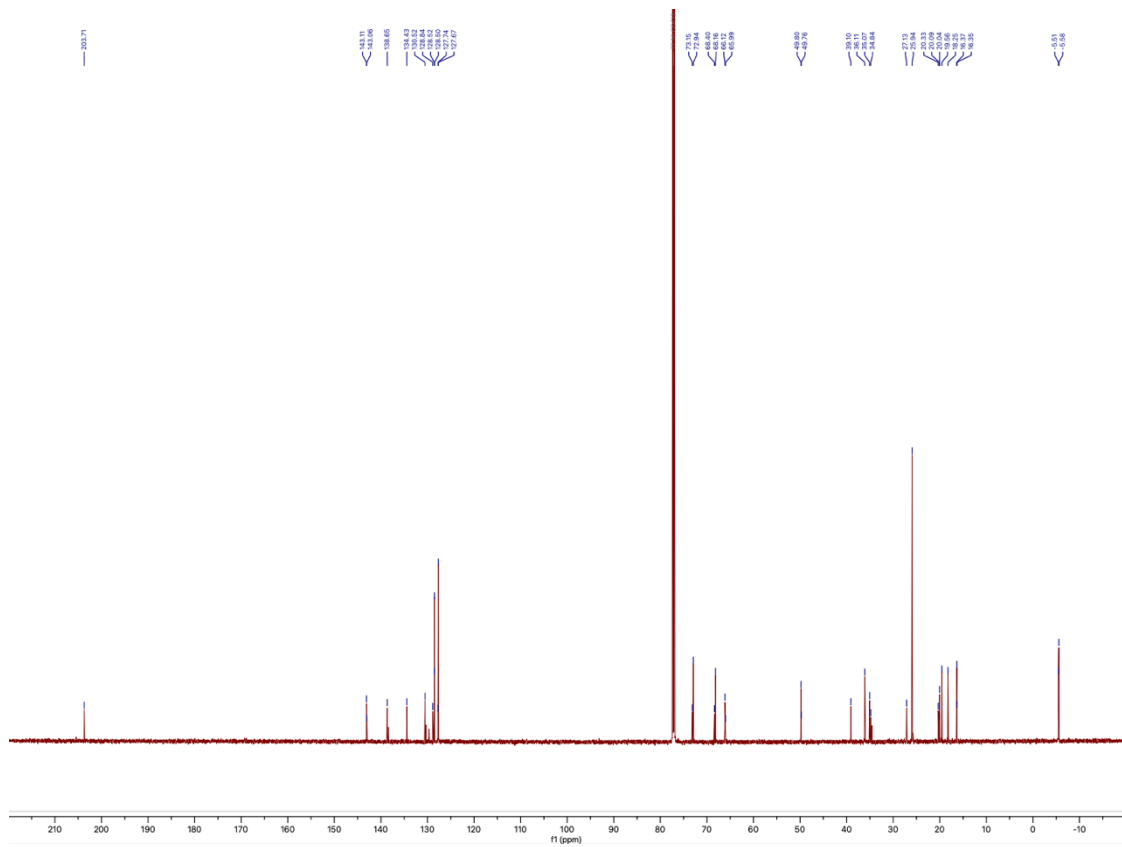


^1H NMR (600 MHz, CDCl_3) (**2.3m**)

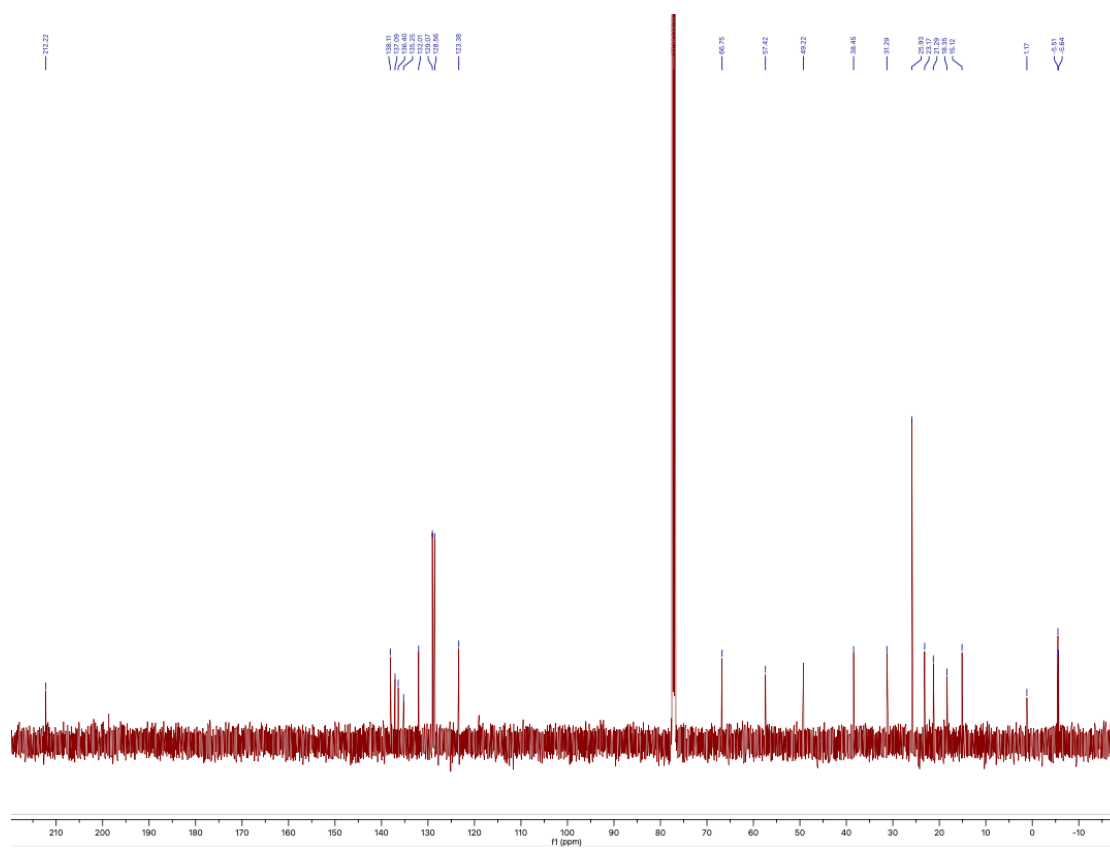


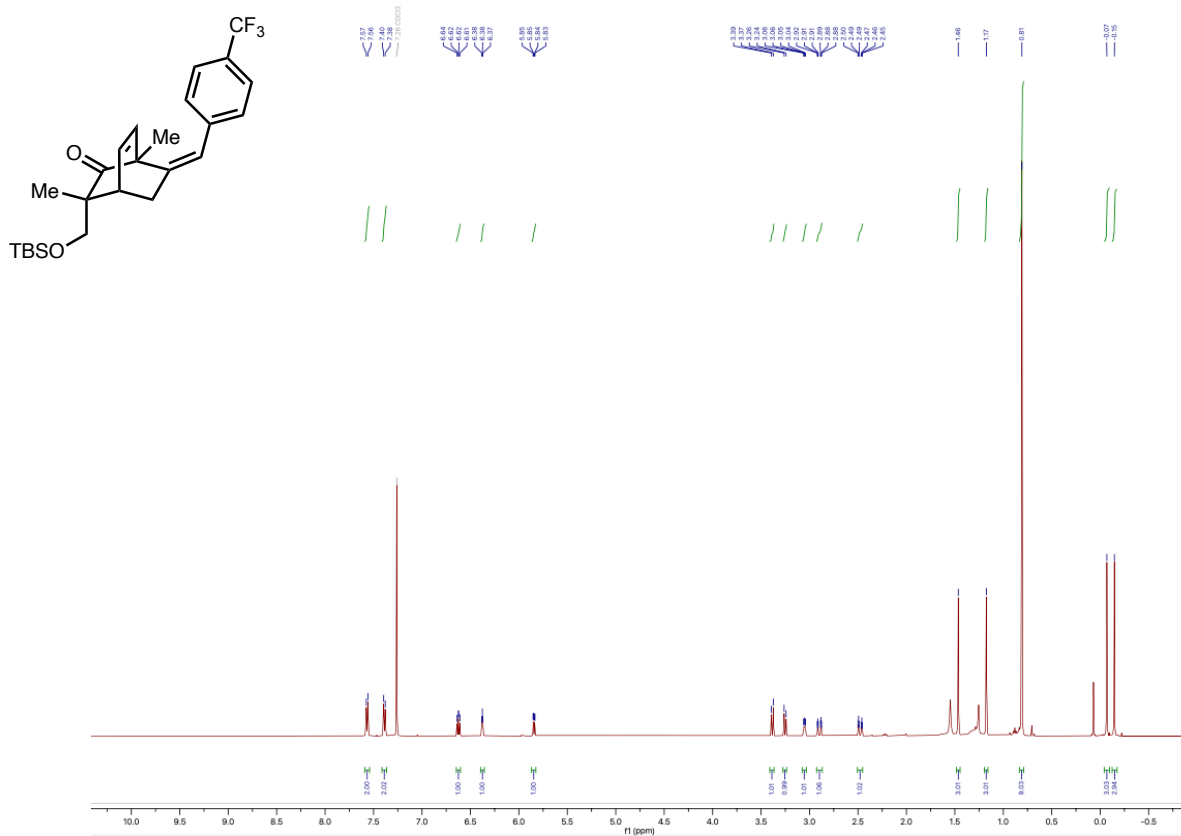
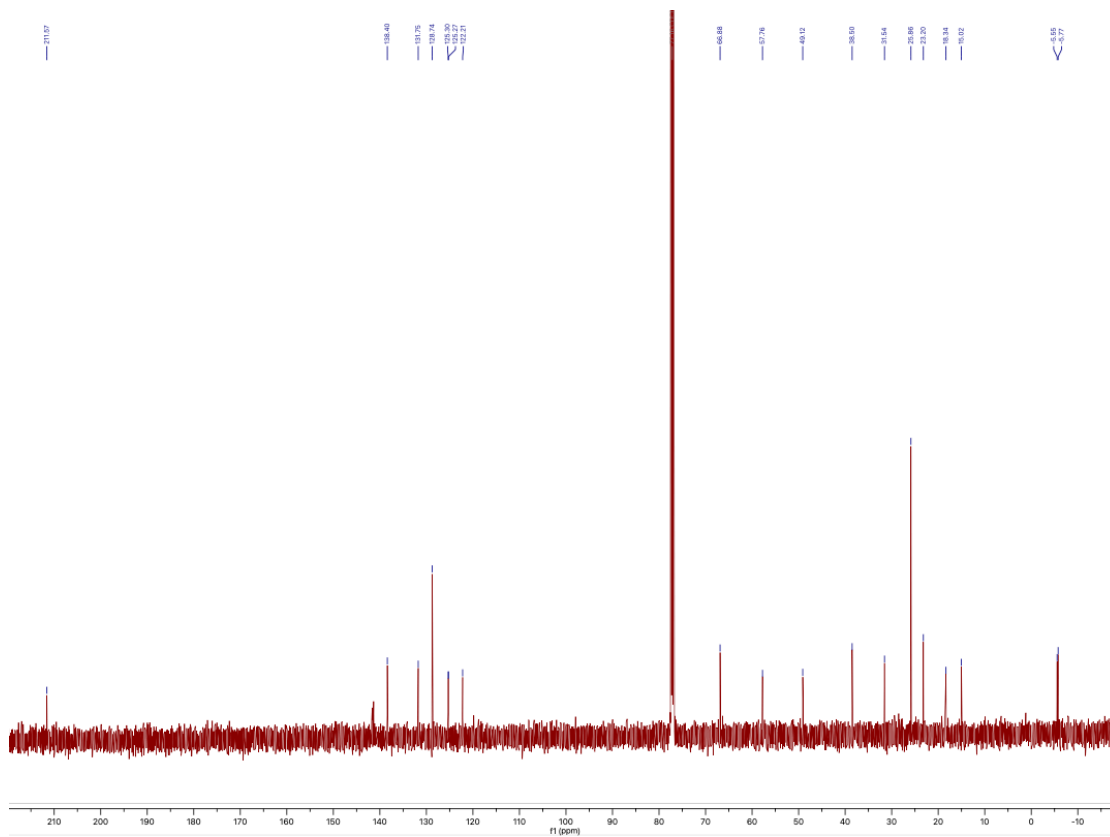
^{13}C NMR (151 MHz, CDCl_3) (**2.3m**)



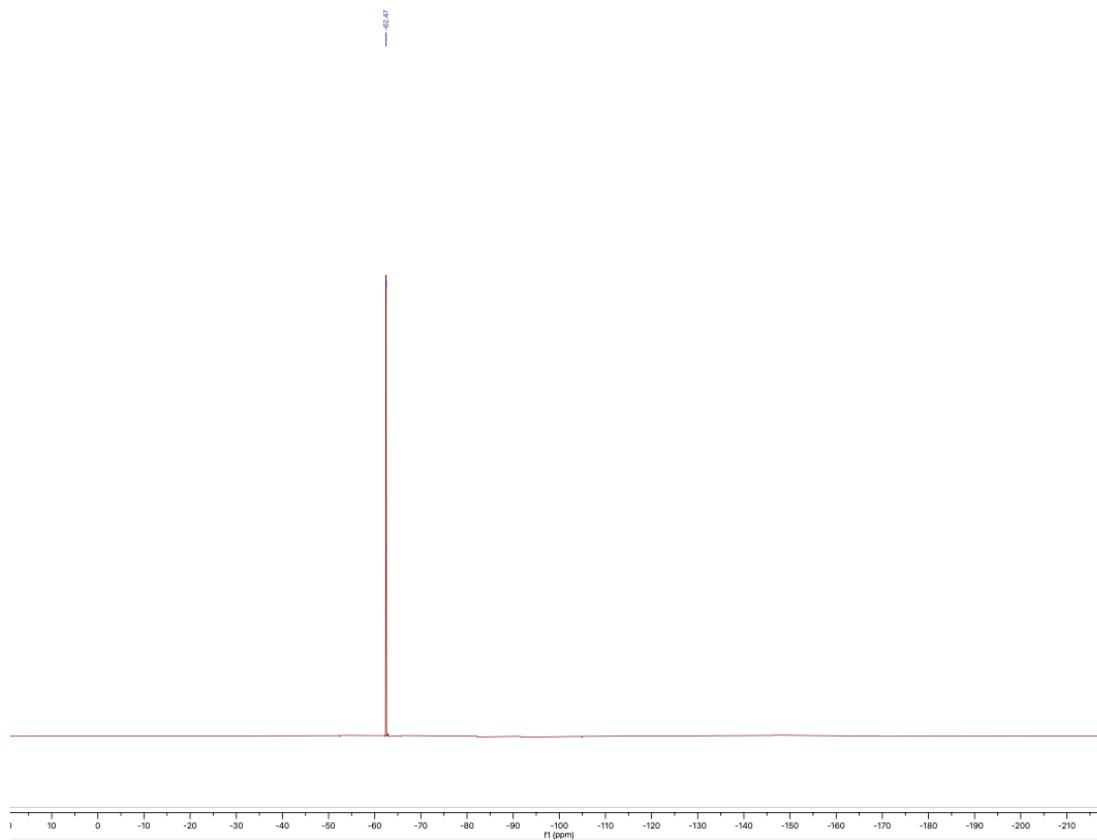
¹H NMR (700 MHz, CDCl₃) (**2.30**) ^{13}C NMR (151 MHz, CDCl_3) (**2.30**)

Chemical structure of compound 10: A bicyclic molecule featuring a TBSO group, a methyl group, and a 4-methylbenzyl group.

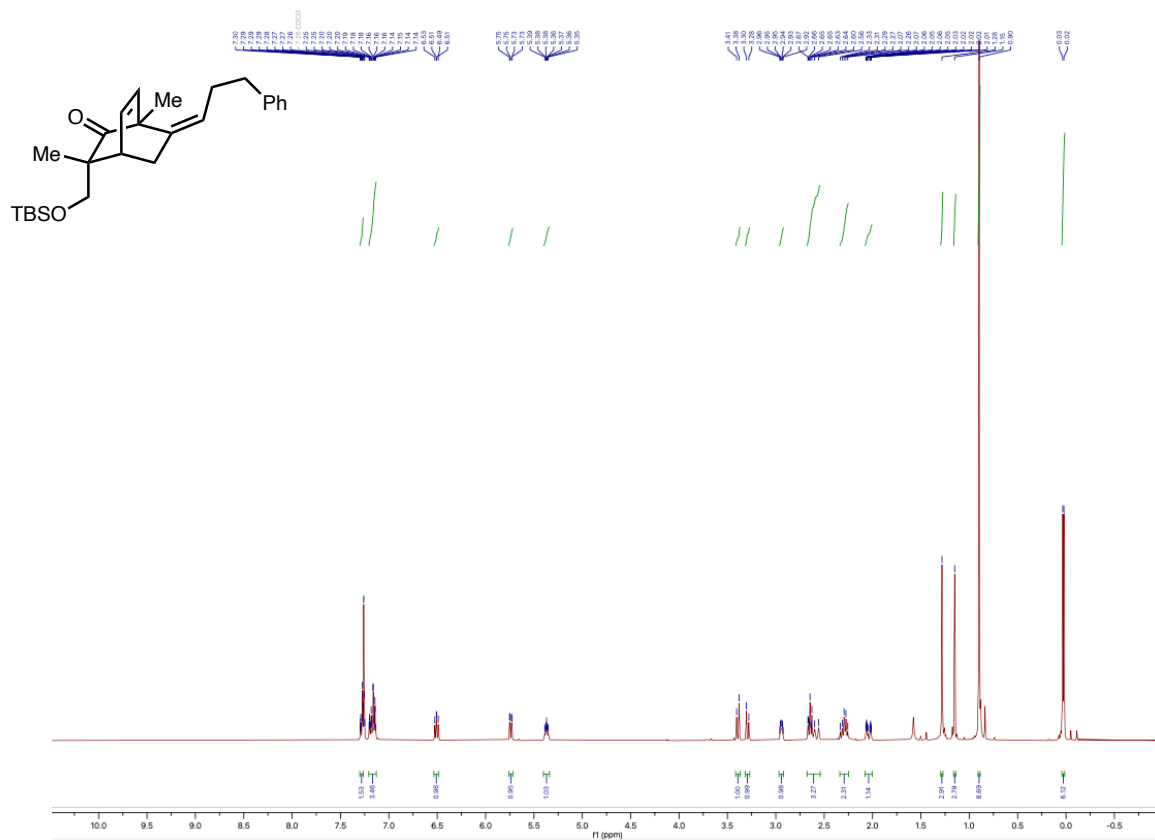


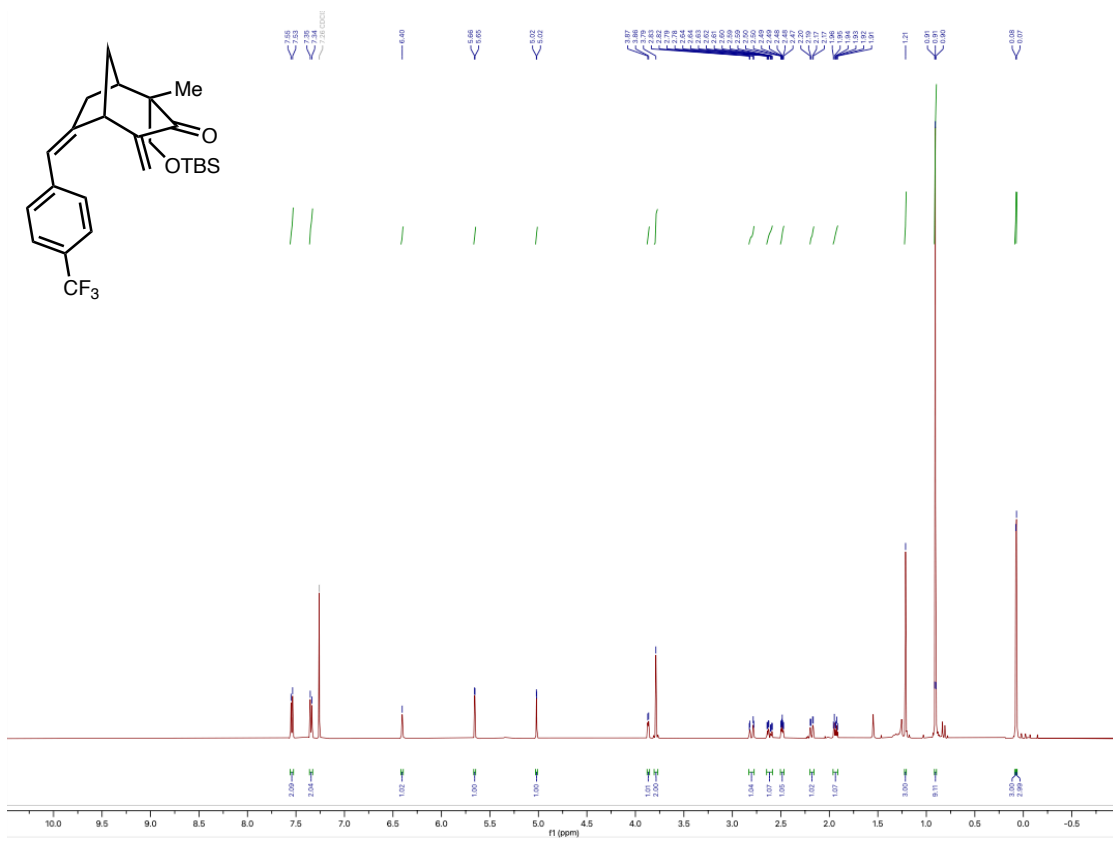
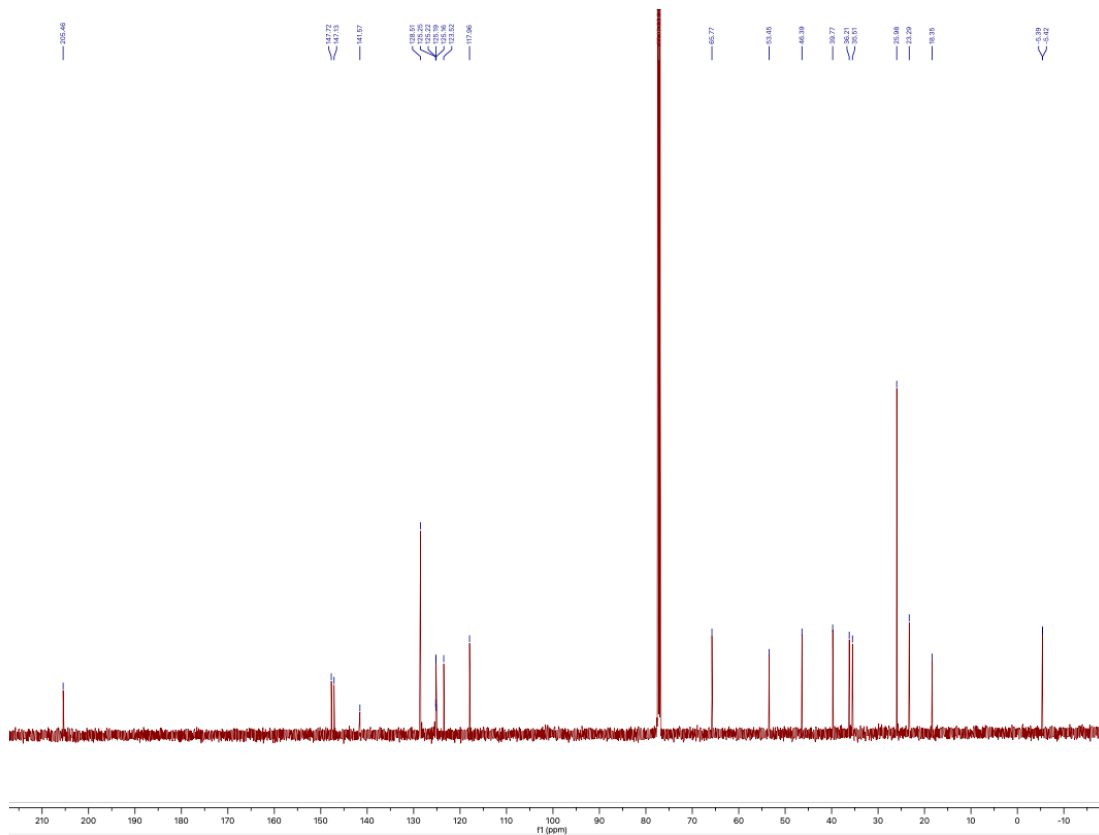
¹H NMR (500 MHz, CDCl₃) (**2.4b**) ^{13}C NMR (126 MHz, CDCl_3) (**2.4b**)

^{19}F NMR (500 MHz, CDCl_3) (**2.4b**)

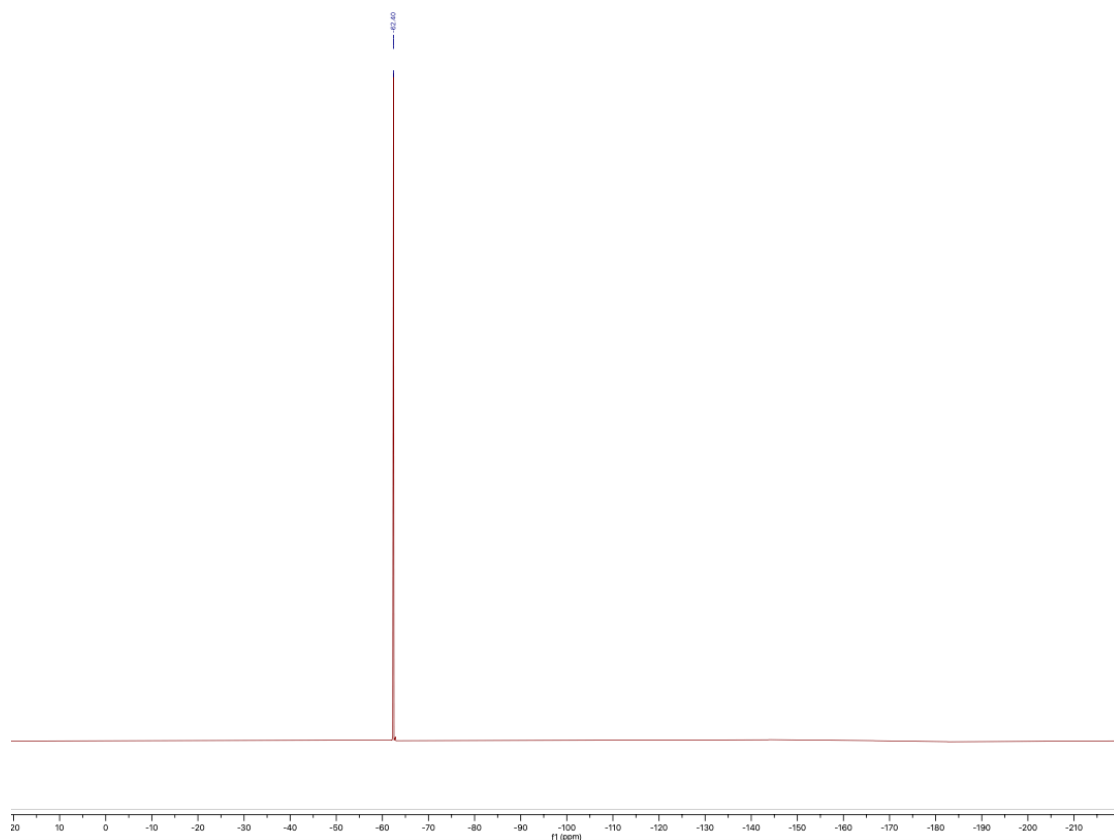


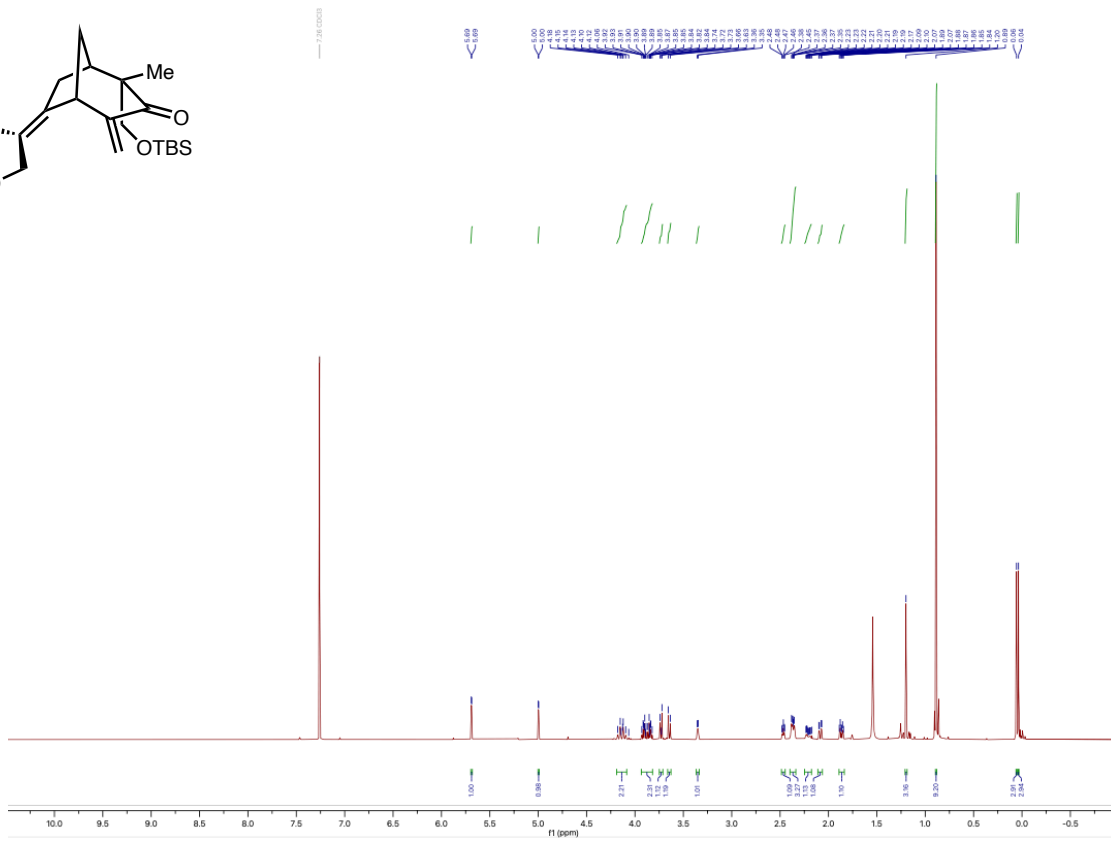
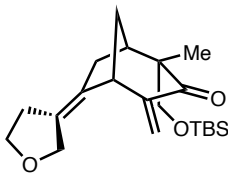
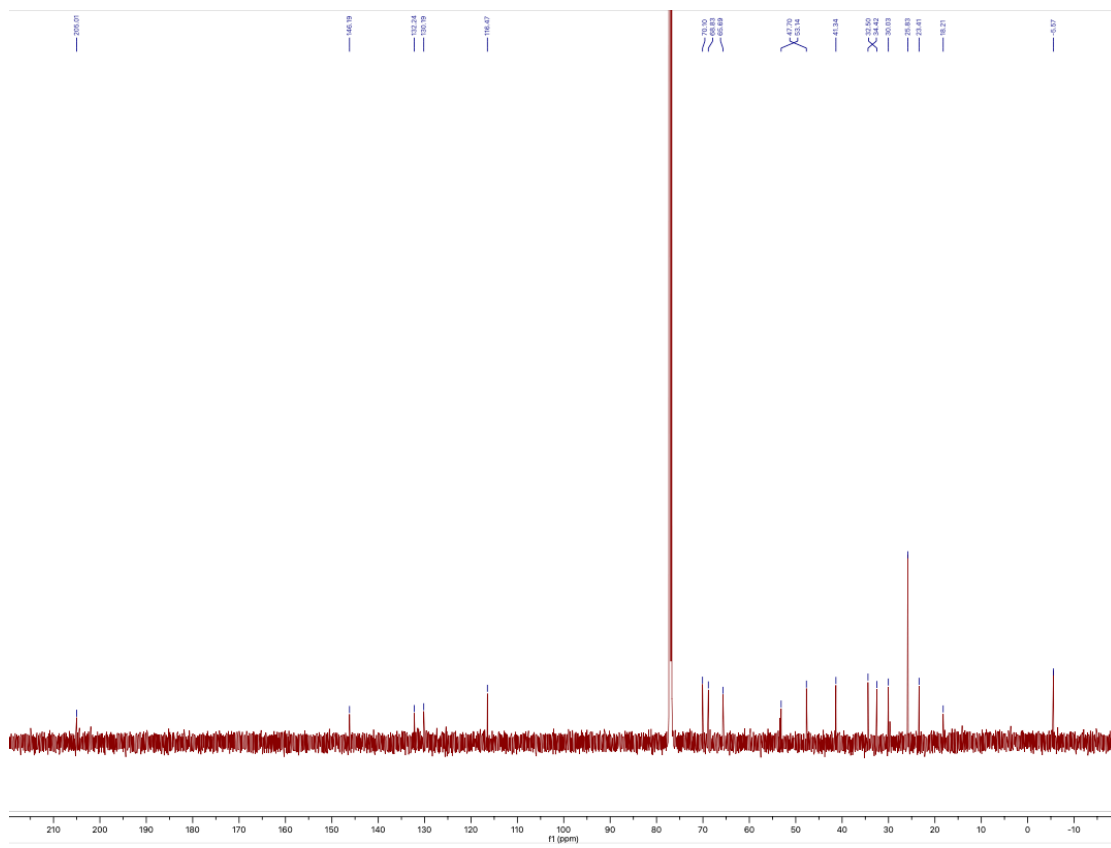
^1H NMR (600 MHz, CDCl_3) (**2.42**)



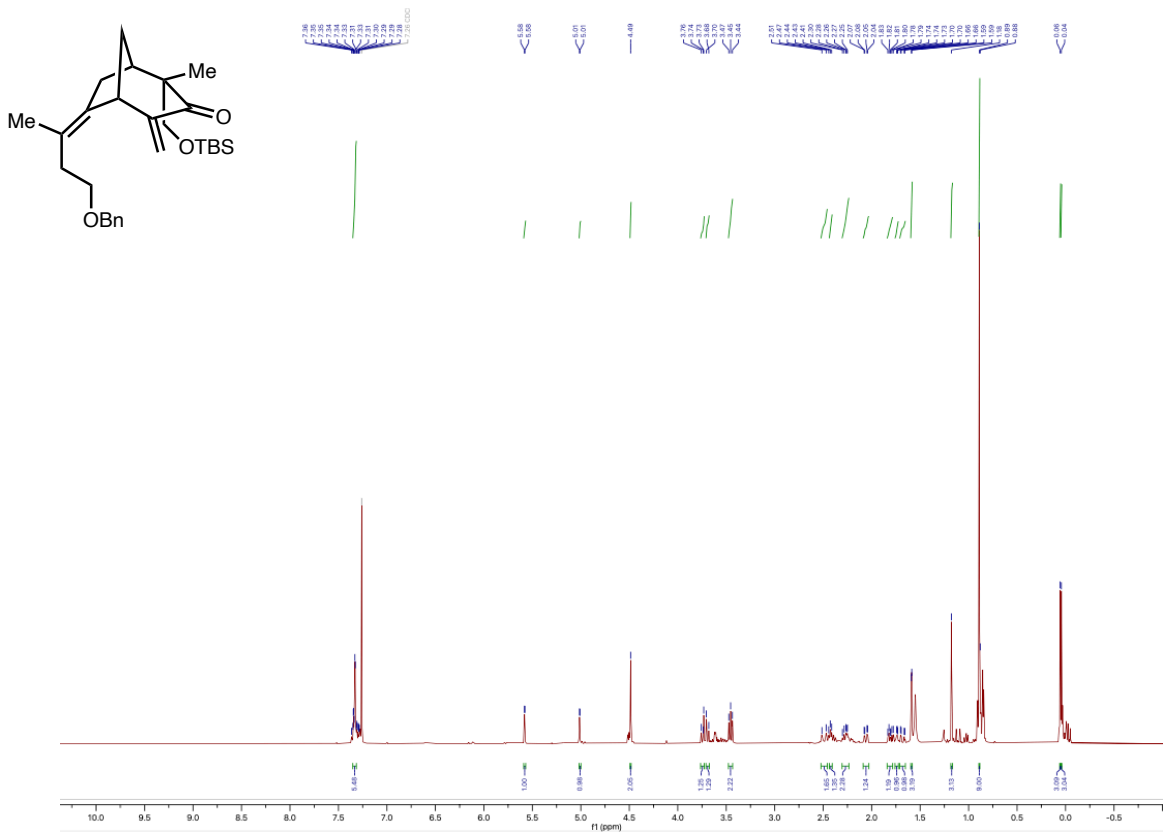
¹H NMR (500 MHz, CDCl₃) (**2.7b**) ^{13}C NMR (126 MHz, CDCl_3) (**2.7b**)

^{19}F NMR (500 MHz, CDCl_3) (**2.42**)

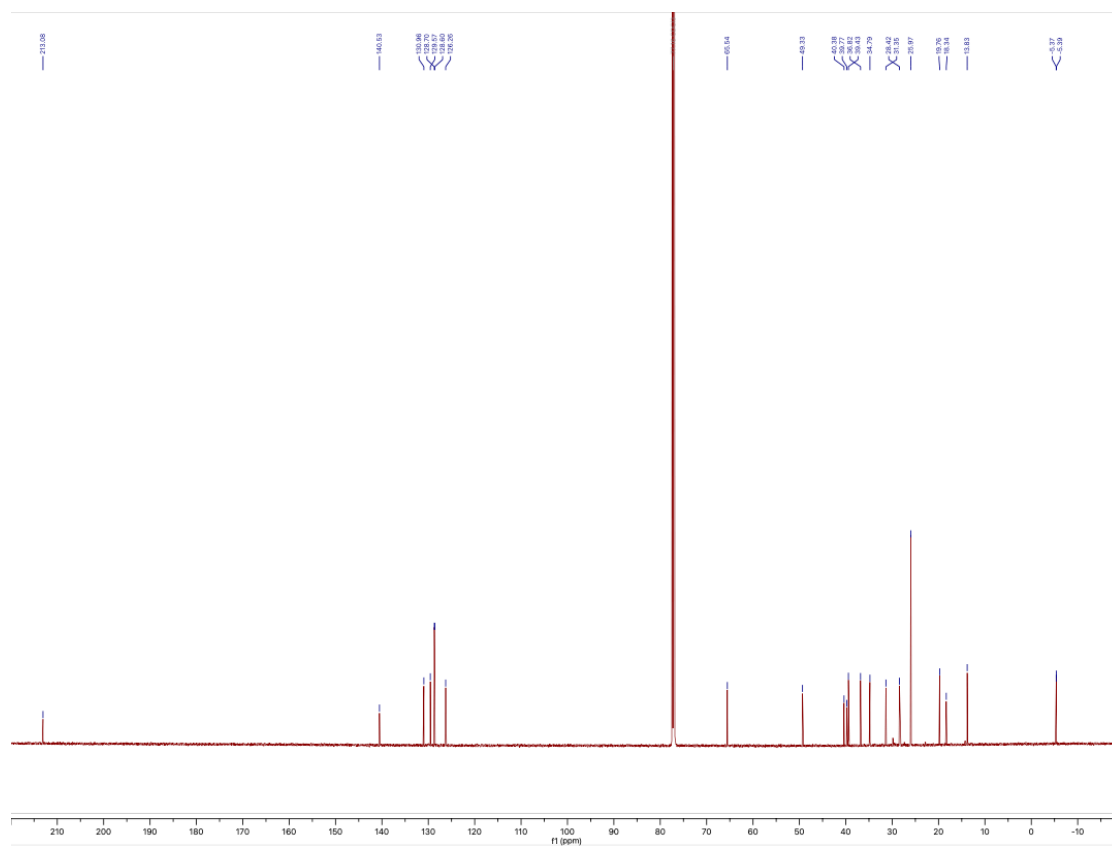


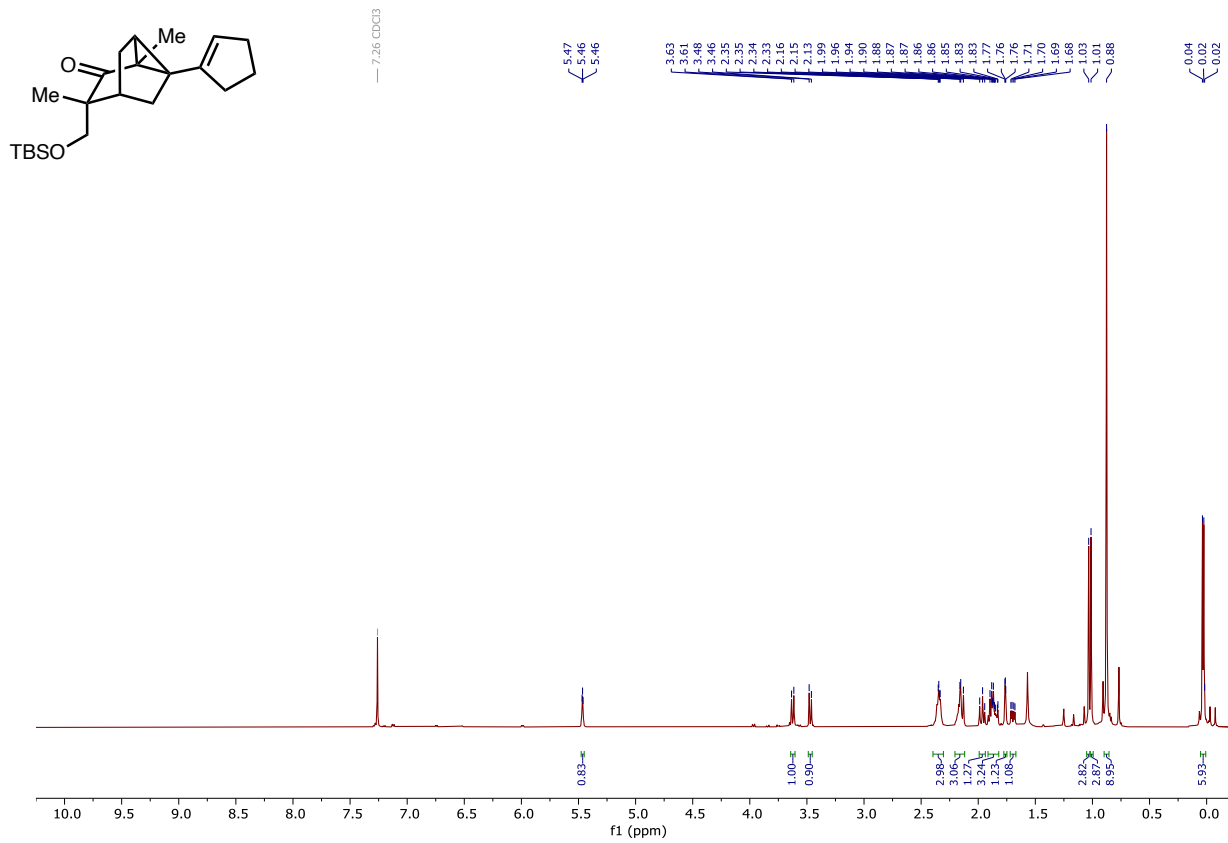
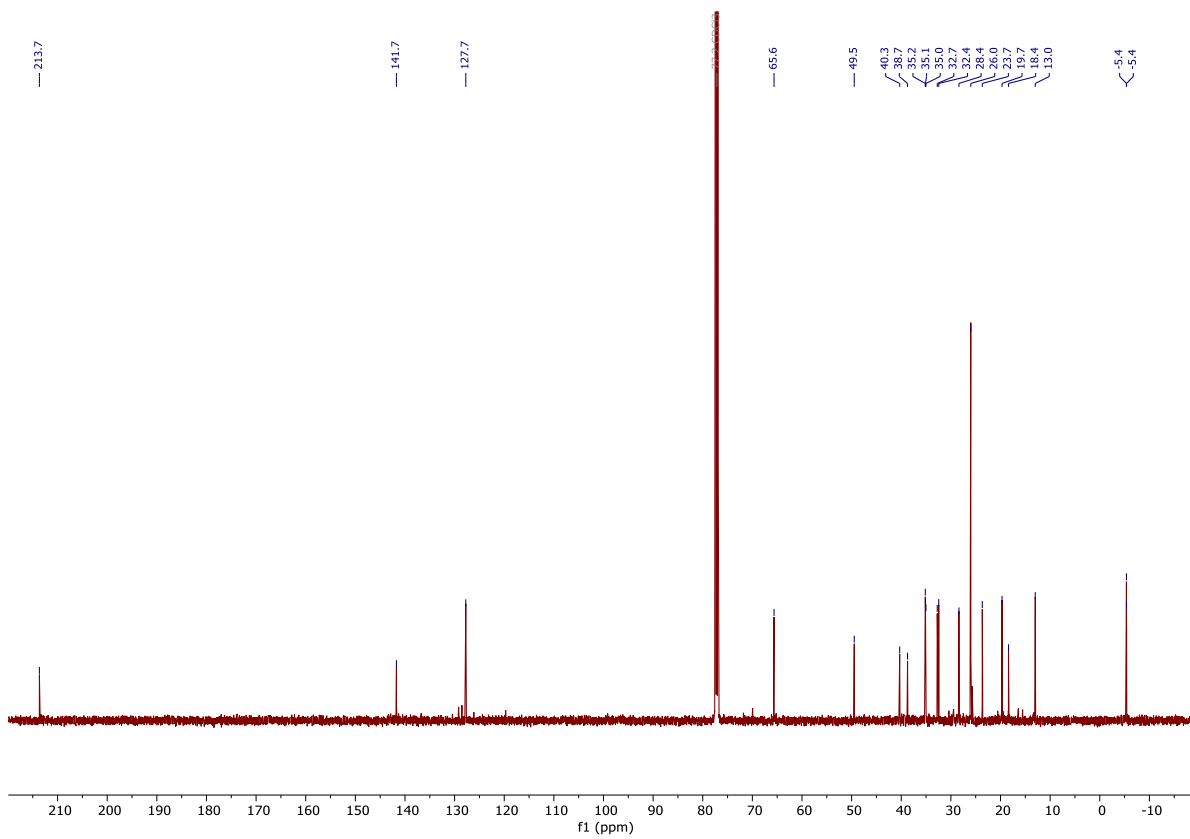
¹H NMR (500 MHz, CDCl₃) (**2.7k**) ^{13}C NMR (151 MHz, CDCl_3) (**2.7k**)

^1H NMR (400 MHz, CDCl_3) (**2.7o**)



Chemical structure of compound 10: A bicyclic ketone (bicyclo[2.2.1]hept-5-en-2-one) with a TBSO group at C1, a methyl group at C2, and a 3-phenylallyl group at C3.

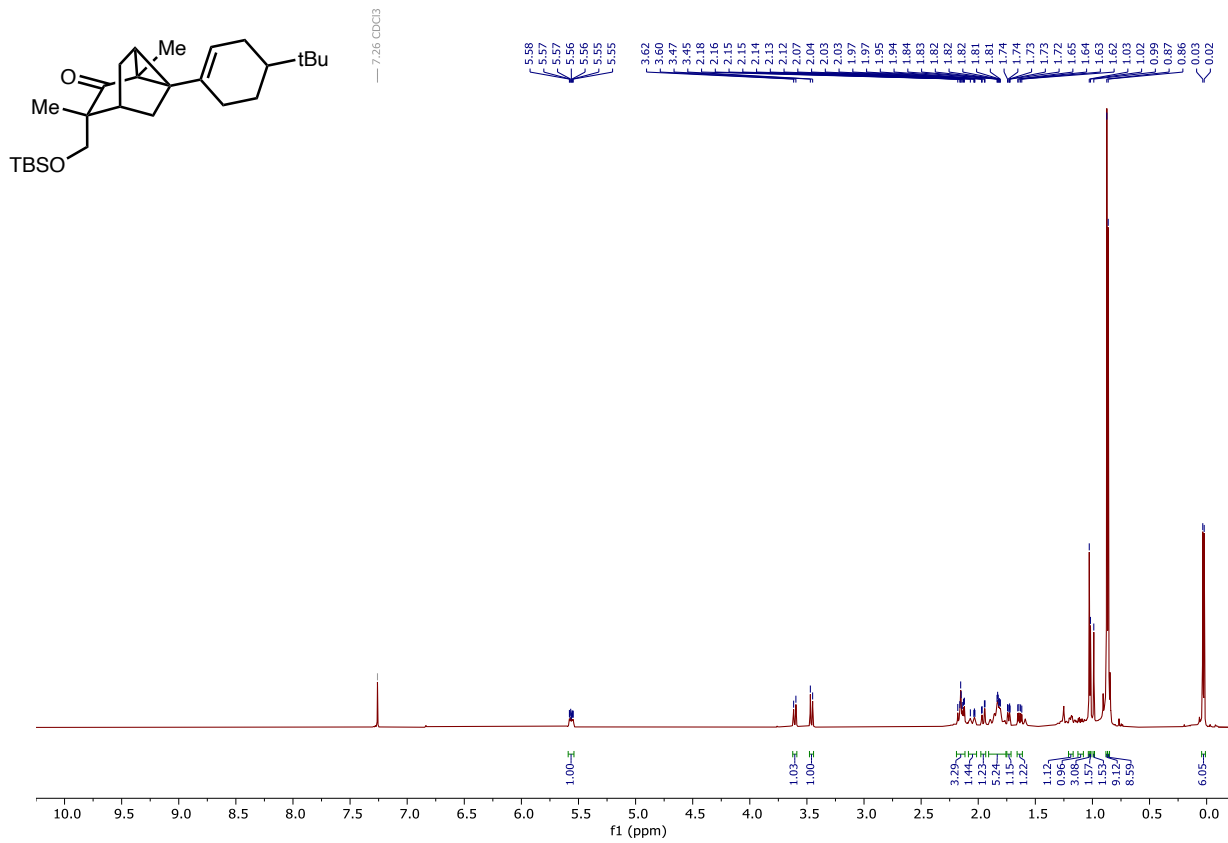
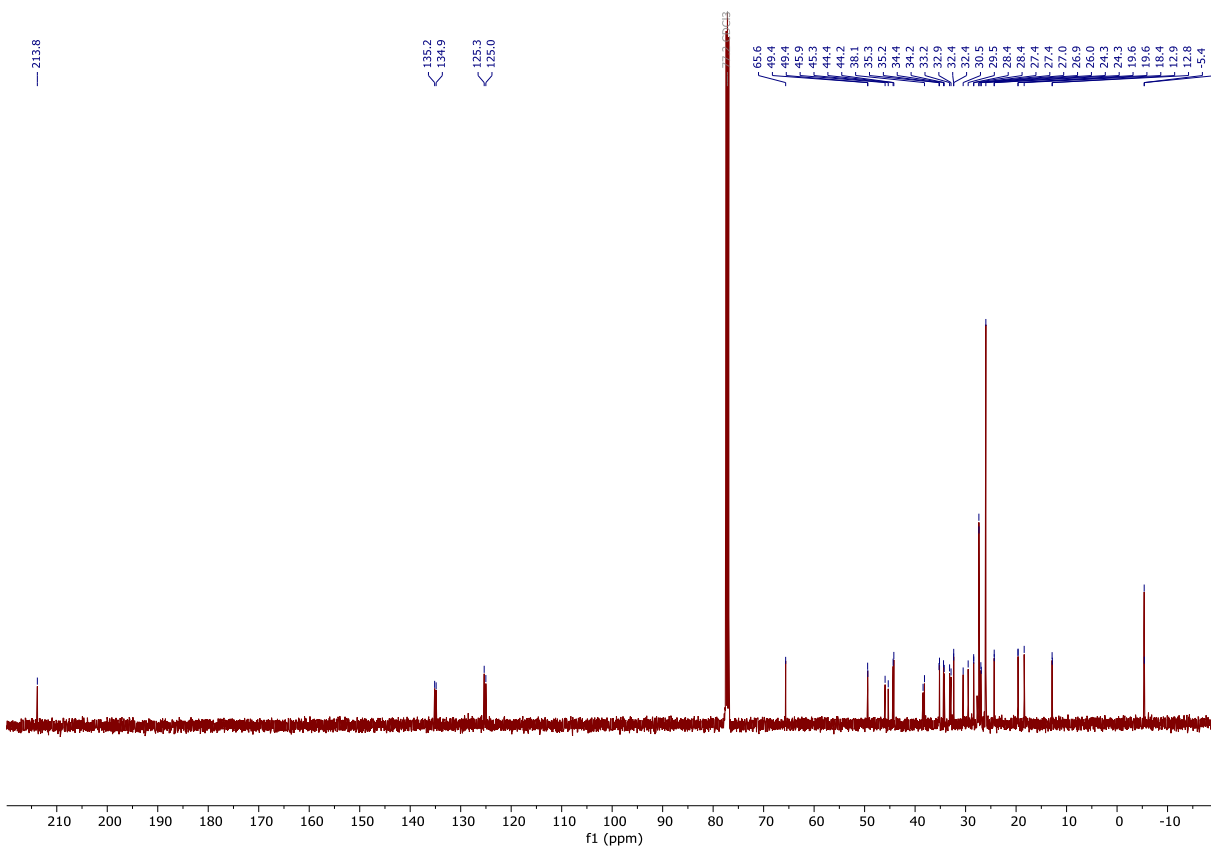


¹H NMR (500 MHz, CDCl₃) (2.46) ^{13}C NMR (126 MHz, CDCl_3) (2.46)

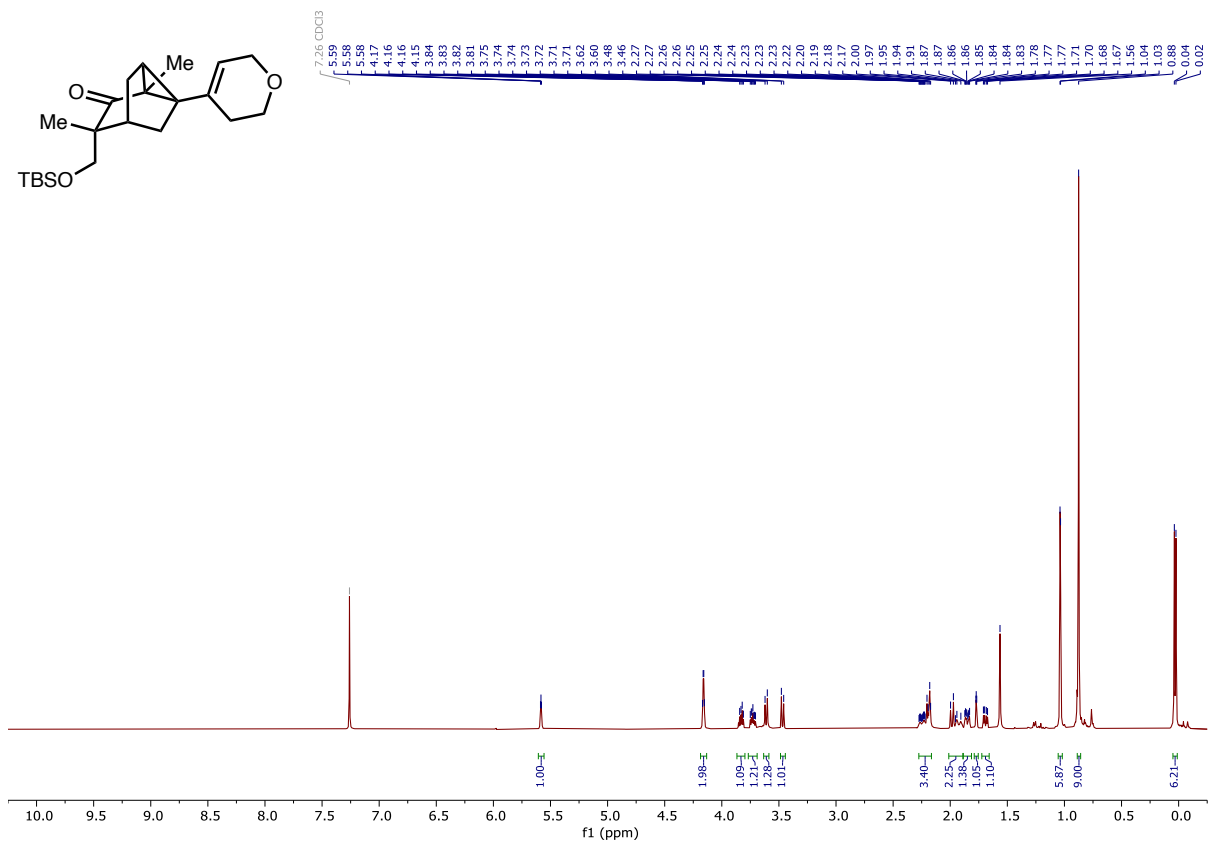
Chemical structure of compound 10 is shown in the top left. The spectrum displays peaks from 0.02 to 6.38 ppm. Key features include a TBSO group, a ketone, a cyclohexene ring, and a cyclopropane ring. Integration values are provided below the baseline, and chemical shifts are listed above the peaks.

Chemical Shift (ppm)	Integration
6.38	6.38
3.61	1.00
3.59	1.02
3.47	
3.45	
3.15	
2.15	
2.14	
2.04	
2.03	
2.03	
2.02	
2.02	
1.97	
1.94	
1.85	
1.84	
1.83	
1.82	
1.81	
1.74	
1.66	
1.65	
1.64	
1.63	
1.03	
1.01	
0.88	
0.87	
0.03	
0.03	
0.02	

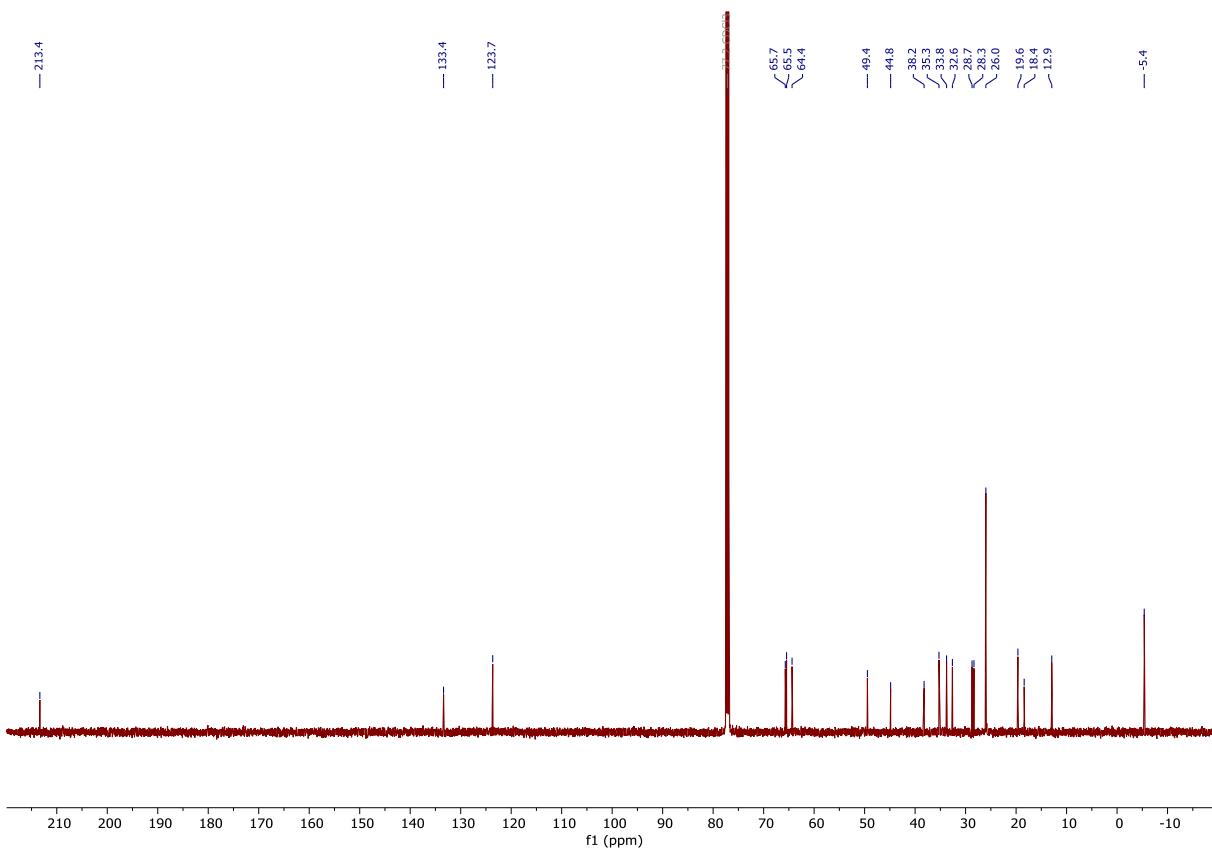
13C NMR spectrum (CDCl₃) of compound 10. The x-axis is labeled 'f1 (ppm)' and ranges from -10 to 210. The spectrum shows several peaks, with the most prominent one at 77.0 ppm (CDCl₃ solvent). Other labeled peaks include 213.9, 135.2, 124.9, 65.6, 49.4, 46.1, 38.3, 35.2, 32.6, 32.0, 28.6, 28.4, 26.0, 25.3, 23.0, 22.6, 18.4, 12.8, -5.4, and -5.4. The peaks are color-coded: blue for aromatic/alkene carbons, red for aliphatic carbons, and green for the solvent peak.

¹H NMR (500 MHz, CDCl₃) (**2.48**) ^{13}C NMR (126 MHz, CDCl_3) (**2.48**)

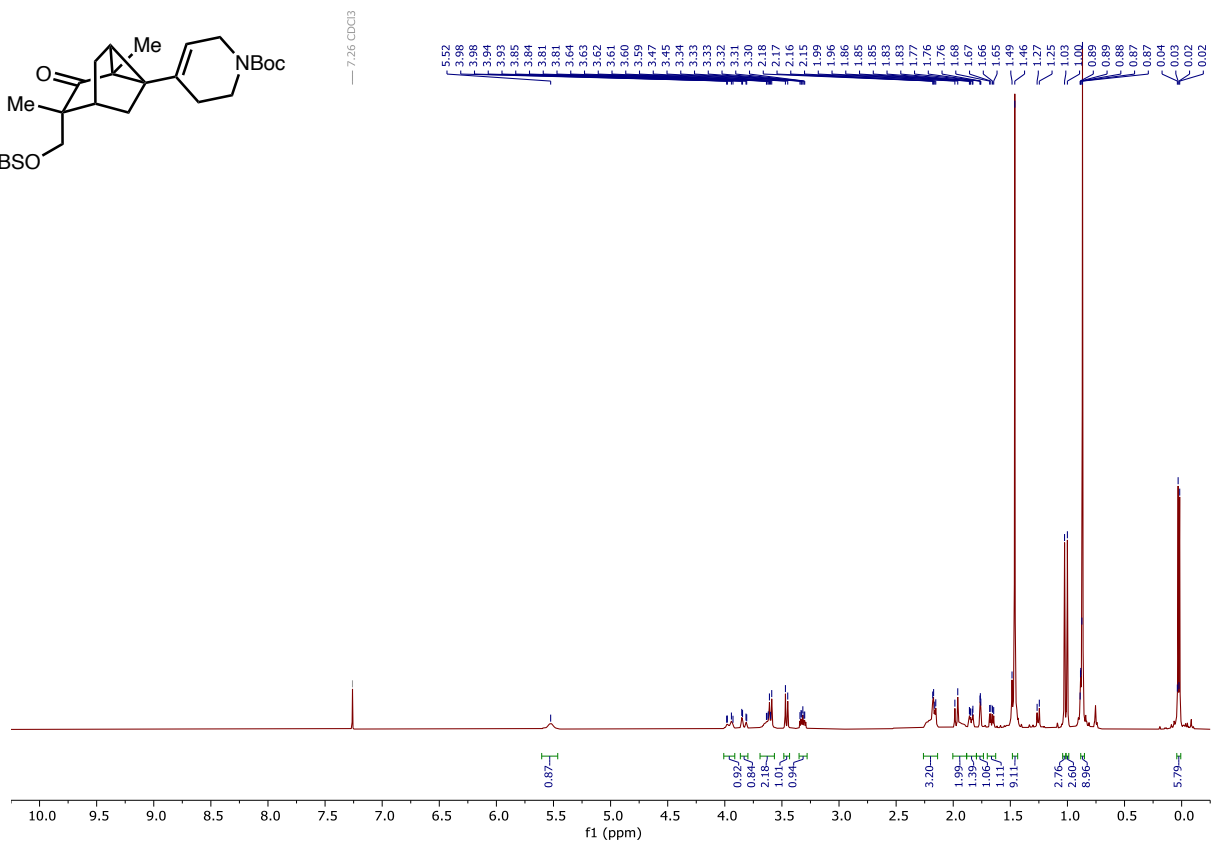
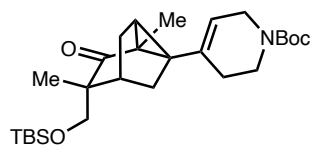
^1H NMR (500 MHz, CDCl_3) (**2.49**)



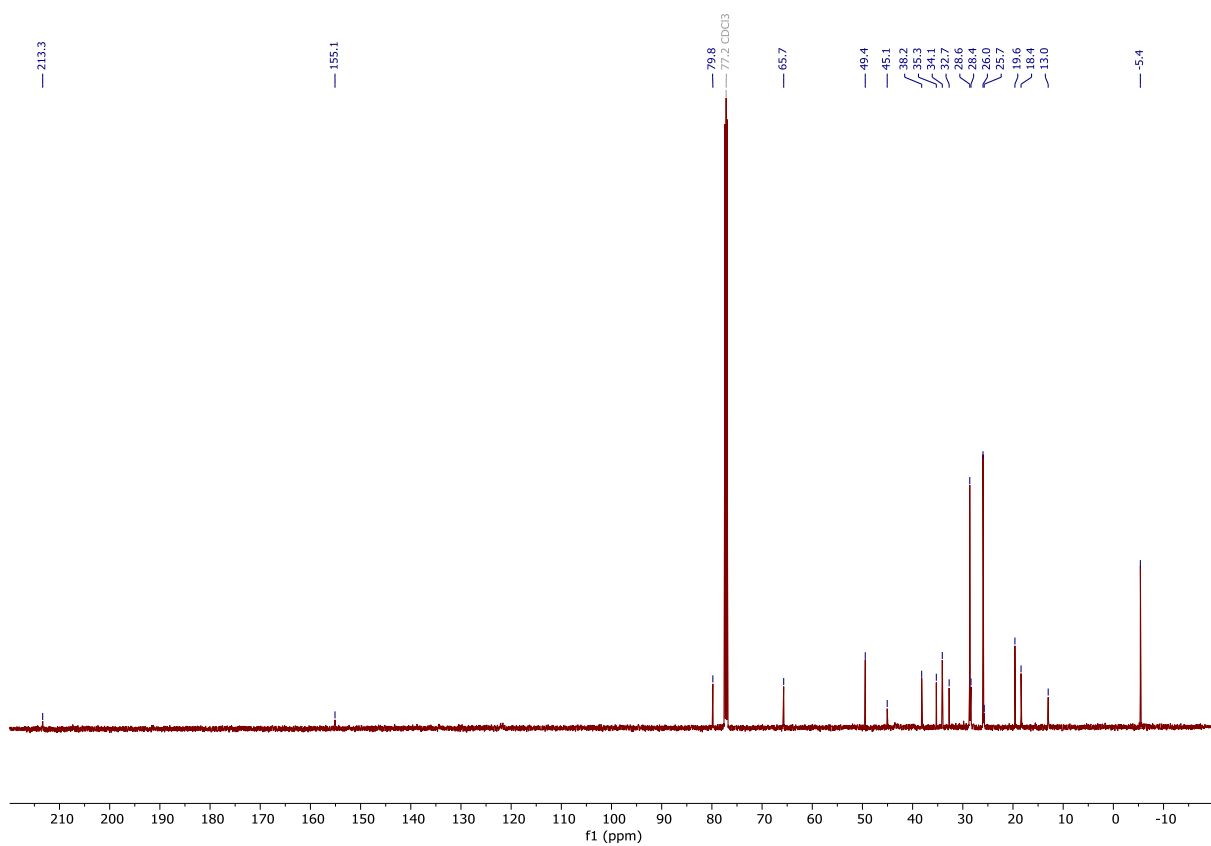
^{13}C NMR (126 MHz, CDCl_3) (**2.49**)

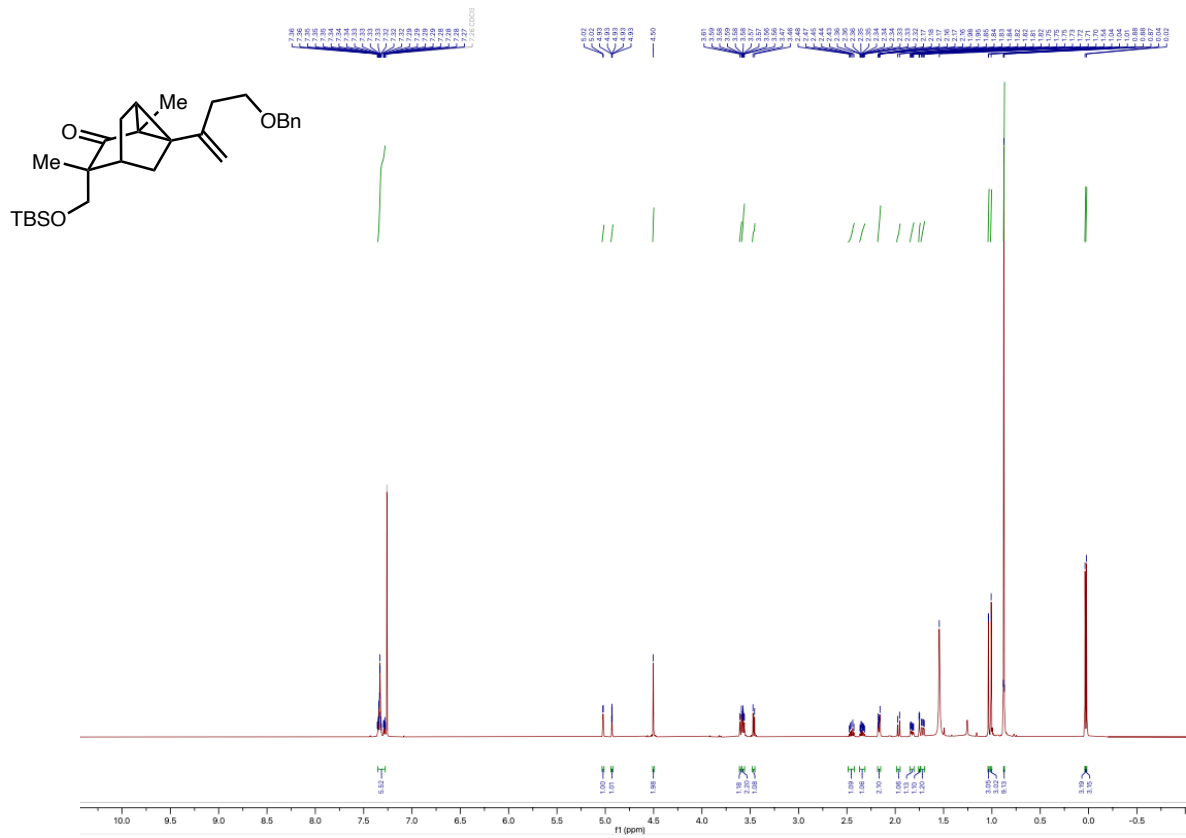
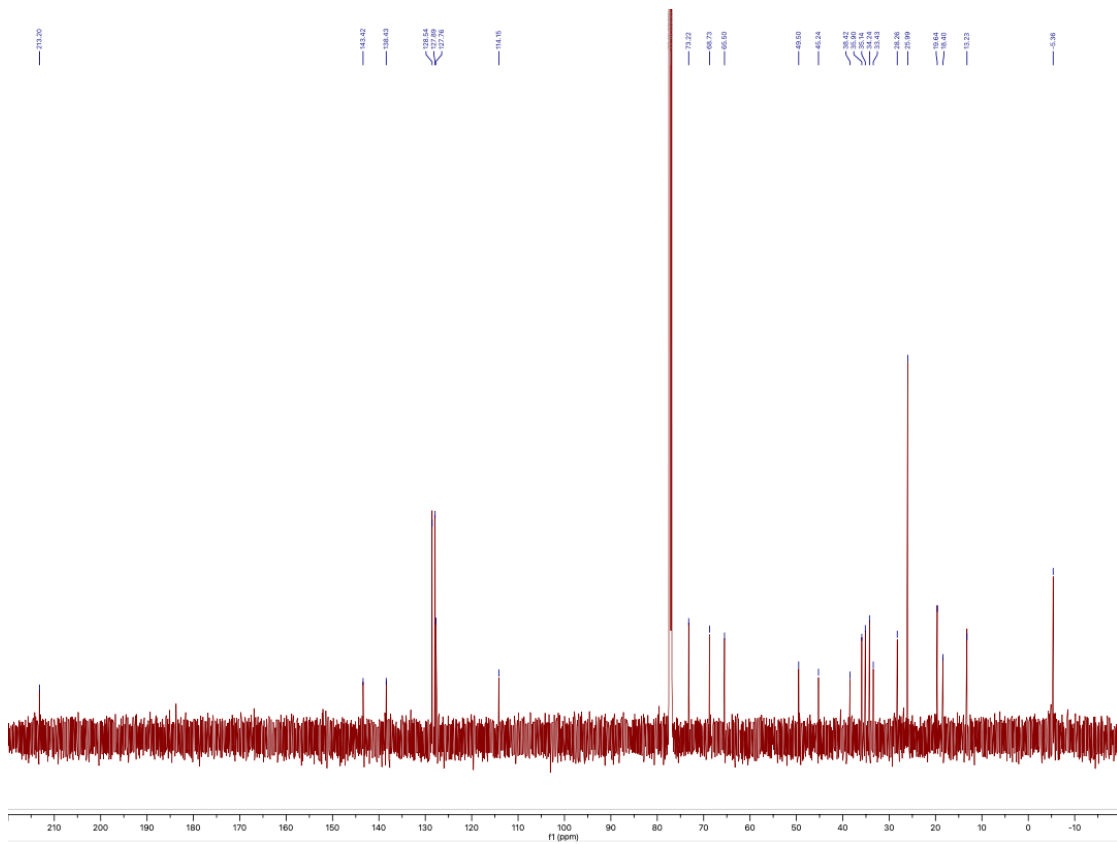


^1H NMR (500 MHz, CDCl_3) (**2.50**)

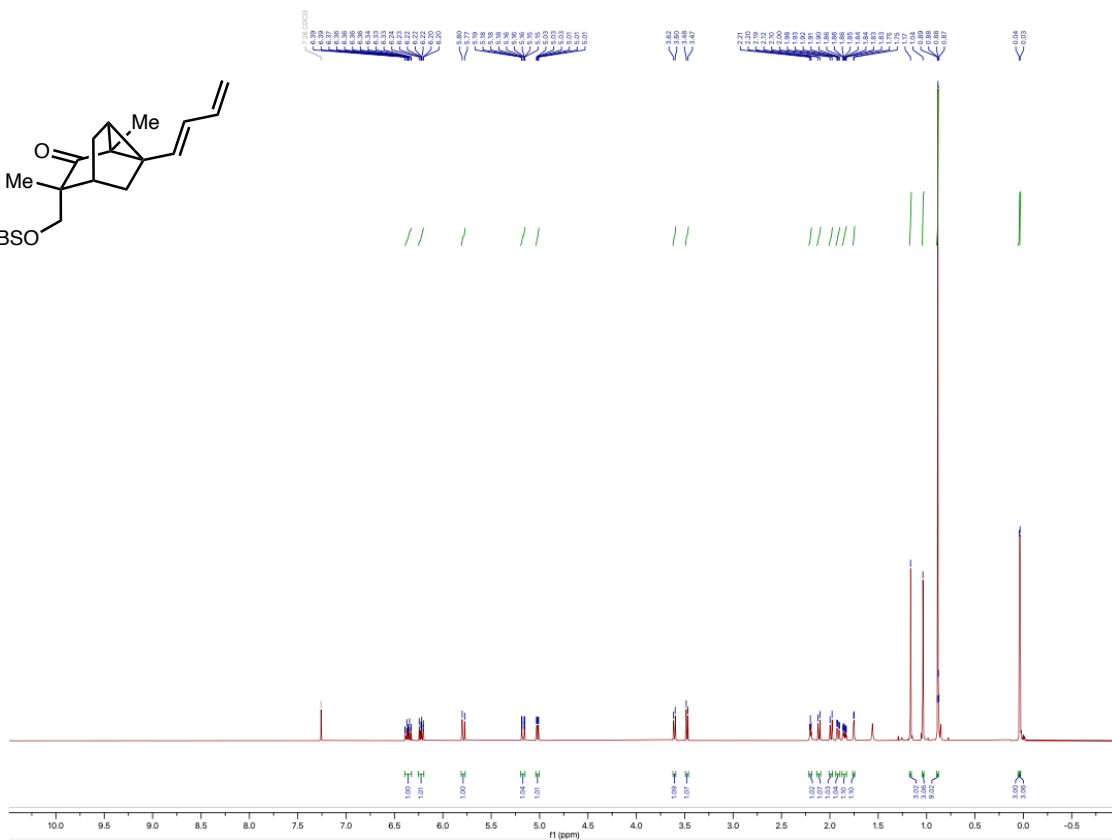
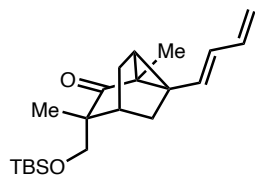


^{13}C NMR (126 MHz, CDCl_3) (**2.50**)

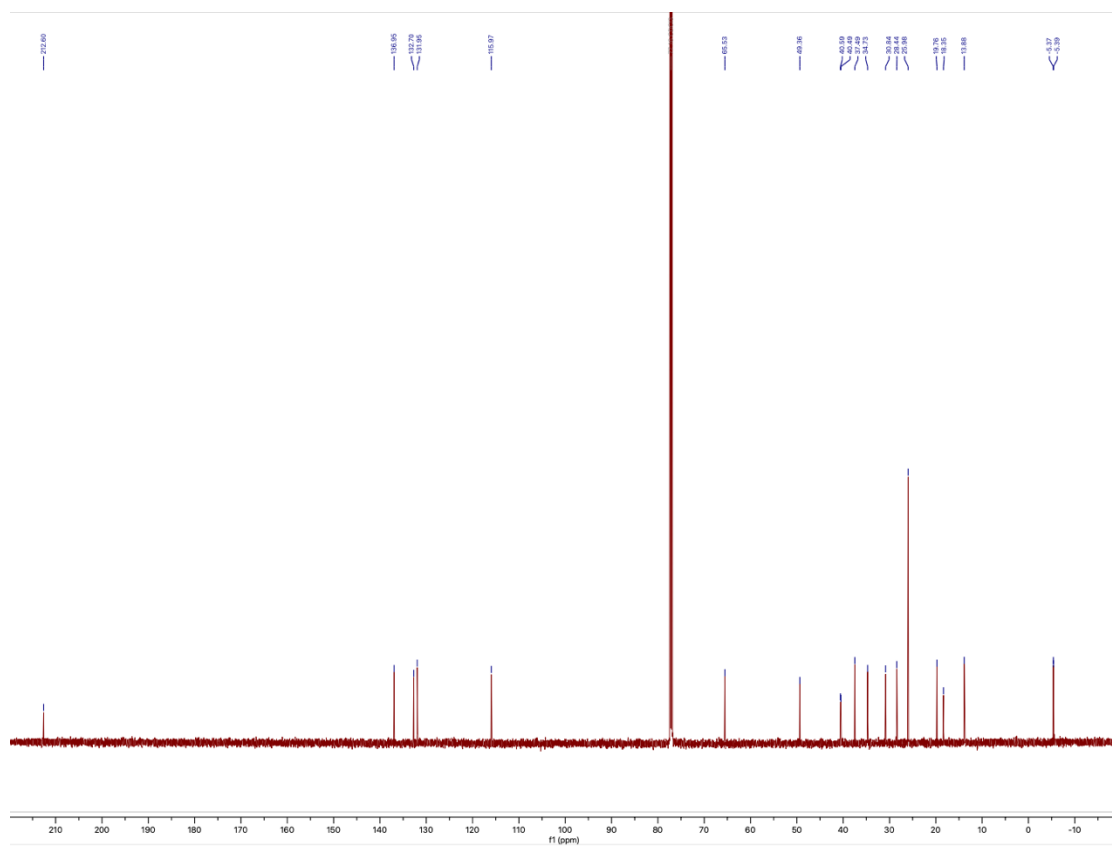


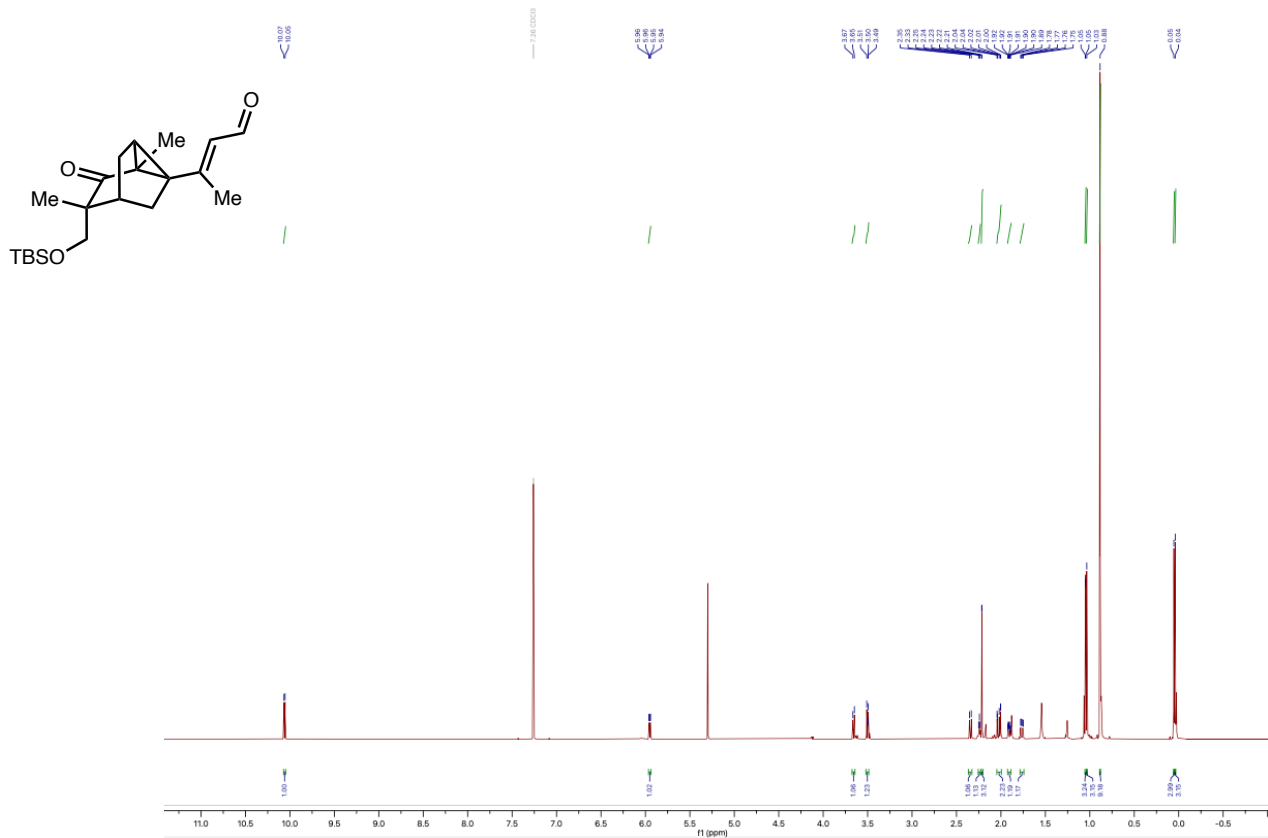
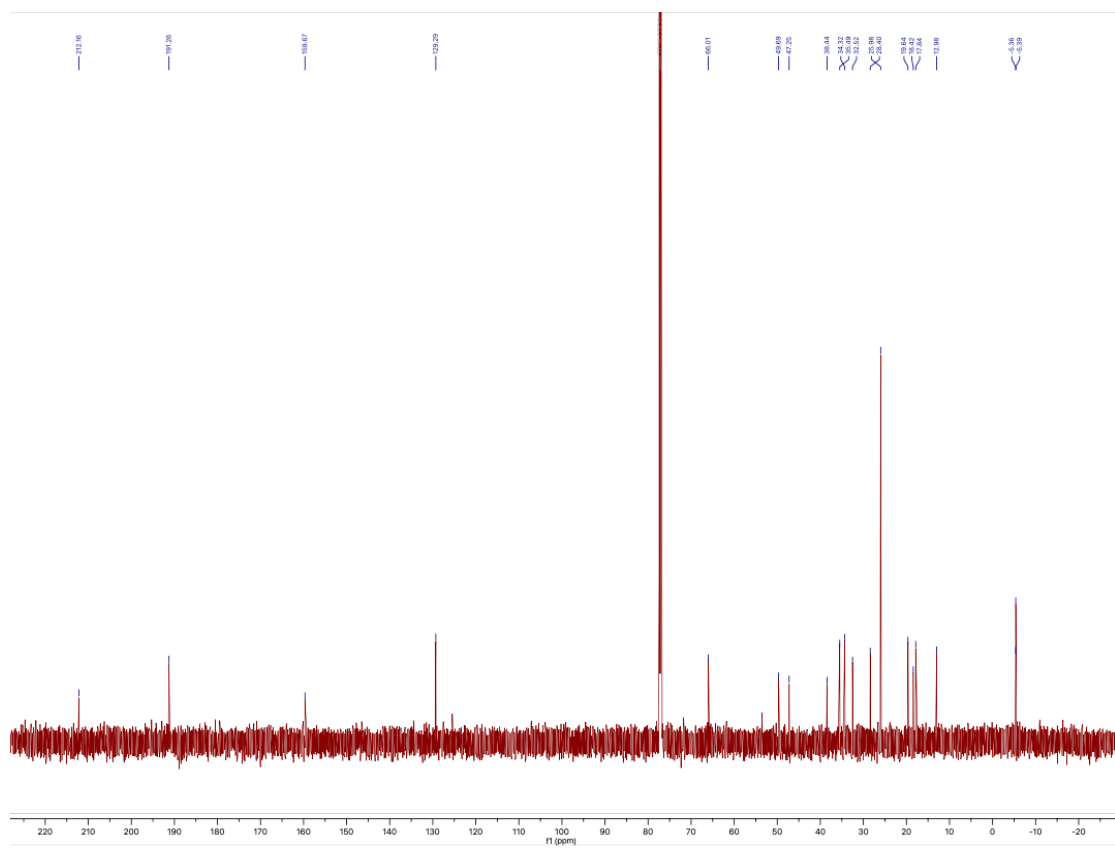
¹H NMR (600 MHz, CDCl₃) (2.70) ^{13}C NMR (151 MHz, CDCl_3) (**2.70**)

^1H NMR (600 MHz, CDCl_3) (**2.59**)

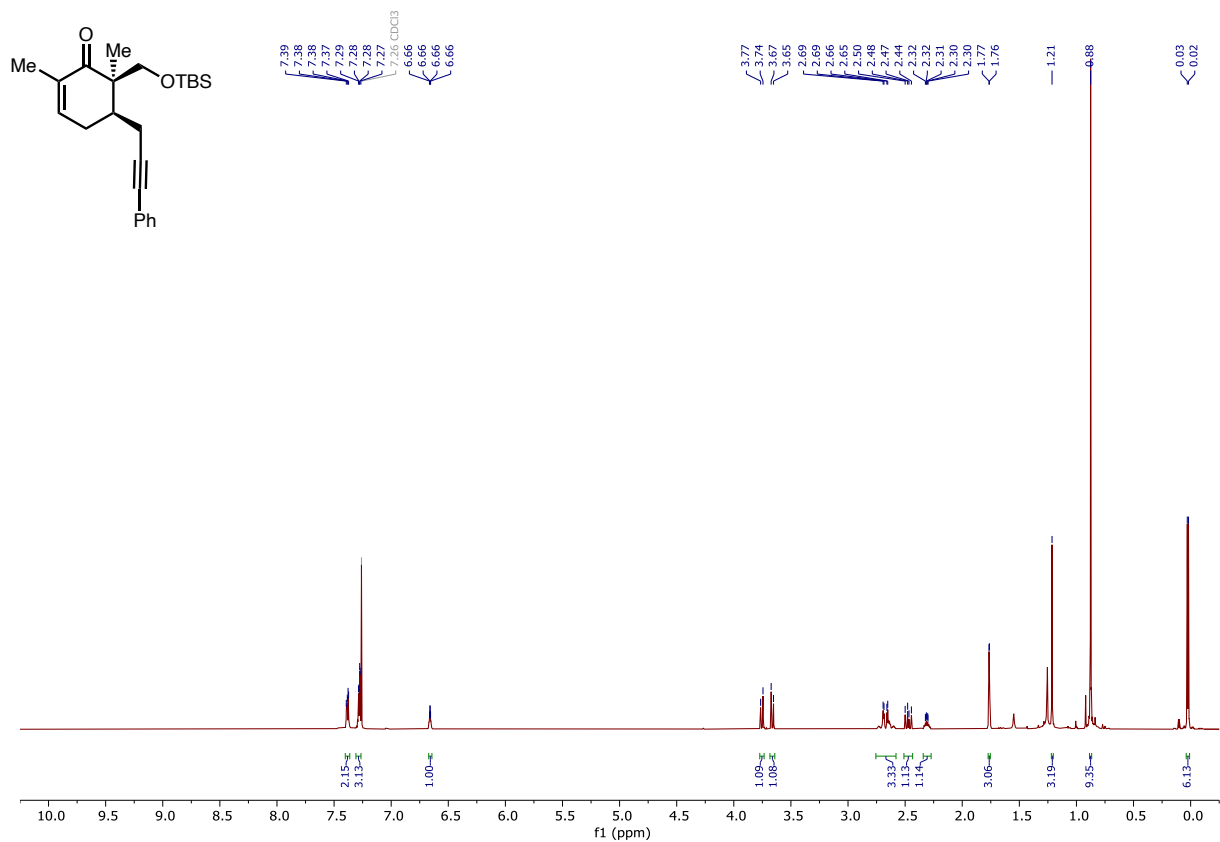


^{13}C NMR (151 MHz, CDCl_3) (**2.59**)

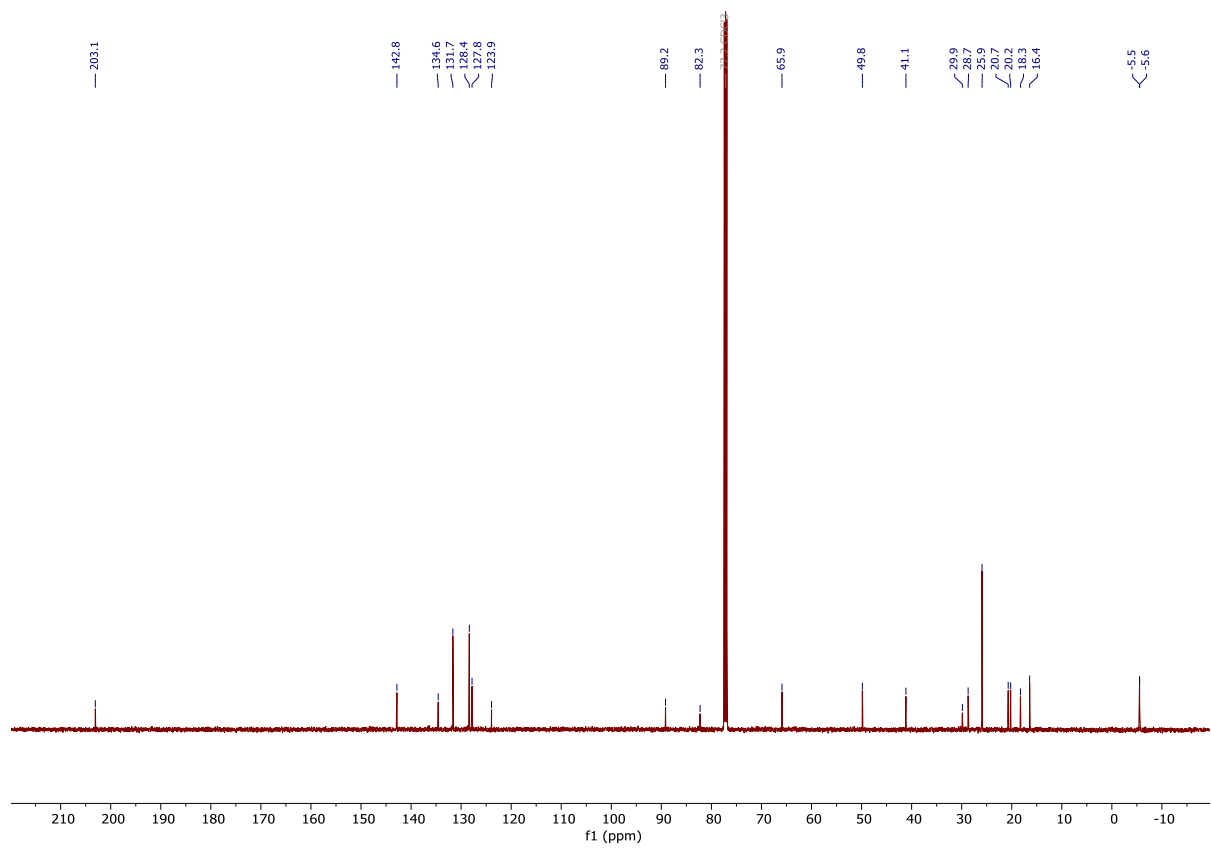


¹H NMR (600 MHz, CDCl₃) (2.61) ^{13}C NMR (151 MHz, CDCl_3) (2.61)

^1H NMR (500 MHz, CDCl_3) (**2.33**)



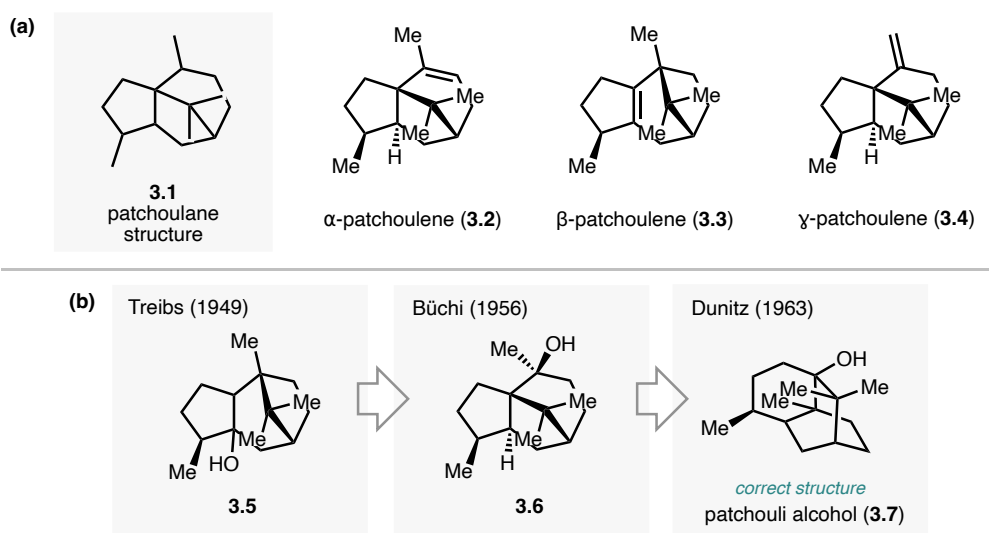
^{13}C NMR (126 MHz, CDCl_3) (**2.33**)



Chapter 3. Background on Patchoulol Natural Products

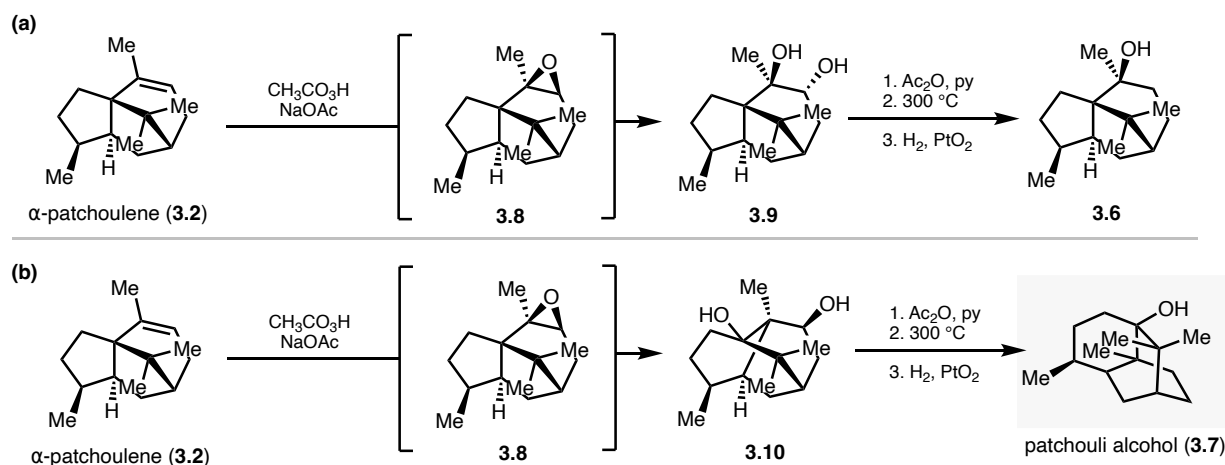
3.1 Introduction

Patchouli alcohol (**3.7**), the major constituent of East Indian patchouli oil, has an intriguing history of structure elucidation despite its relatively simple structure. This tertiary alcohol-containing sesquiterpene is characterized by a caged tricyclo[5.3.1.0^{3,8}]undecane core with five stereogenic centers, two of which are quaternary (Scheme 1). In 1949, Treibs proposed the first structural representation of patchouli alcohol (**3.5**), inferring its structure from β -patchoulene (**3.3**), which was obtained along with the α - and γ -isomers (**3.2** and **3.4**) via dehydration of patchouli alcohol under various conditions.¹



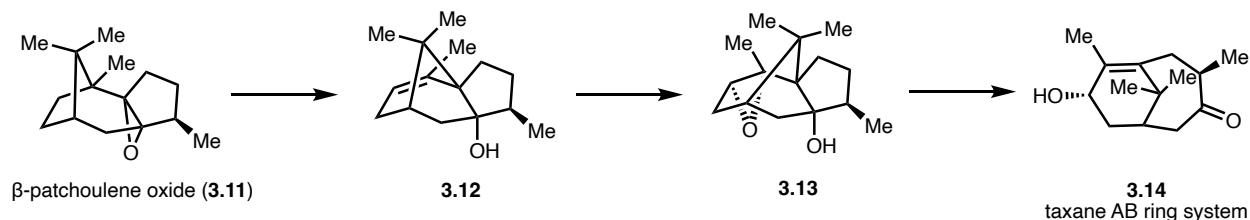
Scheme 1. (a) Patchoulene congeners. (b) Past proposed structures and the correct structure of patchouli oil (**3.7**).

In a Communication published in 1956, Büchi proposed an alternative structure (**3.6**) based on a series of degradation studies.² The suggested Büchi structure was a topological isomer of cedrol. Experimental evidence and reasoning were presented in detail in a full paper published in 1961,³ and the proposed structure appeared to be confirmed Büchi's subsequent total synthesis of the natural product in 1962.⁴ The synthetic material fully corresponded to the authentic patchouli alcohol and was obtained in just four steps from α -patchoulene (**3.2**). However, Büchi's assignment ultimately proved to be incorrect. The following year, Dunitz revised the structure of patchouli alcohol (**3.7**) based on an X-ray crystallographic investigation of chromium-oxygen-carbon bond angles in the patchouli alcohol diester of chromic acid.⁵ In fact, Büchi's completed synthesis provided the correct natural product, but the authors had failed to recognize an unanticipated rearrangement. The discrepancy arose from a cationic skeletal rearrangement that occurred when an intermediate was treated with peracid, fortuitously generating the correct architecture of the natural product (Scheme 2). This unexpected rearrangement was overlooked by the authors and led them to ultimately propose the wrong structure.



Scheme 2. (a) Proposed synthesis sequence of patchouli alcohol (3.7) by Büchi (1961). (b) Revised actual synthesis sequence after structural elucidation by Dunitz and co-workers (1963).

In the Full Article published in 1964,⁶ Büchi recounted the sequence of events and rearrangements that had led to his originally proposed structure, including a detailed discussion of the “reverse rearrangement” of β -patchoulene oxide (3.11). Many years later, this rearrangement became the cornerstone of Holton’s strategy for the synthesis of the taxane skeleton (Scheme 3).⁷

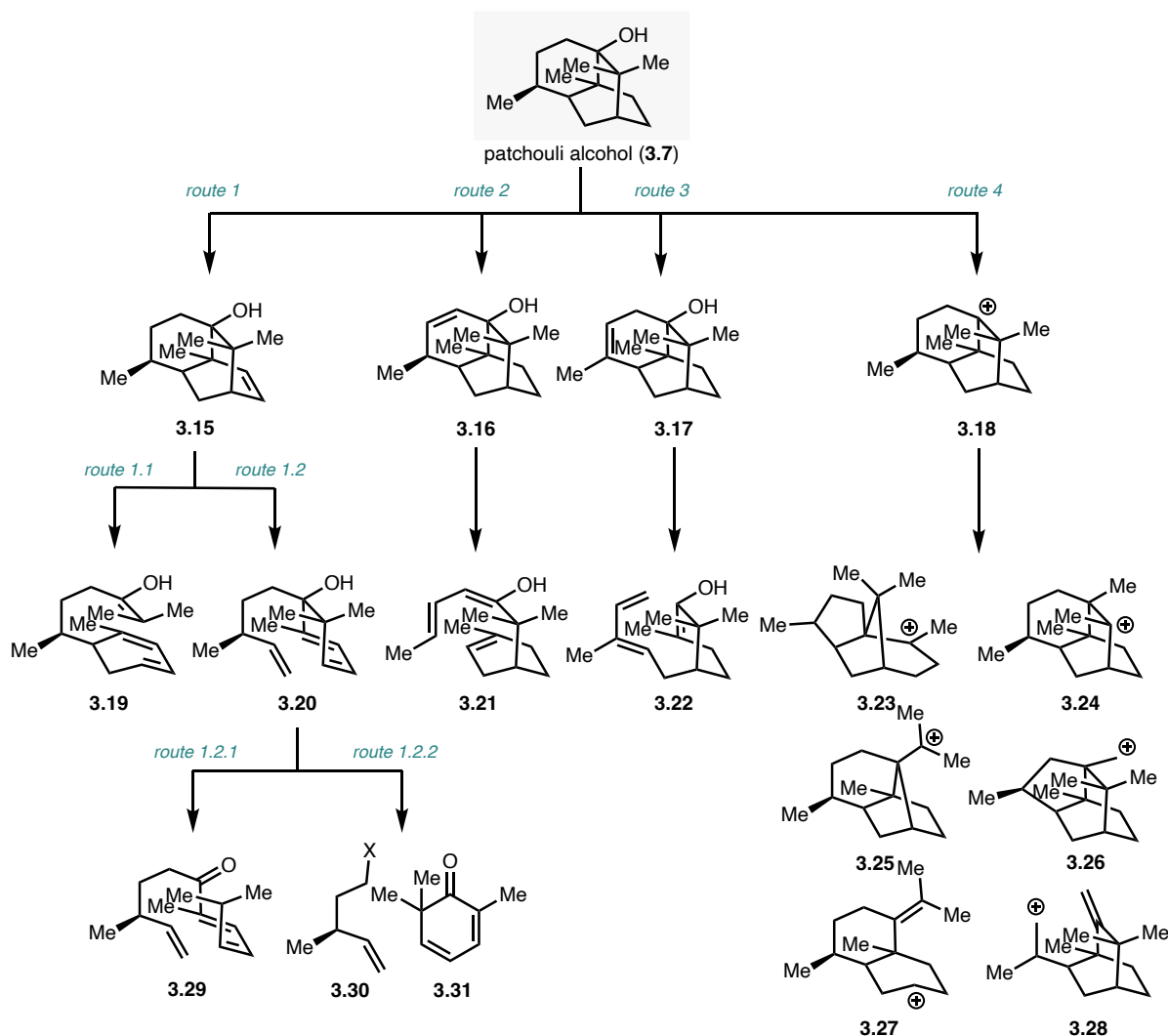


Scheme 3. Reverse rearrangement of β -patchoulene oxide (3.11) in Holton’s taxol synthesis.

