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Cyclic Allenes in the Synthesis of Complex Molecules
and Organic Chemistry for Kids

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy
in Chemistry

by

Laura Grace Wonilowicz

2024

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ABSTRACT OF THE DISSERTATION

Cyclic Allenes in the Synthesis of Complex Molecules and Organic Chemistry for Kids

by

Laura Grace Wonilowicz

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2024

Professor Neil K. Garg, Chair

This dissertation describes the application of strained cyclic allene methodology to the total synthesis of lissodendoric acid A, the further exploration of cyclic allene reactivity, and developments in chemical education. Strained cyclic allenes are fleeting intermediates and valuable synthetic building blocks due to their ability to undergo strain-driven reactions. In particular, heterocyclic allenes can be used to rapidly construct valuable motifs containing nitrogen or oxygen. Herein, the use of a strained azacyclic allene in a stereoselective Diels–Alder cycloaddition that enables the total synthesis of lissodendoric acid A is described. Synthetic strategies toward the natural product and computational studies of the key cycloaddition are also

detailed. Moreover, a methodology study of the Diels–Alder cycloadditions of strained oxacyclic allenes and pyrones is described. Finally, the development of an organic chemistry summer camp for children called Chem Kids is detailed, highlighting an important initiative in STEM outreach.

Chapter one offers a perspective on the field of strained cyclic alkynes and allenes. Despite their validation over fifty years ago, strained cyclic alkynes and allenes have become valuable building blocks for the synthesis of complex small molecules. This chapter highlights recent methodologies and syntheses using strained alkynes, allenes, and alkynes to generate complex products bearing stereodefined quaternary centers or generate products with multiple fused rings in high enantioenrichment.

Chapters two and three describe the total synthesis of lissodendoric acid A, highlighting the use of a key Diels–Alder cycloaddition between a strained azacyclic allene and a pyrone to stereoselectively construct the azadecalin core of the natural product. Chapter two focuses on the optimized asymmetric synthesis of the natural product, which had previously never been synthesized. The synthesis of an enantioenriched silyl bromide allows for a stereoretentive cycloaddition of the resultant allene, which provides the core of the natural product stereoselectively. An efficient synthetic endgame then provides (–)-lissodendoric acid A. Chapter three provides a full account of the total synthesis study. Model system studies are detailed, providing insights into reaction design. Several earlier generation strategies and synthetic routes are also described, showing key challenges and the corresponding solutions developed. In addition, experimental and computational investigations of the key cycloaddition are detailed, revealing substituent effects and interesting selectivity trends.

Chapter four describes the development of Diels–Alder cycloadditions of oxacyclic allenes and pyrones. The results arising from the use of alkyl-substituted oxacyclic allenes and various

pyrones are detailed, showing trends in regioselectivity and a panel of highly functionalized bicyclic products. Next, the reactions of ester-substituted and ester- and methyl-di-substituted oxacyclic allenes provide insight into the effects of allene substitution on reaction outcome. Competition studies between pyrone and furan trapping partners then suggest relative rates of reaction between oxacyclic allenes and different trapping partners. Finally, the use of an enantioenriched oxacyclic allene precursor is described, wherein the cycloaddition proceeds with high stereospecificity and gives rise to a complex, enantioenriched scaffold.

Chapter five details the development of Chem Kids, an organic chemistry summer camp for children. The motivations and objectives behind the program are discussed, as well as descriptions of daily activities. Finally, key takeaways and future directions are highlighted.

The dissertation of Laura Grace Wonilowicz is approved.

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2024

*“If you hear a voice within you say ‘you cannot paint,’ then by all means paint, and that voice
will be silenced.”*

– Vincent van Gogh

For my family.

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LIST OF ABBREVIATIONS

α	alpha
β	beta
γ	gamma
λ	wavelength
μ	micro
π	pi
δ	chemical shift
Δ	heat
(Het)	hetero
[H]	reduction
[O]	oxidation
$[\alpha]_D$	specific rotation at wavelength of sodium D line
$^{\circ}\text{C}$	degrees Celsius
$\text{\AA}$	angstrom
AcOH	acetic acid
Ag	silver
Alk	alkyl
APCI	atmospheric-pressure chemical ionization
app.	apparent
aq.	aqueous
Ar	aryl
Au	gold
BCl_3	boron trichloride
BDP	1,2-bis(diphenylphosphino)benzene
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
B(pin)	pinacol borane
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Boc_2O	di- <i>tert</i> -butyl dicarbonate
Bu	butyl
Bu_4NBr	tetrabutylammonium bromide
Bu_4NBr_3	tetrabutylammonium tribromide
Bz	benzoyl

c	centi
<i>c</i>	concentration for specific rotation measurements
C	carbon
C ₆ D ₆	deuterated benzene
C ₆ H ₆	benzene
CaH ₂	calcium hydride
calcd	calculated
cat.	catalytic or catalyst
CBS	Corey–Bakshi–Shibata
Cbz	benzyl carbamate
CD ₃ CN	deuterated acetonitrile
CDCl ₃	deuterated chloroform
CF ₃	trifluoromethyl
CH ₂ Cl ₂	dichloromethane
CH ₃	methyl
CH ₃ CN	acetonitrile
CHCl ₃	chloroform
CO ₂	carbon dioxide
Co(OAc) ₂ •4H ₂ O	cobalt (II) acetate tetrahydrate
cod	1,5-cyclooctadiene
CsF	cesium fluoride
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DART	direct analysis in real time
DFT	density functional theory
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dr	diastereomeric ratio
eds.	editors
ee	enantiomeric excess
equiv	equivalent
ESI	electrospray ionization

Et	ethyl
Et ₂ O	diethyl ether
Et ₃ N	triethylamine
EtOAc	ethyl acetate
FMO	frontier molecular orbital
FT	Fourier transform
g	gram(s)
GC-MS	gas chromatography mass spectrometry(er)
h	hour(s)
H	proton
$h\nu$	light
HCl	hydrochloric acid
HOMO	highest occupied molecular orbital
HMBC	heteronuclear multiple bond correlation
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum coherence
Hz	hertz
<i>i</i> -Bu	<i>iso</i> -butyl
<i>i</i> -Pr	<i>iso</i> -propyl
<i>i</i> -PrNH ₂	<i>iso</i> -propyl amine
<i>i</i> -PrOAc	<i>iso</i> -propyl acetate
<i>i</i> -PrOH	<i>iso</i> -propyl alcohol
I ₂	iodine
IR	infrared (spectroscopy)
<i>J</i>	coupling constant
kcal	kilocalorie
KF	potassium fluoride
KHMDS	potassium hexamethyldisilazane
K ₃ PO ₄	potassium phosphate tribasic
KOt-Bu	potassium <i>tert</i> -butoxide
L	liter
LDA	lithium diisopropylamide
LiAlH ₄	lithium aluminum hydride

LiCl	lithium chloride
LiHMDS	lithium bis(trimethylsilyl)amide
LUMO	lowest unoccupied molecular orbital
m	multiplet or milli or meter
M	molecular mass, molar, or metal
<i>m</i> -	meta
<i>m/z</i>	mass to charge ratio
Me	methyl
MgSO ₄	magnesium sulfate
MHz	megahertz
min	minute(s)
Mo	molybdenum
mol	mole(s)
mp	melting point
MS	molecular sieves
N	normal
NBS	<i>N</i> -bromosuccinimide
<i>n</i> -Bu ₄ NBF ₄	tetrabutylammonium tetrafluoroborate
<i>n</i> -Bu	butyl (linear)
<i>n</i> -BuLi	butyl (linear) lithium
N ₂	nitrogen gas
Na ⁰	sodium metal
Na ₂ S ₂ O ₃	sodium thiosulfate
Na ₂ SO ₄	sodium sulfate
NaH	sodium hydride
NaHCO ₃	sodium bicarbonate
NaOH	sodium hydroxide
NaOt-Bu	sodium <i>tert</i> -butoxide
NH ₄ Cl	ammonium chloride
NHC	<i>N</i> -heterocyclic carbene
Ni	nickel
nM	nanomolar
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
<i>o</i> -	ortho

OFETs	organic field-effect transistors
OLEDs	organic light-emitting diodes
OMe	methoxy
OPVs	organic photovoltaics
<i>p</i> -	para
PAH	polyaromatic hydrocarbon
Pd	palladium
PDC	pyridinium dichromate
Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
Ph	phenyl
PhH	benzene
PhMe	toluene
PhSiH ₃	phenylsilane
PMHS	polymethylhydrosiloxane
PPh ₃	triphenylphosphine
ppm	parts per million
Pr	propyl
Pt	platinum
PTFE	polytetrafluoroethylene
q	quartet
quint.	quintet
rac	racemic
R _f	retention factor
Rh	rhodium
Rh(COD)(acac)	(acetylacetonato)(1,5-cyclooctadiene)rhodium(I)
rpm/RPM	revolutions per minute
Ru	ruthenium
s	singlet or second
sat.	saturated
sext.	sextet
SFC	supercritical fluid chromatography
(<i>S</i>)-QUINAP	(<i>S</i>)-(-)-1-(2-diphenylphosphino-1-naphthyl)isoquinoline
t	triplet
TA	teaching assistant
TBAF	tetrabutylammonium fluoride

TBDPS	<i>tert</i> -butyldiphenylsilyl
TBDPSCI	<i>tert</i> -butyldiphenylchlorosilane
<i>t</i> -Bu	<i>tert</i> -butyl
<i>t</i> -BuNH ₂	<i>tert</i> -butyl amine
<i>t</i> -BuOH	<i>tert</i> -butyl alcohol
<i>t</i> -BuOOH	<i>tert</i> -butyl hydroperoxide
TCI	Tokyo Chemical Industry Co.
temp	temperature
TFA	trifluoroacetic acid
TfOH	triflic acid
THF	tetrahydrofuran
Ti	titanium
TLC	thin layer chromatography
TMB	1,3,5-trimethoxybenzene
TMSCl	chlorotrimethylsilane
t _R	retention time
Ts	tosyl
UCLA	University of California Los Angeles
UHP	ultra-high purity
UV	ultraviolet
Zr	zirconium

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Finally, I want to give endless thanks to my family. I know that I cannot capture all of my sentiments in words, but I will try. I am grateful for my grandparents who, while not with us today, have watched over me. To my aunts and uncles, thank you for your love and support as I grew up and embarked on my educational journey. Each of you have given me lessons and guidance that I carry with me every day. I am so grateful for my closest and very first friends, my siblings. To my big brother, Kurt, thank you for always believing in me. I could not get through life without your support, your wisdom, and your incredible sense of humor. Thank you for always encouraging me to keep going, and always making me laugh. To my lovely sister-in-law, Lyra: thank you for the joy you bring to my life and my family. Your kindness, creativity, and artistry light up our lives, and I appreciate your love and support over the last five years. Ceili, my big sister, you have always been my idol and my hero. We have journeyed through life hand-in-hand, no matter the distance between us, and I know that we always will. Thank you for always lifting me up, listening to me without judgement, and laughing with me. Andy, I am so blessed to have you as a brother-in-law, husband to Ceili, and father to my nieces. Your incredible work ethic, big heart, and sharp sense of humor are so important to me and my family. To my beautiful nieces, Genevieve and Lillian: whenever you can read this, please know that you can accomplish anything you set your minds to.

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Chapter 4 is a version of Wonilowicz, L. G.;[†] Mehta, M. M.;[†] Kamecke, L.; French, S. A.; Garg, N. K. Diels–Alder Cycloadditions of Oxacyclic Allenes and α -Pyrone. *Manuscript in Preparation*. Wonilowicz, Mehta, Kamecke, and French were responsible for experimental studies.

Chapter 5 is a version of Tena Meza, A.;[†] Wonilowicz, L. G.;[†] Garg, N. K. Organic Chemistry for Kids. *Manuscript in Preparation*. Tena Meza, Wonilowicz, and Garg were responsible for the manuscript.

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- Ph.D. in Organic Chemistry, anticipated Spring 2024
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 - Established a concise new route to enantioenriched azacyclic allene precursors via a Corey–Bakshi–Shibata reduction and silylation sequence.
 - Conducted a systematic study of the origins of selectivity in Diels–Alder cycloadditions of strained cyclic allenes and pyrones.
 - Advanced the development of an asymmetric synthesis of oxacyclic allene precursors to assess enantiospecificity of Diels–Alder cycloadditions.
 - Mentored a younger graduate student and a visiting graduate researcher on laboratory methods and chemistry concepts.
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- Graduate Research Fellowship, National Science Foundation, 2021 – 2024
- Michael E. Jung Excellence in Teaching Award, UCLA, 2021
- Christopher Foote Fellowship, UCLA, 2019 – 2020
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Publications:

1. **Organic Chemistry for Kids.** Arismel Tena Meza,[‡][Laura G. Wonilowicz](#),[‡] and Neil K. Garg. *In preparation*.
2. **Diels–Alder Cycloadditions of Strained Cyclic Allenes and Pyrones.** [Laura G. Wonilowicz](#),[‡] Milauni M. Mehta,[‡] Lisa Kamecke, Sarah A. French, and Neil K. Garg. *In preparation*.
2. **Total Synthesis of Lissodendoric Acid A.** Francesca M. Ippoliti,[‡] [Laura G. Wonilowicz](#),[‡] Nathan J. Adamson, Evan R. Darzi, Joyann S. Donaldson, Daniel J. Nasrallah, Milauni M. Mehta, Andrew V. Kelleghan, K. N. Houk, and Neil K. Garg. *Angew. Chem., Int. Ed.* **2024**, doi: 10.1002/anie.202406676.
3. **Synthesis of a Furoindoline Scaffold via an Interrupted Fischer Indolization.** Georgia M. Scherer, Jordan Gonzalez, [Laura G. Wonilowicz](#), and Neil K. Garg. *Org. Synth.* **2023**, 100, 304–326.
4. **Total Synthesis of Lissodendoric Acid A via Stereospecific Trapping of a Strained Cyclic Allene.** Francesca M. Ippoliti, Nathan J. Adamson, [Laura G. Wonilowicz](#), Daniel J. Nasrallah, Evan R. Darzi, Joyann S. Donaldson, and Neil K. Garg. *Science* **2023**, 379, 261–265.
5. **Leveraging Fleeting Strained Intermediates to Access Complex Scaffolds.** Sarah M. Anthony, [Laura G. Wonilowicz](#),[‡] Matthew S. McVeigh,[‡] and Neil K. Garg. *JACS Au* **2021**, 1, 897–912.
6. **Lipophilic Tail Modifications of (R)-Prolinol Scaffold Reveal Dual Sphingosine Kinase 1 and 2 Inhibitors.** Hao Li, Christopher D. Sibley, Yugesh Kharel, Tao Huang, Anne M. Brown, [Laura G. Wonilowicz](#), David R. Bevan, Kevin R. Lynch, and Webster L. Santos. *Bioorg. Med. Chem.* **2021**, 30, 115941.
7. **Route to Air and Moisture Stable β -Difluoroboryl Acrylamides.** Russell G. Fritzemeier, Eric J. Medici, Connor Szwetkowski, [Laura G. Wonilowicz](#), Christopher D. Sibley, Carla Slebodnick, and Webster L. Santos. *Org. Lett.* **2019**, 21, 8053–8057.
8. **Copper-Catalyzed [4+2] Cycloaddition of 9H-Cyclohepta[b]pyridine-9-one and Electron-Rich Alkenes.** Philipp J. Gritsch, Irene Gimenez-Nueno, [Laura G. Wonilowicz](#), and Richmond Sarpong. *J. Org. Chem.* **2019**, 84, 8717–8723.

Select Outreach Activities:

- Exploring Your Universe (Fall 2023): Designed and hosted an organic chemistry booth with other graduate students at the annual UCLA science outreach event.
- Chem Kids Summer Camp (Summer 2023): Co-developed and carried out camp programming aiming to teach introductory organic chemistry concepts to children ages 9–12.
- ChemMatch (Fall 2021 – Fall 2022): Led a team of graduate and high school students in the creation of a chemistry matching website with the overall goal to aid in learning element symbols, polyatomic ion names, and more.

CHAPTER ONE

Leveraging Fleeting Strained Intermediates to Access Complex Scaffolds

Sarah M. Anthony, Laura G. Wonilowicz,[†] Matthew S. McVeigh,[†] and Neil K. Garg*.

JACS Au **2021**, *1*, 897–912.

1.1 Abstract

Arynes, strained cyclic alkynes, and strained cyclic allenes were validated as plausible intermediates in the 1950s and 1960s. Despite initially being considered mere scientific curiosities, these transient and highly reactive species have now become valuable synthetic building blocks. This Chapter highlights recent advances in the field that have allowed access to structural and stereochemical complexity, including recent breakthroughs in asymmetric catalysis.

1.2 Introduction

In 1902, a provocative proposal was put forth by Stoermer and Kahlert, who contemplated the intermediacy of benzofuranyne **1.1** (Figure 1.1).¹ Although the existence of **1.1** would ultimately be called into question,^{2,3,4} the proposal led chemists to consider if triple bonds could exist in small rings. Roughly fifty years later, benzyne (**1.2**) and cyclohexyne (**1.3**) were validated experimentally, thanks to pioneering efforts by Roberts,^{5,6} Wittig,⁷ and Huisgen,⁸ in particular. Soon thereafter, in 1966, Wittig showed that 1,2-cyclohexadiene (**1.4**), an unusual-looking counterpart to benzyne (**1.2**) and cyclohexyne (**1.3**), could be generated and intercepted in cycloaddition processes.⁹ These results were striking at the time, as **1.2–1.4** possess functional groups (i.e., alkynes and allenes) that would ordinarily be linear. The bent nature of these species renders them transient and highly reactive intermediates that initially received little use in chemical

synthesis. However, over the past few decades, the field of arynes and related strained intermediates has undergone a substantial period of growth, as shown in Figure 1.1.¹⁰

The synthetic utility of arynes and related strained intermediates is often underappreciated, perhaps owing to common misconceptions regarding safety or high reactivity (and consequently, misconceptions regarding low selectivity in aryne reactions). Conversely, we highlight the impact of arynes and related intermediates in the syntheses of **1.5–1.9**. Popular ligands, such as XPhos (**1.5**), are made using aryne chemistry.¹¹ The medicinal chemistry route toward Chantix® (**1.6**) was enabled by an aryne cyclization.¹² Syngenta has prepared isopyrazam (**1.7**), an important fungicide, using an aryne Diels–Alder reaction on multikilogram scale.¹³ Lastly, there are numerous examples of arynes and related intermediates in total synthesis,^{14,15,16} such as the use of an aryne insertion in Sarpong’s synthesis of cossonidine (**1.8**) and a cyclohexyne insertion in Carreira’s synthesis of guanacastepene N (**1.9**).^{17,18} As these examples highlight, arynes and related intermediates can be used to build two new bonds in a single transformation. Moreover, it should be noted that arynes can be generated under exceedingly mild, safe, and operationally simple fluoride-based reaction conditions, thanks to the advent of Kobayashi silyl triflates.^{19,20,21,22} In turn, chemists have sought to leverage the synthetic utility of these once controversial species, in addition to deepening our fundamental understanding through electrophilicity studies²³ and regioselectivity studies.^{24,25,26}

Rather than providing a comprehensive overview of the field, several of which are available elsewhere,^{14,15,16,20,27,28 29,30,31,32,33,34,35,36,37} this Chapter examines some of the quickly emerging areas of aryne chemistry and related strained intermediates. We assess the following recent advances: a) the use of heterocyclic strained alkynes to construct scaffolds of value to medicinal and materials chemistry, b) access to quaternary stereocenters using non-catalytic

reactions of arynes and cyclic alkynes, c) catalytic asymmetric reactions of arynes, d) the assembly of intricate heterocyclic scaffolds via strained cyclic allene intermediates, and e) stereospecific and catalytic asymmetric transformations of strained cyclic allenes. We hope this discussion underscores the current excitement in the field and, moreover, helps to draw researchers into an area that continues to rapidly evolve with opportunities for discovery.

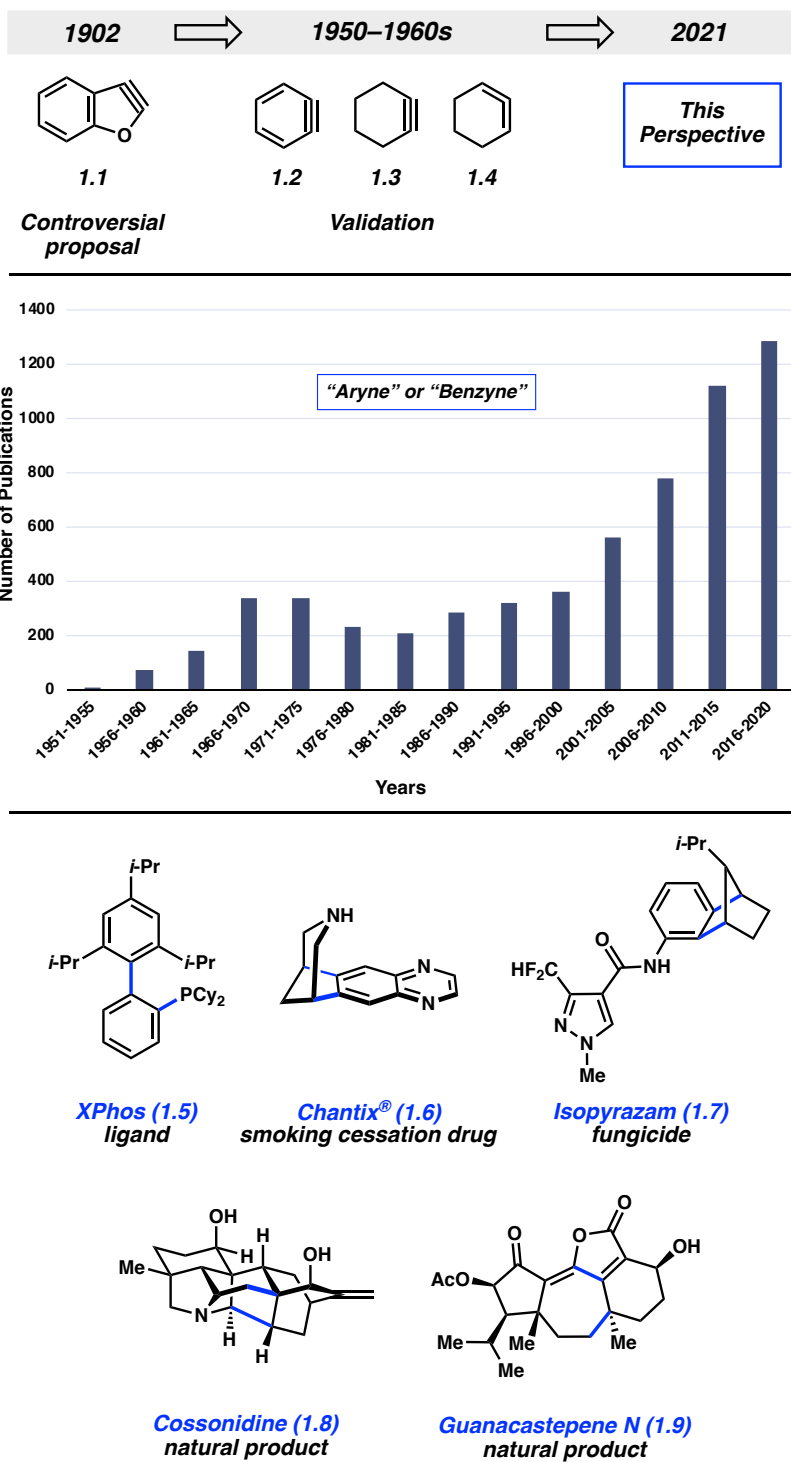


Figure 1.1. Historical perspective, growth of “aryne” or “benzyne” chemistry, and select synthetic applications.

1.3 Use of Heterocyclic Alkynes in the Synthesis of Medicinal and Materials Scaffolds

New strategies to access heterocyclic compounds, especially those with a high degree of sp^3 -rich character, remain highly sought after due to the numerous applications of heterocycles in drugs, agrochemicals, natural products, and materials.^{38,39,40,41,42,43} Just within the pharmaceutical industry, the vast majority of small-molecule drugs approved by the U.S. Food and Drug Administration contain a nitrogen or oxygen-containing heterocycle.^{44,45} A few examples are Plavix[®] (**1.10**), an antiplatelet, rhoeadine (**1.11**), a sedative and antitussive, and the antimalarial drug artemisinin (**1.12**) (Figure 1.2).

Strained cyclic alkynes have emerged as valuable building blocks to access sp^3 -rich³⁸ medicinally relevant heterocycles (Figure 1.2).^{46,47,48,49} Heteroatom-containing cyclohexyne derivatives, such as 2,3-piperidynes **1.13**, 3,4-piperidynes **1.14**, and oxacyclohexyne **1.15** have been far less studied than related aryne counterparts, (e.g., 3,4-pyridyne (**1.16**)).^{50,51,52,53} For comparison, the 3,4-pyridyne (**1.16**) was first disclosed in 1955,⁵⁴ but studies involving 3,4-piperidynes were only reported recently. Specifically, the Danheiser group reported access to **1.13** in 2014⁴⁷ and our group described generation and interception of **1.14** and **1.15** in 2014 and 2016, respectively.^{48,49} These studies demonstrate the synthetic value of transient intermediates **1.13**–**1.16**.

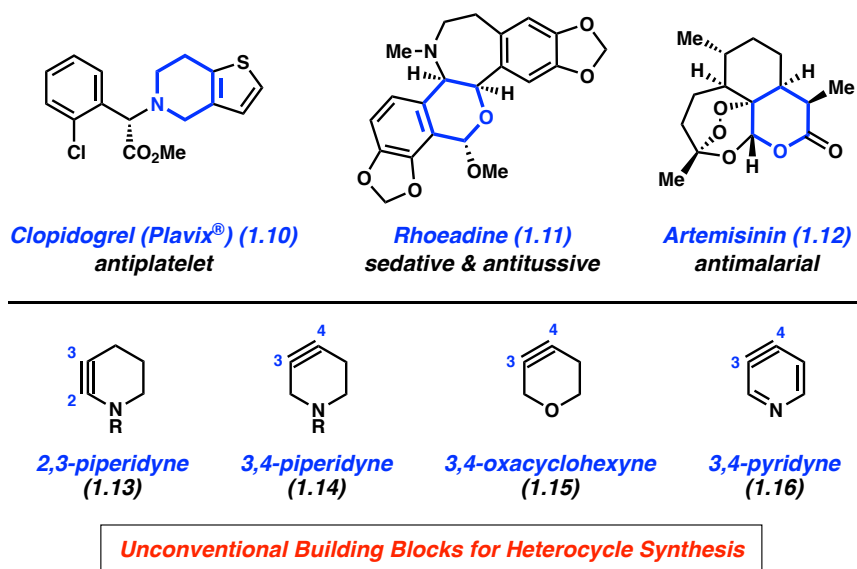


Figure 1.2. Representative natural products and pharmaceuticals containing heterocycles and representative nitrogen- and oxygen-containing strained cyclic alkynes.

The initial breakthrough in this area by Danheiser and coworkers involved piperidyne precursor **1.17** (Figure 1.3). Upon treatment of **1.17** with CsF or KF, in the presence of a cycloaddition partner, a variety of (3+2) and (2+2) cycloadducts **1.20** were obtained. Presumably, these reactions proceed via the regioselective trapping of cyclic alkyne **1.19**. Three examples are shown to highlight the diverse products (i.e., **1.22**, **1.24**, and **1.26**) that can be obtained using this methodology. Moreover, each of the cycloadducts shown were isolated as one major constitutional isomer, with the significant regioselectivity of the reaction being attributed to the electronic effect of the nitrogen atom.

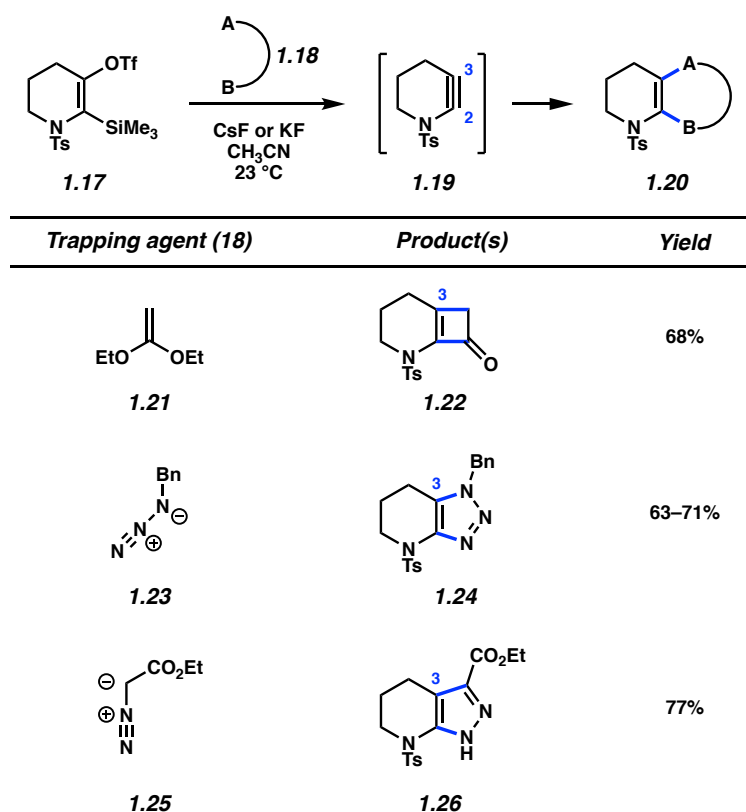


Figure 1.3. Selected trapping experiments involving piperidyne **1.19**.

Our laboratory had simultaneously engaged in complementary studies, which were geared toward accessing cyclic alkynes **1.28** (Figure 1.4). After developing synthetic routes to the requisite silyl triflates **1.27**, we performed experiments to generate and trap the corresponding heterocyclic alkynes. As summarized, strained intermediate trapping via (4+2) and (3+2) cycloadditions led to an array of interesting heterocyclic products, such as aza- and oxa-bicycles **1.30** and **1.32**, respectively, isooxazolines **1.34** and **1.35**, pyrazole **1.36**, and triazole **1.37**. Where applicable, reactions occurred regioselectively, indicative of initial bond formation occurring at C4 of the reactive strained intermediate. It should be emphasized that by strategically varying the trapping partner, one can utilize common silyl triflate precursors (i.e., **1.27**) to rapidly arrive at a variety of diverse heterocyclic scaffolds, including previously unknown scaffolds and analogs of medically relevant compounds.^{55,56,57,58}

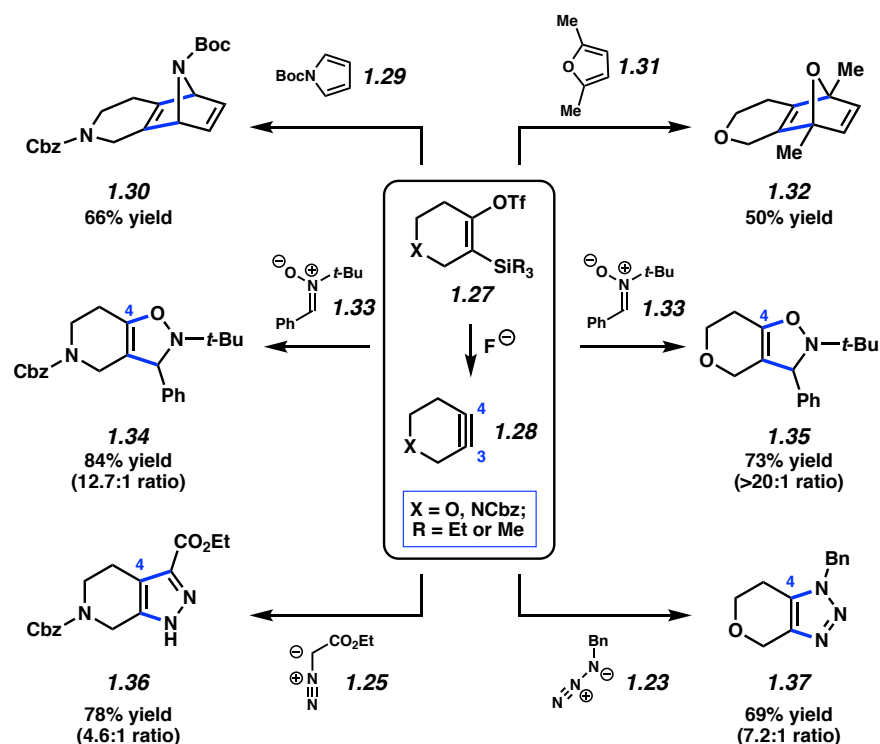


Figure 1.4. Selected trapping experiments of heterocyclic alkynes using silyl triflate precursors.

An attractive feature related to strained cyclic alkyne methodologies is the ability to make reliable predictions regarding regioselectivities using the aryne distortion model. This model, proposed by Houk and coworkers via our earlier collaborative studies,³³ shows that non-symmetrical cyclic alkynes are geometrically distorted in their ground state. Nucleophilic addition occurs more favorably at the alkyne terminus with a larger internal angle (i.e., more distorted toward linearity), which correlates to a lower calculated distortion energy seen in the corresponding transition state. Moreover, larger differences between the internal angles typically correlates with regioselectivities in trapping experiments. Thus, by analyzing the ground state structure of a strained cyclic alkyne, one can typically make meaningful regioselectivity predictions. In the cases of piperidyne **1.14** and oxacyclohexyne **1.15**, both react with a preference for C4 addition (Figure 1.5). Consistent with the distortion model, the ground state geometries of **1.14** and **1.15** shown by DFT calculations demonstrate that the C4 alkyne terminus is more

distorted toward linearity. Furthermore, the difference between the internal angles of **1.14** and **1.15** are 12° and 15° , respectively. The greater angle difference of 15° seen in **1.15** is consistent with observed regioselectivities. For example, as shown in Figure 1.4 the nitron trapping proceeds with higher selectivity when using **1.15** compared to **1.14**.

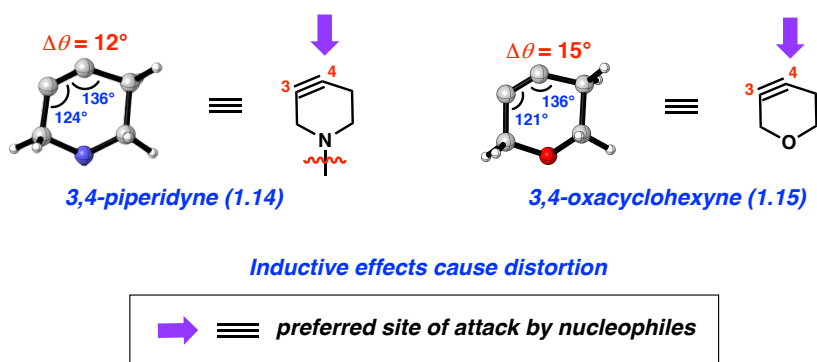


Figure 1.5. Regioselectivity of piperidyne **1.14** and oxacyclohexyne **1.15** trappings.

These methods demonstrate the value of strained heterocyclic alkynes for the synthesis of medicinally relevant scaffolds. Using common building blocks, rapid structural diversification can be achieved, with regioselectivity being predicted using simple calculations. Moreover, this chemistry provides a new and unusual strategy for accessing decorated heterocycles (i.e., using new strained intermediates). We expect these reports to influence future retrosynthetic analyses for the synthesis of heterocycles seen commonly in pharmaceuticals.

In addition to their value for the synthesis of medicinally relevant scaffolds, strained heterocyclic alkynes have seen recent utility in the synthesis of aromatic structures relevant to materials chemistry. Highly conjugated small molecules and polycyclic hydrocarbon frameworks have many potential applications in the field of organic electronics and material science.^{59,60} For example, these conjugated small molecules have been widely used in light-emitting diodes (OLEDs),^{61,62,63,64} field-effect transistors (OFETs),^{65,66,67,68} and photovoltaics (OPVs).^{69,70,71} Two common conjugated small molecules are 9,10-diphenylanthracene (**1.38**) and triphenylene (**1.41**)

(Figure 1.6).^{72,73,74,75} Heteroatom containing-derivatives of these compounds, such as **1.39**, **1.40**, **1.42**, and **1.43**, have been gaining interest as the presence of heteroatoms can modulate electronic properties.^{76,77,78} New synthetic methods to access novel heterocyclic conjugated materials are highly desirable. As such, in 2017, our laboratory synthesized heterohelicene⁷⁹ **1.43** (and derivatives) using an indolyne cyclotrimerization reaction.^{80,81} Indole trimers have been used in various materials applications.^{76,82,83,84,85,86,87} Building on these studies, we sought to access heteroatom-containing 9,10-diarylanthracene scaffolds using arynes and strained alkyne building blocks.

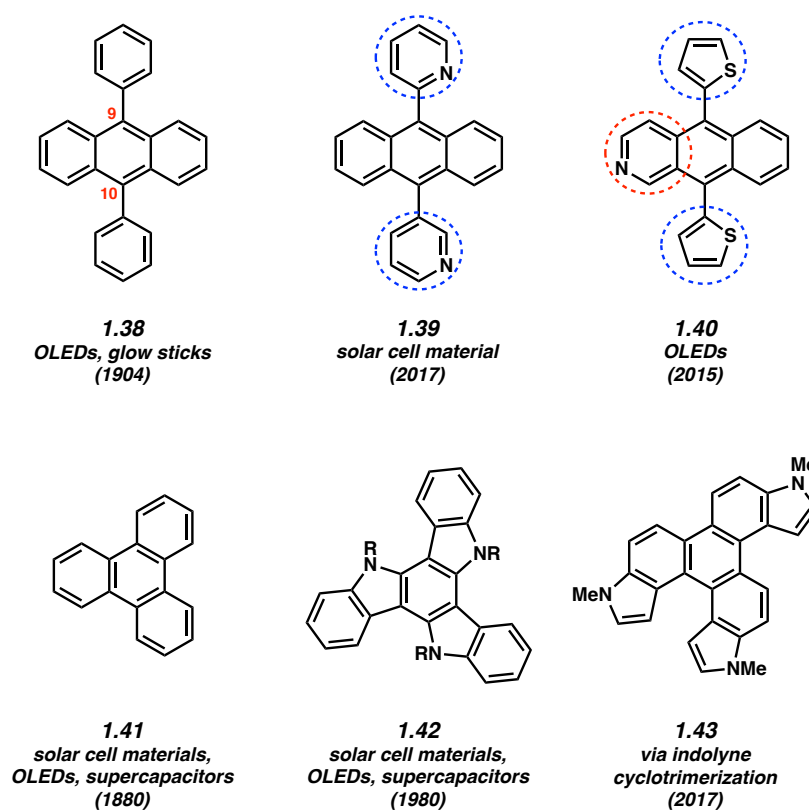


Figure 1.6. Notable polycyclic aromatic hydrocarbons.

In 2019, we disclosed a modular strategy toward *N*-containing 9,10-diphenylanthracene derivatives, wherein all four aryl rings could be easily modified.⁸⁸ The sequence was inspired by the collective seminal studies by Steglich, Nuckolls, and Wudl pertaining to double-aryne

annulations of oxadiazinones.^{89,90,91} As shown in Figure 1.7, our approach involved two steps. First, 3,4-piperidyne (**1.14**), generated in situ from the corresponding silyl triflate, undergoes reaction with oxadiazinones **1.44** to give pyrones **1.45** through a Diels–Alder/retro-Diels–Alder sequence.⁹² The oxadiazinones are easily prepared with two different aryl substituents from readily available starting materials.⁹³ In a second Diels–Alder/retro-Diels–Alder sequence, pyrones **1.45**, which are bench stable and isolable, react with an aryne or non-aromatic strained cyclic alkyne (i.e., **1.46**) to deliver polycyclic hydrocarbon frameworks **1.47**. **1.48–1.50** are representative products. As needed, subsequent oxidation can be performed to access more highly conjugated derivatives.

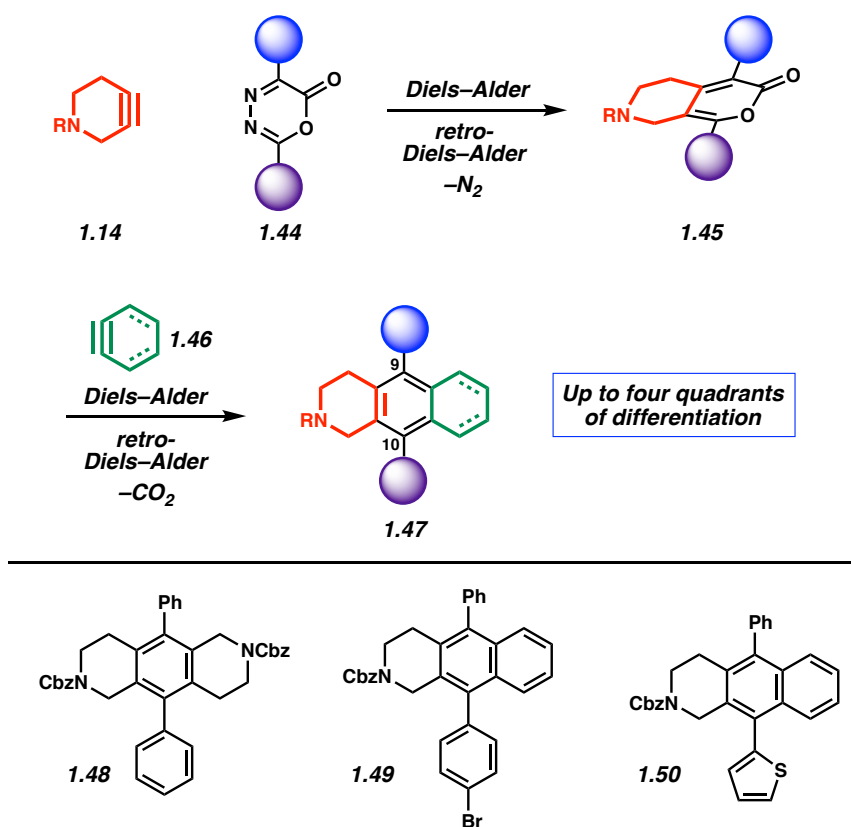


Figure 1.7. Modular strategy to access 9,10-diphenylanthracene derivatives and representative products **1.48–1.50**.

Figure 1.8 highlights two additional aspects of this chemistry. In the first, **1.51**, **1.52**, and **1.53** were shown to react at room temperature in the presence of CsF. This three-component coupling obviates the need to isolate a pyrone intermediate and delivers **1.54** in 56% yield. Additionally, the methodology could be used to access **1.55**, a novel heterocyclic PAH scaffold that fluoresces, displaying a blue emission. In the presence of acid, pyridinium salt **1.56** forms, which displays an orange emission. Stimuli responsive materials are useful in a host of applications such as pH fluorescence sensors^{94,95} and solid-state fluorescent switches.⁹⁶

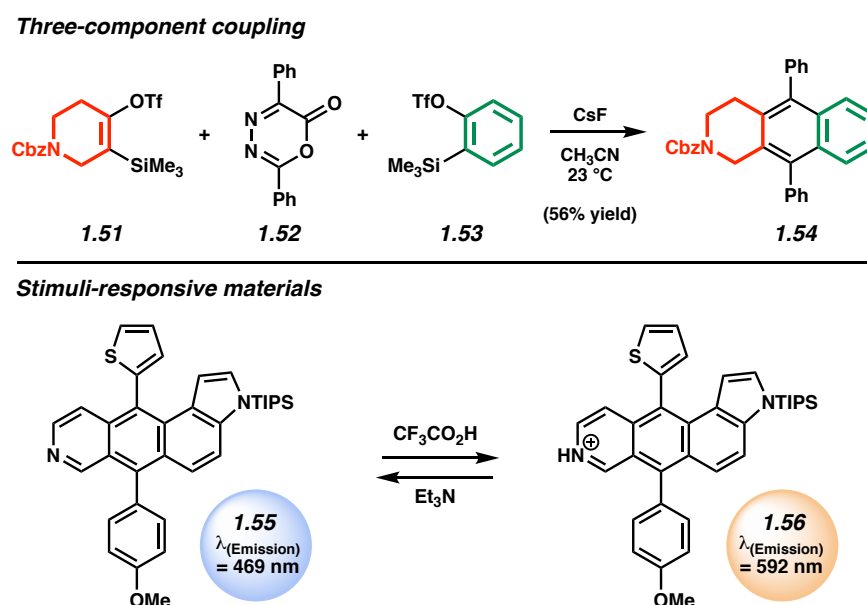


Figure 1.8. Utilizing arynes to access 9,10-diphenylanthracene derivatives.

The chemistry described above pertaining to PAHs showcases an exciting new direction of modern strained intermediate chemistry. Notably, Hosoya and coworkers published a complementary method in 2019 that utilizes a variety of strained intermediates, including thienobenzynes, to access PAH skeletons.⁹⁷ Our group has published a follow-up study as well, which provides additional experimental results, as well as a computational mechanistic investigation.⁹⁸ More specifically, heterocyclic strained intermediates can be strategically leveraged through a cycloaddition cascade sequence to rapidly generate PAH scaffolds. The

transformation enables access to structurally diverse products through the formation of four carbon–carbon bonds. It is expected that this chemistry and variants thereof will prompt the development of related methods that rely on strained intermediates to access compounds of value to materials chemistry.

1.4 Use of Arynes and Cyclic Alkynes to Access Quaternary Stereocenters (Non-Catalytic)

The majority of reported methodologies and synthetic applications that utilize strained cyclic alkynes are intermolecular reactions that generate achiral or racemic products. However, efforts have been put forth to generate enantioenriched products, including those that rely on the use of chiral auxiliaries or reagents. For example, reports by Lautens^{99,100} and Barrett^{101,102} demonstrate stereocontrolled intermolecular reactions of arynes for the introduction of tertiary stereocenters using Oppolzer or Schöllkopf reagents, respectively. As accessing quaternary stereocenters is especially valuable,^{103,104,105,106} we were interested in utilizing arynes and strained cyclic alkynes to access stereodefined quaternary centers in an intermolecular fashion.

Our efforts, which were reported in 2018,¹⁰⁷ concerned the reaction between β -ketoester **1.57** and strained cyclic alkyne **1.46** to yield α -substituted product **1.58**, as shown in Figure 1.9. Prior efforts to achieve this transformation in a racemic sense were accompanied by concomitant C–C bond fragmentation,¹⁰⁸ so we considered an alternative, two-step approach. First, β -ketoester **1.57** would be treated with amine **1.59** to afford the corresponding enamine **1.60**. Enamine **1.60** could then be used to trap aryne **1.46**, affording α -substituted product **1.58** after hydrolysis. We envisioned that employing a chiral amine (i.e., **1.59**) would render the reaction diastereoselective and yield **1.58** in enantioenriched form. It should be noted that enantioselective α -arylation of β -

ketoesters, one of the net transformations we hoped to develop, had remained a challenging synthetic problem.^{109,110,111,112,113,114,115,116}

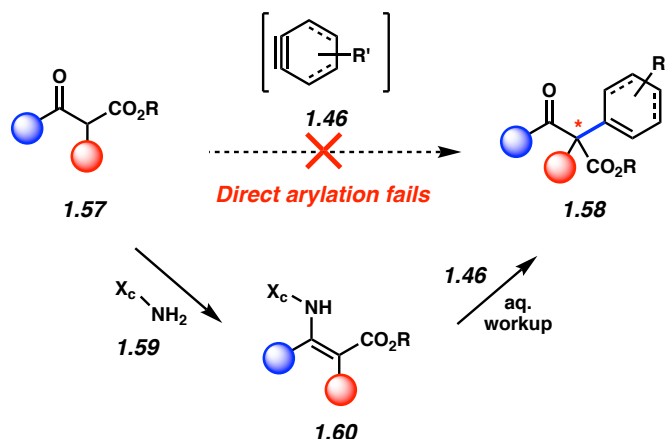


Figure 1.9. Intercepting arynes and cyclic alkynes for the installation of stereodefined quaternary stereocenters.

At the time of our study, the use of enamines and strained cyclic alkynes to construct quaternary stereocenters was unknown; thus, the racemic arylation^{117,118,119} was first developed (Figure 1.10). Benzylamine was condensed onto ketoester **1.61** to afford enamine **1.62** ($R = Bn$). Next, enamine **1.62** was used to trap benzyne, which was generated in situ from silyl triflate **1.53** using CsF in DME. Following hydrolysis with 1 M HCl, α -arylated product **1.63** was obtained in 92% yield. To effect the desired stereoselective variant, we ultimately arrived at the use of an anthracenyl derivative (i.e., $R = \mathbf{1.67}$). Several products that were obtained are shown in Figure 1.10 (i.e., **1.64–1.66**), which highlight the use of heterocyclic arynes and cyclic alkynes as trapping agents, as well as a 7-membered β -ketoester.

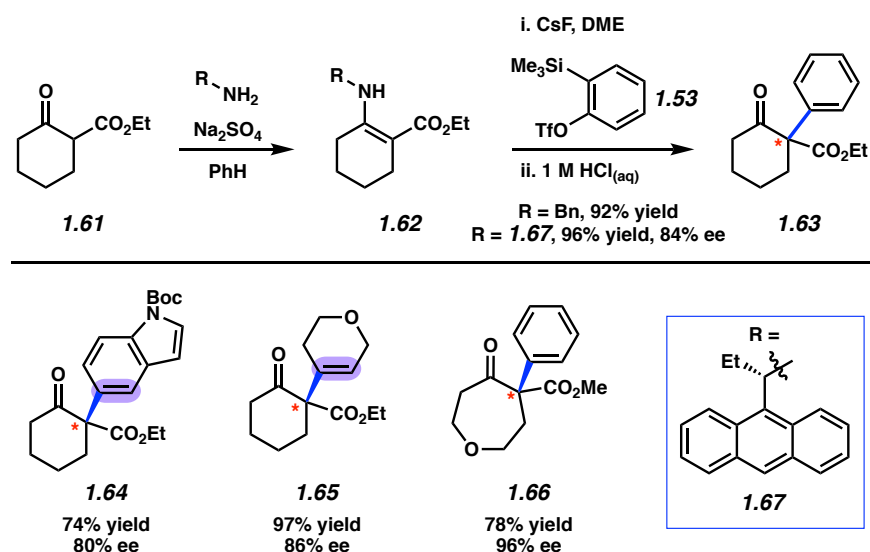


Figure 1.10. Selected substrate scope of α -arylation methodology.

Another attractive aspect of this reaction methodology is the one-pot variant shown in Figure 1.11. Treatment of ketoester **1.68** with chiral amine **1.67** yielded the corresponding enamine, which was not isolated. This intermediate was then subjected to silyl triflate **1.53** and CsF, followed by the addition of aqueous 1 M HCl. The product, ketoester **1.69**, was isolated in 68% yield and 92% ee. Of note, amine **1.67** was recovered in 67% yield. Overall, this methodology provided a means to access stereodefined quaternary stereocenters by the interception of strained intermediates in intermolecular processes. As will be discussed later in this review, an elegant catalytic asymmetric variant of this methodology has subsequently been developed.¹²⁰

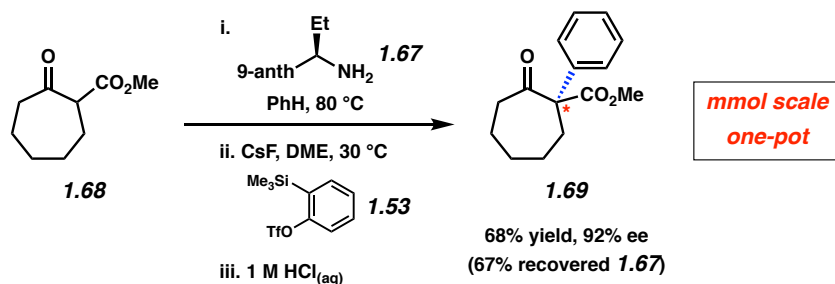
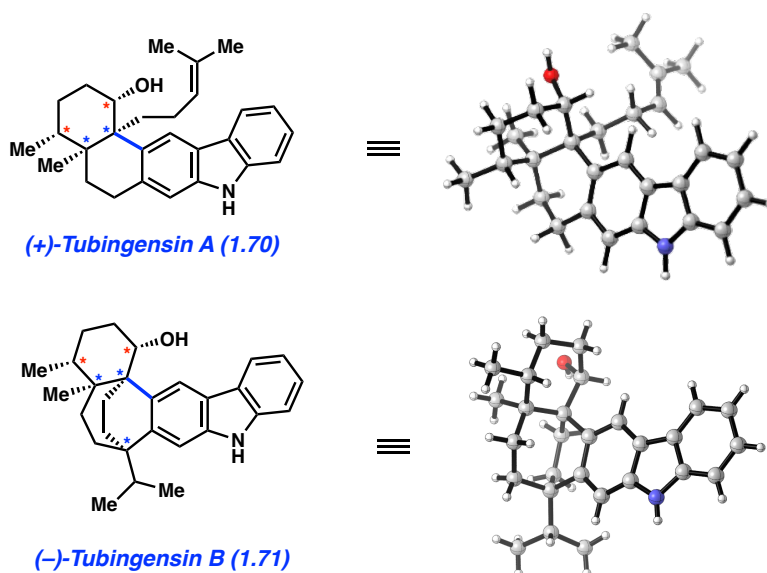


Figure 1.11. α -Arylation reaction demonstrated in one-pot.