Today, patchouli alcohol is often cited as one of the rare cases in which the chemical synthesis of a natural compound, undertaken to verify its structure, ultimately proved misleading.⁸ Nevertheless, it remains a compelling example of the pivotal role that chemical synthesis once played in chemical discovery and structural confirmation, particularly in light of the limitations of the analytical methods available at the time. By the late 1960s, the likelihood of encountering such unanticipated outcomes during efforts towards structure elucidation had decreased dramatically, as the “classical” chemical approach, such as degradation studies, was gradually replaced by far more accurate spectroscopic methods such as NMR, UV, IR, CD, and MS.

In addition to serving as a prime example in discussions of structural misassignment in natural product synthesis, patchouli alcohol has also historically been cited as an illustrative example in early discussions of computer-assisted synthesis.^{9,10} Notably, in 1969, Corey outlined a general theory of chemical synthesis and introduced the concept of applying machine computation to the generation of synthetic pathways for complex organic molecules.⁹ The central question he posed was whether modern computers could be used to derive logic-centered solutions to problems in

molecular syntheses. Together with his co-workers, Corey developed a program capable of rapidly processing molecular structures to generate a retrosynthetic tree, excluding chemically unreasonable or unproductive intermediates while retaining a broad range of plausible pathways. To demonstrate the performance of the initial phase of this study, patchouli alcohol was selected as a target due to its moderate structural complexity (Scheme 4). Notably, the program successfully captured the essence of the logic-centered disconnection approach for this natural product: most of the proposed strategies were based on Diels-Alder cycloadditions and carbocation rearrangements. Among the suggested synthetic routes, two showed strong resemblance to the total syntheses by Danishefsky¹¹ and Ohloff (route 1.2.2),¹² which will be discussed in the following chapters.



Scheme 4. Proposed disconnections from Corey's computer-assisted synthesis work.

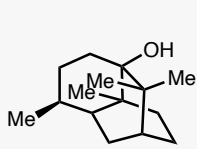
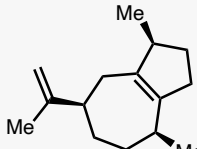
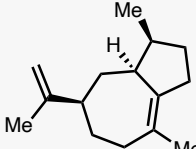
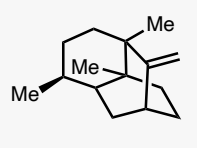
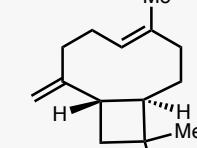
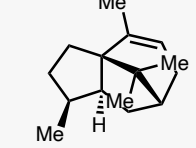
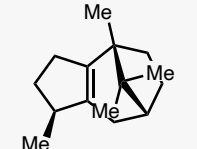
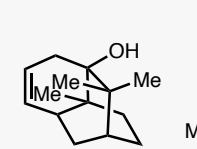
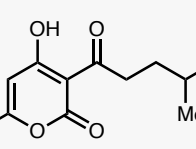
Depending on the target in question, the routes that are suggested by computer may serve as an aspirational goal that inspire creativity, serving as a starting point for synthetic chemists tackling

complex targets, or even as a blueprint for their synthesis.¹³ Previously reported total and formal syntheses of patchouli alcohol are discussed in the following chapters.

3.2 Isolation

The name “patchouli” is derived from the Tamil term “*patch ilia*”, meaning “green leaf”. Patchouli alcohol is a major constituent of the pungent oil from the eastern Indian shrub *Pogostemon patchouli* and is widely used in fragrances. Referred to as patchouli-camphor in the earliest literature, it was first isolated in 1869 by Gal.¹⁴ The leaves of *Pogostemon cablin* (Blanco) Benth. (Lamiaceae) are the source of patchouli essential oil (PEO), a key commodity in the fragrance industry, with an annual production of approximately 1300 tons.¹⁵ Today, about 90 % of global production occurs in Indonesia. PEO is obtained through either steam distillation or hydro-distillation of the dried leaves. It has a unique woody odor and is an indispensable and difficult to replace constituent in many fragrances. By volume, it ranks as approximately the tenth most important essential oil. Due to its low pricing, between \$50-200/kg, attempts to industrially synthesize the sesquiterpene alcohol have proved to be uneconomical.

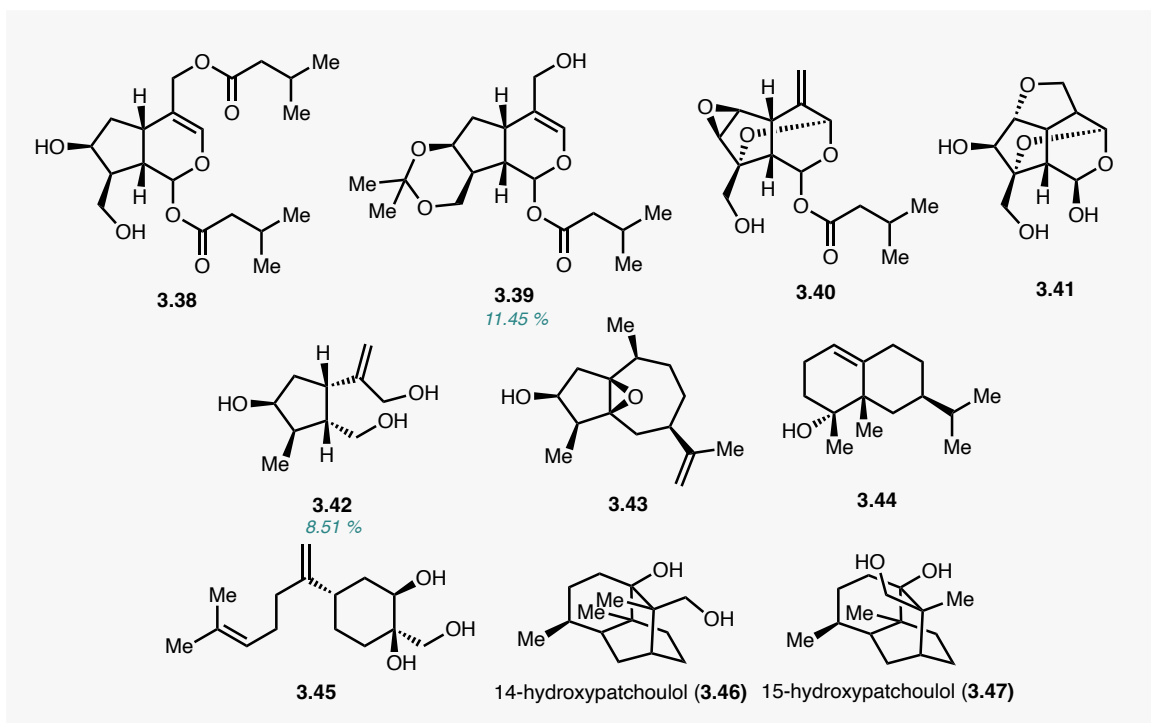
Table 1. Percentage of key constituents in patchouli essential oil (PEO) and their structures.

constituent	percentage in PEO	
patchouli alcohol	62 %	 patchouli alcohol (3.7)
α -guaiene	10 %	 α -guaiene (3.32)
α -bulnesene	9 %	 α -bulnesene (3.33)
seychellene	3 %	 seychellene (3.34)
β -caryophyllene	2 %	 β -caryophyllene (3.35)
α -patchoulene	1 %	 α -patchoulene (3.2)
norpatchoulanol	1 %	 β -patchoulene (3.3)
β -patchoulene	1 %	 norpatchoulanol (3.36)
pogostone	1 %	 pogostone (3.37)

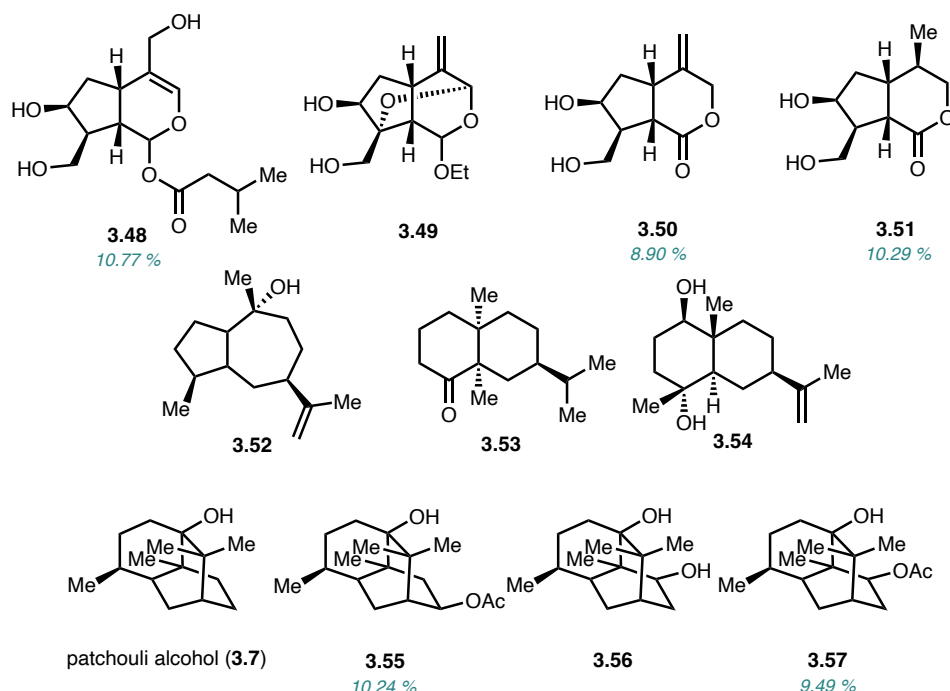
Patchouli leaves entered the European market in the first half of the 19th century, and their distinctive odor soon became popular, particularly in association with the fashion of cashmere shawls.¹⁶ To protect the fine cashmere wool during its journey to Europe, the cloth was layered with patchouli leaves, which were the most effective moth repellent known at the time. The oil's

wood-balsamic scent with its well-balanced herbaceous, earthy, camphoraceous, and floral notes, soon turned out to be as much a draw for buyers as the cashmere itself. PEO is mentioned in the first book on plant constituents, and a brief monograph detailing its constituents and odor was published as early as 1875. More extensive monographs followed towards the end of 19th century and compounds like patchoulol and patchoulene were already included in Beilstein's Handbook of Organic Chemistry.¹⁵ To date, over 130 different chemical compounds have been positively identified to constitute in PEO. Among these, sesquiterpene hydrocarbons constitute a large fraction which are reported to be around 40-60 % and they significantly contribute to its characteristic odor.

While patchoulol is not specific to *Pogostemon* species, its occurrence in high concentrations is relatively rare in other essential oils and is mostly restricted to certain *Valeriana* species. The genus *Valeriana* (family Valerianaceae) contains about 250 species. The roots and rhizomes of some of these species have been used in traditional medicine, primarily for their effects on the central nervous system, especially as mild sedatives and sleep aids in many cultures. Previous phytochemical investigations on *Valeriana* plants resulted in the isolation of acylated iridoids, sesquiterpenoids, essential oils, flavone glycosides, and lignans. For example, patchoulol concentrations were found to be 26.2 % in *Valeriana celtica* leaf oil, up to 50% in *Valeriana wallichii* rhizome oil, in *Valeriana pancicii* root and rhizome oil, and up to 66.7 % in *Valeriana jatamansi* rhizome oil.



Scheme 5. Isolated new compounds from *Valeriana Stenoptera*. NGF-induced differentiation rate in PC12 cells is indicated in green below the compounds that are clinically potent.



Scheme 6. Isolated known compounds from *Valeriana Stenoptera*. NGF-induced differentiation rate in PC12 cells is indicated in green below the compounds that are clinically potent.

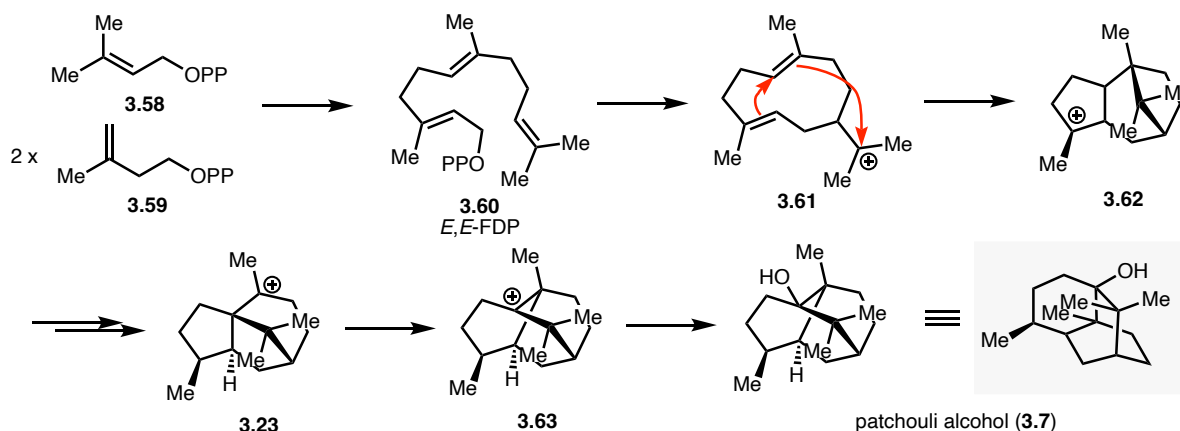
In 2015, Hu and co-workers undertook phytochemical and bioactive investigations of *Valeriana Stenoptera*, an annual herb medicinal plant primarily found in the southwestern regions of China.¹⁷ The essential oil obtained from the roots of the plant is an important resource in the perfumery industry and is also widely used in pharmaceutical and cosmetic industries. They reported the isolation of ten new compounds, including five new iridoids, stenopterins A–E (**3.38**–**3.42**, Scheme 5) and five new sesquiterpenoids, among them the 14- and 15-hydroxypatchoulols (**3.46**, **3.47**, Scheme 5).

14- and 15-Hydroxypatchoulol (**3.46**, **3.47**) are caged tricyclic patchoulane sesquiterpenoids featuring the characteristic bicyclo[2.2.2]octane core with six contiguous stereogenic centers, two of which are quaternary. As differently oxygenated congeners of patchouli alcohol, they have attracted interest from the fragrance industry as potential new fragrance candidates.

3.3 Biosynthesis

As with most sesquiterpene natural products, patchouli alcohol is proposed to originate from farnesyl pyrophosphate (**3.60**), a 15-carbon branched-chain hydrocarbon tethered to an ionizable diphosphate group. Patchoulol synthase, a central enzyme in the biosynthesis of patchouli essential oil, is thought to catalyze the key step in this process, generating patchoulol alongside at least 22 additional sesquiterpenes with varying structural motifs that contribute to the complex composition of PEO. Such a broad product spectrum is uncommon, as the majority (> 80 %) of sesquiterpene synthases typically produce only a single product. The diversity of the product profile of patchoulol

synthase arises from numerous cyclizations, rearrangements, and quenching reactions. Presumably, these reactions are influenced by factors such as pH and temperature, which can lead to different product ratios under varying reaction conditions.¹⁸



Scheme 7. Proposed biosynthesis of patchouli alcohol (3.7).

Regarding 14- and 15-hydroxypatchoulol (3.46, 3.47), no studies have been reported on their possible biosynthesis. On the basis of the high similarity of these compounds to other structurally related patchouli alcohol congeners (3.55, 3.56, and 3.57) that are isolated from the same plant, we propose that these new oxygenated congeners arise from post-synthetic oxidation catalyzed by tailoring oxygenases.¹⁹

3.4 Biological Activity

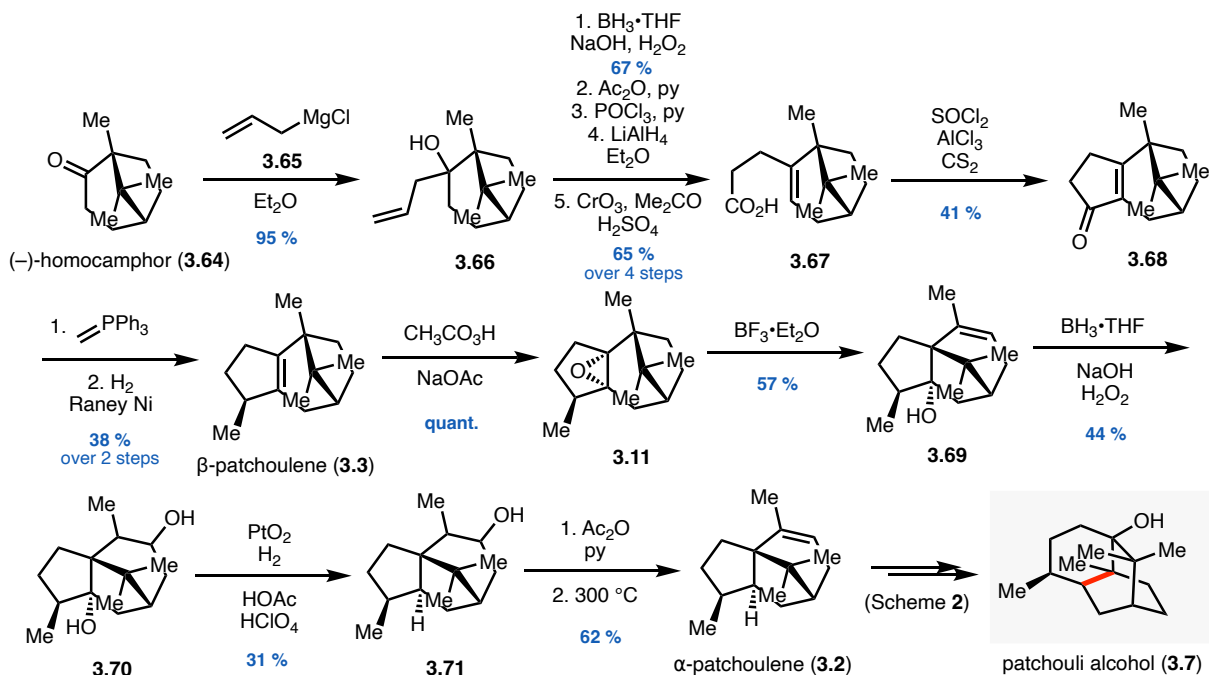
Iridoids and sesquiterpenoids have reportedly shown protective effects against amyloid- β -induced neurotoxicity in pheochromocytoma (PC12) cells, thereby promoting nerve growth factor (NGF)-mediated neurite outgrowth in PC12 cells and protecting against MPP⁺-induced neuronal cell death in human dopaminergic neuroblastoma SH-SY5Y cells. NGF is both theoretically and clinically involved in the central nervous system (CNS) and plays a significant role in the proliferation, differentiation, survival and death of nerve cells. All newly isolated compounds by Hu and co-workers were evaluated for their potential effects on NGF-mediated neurite outgrowth in PC12 cells.¹⁷ Compounds that enhance NGF-induced differentiation in PC12 cells are expected to be useful for the medical treatment of Alzheimer's disease. Among the tested compounds 3.39, 3.42, 3.48, 3.50, 3.51, 3.55, and 3.57 showed potent promoting effects on NGF-induced neurite outgrowth in PC12 cells at a concentration of 10 μ M as indicated in Scheme 5. 14- and 15-Hydroxypatchoulol (3.46 and 3.47) showed differentiation rates of 5.65 % and 5.96 %, respectively.

3.5 Previous Syntheses of Patchouli Alcohol

Patchouli alcohol's intriguing core skeleton and unique structure have attracted significant interest from the synthetic community. To date, nine groups have achieved total syntheses of **3.7**, and two groups have reported formal syntheses. Each synthesis is described in greater detail below, with the key disconnection used to construct the bicyclo[2.2.2]octane core highlighted with red bonds in the natural product. A comparative summary is provided in Chapter 3.5.13, including a tabulated overview of the reported syntheses.

3.5.1 Büchi (1961, 1962, 1964)

The first total synthesis of patchouli alcohol was reported by Büchi and co-workers in 1961.³ As discussed in Chapter 3.1, the structure was initially misassigned due to the occurrence of an unexpected rearrangement following the peracid-mediated epoxidation of α -patchoulene (**3.2**). Although α -patchoulene (**3.2**) and β -patchoulene (**3.3**) are commercially available compounds, the synthesis begins with (–)-homocamphor (**3.64**) which is elaborated to the patchoulene sesquiterpenes. Of note, the use of (–)-homocamphor (**3.64**) as an intermediate in natural product synthesis was first illustrated in this synthesis of patchouli alcohol. The steps leading to α -patchoulene (**3.2**) and β -patchoulene (**3.3**) are shown in Scheme 8, while their conversion to patchouli alcohol is discussed in the Chapter 3.1 (Scheme 2).⁶

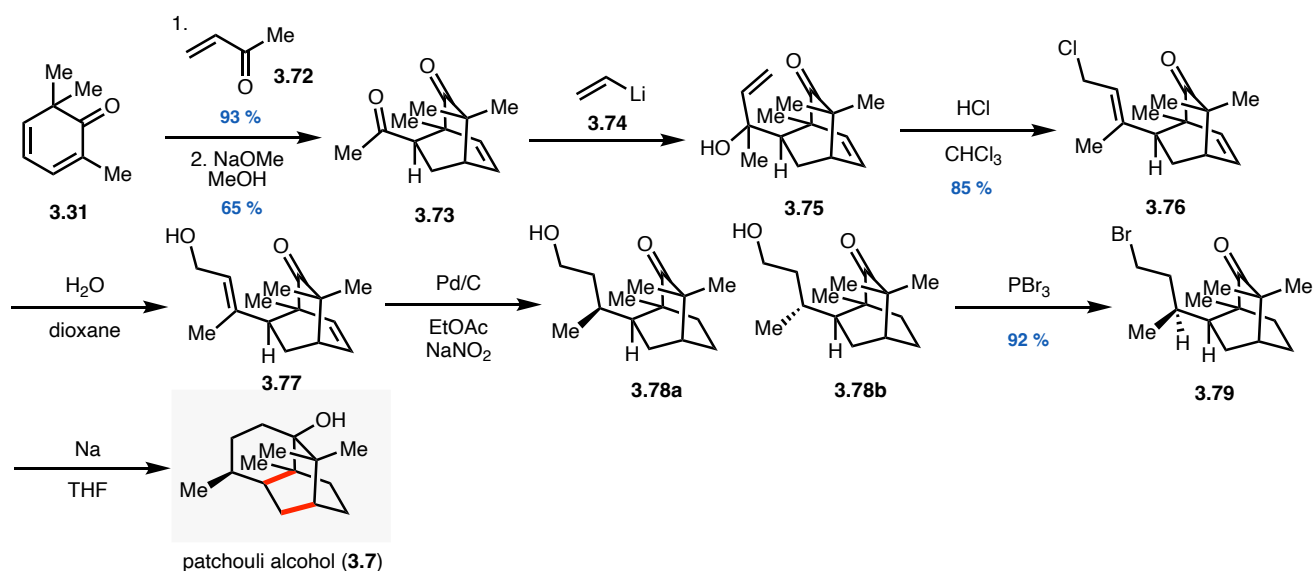


Scheme 8. Büchi's total synthesis of patchouli alcohol (**3.7**).

3.5.2 Danishefsky (1968)

Danishefsky and co-workers reported a synthesis of patchouli alcohol beginning with an intermolecular Diels-Alder cycloaddition between 2,6,6-trimethylcyclohexa-2,4-dien-1-one **3.31**

and methyl vinyl ketone **3.72**, which constructs the bicyclo[2.2.2]octanone **3.73** (Scheme 9).¹¹ Following base-mediated α -epimerization and vinylation, the newly formed tertiary alcohol (**3.75**) was treated with HCl in CHCl_3 to give allylic chloride **3.76**. Solvolysis with H_2O in dioxane and subsequent catalytic hydrogenation afforded a diastereomeric mixture of allylic alcohols **3.78**, whose structures were not assigned until completion of the synthesis. Conversion of **3.78a** to the corresponding bromide **3.79** with PBr_3 , followed by intramolecular cyclization with sodium in THF, furnished the natural product. The stereochemistry of the two diastereomeric alcohols **3.78a** and **3.78b** were established by comparison of synthesized patchouli alcohol upon completion of the synthesis with an authentic sample of patchouli alcohol provided by Büchi. This work inspired numerous subsequent syntheses, particularly through adoption of the final intramolecular cyclization used to construct the tricyclic framework by other researchers, which will be outlined in the following subchapters. Yields on certain reaction steps were not reported in the original literature.

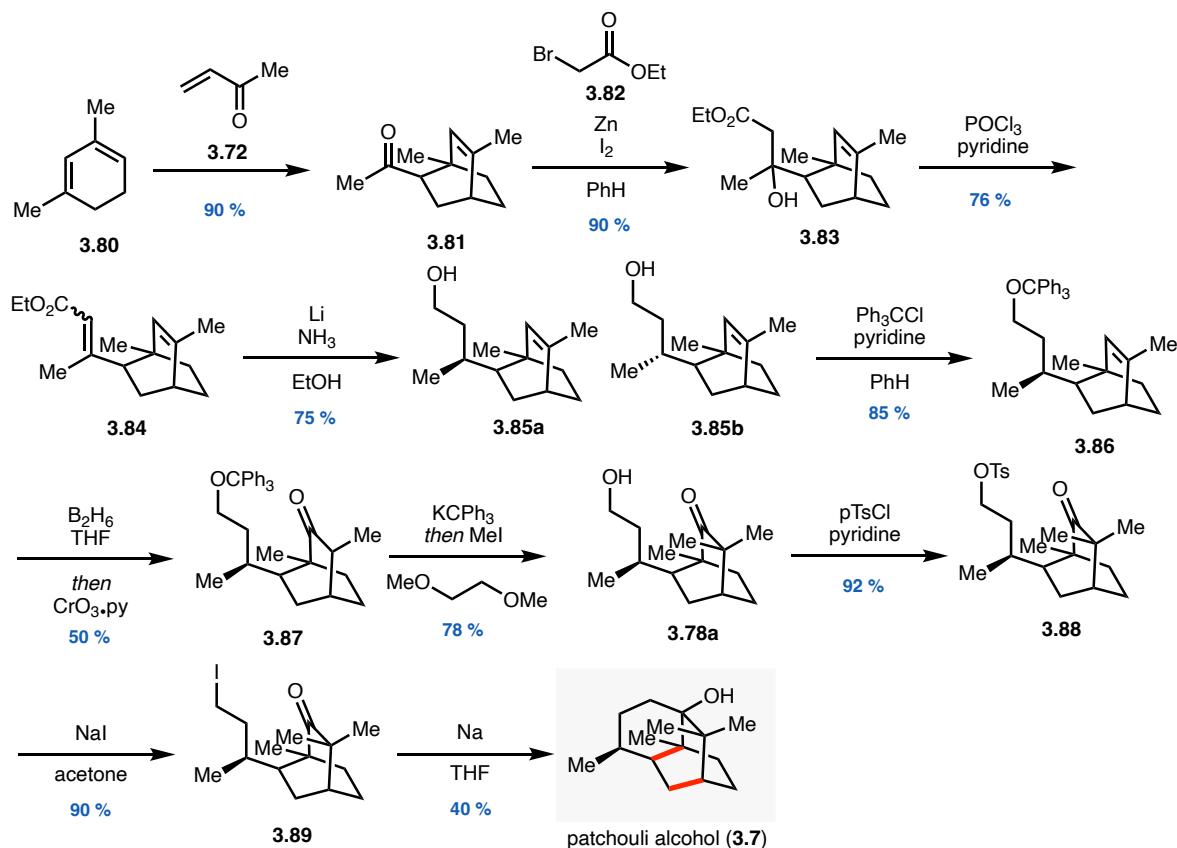


Scheme 9. Danishefsky's total synthesis of patchouli alcohol (**3.7**).

3.5.3 Mirrington (1972)

Mirrington and co-workers reported a synthesis reminiscent of Danishefsky and co-workers' synthesis.²⁰ Beginning from the achiral 1,3-dimethylcyclohexa-1,3-diene **3.80**, an intermolecular Diels-Alder cycloaddition with methyl vinyl ketone **3.72** afforded the bicyclo[2.2.2]octene framework **3.81**. A subsequent Reformatsky reaction yielded tertiary alcohol **3.83**. Following dehydrogenation and reduction, two diastereomers of the primary alcohol **3.85** were obtained. Alcohol **3.85a** led to the desired patchouli alcohol, whereas alcohol **3.85b** led to *epi*-patchouli alcohol. For clarity, the synthetic pathway continuing with **3.85b** is omitted in Scheme 10. After a sequence of alcohol protection, alkene oxidation, methylation and alcohol deprotection, primary alcohol **3.78** was obtained, analogous to the intermediate reported in Danishefsky's synthesis.

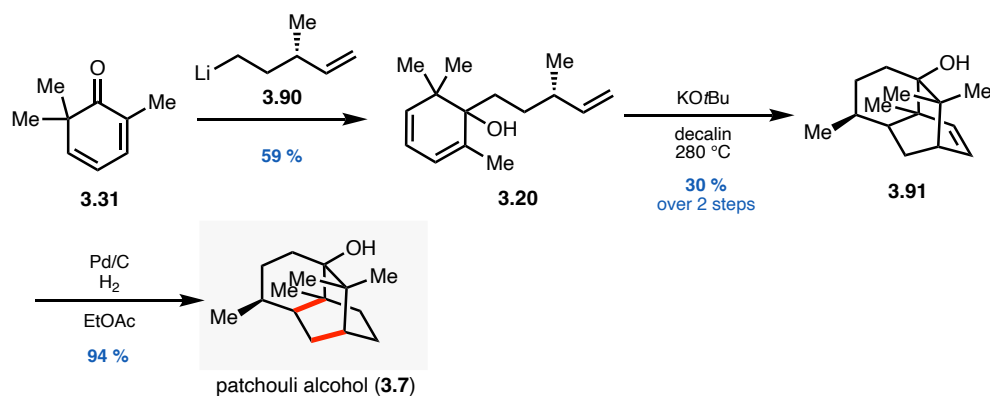
Alcohol **3.78** was then transformed stepwise into the corresponding alkyl iodide **3.89**, which upon treatment with sodium in THF furnished the desired natural product in 10 overall steps.



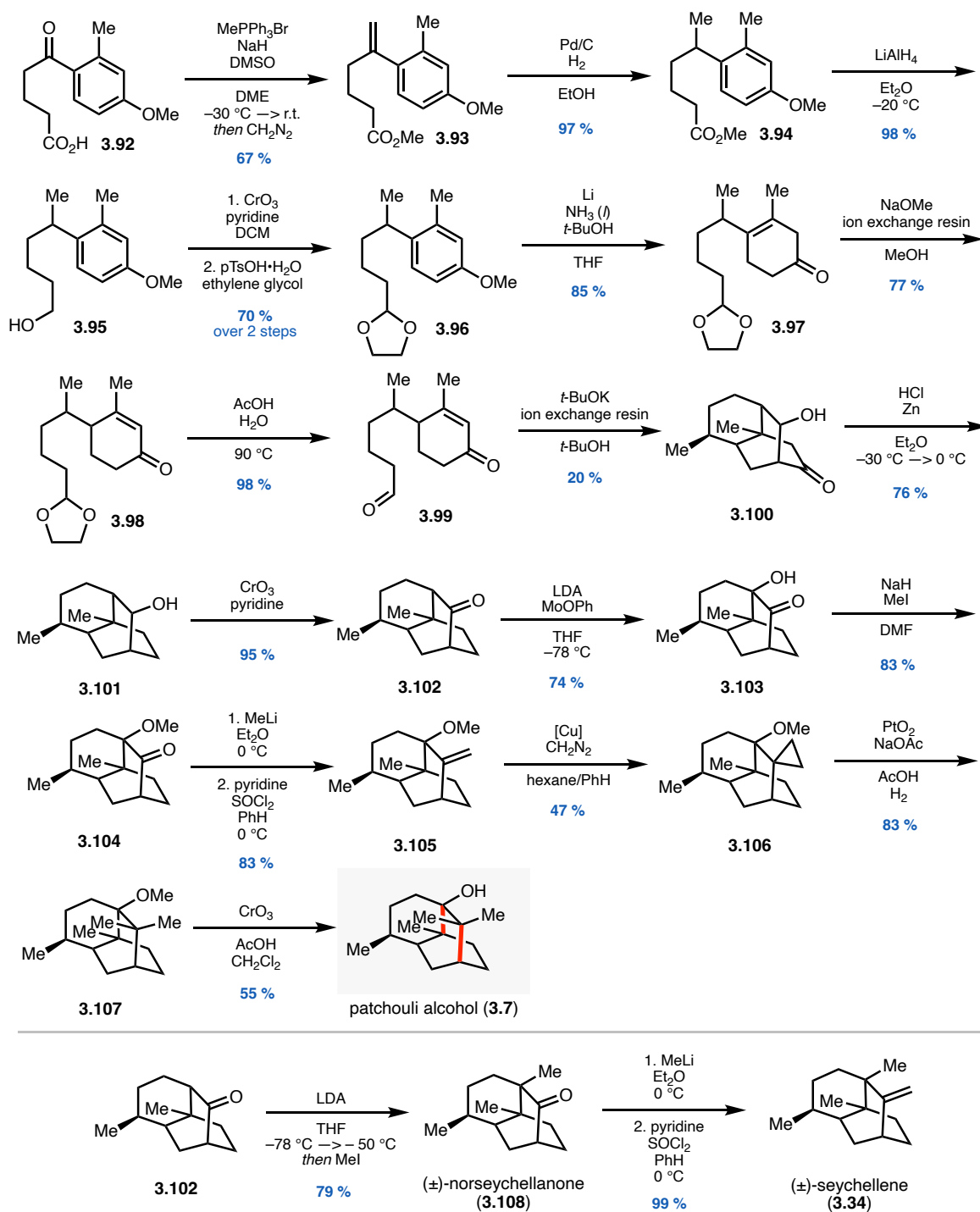
Scheme 10. Mirrington's total synthesis of patchouli alcohol (**3.7**).

3.5.4 Ohloff (1974)

A short stereoselective total synthesis of racemic patchouli alcohol was published by Ohloff and co-workers in 1974.¹² Starting from compounds 2,6,6-trimethyl-2,4-cyclohexadien-1-one **3.31** and alkyl lithiate **3.90**, the precursor for the key intramolecular Diels-Alder reaction was obtained in the first step. Upon treatment with KO^tBu and heating at elevated temperature, intramolecular Diels-Alder cycloaddition gave bicyclo[2.2.2]octane **3.91**. Subsequent catalytic hydrogenation furnished the natural product in four steps overall. This is the shortest total synthesis of patchouli alcohol to date.



3.5.5 Yamada (1979)

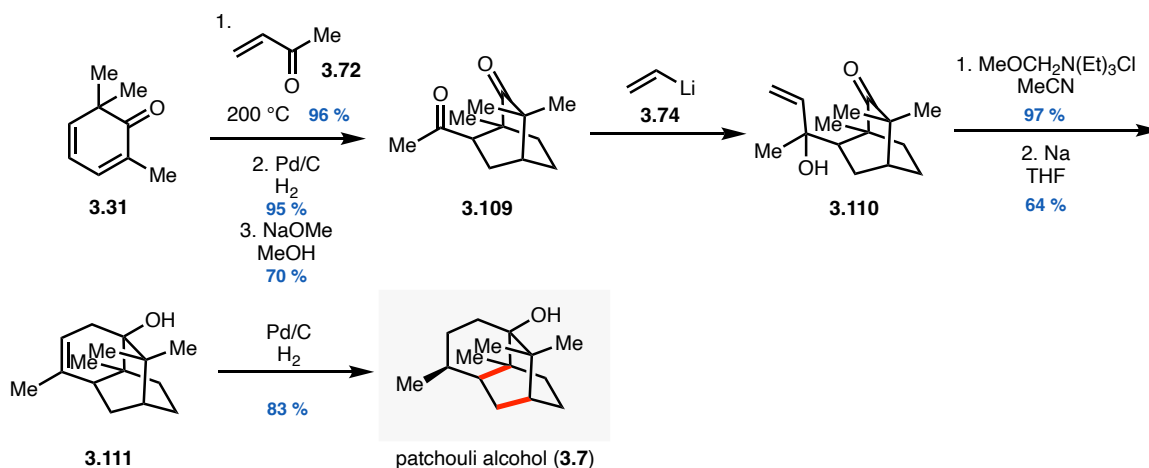


Scheme 12. Yamada's total synthesis of patchouli alcohol (3.7), norseychellانون (3.108), and seychellene (3.34).

3.5.6 Bertrand (1980)

Bertrand's synthesis of patchouli alcohol closely resembles that reported by Danishefsky and co-workers.²² Starting from the same starting materials, the bicyclo[2.2.2]octanone core is

obtained via intermolecular Diels-Alder cycloaddition. Catalytic hydrogenation and epimerization of the methyl ketone afforded diketone **3.109**. Addition of vinyl lithiate to obtain the tertiary alcohol **3.110** (yield not provided in the original literature) and preparation of the methoxymethyl ether intermediate were followed by radical cyclization: treatment with sodium in THF then afforded **3.111**. Final catalytic hydrogenation furnished the natural product patchouli alcohol (**3.7**) in seven steps overall.



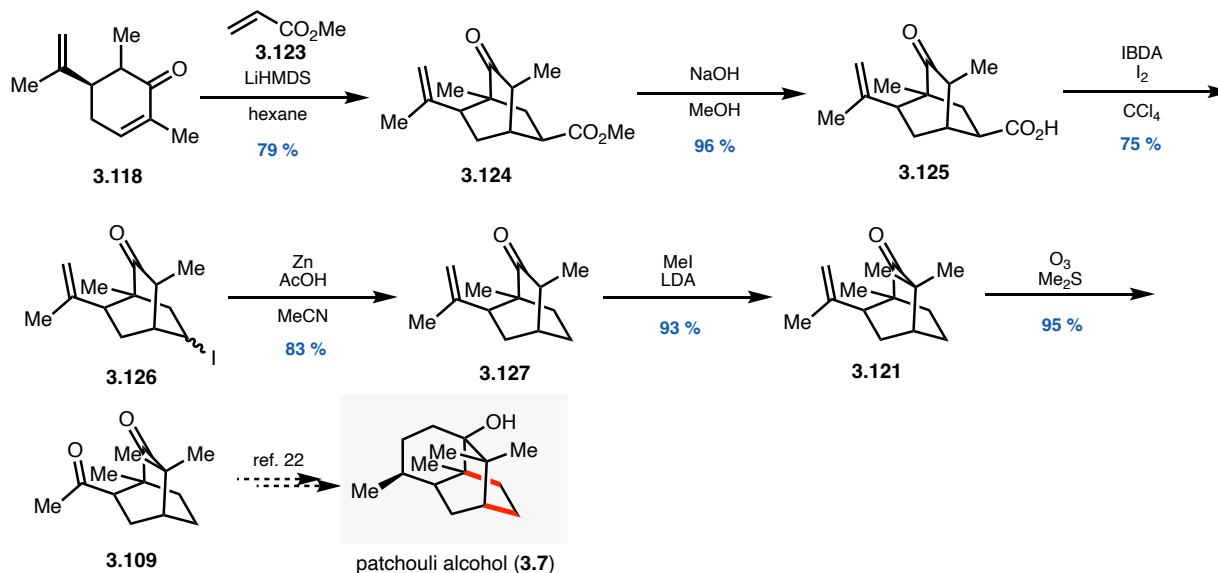
Scheme 13. Bertrand's total synthesis of patchouli alcohol (**3.7**).

3.5.7 Ohloff (1981)

In 1981, Ohloff and co-workers revisited their racemic total synthesis of patchouli alcohol reported in 1974 to render it enantiospecific.²³ Similar to their earlier work, the strategy employs an intramolecular Diels-Alder reaction as the key step. The enantioenriched dienophile fragment was derived from the flash pyrolytic product (+)- α -pinene (**3.112**) (yield not provided in the literature). Epoxide **3.114** was readily isomerized to the corresponding ketone (**3.115**). Autoxidative degradation of ketone **3.115**, followed by reduction with LiAlH_4 , afforded the desired alcohol **3.116**. Subsequent bromination and lithiation provided precursor **3.20** for the intramolecular Diels-Alder reaction, which furnished the bicyclo[2.2.2]octene **3.91** in 48 % yield. After catalytic hydrogenation, the desired natural product was obtained in eight steps overall.

3.5.9 Wu (formal synthesis, 1991)

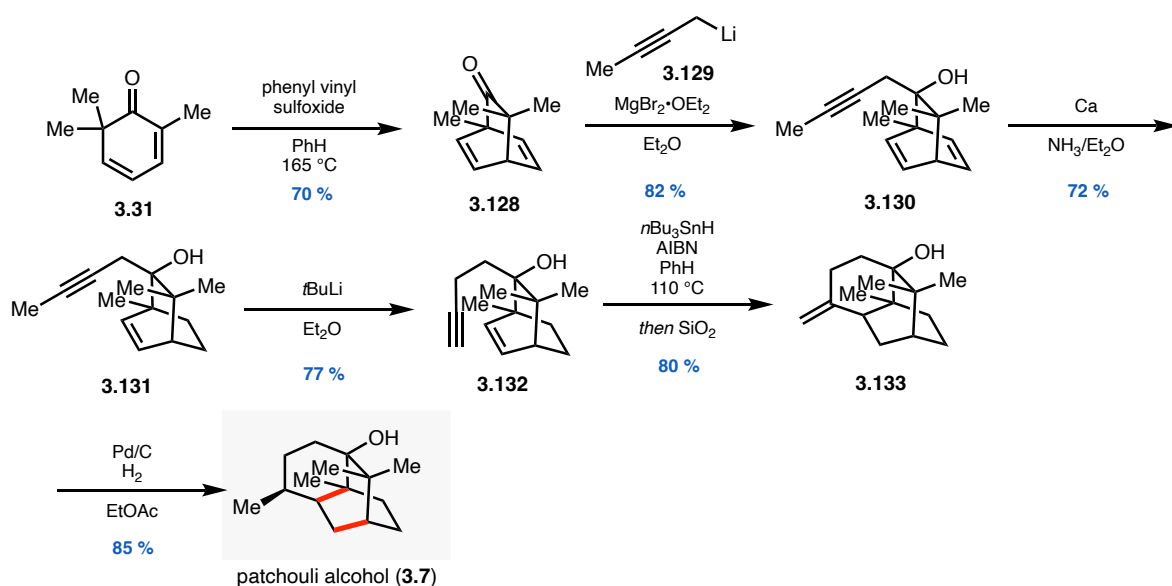
An enantiomerically enriched key intermediate for the synthesis of patchouli alcohol was prepared from (–)-methylcarvone (**3.118**) and methyl acrylate **3.123**.²⁵ A double Michael addition between the two substrates afforded optically pure derivatives of bicyclo[2.2.2]octanone **3.124** in 79 % yield. Subsequent removal of the ester group, followed by oxidative cleavage of the isopropyl group, furnished the known diketone intermediate **3.109**. This intermediate corresponds to that reported in Cory's formal synthesis of patchouli alcohol and was obtained in six steps in 42.6 % overall yield.



Scheme 16. Wu's formal synthesis of patchouli alcohol (**3.7**).

3.5.10 Magee (1995)

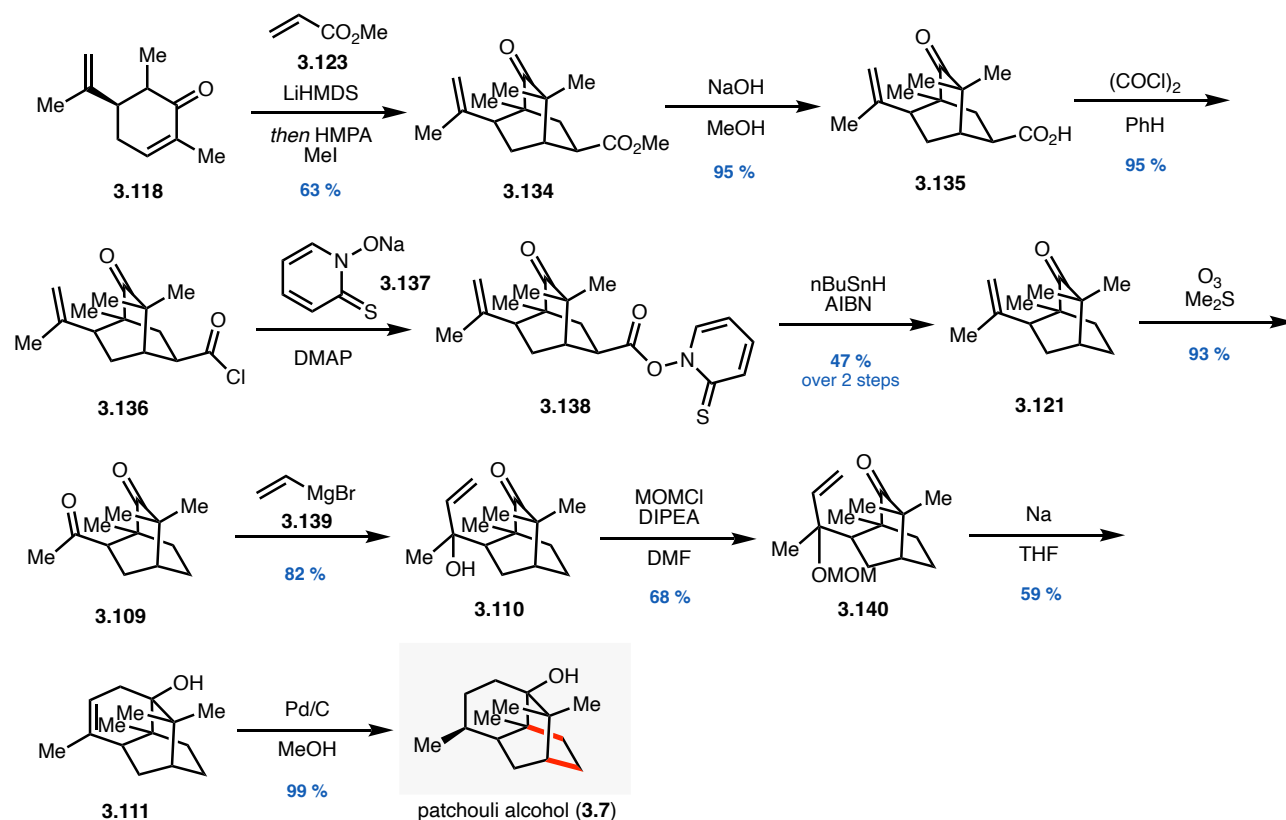
The total synthesis of racemic patchouli oil utilizing a *6-exo-trig* vinyl radical cyclization achieves the 6-membered ring closure required for the tricyclic skeleton.²⁶ Magee's synthesis began with construction of the bicyclo[2.2.2]octane core via cycloaddition of 2,2,6-trimethylcyclohexadiene **3.31** with an acetylene equivalent. Heating dienone **3.31** with phenyl vinyl sulfoxide directly yielded **3.128**, with elimination of sulfenic acid from the cycloadduct occurring in the same pot. Selective olefin reduction of the resulting dienyne was accomplished under carefully controlled dissolving-metal conditions using calcium metal, affording the product (**3.131**) in 72 % yield. Lithiation of the alkyne, accompanied by concomitant migration, furnished **3.132** in 77 % yield. Treatment with *n*Bu₃SnH induced vinyl radical cyclization and concomitant protodestannylation, producing tricycle **3.133** in 80 % yield. Finally, catalytic hydrogenation of the *exo*-methylene group afforded patchouli alcohol in six steps overall.



Scheme 17. Magee's total synthesis of patchouli alcohol (3.7).

3.5.11 Srikrishna (2005)

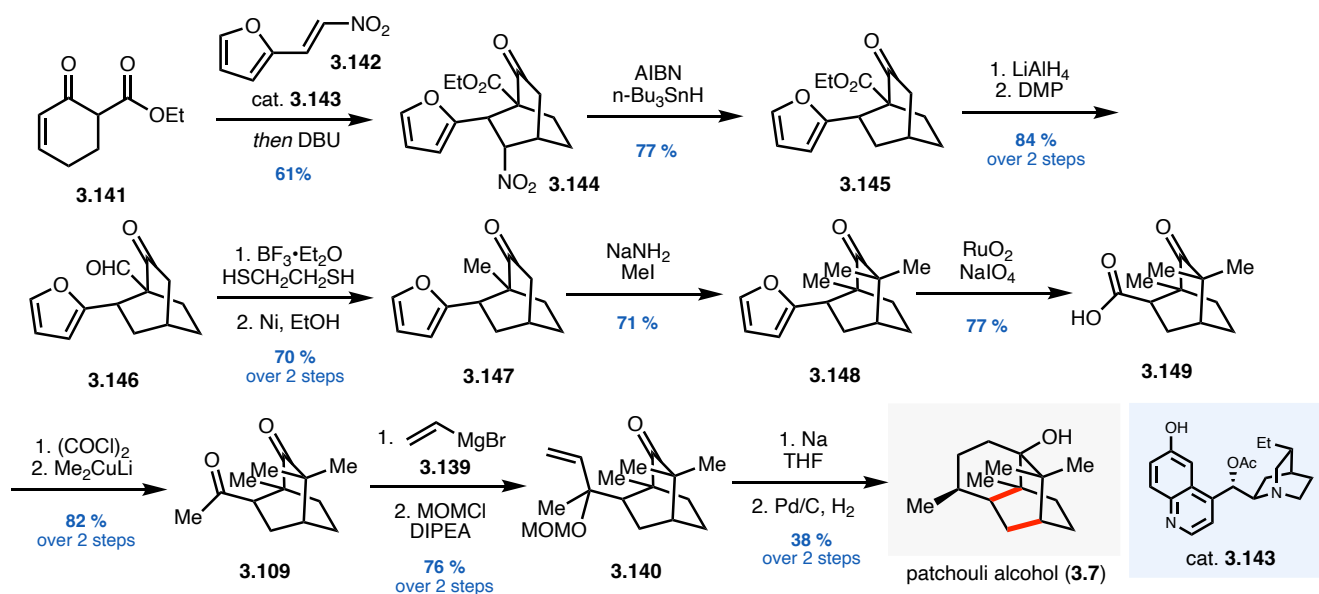
An enantiospecific total synthesis of patchouli alcohol was achieved using a tandem intermolecular Michael addition–intramolecular Michael addition–alkylation sequence, followed by a ketyl radical *6-endo-trig* cyclization initiated via single electron transfer.²⁷ The desired bicyclo[2.2.2]octanone **3.134** was obtained from methylcarvone **3.118** and methyl acrylate **3.123**, similar to the intermediate in Wu's formal synthesis. Different from Wu's synthesis, the additional methyl group was introduced in the same step. After a sequence of transformations to remove the ester and oxidative cleavage of the isopropyl group, the diketone intermediate **3.109**, which is a common intermediate that has been previously accessed in numerous reports, was obtained. Addition of a vinyl Grignard reagent **3.139**, followed by protection of the resulting tertiary alcohol, and treatment of ketone **3.140** with sodium furnished the tricyclic intermediate **3.111**. Catalytic hydrogenation then delivered the natural product in ten steps overall.



Scheme 18. Srikrishna's total synthesis of patchouli alcohol (3.7).

3.5.12 Sun (2017)

The most recent total synthesis of patchouli alcohol was reported by Sun and co-workers in 2017.²⁸ The asymmetric synthesis was accomplished concisely, with key transformations including a highly diastereo- and enantioselective formal organocatalytic [4+2] cycloaddition, radical denitration, and oxidative carbonylation. The formal synthesis of norpatchoulenol was also achieved. Starting from the unsaturated β -keto ester **3.141**, the formal asymmetric [4+2] cycloaddition using organocatalyst **3.143** afforded the desired bicyclo[2.2.2]octanone **3.144** in 61 % yield. Denitration, followed by sequential reduction of the ester, provided intermediate **3.147**. Subsequent double α -methylation of ketone **3.148** and hydrolysis of the furan substituent yielded intermediate **3.149**. Transformation of the resulting carboxylic acid into the methyl ketone furnished diketone intermediate **3.109**, previously employed in earlier syntheses. The steps following the ketone formation were identical to those reported by Srikrishna and co-workers. Overall, patchouli alcohol was obtained in 13 steps.

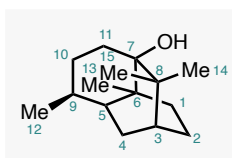


Scheme 19. Sun's total synthesis of patchouli alcohol (3.7).

3.5.13 Summary

A statistical summary of the previous syntheses of patchouli alcohol is shown in Table 2. Analysis of the reported total and formal syntheses of patchouli alcohol and its related congeners reveals that inter- and/or intramolecular Diels-Alder reactions, or formal [4+2] cycloadditions, are a popular strategy for accessing the bicyclo[2.2.2]octane core (7 out of 12 cases), with disconnections at the C3–C4 and C5–C6 bonds being the most common (Table 2). Comparison of the strategies employed in these reports with the disconnections suggested by Corey and co-workers in their computer-assisted retrosynthetic analysis (Chapter 3.1, Scheme 4) indicates that syntheses following the disconnection approach described as route 1.2 are the most represented. In particular, Büchi and Danishefsky exemplify concise and logical disconnections for patchouli alcohol. Inspired by their seminal work, many subsequent syntheses have been strongly influenced by these precedents. Furthermore, an increasing use of chiral pool feedstocks, such as carvone and pinene, as starting materials for enantioselective total synthesis is evident in the more recent reports.

Table 2. Total syntheses and formal syntheses of patchouli alcohol (3.7).



patchouli alcohol (3.7)

year	author	starting material	key step	step count	racemic/ enantioselective/ enantiospecific?
1964	Büchi	homocamphor (3.64) α -patchoulene (3.2)	epoxide rearrangement	19 steps (homocamphor) 4 steps (α -patchoulene)	enantiospecific
1968	Danishefsky	 3.31	intermolecular Diels-Alder	8	racemic
1972	Mirrington	 3.80	intermolecular Diels-Alder	10	racemic
1974	Ohloff	 3.31	intramolecular Diels-Alder	4	racemic
1979	Yamada	 3.92	base-catalyzed double cyclization	18	racemic
1980	Bertrand	 3.31	intermolecular Diels-Alder	7	racemic
1981	Ohloff	α -pinene (3.112)	intramolecular Diels-Alder	8	enantiospecific
1990	Cory	(<i>R</i>)-carvone (1.70)	phosphonium bicycloannulation	formal synthesis	enantiospecific
1991	Wu	(<i>R</i>)-carvone (1.70)	double Michael Addition	formal synthesis	enantiospecific
1995	Magee	 3.31	intermolecular Diels-Alder	6	racemic
2005	Srikrishna	(<i>R</i>)-carvone (1.70)	intermolecular Diels-Alder	10	enantiospecific
2017	Sun	 3.141	asymmetric double Michael Addition	13	enantioselective

3.6 Selected Total Syntheses of Natural Products with Bicyclo[2.2.2]octane Scaffold

Syntheses of select natural products featuring the bicyclo[2.2.2]octane scaffold are described below, highlighting the strategies used to construct their bicyclic core. For brevity, this chapter focuses only on the key transformation leading to the bicyclo[2.2.2]octane scaffold and omits both the preparation of precursors and the endgame synthesis of the natural products. The key disconnections employed for bicycle construction are highlighted with red bonds in the respective structures.

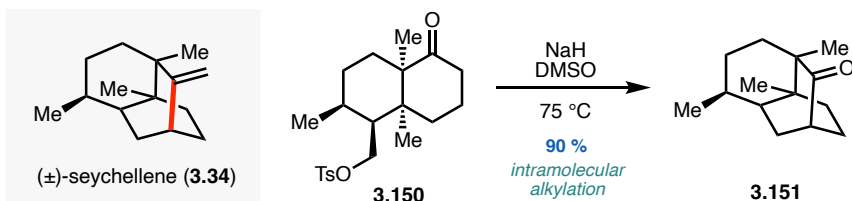
3.6.1 Seychellene

The total synthesis of ($\pm$)-seychellene (**3.34**) reported by Piers and co-workers begins with the well-known Wieland-Miescher ketone.²⁹ The starting material was elaborated to the keto tosylate intermediate **3.150** over 15 steps. Base-promoted intramolecular alkylation then furnished the bicyclo[2.2.2]octanone **3.151** in high yield (90 %), which was subsequently converted to seychellene (**3.34**).

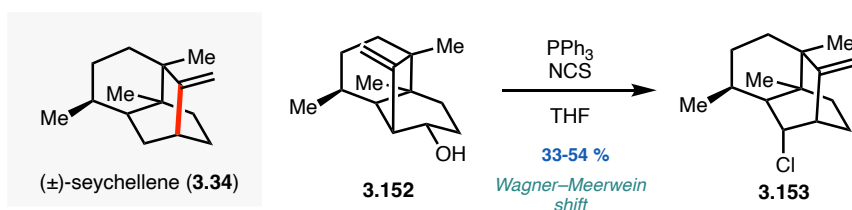
A similar disconnection approach was reported by Welch and co-workers in 1985.³⁰ Starting from a monocyclic ketone substrate and following a sequence of transformations, including a Claisen condensation and an oxidative Prins-ene reaction, they obtained the tricyclic intermediate **3.152** in 30 steps. Treatment of **3.152** with PPh₃ and NCS afforded the desired bicyclo[2.2.2]octane **3.153** in 33-54 % yield via a cationic Wagner-Meerwein shift.

Total syntheses of the same natural product by Yamada (1979)²¹ and Cory (1990)²⁴ are described in the previous chapter and are omitted here to avoid redundancy.

(a) Piers (1971)



(b) Welch (1985)

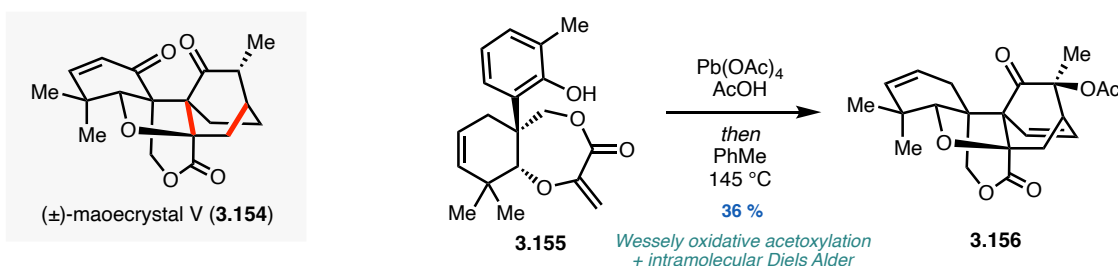


Scheme 20. Key reaction for the construction of bicyclo[2.2.2]octane core in select seychellene (**3.34**) total syntheses.

3.6.2 Maoecrystal V

The first total synthesis of maoecrystal V (**3.154**) was reported by Yang and co-workers in 2010. They later completed an asymmetric synthesis in 2015 using related chemistry.³¹ Namely, the Wessely oxidative acetoxylation of **3.155** yielded a mixture of isomers (not shown). Heating in toluene then afforded the desired Diels-Alder product (**3.156**) in 36 % yield, along with two other isomeric products.

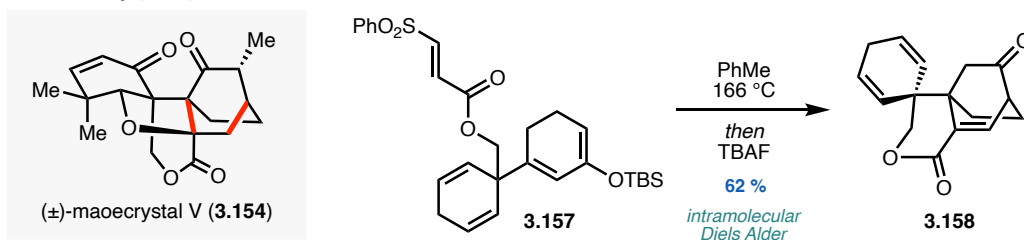
Yang (2010)



Scheme 21. Key reaction for the construction of bicyclo[2.2.2]octane core in Yang's total synthesis of (±)-maoecrystal V (**3.154**).

Following Yang's work, Danishefsky and co-workers reported their synthesis in 2012.³² Their approach also employed an intramolecular Diels-Alder cyclization to construct the bicyclo[2.2.2]octane core. After initial difficulties in achieving the desired facial selectivity, they found that introducing a phenylsulfone group on the dienophile enabled the selective cyclization. Conveniently, the phenylsulfone was subsequently removed in one-pot using TBAF to generate bicyclo[2.2.2]octane **3.158**.

Danishefsky (2012)

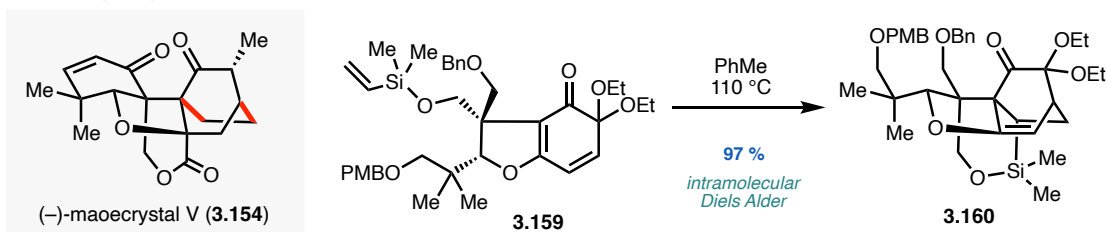


Scheme 22. Key reaction for the construction of bicyclo[2.2.2]octane core in Danishefsky's total synthesis of (±)-maoecrystal V (**3.154**).

The next total synthesis of maoecrystal V was reported by the Zakarian group, first in racemic form in 2013, followed by an enantioselective synthesis in 2014.³³ As in previous approaches, the intramolecular Diels-Alder reaction with **3.159** served as the key step to construct the bicyclo[2.2.2]octane **3.160**. In their synthesis, the tetrahydrofuran ring was assembled with the desired stereochemistry prior to the cycloaddition, enabling the desired facial selectivity and bypassing the challenges encountered by Danishefsky and co-workers. Despite attempts to improve the synthesis by modifying the tether from silicon to boron, Zakarian and co-workers

ultimately settled on a strategy closely resembling their original design in their published work in 2014.

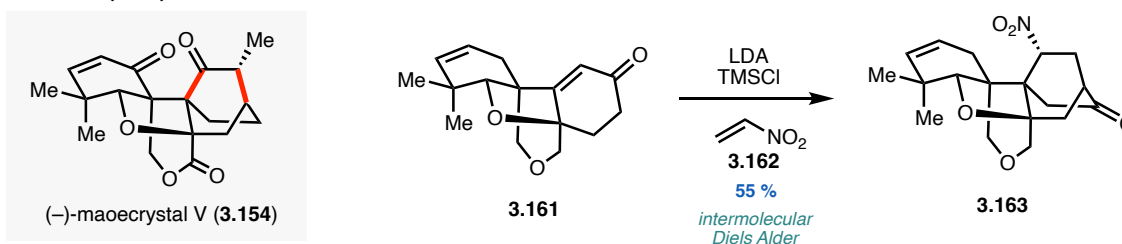
Zakarian (2014)



Scheme 23. Key reaction for the construction of bicyclo[2.2.2]octane core in Zakarian's total synthesis of (-)-maoecrystal V (**3.154**).

Also in 2014, Thomson and co-workers reported an asymmetric synthesis of maoecrystal V.³⁴ Their efficient route relied on a key intermolecular Diels-Alder reaction with tetracycle **3.161** and nitroalkene **3.162** and employed a “west-to-east” strategy for tetrahydrofuran ring assembly. The bond to the cyclohexene ring in the natural product was set early to ensure correct stereochemistry, while the bond to the bicyclo[2.2.2]octane core was formed prior to the cycloaddition via oxidative cyclodearomatization step.

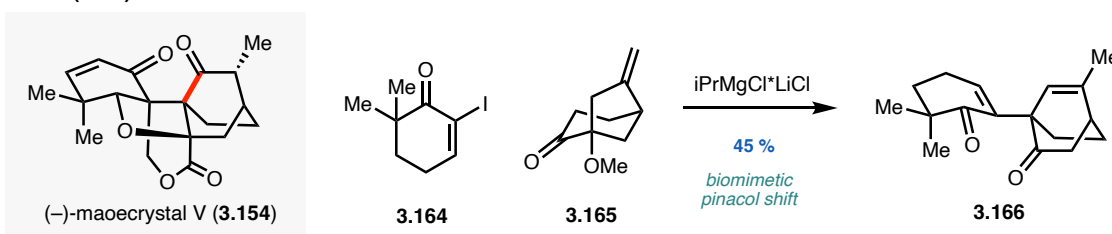
Thomson (2014)



Scheme 24. Key reaction for the construction of bicyclo[2.2.2]octane core in Thomson's total synthesis of (-)-maoecrystal V (**3.154**).

The final successful total synthesis of **3.154** was reported by the Baran group in 2016.³⁵ Departing from the common Diels-Alder approach in the previous synthesis reports, they accessed the bicyclo[2.2.2]octane core via a pinacol rearrangement from a bicyclo[3.2.1]octane (**3.165**), mimicking the originally proposed biosynthetic pathway of the natural product.

Baran (2016)

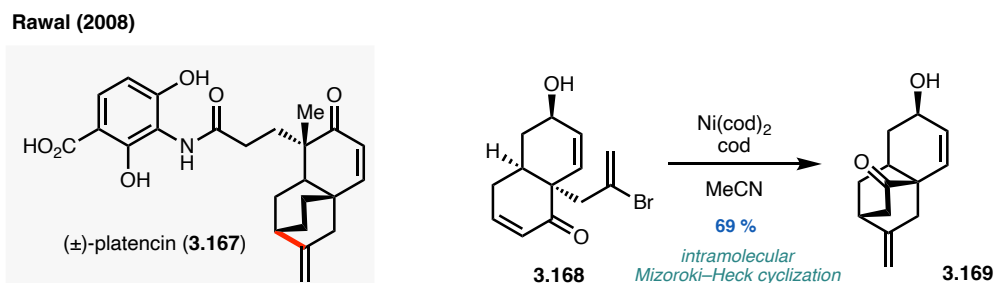


Scheme 25. Key reaction for the construction of bicyclo[2.2.2]octane core in Baran's total synthesis of (-)-maoecrystal V (**3.154**).

In addition to these completed total syntheses, numerous synthetic studies toward maoecrystal V have been published by groups including Danishefsky, Singh, Trauner, Thomson, Nicolaou, Chen, and Chisholm.³⁶ While not discussed in detail here, the majority of these studies utilize inter- and/or intramolecular Diels-Alder reactions to construct the bicyclo[2.2.2]octane core.

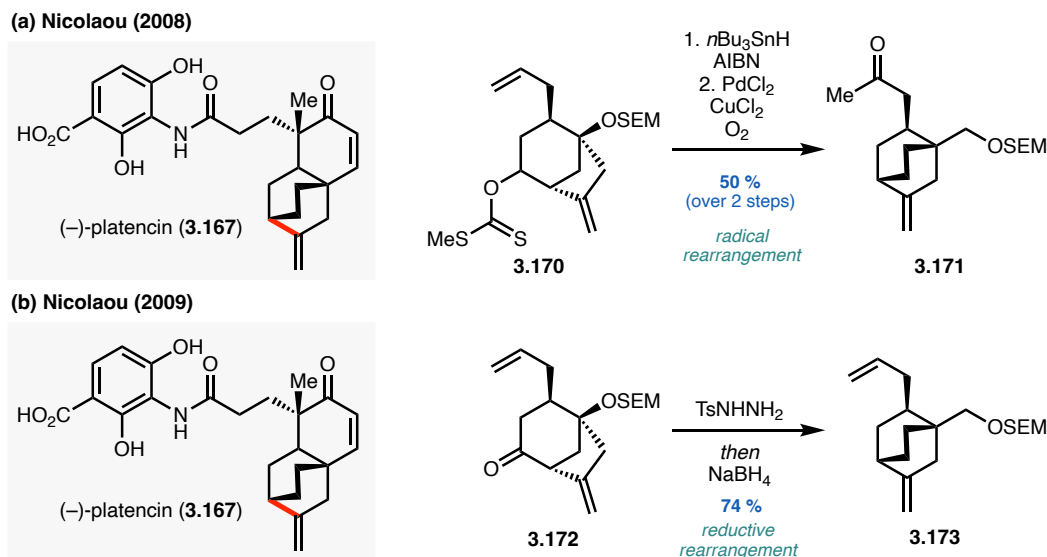
3.6.3 Platencin

In 2008, Rawal and co-workers reported a concise and stereocontrolled route to (±)-platencin (**3.167**).³⁷ Their synthesis features a Diels-Alder reaction with an α -substituted cyclohexanone to obtain intermediate **3.168**, followed by a Ni-promoted 1,4-addition to construct the challenging bicyclo[2.2.2]octanone core in **3.169**.



Scheme 26. Key reaction for the construction of bicyclo[2.2.2]octane core in Rawal's total synthesis of (±)-platencin (**3.167**).

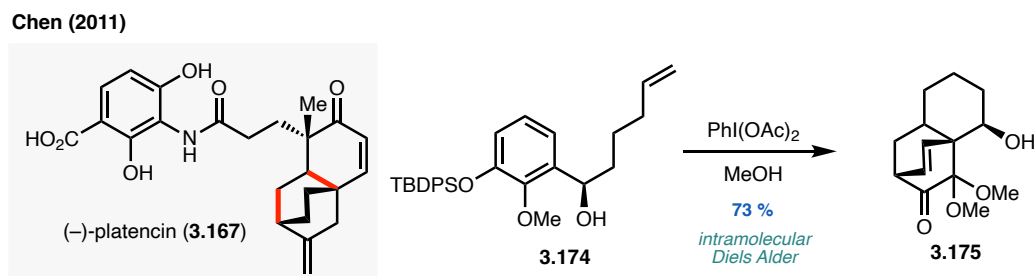
In the same year, Nicolaou and co-workers published their first asymmetric total synthesis of (–)-platencin.³⁸ They prepared an enantioenriched cyclohexanone substrate, which underwent a Co-catalyzed asymmetric Diels-Alder reaction and further transformations to afford intermediate **3.170**. Treatment with $n\text{Bu}_3\text{SnH}$ and AIBN induced a homoallylic radical rearrangement of the bicyclo[3.2.1]octane intermediate **3.170**, yielding bicyclo[2.2.2]octane **3.171**.



Scheme 27. Key reaction for the construction of bicyclo[2.2.2]octane core in Nicolaou's total synthesis of (-)-platencin (**3.167**).

In 2009, Nicolaou and colleagues published a full paper detailing their work on both the racemic and asymmetric synthesis of ($\pm$)- and (-)-platencin, employing the same asymmetric Diels-Alder reaction for precursor preparation.³⁹ In this updated work, a reductive rearrangement of the *in situ* generated tosyl hydrazone from **3.172** using NaBH_4 was reported.

The next total synthesis was published by Chen and co-workers in 2011, featuring the application of a masked *o*-benzoquinone in an intramolecular Diels-Alder reaction.⁴⁰ They carefully investigated the influence of a remote stereocenter from a secondary alcohol on the diastereoselectivity of the cycloaddition, which was obtained from a CBS reduction, and developed three different approaches to assemble the tricyclic core, all utilizing the masked *o*-benzoquinone substrate but with variations in the alkyl tether. Scheme 28 depicts their third-generation approach to desired tricycle **3.175**.

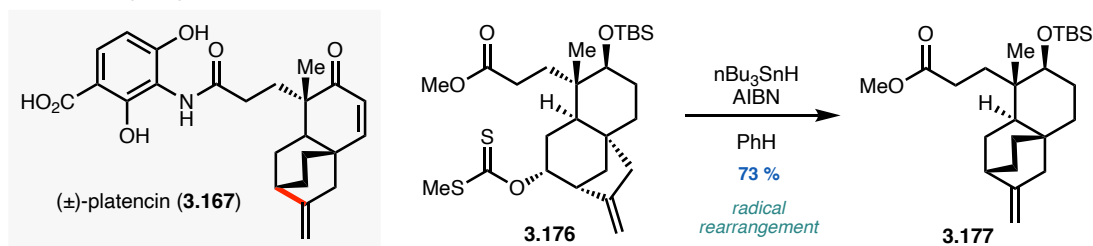


Scheme 28. Key reaction for the construction of bicyclo[2.2.2]octane core in Chen's total synthesis of (-)-platencin (**3.167**).

Finally, the last total synthesis of ($\pm$)-platencin was reported by the Yoshimitsu lab in 2011.⁴¹ Tricyclic intermediate **3.176** was obtained via a Pd-catalyzed Mizoroki-Heck cyclization, followed by a radical skeletal rearrangement with SnBu_3H and AIBN to yield intermediate **3.177**,

analogous to the report by Nicolaou in 2008, but the transformation was applied on a more complex system (Scheme 27a).

Yoshimitsu (2011)

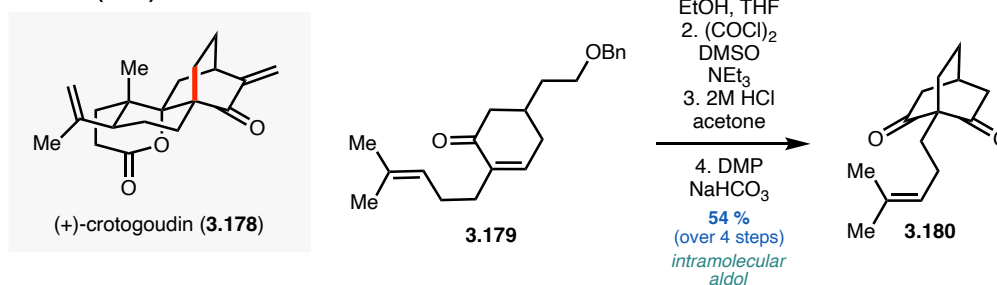


Scheme 29. Key reaction for the construction of bicyclo[2.2.2]octane core in Yoshimitsu's total synthesis of (±)-platencin (**3.167**).

3.6.4 Crotogoudin

In 2013, Carreira and co-workers reported the total synthesis of (+)-crotogoudin (**3.178**).⁴² Their route featured an efficient intramolecular aldol cyclization with **3.179** to construct the bicyclo[2.2.2]octane core **3.180** in good yields. The resulting bicycle (**3.180**) was desymmetrized using Baker's yeast reduction conditions and further elaborated to the tricyclic core required for the natural product.

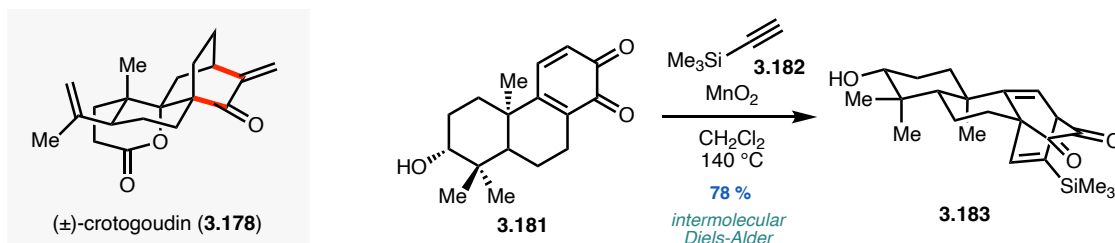
Carreira (2013)



Scheme 30. Key reaction for the construction of bicyclo[2.2.2]octane core in Carreira's total synthesis of (+)-crotogoudin (**3.178**).

The next total synthesis was reported by Qin and co-workers in 2015.⁴³ They employed a [4+2] cycloaddition using unmasked *o*-benzoquinones as carbodienes to construct fully functionalized bicyclo[2.2.2]octanes **3.183**. Utilizing their methodology with podocarpane-type unmasked *o*-benzoquinones, they demonstrated the utility of this reaction across several atisane-type diterpenoids, including (±)-crotobarin, (±)-crotogoudin, atisane-3 β ,16 α -diol, and 16*S*,17-dihydroxy-atisan-3-one. The [4+2] cycloaddition with trimethylsilyl acetylene **3.182** to generate the bicyclic core **3.183** for the (±)-crotogoudin synthesis is shown in Scheme 31.

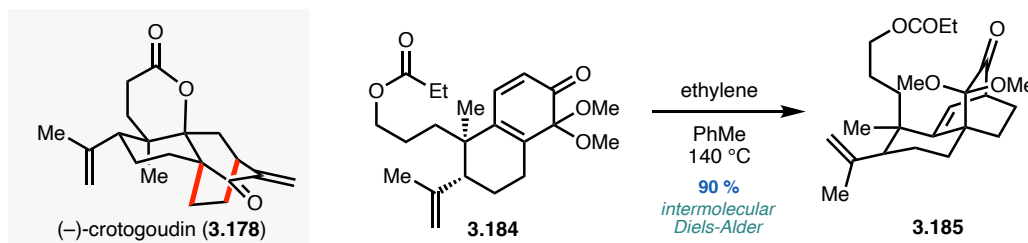
Qin (2015)



Scheme 31. Key reaction for the construction of bicyclo[2.2.2]octane core in Qin's total synthesis of (±)-crotonogoudin (**3.178**).

A notable total synthesis of (–)-crotonogoudin was reported by Sarpong and co-workers in 2017.⁴⁴ The synthesis begins with (*S*)-carvone, which is elaborated into cyclohexadienone **3.184** in nine steps, including an oxidative dearomatization step. Inspired by Fukuyama's synthesis of (–)-lepinine,⁴⁵ the authors designed a diastereoselective [4+2] cycloaddition with ethylene gas. The reaction required increased pressure and elevated temperature to proceed efficiently. With the bicyclo[2.2.2]octanone **3.185** in hand, it was further elaborated to (–)-crotonogoudin in 13 overall steps.

Sarpong (2017)

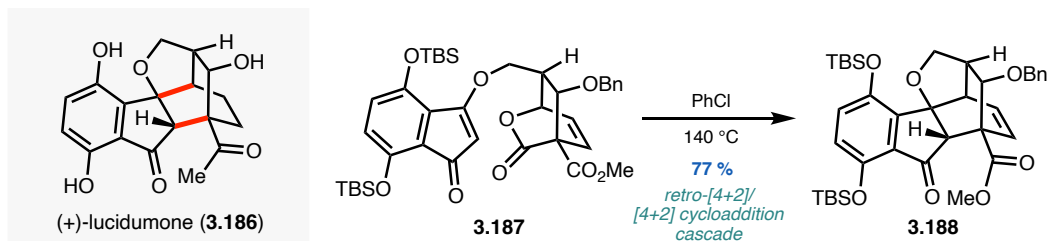


Scheme 32. Key reaction for the construction of bicyclo[2.2.2]octane core in Sarpong's total synthesis of (–)-crotonogoudin (**3.178**).

3.6.5 Lucidumone

The first enantioselective total synthesis of (+)-lucidumone (**3.186**) is reported by de la Torre and co-workers in 2022.⁴⁶ Their key transformation to construct the bicyclo[2.2.2]octane core involved a one-pot retro-[4+2]/[4+2] cycloaddition cascade. Precursor **3.187** for this cascade reaction was obtained via an enantioselective inverse electron-demand Diels-Alder reaction between a 2-pyrone and an enol ether substrate. This efficient cyclization afforded desired bicycle **3.188** in 77 % yield. The concise 13-step total synthesis demonstrated remarkable scalability, enabling the gram-scale synthesis of the natural products with an overall yield of 25.8 %.

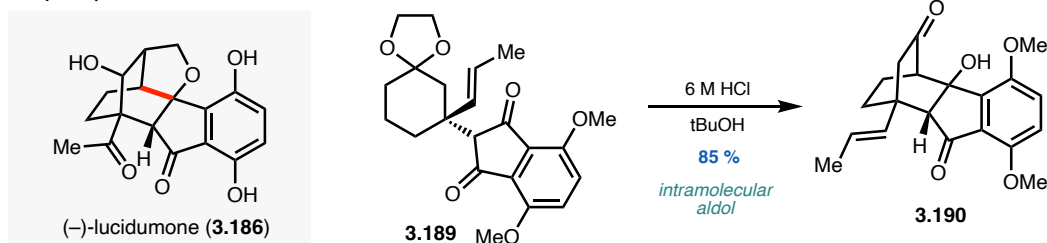
De La Torre (2022)



Scheme 33. Key reaction for the construction of bicyclo[2.2.2]octane core in De La Torre's total synthesis of (+)-lucidumone (**3.186**).

In 2023, Ito and co-workers reported the total synthesis of (–)-lucidumone in 10 steps, constructing the bicyclo[2.2.2]octane core via a stereocontrolled intramolecular aldol reaction with **3.189**.⁴⁷

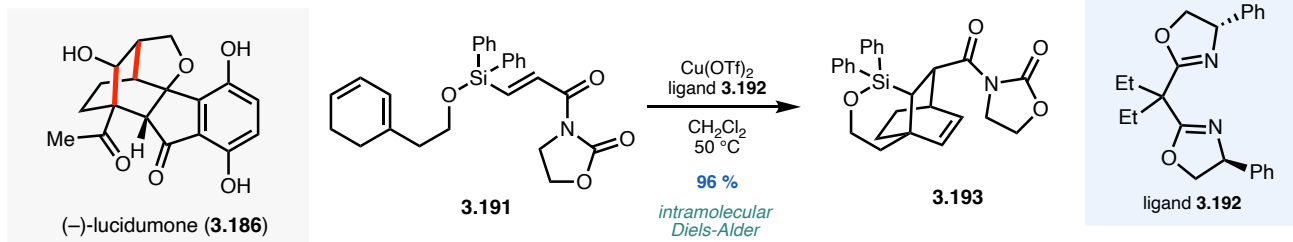
Ito (2023)



Scheme 34. Key reaction for the construction of bicyclo[2.2.2]octane core in Ito's total synthesis of (–)-lucidumone (**3.186**).

Following Ito's work, Li and co-workers completed an enantioselective total synthesis of (–)-lucidumone. Their route features a copper-catalyzed, enantioselective, silicon-tethered intramolecular Diels-Alder cycloaddition to generate the highly functionalized bicyclo[2.2.2]octane **3.193**.⁴⁸

Li (2024)

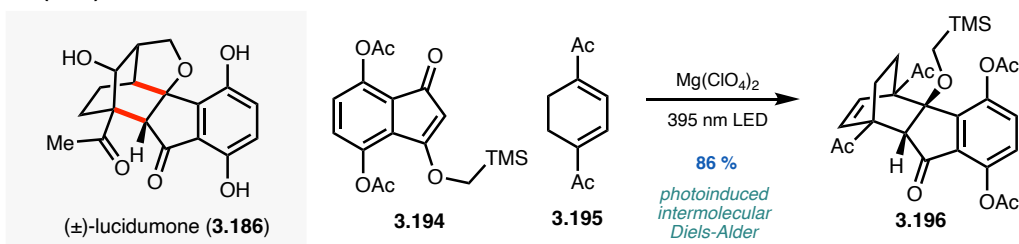


Scheme 35. Key reaction for the construction of bicyclo[2.2.2]octane core in Li's total synthesis of (–)-lucidumone (**3.186**).

In the same year, Hu and co-workers reported their total synthesis of racemic lucidumone using a photoinduced formal [4+2] cycloaddition.⁴⁹ They explored photoinduced cycloadditions between electronically mismatched components, which are underdeveloped reactions under thermal conditions. The intermolecular photoinduced cycloaddition of enone **3.194** with carbodiene **3.195**

afforded the bicyclo[2.2.2]octene **3.196** in 86 % yield. This intermediate was further elaborated to the natural product in nine steps from commercially available starting material.

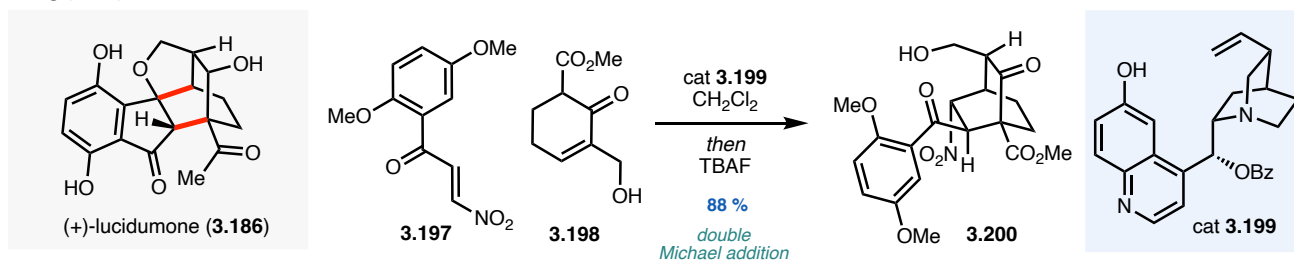
Hu (2024)



Scheme 36. Key reaction for the construction of bicyclo[2.2.2]octane core in Hu's total synthesis of (±)-lucidumone (**3.186**).

Most recently, Yang and co-workers reported a concise enantioselective total synthesis of (+)-lucidumone in 10 steps starting from commercially available 2-cyclohexen-1-one.⁵⁰ The key transformation constructing the bicyclo[2.2.2]octane core was a chiral quinine derivative-catalyzed double Michael addition with enone **3.197** and cyclohexenone **3.198**.

Yang (2025)



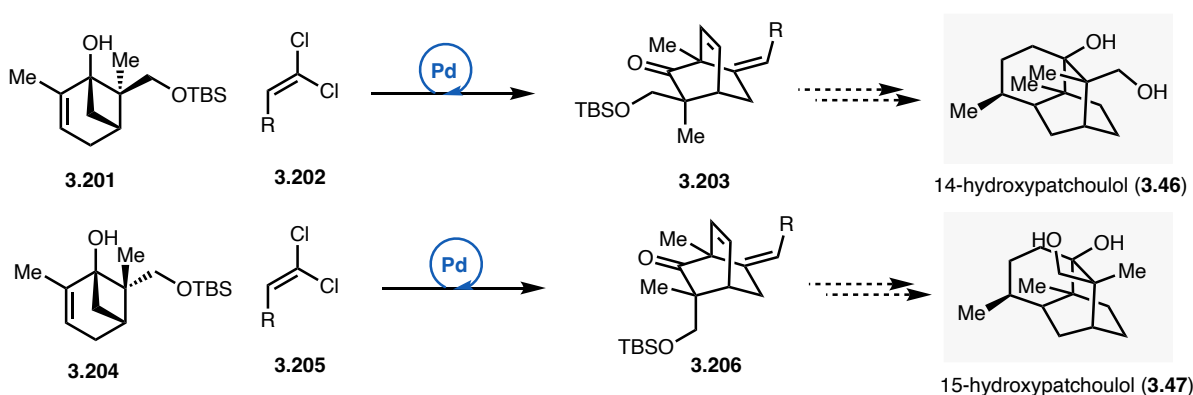
Scheme 37. Key reaction for the construction of bicyclo[2.2.2]octane core in Yang's total synthesis of (+)-lucidumone (**3.186**).

3.6.6 Summary

As observed in the previous chapter on the syntheses of patchouli alcohol, most total syntheses of natural products featuring the bridged bicyclo[2.2.2]octane motif employ inter- and/or intramolecular Diels-Alder reactions. Undeniably, the broad substrates scope, functional group tolerance, and excellent stereocontrol of the Diels-Alder reaction make it a highly effective and powerful transformation for constructing complex, densely functionalized bridged bicyclic frameworks. Consequently, the synthetic approaches to bicyclo[2.2.2]octane cores exhibit limited methodological diversity. To complement these established strategies, the development of new paradigms for bridged bicycle construction could enable more creative and unprecedented approaches to these structurally intricate natural products.

3.7 Our Proposal

Employing our Pd-catalyzed cascade reaction, we envision the first enantiospecific total synthesis of 14- and 15-hydroxypatchoulol (**3.46**, **3.47**) starting from (*R*)-carvone (**1.70**). These two oxygenated congeners of patchouli alcohol were selected as illustrative targets to showcase the utility of the previously discussed, newly developed Pd-catalyzed cascade reaction in natural product synthesis. Compared to previously reported syntheses of patchouli alcohol (**3.7**), our strategy introduces a new paradigm for constructing the bicyclo[2.2.2]octane core (Scheme 38). The palladium-catalyzed cascade reaction is expected to enable rapid assembly of the desired bicycle framework under mild conditions.



Scheme 38. Proposed synthetic approach to 14- and 15-hydroxypatchoulol (**3.46**, **3.47**) using the developed Pd-catalyzed cascade reaction.

3.8 References

1. Reed, J. W.; Hudlicky, T. *The Way of Synthesis: Evolution of Design and Methods for Natural Products*; Wiley-VCH: Weinheim, 2007.
2. Büchi, G.; Erickson, R. E. Terpenes. V. The Structure of Patchouli Alcohol. *J. Am. Chem. Soc.* **1956**, *78*, 1262–1263.
3. Büchi, G.; Erickson, R. E.; Wakabayashi, B. Terpenes. XVI. Constitution of Patchouli Alcohol and Absolute Configuration of Cedrene. *J. Am. Chem. Soc.* **1961**, *83*, 927–938.
4. Büchi, G.; MacLeod, W. D. Synthesis of Patchouli Alcohol. *J. Am. Chem. Soc.* **1962**, *84*, 3205–3206.
5. Dobler, M.; Dunitz, J. D.; Gubler, B.; Weber, H. P.; Büchi, G.; Padilla, O. J. The Structure of Patchouli Alcohol. *Proc. Chem. Soc.* **1963**, 383. <https://doi.org/10.1039/PS9630000357>.
6. Büchi, G.; MacLeod, W. D.; Padilla, O. J. Terpenes. XIX. Synthesis of Patchouli Alcohol. *J. Am. Chem. Soc.* **1964**, *86*, 4438.
7. Holton, R. A. Synthesis of the Taxane Ring System. *J. Am. Chem. Soc.* **1984**, *106*, 5731–5732.
8. Nicolaou, K. C.; Snyder, S. A. Chasing Molecules That Were Never There: Misassigned Natural Products and the Role of Chemical Synthesis in Modern Structure Elucidation. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012–1044.
9. Corey, E. J.; Wipke, W. T. Computer-Assisted Design of Complex Organic Syntheses. *Science* **1969**, *166*, 178–192.
10. Baumer, L.; Sala, G.; Sello, G. Organic Synthesis Planning: A New Algorithm for Strategic Bond Perception. *Tetrahedron* **1988**, *44*, 1195–1206.
11. Danishefsky, S.; Dumas, D. The Total Synthesis of Racemic Patchouli and epi-Patchouli Alcohol. *Chem. Commun.* **1968**, 1287–1288.
12. Näf, F.; Ohloff, G. A Short Stereoselective Total Synthesis of Racemic Patchouli Alcohol. *Helv. Chim. Acta* **1974**, *57*, 1868–1870.
13. Hardy, M. A.; Nan, B.; Wiest, O.; Sarpong, R. Strategic Elements in Computer-Assisted Retrosynthesis: A Case Study of the Pupukeyanane Natural Products. *Tetrahedron* **2022**, *104*, 132584.
14. Gal, H. Über ein Homologes des Borneocamphers. *Justus Liebigs Ann. Chem.* **1869**, *150*, 374–376.
15. (a) T. A. Van Beek; D. Joulain. The Essential Oil of Patchouli (*Pogostemon cablin*): A Review. *Flavour Fragr. J.* **2018**, *33*, 6–51. (b) F. Rochleder. *Phytochemie*; Verlag von Wilhelm Engelmann: Leipzig, 1854; pp 155. (c) R. Hunt; F. W. Rudler. *Ure's Dictionary of Arts, Manufactures, and Mines*, 7th ed.; Longmans, Green, and Co.: London, 1875; Vol. III, pp 516. (d) Anonymous. Patchouli (*Pogostemon patchouli*, var. *suavis*). *Bull. Misc. Inf. (R. Bot. Gard. Kew)* **1889**, 135–139. (e) E. Gildemeister; F. Hoffmann. *Die Aetherischen Oele*; Verlag Julius Springer: Berlin, 1899; pp 855–859. (f) F. Beilstein. *Handbuch der*

Organischen Chemie, 3rd ed.; Vol. 3; Verlag von Leopold Voss: Hamburg and Leipzig, 1897; pp 514, 538.

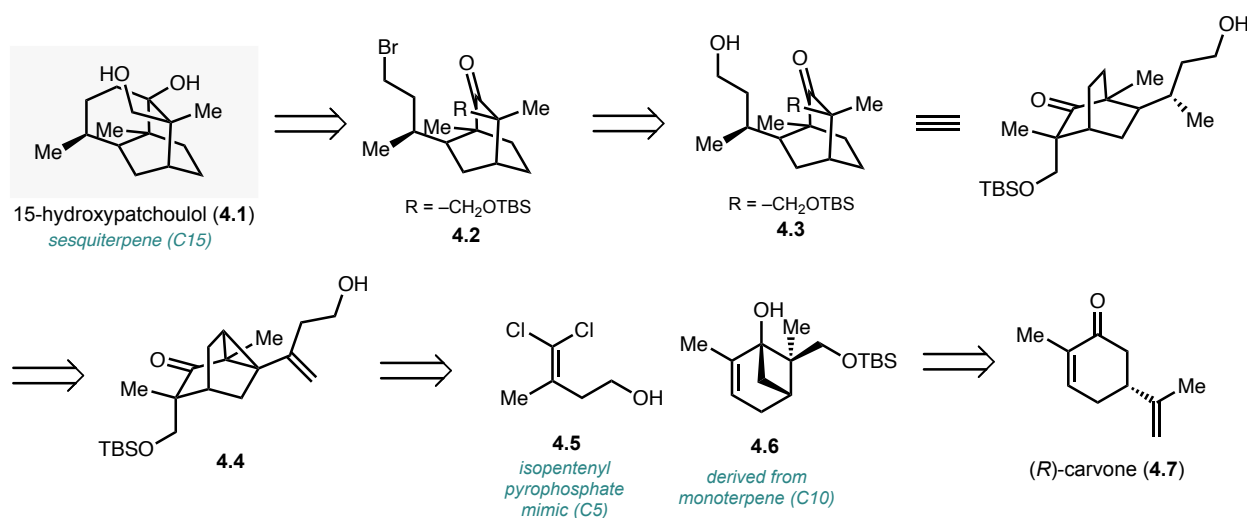
16. Kraft, P.; Wymuth, C.; Nussbaumer, C. Total Synthesis and Olfactory Evaluation of (1R*,3S*,6S*,7S*,8S*)-3-Hydroxy-6,8-dimethyltricyclo[5.3.1.0^{3,8}]undecan-2-one. *Eur. J. Org. Chem.* **2006**, 1403–1412.
17. Dong, F. W.; Wu, Z.-K.; Yang, L.; Zi, C.-T.; Yang, D.; Ma, R. J.; Liu, Z.-H.; Luo, H.-R.; Zhou, J.; Hu, J.-M. Iridoids and Sesquiterpenoids of *Valeriana stenoptera*. *Phytochemistry* **2015**, *118*, 51–60.
18. Faraldos, J. A.; Wu, S.; Chappell, J.; Coates, R. M. Doubly Deuterium-Labeled Patchouli Alcohol. *J. Am. Chem. Soc.* **2010**, *132*, 2998–3008.
19. Weitzel, C.; Simonsen, H. T. Cytochrome P450 Enzymes in Terpene Biosynthesis. *Phytochem. Rev.* **2015**, *14*, 7–24.
20. Mirrington, R. N.; Schmalzl, K. J. Total Synthesis of (±)-Patchouli Alcohol. *J. Org. Chem.* **1972**, *37*, 2871–2877.
21. Yamada, K.; Kyotani, Y.; Manabe, S.; Suzuki, M. Total Synthesis of (±)-Patchouli Alcohol. *Tetrahedron* **1979**, *35*, 293–298.
22. Bertrand, M.; Teisseire, P.; Pelerin, G. Alternative Cyclization Strategy Applied to Patchoulol. *Tetrahedron Lett.* **1980**, *21*, 2055–2056.
23. Näf, F.; Decorzant, R.; Giersch, W.; Ohloff, G. Stereocontrolled Access to Patchouli Alcohol. *Helv. Chim. Acta* **1981**, *64*, 1387–1397.
24. Cory, R. M.; Bailey, M. D.; Tse, D. W. C. A Divergent Approach to Patchouli Sesquiterpenes. *Tetrahedron Lett.* **1990**, *31*, 6839–6842.
25. Zhao, R.-B.; Wu, Y.-L. Formal Synthesis of (–)-Patchouli Alcohol. *Chin. J. Chem.* **1991**, *9*, 377–380.
26. Magee, T. V.; Stork, G.; Fludzinski, P. Total Synthesis of rac-Patchouli Alcohol. *Tetrahedron Lett.* **1995**, *36*, 7607–7610.
27. Srikrishna, A.; Satyanarayana, G. Enantiospecific Total Synthesis of (–)-Patchouli Alcohol. *Tetrahedron: Asymmetry* **2005**, *16*, 3992–3997.
28. Xu, G.-Q.; Lin, G.-Q.; Sun, B.-F. Concise Asymmetric Total Synthesis of (–)-Patchouli Alcohol. *Org. Chem. Front.* **2017**, *4*, 2031–2033.
29. Piers, E.; de Wall, W.; Britton, R. W. Stereoselective Total Synthesis of (±)-Seychellene. *J. Am. Chem. Soc.* **1971**, *93*, 5113–5120.
30. Welch, S. C.; Chou, C.-Y.; Gruber, J. M.; Assercq, J.-M. Total Syntheses of Seychellene Derivatives. *J. Org. Chem.* **1985**, *50*, 2668–2676.
31. (a) Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. Total Synthesis of (±)-Maoecrystal V. *J. Am. Chem. Soc.* **2010**, *132*, 16745–16746. (b) Zhang, W.-B.; Shao, W.-B.; Li, F.-Z.; Gong, J.-X.; Yang, Z. Asymmetric Total Synthesis of (–)-Maoecrystal V. *Chem. Asian J.* **2015**, *10*, 1874–1880.
32. Peng, F.; Danishefsky, S. Total Synthesis of (±)-Maoecrystal V. *J. Am. Chem. Soc.* **2012**, *134*, 18860–18867.

33. Lu, P.; Mailyan, A.; Gu, Z.; Guptill, D. M.; Wang, H.; Davies, H. M. L.; Zakarian, A. Enantioselective Synthesis of (–)-Maoecrystal V. *J. Am. Chem. Soc.* **2014**, *136*, 17738–17749.
34. Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. Enantioselective Total Synthesis of (–)-Maoecrystal V. *J. Am. Chem. Soc.* **2014**, *136*, 17750–17756.
35. Cernijenko, A.; Risgaard, R.; Baran, P. S. 11-Step Total Synthesis of (–)-Maoecrystal V. *J. Am. Chem. Soc.* **2016**, *138*, 9425–9428.
36. Smith, B. R.; Njardarson, J. T. Review of Synthetic Approaches toward Maoecrystal V. *Org. Biomol. Chem.* **2018**, *16*, 4210–4222.
37. Hayashida, J.; Rawal, V. H. Total Synthesis of (±)-Platencin. *Angew. Chem., Int. Ed.* **2008**, *47*, 4373–4376.
38. Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J. Total Synthesis of Platencin. *Angew. Chem.* **2008**, *120*, 1804–1807.
39. Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J.; Kar, M. Total Syntheses of (±)- and (–)-Platencin. *J. Am. Chem. Soc.* **2009**, *131*, 15909–15917.
40. Leung, G. Y. C.; Li, H.; Toh, Q.-Y.; Ng, A. M.-Y.; Sum, R. J.; Bandow, J. E.; Chen, D. Y.-K. Total Synthesis and Biological Evaluation of Platencin. *Eur. J. Org. Chem.* **2011**, 183–196.
41. Yoshimitsu, T.; Nojima, S.; Hashimoto, M.; Tanaka, T. Total Synthesis of (±)-Platencin. *Org. Lett.* **2011**, *13*, 3698–3701.
42. Breitler, S.; Carreira, E. M. Total Synthesis of (+)-Crotogoudin. *Angew. Chem., Int. Ed.* **2013**, *52*, 11168–11171.
43. Song, L.; Zhu, G.; Liu, Y.; Liu, B.; Qin, S. Total Synthesis of Atisane-Type Diterpenoids. *J. Am. Chem. Soc.* **2015**, *137*, 13706–13714.
44. Finkbeiner, P.; Murai, K.; Röpke, M.; Sarpong, R. Total Synthesis of (–)-Crotogoudin. *J. Am. Chem. Soc.* **2017**, *139*, 11349–11352.
45. Nishiyama, Y.; Han-ya, Y.; Yokoshima, S.; Fukuyama, T. Total Synthesis of (–)-Lepenine. *J. Am. Chem. Soc.* **2014**, *136*, 6598–6601.
46. Huang, G.; Kouklovsky, C.; de la Torre, A. Enantioselective Synthesis of (+)-Lucidumone. *J. Am. Chem. Soc.* **2022**, *144*, 17803–17807.
47. Kawamoto, Y.; Noguchi, N.; Kobayashi, T.; Ito, H. Total Synthesis of Lucidumone. *Angew. Chem., Int. Ed.* **2023**, *62*, e202304132.
48. Liao, X.-Z.; Wang, R.; Wang, X.; Li, G. Enantioselective Total Synthesis of (–)-Lucidumone. *Nat. Commun.* **2024**, *15*, 2647.
49. Yu, Z.; Peng, W.; Huang, J.; Shen, J.; Guo, J.-J.; Hu, A. Photoinduced Formal [4+2] Cycloaddition. *Nat. Commun.* **2024**, *15*, 9748.
50. Liang, X.; Jiang, H.-N.; Yang, J.-T.; Duan, Y.-J.; Wei, K.; Yang, Y.-R. Enantioselective Total Synthesis of (+)-Lucidumone. *Org. Lett.* **2025**, *27*, 10619–10624.

Chapter 4. Total Synthesis of 14- and 15-Hydroxypatchoulol

4.1 Initial Synthesis Strategy

Our initial retrosynthetic analysis was based on using an isopentenyl pyrophosphate (IPP) mimic **4.5** as the cross-coupling electrophile in the synthesis of the sesquiterpene natural product 15-hydroxypatchoulol (**4.1**) from monoterpene derivative **4.6** (Scheme 4.1). In this design, the Pd-catalyzed cascade reaction was expected to generate tricyclo[3.2.1.0]octanone **4.4**, while simultaneously introducing all requisite carbons for the natural product. Cyclopropane hydrogenolysis would then afford the desired bicyclo[2.2.2]octanone core, giving alcohol **4.3**, which could be converted to alkyl bromide **4.2**.¹ Following precedent from Danishefsky and co-workers, this late-stage intermediate would undergo reductive cyclization to deliver **4.1**.²



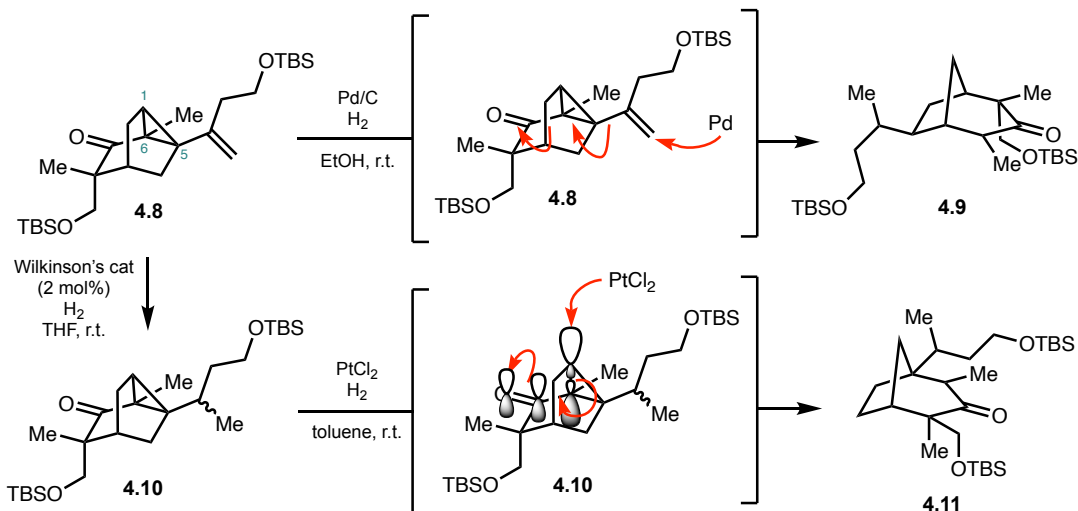
Scheme 4.1. Proposed initial retrosynthetic analysis.

4.2 Initial Attempts with Acyclic Tetrasubstituted *gem*-Dichloroalkene Electrophile

On the basis of the preliminary results obtained during the development of the Pd-catalyzed cascade reaction (discussed in Chapter 2), advancement of cyclobutanol **4.6** to tricycle **4.4** proceeded smoothly. With the desired intermediate in hand, we focused on selective cleavage of the cyclopropane C1–C5 bond to obtain the bicyclo[2.2.2]octanone core.

We investigated literature-reported vinylcyclopropane hydrogenolysis conditions using various metal complexes.¹ Although cleavage of the less substituted C–C bond is typically favored, we instead observed preferential cleavage of the more substituted C5–C6 bond in **4.8** (Scheme 4.2). We hypothesize that this outcome arises from nucleophilic attack by palladium on the vinylcyclopropane moiety, forming a π -allylpalladium intermediate that undergoes selective

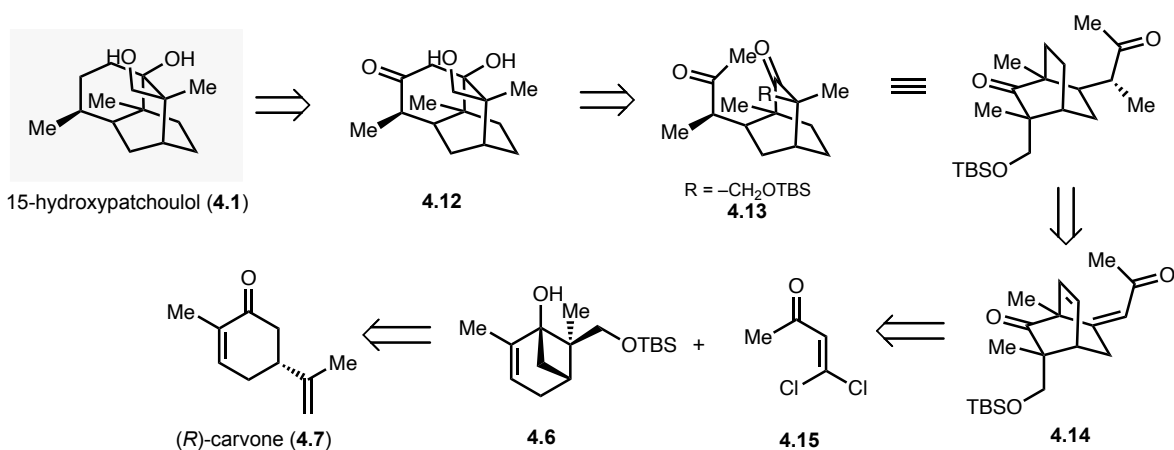
protonation and hydrogenation on the more accessible convex face, affording bicyclo[3.2.1]octanone **4.9**.³ Reducing the olefin group in **4.8** and switching to a platinum catalyst led to the formation of a different bicyclo[3.2.1]octanone (**4.11**).^{1c} We propose that **4.11** arises from nucleophilic attack of the metal catalyst at the C1–C6 bond of **4.10**, which is geometrically aligned to facilitate formation of the C=C bond of the resulting enolate. Attempts to protect the corresponding ketone to prevent engagement of its π -system in the C–C bond cleavage step on **4.8** and **4.10** were unsuccessful, likely due to steric encumbrance from the two adjacent quaternary carbon centers.



Scheme 4.2. Catalytic hydrogenolysis attempts on tricycle **4.8** and **4.10** to obtain bicyclo[2.2.2]octanone **4.3**.

4.3 Retrosynthesis (1st generation)

With repeated failure to obtain the desired bicyclo[2.2.2]octanone **4.3** via C1–C5 bond cleavage, we pivoted to a trisubstituted alkene electrophile **4.15** (Scheme 4.3). To facilitate the selective formation of bicyclo[2.2.2]octanone **4.14** and streamline the synthetic route, the substrate was designed to not possess allylic hydrogens, thereby avoiding the competing formation of tricyclo[3.2.1.0]octanone (Chapter 2.4). The reaction conditions identified from initial coupling studies set the stage for the synthesis of **4.14**, as outlined in the retrosynthetic analysis in Scheme 4.3. We envisioned the patchoulol framework arising from **4.13** via an intramolecular aldol reaction, and accordingly designed a route featuring a key coupling between cyclobutanol **4.6** and *gem*-dichlorovinyl ketone **4.15**. Notably, **4.15** introduces the carbonyl functionality required for aldol cyclization to form the final ring.



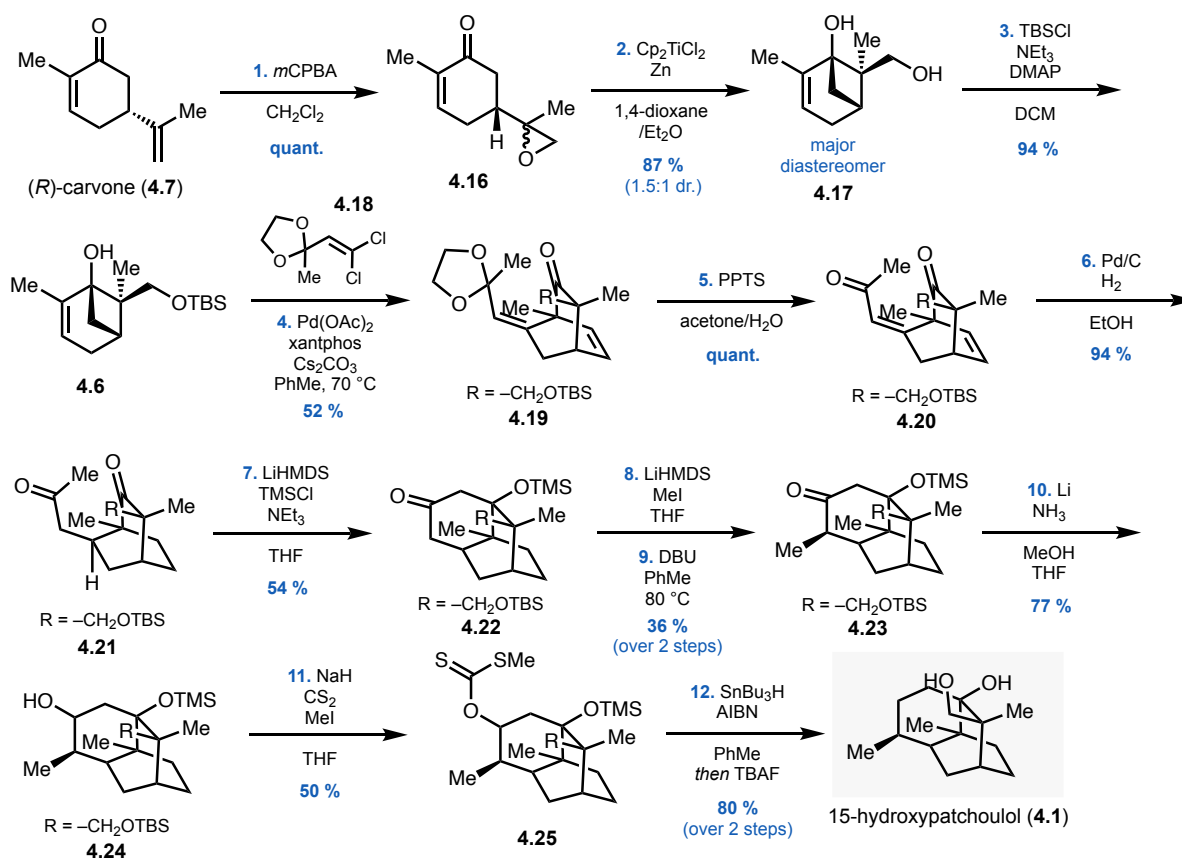
Scheme 4.3. Retrosynthesis employing trisubstituted *gem*-dichloroalkene electrophile **4.15**.

4.4 Total Synthesis of 14- and 15-Hydroxypatchoulol (1st generation)

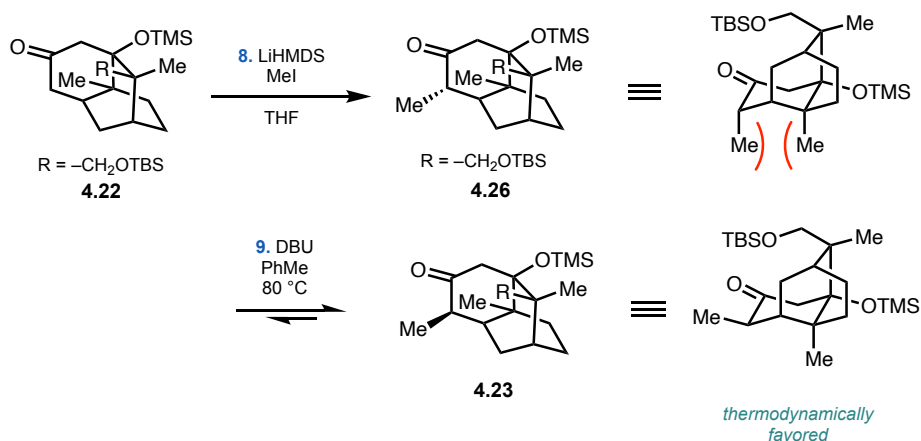
In practice, **4.15** polymerized under the reaction conditions. However, ketal-protected **4.18** proved more robust and afforded bicyclo[2.2.2]octane **4.19** in 53% yield (Scheme 4.4). Cleavage of the dioxolane protecting group in **4.19** with pyridinium *p*-toluenesulfonate (PPTS) provided enone **4.20**. Global hydrogenation of **4.20** using Pd/C and H₂ furnished the fully saturated product (**4.21**) in excellent yield and diastereoselectivity.

In the presence of excess lithium hexamethyldisilazide (LiHMDS), **4.21** underwent aldol cyclization to give the corresponding product.⁴ We found that protection of the resulting hydroxy group was necessary to prevent retro-aldol reaction under basic conditions. Accordingly, *in situ* trapping of the alkoxide formed from aldol cyclization of **4.21** with TMSCl afforded the corresponding silyl ether, along with a mixture of silyl enol ethers (not shown). These silyl enol ethers readily hydrolyzed during silica gel chromatography to give ketone **4.22**. α -Methylation of ketone **4.22** proceeded in moderate yield (49% yield), with significant recovery of the starting material (38%), and favored alkylation on the convex face of the molecule to give the undesired diastereomer **4.26** as the major product (Scheme 4.5). Thermodynamic epimerization with DBU at 70°C provided **4.23** bearing the desired equatorial α -methyl group as a single diastereomer.

Direct removal of the ketone group proved challenging. Attempts at Wolff–Kishner reduction, including the Caglioti and Myers modifications,^{5,6} were unsuccessful, as were efforts to access thiocarbonyl or thioketal intermediates for a Mozingo reduction.⁷ Ultimately, reduction of **4.23** to alcohol **4.24** under dissolving metal conditions, followed by Barton–McCombie deoxygenation, enabled net removal of the carbonyl group. Final cleavage of the silyl protecting groups furnished 15-hydroxypatchoulol (**4.1**).



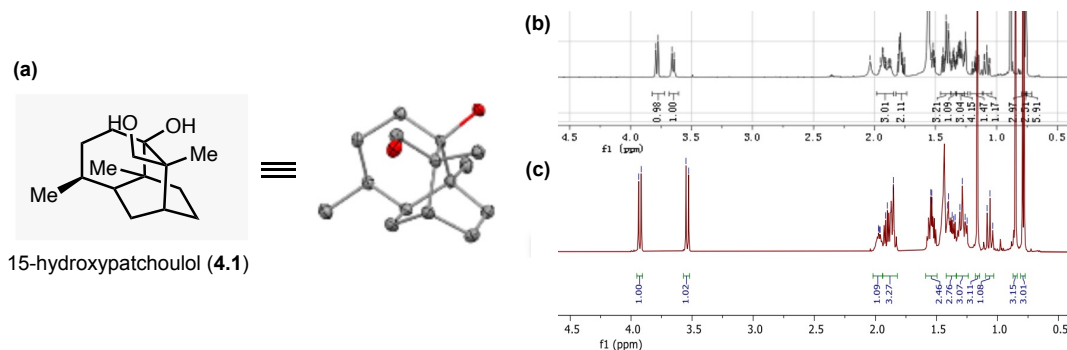
Scheme 4.4. Total synthesis of 15-hydroxypatchoulol (**4.1**).



Scheme 4.5. Epimerization of **4.26**.

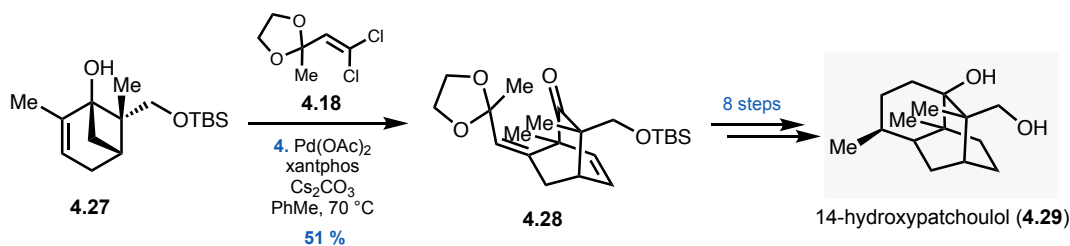
We found that the NMR data for **4.1** did not match those reported in the original isolation report (Scheme 4.6).⁸ Accordingly, we unambiguously characterized **4.1** by X-ray crystallographic analysis. Our results indicate that the compound assigned as **4.1** in the isolated report is in fact a constitutional isomer bearing a primary hydroxy group, rather than the patchoulol skeleton. This conclusion is further supported by the observation that all other hydroxymethyl derivatives of

patchouli alcohol have been reported, none of which exhibit spectroscopic data consistent with those attributed to compound **4.1** in the original report.^{9,10}



Scheme 4.6. (a) X-ray crystallographic structure of 15-hydroxypatchoulol (**4.1**). (b) ¹H NMR of isolated 15-hydroxypatchoulol.⁸ (c) ¹H NMR of synthesized 15-hydroxypatchoulol (**4.1**).

To further support our conclusions, we prepared 14-hydroxypatchoulol (**4.29**) in an analogous manner to our synthesis of 15-hydroxypatchoulol. This route began from diastereomeric cyclobutanol **4.27**, obtained via reductive cyclization of epoxy-carvone (Scheme 4.7). The resulting spectroscopic data likewise did not match those reported from the compound assigned as **4.1** in the isolation report, but matched with the data attributed to compound **4.29**.⁸



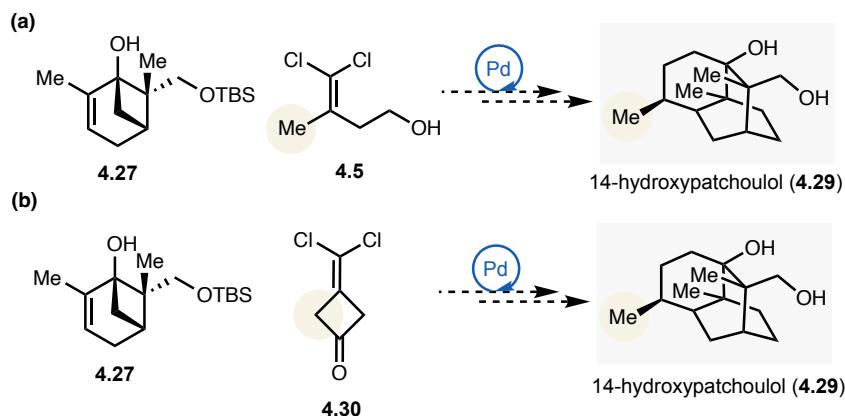
Scheme 4.7. Total synthesis of 14-hydroxypatchoulol (**4.29**).

4.5 Retrosynthesis (2nd Generation)

With the total synthesis of 14- and 15-hydroxypatchoulol in hand, along with additional insights into the product selectivity of the Pd-catalyzed cascade reaction (Chapter 2), we revisited our initial synthetic approach in which the tetrasubstituted alkene electrophile had been a limiting factor. On the basis of previously discussed studies of substituent bond angle dependence on Mizoroki–Heck cyclization selectivity (see Chapter 2.7), we opted to employ the cyclobutanone alkene electrophile **4.30**, a cyclic equivalent of the initially explored *gem*-dichloroalkene (**4.5**, Scheme 4.8).

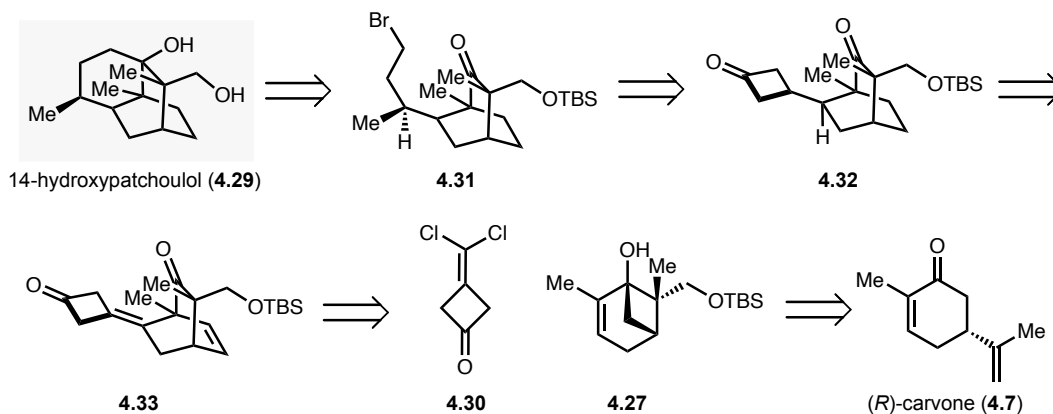
As in our first-generation synthesis, the use of this electrophile introduces the requisite carbons and constructs the bicyclo[2.2.2]octane core in the Pd-catalyzed cross-coupling and cyclization sequence. However, with this electrophile, the methylation, epimerization, and ketone reduction

steps used in the first-generation synthesis of 15-hydroxypatchoulol are no longer necessary, providing an opportunity to streamline the synthesis.



Scheme 4.8. Cyclobutane *gem*-dichloroalkene **4.30** as cyclic equivalent of **4.5** for the total synthesis of 14-hydroxypatchoulol (**4.29**).

Retrosynthetically, we envisioned constructing the tricyclic system of 14-hydroxypatchoulol (**4.29**) via reductive cyclization inspired by the Danishefsky synthesis of patchouli alcohol (**3.7**), as discussed in Chapter 4.1 (Scheme 4.9).² The desired side chain could be obtained via C–C bond cleavage of the cyclobutanone, leveraging its inherent ring strain, using methods reported by Dong or Cramer.^{11,12} Corresponding late-stage intermediate **4.32** can be obtained via global hydrogenation of bicycle **4.33** obtained from the developed cascade reaction with **4.27** and **4.30**.

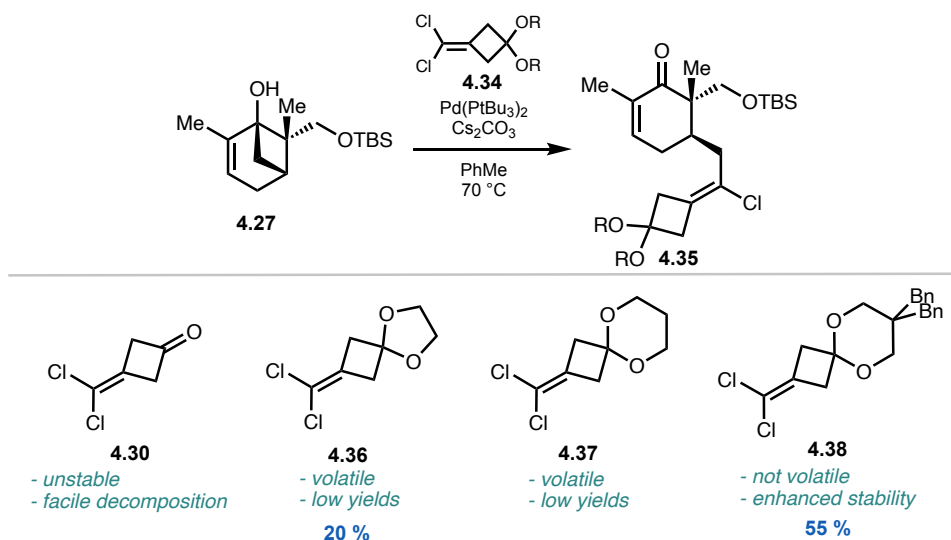


Scheme 4.9. 2nd Generation retrosynthesis of 14-hydroxypatchoulol (**4.29**).

4.6 Total Synthesis of 14-Hydroxypatchoulol (2nd Generation)

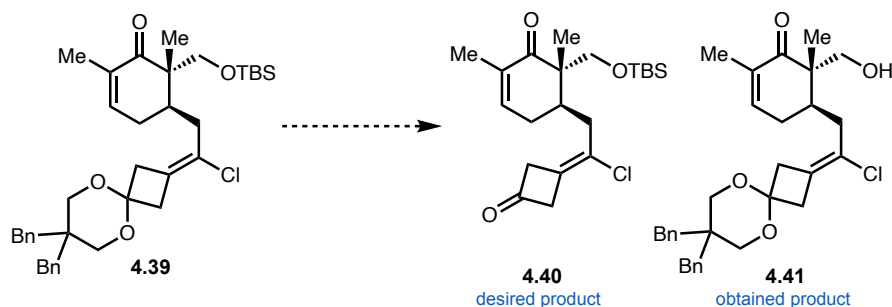
The insights gleaned from our studies set the stage for a synthesis of 14-hydroxypatchoulol (**4.29**) using **4.27**. Due to the instability of **4.30**, the ketone group was protected as a ketal (see **4.34**, Scheme 4.10). However, the corresponding ketal electrophiles **4.36** and **4.37** proved to be volatile, resulting in poor yields or no reaction in the cross-coupling step. This issue was mitigated

by employing 2,2-dibenzylpropane-1,3-diol in the ketalization, affording electrophile **4.38**. Although higher yields in the C–C cleavage/cross-coupling sequence were achieved, subsequent hydrolysis to regenerate the ketone was unsuccessful, with hydrolysis of the silyl ether observed in most cases (Table 4.1).



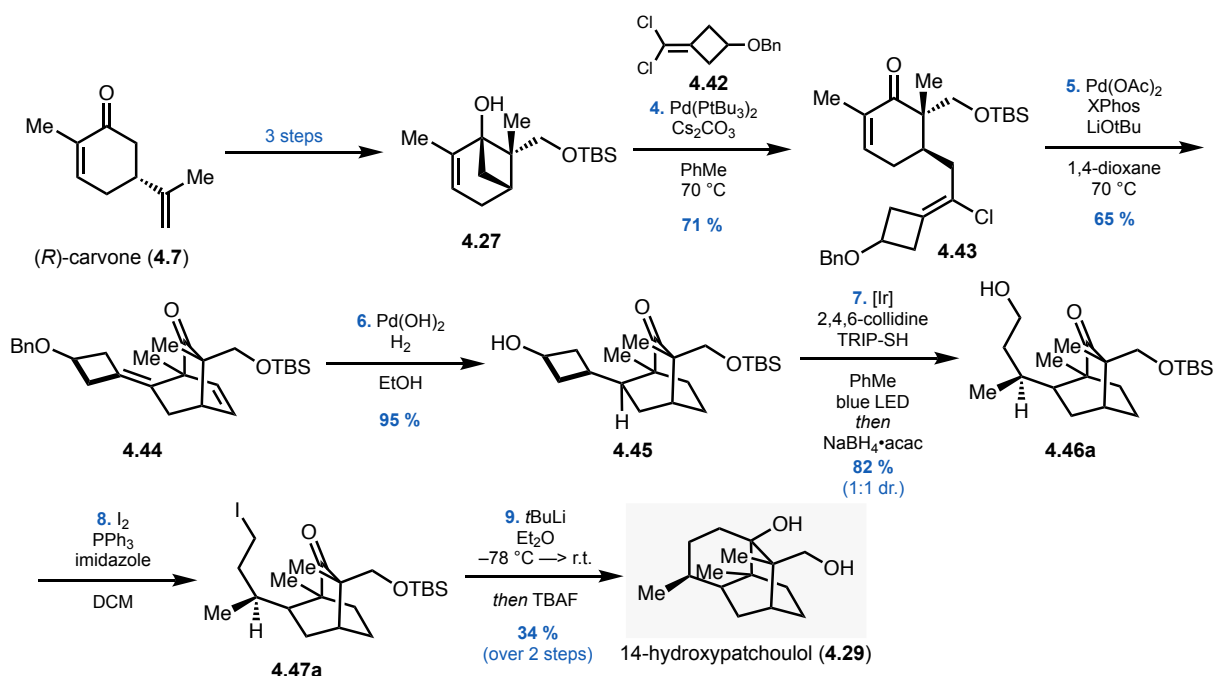
Scheme 4.10. Explored protecting groups for cyclobutanone substrate **4.34**.

Table 4.1. Reaction conditions for cyclobutanone protecting group cleavage.



entry	reaction condition	result
1	PPTS, acetone/H ₂ O, 40 °C, 16 h	no reaction
2	<i>p</i> TsOH•H ₂ O, acetone, 50 °C, 16 h	no reaction
3	H ₂ SO ₄ , acetone/H ₂ O, r.t. 5 h	4.41
4	In(OTf) ₃ , acetone, r.t., 48 h ¹³	4.41
5	Bi(OTf) ₃ , THF/H ₂ O, r.t.→65 °C, 16 h ¹⁴	38 % (4.41)
6	TMSOTf, 2,4,6-collidine, DCM, 0 °C→r.t., 1 h ¹⁵	80 % (4.41)

Instead, we opted to use benzyl ether **4.42** as the cross-coupling electrophile, which provided vinyl chloride **4.43** in 68 % yield (Scheme 4.11). This subsequent Mizoroki–Heck cyclization to give **4.44** proceeded in 65 % yield under the optimized conditions with Xphos and Li^tOBu. Key to the high product selectivity and yield was the increased loading of the base.



Scheme 4.11. 2nd Generation total synthesis of 14-hydroxypatchouol (**4.29**).

With the desired bicyclo[2.2.2]octanone **4.44** in hand, we performed a global hydrogenation with concomitant hydrogenolysis of the benzyl group to afford cyclobutanol **4.45**. Gratifyingly, hydrogenation of the tetrasubstituted alkene occurred exclusively from the side opposite the quaternary center of the two-carbon bridge. Depending on the solvent, palladium catalyst identity/loading, and reaction time, different reduction products were observed (Table 4.2). The product distribution reflects the relative rates of reduction of the various functional groups: the endocyclic alkene group is reduced first (**4.48**), followed by hydrogenolysis of the benzyl protecting group (**4.49**), and lastly the tetrasubstituted alkene (**4.45**), which is the most sterically hindered.

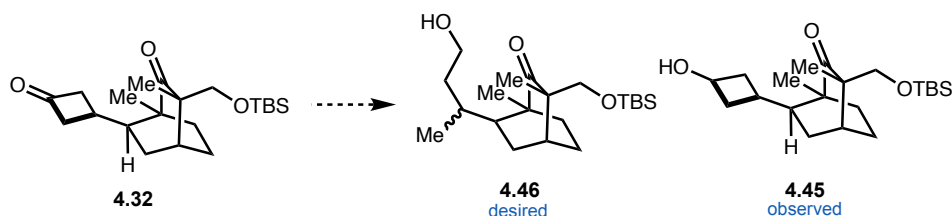
Table 4.2. Hydrogenation and hydrogenolysis conditions.

entry	Reaction condition	4.48	4.49	4.45
1	Pd/C, H ₂ , EtOH, 6 h	mostly	0	0
2	Pd/C, H ₂ , EtOAc, 16 h	0	51 %	0
3	Pd(OH) ₂ , H ₂ , EtOH, 1 h	0	0	95 %

With cyclobutanol **4.45** in hand, we explored a range of conditions to open the cyclobutane, either directly from the cyclobutanol **4.45** or via its corresponding cyclobutanone **4.32**. Selected

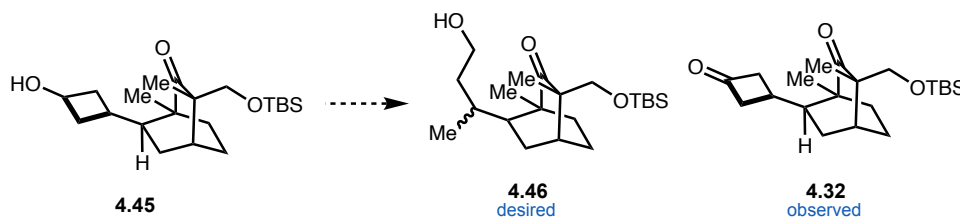
conditions from the literature on transition-metal catalyzed C–C bond cleavage with cyclobutanols or cyclobutanones that were explored are shown in Table 4.3 and Table 4.4, respectively.^{11,12} When employing cyclobutanol **4.45**, the two diastereomers of **4.45** were inseparable and were carried forward as a mixture of diastereomers.

Table 4.3. Reaction conditions for cyclobutanone **4.32** C–C bond cleavage.^{11,12}



entry	reaction condition	result
1	[Rh(cod)(MeCN) ₂]BF ₄ , (<i>R</i>)-BINAP, H ₂ , PhMe, 70 °C, o/n	75 % (4.45)
2	[Rh(cod)(MeCN) ₂]BF ₄ , (<i>R</i>)-BINAP, H ₂ , PhMe, 70 °C, 48 h	73 % (4.45)
3	[Rh(cod)(MeCN) ₂]BF ₄ , (<i>R</i>)-BINAP, NaCO ₂ H, PhMe, 80 °C, o/n	no reaction
4	[Rh(cod)(MeCN) ₂]BF ₄ , (<i>R</i>)-BINAP, NaCO ₂ H, PhMe, 110 °C, o/n	decomposition
5 ¹⁶	[RhCl(cod)] ₂ , dppe, H ₂ 50 atm, 140 °C, o/n	no reaction

Table 4.4. Reaction conditions for cyclobutanol **4.45** C–C bond cleavage.^{11,12}

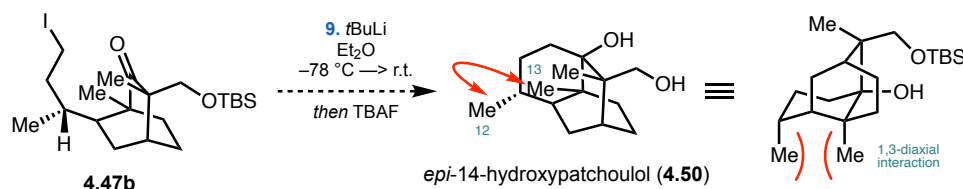


entry	reaction condition	result
1 ¹⁷	Pd(OAc) ₂ , pyridine, NaCO ₂ H, PhMe, 80 °C, o/n	no reaction
2 ¹⁸	Pd(OAc) ₂ , PPh ₃ , K ₂ CO ₃ , NaCO ₂ H, DMF, 80 °C, o/n	no reaction
3	[Rh(OH)(cod)] ₂ , (<i>R</i>)-BINAP, H ₂ , PhMe, 80 °C, o/n	decomposition
3 ¹⁶	[RhCl(cod)] ₂ , dppe, H ₂ 50 atm, 140 °C, o/n	no reaction
4	[Rh(cod)OH] ₂ , MeOH, 60 °C, o/n	no reaction
5	[Rh(cod)OH] ₂ , (<i>R</i>)-BINAP, 110 °C, o/n	no reaction
6	[Rh(cod) ₂]BF ₄ , (<i>R</i>)-BINAP, Ag ₂ CO ₃ , PhMe, 110 °C, o/n	1:1 (4.45 : 4.32)

Ultimately, by using photochemical C–C bond homolysis conditions reported by Knowles and co-workers, the C–C bond cleavage product aldehyde was obtained in excellent yield (95 %, 1:1 dr.) (Scheme 4.11).¹⁹ Attempts to render this step diastereoselective using chiral phosphoric acid were unsuccessful. The aldehydes were reduced to the corresponding alcohol (**4.46a**, only desired diastereomer shown in Scheme 4.11) in the same pot upon cyclobutanol opening using the conditions from Hao.²⁰

After Appel reaction to obtain the corresponding alkyl bromide, the envisioned reductive cyclization using sodium metal reported by Danishefsky and co-workers was unfortunately unsuccessful, with only unreacted starting material recovered.² Alternatively, treatment of the corresponding alkyl iodide (**4.47**) with *t*BuLi furnished 14-hydroxypatchoulol (**4.29**) in 34% yield (over 2 steps). The structure of **4.29** was confirmed by ¹H and ¹³C NMR spectroscopy and matched literature reported values.⁸

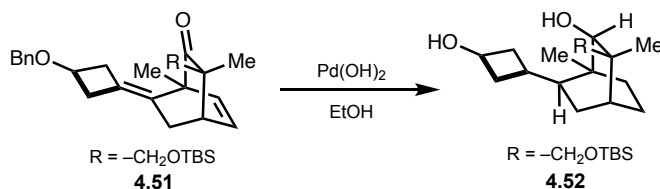
Notably, only diastereomer **4.47a** of the mixture of alkyl iodides yielded 14-hydroxypatchoulol (**4.29**) as the only cyclization product in the final step, while the other diastereomer (**4.47b**) did not undergo cyclization (Scheme 4.12). We hypothesize that unfavorable 1,3-diaxial interactions between the C12 and C13 methyl groups inhibit the cyclization to epi-14-hydroxypatchoulol (**4.50**), leading to kinetic resolution of the epimers.² Accordingly, the corresponding dehalogenated species resulting from **4.47b** was obtained from the reaction.



Scheme 4.12. Kinetic resolution in final cyclization step to 14-hydroxypatchoulol (**4.29**).

4.7 Attempted Total Synthesis of 15-Hydroxypatchoulol

Analogous to our first-generation synthesis, we attempted to access 15-hydroxypatchoulol (**4.1**) using the newly established synthesis route involving cyclobutanol alkene electrophile **4.42**, despite it having been confirmed that this compound does not correspond to the isolated natural product. The synthesis of the corresponding bicyclo[2.2.2]octanone **4.51** proceeded smoothly. An interesting discrepancy was observed in the hydrogenation step, where the established reaction conditions in Table 4.2 (entry 3) also reduced the ketone group of bicycle **4.51** (Scheme 4.13). This unexpected reduction is likely due to the different steric environment of the bicyclic ketone compared to its diastereomeric analogue **4.44** in the 14-hydroxypatchoulol synthesis.



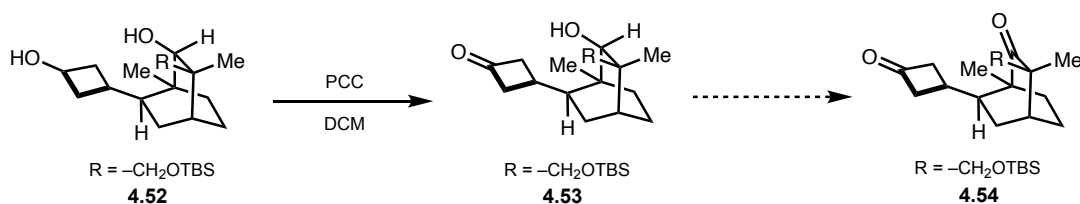
Scheme 4.13. Global hydrogenation and hydrogenolysis of bicycle **4.51**.

To ensure selective cleavage of the cyclobutanol C–C bond in the subsequent alcohol-mediated photochemical homolytic cleavage step, the corresponding alcohol is required to be oxidized to diketone **4.55** (Table 4.5). This transformation proved challenging, as multiple attempts to oxidize

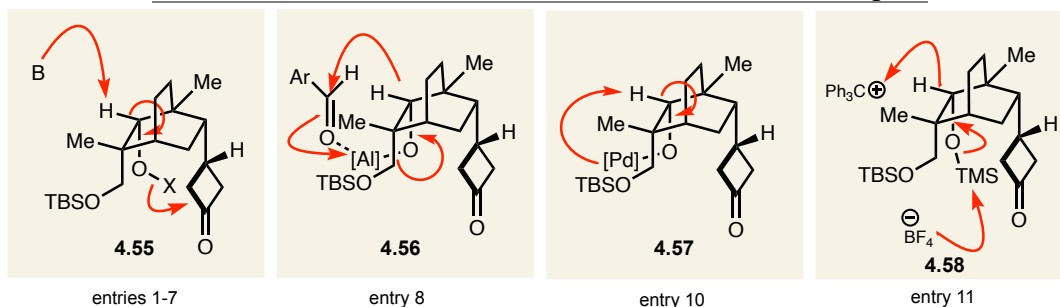
the alcohol were unsuccessful (Table 4.5, entry 1–4). Literature reported procedures known to oxidize sterically hindered alcohols were similarly ineffective (Table 4.5, entry 5–7). Given that approach to the secondary alcohol from the concave face of the molecule is hindered by the bulky silyl ether group and the cyclobutanone substituent, we next explored smaller oxidants and alternatives or activation. These included Oppenauer oxidation (entry 8), Fetizon oxidation (entry 9), Pd-catalyzed oxidation of the secondary alcohol via β -H elimination pathway (entry 10), and trityl cation-mediated oxidation (entry 11).²¹ However, all conditions resulted in no reaction (see bottom of Table 4.5 for the proposed mechanisms).

Likewise, efforts to optimize hydrogenation conditions that would preserve the ketone group while reducing both alkene groups and cleaving the benzyl protecting group were unsuccessful, as hydrogenation of the tetrasubstituted alkene could not be achieved under milder reducing conditions. Other hydrogenation conditions employing homogeneous catalysts were equally unsuccessful in reducing the tetrasubstituted alkene.²⁹ On the basis of these outcomes, we decided to not continue the synthesis of 15-hydroxypatchoulol using this approach.

Table 4.5. Reaction conditions to oxidize **4.53** to **4.54**.

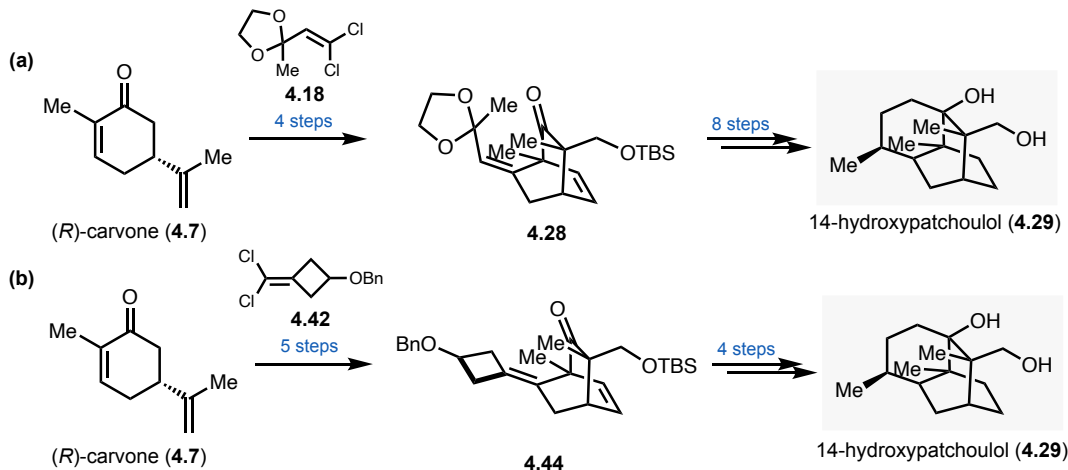


entry	reaction condition	result
1	PCC	no reaction
2	DMP	no reaction
3	(COCl) ₂ , DMSO, NEt ₃	no reaction
4	NaOCl, NaHSO ₄ , H ₂ O, EtOAc ²¹	no reaction
5	AZADO, AcOH, NaNO ₂ ²²	decomposition
6	IBX ²³	no reaction
7	IBS ²⁴	no reaction
8	AlMe ₃ , 3-nitrobenzaldehyde ²⁵	no reaction
9	Ag ₂ CO ₃ , celite, benzene, reflux ²⁶	no reaction
10	Pd(OAc) ₂ , pyridine, MS3A, O ₂ ²⁷	no reaction
11	TMSOTf, PhC ₃ BF ₄ ²⁸	not desired pdt



4.8 Summary and Outlook

In conclusion, we report the first total synthesis of 14- and 15-hydroxypatchoulol (**4.1** and **4.29**) enabled by a Pd-catalyzed Mizoroki–Heck cyclization cascade. Central to this strategy is a concise entry to substituted bicyclo[2.2.2]octanones via Pd-catalyzed cyclobutanol C–C bond cleavage/cross-coupling/Mizoroki–Heck cascade reactions of *gem*-dichloroalkenes. Compared to pioneering syntheses of patchouli sesquiterpenoids, our approach does not rely on Diels–Alder cycloaddition, which has traditionally been the most employed disconnection for constructing such functionalized bicyclo[2.2.2]octane frameworks. The first-generation synthesis employs a trisubstituted alkene electrophile (**4.18**) to access both 14- and 15-hydroxypatchoulol in 12 overall steps (Scheme 4.14a). In addition, we were also able to correct the misassigned structure of 15-hydroxypatchoulol reported in the original literature. Upon revisiting the synthesis with tetrasubstituted alkene electrophile **4.42**, a second-generation synthesis of 14-hydroxypatchoulol was achieved in 9 overall steps (Scheme 4.14b).



Scheme 4.14. Overview of total synthesis of 14-hydroxypatchoulol (**4.29**).

Patchouli alcohol, despite its simple structure, has a history of structural misassignment and thereby resulting confusion in approaches to its synthesis. The more recent misassignment of 15-hydroxypatchoulol further underscores the importance of total synthesis in structure validation, while also illustrating the unexpected complexity in the synthesis of small molecules such as 14- and 15-hydroxypatchoulol. Given the biological and organoleptic properties of patchouli alcohol, we anticipate that this synthetic approach to hydroxylated patchouli alcohol congeners will enable comprehensive functional studies.

4.9 Contributions

This chapter includes content reproduced, with permission, from: Na, C.G.; Kang, S.H.; Sarpong, R. *J. Am. Chem. Soc.* **2022**, 144, 19253–19257.

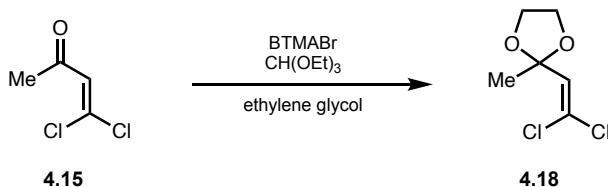
4.10 Experimental Details

4.10.1 General Procedures

For general procedures regarding Solvents and Reagents; Reaction Setup, Monitoring, and Purification; NMR Spectroscopy; Mass Spectrometry; and Optical Rotation, see Chapter 2.10.

4.10.2 Synthetic Procedures and Product Characterization

Synthesis of 15-Hydroxypatchoulol (1st Generation):



2-(2,2-Dichlorovinyl)-2-methyl-1,3-dioxolane (4.18) was prepared using a procedure adapted from the literature.³⁰ In a 50 mL round-bottom flask, benzyltrimethylammonium tribromide (98 mg, 0.25 mmol, 0.01 equiv) was added to a stirring solution of 4,4-dichlorobut-3-en-2-one³¹ (**4.15**; 3.50 g, 25 mmol, 1 equiv) and triethyl orthoformate (8.4 mL, 50 mmol, 2 equiv) in ethylene glycol (14 mL, 0.25 mol, 10 equiv) at 23 °C. The reaction mixture was stirred overnight, then quenched with Et_3N (0.88 mL, 6.3 mmol, 0.25 equiv), and NaBH_4 (0.48 g, 13 mmol, 0.5 equiv) was added portion-wise. After stirring for another 20 min, the resulting mixture was poured into a solution of sat. aq. NaHCO_3 (30 mL) and water (30 mL), which was extracted with ether (50 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, and the solvent was removed under reduced pressure. The resulting residue was purified by silica column chromatography (2.5 % EtOAc /hexanes) to give the title compound as a pale-yellow oil (3.50 g, 76 % yield).

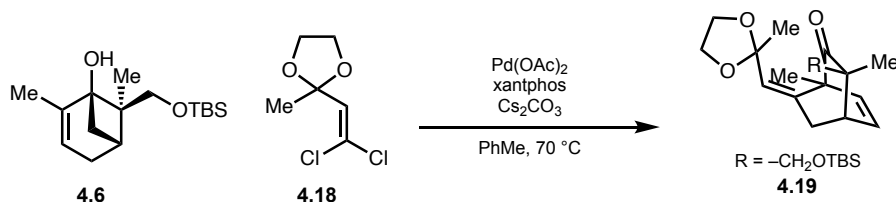
Note: Ketal **4.18** was found to be somewhat volatile, so care should be taken whenever concentrating *in vacuo*.

R_f (10% EtOAc /hexanes, KMnO_4) 0.50.

^1H NMR (500 MHz, CDCl_3) δ 6.02 (s, 1H), 4.04 – 3.86 (m, 4H), 1.58 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 132.0, 123.7, 106.6, 64.7, 24.0.

HRMS (EI) Exact mass calcd for $\text{C}_5\text{H}_5\text{O}_2\text{Cl}_2$ $[\text{M}-\text{CH}_3]^+$, 166.9667. Found 166.9669.



(3*R*,4*S*,*Z*)-3-(((*Tert*-butyldimethylsilyl)oxy)methyl)-1,3-dimethyl-7-((2-methyl-1,3-dioxolan-2-yl)methylene)bicyclo[2.2.2]oct-5-en-2-one (4.19) was prepared using a 20 mL scintillation vial with cyclobutanol **4.6** (452 mg, 1.60 mmol, 1 equiv), Pd(OAc)₂ (36 mg, 0.16 mmol, 0.10 equiv), Xantphos (102 mg, 0.18 mmol, 0.11 equiv), cesium carbonate (2.09 g, 6.40 mmol, 4 equiv), and PhMe (8 mL, 0.2 M). Purification with silica gel chromatography (2.5–5 % EtOAc/hexanes) provided the title compound as a colorless oil (335 mg, 53 % yield).

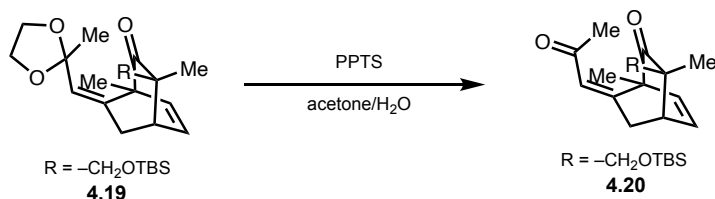
R_f (10% EtOAc/hexanes, CAM) 0.33

[α]_D²⁵ = –28 (*c* = 0.009, CHCl₃)

¹H NMR (500 MHz, CDCl₃) δ 6.54 (t, *J* = 7.1 Hz, 1H), 5.71 (d, *J* = 7.7 Hz, 1H), 5.38 (s, 1H), 3.94 – 3.89 (m, 2H), 3.85 – 3.72 (m, 2H), 3.42 – 3.30 (m, 2H), 3.03 – 2.94 (m, 2H), 2.22 (dt, *J* = 18.3, 3.2 Hz, 1H), 1.43 (s, 3H), 1.27 (s, 3H), 1.16 (s, 3H), 0.90 (s, 9H), 0.04 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ 212.44, 138.93, 138.33, 131.13, 125.43, 108.53, 66.45, 64.32, 64.27, 56.97, 49.39, 37.84, 28.62, 25.97, 24.27, 23.08, 18.39, 14.94, –5.45.

HRMS (ESI) Exact mass calcd for C₂₂H₃₆O₄NaSi [M+Na]⁺, 415.2275. Found 415.2274.



(3*R*,4*S*,*Z*)-3-(((*Tert*-butyldimethylsilyl)oxy)methyl)-1,3-dimethyl-7-(2-oxopropylidene)bicyclo[2.2.2]oct-5-en-2-one (4.20). Pyridinium *p*-toluenesulfonate (PPTS; 16 mg, 0.06 mmol, 0.1 equiv) was added to a solution of **4.19** (243 mg, 0.62 mmol, 1 equiv) in acetone/H₂O (9:1, 6.2 mL, 0.1 M). The reaction mixture was stirred overnight, quenched with sat. aq. NaHCO₃ (0.5 mL), and concentrated. The resulting residue was taken up in a mixture of sat. aq. NaHCO₃ (5 mL) and water (5 mL), which was then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄, and filtered. The solvent was removed under reduced pressure to provide enone **4.20** as a colorless oil (209 mg, 97 % yield), which was taken directly to the next step without further purification.

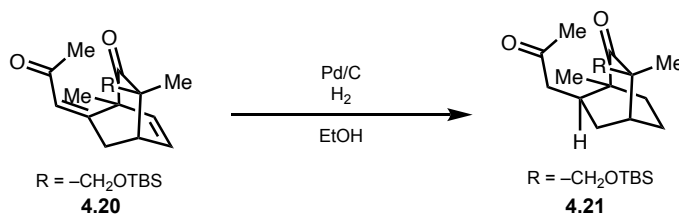
R_f (10 % EtOAc/hexanes, UV or CAM) 0.30

[α]_D²⁵ = –52 (*c* = 0.78 CHCl₃)

¹H NMR (500 MHz, CDCl₃) δ 6.61 (dd, *J* = 7.7, 6.6 Hz, 1H), 6.15 (t, *J* = 2.5 Hz, 1H), 5.72 (dd, *J* = 7.8, 1.1 Hz, 1H), 3.40 – 3.28 (m, 3H), 3.10 – 3.03 (m, 1H), 2.56 (dt, *J* = 20.0, 2.9 Hz, 1H), 2.20 (s, 3H), 1.36 (s, 3H), 1.16 (s, 3H), 0.87 (s, 9H), 0.00 (s, 3H), –0.00 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 210.95, 197.81, 158.88, 139.35, 130.36, 119.68, 66.63, 58.86, 48.96, 38.57, 33.02, 32.00, 25.93, 23.60, 18.36, 14.67, -5.50, -5.55.

HRMS (ESI) Exact mass calcd for $\text{C}_{20}\text{H}_{33}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$, 349.2194. Found 349.2195.



(3*R*,4*R*,6*S*)-3-(((*Tert*-butyldimethylsilyl)oxy)methyl)-1,3-dimethyl-6-(2-oxopropyl)bicyclo[2.2.2]octan-2-one (4.21). Palladium on carbon (10 % wt; 32 mg, 30 μmol , 0.05 equiv) was added to a solution of enone **4.20** (209 mg, 0.60 mmol, 1 equiv) in anhydrous EtOH (6 mL, 0.1 M). The heterogeneous mixture was stirred vigorously at room temperature under a balloon of hydrogen for 2 h. The reaction mixture was then filtered over a plug of Celite®, which was flushed with EtOAc (20 mL), and the filtrate was concentrated *in vacuo*. The resulting residue was purified by silica chromatography (5 % EtOAc/hexanes) to give diol **4.21** as a colorless oil (208 mg, 98 % yield).

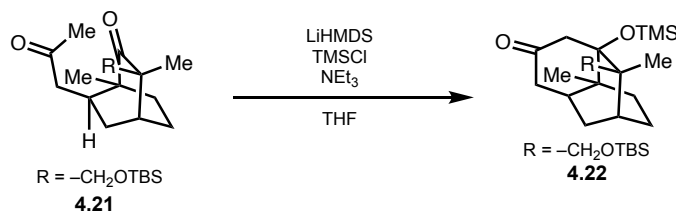
R_f (10 % EtOAc/hexanes, CAM) 0.25; (20 % EtOAc/hexanes, CAM) 0.55

$[\alpha]_{\text{D}}^{25} = -58$ ($c = 1.54$, CHCl_3)

^1H NMR (500 MHz, CDCl_3) δ 3.61 (d, $J = 9.9$ Hz, 1H), 3.55 (d, $J = 9.9$ Hz, 1H), 2.51 (dd, $J = 17.1$, 4.4 Hz, 1H), 2.36 (tt, $J = 10.4$, 5.2 Hz, 1H), 2.11 (s, 3H), 2.07 – 1.96 (m, 3H), 1.89 (tt, $J = 10.4$, 3.6 Hz, 1H), 1.68 (dtt, $J = 18.8$, 10.2, 4.8 Hz, 3H), 1.38 – 1.30 (m, 1H), 1.15 (s, 3H), 0.87 (s, 9H), 0.84 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 207.79, 65.24, 51.50, 48.35, 46.09, 37.28, 32.76, 32.00, 31.26, 30.66, 25.99, 22.13, 20.67, 18.42, 18.16, -5.37, -5.40.

HRMS (ESI) Exact mass calcd for $\text{C}_{20}\text{H}_{37}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$, 353.2507. Found 353.2504.



9-(((*tert*-butyldimethylsilyl)oxy)methyl)-8a,9-dimethyl-1-((trimethylsilyl)oxy)octahydro-1,6-methanonaphthalen-3(2*H*)-one (4.22). LiHMDS (1.0 M in THF; 2.3 mL, 2.27 mmol, 5 equiv)

was added dropwise to a stirring solution of dione **4.21** (160 mg, 0.45 mmol, 1 equiv) in THF (9 mL, 0.05 M) at room temperature. After 3 h, TMSCl (0.58 mL, 4.5 mmol, 10 equiv) was added, followed quickly by Et₃N (0.63 mL, 4.5 mmol, 10 equiv). After stirring for an additional 2 h, the reaction was quenched with sat. aq. NH₄Cl (~0.5 mL), and the contents were moved to a separatory funnel. H₂O (5 mL) and sat. aq. NH₄Cl (5 mL) were added, and the aqueous mixture was extracted with Et₂O (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and filtered. AcOH (0.52 mL, 9.1 mmol, 20 equiv) was added to the filtrate, and the solvent was removed under reduced pressure. The resulting residue was adsorbed onto silica gel to prepare a dry load and purified by silica gel chromatography (2.5 % EtOAc hexanes) to give **39** as a colorless oil (144 mg, 75 % yield).

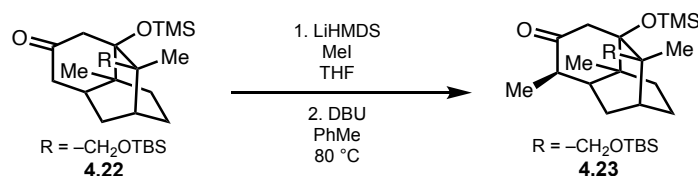
R_f (5 % EtOAc/hexanes, CAM) 0.33

[**a**]_D²⁵ = –83 (*c* = 1.46, CHCl₃)

¹H NMR (500 MHz, CDCl₃) δ 3.49 (d, *J* = 10.0 Hz, 1H), 3.28 (d, *J* = 10.1 Hz, 1H), 2.93 (dd, *J* = 15.6, 2.2 Hz, 1H), 2.55 (dd, *J* = 15.7, 4.8 Hz, 1H), 2.46 (d, *J* = 15.6 Hz, 1H), 2.14 (dt, *J* = 15.6, 2.5 Hz, 1H), 2.02 – 1.88 (m, 2H), 1.84 (t, *J* = 12.6 Hz, 1H), 1.66 (ddd, *J* = 14.7, 11.6, 3.5 Hz, 1H), 1.46 (s, 1H), 1.30 – 1.22 (m, 1H), 1.14 – 1.06 (m, 2H), 1.04 (s, 3H), 0.93 (s, 3H), 0.89 (s, 9H), 0.13 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 211.65, 81.02, 67.85, 49.18, 46.64, 45.21, 37.77, 36.26, 31.88, 30.70, 27.49, 26.16, 23.74, 21.85, 21.36, 18.65, 2.73, –5.23, –5.26.

HRMS (ESI) Exact mass calcd for C₂₃H₄₄O₃NaSi₂ [**M**+Na]⁺, 447.2721. Found 447.2719.



(4*R*)-9-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,8a,9-trimethyl-1-(((trimethylsilyl)oxy)octahydro-1,6-methanonaphthalen-3(2*H*)-one (4.23). A solution of LiHMDS (1.0 M in THF; 0.37 mL, 0.37 mmol, 1.2 equiv) in THF (2 mL) was placed in an acetone/dry ice cooling bath and stirred at –78 °C for 10 min. A solution of **4.22** (130 mg, 0.31 mmol, 1 equiv) in THF (0.6 mL, 0.5 M) was then added dropwise to the anionic solution. The syringe used to add **4.22** was rinsed with THF (0.6 mL), which was also added dropwise to the reaction mixture. After 2 h of stirring at –78 °C, MeI (38 μL, 0.61 mmol, 2 equiv) was added. The reaction mixture was stirred at –78 °C for 15 min before warming to 0 °C and was stirred for an additional 2 h. The reaction was quenched with sat. aq. NH₄Cl (~0.5 mL), and the contents were moved to a separatory funnel. H₂O (2.5 mL) and sat. aq. NH₄Cl (2.5 mL) were added, and the aqueous mixture was extracted with EtOAc (5

mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated.

The resulting residue was resuspended in PhMe (3 mL, 0.1 M), and DBU (0.12 mL, 0.77 mmol, 2.5 equiv) was added. The reaction mixture was heated to 70 °C and left stirring overnight. After cooling to room temperature, sat. aq. NH₄Cl (2.5 mL) and water (2.5 mL) were added, and the aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude mixture was adsorbed onto silica gel to prepare a dry load and was purified by silica gel chromatography (1 % EtOAc hexanes) to give **4.23** as a colorless oil (66 mg, 49 % yield) as well as starting **4.22** (50 mg, 38 % rsm).

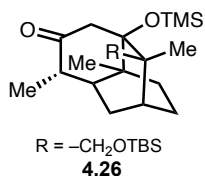
R_f (5 % EtOAc/hexanes, CAM) 0.45

[α]_D²⁵ = −60.0 (*c* = 1.18)

¹H NMR (500 MHz, CDCl₃) δ 3.47 (d, *J* = 9.9 Hz, 1H), 3.27 (d, *J* = 9.9 Hz, 1H), 2.87 (d, *J* = 14.9 Hz, 1H), 2.72 – 2.62 (m, 1H), 2.47 (d, *J* = 14.9 Hz, 1H), 1.96 (ddd, *J* = 13.4, 11.4, 7.7 Hz, 1H), 1.85 – 1.72 (m, 2H), 1.52 – 1.42 (m, 2H), 1.30 – 1.18 (m, 2H), 1.17 – 1.07 (m, 1H), 1.03 (s, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.98 (s, 3H), 0.89 (s, 9H), 0.12 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 212.45, 81.70, 67.36, 48.95, 46.82, 45.48, 43.23, 39.14, 31.45, 27.78, 27.05, 26.18, 23.57, 21.97, 21.86, 18.64, 11.55, 2.71, −5.20, −5.23.

HRMS (ESI) Exact mass calcd for C₂₄H₄₆O₃NaSi₂ [M+Na]⁺, 461.2878. Found 461.2880.



Characterization data for **4.26**:

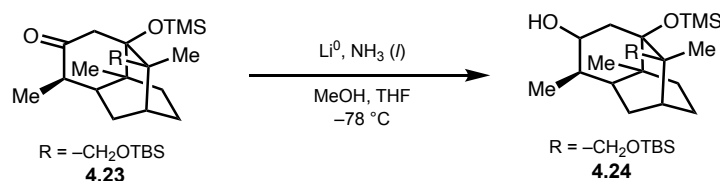
R_f (5 % EtOAc/hexanes, CAM) 0.40

[α]_D²⁵ = −51.6 (*c* = 0.0078)

¹H NMR (500 MHz, CDCl₃) δ 3.48 (d, *J* = 10.1 Hz, 1H), 3.26 (d, *J* = 10.1 Hz, 1H), 3.03 (dd, *J* = 16.7, 1.6 Hz, 1H), 2.61 (d, *J* = 16.8 Hz, 1H), 2.28 (q, *J* = 7.9 Hz, 1H), 1.91 – 1.69 (m, 4H), 1.43 (q, *J* = 3.0 Hz, 1H), 1.27 (d, *J* = 8.0 Hz, 3H), 1.20 (dtd, *J* = 11.4, 5.8, 4.8, 2.4 Hz, 1H), 1.16 – 1.08 (m, 2H), 1.03 (s, 3H), 0.96 (s, 3H), 0.89 (s, 9H), 0.13 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 215.89, 80.70, 68.62, 53.31, 47.06, 46.26, 42.64, 38.23, 34.07, 33.14, 28.50, 26.14, 23.64, 23.34, 21.72, 20.20, 18.63, 2.74, −5.28, −5.32.

HRMS (ESI) Exact mass calcd for $C_{24}H_{46}O_3NaSi_2$ $[M+Na]^+$, 461.2878. Found 461.2880.



(3*R*,4*R*)-9-(((*Tert*-butyldimethylsilyl)oxy)methyl)-4,8*a*,9-trimethyl-1-((trimethylsilyl)oxy)decahydro-1,6-methanonaphthalen-3-ol (4.24). Lithium metal (7.7 mg, 1.1 mmol, 10 equiv) was washed with hexanes and suspended in THF (0.2 mL) and MeOH (22 μ L, 0.55 mmol, 5 equiv) in a 10 mL round-bottom flask equipped with a stir bar and rubber septum with a N_2 balloon. The mixture was cooled to $-78\text{ }^\circ C$ using a dry ice/acetone cooling bath, and ammonia was condensed into the flask until a dark blue color persisted (~ 2 mL). A solution of **4.23** (49 mg, 0.11 mmol, 1 equiv) in THF (0.3 mL) was added dropwise into the blue solution. The syringe was rinsed with THF (0.3 mL), which was also added dropwise to the reaction mixture. If necessary, additional ammonia was condensed into the flask to maintain the dark color. After vigorously stirring for 2 h at $-78\text{ }^\circ C$, the reaction was quenched with a dropwise addition of sat. aq. NH_4Cl (2 mL). After warming to room temperature, the contents were moved to a separatory funnel. H_2O (2 mL) was added, and the mixture was extracted with EtOAc (5 mL $\times$ 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , and filtered. Solvent was removed under reduced pressure to give **4.24** as a colorless oil (45 mg, 92 % yield), which was used directly in the next step without additional purification.

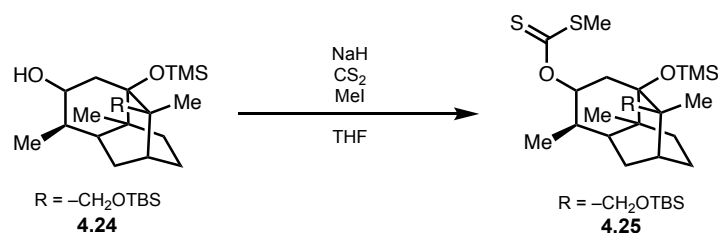
R_f (10% EtOAc/hexanes, CAM) 0.30

$[a]_D^{25}$ = -51.6 ($c = 0.0078$)

1H NMR (500 MHz, $CDCl_3$) δ 3.64 – 3.53 (m, 3H), 2.24 (dd, $J = 13.3, 6.2$ Hz, 1H), 1.87 (ddd, $J = 13.2, 11.4, 7.6$ Hz, 1H), 1.81 – 1.67 (m, 2H), 1.62 – 1.46 (m, 4H), 1.38 – 1.24 (m, 3H), 1.23 – 1.12 (m, 1H), 1.02 (s, 3H), 0.99 (d, $J = 6.6$ Hz, 3H), 0.90 (s, 9H), 0.80 (s, 3H), 0.11 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 80.31, 73.16, 67.31, 45.95, 42.99, 40.53, 38.90, 37.06, 31.47, 28.23, 26.20, 25.65, 24.03, 22.72, 21.86, 18.61, 15.29, 2.83, $-5.10, -5.24$.

HRMS (ESI) Exact mass calcd for $C_{24}H_{48}O_3NaSi_2$ $[M+Na]^+$, 463.3034. Found 463.3031.



***O*-((3*R*,4*R*)-9-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,8*a*,9-trimethyl-1-((trimethylsilyl)oxy)decahydro-1,6-methanonaphthalen-3-yl) *S*-methyl carbonodithioate (4.25).** Dry sodium hydride (90 % wt; 5.4 mg, 0.20 mmol, 2 equiv) was suspended in THF (0.2 mL) in a 1 dram vial equipped with a stir bar and septa cap and cooled to 0 °C in an ice water bath. A solution of **4.24** (45 mg, 0.10 mmol, 1 equiv) in THF (0.4 mL) was added dropwise to the heterogeneous mixture. The syringe was rinsed with additional THF (0.4 mL), which was also added to the reaction mixture. After vigorous stirring at 0 °C for 10 min, CS₂ (61 µL, 1.0 mmol, 10 equiv) was added. The reaction mixture was stirred for an additional 15 min at 0 °C before MeI (63 µL, 1.0 mmol, 10 equiv) was added. The ice bath was removed, and stirring continued at room temperature. Upon completion of the reaction as determined by TLC (typically 3 h), sat. aq. NH₄Cl (2 mL) was added. The contents were moved to a separatory funnel, and H₂O (2 mL) was added. The mixture was extracted with Et₂O (5 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and filtered. The solvent was removed under reduced pressure to give **4.25** as a pale-yellow oil (50 mg, 93 % yield), which was used directly in the next step without further purification.

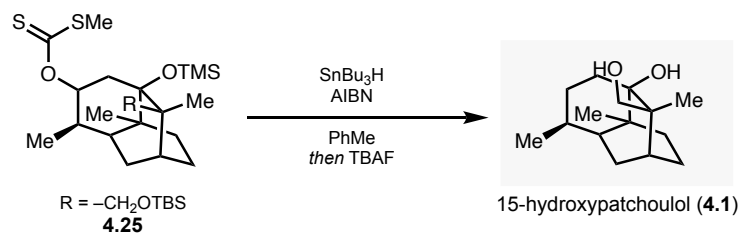
R_f (1% EtOAc/hexanes, UV/I₂/CAM) 0.25

[α]_D²⁵ = −116 (*c* = 0.0062)

¹H NMR (500 MHz, CDCl₃) δ 5.60 (td, *J* = 11.1, 6.3 Hz, 1H), 3.82 (d, *J* = 9.7 Hz, 1H), 3.58 (d, *J* = 9.7 Hz, 1H), 2.58 (s, 3H), 2.42 (dd, *J* = 13.1, 6.3 Hz, 1H), 2.24 – 2.16 (m, 1H), 1.89 (ddd, *J* = 13.4, 11.4, 7.7 Hz, 1H), 1.77 (t, *J* = 12.7 Hz, 1H), 1.70 (dd, *J* = 5.0, 2.8 Hz, 1H), 1.60 (dt, *J* = 12.8, 10.4 Hz, 2H), 1.38 (dd, *J* = 9.0, 3.1 Hz, 2H), 1.24 – 1.14 (m, 1H), 1.03 (s, 3H), 1.02 – 1.00 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 0.85 (s, 3H), 0.09 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 216.53, 86.41, 80.22, 66.98, 46.00, 42.65, 38.81, 34.64, 33.86, 30.69, 28.15, 26.19, 25.48, 23.94, 22.65, 21.74, 19.21, 18.55, 15.03, 2.75, −5.16, −5.17.

HRMS (ESI) Exact mass calcd for C₂₆H₅₀O₃S₂Si₂ [M+Na]⁺, 553.2638. Found 553.2639.



15-Hydroxypatchoulol (4.1). Tributyltin hydride (34 μL , 0.13 mmol, 1.5 equiv) was added to a solution of xanthate **4.25** (45 mg, 0.085 mmol, 1 equiv) and AIBN (1.4 mg, 8.5 μmol , 0.1 equiv) in PhMe (1.7 mL, 0.05 M). The reaction mixture was stirred at 80 $^{\circ}\text{C}$ for 1 h, then cooled to room temperature. The solution was filtered through a short plug of potassium carbonate–silica (10 % wt/wt $\text{K}_2\text{CO}_3/\text{SiO}_2$), which was flushed with hexanes (10 mL), and the filtrate was concentrated. TBAF (1.0 M in THF; 1.7 mL, 1.7 mmol, 20 equiv) was added to the resulting residue, and the solution was stirred at reflux overnight. After cooling to room temperature, the solution was filtered through a short plug of potassium carbonate–silica³² (10 % wt/wt $\text{K}_2\text{CO}_3/\text{SiO}_2$). The resulting residue was purified by preparative TLC (50 % EtOAc/hexanes) to afford 15-hydroxypatchoulol (**4.1**) as a white solid (17 mg, 84 % yield). Single crystals were obtained with vapor diffusion (EtOAc/hexanes as the solvent/anti-solvent, respectively).

mp = 106–107 $^{\circ}\text{C}$

R_f (50% EtOAc/hexanes, CAM) 0.40

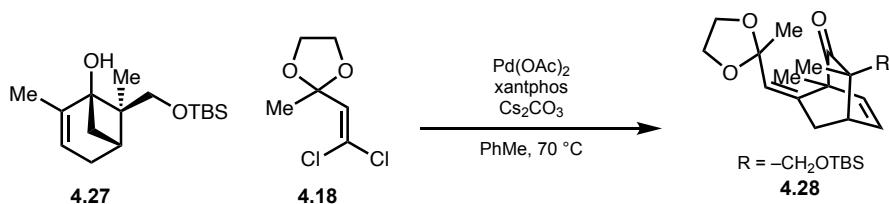
[α]_D²⁵ = –98 (*c* 0.0066, CHCl_3)

¹H NMR (500 MHz, CDCl_3) δ 3.93 (d, *J* = 10.8 Hz, 1H), 3.54 (d, *J* = 10.8 Hz, 1H), 2.01 – 1.82 (m, 4H), 1.59 – 1.50 (m, 2H), 1.49 – 1.23 (m, 6H), 1.17 (s, 3H), 1.06 (t, *J* = 11.5 Hz, 1H), 0.86 (s, 3H), 0.79 (d, *J* = 6.7 Hz, 3H).

¹³C NMR (126 MHz, CDCl_3) δ 75.26, 67.76, 45.22, 43.65, 38.07, 33.04, 31.71, 29.05, 28.90, 27.79, 24.35, 24.25, 20.57, 20.38, 18.72.

HRMS (ESI) Exact mass calcd for $\text{C}_{15}\text{H}_{26}\text{O}_2\text{Na}$ [$\text{M}+\text{Na}$]⁺, 261.1825. Found 261.1823.

Synthesis of 14-Hydroxypatchoulol (1st Generation):



(3*S*,4*S*,*Z*)-3-(((*Tert*-butyldimethylsilyl)oxy)methyl)-1,3-dimethyl-7-((2-methyl-1,3-dioxolan-2-yl)methylene)bicyclo[2.2.2]oct-5-en-2-one (**4.28**) was prepared using a 20 mL scintillation vial

with cyclobutanol **4.27** (212 mg, 0.75 mmol, 1 equiv), Pd(OAc)₂ (17 mg, 75 μmol, 0.10 equiv), Xantphos (48 mg, 83 μmol, 0.11 equiv), cesium carbonate (980 mg, 3.0 mmol, 4 equiv), and PhMe (3.75 mL, 0.2 M). Purification with silica gel chromatography (2.5–5 % EtOAc/hexanes) provided the title compound as a colorless oil (163 mg, 55 % yield).

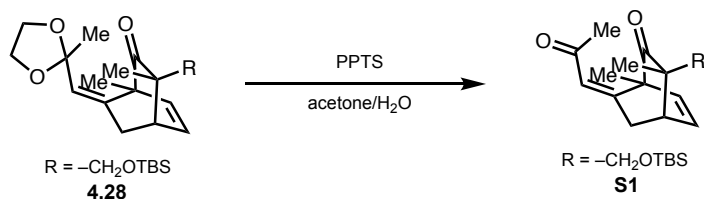
R_f (10 % EtOAc/hexanes, CAM) 0.28

[α]_D²⁵ = –43 (*c* = 0.016, CHCl₃)

¹H NMR (500 MHz, CDCl₃) δ 6.53 (dd, *J* = 7.8, 6.7 Hz, 1H), 5.67 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.38 (dd, *J* = 2.9, 1.7 Hz, 1H), 3.98 – 3.86 (m, 2H), 3.83 – 3.75 (m, 2H), 3.49 – 3.39 (m, 1H), 3.01 – 2.91 (m, 2H), 2.26 – 2.22 (m, 2H), 1.44 (s, 3H), 1.27 (s, 3H), 1.06 (s, 3H), 0.89 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 211.8, 139.1, 138.4, 130.2, 125.2, 108.6, 69.3, 64.4, 64.2, 57.0, 49.2, 37.6, 28.7, 26.0, 24.4, 20.2, 18.4, 15.0, –5.4, –5.4.

HRMS (ESI) Exact mass calcd for C₂₂H₃₆O₄NaSi [M+Na]⁺, 415.2275. Found 415.2273.



(3*S*,4*S*,*Z*)-3-(((*Tert*-butyldimethylsilyl)oxy)methyl)-1,3-dimethyl-7-(2-oxopropylidene)

bicyclo[2.2.2]oct-5-en-2-one (S1). Pyridinium *p*-toluenesulfonate (PPTS; 10 mg, 42 μmol, 0.1 equiv) was added to a solution of **4.28** (163 mg, 414 μmol, 1 equiv) in acetone/H₂O (9:1, 4.2 mL, 0.1 M). The reaction mixture was stirred overnight, quenched with sat. aq. NaHCO₃ (0.5 mL), and concentrated. The resulting residue was taken up in a mixture of sat. aq. NaHCO₃ (5 mL) and water (5 mL), which was then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄, and filtered. The solvent was removed under reduced pressure to provide enone **S1** as a colorless oil (153 mg, >99 % yield), which was taken directly to the next step without further purification.

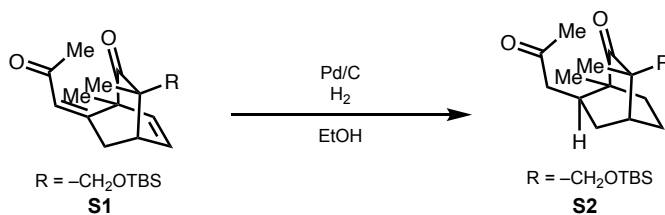
R_f (10 % EtOAc/hexanes, CAM) 0.30

[α]_D²⁵ = –82 (*c* = 0.010, CHCl₃)

¹H NMR (600 MHz, CDCl₃) δ 6.62 (dd, *J* = 7.7, 6.6 Hz, 1H), 6.19 (t, *J* = 2.5 Hz, 1H), 5.68 (ddd, *J* = 7.7, 1.8, 0.9 Hz, 1H), 3.46 (s, 2H), 3.26 (dt, *J* = 19.9, 2.7 Hz, 1H), 3.09 (dq, *J* = 8.0, 2.5 Hz, 1H), 2.57 (dt, *J* = 20.0, 3.0 Hz, 1H), 2.22 (s, 3H), 1.37 (s, 3H), 1.01 (s, 3H), 0.89 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3) δ 210.3, 198.0, 159.1, 139.3, 129.2, 119.8, 69.4, 58.8, 49.0, 37.8, 33.1, 32.0, 26.0, 20.1, 18.4, 14.7, -5.4, -5.4.

HRMS (ESI) Exact mass calcd for $\text{C}_{20}\text{H}_{32}\text{O}_3\text{NaSi}$ $[\text{M}+\text{Na}]^+$, 371.2013. Found 371.2010.



(3*S*,4*R*)-3-(((*Tert*-butyldimethylsilyl)oxy)methyl)-1,3-dimethyl-6-(2-oxopropyl)bicyclo[2.2.2]octan-2-one (S2). Palladium on carbon (10 % wt; 23 mg, 22 μmol , 0.05 equiv) was added to a solution of enone **S1** (150 mg, 0.43 mmol, 1 equiv) in anhydrous EtOH (4.3 mL, 0.1 M). The heterogeneous mixture was stirred vigorously at room temperature under a balloon of hydrogen for 2 h. The reaction mixture was then filtered over a plug of Celite®, which was flushed with EtOAc (20 mL), and the filtrate was concentrated *in vacuo*. The resulting residue was purified by silica chromatography (5 % EtOAc/hexanes) to give dione **S2** as a colorless oil (142 mg, 94 % yield).

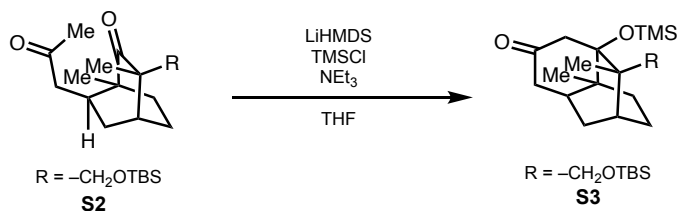
R_f (10 % EtOAc/hexanes, CAM) 0.26

$[\alpha]_D^{25} = -81$ ($c = 0.010$, CHCl_3)

^1H NMR (600 MHz, CDCl_3) δ 3.62 (d, $J = 9.7$ Hz, 1H), 3.42 (d, $J = 9.7$ Hz, 1H), 2.52 (dd, $J = 17.2, 4.2$ Hz, 1H), 2.35 (tdd, $J = 10.4, 5.8, 4.2$ Hz, 1H), 2.11 (s, 3H), 2.07 – 2.02 (m, 2H), 1.98 – 1.93 (m, 2H), 1.75 – 1.71 (m, 1H), 1.67 – 1.57 (m, 2H), 1.31 (ddt, $J = 14.2, 5.9, 3.0$ Hz, 1H), 1.10 (s, 3H), 0.87 (s, 9H), 0.83 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 220.5, 207.9, 67.1, 51.9, 48.6, 45.9, 37.8, 34.2, 32.3, 31.3, 30.7, 25.9, 22.3, 18.7, 18.4, 18.3, -5.5, -5.5.

HRMS (ESI) Exact mass calcd for $\text{C}_{20}\text{H}_{36}\text{O}_3\text{SiNa}$ $[\text{M}+\text{Na}]^+$, 375.2326. Found 375.2329.



9-(((*Tert*-butyldimethylsilyl)oxy)methyl)-8a,9-dimethyl-1-((trimethylsilyl)oxy)octahydro-1,6-methanonaphthalen-3(2*H*)-one (S3). LiHMDS (1.0 M in THF; 1.8 mL, 1.82 mmol, 5 equiv)

was added dropwise to a stirring solution of dione **S2** (128 mg, 0.36 mmol, 1 equiv) in THF (7.3 mL, 0.05 M) at room temperature. After 3 h, TMSCl (0.46 mL, 3.6 mmol, 10 equiv) was added, followed quickly by Et₃N (0.51 mL, 3.6 mmol, 10 equiv). After stirring for an additional 2 h, the reaction was quenched with sat. aq. NH₄Cl (~0.5 mL), and the contents were moved to a separatory funnel. H₂O (5 mL) and sat. aq. NH₄Cl (5 mL) were added, and the aqueous mixture was extracted with Et₂O (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and filtered. AcOH (0.42 mL, 7.3 mmol, 20 equiv) was added to the filtrate, and the solvent was removed under reduced pressure. The resulting residue was adsorbed onto silica gel to prepare a dry load and purified by silica gel chromatography (2.5 % EtOAc hexanes) to give **S3** as a colorless solid (84 mg, 54 % yield) as well as **S2** (19 mg, 15 % rsm).

mp = 91–98 °C

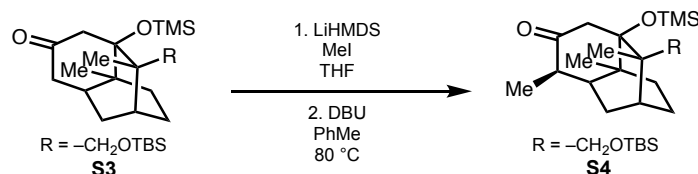
R_f (5 % EtOAc/hexanes, CAM) 0.18

[α]_D²⁵ = –51 (*c* = 0.009, CHCl₃)

¹H NMR (600 MHz, CDCl₃) δ 3.79 (d, *J* = 10.0 Hz, 1H), 3.21 (d, *J* = 10.0 Hz, 1H), 2.87 (dd, *J* = 15.1, 2.1 Hz, 1H), 2.55 (dd, *J* = 15.5, 4.7 Hz, 1H), 2.46 (d, *J* = 15.1 Hz, 1H), 2.16 (dt, *J* = 15.8, 2.5 Hz, 1H), 2.00 – 1.90 (m, 2H), 1.90 – 1.83 (m, 1H), 1.72 (ddd, *J* = 14.8, 11.5, 3.7 Hz, 1H), 1.46 (dp, *J* = 4.2, 2.1 Hz, 1H), 1.26 (tdd, *J* = 12.7, 7.1, 1.8 Hz, 1H), 1.17 (td, *J* = 12.5, 11.6, 1.9 Hz, 1H), 1.06 (ddt, *J* = 14.3, 5.8, 2.9 Hz, 1H), 0.94 (s, 3H), 0.93 (s, 3H), 0.88 (s, 9H), 0.12 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 211.4, 82.3, 68.3, 50.8, 45.5, 45.4, 37.2, 36.6, 32.2, 30.5, 28.5, 26.0, 23.6, 21.3, 20.0, 18.4, 2.6, –5.4, –5.4.

HRMS (ESI) Exact mass calcd for C₂₃H₄₄O₃Si₂Na [M+Na]⁺, 447.2721. Found 447.2727.



(4*R*)-9-(((*Tert*-butyldimethylsilyl)oxy)methyl)-4,8a,9-trimethyl-1-((trimethylsilyl)oxy)octahydro-1,6-methanonaphthalen-3(2*H*)-one (S4). A solution of LiHMDS (1.0 M in THF; 0.21 mL, 0.22 mmol, 1.2 equiv) in THF (0.6 mL) was placed in an acetone/dry ice cooling bath and stirred at –78 °C for 10 min. A solution of **S3** (75 mg, 0.18 mmol, 1 equiv) in THF (0.3 mL, 0.2 M) was then added dropwise to the anionic solution. The syringe used to add **S3** was rinsed with THF (0.3 mL), which was also added dropwise to the reaction mixture. After 2 h of stirring at –78 °C, MeI (23 μL, 0.35 mmol, 2 equiv) was added. The reaction mixture was stirred at –78 °C for 15 min before warming to 0 °C and was stirred for an additional 2 h. The reaction was quenched

with sat. aq. NH_4Cl (~0.5 mL), and the contents were moved to a separatory funnel. H_2O (2.5 mL) and sat. aq. NH_4Cl (2.5 mL) were added, and the aqueous mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated.

The resulting residue was resuspended in PhMe (1.8 mL, 0.1 M), and DBU (66 μL , 0.44 mmol, 2.5 equiv) was added. The reaction mixture was heated to 70 $^\circ\text{C}$ and left stirring overnight. After cooling to room temperature, sat. aq. NH_4Cl (2.5 mL) and water (2.5 mL) were added, and the aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude mixture was adsorbed onto silica gel to prepare a dry load and was purified by silica gel chromatography (1 % EtOAc hexanes) to give **S4** as a colorless crystalline solid (28 mg, 36 % yield) as well as starting **S3** (18 mg, 24 % rsm).

mp = 79–83 $^\circ\text{C}$

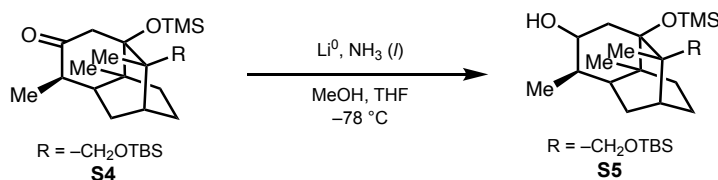
R_f (10 % EtOAc/hexanes, CAM) 0.62

$[\alpha]_D^{25} = -53$ ($c = 0.007$, CHCl_3)

^1H NMR (600 MHz, CDCl_3) δ 3.79 (dd, $J = 10.0, 1.0$ Hz, 1H), 3.20 (d, $J = 10.0$ Hz, 1H), 2.86 (d, $J = 14.5$ Hz, 1H), 2.47 (d, $J = 14.4$ Hz, 1H), 1.98 – 1.92 (m, 1H), 1.88 – 1.83 (m, 1H), 1.78 (ddd, $J = 11.2, 6.0, 4.1$ Hz, 1H), 1.52 (m, 1H), 1.44 (dp, $J = 4.1, 1.9$ Hz, 1H), 1.26 – 1.16 (m, 3H), 1.00 (d, $J = 6.5$ Hz, 3H), 0.98 (s, 3H), 0.90 (d, $J = 0.9$ Hz, 3H), 0.88 (s, 9H), 0.12 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3) δ 211.9, 82.7, 68.2, 50.3, 45.6, 45.5, 43.4, 38.4, 32.1, 28.7, 26.8, 25.9, 23.3, 21.8, 19.5, 18.2, 11.3, 2.4, -5.6, -5.6.

HRMS (ESI) Exact mass calcd for $\text{C}_{24}\text{H}_{46}\text{O}_3\text{NaSi}_2$ $[\text{M}+\text{Na}]^+$, 461.2878. Found 461.2883.



(4R)-9-(((Tert-butyltrimethylsilyl)oxy)methyl)-4,8a,9-trimethyl-1-((trimethylsilyl)oxy)decahydro-1,6-methanonaphthalen-3-ol (S5). Lithium metal (3.3 mg, 0.48 mmol, 10 equiv) was washed with hexanes and suspended in THF (0.2 mL) and MeOH (10 μL , 0.24 mmol, 5 equiv) in a 4 mL scintillation vial equipped with a stir bar and cap with a N_2 balloon. The mixture was cooled to -78 $^\circ\text{C}$ using a dry ice/acetone cooling bath, and ammonia was condensed into the flask until a dark blue color persisted (~2 mL). A solution of **S4** (21 mg, 0.48 mmol, 1 equiv) in THF (0.2 mL) was added dropwise into the blue solution. The syringe was rinsed with THF (0.2 mL), which was

also added dropwise to the reaction mixture. If necessary, additional ammonia was condensed into the flask to maintain the dark color. After vigorously stirring for 2 h at $-78\text{ }^{\circ}\text{C}$, the reaction was quenched with a dropwise addition of sat. aq. NH_4Cl (2 mL). After warming to room temperature, the contents were moved to a separatory funnel. H_2O (2 mL) was added, and the mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , and filtered. Solvent was removed under reduced pressure to give **S5** as a colorless oil (16 mg, 77 % yield), which was used directly in the next step without additional purification.

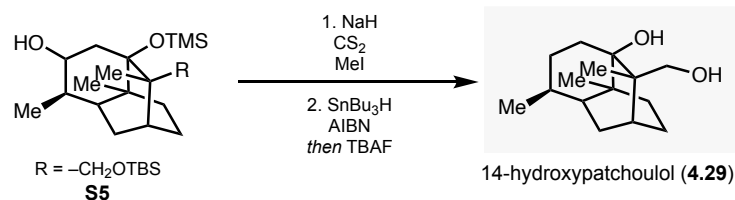
R_f (10 % EtOAc /hexanes, CAM) 0.24

$[\alpha]_D^{25} = -61$ ($c = 0.001$, CHCl_3)

^1H NMR (600 MHz, CDCl_3) δ 3.78 (d, $J = 10.0$ Hz, 1H), 3.64 (dt, $J = 10.6, 5.3$ Hz, 1H), 3.16 (d, $J = 10.0$ Hz, 1H), 2.25 (dd, $J = 12.9, 6.0$ Hz, 1H), 1.89 – 1.79 (m, 2H), 1.73 (ddd, $J = 10.1, 6.7, 3.4$ Hz, 1H), 1.55 (m, 4H), 1.45 (d, $J = 3.4$ Hz, 1H), 1.37 (ddd, $J = 14.7, 11.5, 3.4$ Hz, 1H), 1.25 (s, 1H), 1.16 (dtd, $J = 12.0, 6.2, 2.2$ Hz, 1H), 1.06 (d, $J = 1.0$ Hz, 2H), 0.99 (d, $J = 6.6$ Hz, 3H), 0.89 (s, 9H), 0.81 (s, 3H), 0.11 (s, 9H), 0.03 (d, $J = 1.6$ Hz, 6H).

^{13}C NMR (150 MHz, CDCl_3) δ 81.6, 72.3, 68.5, 44.5, 43.1, 41.9, 38.1, 37.1, 32.6, 29.7, 29.1, 25.9, 25.3, 23.9, 21.7, 18.6, 18.2, 15.0, 2.5, -5.6, -5.6.

HRMS (ESI) Exact mass calcd for $\text{C}_{24}\text{H}_{47}\text{O}_3\text{Si}_2$ $[\text{M}-\text{H}]^-$, 439.3069. Found 439.3069.



14-Hydroxypatchoulol (4.29). Dry sodium hydride (90% wt; 1.8 mg, 68 μmol , 2 equiv) was suspended in THF (0.2 mL) in a 1 dram vial equipped with a stir bar and septa cap and cooled to $0\text{ }^{\circ}\text{C}$ in an ice water bath. A solution of **S5** (15 mg, 34 μmol , 1 equiv) in THF (0.2 mL) was added dropwise to the heterogeneous mixture. The syringe was rinsed with additional THF (0.4 mL), which was also added to the reaction mixture. After vigorous stirring at $0\text{ }^{\circ}\text{C}$ for 10 min, CS_2 (21 μL , 0.34 mmol, 10 equiv) was added. The reaction mixture was stirred for an additional 15 min at $0\text{ }^{\circ}\text{C}$ before MeI (22 μL , 0.34 mmol, 10 equiv) was added. The ice bath was removed, and stirring continued at room temperature overnight. Upon completion of the reaction as determined by TLC, sat. aq. NH_4Cl (2 mL) was added. The contents were moved to a separatory funnel, and H_2O (2 mL) was added. The mixture was extracted with Et_2O (5 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and filtered. The solvent was removed

under reduced pressure to give the intermediary xanthate as a pale-yellow oil (8 mg, 50 % yield), which was purified over a short plug of silica eluting with hexanes.

Tributyltin hydride (14 μ L, 51 μ mol, 1.5 equiv) was added to a solution of xanthate (8 mg, 17 μ mol, 1 equiv) and AIBN (0.6 mg, 3.4 μ mol, 0.1 equiv) in PhMe (0.34 mL, 0.05 M). The reaction mixture was stirred at 80 $^{\circ}$ C for 1 h, then cooled to room temperature. The solution was filtered through a short plug of potassium carbonate–silica³² (10 % wt/wt K₂CO₃/SiO₂), which was flushed with hexanes (10 mL), and the filtrate was concentrated. TBAF (1.0 M in THF; 0.68 mL, 0.68 mmol, 20 equiv) was added to the resulting residue, and the solution was stirred at reflux overnight. After cooling to room temperature, the solution was filtered through a short plug of potassium carbonate–silica (10 % wt/wt K₂CO₃/SiO₂). The resulting residue was purified by preparative TLC (50% EtOAc/hexanes) to afford 14-hydroxypatchoulol (**4.29**) as a white solid (3 mg, 40 % yield over 2 steps).

mp = 144–164 $^{\circ}$ C

R_f (50 % EtOAc/hexanes, CAM) 0.45

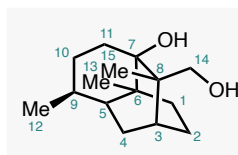
[α]_D²⁵ = –53 (*c* = 0.002, MeOH); Reported: **[α]_D²³** = –104.84 (*c* = 0.1, MeOH).

¹H NMR (600 MHz, CDCl₃) δ 4.24 (d, *J* = 10.6 Hz, 1H), 3.10 (d, *J* = 10.7 Hz, 1H), 2.02 – 1.93 (m, 2H), 1.82 – 1.77 (m, 1H), 1.77 – 1.70 (m, 1H), 1.55 – 1.48 (m, 1H), 1.48 – 1.43 (m, 2H), 1.43 – 1.33 (m, 2H), 1.33 – 1.23 (m, 3H), 1.22 (s, 3H), 1.06 (ddd, *J* = 13.9, 12.0, 2.3 Hz, 1H), 0.87 (s, 3H), 0.80 (d, *J* = 6.7 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 77.7, 71.6, 44.0, 43.3, 38.1, 36.5, 34.5, 29.0, 28.8, 28.2, 25.0, 23.3, 20.1, 18.7, 18.6.

HRMS (ESI) Exact mass calcd for C₁₅H₂₅O₂ [*M*–H][–], 237.1860. Found 237.1859.

Table S1. Comparison of NMR data of natural and synthetic 14-hydroxypatchoulol (4.29):

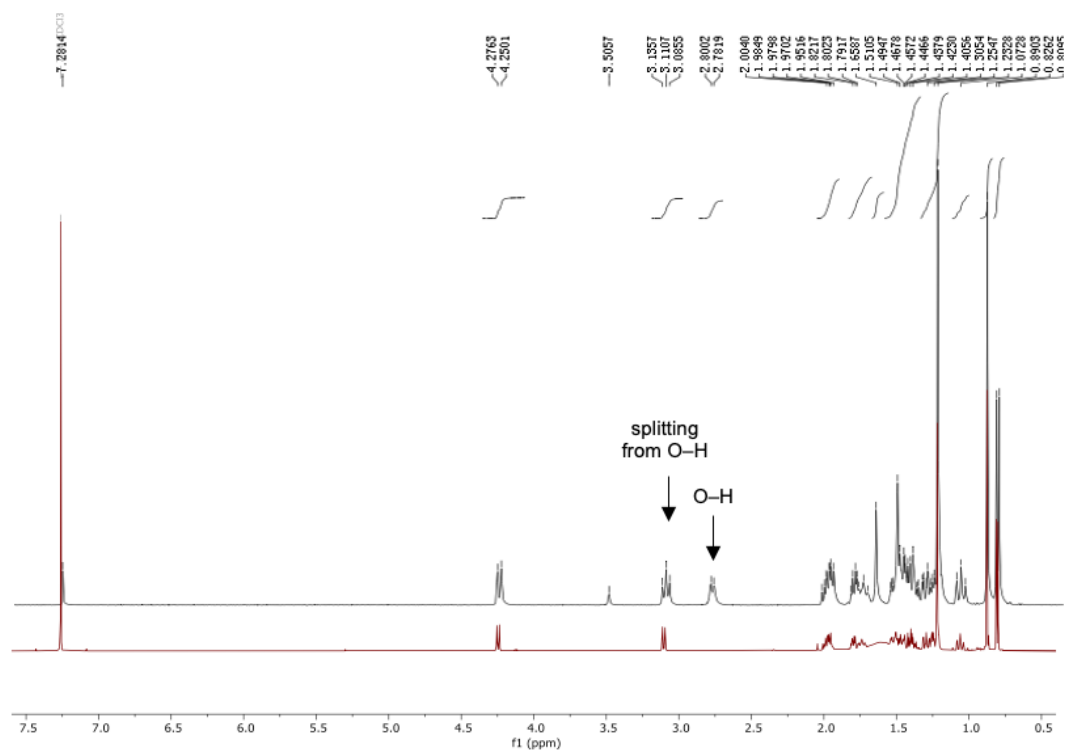


14-hydroxypatchoulol (4.29)

Position	Natural $\delta_{\text{H}}^{\text{a}}$ (500 MHz, CDCl_3)	Synthetic δ_{H} (700 MHz, CDCl_3)	Natural $\delta_{\text{H}}^{\text{b}}$ (125 MHz, CDCl_3)	Synthetic δ_{H} (150 MHz, CDCl_3)
1	1.97, overlap 1.04, t (15.3)	1.98, overlap 1.06, ddd (13.9, 12.0, 2.3 Hz)	28.7	29.0
2	1.72, m 1.22, m	1.74, m 1.25, m	23.1	23.3
3	1.20, m	1.22, m	36.3	36.5
4	1.51, m 1.28, m	1.52, m 1.30, m	24.7	25.0
5	1.45, m	1.45, m	43.0	43.3
6			37.9	38.1
7			77.5	77.7
8			43.8	44.0
9	1.95, m	1.96, m	28.0	28.2
10	1.48, m 1.37, m	1.47, m 1.39, m	28.5	28.8
11	1.79, dd (15.0, 5.3) 1.38, overlap	1.80, m 1.41, overlap	34.3	34.5
12	0.81, d (6.7)	0.80, d (6.7)	18.5	18.7
13	1.23, s	1.22, s	18.4	18.6
14	4.25, d (13.1) 3.09, t (13.1)	4.24, d (10.6) 3.10, d (10.7)	71.4	71.6
15	0.89, s	0.87, s	19.9	20.1

Figure S1. Overlay of synthetic (red) with natural (black) 14-hydroxypatchoulol (**4.29**):

^1H NMR (700 MHz, CDCl_3)



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

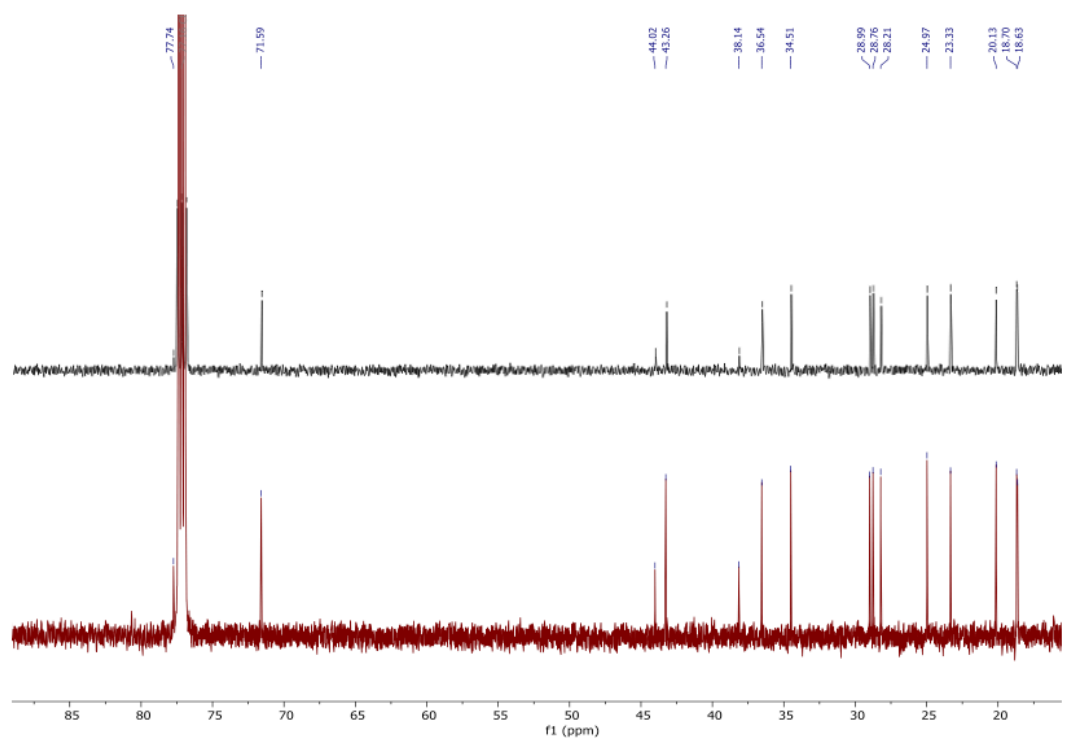
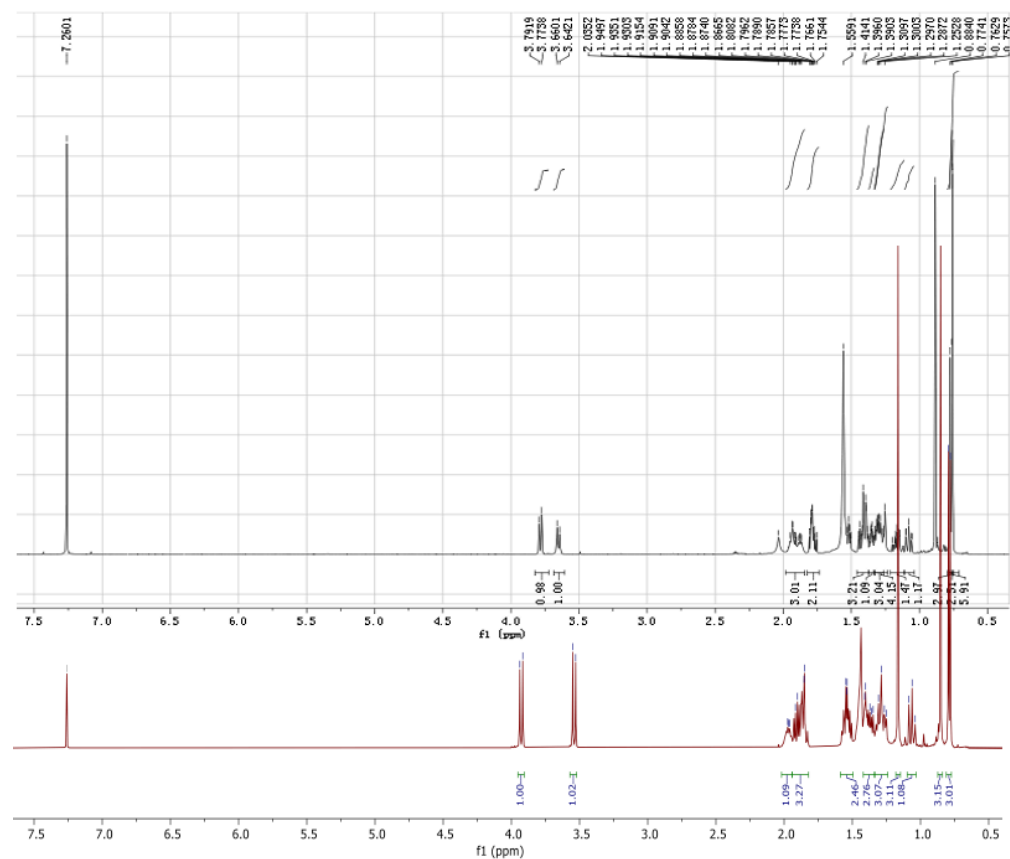
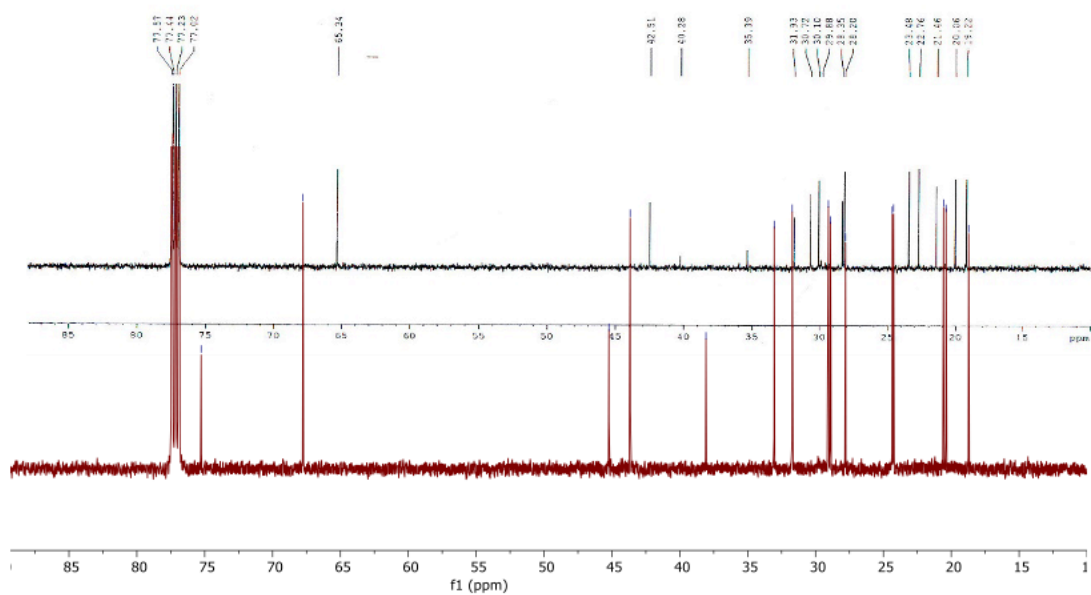


Figure S2. Overlay of synthetic (red) with reported (black) 15-hydroxypatchoulol (**4.1**):

^1H NMR (700 MHz, CDCl_3)



^{13}C NMR (126 MHz, CDCl_3)



X-Ray Crystallographic Information

X-Ray Analysis of **4.1**

A colorless block 0.14 x 0.09 x 0.07 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 33.00 mm and exposure time was 0.50 seconds per frame at low angles and 0.75 seconds at high angles, using a scan width of 0.5°. Data collection was 99% complete to 74.000° in θ . A total of 60217 reflections were collected covering the indices $-8 \leq h \leq 9$, $-32 \leq k \leq 32$, $-17 \leq l \leq 16$. 10649 reflections were founded to be symmetry independent, with an R_{int} of 0.0357. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21 (No. 4). The data were integrated using the CrysAlis^{Pro} 1.172.42.51a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

[Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172.]