The synthesis of natural products and their derivatives also provides an opportunity to use arynes in complex settings, as has been well demonstrated in the literature.^{14,16,32,33} With regard to several recent efforts, the Hoyer group has used arynes generated from hexadehydro-Diels–Alder reactions with readily abundant natural products to access complex derivatives.¹²¹ Additionally, our laboratory has performed late-stage intermolecular aryne cycloadditions to access derivatives of strictosidine, the last common biosynthetic precursor to all monoterpene indole alkaloids.¹²² More commonly, natural products have been accessed through diastereoselective intramolecular aryne trappings of enantioenriched substrates. Early on, our laboratory used an “indolyne” cyclization to build the complex bridged bicyclic core of coveted welwitindolinone natural products.^{123,124,125,126,127} Subsequently, we targeted the tubingensin alkaloids, wherein we envisioned using an aryne cyclization to access a quaternary center.

Tubingensins A and B (**1.70** and **1.71**, respectively) are complex indole diterpenoids first isolated from *Aspergillus tubingensis* in 1989 (Figure 1.12).^{128,129} Both natural products feature disubstituted carbazole moieties. In tubingensin A (**1.70**), the carbazole is fused to a *cis*-decalin containing four contiguous stereocenters, two of which are vicinal quaternary stereocenters. Tubingensin B (**1.71**), however, contains a carbazole fused to a [3.2.2]-bridged bicycle containing five stereocenters, four of which are contiguous. As an additional layer of complexity, three of the stereocenters are quaternary, two of which are vicinal. Moreover, tubingensins A and B (**1.70** and **1.71**, respectively) possess antiviral activity against herpes simplex virus type 1 (HSV-1) along with pesticidal activity.^{128,129} At the time we began our efforts, there were no total syntheses of tubingensins A or B, although Li and Nicolaou reported an elegant route to (±)-**1.70** in 2012.¹³⁰



Quaternary centers accessed through aryne cyclizations

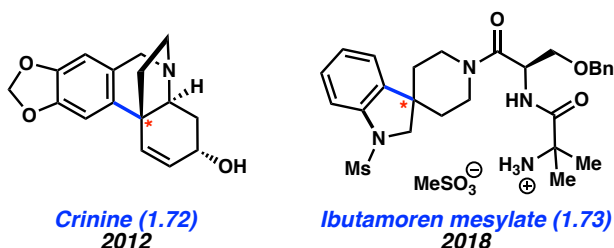


Figure 1.12. The tubingensin alkaloids and natural products with quaternary stereocenters introduced using aryne chemistry.

Given the intriguing structural features of tubingensins A and B, our group proposed synthetic routes to these compounds during a ‘Molecule of the Month’ (MOM) exercise in a 2009 group meeting. Several routes that would employ aryne intermediates were proposed, some of which were tested in the laboratory. Although our initial strategies proved unsuccessful in the laboratory, they helped us appreciate the challenge of establishing quaternary stereocenters in complex frameworks using arynes. Prior studies had largely focused on the use of arynes to access tertiary stereocenters.^{123,131,132,133,134} With regard to setting quaternary centers of natural products and drug candidates using arynes, notable precedent was available in the synthesis of crinine (**1.72**)¹³⁵ and ibutamoren mesylate (**1.73**)¹³⁶ (Figure 1.12). There were no such examples where

scaffolds bearing vicinal quaternary stereocenters, like those seen in the tubingensin alkaloids, were accessed using aryne cyclizations.

Following our initial total synthesis of (+)-tubingensin A (**1.70**),¹³⁷ we were well-poised to address the more complex family member, (–)-tubingensin B (**1.71**). As summarized in Figure 1.13, (+)-dihydrocarvone (**1.74**), an abundant chiral terpene building block, and 2-hydroxycarbazole (**1.75**) were used as starting materials and elaborated to give carbazolyne precursor **1.76**. Of note, **1.76** possesses all of the carbons that would be needed to complete the total synthesis. This key intermediate was subjected to sodium amide and *tert*-butanol in THF^{138,139} at 23 °C to effect carbazolyne cyclization. Although we were expecting to form a single C–C bond, we instead observed the formation of two new C–C bonds as evident by product cyclobutenol **1.78**. Although this outcome was undesired, the formation of **1.78** highlights the structural complexity accessible using aryne chemistry. The reaction likely proceeds via a formal [2+2] cycloaddition (e.g., **1.77**) and occurs with excellent diastereoselectivity. Nonetheless, this transformation served to establish the necessary vicinal quaternary stereocenter framework, construct the natural product’s seven-membered ring, and preserve the phenylselenide moiety necessary for a late-stage radical cyclization. To complete the synthesis, cyclobutenol **1.78** was subjected to Murakami’s Rh-catalyzed fragmentation conditions,¹⁴⁰ which delivered the ketone **1.79** in 53% yield via fragmentation of the cyclobutenol ring. In turn, ketone **1.79** could be elaborated to (–)-tubingensin B (**1.71**).¹⁴¹ This effort demonstrates the utility of highly reactive aryne intermediates for the assembly of sterically congested carbon–carbon bonds in natural products.

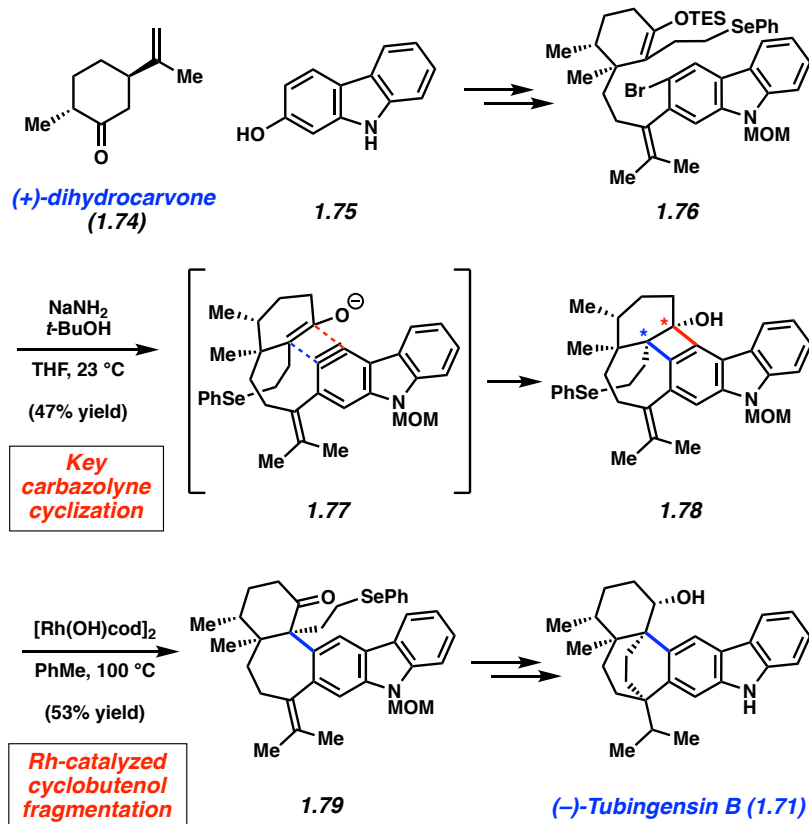


Figure 1.13. Overview of (-)-tubingensin B total synthesis.

1.5 Arynes in Asymmetric Catalysis

The aforementioned section highlights two key tactics for accessing enantioenriched products using aryne intermediates. More specifically, the use of chiral auxiliaries, chiral reagents, or enantioenriched substrates have been most common and successfully used to build intricate scaffolds and quaternary stereocenters. In turn, chemists have questioned: is it possible to leverage asymmetric catalysis in aryne trapping experiments? Such processes may be very challenging, as they could require two transiently generated intermediates,^{29,32} including a highly reactive aryne, to come together and undergo a productive reaction with stereocontrol. In addition to the fundamental scientific interest of using a fleeting aryne intermediate in a catalytic reaction, there are also practical advantages of asymmetric catalysis.^{142,143,144} We highlight three key studies in

this emerging field involving the synthesis of helicenes (axial chirality)^{145,146} and the introduction of quaternary stereocenters (point chirality).¹²⁰

A breakthrough involving the use of arynes in asymmetric catalysis was reported by Guitián and coworkers in 2006.¹⁴⁵ More specifically, the authors studied [2+2+2] cycloadditions of arynes and alkynes to access enantioenriched helicenes. Accessing helicenes in an enantioselective manner has remained an important area of research^{79,147,148} and prior aryne-based approaches had given rise to racemic products.^{149,150} As shown in Figure 1.14, silyl triflate **1.80** was treated with CsF, alkyne **1.81**, catalytic Pd₂(dba)₃, and BINAP to afford helicene **1.82**. The reaction likely proceeds through a palladium-catalyzed cyclotrimerization of two in situ-generated aryne intermediates (from silyl triflate **1.80**) and alkyne **1.81**. Although the yield was modest, helicene **1.82** was obtained in 67% ee. This study demonstrated an important proof-of-concept with regard to arynes and their use in asymmetric catalysis.

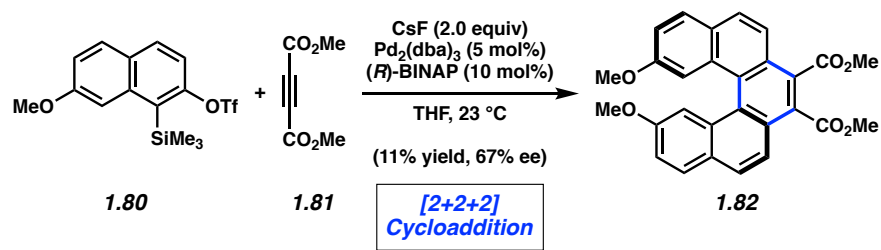


Figure 1.14. Enantioselective synthesis of helicenes using arynes and asymmetric catalysis.

Building upon this pioneering study and their own prior work in this area,¹⁵¹ the Kamikawa group published an enantioselective synthesis of helicenes in 2020.¹⁴⁶ For example, as shown in Figure 1.15, a cyclotrimerization was effected between aryne precursor **1.83** and alkyne **1.84** using Pd₂dba₃•CHCl₃, CsF, and (*S*)-QUINAP (**1.86**).¹⁵² This transformation features a design similar to the aforementioned example by Guitián and coworkers, and affords triple helicene (*M,P,M*)-**1.85** in 49% yield and 96% ee. Notably, despite using racemic aryne precursor **1.83**, both terminal helicenes exclusively formed the (*M*)-[5]-helicenyl moiety, which suggests a kinetic resolution or

dynamic kinetic resolution occurs in the reaction. Overall, this study achieved the first enantioselective synthesis of a triple helicene, while also providing the first practical catalytic asymmetric aryne trapping reaction.

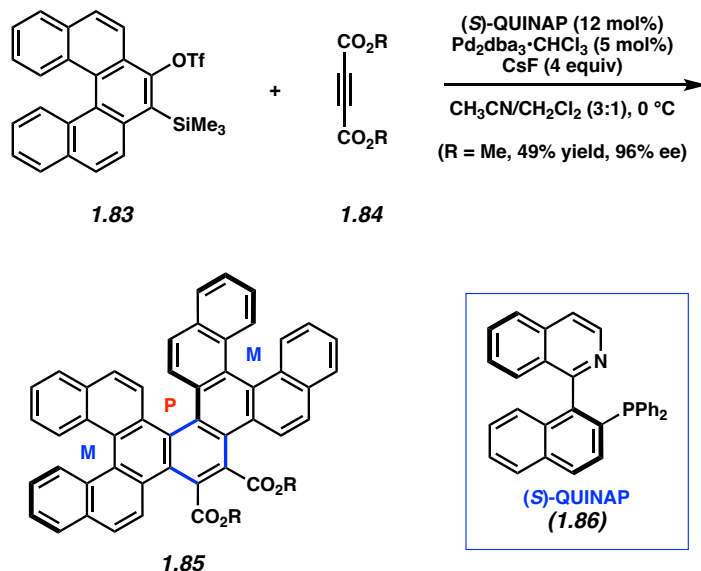


Figure 1.15. Enantioselective synthesis of triple helicenes via the catalytic asymmetric trapping of arynes.

Also in 2020, the Luo group reported a pioneering study in the catalytic asymmetric trapping of arynes and related strained intermediates.¹²⁰ Their methodology strategically blends organocatalysis and electrochemistry to achieve the α -functionalization of 1,3-dicarbonyl substrates and establish point chiral stereochemistry. For example, treatment of ketoester **1.61** with 1-aminobenzotriazole (**1.87**) and amine catalyst **1.88**, under their optimal electrochemical oxidation conditions, afforded α -arylated ketoester **1.63** in 71% yield and 94% ee (Figure 1.16). Mechanistically, the reaction is thought to proceed by way of an intermediate enamine species, which reacts with the aryne generated by electrochemical oxidation of **1.87**. The cobalt catalyst is proposed to bind the aryne triple bond and stabilize excess benzyne intermediate that is generated.^{153,154,155} Products **1.89–1.92** provide further examples of the products that were generated using this methodology. These studies demonstrate an electrochemical oxidation

approach to access benzyne and related strained intermediates, which nicely complements prior studies involving the use of non-electrochemical oxidation conditions for aryne generation.^{156,157,158,159,160} Moreover, this study demonstrates that arynes can be engaged in asymmetric catalysis to provide access to point chiral products in synthetically useful enantioselectivities. The ability to access stereodefined quaternary stereocenters is especially notable.

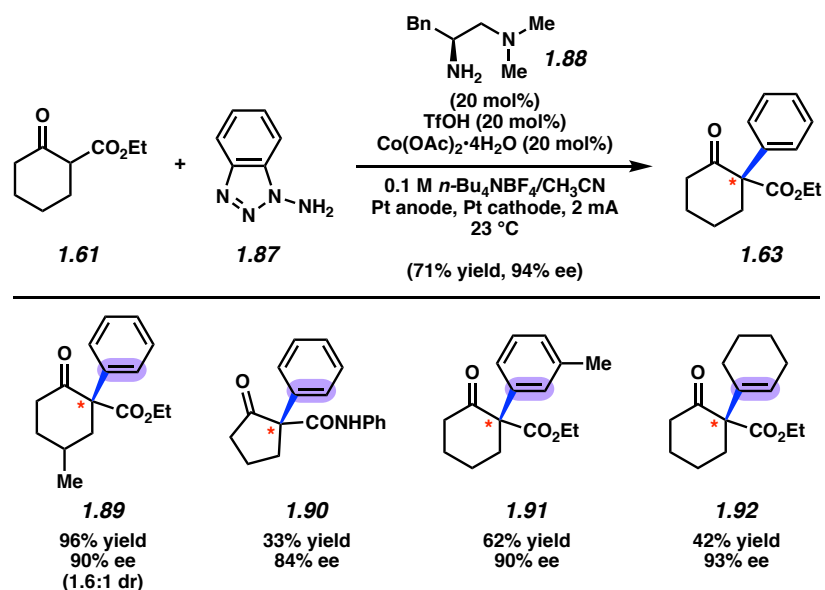


Figure 1.16. Catalytic enantioselective α -arylation of 1,3-dicarbonyls.

1.6 Use of Strained Cyclic Allenes to Access Polycyclic Scaffolds

Whereas arynes and strained cyclic alkynes have been studied extensively, a related counterpart, strained cyclic allenes (i.e., **1.4**, **1.93**, **1.94**, Figure 1.17), have received significantly less attention. Of note, the discovery of 1,2-cyclohexadiene (**1.4**) by Wittig was reported in 1966,⁹ only nine years after the validation of cyclohexyne (and thirteen years after the validation of benzyne in 1953).^{27,31,14} Theoretical investigations of these species have been reported,^{161,162,163,164,165,166,167,168,169} as well as synthetic advances, most notably by Christl.^{170,171,172,173,174,175,176} In a key finding, Guitián and coworkers developed Kobayashi

precursors to strained cyclic allenes and demonstrated their utility in several transformations, such as [4+2] cycloadditions.^{177,178} Subsequently, our laboratory and West's expanded the synthetic utility of Kobayashi cyclic allene precursors to encompass other intermolecular cycloadditions, especially [3+2] cycloadditions.^{179,180,181,182}

Here, we feature selected recent efforts aimed at harnessing strained cyclic allenes to build complex polycyclic scaffolds bearing heteroatoms and sp^3 centers. Generally speaking, these reactions proceed by treating silyl triflate precursors **1.95** with a fluoride source to generate cyclic allenes **1.96**. In situ trapping with cycloaddition partners **1.18** provides adducts **1.97** (Figure 1.17). As will be discussed in the remaining sections of this Chapter, strained cyclic allene chemistry provides exciting opportunities for study related to regiochemistry, pertaining to which olefin of the allene undergoes reaction, and stereochemistry, due to the inherent chirality of cyclic allenes and generation of a new sp^3 center.

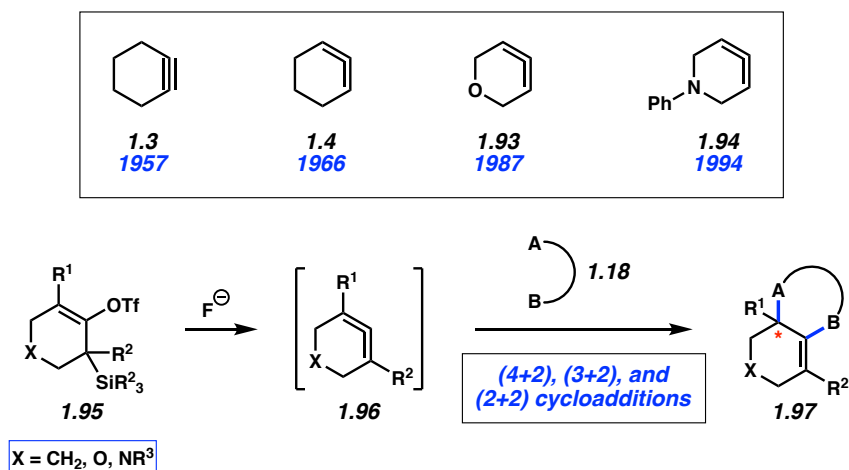


Figure 1.17. Strained cyclic allenes and representative trapping reactions.

A striking example of cyclic allene chemistry was reported by West and co-workers in 2019, where in situ-generated 1,2-cyclohexadienes underwent (4+2) cycloaddition with tethered furans to access complex tetracyclic products (Figure 1.18).¹⁸³ Substrates **1.98** were subjected to

TBAF to afford cycloadducts **1.100**, presumably by way of cyclic allene intermediate **1.99**. The products contain three stereocenters, set in a relative sense, including a quaternary center. Representative products **1.101** and **1.102** highlight that the linker length could be varied ($n = 1$ or 2). In addition, heteroatoms were tolerated in the linker, as shown by cycloadducts **1.103** and **1.104**. Of note, the transformations proceeded diastereoselectively in favor of the *endo* product and regioselectively, with the latter being governed by the tether. This methodology provides the first examples of an intramolecular cycloaddition with a six-membered cyclic allene and showcases the structural complexity that is accessible using cyclic allene chemistry.

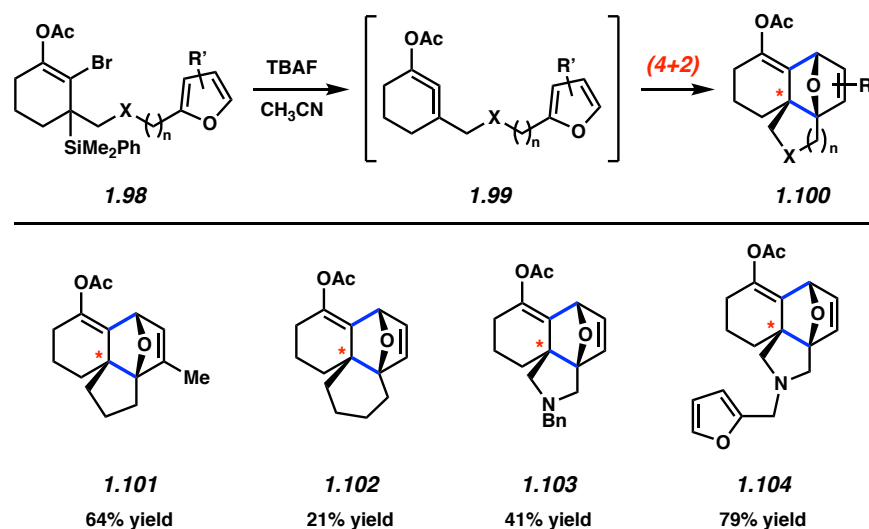


Figure 1.18. Intramolecular Diels–Alder reactions afford tetracyclic products.

Our laboratory was particularly interested in heterocyclic allenes and the possibility of accessing them using Kobayashi-type precursors. Many heterocyclic allenes had been accessed previously, but never using a silyl triflate as the precursor.^{184,185,186,187,188,189,190} After developing syntheses of the appropriate precursors to azacyclic and oxacyclic allenes (i.e. **1.105** and **1.106**, respectively), we demonstrated their use in cycloaddition reactions, with select results shown in Figure 1.19.^{191,192} Operationally, reactions are performed by treating the appropriate silyl triflate precursor (**1.105**, X = NCbz; or **1.106**, X = O) with a trapping agent **1.18** in the presence of CsF at

23 °C, ultimately leading to cycloadducts **1.108**. Three cycloadducts arising from azacyclic allene precursor **1.105** are shown reflective of (4+2), (3+2), and (2+2) cycloadditions (entries 1–3). The cycloadducts, **1.109**, **1.111**, and **1.112**, are formed in good yield and useful diastereoselectivities (when applicable). Similarly, oxacyclic allene precursor **1.106** could be employed in (4+2), (3+2), and (2+2) cycloadditions, thus giving rise to cycloadducts **1.114**, **1.116**, and **1.118**, respectively (entries 4–6). Overall, by varying the heterocyclic allene precursor and the trapping agent, one can now use strained cyclic allene chemistry as a strategy to synthesize structurally complex heterocyclic compounds.

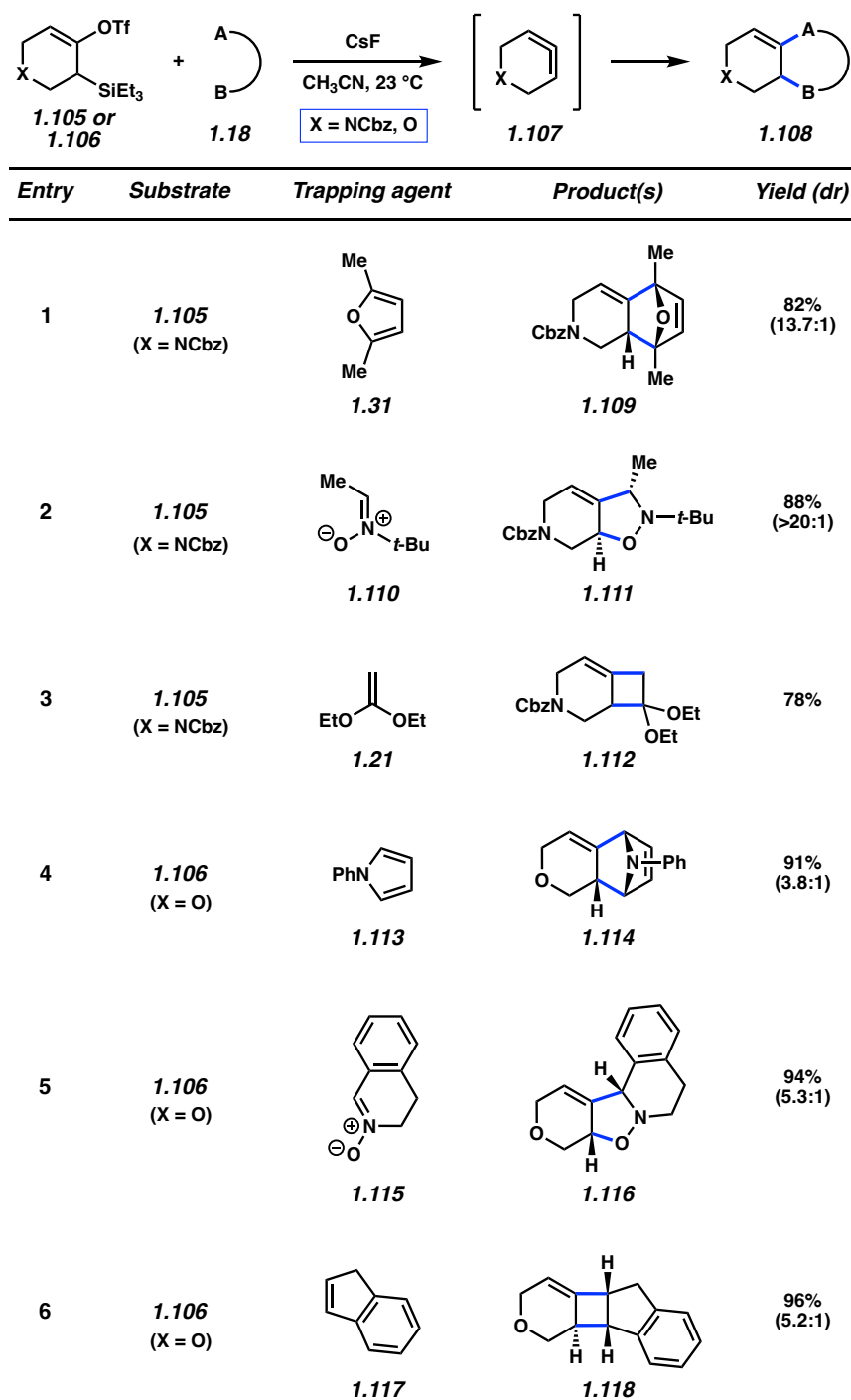


Figure 1.19. Representative azacyclic and oxacyclic allene trapping experiments.

Whereas the results shown in Figure 1.19 showcase reactions of unsubstituted strained cyclic allenes, another important facet of these compounds is observing and understanding what happens when substituents are present on the allene carbons in intermolecular trapping

experiments. Our laboratory has probed this issue in the context of azacyclic allenes,¹⁹¹ with key results provided in Figure 1.20. Silyl triflate **1.119**, **1.122**, and **1.125** were accessed as precursors to the corresponding cyclic allenes **1.120**, **1.123**, and **1.126**, in order to probe the influence of electron-donating and electron-withdrawing substituents (i.e., alkyl and ester groups, respectively). As shown by the formation of **1.121**, cycloaddition occurs on the olefin of **1.120** distal to the methyl group, whereas the cycloaddition takes place on the olefin proximal to the ester of **1.123**. When both methyl and ester substituents were present, cycloaddition occurs proximal to the ester and distal to the methyl of cyclic allene **1.126**, as one might expect in this matched scenario (**1.125** + **1.113** → **1.127**). All three reactions proceeded in good yields and excellent diastereoselectivities to give structurally complex products, including two with quaternary centers (i.e., **1.124** and **1.127**), further highlighting the synthetic utility of this methodology. In a collaboration with the Houk group at UCLA, a distortion-interaction analysis demonstrated that interaction energies, related to electron-factors, likely govern regioselectivity.¹⁹¹ With regard to diastereoselectivity, reactions proceed with *endo* selectivity with respect to the unreactive cyclic allene double bond.^{191,193} Given the synthetic utility of this methodology and the ability to understand the regiochemical and stereochemical outcomes, we expect this methodology will see increased usage in chemical synthesis. For example, Schreiber and coworkers have recently harnessed heterocyclic allene chemistry for the synthesis of DNA-encoded libraries.¹⁹⁴

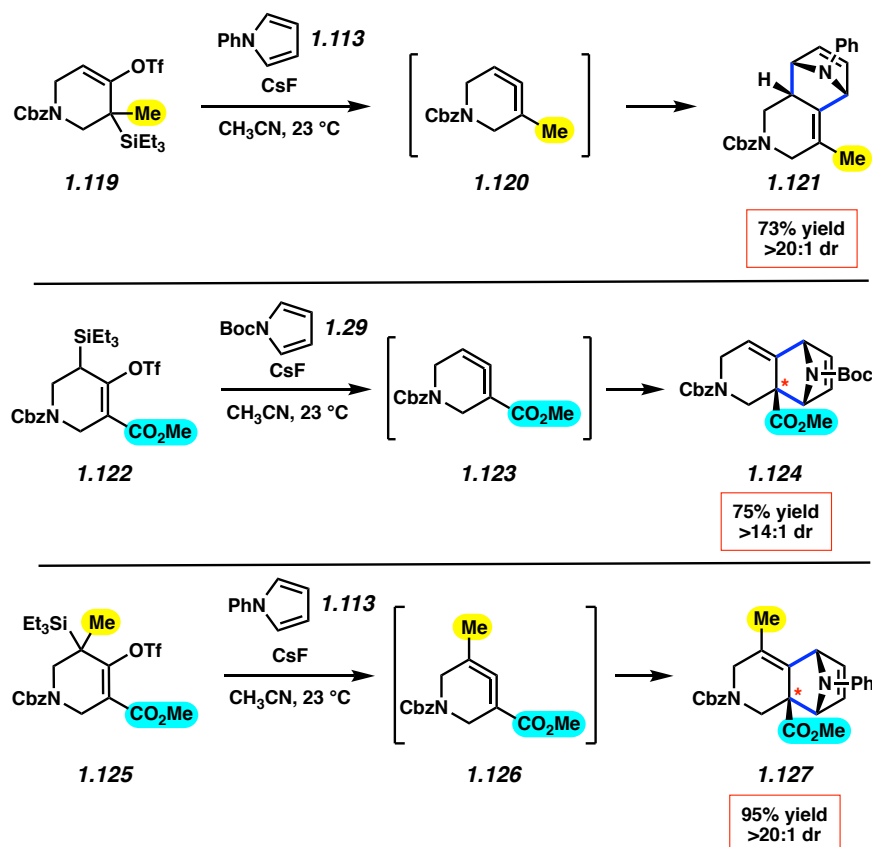


Figure 1.20. Regioselectivity investigation of substituted azacyclic allenes.

1.7 Strained Cyclic Allenes in Enantioselective and Stereospecific Reactions

The aforementioned studies demonstrate that cyclic allenes can undergo regio- and diastereoselective trapping to give polycyclic heterocyclic products. In an emerging area, efforts have also been put forth to control absolute stereochemistry in reactions of strained cyclic allenes. Seminal studies performed by Christl and coworkers demonstrated that enantioenriched cyclic allenes can be generated and intercepted using the Skattebøl rearrangement.^{171,172} Our laboratory devised the alternative approach shown in Figure 1.21.^{191,192} Silyl triflates **1.128** would be prepared with control of absolute stereochemistry and subjected to mild fluoride-based conditions. This could lead to the transmission of stereochemical information to cyclic allenes **1.129**, which in turn, could undergo stereospecific trapping with **1.18** to yield cycloadducts **1.130**. Of note, this overall

process would proceed with the transfer of point chirality from **1.128** to **1.130**, via the intermediacy of axially chiral intermediates (i.e., **1.129**), with potential ablation of the sole stereocenter present in the substrate. This approach involving enantioenriched silyl triflate precursors had not been examined previously.

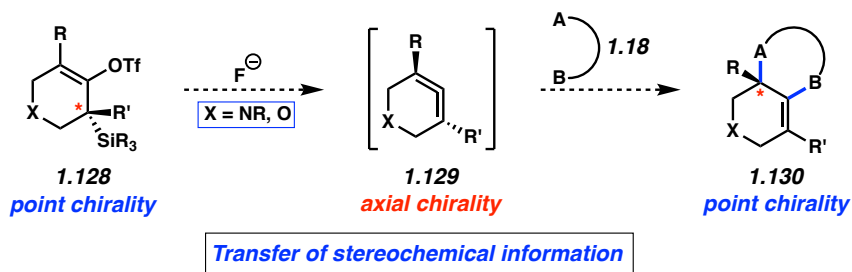


Figure 1.21. Transfer of stereochemical information in allene cycloadditions.

As shown in Figure 1.22, the success of the aforementioned approach was validated in the context of both aza- and oxacyclic allenes. In the first example, silyl triflate (+)-**1.119** was accessed in >99% ee by performing preparative chiral supercritical fluid chromatography (SFC) on a synthetic precursor. Under standard cyclic allene generation and trapping conditions, with diene **1.31** as the trapping agent, Diels–Alder adduct (+)-**1.131** was obtained in 98% ee (98% stereoretention).¹⁹¹ In the second example, silyl triflate (–)-**1.132** was obtained in 81% ee. The absolute stereochemistry was introduced by performing asymmetric allylic alkylation^{195,196,197,198,199} of a ketone precursor in collaboration with Stoltz and coworkers, thus obviating the need for preparative chiral chromatography. Nonetheless, cyclic allene generation and trapping provided (+)-**1.134** in 81% ee, reflective of >99% stereoretention.¹⁹² Collectively, these results demonstrate the feasibility of transferring stereochemical information from the silyl triflate to the cycloadduct through an axially chiral cyclic allene, while providing access to enantioenriched polycyclic products.

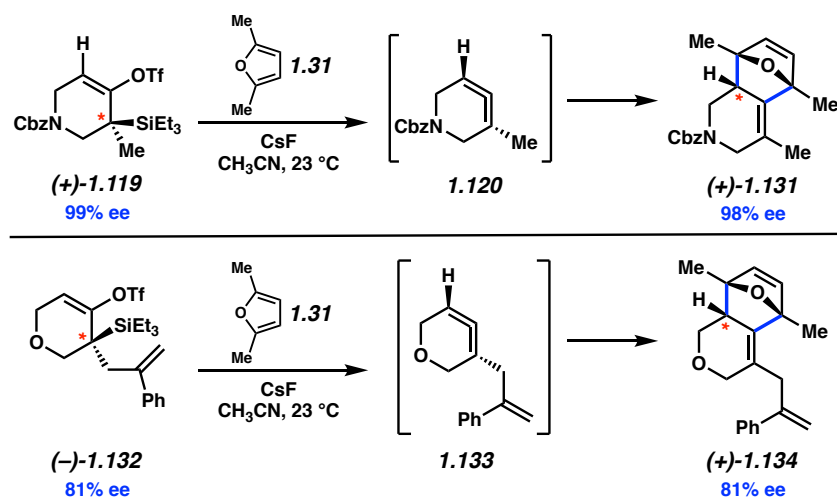


Figure 1.22. Stereospecific cycloadditions of heterocyclic allenes using enantioenriched silyl triflates.

An exciting new approach to control the absolute stereochemistry in reactions of cyclic allenes was recently demonstrated. This strategy was motivated by an interest in cyclic allene racemization, in contrast to the aforementioned approach involving transfer of stereochemical information. A key result that prompted this study is shown in Figure 1.23. Silyl triflate **1.122**, accessible in 87% ee (via chiral separation of a precursor), was subjected to cyclic allene generation and trapping.¹⁹¹ However, cycloadduct **1.135** was obtained racemically. This result suggested the importance of substituent effects and that racemization could plausibly outcompete cyclic allene trapping. Interestingly, computational studies suggest that ester-substituted cyclic allene **1.122** undergoes racemization readily, with an estimated barrier of only 14.1 kcal/mol.¹⁹¹ Thus, efforts were put forth toward developing an asymmetric trapping of cyclic allene intermediates using transition metal catalysis.

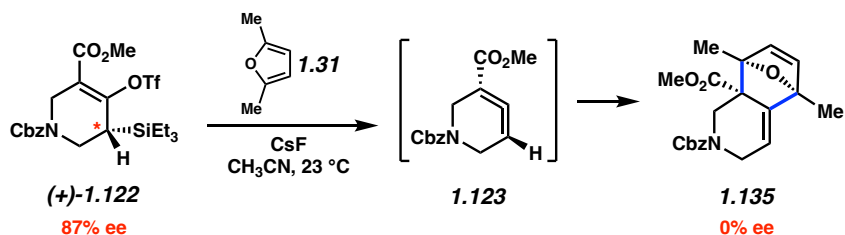


Figure 1.23. Cyclic allene racemization.

Only one prior example of a transition metal-mediated strained cyclic allene reaction was known in the literature, which involved a cyclotrimerization process.¹⁷⁷ Our laboratory has since developed two variants of asymmetric transition metal-catalyzed annulations of cyclic allenes, as shown in Figure 1.24. It was found that under nickel-catalyzed annulation conditions,²⁰⁰ cyclic allene precursor **1.136** and benzotriazinone **1.137** afforded tricycle **1.139** in 85% yield and 94% ee.²⁰¹ More recently, we demonstrated that reaction of silyl triflate **1.140** and iodopyridine **1.141** under palladium-catalyzed annulation conditions afforded tricycle **1.143** in 64% yield and 90% ee.²⁰² These transformations are thought to proceed via the reaction of an in situ-generated, racemic cyclic allene and a transient metallocycle formed by oxidative addition. Mechanistic details, including how absolute stereochemistry is introduced, have been proposed for the nickel-catalyzed annulation based on computations.²⁰¹ As such, these methodologies not only provide an advance in strained cyclic allene chemistry, but are also some of the few catalytic asymmetric reactions across the larger family of transiently-generated cyclic intermediates (e.g., arynes, cyclic alkynes, cyclic allenes).

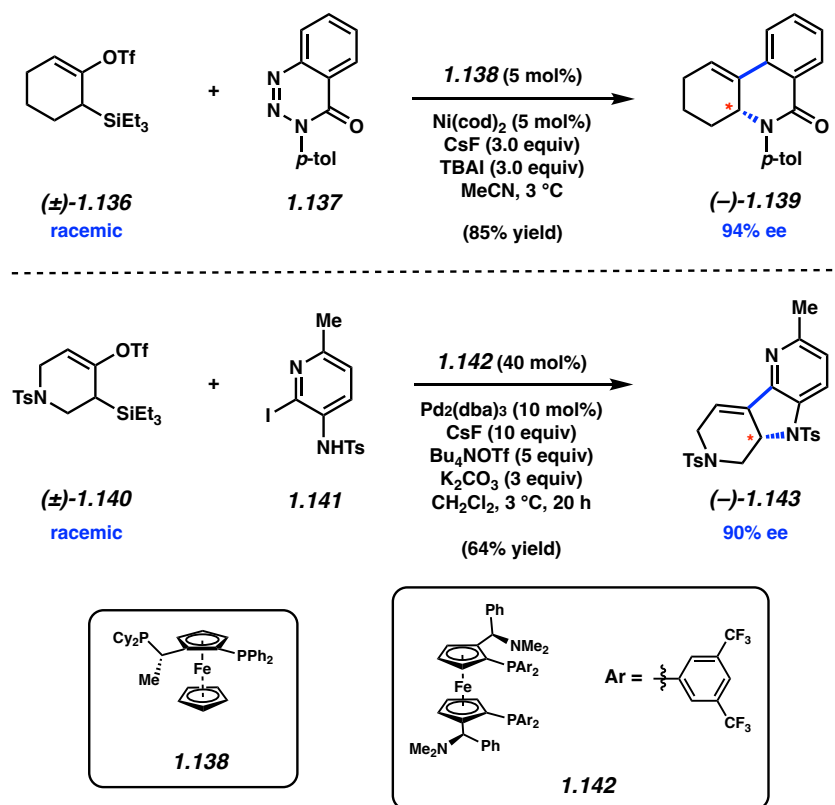


Figure 1.24. Catalytic asymmetric reactions of cyclic allenes.

1.8 Outlook and Future Directions

The study of arynes, strained cyclic alkynes, and strained cyclic allenes has seen tremendous growth in recent years. As highlighted in this Chapter, such strained intermediates were contemplated as early as 1902, and validated 50+ years later. In the modern era, these species can be strategically employed in a host of impressive synthetic applications. The increase in practical use can be attributed to a combination of factors, including the mild conditions used for their generation, the commercial availability of silyl triflate precursors,²⁰³ and advances in our ability to understand and predict how strained cyclic intermediates will react in complexity-generating transformations.^{24,25,26}

What does the future hold for arynes, cyclic alkynes, and cyclic allenes? We have shown in this Chapter how these transient species can be strategically leveraged to build complexity in

the form of polycyclic scaffolds. Notably, many of newly developed methods discussed herein have potential applications in drug discovery and materials, as well as in the synthesis of heterocycles, natural products, and sp^3 -rich compounds. Moreover, key advances to control absolute stereochemistry using asymmetric catalysis recently emerged and represent a particularly exciting area for future reaction development. As such, we curiously and enthusiastically await further advances from the synthetic community in the chemistry of arynes, strained cyclic alkynes, and strained cyclic allenes.

1.9 Notes and References

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CHAPTER TWO

Total Synthesis of Lissodendoric Acid A via Stereospecific

Trapping of a Strained Cyclic Allene

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2.1 Abstract

Small rings that contain allenes are unconventional transient compounds that have been known since the 1960s. Despite being discovered around the same time as benzyne and offering a number of synthetically advantageous features, strained cyclic allenes have seen relatively little use in chemical synthesis. We report a concise total synthesis of the manzamine alkaloid lissodendoric acid A, which hinges on the development of a regioselective, diastereoselective, and stereospecific trapping of a fleeting cyclic allene intermediate. This key step swiftly assembles the cis-azadecalin framework of the natural product, allows for a succinct synthetic endgame, and enables a 12-step total synthesis (longest linear sequence; 0.8% overall yield). These studies demonstrate that strained cyclic allenes are versatile building blocks in chemical synthesis.

2.2 Introduction

Geometrically-constrained organic molecules have long fascinated chemists. One subclass of such compounds are small cyclic molecules that bear functional groups of typically linear geometry. Embedding typically linear functional groups within small ring systems forces bent geometries, thereby leading to a high degree of strain. Small rings that contain triple-bonds were speculated in the early 1900s,¹ ultimately leading to the validation of benzyne (**2.1**)^{2,3} and cyclohexyne (**2.2**)⁴ in the 1950s (Figure 2.1A).^{5,6,7,8,9} Despite that these in situ generated intermediates exhibit significant strain energies of ~40–50 kcal/mol^{10,11} and short lifetimes,^{12,13} scientists have learned how to leverage these highly reactive intermediates in a range of useful chemical transformations and biological applications. Indeed, examples of aromatic and non-aromatic cyclic alkyne trapping experiments can be seen in the synthesis of important ligands, such as XPhos, medicines, agrochemicals, materials, naturally-occurring compounds, and other areas.⁹ Moreover, biorthogonal chemistry,¹⁴ recently recognized by the Nobel Prize in Chemistry, relies on cyclooctynes (**2.3**) and other strained intermediates.

Cyclic allenes, such as 1,2-cyclohexadiene (**2.4**), are a related class of strained molecules that contain a typically linear functional group that is constrained in a small ring (Figure 2.1A). Cyclic allene **2.4** was first validated in 1964¹⁵ and again in 1966.¹⁶ This intermediate, along with other cyclic allenes, has received far less attention compared to strained cyclic alkynes, despite having a number of advantages that warrant their further investigation. Our laboratory has been interested in heterocyclic allenes, such as azacyclic allene **2.5**, due to their properties and potential use in chemical synthesis.^{9,17,18} The geometry-optimized structure of this species is depicted in Figure 2.1B. As shown, the allene C=C bonds are each 1.32 Å and the central allene carbon bears an internal angle of 133°. Additionally, the allene C–H and C–CH₃ bonds are twisted out of the

allene C=C=C plane by 39° and 36°, respectively. Several features result from this unique structure, including the high reactivity of cyclic allenes due to strain, their capacity to undergo cycloadditions, nucleophilic additions, or metal-catalyzed reactions, and the capability to form two new bonds in a single transformation, with introduction of up to three C(sp³) stereocenters. As such, strained cyclic allenes have recently been used to prepare highly substituted, sp³-rich compounds^{9,17,18,19,20,21,22,23,24} and have even been used to access DNA-encoded libraries.²⁵ Further underscoring their attractiveness is the fact that cyclic allenes are axially chiral and could serve as unconventional, yet valuable building blocks for stereoselective synthesis. Moreover, from a practical perspective, strained cyclic allenes can possess heteroatoms within the ring and can be accessed under mild conditions (e.g., fluoride-based reactions, ambient temperatures).¹⁹ Lastly, because of the relatively scarce body of literature surrounding strained cyclic allenes, there exist numerous opportunities for discovery with regard to reactivity and selectivity patterns in synthetic applications. Cyclic allenes have rarely been used in the synthesis of complex natural products, which is notable given that their close relatives, arynes and strained cyclic alkynes, have been employed in more than one hundred total syntheses to date.^{6,7,8} One notable example of the use of a cyclic allene in total synthesis was reported in 1997 by Marshall and Sehn and involves a relatively unstrained allene embedded in a macrocyclic 14-membered ring.²⁶

With the aim of developing the chemistry of strained cyclic allenes and evaluating their utility in total synthesis, we considered lissodendoric acid A (**2.6**),²⁷ a structurally-complex member of the manzamine family of alkaloids²⁸ (Figure 2.1C). Manzamine alkaloids have been popular targets for total synthesis due to their complex structures and promising biological activities.^{29,30} The cumulative synthetic efforts toward manzamine alkaloids, as recently highlighted by Dixon and coworkers,²⁹ have involved more than 25 research groups to date. With

regard to lissodendoric acid A (**2.6**), this natural product was isolated in 2017 from the marine sponge *Lissodendoryx florida* and has been shown to reduce reactive oxygen species (ROS) in a Parkinson's disease model consisting of Neuro 2a cells treated with 6-hydroxydopamine (~50% reduction in ROS levels at concentrations of 0.1 and 10 mM).²⁷ The natural product's complex structure poses a daunting synthetic challenge which, in turn, would push the limits of strained cyclic allene chemistry. The core of lissodendoric acid A (**2.6**) is an azadecalin scaffold bearing a conjugated diene, a carboxylic acid substituent, and two stereogenic centers, one of which is quaternary at C8a. In addition, the natural product bears a 14-membered macrocycle tethered beneath the C8a aminodecane substituent. A total synthesis of lissodendoric acid A (**2.6**) has not been reported.

We questioned if the azadecalin core and C8a quaternary stereocenter (e.g., **2.7**) could be introduced simultaneously via a [4+2] cycloaddition between cyclic allene **2.8** and 2-pyrone **2.9** (Figure 2.1C).³¹ The strain associated with cyclic allene **2.8** would be crucial to the success of the proposed reaction, as such intermolecular cycloadditions using analogous cyclic alkene substrates are challenging.^{32,33} The use of 2-pyrones in [4+2] cycloadditions with cyclic allenes was previously unknown, but if successful could enable control of regioselectivity via an inverse electron-demand Diels–Alder process. In addition, the use of a pyrone would furnish a [2.2.2]-bicyclic product (**2.7**), which in turn, would function as a masked 1,3-diene, enabling the strategic unveiling of this potentially sensitive motif at a later stage via thermal expulsion of CO₂. Lastly, we were intrigued by the possibility of accessing cyclic allene **2.8** in enantioenriched form and developing enantiospecific trapping reactions.

Our successful total synthesis of lissodendoric acid A (**2.6**) was indeed enabled by the development of a regioselective, diastereoselective, and stereospecific trapping reaction of a fleeting cyclic allene intermediate. The total synthesis is concise owing to generation of substantial structural complexity in the key cyclic allene trapping step.

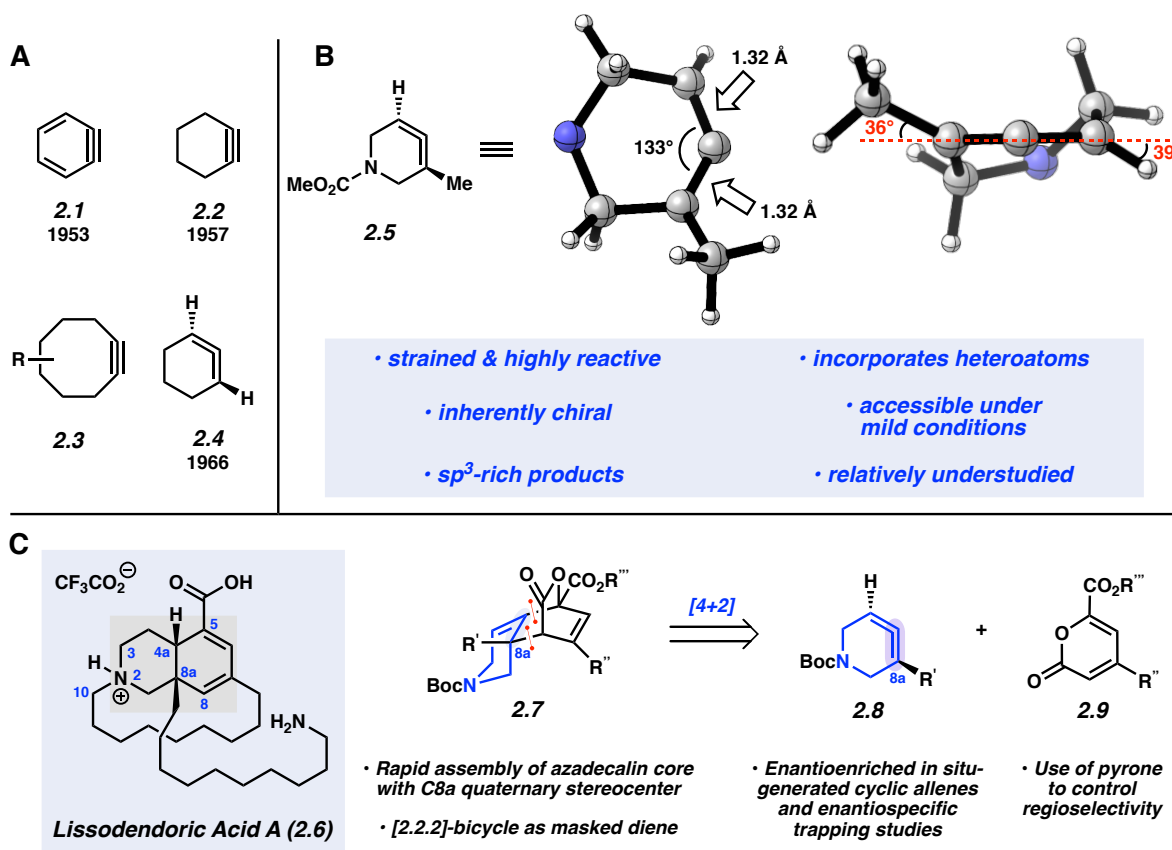


Figure 2.1. Strained intermediates and overview of current study. **(A)** Seminal strained cyclic intermediates **2.1**, **2.2**, and **2.4** and biorthogonal cyclooctyne reagents **2.3**. **(B)** Geometry-optimized structure of strained azacyclic allene **2.5** (ω B97XD/6-31G(d)) and key features. CO_2Me is omitted from the 3D representations for clarity. **(C)** Our synthetic target, lissodendoric acid A (**2.6**), and our synthetic approach using a [4+2] cycloaddition to access **2.7** from cyclic allene **2.8** and pyrone **2.9** (R' , R'' , R''' = alkyl).

2.3 Results and Discussion

2.3.1 Development of regio- and stereoselective cycloadditions

As the success of our approach would hinge on the ability to control the regioselectivity and stereoselectivity in the key [4+2] cycloaddition step, we performed preliminary studies with furan **2.11** and pyrone **2.13** (Figure 2.2). These dienes were selected so that we could compare and contrast the electronic effects of the cyclic allene trapping partners (i.e. electron-rich furan vs. electron-poor pyrones). Pyrone **2.13** was chosen because it was easily accessible and possesses potentially useful synthetic handles, whereas furan (**2.11**) had previously been used in cyclic allene [4+2] cycloadditions.¹⁷ The syntheses of **2.12**, **2.16**, and **2.18**, which function as precursors to cyclic allene **2.8** (see Figure 2.1C), are detailed Section 2.5.2.1, and relied on chiral separation technology to access enantioenriched material. Treatment of silyl triflate **2.12** with furan (**2.11**) and CsF in acetonitrile at 23 °C delivered the undesired regioisomer **2.10**, consistent with prior experiments using the N-Cbz derivative of **2.12**.¹⁷ In a crucial result, we found that treatment of **2.12** with readily available pyrone **2.13**³⁴ gave cycloadduct **2.14**, which possesses the desired connectivity and the necessary C8a quaternary center, without significant loss of stereochemical integrity. The reaction is *endo*-selective, consistent with theoretical studies of 1,2-cyclohexadienes,³⁵ and occurs with the expected regioselectivity based on this being an inverse-electron demand process. These results demonstrate that regioselectivity in cyclic allene [4+2] cycloadditions can be modulated by judicious selection of the trapping agent.