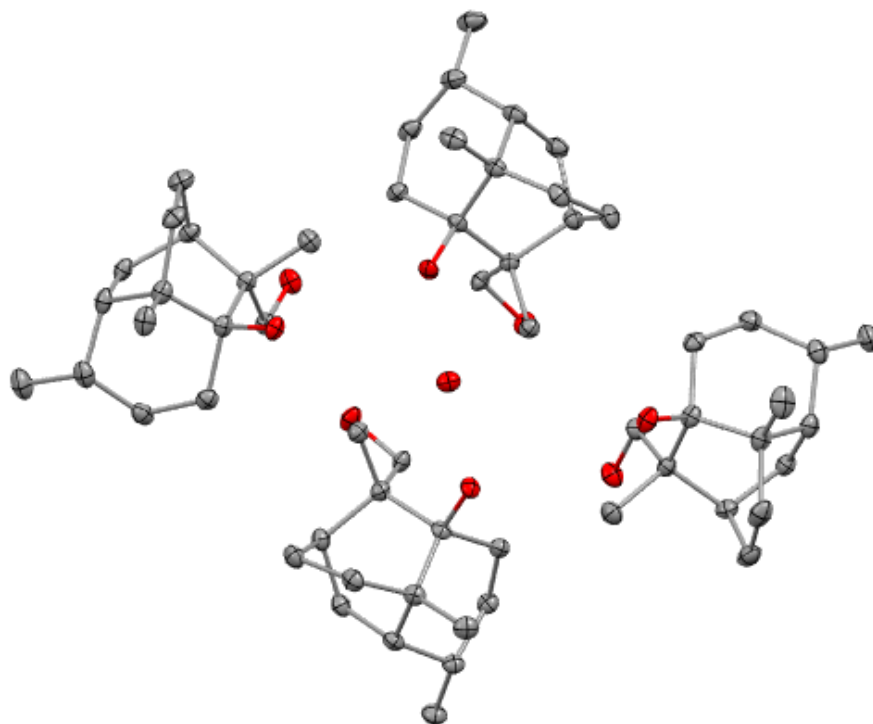


Figure S3. X-ray crystal structure showing four molecules of **4.1** organized by H-bonding around water.

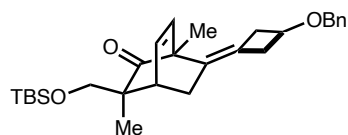
This crystal structure has been deposited at the Cambridge Crystallographic Data Center under CCDC 2203888.

Table S4. Crystal data and structure refinement for CNa03_Sarpong.

Identification code	CNa03_Sarpong
Empirical formula	C ₆₀ H ₁₀₆ O ₉
Formula weight	971.44
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	P 21
Unit cell dimensions	a = 7.29320(10) Å a = 90°. b = 26.0768(2) Å b = 104.0890(10)°. c = 14.53990(10) Å g = 90°.
Volume	2682.06(5) Å ³
Z	2
Density (calculated)	1.203 Mg/m ³
Absorption coefficient	0.611 mm ⁻¹
F(000)	1076
Crystal size	0.140 x 0.090 x 0.070 mm ³
Theta range for data collection	3.134 to 74.473°.
Index ranges	-8<= <i>h</i> <=9, -32<= <i>k</i> <=32, -17<= <i>l</i> <=16
Reflections collected	60217
Independent reflections	10649 [R(int) = 0.0357]
Completeness to theta = 74.000°	98.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.83100

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10649 / 1 / 674
Goodness-of-fit on F^2	1.045
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0294$, $wR_2 = 0.0750$
R indices (all data)	$R_1 = 0.0308$, $wR_2 = 0.0764$
Absolute structure parameter	-0.03(4)
Extinction coefficient	n/a
Largest diff. peak and hole	0.154 and -0.174 e.Å ⁻³

Synthesis of 14-Hydroxypatchoulol 4.29 (2nd Generation):



(1*S*,3*S*,4*S*,*E*)-7-((*S*)-3-(benzyloxy)cyclobutylidene)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,3-dimethylbicyclo[2.2.2]oct-5-en-2-one (4.44):

The title compound was prepared using General Procedure F (Chapter 2.10) with **4.43** as starting material (65 % yield). Product was isolated as a mixture of two diastereomers that were inseparable. Reported are the chemical shifts of the mixture of diastereomers.

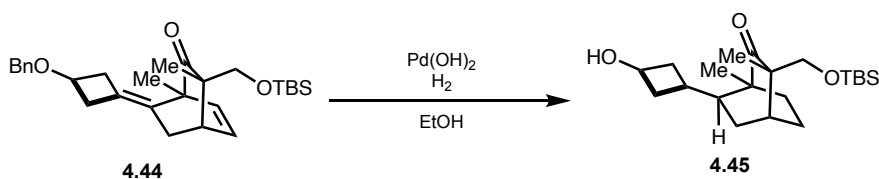
R_f (25 % EtOAc/hexanes, *p*-anisaldehyde) 0.40

[α]_D²⁵ = + 4.14 (*c* = 0.0066, CH₂Cl₂)

¹H NMR (600 MHz, CDCl₃) δ 7.36 – 7.26 (m, 5H), 6.49 (dd, *J* = 7.9, 6.5 Hz, 1H), 5.67 (dd, *J* = 7.8, 1.8 Hz, 1H), 4.43 (d, *J* = 1.0 Hz, 2H), 4.12 (tt, *J* = 7.0, 5.6 Hz, 1H), 3.45 – 3.40 (m, 2H), 3.19 – 3.12 (m, 1H), 2.92 – 2.85 (m, 2H), 2.78 (ddt, *J* = 16.0, 6.1, 3.1 Hz, 1H), 2.62 (ddd, *J* = 16.1, 5.6, 2.8 Hz, 1H), 2.34 (d, *J* = 16.4 Hz, 1H), 2.03 – 1.97 (m, 1H), 1.34 (s, 3H), 1.07 (s, 3H), 0.89 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 211.89, 138.25, 138.06, 131.67, 128.56, 128.01, 127.82, 127.08, 127.03, 70.50, 69.89, 69.29, 56.90, 49.37, 40.22, 39.57, 37.72, 30.36, 26.00, 20.17, 18.41, 15.55, -5.36, -5.41.

HRMS (ESI) Exact mass calcd for C₂₈H₄₁O₃Si [M+H]⁺, 453.27. Found 453.28.



(1*S*,3*S*,4*R*,6*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-(3-hydroxycyclobutyl)-1,3-dimethylbicyclo[2.2.2]octan-2-one (4.45): In a flame-dried scintillation vial, **4.44** (300 mg, 623 μ mol, 1.0 equiv) was charged with Pd(OH)₂/C (20 wt %, 233 mg, 331 μ mol, 0.5 equiv) and anhydrous EtOH (6.63 mL, 0.1 M) with a H₂ balloon attached to it. The reaction was stirred at room temperature overnight. After filtration over a pad of celite and washing with EtOAc, the crude was concentrated and purified with silica gel chromatography (25 – 50 % EtOAc/hexane). The title compound was obtained as colorless oil (231 mg, 95 %).

R_f (25 % EtOAc/hexanes, *p*-anisaldehyde) 0.25

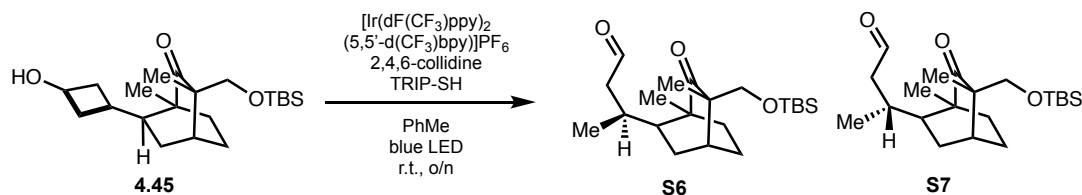
$[\alpha]_D^{25} = -54.71$ ($c = 0.019$, CH_2Cl_2)

The title compound was isolated as a mixture of two diastereomers that were inseparable. Reported are the chemical shifts of the mixture of diastereomers.

^1H NMR (600 MHz, CDCl_3) δ 4.05 – 3.99 (m, 1H), 3.60 (d, $J = 10.3$ Hz, 1H), 3.41 (dd, $J = 9.7$, 1.5 Hz, 1H), 2.50 – 2.38 (m, 2H), 2.33 (q, $J = 9.9$ Hz, 1H), 2.20 (dt, $J = 17.2$, 8.0 Hz, 1H), 2.07 – 1.89 (m, 4H), 1.84 – 1.62 (m, 5H), 1.61 – 1.46 (m, 4H), 1.40 – 1.32 (m, 2H), 1.08 (d, $J = 1.3$ Hz, 3H), 0.87 (s, 9H), 0.86 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 220.63, 67.03, 63.78, 51.81, 49.51, 47.62, 42.34, 37.97, 33.70, 32.71, 29.93, 29.71, 28.04, 25.80, 18.86, 18.22, -5.59, -5.63.

HRMS (ESI) Exact mass calcd for $\text{C}_{21}\text{H}_{39}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$, 367.26. Found 367.27.



In a flame-dried 1 dram scintillation vial, **4.45** (40.0 mg, 109 μmol , 1.0 equiv) was charged with Ir photocatalyst (3.75 mg, 3.27 μmol , 0.03 equiv), TRIP-SH (5.19 mg, 27.3 μmol , 0.25 equiv), 2,4,6-collidine (3.31 mg, 27.3 μmol , 0.25 equiv). The reagents were dissolved in anhydrous PhMe (2.18 mL, 0.05 M) and stirred at room temperature in a photoreactor (425 nm) overnight. Upon completion of the reaction, the crude mixture was filtered over a pad of celite and concentrated. Purification with silica gel chromatography (25 % EtOAc/hexane) provided the title compound **S6** (19.1 mg, 48 % yield) and **S7** (19.0 mg, 48 % yield) and colorless oils.

(3S)-3-((4R,5S)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1,5-dimethyl-6-oxobicyclo[2.2.2]octan-2-yl)butanal (S6):

R_f (25 % EtOAc/hexanes, *p*-anisaldehyde) 0.75

$[\alpha]_D^{25} = -37.27$ ($c = 0.018$, CH_2Cl_2)

^1H NMR (600 MHz, CDCl_3) δ 9.65 (d, $J = 3.3$ Hz, 1H), 3.59 (d, $J = 9.6$ Hz, 1H), 3.44 (d, $J = 9.7$ Hz, 1H), 2.42 (d, $J = 5.7$ Hz, 1H), 2.15 – 2.07 (m, 1H), 2.03 – 1.90 (m, 3H), 1.74 (ddd, $J = 14.7$, 10.7, 4.3 Hz, 1H), 1.67 – 1.62 (m, 2H), 1.48 – 1.41 (m, 1H), 1.16 (s, 3H), 0.95 (s, 3H), 0.90 (d, $J = 6.9$ Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 222.31, 201.92, 67.64, 52.37, 47.52, 46.61, 45.21, 34.91, 33.36, 28.28, 25.95, 25.13, 21.58, 18.78, 18.62, 18.38, 17.98, -5.48, -5.43.

HRMS (ESI) Exact mass calcd for $\text{C}_{21}\text{H}_{39}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$, 367.26. Found 367.27.

(3*R*)-3-(((4*R*,5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,5-dimethyl-6-oxobicyclo[2.2.2]octan-2-yl)butanal (S7):

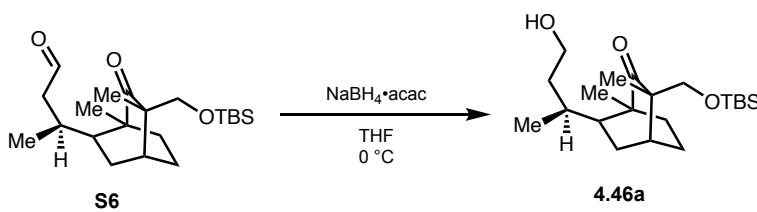
R_f (25 % EtOAc/hexanes, *p*-anisaldehyde) 0.70

[α]_D²⁵ = − 67.33 (c = 0.012, CH₂Cl₂)

¹H NMR (700 MHz, CDCl₃) δ 9.75 – 9.73 (m, 1H), 3.57 (d, *J* = 9.6 Hz, 1H), 3.43 (dd, *J* = 9.7, 2.2 Hz, 1H), 2.52 – 2.45 (m, 1H), 2.34 – 2.25 (m, 2H), 2.01 (s, 1H), 1.96 – 1.85 (m, 2H), 1.66 – 1.57 (m, 2H), 1.55 – 1.51 (m, 1H), 1.15 (d, *J* = 2.2 Hz, 3H), 0.97 (d, *J* = 2.1 Hz, 3H), 0.88 (dd, *J* = 6.6, 2.5 Hz, 9H), 0.67 (dd, *J* = 7.0, 2.1 Hz, 3H), 0.04 (s, 3H), 0.02 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 221.58, 202.28, 67.76, 52.19, 49.47, 46.43, 46.28, 34.90, 33.30, 28.58, 25.95, 23.87, 21.70, 18.75, 18.37, 17.92, 14.34, −5.49, −5.43.

HRMS (ESI) Exact mass calcd for C₂₁H₃₉O₃Si [M+H]⁺, 367.26. Found 367.27.



(3*S*,4*R*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-((*S*)-4-hydroxybutan-2-yl)-1,3-dimethyl bicyclo[2.2.2]octan-2-one (4.46a): In a flame-dried 1 dram scintillation vial, **S6** (19.1 mg, 51.8 μmol, 1.0 equiv) was dissolved in anhydrous THF (260 μL, 0.2 M) under N₂ atmosphere at 0 °C. The NaBH₄*acac complex was prepared according to the literature.²⁰ After careful addition of the reagent, the reaction was stirred at 0 °C for 15 min and was monitored by TLC. Upon completion of the reaction, the reaction was quenched with saturated aqueous solution of NH₄Cl and extracted with EtOAc (2 x 500 μL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Purification with preparatory silica chromatography (25 % EtOAc/hexane) provided the title compound as a colorless oil (13.4 mg, 70 % yield).

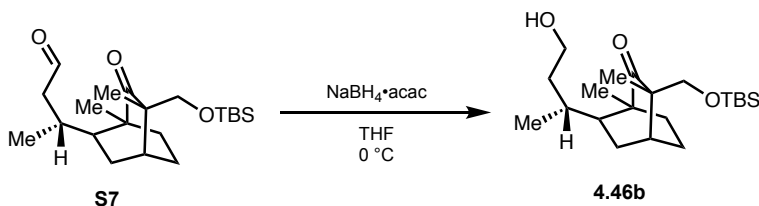
R_f (25 % EtOAc/hexanes, *p*-anisaldehyde) 0.25

[α]_D²⁵ = − 42.11 (c = 0.036, CH₂Cl₂)

¹H NMR (600 MHz, CDCl₃) δ 3.66 (ddd, *J* = 10.7, 7.3, 4.4 Hz, 1H), 3.59 – 3.56 (m, 1H), 3.54 (ddd, *J* = 10.7, 8.5, 6.2 Hz, 1H), 3.44 (d, *J* = 9.6 Hz, 1H), 2.01 – 1.98 (m, 1H), 1.92 (dq, *J* = 6.9, 4.3 Hz, 3H), 1.70 (ddd, *J* = 14.7, 10.7, 4.3 Hz, 1H), 1.65 – 1.60 (m, 2H), 1.53 – 1.48 (m, 2H), 1.29 – 1.22 (m, 2H), 1.15 (d, *J* = 0.7 Hz, 3H), 1.08 (dddd, *J* = 13.1, 11.0, 6.2, 4.5 Hz, 1H), 0.93 (s, 3H), 0.88 (s, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 222.62, 67.76, 61.62, 52.22, 48.49, 46.66, 35.22, 33.58, 33.34, 30.01, 25.95, 24.82, 21.67, 18.87, 18.37, 18.06, 18.01, -5.42, -5.48.

HRMS (ESI) Exact mass calcd for $\text{C}_{21}\text{H}_{41}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$, 369.27. Found 369.28.



(3*S*,4*R*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-((*R*)-4-hydroxybutan-2-yl)-1,3-dimethyl bicyclo[2.2.2]octan-2-one (4.46b): In a flame-dried 1 dram scintillation vial, **S7** (19.1 mg, 51.8 μmol , 1.0 equiv) was dissolved in anhydrous THF (260 μL , 0.2 M) under N_2 atmosphere at 0 $^\circ\text{C}$. The $\text{NaBH}_4\cdot\text{acac}$ complex was prepared according to the literature.²⁰ After careful addition of the reagent, the reaction was stirred at 0 $^\circ\text{C}$ for 15 min and was monitored by TLC. Upon completion of the reaction, the reaction was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc (2 x 500 μL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification with preparatory silica chromatography (25 % EtOAc /hexane) provided the title compound as a colorless oil (13.4 mg, 70 % yield).

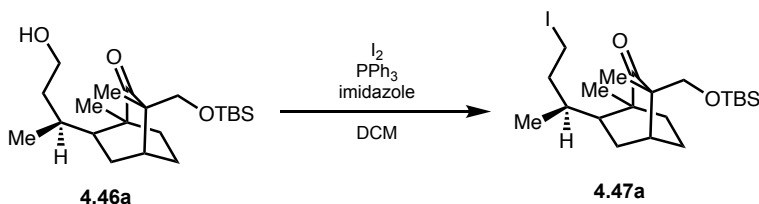
R_f (25 % EtOAc /hexanes, *p*-anisaldehyde) 0.25

[α]_D²⁵ = - 28.12 (*c* = 0.019, CH_2Cl_2)

^1H NMR (600 MHz, CDCl_3) δ 3.71 – 3.62 (m, 2H), 3.58 (d, *J* = 9.6 Hz, 1H), 3.44 (d, *J* = 9.6 Hz, 1H), 2.23 (qd, *J* = 15.1, 7.4 Hz, 1H), 2.03 – 1.85 (m, 4H), 1.68 – 1.38 (m, 5H), 1.18 – 1.12 (m, 3H), 0.92 (s, 3H), 0.88 (s, 9H), 0.61 (d, *J* = 6.8 Hz, 3H), 0.04 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 222.20, 67.80, 61.22, 52.15, 46.62, 46.49, 38.21, 35.10, 33.30, 29.75, 25.95, 23.92, 21.82, 18.79, 18.38, 18.00, 13.94, -5.42, -5.48.

HRMS (ESI) Exact mass calcd for $\text{C}_{21}\text{H}_{41}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$, 369.27. Found 369.28.



(3*S*,4*R*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-((*S*)-4-iodobutan-2-yl)-1,3-dimethyl bicyclo[2.2.2]octan-2-one (4.47a): In a flame-dried 1 dram scintillation vial, **4.46a** (6.50 mg, 17.6 μ mol, 1.0 equiv) was dissolved in anhydrous dichloromethane (350 μ L, 0.05 M) with iodine (4.48 mg, 17.6 μ mol, 1.0 equiv), triphenylphosphine (9.25 mg, 35.3 μ mol, 2.0 equiv), and imidazole (4.80 mg, 70.5 μ mol, 4.0 equiv) and stirred at 35 °C for 30 min. Upon completion of the reaction, it was quenched with H₂O and extracted with Et₂O (3 x 500 μ L). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. Purification over a quick plug of silica gel provided the title compound **4.47a** as colorless oil.

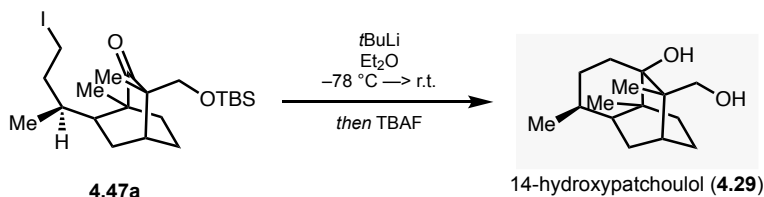
R_f (25 % EtOAc/hexanes, *p*-anisaldehyde) 0.90

[α]_D²⁵ = – 28.83 (*c* = 0.006, CH₂Cl₂)

¹H NMR (700 MHz, CDCl₃) δ 3.57 (d, *J* = 9.8 Hz, 1H), 3.44 (dd, *J* = 9.6, 2.2 Hz, 1H), 3.29 (ddd, *J* = 9.4, 7.1, 3.8 Hz, 1H), 3.02 (qd, *J* = 8.3, 5.1 Hz, 1H), 1.99 (s, 1H), 1.94 – 1.86 (m, 3H), 1.71 (td, *J* = 11.7, 4.3 Hz, 1H), 1.64 – 1.60 (m, 2H), 1.57 – 1.45 (m, 2H), 1.13 (d, *J* = 2.1 Hz, 3H), 0.96 (d, *J* = 2.1 Hz, 3H), 0.88 (d, *J* = 2.2 Hz, 9H), 0.85 (dd, *J* = 6.9, 2.2 Hz, 3H), 0.04 (d, *J* = 2.2 Hz, 3H), 0.02 (d, *J* = 2.2 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 221.94, 67.75, 52.17, 48.11, 46.60, 35.25, 34.41, 33.42, 33.17, 25.95, 25.43, 21.60, 18.83, 18.38, 18.11, 16.66, 6.05, –5.42, –5.48.

HRMS (ESI) Exact mass calcd for C₂₁H₄₀IO₂Si [*M*+H]⁺, 479.18. Found 479.18.



14-Hydroxypatchoulol (4.29) In a flame-dried 1 dram scintillation vial, **4.47a** (7.61 mg, 15.9 μ mol, 1.0 equiv) was dissolved in anhydrous Et₂O (318 μ L, 0.05 M) and cooled down to –78 °C using a dry ice-acetone bath. To this solution, *t*BuLi (2.0 equiv, 1.7 M in pentane) was added slowly and the reaction was allowed to slowly warm up room temperature. After stirring for 30 min, the completion of the reaction was confirmed by TLC. After quenching the reaction with saturated aqueous solution of NH₄Cl and extracting with EtOAc (3 x 500 μ L), the combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*.

The crude material was subjected to TBAF in THF (1.0 M, 318 μ L, 20 equiv) and stirred at room temperature overnight. Purification with preparatory silica chromatography provided the title compound (1.3 mg, 34 % yield) as colorless solid. Spectral data was consistent with that reported in the literature.⁸

¹H NMR (600 MHz, CDCl₃) δ 4.24 (d, *J* = 10.6 Hz, 1H), 3.10 (d, *J* = 10.7 Hz, 1H), 2.02 – 1.93 (m, 2H), 1.82 – 1.77 (m, 1H), 1.77 – 1.70 (m, 1H), 1.55 – 1.48 (m, 1H), 1.48 – 1.43 (m, 2H), 1.43 – 1.33 (m, 2H), 1.33 – 1.23 (m, 3H), 1.22 (s, 3H), 1.06 (ddd, *J* = 13.9, 12.0, 2.3 Hz, 1H), 0.87 (s, 3H), 0.80 (d, *J* = 6.7 Hz, 3H).

4.11 References

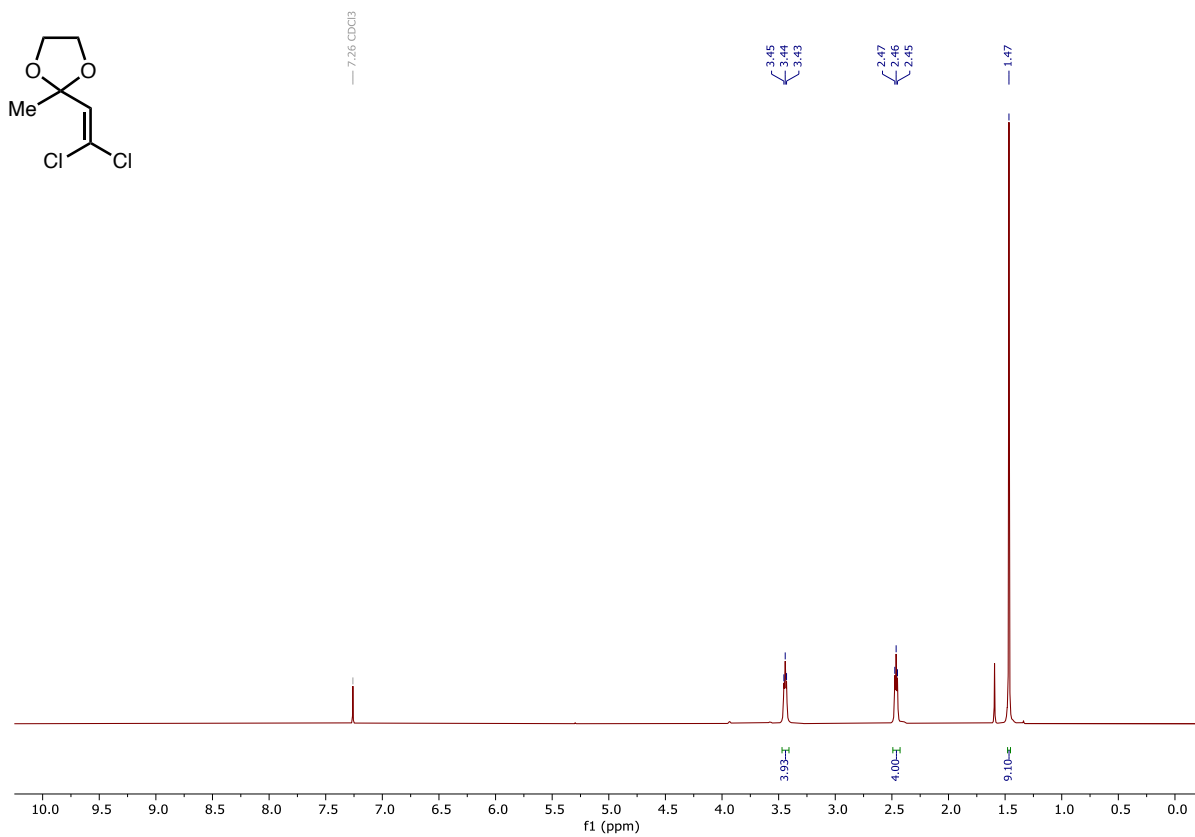
1. (a) Poulter, S. R.; Heathcock, C. H. Catalytic hydrogenation of cyclopropyl alkenes. I. Effect of alkyl substitution on the heterogeneous hydrogenolysis reaction. *Tetrahedron Lett.* **1968**, 9, 5339. (b) Barrett, A. G. M.; Tam, W. Regioselective ring opening of vinylcyclopropanes by hydrogenation with palladium on activated carbon. *J. Org. Chem.* **1997**, 62, 7673. (c) Hours, A. E.; Snyder, J. K. PtCl₂-mediated cyclopropane opening: A mechanistic study. *Organometallics* **2008**, 27, 410–417.
2. Danishefsky, S.; Dumas, D. The total synthesis of racemic patchouli and epi-patchouli alcohol. *Chem. Commun.* **1968**, 1287–1288.
3. Rubin, M.; Rubina, M.; Gevorgyan, V. Transition metal chemistry of cyclopropenes and cyclopropanes. *Chem. Rev.* **2007**, 107, 3117.
4. Corey, R. M.; Bailey, M. D.; Tse, D. W. C. A divergent approach to patchouli sesquiterpenes: Synthesis of 3-oxopatchouli alcohol, 5-oxo-7-hydroxy-13-norcyloseychellene, 6-methoxy-4,12-dehydro-13-norcyloseychellene, and patchouli alcohol. *Tetrahedron Lett.* **1990**, 31, 6839.
5. Caglioti, L.; Magi, M. The reaction of tosylhydrazones with lithium aluminium hydride. *Tetrahedron* **1963**, 19, 1127.
6. Furrow, M. E.; Myers, A. G. Practical procedures for the preparation of *N*-tert-butyltrimethylsilylhydrazones and their use in modified Wolff–Kishner reductions and in the synthesis of vinyl halides and gem-dihalides. *J. Am. Chem. Soc.* **2004**, 126, 5436.
7. (a) du Vigneaud, V.; Melville, D. B.; Folkers, K.; Wolf, D. E.; Mozingo, R.; Keresztesy, J. C.; Harris, S. A. The structure of biotin: A study of desthiobiotin. *J. Biol. Chem.* **1942**, 146, 475–485. (b) Wolfrom, M. L.; Karabinos, J. V. Carbonyl reduction by thioacetal hydrogenolysis. *J. Am. Chem. Soc.* **1944**, 66, 909–911.
8. Dong, F.-W.; Wu, Z.-K.; Yang, L.; Zi, C.-T.; Yang, D.; Ma, R.-J.; Liu, Z.-H.; Luo, H.-R.; Zhou, J.; Hu, J.-M. Iridoids and sesquiterpenoids of *Valeriana stenoptera* and their effects on NGF-induced neurite outgrowth in PC12 cells. *Phytochemistry* **2015**, 118, 51–60.
9. Aleu, J.; Hanson, J. R.; Galán, R. H.; Collado, I. G. Biotransformation of the fungistatic sesquiterpenoid patchoulol by *Botrytis cinerea*. *J. Nat. Prod.* **1999**, 62, 437.
10. Ding, W.-B.; Lin, L.-D.; Liu, M.-F.; Wei, X.-Y. Two new sesquiterpene glycosides from *Pogostemon cablin*. *J. Asian Nat. Prod. Res.* **2011**, 13, 599.
11. Hou, S. H.; Yu, X.; Zhang, R.; Wagner, C.; Dong, G. Rhodium-catalyzed diastereo- and enantioselective divergent annulations between cyclobutanones and 1,5-enynes: Rapid construction of complex C(sp³)-rich scaffolds. *J. Am. Chem. Soc.* **2022**, 144, 22159–22169.
12. (a) Seiser, T.; Cramer, N. Rhodium-catalyzed C–C bond cleavage: Construction of acyclic methyl-substituted quaternary stereogenic centers. *J. Am. Chem. Soc.* **2010**, 132, 5340–5342. (b) Seiser, T.; Cramer, N. Rhodium(I)-catalyzed enantioselective activation of cyclobutanols: Formation of cyclohexane derivatives with quaternary stereogenic centers. *Chem. Eur. J.* **2010**, 16, 3383–3391. (c) Souillart, L.; Cramer, N. Highly

- enantioselective rhodium(I)-catalyzed carbonyl carboacylations initiated by C–C bond activation. (d) Souillart, L.; Cramer, N. Enantioselective rhodium-catalyzed C–C bond activation of cyclobutanones. *Chimia* **2015**, *69*, 187–190.
13. Gregg, B. T.; Golden, K. C.; Quinn, J. F. Indium(III) trifluoromethanesulfonate as an efficient catalyst for the deprotection of acetals and ketals. *J. Org. Chem.* **2007**, *72*, 5890–5893.
 14. Carrigan, M. D.; Sarapa, D.; Smith, R. C.; Wieland, L. C.; Mohan, R. S. A simple and efficient chemoselective method for the catalytic deprotection of acetals and ketals using bismuth triflate. *J. Org. Chem.* **2002**, *67*, 1027–1030.
 15. Fujioka, H.; Minamitsuji, Y.; Kubo, O.; Senami, K.; Maegawa, T. The reaction of acetal-type protective groups in combination with TMSOTf and 2,2'-bipyridyl: Mild and chemoselective deprotection and direct conversion to other protective groups. *Tetrahedron* **2011**, *67*, 2949–2960.
 16. Murakami, M.; Amii, H. Selective activation of carbon–carbon bonds next to a carbonyl group. *Nature* **1994**, *370*, 540.
 17. Nishimura, T.; Uemura, S. Palladium-catalyzed arylation of tert-cyclobutanols with aryl bromides via C–C bond cleavage: A new approach for γ -arylated ketones. *J. Am. Chem. Soc.* **1999**, *121*, 11010.
 18. 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*, 2647–2650.
 19. Ota, E.; Wang, H.; Frye, N. L.; Knowles, R. R. A redox strategy for light-driven, out-of-equilibrium isomerizations and application to catalytic C–C bond cleavage reactions. *J. Am. Chem. Soc.* **2019**, *141*, 1457–1462.
 20. Sui, G.; Lv, Q.; Song, X.; Guo, H.; Dai, J.; Ren, L.; Lee, C.-S.; Zhou, W.; Hao, H.-D. Chemoselective reduction of aldehydes via a combination of NaBH₄ and acetylacetone. *New J. Chem.* **2019**, *43*, 15793–15796.
 21. Vitaku, E.; Christie, H. S. Improved procedure for bleach-based alcohol oxidation in undergraduate laboratories. *J. Chem. Educ.* **2019**, *96*, 1042–1045.
 22. Hayashi, M.; Sassano, Y.; Nagasawa, S.; Shibuya, M.; Iwabuchi, Y. 9-Azanoradamantane *N*-oxyl (nor-AZADO): A highly active organocatalyst for alcohol oxidation. *Chem. Pharm. Bull.* **2011**, *59*, 1570–1573.
 23. Frigerio, M.; Santagostino, M. A mild oxidizing reagent for alcohols and 1,2-diols: *o*-Iodoxybenzoic acid (IBX) in DMSO. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.
 24. Uyanik, M.; Akakura, M.; Ishihara, K. 2-Iodoxybenzenesulfonic acid as an extremely active catalyst for the selective oxidation of alcohols to aldehydes, ketones, carboxylic acids, and enones with Oxone. *J. Am. Chem. Soc.* **2009**, *131*, 251–262.
 25. Graves, C. R.; Zeng, B.; Nguyen, S. B. T. Efficient and selective Al-catalyzed alcohol oxidation via Oppenauer chemistry. *J. Am. Chem. Soc.* **2006**, *128*, 12596–12597.
 26. Jurberg, I. D. Silver carbonate. *Synlett* **2011**, 3053–3054.

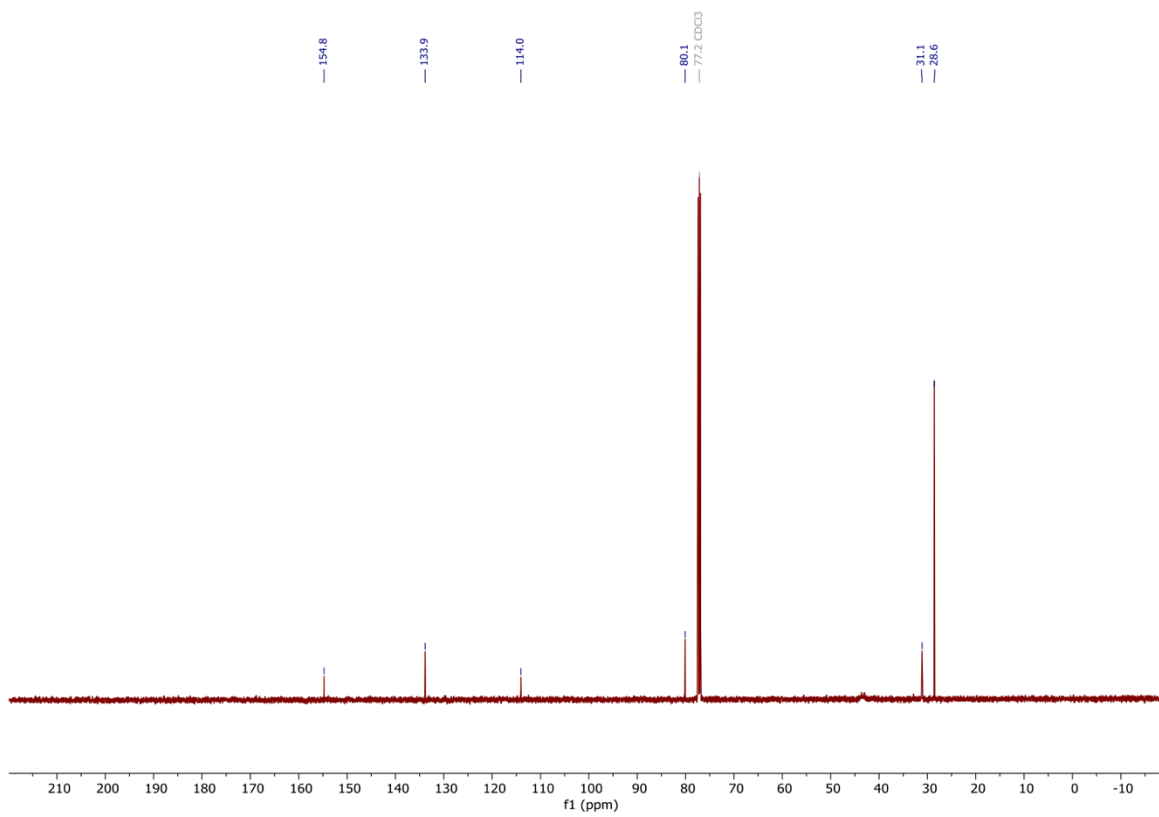
27. Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. Palladium(II)-catalyzed oxidation of alcohols to aldehydes and ketones by molecular oxygen. *J. Org. Chem.* **1999**, *64*, 6750–6755.
28. (a) Jung, M. E.; Speltz, L. Oxidation of ethers via hydride abstraction: A new procedure for selective oxidation of primary, secondary diols at the secondary position. *J. Am. Chem. Soc.* **1976**, *98*, 7882–7884. (b) Jung, M. E. Oxidation of trimethylsilyl ethers via hydride abstraction: A new method for alcohol oxidation. *J. Org. Chem.* **1976**, *41*, 1479–1480.
29. (a) Zhang, Y.; Xue, Y.; Li, G.; Yuan, H.; Luo, T. Enantioselective synthesis of iboga alkaloids and vinblastine via rearrangements of quaternary ammoniums. *Chem. Sci.* **2016**, *7*, 5530–5536. (b) Dethe, D. H.; Mahapatra, S.; Sau, S. K. Enantioselective total synthesis and assignment of the absolute configuration of the meroterpenoid (+)-taondiol. *Org. Lett.* **2018**, *20*, 2766–2769.
30. Zhu, Z.; Odagi, M.; Zhao, C.; Abboud, K. A.; Kirm, H. U.; Saame, J.; Lõkov, M.; Leito, I.; Seidel, D. Highly acidic conjugate-base-stabilized carboxylic acids catalyze enantioselective oxa-Pictet–Spengler reactions with ketals. *Angew. Chem., Int. Ed.* **2020**, *59*, 2028.
31. Barker, D.; Brimble, M. A.; Do, P.; Turner, P. Addition of silyloxydienes to 2,6-dibromo-1,4-benzoquinone: An approach to highly oxygenated bromonaphthoquinones for the synthesis of thysanone. *Tetrahedron* **2003**, *59*, 2441.
32. Harrowven, D. C.; Curran, D. P.; Kostiuk, S. L.; Wallis-Guy, I. L.; Whiting, S.; Stenning, K. J.; Tang, C.; Packard, E.; Nanson, L. Potassium carbonate–silicas: A highly effective stationary phase for the chromatographic removal of organotin impurities. *Chem. Commun.* **2010**, *46*, 6335.

Appendix 4A. NMR Spectra for Chapter 4

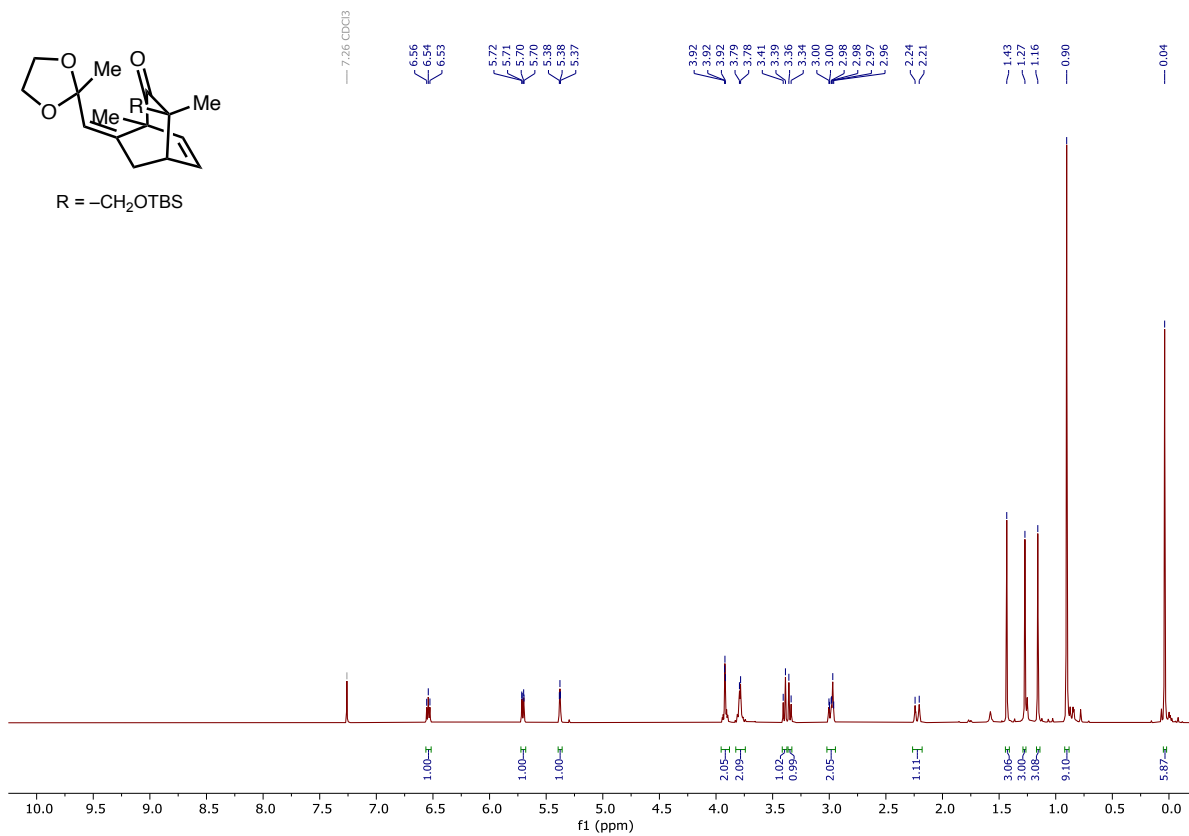
^1H NMR (500 MHz, CDCl_3) (4.18)



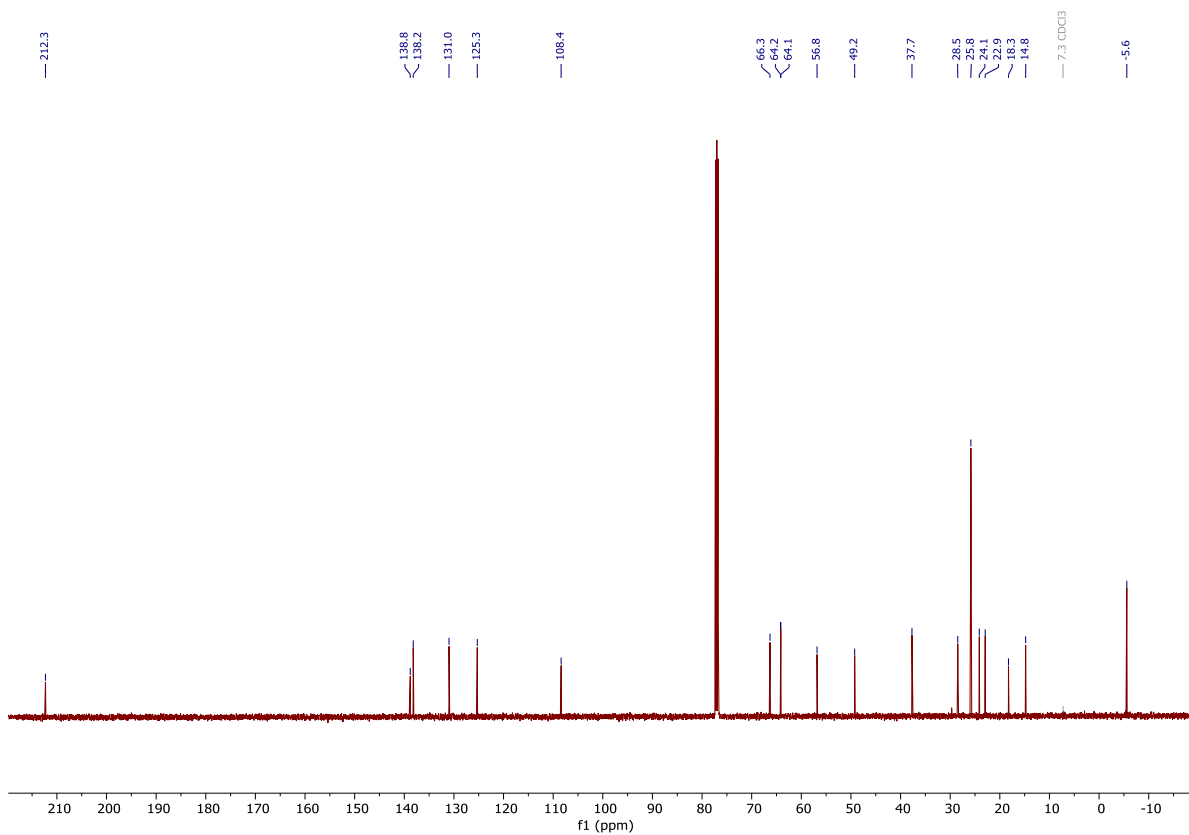
^{13}C NMR (126 MHz, CDCl_3) (4.18)



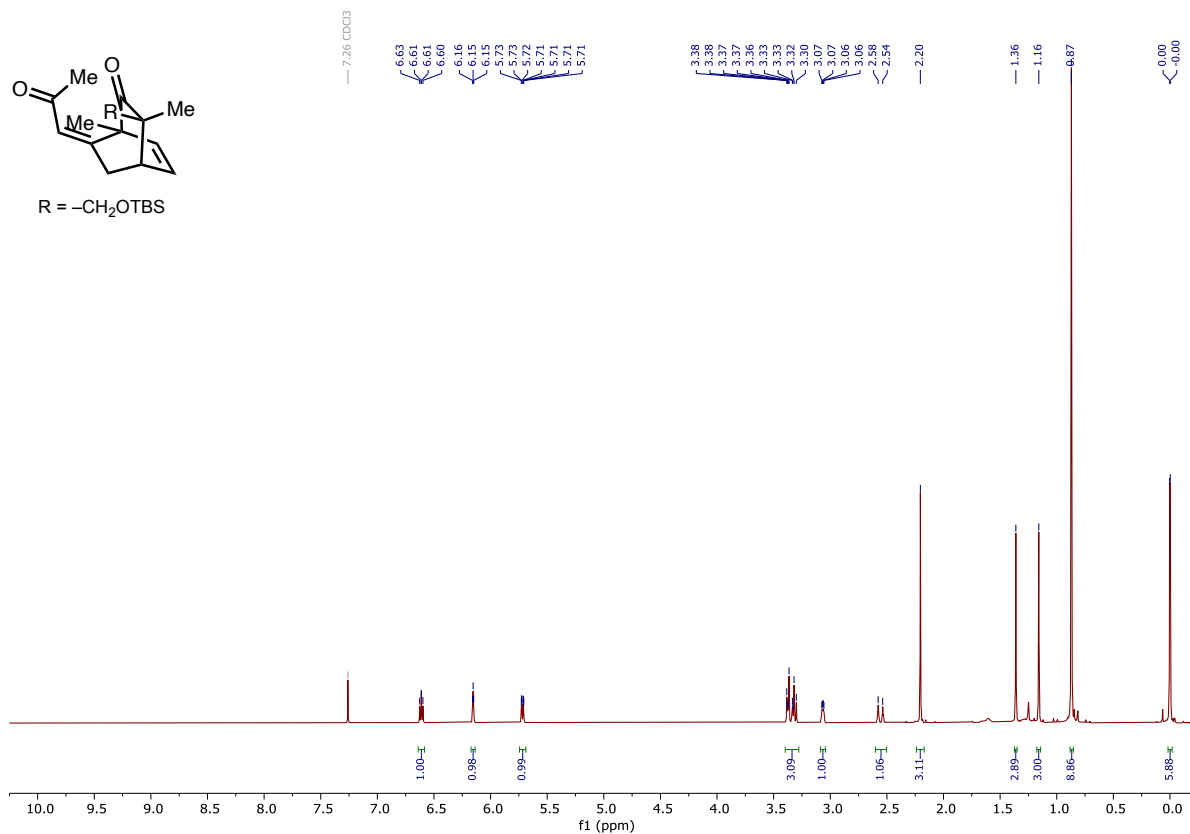
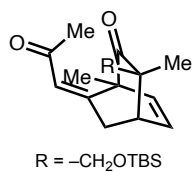
¹H NMR (500 MHz, CDCl₃) (**4.19**)



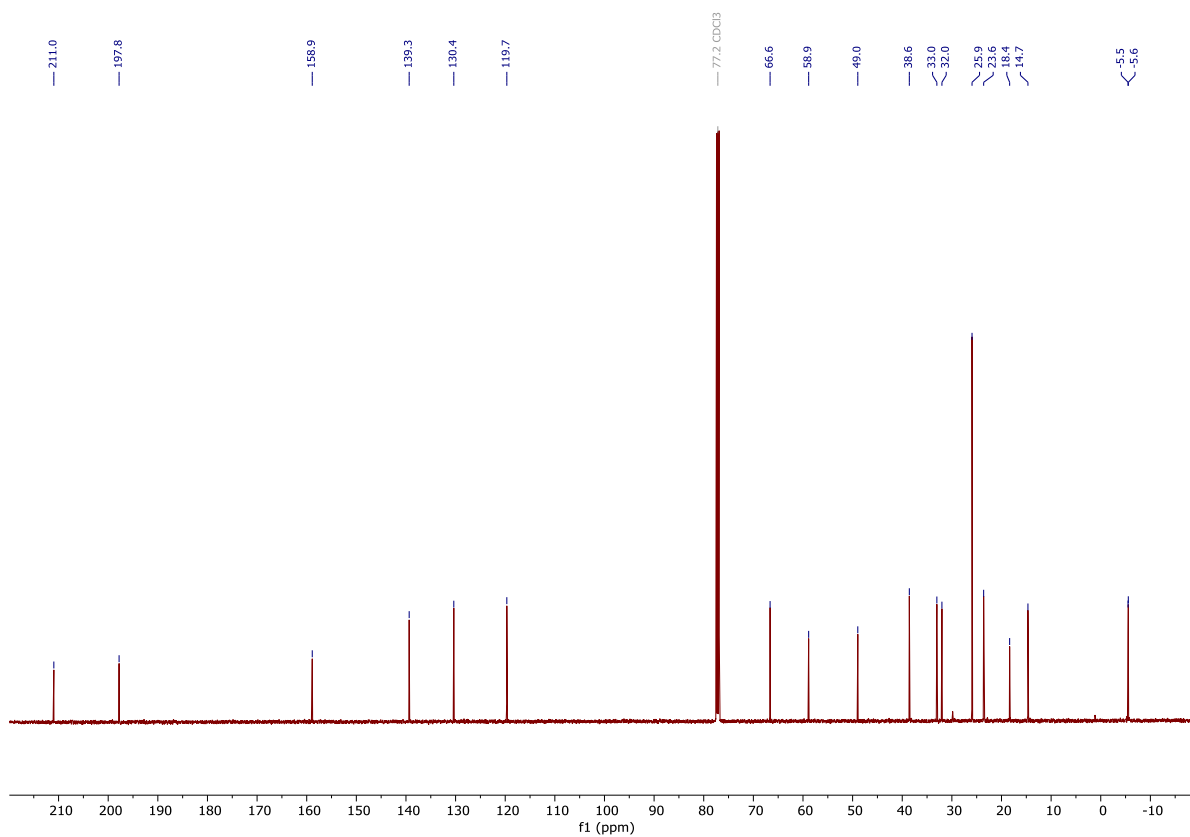
¹³C NMR (126 MHz, CDCl₃) (**4.19**)



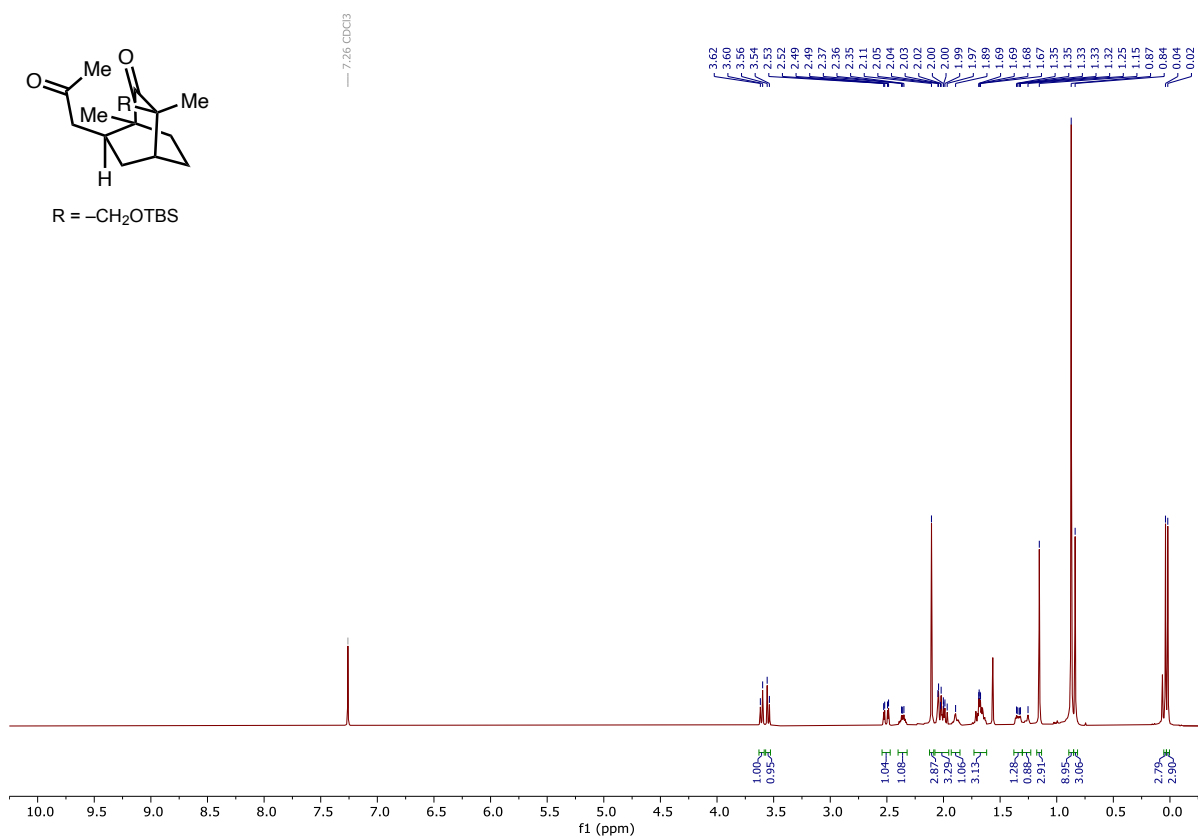
¹H NMR (500 MHz, CDCl₃) (4.20)



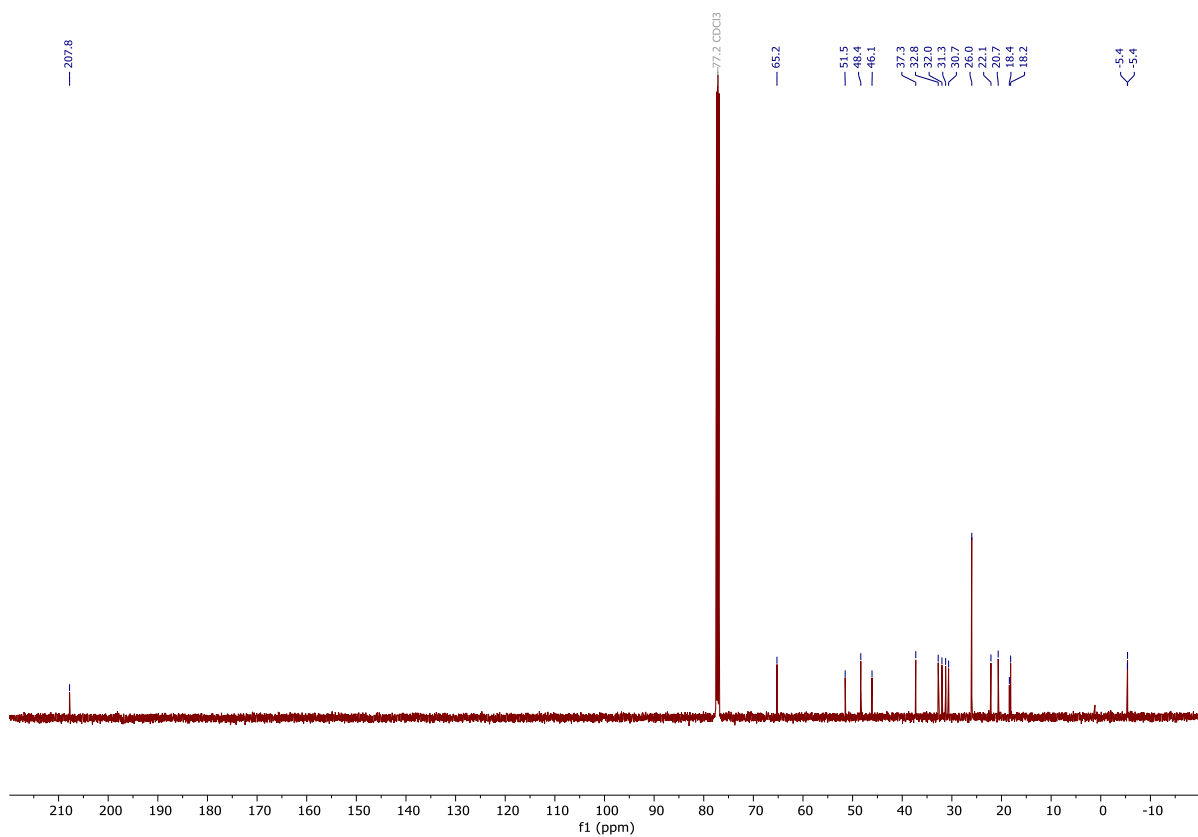
¹³C NMR (126 MHz, CDCl₃) (4.20)



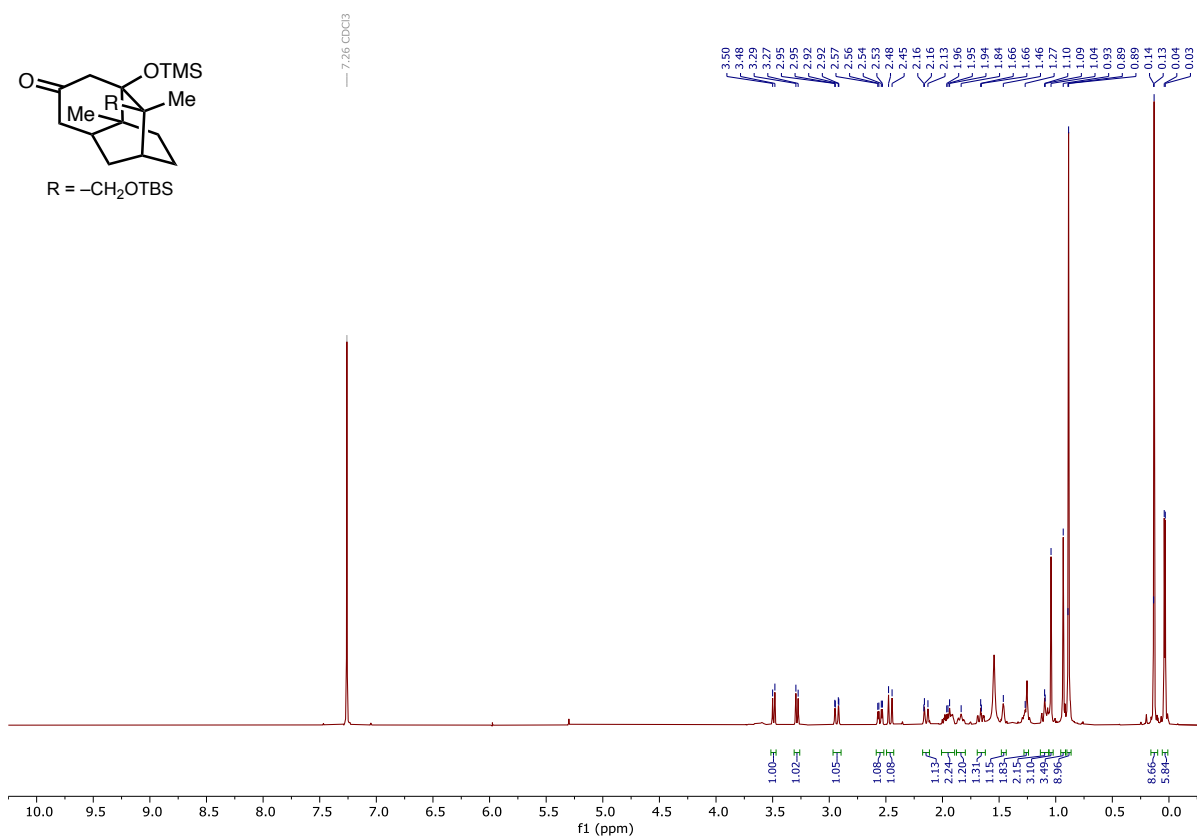
^1H NMR (500 MHz, CDCl_3) (**4.21**)



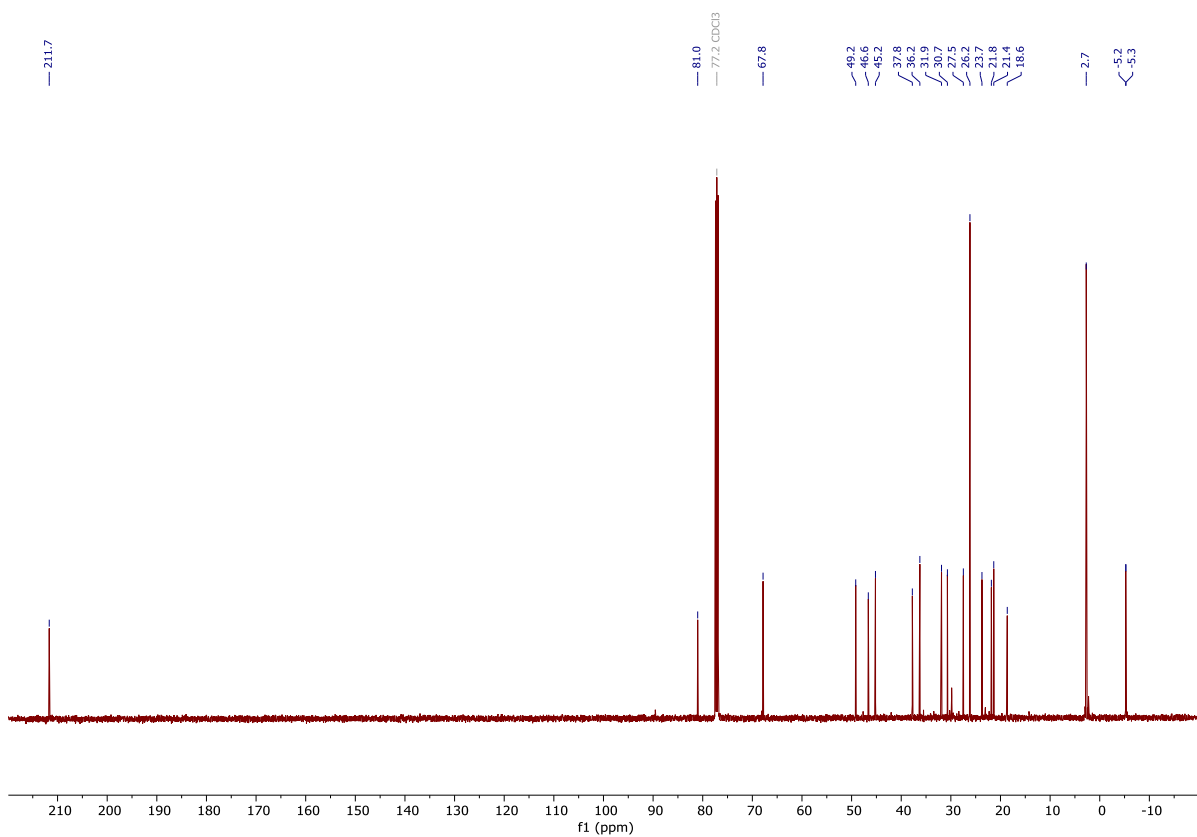
^{13}C NMR (126 MHz, CDCl_3) (**4.21**)



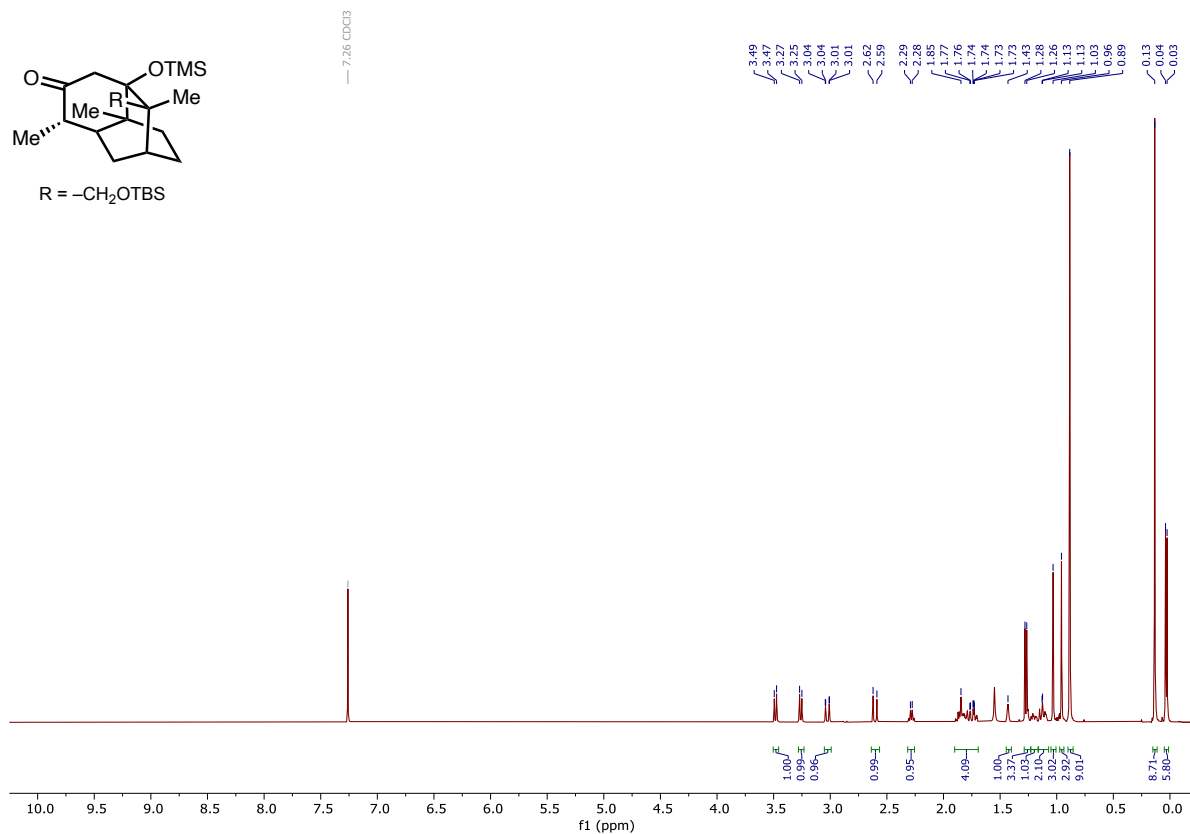
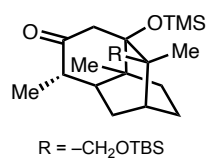
^1H NMR (500 MHz, CDCl_3) (**4.22**)



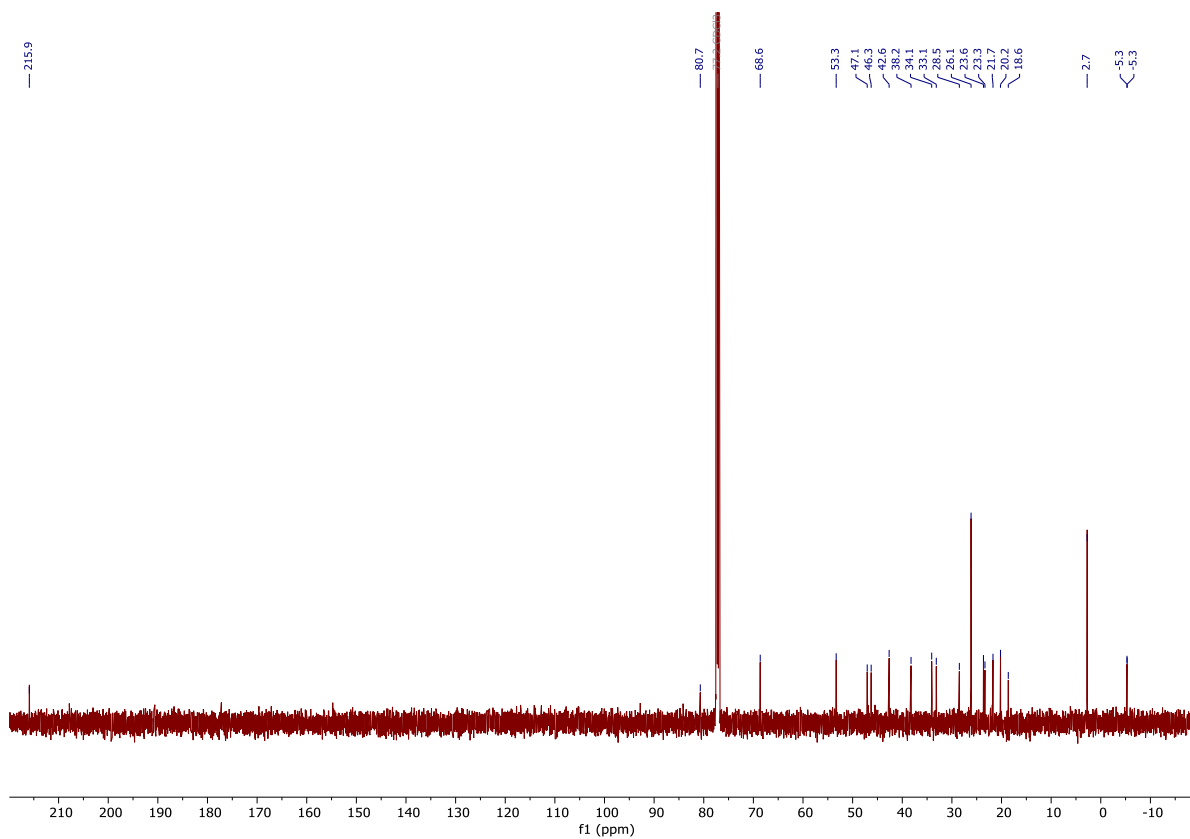
^{13}C NMR (126 MHz, CDCl_3) (**4.22**)



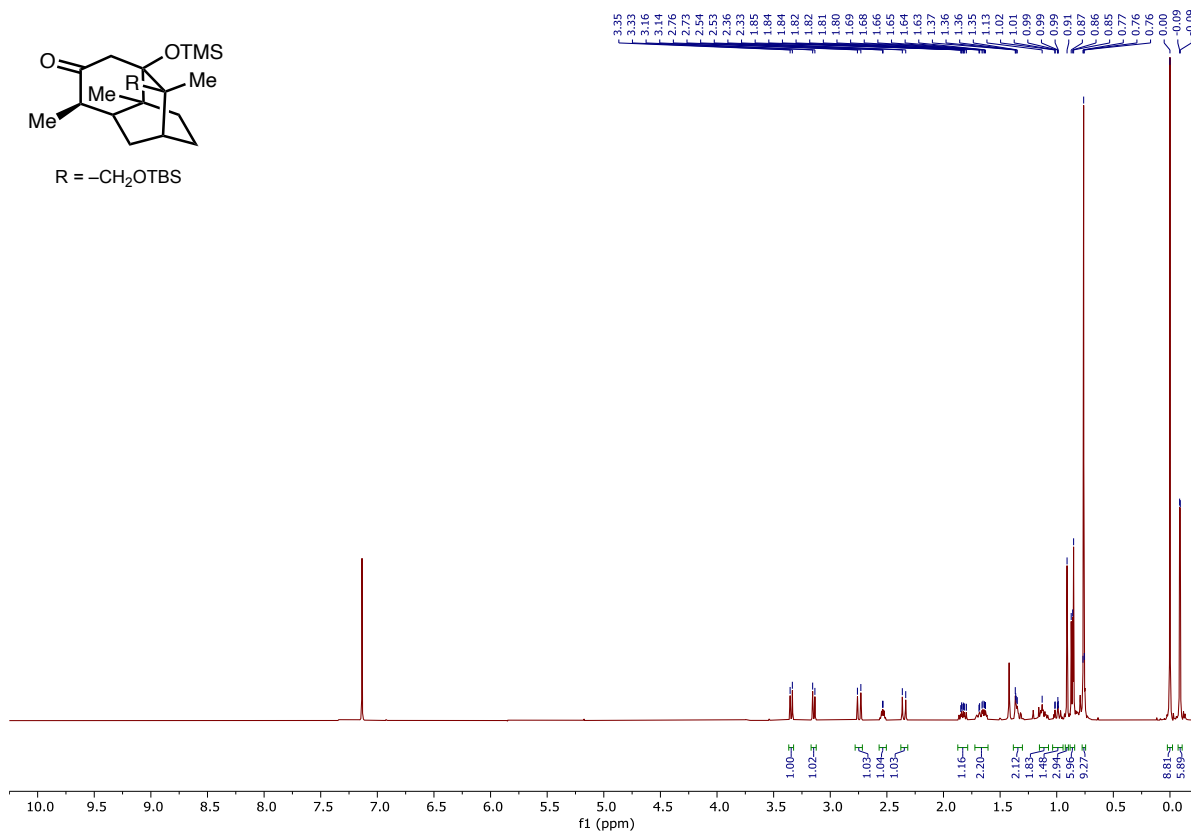
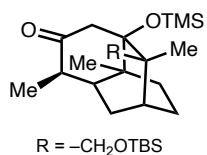
^1H NMR (500 MHz, CDCl_3) (4.26)



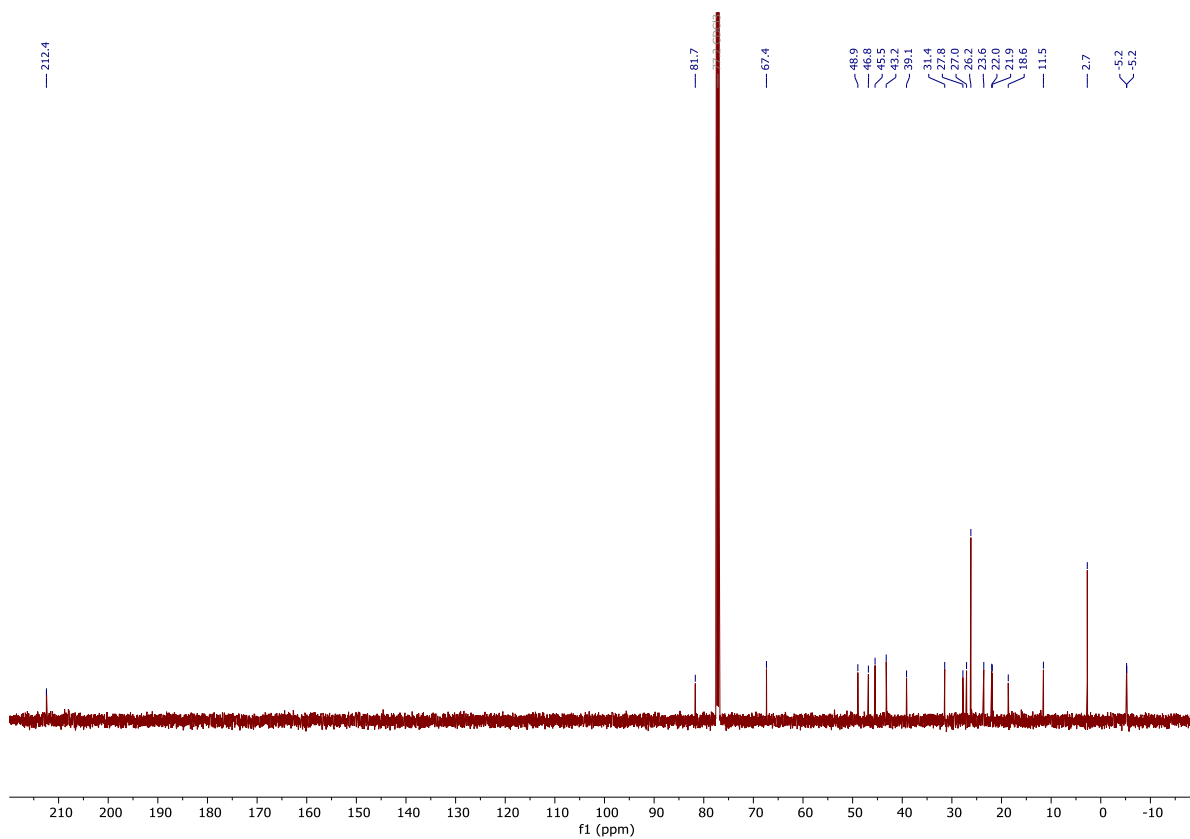
^{13}C NMR (126 MHz, CDCl_3) (4.26)



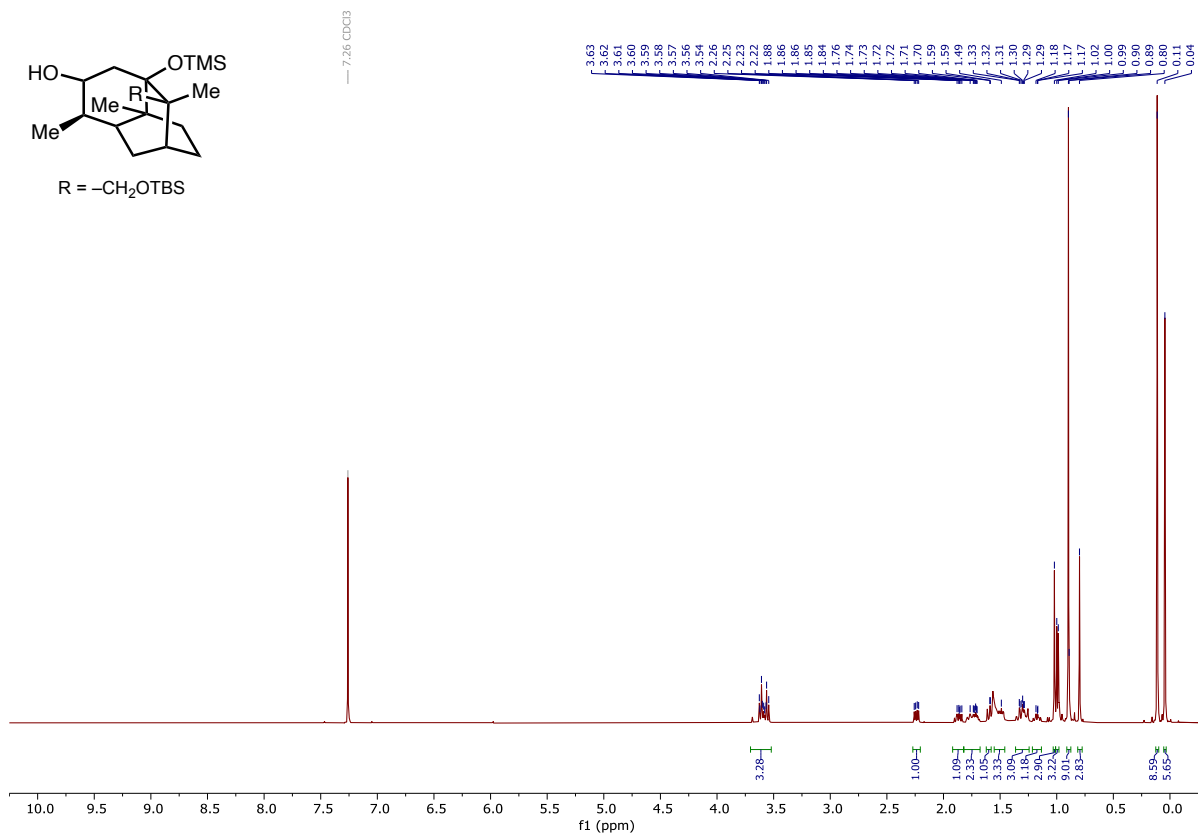
^1H NMR (500 MHz, CDCl_3) (**4.23**)



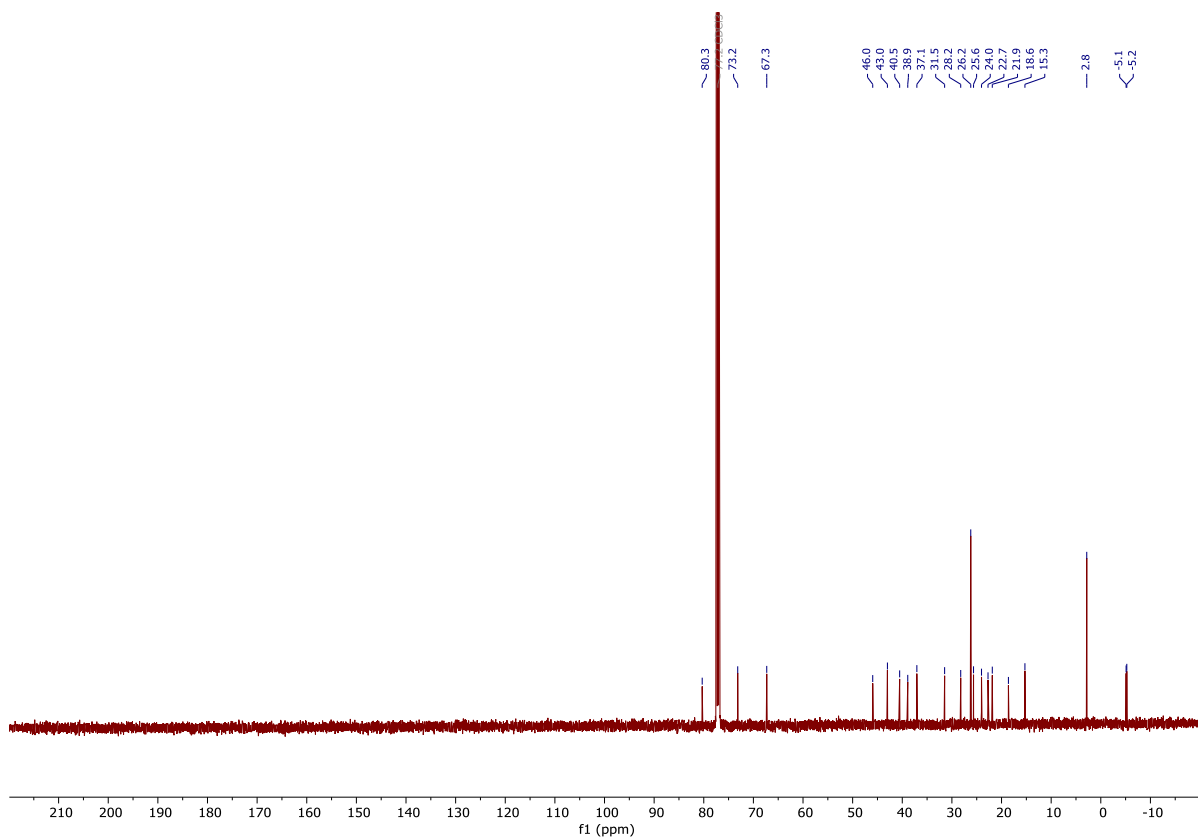
^{13}C NMR (126 MHz, CDCl_3) (**4.23**)

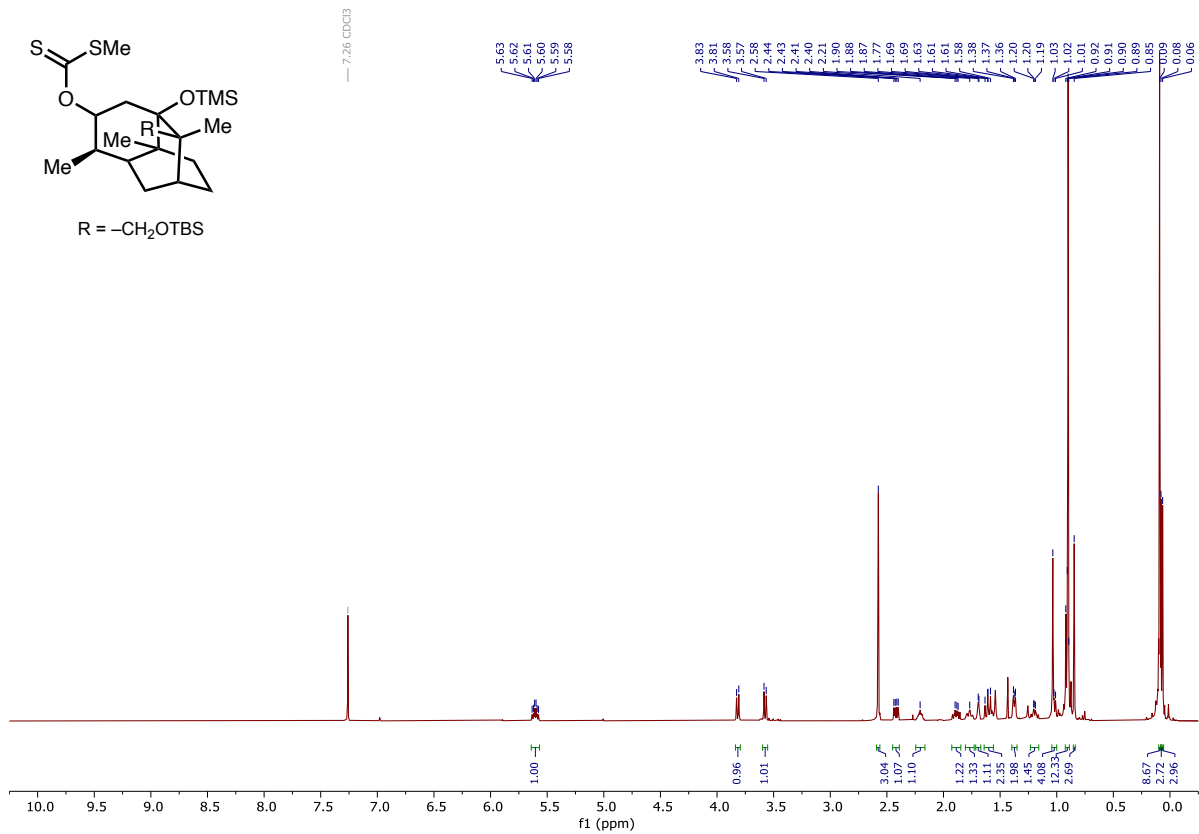
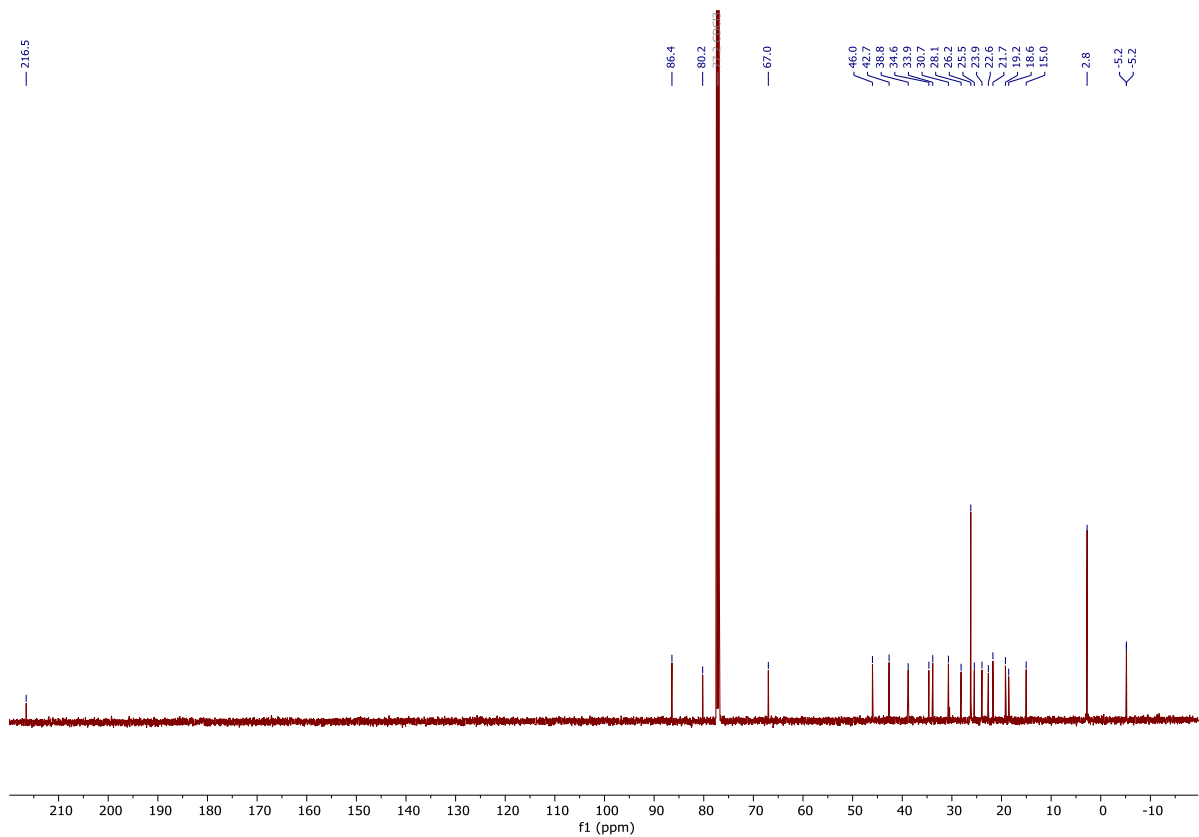


^1H NMR (500 MHz, CDCl_3) (4.24)

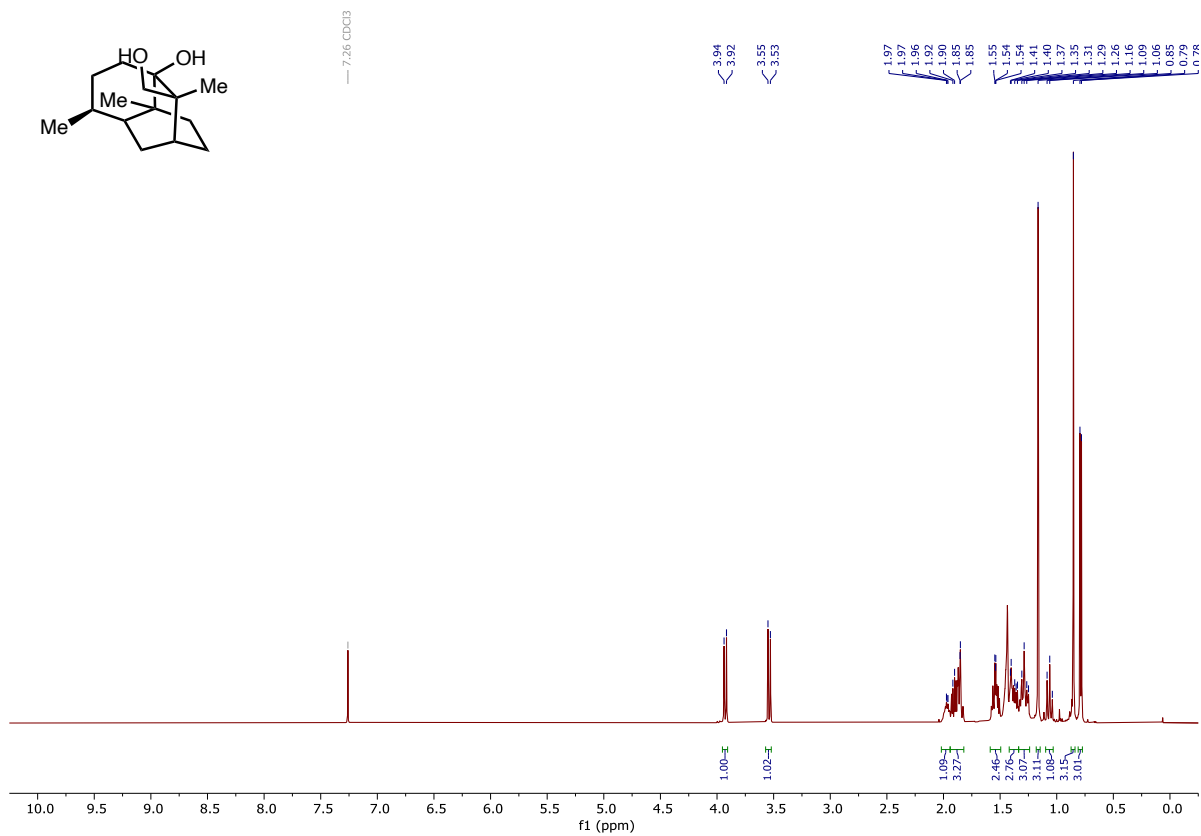


^{13}C NMR (126 MHz, CDCl_3) (4.24)

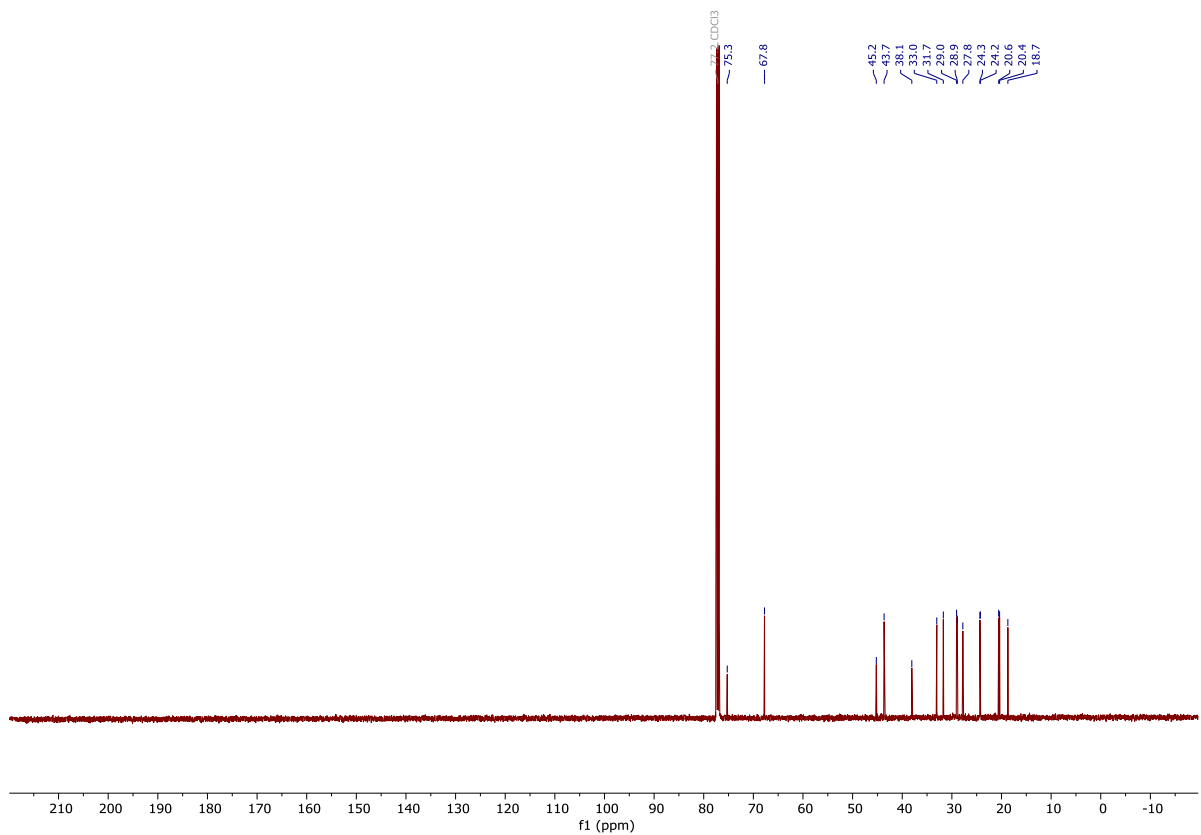


¹H NMR (500 MHz, CDCl₃) (4.25) ^{13}C NMR (126 MHz, CDCl_3) (4.25)

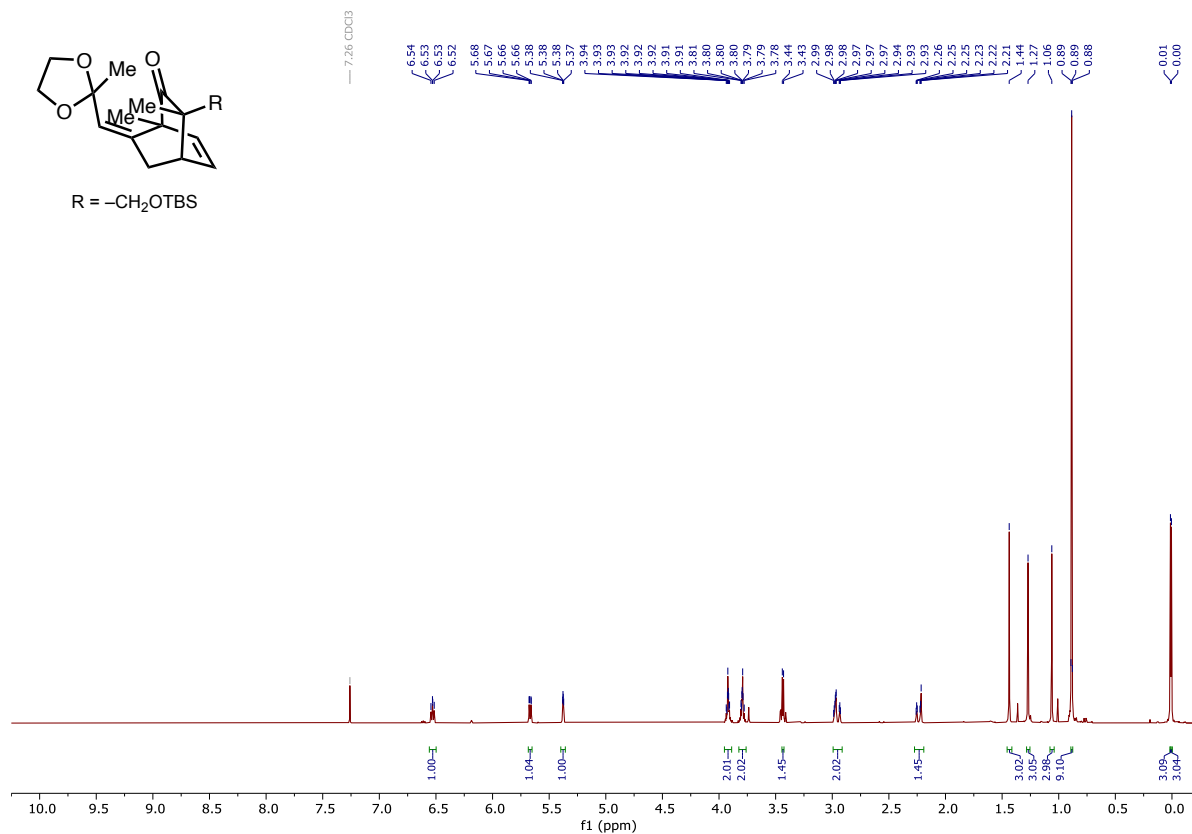
^1H NMR (500 MHz, CDCl_3) (**4.1**)



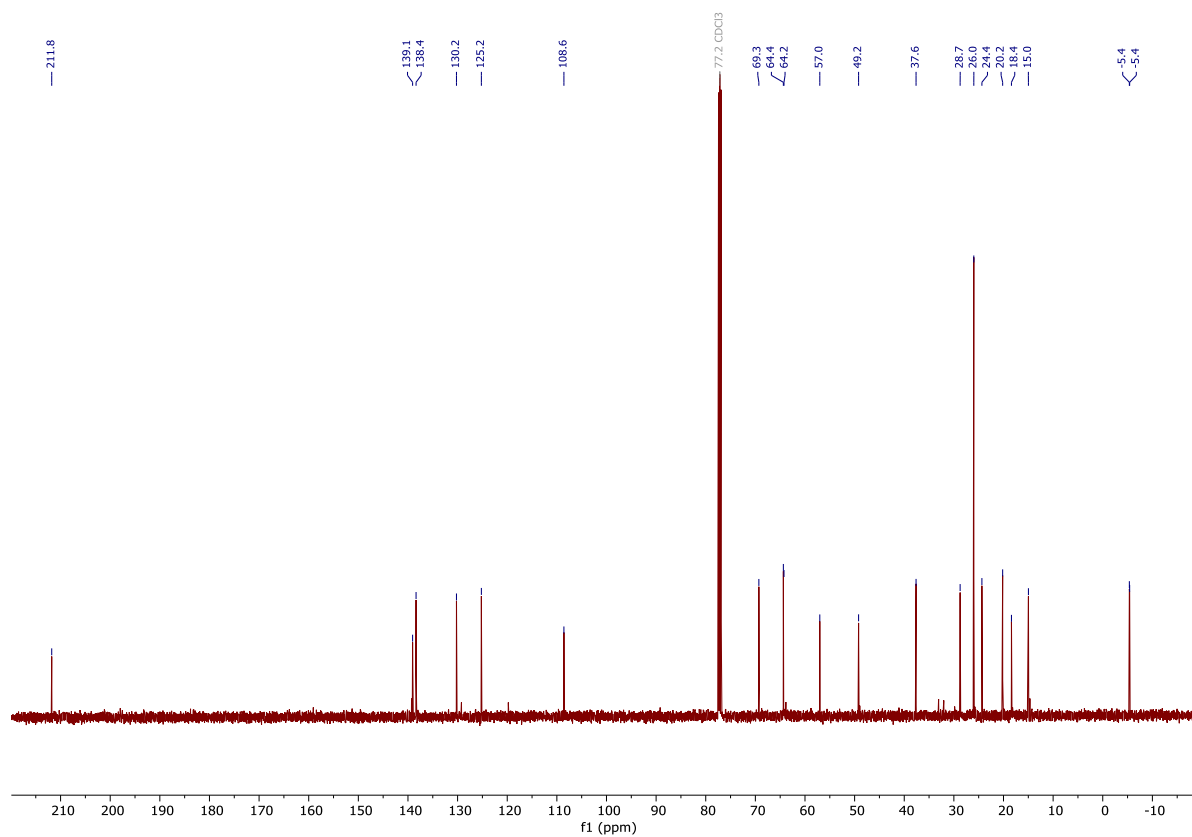
^{13}C NMR (126 MHz, CDCl_3) (**4.1**)



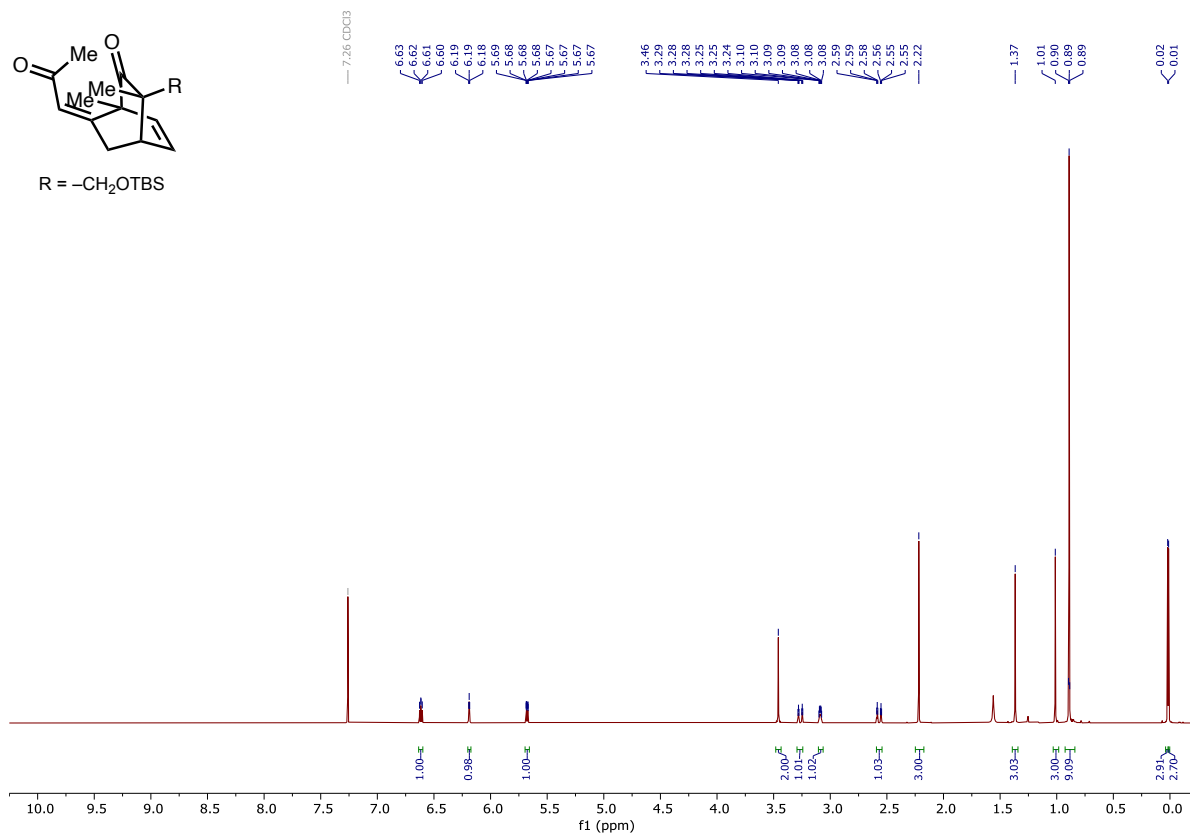
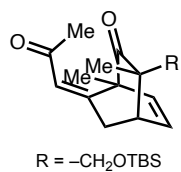
^1H NMR (500 MHz, CDCl_3) (4.28)



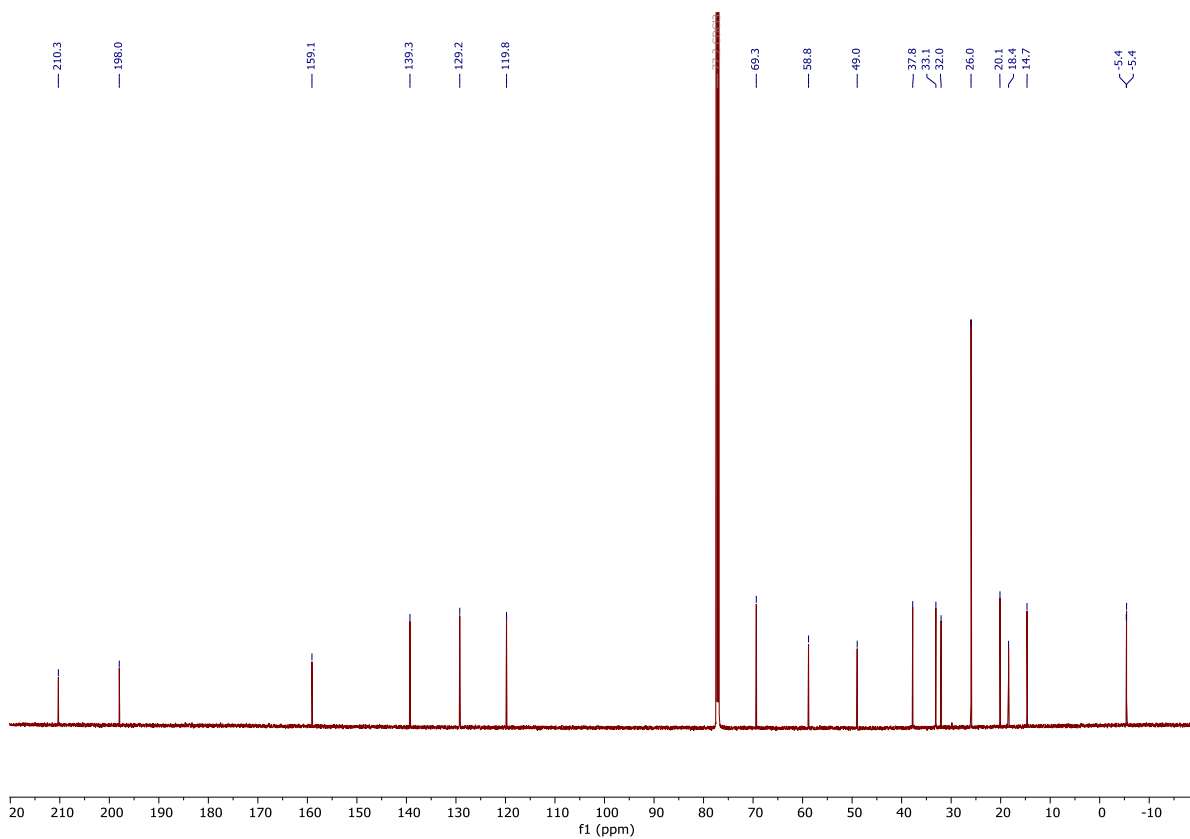
^{13}C NMR (126 MHz, CDCl_3) (4.28)



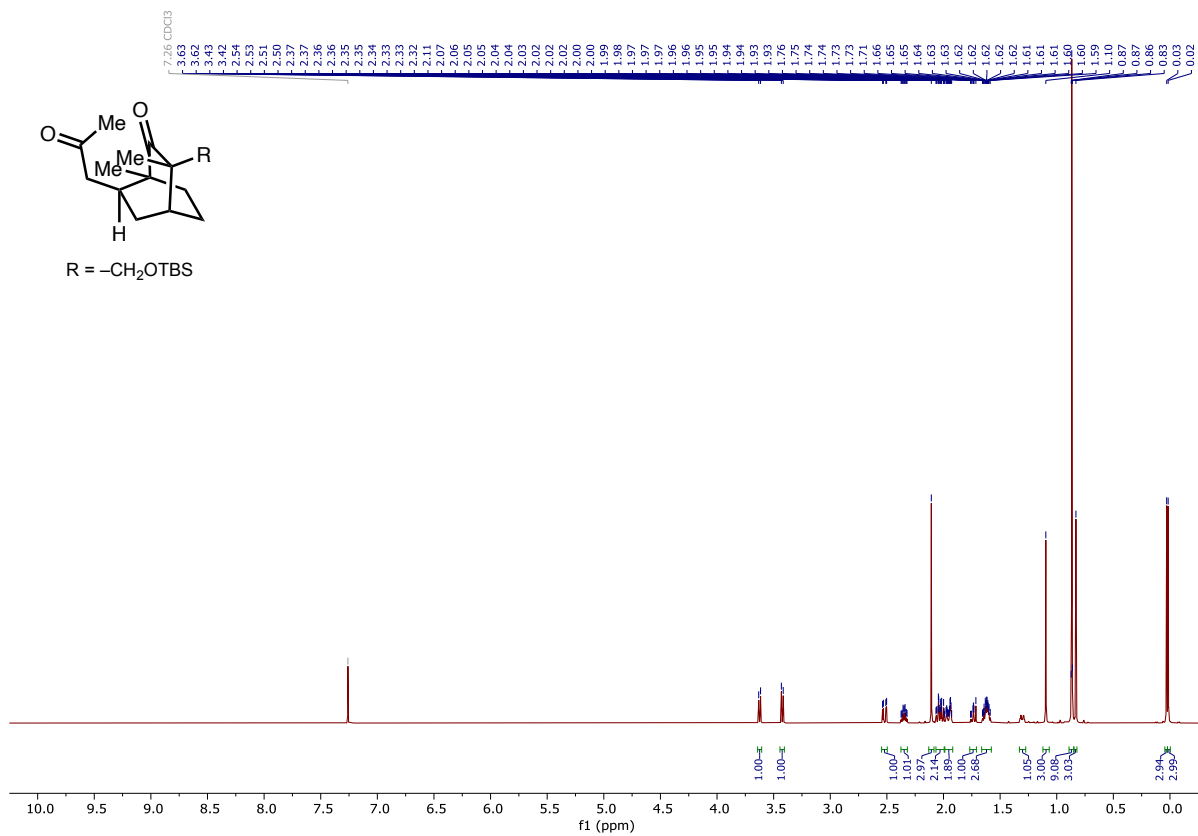
^1H NMR (600 MHz, CDCl_3) (**S1**)



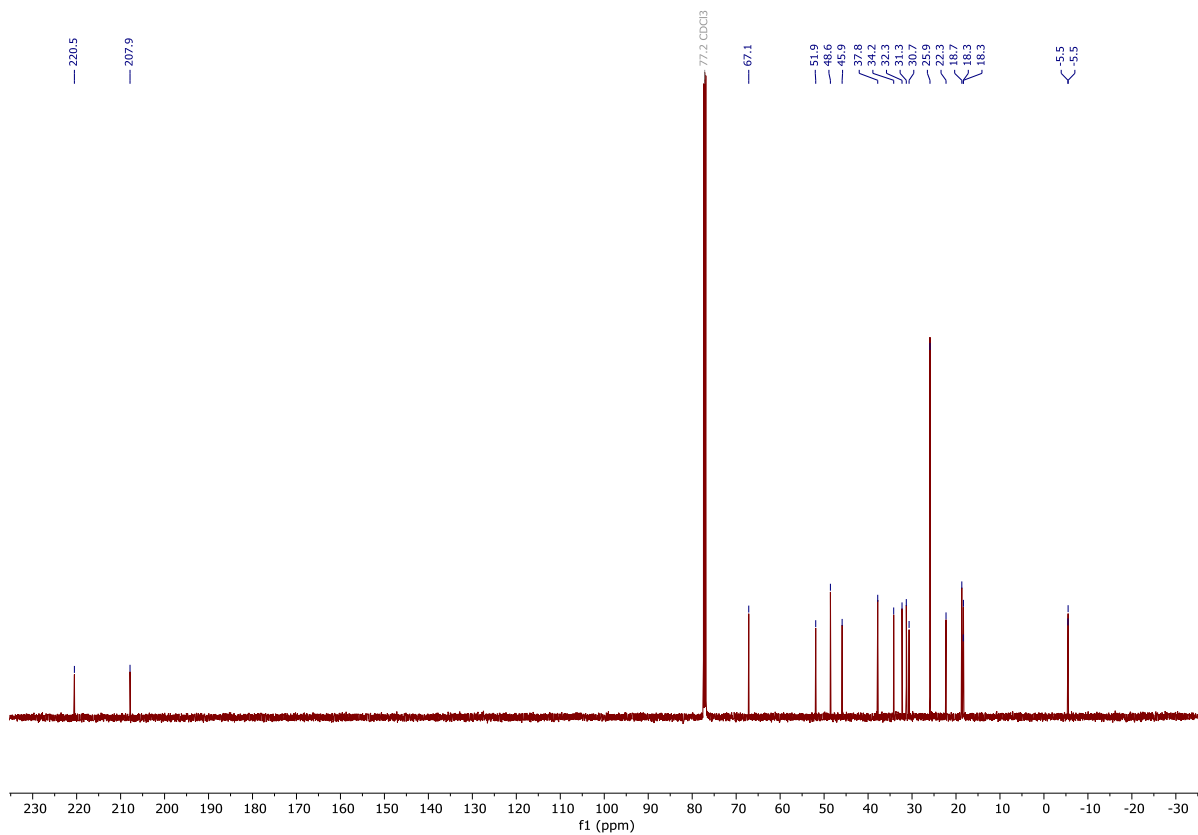
^{13}C NMR (150 MHz, CDCl_3) (**S1**)



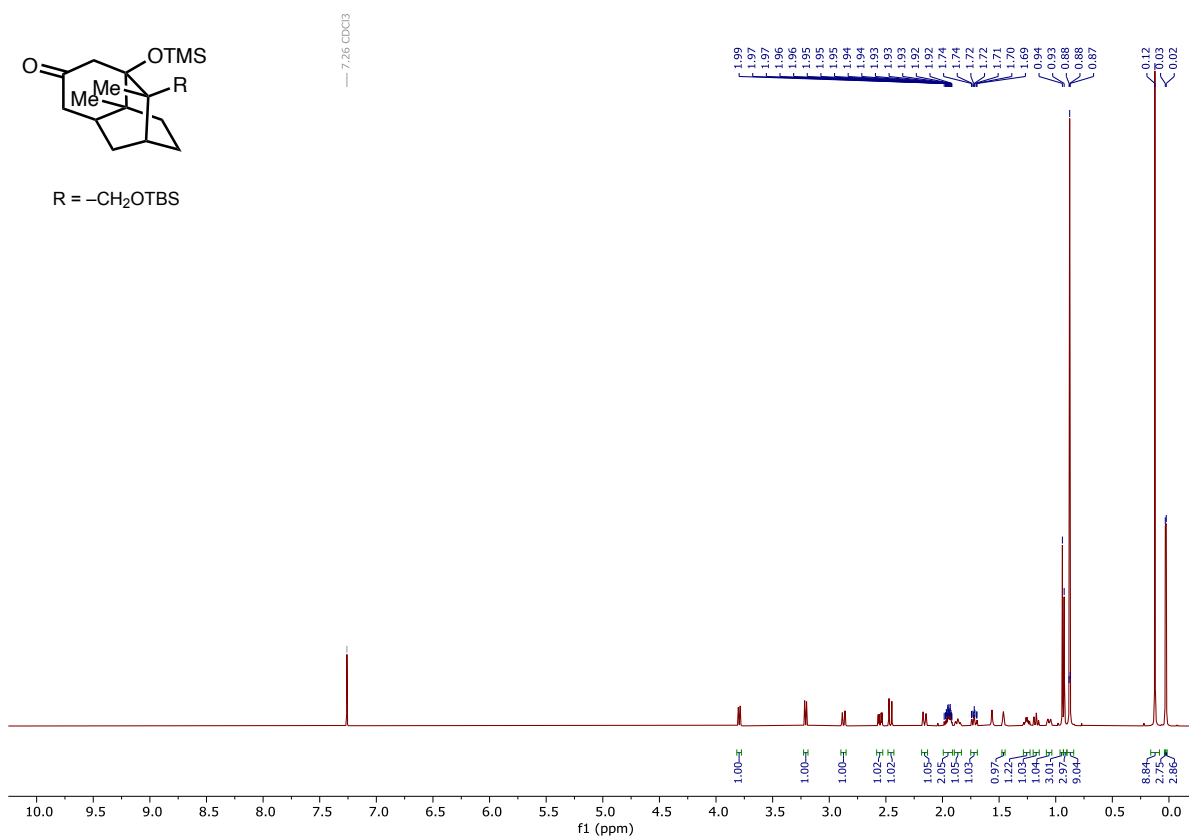
^1H NMR (600 MHz, CDCl_3) (S2)



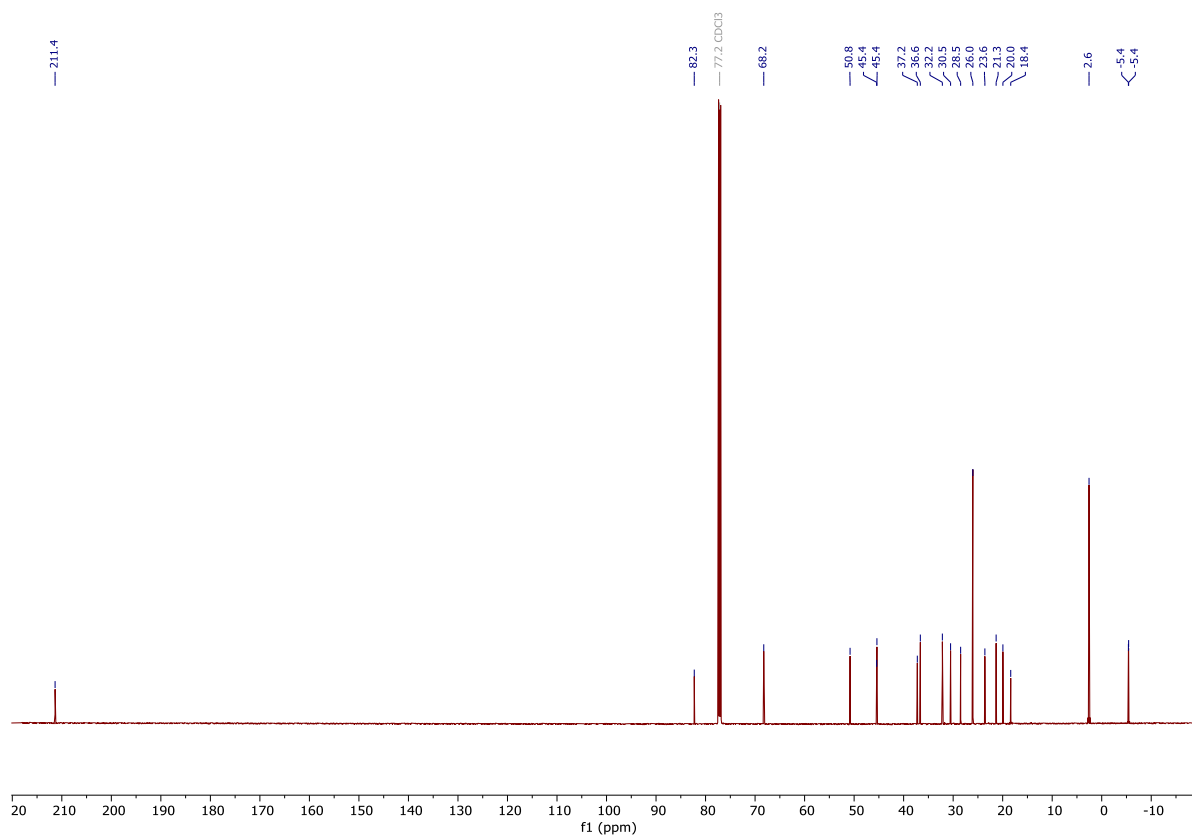
^{13}C NMR (150 MHz, CDCl_3) (S2)

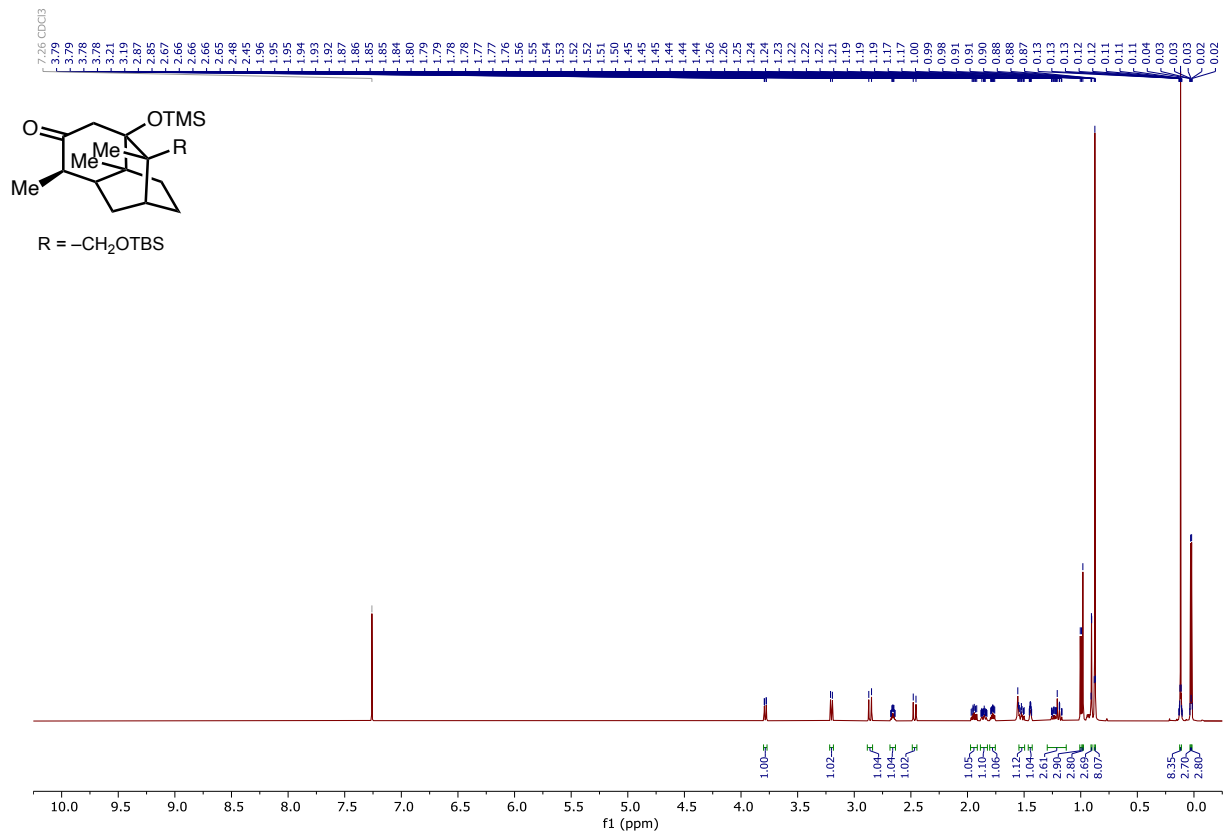
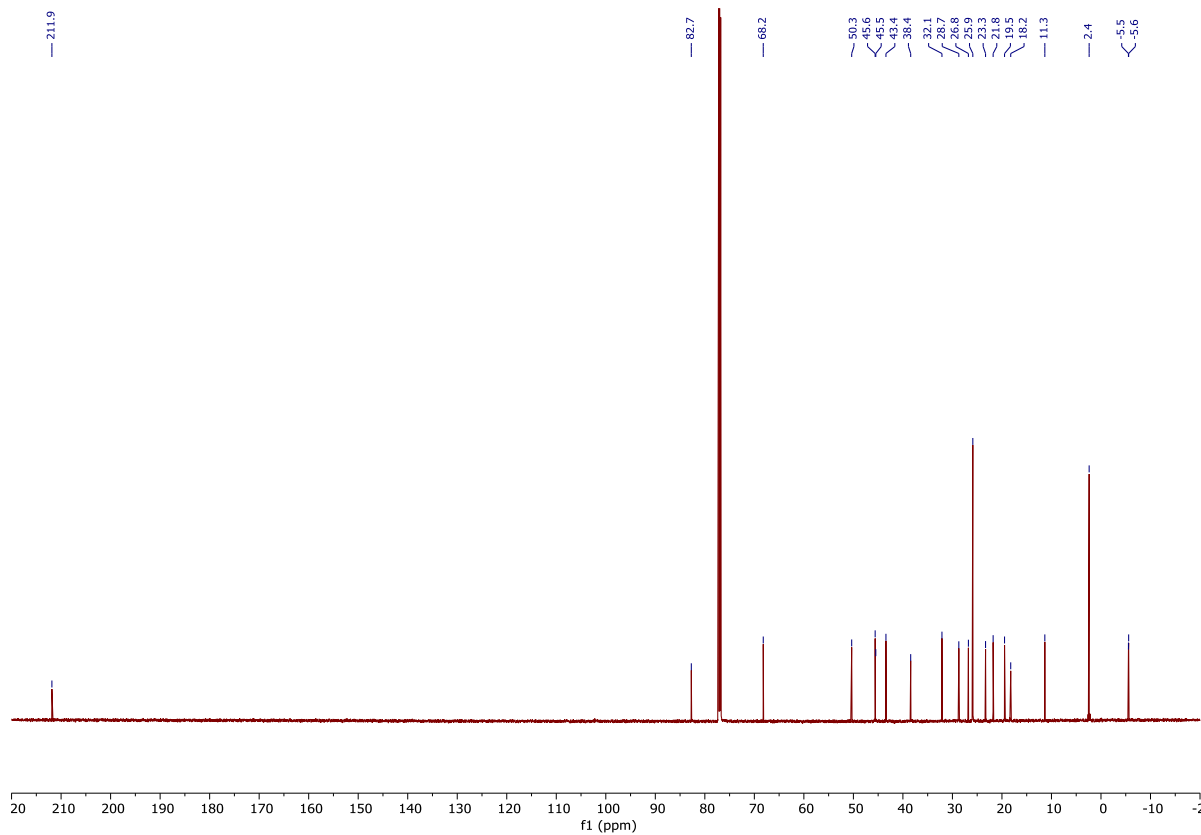


^1H NMR (600 MHz, CDCl_3) (**S3**)

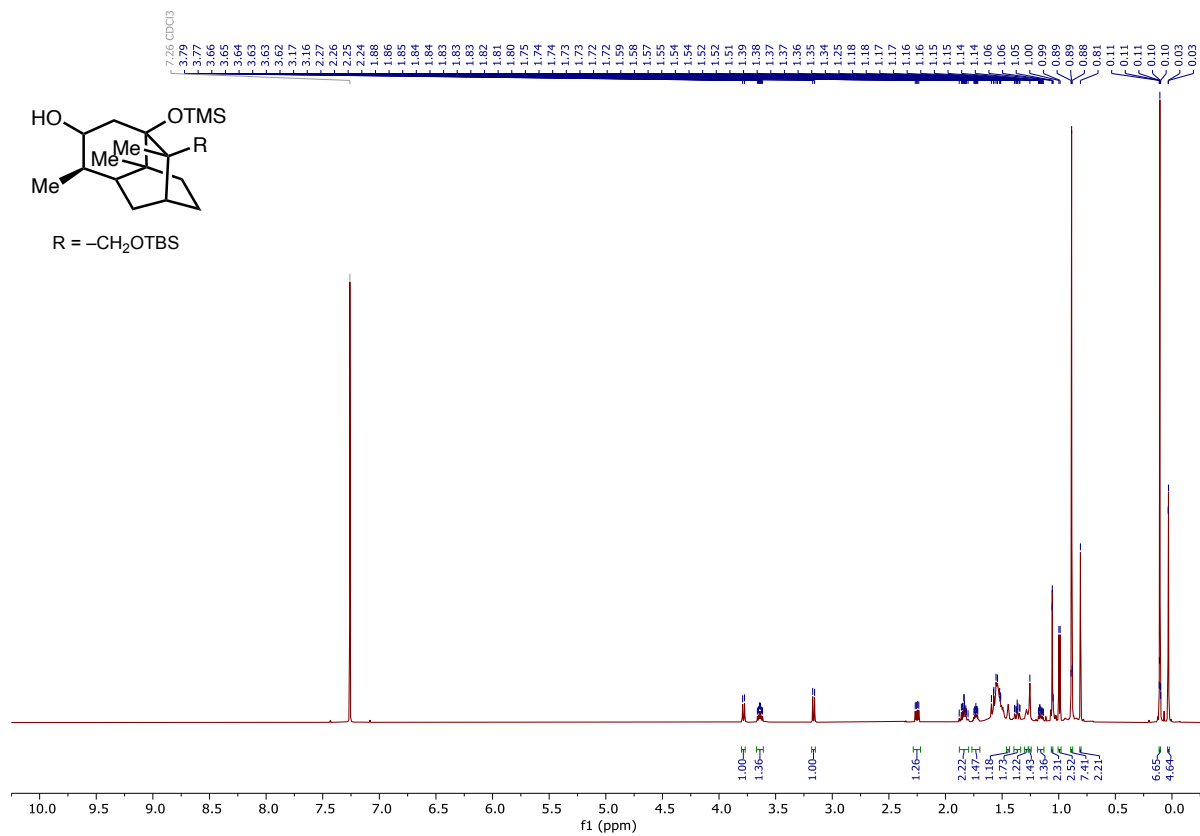


^{13}C NMR (150 MHz, CDCl_3) (**S3**)

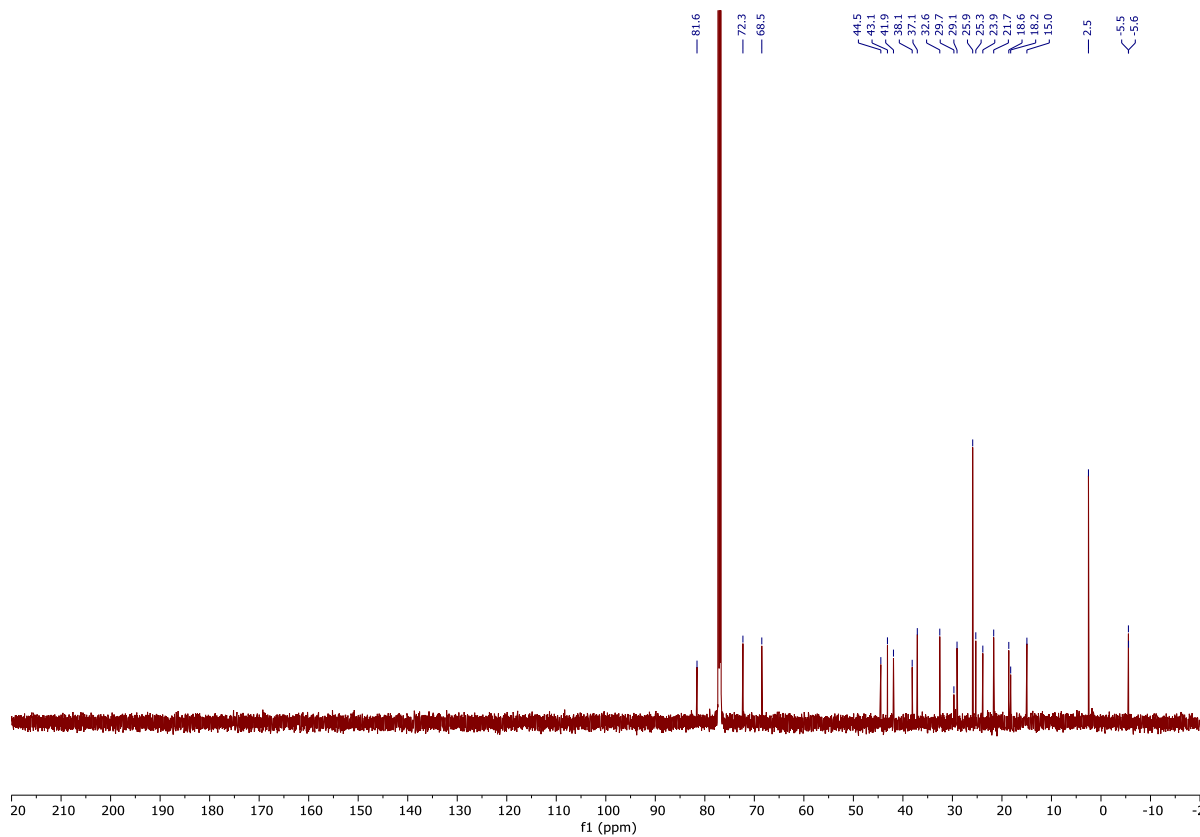


¹H NMR (600 MHz, CDCl₃) (**S4**) ^{13}C NMR (150 MHz, CDCl_3) (**S4**)

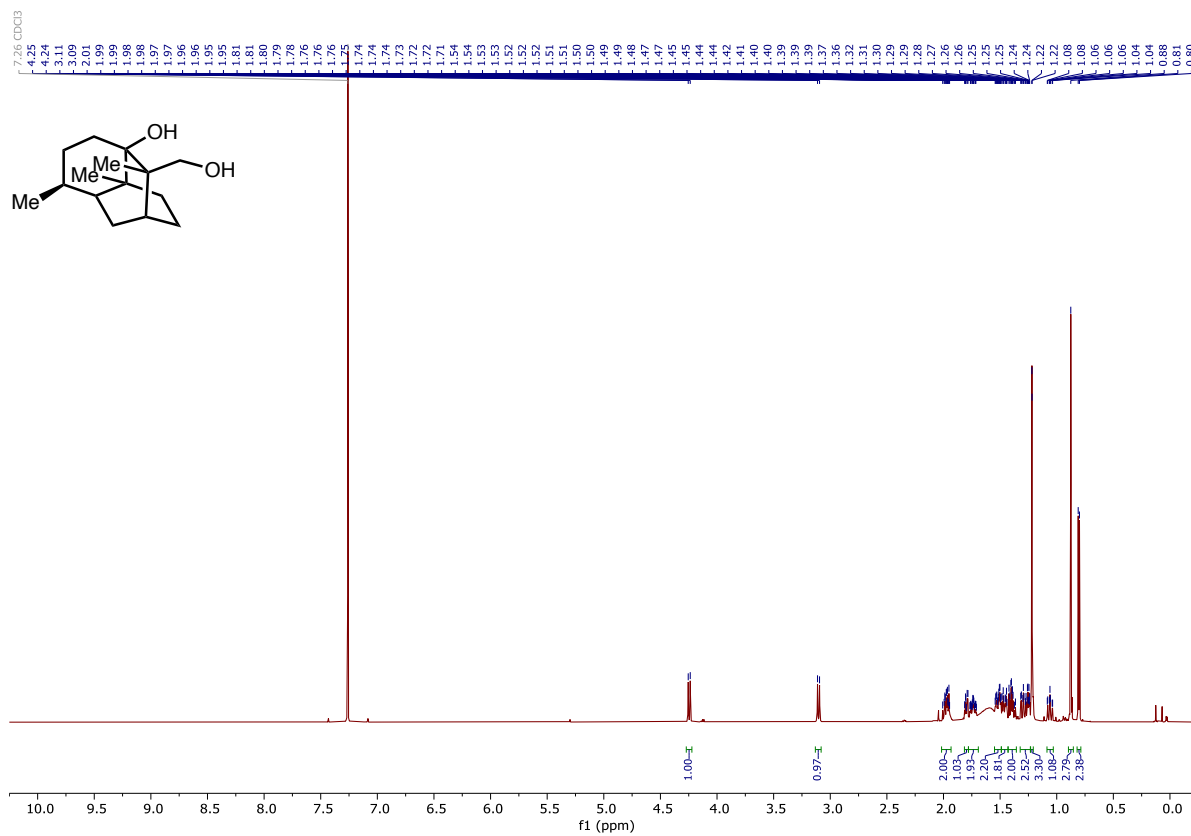
^1H NMR (600 MHz, CDCl_3) (**S5**)



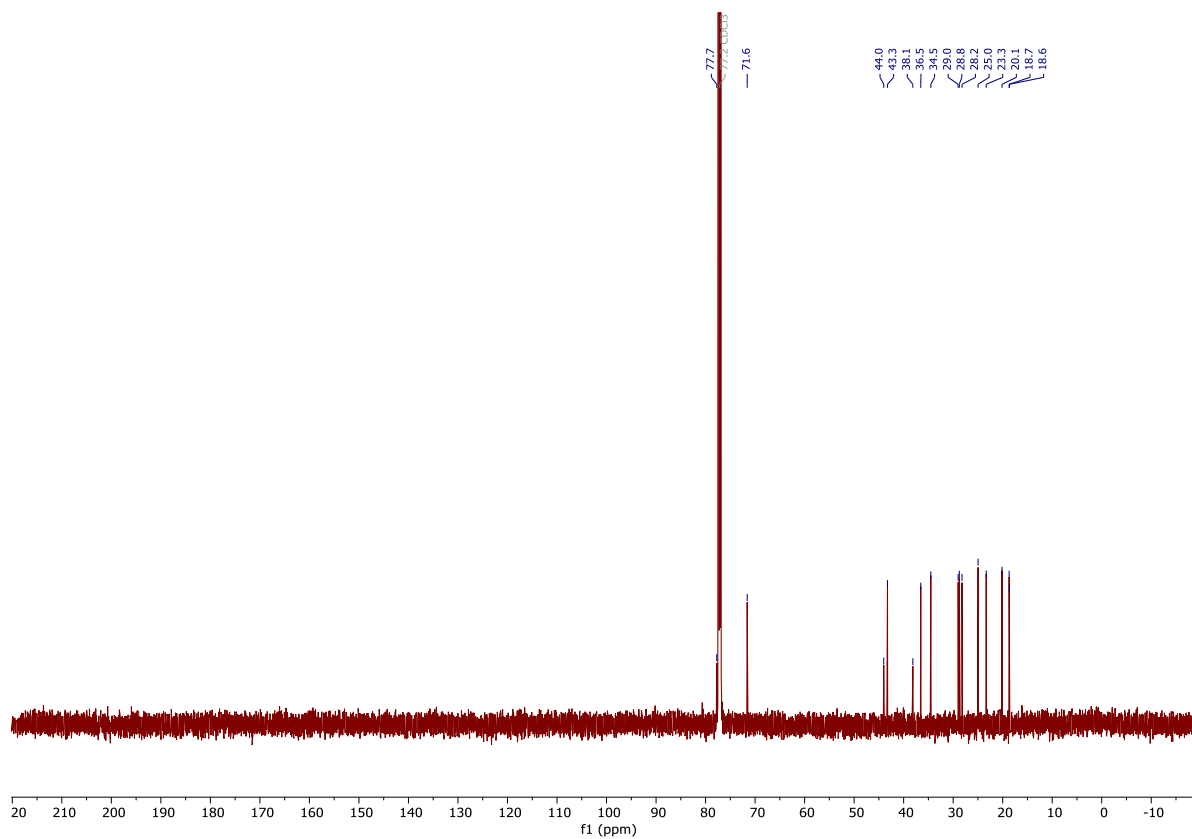
^{13}C NMR (150 MHz, CDCl_3) (**S5**)



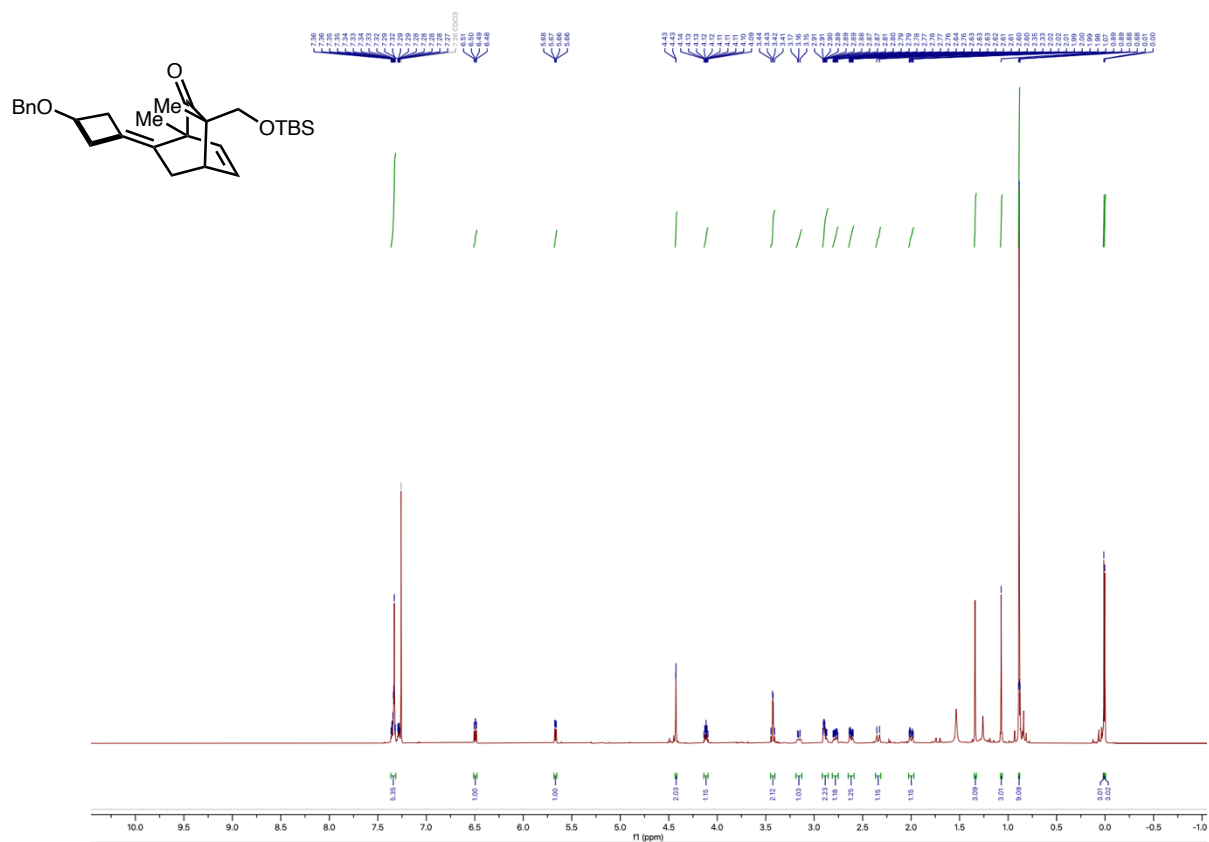
^1H NMR (600 MHz, CDCl_3) (4.29)



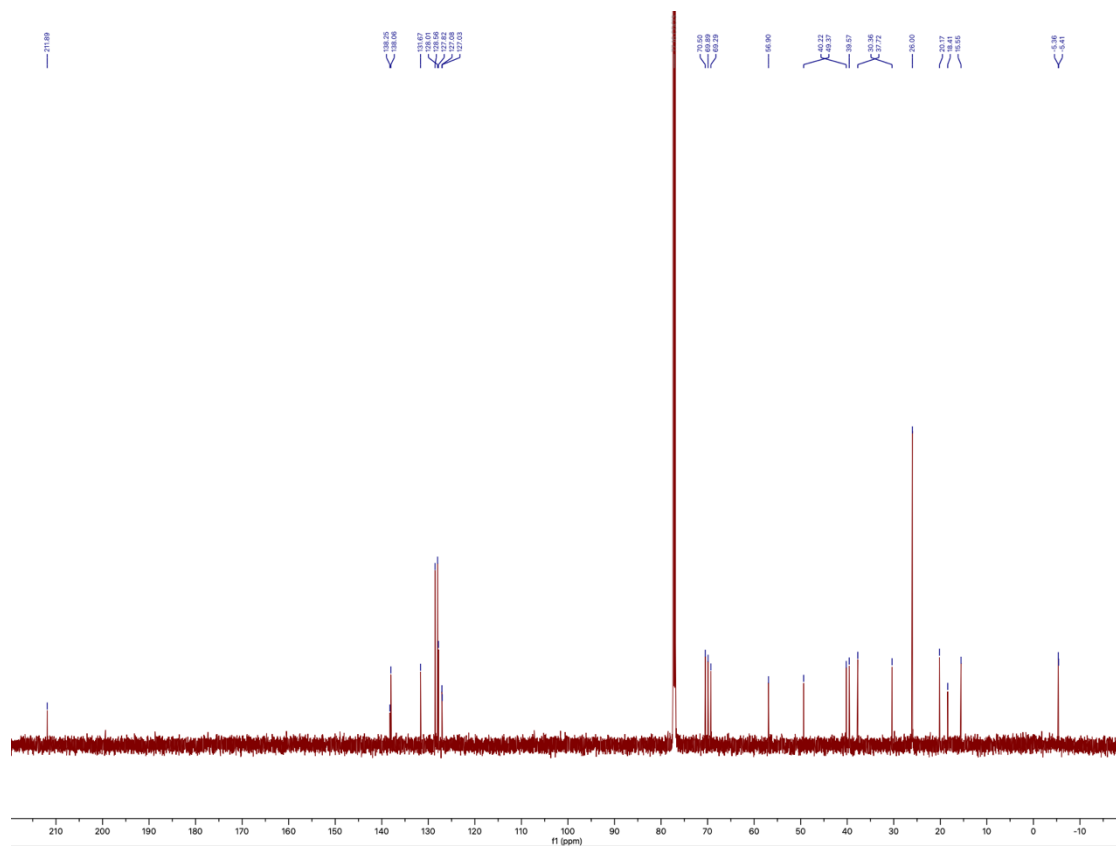
^{13}C NMR (150 MHz, CDCl_3) (4.29)



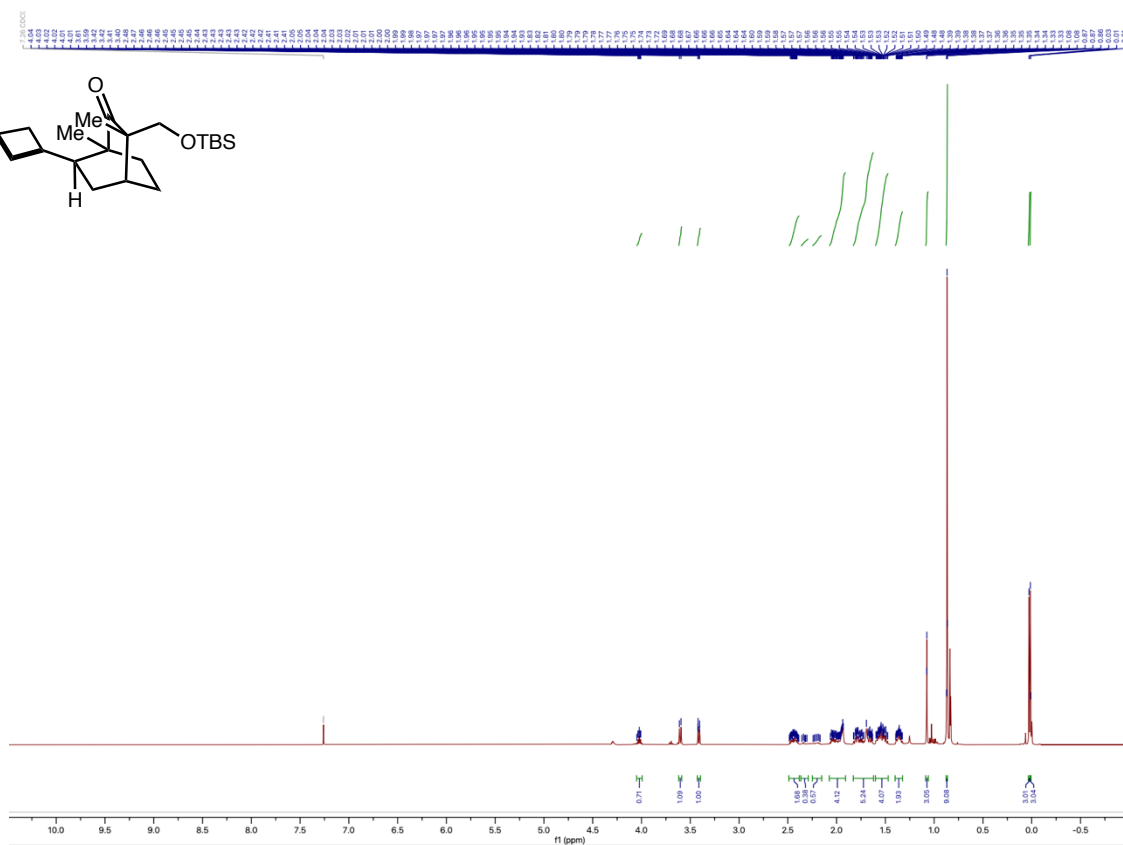
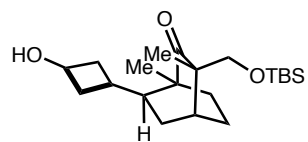
^1H NMR (600 MHz, CDCl_3) (**4.44**)



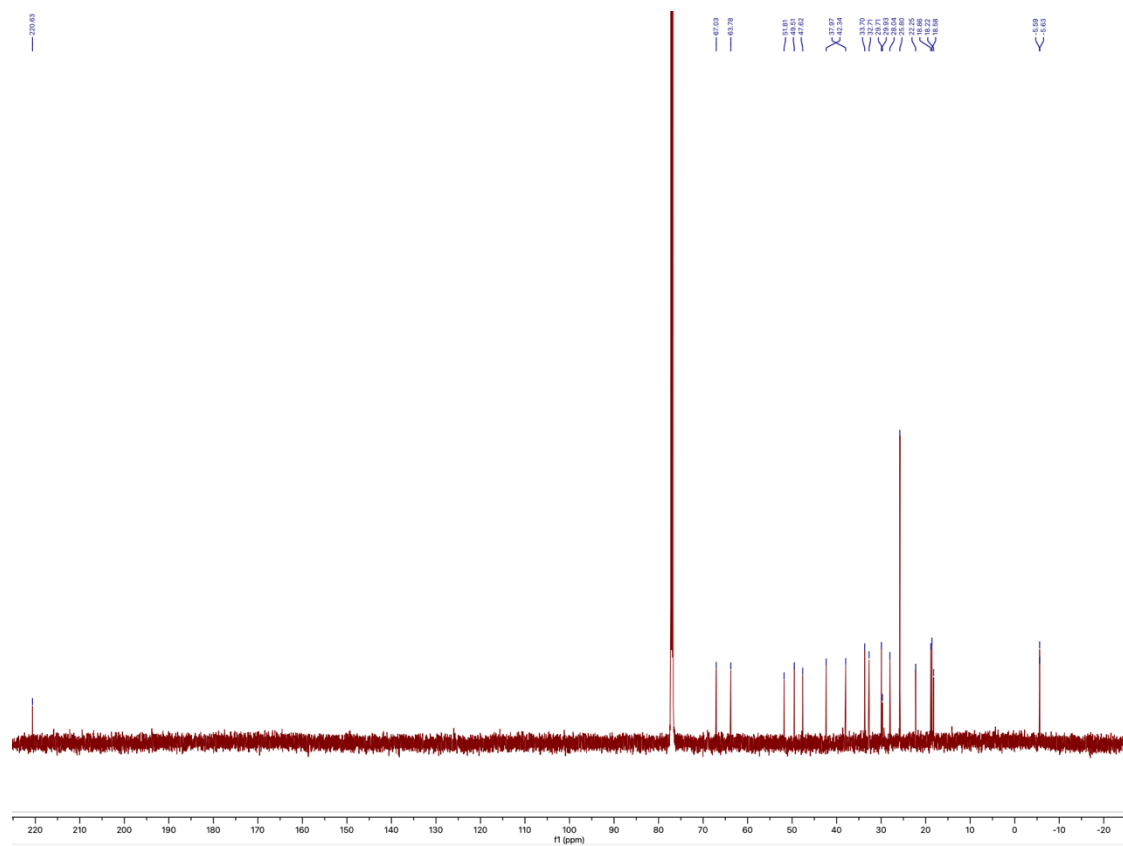
^{13}C NMR (151 MHz, CDCl_3) (**4.44**)

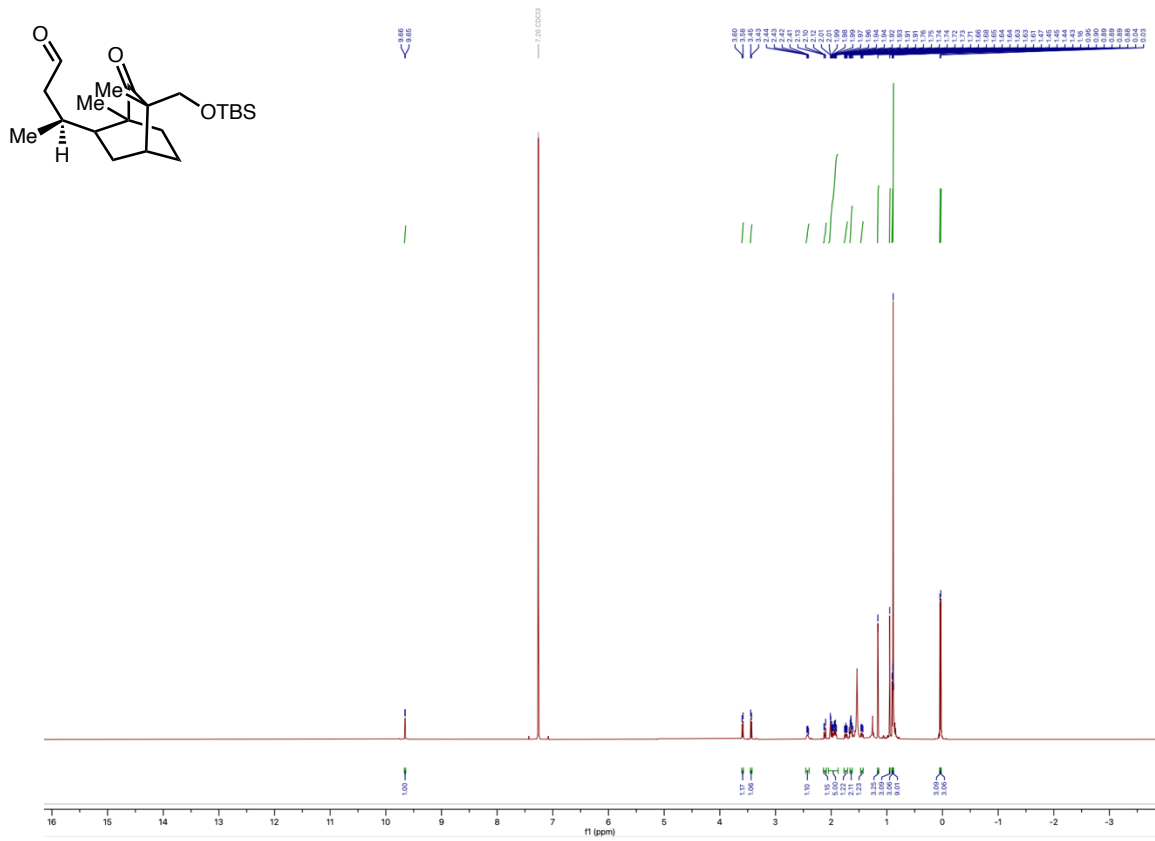
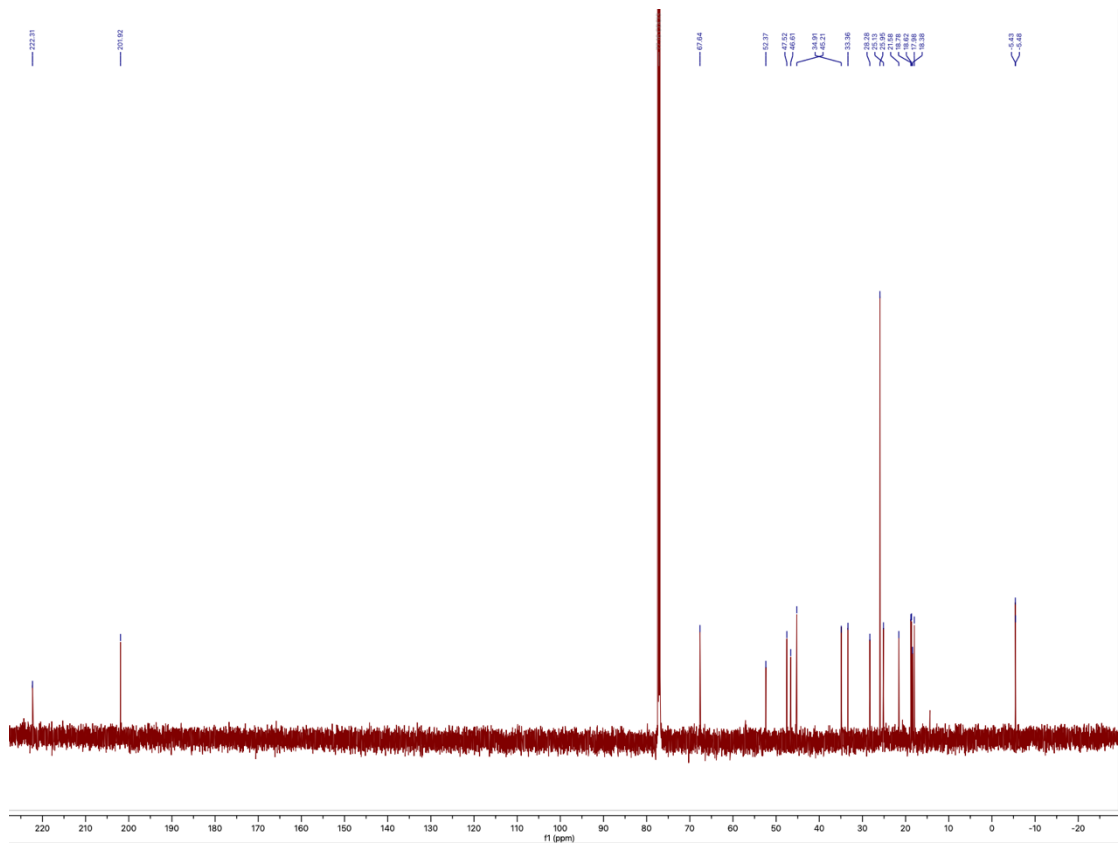


^1H NMR (600 MHz, CDCl_3) (**4.45**)

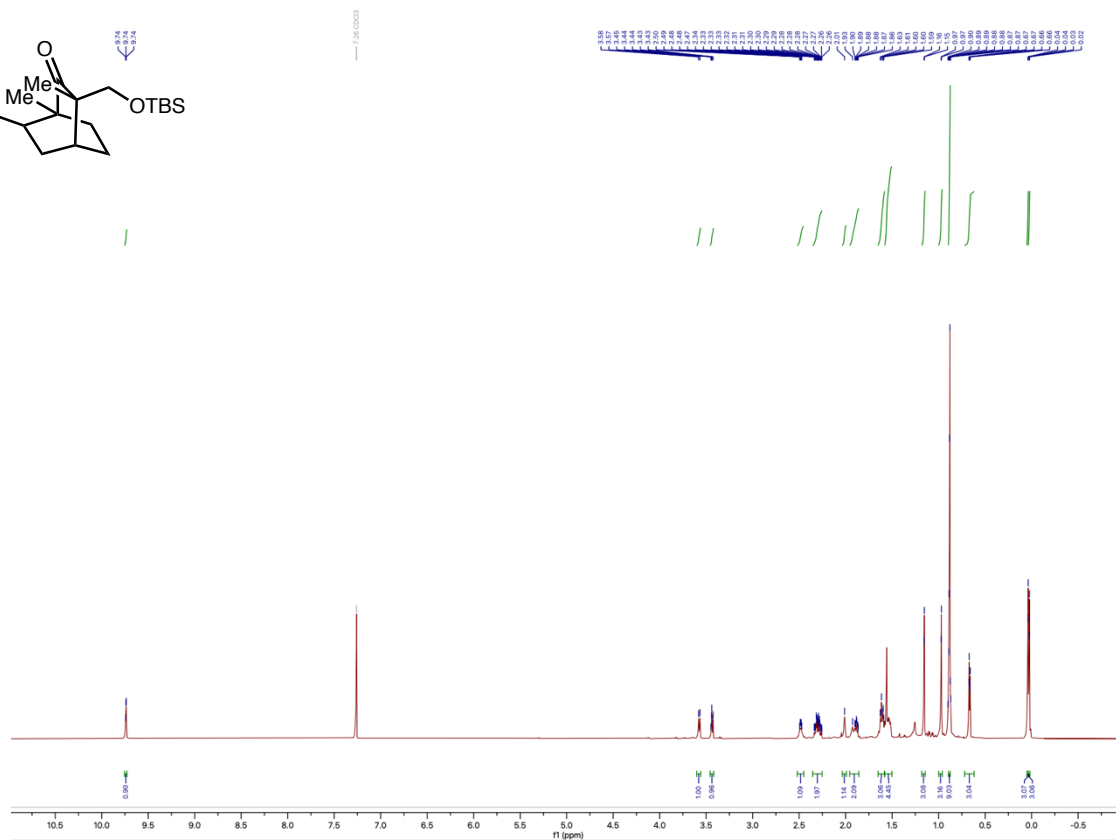
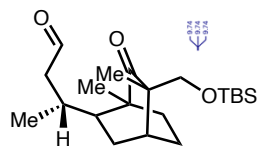


^{13}C NMR (151 MHz, CDCl_3) (**4.45**)

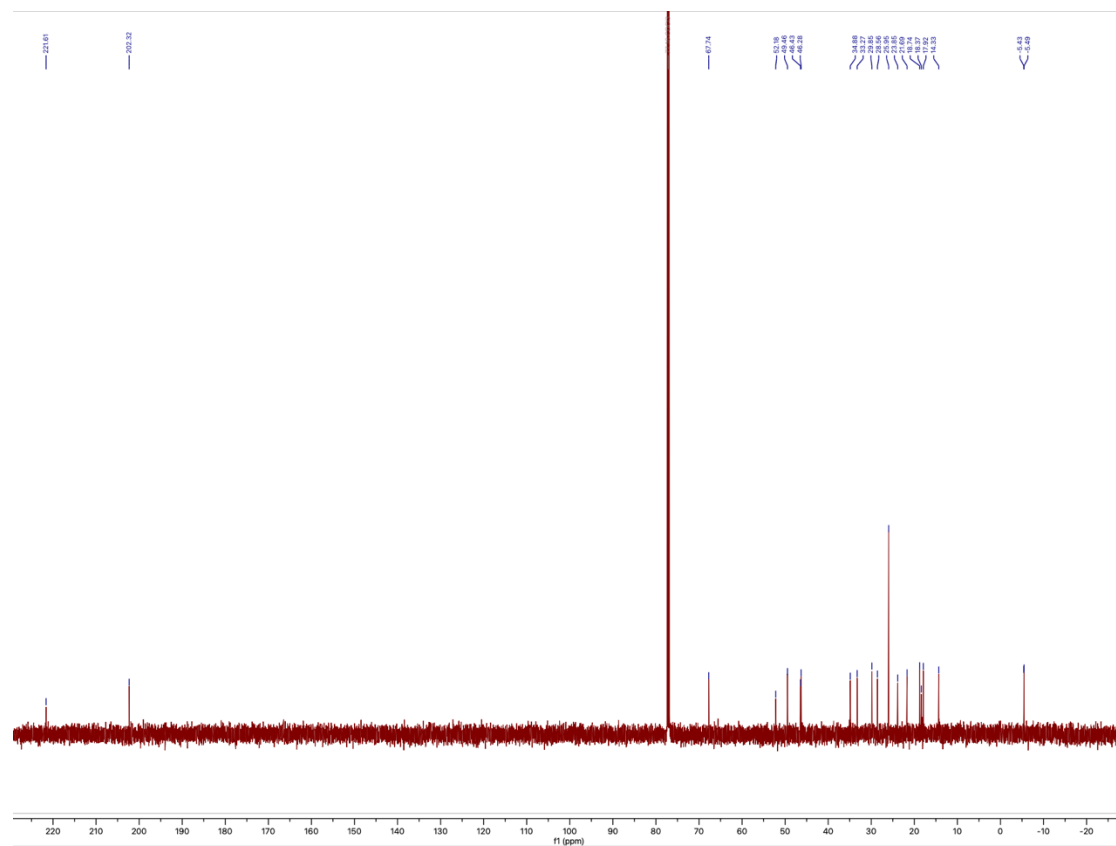


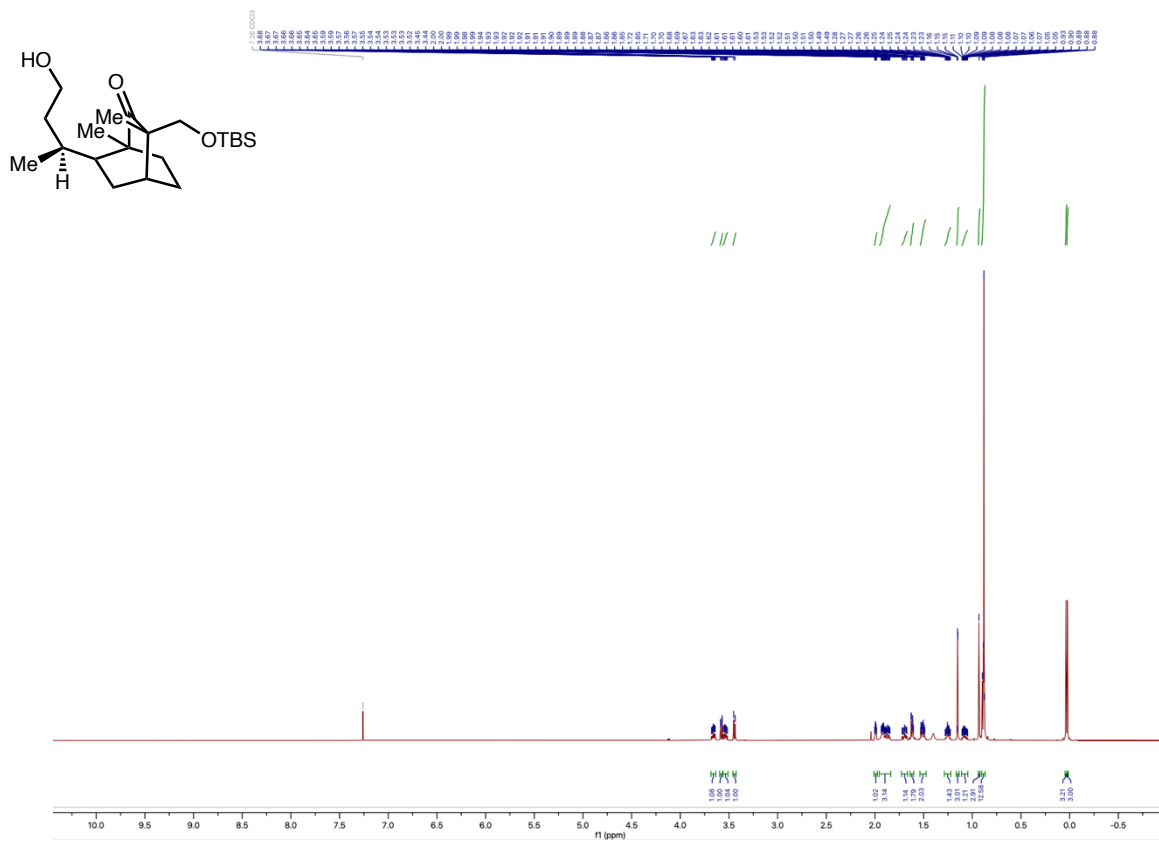
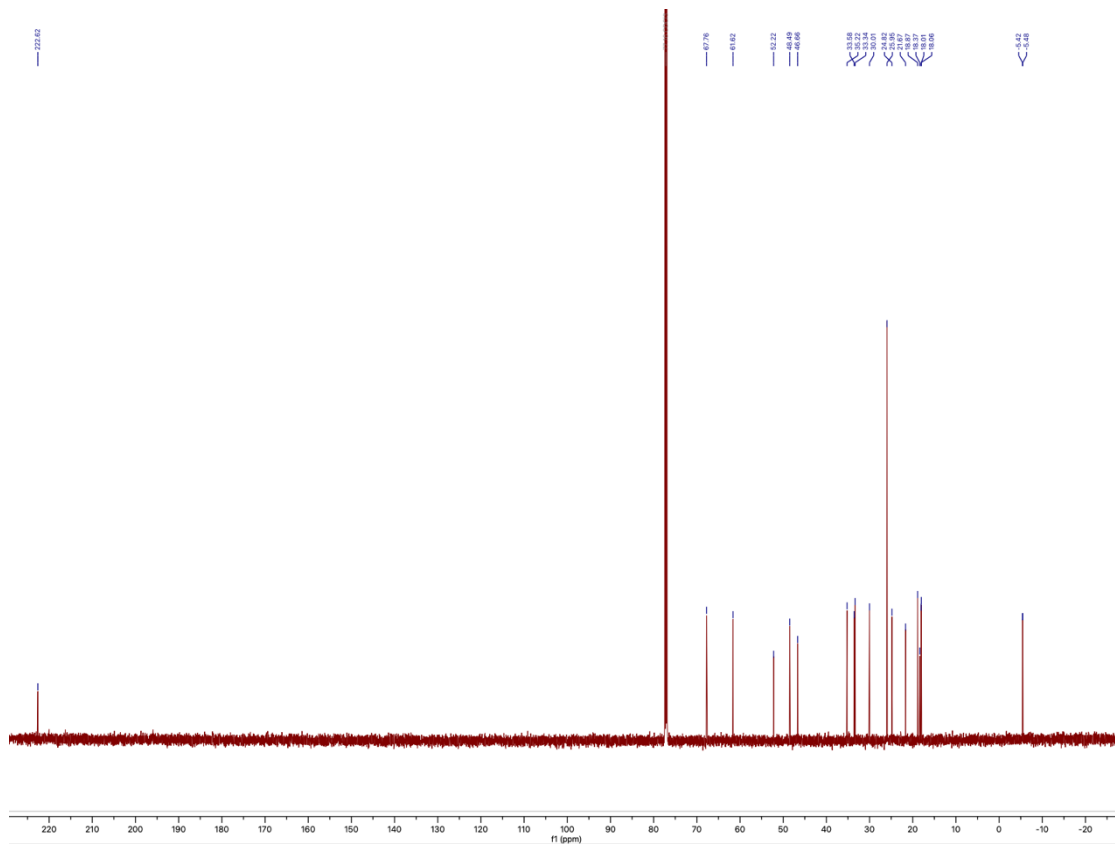
¹H NMR (600 MHz, CDCl₃) (**S6**) ^{13}C NMR (151 MHz, CDCl_3) (**S6**)

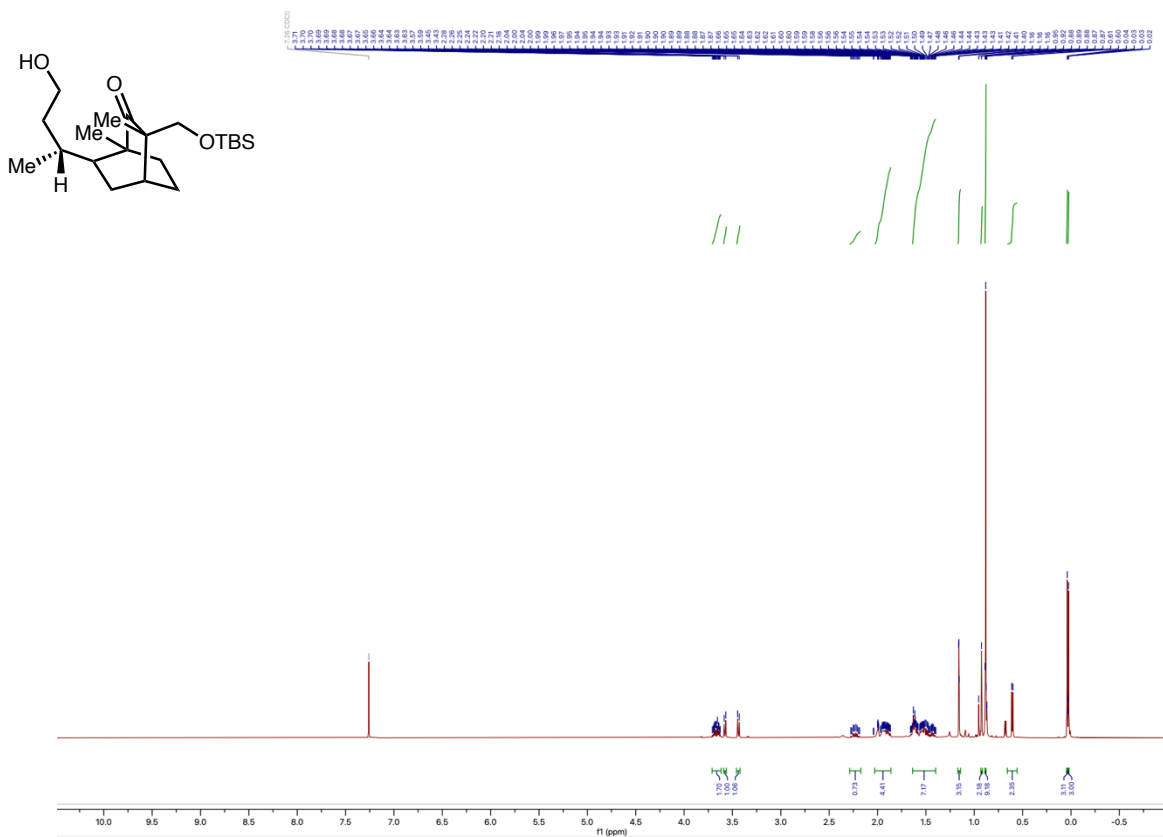
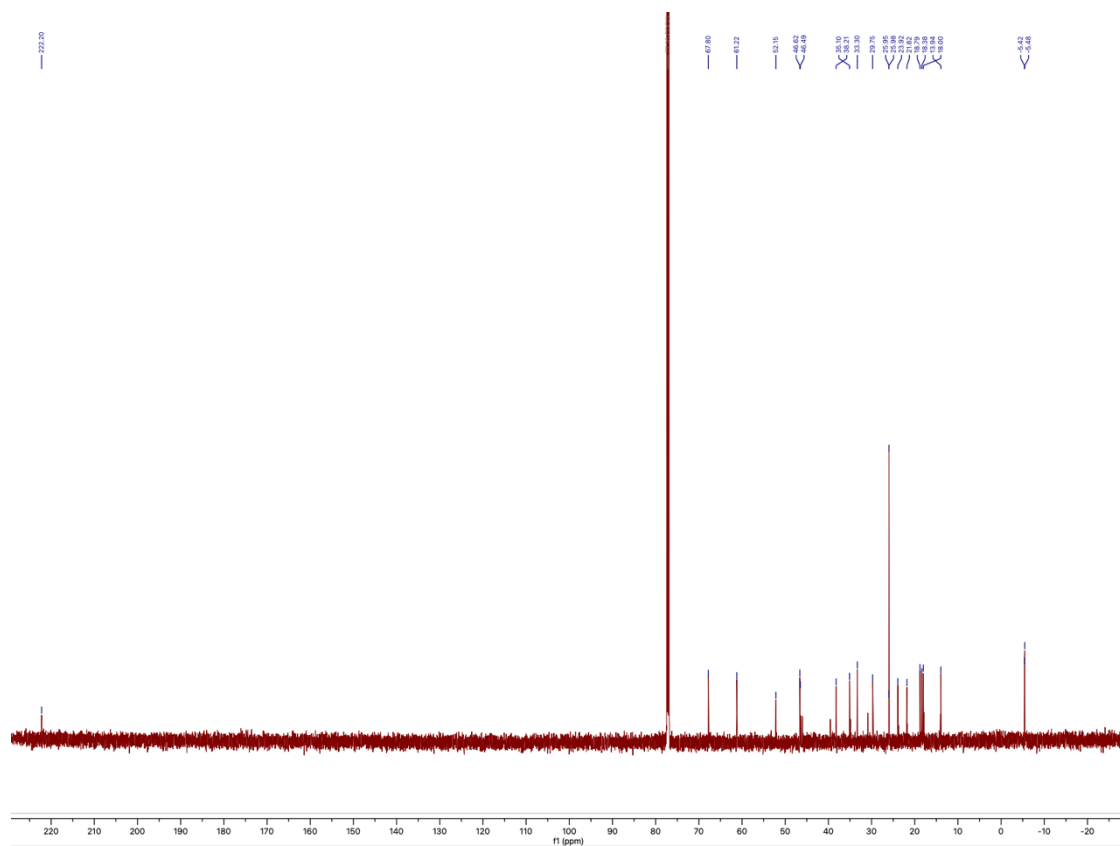
^1H NMR (700 MHz, CDCl_3) (**S7**)



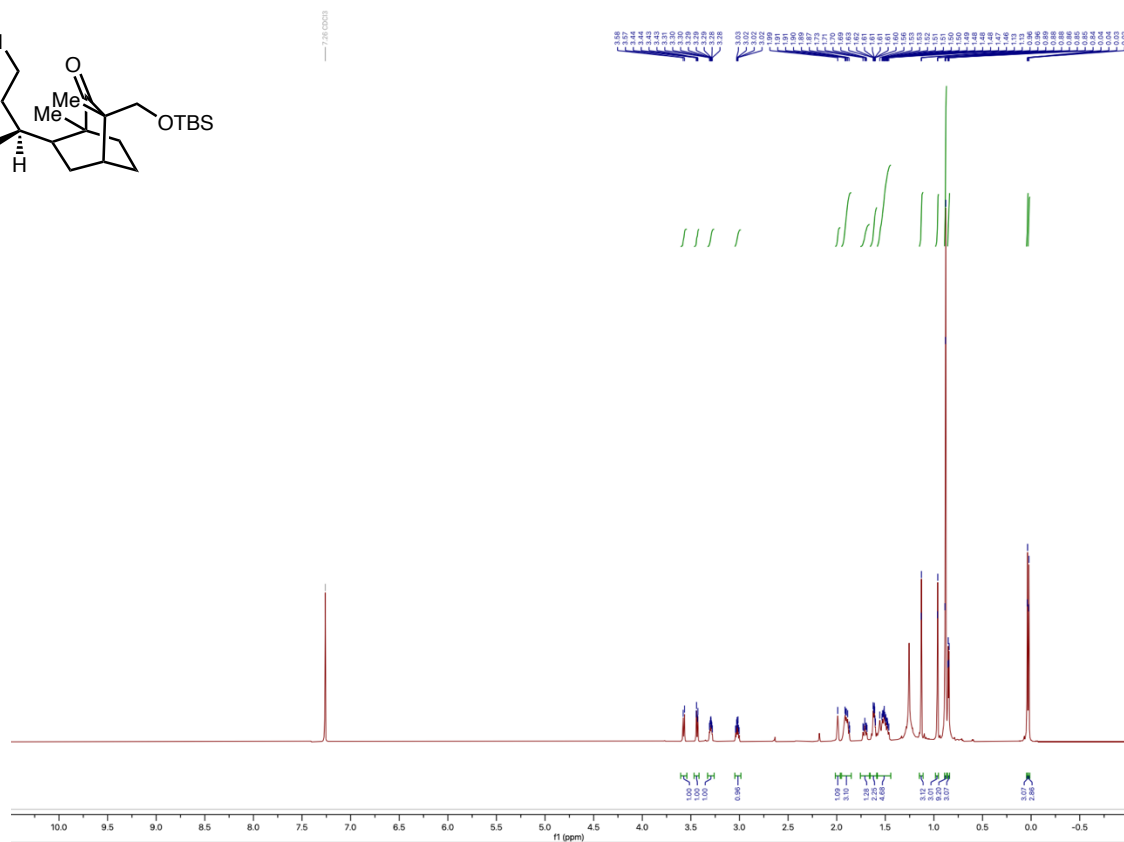
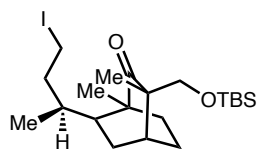
^{13}C NMR (151 MHz, CDCl_3) (**S7**)



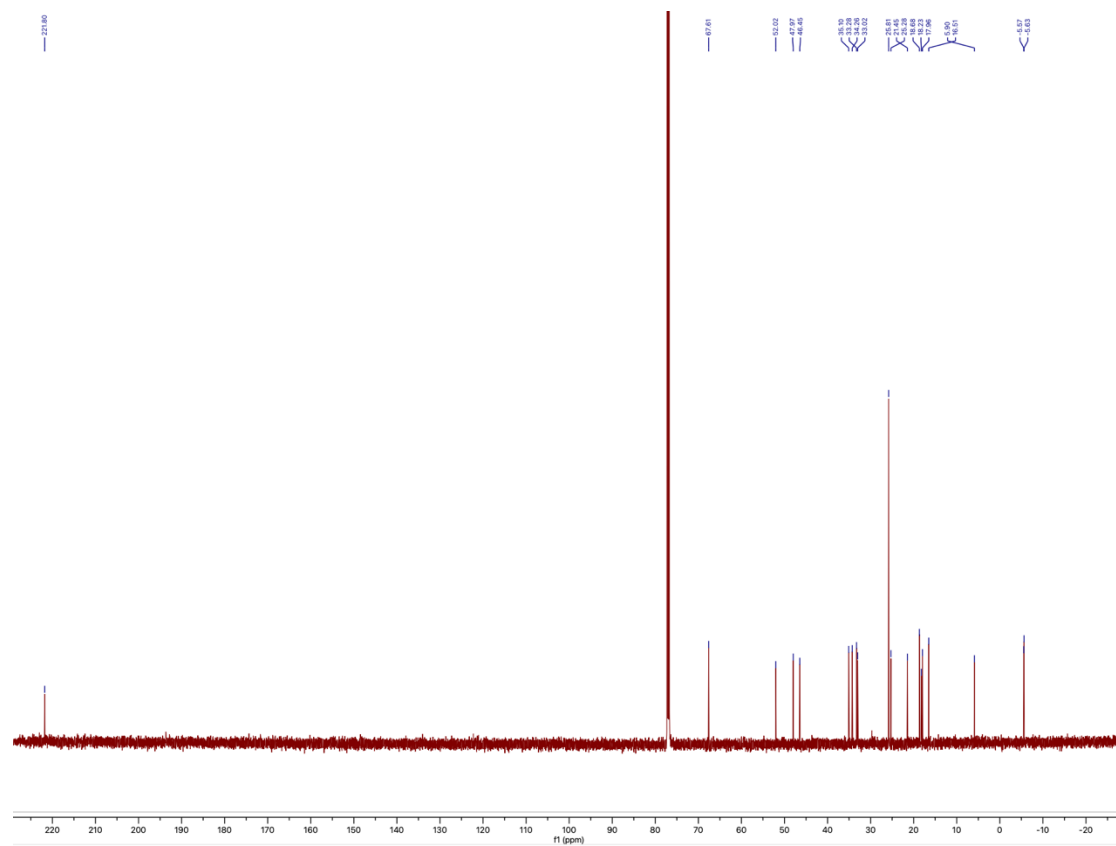
¹H NMR (600 MHz, CDCl₃) (**4.46a**) ^{13}C NMR (151 MHz, CDCl_3) (**4.46a**)

¹H NMR (600 MHz, CDCl₃) (4.46b) ^{13}C NMR (151 MHz, CDCl_3) (**4.46b**)

^1H NMR (600 MHz, CDCl_3) (**4.47a**)



^{13}C NMR (151 MHz, CDCl_3) (**4.47a**)



Chapter 5. Background on Xenicane Diterpenoid Natural Product Family

5.1 Introduction

Natural products of marine origin occupy a distinct position among bioactive molecules of pharmaceutical interest due to their remarkable structural and biological diversity. Organisms such as Archaea, Bacteria, Protozoa, Chromista, and Fungi, as well as many Algae and lower animals from the phyla Porifera and Cnidaria, often lack sufficiently protective membranes or cell walls.¹ Instead, they rely on the release of secondary metabolites, such as toxins, as a chemical defense mechanism.^{2,3} These substances may be synthesized by the organism itself, produced by associated symbionts, or acquired from other organisms.⁴ Marine secondary metabolites exhibit a wide range of biological activities, including cytotoxic, antiproliferative, antibacterial, antifungal, and algicidal effects.⁵

The xenicane diterpenoids, also known as *Xenia* diterpenoids, constitute a large class of predominantly bicyclic marine diterpenoids characterized by a cyclononane ring as a shared structural feature.⁶ Notably, the term “*Xenia* diterpenoids” refers to compounds grouped by their species of origin rather than by strict structural features.⁵ As a result, this class includes the structurally diverse xenicanes (**5.1**), xeniaphyllanes (**5.2**), and germacrenes such as germacrene A (**5.3**), among others (Figure 5.1).

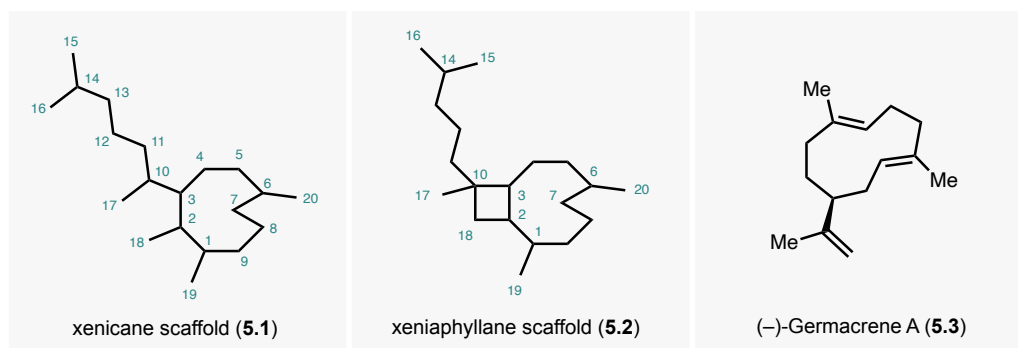


Figure 5.1. Structural scaffolds of xenicane diterpenoids.

Since the isolation of xenicin (**5.4**) in 1977 by Schmitz, van der Helm and co-workers, the first xenicane diterpenoid identified from the soft coral *Xenia elongata*, more than a hundred structurally diverse members of this family have been discovered, displaying a wide range of oxidation patterns and biological activities (Figure 5.2).⁷ In most xenicane diterpenoids, carbon atoms C17 and C18 are often linked by an oxa-bridge, such as a pyran or lactone, resulting predominantly in polycyclic structures. Structurally, the xenicane family comprises two major subclasses based on the nature of the additional six-membered ring: xenicin-type and xeniolide-type. The former features a dihydropyran moiety possessing a *trans*-fused ring junction to the nine-membered ring (e.g., xenicin (**5.4**)). In contrast, xeniolides **5.5** and **5.6** incorporate a δ -lactone ring

in place of the pyranoside moiety, with either C17 or C18 being oxidized to form the ester moiety. Common differences among xenicin-type compounds include the degree of acetylation and hydroxylation, as well as the configuration of the acetyl acetal moiety. Additionally, much of the structural variation within the xenicin and xeniolide subclasses of xenicane diterpenoids arises from the number, position, and geometry of unsaturations in the side chain.⁵

In addition to xenicins and xeniolides, which represent bicyclic xenicane diterpenoids, a few monocyclic examples have also been reported. One such example is dictyodial (**5.7**), which was first isolated in 1979 from *Dictyota crenulate* (Figure 5.2).⁸

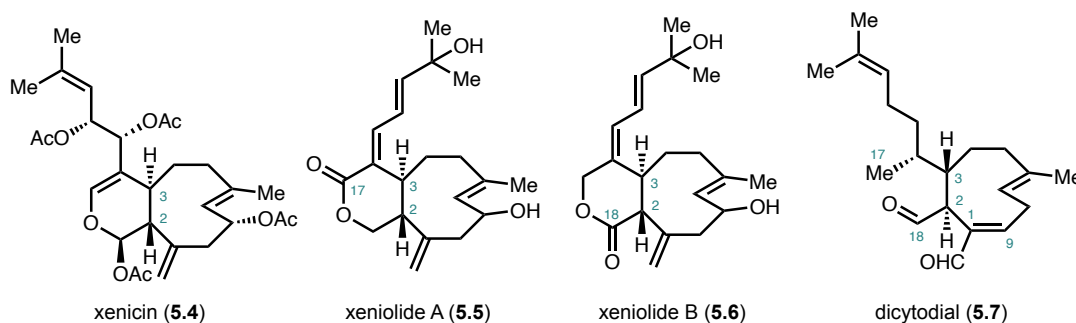


Figure 5.2. Selected examples of xenicane diterpenoid natural products.

Importantly, the absolute configuration of the xenicane skeleton can vary among members of this family depending on the producing organism. Available data from isolated samples indicate that xenicanes isolated from brown algae and soft corals exhibit opposite configurations at the C2 and C3 stereocenters.^{9,10}

Compared with other members of the xenicin subtype families, (+)-crisaxenicin A (**5.8**) exhibits a unique oxidation pattern (Figure 5.3).¹¹ Specifically, the C11 and C20 carbons are oxidized to a ketone and an aldehyde, respectively. Further, while representative xenicane diterpenoids typically feature a *trans*-cyclononene framework with a C6–C7 double bond, crisaxenicin A features a *cis*-cyclononene with a C5–C6 double bond. Its promising biological activity, combined with its distinctive structure, has attracted considerable interest from synthetic chemists. However, to date, only one total synthesis has been published.¹¹

Other structurally more complex xenicane diterpenoids have also been isolated from the soft corals, including sarcoglance (**5.9**) and xeniafaraunol (**5.10**), which feature additional all-carbon cycles fused to the central cyclononane (Figure 5.3).^{12,13}

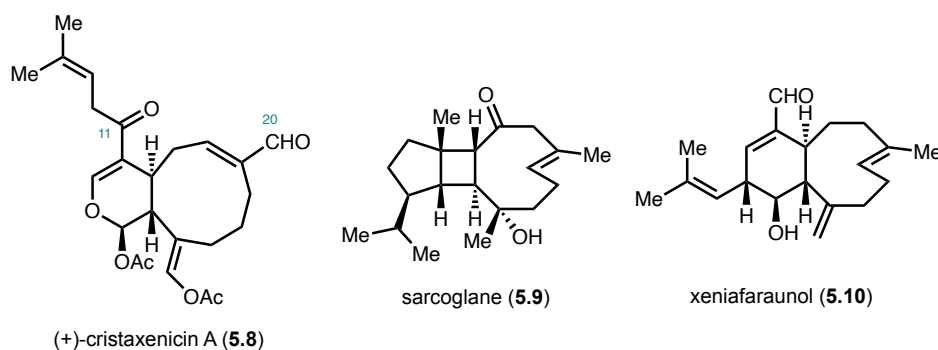


Figure 5.3. Selected examples of xenicane diterpenoid natural products.

Among the more complex xenicane diterpenoids, plumisclerin A (**5.11**), first isolated in 2010, stands out due to its structural complexity and unusual core skeleton (Figure 5.4).¹⁴ It features a compact tetracyclic 6/5/4/6-fused ring system that includes a cyclobutane ring bearing one fully substituted and two quaternary carbon centers, as well as seven contiguous stereocenters, making it an attractive synthetic target. To date, only one total synthesis of **5.11** has been reported.¹⁵

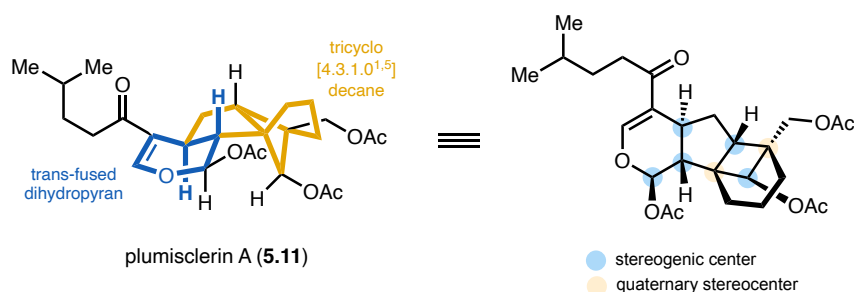


Figure 5.4. Structure of plumisclerin A.

5.2 Isolation

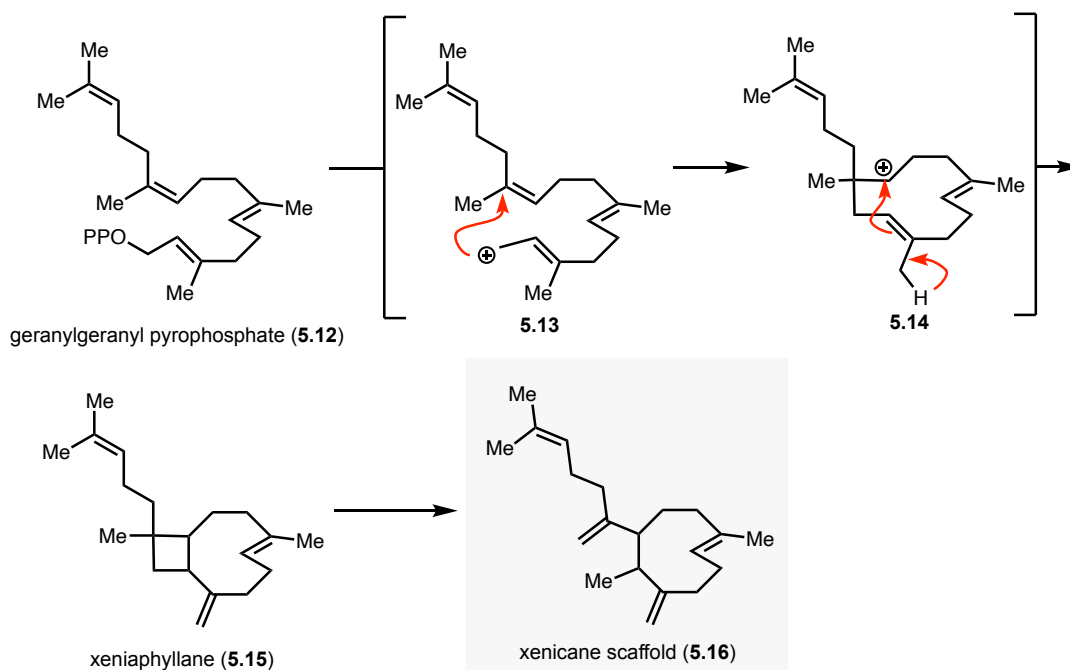
To date, xenicane diterpenoids have been identified exclusively in marine organisms, most commonly in soft corals of the genera *Xenia* and *Acanthogorgia* and in brown algae of the genus *Dictyota*.⁵ Additionally, less common sources include sea slugs of the genus *Aplysia*, brown algae of the genera *Dilophus*, *Padina* and *Glossophora*, and soft corals of the genera *Asterospicularia*, *Capnella*, *Eleutherobia*, *Acanthoprimnoa*, *Alcyonium*, *Anthelia*, and *Clavularia*.¹⁶

Specifically, plumisclerin A (**5.11**) was isolated and characterized by Cuevas and co-workers from cytotoxic crude extracts of soft coral *Plumigorgia terminosclera* in 2010.¹⁴ As part of a screening program for identifying new marine-derived anticancer compounds, the authors isolated the compound from extracts collected at Mayotte Island off the coast of Madagascar. Bioassay-guided fractionation of 2-propanol extracts of frozen specimens, involving RP-18 VLC chromatography followed by reversed-phase HPLC, led to the isolation of this new natural product. Plumisclerin A was obtained as an optically active white amorphous solid.

5.3 Biosynthesis

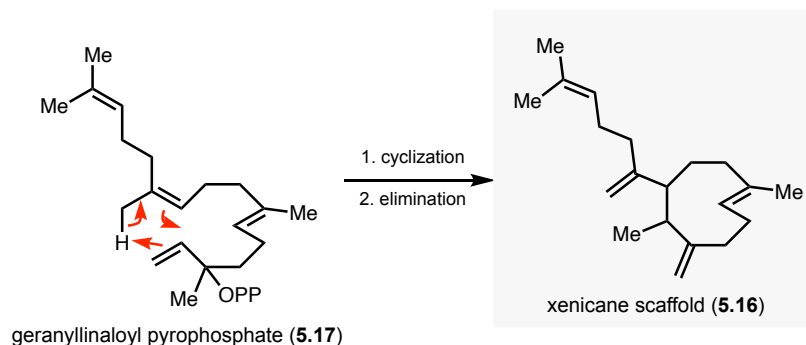
While significant advances have been made in elucidating biosynthetic pathways in terrestrial organisms, the biosynthesis of marine natural products remains comparatively poorly understood. This is largely due to the difficulty of cultivating certain marine organisms.⁵

According to the biogenetic isoprene rule,¹⁷ xenicanes are regular, i.e., non-rearranged diterpenes. The biosynthesis of xenicanes has been proposed to proceed from geranylgeranyl pyrophosphate (**5.12**) or geranylgeranyl pyrophosphate (**5.17**) as precursors (Scheme 5.1 and 5.2).⁷ By analogy with the biosynthesis of structurally similar caryophyllene, cyclization of a linear allylic cation **5.13** has been suggested.¹⁸ Following initial formation of xeniaphyllane (**5.15**), cleavage of the cyclobutane ring would lead to the xenicanes scaffold (Scheme 5.1).⁷



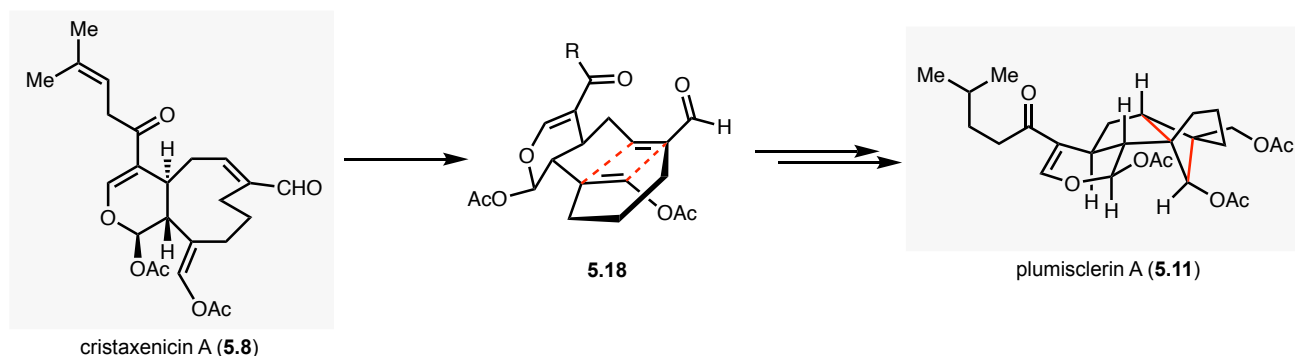
Scheme 5.1. Proposed biosynthesis of xenicanes diterpenoid natural products.

Alternatively, direct ring closure via a formal ene-reaction has been proposed (Scheme 5.2). The characteristic *exo*-methylene group would then arise through elimination of the tertiary pyrophosphate group.⁷ The co-isolation of xeniaphyllanes and xenicanes suggests that the “xeniaphyllane pathway” may be the more likely route for formation of the nine-membered ring.^{19,20} However, this does not conclusively exclude alternative pathways. The exact sequence of steps leading to formation of the nine-membered ring therefore remains unresolved.⁵



Scheme 5.2. Proposed biosynthesis of xenicane diterpenoid natural products.

The previously mentioned more complex xenicane diterpenoids, such as sarcoglance (**5.9**) and xenifaraunol (**5.10**), are proposed to arise via subsequent transannular cyclizations.¹³ In particular, plumisclerin A (**5.11**), which features a novel carbon skeleton in this class of natural products, is proposed to be biosynthetically derived from cristaxenicin A (**5.8**) (Scheme 5.3).¹⁴ Cuevas and co-workers proposed an intramolecular [2+2] cycloaddition between double bonds placed at the Δ_6 and Δ_{11} double bonds of cristaxenicin A. Subsequent reduction and acetylation of the C19 aldehyde group would then lead to the formation of plumisclerin A (**5.11**). This biosynthetic hypothesis is supported by computational studies by Tantillo and co-workers.²¹



Scheme 5.3. Proposed biosynthesis of plumisclerin A from cristaxenicin A.