Our excitement for these results was somewhat dampened by our inability to access compounds such as **2.12** in high ee without the use of chiral separation technologies. As such, we evaluated alternative precursors **2.16** and **2.18**, where the silicon substituent would be placed on a less-substituted carbon, in the corresponding cycloaddition reactions.³⁶ As shown in Figure 2.2B,

the use of pseudo-isomeric silyltriflate **2.16** (albeit with Et in place of Me due to substrate synthesis logistics), furnished the expected cycloadducts **2.15** and **2.17**. However, regardless of the trapping agent, poor stereoretention was observed for reasons that are not well understood presently. Lastly, we examined silylbromide **2.18**, analogous to an approach to cyclic allene generation developed by West and co-workers²² (Figure 2.2C). Although yields were modest in these initial studies, significant stereoretention was observed in the formation of cycloadducts **2.10** and **2.14**.³⁷ Silylbromide precursors to cyclic allenes had not been synthesized previously in enantioenriched fashion, but we were optimistic that derivatives of **2.18** could be prepared without the need for chiral separations. Before describing the translation of these studies to the total synthesis of lissodendoric acid A (**2.6**), we also highlight several key features of cyclic allene chemistry that are reflected in the results shown in Figure 2.2. Specifically, all reactions proceed under mild conditions, lead to the formation of two C–C bonds, occur with high *endo* diastereoselectivity,³⁵ and provide access to complex heterocyclic products containing three stereocenters, one of which is quaternary in the cases of the pyrone cycloadducts.

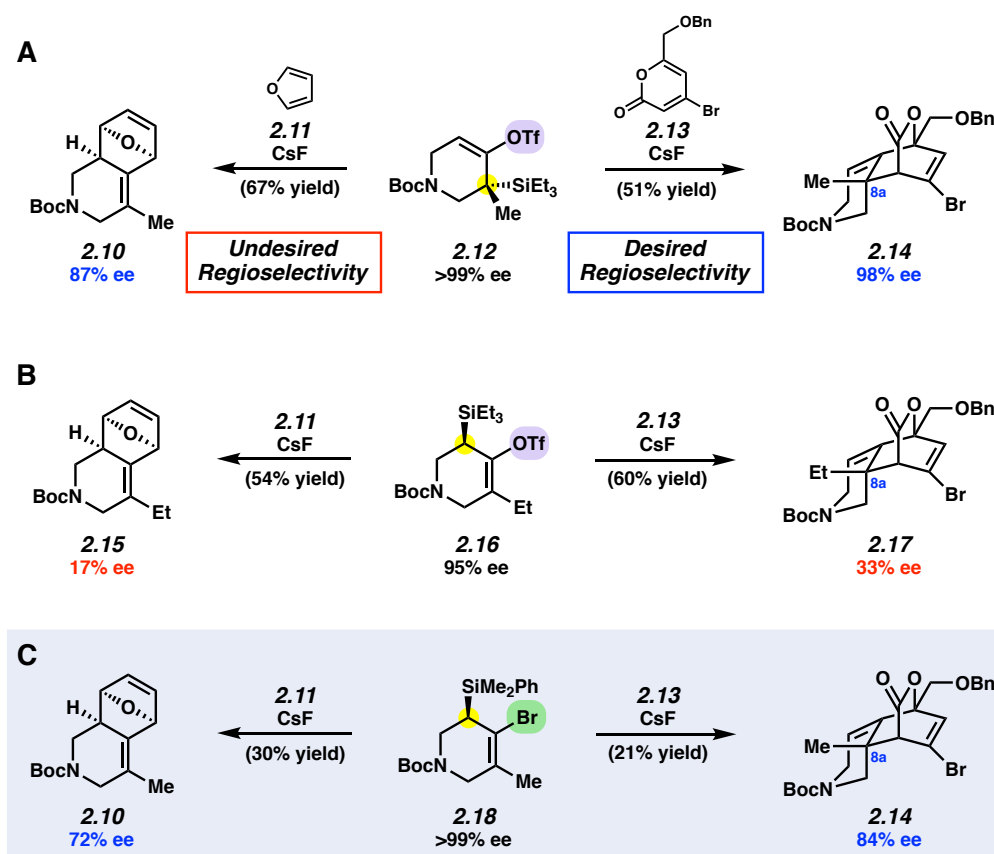


Figure 2.2. Regioselectivity and stereospecificity studies using variable cyclic allene precursors and [4+2] cycloaddition partners. **(A)** Use of cyclic allene precursor **2.12** allows for efficient and stereospecific cycloadditions. **(B)** Stereospecificity is modest when employing pseudo-isomeric silyltriflate **2.16**. **(C)** Switching to silylbromide **2.18** as the cyclic allene precursor allows for regioselective and stereospecific cycloaddition reactions, while providing a plausible entryway to enantioenriched material. Highlights depict the primary differences between cyclic allene precursors **2.12**, **2.16**, and **2.18**. See Section 2.5.2.3 for reaction conditions.

2.3.2 Fragment synthesis and assembly of azadecalin core

Having established the feasibility of the key cyclic allene trapping step, we sought to perform analogous studies on a more elaborate substrate. Pursuing this endeavor could allow us to

push the limits of strained cyclic allene chemistry, while enabling the synthesis of lissodendoric acid A (**2.6**). Pyrone **2.22** was prepared in two steps from commercially available carboxylic acid **2.19** (Figure 2.3A). Double tosylation, followed by the addition of *t*-BuOH, furnished tosylate **2.20**, bearing a *t*-butyl ester substituent. Subsequent Negishi coupling with organozinc reagent **2.21** provided the alkylated pyrone **2.22**, which contains a terminal alkene necessary for the eventual installation of the macrocycle using ring-closing metathesis. The desired cyclic allene precursor, silylbromide **2.27**, was prepared from bromotriflate **2.23**, which was obtained commercially (Figure 2.3B). Treatment of **2.23** with alkylzirconium reagent **2.24** gave ketone **2.25** via 1,4-addition and ejection of the triflate leaving group.³⁸ CBS reduction,³⁹ followed by treatment with ethylchloroformate, gave **2.26** in 90–92% ee. Displacement of the carbonate with a silyl cuprate nucleophile^{22,40,41} delivered cyclic allene precursor **2.27** without loss in enantioenrichment. This step was thought to proceed with inversion of stereochemistry based on prior studies by Oestreich.⁴¹ Of note, the conversion of bromoketone **2.25** to silylbromide **2.27** parallels a general racemic strategy pioneered by West²² but the enantioselective reduction and stereospecific displacement of the carbonate had not been demonstrated previously.

With pyrone **2.22** and cyclic allene precursor **2.27** in hand, we evaluated the key [4+2] cycloaddition (Figure 2.3C). We were delighted to find that, by simply treating these reactants with CsF, the desired cycloadduct, **2.28**, could be obtained. Through optimization, it was found that the optical yield,^{42,43} or % stereoretention, was greatly improved at lower reaction temperatures, which, in turn, required the use of Bu₄NBr to improve the solubility of fluoride ion in solution. Ultimately, –20 °C was found to be the optimal temperature, enabling the formation of **2.28** in 73% isolated yield, presumably via the depicted transition structure proposed based on prior computational studies of cyclic allene Diels–Alder reactions.^{17,35,44}

Several aspects of this complexity-generating step should be noted, especially the regioselectivity and stereoselectivity. The regioselectivity is thought to depend upon both the cyclic allene and pyrone components. First considering the cyclic allene component, either olefin of the allene could potentially undergo trapping; however, the more electron-rich substituted olefin of the cyclic allene engages with the electron-deficient pyrone, presumably due to the inverse electron-demand nature of this cycloaddition. With regards to the pyrone component, the diene in pyrone **2.22** aligns with the cyclic allene to promote bond-formation between C8a and C8. The pyrone carbonyl, which is conjugated to the diene in **2.22**, is thought to provide a dominant electronic effect that leads to this selectivity. The origins of stereoselectivity in this transformation are also notable. The reaction is thought to proceed in an *endo* fashion, with favorable orbital overlap between the diene and the non-reactive olefin of the cyclic allene, and with favorable approach of the pyrone opposite the C8a alkyl substituent. This gives rise to **2.28** in >20:1 dr. The *endo* approach and facial selectivity are consistent with prior computational studies of cyclic allene Diels–Alder reactions.^{17,35} Despite that four cycloadducts could be envisioned (not accounting for enantiomers discussed below), cycloadduct **2.28**, which bears considerable structural complexity and functionality, is formed selectively as the sole observable product of the reaction.

The topics of absolute stereochemistry and optical yield also deserve special attention. Cyclic allene precursor **2.27** bears a single stereocenter (marked *). Upon generation of the cyclic allene intermediate, point chirality in **2.27** is transmitted to axial chirality in the cyclic allene intermediate. Then, cycloaddition re-introduces point chirality, with the generation of two tertiary stereocenters and the C8a quaternary stereocenter. The sole stereocenter present in reactant **2.27** is ablated in this process. It is also notable that the optical yield,^{42,43} or stereoretention, in forming **2.28** at –20 °C is 88%, indicating that strain-driven cycloaddition between two highly substituted

reactants is favorable over facile enantiomerization of the strained cyclic allene at low temperature. The barrier for enantiomerization for related cyclic allenes has been estimated to be ~14 kcal/mol.⁴⁵

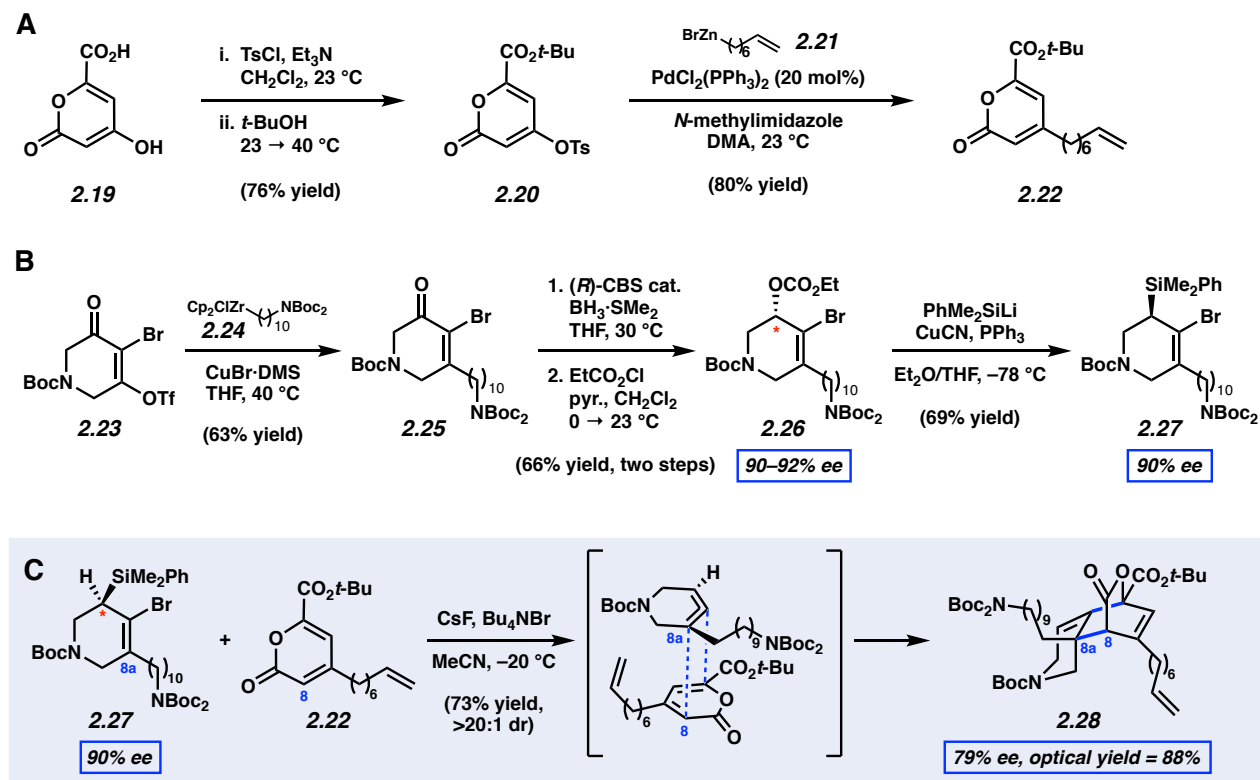


Figure 2.3. Assembly of the azadecalin core of lissodendoric acid A (**2.6**) using a strained cyclic allene. (A) Synthesis of pyrone **2.22**. (B) Enantioselective route to silyltriflate **2.27**. (C)

Cycloaddition of the strained cyclic allene derived from **2.27** with pyrone **2.22** proceeds with regioselectivity, diastereoselectivity, and stereospecificity to deliver enantioenriched adduct **2.28** with the desired quaternary stereocenter at C8a.

2.3.3 Completion of total synthesis

To complete the total synthesis of lissodendoric acid A (**2.6**), we developed the concise late-stage sequence shown in Figure 2.4 using (±)-**2.28**. The first challenge was to introduce the

C4a hydrogen substituent chemoselectively, without reduction of the other olefins. The C4/C4a olefin proved recalcitrant toward a range of reduction conditions; however, we ultimately achieved a selective reduction by first oxidizing C3 with pyridinium dichromate (PDC) / *t*-BuOOH^{46,47} and then treating the resulting α,β -unsaturated lactam intermediate with a copper hydride source⁴⁸ to effect diastereoselective 1,4-reduction and furnish cis-azadecalin **2.29**. The CO₂ bridge embedded in the [2.2.2]-bicycle of **2.28** (installed in the aforementioned cyclic allene trapping) was important for the success of this sequence as it masked the 1,3-diene motif that would otherwise be in conjugation with the C4/C4a olefin. Next, we arrived at tetraene **2.30** via a sequence involving thermal extrusion of CO₂,⁴⁹ copper triflate-promoted removal of two of the three Boc groups,⁵⁰ and amidation of the piperidine nitrogen with acryloyl chloride. Access to **2.30** set the stage for macrocyclization, which was achieved using ring-closing metathesis promoted by the robust Grubbs' 2nd Generation catalyst.^{51,52} The desired macrocycle **2.31** was obtained in 83% yield and as an inconsequential 2:1 mixture of *E*:*Z* olefin isomers. All that remained to complete the total synthesis was to selectively reduce the α,β -unsaturated imide and perform a global deprotection. The former was achieved using a reduction protocol reported by Beller,⁵³ which led to saturation of the C3 amide and the C10 α,β -unsaturated amide selectively without reduction of the ester or diene functional groups. Although the overall yield of this transformation is modest (38%), given that three functional groups are being reduced (~72% yield per reduction), we deemed the yield acceptable. Finally, treatment of the reduced intermediate with TFA furnished lissodendoric acid A (**2.6**). The total synthesis is 12 steps from **2.23** (longest linear sequence; 0.8% overall yield).

Another matter of interest is the absolute stereochemical configuration of lissodendoric acid A. On the basis of experimental and computational circular dichroism studies, the isolation chemists had postulated the absolute configuration of (–)-**2.6** to be as we have depicted throughout

the manuscript.²⁷ To validate this hypothesis, our enantioenriched material was elaborated to the natural product. Much to our delight, the circular dichroism spectrum for our synthetic sample matched that of a natural sample. We conclude that the natural configuration of (–)-**2.6** proposed by the isolation chemists was indeed correct.

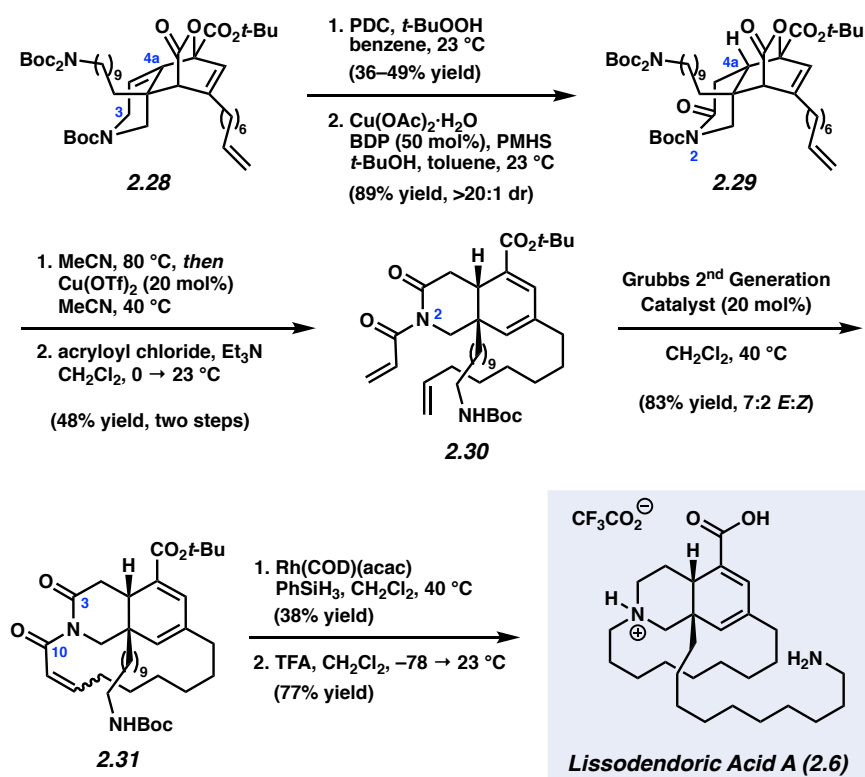


Figure 2.4. Completion of the total synthesis of lissodendoric acid A (**2.6**).

2.4 Conclusions

These studies demonstrate that cyclic allenes are powerful tools for complex molecule synthesis and should prompt the further investigation and application of these unusual compounds.

2.5 Experimental Section

2.5.1 Materials and Methods

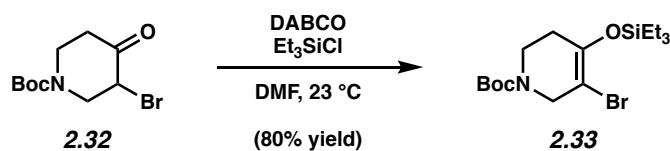
Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received unless otherwise specified. 1,4-Diazabicyclo[2.2.2]octane (DABCO), $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, and $\text{CuBr} \cdot \text{DMS}$ were purchased from Acros Organics. AgOTf , NBS, *n*-Butyllithium 2.5 M solution in hexanes (*n*-BuLi), allyl chloroformate, *n*- Bu_4NBr_3 , NaBH_4 , ethyl chloroformate, alkynyl trifluoroborate **2.35**, anhydrous *t*-BuOH, AIBN, NaH, Grubbs' 2nd generation catalyst, KHMDS, PDC, *t*-BuOOH 70 wt% in H_2O , *N*-methylimidazole, LiAlH_4 2.0 M solution in THF, acryloyl chloride, PhSiH_3 , and TsCl were obtained from Sigma-Aldrich. AgNO_3 , *N*-Phenyl-bis(trifluoromethanesulfonimide) (PhNTf_2), triethylsilyl chloride (Et_3SiCl), PPh_3 , azetidinone **2.34**, DMAP, Tf_2O , Cs_2CO_3 , and trifluoroacetic acid (TFA) were purchased from Oakwood Chemical. CsF, $(\text{PPh}_3)\text{AuCl}$, $\text{Pd}(\text{PPh}_3)_4$, $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$, $\text{Cu}(\text{OTf})_2$, $\text{Rh}(\text{COD})(\text{acac})$, $\text{Ni}(\text{cod})_2$, zirconocene hydrochloride, and 1,2-bis(diphenylphosphino)benzene (BDP) were purchased from Strem Chemicals. Copper(II) acetate monohydrate ($\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$) and 10-bromodec-1-ene (**2.41**) were purchased from TCI chemicals. Poly(methylhydrosiloxane) (PMHS), triethylamine, diisopropylamine, and $\text{BH}_3 \cdot \text{SMe}_2$ were purchased from Alfa-Aesar. *t*-BuOH was purchased from Fisher Scientific. α -Bromo ketone **2.32**, Comins' reagent, diketone **2.40**, and (*R*)-CBS catalyst were purchased from Combi-Blocks. Bromotriflate **2.23** was purchased from WuXi or could be synthesized using the procedure described herein. Di-*tert*-butyl iminodicarbonate ($\text{NH}(\text{Boc})_2$) was purchased from Ambeed. Et_3SiCl , allyl chloroformate, pyridine, diisopropylamine, and acryloyl chloride were distilled over CaH_2 prior to use. PMHS and *t*-BuOH were sparged with N_2 prior to use. NBS was recrystallized

from H₂O prior to use. Unless stated otherwise, reactions were performed at 23 °C. Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using anisaldehyde or potassium permanganate staining. Silicycle Siliaflash P60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ¹H-NMR spectra were recorded on Bruker spectrometers (at 400, 500, or 600 MHz) and are reported relative to the residual solvent signal. Data for ¹H-NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ¹³C-NMR spectra were recorded on Bruker spectrometers (at 100, 125 or 150 MHz) and are reported relative to the residual solvent signal. Data for ¹³C-NMR spectra are reported in terms of chemical shift (δ ppm). IR spectra were obtained on a Perkin-Elmer UATR Two FT-IR spectrometer and are reported in terms of frequency of absorption (cm⁻¹). DART-MS spectra were collected on a Thermo Exactive Plus MSD (Thermo Scientific) equipped with an ID-CUBE ion source, a Vapur Interface (IonSense Inc.), and an Orbitrap mass analyzer. Both the source and MSD were controlled by Excalibur software v. 3.0. The analyte was spotted onto OpenSpot sampling cards (IonSense Inc.) using CDCl₃ as the solvent. Ionization was accomplished using UHP He (Airgas Inc.) plasma with no additional ionization agents. The mass calibration was carried out using Pierce LTQ Velos ESI (+) and (–) Ion calibration solutions (Thermo Fisher Scientific). ESI-TOF measurements were carried out in positive ionization mode on a Waters LCT-Premier XE Time of Flight Instrument controlled by MassLynx 4.1 software (Waters Corporation, Milford MA). The instrument was equipped with the Multi Mode Ionization source operated in the electrospray mode. A solution of Leucine Enkephalin (Sigma Chemical, L9133) was used in the Lock-Spray to obtain accurate mass measurements. Samples were infused using direct loop injection on a Waters Acquity UPLC system. Determination of enantiopurity was carried out on a JASCO SFC (supercritical fluid

chromatography) using Daicel ChiralPak IA and IB columns and an Agilent 1200 series HPLC using a Daicel ChiralPak ID column. ECD spectra were obtained on a AppliedPhotophysics Chirascan V100 Circular Dichroism spectrometer with Chirascan software.

2.5.2 Experimental Procedures⁵⁴

2.5.2.1 Synthesis of Cyclic Allene Precursors 2.12, 2.16, and 2.18

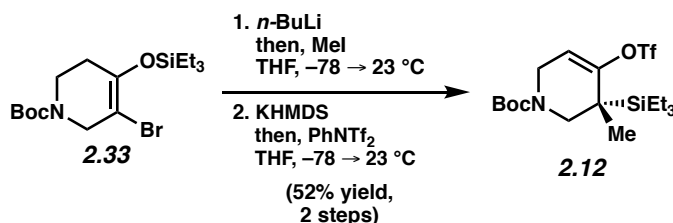


Bromo silyl enol ether 2.33. Silyl enol ether **2.33** was prepared by a previously reported method.⁵⁵

To a solution of α -bromo ketone **2.32** (4.51 g, 16.2 mmol, 1.00 equiv) dissolved in DMF (14.7 mL, 1.10 M) using sonication, was added triethylsilyl chloride (4.40 mL, 25.9 mmol, 1.60 equiv) and DABCO (4.18 g, 37.3 mmol, 2.30 equiv). Then, the reaction was allowed to stir for 23.5 h at 23 °C before being quenched with a saturated aqueous solution of NaHCO₃ (10 mL). The reaction mixture was then transferred to a separatory funnel and diluted with water (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were sequentially washed with water (2 x 20 mL) and brine (1 x 20 mL), dried with MgSO₄, filtered, and concentrated under reduced pressure to provide the crude residue. The crude residue was purified via flash chromatography (100% hexanes $\rightarrow$ 39:1 hexanes:EtOAc) to obtain bromo silyl enol ether **2.33** (5.07 g, 80% yield) as a colorless oil. Bromo silyl enol ether **2.33**: R_f 0.67 (5:1 hexanes:EtOAc); ¹H NMR (600 MHz, CDCl₃): δ 4.07 (br s, 2H), 3.57 (br s, 2H), 2.28 (br s, 2H), 1.46 (s, 9H), 1.00 (t, J = 7.9, 9H), 0.71 (q, J = 7.9, 6H); ¹³C NMR (150 MHz, CDCl₃):

δ 154.3, 146.0, 97.5, 96.9, 80.3, 49.0, 48.4, 41.7, 40.4, 31.5, 28.5, 6.8, 5.7; IR (film): 2957, 2877, 1700, 1412, 1226, 1166 cm^{-1} ; HRMS-APCI (m/z) [$M + H$] $^+$ calc'd for $\text{C}_{16}\text{H}_{31}^{79}\text{BrNO}_3\text{Si}^+$, 392.1251; found 392.1243.

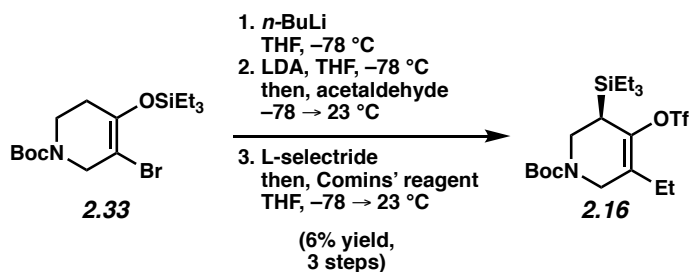
Note: 2.33 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.



Silyl Triflate 2.12. A solution of silyl enol ether **2.33** (3.00 g, 7.65 mmol, 1.00 equiv) in THF (76.5 mL, 0.10 M) was cooled to $-78\text{ }^\circ\text{C}$. Then, $n\text{-BuLi}$ (3.53 mL, 2.38 M solution in hexanes, 8.41 mmol, 1.10 equiv) was added dropwise over 40 min, then the reaction was allowed to stir at $-78\text{ }^\circ\text{C}$ for 3 h. MeI (4.78 mL, 76.5 mmol, 10.0 equiv) was added as a neat liquid dropwise over 5 min, and the reaction was allowed to stir at $-78\text{ }^\circ\text{C}$ for 20 min before warming to $23\text{ }^\circ\text{C}$ and stirring for an additional 14 h. The reaction was then quenched with water (30 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were then dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (4:1 hexanes: EtOAc) to afford the α -silyl ketone. The α -silyl ketone enantiomers were separated by chiral SFC by Lotus Separations (enantiopurity of the α -silyl ketone was determined to be $>99\%$ ee by Lotus Separations). To a flask in the glovebox was added KHMDS (110 mg, 0.551 mmol, 1.21 equiv) and the flask was then removed from the glovebox. The powder was then dissolved in THF (1.5 mL) and cooled to $-78\text{ }^\circ\text{C}$ for 20 min. To the solution was added a solution

of the α -silyl ketone (150 mg, 0.457 mmol, 1.00 equiv, >99% ee) in THF (1.5 mL) dropwise over 5 min and the subsequent mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for an additional 1 h. To the reaction mixture was added a solution of Comins' reagent (215 mg, 0.548 mmol, 1.20 equiv) in THF (1.5 mL) dropwise over 5 min. The cold bath was then removed and the reaction was allowed to warm to $23\text{ }^{\circ}\text{C}$. After stirring for 1 h, the reaction was quenched with saturated aq. NaHCO_3 (20 mL) and was extracted with ether (3 x 30 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (1:1 hexanes:benzene $\rightarrow$ 99:1 benzene:EtOAc) to afford silyl triflate (**2.12**, 121 mg, 52% yield over two steps, >99% ee) as a colorless oil. Silyl triflate **2.12**: R_f 0.51 (9:1 hexanes:EtOAc); ^1H NMR (600 MHz, CDCl_3): δ 5.61 (d, $J = 29.5$, 1H), 4.07 (t, $J = 16.8$, 1H), 4.00–3.89 (m, 1H), 3.68 (d, $J = 12.9$, 1H), 3.35 (dd, $J = 36.1, 12.3$, 1H), 1.47 (s, 9H), 1.17 (s, 3H), 0.99 (t, $J = 7.9$, 9H), 0.74–0.65 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ 155.1, 154.7, 154.5, 154.3, 118.4 (q, $J = 322.4$), 110.5, 109.9, 80.5, 50.5, 49.5, 42.7, 42.1, 31.4, 28.51, 28.48, 18.6, 7.9, 2.5; IR (film): 2960, 2882, 1702, 1417, 1246, 1214 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calc'd for $\text{C}_{18}\text{H}_{33}\text{F}_3\text{NO}_5\text{SSi}^+$, 460.17953; found 460.18305.

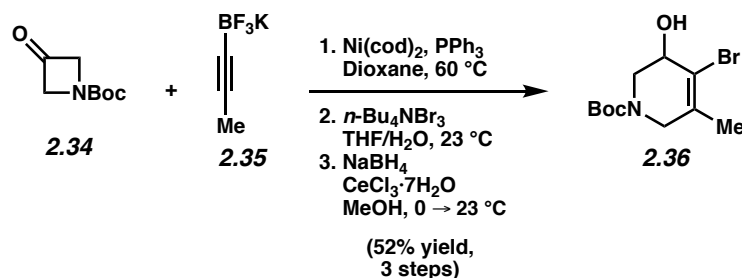
Note: 2.12 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.



Silyl Triflate 2.16. A solution of silyl enol ether **2.33** (2.80 g, 7.14 mmol, 1.00 equiv) in THF (60 mL, 0.12 M) was cooled to $-78\text{ }^{\circ}\text{C}$ and stirred for 5 min. To this solution was added *n*-butyllithium (4.9 mL, 11 mmol, 2.2 M in hexanes, 1.5 equiv) dropwise over 2 min and then the solution was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 2.5 h. The reaction was quenched by the addition of saturated aq. NaHCO_3 (20 mL) and then the reaction mixture was allowed to warm to $23\text{ }^{\circ}\text{C}$. The reaction was diluted with H_2O (50 mL) and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were then dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (20:1 hexanes:EtOAc $\rightarrow$ 5:1 hexanes:EtOAc) to afford the silyl ketone. A solution of diisopropylamine (0.34 mL, 2.4 mmol, 1.5 equiv) and in THF (7 mL) was cooled to $-78\text{ }^{\circ}\text{C}$ for 10 min. To this solution was added *n*-butyllithium (1.10 mL, 2.20 M in hexanes, 2.42 mmol, 1.52 equiv) dropwise over 5 min. The resulting LDA solution was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 30 min and then allowed to warm to $23\text{ }^{\circ}\text{C}$ and stirred for 10 min. The solution was then cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of the silyl ketone (500 mg, 1.59 mmol, 1.00 equiv) in THF (7 mL) was added dropwise over 5 min. The resulting mixture was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 1 h. After this time, acetaldehyde (892 μL , 15.9 mmol, 10.0 equiv) was added to the solution. The reaction mixture was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 15 min and then allowed to warm to $23\text{ }^{\circ}\text{C}$ and stir for 1 h. After this time, the reaction mixture was quenched with saturated aq. NaHCO_3 (20 mL) and then diluted with Et_2O (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (19:1 $\rightarrow$ 9:1 hexanes:EtOAc) to afford the enone. The enone enantiomers were separated by chiral SFC by Lotus Separations (enantiopurity of the enone was determined to be 95% ee by Lotus Separations). A solution of the enone (155 mg, 0.456

mmol, 1.00 equiv, 95% ee) in THF (2.0 mL, 0.23 M) and was cooled to $-78\text{ }^{\circ}\text{C}$. To this solution was added L-selectride (0.50 mL, 1.0 M in THF, 0.50 mmol, 1.1 equiv) dropwise over 2 min and the resulting solution was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 1 h. To the reaction mixture was then added a solution of Comins' reagent (199 mg, 0.506 mmol, 1.1 equiv) in THF (2 mL) dropwise over 5 min and then the reaction was allowed to warm to $23\text{ }^{\circ}\text{C}$ and stir for 20 h. After this time, the reaction was quenched with saturated aq. NaHCO_3 (20 mL) and diluted with Et_2O (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (1:1 benzene:hexanes $\rightarrow$ 99:1 benzene:EtOAc) to afford silyl triflate **2.16** (35.0 mg, 6% yield over three steps, 95% ee) as a colorless oil. Silyl triflate **2.16**: R_f 0.40 (9:1 hexanes:EtOAc); ^1H NMR (600 MHz, CDCl_3): δ 4.28–2.15 (m, 1H), 4.15–4.02 (m, 1H), 3.77–3.64 (m, 1H), 3.35–3.18 (m, 1H), 2.38–2.24 (m, 1H), 2.12–2.03 (m, 1H), 1.98 (bs, 1H), 1.48 (s, 9H), 1.05 (t, $J = 7.6$, 3H), 0.97–0.88 (m, 9H), 0.64 (q, $J = 8.0$, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ 154.4, 143.6, 142.9, 125.5, 125.2, 118.4 (q, $J = 318.8$), 80.6, 80.5, 45.4, 45.1, 43.3, 42.2, 28.5, 21.9, 12.2, 7.2, 2.8; IR (film): 2959, 2880, 1705, 1412, 1212, 1142 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calc'd for $\text{C}_{19}\text{H}_{35}\text{F}_3\text{NO}_5\text{SSi}^+$, 474.19518; found 474.19987.

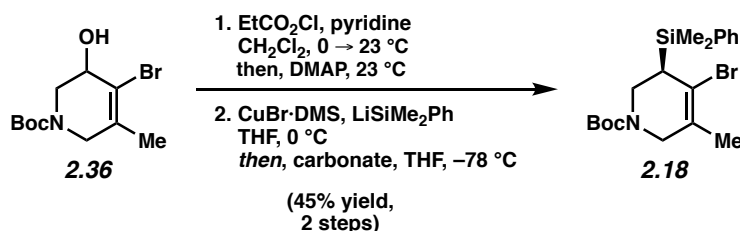
Note: 2.16 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.



Alcohol 2.36. The procedure for accessing alcohol **2.36** was adapted from the work of Aïssa and co-workers.⁵⁶ Three vials containing triphenylphosphine (162 mg, 617 μmol , 37.0 mol%), azetidinone **2.34** (493 mg, 2.88 mmol, 1.73 equiv), and alkynyl trifluoroborate **2.35** (243 mg, 1.67 mmol, 1.00 equiv), respectively, were brought into the glovebox. Inside the glovebox, Ni(cod)_2 (56.5 mg, 206 μmol , 12.3 mol%) and dioxane (1.7 mL, 0.12 M) were added to the vial containing triphenylphosphine. The mixture was allowed to stir inside the glovebox for 10 min. Next, azetidinone **2.34**, alkynyl trifluoroborate **2.35**, and dioxane (5.1 mL, 0.40 M) were added to the catalyst solution. The vial was capped with a Teflon-coated cap and brought out of the glovebox. The reaction mixture was then warmed to 60 $^\circ\text{C}$ and stirred for 18 h. After 18 h, the reaction was allowed to cool to 23 $^\circ\text{C}$, then diluted with acetonitrile (15 mL) and concentrated under reduced pressure. Next, acetone (10 mL) and Et_2O (80 mL) were added to the reaction mixture to induce precipitation. The solution was filtered through a sintered Buchner funnel, rinsing with Et_2O (30 mL). The solid was collected from the filter and dried under vacuum. The product was triturated with Et_2O (3 x 5 mL) to provide the enone trifluoroborate potassium salt. To a solution of the enone trifluoroborate potassium salt (764 mg, 2.41 mmol, 1.00 equiv) in THF (12.0 mL) and water (12.0 mL) was added tetra-*n*-butylammonium tribromide (1.16 g, 2.41 mmol, 1.00 equiv) in one portion. The mixture was stirred at 23 $^\circ\text{C}$ for 1.5 h. After 1.5 h, the reaction was diluted with Et_2O (15 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer

was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated. The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc) to provide the bromoenone. To a solution of the bromoenone (80 mg, 0.28 mmol, 1.0 equiv) in methanol (0.70 mL) was added cerium(iii)chloride heptahydrate (0.11 g, 29 μ L, 0.30 mmol, 1.1 equiv). The solution was cooled to 0 °C and sodium borohydride (13 mg, 1.2 Eq, 0.33 mmol, 1.2 equiv) was added in 3 portions over 5 min. The reaction was stirred at 0 °C for 1 h, then allowed to warm to 23 °C and stirred for an additional 1 h. The reaction was cooled to 0 °C and quenched with the addition of 1 M HCl (1 mL) added dropwise over 1 min. The mixture was transferred to a separatory funnel with Et₂O, the layers were separated, and the aqueous layer was extracted with Et₂O (3 x 6 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated. The crude residue was purified via flash chromatography (3:1 hexanes:EtOAc) to afford alcohol **2.36** (68.0 mg, 52% yield over three steps) as a white sticky foam. Alcohol **2.36**: *R_f* 0.28 (3:1 hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃): δ 4.22 (bs, 1H), 4.06 (bs, 1H), 3.84 (bs, 1H), 3.72 (d, *J* = 17.8, 1H), 3.49 (dd, *J* = 13.5, 2.9, 1H), 2.16 (bs, 1H), 1.83 (d, *J* = 0.8, 3H), 1.47 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 154.8, 134.8, 120.0, 80.7, 69.9, 48.5, 47.8, 28.4, 20.3; IR (film): 3406, 2920, 2850, 1681, 1423, 1244, 1146 cm⁻¹; HRMS-APCI (*m/z*) [*M* + H]⁺ calc'd for C₁₁H₁₉⁷⁹BrNO₃, 292.05428; found 292.05255.

Note: 2.36 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ¹H and ¹³C NMR spectra.

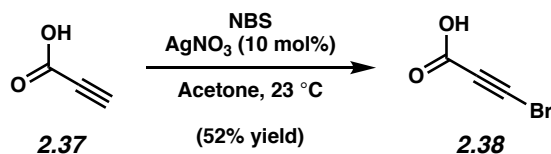


Silyl bromide 2.18. The procedure for accessing silyl bromide **2.18** was derived from a method developed by West and coworkers.^{20,22} A solution of alcohol **2.36** (414 mg, 1.42 mmol, 1.00 equiv) in CH₂Cl₂ (14.2 mL, 0.100 M) was cooled to 0 °C. To the solution was added pyridine (172 µL, 2.13 mmol, 1.50 equiv) dropwise over 1 minute. Next, ethyl chloroformate (163 µL, 1.70 mmol, 1.20 equiv) was added to the solution dropwise over 1 minute. The reaction was stirred at 0 °C for 5 min and then allowed to warm to 23 °C and stirred for 1.25 h. DMAP (52.0 mg, 426 µmol, 30.0 mol%) was added to the reaction in one portion and the reaction mixture was stirred for an additional 1 h at 23 °C. The reaction mixture was then cooled to 0 °C and quenched by the addition of 1 M HCl (5 mL) and water (10 mL). The reaction mixture was warmed to 23 °C, the layers were separated, and the aqueous layer was extracted with Et₂O (3 x 10 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (9:1 → 5:1 hexanes:EtOAc) to afford the carbonate. A solution of bromocopper methylsulfanylmethane (50.2 mg, 244 µmol, 1.30 equiv) in THF (1.6 mL) was cooled to 0 °C. To the solution was added (dimethyl(phenyl)silyl)lithium²⁰ (2.12 mL, 0.23 M, 488 µmol, 2.60 equiv) dropwise over 3 min and the mixture was stirred at 0 °C for 40 min. The reaction mixture was cooled to –78 °C and to the solution was added the carbonate (68.4 mg, 188 µmol, 1.00 equiv) in THF (0.45 mL) dropwise over 2 minutes. The reaction mixture was allowed to stir at –78 °C for 3 h. After this time, the reaction was diluted with Et₂O (2 mL) and quenched with water (2 mL) at –78 °C, then allowed to warm to 23 °C. The reaction mixture was then transferred to a separatory funnel containing Et₂O (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with Et₂O (2 x 5 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (50:1 → 9:1 hexanes:EtOAc) to afford silyl bromide **2.18** (42.0

mg, 45% yield over two steps) as a colorless oil. The silyl bromide enantiomers were separated by chiral SFC by Lotus Separations (enantiopurity of the silyl bromide was determined to be >99% ee by Lotus Separations). Silyl bromide **2.18**: R_f 0.61 (5:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 7.49 (d, $J = 6.6$, 2H), 7.41–7.28 (m, 3H), 4.25–3.88 (m, 1H), 3.64–3.26 (m, 2H), 3.26–3.04 (m, 1H), 2.24 (s, 1H), 1.70 (d, $J = 26.6$, 3H), 1.44 (s, 9H), 0.54–0.33 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ 154.2, 137.4, 133.8, 129.1, 127.8, 127.6, 127.5, 79.9, 48.8, 48.6, 44.2, 43.1, 38.0, 28.5, 28.4, 20.4, –2.4, –2.7, –3.1, –3.5; IR (film): 2979, 1698, 1407, 1256, 1148, 818 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calc'd for $\text{C}_{19}\text{H}_{29}^{79}\text{BrNO}_2\text{Si}^+$, 410.11454; found 410.11383.

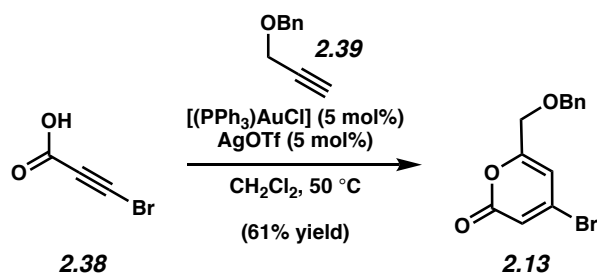
*Note: **2.18** was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.*

2.5.2.2. Synthesis of Pyrone 2.13



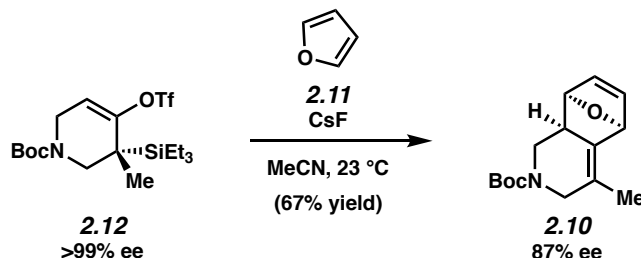
3-Bromopropiolic acid (2.38). To a solution of propiolic acid (**2.37**, 0.890 mL, 14.0 mmol, 1.00 equiv) in acetone (27 mL, 0.50 M) was added silver nitrate (0.24 g, 1.4 mmol, 10 mol%). The solution was allowed to stir for 5 min before NBS (3.1 g, 17 mmol, 1.2 equiv) was added in one portion. The reaction mixture was allowed to stir at 23 °C for 20 h. After this time, the reaction mixture was filtered through a pad of celite (3 x 5 cm) rinsing with acetone (50 mL) and the filtrate was concentrated under reduced pressure. The crude residue was purified via flash chromatography (7:3 hexanes:EtOAc) to afford 3-bromopropiolic acid (**2.38**, 1.11 g, 52% yield) as a white solid. 3-Bromopropiolic acid (**2.38**): R_f 0.17 (98:2 EtOAc:AcOH); ^1H NMR (400 MHz,

CDCl₃): δ 10.46 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 156.8, 72.1, 56.2; spectral data match those previously reported.³⁴



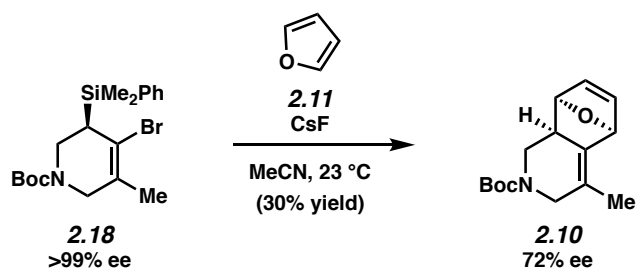
Pyrone 2.13. The preparation of pyrone **2.13** was accomplished using a method developed by Schreiber and coworkers.³⁴ To a solution of 3-bromopropiolic acid (**2.38**, 991 mg, 6.65 mmol, 1.00 equiv), benzyl propargyl alcohol⁵⁷ (**2.39**, 4.86 g, 33.3 mmol, 5.00 equiv), and (PPh₃)AuCl (165 mg, 0.333 mmol, 5.00 mol%) in CH₂Cl₂ (34 mL, 0.20 M) was added AgOTf (85.5 mg, 0.333 mmol, 5.00 mol%). Then, the flask was equipped with a reflux condenser and the reaction mixture was heated to 50 °C and allowed to stir for 14.5 h. After 14.5 h, the reaction was allowed to cool to 23 °C, filtered over celite (1 cm) with CH₂Cl₂ (~20 mL) to remove the black precipitate, and concentrated under reduced pressure to afford a crude oil. The crude oil was purified by flash chromatography (19:1 → 9:1 hexanes:EtOAc) to obtain pyrone **2.13** (1.21 g, 61% yield) as an orange oil. Pyrone **2.13**: *R_f* 0.31 (9:1 hexanes:EtOAc); ¹H NMR (600 MHz, CDCl₃): δ 7.39–7.31 (m, 5H), 6.50–6.49 (m, 2H), 4.62 (s, 2H), 4.28 (t, *J* = 1.0, 2H); ¹³C NMR (150 MHz, CDCl₃): δ 161.4, 159.7, 141.1, 136.7, 128.6, 128.3, 127.9, 116.0, 107.4, 73.5, 67.2; IR (film): 3090, 3031, 2863, 1732, 1622, 1549, 1107 cm⁻¹; HRMS-APCI (*m/z*) [*M* + *H*]⁺ calc'd for C₁₃H₁₂⁷⁹BrO₃⁺, 294.9964; found 294.9964.

2.5.2.3. Diels–Alder Cycloadditions on Model Systems

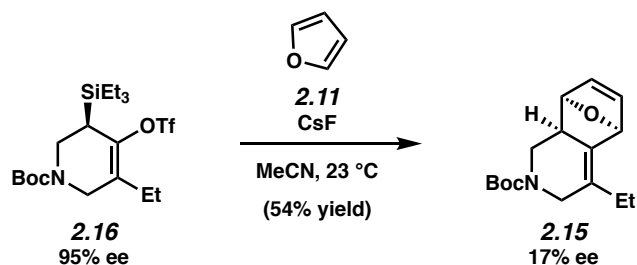


Methyl-Substituted Furan Cycloadduct 2.10. From silyl triflate **2.12**: To a solution of silyl triflate **2.12** (20.9 mg, 45.5 μmol , 1.00 equiv) in acetonitrile (0.45 mL, 0.10 M) was added furan (**2.11**, 16.5 μL , 227 μmol , 5.00 equiv). Then, cesium fluoride (34.5 mg, 227 μmol , 5.00 equiv) was added to the solution, the vial was capped with a Teflon-lined screw cap, and the reaction was allowed to stir for 16.5 h at 23 °C. After 16.5 h, the reaction was filtered over a 2.5 cm plug of silica gel (monster pipette) with EtOAc (10 mL) and concentrated to a crude oil. The crude residue was purified via preparative TLC (4:1 hexanes:EtOAc) to obtain cycloadduct **2.10** (8.0 mg, 67% yield, 87% ee) as a colorless oil. Cycloadduct **2.10**: R_f 0.26 (4:1 hexanes:EtOAc); ^1H NMR (500 MHz, C_6D_6): δ 5.97–5.85 (m, 1H), 5.56–5.45 (m, 1H), 4.99 (s, 1H), 4.66–4.26 (m, 2H), 4.22–3.98 (m, 1H), 3.29–3.10 (m, 1H), 2.47–2.37 (m, 1H), 1.50 (s, 9H), 1.27–1.17 (m, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 154.9, 154.6, 135.4, 134.8, 133.2, 132.3, 129.7, 129.3, 128.6, 127.5, 121.2, 120.2, 80.2, 80.1, 79.2, 78.6, 47.7, 47.5, 46.0, 45.0, 40.2, 40.1, 28.6, 27.93, 27.88, 16.5; IR (film): 2976, 2927, 2858, 1691, 1395, 1159 cm^{-1} ; HRMS-APCI (m/z) [$\text{M} + \text{H}$] $^+$ calc'd for $\text{C}_{15}\text{H}_{22}\text{NO}_3^+$, 264.15942; found 264.16156. For representative SFC chromatogram see Section 2.6.

*Note: **2.10** was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.*



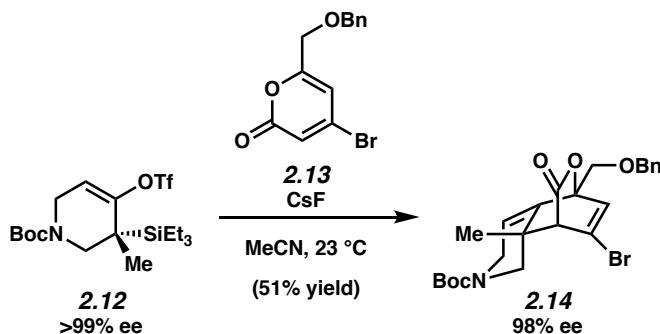
Methyl-Substituted Furan Cycloadduct 2.10. From silyl bromide **2.18**: To a solution of silyl bromide **2.18** (3.2 mg, 7.8 μmol , 1.0 equiv) in acetonitrile (0.20 mL, 0.10 M) was added furan (**2.11**, 23 μL , 39 μmol , 5.0 equiv). Then, cesium fluoride (5.9 mg, 39 μmol , 5.0 equiv) was added to the solution, the vial was capped with a Teflon-lined screw cap, and the reaction was allowed to stir for 16 h at 23 °C. After 16 h, the reaction was filtered over a 2.5 cm plug of silica gel (monster pipette) with EtOAc (10 mL) and concentrated to afford a crude oil. The crude residue was purified via preparative TLC (4:1 hexanes:EtOAc) to obtain cycloadduct **2.10** (0.7 mg, 30% yield, 72% ee) as a colorless oil. Spectral data matched those provided above. For representative SFC chromatogram see Section 2.6.



Ethyl-Substituted Furan Cycloadduct 2.15. To a solution of silyl triflate **2.16** (9.2 mg, 19 μmol , 1.0 equiv) in acetonitrile (0.19 mL, 0.10 M) was added furan (**2.11**, 7.1 μL , 97 μmol , 5.0 equiv). Then, cesium fluoride (15 mg, 97 μmol , 5.0 equiv) was added to the solution, the vial was capped with a Teflon-lined screw cap, and the reaction was allowed to stir for 16 h. After 16 h, the reaction was filtered over a 2.5 cm plug of silica gel (monster pipette) with EtOAc (10 mL) and

concentrated to a crude oil. The crude residue was purified via preparative TLC (4:1 hexanes:EtOAc) to obtain cycloadduct **2.15** (2.9 mg, 54% yield, 17% ee). Cycloadduct **2.15**: R_f 0.30 (4:1 hexanes:EtOAc); ^1H NMR (500 MHz, C_6D_6): δ 5.97–5.86 (m, 1H), 5.57–5.46 (m, 1H), 5.04 (s, 1H), 5.63–4.31 (m, 2H), 4.21–4.05 (m, 1H), 3.47–3.28 (m, 1H), 2.47–2.38 (m, 1H), 1.75–1.58 (m, 2H), 1.51 (s, 9H), 0.77–0.66 (m, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 155.1, 154.7, 135.7, 135.2, 132.8, 131.9, 129.7, 129.3, 128.9, 128.6, 127.5, 127.3, 126.4, 80.04, 79.96, 79.24, 79.18, 78.6, 46.0, 45.7, 45.0, 40.0, 39.9, 30.22, 30.15, 28.62, 28.57, 28.4, 28.0, 27.9, 25.1, 13.7, 13.6; IR (film): 2973, 2932, 1689, 1400, 1160 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calc'd for $\text{C}_{16}\text{H}_{24}\text{NO}_3^+$, 278.17507; found 278.17769. For representative SFC chromatogram see Section 2.6.

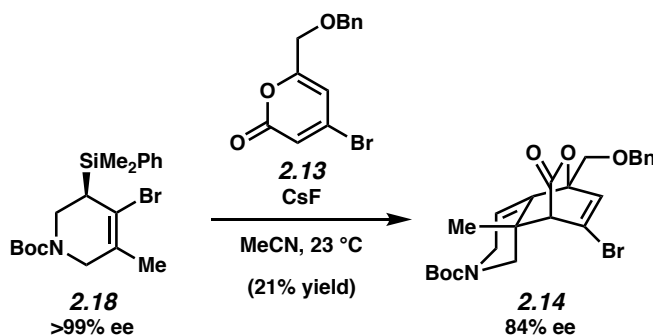
Note: 2.15 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.