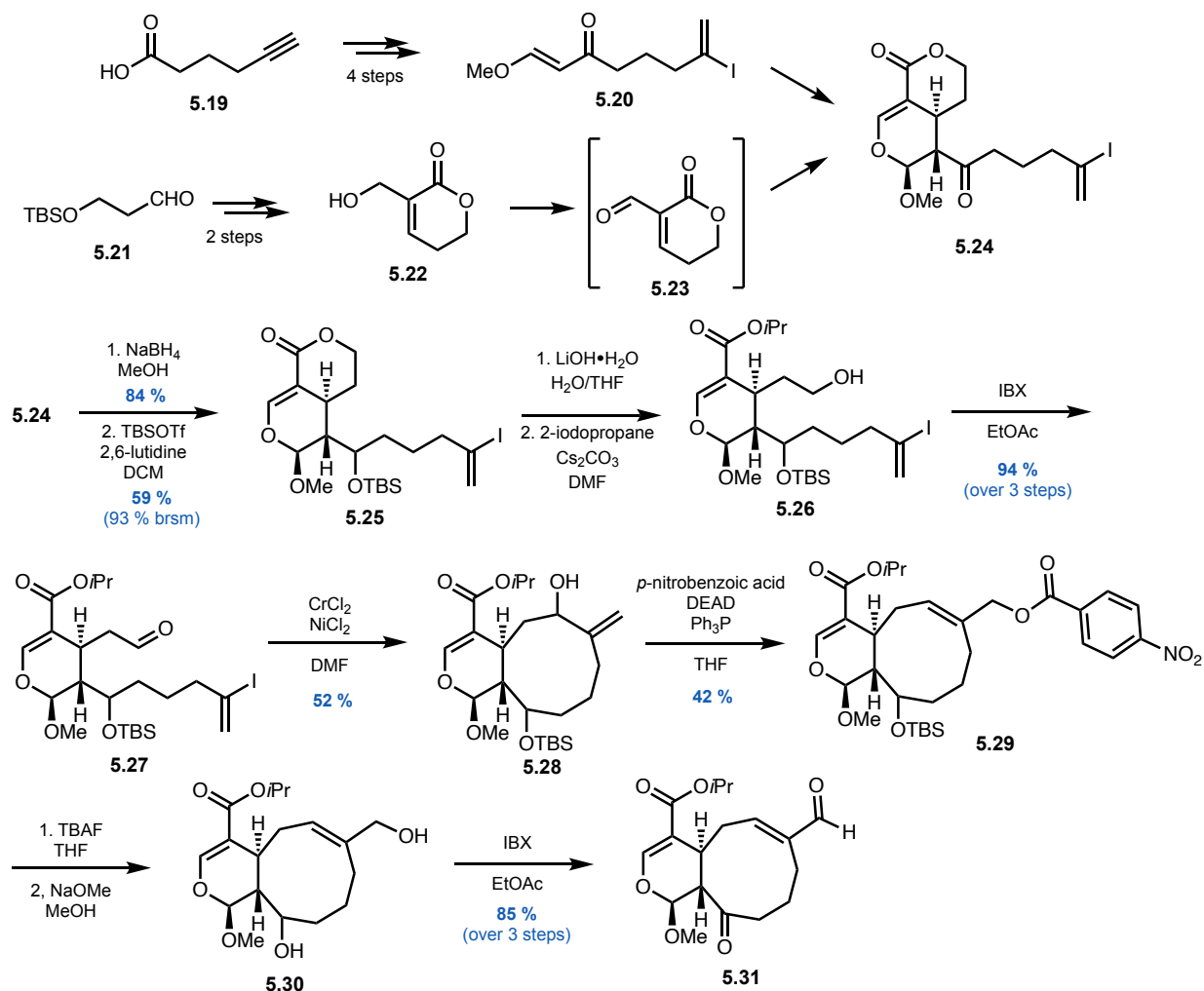
5.4 Biological Activity

The cytotoxic activity of **5.11** was evaluated against three human tumor cell lines, including lung (A549), colon (HT29), and breast (MDA-MB-231) cancer cells. The compound exhibited moderate cytotoxic activity, with GI_{50} values of 4.7, 2.1, and 6.1 μ M, respectively, and showed no tissue selectivity.¹⁴ Further studies on tissue selectivity and mode of action have not yet been reported and remain to be investigated.

5.5 Previous Synthetic Studies on Cristaxenicin A (5.8)

Although successful total syntheses of numerous xeniolide-type compounds have been reported, those of xenicin-type compounds were not published until recently. Given the close structural similarity of cristaxenicin A (5.8) and plumisclerin A (5.11), the total syntheses and synthetic studies on these two natural products will be summarized herein.

5.5.1 Hosokawa's Synthesis of Cristaxenicin A's core (2016)



Scheme 5.4. Hosokawa's synthetic studies toward the core structure of cristaxenicin A.

In 2016, Hosokawa and co-workers reported the synthesis of the core structure of cristaxenicin A (5.8) using a [4+2] cycloaddition reaction between an unsaturated aldehyde **5.23** and a β-alkoxy-α,β-unsaturated ketone **5.20**.²²

Starting from propargylic carboxylic acid **5.19** and β-siloxyaldehyde **5.21**, the respective substrates were converted into vinyl iodide **5.20** and allylic alcohol **5.22**. Mild oxidation of alcohol **5.22** to the corresponding aldehyde, followed by an *in situ* hetero-Diels-Alder cycloaddition with

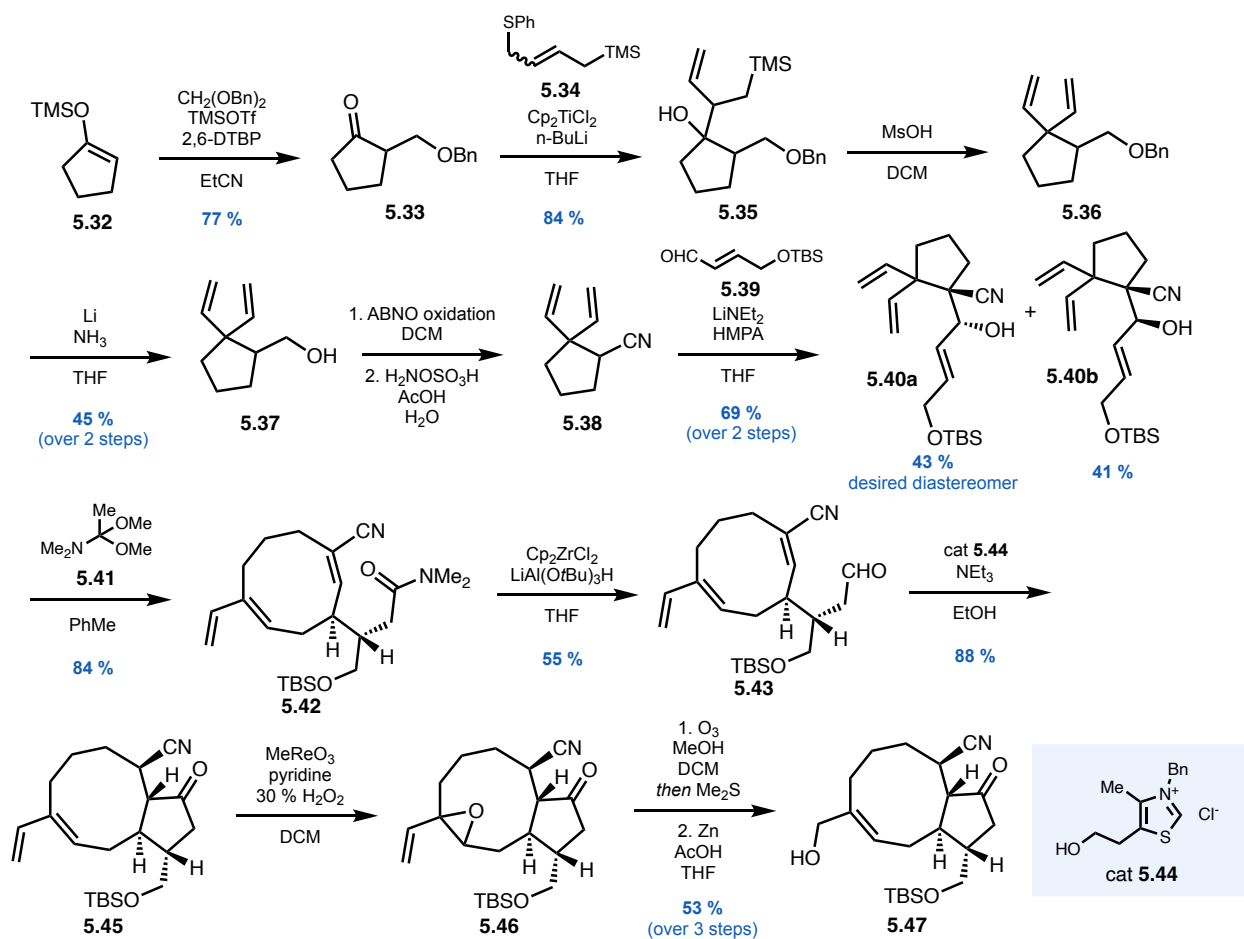
vinyl iodide **5.20**, afforded bicyclic intermediate **5.24**. Due to the instability of the aldehyde intermediate **5.23**, oxidation and cycloaddition were performed in a one-pot sequence.

With intermediate **5.24** in hand, reduction of the ketone group followed by protection as the TBS ether gave intermediate **5.25**. Subsequent hydrolysis of the lactone and esterification of the resulting carboxylic acid yielded primary alcohol **5.26**. Oxidation to the corresponding aldehyde enabled an intramolecular Nozaki-Hiyama-Kishi (NHK) reaction, furnishing the nine-membered cyclic allylic alcohol **5.28** in moderate yield (52 % yield). The resulting intermediate underwent a Mitsunobu rearrangement to give *endo*-olefin **5.29**. After removal of the TBS and *p*-nitrobenzoyl protecting groups, oxidation of the primary and secondary alcohols afforded aldehyde **5.31**, corresponding to the core structure of cristaxenicin A (**5.8**). Overall, the racemic core structure **5.31** was obtained in 15 steps. The synthesized intermediate was subsequently evaluated for anti-leishmanial activity.

5.5.2 Tanino's Total Synthesis of Cristaxenicin A (2025)

The first racemic total synthesis of cristaxenicin A was reported by Tanino and co-workers in 2025.¹¹ The key strategy for constructing the nine-membered ring involved an addition reaction between 2,2,-divinylcyclopentanecarbonitrile **5.38** and 4-(tert-butyldimethylsilyl)oxy-2-butenal **5.39**, followed by a one-pot sequence of Eschenmoser-Claisen and Cope rearrangements.

The synthesis commenced with the preparation of a five-membered nitrile from commercially available silyl enol ether **5.32**. A Mukaiyama aldol reaction between **5.32** and di(benzyloxy)methane afforded ketone **5.33**, which was converted in two-steps into divinyl compound **5.36**. Removal of the benzyl group through dissolving metal reduction yielded primary alcohol **5.37**, which was transformed into nitrile **5.38** via ABNO-mediated oxidation conditions (Stahl conditions), followed by condensation with hydroxylamine-O-sulfonic acid. Treatment of the resulting nitrile with **5.39** afforded a mixture of diastereomers **5.40a** and **5.40b**. Upon heating with dimethylacetamide dimethyl acetal (DMF-DMA), diastereomer **5.40a** underwent a cascade Eschenmoser-Claisen and Cope rearrangement sequence to afford desired nine-membered nitrile **5.42** as the sole product in 84 % yield. Reduction of the nitrile with *in situ*-generated Schwartz's reagent furnished the corresponding aldehyde (**5.43**), which was subsequently subjected to an intramolecular Stetter reaction with thiazolium salt **5.44** to afford bicyclic intermediate **5.45**. Epoxidation of **5.45** using methyltrioxorhenium and hydrogen peroxide in the presence of pyridine yielded intermediate **5.46**, which was then subjected to ozonolysis followed by reductive opening of the epoxide with Zn and acetic acid to give allylic alcohol **5.47**.

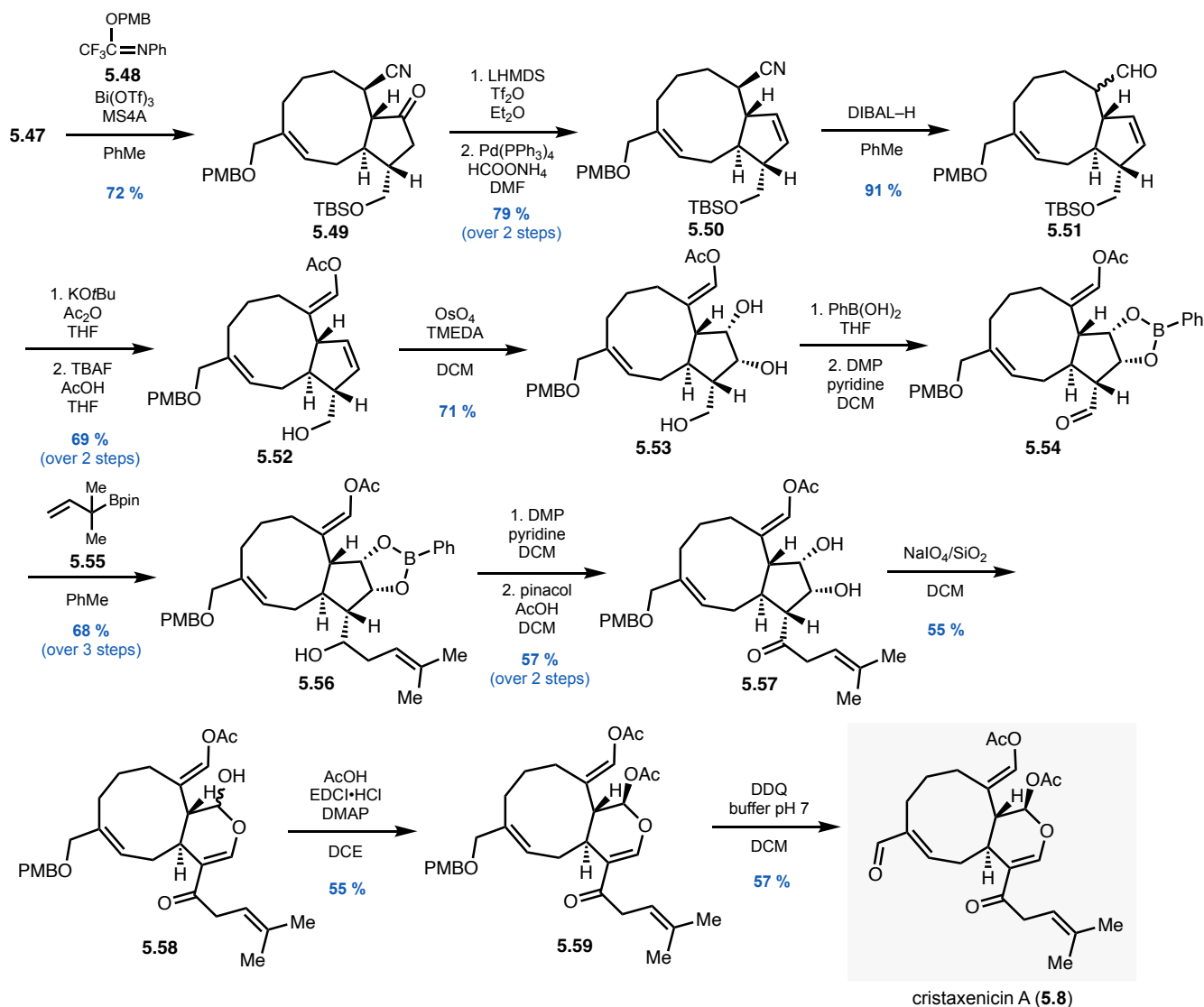


Scheme 5.5. Tanino's total synthesis of cristaxenicin A (part 1).

Following protection of the primary allylic alcohol group as a PMB ether, cyclopentanone **5.49** was converted into cyclopentene **5.50** via formation of an enol triflate, followed by reduction with $\text{Pd}(\text{PPh}_3)_4$ and ammonium formate. Reduction of the nitrile to the corresponding aldehyde with DIBAL-H afforded intermediate **5.51**, which was subsequently transformed into the corresponding enol acetate. Removal of the TBS group with TBAF then provided alcohol **5.52** in 69% yield over two steps.

This intermediate was subjected to OsO_4 -mediated dihydroxylation, in which the adjacent primary alcohol served as a directing group to enable site- and stereoselective oxidation of the neighboring double bond, affording triol **5.53** in 71% yield. Protection of the 1,2-diol moiety as a cyclic phenylboronic ester (**5.54**) enabled installation of the side chain via a five-step sequence. The boronate was subsequently removed using pinacol under mildly acidic conditions to yield diol **5.57**.

Oxidative cleavage of diol **5.57** with NaIO_4 afforded dihydropyran **5.58**, which was acetylated using $\text{EDCI} \cdot \text{HCl}$. Finally, removal of the PMB protecting group furnished natural product (**5.8**). Overall, the synthesis required 28 steps.



Scheme 5.6. Tanino's total synthesis of cristaxenicin A (part 2).

5.6 Previous Synthetic Studies on Plumisclerin A (5.11)

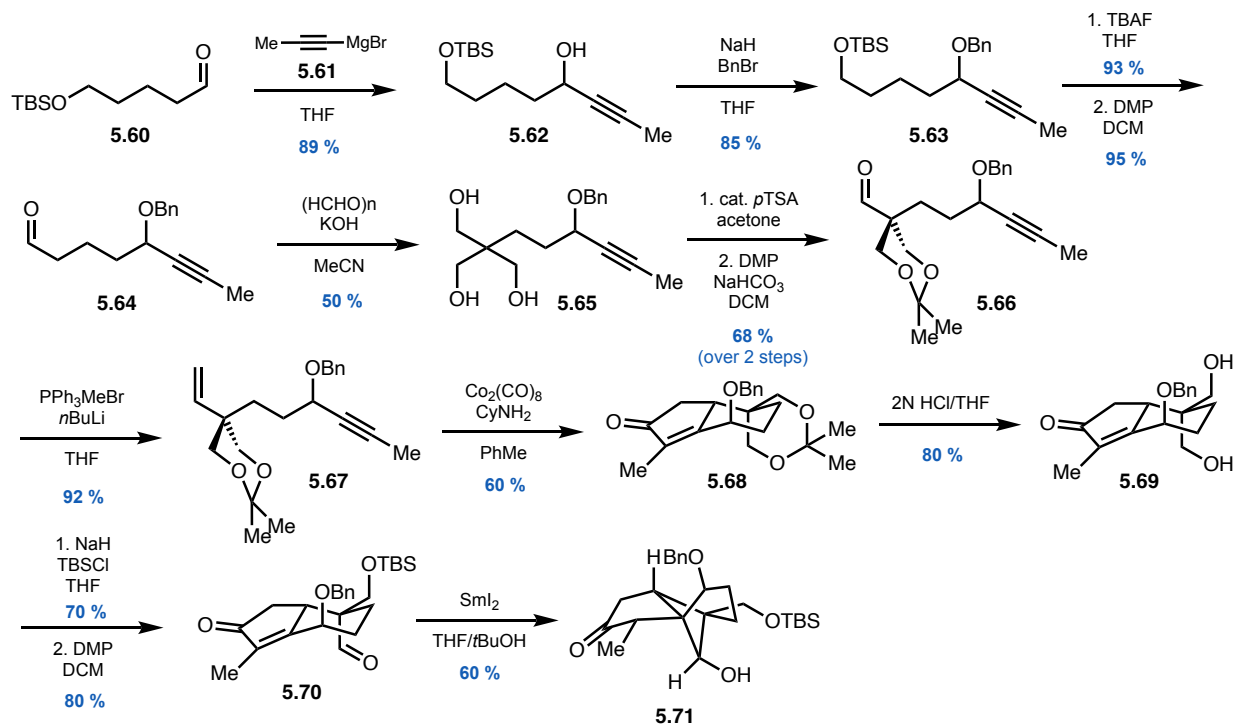
5.6.1 Yao's Synthetic Studies Toward Plumisclerin A (2015)

Yao and co-workers reported synthetic studies toward plumisclerin A in 2015, in which a Pauson-Khand reaction was applied for the construction of the 5/6-fused bicyclic core.²³

The study commenced with the preparation of alcohol **5.62** via addition of propynyl magnesium bromide **5.61** to aldehyde **5.60**. Protection of the resulting secondary alcohol as a benzyl ether afforded compound **5.63**, which was converted into the corresponding aldehyde (**5.64**) through removal of the TBS protecting group followed by DMP oxidation. Reaction of aldehyde **5.64** with excess paraformaldehyde in the presence of KOH afforded triol **5.65** in moderate yield (50 %). Protection of the diol as an acetonide enabled selective oxidation of the remaining primary

alcohol to the corresponding aldehyde (**5.66**), which was then converted into desired enyne precursor **5.67** via treatment with methyltriphenylphosphonium bromide and *n*BuLi in THF.

Subjecting intermediate **5.67** to Pauson-Khand reaction constructed the designed B/D-ring system **5.68** containing an α,β -unsaturated cyclopentenone moiety. Removal of the acetonide group under acidic condition revealed diol **5.69**, which was selectively protected and oxidized to afford intermediate **5.70**. With enone-aldehyde **5.70** in hand, formation of the cyclobutane ring was achieved via SmI₂-mediated ketyl radical cyclization. The resulting tricyclic intermediate (**5.71**) was obtained in 13 overall steps.



Scheme 5.9. Yao's synthetic studies toward plumisclerin A.

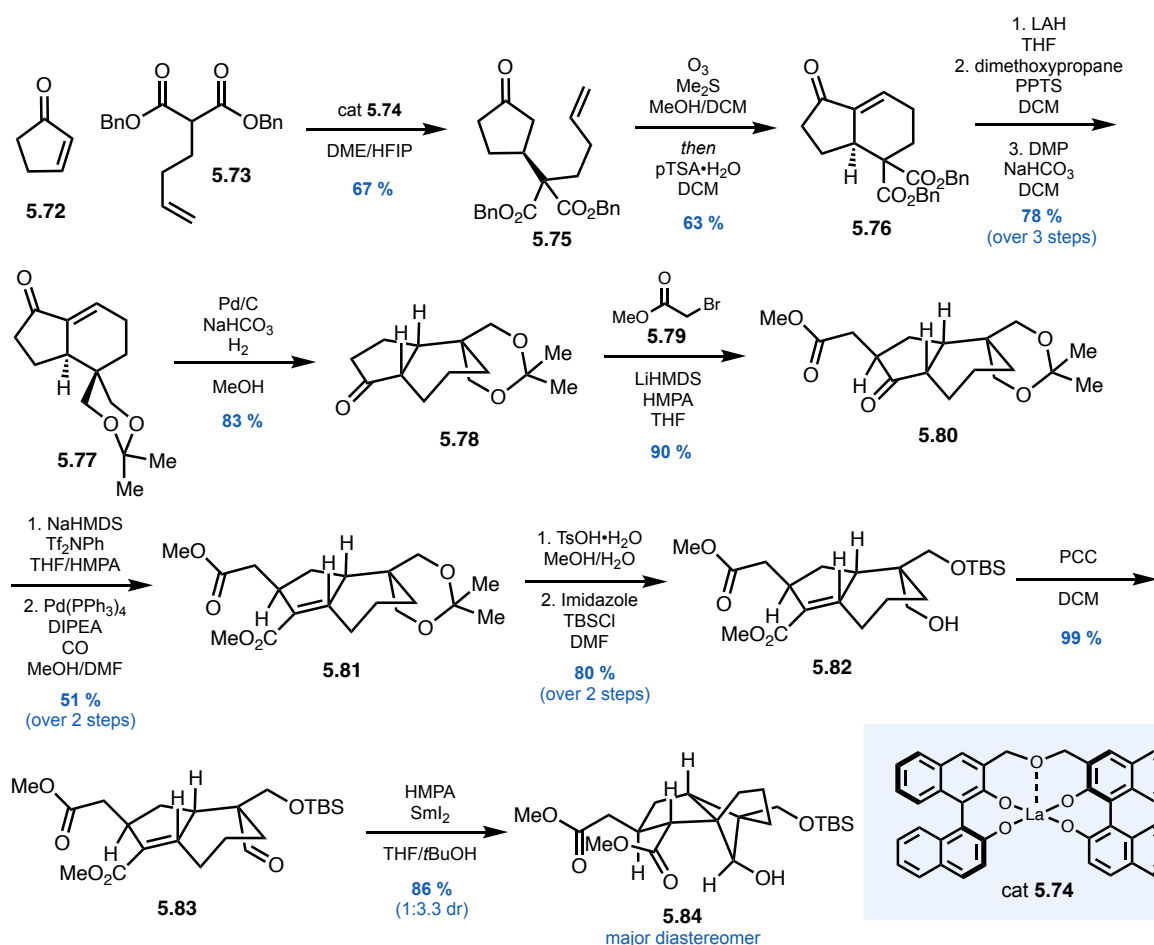
5.6.2 Yao's Total Synthesis of Plumisclerin A (2018)

In 2018, Yao and co-workers accomplished the first enantioselective synthesis of plumisclerin A (**5.11**).¹⁵ Similar to their previously reported synthetic studies, the synthesis features a SmI₂-mediated ketyl radical cyclization as the key step for constructing the cyclobutane ring.

The synthesis commenced with an enantioselective catalytic asymmetric conjugate addition of malonate **5.73** to cyclopentenone **5.72** using (*S,S*)-La-bis-BINOL **5.74** as the catalyst, affording the desired product (**5.76**) on decagram scale with high enantioselectivity (>98% ee). Ozonolysis of the terminal olefin group, followed by intramolecular aldol condensation in the presence of catalytic *p*TSA·H₂O, furnished enone **5.76**. Complete reduction of the diester afforded a 1,3-diol, which was selectively protected as the corresponding acetonide using 2,2-dimethoxypropane.

Oxidation of the cyclopentanol moiety to **5.77** followed by catalytic hydrogenation with Pd/C provided cyclopentanone **5.78** in 83 % yield.

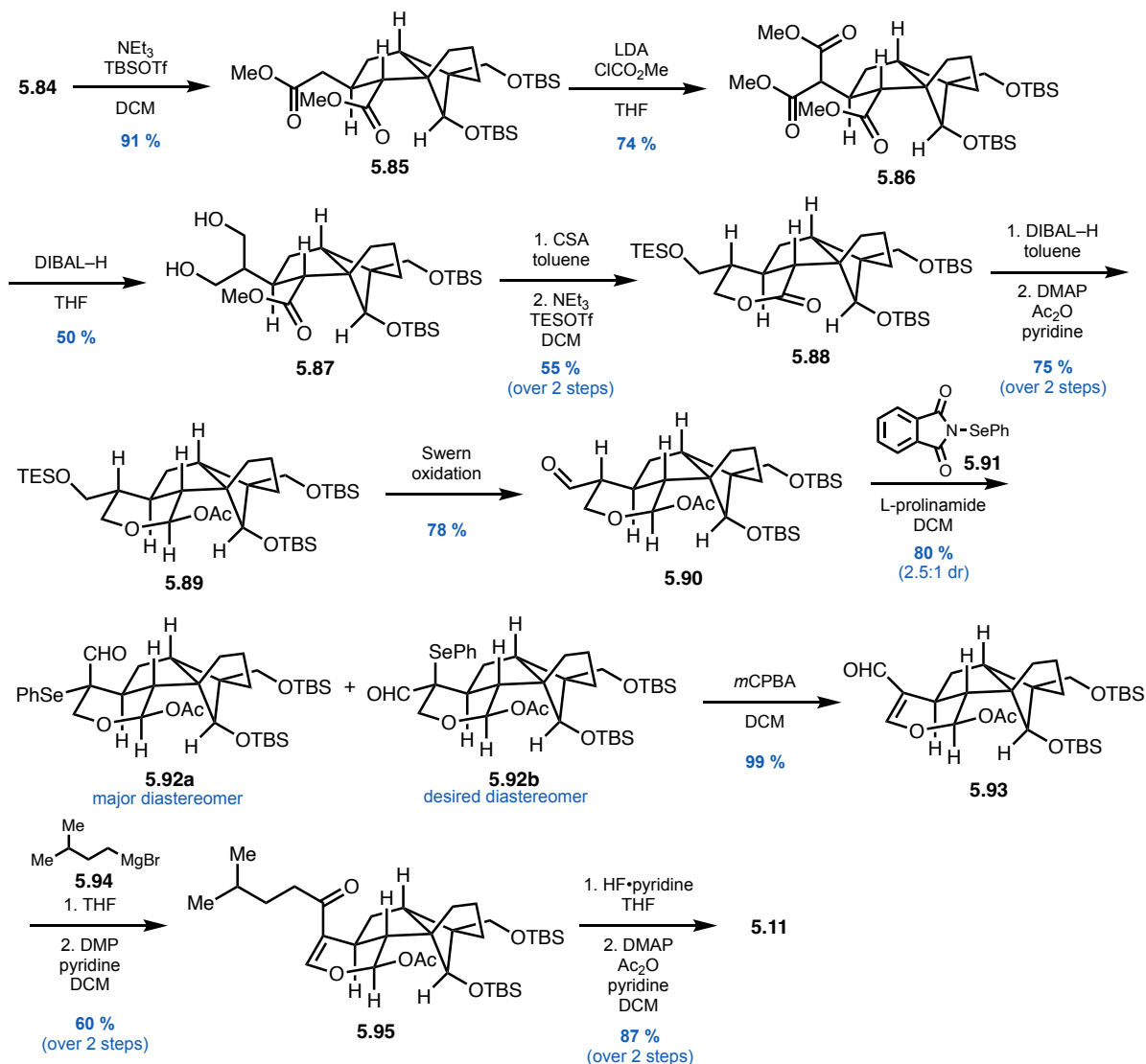
A diastereoselective alkylation of bicyclic ketone **5.78** with methyl bromoacetate **5.79** afforded ketone **5.80** in 90 % yield as a single diastereomer with the desired stereochemistry. Subsequent formation of an enol triflate followed by Pd-catalyzed carbonylation furnished α,β -unsaturated ester **5.81**. Removal of the acetonide under acidic conditions and selective protection of one primary alcohol provided intermediate **5.82**, which was oxidized to the corresponding aldehyde **5.83** with PCC. This intermediate served as the precursor for construction of the rigid tricyclodecane framework via a SmI_2 -mediated ketyl radical 1,4-addition.



Scheme 5.7. Yao's total synthesis of plumisclerin A (part 1).

The final stage of the synthesis focused on the formation of the trans-fused dihydropyran ring. Treatment of **5.85** with LDA and methyl chloroformate afforded malonate **5.86** selectively. Chemoselective reduction of malonate **5.86** was achieved using DIBAL-H at -40°C . The resulting diol was subjected to lactonization using a substoichiometric amount of CSA, and the remaining hydroxy group was protected as the TES ether using TESOTf to provide a stable tetracyclic lactone **5.88** in 55 % yield.

Reduction of lactone **5.88** to the corresponding lactol followed by acetylation afforded intermediate **5.89**. Removal of the TES group and subsequent Swern oxidation furnished aldehyde **5.90** in 78 % yield in a one-pot sequence. Installation of the endocyclic alkene was achieved via L-prolinamide-promoted α -selenenylation of aldehyde **5.90** followed by oxidative elimination, giving desired α,β -unsaturated aldehyde **5.93**. 1,2-Addition of isopentyl Grignard reagent **5.94** to the enal was followed by oxidation with DMP to afford the corresponding ketone (**5.95**). Finally, removal of all silyl protecting groups and global acetylation furnished the natural product (plumisclerin A, **5.11**). Overall, the synthesis was completed in 27 steps.

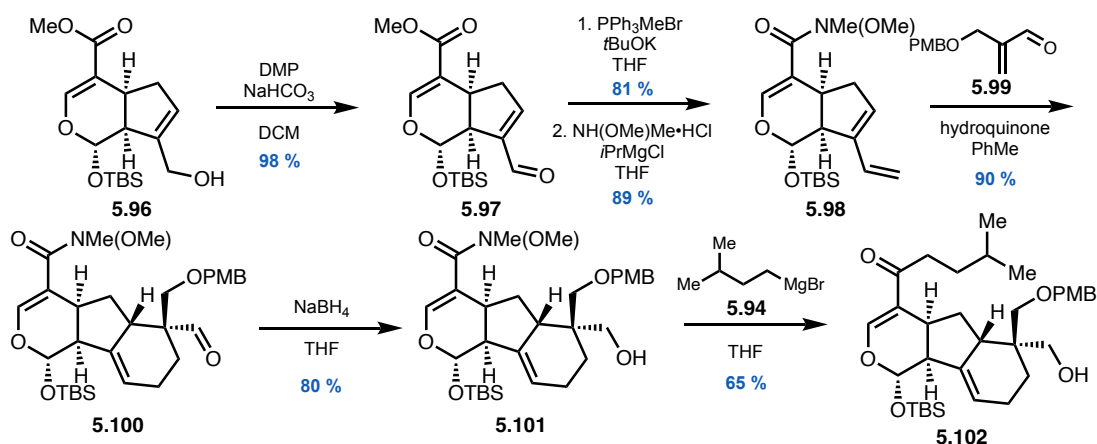


Scheme 5.8. Yao's total synthesis of plumisclerin A (part 2).

5.6.3 Ma's Synthetic Studies Toward Plumisclerin A (2019)

In 2019, Ma and co-workers reported synthetic studies toward plumisclerin A, featuring a highly selective intramolecular Diels-Alder reaction and a SmI₂-mediated reductive coupling.²⁴

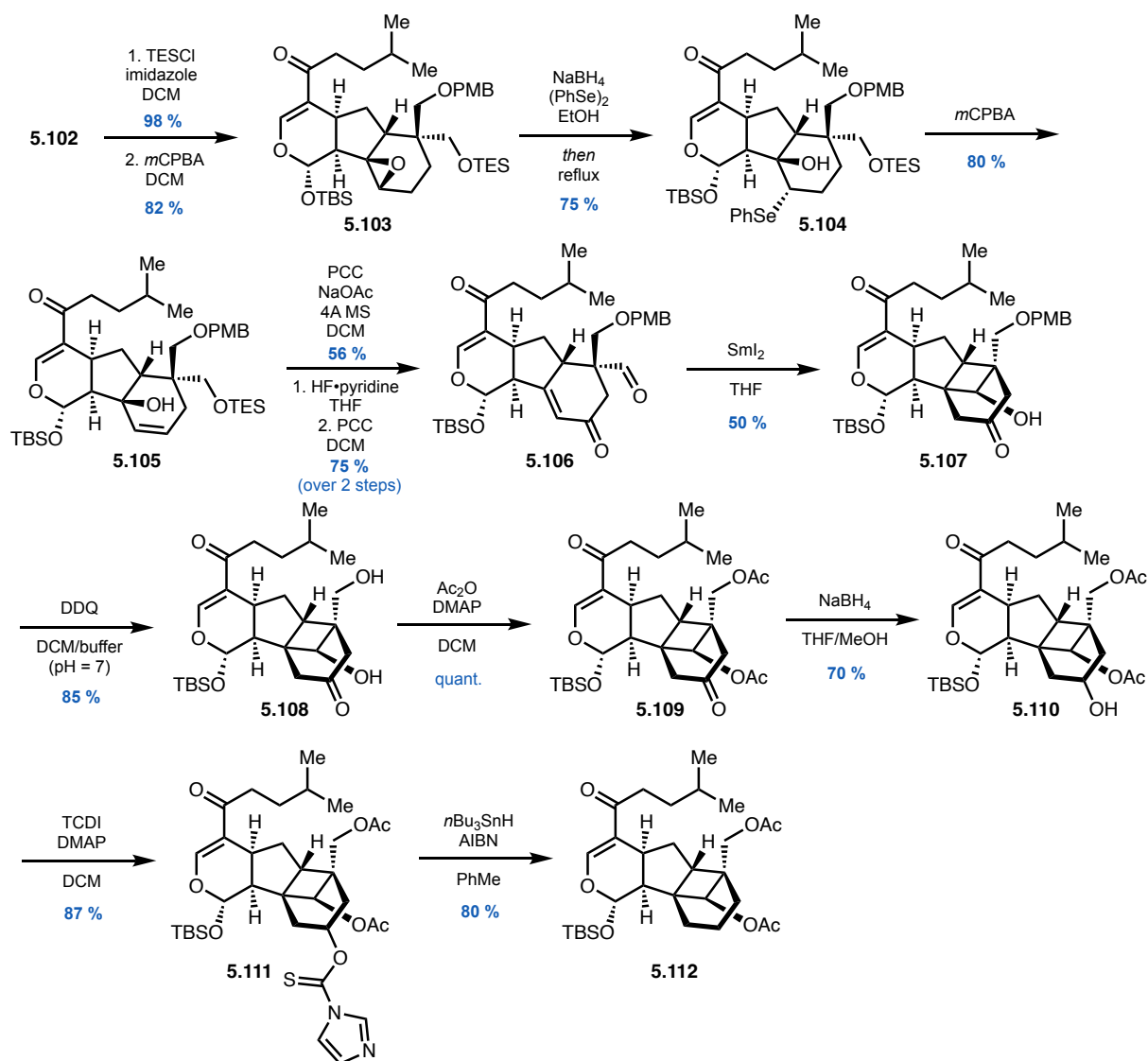
Starting from inexpensive iridoid TBS-protected genipin (**5.96**), DMP oxidation of the allylic alcohol group afforded aldehyde **5.97**, which was subjected to a Wittig reaction followed by Weinreb amide formation to give diene **5.98**. The key Diels-Alder reaction between diene **5.98** and the known dienophile **5.99** proceeded smoothly in toluene at 80 °C for 3 days in the presence of a small amount of hydroquinone, affording cycloadduct **5.100**. Reduction of the aldehyde with NaBH₄ and 1,2-addition of isopentyl Grignard reagent **5.94** to the Weinreb amide provided intermediate **5.102**. The resulting alcohol was protected as the TES ether, and the trisubstituted alkene moiety was oxidized with *m*CPBA to give epoxide **5.103** as a single diastereomer in 82 % yield.



Scheme 5.10. Ma's synthetic studies toward plumisclerin A (part 1).

Next, epoxide **5.103** was rearranged to the corresponding tertiary allylic alcohol **5.105**, which was further transformed via a PCC-mediated Dauben oxidative rearrangement to an enone. Subsequent selective desilylation and oxidation furnished desired enone-aldehyde **5.106** in 75 % yield. This intermediate was then subjected to SmI₂-mediated ketyl radical cyclization to afford cyclobutanol **5.107**.

Finally, removal of the PMB protecting group followed by global acetylation furnished intermediate **5.109**. Reduction of the ketone with NaBH₄ and a Barton-McCombie deoxygenation sequence provided intermediate **5.112** in 19 overall steps. This intermediate requires only a late-stage epimerization at C18 to access plumisclerin A.



Scheme 5.11. Ma's synthetic studies toward plumisclerin A (part 2).

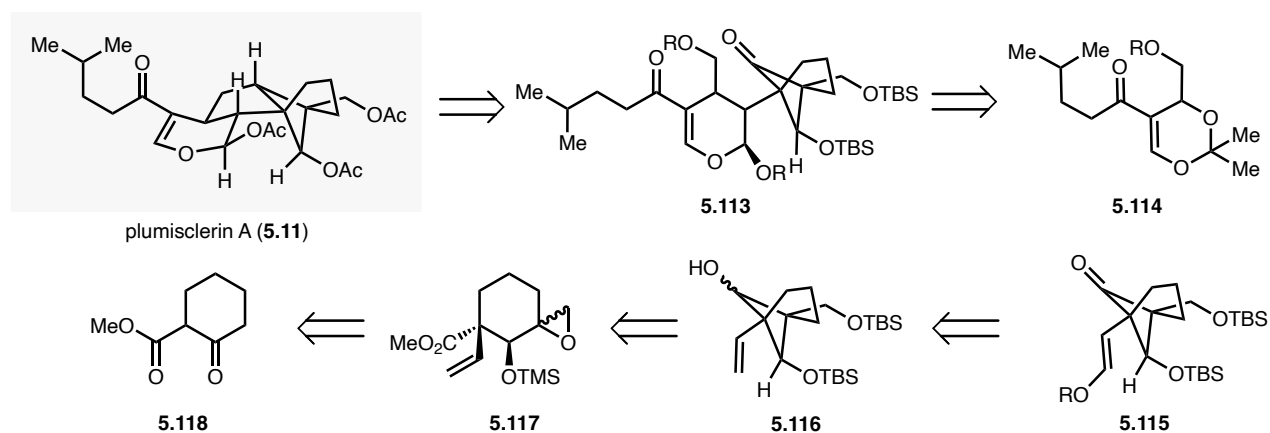
5.7 Our Proposal

We recognize two primary structural challenges in the synthesis of plumisclerin A (**5.11**): the highly congested and rigid tricyclo[4.3.2.0^{1,5}]decane, and the *trans*-fused dihydropyran ring appended to the central cyclopentane. The previous total synthesis and synthetic studies toward plumisclerin A have demonstrated a range of creative and efficient strategies for construction of this scaffold. However, formation of the central cyclobutane moiety has predominantly relied on SmI₂-mediated ketyl radical cyclization.

In this study, we sought to explore alternative approaches to constructing the rigid tricyclo[4.3.2.0^{1,5}]decane framework. Drawing inspiration from prior work in the Sarpong group

on titanocene-mediated bicyclo[3.1.1]heptane **1.84** formation using epoxy-carvone, we designed compound **5.117** as the precursor to the bicyclic intermediate (**5.116**) of plumisclerin A. This intermediate can be obtained from commercially available β -keto ester **5.118**.

For the construction of the dihydropyran moiety, we envisioned a hetero-Diels-Alder cycloaddition with dioxine **5.114** as a masked diene, inspired by the synthesis of euplotin A reported by Funk and co-workers.^{25,26} To construct the final cyclopentane ring, we proposed a reductive cyclization between the cyclobutanone and a primary halide derived from the methylene alcohol in **5.113**. Subsequent deoxygenation would furnish the desired natural product.



Scheme 5.12. Proposed retrosynthesis of plumisclerin A.

With this convergent approach, we aim to achieve a concise and efficient total synthesis of plumisclerin A. Efforts toward the natural product are discussed in the following chapter.

5.8 References

1. Coll, J. C. The Chemistry and Chemical Ecology of Octocorals (Coelenterata, Anthozoa, Octocorallia). *Chem. Rev.* **1992**, 92, 613–631.
2. Fram, F. Chemical Prospectors Scour the Seas for Promising Drugs. *Science* **1994**, 266, 1324–1325.
3. Kelman, D.; Kashman, Y.; Hill, R. T.; Rosenberg, E.; Loya, Y. Chemical Warfare in the Sea: The Search for Antibiotics from Red Sea Corals and Sponges. *Pure Appl. Chem.* **2009**, 81, 1113–1121.
4. Haefner, B. Drugs from the Deep: Marine Natural Products as Drug Candidates. *Drug Discovery Today* **2003**, 8, 536–544.
5. Bertschart, L.; Altmann, K.-H. Xenicane Natural Products: Biological Activity and Total Synthesis. *Curr. Pharm. Des.* **2015**, 21, 5467–5488.
6. Breitmaier, E. Diterpenes. In *Terpenes*, 2nd ed.; Breitmaier, E., Ed.; Wiley-VCH: Weinheim, Germany, 2006; pp 52–81.
7. Vanderah, D. J.; Steudler, P. A.; Ciereszko, L. S.; Schmitz, F. J.; Ekstrand, J. D.; Van der Helm, D. Marine Natural Products. Xenicin: A Diterpenoid Possessing a Nine-Membered Ring from the Soft Coral *Xenia elongata*. *J. Am. Chem. Soc.* **1977**, 99, 5780–5784.
8. Finer, J.; Clardy, J.; Fenical, W.; Minale, L.; Riccio, R.; Battaile, J.; Kirkup, M.; Moore, R. E. Structures of Dictyodial and Dictyolactone, Unusual Marine Diterpenoids. *J. Org. Chem.* **1979**, 44, 2044–2047.
9. Ohtani, I.; Kusumi, T.; Ishitsuka, M. O.; Kakisawa, H. Absolute Configurations of Marine Diterpenes Possessing a Xenicane Skeleton: An Application of an Advanced Mosher's Method. *Tetrahedron Lett.* **1989**, 30, 3147–3150.
10. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. High-Field FT NMR Application of Mosher's Method: The Absolute Configurations of Marine Terpenoids. *J. Am. Chem. Soc.* **1991**, 113, 4092–4096.
11. Kiuchi, W.; Tsunoda, Y.; Ishikura, K.; Kato, K.; Takino, J.; Suzuki, T.; Tanino, K. Total Synthesis of (±)-Cristaxenicin A: Construction of a Nine-Membered Ring by an Eschenmoser–Claisen/Cope Rearrangement Cascade. *Angew. Chem., Int. Ed.* **2026**, 65, e24855.
12. Fridkovsky, E.; Rudi, A.; Benayahu, Y.; Kashman, Y.; Schleyer, M. Sarcoglance, a New Cytotoxic Diterpene from *Sarcophyton glaucum*. *Tetrahedron Lett.* **1996**, 37, 6909–6910.
13. Kashman, Y.; Saltoun, M.; Rudi, A.; Benayahu, Y. Xeniafaraunol A and B, and Faraunatin: Three New Cytotoxic Diterpenes from the Soft Coral *Xenia faraunensis*. *Tetrahedron Lett.* **1994**, 35, 8855–8858.
14. Martín, M.; Fernández, R.; Francesch, A.; Amade, P.; de Matos-Pita, S. S.; Reyes, F.; Cuevas, C. Plumisclerin A, a Diterpene with a New Skeleton from the Soft Coral *Plumigorgia terminosclera*. *Org. Lett.* **2010**, 12, 912–914.

15. Gao, M.; Wang, Y.-C.; Yang, K.-R.; He, W.; Yang, X.-L.; Yao, Z.-J. Enantioselective Total Synthesis of (+)-Plumisclerin A. *Angew. Chem., Int. Ed.* **2018**, *57*, 13497–13502.
16. (a) Finer, J.; Clardy, J.; Fenical, W.; et al. Structures of Dictyodial and Dictyolactone, Unusual Marine Diterpenoids. *J. Org. Chem.* **1979**, *44*, 2044–2047. (b) Schlenk, D.; Gerwick, W. Dilophic Acid, a Diterpenoid from the Tropical Brown Seaweed *Dilophus guineensis*. *Phytochemistry* **1987**, *26*, 1081–1084. (c) Bouaicha, N.; Pesando, D.; Puel, D. Cytotoxic Diterpenoids from the Brown Alga *Dilophus ligulatus*. *J. Nat. Prod.* **1993**, *56*, 1747–1752. (d) Suzuki, M.; Yamada, H.; Kurata, K. Dictyterpenoids A and B, Two Novel Diterpenoids with Feeding-Deterrent Activity from the Brown Alga *Dilophus okamurae*. *J. Nat. Prod.* **2002**, *65*, 121–125. (e) Awad, N. E.; Selim, M. A.; Metawe, H. M.; Matloub, A. A. Cytotoxic Xenicane Diterpenes from the Brown Alga *Padina pavonia*. *Phytother. Res.* **2008**, *22*, 1610–1613. (f) De Nys, R.; Wright, A. D.; König, G. M.; Sticher, O. A Diterpene from the Marine Alga *Glossophora kunthii*. *Phytochemistry* **1993**, *32*, 463–465. (g) Bowden, B. F.; Cusack, B. J.; Dangel, A. 13-Epi-9-deacetoxynenicin from the Soft Coral *Asterospicularia laurae*. *Mar. Drugs* **2003**, *1*, 18–26. (h) Lin, Y.-C.; El-Razek, M. H. A.; Hwang, T.-L.; et al. Asterolaurins A–F, Xenicane Diterpenoids from the Taiwanese Soft Coral *Asterospicularia laurae*. *J. Nat. Prod.* **2009**, *72*, 1911–1916. (i) Grkovic, T.; Whitson, E. L.; Rabe, D. C.; et al. Identification and Evaluation of Soft Coral Diterpenes as Inhibitors of HIF-2 α -Induced Gene Expression. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2113–2115. (j) Hooper, G. J.; Davies-Coleman, M. T. New Metabolites from the South African Soft Coral *Capnella thyrsoidea*. *Tetrahedron* **1995**, *51*, 9973–9984. (k) Hooper, G. J.; Davies-Coleman, M. T.; Schleyer, M. New Diterpenes from the South African Soft Coral *Eleutherobia aurea*. *J. Nat. Prod.* **1997**, *60*, 889–893. (l) Ishigami, S.; Goto, Y.; Inoue, N.; et al. Cristaxenicin A, an Antiprotozoal Xenicane Diterpenoid from the Deep-Sea Gorgonian *Acanthoprimnoa cristata*. *J. Org. Chem.* **2012**, *77*, 10962–10966. (m) Rudi, A.; Ketzinel, S.; Goldberg, I.; Stein, Z.; Kashman, Y. Antheliatin and Zahavins A and B, Three New Cytotoxic Xenicane Diterpenes from Two Soft Corals. *J. Nat. Prod.* **1995**, *58*, 1581–1586. (n) Wang, S.-K.; Huang, M.-J.; Duh, C.-Y. Cytotoxic Constituents from the Formosan Soft Coral *Clavularia inflata* var. *luzoniana*. *J. Nat. Prod.* **2006**, *69*, 1411–1416.
17. Ruzicka, L. The Isoprene Rule and the Biogenesis of Terpenic Compounds. *Experientia* **1953**, *9*, 357–367.
18. Hendrickson, J. B. Stereochemical Implications in Sesquiterpene Biogenesis. *Tetrahedron* **1959**, *7*, 82–89.
19. Kashman, Y.; Groweiss, A. Xeniolide A and Xeniolide B, Two New Diterpenoids from the Soft Coral *Xenia macrospiculata*. *Tetrahedron Lett.* **1978**, *19*, 4833–4836.
20. Groweiss, A.; Kashman, Y. Xeniculin, Xeniaphyllenol, and Xeniaphyllenol Oxide: New Diterpenoids from the Soft Coral *Xenia macrospiculata*. *Tetrahedron Lett.* **1978**, *19*, 2205–2208.
21. Sio, V.; Harrison, J. G.; Tantillo, D. J. Theoretical Assessment of the Viability of Thermal [2+2] Processes for Formation of Plumisclerin A. *Tetrahedron Lett.* **2012**, *53*, 6919–6922.

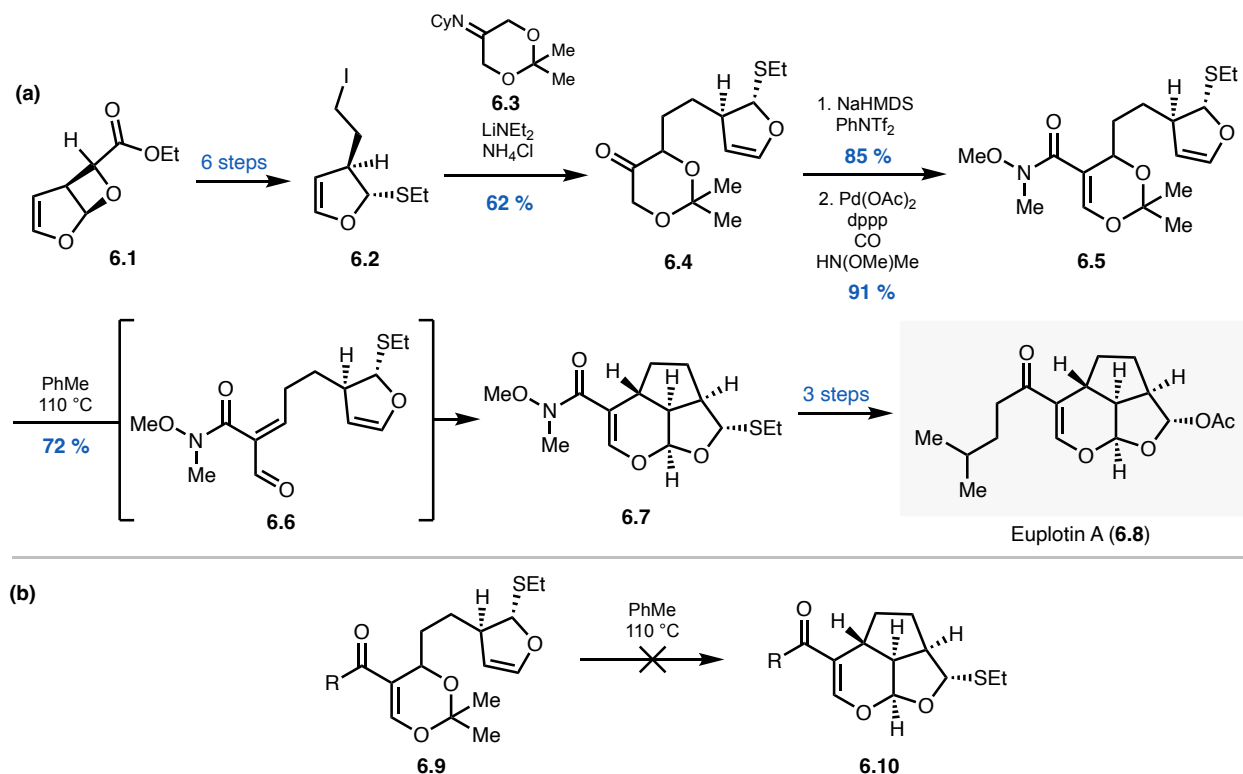
22. Fumiyama, H.; Sadayuki, T.; Osada, Y.; Goto, Y.; Nakao, Y.; Hosokawa, S. Synthesis and Antileishmanial Activity of the Core Structure of Cristaxenicin A. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 4355–4357.
23. Chen, J. P.; He, W.; Yang, Z.-Y.; Yao, Z.-J. Synthesis of Tricyclo[4.3.1.0^{1,5}]decane Core for Plumisclerin A Using Pauson–Khand Annulation and SmI₂-Mediated Radical Cyclization. *Org. Lett.* **2015**, *17*, 3379–3381.
24. Gao, Y.; Wei, Y.; Ma, D. Synthetic Studies toward Plumisclerin A. *Org. Lett.* **2019**, *21*, 1384–1387.
25. Funk, R. L.; Fearnley, S. P.; Gregg, R. Preparation of 2-Alkyl- and 2-Acylpropenals from 5-(Trifluoromethanesulfonyloxy)-4H-1,3-dioxin: A Versatile Acrolein α -Cation Synthon. *Tetrahedron* **2000**, *56*, 10275–10281.
26. Aungst, R. A.; Funk, R. L. Synthesis of (Z)-2-Acyl-2-enals via Retrocycloadditions of 5-Acyl-4-alkyl-4H-1,3-dioxins: Application in the Total Synthesis of ($\pm$)-Euplotin A. *J. Am. Chem. Soc.* **2001**, *123*, 9455–9456.

Chapter 6. Synthetic Studies Toward Plumisclerin A

6.1 Hetero-Diels–Alder Approach

6.1.1 Background and Retrosynthesis

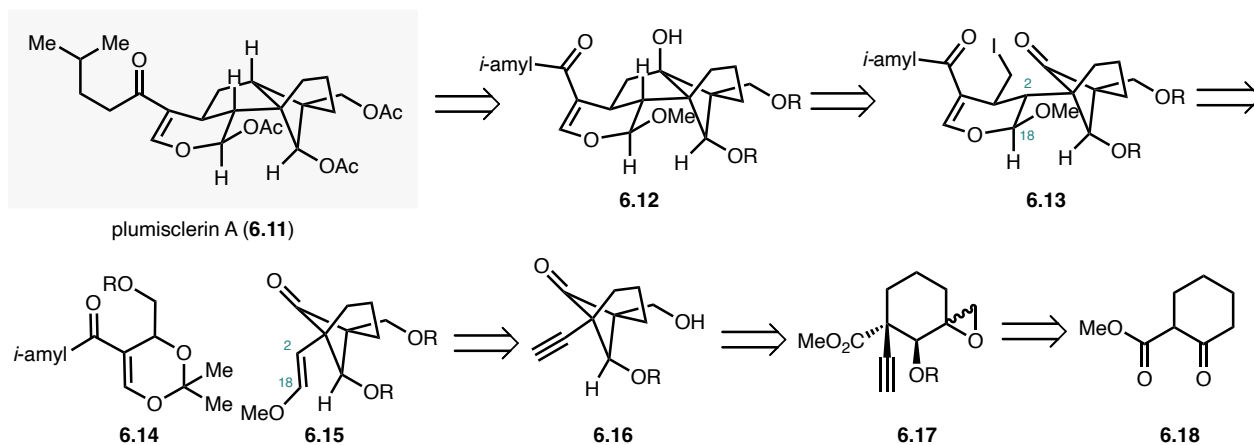
Our strategy to employ dioxine fragment **6.14** in a retro-cycloaddition-cycloaddition sequence for the construction of the *trans*-fused dihydropyran ring was inspired by Funk's total synthesis of euplotin A (**6.8**), in which the natural product features a molecular architecture closely related to that of plumisclerin A (**6.11**, Scheme 6.1).¹ Fragment **6.5** was synthesized from alkylated dioxanone **6.4** through conversion to the corresponding vinyl triflate, followed by Pd-catalyzed carbonylative amination to furnish Weinreb amide **6.5** (Scheme 6.1a). Additional studies by Funk and co-workers demonstrated that the ketone analog of **6.9** is unstable under prolonged heating and does not undergo the desired intramolecular hetero-Diels–Alder cycloaddition.² In contrast to **6.9**, the corresponding Weinreb amide substrates exhibited greater stability and could be readily isolated and were therefore employed in the total synthesis.



Scheme 6.1. Total synthesis of euplotin A (**6.8**) by Funk.¹

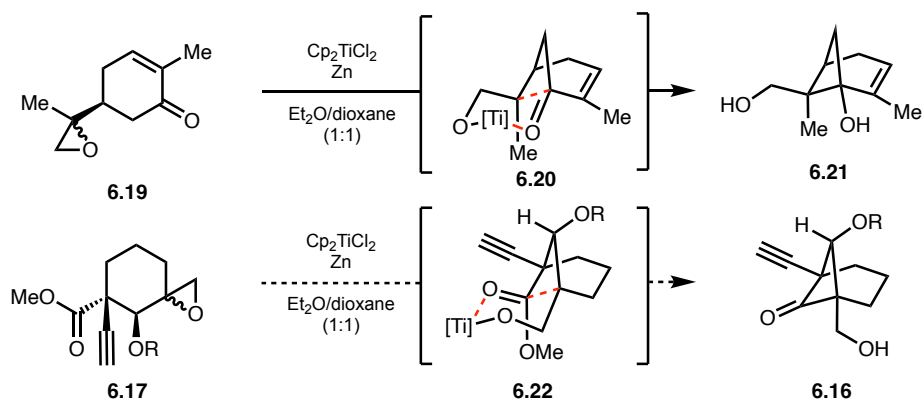
On the basis of this precedent, we sought to apply this cycloaddition strategy toward plumisclerin A (**6.11**). Our initial approach involved the independent preparation of two fragments, **6.14** and **6.15**, followed by an intermolecular retro-cycloaddition-cycloaddition sequence to furnish intermediate **6.13** (Scheme 6.2). Regarding the construction of the final cyclopentane ring, we envisioned converting the methylene alcohol group into an alkyl halide upon deprotection,

which would then undergo nucleophilic addition into the ketone to form the cyclopentane ring in **6.12**. Subsequent deoxygenation of the resulting tertiary alcohol would ultimately furnish **6.11**.



Scheme 6.2. Proposed retrosynthesis of plumisclerin A (**6.11**) using intermolecular hetero-Diels–Alder approach.

For the construction of bicyclo[3.1.1]heptane system **6.16**, we drew inspiration from the synthesis of the structurally related compound **6.21** from epoxy-carvone **6.19** (see Chapter 2). Careful comparison and structural overlay with **6.21** led us to identify compound **6.17** as a suitable precursor for the key titanocene-mediated reductive cyclization step (Scheme 6.3).

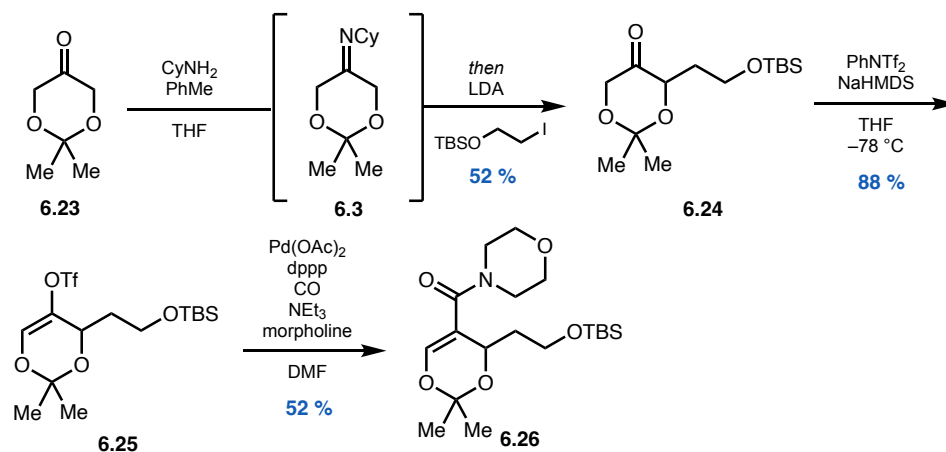


Scheme 6.3. Comparison of reductive cyclization with epoxy-carvone **6.19** and proposed epoxy ester precursor **6.17**.

With the installation of the alkynyl substituent in **6.17**, we envisioned that this functional group can be leveraged for hydrosilylation or other related transformations to access the corresponding enol ether (i.e., **6.15**). To establish the desired trans-substitution pattern at C2 and C18 in **6.12**, a trans-alkene geometry of the parent alkyl enol ether **6.15** was required. Ultimately, we anticipated that precursor **6.17** could be accessed from commercially available β -keto ester **6.18**.

6.1.2 Synthesis of the Dioxine Fragment

By adapting the procedure reported by Funk and co-workers, we were able to access amide **6.26** from dioxanone **6.23** in three steps (Scheme 6.4).¹ In contrast to the original report, morpholine was employed in the carbonylative amination step in place of NHMe(OMe), as it provided improved yields and is likewise known to provide reactivity and selectivity comparable to those of a classical Weinreb amide.³

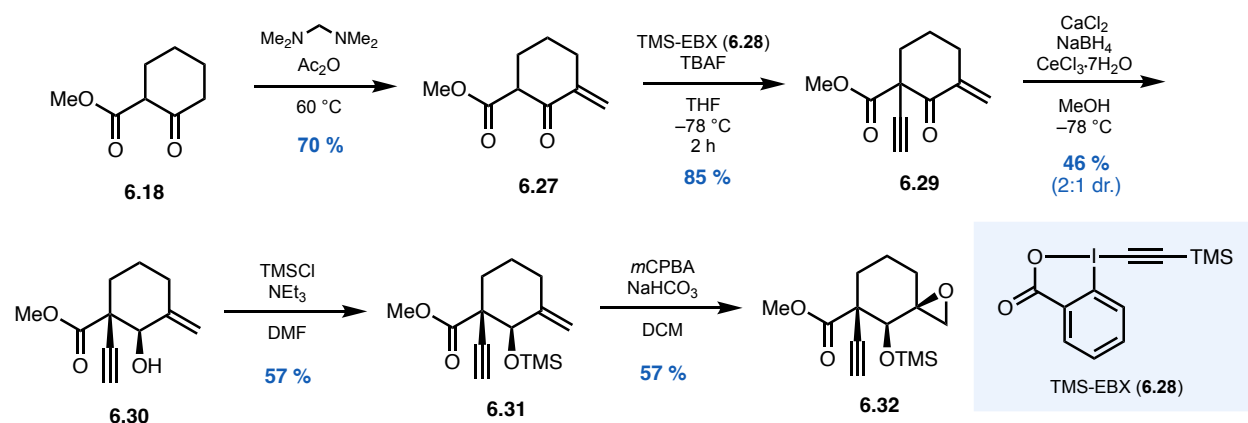


Scheme 6.4. Preparation of the dioxine fragment with modified procedure by Funk.

The OTBS-substituted alkyl side chain appended to the dioxine fragment **6.26** will ultimately require further functional group manipulation to achieve formation of the cyclopentane ring present in the natural product. However, for the initial evaluation of the feasibility of the envisioned hetero-Diels–Alder strategy using this fragment, we elected to proceed with the known compound and explore side-chain derivatization studies at a later stage.

6.1.3 Synthesis of the Bicyclo[3.1.1]heptane Fragment

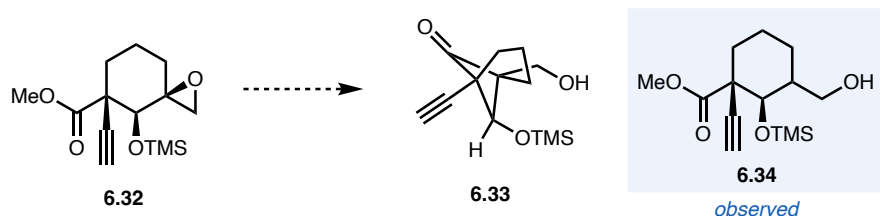
The synthesis of the desired bicyclo[3.1.1]heptane fragment commenced with an Eschenmoser methenylation of commercially available β -keto ester **6.18** (Scheme 6.5).⁴ Subsequent electrophilic alkynylation using Waser's reagent (TMS-EBX , **6.28**) furnished the corresponding alkynylated product (**6.29**) in 85 % yield.⁵ Luche reduction of the enone afforded alcohol **6.30**, which upon protection with TMSCl underwent epoxidation with $m\text{CPBA}$ to provide intermediate **6.32**.⁶



Scheme 6.5. Preparation of alkynyl ester precursor **6.32**.

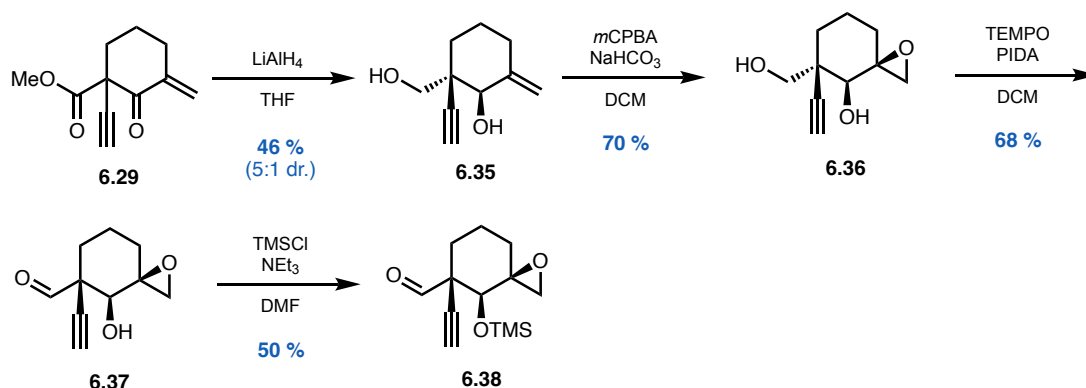
Our initial objective was to exploit the ester functionality as the electrophile in the titanocene-mediated cyclization step, as the resulting hemiacetal could be readily hydrolyzed to the corresponding ketone (see **6.16**) during work-up, thus avoiding a separate oxidation step. However, despite extensive screening of reductive cyclization conditions using Cp_2TiCl_2 and various metal reductants, desired bicyclic product **6.33** could not be obtained. Instead, the only identifiable product was reduction product **6.34**, suggesting that addition of the tertiary radical to the ester functionality was not viable.

Table 6.1. Reductive cyclization with alkynyl ester precursor **6.32**.



entry	Reaction conditions	Result
1	Cp_2TiCl_2 , Zn, TMSCl, dioxane/ Et_2O (1:1), r.t., 16 h	no reaction
2	Cp_2TiCl_2 , Zn, collidine·HCl, THF, r.t., 16 h	no reaction
3	Cp_2TiCl_2 , Mn, TMSCl, THF, r.t., 16 h	6.34
4	Cp_2TiCl_2 , Mn, TMSCl, THF, 55 °C, 16 h	decomposition

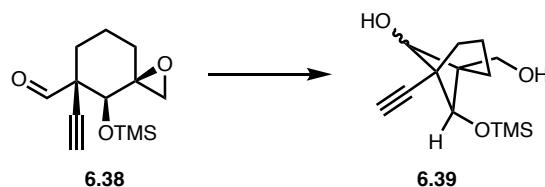
Recognizing the relatively low electrophilicity of the ester group, we opted to replace it with a more reactive aldehyde. Accordingly, the synthesis sequence was modified as outlined in Scheme 6.6. In place of Luche reduction conditions, global reduction with LiAlH_4 was performed to obtain diol **6.35**,⁷ which underwent sequential chemoselective TEMPO oxidation of the primary hydroxy group. Protection of the remaining secondary alcohol with TMSCl afforded **6.38**.



Scheme 6.6. Preparation of alkynyl aldehyde precursor **6.38**.

With corresponding aldehyde precursor **6.38** in hand, we next evaluated the proposed reductive cyclization reaction (Table 6.2). The use of Zn as the reductant resulted in a generally messier reaction profile, indicating competing decomposition pathways under these reaction conditions. In contrast, switching to Mn as the reductant, which is known to reduce Ti(IV) to Ti(III) slower than Zn, led to a cleaner overall reaction outcome.⁸ Further, benzene was employed as a co-solvent, in which Ti(IV) species are less soluble and consequently exhibit diminished reactivity. Under these optimized conditions, the product yield and reaction profile were generally improved (Table 6.2, entry 4).

Table 6.2. Reductive cyclization with alkynyl aldehyde precursor **6.38**.

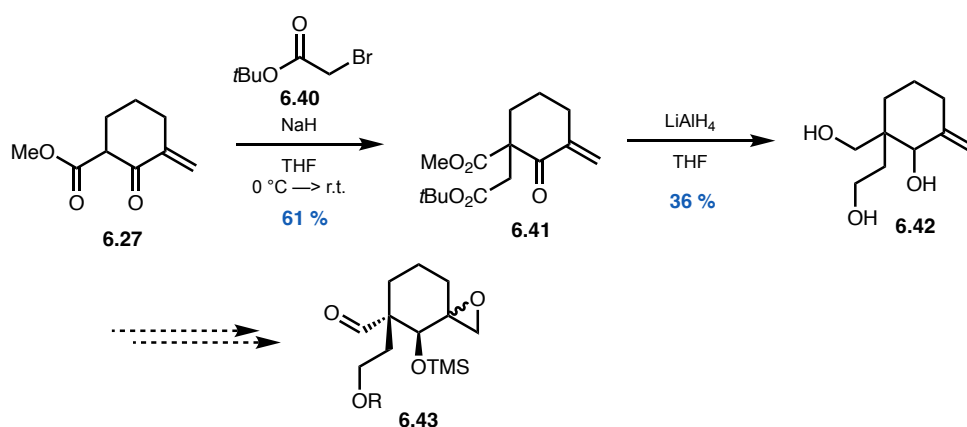


entry	Reaction conditions	Result
1	Cp ₂ TiCl ₂ , Mn, TMSCl, THF, r.t., 16 h	6 %
2	Cp ₂ TiCl ₂ , Mn, THF, r.t., 16 h	11 %
3	Cp ₂ TiCl ₂ , Zn, THF, r.t., 16 h	4 %
4	Cp ₂ TiCl ₂ , Mn, PhH:THF (5:1), 16 h	39 %
5	Cp ₂ TiCl ₂ , Mn, PhH:THF (10:1), 16 h	12 %
6	Cp ₂ TiCl ₂ (20 mol%), Mn, THF, 16 h	no reaction
7	Cp ₂ TiCl ₂ (20 mol%), Mn, PhH:THF (5:1), 16 h	no reaction
8	Cp ₂ TiCl ₂ (20 mol%), Mn, 2,4,6-collidine·HCl, PhH:THF (5:1), r.t., 16 h	no reaction

However, despite further screening of reaction conditions aimed at improving the yield, no conditions provided the product beyond 39 %. We began to consider whether the alkynyl group might be responsible for alternative reaction pathways, potentially due to its propensity to

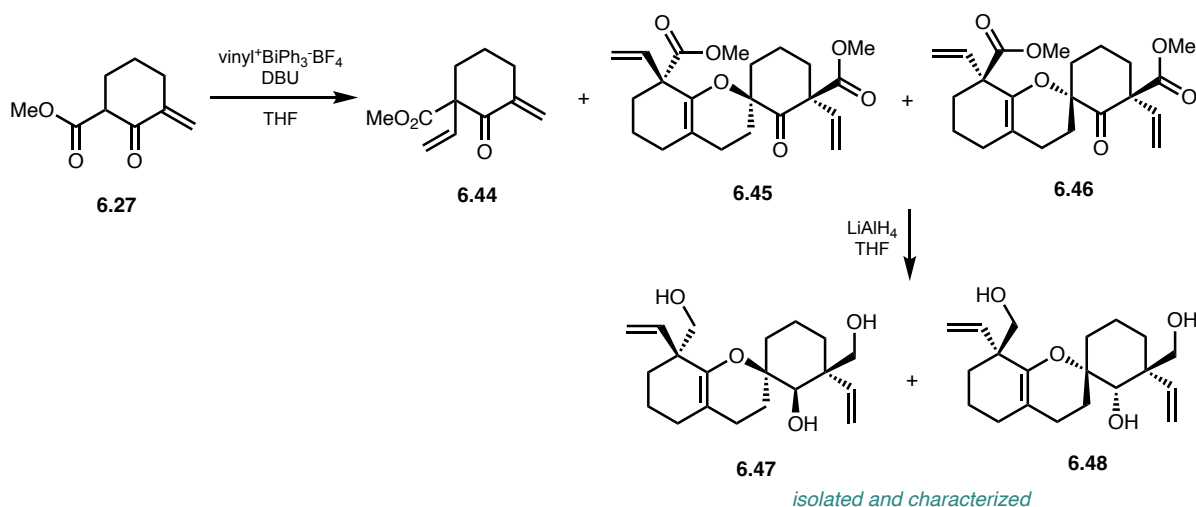
coordinate to the titanocene reagent.⁹ Consequently, we sought to explore alternative functional groups appended to the precursor in place of the alkynyl moiety.

Regarding the necessary oxidation of the vinyl side chain to install the alkyl enol ether functionality, we initially considered introducing an oxidized side chain on β -keto ester **6.18**. Alkylation with *t*-butyl 2-bromoacetate **6.40** proceeded smoothly, affording the desired product in 61 %. However, subsequent global reduction gave rise to a triol (**6.42**) as a diastereomeric mixture, which proved challenging to separate and characterize. Furthermore, differentiation of the individual alcohol groups in **6.42** did not appear straightforward. Since stepwise, selective protection and deprotection of the alcohols downstream in the synthesis would significantly lengthen the overall synthesis sequence toward the corresponding reductive cyclization precursor analog **6.43**, this route was ultimately abandoned.



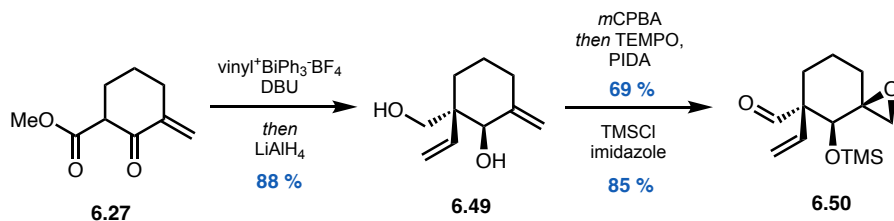
Scheme 6.7. Attempted preparation of alkylated precursor **6.43**.

Accordingly, we switched to preparation of vinyl analog **6.50** (Scheme 6.9). The synthesis was reinitiated with an Eschenmoser methenylation on β -keto ester **6.18**, followed by electrophilic vinylation using the vinyl bismuth reagent reported by Rawal and co-workers, which afforded the desired product in good yield.¹⁰ However, during scale-up to multigram quantities, we observed undesired dimerization of **6.44** via a hetero-Diels–Alder cycloaddition. The resulting cycloadduct diastereomers **6.47** and **6.48** were isolated and characterized following global reduction with LiAlH₄ (Scheme 6.8).



Scheme 6.8. Electrophilic vinylation of β -keto ester **6.27** and subsequent hetero-Diels–Alder reaction.

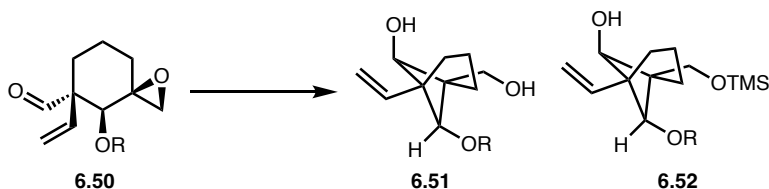
This issue was addressed by performing a one-pot vinylation and global reduction protocol, which afforded diol **6.49** in 88 % yield (Scheme 6.9). Subsequent one-pot epoxidation and TEMPO oxidation, followed by alcohol protection with TMSCl were carried out under the previously established reaction conditions. In total, we were able to prepare **6.50** in 4 steps from **6.18**.



Scheme 6.9. Preparation of vinyl aldehyde precursor **6.50**.

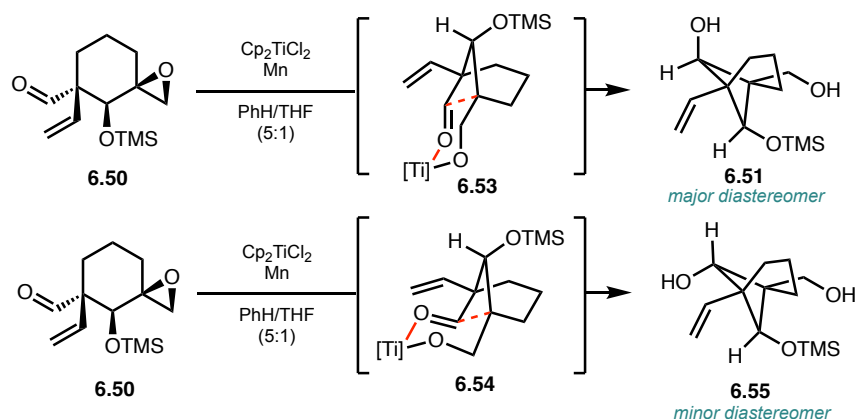
Epoxy-aldehyde precursor **6.50** afforded the desired bicyclic product (**6.51**) in up to 65 % yield upon optimization (Table 6.3). Attempts to achieve cyclization using alternative protecting groups in place of TMS, such as MOM or TES, either did not lead to conversion of starting material or afforded the desired product in lower yield (Table 6.3, entries 2 and 3). Moreover, a one-pot cyclization and *in situ* protection of the primary alcohol via addition of TMSCl proved unsuccessful: addition of TMSCl either prior to or after completion of the cyclization led to no protection (Table 6.3, entry 4). Consequently, **6.51** was protected as the corresponding TBS silyl ether (see **6.52**) in a separate step (Scheme 6.11).

Table 6.3. Reductive cyclization with vinyl aldehyde precursor **6.50**.



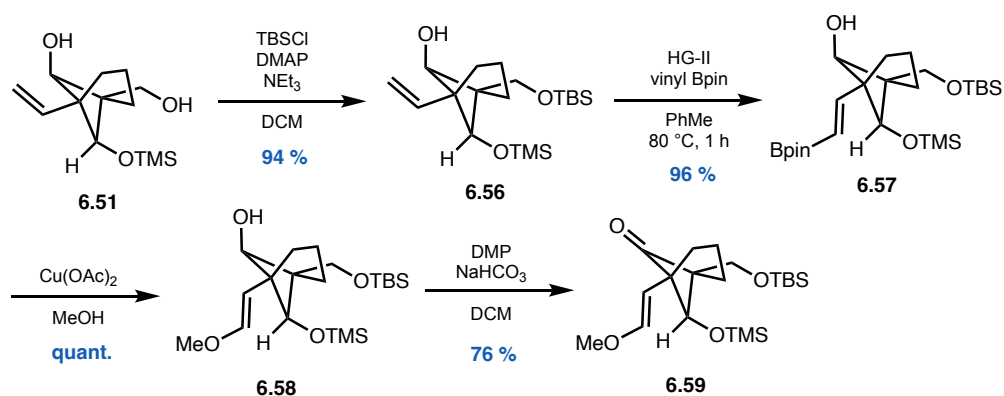
entry	R	Reaction condition	Result
1	TMS	Cp ₂ TiCl ₂ , Mn, PhH:THF, r.t., 16 h	65 % (6.51)
2	TES	Cp ₂ TiCl ₂ , Mn, PhH:THF, r.t., 16 h	20 % (rsm 6.50)
3	MOM	Cp ₂ TiCl ₂ , Mn, PhH:THF, r.t., 16 h	20 % (6.51)
4	TMS	Cp ₂ TiCl ₂ , Mn, TMSCl, PhH:THF, r.t., 16 h	47 % (6.51)

Similar to the reductive cyclization of the alkyne precursor **6.38**, the cyclization product was obtained as a mixture of diastereomers (Scheme 6.10). We propose that a possible syn-pentane interaction between the hydroxy group and the bridging methine favored the formation of **6.51** as the major product. Additionally, eclipsing interactions between the aldehyde group and the vinyl group in **6.54** may be energetically less favorable than those in transition state **6.53**, thereby leading to higher yields of **6.51**.



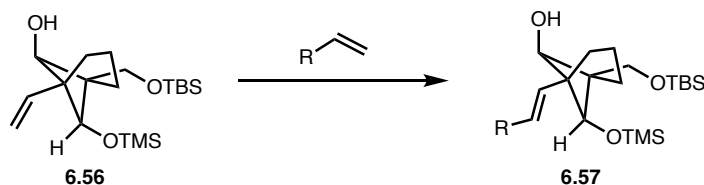
Scheme 6.10. Diastereoselectivity of reductive cyclization.

Next, we focused on the construction of the enol ether on bicycle **6.51**. The most straightforward approach involved cross metathesis. However, as cross metathesis reactions with vinyl acetates are not well preceded in the literature, we instead considered more general alkyl enol ethers, such as methyl or ethyl enol ether, which could be readily hydrolyzed and subsequently acetylated following cycloaddition as in the natural product. Ultimately, cross metathesis employing ethyl enol ether did not furnish the desired product (Table 6.4). Consequently, we pursued a stepwise strategy and first subjected the substrate to cross-metathesis with vinyl pinacol boronate, affording the corresponding product in 96 % yield (Table 6.4, entry 4). Subjection of the vinyl pinacol boronate intermediate **6.57** to Chan–Lam coupling conditions using Cu(OAc)₂, NEt₃, and MeOH afforded enol ether **6.58**.¹¹ This intermediate was transformed to the corresponding ketone (**6.59**) under Dess–Martin oxidation conditions.



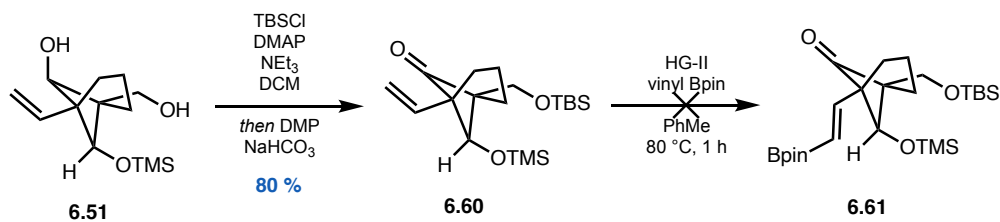
Scheme 6.11. Preparation of methyl enol ether bicycle **6.59**.

Table 6.4. Cross metathesis screening table.



entry	Reaction conditions	R	Result
1	Grubbs-II, DCM, 40 °C, 16 h	OEt	no reaction
2	HG-II, DCM, 40 °C, 16 h	OEt	no reaction
3	HG-II, PhMe, r.t., 16 h	Bpin	64 %
4	HG-II, PhMe, 80 °C, 2 h	Bpin	96 %

In the interest of streamlining the synthesis and reducing the step count, we carried out the protection of primary alcohol **6.51** in the same pot as the oxidation step, affording ketone **6.60** in 80 % yield. However, the metathesis reaction did not proceed to give borylated ketone **6.61** (Scheme 6.12).



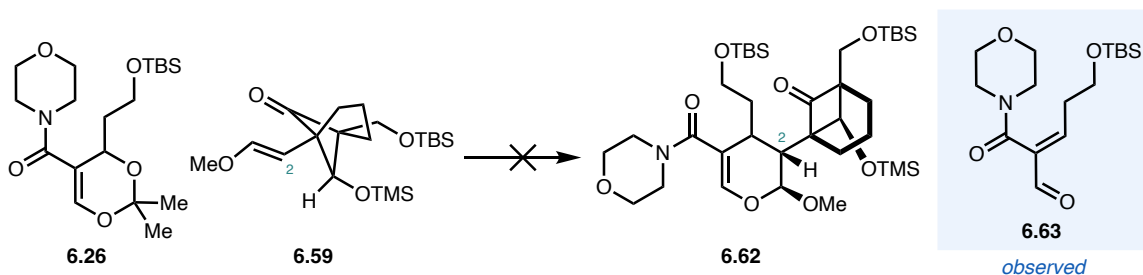
Scheme 6.12. Alternative attempt to access vinyl pinacol boronate **6.61**.

6.1.4 Intermolecular Hetero-Diels–Alder

With the two hetero-Diels–Alder precursors (**6.26** and **6.59**) in hand, we next evaluated the feasibility of the cycloaddition. Despite extensive screening of reaction conditions, the desired

cycloaddition product (**6.62**) was not obtained (Table 6.5). Instead, only formation of the corresponding enal (**6.63**), arising from retro-cycloaddition, was observed.

Table 6.5. Intermolecular hetero-Diels–Alder.



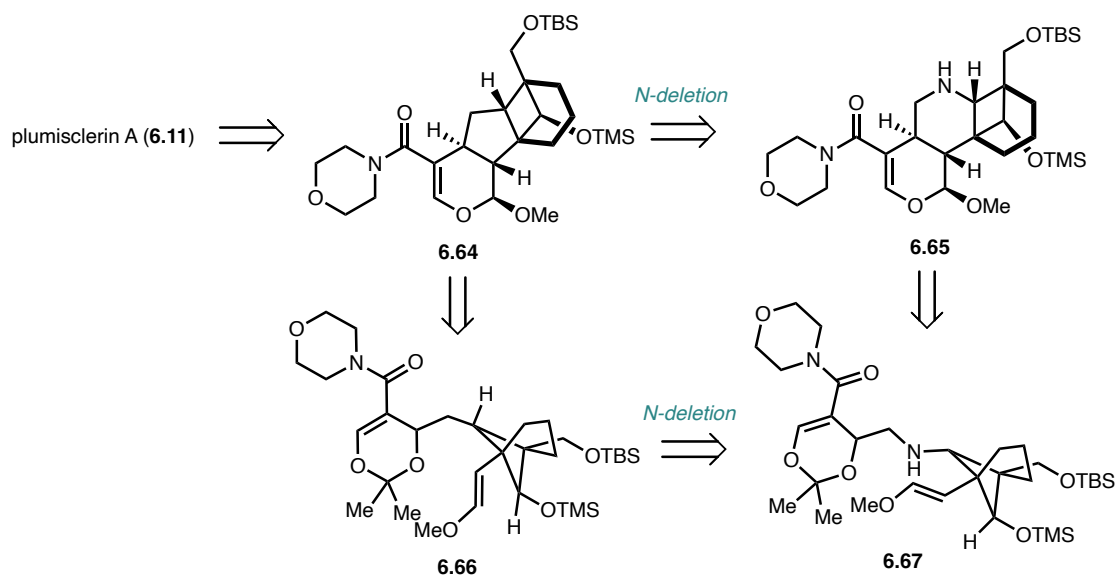
entry	Reaction conditions	Result
1	PhMe, 110 °C, 1 h	no reaction
2	PhMe, 110 °C, 16 h	no reaction
3	PhMe, 150 °C, microwave, 1 h	no reaction
4	1,2-dichlorobenzene, 200 °C, microwave, 1 h	no reaction
5	Yb(fod) ₃ , PhH, 80 °C, 16 h ^{a 12}	no reaction
6	Yb(fod) ₃ , DCM, r.t., 16 h ^{a 12}	no reaction
7	EtAlCl ₂ , DCM, −78 °C → 0 °C, 1 h ^a	decomposition
8	AlCl ₃ , PhH, 90 °C, 16 h ^{a 13}	decomposition
9	ZnCl ₂ , PhH, 90 °C, 16 h ^{a 14}	decomposition
10	Cr-Jacobsen catalyst, neat, r.t., 16 h ^{a 15}	no reaction
11	Cu(OTf) ₂ , box ligand, DCM, −78 °C → r.t ^{a 16}	no reaction

^a enal **6.63** was used for the reaction

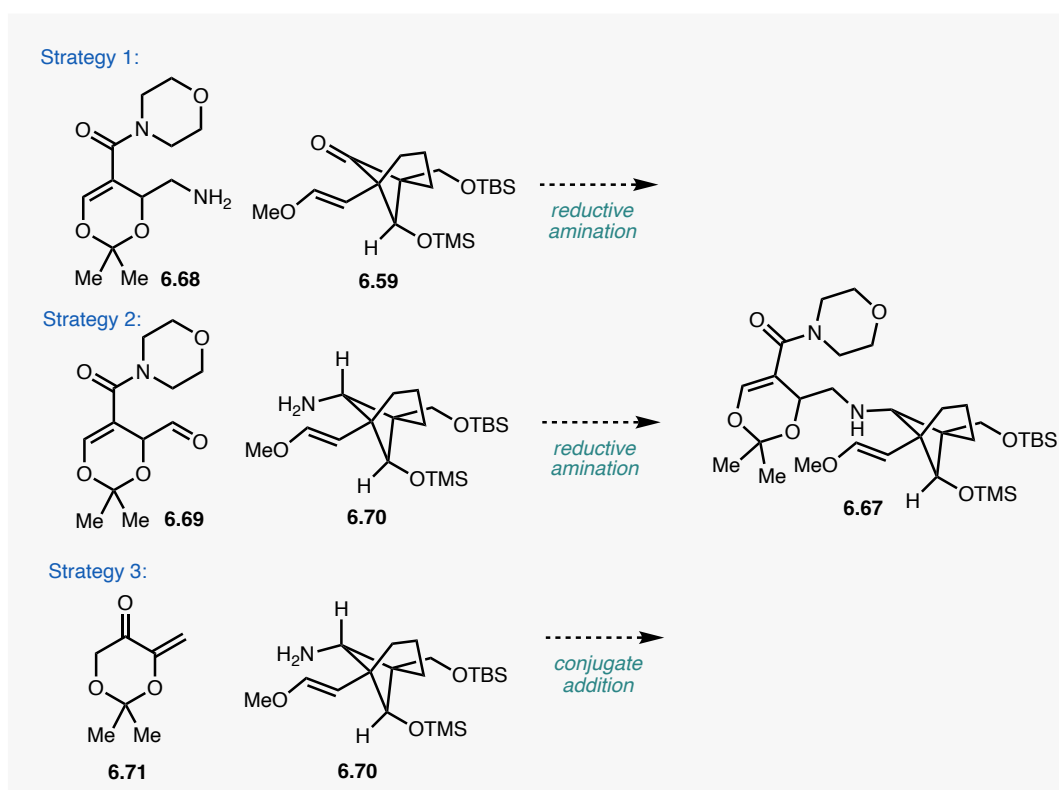
On the basis of repeated recovery of unreacted starting material and the generally clean reaction profiles, we hypothesized that the neopentyl-like steric environment of the methyl enol ether dienophile at C2 hindered productive approach of the diene required for cycloaddition (see structure in Table 6.5). Therefore, our attention shifted toward tethering the two fragments to facilitate an intramolecular hetero-Diels–Alder reaction, similar to reports by Funk and co-workers in their euplotin A synthesis.¹ To this end, several tethering strategies were explored and are discussed herein.

6.1.5 Nitrogen Deletion-Intramolecular Hetero-Diels–Alder Approach

One potential strategy for tethering the two fragments involved the preparation of intermediate **6.67** via C–N bond formation (Scheme 6.13). This approach was inspired by the recent work of Renata and co-workers on lycoposerramine congeners, in which they leveraged a late-stage nitrogen deletion approach to access their key intermediate following reductive amination to join two addends.¹⁷ From intermediate **6.67**, either direct nitrogen deletion to **6.66** could be envisioned, or alternatively, the cycloaddition could be first performed prior to subsequent removal of the nitrogen atom from the piperidine ring to obtain **6.65** (Scheme 6.13).



Scheme 6.13. Retrosynthesis of nitrogen deletion strategy.

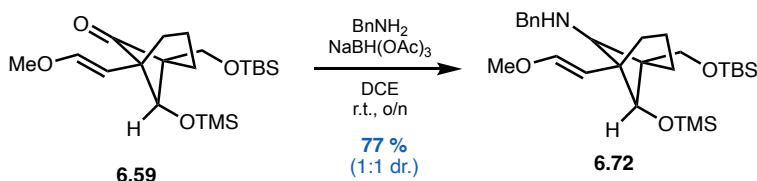


Scheme 6.14. Explored strategies to access C–N tethered intermediate **6.67**.

Several potential strategies for the formation of the desired C–N bond were considered, and the corresponding approaches are summarized in Scheme 6.14. Analogous to the strategy reported by Renata and co-workers, our initial approach involved reductive amination between amine **6.68** and ketone **6.59** (Strategy 1). A related disconnection was also envisioned employing aldehyde

6.69 and amine **6.70** to forge the same C–N bond (Strategy 2). As an alternative strategy, we considered preparation of intermediate **6.67** via Eschenmoser methenylation on **6.23** to enable subsequent conjugate addition, although this approach is less convergent (Strategy 3).

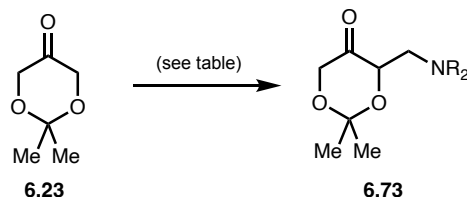
The successful preliminary reductive amination with **6.59** and benzylamine provided support for the viability of the proposed strategy and nitrogen deletion approach (Scheme 6.15).



Scheme 6.15. Reductive amination with benzylamine.

Accordingly, we initiated the preparation of literature-reported amine-substituted dioxanones to explore Strategy 1 (Table 6.6, entries 1 and 2). Other alkylation precursors, such as **6.76** and **6.77**, were also employed in the pursuit of other primary amine precursors, however these efforts did not provide the desired product (Table 6.6, entries 3 and 4).

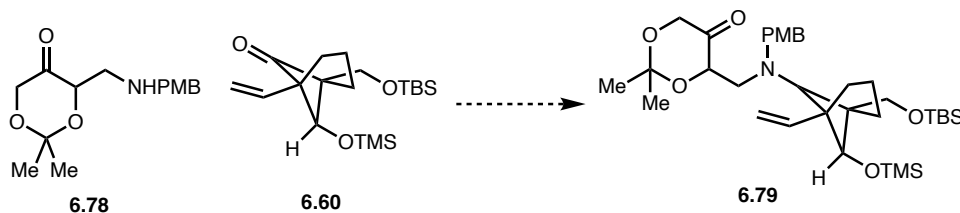
Table 6.6. Alkylamination of dioxanone.



entry	Amine precursor	Reaction condition	Result
1	 6.74	6.74 , formaldehyde, DMF ¹⁸	82 %
2	 6.75	6.75 , proline, DMF ¹⁹	complex mixture
3	 6.76	NH_2Cy , PhMe, <i>then</i> LDA, 6.76 ¹	complex mixture
4	 6.77	NH_2Cy , PhMe, <i>then</i> LDA, 6.77 ¹	complex mixture

As methyl enol ether **6.59** contains an acid-labile functional group, we explored reductive amination conditions with the more stable cyclobutanone (**6.60**). Reductive amination with the obtained PMB protected dioxanone **6.78** and cyclobutanone **6.60** was attempted but proved unsuccessful (Table 6.7). We hypothesized that the steric demand associated with the secondary amine impeded productive amination with ketone **6.60**. As a result, our efforts shifted toward accessing the corresponding primary amine following deprotection.

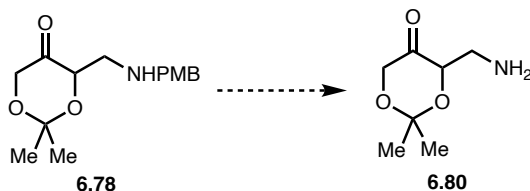
Table 6.7. Reductive amination with secondary amine **6.78** and cyclobutanone **6.60**.



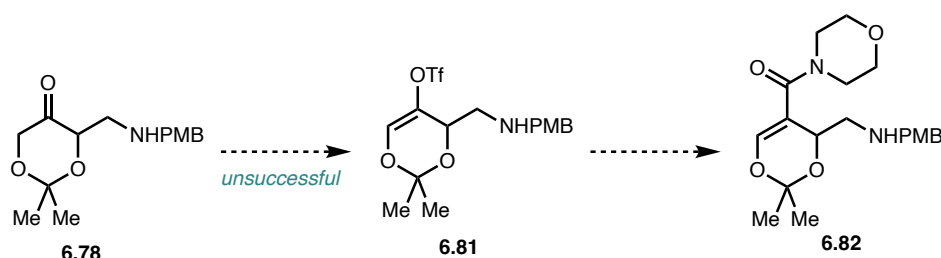
entry	Reaction conditions	Result
1	NaBH(OAc) ₃ , DCE, mol sieves, r.t., 16 h	no reaction
2	NaBH(OAc) ₃ , DCE, mol sieves, 65 °C, 16 h	no reaction
3	NaBH(OAc) ₃ , AcOH, DCE, mol sieves, r.t., 16 h	no reaction
4	NaBH(OAc) ₃ , NEt ₃ , DCE, mol sieves, r.t., 16 h	no reaction
5	Re ₂ O ₇ , NaBF ₄ , DCE, r.t., 16 h ²⁰	decomposition
6	B(OCH ₂ CF ₃) ₃ , THF, <i>then</i> NaBH(OAc) ₃ ²¹	decomposition

To our surprise, deprotection of the amine proved unsuccessful, predominantly resulting in either recovery of starting material or decomposition (Table 6.8). With the goal of exploring PMB deprotection after obtaining corresponding amide **6.82**, we attempted to advance this intermediate (Scheme 6.16). However, conversion of amine **6.78** to the corresponding amide (**6.82**) was also unsuccessful.

Table 6.8. Amine deprotection

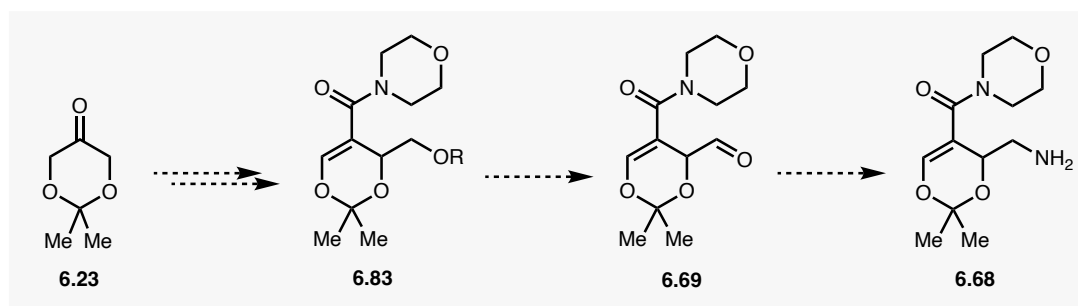


entry	Reaction conditions	Result
1	CAN, MeCN/H ₂ O, 0 °C	decomposition
2	PIDA, MeOH, r.t.	decomposition
3	DDQ, DCM/H ₂ O, r.t.	decomposition
4	Pd/C, H ₂ , MeOH, r.t.	no reaction
5	Pd(OH) ₂ , H ₂ , MeOH, r.t.	no reaction



Scheme 6.16. Attempted preparation of PMB amine dioxine fragment **6.82**.

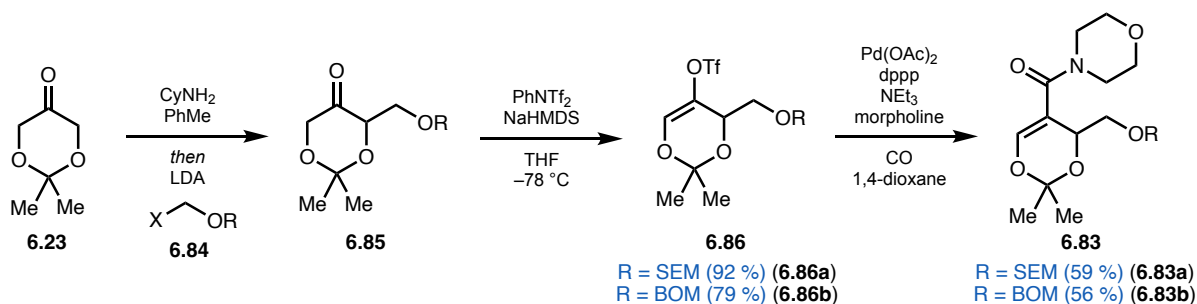
After repeated unsuccessful attempts to access primary amine **6.80** directly from dioxanone **6.23**, we turned to accessing primary amine **6.68** from aldehyde **6.69** via reductive amination (Scheme 6.17). In addition to its role as an intermediate for Strategy 1, we also saw aldehyde **6.69** as relevant for the exploration of Strategy 2.



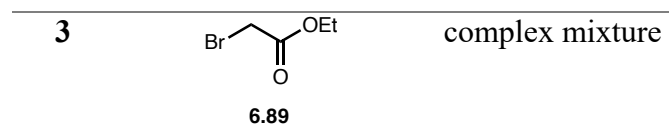
Scheme 6.17. Synthesis outline of primary amine **6.68** preparation using reductive amination approach.

Using available alkyl halides **6.87** and **6.88**, we were able to prepare the corresponding alkylation products in low to moderate yields, which were subsequently converted to their corresponding amides **6.83a** and **6.83b**, respectively (Table 6.9).

Table 6.9. Alkylation of dioxanone.

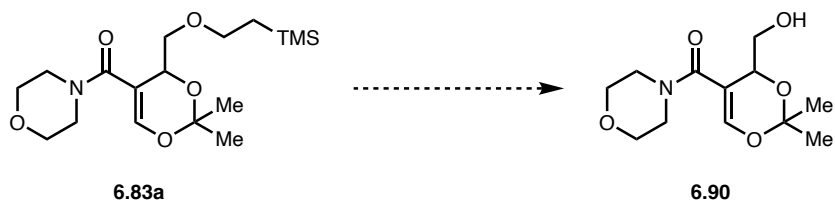


entry	Alkylation precursor	Result
1	<chem>ClCCOBn</chem> 6.87	51 %
2	<chem>ClCCOSEM</chem> 6.88	28 %



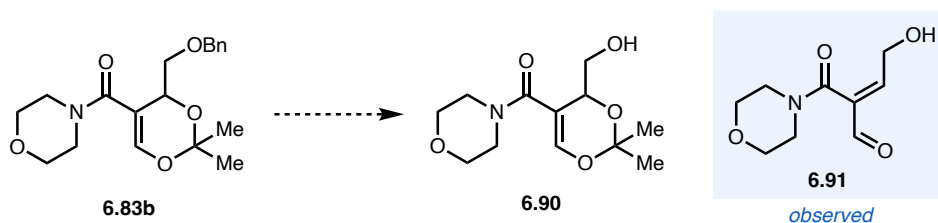
However, to our surprise, deprotection of **6.83a** and **6.83b** to afford the primary alcohol once again was unsuccessful. The explored deprotection conditions with **6.83a** predominantly afforded recovered starting material or decomposition (Table 6.10). Under mild deprotection conditions with $\text{BCl}_3 \cdot \text{DMS}$, we were able to observe deprotection with concomitant hydrolysis of the dioxine moiety to afford enal **6.91** (Table 6.11, entry 3).²² Similar results were obtained when exploring oxidative debenzoylation conditions on **6.83b**, with observation of the corresponding enal aldehyde (**6.92**) in the crude mixture (Table 6.12, entry 1).