Methyl-Substituted Pyrone Cycloadduct 2.14. From silyl triflate **2.12**: To a solution of silyl triflate **2.12** (14.4 mg, 31.3 μmol , 1.00 equiv) and pyrone **2.13** (46.0 mg, 156 μmol , 5.00 equiv) in acetonitrile (0.31 mL, 0.10 M) was added cesium fluoride (23.8 mg, 157 μmol , 5.00 equiv). The vial was capped with a Teflon-lined screw cap and the reaction was allowed to stir for 16.5 h at 23 °C. After 16.5 h, the reaction was filtered over a 3 cm plug of silica gel (monster pipette) with EtOAc (10 mL) and concentrated to afford a crude oil. The crude residue was purified via

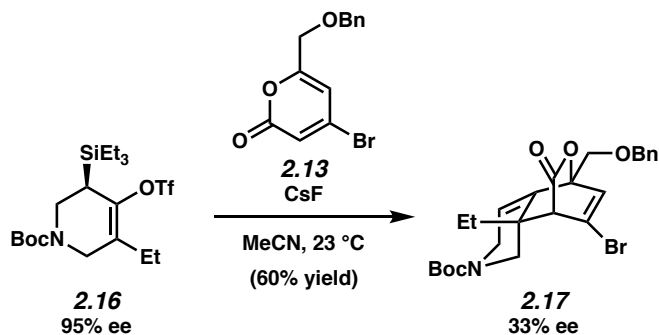
preparative TLC (4:1 hexanes:EtOAc) to obtain cycloadduct **2.14** (7.8 mg, 51% yield, 98% ee). Cycloadduct **2.14**: R_f 0.27 (4:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 7.40–7.33 (m, 5H), 6.54 (dd, $J = 21.4, 2.4$, 1H), 5.77–5.67 (m, 1H), 4.67 (s, 2H), 4.30–4.11 (m, 1H), 4.11–4.02 (m, 2H), 3.95–3.87 (m, 2H), 3.72–3.60 (m, 1H), 3.55–3.50 (m, 1H), 2.46 (dd, $J = 33.5, 11.6$, 1H), 1.78–1.74 (m, 1H), 1.50–1.41 (m, 13H), 1.16–1.11 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 169.33, 169.30, 155.5, 155.2, 137.7, 137.3, 137.23, 137.21, 133.1, 132.7, 128.8, 128.6, 128.31, 128.29, 128.14, 128.11, 128.0, 119.3, 118.9, 117.9, 117.5, 85.2, 85.1, 80.7, 80.5, 74.2, 67.9, 67.8, 60.5, 60.4, 50.0, 48.9, 43.0, 42.5, 37.5, 37.4, 36.0, 35.6, 29.9, 28.6, 28.5, 28.4, 28.3, 22.8, 22.1, 22.0, 21.9, 14.3; IR (film): 2976, 2929, 1763, 1697, 1394, 1145 cm^{-1} ; HRMS-APCI (m/z) [$M + \text{H}$] $^+$ calc'd for $\text{C}_{24}\text{H}_{29}^{79}\text{BrNO}_5^+$, 490.12236; found 490.12632. For representative SFC chromatogram see Section 2.6.

Note: 2.14 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.



Methyl-Substituted Pyrone Cycloadduct 2.14. From silyl bromide **2.18**: To a solution of silyl bromide **2.18** (4.4 mg, 11 μmol , 1.0 equiv) and pyrone **2.13** (16 mg, 54 μmol , 5.0 equiv) in acetonitrile (0.20 mL, 0.10 M) was added cesium fluoride (8.1 mg, 54 μmol , 5.0 equiv). The vial was capped with a Teflon-lined screw cap and the reaction was allowed to stir for 15 h at 23 °C.

After 15 h, the reaction was filtered over a 2.5 cm plug of silica gel (monster pipette) with EtOAc (10 mL) and concentrated to afford a crude oil. The crude residue was purified via preparative TLC (4:1 hexanes:EtOAc) to obtain cycloadduct **2.14** (1.1 mg, 21% yield, 84% ee). Spectral data matched those provided above. For representative SFC chromatogram see Section 2.6.

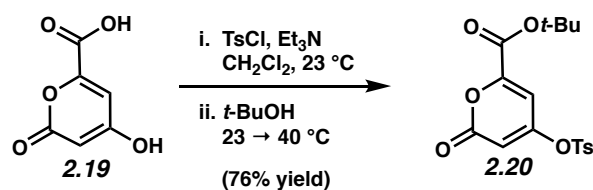


Ethyl-Substituted Pyrone Cycloadduct 2.17. To a solution of silyl triflate **2.16** (0.80 mg, 1.7 μ mol, 1.0 equiv) and pyrone **2.13** (2.5 mg, 8.4 μ mol, 5.0 equiv) in acetonitrile (0.20 mL, 0.020 M) was added cesium fluoride (2.6 mg, 17 μ mol, 10 equiv). The vial was capped with a Teflon-lined screw cap and the reaction was allowed to stir for 18 h at 23 °C. After 18 h the reaction was filtered over a 2.5 cm plug of silica gel (monster pipette) with EtOAc (10 mL) and concentrated to afford a crude oil. The crude residue was purified via preparative TLC (4:1 hexanes:EtOAc) to obtain cycloadduct **2.17** (0.5 mg, 60% yield, 33% ee). Cycloadduct **2.17**: R_f 0.28 (4:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 7.41–7.33 (m, 5H), 6.55 (dd, J = 22.6, 2.3, 1H), 5.73–5.64 (m, 1H), 4.67 (s, 2H), 4.39–4.08 (m, 2H), 4.07–4.01 (m, 1H), 3.96–3.90 (m, 1H), 3.72–3.54 (m, 2H), 2.38–2.26 (m, 1H), 1.50–1.45 (m, 11H), 1.25 (s, 4H), 0.97 (t, J = 7.6, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 169.21, 169.17, 155.2, 155.0, 138.8, 138.3, 137.3, 137.2, 133.6, 133.1, 128.8, 128.29, 128.27, 128.13, 128.10, 119.2, 118.8, 117.6, 117.3, 85.2, 85.1, 80.7, 80.4, 74.2, 67.9, 67.8, 57.0, 56.9, 45.1, 44.3, 43.0, 42.5, 41.04, 40.95, 33.2, 32.1, 29.9, 29.7, 29.6, 29.5, 29.4, 29.2, 28.6, 28.5, 28.2, 27.3,

27.1, 24.9, 22.8, 14.3, 8.0, 7.9; IR (film): 2974, 2926, 1763, 1697, 1401, 1139 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calc'd for $\text{C}_{25}\text{H}_{31}^{79}\text{BrNO}_5^+$, 504.13801; found 504.14232. For representative SFC chromatogram see Section 2.6.

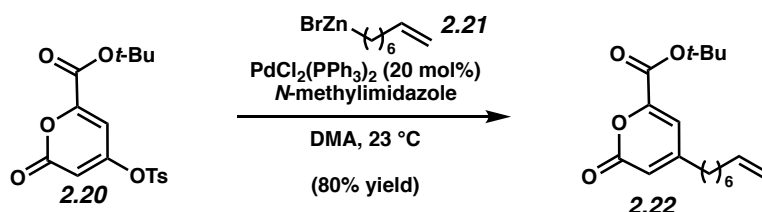
Note: 2.17 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.

2.5.2.4. Synthesis of Pyrone 2.22 and Silyl Bromide 2.27



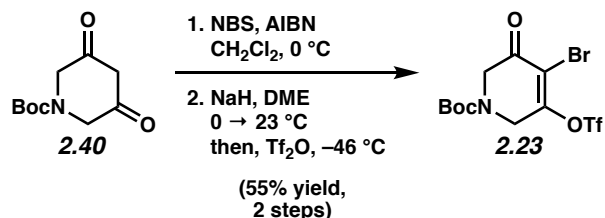
Vinyl tosylate 2.20. To a solution of pyrone **2.19** (544 mg, 3.48 mmol, 1.00 equiv) in CH_2Cl_2 (23 mL, 0.15 M) was added triethylamine (1.90 mL, 13.6 mmol, 3.91 equiv) dropwise over 5 min. The reaction mixture was allowed to stir at $23\text{ }^\circ\text{C}$ until homogenous (~ 5 min) and then *p*-toluenesulfonyl chloride (1.46 g, 2.20 equiv, 7.67 mmol) was added as a solution in CH_2Cl_2 (18 mL) via cannula transfer over 5 min. The reaction mixture was allowed to stir at $23\text{ }^\circ\text{C}$ for 21.5 h. After this time, anhydrous *tert*-butanol (2.56 g, 3.30 mL, 9.91 equiv, 34.5 mmol) was added in one portion and the reaction mixture was allowed to stir at $23\text{ }^\circ\text{C}$ for 30 min. The flask was then fitted with a reflux condenser and heated to $40\text{ }^\circ\text{C}$ for 4 h. After this time, the reaction mixture was quenched with saturated aq. NaHCO_3 (50 mL) and diluted with CH_2Cl_2 (50 mL). The aqueous layer was separated from the organics and washed with CH_2Cl_2 (2 x 50 mL). The combined organic fractions were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (4:1 $\rightarrow$ 7:3 hexanes:EtOAc) to afford vinyl tosylate **2.20** (971 mg, 76% yield) as a white solid. Vinyl tosylate **2.20**: R_f 0.37 (4:1 Hexanes:EtOAc); ^1H

NMR (400 MHz, CDCl₃): δ 7.83 (d, J = 8.4, 2H), 7.41 (d, J = 8.2, 2H), 6.88 (d, J = 2.2, 1H), 6.18 (d, J = 2.2, 1H), 2.48 (s, 3H), 1.55 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 160.51, 160.46, 157.3, 151.5, 147.1, 131.3, 130.5, 128.5, 106.9, 106.7, 84.8, 27.9, 21.9; IR (film): 3107, 2982, 1743, 1334, 1175 cm⁻¹; HRMS-APCI (m/z) [$M + H$]⁺ calc'd for C₁₇H₁₉O₇S⁺, 367.08460; found 367.08067.



Pyrone 2.22. To a vial containing vinyl tosylate **2.20** (503 mg, 1.00 equiv, 1.37 mmol) was added bis(triphenylphosphine)palladium(II) chloride (192 mg, 20.0 mol%, 274 μ mol), 1-methylimidazole (0.34 g, 0.33 mL, 3.0 equiv, 4.1 mmol), and a solution of alkylzinc bromide⁵⁸ **2.21** in DMA (1.1 g, 5.8 mL, 0.71 M, 3.0 equiv, 4.1 mmol). The reaction mixture was stirred at 23 °C for 21.5 h. After this time, the reaction was quenched with saturated aq. NH₄Cl (30 mL) and diluted with Et₂O (30 mL). The layers were separated and the aqueous layer was extracted with Et₂O (2 x 30 mL). The combined organic fractions were washed with water (3 x 30 mL) and brine (10 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (9:1 pentane:EtOAc) to afford pyrone **2.22** (336 mg, 80% yield) as a pale yellow oil. Pyrone **2.22**: R_f 0.55 (4:1 Hexanes:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 6.89 (d, J = 1.6, 1H), 6.26 (d, J = 1.5, 1H) 5.80 (ddt, J = 17.1, 10.2, 6.7, 1H), 5.03–4.90 (m, 2H), 2.45 (t, J = 7.7, 2H), 2.04 (q, J = 7.1, 2H), 1.57 (s, 9H), 1.51–1.40 (m, 2H), 1.39–1.30 (6H); ¹³C NMR (125 MHz, CDCl₃): δ 161.0, 158.67, 158.65, 149.7, 116.6, 114.5, 111.5, 84.0,

35.2, 33.7, 28.9, 28.8, 28.7, 28.1, 28.0; IR (film): 3082, 2981, 2929, 1732, 1117 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calc'd for $\text{C}_{18}\text{H}_{27}\text{O}_4^+$, 307.19039; found 307.18763.

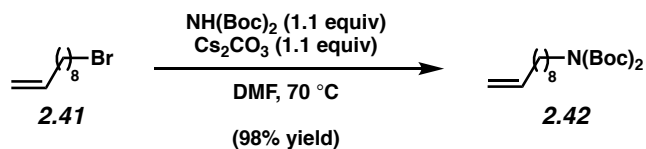


Bromotriflate 2.23. This compound was obtained from commercial sources, but could also be prepared in two steps as follows. A solution of diketone **2.40** (2.00 g, 9.38 mmol, 1.00 equiv) in CH_2Cl_2 (40 mL, 0.23 M) was cooled to 0 °C. To the solution was added NBS (1.67 g, 9.38 mmol, 1.00 equiv) in one portion and AIBN (108 mg, 657 μmol , 7.00 mol%) in one portion. The reaction mixture was allowed to stir at 0 °C for 3.5 h. Then, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and water (100 mL) and allowed to warm to 23 °C. The solution was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with water (3 x 50 mL) and then dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (1:1 hexanes:EtOAc) to afford the bromide (2.19 g 7.49 mmol, 79.9% yield).

A solution of sodium hydride (0.58 g, 60% Wt, 14 mmol, 1.2 equiv) in DME (70 mL) was cooled to 0 °C. To this solution was added the above bromide (3.40 g, 11.6 mmol, 1.00 equiv) as a solid in portions over 15 min. The solution was allowed to stir at 0 °C for 15 min and then allowed to warm to 23 °C and stir for 1 h. After this time, the reaction mixture was cooled to -46 °C and trifluoromethanesulfonic anhydride (1.87 mL, 11.1 mmol, 0.950 equiv) was added dropwise over 15 min. The reaction mixture was allowed to stir at -46 °C for 1 h. After this time, the reaction

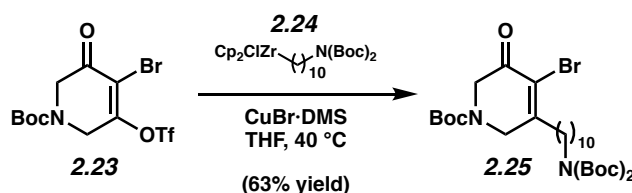
mixture was quenched with Et₂O (5 mL) and water (5 mL) and allowed to warm to 23 °C. The reaction mixture was transferred to a separatory funnel with Et₂O (100 mL) and water (100 mL). The layers were separated and the aqueous layer was extracted with Et₂O (2 x 50 mL). The combined organic fractions were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc) to afford bromo triflate **2.23** (3.38 g, 7.97 mmol, 69% yield; 55% yield over two steps) as a pale yellow solid. Bromo triflate **2.23**: R_f 0.55 (4:1 hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃): δ 4.56 (s, 2H), 4.33 (s, 2H), 1.49 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 185.9, 153.4, 118.4 (q, *J* = 322.2), 116.8, 83.2, 52.0, 45.9, 28.5; IR (film): 2981, 1704, 1432, 1214, 1131 cm⁻¹; HRMS-APCI (*m/z*) [M + H]⁺ calc'd for C₁₁H₁₃⁷⁹BrF₃NO₆SK⁺, 461.92306; found 461.92398.

Note: 2.23 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ¹H and ¹³C NMR spectra.



Alkene 2.42. To a solution of 10-bromodec-1-ene (**2.41**, 1.99 g, 9.11 mmol, 1.00 equiv) in DMF (45 mL, 0.20 M) was added di-*tert*-butyl iminodicarbonate (2.18 g, 10.0 mmol, 1.10 equiv) and cesium carbonate (3.26 g, 10.0 mmol, 1.10 equiv). The flask was equipped with a reflux condenser and the reaction mixture was heated to 70 °C for 2.5 h. After this time, the mixture was allowed to cool to room temperature and then was transferred to a separatory funnel with water (50 mL) and Et₂O (50 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 30 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (19:1 hexanes:EtOAc)

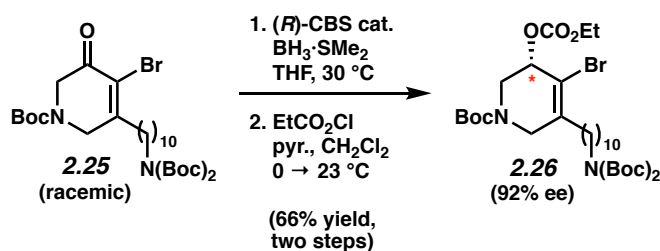
to afford alkene **2.42** (3.18 g, 98% yield) as a colorless oil. Alkene **2.42**: R_f 0.60 (9:1 hexanes:EtOAc); ^1H NMR (600 MHz, CDCl_3): δ 5.80 (ddt, $J = 17.2, 10.2, 6.7$, 1H), 4.98 (ddt, $J = 17.2, 1.9, 1.7$, 1H), 4.95–4.89 (m, 1H), 3.59–3.50 (m, 2H), 2.08–2.00 (m, 2H), 1.58–1.52 (m, 2H), 1.50 (s, 18H), 1.40–1.33 (m, 2H), 1.31–1.24 (m, 8H); ^{13}C NMR (125 MHz, CDCl_3): δ 152.9, 139.3, 114.3, 82.1, 46.6, 33.9, 29.6, 29.4, 29.2, 29.0, 28.2, 26.9; ^{19}F NMR (376 MHz, CDCl_3): δ -73.3; IR (film): 2979, 2927, 2856, 1697, 1367, 1126 cm^{-1} ; HRMS-APCI (m/z) [$\text{M} + \text{H}$] $^+$ calc'd for $\text{C}_{20}\text{H}_{38}\text{NO}_4^+$, 356.27954; found 356.28069.



Bromoenone 2.25. The synthesis of bromoenone **2.25** was inspired by the work of West and coworkers.²² To first prepare alkylzirconium reagent **2.24**, a flask was brought into the glovebox where zirconocene hydrochloride (Schwartz's reagent) (678 mg, 2.63 mmol, 3.00 equiv) was added. The flask was removed from the glovebox and a solution of alkene **2.42** (941 mg, 2.65 mmol, 3.00 equiv) in THF (3.8 mL) was added via rapid cannula transfer. The flask was equipped with a reflux condenser and the suspension was heated to $40\text{ }^\circ\text{C}$ for 30 min during which time the solution became homogenous. After this time, the reaction mixture was allowed to cool to $23\text{ }^\circ\text{C}$ giving **2.24**. To a separate solution of vinyl tosylate **2.23** (374 mg, 883 μmol , 1.00 equiv) in THF (1.9 mL) was added the solution of freshly prepared alkylzirconium reagent **2.24** rapidly via cannula transfer. After 3 min, a solution of $\text{CuBr}\cdot\text{DMS}$ (541 mg, 2.63 mmol, 3.00 equiv) in THF (4 mL) was added rapidly via syringe. The resulting reaction mixture was allowed to stir at $40\text{ }^\circ\text{C}$ for 3 min, after which the reaction was immediately removed from heat and diluted with Et_2O (3

mL) and water (5 mL). The mixture was transferred to a separatory funnel, washing the reaction vial with additional Et₂O (15 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with Et₂O (2 x 20 mL). The combined organic fractions were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (9:1 → 85:15 hexanes:EtOAc) to afford bromoenone **2.25** (349 mg, 63% yield) as a pale yellow oil. Bromoenone **2.25**: *R_f* 0.37 (4:1 hexanes:EtOAc); ¹H NMR (600 MHz, CDCl₃): δ 4.35–4.20 (m, 4H), 3.59–3.50 (m, 2H), 2.52–2.41 (m, 2H), 1.63–1.52 (m, 5H), 1.52–1.44 (m, 27H), 1.42–1.35 (m, 2H), 1.35–1.22 (m, 11H); ¹³C NMR (125 MHz, CDCl₃): δ 186.0, 161.7, 153.7, 152.8, 129.0, 128.2, 125.3, 120.3, 82.0, 81.5, 51.8, 47.6, 46.5, 36.4, 29.6, 29.5, 29.4, 29.29, 29.25, 29.0, 28.3, 28.1, 26.9, 26.8; IR (film): 2978, 2929, 1694, 1367, 1127 cm⁻¹; HRMS-APCI (*m/z*) [*M* + H]⁺ calc'd for C₃₀H₅₁⁷⁹BrN₂O₇Na⁺, 653.2777; found 653.2845.

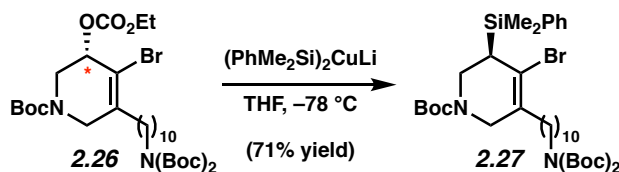
Note: 2.25 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ¹H and ¹³C NMR spectra.



Carbonate 2.26. The synthesis of carbonate **2.26** was inspired by the work of West and coworkers.²² To a vial in the glovebox was added (*R*)-CBS catalyst (24.7 mg, 89.3 μmol, 20.0 mol%). The vial was brought out of the glovebox and the CBS catalyst was dissolved in THF (3 mL). To a solution of bromoenone **2.25** (300 mg, 446 μmol, 1.00 equiv) in THF (3 mL) was added the CBS catalyst solution via rapid cannula transfer. The reaction mixture was heated to 30 °C (oil bath) and to this mixture was added borane-methyl sulfide complex (335 μL, 2.00 M, 670 μmol,

1.50 equiv) dropwise over 5 min at 30 °C. The mixture was allowed to stir at 30 °C for 0.5 h. After this time, the reaction was quenched with methanol (1 mL) and then the mixture was transferred to a separatory funnel with Et₂O (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with Et₂O (2 x 20 mL). The combined organic layers were then dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc) to afford the enantioenriched alcohol (92% ee) as a pale yellow oil. Note ee's ranged from 90–92% for this step. A solution of the alcohol (181 mg, 271 μmol, 1.00 equiv) in CH₂Cl₂ (2.5 mL, 0.11 M) was cooled to 0 °C. To the solution was added pyridine (32.9 μL, 407 μmol, 1.50 equiv) dropwise over 1 min and ethyl carbonochloridate (31.0 μL, 326 μmol, 1.20 equiv) dropwise over 1 minute. The reaction was stirred for at 0 °C for 5 min and then allowed to warm to 23 °C and stirred for 1.5 h. After this time, the reaction mixture was diluted with Et₂O (20 mL) quenched with saturated aq. NaHCO₃ (20 mL). The layers were separated and the aqueous layer was extracted with Et₂O (2 x 20 mL). The combined organic flayers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (85:15 hexanes:EtOAc) to afford carbonate **2.26** (157 mg, 66% yield over two steps, 92% ee) as a colorless oil. Carbonate **2.26**: R_f 0.47 (4:1 hexanes:EtOAc); ¹H NMR (600 MHz, CDCl₃): δ 5.28–5.07 (m, 1H), 4.44 (app. d, *J* = 17.6, 1H), 4.30 (dd, *J* = 14.5, 2.1, 1H), 4.24 (q, *J* = 7.1, 2H), 3.69–3.50 (m, 3H), 3.25 (dd, *J* = 14.5, 2.8, 1H), 2.26–2.11 (m, 2H), 1.58–1.52 (m, 2H), 1.50 (s, 18H), 1.48–1.41 (m, 9H), 1.36–1.24 (m, 17H); ¹³C NMR (125 MHz, CDCl₃): δ 154.7, 154.4, 152.9, 143.2, 128.5, 112.8, 82.1, 80.5, 75.8, 68.1, 66.0, 64.5, 47.9, 47.1, 46.7, 46.3, 45.3, 34.5, 30.5, 29.7, 29.6, 29.4, 29.2, 28.4, 28.2, 27.2, 27.0, 25.8, 15.4, 14.4; IR (film): 2978, 2929, 1744, 1698, 1256 cm⁻¹; HRMS-APCI (*m/z*) [*M* + *H*]⁺ calc'd for C₃₃H₅₈⁷⁹BrN₂O₉⁺, 705.33202; found 705.33299.

Note: **2.26** was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.



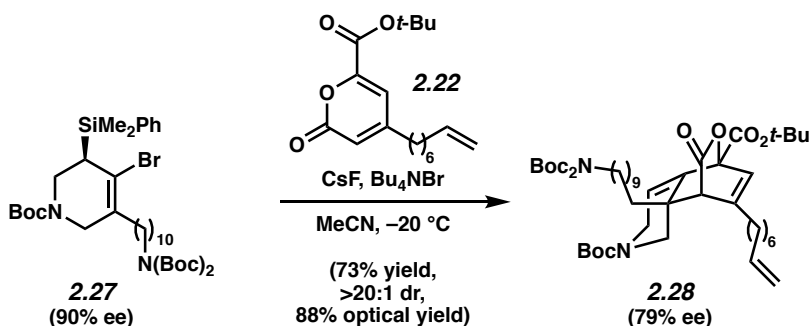
Silyl Bromide 2.27. The synthesis of silyl bromide **2.27** was inspired by the work of West and coworkers.^{20,22} A solution of bromocopper methylsulfanylmethane (7.5 mg, 36 μmol , 1.4 equiv) in THF (0.5 mL) was cooled to 0 $^\circ\text{C}$. Then, (dimethyl(phenyl)silyl)lithium²⁰ (0.27 mL, 0.26 M, 70 μmol , 2.6 equiv) was added dropwise over 3 min and then the mixture was stirred at 0 $^\circ\text{C}$ for 30 min. The reaction mixture was cooled to $-78\text{ }^\circ\text{C}$ and a solution of carbonate **2.26** (20.0 mg, 26.9 μmol , 1.00 equiv) in THF (0.3 mL) was added dropwise over 2 minutes. The reaction was allowed to stir at $-78\text{ }^\circ\text{C}$ for 1 h. After this time, the reaction was diluted with Et_2O (1 mL), quenched with water (1 mL), and allowed to warm to 23 $^\circ\text{C}$. The reaction mixture was then transferred to a separatory funnel containing Et_2O (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified via preparative TLC (4:1 hexanes: EtOAc) to afford silyl bromide **2.27** (14.4 mg, 19.2 μmol , 71% yield) as a colorless oil. Silyl bromide **2.27**: R_f 0.69 (4:1 hexanes: EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 7.53–7.47 (m, 2H), 7.36–7.29 (m, 3H), 4.20–3.93 (m, 1H), 3.76–3.60 (m, 1H), 3.58–3.43 (m, 3H), 3.15 (bs, 1H), 2.27–2.04 (m, 2H), 1.97 (bs, 1H), 1.58–1.53 (m, 2H), 1.50 (s, 16H), 1.44 (bs, 9H), 1.34–1.18 (m, 14H), 0.49–0.36 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ 154.3, 152.7, 137.3, 134.2, 133.9, 133.6, 130.6, 130.1, 129.3, 129.1, 128.3, 127.9, 127.8, 127.6, 118.5, 117.6, 82.0, 80.0, 47.7, 47.5, 46.5, 44.1, 43.2, 37.9, 34.7, 29.6, 29.5, 29.4, 29.3, 29.1, 28.4, 28.1,

27.6, 26.9, -2.4, -2.5, -3.1, -3.2, -3.3; IR (film): 2979, 2929, 1748, 1698, 1366, 1131 cm^{-1} ; HRMS-APCI (m/z) [$M + H$] $^{+}$ calc'd for $\text{C}_{38}\text{H}_{64}^{79}\text{BrN}_2\text{O}_6\text{Si}^{+}$, 751.3717; found 751.3689.

Note: 2.27 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra. For representative SFC chromatogram see Section 2.6.

Alternative Large-Scale Procedure. A suspension of copper (I) cyanide (47.4 mg, 0.529 mmol, 1.31 equiv) and triphenylphosphine (277 mg, 1.06 mmol, 2.61 equiv) in Et_2O (7.0 mL) was cooled to 0 $^{\circ}\text{C}$. Then, (dimethyl(phenyl)silyl)lithium²⁰ (2.40 mL, 0.44 M in THF, 1.06 mmol, 2.61 equiv) was added dropwise over 5 min and then the mixture was stirred at 0 $^{\circ}\text{C}$ for 30 min. The reaction mixture was cooled to -78 $^{\circ}\text{C}$ and a solution of carbonate **2.26** (300 mg, 0.425 mmol, 1.00 equiv) in Et_2O (3.0 mL) was added dropwise over 5 minutes. The reaction was allowed to stir at -78 $^{\circ}\text{C}$ for 1 h. After this time, the reaction was diluted with Et_2O (5 mL), quenched with water (1 mL), and allowed to warm to 23 $^{\circ}\text{C}$. The reaction mixture was then transferred to a separatory funnel containing Et_2O (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (20:1 hexanes: EtOAc) to afford silyl bromide **2.27** (219 mg, 0.292 mmol, 69% yield) as a colorless oil. The characterization for silyl bromide **2.27** match those reported above.

2.5.2.5. Key Diels–Alder Cycloaddition



Cycloadduct 2.28. A vial containing pyrone **2.22** (20.7 mg, 67.6 μ mol, 5.5 equiv) was brought into the glovebox. To this vial was added Bu₄NBr (1.5 mg, 4.7 μ mol, 40 mol%), CsF (13.9 mg, 91.5 μ mol, 7.5 equiv), and MeCN (0.1 mL). The vial was sealed with a septa cap, removed from the glovebox, and then cooled to -20 °C in a carefully controlled dry ice/acetone bath. To this vial was added silyl bromide **2.27** (9.2 mg, 12 μ mol, 1.0 equiv, 90% ee) as a solution in MeCN (0.2 mL, 0.04 M final concentration) via rapid cannula transfer. Meanwhile, a -20 °C freezer was equipped with an IKA brand Topolino stir plate, with a sand bath resting on top of the stir plate (the electrical cord was passed between the door opening and the freezer door's rubber stripping such that the freezer maintained a good seal). The aforementioned reaction vial was transferred to the pre-cooled sand bath in the -20 °C freezer and then allowed to stir vigorously for 21.5 h. After this time, the reaction vessel was removed from the freezer and immediately diluted with EtOAc (1 mL), filtered through a 1 x 4 cm plug of silica gel eluting with 2:1:1 hexanes:CH₂Cl₂:Et₂O (50 mL), and then concentrated under reduced pressure. The crude residue was purified via flash silica gel chromatography (8:1:1 → 2:1:1 hexanes:CH₂Cl₂:Et₂O to afford the cycloadduct **2.28** (7.5 mg, 73% yield, 79% ee, 88% optical yield) as a yellow oil. Cycloadduct **2.28**: *R*_f 0.31 (5:1:1 Hexanes:CH₂Cl₂:Et₂O); ¹H NMR (500 MHz, CDCl₃): δ 6.35–6.25 (m, 1H), 5.79 (ddt, *J* = 17.2, 10.2, 6.7, 1H), 5.58–5.46 (m, 1H), 4.98 (dq, *J* = 17.1, 1.8, 1H), 4.93 (d, *J* = 10.2, 1H), 4.32–4.08 (m, 2H), 3.67–3.49 (m, 3H), 3.38 (d, *J* = 13.2, 1H), 2.26–2.08 (m, 3H), 2.06–1.99 (m, 2H), 1.61–

1.58 (m, 2H), 1.58–1.55 (m, 8H), 1.54–1.51 (m, 2H), 1.50 (s, 9H), 1.48–1.45 (m, 9H), 1.41–1.10 (m, 22H); ^{13}C NMR (125 MHz, CDCl_3): δ 165.0, 155.2, 154.9, 152.9, 142.2, 139.11, 139.08, 126.2, 115.5, 115.2, 114.49, 114.47, 84.1, 84.0, 83.9, 83.8, 82.09, 82.08, 80.4, 80.3, 52.28, 52.26, 46.7, 46.4, 42.9, 42.5, 38.8, 38.7, 34.7, 34.6, 34.3, 34.2, 33.8, 30.1, 30.0, 29.84, 29.78, 29.73, 29.69, 29.5, 29.4, 29.2, 29.10, 29.08, 28.91, 28.88, 28.8, 28.6, 28.5, 28.23, 28.16, 27.14, 27.10, 27.00, 26.99, 23.8, 23.6; IR (film): 2979, 2924, 1736, 1698, 1367, 1033 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calc'd for $\text{C}_{48}\text{H}_{79}\text{N}_2\text{O}_{10}^+$, 843.57292; found 843.56626. For representative SFC chromatogram see Section 2.6.

Note: 2.28 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra. The IKA Topolino stir plate provides an ideal option for cooling the reaction to $-20\text{ }^\circ\text{C}$ for a prolonged period of time. Per the manufacturer, operating this stir plate at $-20\text{ }^\circ\text{C}$ is permissible. In addition, humidity in the freezer was determined to be below 20%, which is well below the Topolino's humidity threshold of 80%.

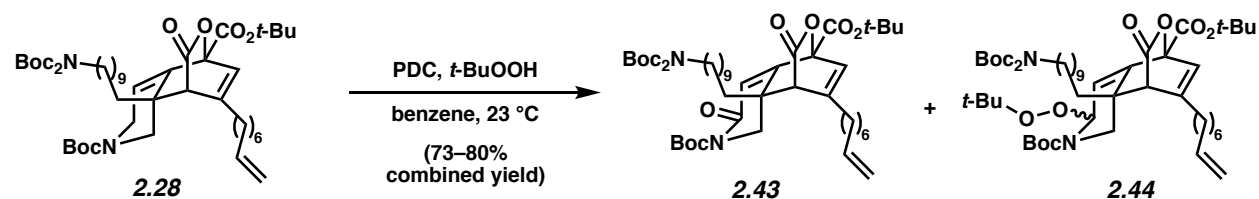
The cyclic allene Diels–Alder step could also be performed on larger scale. A representative procedure is as follows.

Cycloadduct 2.28. A vial containing pyrone **2.22** (341 mg, 1.11 mmol, 5.0 equiv) was brought into the glovebox. To this vial was added Bu_4NBr (21.5 mg, 66.7 μmol , 30 mol%), CsF (236 mg, 1.56 mmol, 7.0 equiv), and MeCN (2.2 mL). The vial was sealed with a septa cap, removed from the glovebox, and then cooled to $-20\text{ }^\circ\text{C}$ in a carefully controlled dry ice/acetone bath. To this vial was added silyl bromide **2.27** (167 mg, 0.222 mmol, 1.0 equiv, 91% ee) as a solution in MeCN (3.3 mL, 0.04 M final concentration) via rapid cannula transfer. Meanwhile, a $-20\text{ }^\circ\text{C}$ freezer was

equipped with an IKA brand Topolino stir plate, with a sand bath resting on top of the stir plate (the electrical cord was passed between the door opening and the freezer door's rubber stripping such that the freezer maintained a good seal). The aforementioned reaction vial was transferred to the pre-cooled sand bath in the $-20\text{ }^{\circ}\text{C}$ freezer and then allowed to stir vigorously for 18 h. After this time, the reaction vessel was removed from the freezer and immediately diluted with EtOAc (1 mL), filtered through a 1.5 x 2 cm plug of silica gel eluting with 2:1:1 hexanes: CH_2Cl_2 :Et₂O (50 mL), and then concentrated under reduced pressure. The crude residue was purified via flash silica gel chromatography (8:1:1 $\rightarrow$ 6:1:1 $\rightarrow$ 3:1:1 hexanes: CH_2Cl_2 :Et₂O to afford the cycloadduct **2.28** (122 mg, 65% yield, 81% ee, 89% optical yield) as a pale yellow oil.

2.5.2.6. Elaboration to Lissodendoric Acid A (2.6)

The elaboration of **2.28** to **2.6** was first developed on racemic material as noted in the manuscript text. The procedures shown below reflect those studies. However, the same procedures were used to carry forward enantioenriched **2.28** to (–)-**2.6**, thus allowing for the validation of the absolute stereochemistry of lissodendoric acid A.

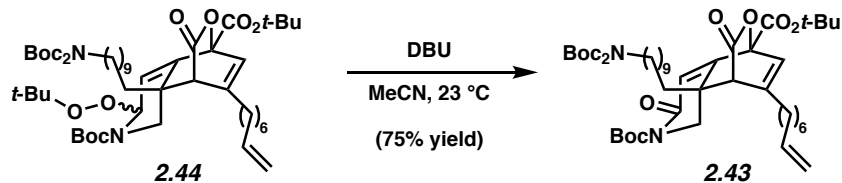


Enamide 2.43. The oxidation of **2.28** was inspired by the work of Chandrasekaran and coworkers.⁴⁷ To a solution of cycloadduct **2.28** (30.0 mg, 33.8 μmol , 1.00 equiv) in benzene (3.3 mL, 0.01 M) was added PDC (38.1 mg, 101 μmol , 3.00 equiv). The suspension was stirred rapidly (1000 rpm) and then tert-butyl hydroperoxide in water (13.1 mg, 14 μL , 70 wt%, 101 μmol , 3.00

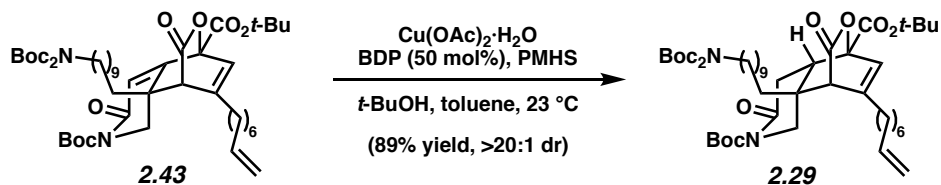
equiv). The reaction mixture was stirred at 23 °C for 17 h. After this time, celite (50 mg) was added to the reaction and was stirred for 30 min at which point it was filtered through a celite plug (1 cm), rinsed with EtOAc (20 mL), and diluted with saturated aq. sodium thiosulfate (20 mL) to quench any remaining peroxides. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic fractions were dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The crude residue was purified via flash chromatography (9:1 → 4:1 hexanes:EtOAc) to afford enamide **2.43** (14.1 mg, 16.5 μmol, 49% yield) and peroxide side product **2.44** (7.7 mg, 8.3 μmol, 24% yield). The peroxide side product **2.44** can be converted into amide **2.43** by treatment with DBU in a separate step (see below). Enamide product (**2.43**): *R_f* 0.60 (4:1 Hexanes:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 6.45 (d, 1.8 Hz, 1H), 5.79 (ddt, *J* = 17.0, 10.3, 6.7 Hz), 5.64 (s, 1H), 4.98 (app. dq, *J* = 17.0, 1.7 Hz, 1H), 4.93 (ddt, *J* 10.3, 2.1, 1.3 Hz, 1H), 4.32 (d, *J* = 12.5 Hz, 1H), 3.53 (app. t, *J* = 7.5 Hz, 2H), 3.42 (d, *J* = 1.3 Hz, 1H), 3.02 (d, *J* = 12.5 Hz, 1H), 2.22–2.14 (m, 2H), 2.07–1.99 (m, 2H), 1.98–1.86 (m, 1H), 1.57 (s, 9 H), 1.52 (s, 9H), 1.51–1.43 (m, 22H), 1.42–1.16 (m, 21H); ¹³C NMR (125 MHz, CDCl₃): δ 169.3, 163.5, 162.6, 157.9, 152.9, 152.4, 145.3, 139.0, 127.2, 115.2, 114.6, 85.2, 83.8, 82.8, 82.1, 52.0, 50.6, 46.6, 39.1, 34.8, 34.4, 33.8, 29.8, 29.6, 29.2, 28.8, 28.8, 28.2, 28.1, 28.1, 27.0, 26.8, 23.8; IR (film): 2930, 1774, 1718, 1458, 1368, 1288, 1129, 1075 cm⁻¹; HRMS-APCI (*m/z*) [*M* + *H*]⁺ calc'd for C₄₈H₇₆N₂O₉, 857.55219; found 857.55490. Peroxide product (**2.44**) (note: **2.44** is isolated as a 3:2 mixture of diastereomers and data is reported as a reflection of this): *R_f* 0.47 (4:1 Hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃): δ 6.42 (s, 0.4H), 6.39 (s, 0.6H), 5.99 (d, *J* = 1.9 Hz, 0.4H), 5.90 (d, *J* = 2.0 Hz, 0.6H), 5.79 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.54 (d, *J* = 1.3 Hz, 0.4H), 5.46 (d, *J* = 1.2 Hz, 0.6H), 4.98 (d, *J* = 17.1 Hz, 1H), 4.27 (d, *J* = 11.9 Hz, 0.6H), 4.07 (d, *J* = 12.9 Hz, 0.4H), 3.53 (t, *J* = 7.4 Hz, 2H), 3.39–3.32 (m, 1H), 2.57–2.48 (m, 0.6H), 2.36

(d, $J = 12.2$ Hz, 0.4H), 2.21–2.07 (m, 2H), 2.06–1.97 (m, 2H), 1.60–1.55 (m, 10H), 1.54–1.52 (m, 2H), 2.51–1.45 (m, 28H), 1.44–1.40 (m, 2H), 1.39–1.32 (m, 3H), 1.32–1.19 (m, 20H), 1.18–1.13 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ 170.9, 170.6, 164.7, 164.7, 155.5, 155.5, 154.8, 153.1, 153.0, 145.6, 144.4, 142.9, 142.9, 142.4, 139.3, 139.3, 139.2, 127.5, 127.2, 116.3, 115.2, 114.8, 114.7, 84.5, 84.3, 84.3, 84.2, 83.7, 82.3, 82.3, 82.0, 81.7, 81.3, 81.2, 80.8, 80.4, 53.7, 52.1, 52.1, 50.8, 50.2, 46.9, 46.9, 45.0, 43.4, 39.3, 38.4, 38.3, 35.7, 35.5, 35.0, 34.5, 34.4, 34.0, 34.0, 30.4, 30.2, 30.1, 30.0, 30.0, 29.9, 29.9, 29.8, 29.7, 29.7, 29.6, 29.4, 29.3, 29.2, 29.1, 29.0, 29.0, 28.7, 28.6, 28.4, 28.3, 27.3, 27.3, 27.2, 27.2, 26.9, 26.7, 26.6, 24.0, 23.8; IR (film): 2978, 2930, 2856, 1772, 1734, 1702, 1458, 1393, 1366, 1250, 1131, cm^{-1} ; HRMS-ESI (m/z) $[\text{M} + \text{Na}]^+$ calc'd for $\text{C}_{52}\text{H}_{86}\text{N}_2\text{O}_{12}\text{Na}^+$, 953.6073; found 953.6069.

Alternative Large-Scale Procedure. To a solution of cycloadduct **2.28** (825 mg, 0.920 mmol, 1.00 equiv) in benzene (80 mL, 0.01 M) was added PDC (1.027 g, 2.73 mmol, 2.97 equiv). The suspension was stirred rapidly (1000 rpm) and then tert-butyl hydroperoxide in water (0.380 mL, 70 wt%, 2.76 mmol, 3.00 equiv). The reaction mixture was stirred at 23 °C for 22.5 h. After this time, celite (1.5 g) was added to the reaction and was stirred for 30 min at which point it was filtered through a pad of celite (3 x 4 cm), rinsed with EtOAc (100 mL), and diluted with saturated aq. sodium thiosulfate (50 mL) to quench any remaining peroxides. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic fractions were dried over MgSO_4 , filtered, and the solvent was removed under reduced pressure. The crude residue was purified via flash chromatography (9:1 $\rightarrow$ 4:1 hexanes:EtOAc) to afford the enamide **2.43** (285 mg, 0.332 mmol, 36% yield) and peroxide side product **2.44** (380 mg, 0.408 mmol, 44% yield). The characterization data match those reported above.

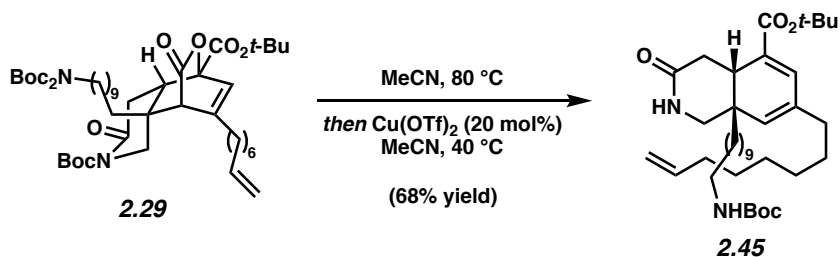


Enamide 2.43. To a 20 mL vial equipped with a stirbar was added peroxide **2.44** (378 mg, 0.398 mmol, 1.00 equiv) and MeCN (6 mL). To this solution was added DBU (30 μ L, 0.20 mmol, 0.50 equiv) and the reaction mixture was allowed to stir at 23 $^{\circ}$ C for 40 min. After this time, the reaction mixture was filtered through a short plug of silica gel (1.5 x 4 cm) eluting with 1:1 hexanes:EtOAc (80 mL) and then concentrated under reduced pressure. The crude residue was purified by flash chromatography (9:1 $\rightarrow$ 4:1 hexanes:EtOAc) to afford the enamide **2.43** (260 mg, 0.303 mmol, 75% yield). Characterization data for **2.43** matches that which is reported above.



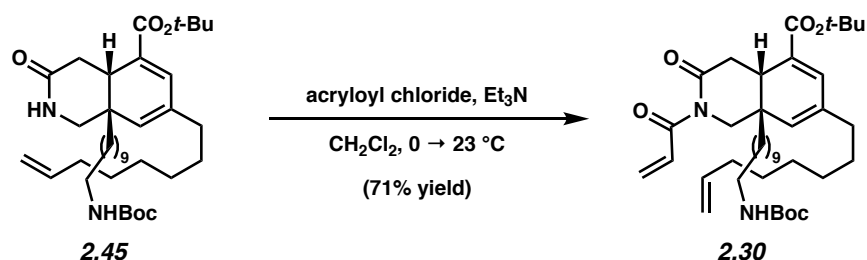
Amide 2.29. The procedure for the reduction of amide **2.29** is based on previous work reported by Lipshutz and coworkers.⁴⁸ To a flask was added copper(II) acetate monohydrate (80.2 mg, 402 μ mol, 0.990 equiv) and 1,2-bis(diphenylphosphaneyl)benzene (BDP) (88.5 mg, 198 μ mol, 50.0 mol%). These were dissolved in sparged *t*-BuOH (602 mg, 0.77 mL, 8.12 mmol, 20.0 equiv) and toluene (5 mL) and the reaction was stirred for 20 minutes to give a blue solution. At this point PMHS (2.30 mL, 1.22 mmol, 3.00 equiv) was added dropwise over 3 min and the solution gradually turned from blue to a yellow/green color (30 min). A separate vial was charged with the enamide (355 mg, 406 μ mol, 1.00 equiv) and toluene (5 mL). The enamide solution was then added to the Stryker's reagent dropwise over 3 min. The reaction was stirred at 23 $^{\circ}$ C for 21.5 h.

After this time, the reaction mixture was filtered through a plug of silica gel (1.5 x 5 cm silica) eluting with 1:1 hexanes:EtOAc (100 mL). The crude residue was purified via flash chromatography (9:1 → 6:1 → 4:1 hexanes:EtOAc) to afford amide **2.29** (310 mg, 0.361 mmol, 89% yield) as a colorless oil. Amide **2.29**: R_f 0.38 (4:1 Hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 6.38–6.34 (m, 1H), 5.79 (ddt, J = 17.1, 10.3, 6.7, 1H), 4.99 (ddt, J = 17.1, 3.9, 1.6, 1H), 4.96–4.91 (m, 1H), 4.16 (d, J = 13.7, 1H), 3.56–3.50 (m, 2H), 3.29–3.25 (m, 2H), 2.90 (d, J = 13.8, 1H), 2.44 (dd, J = 14.5, 5.7, 1H), 2.31 (dd, J = 11.7, 5.6, 1H), 2.23–2.17 (m, 1H), 2.13–2.07 (m, 1H), 2.07–2.01 (m, 2H), 1.68–1.61 (m, 2H), 1.53 (s, 9H), 1.52 (s, 9H), 1.50 (s, 18H), 1.41–1.18 (m, 24H); ^{13}C NMR (125 MHz, CDCl_3): δ 170.8, 168.9, 165.8, 152.9, 151.5, 146.0, 139.0, 122.8, 114.5, 84.36, 84.35, 84.0, 82.1, 51.6, 47.0, 46.7, 46.2, 41.8, 38.7, 37.7, 34.9, 33.8, 30.0, 29.74, 29.69, 29.52, 29.49, 29.4, 29.2, 29.1, 28.9, 28.8, 28.2, 28.08, 28.06, 27.0, 26.9, 23.4; IR (film): 2978, 2930, 1770, 1731, 1368, 1152 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calc'd for $\text{C}_{48}\text{H}_{79}\text{N}_2\text{O}_{11}^+$, 859.56784; found 859.56714.



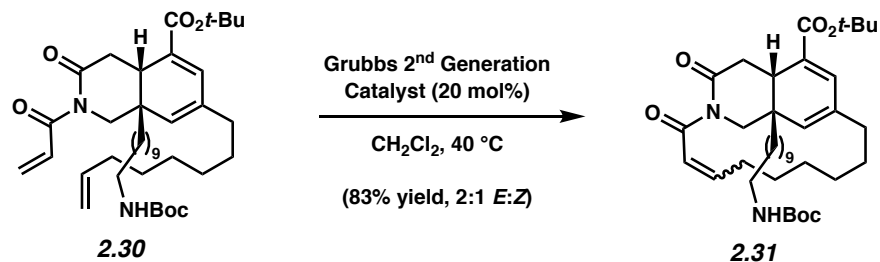
Diene 2.45. Inspiration for the deprotection strategy used in this procedure comes from Webster and coworkers.⁵⁰ A vial containing a solution of amide **2.29** (10.0 mg, 11.6 μmol , 1.00 equiv) in acetonitrile (0.39 mL, 0.30 M) was sealed with a Teflon-lined cap and heated to 80 $^\circ\text{C}$ for 14.25 h. The solution was then cooled to 23 $^\circ\text{C}$ and to the solution was added copper(II) triflate (0.8 mg, 2.3 μmol , 20 mol%) in one portion and the vial was resealed with a Teflon-lined cap. The vial was heated to 40 $^\circ\text{C}$ for 1.5 h. The reaction mixture was then allowed to cool to 23 $^\circ\text{C}$ and filtered

through a short plug of silica gel (0.9 x 2.5 cm silica) eluting with EtOAc (10 mL) and then concentrated under reduced pressure. The crude residue was purified via preparative TLC (1:1 hexanes:EtOAc) to afford diene **2.45** (4.9 mg, 0.012 mmol, 68% yield) as a colorless oil. R_f 0.60 (1:1 Hexanes:EtOAc); ^1H NMR (400 MHz, CDCl_3): δ 6.78 (d, J = 1.0 Hz, 1H), 6.02 (br s, 1H), 5.79 (ddt, J = 17.2, 10.3, 6.7 Hz, 1H), 5.52 (s, 1H), 4.98 (app. dq, J = 17.2, 1.8 Hz, 1H), 4.93 (ddt, J = 10.3, 2.1, 1.2 Hz, 1H), 4.49 (br s, 1H), 3.35–3.24 (m, 2H), 3.14–3.02 (m, 2H), 2.82 (dd, J = 10.1, 7.2 Hz, 1H), 2.53 (dd, J = 17.7, 7.1 Hz, 1H), 2.14–1.98 (m, 5H), 1.73–1.57 (m, 2H), 1.50 (s, 9H), 1.47–1.39 (m, 13H), 1.32–1.06 (m, 20H); ^{13}C NMR (125 MHz, CDCl_3): δ 173.8, 166.0, 156.1, 139.2, 137.2, 133.8, 133.5, 133.2, 114.4, 81.0, 50.7, 40.8, 38.3, 37.9, 36.0, 35.0, 33.9, 30.5, 30.2, 29.8, 29.6, 29.6, 29.6, 29.5, 29.4, 29.0, 29.0, 29.0, 28.6, 28.5, 28.3, 26.9, 24.4; IR (film): 3315, 2927, 2855, 1698, 1671, 1163 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calc'd for $\text{C}_{37}\text{H}_{63}\text{N}_2\text{O}_5^+$, 615.47315; found 615.47783. For representative SFC chromatogram see Section 2.6.