Table 6.10. SEM deprotection.



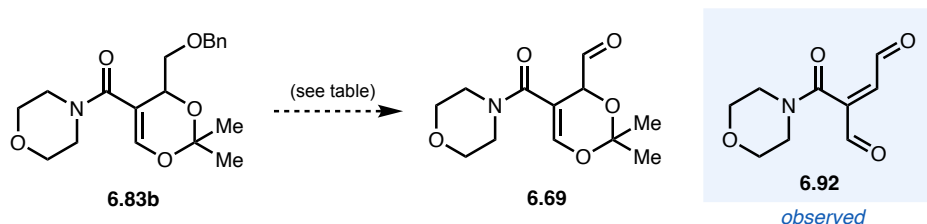
entry	Reaction conditions	Result
1	TBAF, THF	no reaction
2	HF · py, MeCN, 16 h	no reaction
3	HF · py, MeCN, 3 d	no reaction
3	$\text{BF}_3 \cdot \text{OEt}_2$, DCM, 0 °C → r.t.	decomposition

Table 6.11. Benzyl alcohol deprotection.



entry	Reaction conditions	Result
1	Pd/C, H_2 , EtOH	no reaction
2	$\text{Pd}(\text{OAc})_2$, Et_3SiH , NEt_3 , DCM ²²	no reaction
3	$\text{BCl}_3 \cdot \text{DMS}$, DCM ²³	65 % (6.91)
4	I_2 , Et_3SiH , EtOAc ²⁴	decomposition

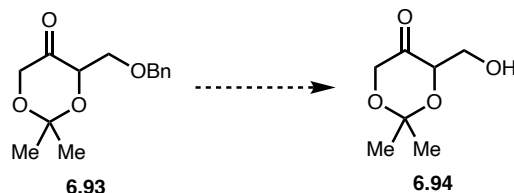
Table 6.12. Oxidative debenzoylation.



entry	Reaction conditions	Result
1	Bobbitt's salt, MeCN/H ₂ O ²⁵	6.92 observed in crude
2	KBr, oxone, MeCN ²⁶	decomposition

Likewise, attempted hydrogenolysis of dioxanone **6.93** gave no conversion of starting material (Table 6.13).

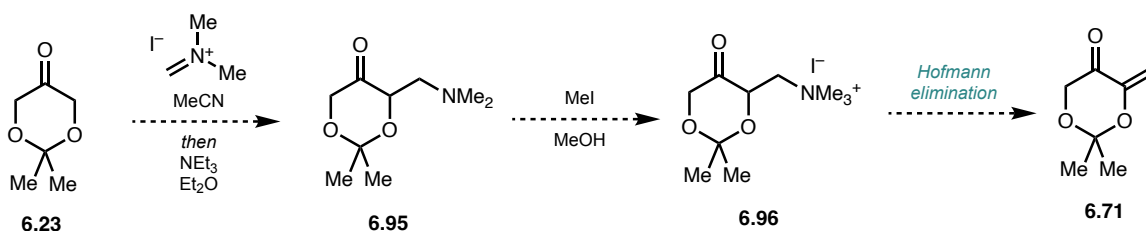
Table 6.13. Hydrogenolysis.



entry	Reaction conditions	Result
1	Pd/C, H ₂ , MeOH, 16 h	no reaction
2	Pd(OH) ₂ , H ₂ , MeOH, 16 h	no reaction
3	PtO ₂ , H ₂ , MeOH, 16 h	no reaction

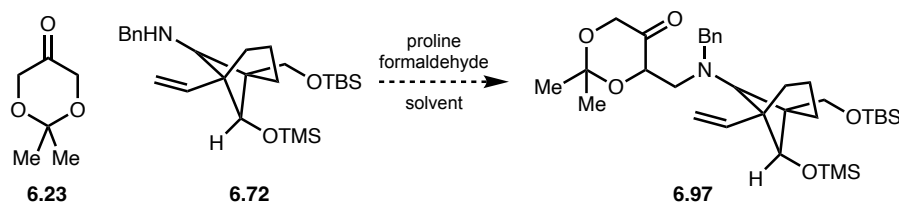
From these results, it became apparent that the dioxine moiety is sensitive to both elevated temperatures and acidic conditions, thereby significantly limiting the range of compatible reaction conditions for the desired deprotection.

Lastly, regarding formation of the desired C–N bond without the involvement of protecting groups, we considered a conjugate addition of amine **6.72** to α,β -unsaturated dioxanone **6.71**, which corresponds to Strategy 3 (Scheme 6.14). Our attempts to access intermediate **6.71** via Eschenmoser methenylation, previously performed on β -keto ester **6.18** (Scheme 6.5), were unsuccessful. Alternatively, a stepwise sequence to install the *exo*-methylene group via Mannich reaction, amine methylation, and Hofmann elimination was explored (Scheme 6.18).²⁷ However, this approach failed at the first step of the proposed sequence.



Scheme 6.18. Hofmann elimination sequence on dioxanone **6.23**.

With repeated failure to install the *exo*-methylene group, we attempted a Mannich reaction with dioxanone **6.23** and benzylamine **6.72**, which resulted in recovery of the starting material **6.72** (Scheme 6.19).

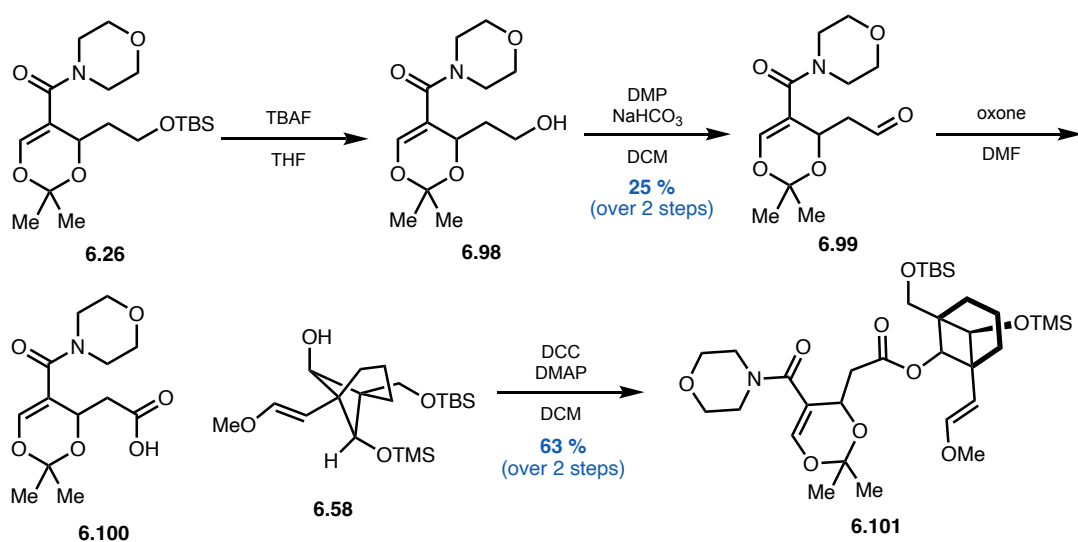


Scheme 6.19. Mannich reaction with dioxanone **6.23** and benzylamine **6.72**.

In conclusion, despite the initial success of reductive amination of cyclobutanone **6.60** using benzylamine, we were unable to access the desired primary amine (**6.68**) required to evaluate the nitrogen deletion strategy. The high instability of the dioxanone moiety under both acidic and Lewis acidic conditions significantly limited our attempts to derivatize the alkyl side chain, which is critical for the preparation of amine **6.68**.

6.1.6 Esterification-Intramolecular Hetero-Diels–Alder Approach

Given the challenges associated with derivatizing the alkyl side chain of the dioxine fragment, we instead turned to leverage intermediate **6.26**, which we had successfully prepared using a modified literature procedure (Chapter 6.1.2).¹ From the available intermediates, we assessed that the most straightforward strategy for introducing a tether to evaluate the hetero-Diels–Alder approach involved esterification between carboxylic acid **6.100** and cyclobutanol **6.58**. Gratifyingly, the corresponding carboxylic acid (**6.100**) was accessed from **6.26** in 3 steps (Scheme 6.20).²⁸ Subsequent Steglich esterification afforded desired ester **6.101** in 63 % yield.

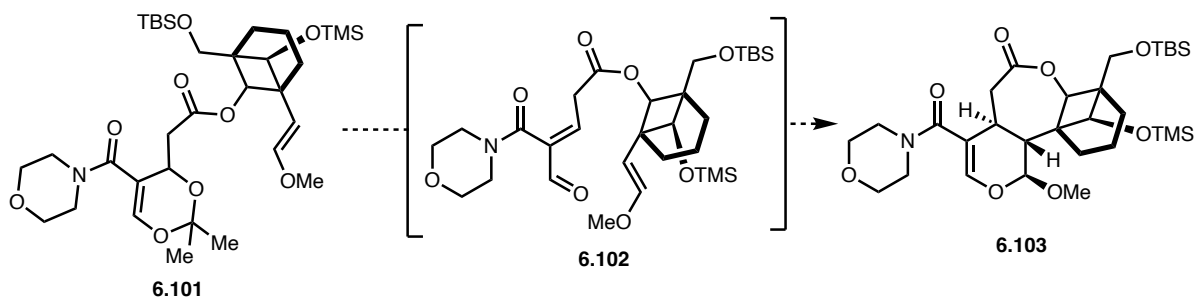


Scheme 6.20. Esterification approach.

With ester **6.101** in hand, we next evaluated hetero-Diels–Alder reaction conditions. However, to our disappointment, the desired cycloadduct (**6.103**) was not observed. Prolonged reaction times and elevated temperatures resulted in decomposition of the starting material (Table 6.14, entry 2). Even when enal **6.102** was subjected to room temperature conditions or Lewis acid at lower temperature, decomposition was still observed (Table 6.14, entries 3 and 4).

Although the diene and dienophile are formally tethered, we assume that the rigidity imposed by the ester linkage possibly prevents effective spatial proximity required for cycloaddition. In spite of the potential for rotational flexibility around the ester linkage, we assume that ester **6.103** is less stable than ketone **6.59** at the timescales required for cycloaddition conditions and therefore predominantly undergoes decomposition.

Table 6.14. Intramolecular hetero-Diels–Alder with ester **6.103**.



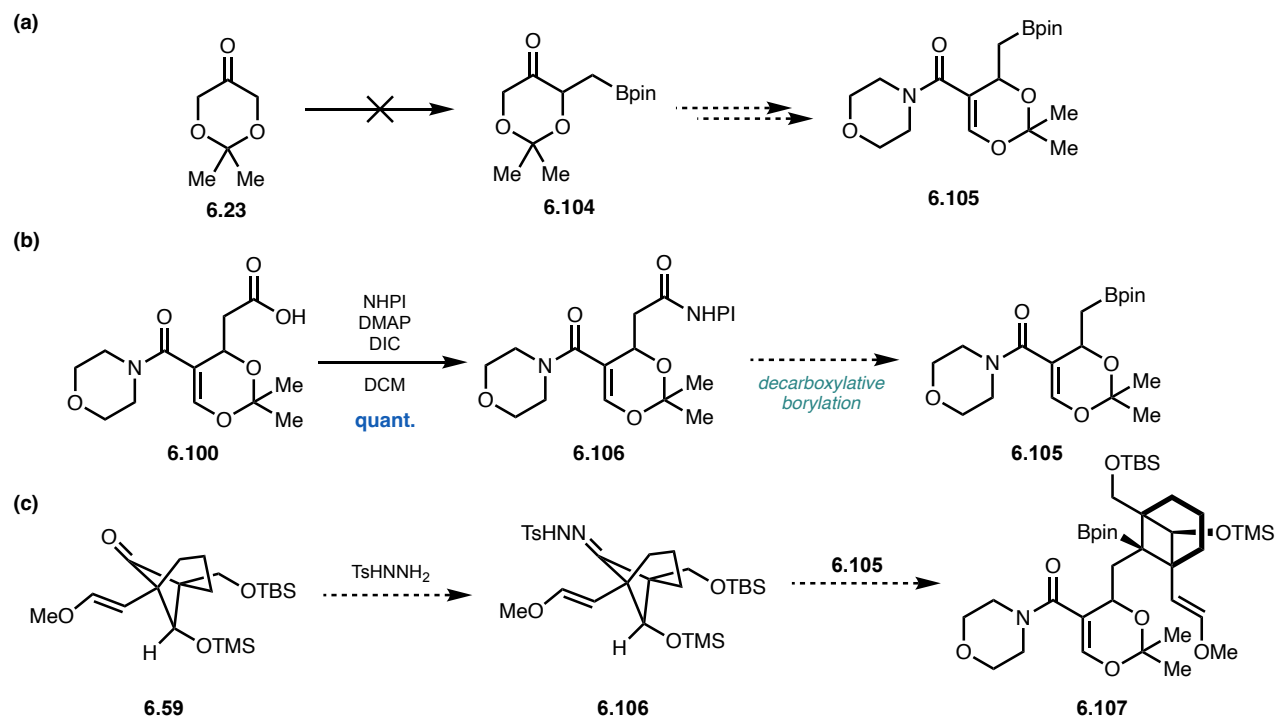
entry	Reaction conditions	Result
1	110 °C, PhMe, 1 h	enal 6.102
2	110 °C, PhMe, 16 h	decomposition
3	r.t., PhMe, 16 h ^a	decomposition
4	Et ₂ AlCl (50 mol%), DCM, –78 °C → r.t., 1 h ^a	decomposition

^a recovered enal **6.102** from entry 1 was used.

6.1.7 Matteson Coupling-Intramolecular Hetero-Diels–Alder Approach

On the basis of the hypothesis regarding the rigidity of the ester linkage in **6.103**, we also considered the formation of a direct C–C bond linkage to intermediate **6.107** using Matteson coupling conditions reported by Barluenga and co-workers (Scheme 6.21).²⁹ Consistent with the previously discussed challenges associated with derivatization of the dioxine side chain, direct access to the corresponding alkyl pinacol boronate intermediate (**6.104**) from dioxanone **6.23** proved unsuccessful (Scheme 6.21a). Consequently, we sought to obtain **6.105** from carboxylic acid **6.100** via decarboxylative borylation of redox-active ester **6.106** following the protocol reported by Baran and co-workers (Scheme 6.21b).³⁰ The corresponding redox-active ester (**6.106**) was obtained in quantitative yield. However, the desired pinacol boronate **6.105** could neither be successfully isolated nor characterized. It remains unclear whether the borylation proceeded successfully to give an unstable boronate product, or whether the substrate instead underwent decomposition under the explored reaction conditions.

On the complementary coupling partner, preparation of tosylhydrazone **6.106** from ketone **6.59** was likewise unsuccessful and only led to recovered starting material (Scheme 6.21c). As a result, the proposed Matteson coupling to furnish intermediate **6.107** including the subsequent hetero-Diels–Alder reaction could not be evaluated.



Scheme 6.21. (a) Direct alkylboronate formation with dioxanone **6.23**. (b) Decarboxylative borylation approach. (c) Tosylhydrazone formation.

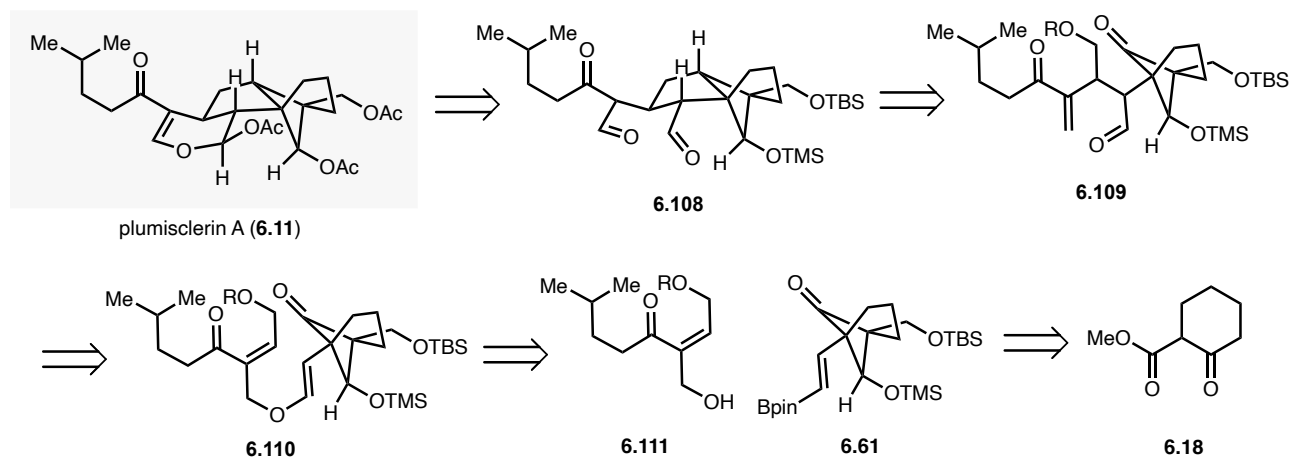
6.2 Chan–Lam Coupling–Claisen Rearrangement Approach

6.2.1 Retrosynthesis

Following repeated challenges in trying to derivatize dioxine fragment **6.26** and evaluate the key hetero-Diels–Alder reaction step, we were prompted to investigate an alternative strategy for construction of the dihydropyran moiety of the natural product. In light of our hypothesis that steric encumbrance surrounding the vinyl enol ether moiety of ketone **6.59** impeded cycloaddition, we pursued a different strategy to forge the C–C bond at C2 of bicycle **6.59**.

By leveraging intermediates accessible from the previously explored route, we opted to investigate a Claisen rearrangement to form the C–C bond at the neopentyl-like carbon of bicycle **6.59** (Scheme 6.22). Given the partial radical character associated with the Claisen rearrangement, we anticipated that formation of this sterically demanding C–C bond would proceed more readily than in the previously investigated hetero-Diels–Alder approach, thereby potentially circumventing the steric limitations associated with the cycloaddition strategy.³¹

The precursor of the Claisen rearrangement, **6.110**, could be accessed through a Chan–Lam coupling with vinyl pinacol boronate **6.61** and corresponding allylic alcohol **6.111**. Following the Claisen rearrangement, the resulting product (**6.109**) could be further elaborated to dialdehyde **6.108**, serving as a suitable intermediate for construction of the desired dihydropyran moiety following the cyclization strategy reported by Tanino and co-workers in their total synthesis of cristaxenicin A (see Chapter 5).³² For the construction of the cyclopentane ring, we are envisioning the strategy described in Chapter 6.1.1 (Scheme 6.2).



Scheme 6.22. Retrosynthesis of Claisen rearrangement approach.

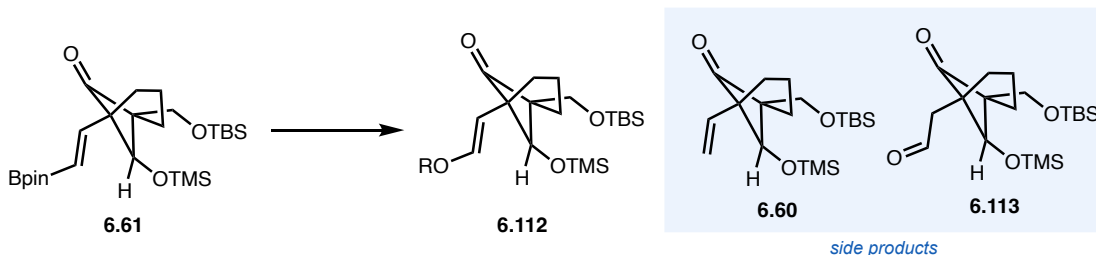
6.2.2 Chan–Lam–Coupling

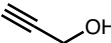
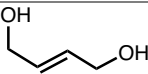
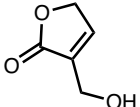
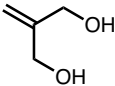
We next set out to investigate Chan–Lam coupling conditions using a range of allylic alcohols. Notably, most reported Chan–Lam couplings in the literature are conducted under relatively harsh conditions, with superstoichiometric quantities of $\text{Cu}(\text{OAc})_2$ or using the alcohol substrate as the reaction solvent. Consequently, the scope of viable alcohol substrates reported in the literature are

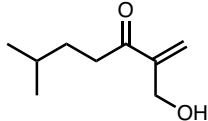
rather limited. In our earlier synthesis of methyl enol ether **6.58**, the use of $\text{Cu}(\text{OAc})_2$ and methanol as reaction solvent afforded the desired product in good yield (Table 6.15, entry 1).¹¹ However, such conditions are less suited to more structurally elaborate allylic alcohols to achieve a more convergent synthesis, particularly when the alcohol substrates require multistep preparation (e.g. **6.111**). Moreover, under these conditions, side reactions such as protodeboration to afford **6.60** and hydrolysis of the resulting alkyl enol ether to the corresponding aldehyde (**6.113**) were observed (Table 6.15).

Upon further perusal of the literature, we identified a recent report by McDonald and co-workers describing Chan–Lam coupling conditions employing substoichiometric amounts of $\text{Cu}(\text{OAc})_2$ that tolerate a variety of allylic alcohols without requiring the alcohol to serve as the reaction solvent.³³ Application of these conditions to allylic alcohol **S5** afforded the corresponding product in 22 % yield. However, more structurally elaborate allylic alcohols such as **S6** led to no conversion to the desired coupling product.

Table 6.15. Chan–Lam coupling and allylic alcohol substrate scope.^{11,33}

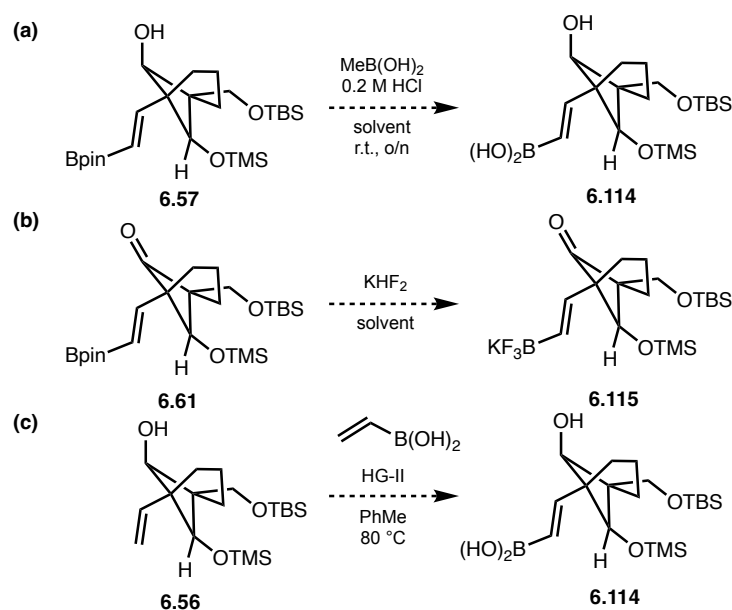


entry	Alcohol substrate	Reaction conditions	Result
1	MeOH	$\text{Cu}(\text{OAc})_2$, NEt_3 , MeOH	quant.
2	 S1	$\text{Cu}(\text{OAc})_2$, NEt_3 , MeOH	62 % (6.112) 31 % (6.113)
3	 S2	$\text{Cu}(\text{OAc})_2$, NEt_3 , MeOH	trace (6.112)
4	 S3	$\text{Cu}(\text{OAc})_2$, NEt_3 , MeOH	30 % (6.112)
5	 S4	$\text{Cu}(\text{OAc})_2$, NEt_3 , MeOH	no reaction
6	 S5	$\text{Cu}(\text{OAc})_2$, NPI, dicumyl peroxide, <i>t</i> BuOH, PhCF ₃ , 60 °C	22 % (6.112)

7		$\text{Cu}(\text{OAc})_2$, NPI, dicumyl peroxide, <i>t</i> BuOH, PhCF_3 , 60 °C	no reaction
	S6		

Given the greater number of literature reports on C–O bond coupling reactions employing vinyl boronic acids and vinyl potassium trifluoroborate salts (BF_3K), as well as their higher intrinsic reactivity relative to vinyl pinacol boronates in such transformations, we also investigated conversion of **6.57** and **6.61** to the corresponding boronate analogues.³⁴ However, these transformations were unsuccessful and resulted in complete decomposition of the starting material (Scheme 6.23a and b).

Likewise, direct installation of the vinyl boronic acid functionality via cross-metathesis with ketone **6.56** was unsuccessful and similarly led to decomposition of the starting material (Scheme 6.23c).

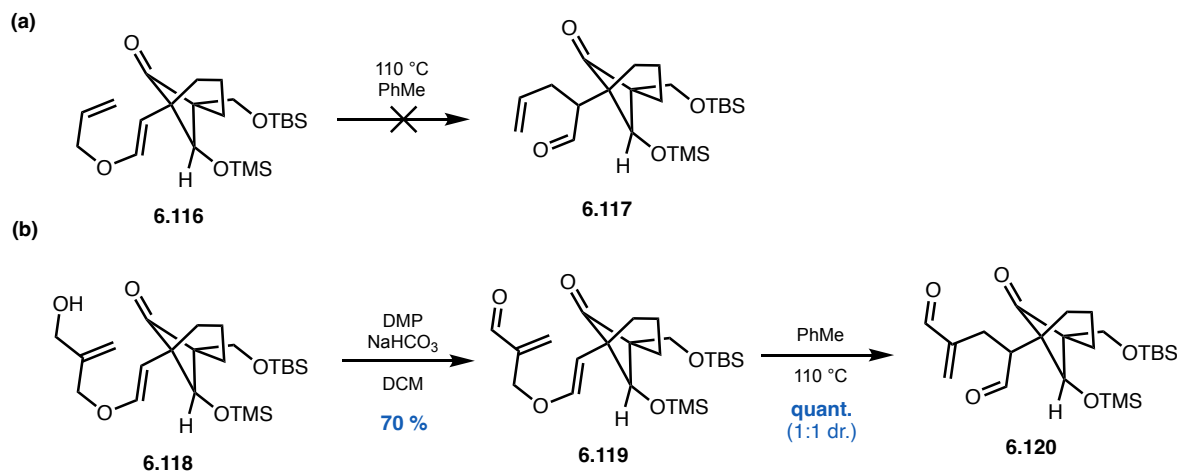


Scheme 6.23. Attempts to access vinyl boronic acid or vinyl potassium trifluoroborate intermediates.

6.2.3 Claisen Rearrangement

With the allyl enol ether intermediates **6.112** accessed through Chan–Lam coupling reactions in hand, we next evaluated the Claisen rearrangement. Allyl enol ether **6.116** unfortunately did not furnish the Claisen rearrangement product, even at elevated temperatures. Gratifyingly, allyl enol ether **6.119**, obtained from **6.118** following DMP oxidation, underwent Claisen rearrangement smoothly to afford **6.120** in quantitative yield as a 1:1 diastereomeric mixture. The electron-withdrawing aldehyde group of **6.119** activated the terminal alkene group, thereby facilitating the Claisen rearrangement; reactivity that was not observed for **6.116**. Notably, this Claisen

rearrangement represents the first functionalization of the C2 position with an alkyl side chain in our studies.

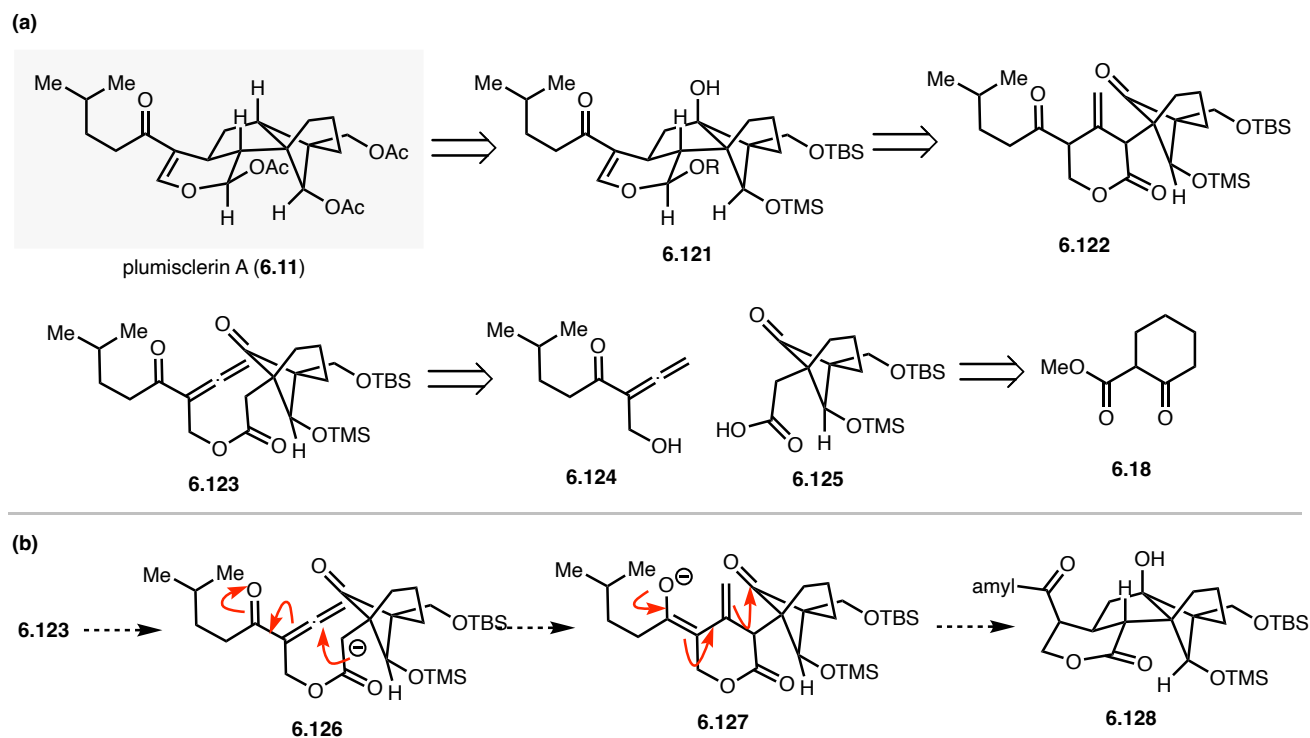


Scheme 6.24. Claisen rearrangement.

6.3 Intramolecular Michael Addition

6.3.1 Retrosynthesis

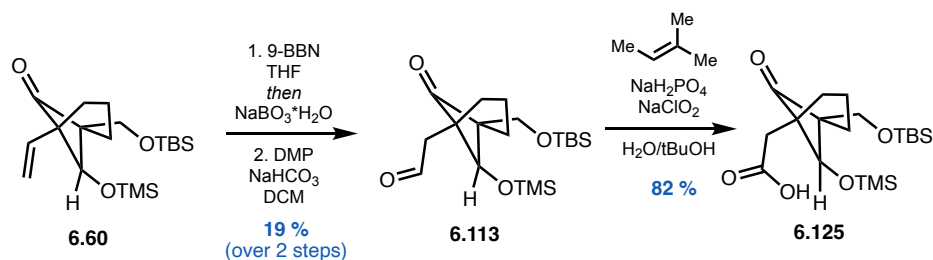
While exploring the Claisen rearrangement strategy, we recognized that accessing bicyclo[3.1.1]heptanoic acid **6.125** and coupling it with allenolate alcohol **6.123** to form the corresponding ester could provide an opportunity for an intramolecular Michael addition, potentially enabling direct formation of the framework of the desired dihydropyran ring (Scheme 6.25a). Furthermore, subsequent cyclization of the resulting enolate onto the cyclobutanone could furnish the cyclopentane ring in intermediate **6.128** through a cascade reaction (Scheme 6.25b). This approach offers the advantage that, in addition to enabling the functionalization at the C2 position and potential formation of the cyclopentane moiety, it retains the original C–O bond of the ester, which needs to be re-formed in a separate step in the Claisen rearrangement approach.



Scheme 6.25. (a) Retrosynthesis of intramolecular Michael addition strategy with ester **6.123**. (b) Envisioned cyclization cascade with allenolate ester **6.123**.

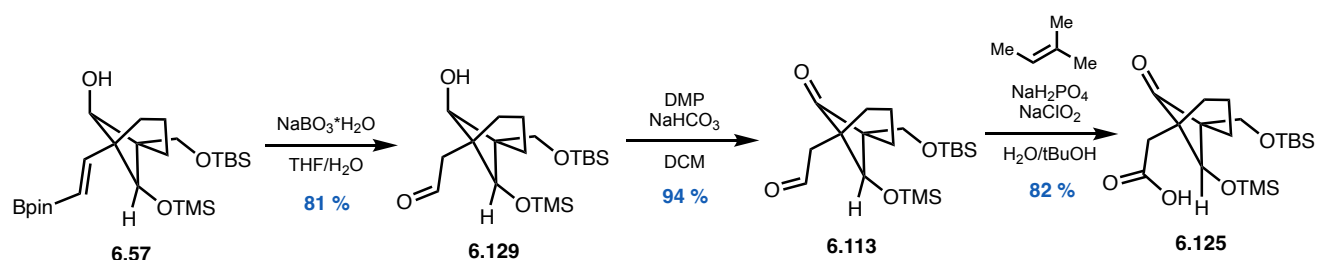
6.3.2 Preparation of bicyclo[3.1.1]heptanoic acid

Starting from ketone **6.60**, a hydroboration-oxidation sequence smoothly furnished the corresponding ketone (**6.113**) in 74 % yield over 2 steps (Scheme 6.26). However, this reaction proved difficult to scale, as larger-scale attempts resulted in undefined decomposition and a significantly complex reaction profile, only providing the desired product in 19 % yield.



Scheme 6.26. Preparation of carboxylic acid **6.125** from ketone **6.60**.

To achieve more reliable and reproducible results, we instead employed the vinyl pinacol boronate intermediate **6.57**, which was oxidized to the corresponding aldehyde using NaBO_3 (Scheme 6.27).³⁵ Subsequent oxidation of the alcohol **6.129** to ketone **6.113**, followed by Pinnick oxidation, afforded the desired carboxylic acid **6.125** in 82 % yield.

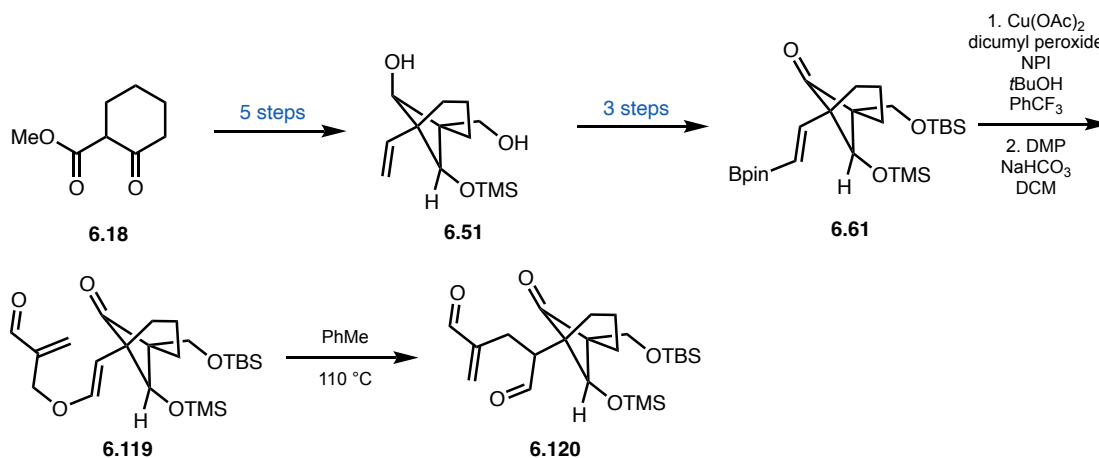


Scheme 6.27. Preparation of carboxylic acid **6.125** from vinyl pinacol boronate **6.57**.

Attempts to access the corresponding ester from coupling carboxylic acid **6.125** with allenolate alcohol **6.124** have remained unsuccessful due to the high electrophilicity of the allenolate functional group. Efforts to identify suitable esterification conditions are underway.

6.4 Summary and Outlook

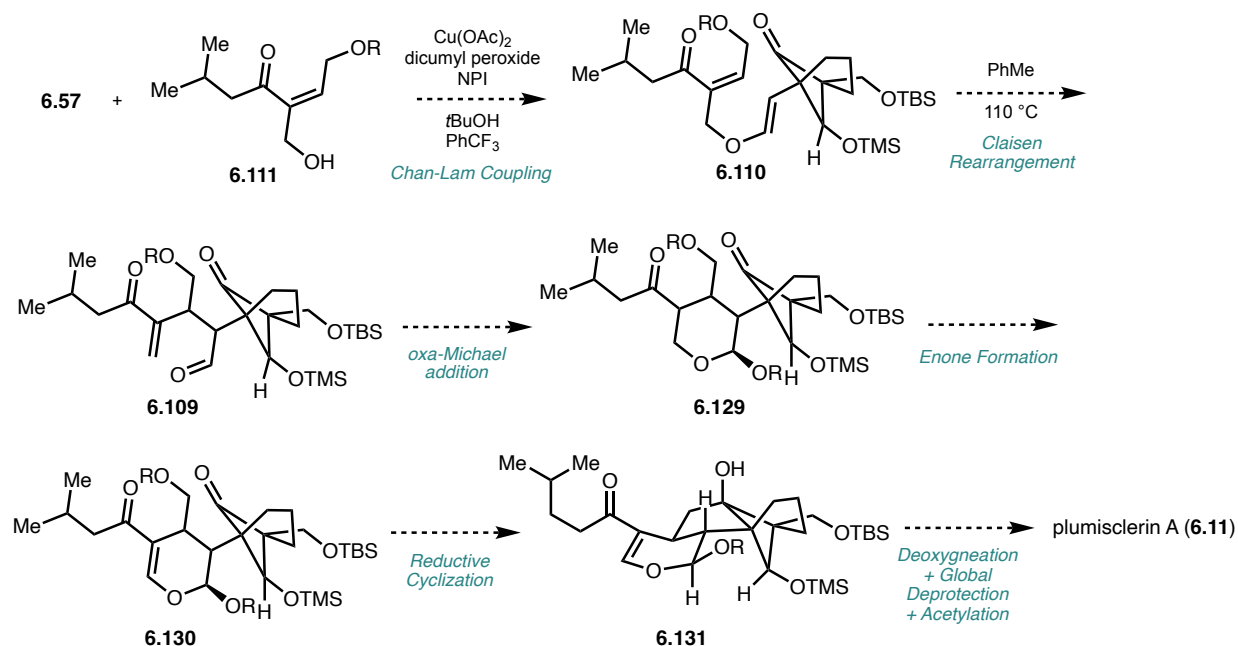
In summary, we explored two different strategies toward the total synthesis of plumisclerin A (**6.11**). Unlike previous approaches to this natural product, our strategy employed a titanocene-mediated reductive cyclization to access the highly functionalized bicyclo[3.1.1.]heptane core at an early stage (5 steps from commercially available **6.18**, Scheme 6.25). Attempts to introduce the dihydropyran moiety through inter- and intramolecular hetero-Diels–Alder reactions were unsuccessful. However, a new strategy leveraging a Claisen rearrangement following a Chan–Lam coupling enabled functionalization at the C2 position of the enol ether moiety, a transformation that had previously proven challenging.



Scheme 6.28. Progress toward Plumisclerin A.

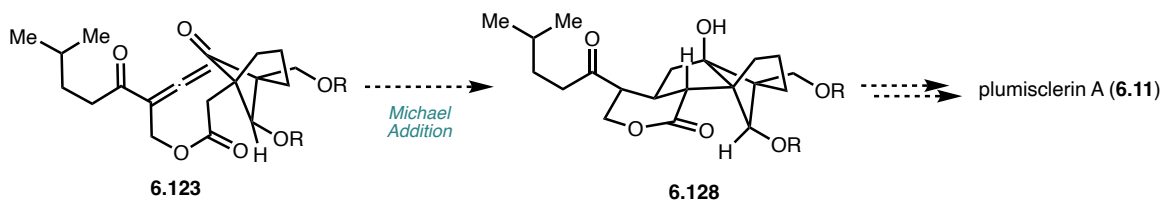
Regarding future directions for the Claisen rearrangement strategy, we envision that coupling vinyl pinacol boronate **6.57** with alcohol **6.111** under Chan–Lam coupling conditions would set the stage for a subsequent Claisen rearrangement to access **6.110**. We further anticipate that an oxa-Michael addition could enable formation of the dihydropyran ring,³⁶ followed by enone

formation. A sequence involving alcohol deprotection, halogenation, and reductive cyclization would furnish intermediate **6.131**, which could then be advanced to plumisclerin A (**6.11**) through literature-known procedures for deoxygenation, global deprotection, and acetylation.³⁷



Scheme 6.29. Future directions for the Claisen rearrangement strategy.

Regarding future directions for the intramolecular Michael addition strategy, the primary focus will be the synthesis of ester **6.123** (Scheme 6.30). Reaction conditions for the envisioned cyclization cascade from **6.123** could then be investigated by evaluation of a range of bases and solvent systems. The late-stage modifications at the periphery of the scaffold, as outlined for the Claisen rearrangement strategy, would also apply to intermediate **6.128** obtained through this approach.



Scheme 6.30. Future directions for the intramolecular Michael addition strategy.

6.5 Contributions

Experiments were carried out by Suh Hyun Kang, Hayato Inoue, and David Benko. Experimental designs were conceived by joint efforts of SHK and Professor Richmond Sarpong.

6.6 Experimental Details

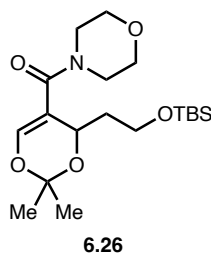
6.6.1 General Procedures

For general procedures regarding Solvents and Reagents; Reaction Setup, Monitoring, and Purification; NMR Spectroscopy; Mass Spectrometry; and Optical Rotation, see Chapter 2.10.

6.6.2 Synthetic Procedures and Product Characterization

General Procedure for Preparation of the Dioxine Fragment

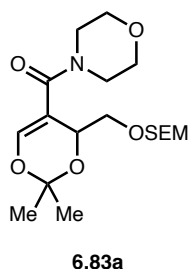
The following amides **6.26**, **6.83a**, and **6.83b** were prepared using the procedure reported by Funk and co-workers.¹



(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-5-yl)(morpholino)methanone (**6.26**)

R_f (25 % EtOAc/hexanes, *p*-anisaldehyde) 0.30

¹H NMR (400 MHz, C₆D₆) δ 6.38 (s, 1H), 5.02 (d, J = 9.4 Hz, 1H), 3.96 (q, J = 8.2 Hz, 1H), 3.88 – 3.79 (m, 1H), 3.31 (s, 2H), 3.23 – 3.05 (m, 6H), 2.21 (dd, J = 13.9, 7.8 Hz, 1H), 1.88 – 1.75 (m, 1H), 1.43 (s, 3H), 1.35 (s, 3H), 0.99 (s, 9H), 0.09 (d, J = 2.7 Hz, 6H).

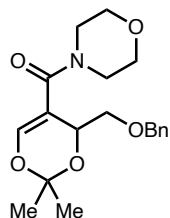


(2,2-dimethyl-4-(((2-(trimethylsilyl)ethoxy)methoxy)methyl)-4*H*-1,3-dioxin-5-yl)(morpholino)methanone (**6.83a**)

R_f (25 % EtOAc/hexanes, *p*-anisaldehyde) 0.45

¹H NMR (600 MHz, C₆D₆) δ 6.44 (d, J = 1.5 Hz, 1H), 4.98 (ddd, J = 4.5, 2.5, 1.5 Hz, 1H), 3.81 (dd, J = 10.6, 4.7 Hz, 1H), 3.62 (dd, J = 10.6, 2.6 Hz, 1H), 3.51 (ddd, J = 8.7, 6.9, 2.9 Hz, 2H),

3.38 – 3.24 (m, 8H), 3.06 – 2.95 (m, 3H), 1.44 (s, 3H), 1.31 (s, 3H), 0.94 (q, $J = 7.1$ Hz, 4H), -0.01 (s, 9H).

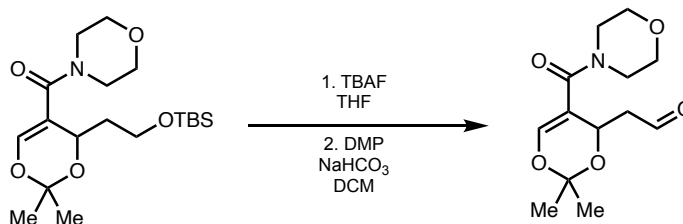


6.83b

(4-((benzyloxy)methyl)-2,2-dimethyl-4H-1,3-dioxin-5-yl)(morpholino)methanone (6.83b)

R_f (25 % EtOAc/hexanes, p-anisaldehyde) 0.20

¹H NMR (700 MHz, C₆D₆) δ 7.36 – 7.24 (m, 3H), 7.10 – 6.99 (m, 2H), 6.41 (d, $J = 1.7$ Hz, 1H), 4.97 (ddd, $J = 4.2, 2.7, 1.6$ Hz, 1H), 4.45 – 4.41 (m, 1H), 4.37 (t, $J = 12.0$ Hz, 1H), 3.93 – 3.87 (m, 1H), 3.65 (dd, $J = 11.2, 2.9$ Hz, 1H), 3.40 (s, 2H), 3.22 – 3.18 (m, 8H), 1.44 (d, $J = 2.1$ Hz, 3H), 1.29 (d, $J = 2.0$ Hz, 3H).



6.26

6.99

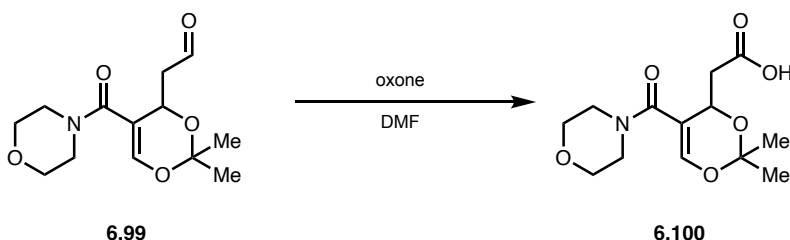
2-(2,2-dimethyl-5-(morpholine-4-carbonyl)-4H-1,3-dioxin-4-yl)acetaldehyde (6.99)

In a 1 dr vial, **6.26** (100.0 mg, 259.4 μ mol, 1.0 equiv) was dissolved in TBAF (678.12 mg, 2.60 mL, 1.0 molar, 2.60 mmol, 10 equiv) and stirred for 1 hour. Upon full consumption of the starting material, the reaction was quenched with an aqueous solution of NaHCO₃ and extracted three times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure.

The resulting residue was dissolved in DCM (1.30 mL) with DMP (165.0 mg, 389.02 μ mol, 1.5 equiv) and sodium bicarbonate (32.7 mg, 389.02 μ mol, 1.5 equiv). The reaction was stirred at room temperature for 1 hour until it was quenched with an aqueous solution of Na₂S₂O₃. The layers were separated and the aqueous layer was washed three times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to afford **6.99** as a yellow oil (18.4 mg, 68.3 μ mol, 25%).

R_f (25 % EtOAc/hexanes, p-anisaldehyde) 0.45

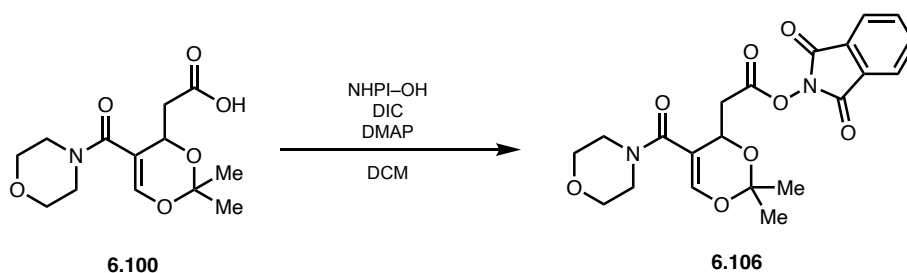
¹H NMR (400 MHz, C₆D₆) δ 9.54 (t, *J* = 2.4 Hz, 1H), 6.27 (s, 1H), 5.12 (t, *J* = 5.7 Hz, 1H), 3.36 – 3.26 (m, 2H), 3.22 (t, *J* = 4.7 Hz, 4H), 3.09 – 2.99 (m, 2H), 2.58 – 2.52 (m, 1H), 2.47 – 2.32 (m, 1H), 1.32 (s, 3H), 1.22 (s, 3H).



2-(2,2-dimethyl-5-(morpholine-4-carbonyl)-4H-1,3-dioxin-4-yl)acetic acid (6.100)

In a 1 dr vial, **6.99** (65.00 mg, 241.4 μmol, 1.0 equiv) was dissolved in DMF (1.2 mL) with oxone (148.4 mg, 241.4 μmol, 1.0 equiv). The reaction was stirred at room temperature for 1 hour. After completion of the reaction, H₂O (2 mL) was added and the reaction was kept stirring for another 10 min. The reaction was extracted three times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The product **6.100** was obtained as a yellow oil and carried forward to the next step without further purification.

¹H NMR (600 MHz, C₆D₆) δ 6.31 (d, *J* = 1.5 Hz, 1H), 5.29 (ddd, *J* = 7.5, 4.0, 1.5 Hz, 1H), 3.34 (s, 2H), 3.25 (qd, *J* = 7.4, 5.0 Hz, 4H), 3.12 (ddd, *J* = 13.1, 6.2, 3.4 Hz, 2H), 2.86 (dd, *J* = 15.2, 4.0 Hz, 1H), 2.71 (dd, *J* = 15.2, 7.5 Hz, 1H), 1.37 (s, 3H), 1.30 (s, 3H).

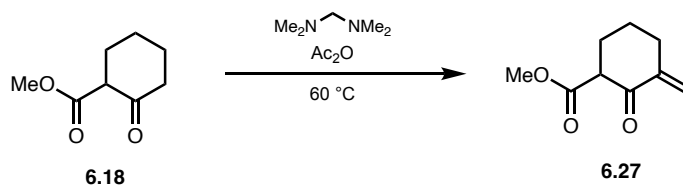


1,3-dioxoisindolin-2-yl
2-(2,2-dimethyl-5-(morpholine-4-carbonyl)-4H-1,3-dioxin-4-yl)acetate (6.106)

In a 1 dr vial, **6.100** (10.0 mg, 35.1 μmol, 1.0 equiv) was dissolved in DCM (175.3 μL) with DMAP (428.2 μg, 3.50 μmol, 0.1 equiv), N-Hydroxyphthalimide (6.86 mg, 42.1 μmol, 1.2 equiv), and DIC (4.87 mg, 6.04 μL, 38.6 μmol, 1.1 equiv) and stirred at room temperature for about 2 hours. The reaction was filtered over a plug of celite and washed with DCM. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The

resulting residue was purified by fluorsil column chromatography (2:1 hexanes/EtOAc) to afford the desired product as a pale yellow solid.

¹H NMR (600 MHz, C₆D₆) δ 7.24 (dd, J = 5.4, 3.1 Hz, 2H), 6.73 (dd, J = 5.5, 3.1 Hz, 2H), 6.40 (d, J = 1.4 Hz, 1H), 5.19 (ddd, J = 5.8, 4.1, 1.5 Hz, 1H), 3.43 – 3.36 (m, 2H), 3.25 (dd, J = 5.6, 3.9 Hz, 4H), 3.21 – 3.14 (m, 2H), 2.98 (dd, J = 14.8, 4.1 Hz, 1H), 2.85 (dd, J = 14.8, 6.2 Hz, 1H), 1.55 (s, 3H), 1.25 (s, 3H).



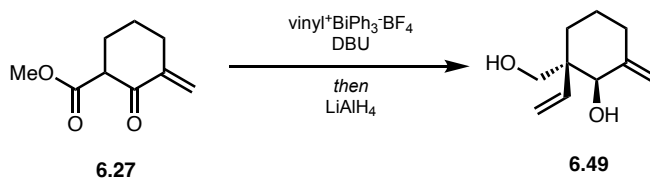
methyl 3-methylene-2-oxocyclohexane-1-carboxylate (6.27)

A solution of 4-oxo-tetrahydrothiopyran-3-carboxylic acid methyl ester **6.18** (30.0 g, 192 mmol, 1.0 equiv) in acetic anhydride (98.1 g, 90.6 mL, 5.0 equiv) was treated with N,N,N',N'-tetramethyl diamino methane (29.4 g, 288 mmol, 1.5 equiv) added dropwise at room temperature, and the mixture was stirred at 60 °C for 15 min. After cooling to room temperature, the mixture was slowly added to saturated aqueous sodium hydrogen carbonate, and the mixture was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (25 % EtOAc/hex) to afford the desired product (26.2g, 192 mmol, 81 %).

R_f (25 % EtOAc/hexanes, p-anisaldehyde) 0.50

¹H NMR (500 MHz, CDCl₃) δ 12.01 (s, 1H), 5.82 (t, J = 1.8 Hz, 1H), 5.18 (t, J = 1.9 Hz, 1H), 3.78 (s, 3H), 2.42 (tt, J = 6.0, 1.5 Hz, 2H), 2.36 (t, J = 6.1 Hz, 2H), 1.68 (p, J = 6.1 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 173.45, 164.16, 138.77, 115.84, 100.13, 51.81, 31.39, 23.64, 22.70.



(1R,2R)-2-(hydroxymethyl)-6-methylene-2-vinylcyclohexan-1-ol (6.49)

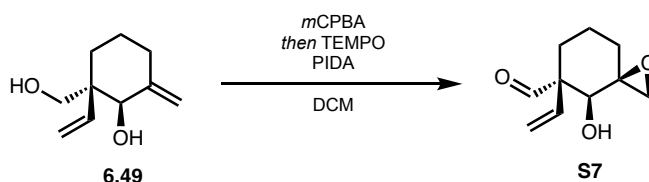
In a 1 L round bottom flask, methyl 3-methylene-2-oxocyclohexane-1-carboxylate **6.27** (9.00 g, 53.5 mmol, 1.0 equiv) was dissolved in THF (535 mL) and DBU (8.96 g, 8.87 mL, 58.9 mmol, 1.1 equiv) was added. After stirring for 5 min, the vinylating reagent (35.6 g, 64.2 mmol, 1.2 equiv) was added in one portion and the reaction was stirred for 1 hour. Upon completion of the

reaction, the reaction mixture was transferred to a separate 2 L round bottom flask charged with LiAlH_4 (4.06 g, 107 mL, 1.0 molar, 107 mmol, 2.0 equiv) in 200 mL THF at 0 °C via cannula. Upon completion of the addition, the reaction was allowed to warm up to r.t. and stirred for 1 h. The reaction was cooled down to 0 °C and quenched by slow addition of EtOAc and 1 M aqueous solution of NaOH. After warming it up to room temperature, the reaction was filtered and extracted with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (25 % EtOAc/hex $\rightarrow$ 100 % EtOAc) to afford the desired product as a pale yellow oil (7.89 g, 46.9 mmol, 88 %).

R_f (50 % EtOAc/hexanes, p-anisaldehyde) 0.25

^1H NMR (500 MHz, CDCl_3) δ 5.92 (dd, J = 18.1, 11.3 Hz, 1H), 5.33 (dd, J = 11.3, 1.3 Hz, 1H), 5.22 (dd, J = 18.1, 1.3 Hz, 1H), 4.92 (dq, J = 38.7, 1.8 Hz, 2H), 4.15 (d, J = 1.9 Hz, 1H), 3.74 (d, J = 11.0 Hz, 1H), 3.61 (d, J = 11.0 Hz, 1H), 2.81 (s, 1H), 2.38 (dtd, J = 13.5, 4.2, 1.9 Hz, 2H), 2.06 – 1.97 (m, 1H), 1.67 – 1.41 (m, 4H).

^{13}C NMR (126 MHz, CDCl_3) δ 147.85, 138.05, 116.92, 107.43, 77.21, 70.23, 48.30, 33.57, 31.74, 22.34.



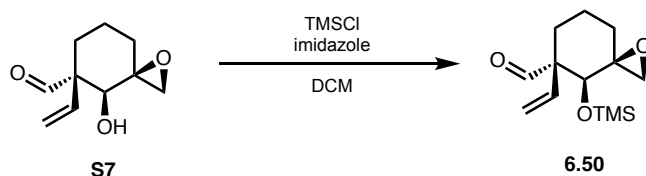
(3*S*,4*S*,5*S*)-4-hydroxy-5-vinyl-1-oxaspiro[2.5]octane-5-carbaldehyde (S7)

In a 1 L RBF, **6.49** (1.26 g, 7.51 mmol, 1.0 equiv) was dissolved in DCM (94 mL) with sodium bicarbonate (694.3 mg, 8.26 mmol, 1.1 equiv) and 3-Chloroperoxybenzoic acid (2.04 g, 3.6 mL, 70% wt, 8.26 mmol, 1.1 equiv). The reaction was stirred at room temperature for 1 h. Upon full consumption of **6.49** as monitored by TLC, another portion of DCM (94 mL) was added along with PIDA (1.70 g, 5.26 mmol, 0.7 equiv) and TEMPO (352.2 mg, 2.25 mmol, 0.3 equiv) and continued stirring overnight. The reaction was quenched by addition aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution and was extracted three times with Et_2O . The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (50 % EtOAc/hex) to afford the desired product as a transparent orange oil (932.8 mg, 5.12 mmol, 68 %).

R_f (50 % EtOAc/hexanes, p-anisaldehyde) 0.48

^1H NMR (500 MHz, CDCl_3) δ 9.50 (s, 1H), 6.02 (dd, J = 18.0, 11.1 Hz, 1H), 5.52 (d, J = 11.1 Hz, 1H), 5.32 (d, J = 18.0 Hz, 1H), 4.11 (s, 1H), 3.05 (d, J = 4.9 Hz, 1H), 2.62 (d, J = 4.9 Hz, 1H), 2.31 (t, J = 7.1 Hz, 1H), 2.00 (ddd, J = 15.1, 5.3, 2.8 Hz, 1H), 1.84 – 1.50 (m, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 200.99, 132.17, 119.85, 70.69, 59.13, 58.85, 50.45, 30.98, 27.99, 19.62.

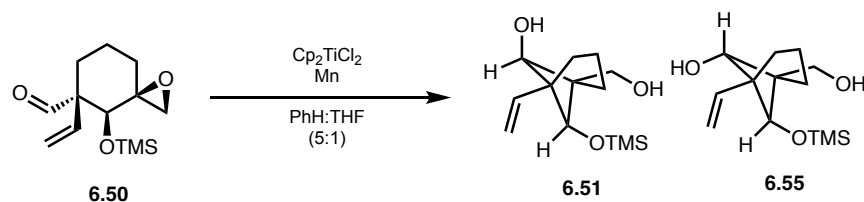


(3*S*,4*S*,5*S*)-4-((trimethylsilyl)oxy)-5-vinyl-1-oxaspiro[2.5]octane-5-carbaldehyde (6.50)

In a 100 mL round bottomed flask, **S7** (855.0 mg, 4.69 mmol, 1.0 equiv) was dissolved in DCM (24 mL) with imidazole (479.2 mg, 7.04 mmol, 1.5 equiv) and chlorotrimethylsilane (560.73 mg, 655 μL , 5.16 mmol, 1.1 equiv). The reaction was stirred at room temperature overnight. The reaction was quenched by adding H_2O (40 mL). After separating the layers, the aqueous layer was extracted three times with Et_2O . The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (25 % EtOAc /hex) to afford the desired product as a transparent pale yellow oil (1.01 g, 3.96 mmol, 85 %).

^1H NMR (600 MHz, CDCl_3) δ 9.47 (s, 1H), 6.02 (dd, J = 18.1, 11.1 Hz, 1H), 5.43 (d, J = 11.1 Hz, 1H), 5.20 (dd, J = 18.1, 0.9 Hz, 1H), 3.99 (s, 1H), 2.86 (d, J = 5.3 Hz, 1H), 2.52 (d, J = 5.3 Hz, 1H), 1.93 – 1.85 (m, 1H), 1.74 – 1.52 (m, 5H), 0.09 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 201.25, 133.92, 118.61, 72.28, 59.65, 58.94, 50.35, 30.69, 27.95, 19.70, -0.10.



In a 50 mL round-bottom flask, di(cyclopenta-1,3-dien-1-yl)titanium(IV) chloride (2.15 g, 8.65 mmol, 2.2 equiv) and manganese (1.43 g, 25.94 mmol, 6.6 equiv) were dissolved in degassed THF (13.1 mL) and benzene (65.5 mL). After stirring the mixture at room temperature for 30 min, **6.50** (1.00 g, 3.93 mmol, 1.0 equiv) dissolved in anhydrous benzene (65.5 mL) was added dropwise at room temperature. The reaction color was monitored to maintain its dark green color for about 30

min and the reaction was stirred at room temperature overnight. The reaction was quenched by adding aqueous NaHPO₄ solution (100 mL). The reaction mixture was extracted three times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (50 % EtOAc/hex).

(6*R*)-1-(hydroxymethyl)-7-((trimethylsilyl)oxy)-5-vinylbicyclo[3.1.1]heptan-6-ol (6.51)

The title compound was isolated as yellow oil (547.4 mg, 2.14 mmol, 54 %).

R_f (50 % EtOAc/hexanes, p-anisaldehyde) 0.35

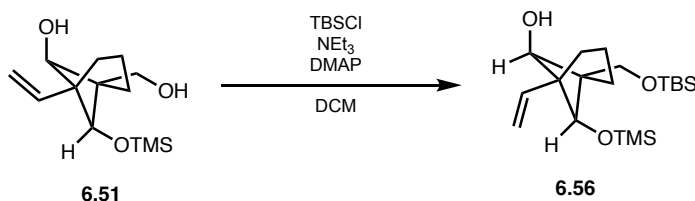
¹H NMR (700 MHz, CDCl₃) δ 5.80 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.03 – 4.97 (m, 2H), 3.64 (s, 1H), 3.49 (t, *J* = 5.5 Hz, 2H), 3.42 (d, *J* = 11.1 Hz, 1H), 1.91 – 1.86 (m, 1H), 1.85 – 1.76 (m, 3H), 1.72 – 1.61 (m, 2H), 0.08 (s, 9H).

(6*S*)-1-(hydroxymethyl)-7-((trimethylsilyl)oxy)-5-vinylbicyclo[3.1.1]heptan-6-ol (6.55)

The minor diastereomer was isolated as a yellow oil (172.6 mg, 673.1 μmol, 17 %).

R_f (50 % EtOAc/hexanes, p-anisaldehyde) 0.45

¹H NMR (700 MHz, CDCl₃) δ 5.78 (dd, *J* = 17.7, 10.8 Hz, 1H), 5.26 (dd, *J* = 10.8, 1.6 Hz, 1H), 5.14 (dd, *J* = 17.7, 1.6 Hz, 1H), 4.54 (s, 1H), 4.09 (s, 1H), 3.68 (d, *J* = 11.7 Hz, 1H), 3.51 (d, *J* = 11.7 Hz, 1H), 2.16 – 2.06 (m, 1H), 1.89 – 1.74 (m, 1H), 1.75 – 1.44 (m, 19H), 0.11 (s, 6H).



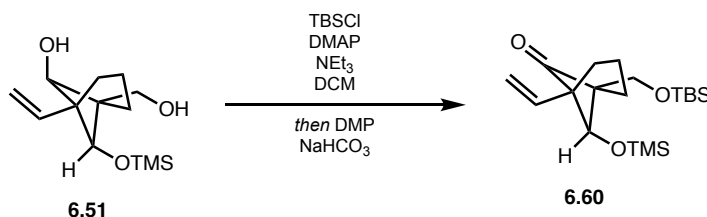
(6*R*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-((trimethylsilyl)oxy)-5-vinylbicyclo[3.1.1]heptan-6-ol (6.56)

In a 20 mL vial, **6.51** (720.0 mg, 2.81 mmol, 1.0 equiv) was dissolved in DCM (12.8 mL) with DMAP (34.3 mg, 280.8 μmol, 1.0 equiv) and triethylamine (568.3 mg, 783 μL, 5.62 mmol, 2.0 equiv) and TBS-Cl (465.5 mg, 3.09 mmol, 1.1 equiv). The reaction was stirred at room temperature for 1 h. The reaction was quenched with H₂O and extracted three times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (10 % EtOAc/hex). The product was isolated as a pale yellow oil (989 mg, 2.67 mmol, 95 %).

R_f (25 % EtOAc/hexanes, p-anisaldehyde) 0.75

¹H NMR (500 MHz, C₆D₆) δ 5.88 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.10 (dd, *J* = 17.5, 1.6 Hz, 1H), 5.02 (dd, *J* = 10.7, 1.6 Hz, 1H), 3.76 (s, 1H), 3.67 (s, 1H), 3.37 (d, *J* = 10.5 Hz, 1H), 3.32 (d, *J* = 10.5 Hz, 1H), 2.12 – 2.02 (m, 1H), 2.01 – 1.90 (m, 1H), 1.85 – 1.76 (m, 1H), 1.75 – 1.67 (m, 2H), 0.99 (s, 9H), 0.16 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

¹³C NMR (126 MHz, C₆D₆) δ 143.81, 112.38, 69.23, 68.52, 64.07, 52.94, 52.64, 26.16, 24.26, 22.15, 18.51, 15.31, 0.32, -5.30, -5.37.



1-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-((trimethylsilyl)oxy)-5-vinylbicyclo[3.1.1]heptan-6-one (6.60)

In a 20 mL vial, **6.51** (148.6 mg, 579.5 μmol, 1.0 equiv) was dissolved in DCM (2.65 mL) with DMAP (7.1 mg, 58.0 μmol, 0.1 equiv) and triethylamine (117.3 mg, 162 μL, 1.16 mmol, 2.0 equiv) and TBS-Cl (96.1 mg, 637.5 μmol, 1.1 equiv). The reaction was stirred at room temperature overnight. To this reaction, DMP (268.7 mg, 869.3 μmol, 1.5 equiv) and NaHCO₃ (97.4 mg, 1.16 mmol, 2.0 equiv) were added and the reaction was stirred for another 1 h. The reaction was quenched with H₂O and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (25 % EtOAc/hex). The product was isolated as a colorless transparent oil (156 mg, 421 μmol, 73 %).

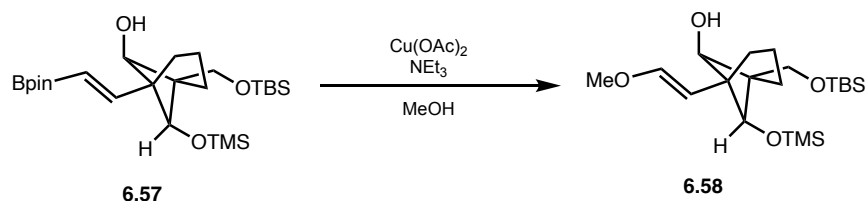
R_f (25 % EtOAc/hexanes, *p*-anisaldehyde) 0.70

¹H NMR (400 MHz, C₆D₆) δ 5.83 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.27 (dd, *J* = 17.6, 1.5 Hz, 1H), 5.07 (dd, *J* = 10.9, 1.5 Hz, 1H), 4.66 (s, 1H), 3.71 (d, *J* = 11.0 Hz, 1H), 3.20 (d, *J* = 11.1 Hz, 1H), 2.67 – 2.55 (m, 1H), 2.39 – 2.28 (m, 1H), 1.87 (dd, *J* = 12.1, 6.4 Hz, 1H), 1.42 (dq, *J* = 23.3, 6.9 Hz, 3H), 0.97 (s, 9H), 0.16 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H).

¹³C NMR (151 MHz, C₆D₆) δ 211.93, 135.95, 115.57, 68.80, 68.60, 66.00, 60.78, 31.80, 28.81, 26.08, 18.50, 0.17, -5.33, -5.38.

¹H NMR (400 MHz, C₆D₆) δ 7.03 (d, *J* = 18.5 Hz, 1H), 6.05 (d, *J* = 18.3 Hz, 1H), 4.78 (s, 1H), 3.70 (d, *J* = 11.1 Hz, 1H), 3.22 (d, *J* = 11.0 Hz, 1H), 2.76 – 2.57 (m, 1H), 2.32 (d, *J* = 8.3 Hz, 1H), 1.96 – 1.87 (m, 1H), 1.38 (d, *J* = 9.7 Hz, 3H), 1.03 (s, 12H), 0.93 (s, 9H), 0.15 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

¹³C NMR (151 MHz, C₆D₆) δ 211.33, 170.00, 149.87, 126.03, 115.56, 83.16, 70.39, 68.69, 65.85, 60.96, 60.06, 31.92, 28.92, 26.08, 24.89, 24.87, 20.56, 18.51, 14.24, 0.18, -5.31, -5.43.

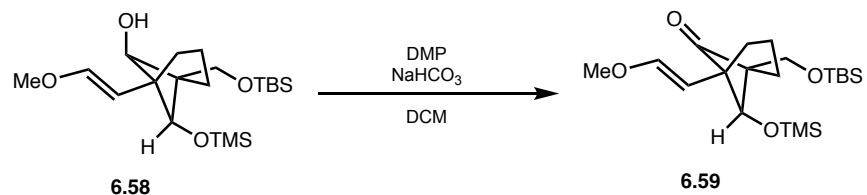


(*E*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(2-methoxyvinyl)-7-((trimethylsilyl)oxy)bicyclo[3.1.1]heptan-6-ol (6.58)

In a 20 mL vial, **6.57** (68.9 mg, 139 μmol, 1.0 equiv) was dissolved in MeOH (462 μL) with diacetyoxycopper hydrate (55.4 mg, 277 μmol, 2.0 equiv) and triethylamine (56.2 mg, 77.3 μL, 555 μmol, 4.0 equiv). The reaction was stirred at room temperature overnight. The reaction was quenched with H₂O and extracted three times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The product was obtained as a colorless oil (55.6 mg, 139 μmol, quantitative yield).

R_f (25 % EtOAc/hexanes, *p*-anisaldehyde) 0.65

¹H NMR (400 MHz, C₆D₆) δ 6.49 (d, *J* = 13.0 Hz, 1H), 4.87 (d, *J* = 13.0 Hz, 1H), 3.72 (s, 1H), 3.65 (s, 1H), 3.40 (d, *J* = 10.4 Hz, 1H), 3.35 (d, *J* = 10.5 Hz, 1H), 3.18 (s, 3H), 2.07 – 1.89 (m, 4H), 1.86 – 1.68 (m, 2H), 0.99 (s, 9H), 0.18 (s, 9H), 0.05 (d, *J* = 2.3 Hz, 6H).



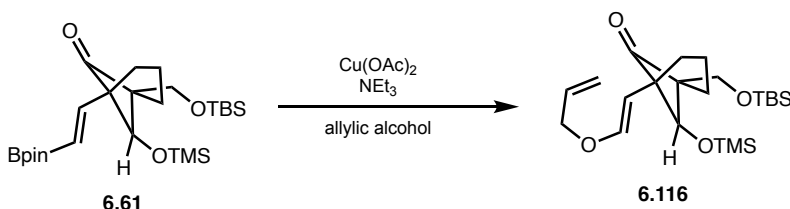
(*E*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(2-methoxyvinyl)-7-((trimethylsilyl)oxy)bicyclo[3.1.1]heptan-6-one (6.59)

In a 1 dram vial, **6.58** (86.80 mg, 216.6 μmol, 1.0 equiv) was dissolved in DCM (2.2 mL) and DMP (137.8 mg, 324.9 μmol, 1.5 equiv) and sodium bicarbonate (45.5 mg, 541.5 μmol,

2.5 equiv) were added. The reaction was stirred at room temperature for 1 hour. The reaction was quenched with aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ and diluted with Et_2O . After separating the layers, the aqueous layer was extracted three times with Et_2O . The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (25 % EtOAc /hex). The product was isolated as a colorless transparent oil (66.7 mg, 167 μmol , 77 %).

R_f (25 % EtOAc /hexanes, p-anisaldehyde) 0.65

^1H NMR (400 MHz, C_6D_6) δ 6.74 (d, J = 13.0 Hz, 1H), 4.80 (d, J = 13.1 Hz, 1H), 4.55 (s, 1H), 3.74 (d, J = 11.0 Hz, 1H), 3.24 (d, J = 10.9 Hz, 1H), 3.10 (s, 3H), 2.70 – 2.59 (m, 1H), 2.35 (d, J = 7.8 Hz, 1H), 1.81 (d, J = 9.7 Hz, 1H), 1.44 (dd, J = 17.1, 9.8 Hz, 3H), 0.97 (s, 9H), 0.18 (d, J = 0.9 Hz, 9H), 0.14 (s, 3H), 0.10 (s, 3H).

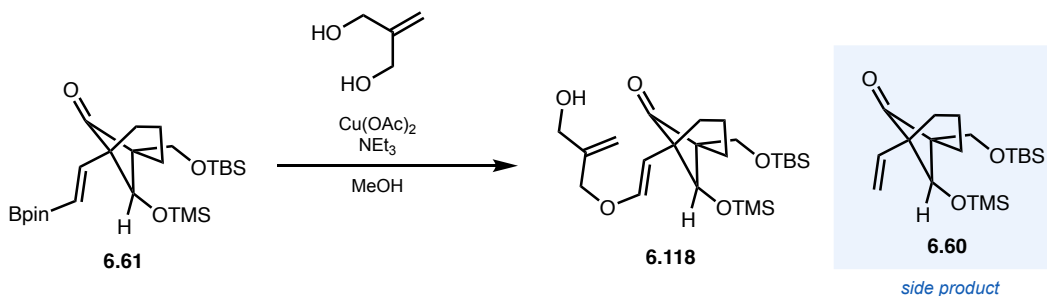


(5*S*)-1-((*E*)-2-(allyloxy)vinyl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-((trimethylsilyl)oxy)bicyclo[3.1.1]heptan-6-one (6.116)

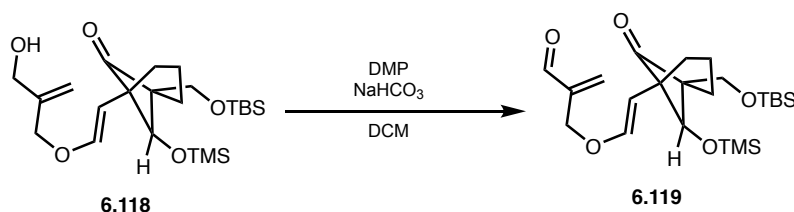
In a 20 mL vial, **6.61** (9.50 mg, 19.2 μmol , 1.0 equiv) was dissolved in allyl alcohol (462 μL) with diacetyoxycopper hydrate (6.98 mg, 38.4 μmol , 2.0 equiv) and triethylamine (7.77 mg, 10.7 μL , 76.8 μmol , 4.0 equiv). The reaction was stirred at room temperature overnight. The reaction was quenched with H_2O and extracted three times with EtOAc . The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The product was obtained as a colorless oil (4.2 mg, 9.9 μmol , 51 %).

R_f (50 % EtOAc /hexanes, p-anisaldehyde) 0.65

^1H NMR (600 MHz, C_6D_6) δ 6.67 (d, J = 12.9 Hz, 1H), 5.70 (ddd, J = 17.4, 10.6, 5.3 Hz, 1H), 5.14 (dt, J = 17.3, 1.7 Hz, 1H), 5.01 – 4.95 (m, 1H), 4.94 (s, 1H), 4.55 (s, 1H), 3.89 (dt, J = 5.3, 1.6 Hz, 2H), 3.74 (d, J = 11.0 Hz, 1H), 3.24 (d, J = 11.0 Hz, 1H), 2.71 – 2.58 (m, 1H), 2.38 – 2.27 (m, 1H), 1.83 (dd, J = 12.6, 6.9 Hz, 1H), 1.51 – 1.39 (m, 3H), 0.97 (d, J = 1.6 Hz, 9H), 0.18 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H).



(1*S*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-((*E*)-2-((2-(hydroxymethyl)allyl)oxy)vinyl)-7-((trimethylsilyl)oxy)bicyclo[3.1.1]heptan-6-one (6.118)



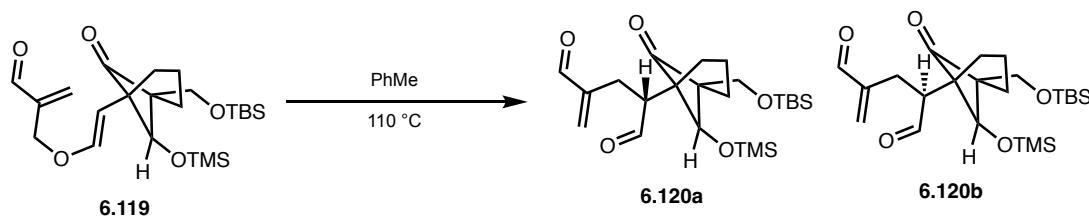
2-((((*E*)-2-((5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-oxo-7-(((trimethylsilyl)oxy)bicyclo[3.1.1]heptan-1-yl)vinyl)oxy)methyl)acrylaldehyde (6.119)

by preparative TLC (25 % EtOAc/hex). The product was isolated as a colorless transparent oil (2.8 mg, 6.2 μ mol, 70 %)

R_f (25 % EtOAc/hexanes, p-anisaldehyde) 0.45

¹H NMR (600 MHz, C₆D₆) δ 9.08 (s, 1H), 6.63 (d, *J* = 12.9 Hz, 1H), 6.01 (s, 1H), 5.32 (s, 1H), 4.94 (d, *J* = 12.9 Hz, 1H), 4.52 (s, 1H), 3.72 (d, *J* = 11.0 Hz, 1H), 3.23 (d, *J* = 11.0 Hz, 1H), 2.67 – 2.57 (m, 1H), 2.34 (p, *J* = 6.9 Hz, 1H), 1.78 (dt, *J* = 11.9, 6.0 Hz, 1H), 1.42 (q, *J* = 7.1 Hz, 3H), 0.96 (s, 9H), 0.17 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H).

¹³C NMR (151 MHz, C₆D₆) δ 191.88, 170.02, 147.70, 133.01, 103.72, 67.45, 65.20, 60.06, 33.29, 28.70, 26.09, 20.55, 18.59, 14.23, 0.18, -5.32. (aldehyde carbonyl is missing)



(2*R*)-2-((5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-oxo-7-((trimethylsilyl)oxy)bicyclo[3.1.1] heptan-1-yl)-4-methylenepentanedial (6.120a)

(2*S*)-2-((5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-oxo-7-((trimethylsilyl)oxy)bicyclo[3.1.1] heptan-1-yl)-4-methylenepentanedial (6.120b)

In a 1 dram vial, **6.119** (2.80 mg, 6.18 μ mol, 1.0 equiv) was dissolved in anhydrous PhMe (61.8 μ L) and stirred at 110 °C for 1 h. The reaction was concentrated under reduced pressure. The product was obtained as a mixture of diastereomers **6.120a** and **6.120b** in quantitative yield.

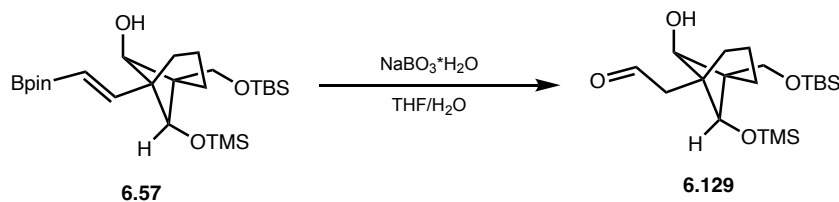
R_f (25 % EtOAc/hexanes, p-anisaldehyde) 0.35

Reported are chemical shifts of both diastereomers.

¹H NMR (600 MHz, C₆D₆) δ 9.88 (d, *J* = 2.3 Hz, 1H), 9.74 (d, *J* = 2.8 Hz, 1H), 9.06 (s, 1H), 9.04 (s, 1H), 5.82 (s, 1H), 5.69 (d, *J* = 1.5 Hz, 1H), 5.23 (s, 1H), 5.21 (s, 1H), 4.85 (s, 1H), 4.76 (s, 1H), 4.67 (s, 1H), 3.68 (d, *J* = 11.0 Hz, 1H), 3.65 (d, *J* = 11.0 Hz, 1H), 3.15 (d, *J* = 11.1 Hz, 1H), 3.11 (d, *J* = 11.0 Hz, 1H), 2.79 (dt, *J* = 11.4, 2.2 Hz, 1H), 2.72 (dt, *J* = 10.6, 2.9 Hz, 1H), 2.70 (s, 1H), 2.68 (s, 1H), 2.64 – 2.59 (m, 2H), 2.58 – 2.53 (m, 1H), 2.50 (d, *J* = 14.1 Hz, 1H), 2.21 – 2.15 (m, 2H), 1.81 (dd, *J* = 12.6, 7.1 Hz, 1H), 1.70 – 1.64 (m, 1H), 1.00 (s, 9H), 0.98 (s, 9H), 0.24 (s, 9H), 0.21 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H).

¹³C NMR (151 MHz, C₆D₆) δ 212.70, 200.95, 200.68, 193.36, 193.21, 147.54, 135.54, 134.88, 129.34, 129.13, 128.52 (d, *J* = 14.9 Hz), 125.70, 68.62, 66.60, 64.09, 62.78, 60.58, 60.53, 53.87,

53.33, 31.02, 29.80, 28.94, 26.09, 26.04, 23.48, 22.89, 21.43, 18.60, 18.50, 18.45, 1.42, 0.15 (d, J = 10.3 Hz), -5.32, -5.37, -5.41, -5.49.

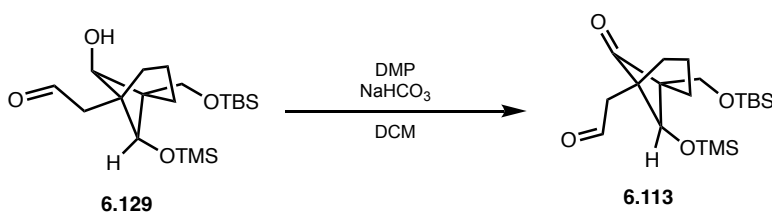


2-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-hydroxy-7-((trimethylsilyl)oxy)bicyclo[3.1.1]heptan-1-yl)acetaldehyde (6.129)

In a 1 dr vial, **6.57** (6.00 mg, 12.1 μmol , 1.0 equiv) was dissolved in THF (121 μL) and H_2O (121 μL) with sodium perborate 1-hydrate (3.62 mg, 36.2 μmol , 3.0 equiv). The reaction was stirred at room temperature for 2 h. The reaction was quenched with brine and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (25 % EtOAc/hex). The product was isolated as a colorless transparent oil (3.82 mg, 9.88 μmol , 81 %).

R_f (25 % EtOAc/hexanes, *p*-anisaldehyde) 0.75

¹H NMR (400 MHz, C₆D₆) δ 9.28 (s, 1H), 3.61 (s, 1H), 3.53 (s, 1H), 3.42 (d, J = 10.6 Hz, 1H), 3.30 (d, J = 10.9 Hz, 1H), 2.17 (d, J = 17.4 Hz, 1H), 1.91 – 1.66 (m, 7H), 0.99 (d, J = 2.2 Hz, 9H), 0.13 (d, J = 2.1 Hz, 9H), 0.06 (d, J = 2.0 Hz, 6H).



2-((5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-oxo-7-((trimethylsilyl)oxy)bicyclo[3.1.1]heptan-1-yl)acetaldehyde (6.113)

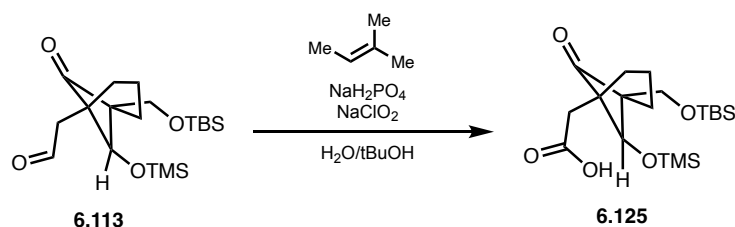
In a 1 dram vial, **6.129** (15.0 mg, 38.79 μmol , 1.0 equiv) was dissolved in DCM (390 μL) and DMP (24.68 mg, 58.19 μmol , 1.5 equiv) and sodium bicarbonate (9.78 mg, 116.4 μmol , 3.0 equiv) were added. The reaction was stirred at room temperature for 1 hour. The reaction was quenched with aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ and diluted with Et_2O . After separating the layers, the aqueous layer was extracted three times with Et_2O . The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was

purified by silica gel column chromatography (25 % EtOAc/hex). The product was isolated as a colorless transparent oil (14.1 mg, 36.7 μmol , 94 %).

R_f (25 % EtOAc/hexanes, p-anisaldehyde) 0.60

^1H NMR (500 MHz, C_6D_6) δ 9.58 (s, 1H), 4.60 (s, 1H), 3.68 (d, J = 11.0 Hz, 1H), 3.16 (d, J = 11.0 Hz, 1H), 2.47 (ddd, J = 12.2, 10.2, 7.1 Hz, 1H), 2.29 – 2.21 (m, 1H), 2.15 (dd, J = 15.9, 2.3 Hz, 1H), 2.07 (dd, J = 15.9, 2.6 Hz, 1H), 1.51 (dd, J = 13.0, 6.9 Hz, 2H), 1.41 – 1.27 (m, 4H), 0.98 (s, 9H), 0.14 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (151 MHz, C_6D_6) δ 212.15, 198.40, 68.90, 64.39, 63.15, 60.73, 45.66, 32.72, 28.77, 26.08, 18.50, 0.02, -5.34, -5.44.

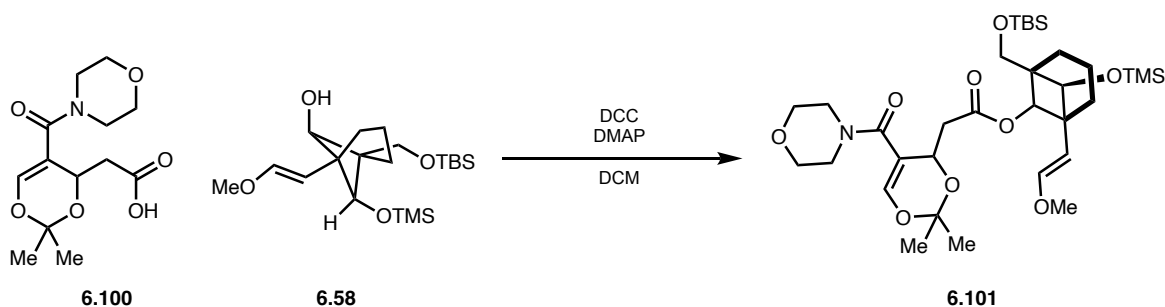


2-((5S)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-oxo-7-((trimethylsilyl)oxy)bicyclo[3.1.1]heptan-1-yl)acetic acid (6.125)

In a 1 mL vial, to a stirred solution of **6.113** (1.00 mg, 2.60 μmol , 1.0 equiv) in *t*BuOH (18.6 μL) and H_2O (18.6 μL) were added 2-methyl-2-butene (18.2 mg, 27.5 μL , 260 μmol , 100 equiv) and sodium dihydrogen phosphate (3.12 mg, 26.0 μmol , 10 equiv) and sodium chlorite (940 μg , 10.4 μmol , 10 equiv) at room temperature. The reaction was stirred for 1 hour. The reaction was quenched with aqueous solution of NaHSO_3 . The aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The product was obtained as a colorless oil (0.84 mg, 2.1 μmol , 81 %).

R_f (100 % EtOAc, bromo cresol green) 0.75

^1H NMR (400 MHz, C_6D_6) δ 4.73 (s, 1H), 3.69 (d, J = 10.9 Hz, 1H), 3.20 (d, J = 11.3 Hz, 1H), 2.61 – 2.50 (m, 1H), 2.34 (d, J = 15.5 Hz, 1H), 2.28 (d, J = 9.6 Hz, 1H), 2.20 (d, J = 15.7 Hz, 1H), 1.63 (d, J = 18.2 Hz, 1H), 1.34 (s, 3H), 0.99 (d, J = 2.3 Hz, 9H), 0.18 (d, J = 2.2 Hz, 9H), 0.14 (s, 3H), 0.10 (s, 3H).



(1*S*,5*R*,6*R*,7*S*)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-((*E*)-2-methoxyvinyl)-7-(((trimethylsilyl)oxy)bicyclo[3.1.1]heptan-6-yl 2-(2,2-dimethyl-5-(morpholine-4-carbonyl)-4*H*-1,3-dioxin-4-yl)acetate (6.101)

In a 1 dr vial, **6.100** (7.50 mg, 18.7 μ mol, 1.0 equiv) was dissolved in anhydrous DCM (93.6 μ L) with **6.58** (5.87 mg, 20.6 μ mol, 1.1 equiv) and DMAP (229 μ g, 1.87 μ mol, 0.1 equiv) and DCC (4.25 mg, 20.6 μ mol, 1.1 equiv) at room temperature for 1 h. The reaction was filtered with an HPLC filter and concentrated under reduced pressure. The product was obtained as a colorless oil (7.8 mg, 12 μ mol, 62 %).

R_f (25 % EtOAc/hexanes, p-anisaldehyde) 0.1

¹H NMR (500 MHz, C₆D₆) δ 6.65 (dd, J = 13.0, 2.8 Hz, 1H), 6.41 – 6.30 (m, 1H), 5.37 – 5.27 (m, 1H), 5.04 (d, J = 15.7 Hz, 1H), 5.00 – 4.91 (m, 1H), 3.99 (d, J = 9.6 Hz, 1H), 3.57 (dd, J = 13.4, 10.4 Hz, 1H), 3.40 (dd, J = 10.4, 3.4 Hz, 2H), 3.31 – 3.22 (m, 5H), 3.15 (d, J = 1.5 Hz, 3H), 2.87 (ddd, J = 14.7, 9.4, 3.9 Hz, 1H), 2.69 – 2.58 (m, 1H), 2.15 (dd, J = 12.9, 7.8 Hz, 1H), 2.09 – 1.98 (m, 1H), 1.92 (d, J = 7.6 Hz, 1H), 1.88 – 1.77 (m, 1H), 1.42 (d, J = 11.9 Hz, 4H), 1.29 (d, J = 11.5 Hz, 4H), 1.04 (d, J = 3.5 Hz, 9H), 0.20 (d, J = 1.8 Hz, 9H), 0.18 (d, J = 1.4 Hz, 3H), 0.15 (d, J = 3.5 Hz, 3H), 0.13 (d, J = 2.3 Hz, 3H).

6.7 References

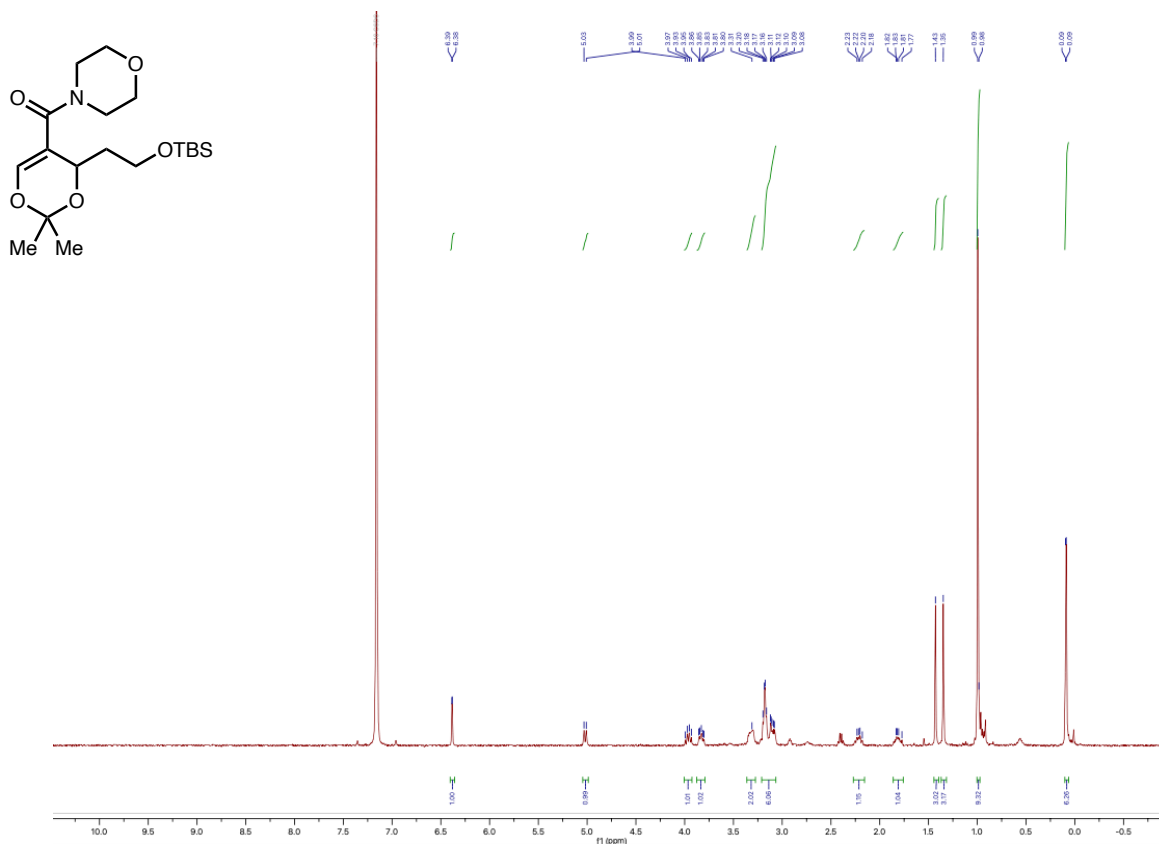
1. Aungst, R. A.; Funk, R. L. Synthesis of (Z)-2-Acyl-2-enals via Retrocycloadditions of 5-Acyl-4-alkyl-4H-1,3-dioxins: Application in the Total Synthesis of the Cytotoxin ($\pm$)-Euplotin A. *J. Am. Chem. Soc.* **2001**, *123*, 9455–9456.
2. Fearnley, S. P.; Funk, R. L.; Gregg, R. J. Preparation of 2-Alkyl- and 2-Acylpropenals from 5-(Trifluoromethanesulfonyloxy)-4H-1,3-dioxin: A Versatile Acrolein α -Cation Synthon. *Tetrahedron* **2000**, *56*, 10275.
3. Ogiwara, Y. Morpholine Amides: Classical but Underexplored Acylating Intermediates in Organic Synthesis. *Synthesis* **2025**, *57* (24), 3639–3648.
4. Meiji Seika Kaisha, Ltd. Poly(ADP-ribose) Polymerase Inhibitors Consisting of Pyrimidine Derivatives; WO2000042025A1, 2000.
5. Le Du, E.; Waser, J. Recent Progress in Alkynylation with Hypervalent Iodine Reagents. *Chem. Commun.* **2023**, *59*, 1589–1604.
6. Shao, W.; Huang, J.; Guo, K.; Gong, J.; Yang, Z. Total Synthesis of Sinensilactam A. *Org. Lett.* **2018**, *20*, 1857–1860.
7. Zhang, J.; Wang, X.; Li, S.; Li, D.; Liu, S.; Lan, Y.; Gong, J.; Yang, Z. Diastereoselective Synthesis of Cyclopentanoids: Applications to the Construction of the ABCD Tetracyclic Core of Retigeranic Acid A. *Chem. Eur. J.* **2015**, *21*, 12596–12600.
8. Gansäuer, A.; Bluhm, H.; Pierobon, M. Emergence of a Novel Catalytic Radical Reaction: Titanocene-Catalyzed Opening of Epoxides. *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859.
9. Ogata, A.; Nemoto, M.; Kobayashi, K.; Tsubouchi, A.; Takeda, T. Titanocene(II)-Promoted Multicomponent Reactions Utilizing Alkynyl Sulfones, Alkenyl Sulfones, and Carbonyl Compounds: A Novel Method for the Synthesis of Vinylallenes. *Chem. Eur. J.* **2007**, *13*, 1320–1325.
10. Li, L.; Hu, L.; Sae-Jew, J.; Rawal, V. H. Vinyltriarylbi-muthonium Salts: Powerful Vehicles for α -Vinylolation of Carbonyl Compounds. *J. Am. Chem. Soc.* **2024**, *146*, 18672–18681.
11. Shade, R. E.; Hyde, A. M.; Olsen, J.-C.; Merlic, C. A. Copper-Promoted Coupling of Vinyl Boronates and Alcohols: A Mild Synthesis of Allyl Vinyl Ethers. *J. Am. Chem. Soc.* **2010**, *132*, 1202–1203.
12. Saito, T.; Kawamura, M.; Nishimura, J. Ytterbium Triflate-Catalyzed Asymmetric Hetero Diels–Alder Cycloaddition of a 1-Thiabuta-1,3-diene with a Chiral N-Acryloyloxazolidinone Dienophile. *Tetrahedron Lett.* **1997**, *38*, 3231–3234.
13. Jian, W.; Qian, B.; Bao, H.; Li, D. AlCl₃-Catalyzed Oxa-Diels–Alder Reaction of Aromatic Aldehydes with Simple Dienes. *Tetrahedron* **2017**, *73*, 4039–4044.
14. Kutsumura, N.; Koyama, Y.; Tateno, K.; Yamamoto, N.; Nagase, H.; Saito, T. ZnCl₂-Promoted Intramolecular Hetero-Diels–Alder Reaction of o-Alkynylphenylcarbodiimides for Synthesis of Dihydrodibenzo[b,g][1,8]naphthyridines. *Chem. Pharm. Bull.* **2016**, *64*, 1364–1369.

15. Schaus, S. E.; Brannalt, J.; Jacobsen, E. N. Asymmetric Hetero-Diels–Alder Reactions Catalyzed by Chiral (salen)Chromium(III) Complexes. *J. Org. Chem.* **1998**, *63*, 403–405.
16. Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. Chiral Bis(oxazoline)copper(II) Complexes as Lewis Acid Catalysts for the Enantioselective Diels–Alder Reaction. *J. Am. Chem. Soc.* **1999**, *121*, 7559–7573.
17. Yokai, K.; Renata, H. Enantioselective Total Synthesis of Lycoposerramine Congeners through Late-Stage Nitrogen Deletion. *Nat. Commun.* **2025**, *16*, 1659.
18. Ibrahim, I.; Zou, W.; Casas, J.; Sundén, H.; Córdova, A. Direct Organocatalytic Enantioselective α -Aminomethylation of Ketones. *Tetrahedron* **2006**, *62*, 357.
19. Ibrahim, I.; Dziedzic, P.; Córdova, A. Organocatalytic Asymmetric α -Aminomethylation of Cyclohexanones. *Synthesis* **2006**, *23*, 4060.
20. Das, B. G.; Ghorai, P. Stereoselective Direct Reductive Amination of Ketones with Electron-Deficient Amines Using $\text{Re}_2\text{O}_7/\text{NaPF}_6$ Catalyst. *Org. Biomol. Chem.* **2013**, *26*, 4379–4382.
21. Reeves, J. T.; Visco, M. D.; Marsini, M. A.; Grinberg, N.; Busacca, C. A.; Mattson, A. E.; Senanayake, C. H. A General Method for Imine Formation Using $\text{B}(\text{OCH}_2\text{CF}_3)_3$. *Org. Lett.* **2015**, *17*, 2442–2445.
22. Coleman, R. S.; Shah, J. A. Chemoselective Cleavage of Benzyl Ethers, Esters, and Carbamates in the Presence of Other Easily Reducible Groups. *Synthesis* **1999**, 1399–1400.
23. Congreve, M. S.; Davison, E. C.; Fuhry, M. A. M.; Holmes, A. B.; Payne, A. N.; Robinson, R. A.; Ward, S. Selective Cleavage of Benzyl Ethers. *Synlett* **1993**, *9*, 663–664.
24. Jiang, J.; Wang, Z. Diiodine–Triethylsilane System: A Practical Method for Deprotection of Aryl Benzyl Ethers. *Synlett* **2025**, *36*, 845–848.
25. Pradhan, P. P.; Bobbitt, J. M.; Bailey, W. F. Oxidative Cleavage of Benzylic and Related Ethers Using an Oxoammonium Salt. *J. Org. Chem.* **2009**, *74*, 9524–9527.
26. Moriyama, K.; Nakamura, Y.; Togo, H. Oxidative Debenzylation of N-Benzyl Amides and o-Benzyl Ethers Using Alkali Metal Bromide. *Org. Lett.* **2014**, *16*, 3812–3815.
27. Han, W.; Ding, Y.; Chen, Z.; Langowski, J. L.; Bellamacina, C.; Rico, A.; Nishiguchi, G. A.; Lan, J.; Atallah, G.; Lindvall, M.; Lin, S.; Zang, R.; Feucht, P.; Zavorotinskaya, T.; Dai, Y.; Garcia, P.; Burger, M. T. Synthesis and Structure–Activity Relationship of Tetra-Substituted Cyclohexyl Diol Inhibitors of Proviral Insertion of Moloney Virus (PIM) Kinases. *J. Med. Chem.* **2020**, *63*, 14885–14904.
28. Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. Facile Oxidation of Aldehydes to Acids and Esters with Oxone. *Org. Lett.* **2003**, *5*, 1031–1034.
29. Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés. Metal-Free Carbon–Carbon Bond-Forming Reductive Coupling between Boronic Acids and Tosylhydrazones. *Nat. Chem.* **2009**, *1*, 494–499.
30. Li, C.; Wang, J.; Barton, L. M.; Yu, S.; Tian, M.; Peters, D. S.; Kumar, M.; Yu, A. W.; Johnson, K. A.; Chatterjee, A. K.; Yan, M.; Baran, P. S. Decarboxylative Borylation. *Science* **2017**, *356*, eaam7355.