Imide 2.30. A solution of diene **2.45** (55.0 mg, 1.00 equiv, 89.4 μmol) in CH_2Cl_2 (0.90 mL, 0.10 M) was cooled to 0 $^\circ\text{C}$. To this solution was added triethylamine (37.4 μL , 268 μmol , 3.00 equiv) followed by acryloyl chloride (21.9 μL , 268 μmol , 3.00 equiv) dropwise over 1 min. The reaction was allowed to warm to 23 $^\circ\text{C}$ and stir for 15 h. The reaction mixture was quenched with water (1 mL) and saturated aq. NaHCO_3 (1 mL) and diluted with Et_2O (2 mL). The layers were separated and the aqueous layer was washed with Et_2O (3 x 1 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified by

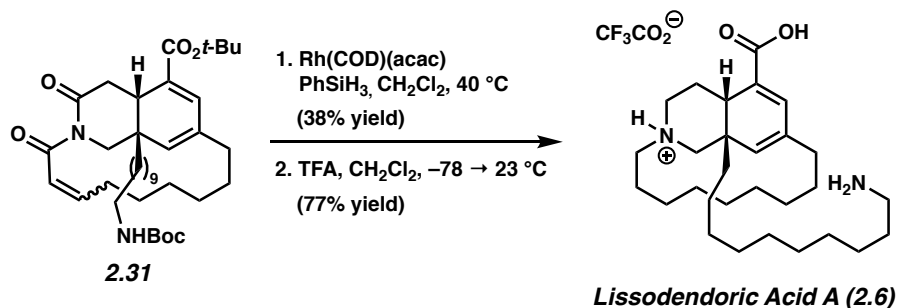
flash chromatography (5:1 hexanes:EtOAc) to afford imide **2.30** (42.5 mg, 0.0894 mmol, 71% yield, 48% yield over two steps from **2.29**) as a colorless oil. Imide **2.30**: R_f 0.64 (2:1 Hexanes:EtOAc); ^1H NMR (600 MHz, CDCl_3): δ 7.12 (dd, $J = 16.9, 10.3$, 1H), 6.76 (s, 1H), 6.38 (dd, $J = 16.9, 1.7$, 1H), 5.83–5.74 (m, 2H), 5.23 (s, 1H), 4.98 (dq, $J = 17.1, 1.7$, 1H), 4.96–4.90 (m, 1H), 4.50 (br s, 1H), 4.03 (d, $J = 13.6$, 1H), 3.61 (d, $J = 13.6$, 1H), 3.15–3.04 (m, 2H), 2.93 (t, $J = 7.7$, 1H), 2.74 (dd, $J = 16.1, 7.9$, 1H), 2.33 (dd, $J = 16.1, 7.0$, 1H), 2.10–2.05 (m, 2H), 2.05–2.00 (m, 2H), 1.51 (s, 9H), 1.43 (s, 9H), 1.39–1.32 (m, 4H), 1.32–1.15 (m, 22H); ^{13}C NMR (125 MHz, CDCl_3): δ 174.1, 168.2, 165.9, 156.1, 139.2, 136.11, 134.17, 131.4, 130.8, 130.7, 129.5, 114.4, 81.2, 79.2, 50.0, 40.8, 40.7, 39.8, 38.5, 35.6, 35.1, 33.9, 30.3, 30.2, 29.6, 29.5, 29.42, 29.37, 29.00, 28.95, 28.8, 28.6, 28.4, 28.3, 26.9, 23.7; IR (film): 2925, 2854, 1713, 1463, 1366, 1163 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calc'd for $\text{C}_{40}\text{H}_{65}\text{N}_2\text{O}_6^+$, 669.48371; found 669.48489.



Macrocycle 2.31. To a flask in the glovebox was added the Grubbs' 2nd generation catalyst (2.4 mg, 2.9 μmol , 20 mol%). The flask was then removed from the glovebox and imide **2.30** (9.6 mg, 14 μmol , 1.0 equiv) dissolved in CH_2Cl_2 (14.0 mL, 0.00100 M) was added to the flask containing Grubbs' catalyst. The flask was equipped with a reflux condenser and heated to 40 $^\circ\text{C}$ for 16 h. After 16 h, the reaction was cooled to 23 $^\circ\text{C}$ and the solvent was evaporated under reduced pressure. The crude residue was purified via preparative TLC (3:1 hexanes:EtOAc) to afford macrocycle **2.31** (7.6 mg, 83%) as an colorless oil. This was isolated as a 2:1 mixture of *E:Z* olefin

isomers, as judged by ^1H NMR analysis (see ^1H NMR spectrum in Section 2.7). Macrocycle **2.31**: R_f 0.28 (4:1 Hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 7.21 (d, $J = 15.3$, 1H, *E* isomer), 6.95 (ddd, $J = 15.4$, 10.8, 4.3, 1H, *E* isomer), 6.70 (s, 1H, *E* isomer), 6.66 (s, 0.5H, *Z* isomer), 6.60 (dd, $J = 11.6$, 2.2, 0.5H, *Z* isomer), 5.90 (td, $J = 12.0$, 4.1, 0.5H, *Z* isomer), 5.13 (s, 0.5H, *Z* isomer), 4.99 (s, 1H, *E* isomer), 4.70 (d, $J = 13.5$, 0.5H, *Z* isomer), 4.49 (br s, 1H, *E* isomer), 4.42 (d, $J = 13.5$, 1H, *E* isomer), 3.21–3.14 (m, 1.5H, mixture), 3.13–3.04 (m, 4H, mixture), 3.01–2.92 (m, 0.5H, *Z* isomer), 2.86–2.76 (m, 1.5H, mixture), 2.46–2.35 (m, 2H, *E* isomer), 2.27 (d, $J = 15.0$, 0.5H, *Z* isomer), 2.23–2.09 (m, 3H, mixture), 1.94–1.80 (m, 1.5H, mixture), 1.76–1.67 (m, 1H, *E* isomer), 1.52–1.48 (m, 14.5H, mixture), 1.43 (s, 15H, mixture), 1.39–1.10 (m, 29.5H, mixture), 1.03–0.66 (m, 2.5H, mixture); ^{13}C NMR (125 MHz, CDCl_3): δ 174.3, 173.3, 168.8, 167.4, 166.0, 165.9, 151.6, 143.2, 136.0, 135.7, 135.5, 134.0, 131.9, 130.6, 130.4, 126.6, 125.3, 81.1, 81.0, 50.9, 49.3, 43.2, 43.0, 41.2, 40.9, 40.8, 40.0, 39.4, 35.5, 35.1, 34.8, 34.1, 33.2, 30.30, 30.26, 30.24, 30.19, 29.6, 29.51, 29.46, 29.39, 29.36, 28.7, 28.6, 28.3, 28.2, 27.9, 27.54, 27.51, 27.2, 26.9, 26.6, 26.3, 26.2, 23.34, 23.28; IR (film): 3385, 2927, 2854, 1699, 1251, 1160 cm^{-1} ; HRMS-APCI (m/z) [$M + H$] $^+$ calc'd for $\text{C}_{38}\text{H}_{61}\text{N}_2\text{O}_6^+$, 641.45241; found 641.45533.

Note: These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra (see Section 2.7). The integrations for the ^1H NMR spectrum were calibrated such that one proton of the major isomer integrates to 1, while one proton of the minor isomer integrates to 0.5.



Lissodendoric Acid A (2.6). The procedure of the Rh-catalyzed reduction of **2.31** is derived from the work of Beller and coworkers.⁵³ A vial containing macrocycle **2.31** (4.4 mg, 6.9 μ mol, 1.00 equiv). was brought into the glovebox and Rh(COD)(acac) (1.1 mg, 3.4 μ mol, 50 mol%) was added. The vial was then removed from the glovebox and the mixture was dissolved in CH₂Cl₂ (0.3 mL) and to this solution was added phenylsilane (8.5 μ L, 69 μ mol, 10 equiv). The vial was sealed with a Teflon-coated cap and the reaction mixture was heated to 40 °C and stirred for 15 h. After this time, the reaction mixture allowed to cool to 23 °C and was then quenched slowly with saturated aq. ammonium fluoride (0.5 mL). The reaction mixture was allowed to stir for 3 h at 23 °C and then diluted with Et₂O (1 mL), water (1 mL) and 1 M aq NaOH (1 mL). The layers were separated and the aqueous layer was washed with Et₂O (3 x 1 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified via preparative TLC (4:1 hexanes:EtOAc with 2% triethylamine) to afford the tertiary amine (1.6 mg, 6.9 μ mol, 38% yield). A vial containing a solution of the tertiary amine (2.1 mg, 3.4 μ mol, 1.00 equiv) in CH₂Cl₂ (0.20 mL, 0.017 M) was cooled to –78 °C. To the vial was added trifluoroacetic acid (0.10 mL, 0.034 M) dropwise over 2 min. The reaction was subsequently stirred at –78 °C for 1 min and then warmed to 23 °C and stirred for 2.75 h. At this point, a nitrogen inlet and vent needle were added to the septum and the reaction mixture was concentrated. CH₂Cl₂ (0.5 mL) was added to resuspended the crude material and was subsequently evaporated off with a nitrogen inlet and vent needle. This was repeated twice more. The crude residue was purified via reversed-phase filtration through a Sep-Pak reverse phase C18 cartridge (6 cc, 500 mg): column flushed with 100% MeCN, then the crude residue was loaded with 20% MeCN in H₂O, then filtered with 20% MeCN in H₂O containing 0.1% TFA → 100% MeCN containing 0.1% TFA (**2.6** collected in 35% MeCN in H₂O containing 0.1% TFA) to afford lissodendoric acid A (**2.6**, 1.5 mg,

3.4 μmol , 77% yield; 29% yield over two steps). Lissodendoric Acid A (**2.6**): R_f 0.47 (1:1 $\text{CH}_2\text{Cl}_2\text{:MeOH}$); ^1H NMR (500 MHz, CD_3OD): δ 6.98–6.92 (m, 1H), 5.89 (s, 1H), 3.56 (d, $J = 13.5$, 1H), 3.47–3.38 (m, 3H), 2.90 (t, $J = 7.7$, 2H), 2.82 (dd, $J = 12.3, 4.2$, 1H), 2.45–2.36 (m, 1H), 2.30–2.1 (m, 1H), 1.97–1.83 (m, 2H), 1.80–1.12 (42H); ^{13}C NMR (125 MHz, CD_3OD): δ 169.4, 135.9, 135.6, 134.5, 132.2, 57.3, 52.6, 40.8, 39.5, 38.7, 37.7, 33.6, 31.4, 30.6, 30.5, 30.5, 30.3, 28.6, 27.9, 27.5, 27.4, 26.8, 26.8, 26.1, 24.9, 24.4, 23.6, 22.0; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calc'd for $\text{C}_{29}\text{H}_{51}\text{N}_2\text{O}_2^+$, 459.39451; found 459.39411; spectral data match those previously reported (see Figure 2.74 in Section 2.7.1 ^1H NMR comparison spectra).²⁷ For comparative ECD spectra, see Section 2.7.2.

For comparison, the ^{13}C NMR data for the natural sample of lissodendoric acid A as reported by the isolation chemists²⁷ is listed as follows: ^{13}C NMR (176 MHz, CD_3OD): δ 169.4, 135.9, 135.5, 134.5, 132.2, 57.3, 52.6, 49.0, 40.8, 39.5, 38.7, 37.7, 33.5, 31.3, 30.5, 30.5, 30.4, 30.2, 28.6, 27.9, 27.5, 27.4, 26.8, 26.8, 26.1, 24.9, 24.3, 23.6, 22.0. All ^{13}C NMR peaks from synthetic lissodendoric acid A match those reported above (within ± 0.1 ppm). In our hands, we could not observe the peak at δ 49.0 due to overlap with the CD_3OD solvent peak and the carbonyl peak at δ 169.4 is in low abundance.

2.5.3. Control Experiments for pyrone / alkene Diels–Alder

As noted in the manuscript, intermolecular Diels–Alder cycloadditions of 2-pyrones with alkenes are known to be challenging. These reactions, as reviewed by Posner and coworkers³³ often require high temperatures and long reaction times, only to give low yields of products. In addition, it can be difficult to control decarboxylation from occurring in the same pot as the desired

Diels–Alder cycloaddition, which can lead to undesirable product mixtures. Lastly, intermolecular Diels–Alder cycloadditions of 2-pyrones with cyclic non-activated alkenes are rare and require the presence of several strongly electron-withdrawing groups on the pyrone, as shown by Martin et al.⁵⁹

Nonetheless, we attempted the Diels–Alder reaction between alkene **2.46** and pyrone **2.13** (see below). A variety of thermal- (up to 160 °C) and Lewis acid-based conditions were assessed based on literature protocols,³³ but failed to deliver the desired cycloadduct **2.47**. Given the aforementioned challenges, the growing interest in strained intermediate chemistry by the synthetic community, and the desire to develop and study stereoretentive transformations of cyclic allenes, we opted to focus our efforts on the use of cyclic allenes to construct the azadecalin core of lissodendoric acid A (**2.6**).

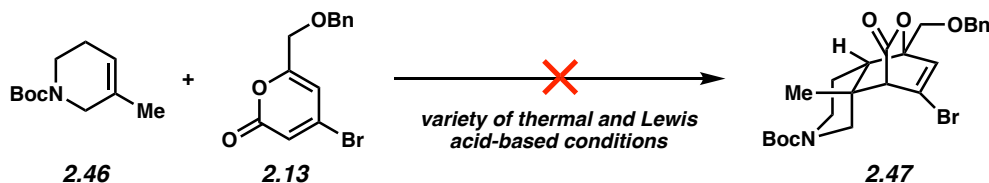
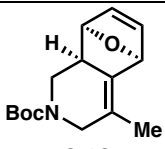
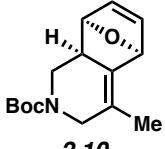
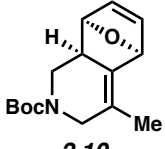
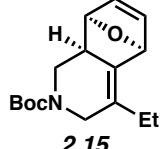
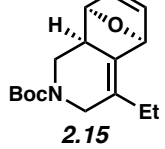
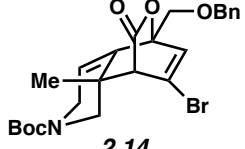
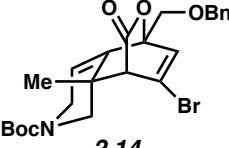
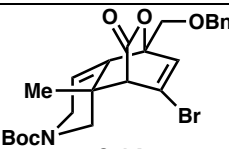
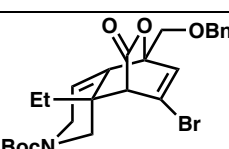
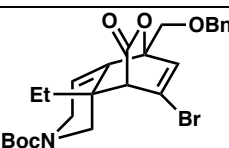
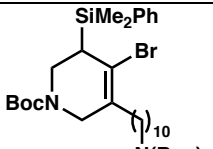
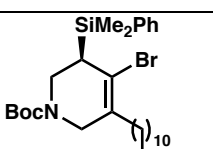
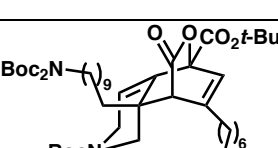


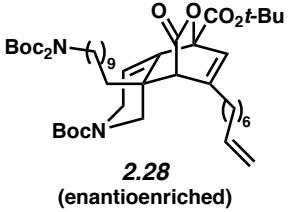
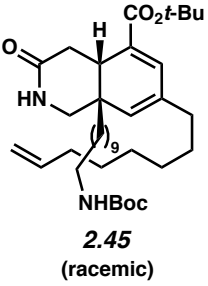
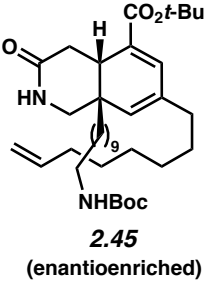
Figure 2.5. Summary of control experiments for pyrone/alkene Diels–Alder reactions.

2.6 Chiral SFC and HPLC Data

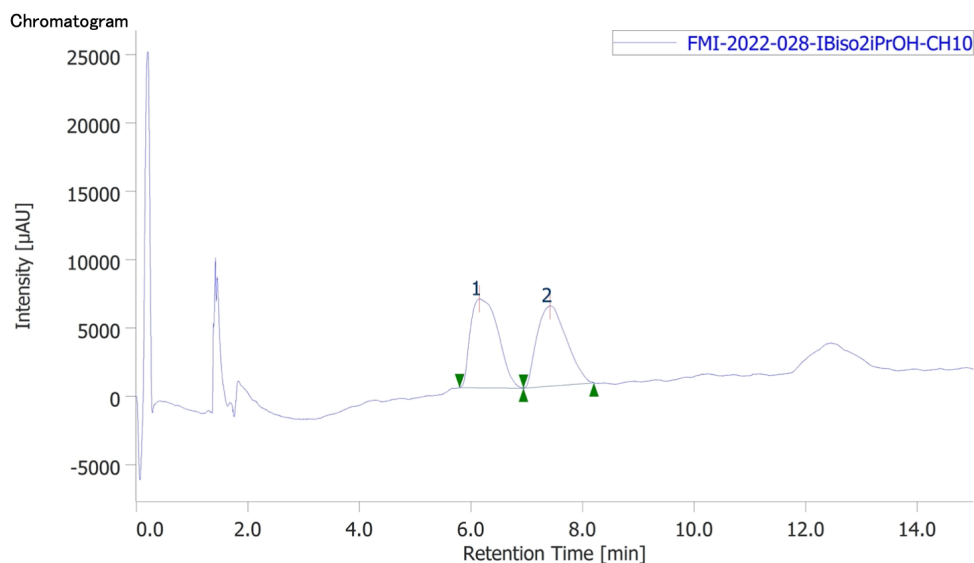
Table 2.1. Chiral SFC and HPLC information.

Compound	Method Column/Temp.	Solvent	Method Flow Rate	Retention Times (min)	Enantiomeric Ratio (er)
 2.10 (racemic)	Diacel ChiralPak IB / 30 °C	2% isopropanol in CO ₂	4 mL/min	6.15/7.42	~51.1:48.9
 2.10 (enantioenriched, from silyl triflate 2.12)	Diacel ChiralPak IB / 30 °C	2% isopropanol in CO ₂	4 mL/min	6.16/7.32	~6.3:93.7
 2.10 (enantioenriched, from silyl bromide 2.18)	Diacel ChiralPak IB / 30 °C	2% isopropanol in CO ₂	4 mL/min	6.38/7.46	~14.2:85.8
 2.15 (racemic)	Diacel ChiralPak IB / 30 °C	2% isopropanol in CO ₂	10 mL/min	12.0/15.0	~49.8:50.2
 2.15 (enantioenriched)	Diacel ChiralPak IB / 30 °C	2% isopropanol in CO ₂	10 mL/min	12.0/15.0	~41.6:58.4
 2.14 (racemic)	Diacel ChiralPak IA / 30 °C	5%–40% isopropanol in CO ₂	4 mL/min	5.49/5.88	~50.0:50.0

 2.14 (enantioenriched, from silyl triflate 2.12)	Diacel ChiralPak IA / 30 °C	5%–40% isopropanol in CO ₂	4 mL/min	5.41/5.85	~99.0:1.0
 2.14 (enantioenriched, from silyl bromide 2.18)	Diacel ChiralPak IA / 30 °C	5%–40% isopropanol in CO ₂	4 mL/min	5.50/5.89	~92.1:7.9
 2.17 (racemic)	Diacel ChiralPak IA / 30 °C	10% isopropanol in CO ₂	10 mL/min	10.76/12.34	~50.4:49.6
 2.17 (enantioenriched)	Diacel ChiralPak IA / 30 °C	10% isopropanol in CO ₂	10 mL/min	10.82/12.43	~66.6:33.4
 2.27 (racemic)	Diacel ChiralPak IA / 30 °C	5% isopropanol in CO ₂	4 mL/min	7.90/9.09	~50.0:50.0
 2.27 (enantioenriched)	Diacel ChiralPak IA / 30 °C	5% isopropanol in CO ₂	4 mL/min	7.76/8.88	~5.1:94.9
 2.28 (racemic)	Diacel ChiralPak ID / 23 °C	10% isopropanol in hexanes	1 mL/min	7.86/8.44	~46.7:53.3

 2.28 (enantioenriched)	Diacel ChiralPak ID / 23 °C	10% isopropanol in hexanes	1 mL/min	7.94/8.38	89.5:10.5
 2.45 (racemic)	Diacel Chiralpak IB / 30 °C	20% isopropanol in CO₂	4.0 mL/min	4.07/5.75	50:50
 2.45 (enantioenriched)	Diacel Chiralpak IB / 30 °C	20% isopropanol in CO₂	4.0 mL/min	4.08/5.72	10.4:89.6

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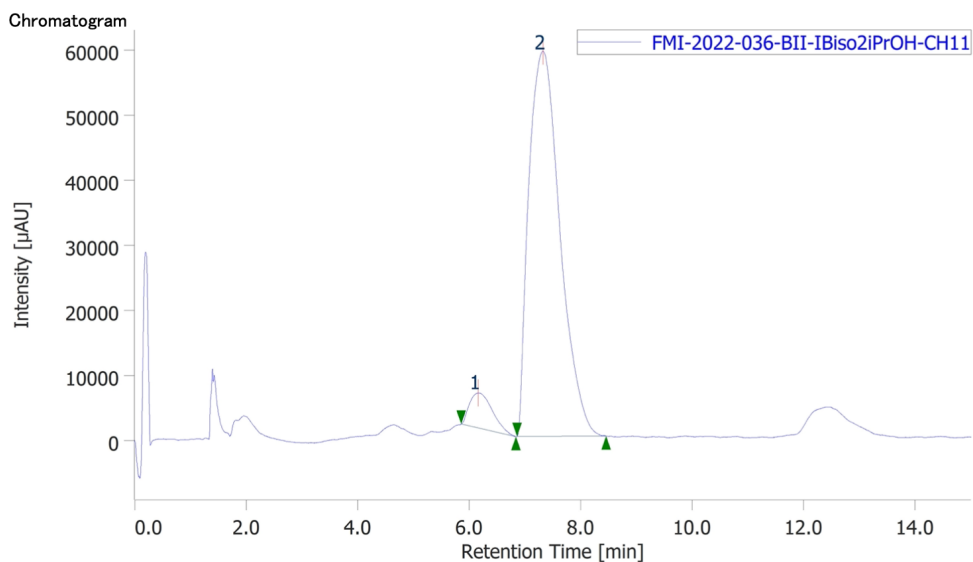


Peak Information

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1	Unknown	10	6.147	224793	6485	51.128	52.522	N/A	617	1.259	1.640	
2	Unknown	10	7.417	214872	5862	48.872	47.478	N/A	824	N/A	1.322	

Figure 2.6. SFC trace of racemic **2.10**.

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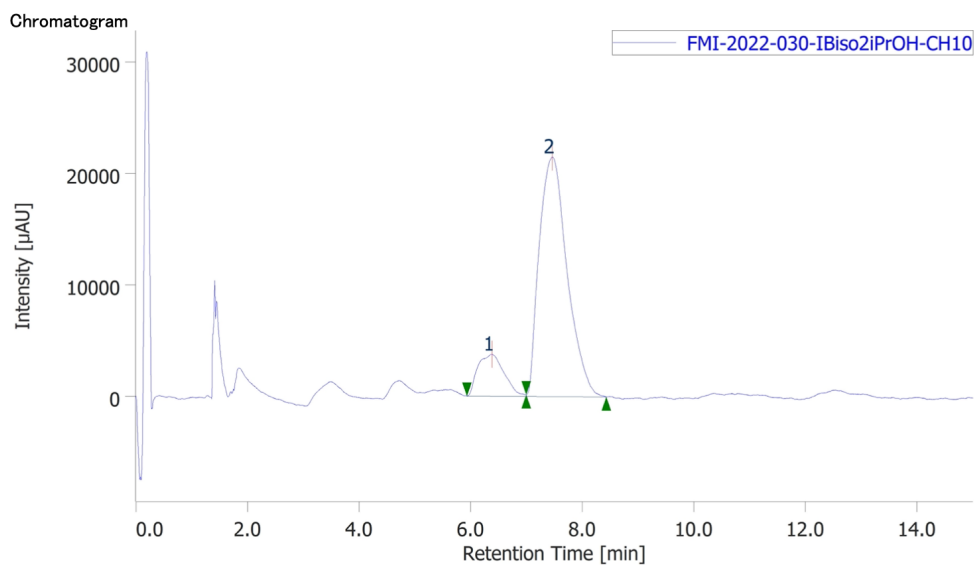


Peak Information

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1	Unknown	11	6.160	155390	5383	6.333	8.341	N/A	940	1.255	1.507	
2	Unknown	11	7.323	2298110	59151	93.667	91.659	N/A	772	N/A	1.424	

Figure 2.7. SFC trace of enantioenriched **2.10** from silyl triflate **2.12**.

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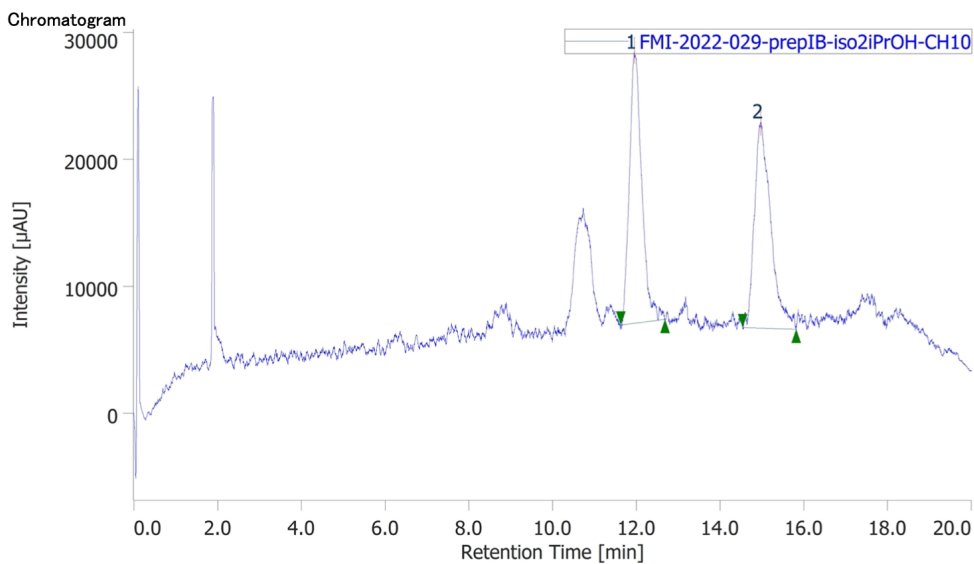


Peak Information

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1	Unknown	10	6.380	122997	3759	14.158	14.899	N/A	745	1.163	1.209	
2	Unknown	10	7.463	745738	21472	85.842	85.101	N/A	1022	N/A	1.329	

Figure 2.8. SFC trace of enantioenriched **2.10** from silyl bromide **2.18**.

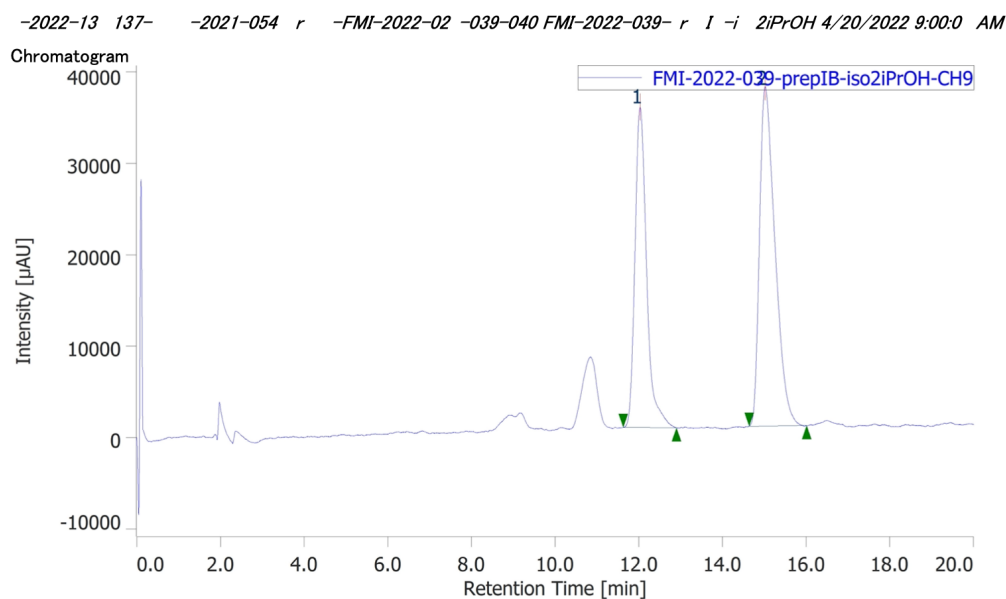
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Peak Information

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2	Unknown	10	14.963	440079	16227	50.155	43.030	N/A	6864	N/A	1.526	

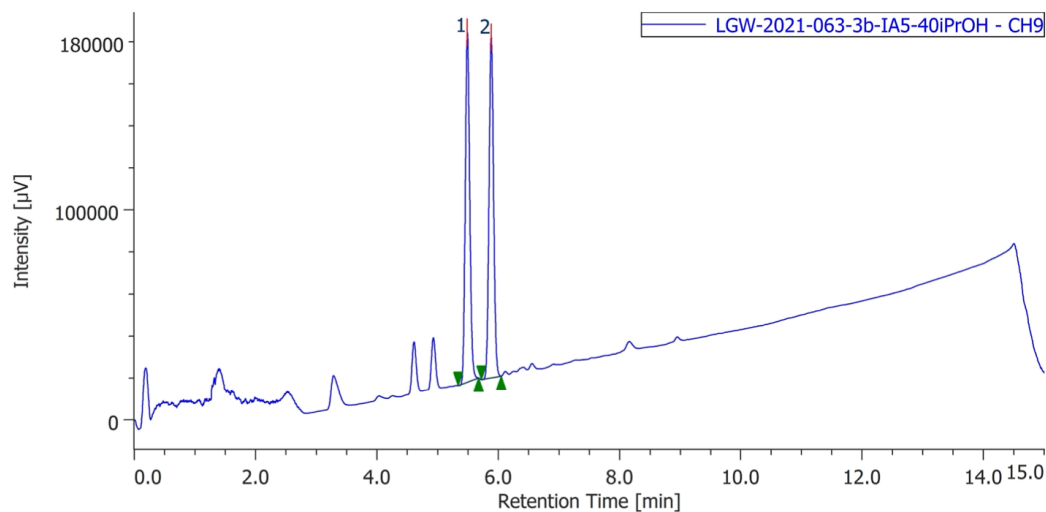
Figure 2.9. SFC trace of racemic **2.15**.



Peak Information

#	Peak Name	CH	tR [min]	Area [μ V-sec]	Height [μ V]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	12.030	677407	35006	41.607	48.556	N/A	9851	5.150	1.432	
2	Unknown	9	15.010	950687	37088	58.393	51.444	N/A	7897	N/A	1.599	

Figure 2.10. SFC trace of enantioenriched 2.15.



#	Peak Name	CH	tR [min]	Area [μ V-sec]	Height [μ V]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	5.487	851401	166444	50.042	50.681	N/A	26876	2.899	1.123	
2	Unknown	9	5.880	849977	161975	49.958	49.319	N/A	28968	N/A	1.067	

Figure 2.11. SFC trace of racemic 2.14.

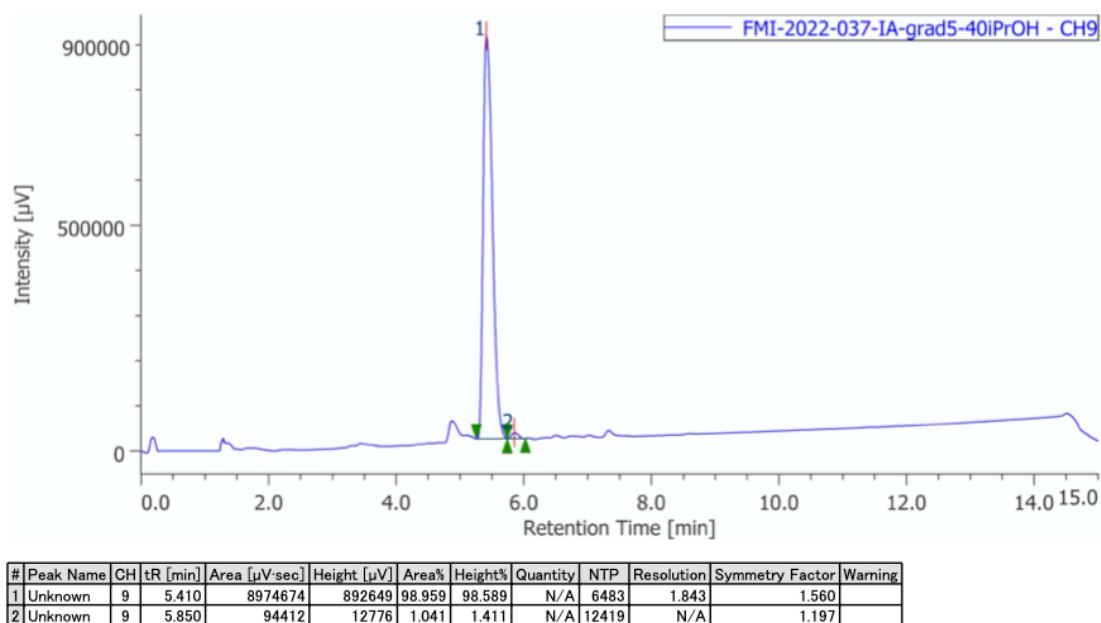


Figure 2.12. SFC trace of enantioenriched **2.14** from silyl triflate **2.12**.

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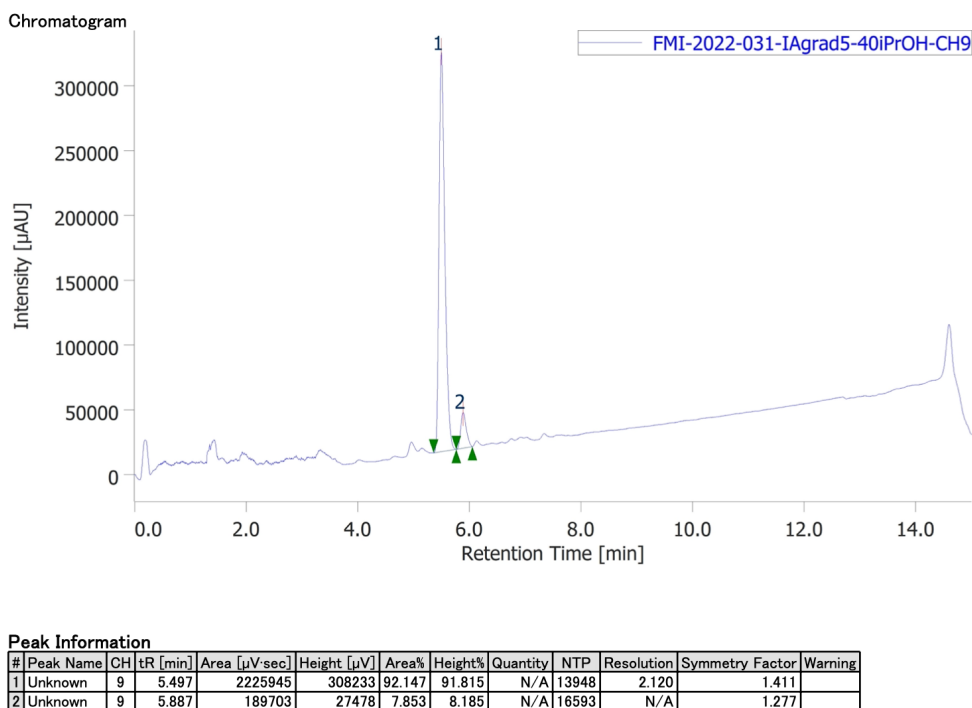
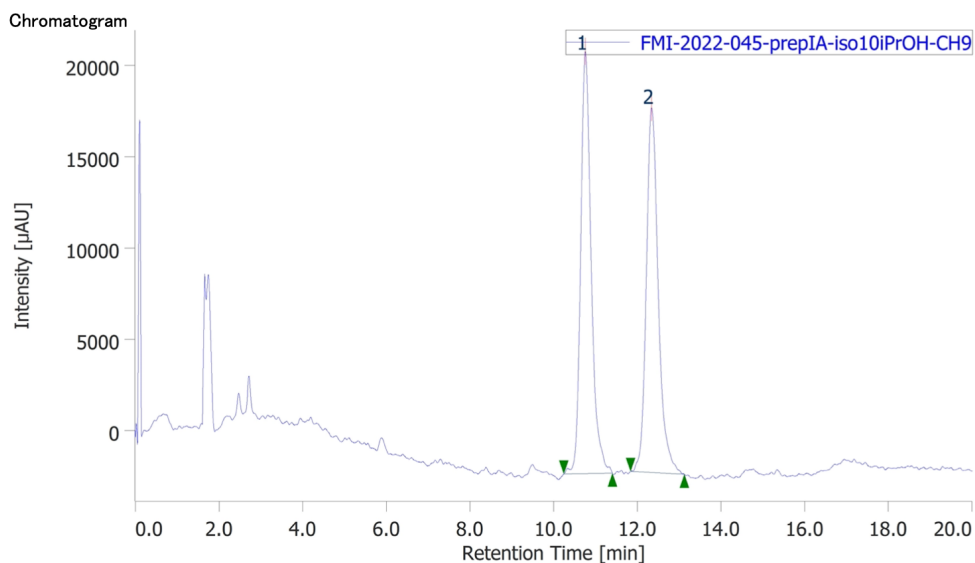


Figure 2.13. SFC trace of enantioenriched **2.14** from silyl bromide **2.18**.

FMI-2022-045 FMI-2022-045-prepIA-iso10iPrOH 4/24/2022 2:44:43 PM

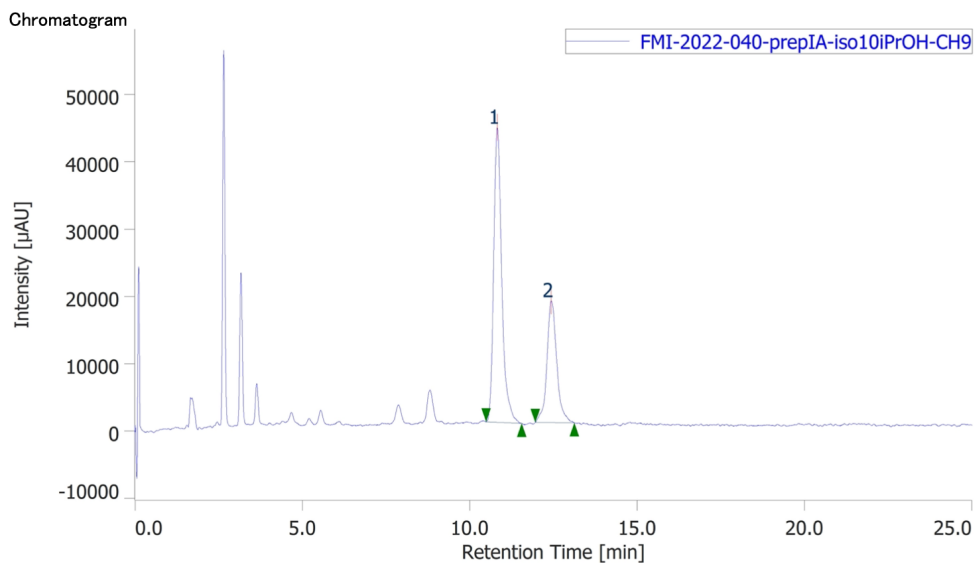


Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	10.757	403689	23110	50.392	53.642	N/A	9816	3.409	1.320	
2	Unknown	9	12.337	397406	19971	49.608	46.358	N/A	9934	N/A	1.283	

Figure 2.14. SFC trace of racemic 2.17.

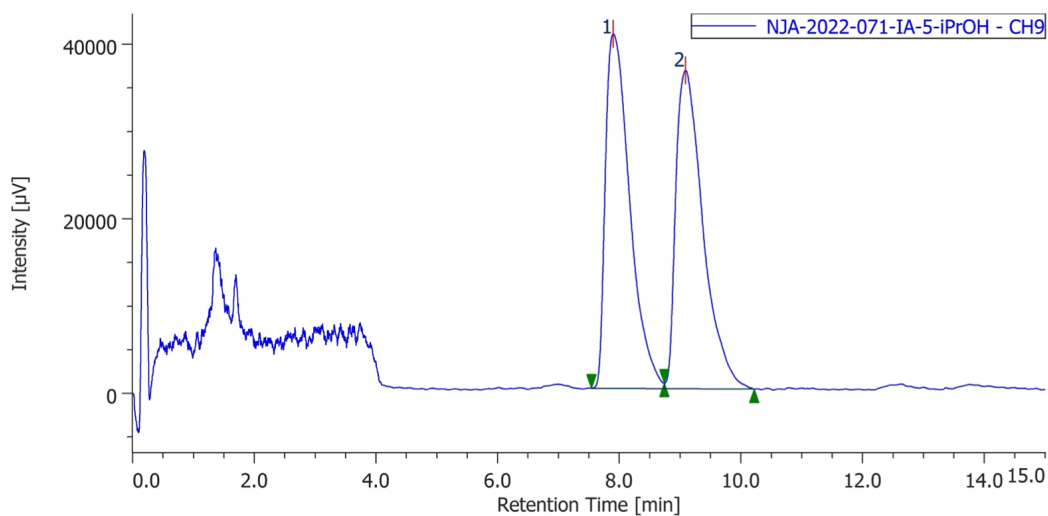
-2022-13 137- -2021-054 r -FMI-2022-02 -039-040 FMI-2022-040- r IA-i 10iPrOH 4/20/2022 9:03:0 AM



Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	10.823	734376	43765	66.608	70.786	N/A	10618	3.490	1.357	
2	Unknown	9	12.430	368164	18062	33.392	29.214	N/A	9765	N/A	1.122	

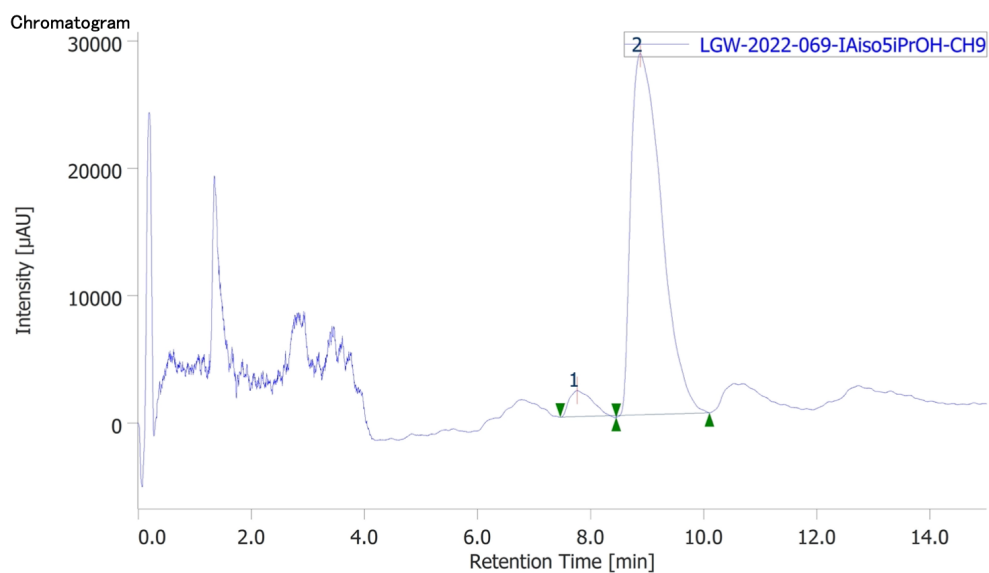
Figure 2.15. SFC trace of enantioenriched 2.17.



#	Peak Name	CH	tR [min]	Area [μV-sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	7.900	1129612	40602	49.980	52.696	N/A	1879	1.557	1.958	
2	Unknown	9	9.087	1130514	36448	50.020	47.304	N/A	2069	N/A	1.855	

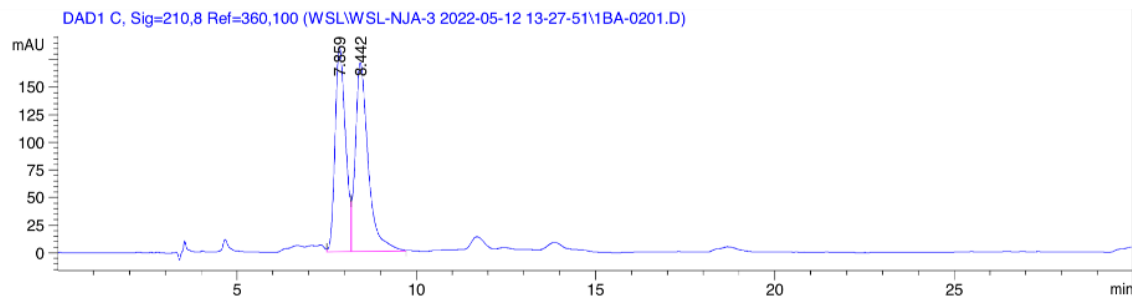
Figure 2.16. SFC trace of racemic **2.27**.

LGW-2022-069-FMI-2022-028-039-040 LGW-2022-069-IAiso5iPrOH 4/26/2022 6:22:35 PM



Peak Information												
#	Peak Name	CH	tR [min]	Area [μV-sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	7.763	57096	2049	5.091	6.738	N/A	1528	1.233	1.584	
2	Unknown	9	8.877	1064505	28362	94.909	93.262	N/A	1219	N/A	2.004	

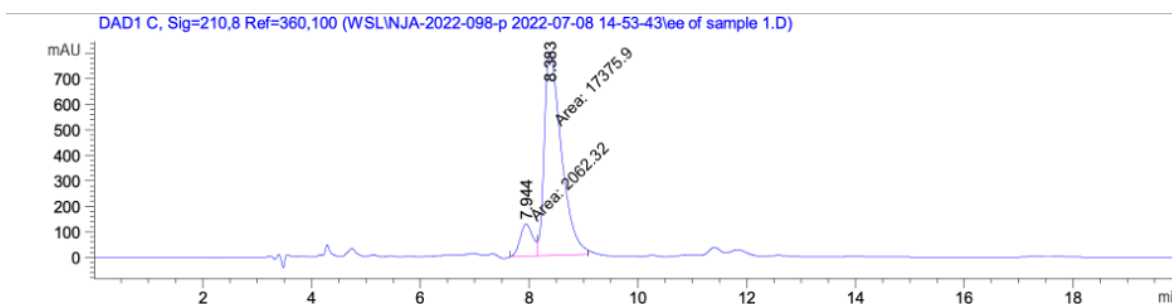
Figure 2.17. SFC trace of enantioenriched **2.27**.



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.859	VV	0.3070	3735.18506	185.40475	46.7099
2	8.442	VB	0.3691	4261.37842	170.76860	53.2901

Figure 2.18. HPLC trace of racemic **2.28**.

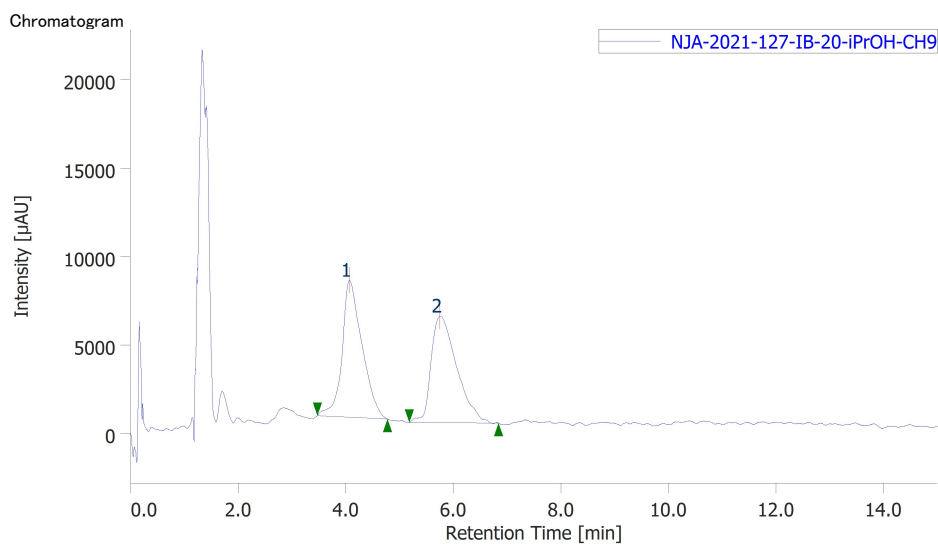


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.944	MF	0.2752	2062.32153	124.88895	10.6096
2	8.383	FM	0.3631	1.73759e4	797.59052	89.3904

Figure 2.19. HPLC trace of enantioenriched **2.28**.

NJA-2022-121-IA_and_NJA-2021-127_column-screen NJA-2021-127-IB-20-iPrOH 10/12/2022 11:37:05 AM

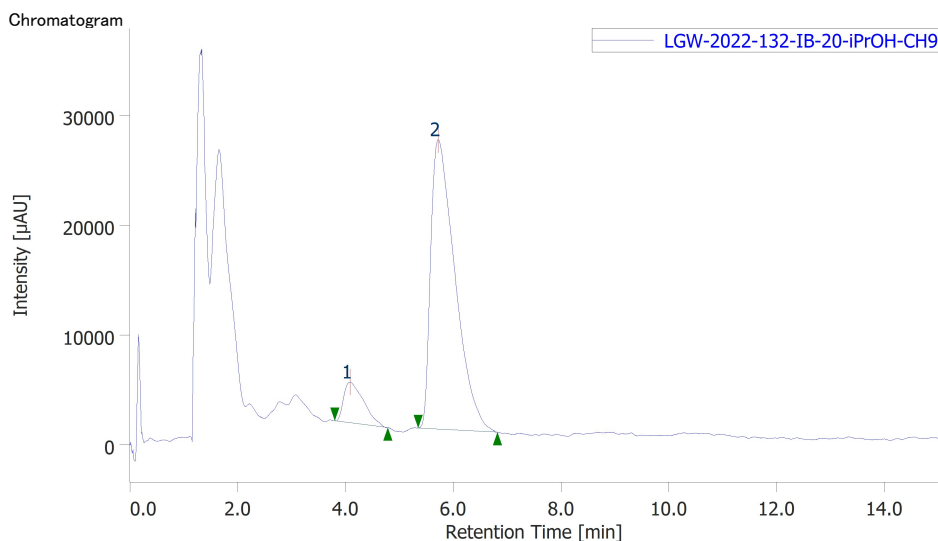


Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	4.067	199285	7736	50.058	56.268	N/A	638	2.246	1.176	
2	Unknown	9	5.750	198822	6012	49.942	43.732	N/A	717	N/A	1.595	

Figure 2.20. SFC trace of racemic **2.45**.

LGW-2022-132-135-IB-2 LGW-2022-132-IB-20-iPrOH 10/12/2022 11:38:07 AM



Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	4.083	95409	3704	10.365	12.331	N/A	515	2.115	1.829	
2	Unknown	9	5.720	825067	26333	89.635	87.669	N/A	755	N/A	1.999	

Figure 2.21. SFC trace of enantioenriched **2.45**.

2.7 Spectra Relevant to Chapter Two:

Total Synthesis of Lissodendoric Acid A via Stereospecific

Trapping of a Strained Cyclic Allene

Francesca M. Ippoliti,[†] Nathan J. Adamson,[†] Laura G. Wonilowicz, Daniel J. Nasrallah,

Evan R. Darzi, Joyann S. Donaldson, and Neil K. Garg.

Science **2023**, 379, 261–265.

2.7.1 NMR Spectra

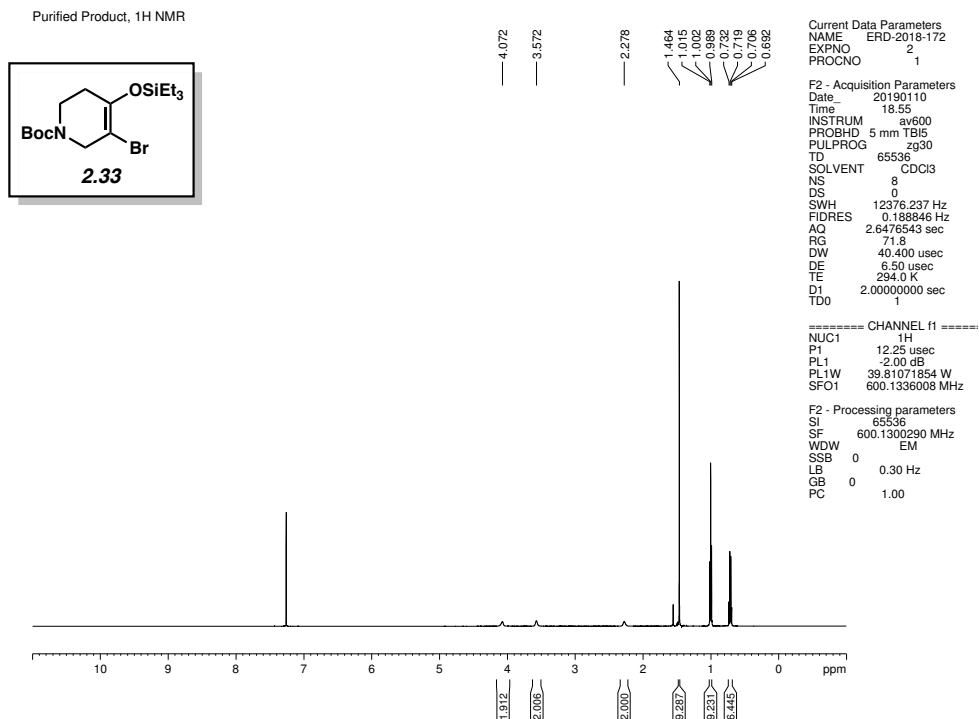


Figure 2.22. ^1H NMR (600 MHz, CDCl_3) of compound 2.33.