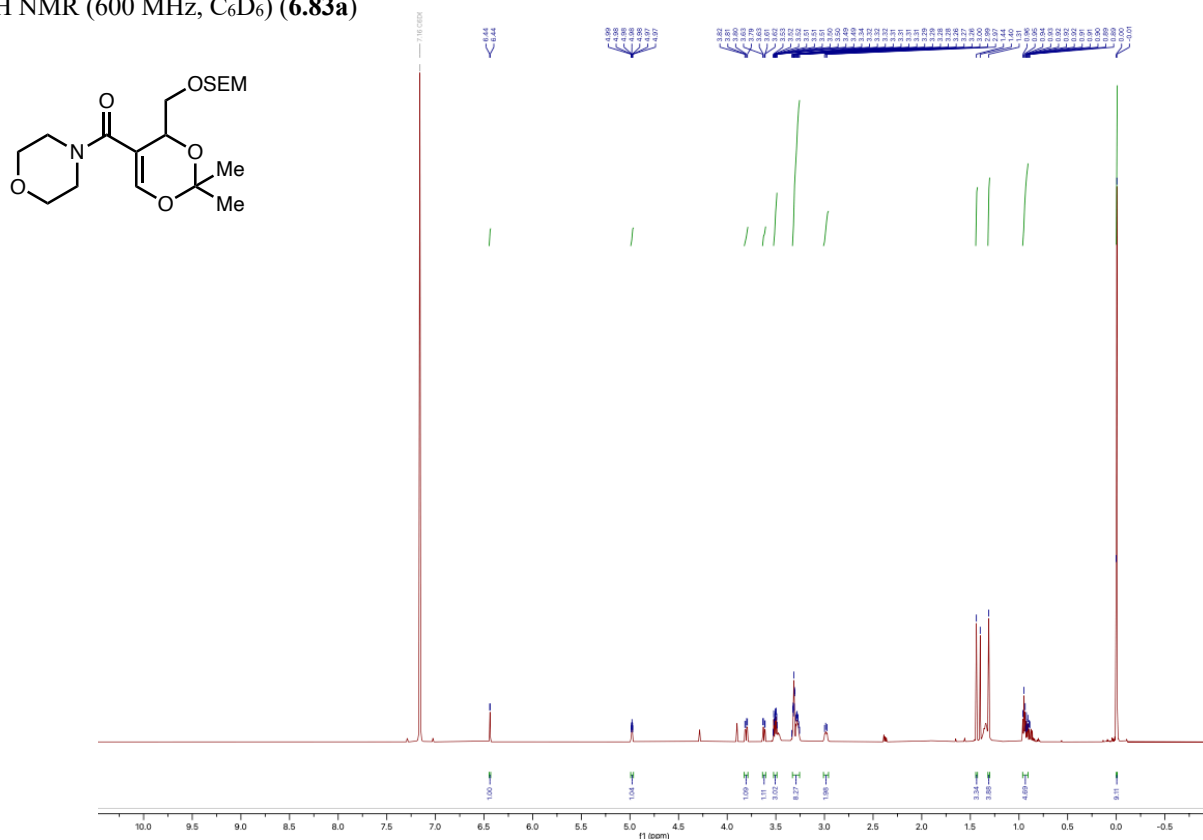
31. Gajewski, J. J. The Claisen Rearrangement: Response to Solvents and Substituents. *Acc. Chem. Res.* **1997**, *30*, 219–225.
32. Kiuchi, W.; Tsunoda, Y.; Ishikura, K.; Kato, K.; Takino, J.; Suzuki, T.; Tanino, K. Total Synthesis of (±)-Cristaxenicin A: Construction of a Nine-Membered Ring by an Eschenmoser–Claisen/Cope Rearrangement Cascade. *Angew. Chem., Int. Ed.* **2026**, *65*, e24855.
33. Pham, S. L.; McDonald, F. E. Chan–Evans–Lam Cu(II)-Catalyzed C–O Cross-Couplings: Broadening Synthetic Access to Functionalized Vinylic Ethers. *Org. Lett.* **2025**, *27*, 7326–7330.
34. Yu, I. F.; Manske, J. L.; Diéguez-Vázquez, A.; Misale, A.; Pashenko, A. E.; Mykhailiuk, P. K.; Ryabukhin, S. V.; Volochnyuk, D. M.; Hartwig, J. F. Catalytic Undirected Borylation of Tertiary C–H Bonds in Bicyclo[1.1.1]pentanes and Bicyclo[2.1.1]hexanes. *Nat. Chem.* **2023**, *15*, 685–693.
35. Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. Sodium Perborate: A Mild and Convenient Reagent for Efficient Oxidation of Organoboranes. *J. Org. Chem.* **1989**, *54*, 5930–5933.
36. (a) Parhi, B.; Maity, S.; Ghorai, P. Catalytic Asymmetric Conjugate Addition of Carboxylic Acids via Oxa-Michael Reaction of Peroxy Hemiacetals Followed by Kornblum–DeLaMare Fragmentation. *Org. Lett.* **2016**, *18*, 5220–5223. (b) Fuwa, H.; Ichinokawa, N.; Noto, K.; Sasaki, M. Stereoselective Synthesis of 2,6-Cis-Substituted Tetrahydropyrans. *J. Org. Chem.* **2012**, *77*, 2588–2607. (c) Karmakar, R.; Pahari, P.; Mal, D. A Synthetic Route to 1,3-Dihydroisobenzofuran Natural Products. *Tetrahedron Lett.* **2009**, *50*, 4042–4045. (d) Mal, D.; Pahari, P.; De, S. R. Regiospecific Synthesis of 3-(2,6-Dihydroxy phenyl)phthalides. *Tetrahedron* **2007**, *63*, 11781–11792.
37. Gao, M.; Wang, Y.-C.; Yang, K.-R.; He, W.; Yang, X.-L.; Yao, Z.-J. Enantioselective Total Synthesis of (+)-Plumisclerin A. *Angew. Chem., Int. Ed.* **2018**, *57*, 13497–13502.

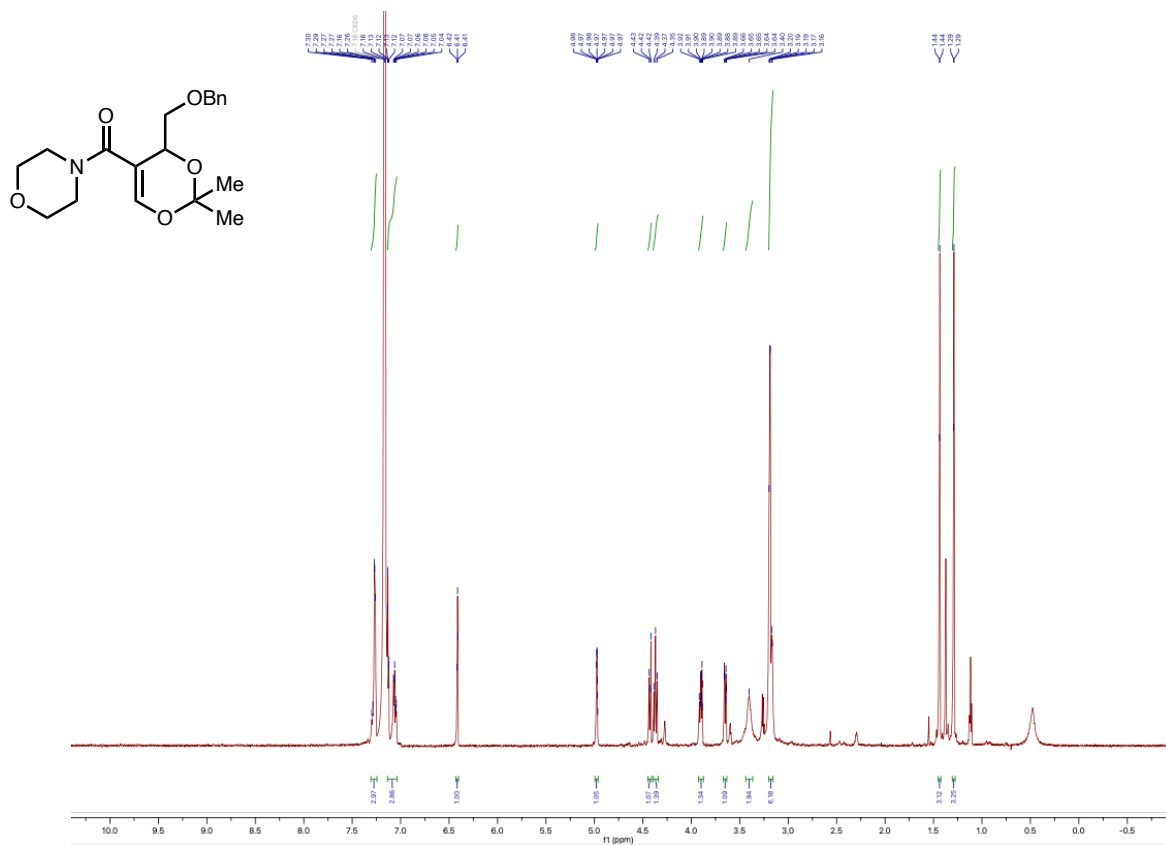
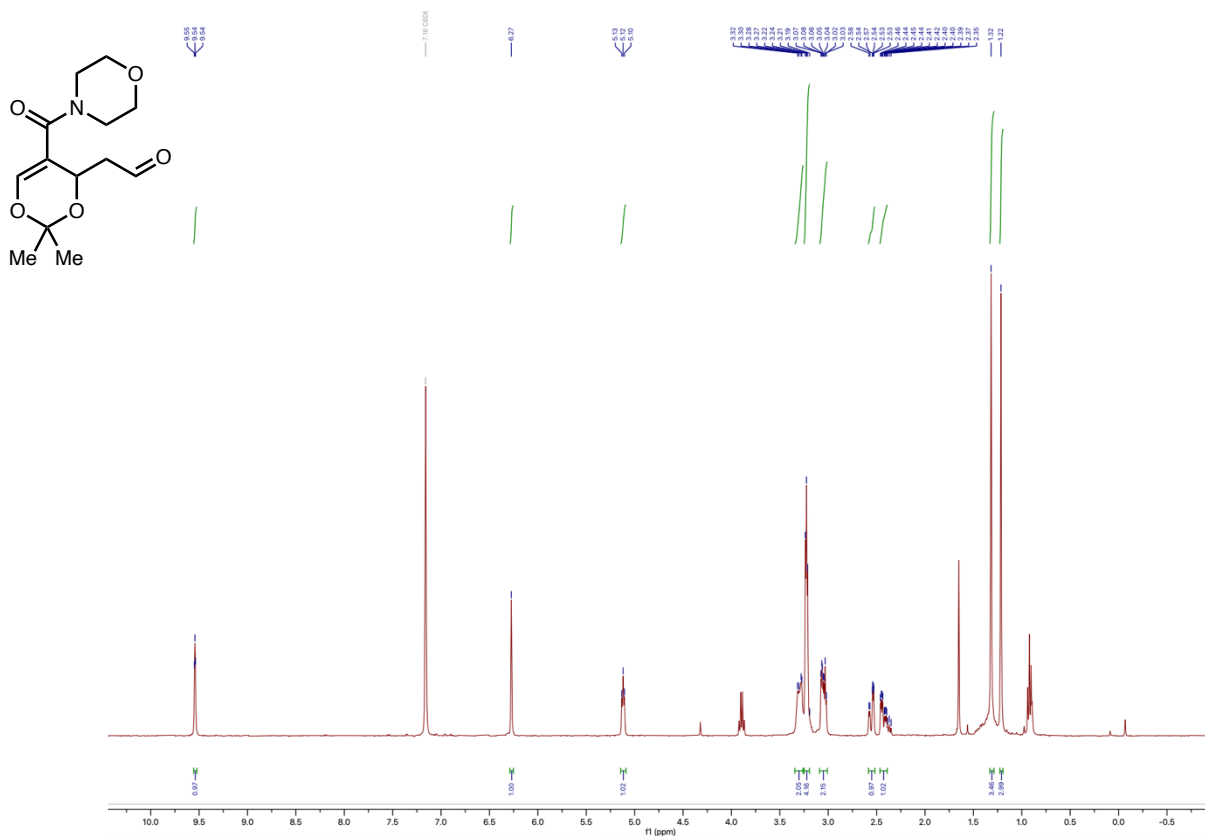
Appendix 6A. NMR Spectra for Chapter 6

^1H NMR (400 MHz, C_6D_6) (**6.26**)

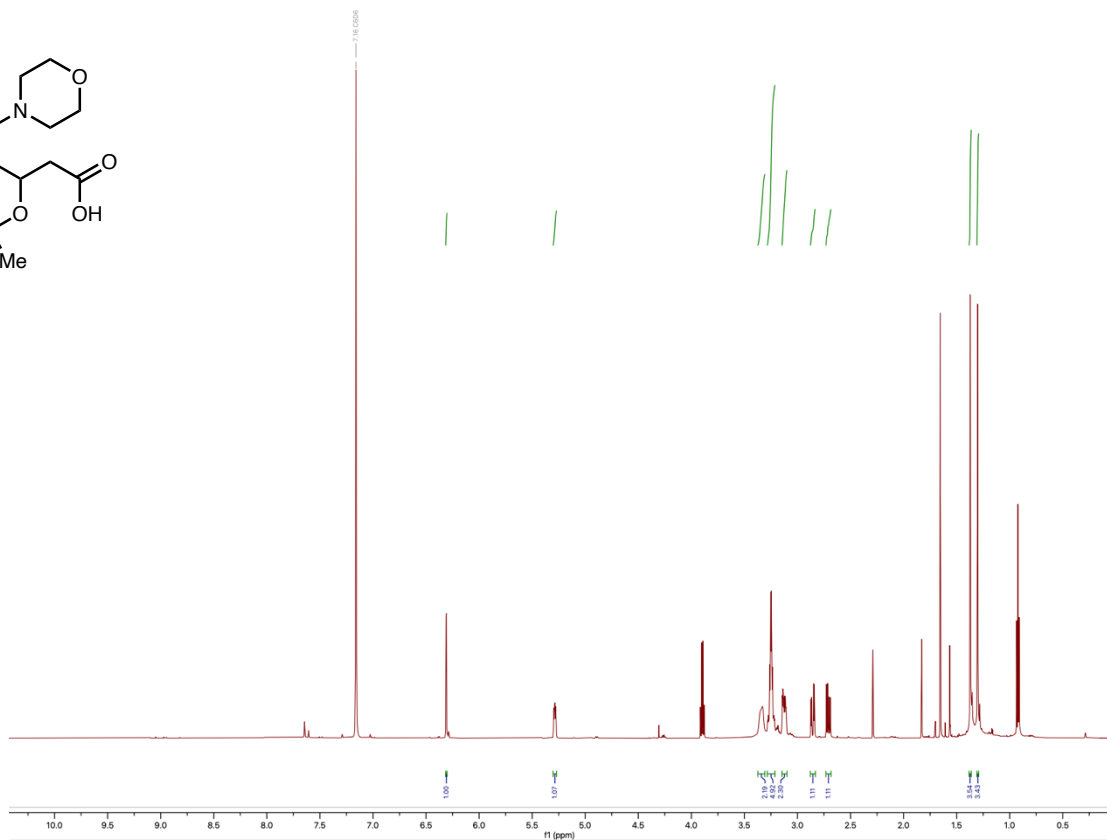
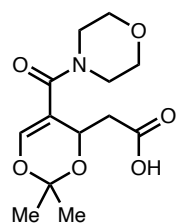


^1H NMR (600 MHz, C_6D_6) (**6.83a**)

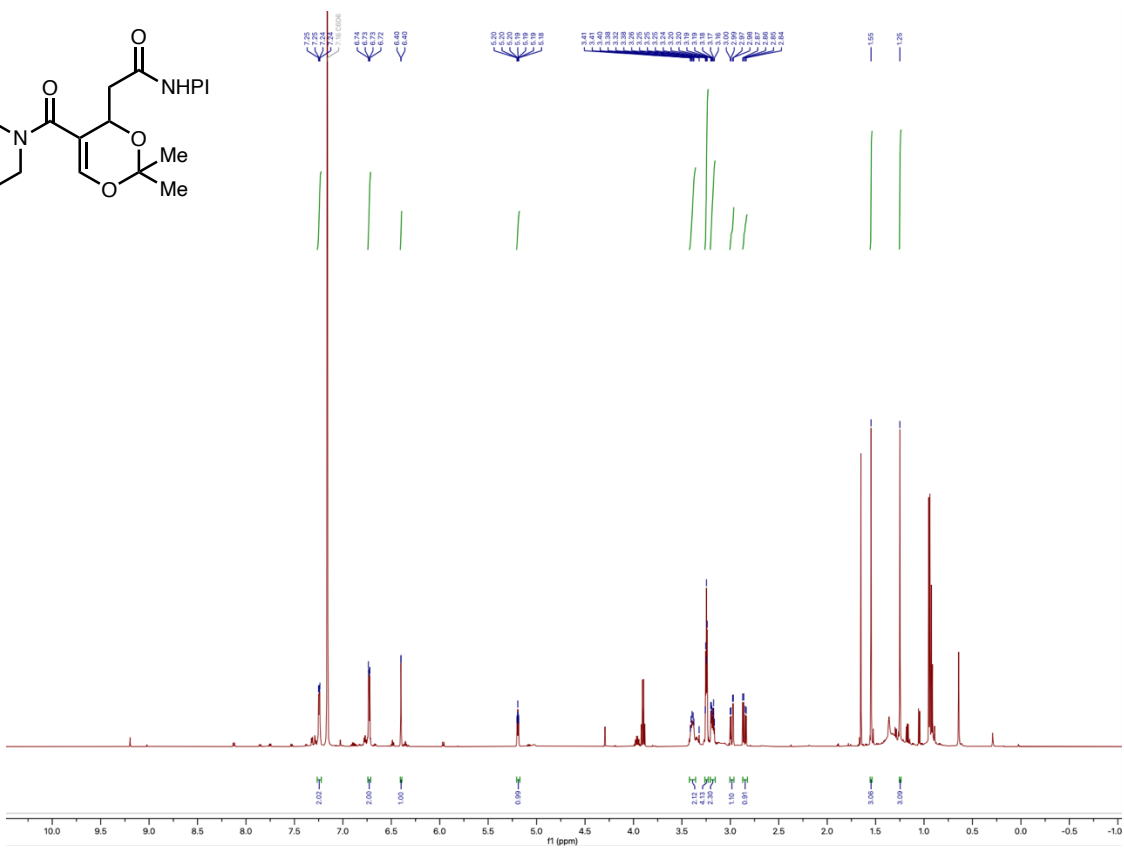
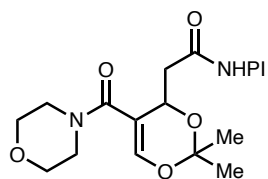


¹H NMR (700 MHz, C₆D₆) (**6.83b**)¹H NMR (400 MHz, C₆D₆) (**6.99**)

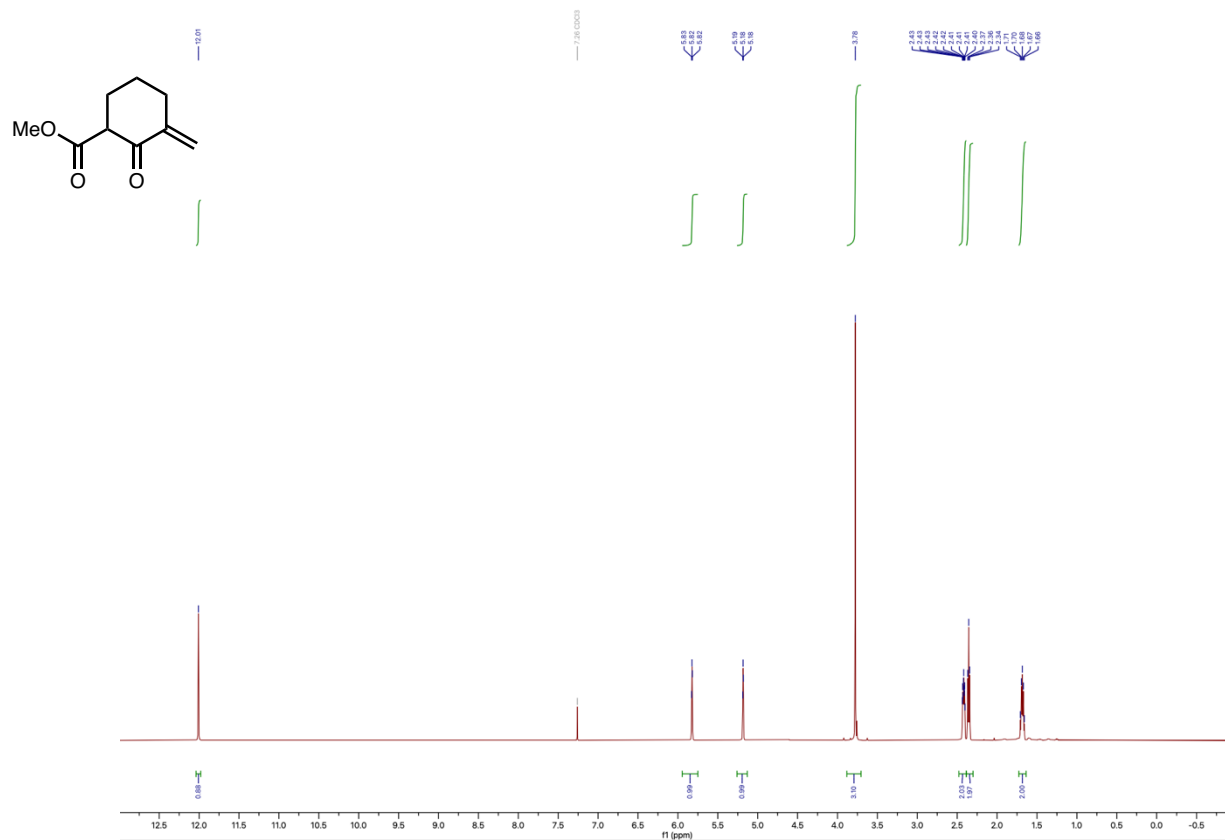
^1H NMR (600 MHz, C_6D_6) (**6.100**)



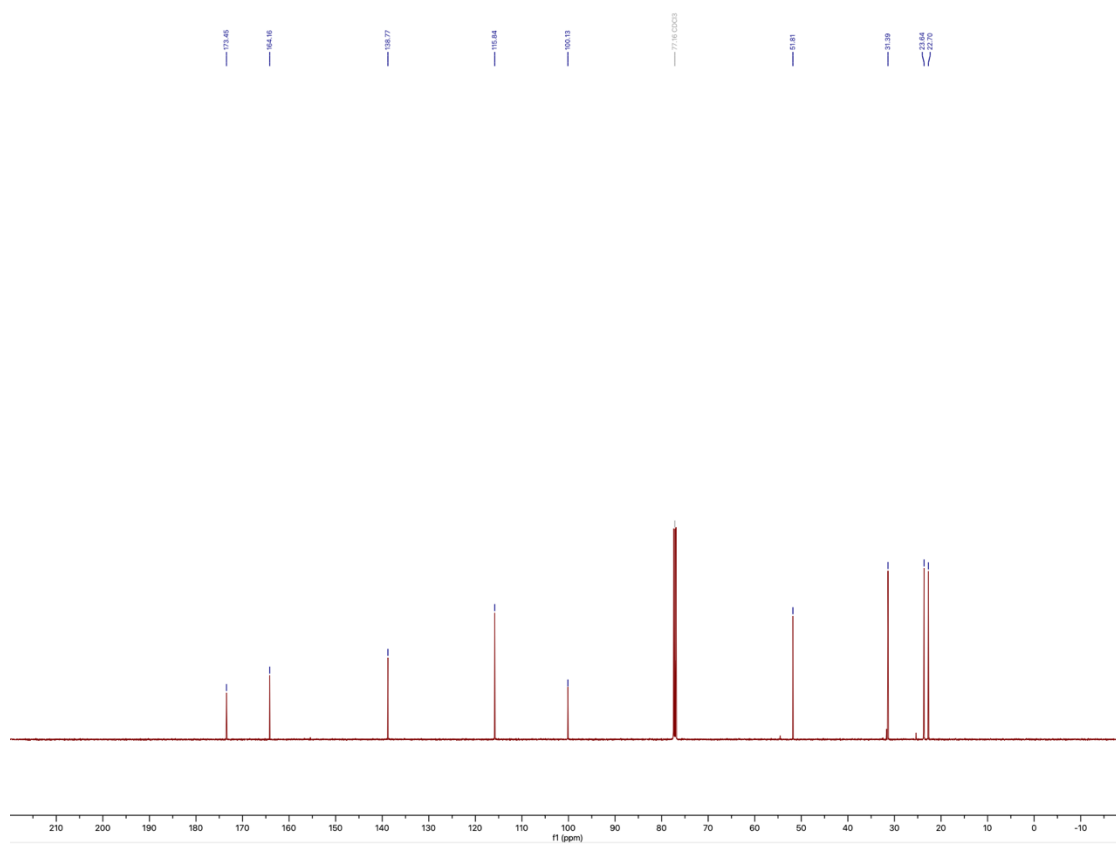
^1H NMR (600 MHz, C_6D_6) (**6.106**)



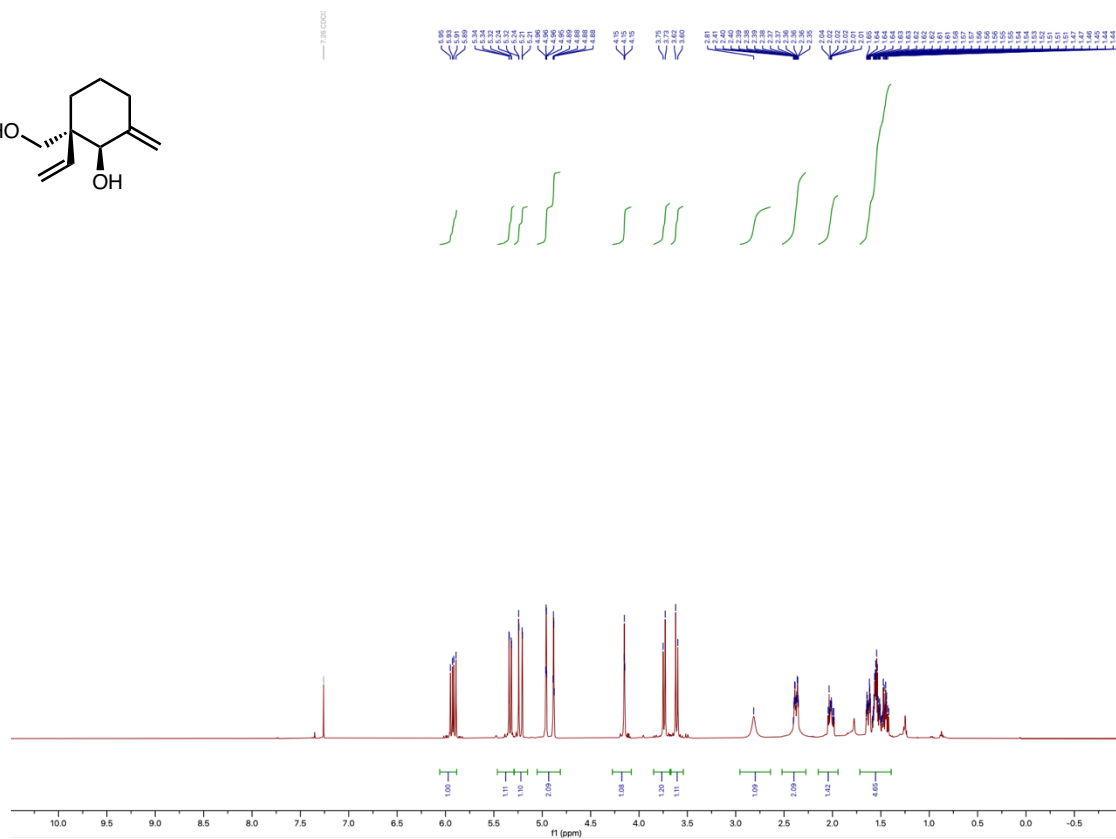
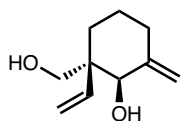
^1H NMR (500 MHz, CDCl_3) (**6.27**)



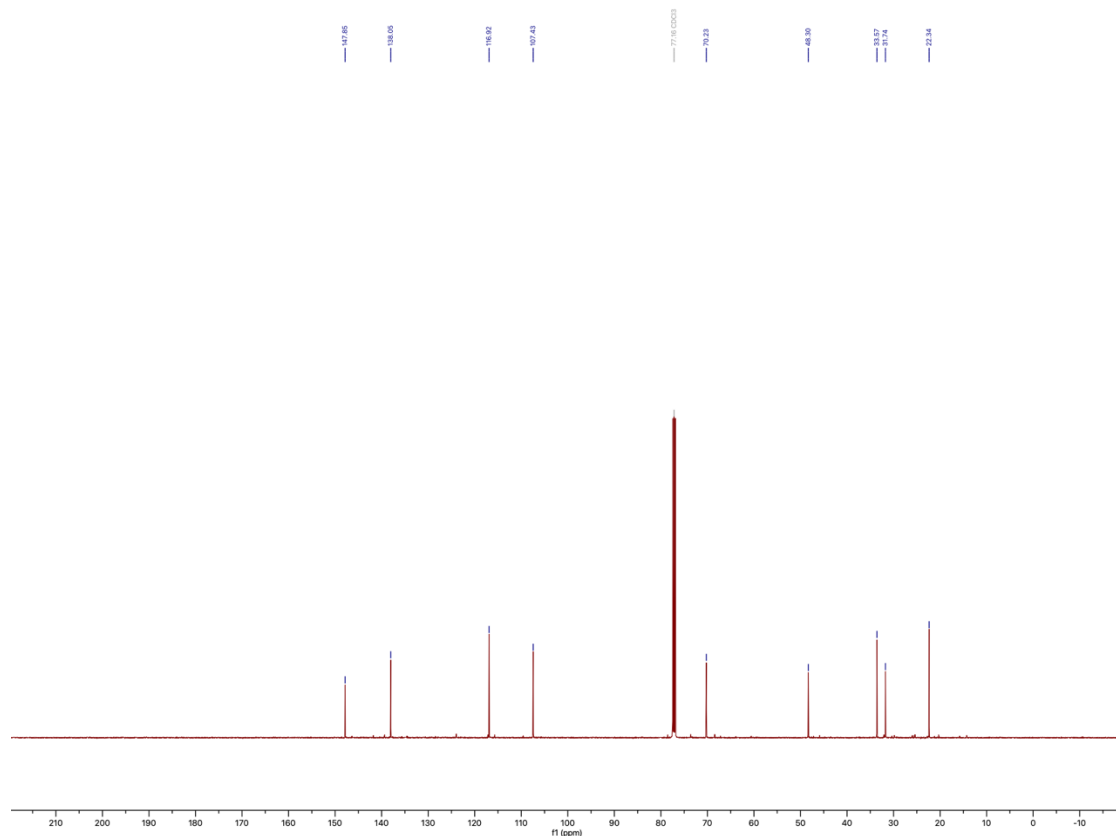
^{13}C NMR (126 MHz, CDCl_3) (**6.27**)



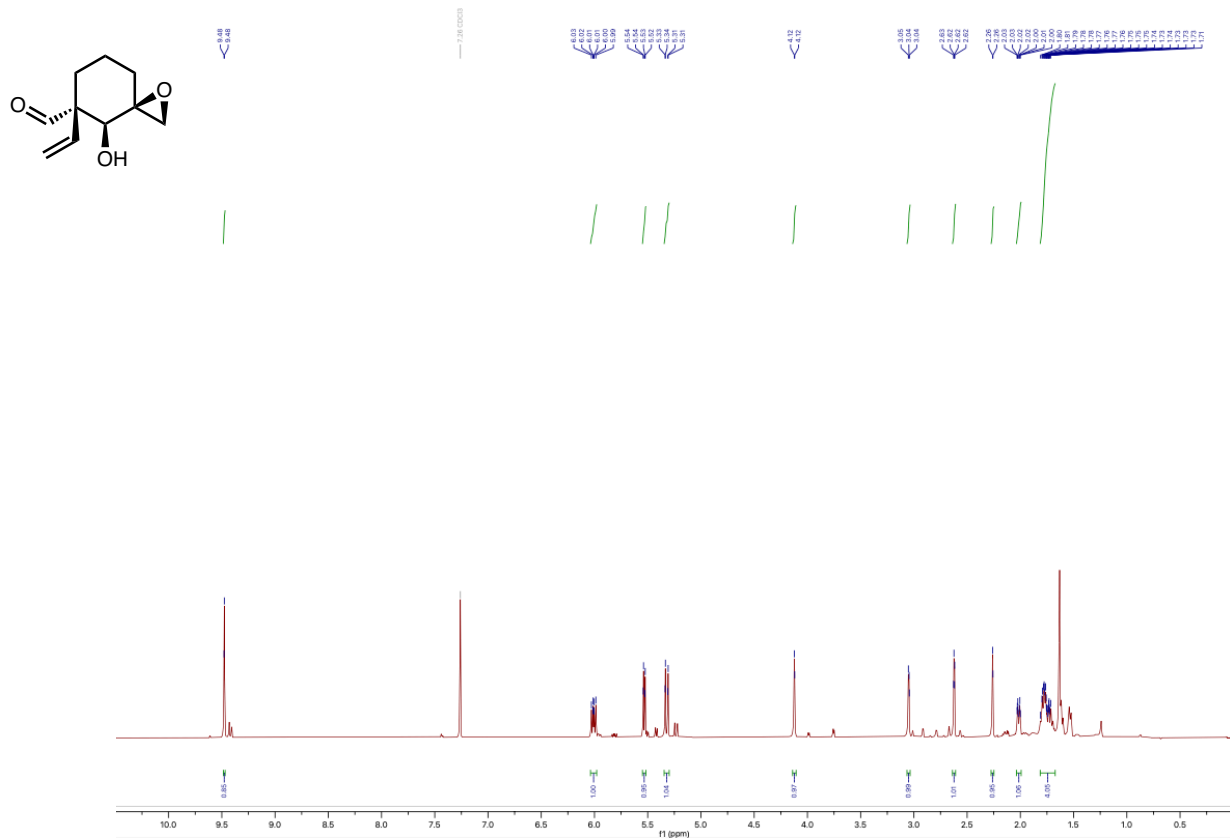
^1H NMR (500 MHz, CDCl_3) (**6.49**)



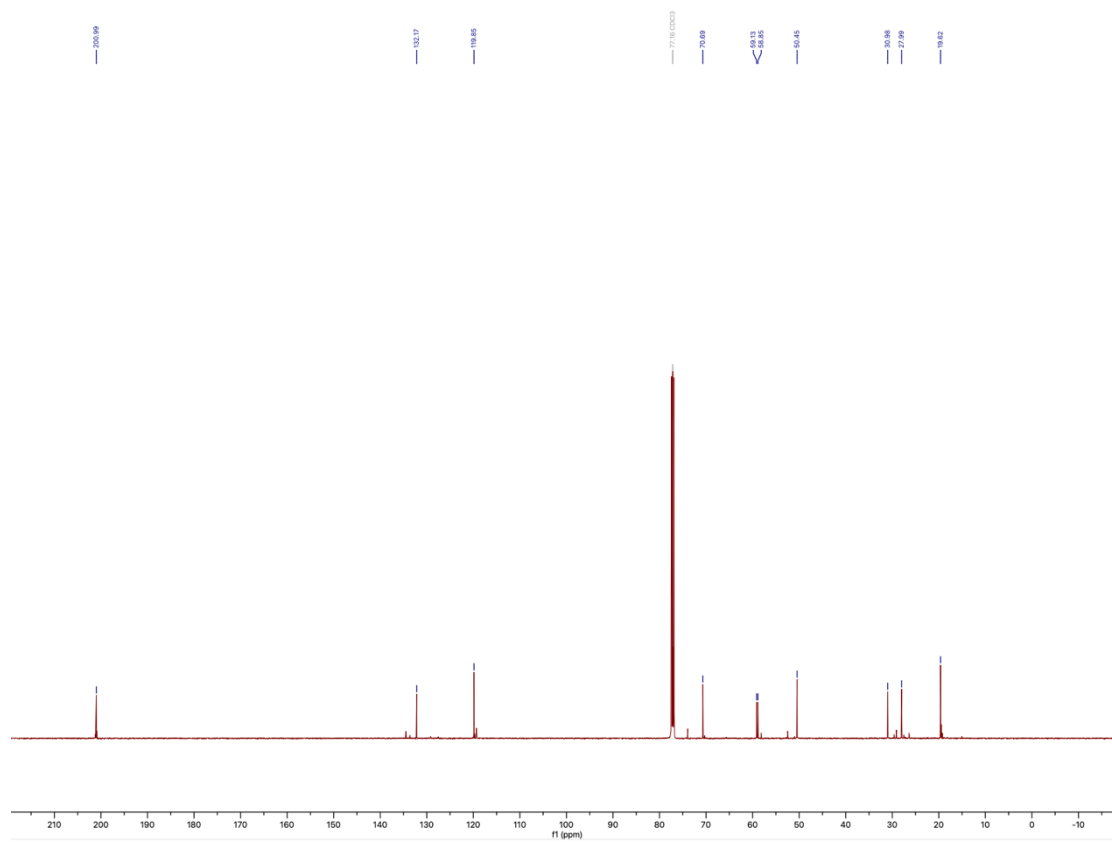
^{13}C NMR (126 MHz, CDCl_3) (**6.49**)

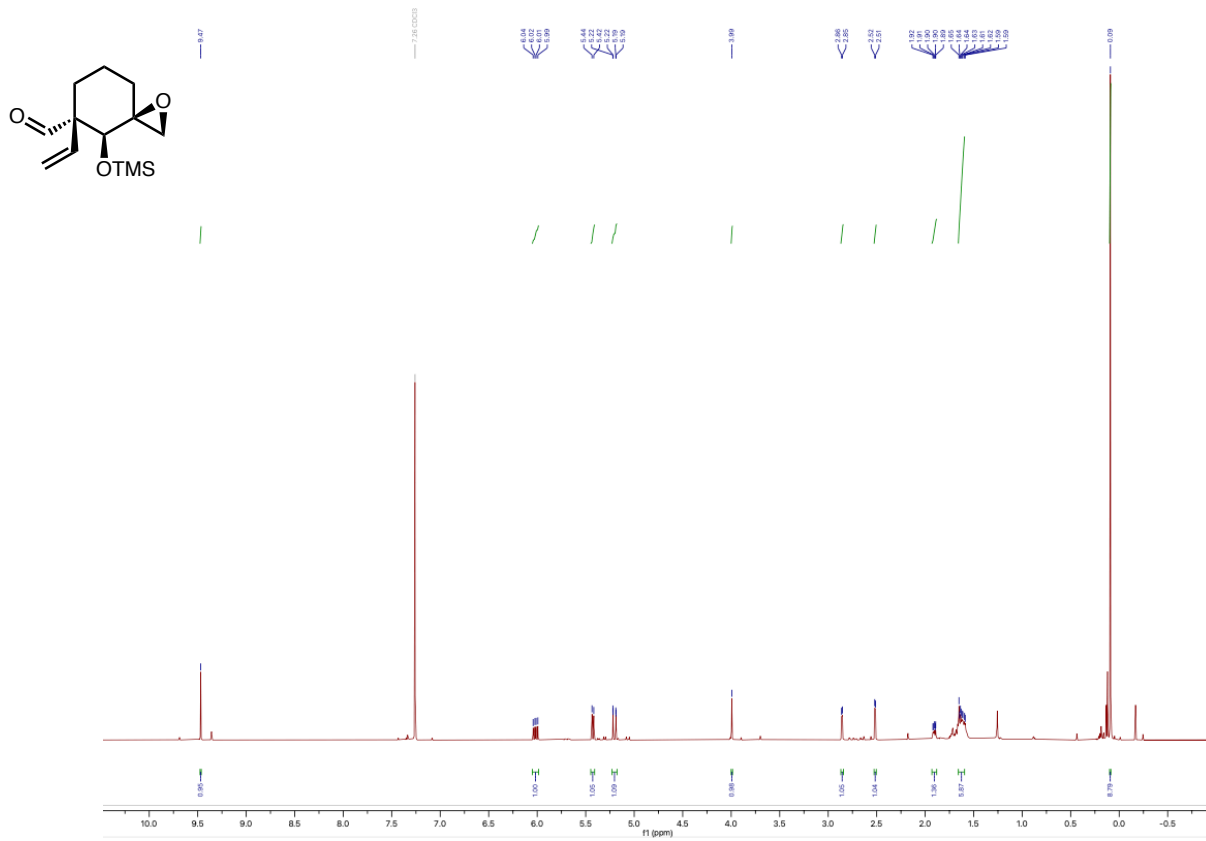
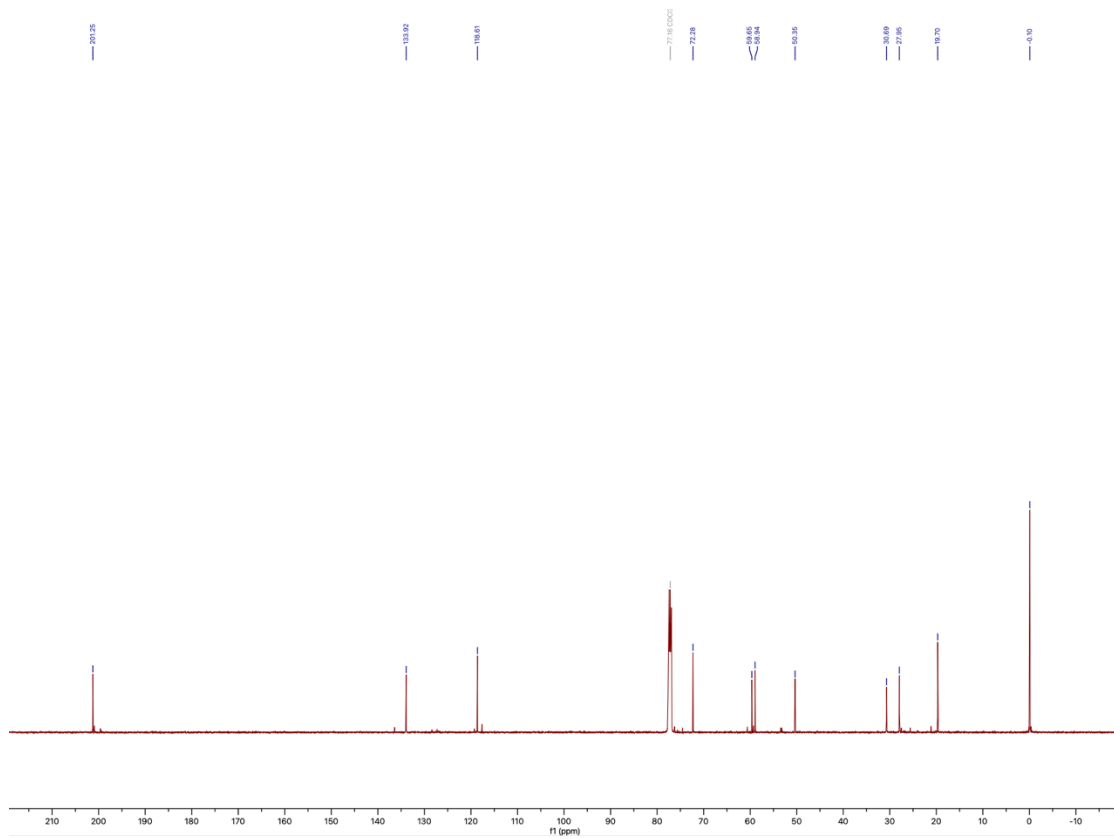


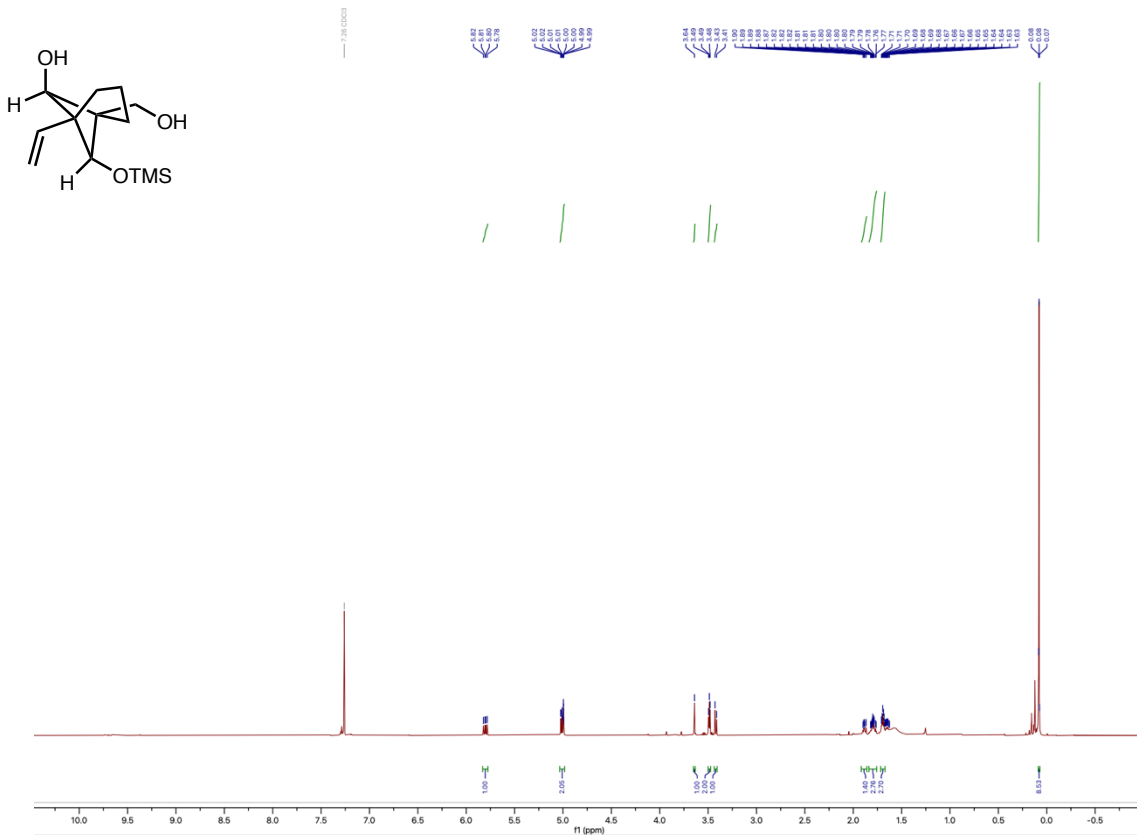
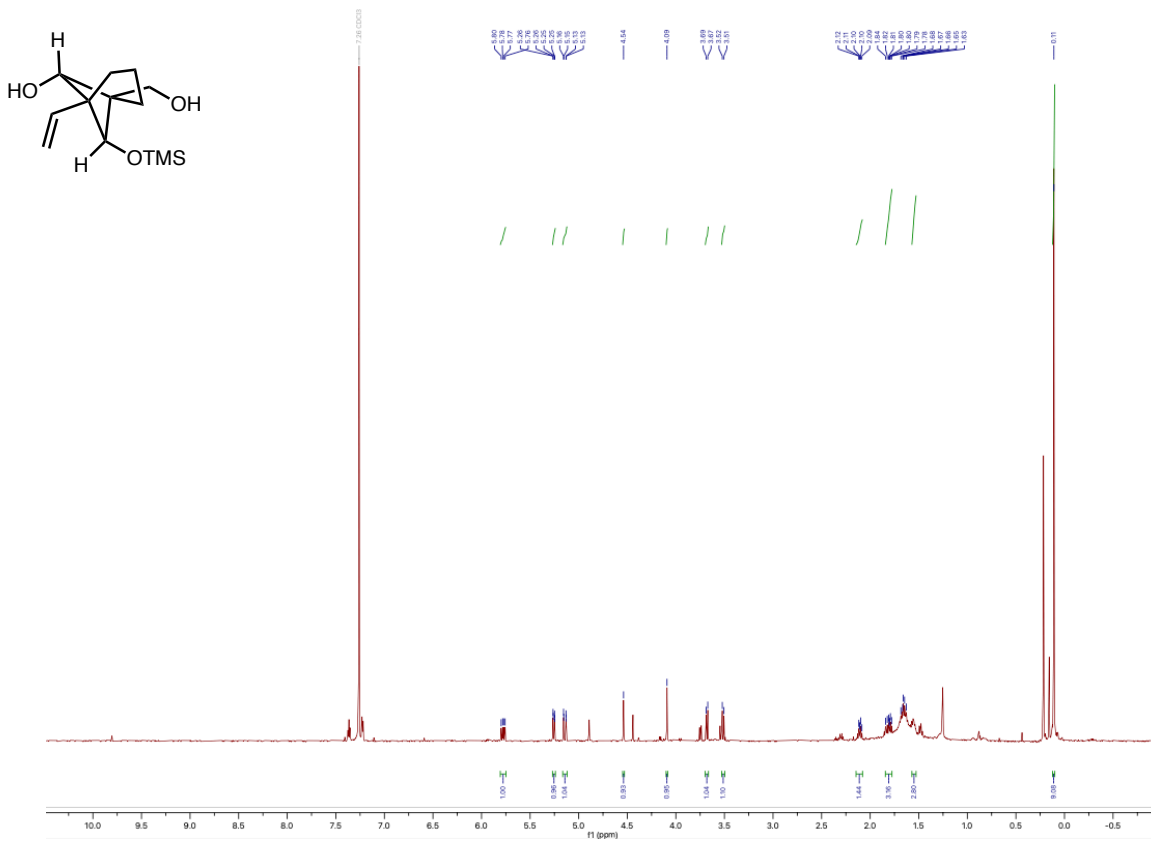
^1H NMR (500 MHz, CDCl_3) (S7)



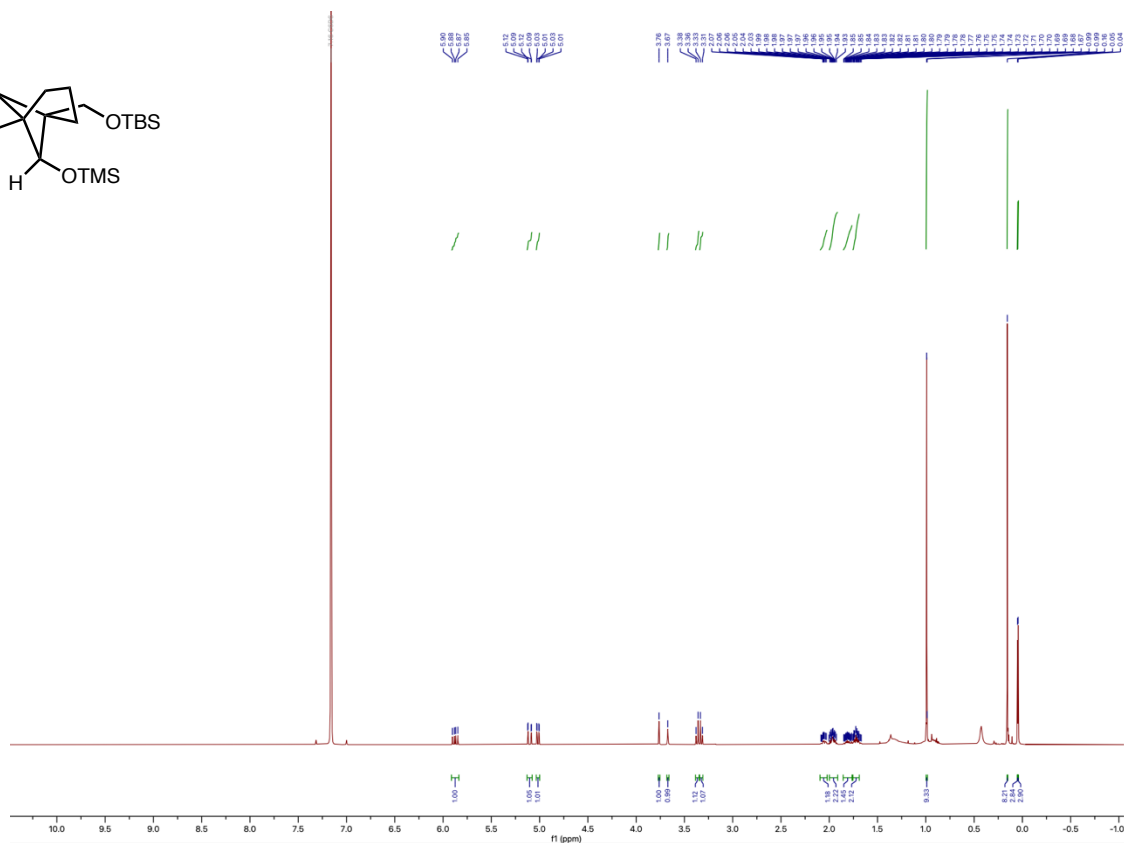
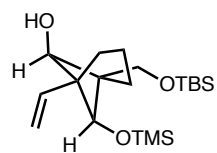
^{13}C NMR (126 MHz, CDCl_3) (S7)



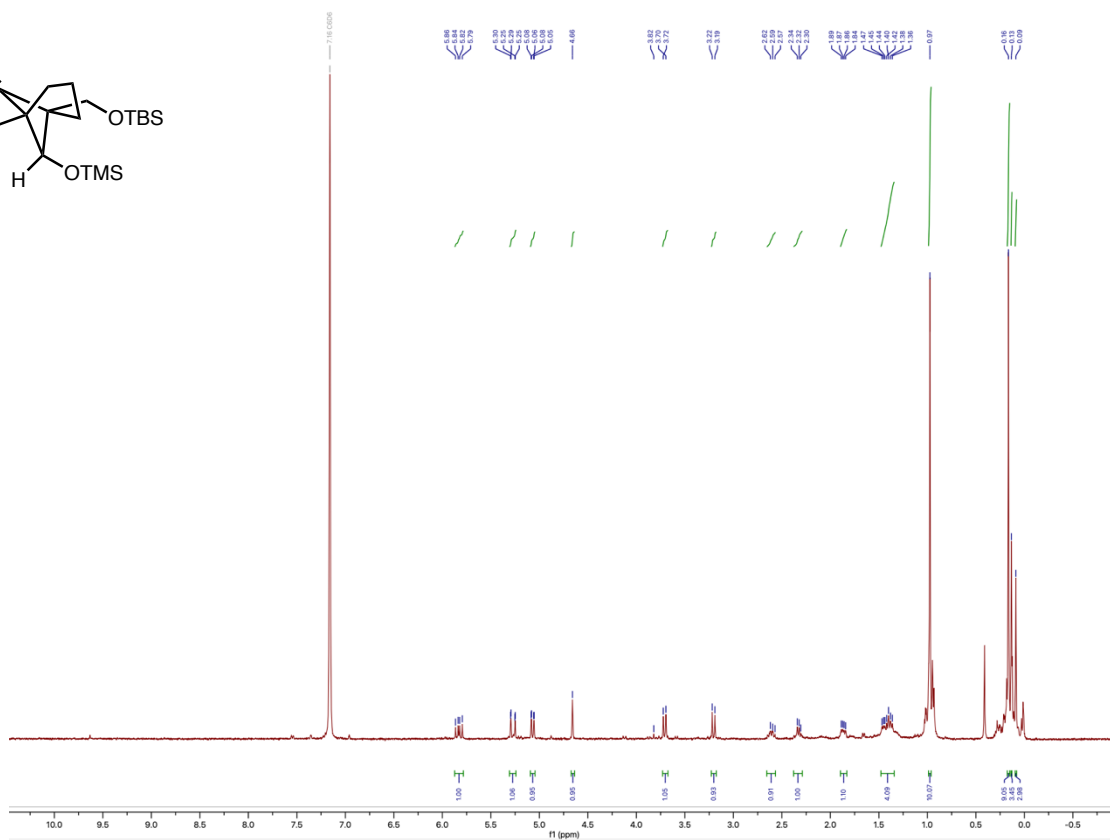
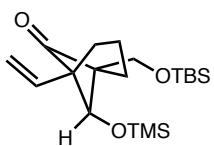
¹H NMR (600 MHz, CDCl₃) (6.50) ^{13}C NMR (126 MHz, CDCl_3) (6.50)

¹H NMR (700 MHz, CDCl₃) (6.51)¹H NMR (700 MHz, CDCl₃) (6.55)

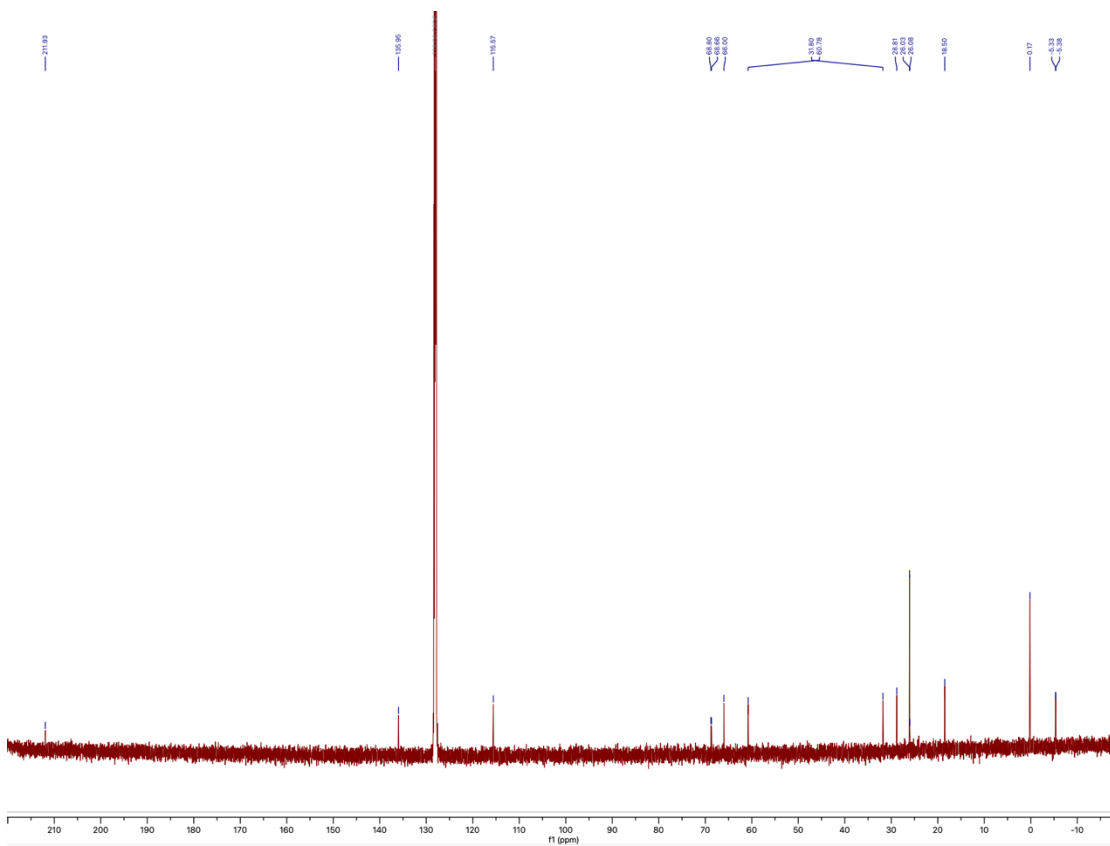
^1H NMR (500 MHz, C_6D_6) (**6.56**)

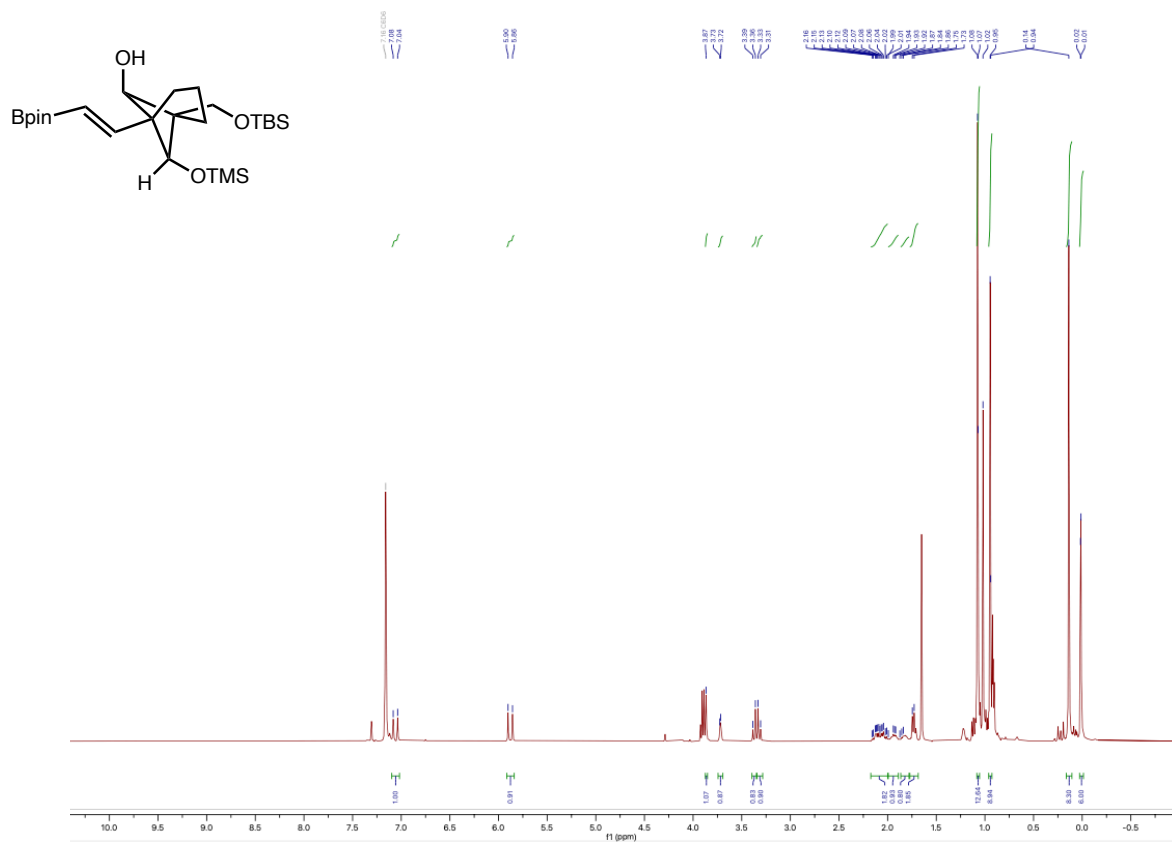


^1H NMR (400 MHz, C_6D_6) (**6.60**)

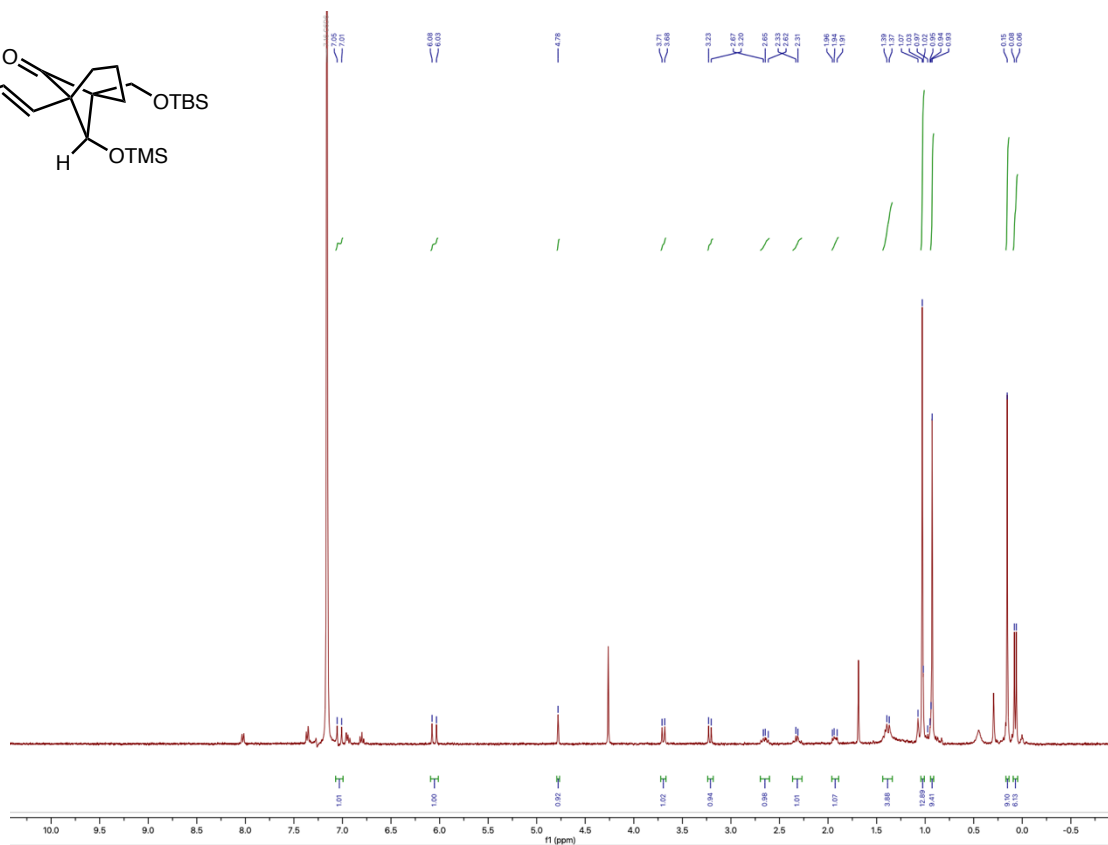
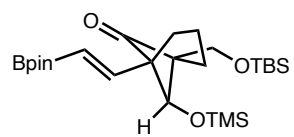


^{13}C NMR (151 MHz, C_6D_6) (**6.60**)

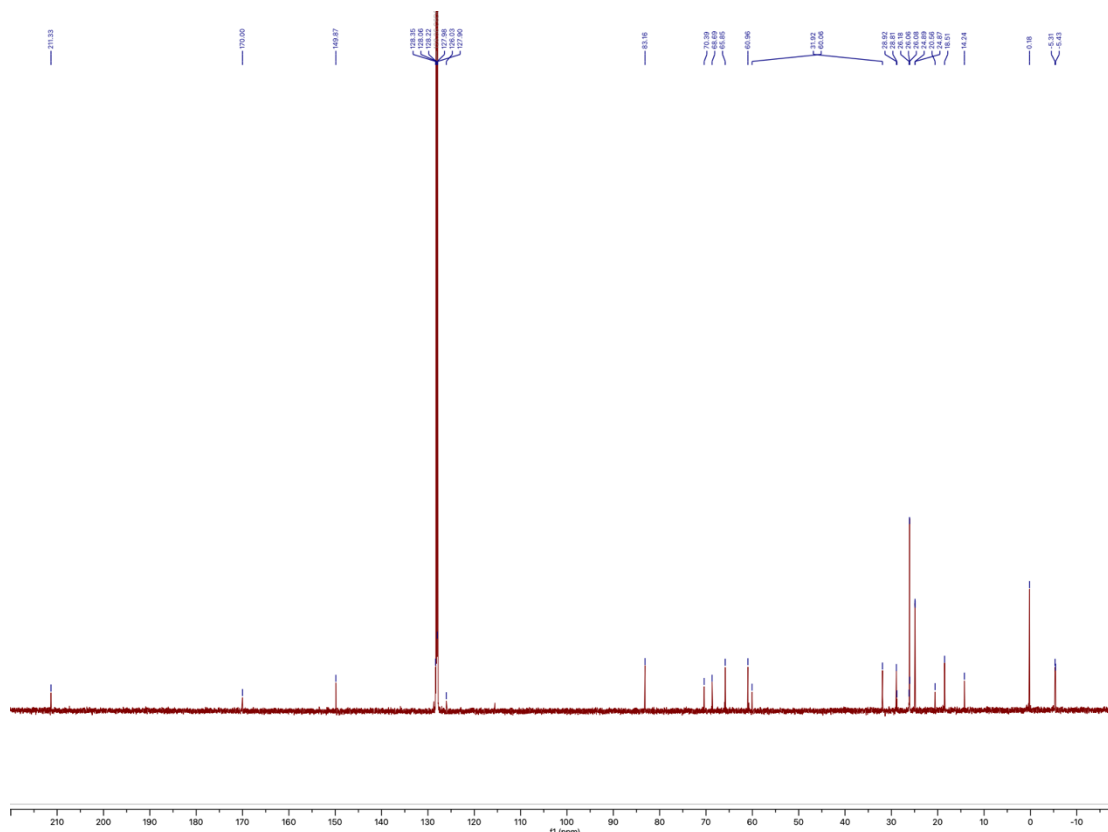


¹H NMR (400 MHz, C₆D₆) (6.57)

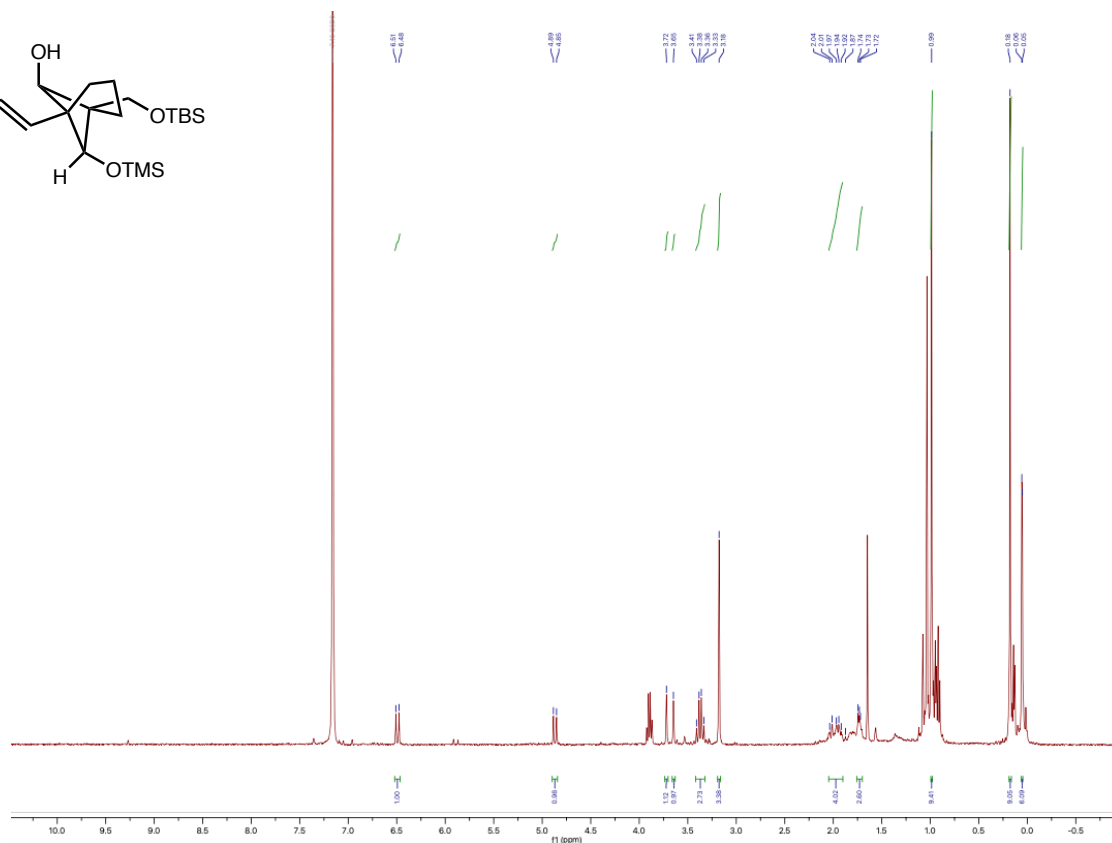
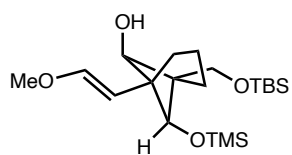
^1H NMR (400 MHz, C_6D_6) (**6.61**)



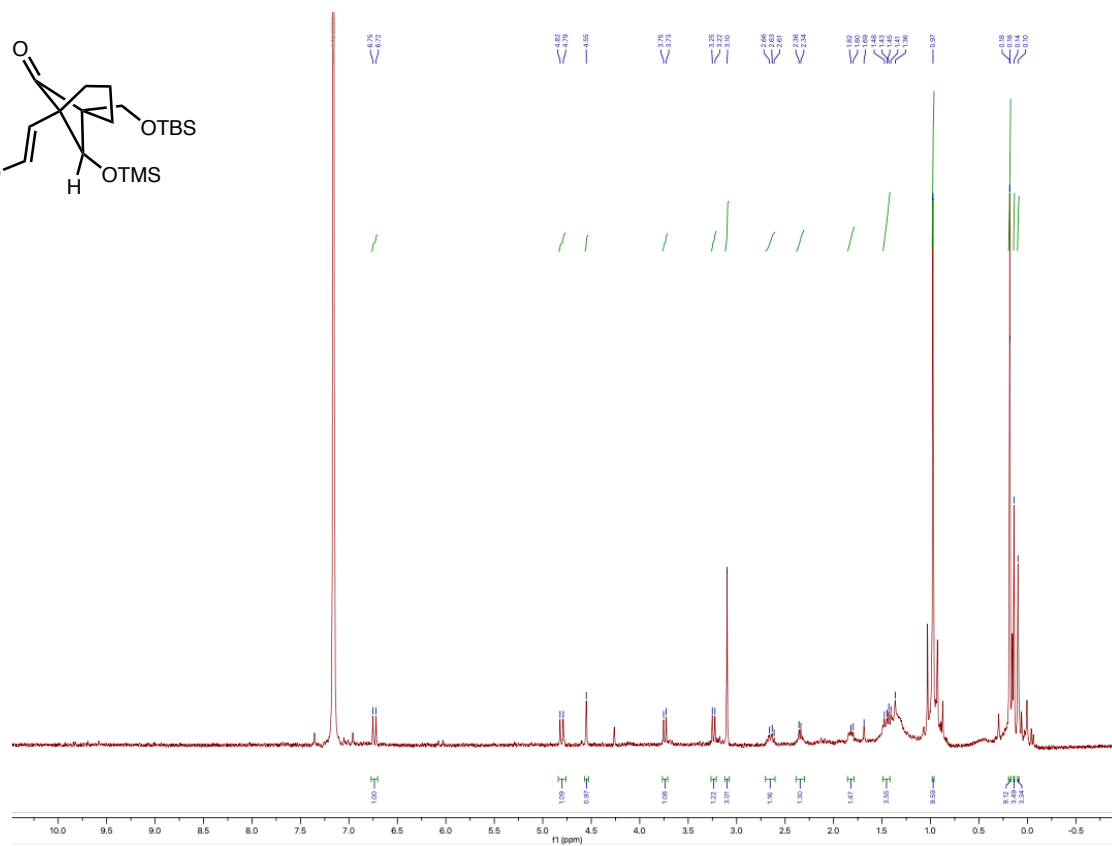
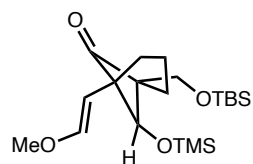
^{13}C NMR (151 MHz, C_6D_6) (**6.61**)



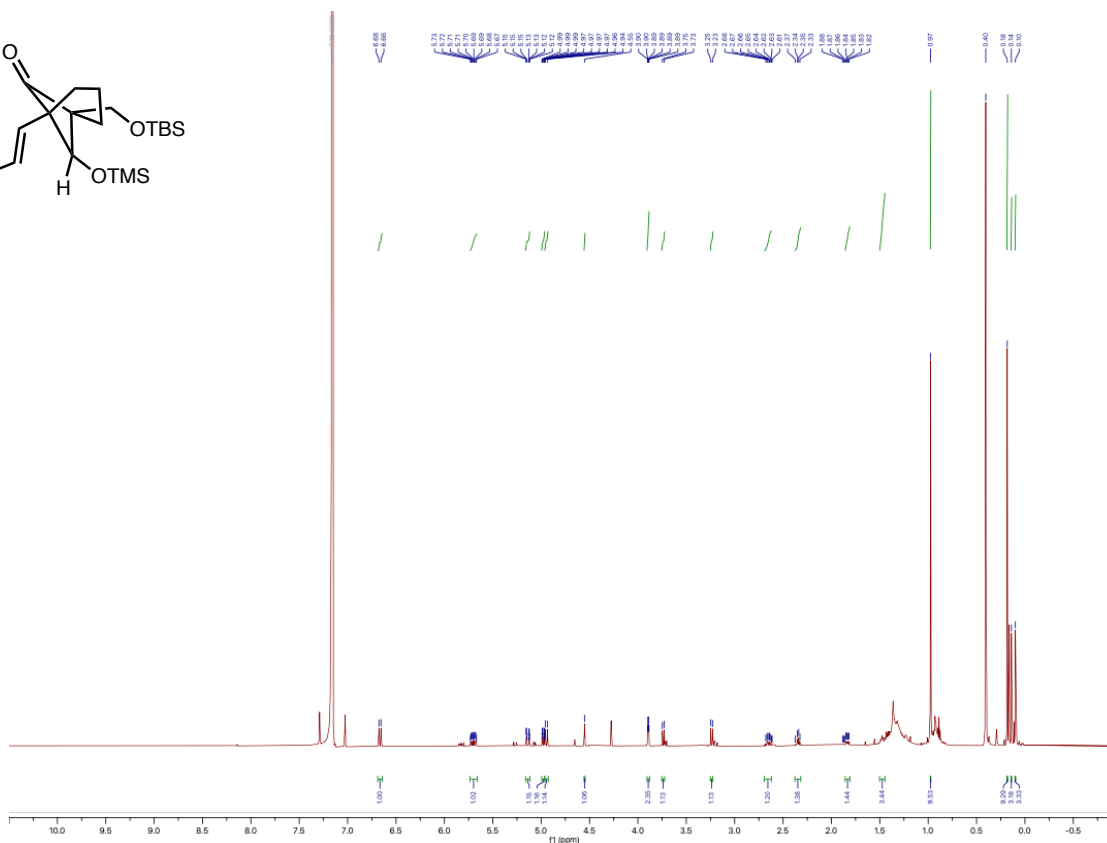
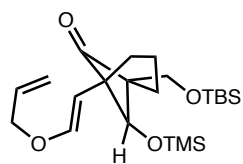
^1H NMR (400 MHz, C_6D_6) (**6.58**)



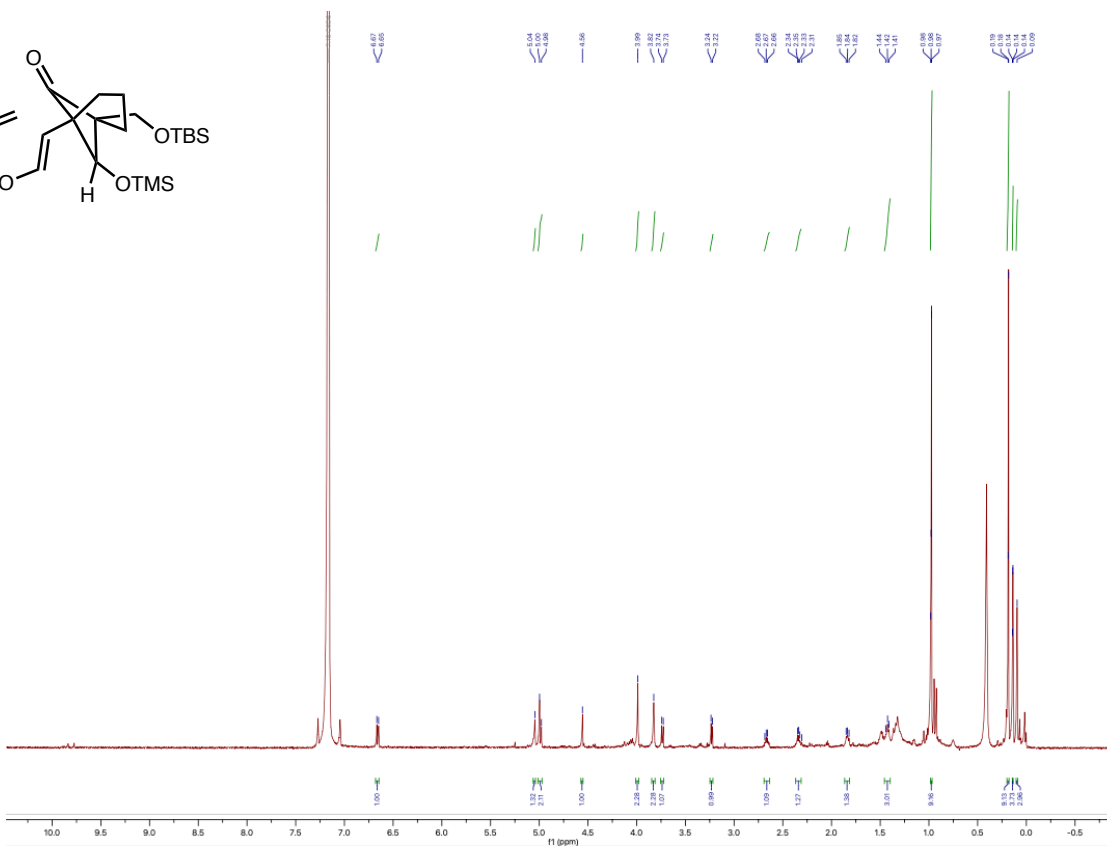
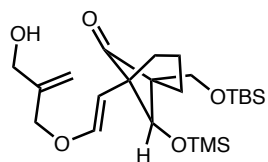
^1H NMR (400 MHz, C_6D_6) (**6.59**)

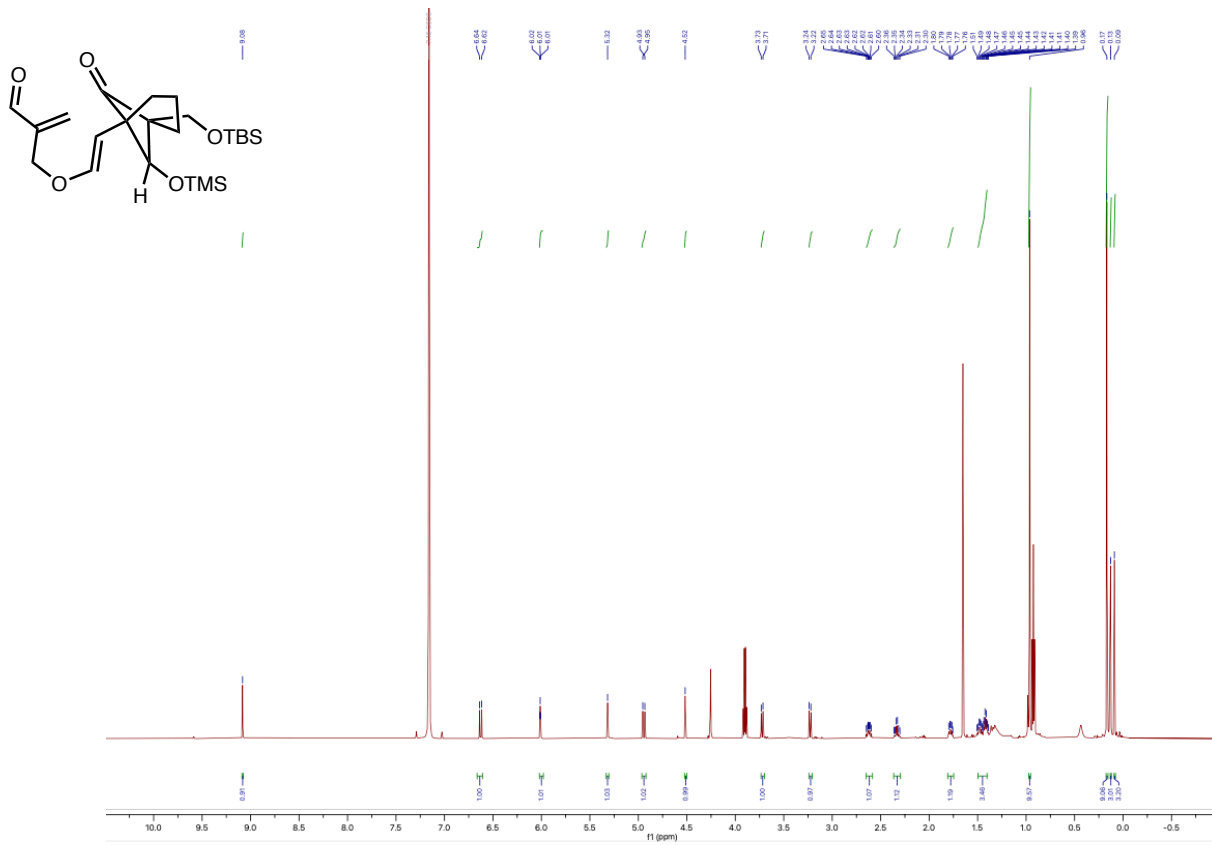
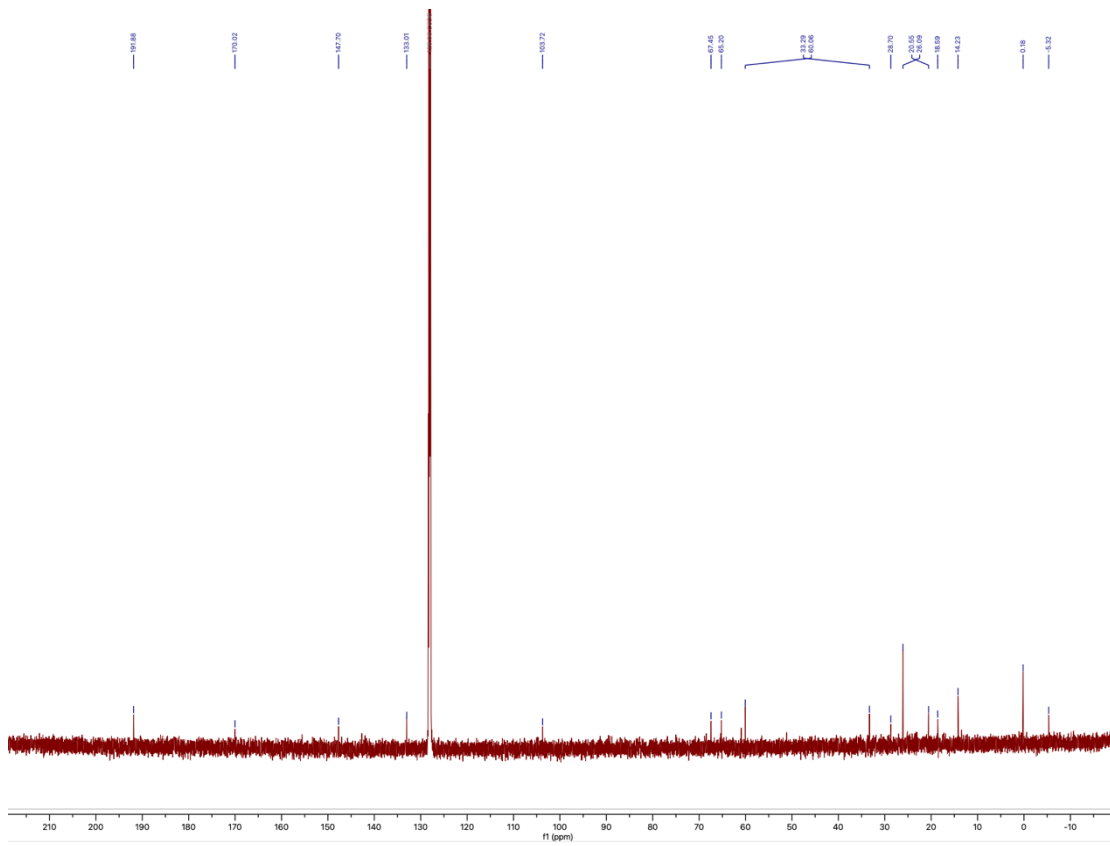


^1H NMR (600 MHz, C_6D_6) (**6.116**)

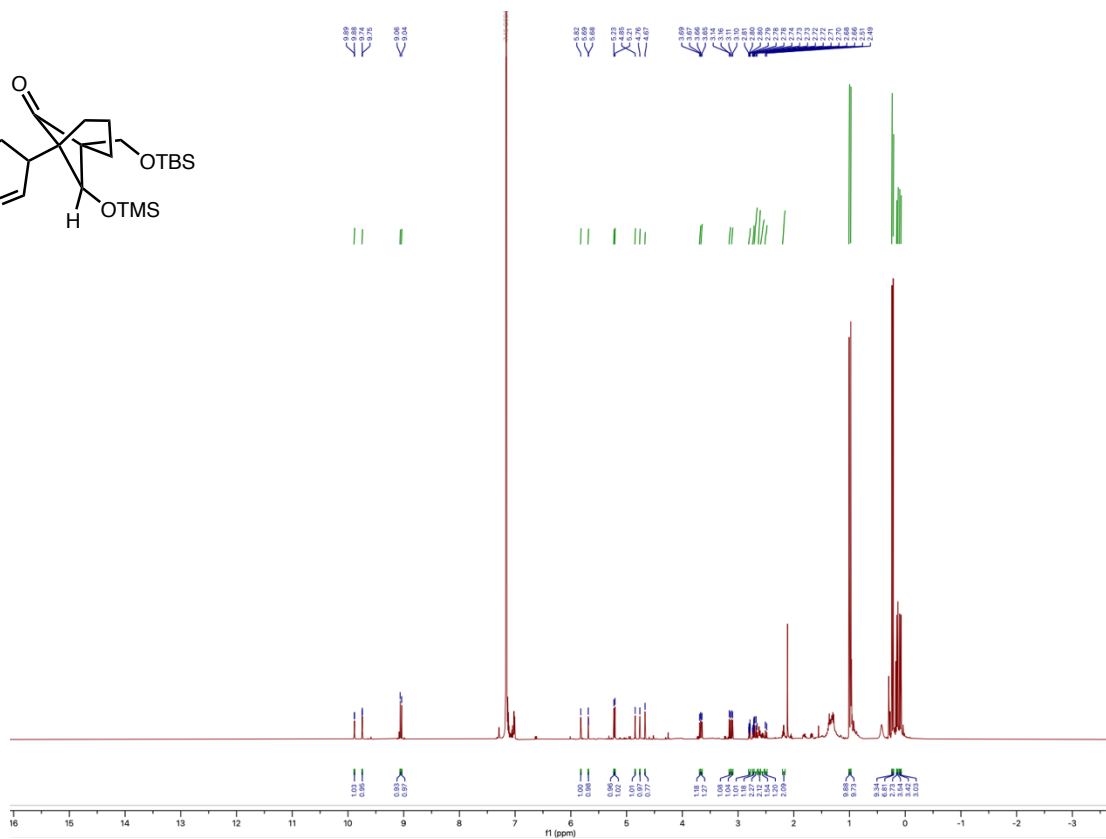
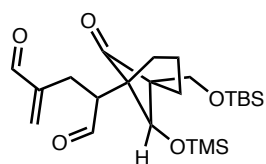


^1H NMR (700 MHz, C_6D_6) (**6.118**)

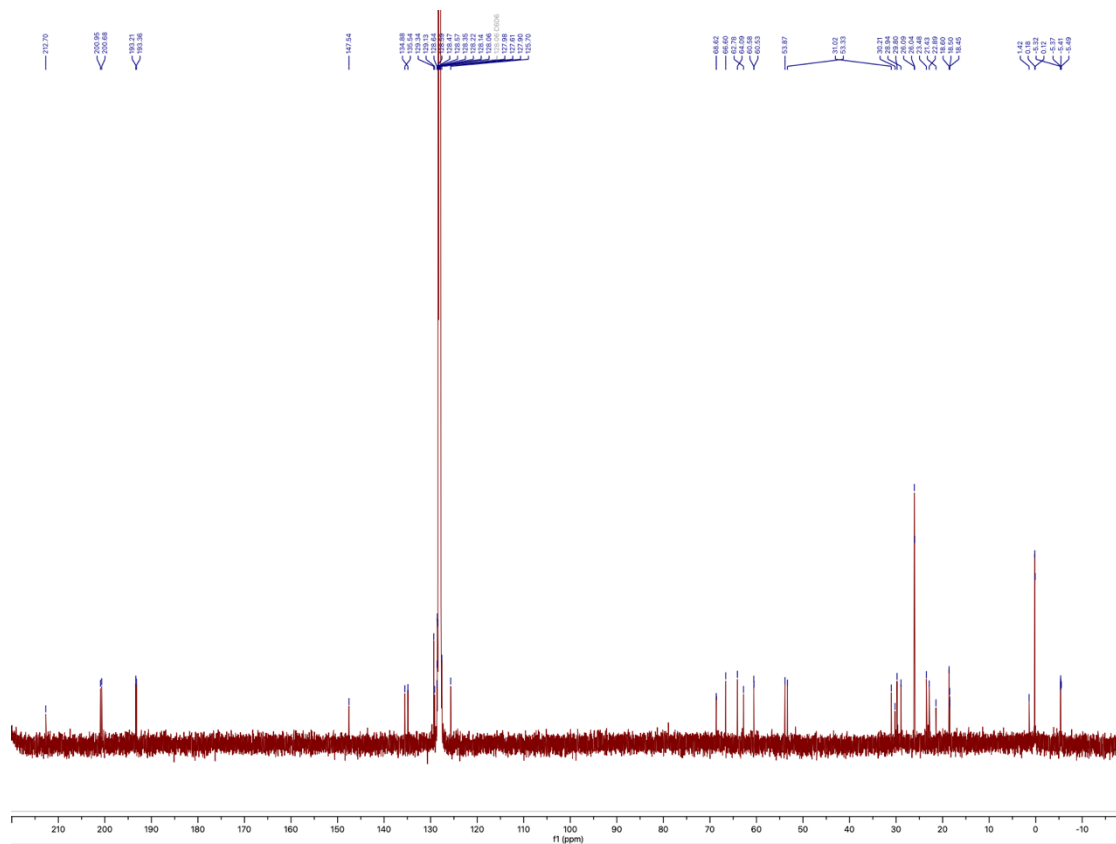


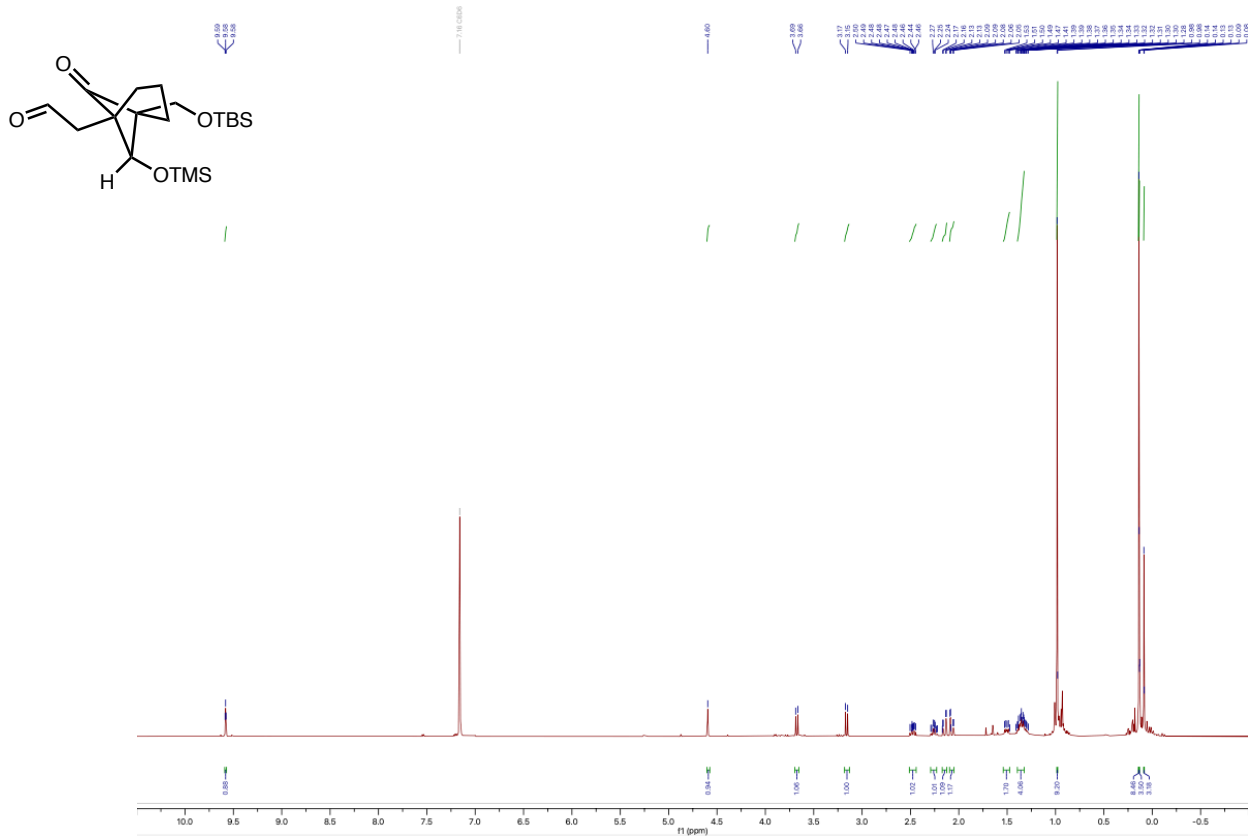
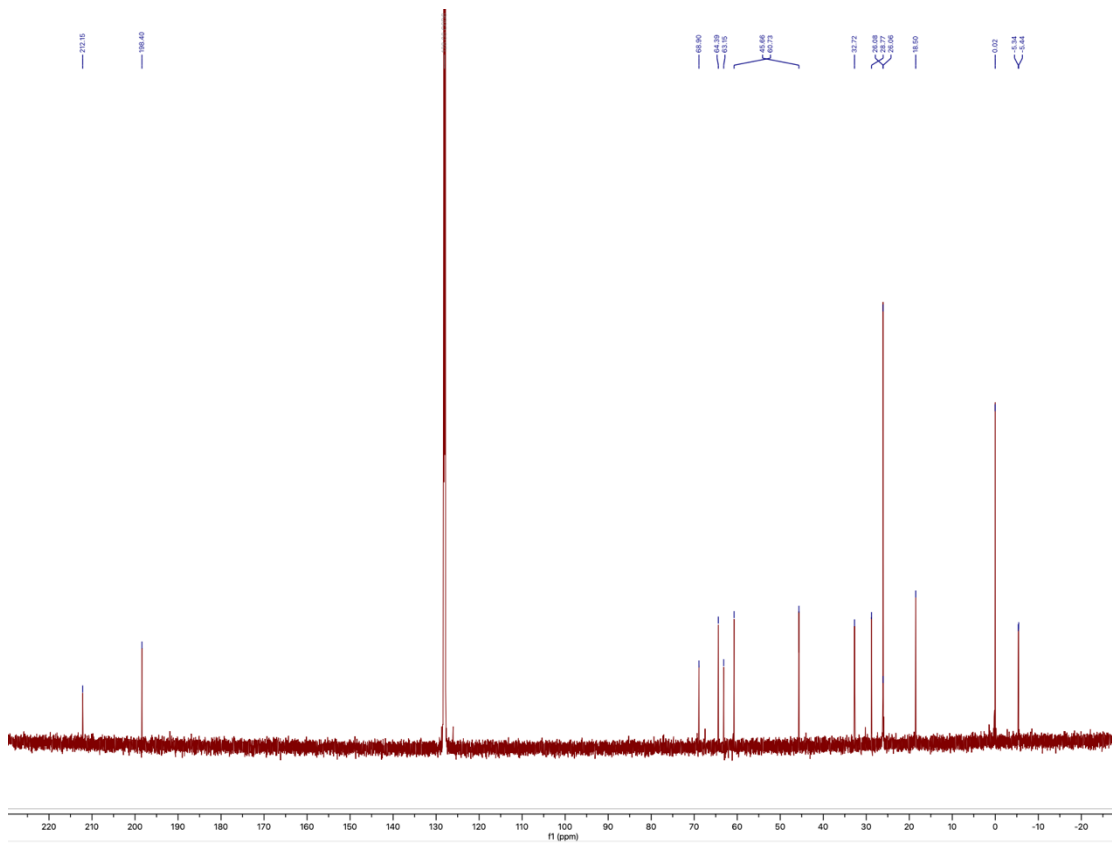
¹H NMR (600 MHz, C₆D₆) (**6.119**) ^{13}C NMR (151 MHz, C_6D_6) (6.119)

^1H NMR (600 MHz, C_6D_6) (**6.120**)

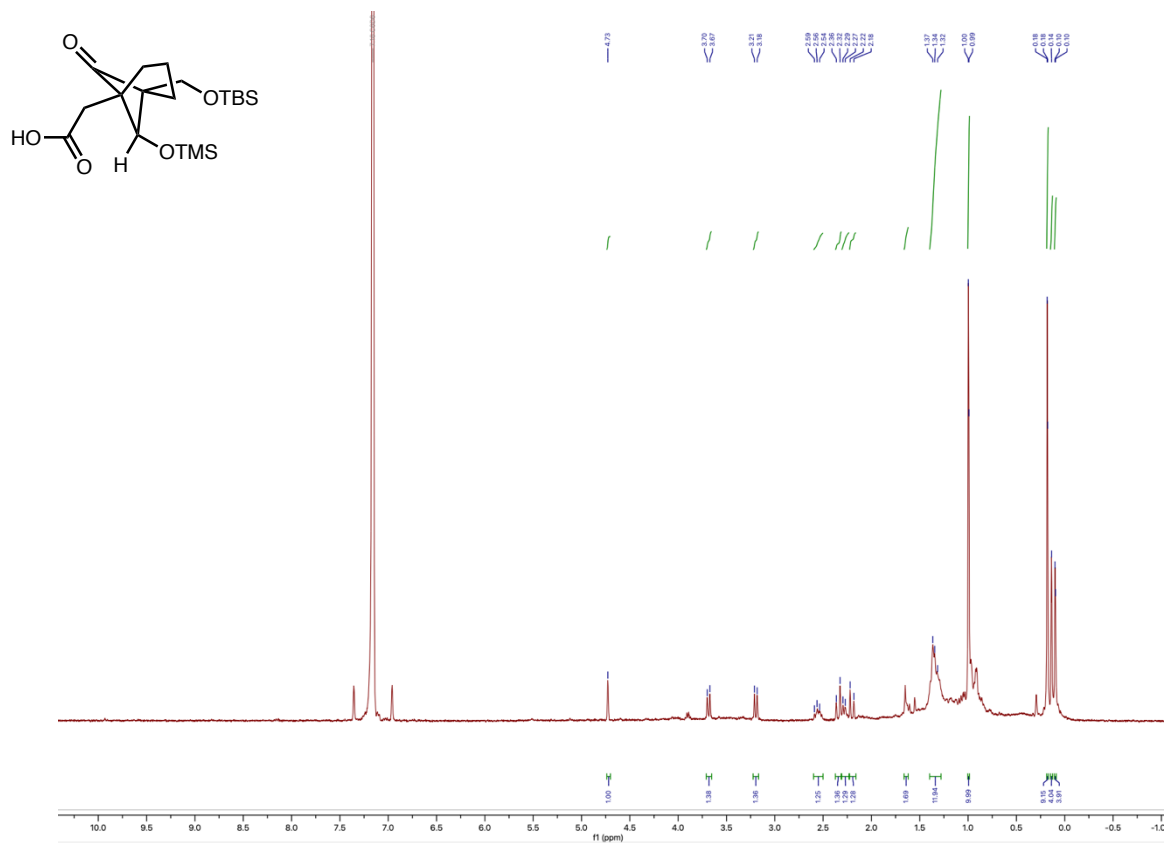


^{13}C NMR (151 MHz, C_6D_6) (**6.120**)



¹H NMR (500 MHz, C₆D₆) (**6.113**) ^{13}C NMR (151 MHz, C_6D_6) (**6.113**)

^1H NMR (400 MHz, C_6D_6) (**6.125**)



^1H NMR (500 MHz, C_6D_6) (**6.101**)