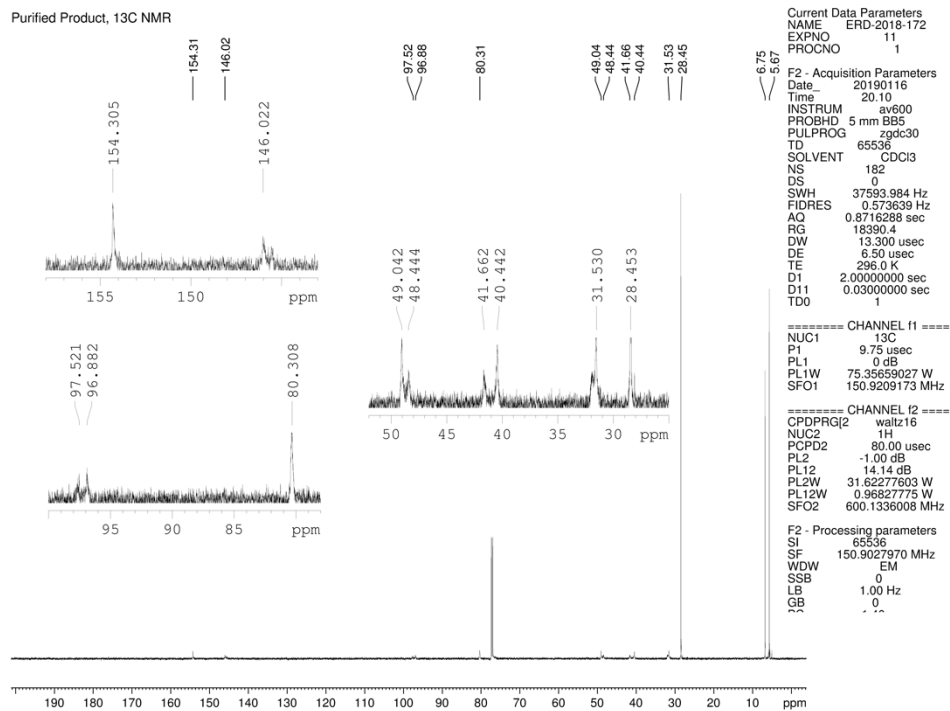


Figure 2.23. ^{13}C NMR (150 MHz, CDCl_3) of compound 2.33.

Purified Product, ¹H NMR

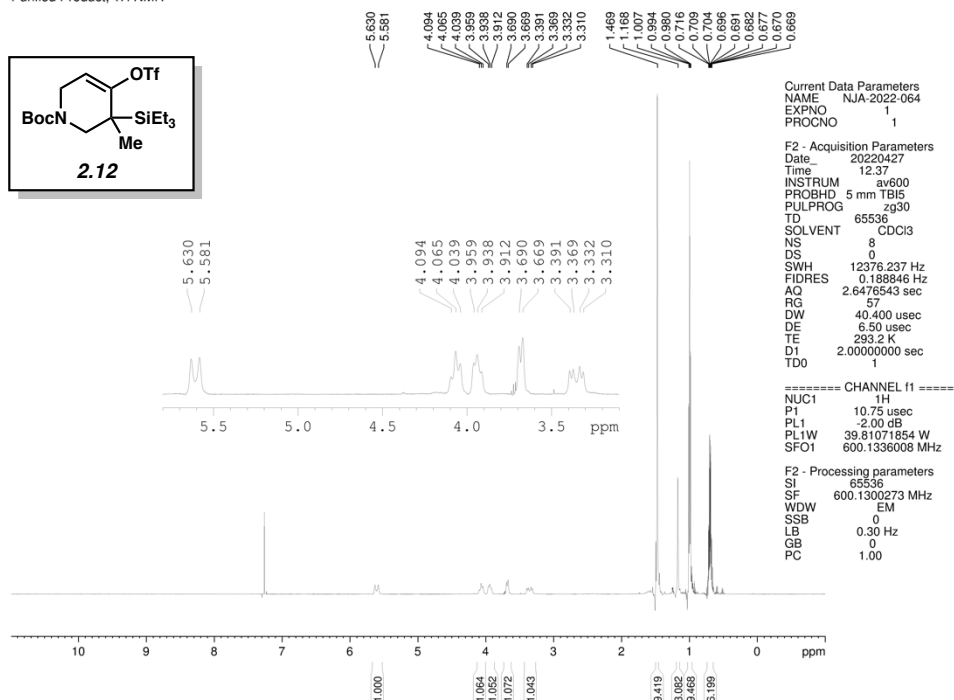


Figure 2.24. ¹H NMR (600 MHz, CDCl₃) of compound **2.12**.

Purified Product, ¹³C NMR

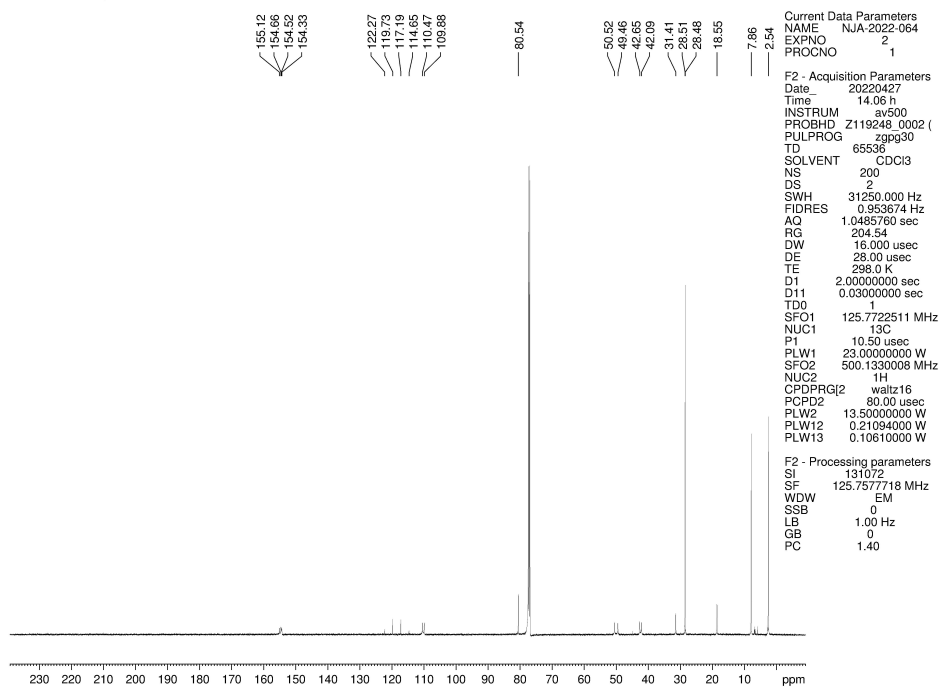


Figure 2.25. ¹³C NMR (125 MHz, CDCl₃) of compound **2.12**.

Purified Product, ¹H NMR

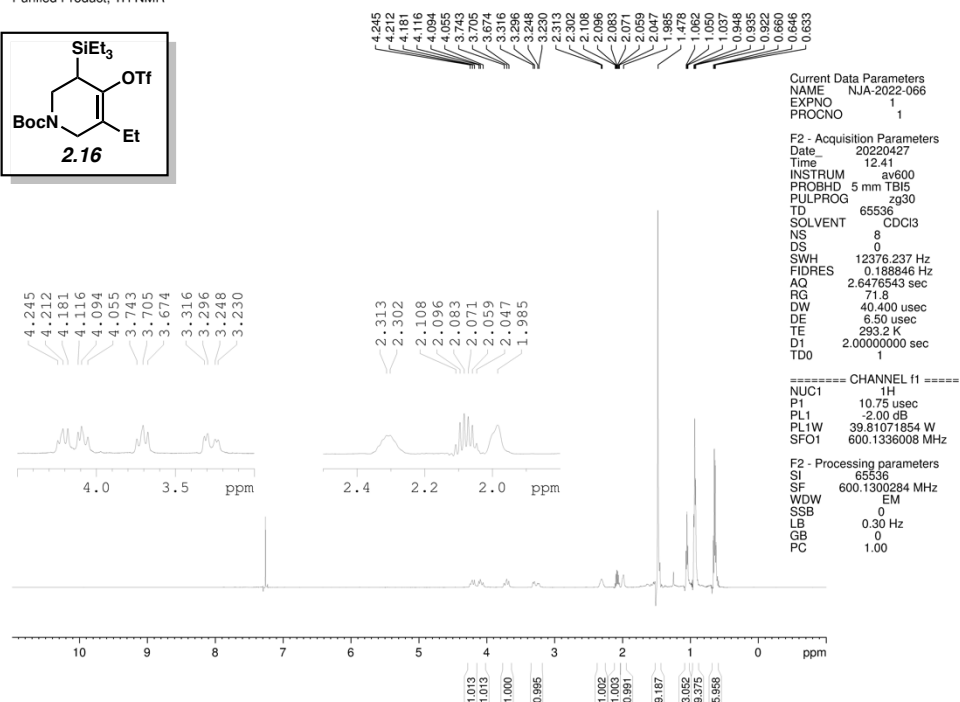
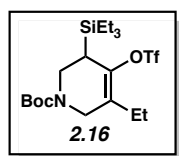


Figure 2.26 ¹H NMR (600 MHz, CDCl₃) of compound **2.16**.

Purified Product, ¹³C NMR

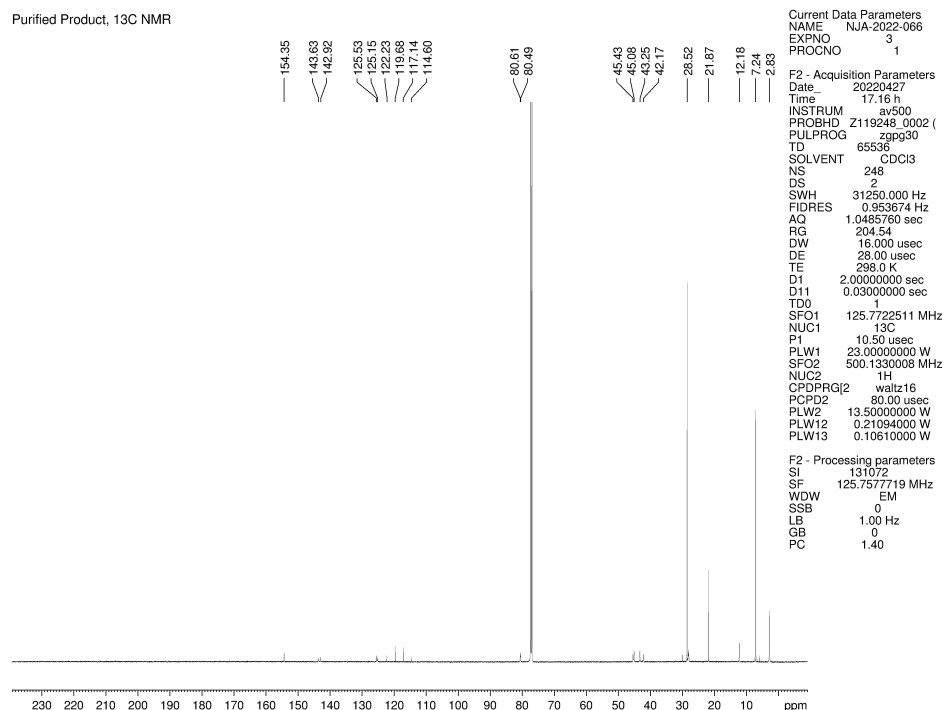


Figure 2.27 ¹³C NMR (125 MHz, CDCl₃) of compound **2.16**.

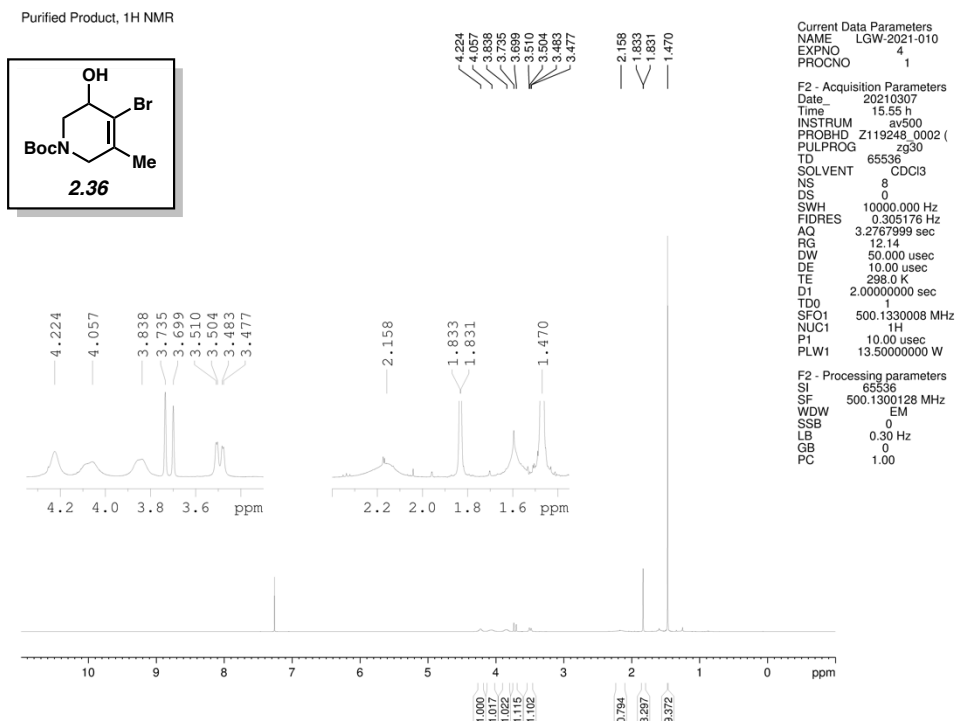


Figure 2.28. ^1H NMR (500 MHz, CDCl_3) of compound **2.36**.

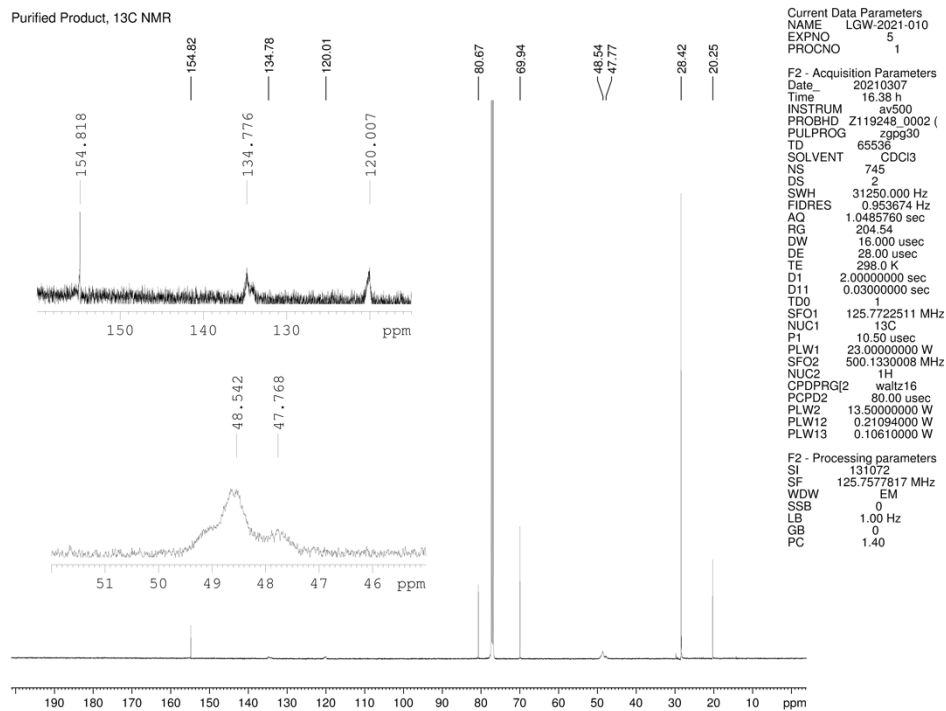


Figure 2.29. ^{13}C NMR (125 MHz, CDCl_3) of compound **2.36**.

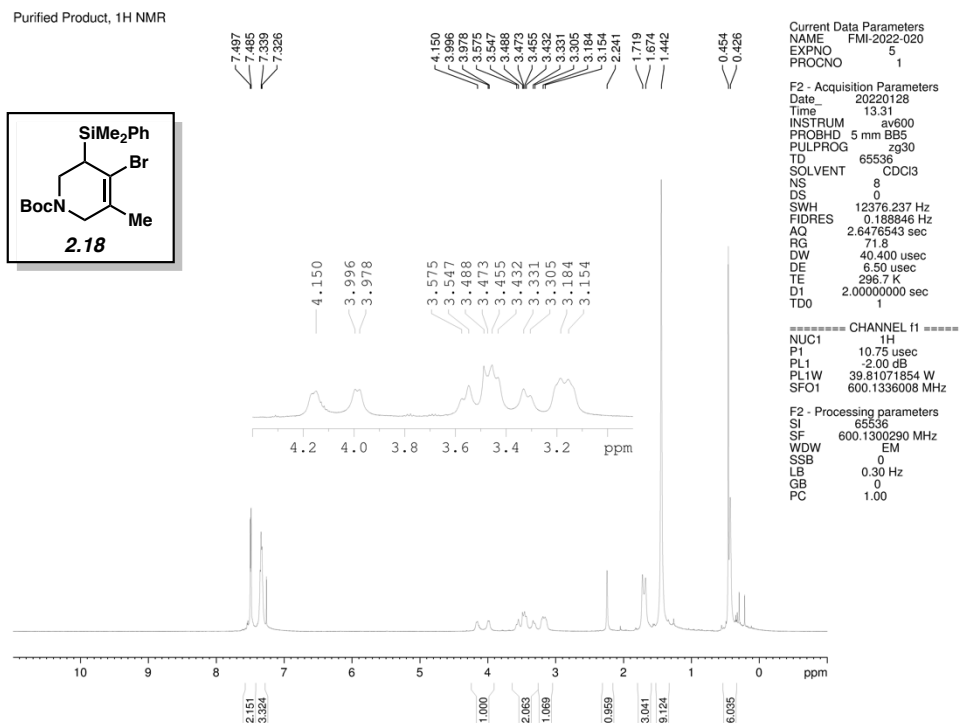


Figure 2.30. ^1H NMR (600 MHz, CDCl_3) of compound **2.18**.

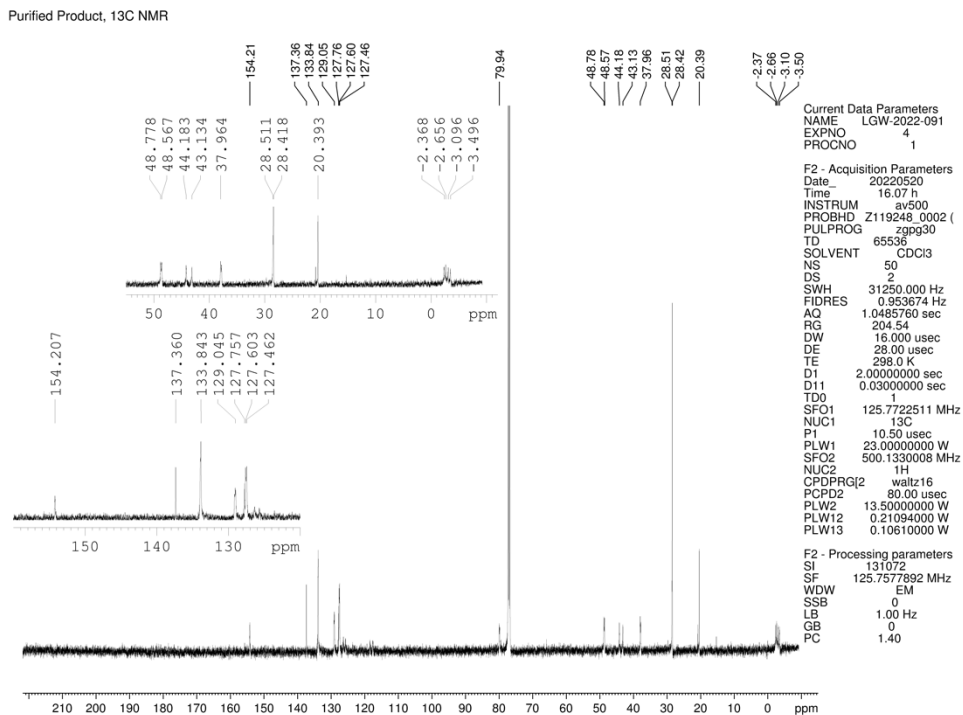


Figure 2.31. ^{13}C NMR (125 MHz, CDCl_3) of compound **2.18**.

Purified Product, ¹H NMR

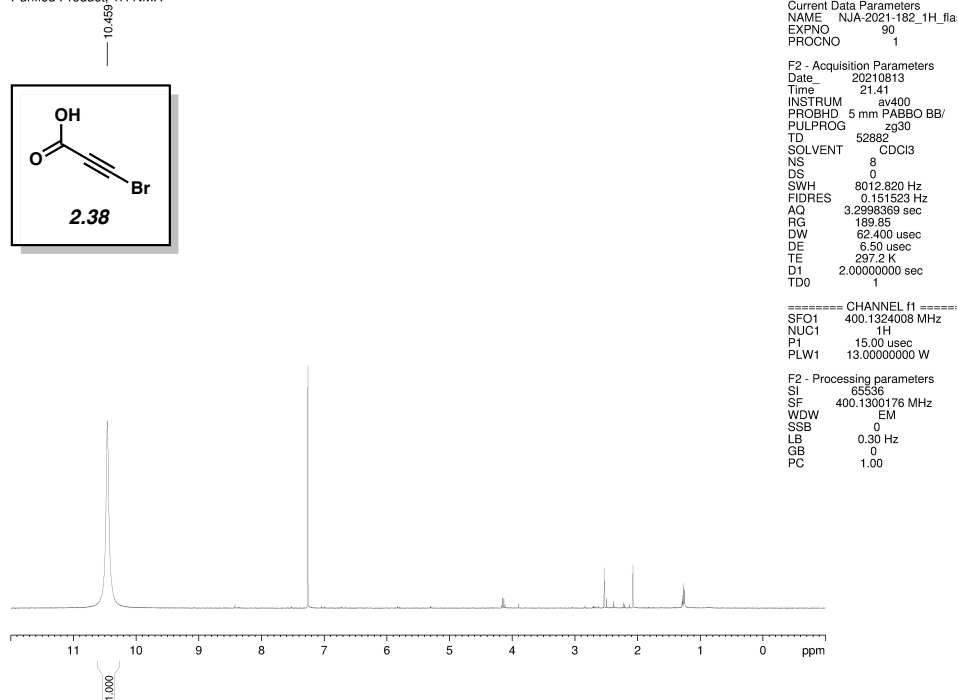


Figure 2.32. ¹H NMR (400 MHz, CDCl₃) of compound **2.38**.

Purified Product, ¹³C NMR

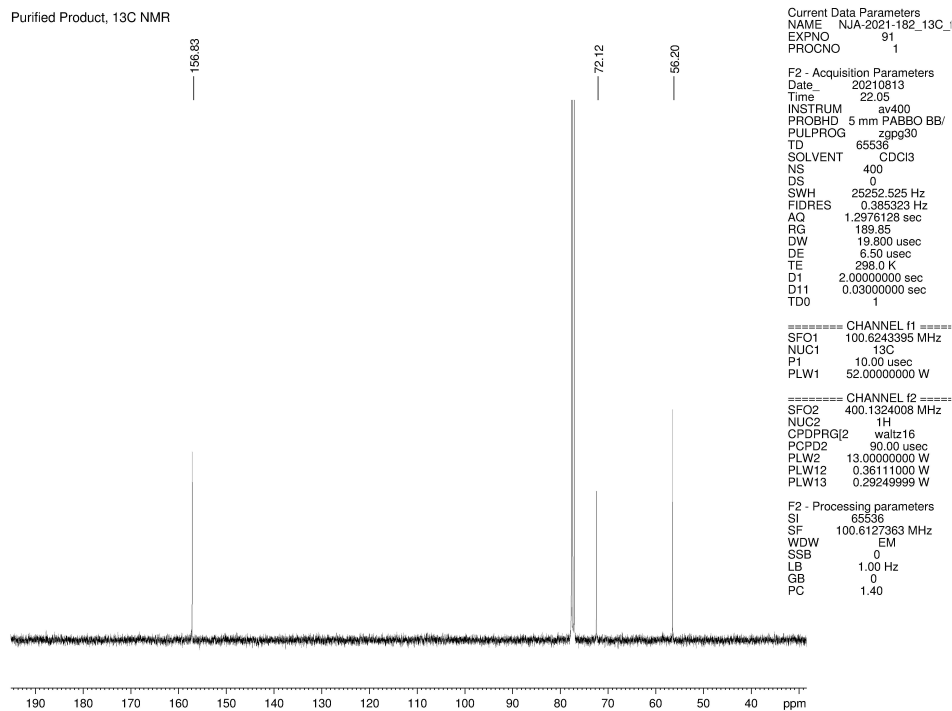


Figure 2.33. ¹³C NMR (100 MHz, CDCl₃) of compound **2.38**.

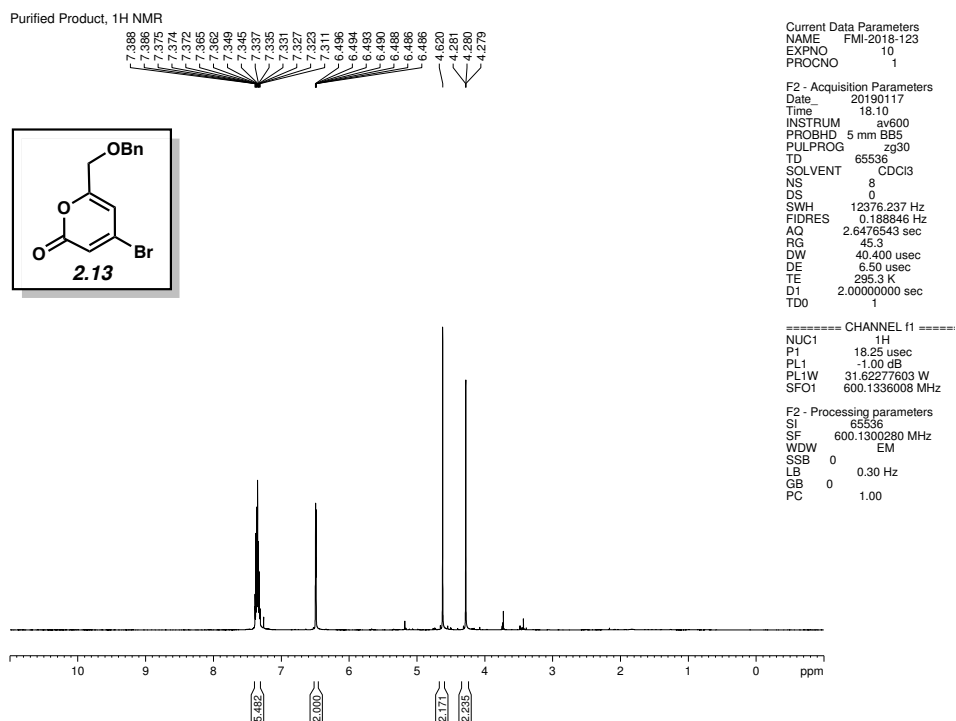


Figure 2.34. ¹H NMR (600 MHz, CDCl₃) of compound 2.13.

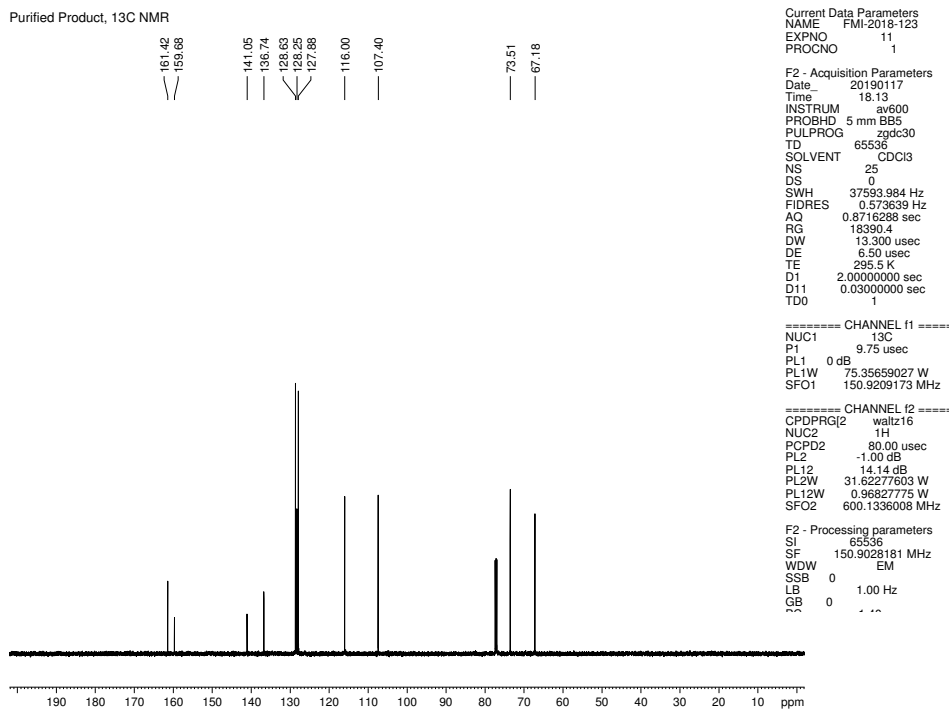


Figure 2.35. ¹³C NMR (150 MHz, CDCl₃) of compound 2.13.

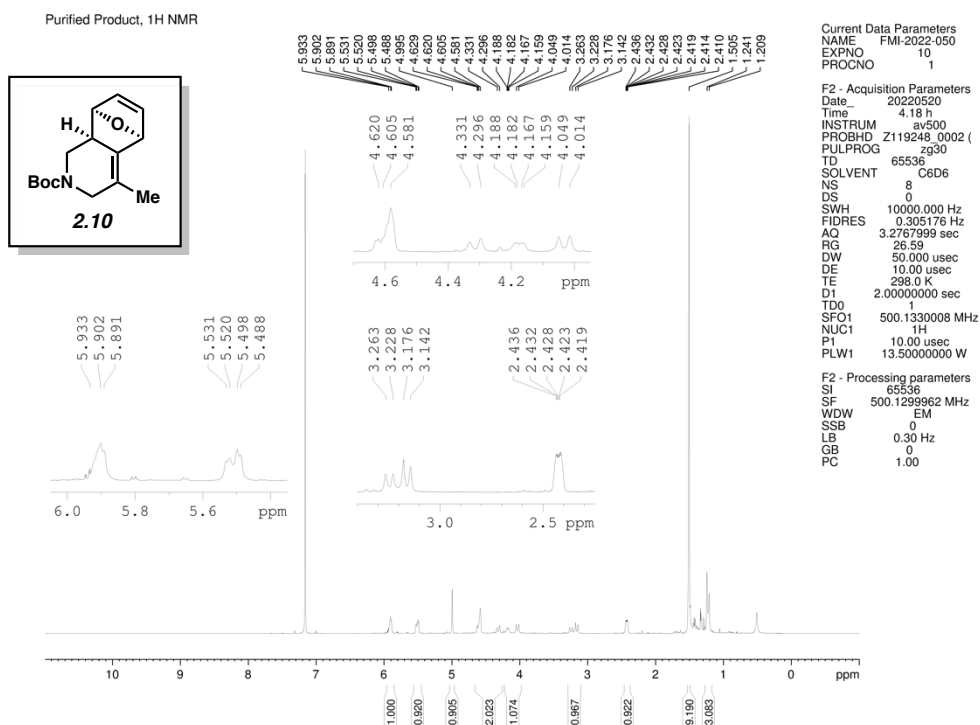


Figure 2.36. ¹H NMR (500 MHz, C₆D₆) of compound **2.10**.

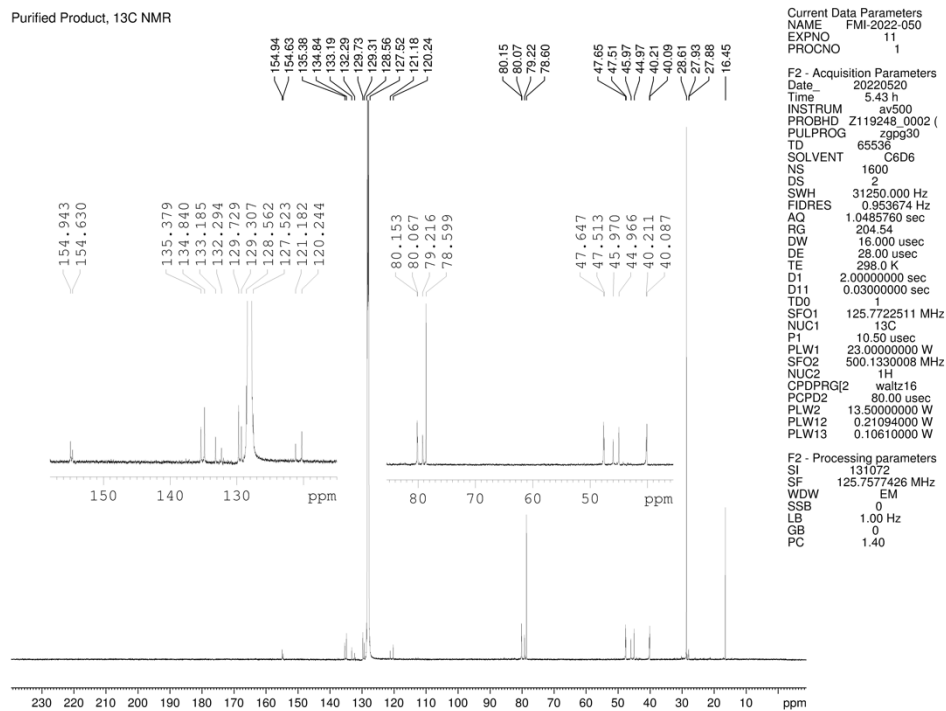


Figure 2.37. ¹³C NMR (125 MHz, C₆D₆) of compound **2.10**.

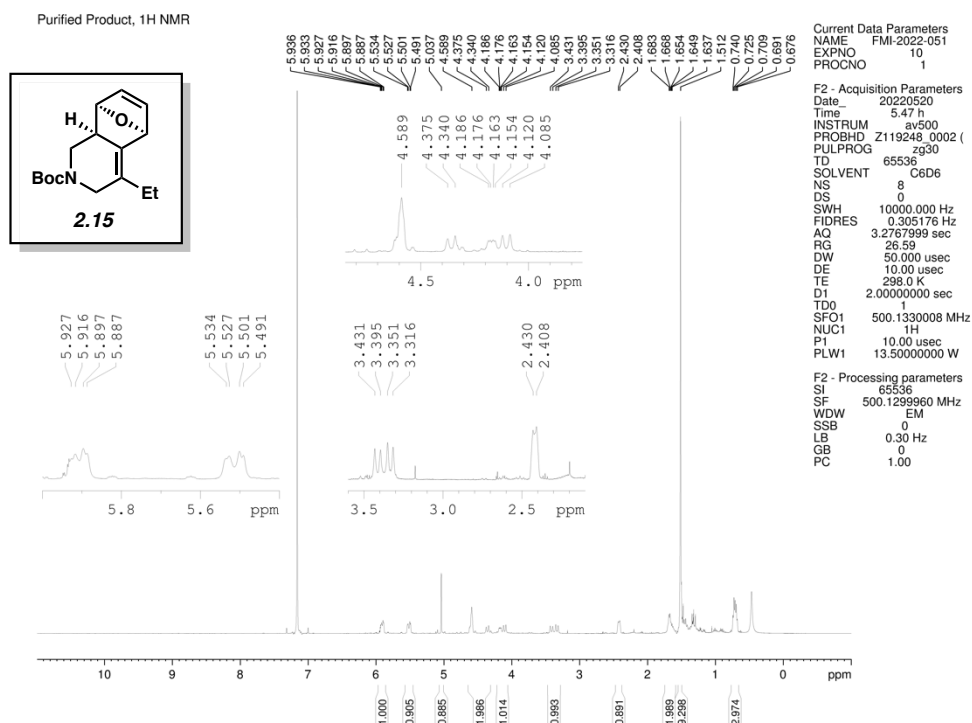


Figure 2.38. ^1H NMR (500 MHz, C_6D_6) of compound **2.15**.

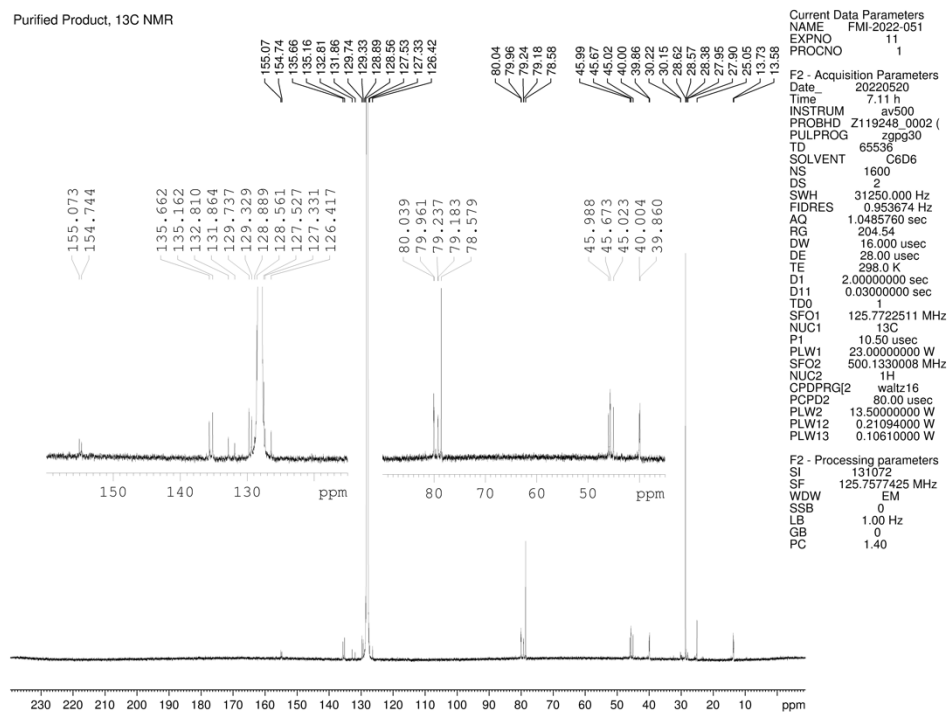


Figure 2.39. ^{13}C NMR (125 MHz, C_6D_6) of compound **2.15**.

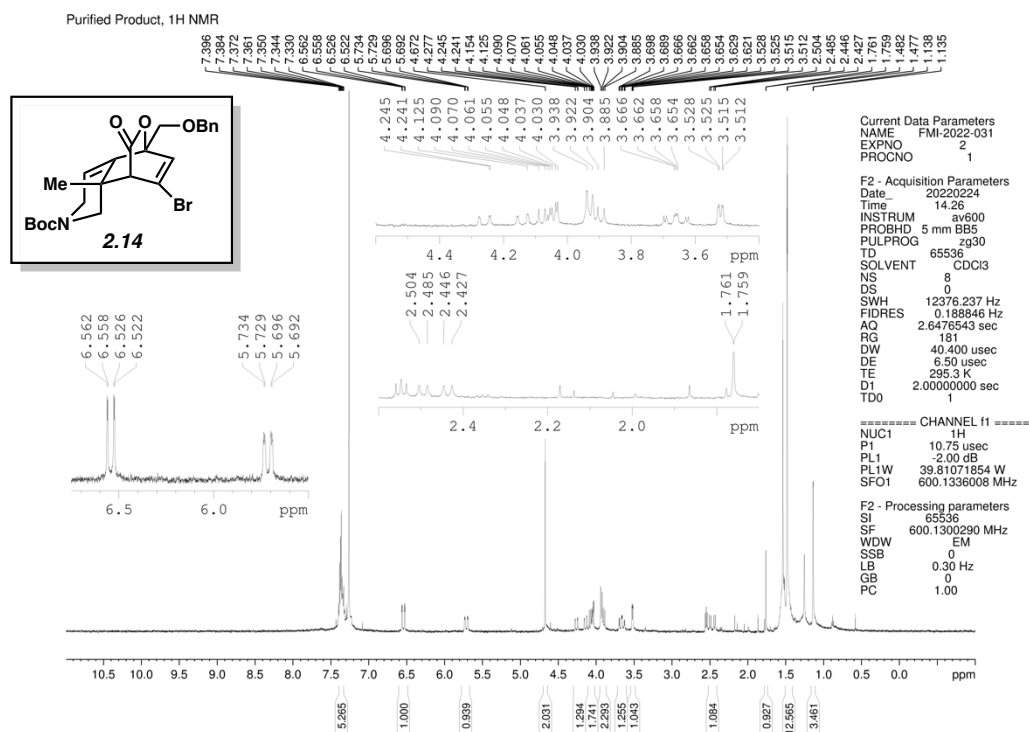


Figure 2.40. ¹H NMR (600 MHz, CDCl₃) of compound 2.14.

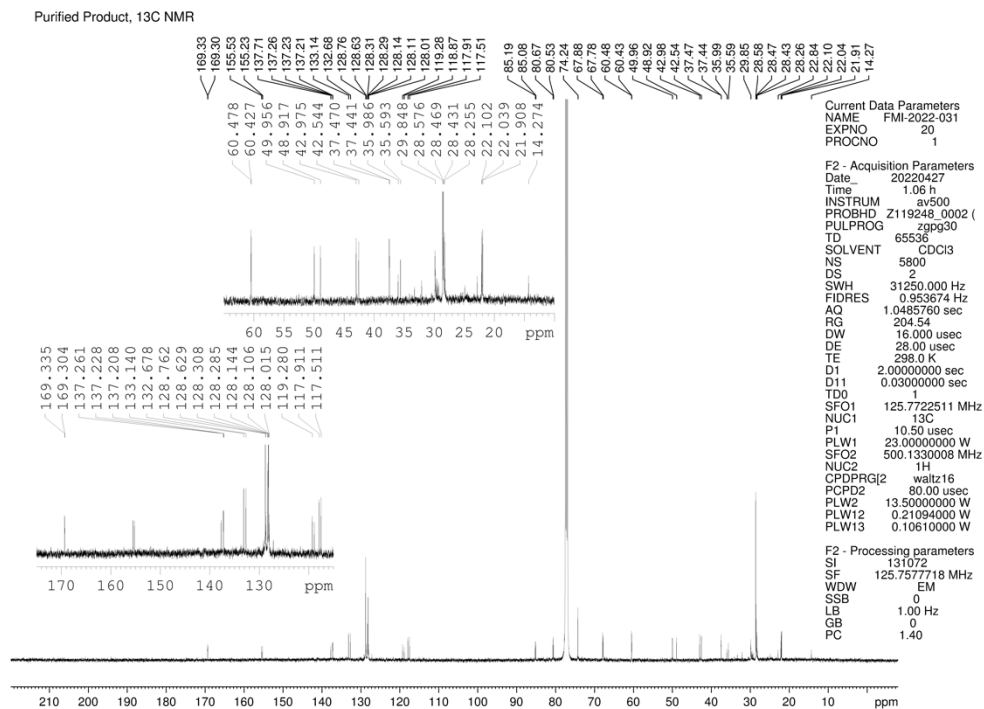


Figure 2.41. ¹³C NMR (125 MHz, CDCl₃) of compound 2.14.

Purified Product, ¹H NMR

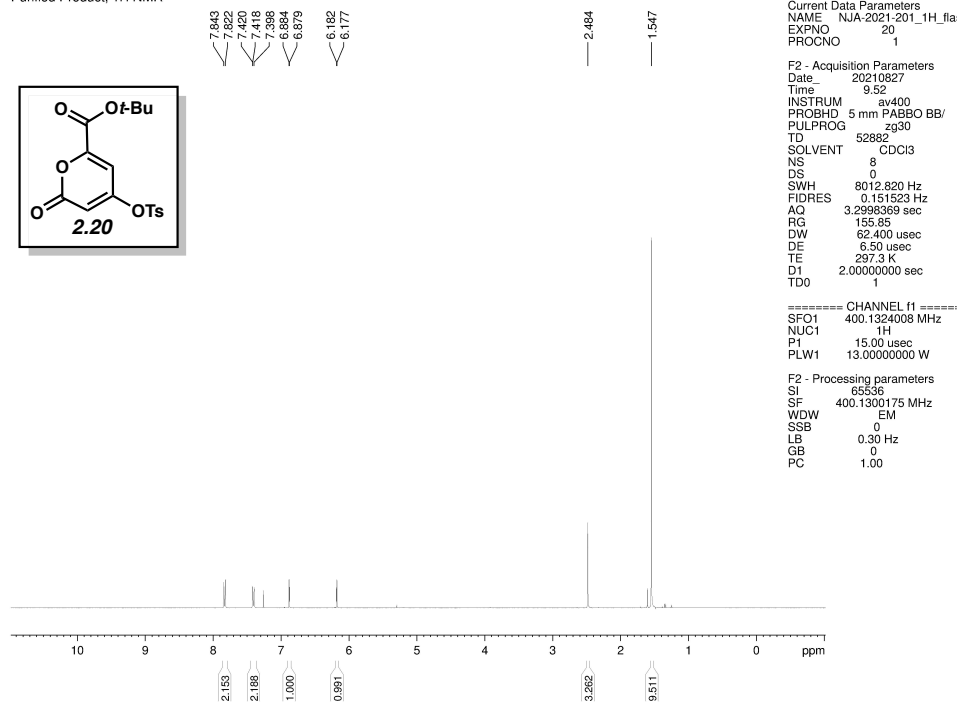
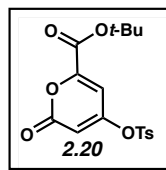


Figure 2.44. ¹H NMR (400 MHz, CDCl₃) of compound **2.20**.

Purified Product, ¹³C NMR

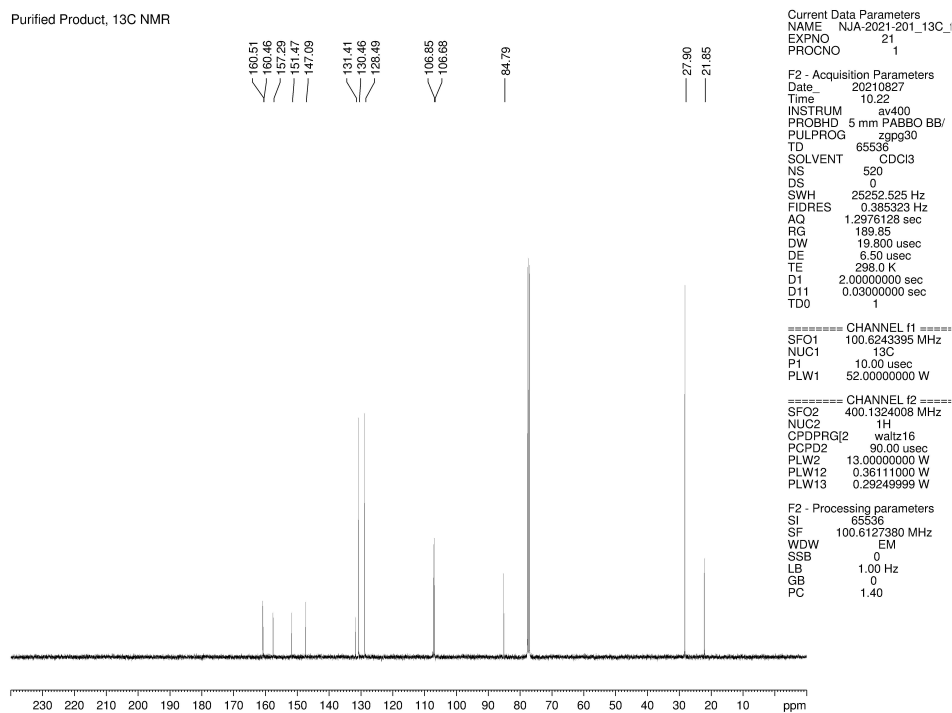


Figure 2.45. ¹³C NMR (100 MHz, CDCl₃) of compound **2.20**.

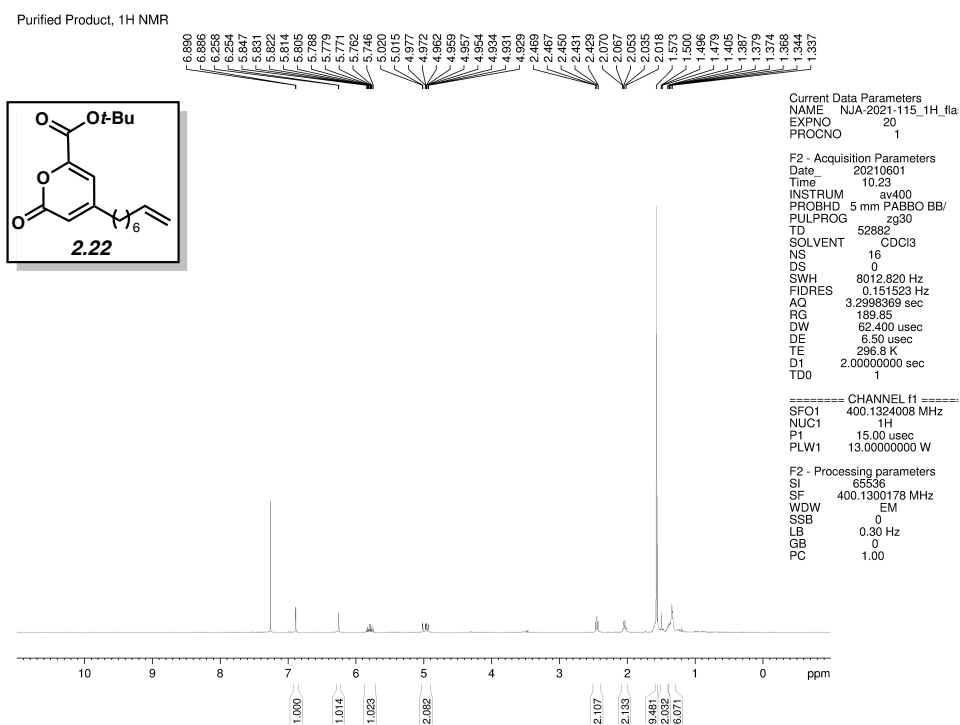


Figure 2.46. ^1H NMR (400 MHz, CDCl_3) of compound **2.22**.

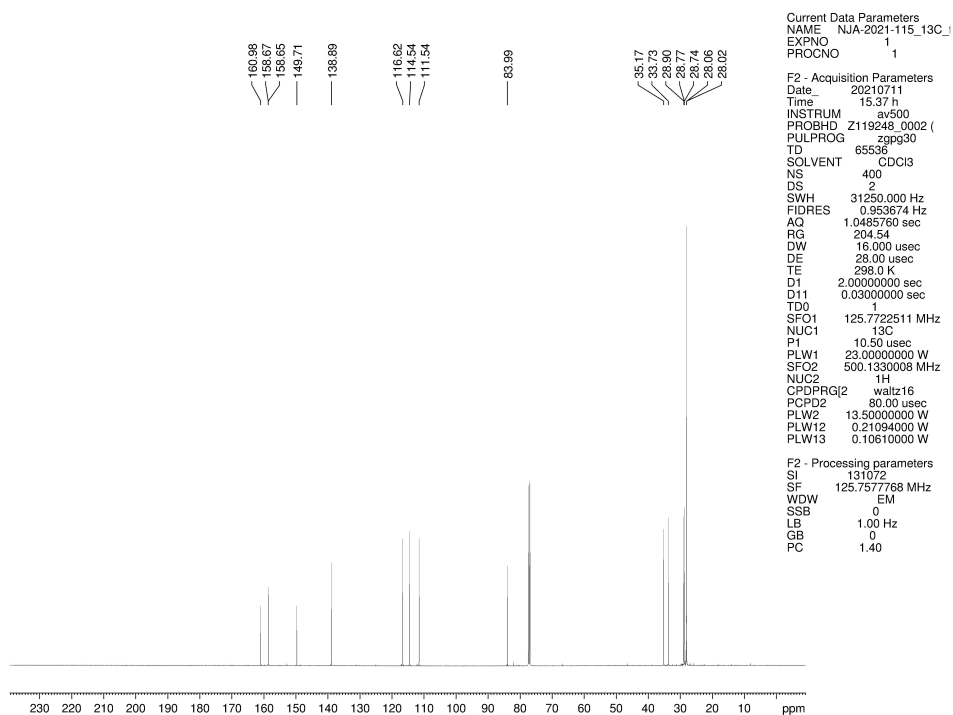


Figure 2.47. ^{13}C NMR (100 MHz, CDCl_3) of compound **2.22**.

Purified Product, ^1H NMR

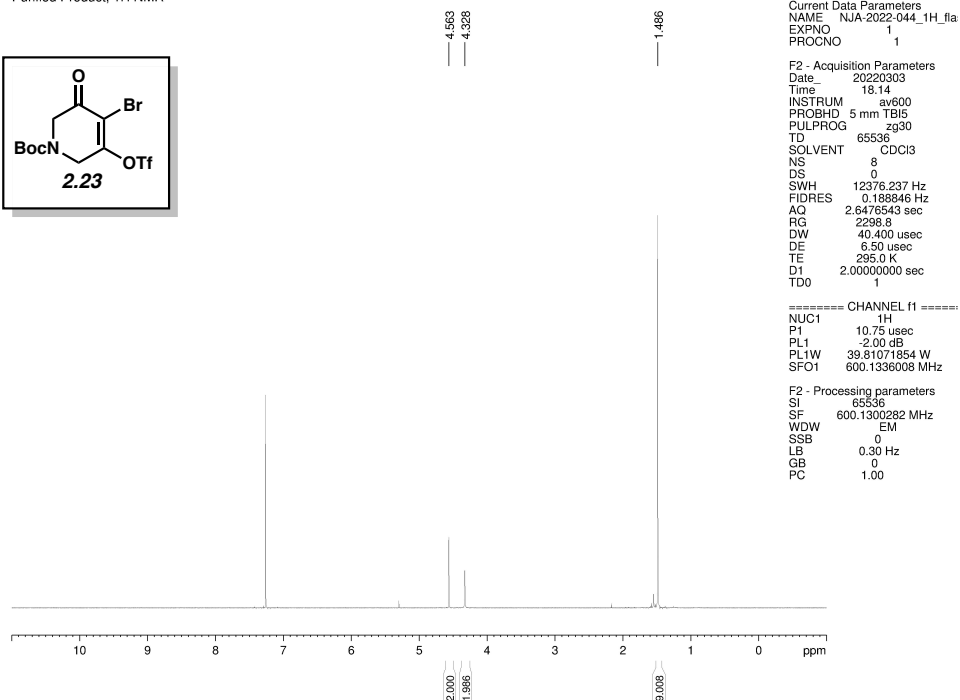
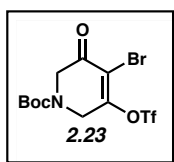


Figure 2.48. ^1H NMR (600 MHz, CDCl_3) of compound **2.23**.

Purified Product, ^{13}C NMR

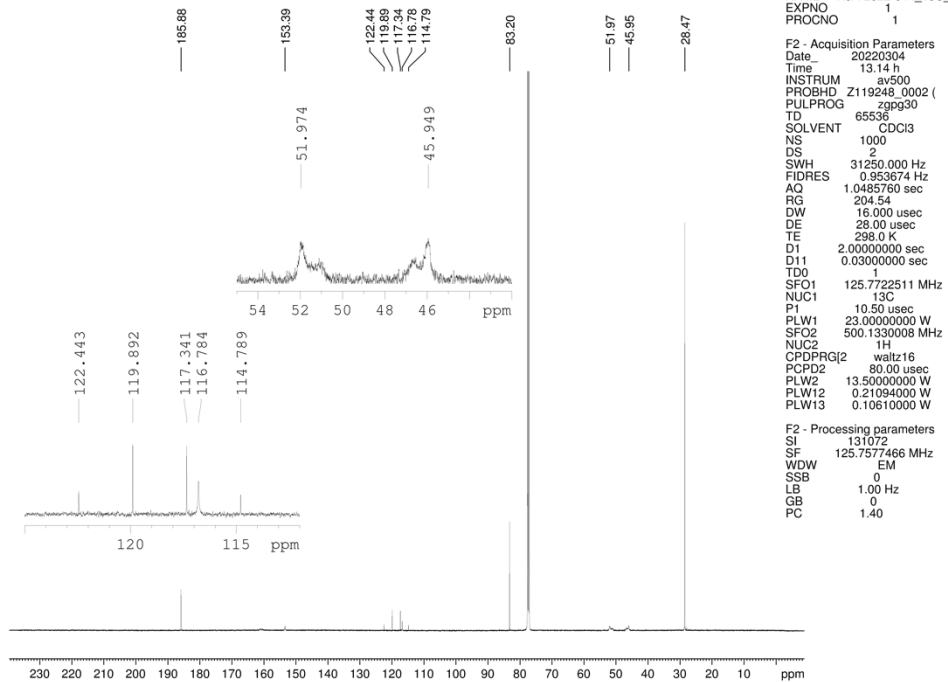


Figure 2.49. ^{13}C NMR (125 MHz, CDCl_3) of compound **2.23**.

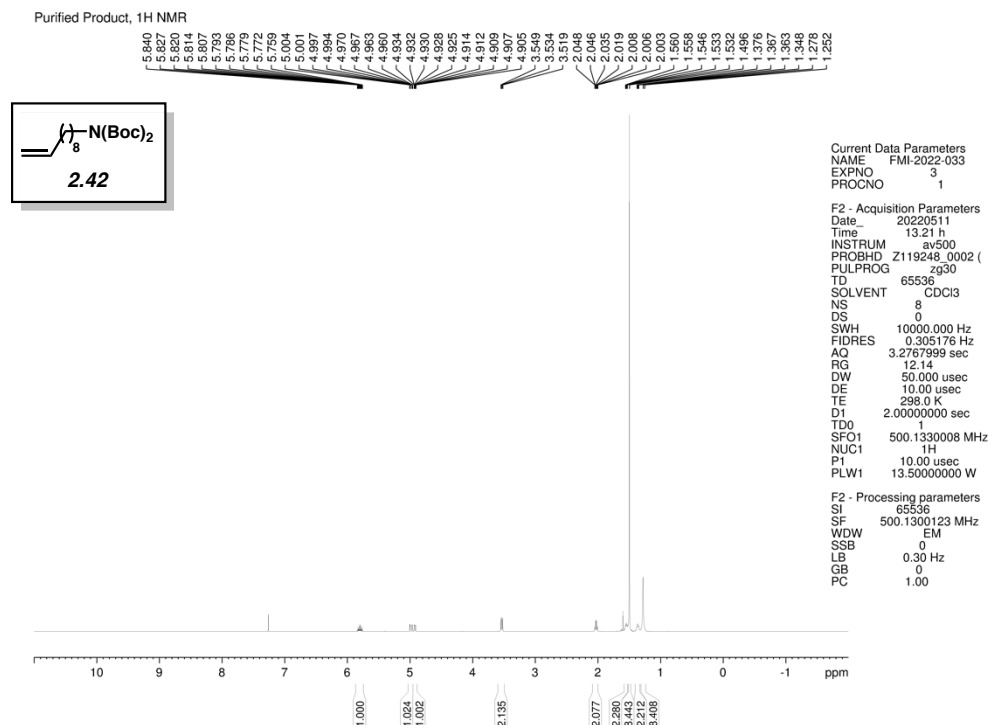


Figure 2.50. ¹H NMR (500 MHz, CDCl₃) of compound 2.42.

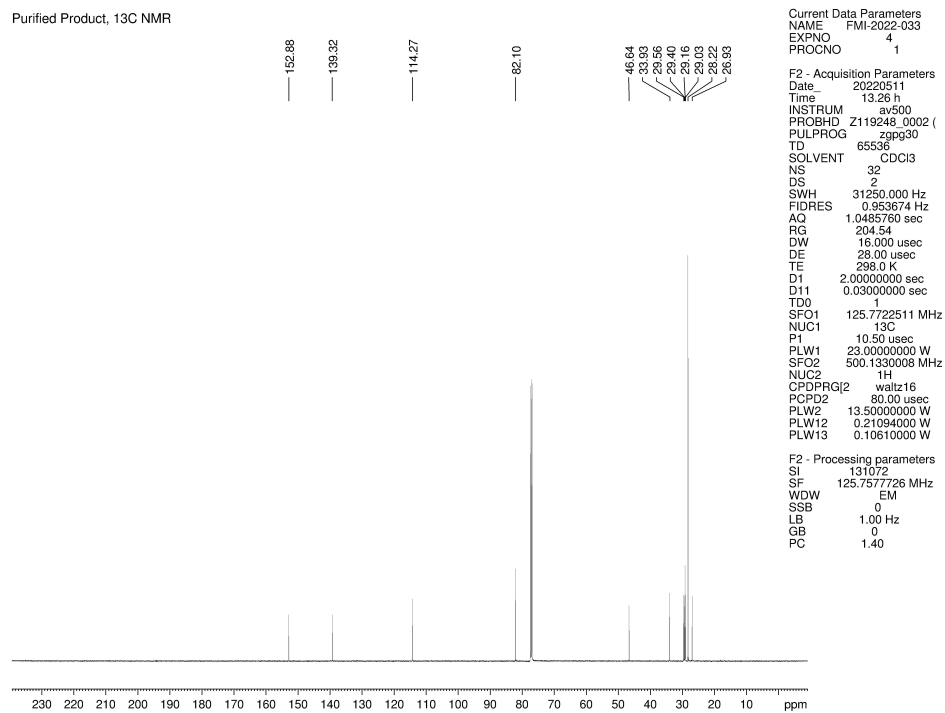


Figure 2.51. ¹³C NMR (125 MHz, CDCl₃) of compound 2.42.







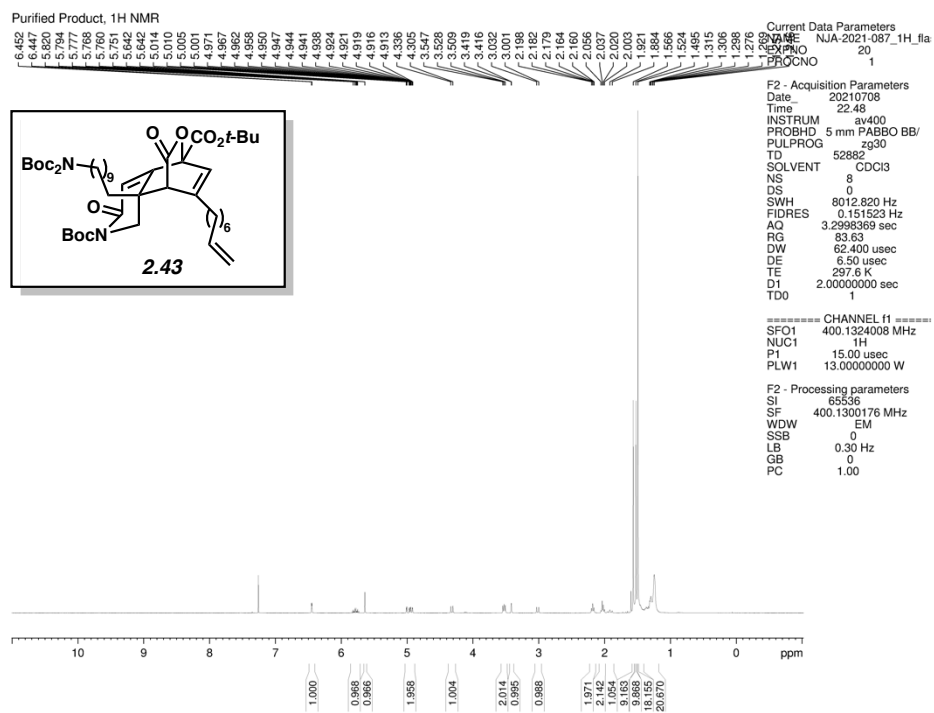


Figure 2.60. ¹H NMR (400 MHz, CDCl₃) of compound 2.43.

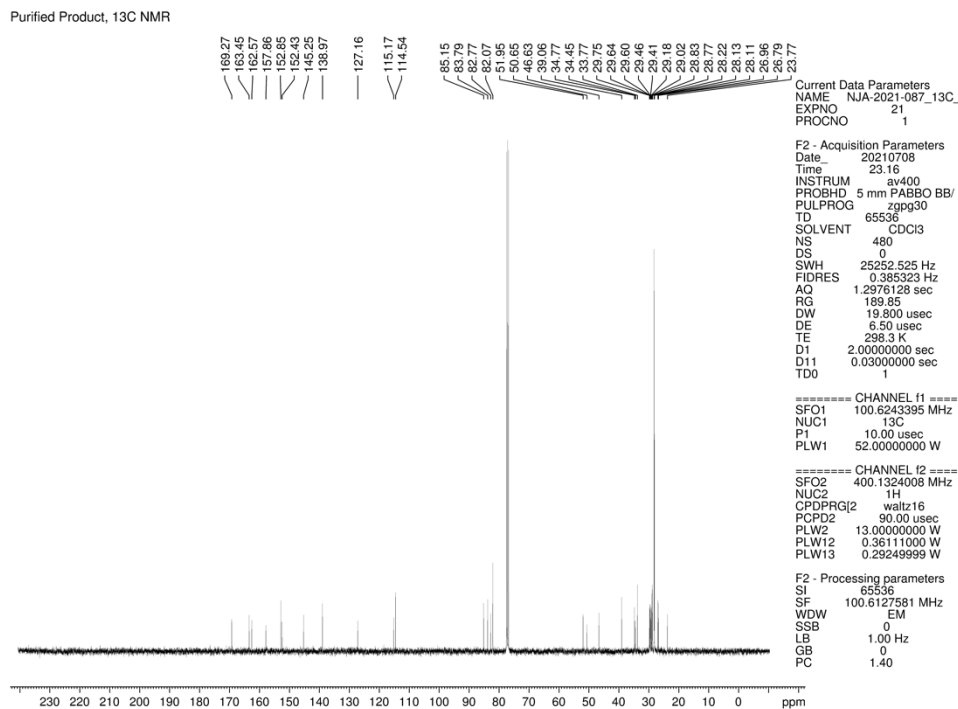


Figure 2.61. ¹³C NMR (125 MHz, CDCl₃) of compound 2.43.

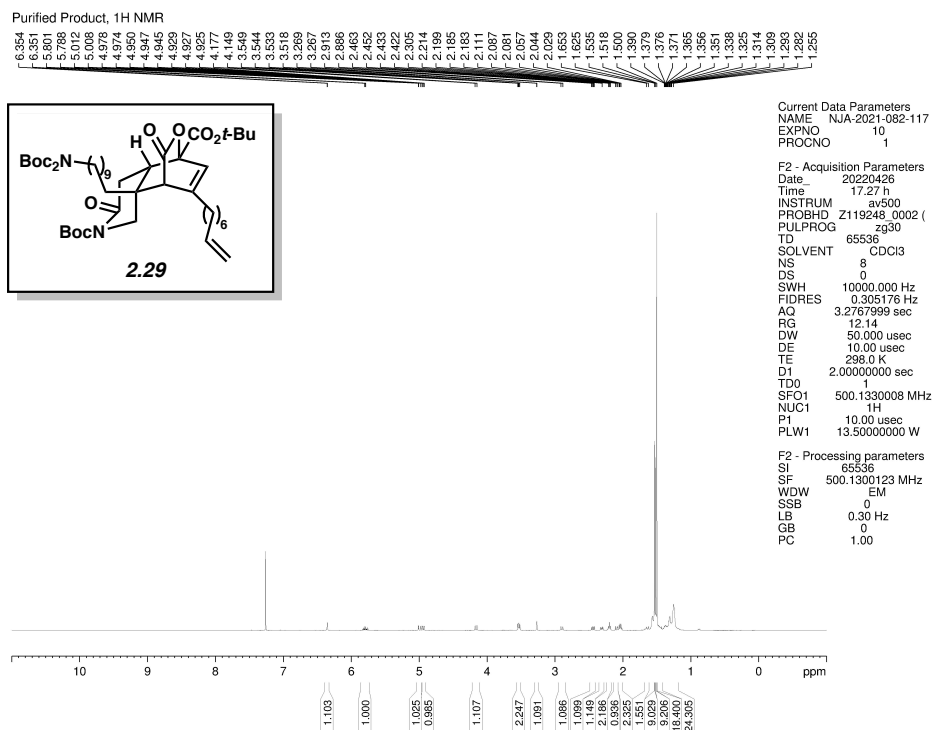


Figure 2.64. ¹H NMR (500 MHz, CDCl₃) of compound 2.29.

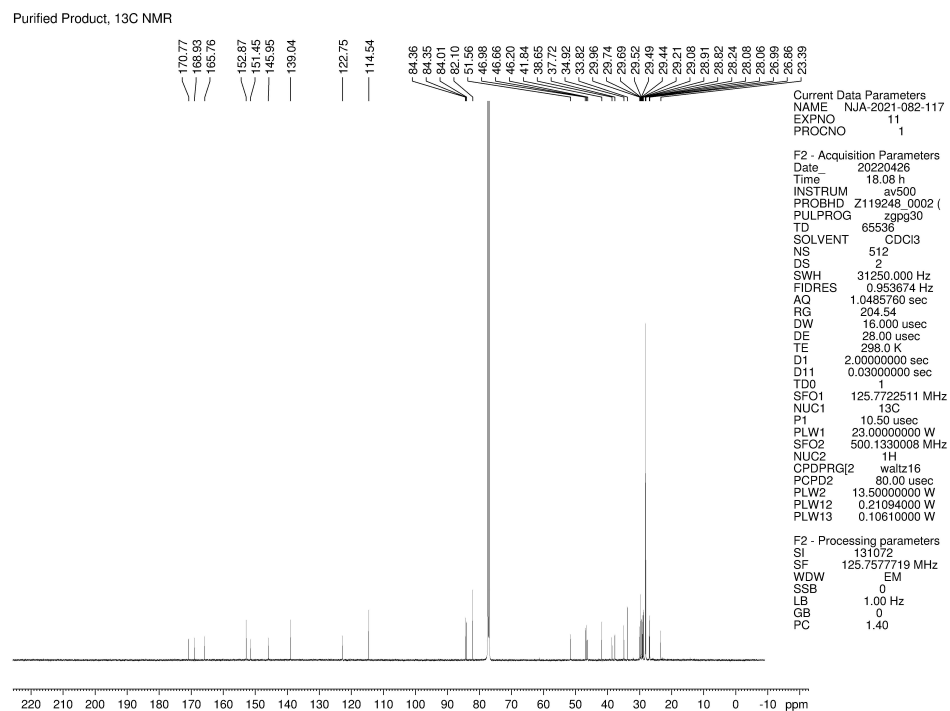


Figure 2.65. ¹³C NMR (125 MHz, CDCl₃) of compound 2.29.

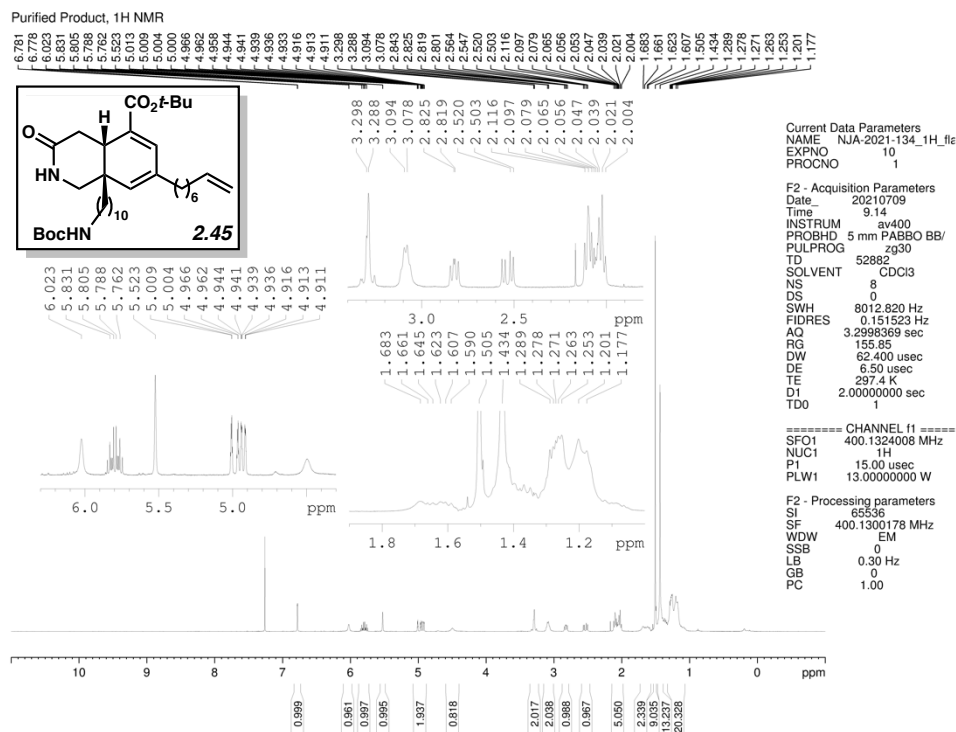


Figure 2.66. ¹H NMR (400 MHz, CDCl₃) of compound 2.45.

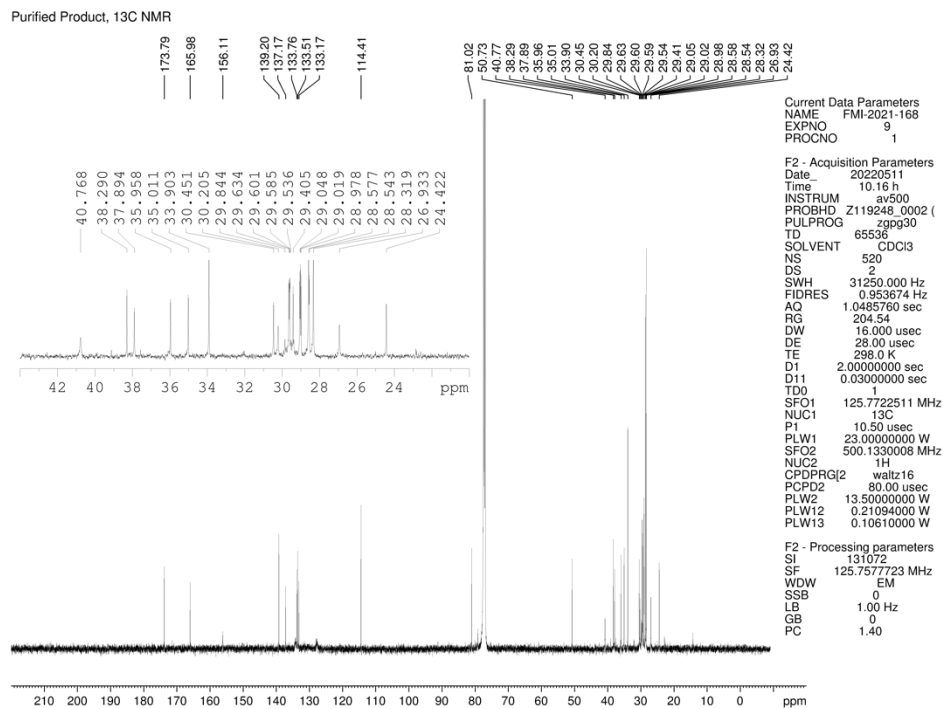


Figure 2.67. ¹³C NMR (125 MHz, CDCl₃) of compound 2.45.

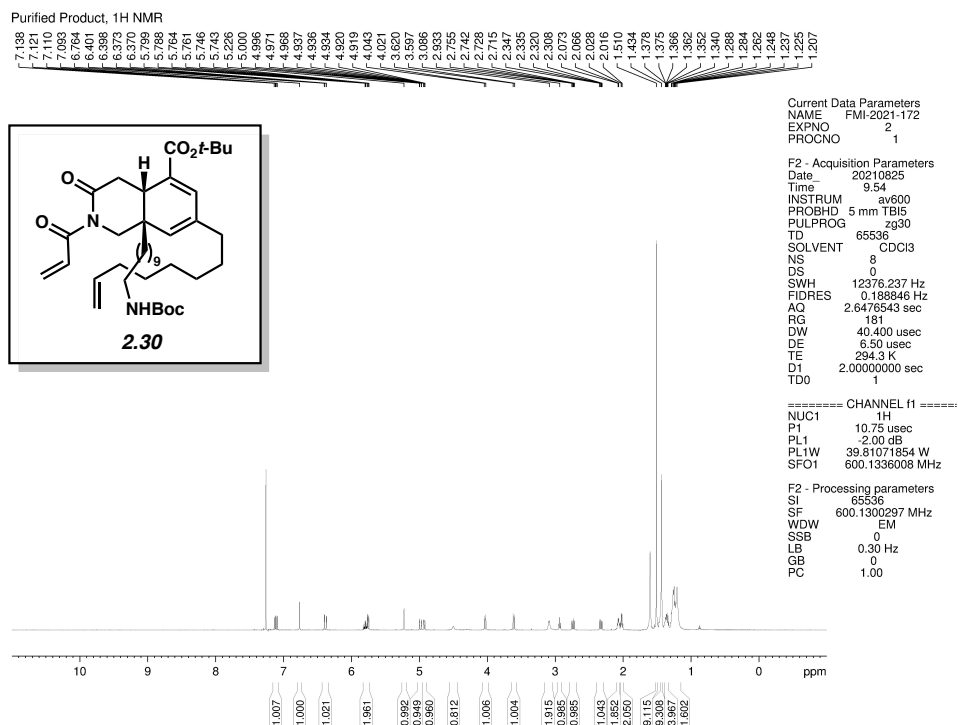


Figure 2.68. ¹H NMR (600 MHz, CDCl_3) of compound 2.30.

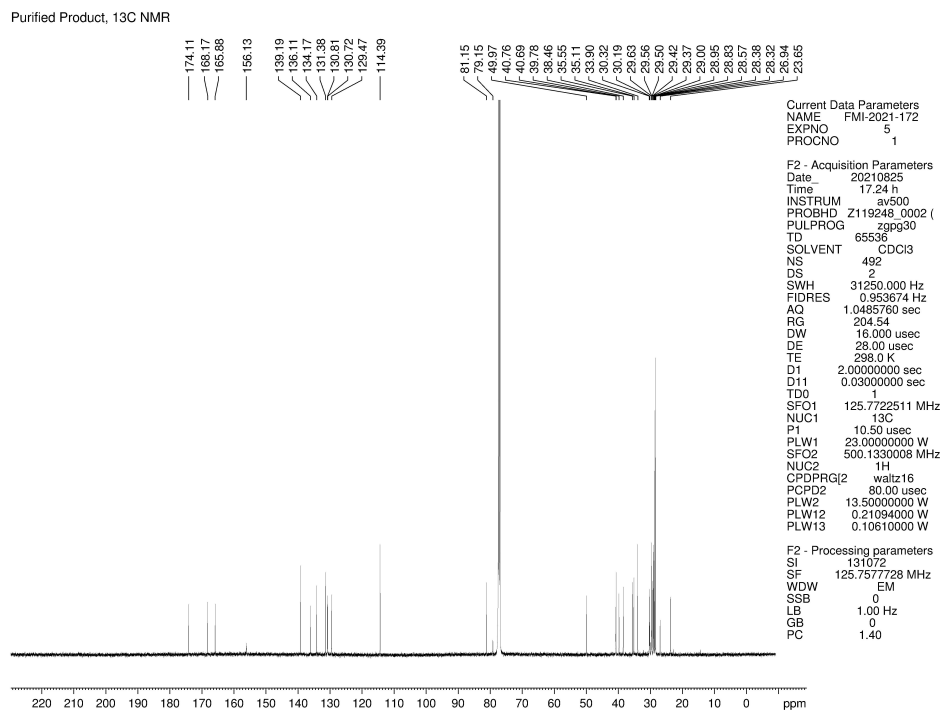


Figure 2.69. ¹³C NMR (125 MHz, CDCl_3) of compound 2.30.

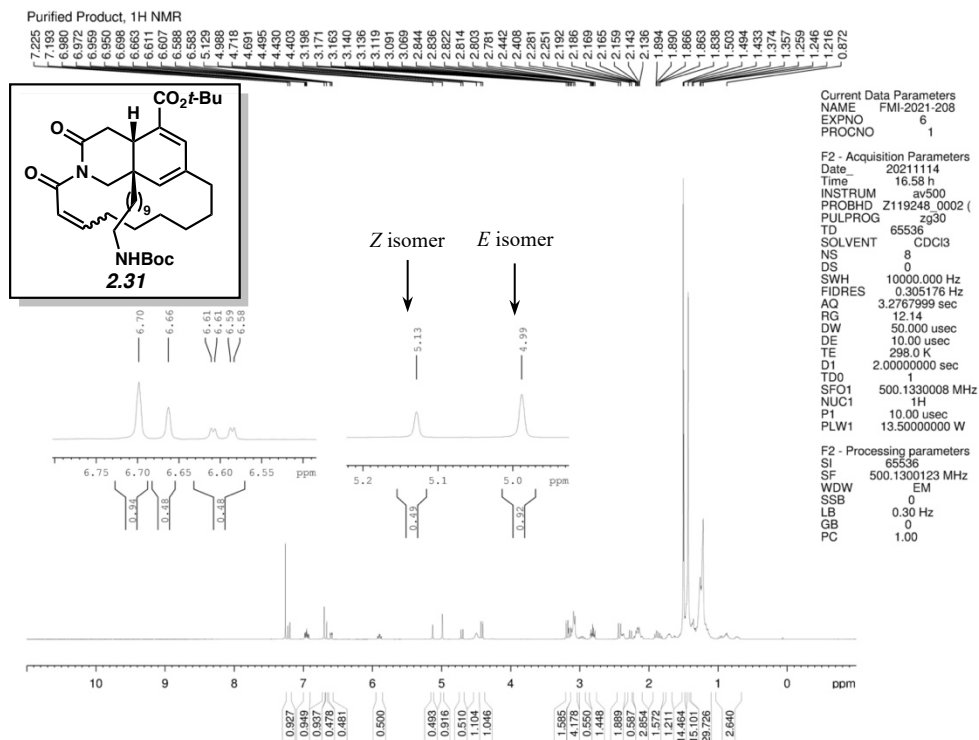


Figure 2.70. ^1H NMR (500 MHz, CDCl_3) of compound **2.31**.

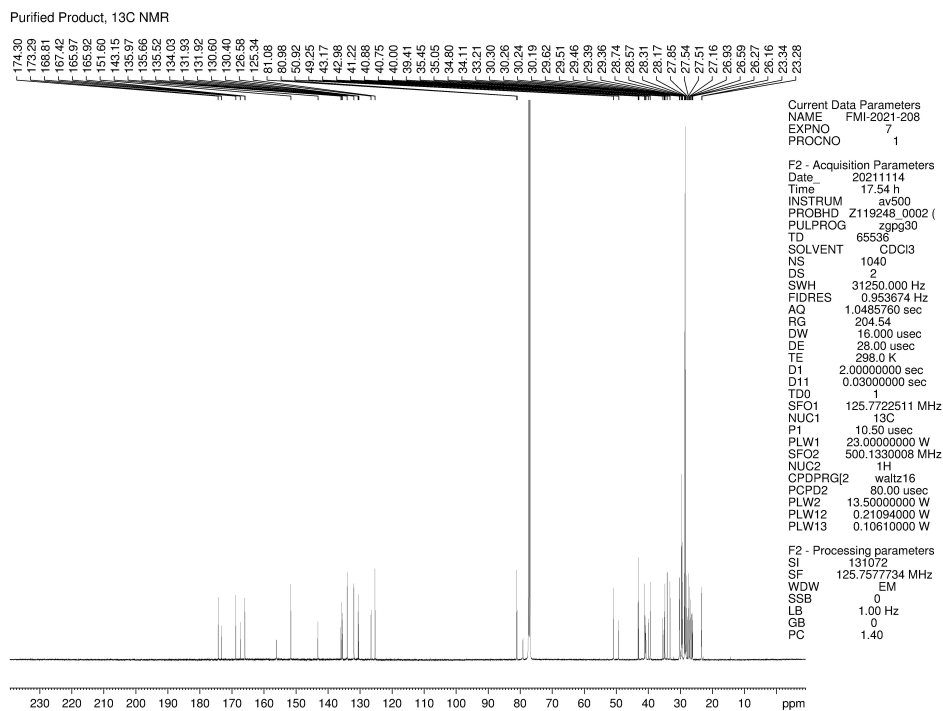


Figure 2.71. ^{13}C NMR (125 MHz, CDCl_3) of compound **2.31**.

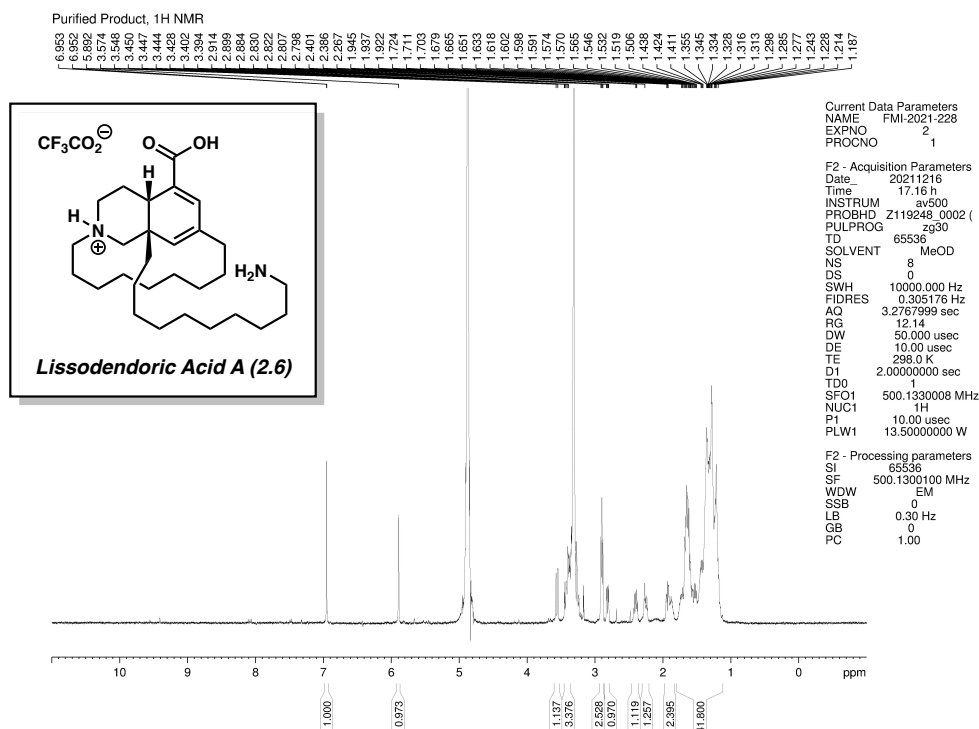


Figure 2.72. ¹H NMR (500 MHz, CD₃OD) of synthetic lissodendoric acid A (2.6).

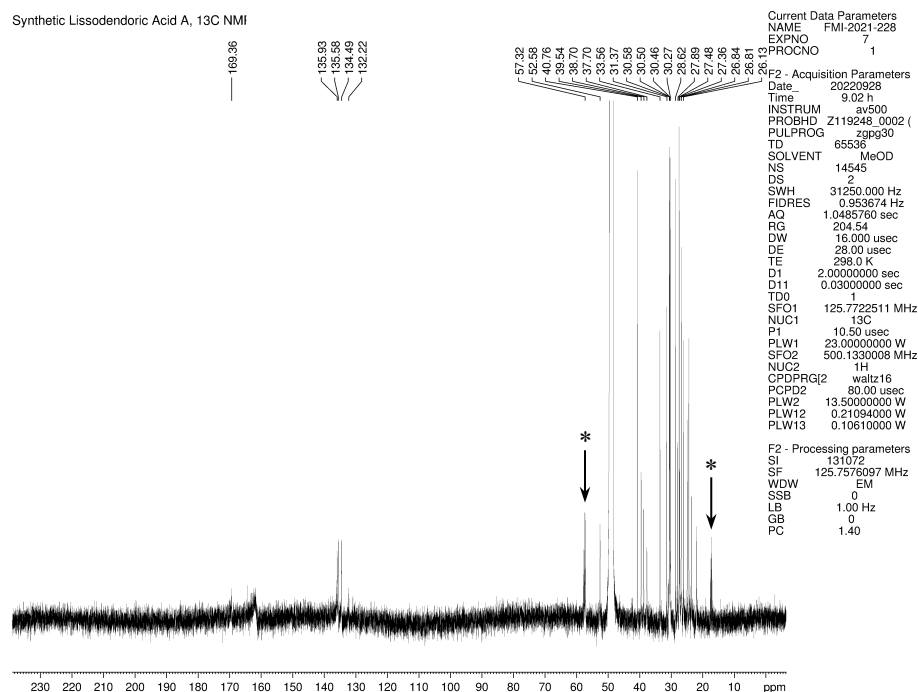


Figure 2.73. ¹³C NMR (125 MHz, CD₃OD) of synthetic lissodendoric acid A (2.6).

* CD₃CD₂OD impurity thought to originate from commercial CD₃OD

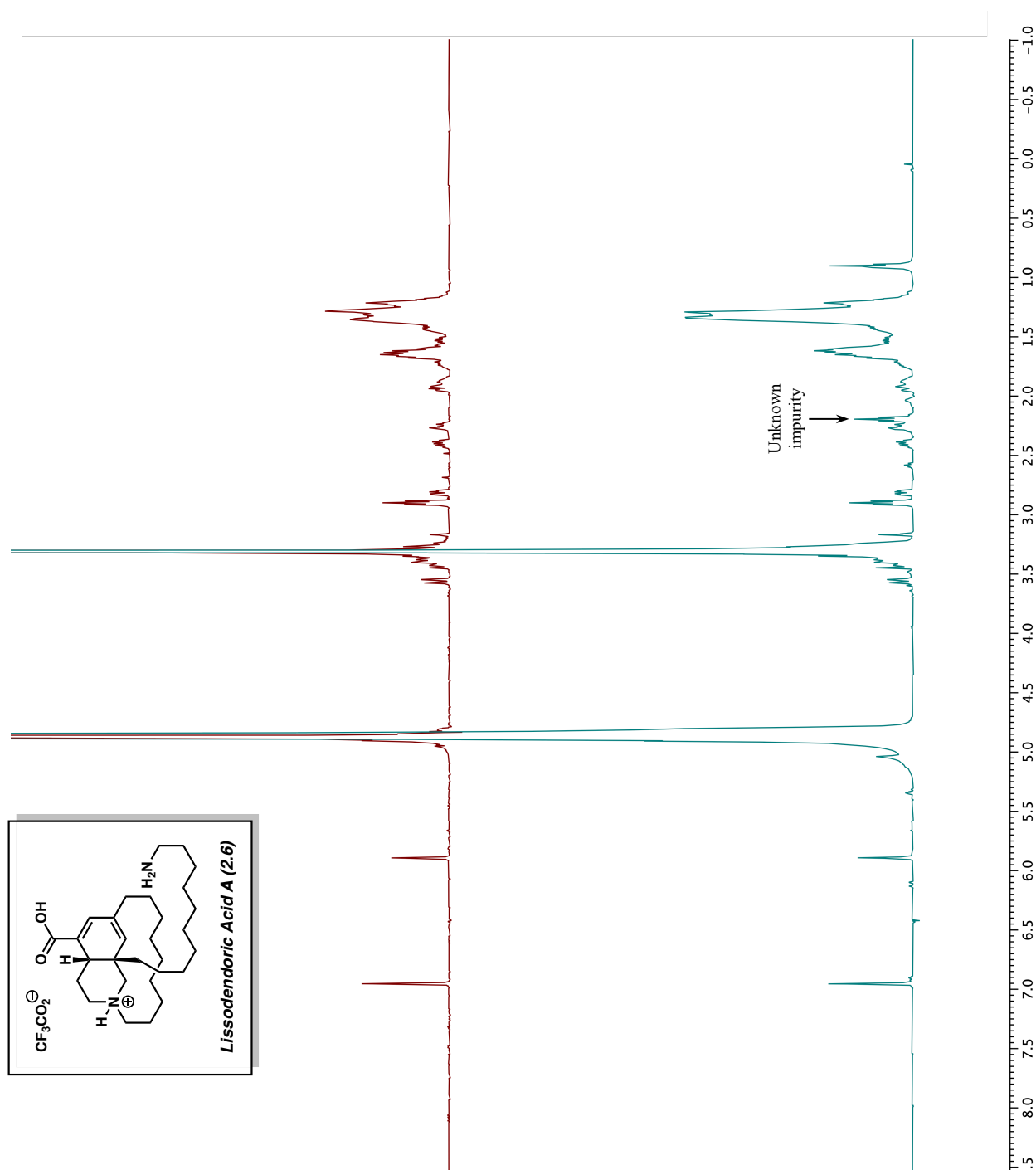


Figure 2.74. ¹H NMR (500 MHz, CD₃OD) spectra of synthetic sample (top) and repurified authentic sample (bottom) of lissodendoric acid A (**2.6**). An unknown impurity (2.25 ppm, triplet) in the authentic sample is noted.

2.7.2 ECD Spectra

Sample Preparation and Data Collection:

Synthetic and authentic samples of enantioenriched **2.6** were analyzed by electronic circular dichroism. To prepare samples, compound was dissolved in CH₃OH and placed in a 1 cm cuvette. ECD measurements were obtained from 200 nm to 600 nm with an interval of 1 nm. A baseline ECD spectrum was obtained for the CH₃OH solvent and used to correct ECD values for **2.6** at each corresponding wavelength. The corrected ECD values were plotted against wavelength ranging from 200 to 600 nm. A moving average trendline was applied to the resulting ECD spectrum, with period values of three and seven for the natural and synthetic samples of **2.6**, respectively.

In comparison to the data as reported by the isolation chemists (see Figure 2.75),²⁷ the ECD spectrum for a sample of authentic **2.6** was in reasonable accord (see Figure 2.76). Additionally, the ECD spectrum for synthetic **2.6** matched in both sign and shape of the curve (see Figure 2.77). As such, we conclude that the absolute configuration of (–)-lissodendoric acid A (**2.6**) is as depicted and as proposed by the isolation chemists.²⁷

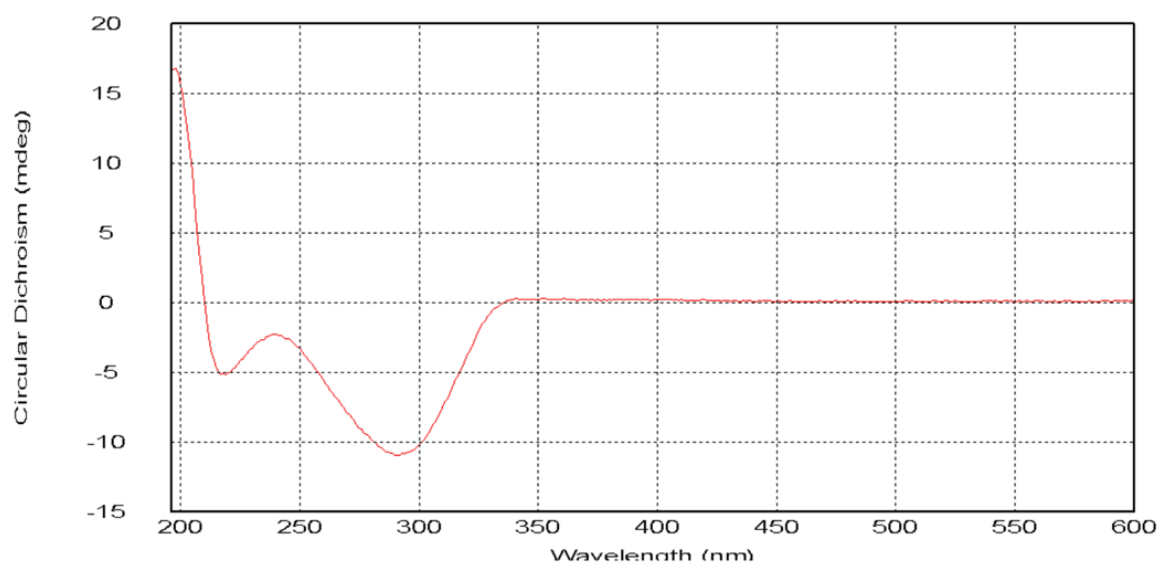


Figure 2.75. ECD spectrum of authentic lissodendoric acid A (**2.6**) reported by Lyakhova and coworkers.²⁷

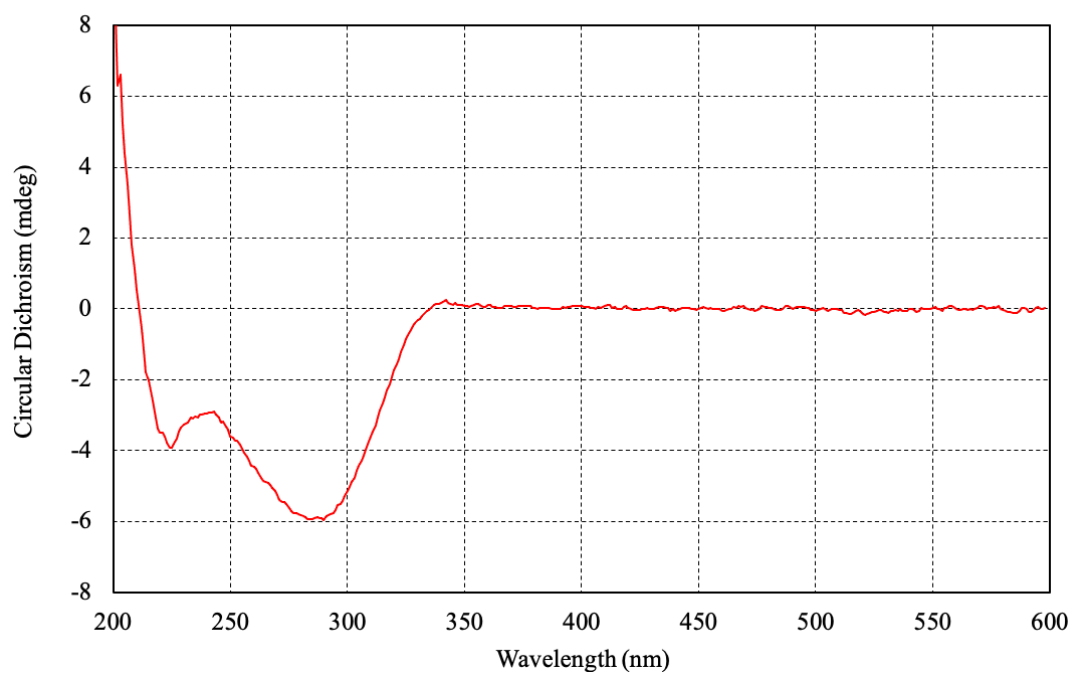


Figure 2.76. ECD spectrum of authentic lissodendoric acid A (**2.6**)

obtained for this study.

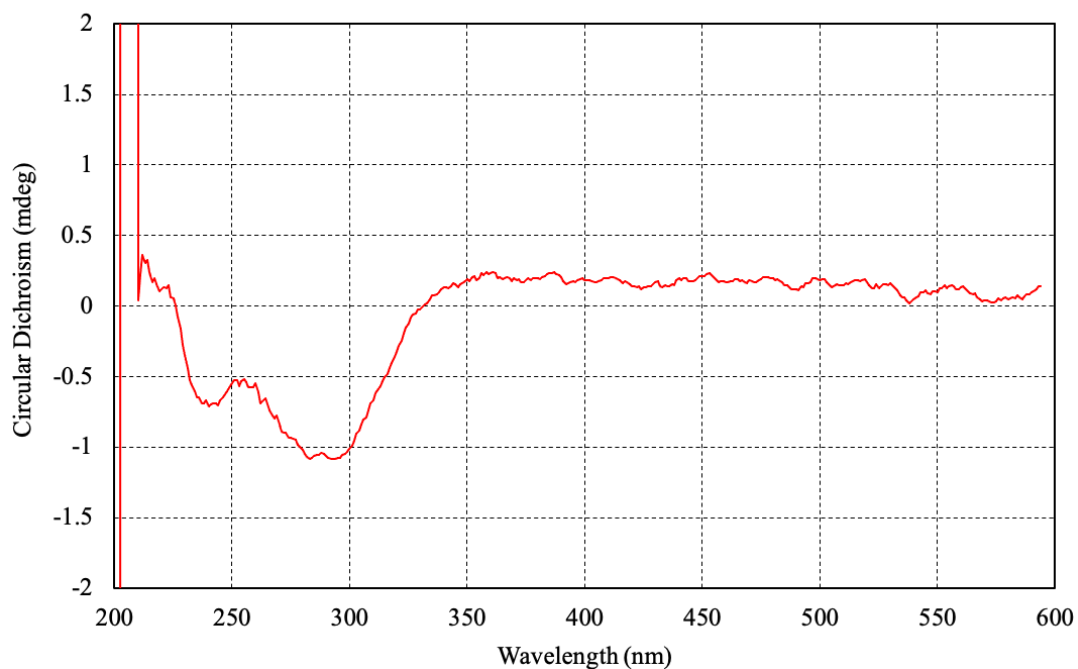


Figure 2.77. ECD spectrum of synthetic (-)-lissodendoric acid A (**2.6**).

2.8 Notes and References

- (1) Stoermer, R.; Kahlert, B. Ueber das 1- und 2-brom-cumaron. *Ber. Dtsch. Chem. Ges.* **1902**, 35, 1633–1640.
- (2) Roberts, J. D.; Simmons, H. E.; Carlsmith, L. A.; Vaughan, C. W.; Rearrangement in the reaction of chlorobenzene-1-C14 with potassium amide. *J. Am. Chem. Soc.* **1953**, 75, 3290–3291.
- (3) Wittig, G.; Pohmer, L. Intermediäre Bildung von Dehydrobenzol (Cyclohexa-dienin). *Angew. Chem.* **1955**, 67, 348.
- (4) Scardiglia, F.; Roberts, J. D. Evidence for cyclohexyne as an intermediate in the coupling of phenyllithium with 1-chlorocyclohexene. *Tetrahedron* **1957**, 1, 343–344.
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- (6) Tadross, P. M.; Stoltz, B. M. A comprehensive history of arynes in natural product total synthesis. *Chem. Rev.* **2012**, 112, 3550–3577.
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CHAPTER THREE

Total Synthesis of Lissodendoric Acid A

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3.1 Abstract

We describe a full account of our synthetic strategy leading to the first total synthesis of the manzamine alkaloid lissodendoric acid A. These efforts demonstrate that strained cyclic allenes are valuable synthetic building blocks and can be employed efficiently in total synthesis.

3.2 Introduction

A valuable synthetic strategy involves constraining a functional group of typically linear geometry into a small or medium-sized ring. This structural contortion leads to high strain energies and fleeting lifetimes of the resultant reactive intermediates. Nonetheless, scientists have learned to leverage them in chemical synthesis. Arynes (**3.1**, Figure 3.1A) in particular, have been used in natural products synthesis for the past half-century.^{1,2,3,4,5} An early example involved the use of an aryne in the synthesis of cryptaustoline (**3.4**) in 1967.⁶ More recently, an indolyne (e.g., **3.2**) proved crucial in our synthesis of **3.5**⁷ and related natural products.^{8,9,10} Cyclohexynes such as **3.3**, have also been enabling in total synthesis, demonstrated by Carreira's synthesis of guanacastepene N (**3.6**).¹¹ Arynes and cyclic alkynes have been used in more than 100 total syntheses to date.^{1,2,3}

Cyclic allenes are a related class of strained intermediates that are less well studied. 1,2-Cyclohexadiene (**3.7**, Figure 3.1A) was first validated in 1964^{12,13} and subsequently in 1966.¹⁴ In spite of the demonstrated value of cyclic allenes in cycloaddition reactions, advancements in their generation and synthetic use were minimal for decades. The first strained azacyclic allene (**3.8**) was generated by Christl and coworkers in 1994.¹⁵ A notable advance was reported in 2009 when Guitián showed that 1,2-cyclohexadiene (**3.7**) could be generated from a silyl triflate precursor using mild fluoride-based reaction conditions.¹⁶ Despite further advances by West,^{17,18,19,20} Christl,^{21,22,23,24} our group,^{25,26} and others^{27,28}, cyclic allenes have scarcely been used in natural products synthesis.²⁹

We surmised that strained cyclic allenes were ideally suited for total synthesis. The ground state structure of azacyclic allene **3.9** (Figure 3.1B) highlights several key structural features. The six-membered cyclic allene functional group contains cumulated C=C bonds of 1.32 Å and a restricted internal angle of 133°, giving rise to high reactivity. In addition, strained cyclic allenes are axially chiral. Substituents are contorted out of the allene C=C=C plane, demonstrated by the C–H and C–CH₃ bonds twisted 39° and 36° out-of-plane, respectively. By leveraging the high reactivity and axial chirality of strained cyclic allenes, we reasoned that complex products could be accessible with control of relative and absolute stereochemistry.^{25,30}

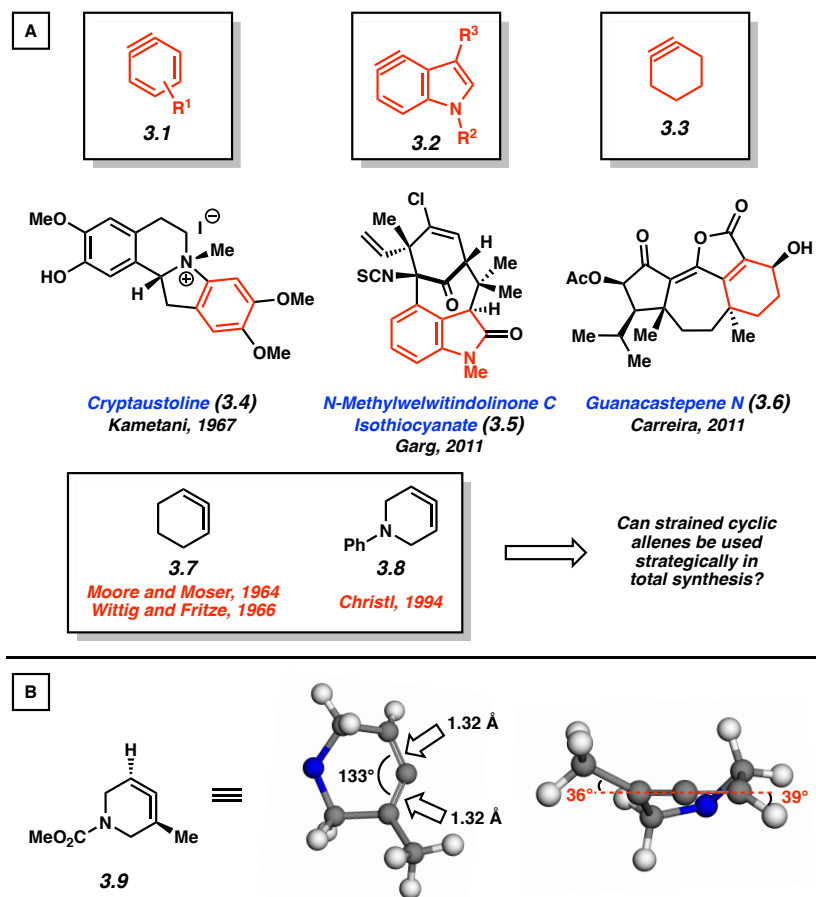


Figure 3.1. (A) Select strained intermediates **3.1–3.3**, their use in total synthesis, and underutilized strained cyclic allenes **3.7** and **3.8**. (B) Geometry-optimized structure of strained azacyclic allene **3.9** (ω B97XD/6-31G(d)). The CO₂Me is omitted from the three-dimensional representations for clarity.

A representative example of a cyclic allene engaging in a Diels–Alder cycloaddition is shown in Figure 3.2A. Trapping of in situ-generated cyclic allenes **3.10** with dienes **3.11** generates products **3.12** by virtue of strain-driven reactivity. Products **3.12** contain two newly formed C–C bonds. Products **3.12** bear three new stereocenters and are significantly saturated, which is

desirable in drug discovery.³¹ Furthermore, we recognized that the inherent axial chirality of the strained cyclic allene could be harnessed in asymmetric synthesis.^{25,30} Finally, heteroatom tolerance broadens the appeal of potentially utilizing strained cyclic allenes in synthesis. Overall, these factors make cyclic allenes excellent subjects for methodological and applicative studies.^{17,18,19,20,21,22,23,24,25,26,27,28,32}

We questioned whether strained cyclic allenes could be leveraged strategically in total synthesis.³³ We were particularly drawn to the manzamine family of alkaloids,^{34,35} which typically contain a highly functionalized piperidine as part of an azadecalin core and possess biological activity.³⁶ Serendipitously, as we considered manzamine targets, the isolation of lissodendoric acid A (**3.15**) was reported in 2017.³⁷ Structurally, **3.15** contains the aforementioned azadecalin core that is generally conserved across the family of manzamine alkaloids. Additionally, it contains two stereocenters, one of which is quaternary, as well as a 14-membered macrocycle and a conjugated diene moiety, which pose additional synthetic challenges. Whereas many manzamine alkaloids have been the subject of total syntheses,³⁴ there were no published syntheses of **3.15** at the time, given its recent isolation. As such, we undertook a total synthesis campaign and communicated our final approach to **3.15** in 2023.³⁰ Herein, we describe a full account of our efforts to leverage strained cyclic allenes to achieve the total synthesis of lissodendoric acid A (**3.15**).

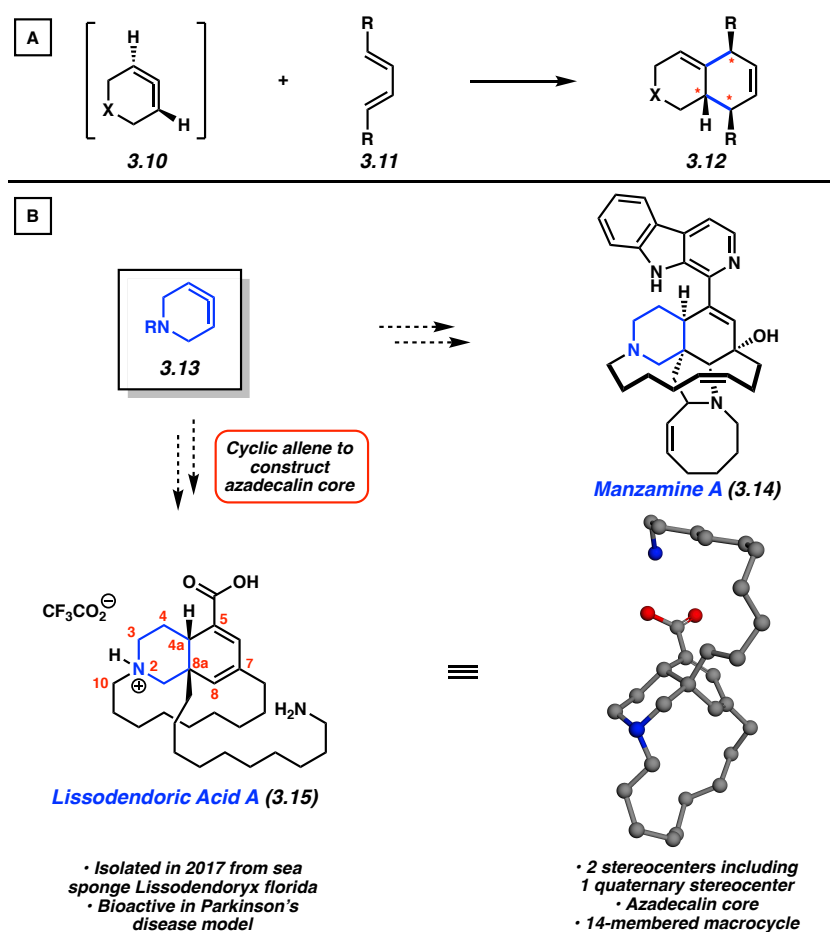


Figure 3.2 (A) General structure of cycloadducts **3.12** arising from strained cyclic allene **3.10** and trapping partner **3.11**. (B) Envisioned use of an azacyclic allene to construct core of lissodendoric acid A (**3.15**) and geometry-optimized structure of **3.15** (B3LYP/6-31G*). Charges, hydrogens, and the trifluoroacetate counterion are omitted from the three-dimensional representation of **3.15** for clarity.

3.3 Results and Discussion

3.3.1 Design of the Key Azacyclic Allene Cycloaddition

A key consideration in leveraging a cyclic allene in building the azadecalin core of lissodendoric acid A (**3.15**) was the regioselectivity of the planned cycloaddition. Our laboratory had previously studied Diels–Alder reactions of alkyl-substituted azacyclic allenes with electron-rich dienes (e.g., **3.16** and furan (**3.17**), respectively, Figure 3.3A). Such trappings occur with excellent regioselectivity favoring reaction of the allene double bond distal to the alkyl group, as shown in Figure 3.3A.^{17a} To achieve the synthesis of **3.15**, the reaction would instead need to occur on the alkene proximal to the alkyl substituent.³⁸ As the proximal alkene was considered to be more electron-rich compared to the distal alkene of the cyclic allene, we hypothesized that the use of an electron-deficient diene could provide access to the desired scaffold. Thus, we thought to design an inverse-electron demand Diels–Alder cycloaddition of azacyclic allene **3.16**.

Our resultant design of the key step is shown in Figure 3.3B and features the use of 2-pyrones. 2-Pyrones have previously been used in inverse-electron demand Diels–Alder reactions, but never with strained cyclic allenes.^{39,40,41} As shown in Figure 3.3B, the cycloaddition between cyclic allenes **3.19** and 2-pyrones **3.20** would deliver cycloadducts **3.21**, possessing the desired regiochemistry, and introducing the necessary quaternary stereocenter. Although intermolecular cycloadditions of alkenes and pyrones can be challenging,³⁰ we surmised that the strain present in cyclic allenes **3.19** would promote the desired bond formations.

Two additional features should be noted. First, the resulting bridged ring system in **3.21** would prove strategic, as CO₂ could be readily extruded later to unveil a diene, as is present in **3.15**.⁴² In addition, the inherent axial chirality of cyclic allenes **3.19** could provide an opportunity for an asymmetric synthesis of (–)-**3.15** if allenes **3.19** could be generated in enantioenriched form

and trapped stereospecifically. Limited examples of stereospecific cyclic allene trappings to deliver enantioenriched products were available.^{5,23,24,25,26}

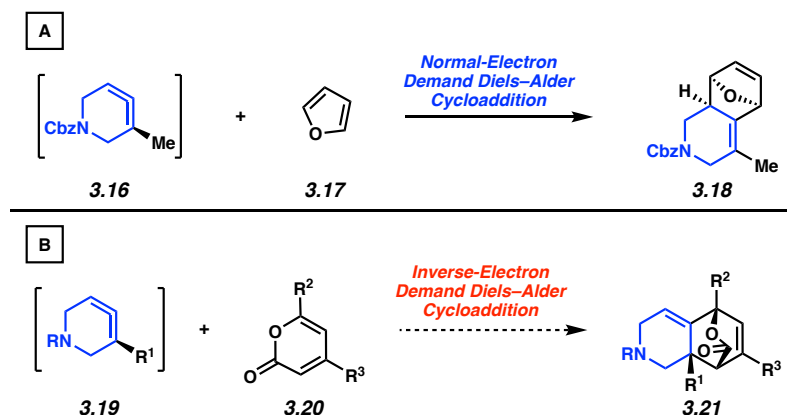


Figure 3.3. (A) Known cycloaddition of azacyclic allene **3.16**. (B) Envisioned Diels–Alder cycloaddition of allenes **3.19**.

3.3.2 Molecular Orbital Analysis of Azacyclic Allene **3.9** and Transition State Analysis Using a Pyrone Trap

The electronic structure of azacyclic allene **3.9**, which serves as a simplified system, was analyzed using density functional theory (DFT). Geometry optimizations were carried out at the ω B97X-D /6-311+G(d,p)/SMD(MeCN) level of theory. Molecular orbitals and orbital energies were then calculated using HF/6-31G(d), consistent with prior studies of strained cyclic allenes.⁴³ Figure 3.4A depicts the localized highest occupied molecular orbital (HOMO) and lowest occupied molecular orbital (LUMO), as well as the corresponding computationally-determined delocalized frontier molecular orbitals (FMOs) of **3.9**. The FMOs showcase the bending and twisting present in the cyclic allene structure. The LUMO is 11.3 eV higher in energy than the HOMO.

Figures 3.4B and C provide a comparison of the known reaction outcome between azacyclic allene **3.16** and furan (**3.17**), as well as a computational study of the corresponding

reaction using pyrone **3.24**. In a prior study,²⁵ we showed that treatment of silyltriflate **3.22** with furan (**3.17**) gives adduct **3.18** as the major observed product. Of note, the reaction occurs on the alkene of allene intermediate **3.16** distal to the alkyl substituent and with selectivity for formation of the endo product shown to give ‘distal’ product **3.18**. Adduct **3.23** (a.k.a., ‘proximal’ product) was not observed. DFT transition state analysis (ω B97XD/6-311+G(d,p)/SMD(MeCN)), using CO₂Me in place of benzylcarbamate (Cbz), showed that that $\Delta\Delta G^\ddagger$ for the two competing endo pathways (distal vs proximal selectivity) was 1.5 kcal/mol, favoring the observed distal product, consistent with experimental results. We have performed the analogous calculation using pyrone **3.24** in place of furan, which could yield ‘distal’ product **3.25** or ‘proximal’ adduct **3.26**. Endo products are most energetically favorable and are depicted (see Section 3.8 for details). The two competing transition states leading to **3.25** or **3.26** were calculated and are depicted: **TS3.1** and **TS3.2**, respectively. The $\Delta\Delta G^\ddagger$ for these two competing endo pathways (distal vs proximal selectivity) was 0.2 kcal/mol. Both **TS3.1** and **TS3.2** reflect concerted asynchronous processes, favoring initial bond formation on the central carbon of the allene. This is consistent with prior computational studies of strained cyclic allene Diels–Alder trapping reactions with furan.^{25,43} The calculations suggest that the desired proximal cycloaddition pathway could be viable.

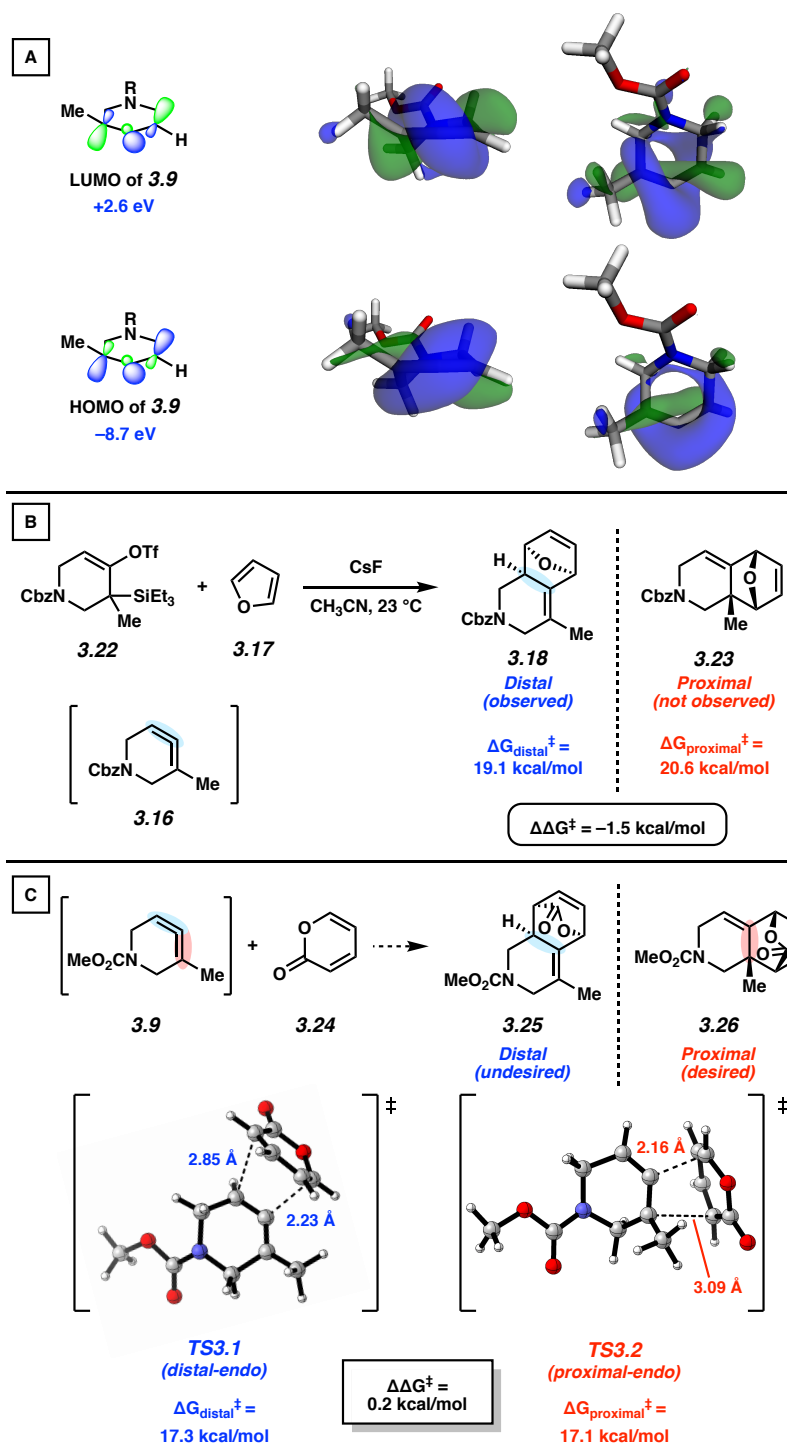


Figure 3.4. (A) Localized and delocalized (canonical) HOMO and LUMO of azacyclic allene **3.9** (R=CO₂Me). Front view (left) and top view (right) of the FMOs are shown. MOs obtained at the HF/6-31G(d)//ωB97XD/6-311+G(d,p)/SMD(MeCN) level of theory. (B) Experimental result

and summary of computational study of Diels–Alder trapping of azacyclic allene **3.16** and furan (**3.17**). (C) Diels–Alder reaction of **3.9** and pyrone **3.24** is predicted to give products **3.25** (distal) and **3.26** (proximal), via **TS3.1** and **TS3.2**, respectively. Energies in kcal mol⁻¹ at the ωB97X-D/6-311+G(d,p)/SMD(MeCN) level of theory. The energetically favorable endo pathways are shown.

3.3.3 Model System Studies and Retrosynthetic Analysis

To validate the predicted regiochemical outcome of the Diels–Alder reaction, we tested our hypothesis in a model system (Figure 3.5 A and B). To this end, we designed pyrone **3.30**, which contains a vinyl bromide as a potential cross-coupling handle, as well as a benzyl-protected alcohol that could be later unveiled and oxidized to install the carboxylic acid found in **3.15**. Pyrone **3.30** was accessed via the sequence shown in Figure 3.5A.^{44,45}

Upon treatment of silyl triflate **3.22** with CsF and pyrone **3.30**, cycloadduct **3.31** was formed as the only observable product (Figure 3.5B). The transformation occurred presumably via a Diels–Alder reaction between the in situ-generated cyclic allene and the diene in **3.30** via the depicted transition structure. This leads to the formation of two new C–C bonds, three new stereocenters, and the desired azadecalin scaffold. The regioselectivity presumably results from an inverse-electron demand Diels–Alder reaction involving electron-poor diene **3.30** and the more electron-rich double bond (C4a=C8a) of allene **3.16**. Additionally, the orientation of pyrone **3.30** in the transition structure is presumably dictated by the electronic matching of electron-rich C4a with electron-poor C5, leading to the observed orientation of the lactone bridge in cycloadduct **3.31**. Also, the reaction is thought to proceed such that secondary orbital overlap occurs between the unreactive double bond (C4=C4a) of allene **3.16** with pyrone **3.30**, resulting in excellent

diastereoselectivity. Analogous endo selectivity has been observed in normal-electron demand Diels–Alder trappings of strained cyclic allenes and has been studied computationally.⁴³

We accessed silyl triflate **3.22** in enantioenriched form by separating the racemate using chiral supercritical fluid chromatography (SFC). Upon generation of cyclic allene **3.16**, the point chirality present at C8a in silyl triflate **3.22** is relayed to axial chirality. Trapping of allene **3.16** in a cycloaddition with pyrone **3.30** reestablishes point chirality with the introduction of three new stereocenters in cycloadduct **3.31**, one of which is quaternary and two of which are tertiary. The sole stereocenter present in silyl triflate **3.22** is ablated during the reaction. The process occurs with quantitative optical yield (i.e., complete stereoretention),^{46,47} indicating that the cycloaddition occurs more readily than the enantiomerization of axially chiral allene **3.16**.

In our first-generation retrosynthetic analysis, we envisioned accessing **3.15** from macrocycle **3.32** through a series of redox and protecting group manipulations (Figure 3.5C). Macrocycle **3.32** would be derived from azadecalin **3.33** using a ring-closing metathesis strategy. Diene **3.33** could arise from cycloadduct **3.34** via selective reduction of the tri-substituted olefin in the piperidyl ring, followed by retro-Diels–Alder extrusion of CO₂. Finally, cycloadduct **3.34** could be forged through Diels–Alder reaction between cyclic allene **3.35** and readily accessible pyrone **3.30**.

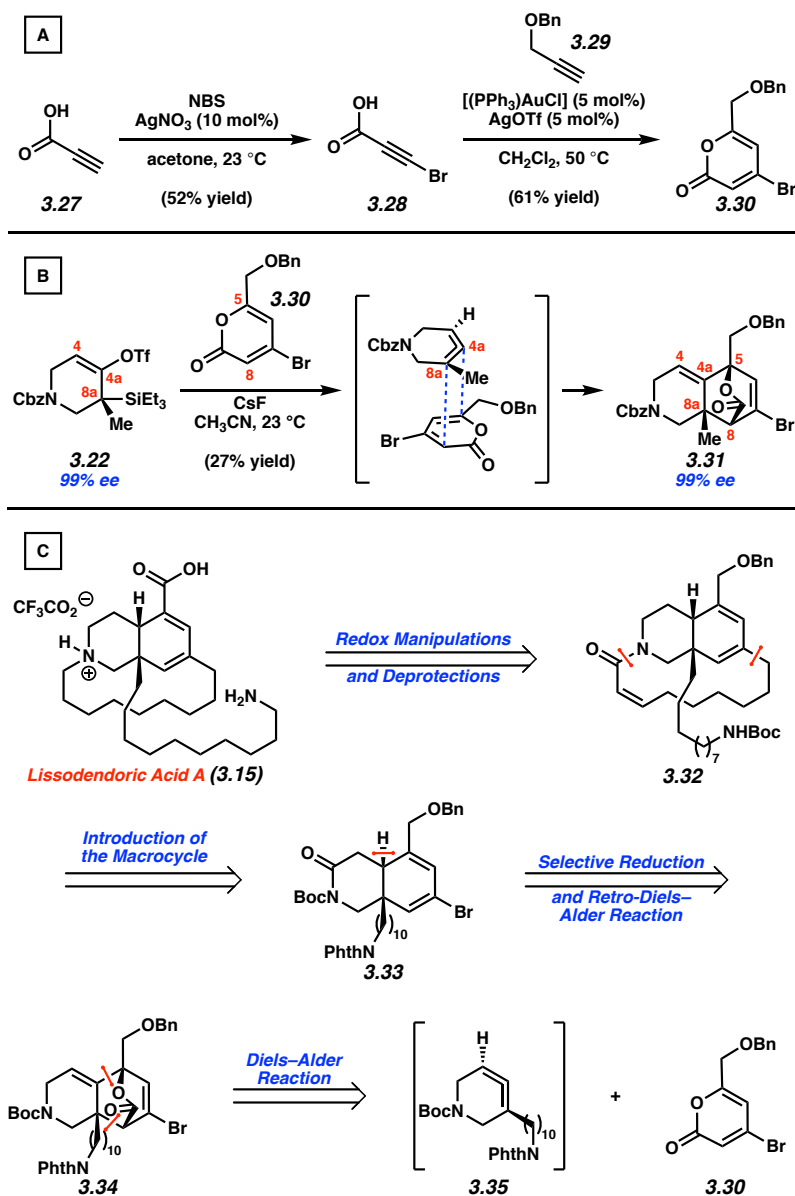


Figure 3.5. (A) Synthesis of pyrone **3.30**. (B) Diels–Alder reaction on model system.

(C) First-generation retrosynthetic analysis of **3.15**.

3.3.4 Synthesis of the Cyclic Allene Precursor and Key Cycloaddition

To access cyclic allene **3.35** (see Figure 3.5C), we targeted silyl triflate **3.41** using the sequence shown in Figure 3.6. Initial studies were performed using racemic materials. From commercially available α -bromo ketone **3.36**, carbonate **3.37** was prepared in 73% yield over two steps. Upon treatment with $\text{Pd}(\text{PPh}_3)_4$, **3.37** underwent allylic alkylation to afford allyl ketone **3.38**.^{48,49} Next, olefin cross-metathesis^{50,51} with alkene **3.39**, followed by hydrogenation, provided ketone **3.40**. Finally, triflation of **3.40** occurred readily to deliver silyl triflate **3.41**.⁵² The key azacyclic allene Diels–Alder reaction was then evaluated. Treatment of **3.41** with **3.30** in the presence of CsF afforded desired cycloadduct **3.34** in 75% yield with excellent diastereoselectivity. Notably, adduct **3.34** contains the desired azadecalin core, the C8a quaternary stereocenter bearing the necessary aminoalkyl side chain, as well as sufficient other functionality.

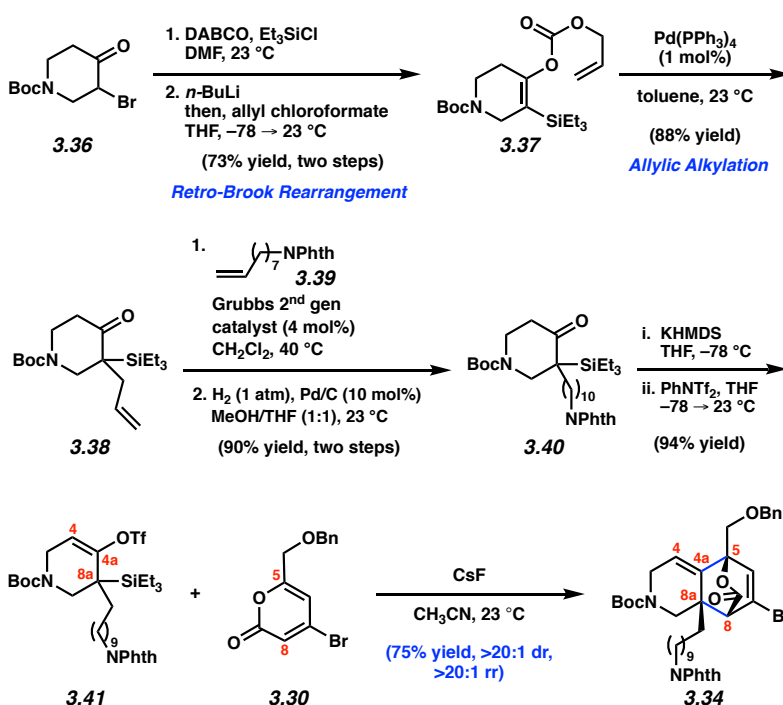


Figure 3.6. Synthesis of silyl triflate **3.41** and application in Diels–Alder cycloaddition with pyrone **3.30** to furnish cycloadduct **3.34**.

3.3.5 Elaboration of the Cycloadduct

To transform cycloadduct **3.34** to diene **3.33**, we first envisioned a selective reduction of the C4–C4a alkene over the reduction of the C6–C7 alkene (Figure 3.7). Unfortunately, efforts to reduce the olefin using traditional metal-catalyzed hydrogenation, hydrogen atom transfer (HAT) protocols,⁵³ or diimide reduction conditions were unsuccessful. To distinguish the olefins electronically, cycloadduct **3.34** was subjected to allylic oxidation conditions,⁵⁴ which provided **3.42**. Next, a modified Stryker reduction⁵⁵ was employed to afford **3.43** in excellent diastereoselectivity. Heating bicycle **3.43** in DMSO-*d*₆ allowed for the extrusion of CO₂ in a retro-Diels–Alder reaction to provide diene **3.33**.⁴²

Toward the goal of introducing the macrocycle, we prepared intermediate **3.48** using the route shown in Figure 3.7. Negishi coupling between vinyl bromide **3.33** and readily available alkylzinc bromide⁵⁶ **3.44** proceeded smoothly, delivering alkene **3.45**. Cross-electrophile coupling reactions⁵⁷ were also considered, however, most led to poor yields. Next, it was necessary to reduce amide **3.45** to the corresponding amine, which, in turn, necessitated protecting group manipulations. Removal of the Boc and phthalimide protecting groups from **3.45** over two steps afforded the corresponding primary amine. The primary amine was converted to the corresponding carbamate upon treatment with Boc anhydride. The amide was then reduced with LiAlH₄ to give secondary amine **3.46**. Finally, secondary amine **3.46** was acylated using **3.47** to yield **3.48**, which was primed for macrocyclization.

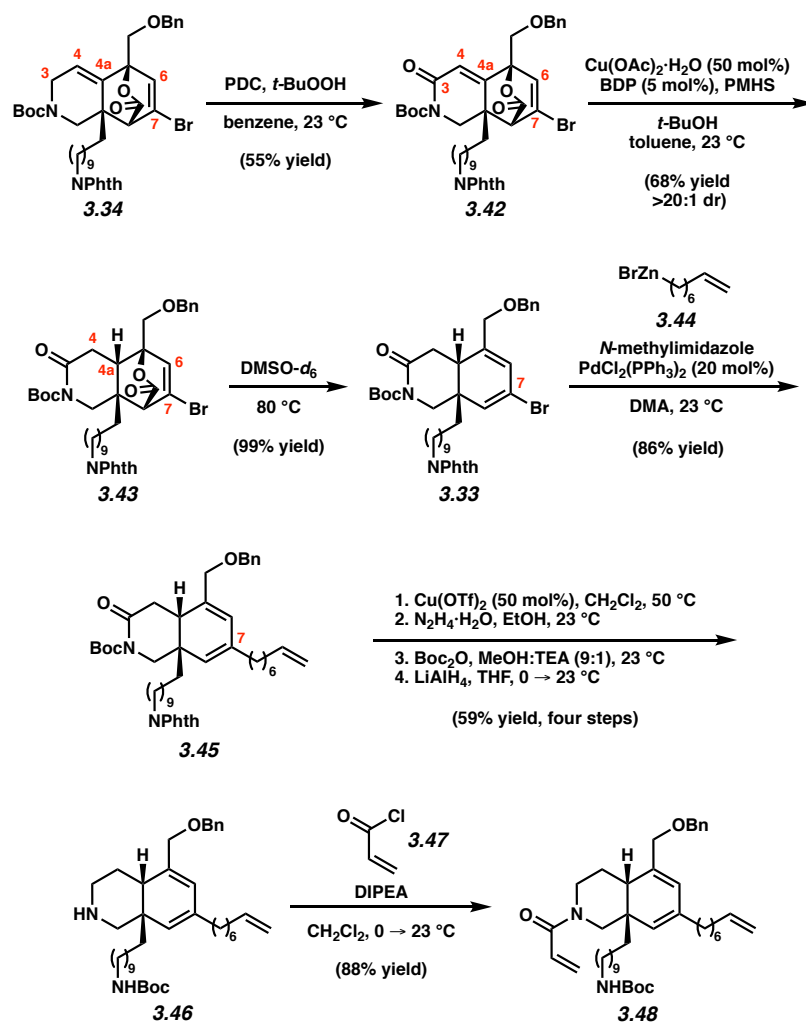


Figure 3.7. Elaboration of cycloadduct **3.34** to **3.48**.

3.3.6 Macrocyclization, Functional Group Manipulations, and Revised Strategy

With alkene **3.48** in hand, the key macrocyclization and functional group manipulations en route to **3.15** were performed. First, olefin **3.48** was treated with Grubbs' 2nd generation catalyst to afford the corresponding 14-membered macrocycle,^{50,58} which was subsequently reduced to give tertiary amine **3.49** (Figure 3.8A).⁵⁵ Having corrected the oxidation state on the western portion of the molecule, alcohol **3.49** was deprotected using BCl₃ to furnish **3.50**. Unfortunately,

and despite our best efforts employing different oxidants,^{59,60,61} oxidation of alcohol **3.50** to aldehyde **3.51** (or the corresponding acid) proved impossible.

Recognizing the notorious challenge of performing oxidation chemistry in the presence of a tertiary amine, we delayed the unveiling of the tertiary amine. Thus, **3.48** was converted to amide **3.52** using a three-step sequence⁵⁵ (Figure 3.8B). We were gratified to find that treatment of **3.52** with MnO₂ facilitated smooth oxidation and delivered aldehyde **3.53** in 70% yield.⁶² Although access to **3.53** was exciting, initial efforts to further elaborate this compound were thwarted by practical considerations.

We revised our strategy to target Diels–Alder cycloadduct **3.54** instead of **3.34** (Figure 3.8C). Rather than carrying a benzyl-protected alcohol through the synthesis, an ester was used to allow for hydrolysis to yield a carboxylic acid in the final step of the synthesis. In addition, we targeted early installation of the C7-alkyl chain, which would allow for greater convergence and fewer late-stage manipulations. Finally, the primary amine protecting group was changed from phthalimide to bis(Boc), with the hope that a final global deprotection mediated by acid could give **3.15**.

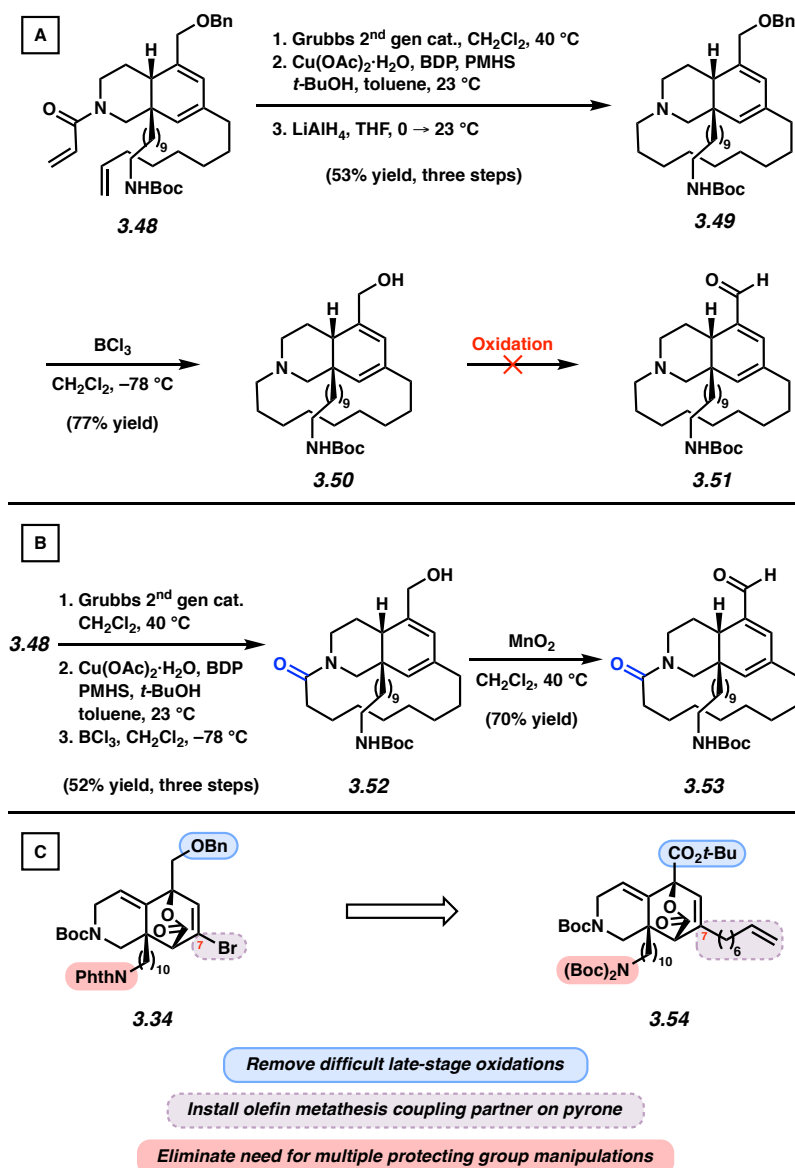


Figure 3.8. (A) Macrocyclization and attempted oxidation. (B) Synthesis of amide **3.52** allows for oxidation to aldehyde **3.53**. (C) Revision of strategy to pursue cycloadduct **3.54**.

3.3.7 Synthesis of the Modified Key Cycloadduct

With a newly designed cycloadduct to target (i.e., **3.54**), syntheses of the necessary pyrone and allene precursor fragments were pursued (Figures 3.9A and B). The desired pyrone, **3.57**, was

prepared from commercially available pyrone **3.55** (Figure 3.9A). Silyl triflate **3.60** was thought to serve as a precursor to azacyclic allene **3.61** (Figure 3.9B). In a sequence similar to the one used to prepare silyl triflate **3.41** (see Figure 3.9B), allyl ketone **3.38** was elaborated to ketone **3.59**.⁶³ Deprotonation and triflation of ketone **3.59** using bis(trimethylsilyl)amide (KHMDs) and Comins' reagent, respectively, delivered silyl triflate **3.60**.

Next, the key Diels–Alder cycloaddition was attempted (Figure 3.9C). The cycloaddition between pyrone **3.57** and in situ-generated allene **3.61** delivered cycloadduct **3.54** in 81% yield. This cycloaddition not only provided the desired azadecalin core of the natural product, but also pushed the limits of known strained cyclic allene chemistry with respect to complexity and functional group tolerance.

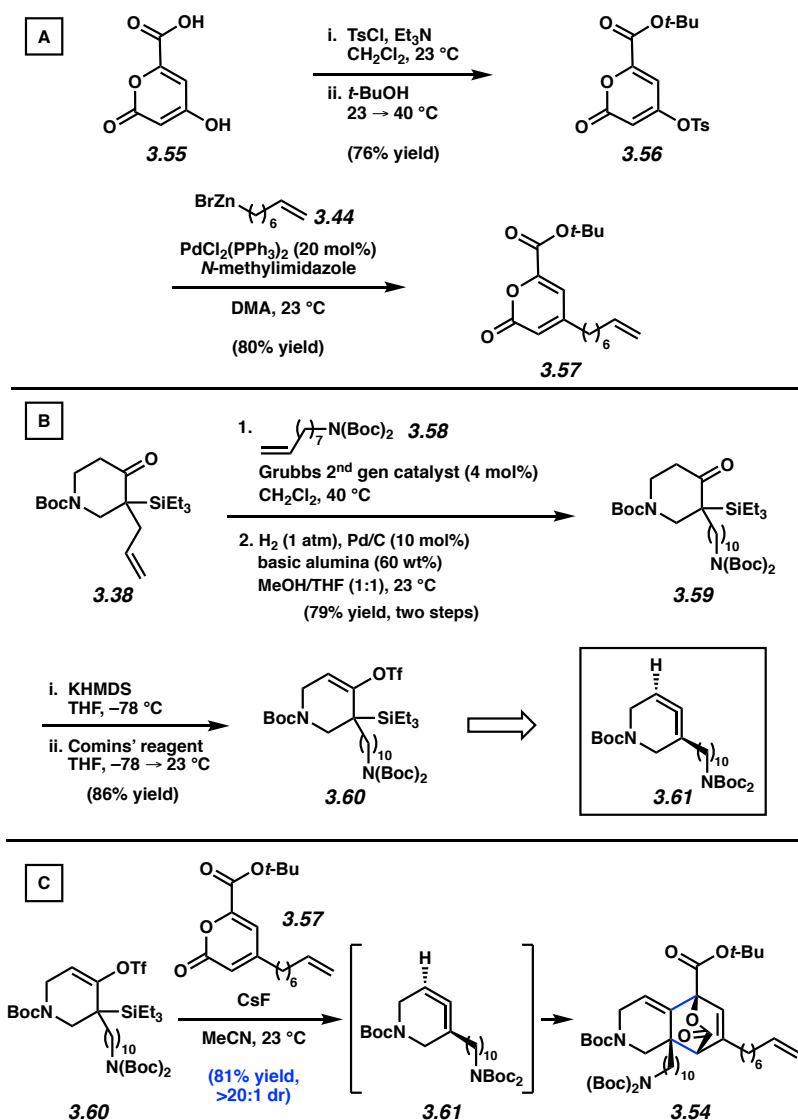


Figure 3.9. (A) Synthesis of ester-containing pyrone **3.57**. (B) Synthesis of silyl triflate **3.60**. (C)

Diels–Alder trapping of cyclic allene **3.61** delivers cycloadduct **3.54**.

3.3.8 DFT Calculations of Key Pyrone Trapping

DFT calculations were performed to study the cycloaddition between cyclic allene **3.61** and pyrone **3.57** using azacyclic allene **3.9** and pyrone **3.62** as reasonable model substrates (Figure 3.10A). Calculations correctly predict the regio- and diastereoselectivity observed in the key step

shown in Figure 3.9C. Although exo pathways were considered, they were found to be disfavored (see Section 3.8). The competing endo products resulting from distal and proximal cycloaddition are adducts **3.63** and **3.64**, respectively. The corresponding transition states, **TS3.3** and **TS3.4** are shown, both of which reflect concerted asynchronous processes. **TS3.4** is favored by 2.4 kcal/mol, consistent with the observed proximal cycloaddition pathway. The length of the C4a–C5 forming bond distance in **TS3.4** is 2.13 Å, reflective of initial bond formation occurring at the central carbon of the allene (vs 3.01 Å for the forming C8a–C8 bond).

Figure 3.10B shows the calculated molecular orbitals for allene **3.9** (HOMO) and pyrone **3.62** (LUMO) using their **TS3.4** transition state geometries.⁶⁴ Favorable orbital overlap for the Diels–Alder reaction is readily apparent (blue), leading to productive bond formation. In addition, a stabilizing secondary orbital interaction is observed between the orbitals of allene C4 and pyrone C6 (green), which we surmise leads to the observed endo-selectivity. Analogous stabilizing secondary orbital interactions are seen in normal electron-demand Diels–Alder reactions between strained cyclic allenes and furan.⁴³ The origins of endo selectivity in inverse electron-demand cycloadditions of strained cyclic allenes had not been investigated previously.

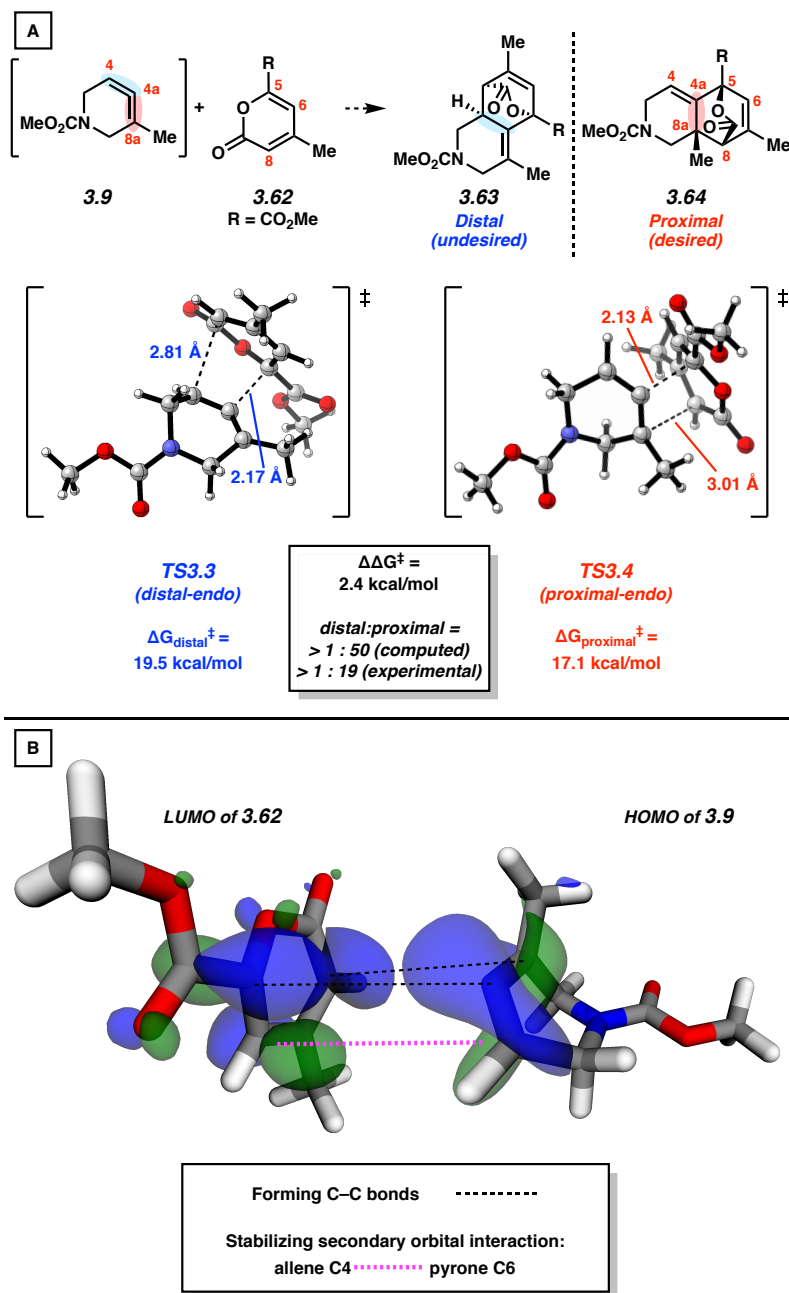


Figure 3.10. (A) Computational study of Diels–Alder trapping of azacyclic allene **3.9** and pyrone **3.62**. The energetically favorable endo transition states, **TS3.3** and **TS3.4**, are shown (the CO₂Me groups are omitted for clarity). Energies in kcal mol^{−1} are for the ωB97X-D/6-311+G(d,p)/SMD(MeCN) level. (B) Frontier molecular orbitals of allene **3.9** (HOMO) and

pyrone **3.62** (LUMO) in their transition state geometries are depicted. This HOMO–LUMO gap is smallest,⁶⁴ reflecting an inverse-electron demand Diels–Alder pathway. Structures are oriented to visualize stabilizing secondary orbital interaction (pink). MOs are calculated with HF/6-31G(d).

3.3.9 Pyrone Cycloadditions

We surveyed several pyrones in the trapping of strained cyclic allenes **3.66** (Figure 3.11). As such, silyl triflates **3.65** were treated with pyrones in acetonitrile at room temperature and reaction outcomes were analyzed by NMR spectroscopy. Unsubstituted pyrone **3.24**, 4-chloro pyrone **3.71**, pyrone **3.74** with electron-donating groups, and pyrone **3.76** with an electron-withdrawing substituent were examined. The use of unsubstituted pyrone **3.24** led to a 1:1 ratio of proximal and distal products **3.69a** and **3.70a** (entry 1), consistent with the computations we described earlier (see Figure 3.4C). Similar results were observed for the analogous allyl-substituted cycloadducts **3.69b** and **3.70b** (entry 2). In the case of using 4-chloro pyrone **3.71**, again a mixture of products was observed; however, the formation of proximal product **3.72** was favored (entry 3). Our efforts to employ pyrone **3.74** as a trapping partner for the azacyclic allene were unsuccessful and led to formation of dimer **3.75** in 49% yield (entry 4). We presume the presence of electron-donating groups on the pyrone make it less electron-deficient, leading to poor reactivity with the cyclic allene intermediate. However, significant selectivity was observed when ester-substituted pyrone **3.76** was examined in trapping experiments. This led to the formation of proximal adduct **3.77**, with no other cycloaddition products observed (entry 5). Lastly, the analogous selectivity was seen when the cyclic allene precursor with R=allyl was used in place of its methyl substituted analog (entry 6).

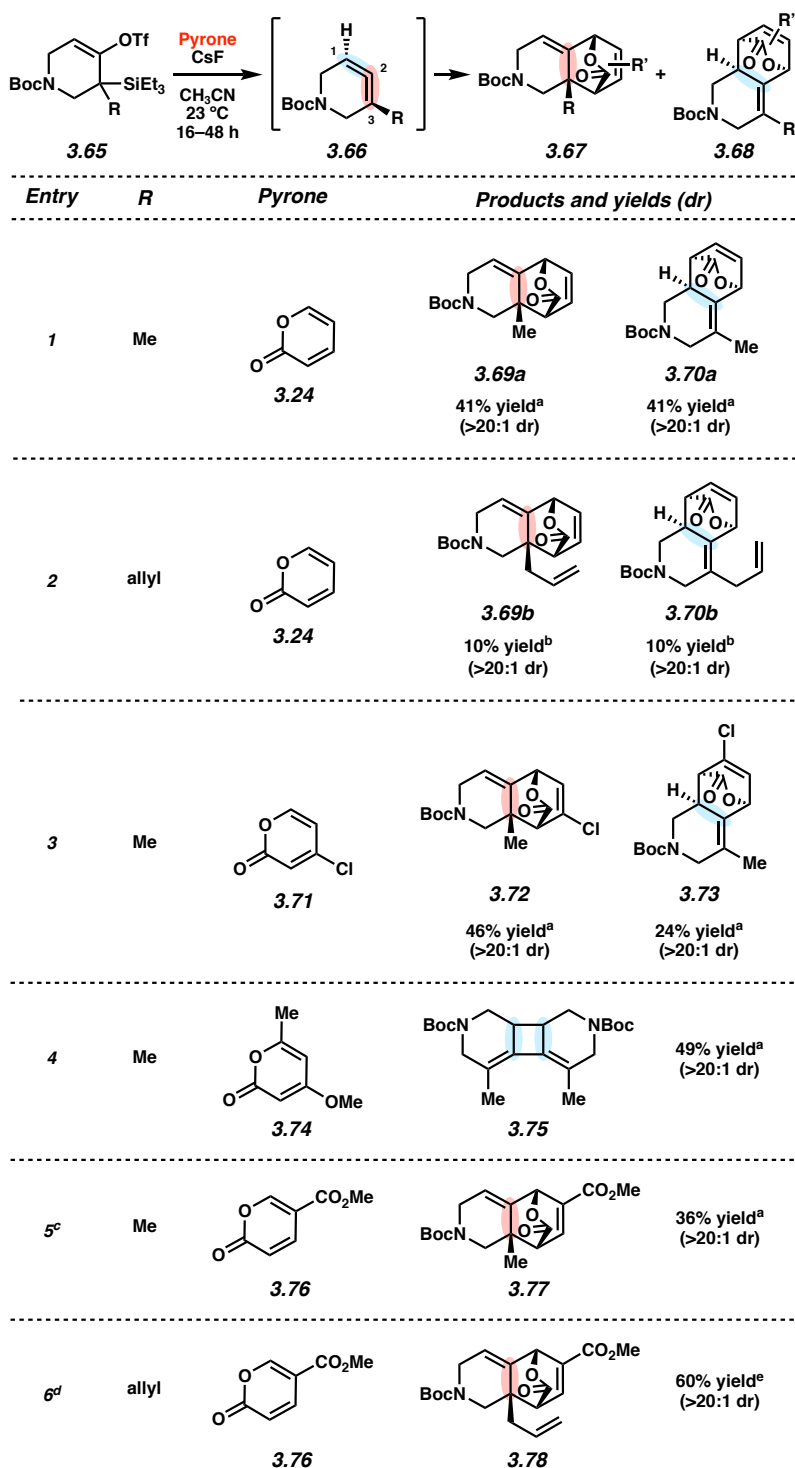


Figure 3.11. Experimental study of azacyclic allene trapping with various pyrones. Conditions unless otherwise stated: silyl triflate substrate (1.0 equiv), pyrone (5.0 equiv), CsF (5.0 equiv),

acetonitrile (0.1 M) at 23 °C for 16 h. ^aYields determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an external standard and reflect the average of two experiments.

^bUnoptimized isolated yields. A 1:1 ratio of **3.69b**:**3.70b** was observed by ¹H NMR analysis of the crude reaction mixture. ^cReaction performed with 10.0 equiv CsF for 48 h. ^dConditions: silyl triflate substrate (1.0 equiv), pyrone (5.0 equiv), TBAF (2.5 equiv), THF (0.1 M) at 23 °C for 16 h. ^eIsolated yield.

DFT calculations were performed to gauge correlations between experimental results and computational predictions (Figure 3.12). In all but one case, endo pathways were found to be favorable (see Section 3.8). In the case of unsubstituted pyrone **3.24**, the computational results are reported earlier in this manuscript (see Figure 3.4C). The computational prediction and experimentally observed selectivities are in good accord (1.3:1 favoring proximal adduct **3.26** vs 1:1 observed in the real system, respectively). A comparison of the experimental and computational results for the proximal vs distal pathways for other pyrone trappings are shown in Figure 3.12. Azacyclic allene **3.9** was again employed as a model compound. Regarding the use of 4-chloro pyrone **3.71**, calculations yield a $\Delta\Delta G^\ddagger$ of 0.7 kcal/mol, favoring the formation of proximal product **3.80** (see **TS3.5** and **TS3.6**). This is reasonably consistent with the experimentally-observed regioselectivity of 1:2, favoring proximal product **3.72** (see Figure 3.11A, entry 2). Lastly, the calculated $\Delta\Delta G^\ddagger$ when ester substituted pyrone **3.76** is employed is 2.2 kcal/mol (see **TS3.7** and **TS3.8**), which is consistent with the observed formation of proximal adducts **3.77** and **3.78** with high selectivity (see Figure 3.11A, entries 4 and 5, respectively). The calculated activation barrier for the favorable reaction between azacyclic allene **3.9** and ester-substituted pyrone **3.76** (i.e., 14.4 kcal/mol) is significantly lower compared to when unsubstituted pyrone **3.24** is used in the

corresponding calculation (i.e., 17.1 kcal/mol; see Figure 3.4C). This is consistent with the proposed inverse-electron demand Diels–Alder pathway.

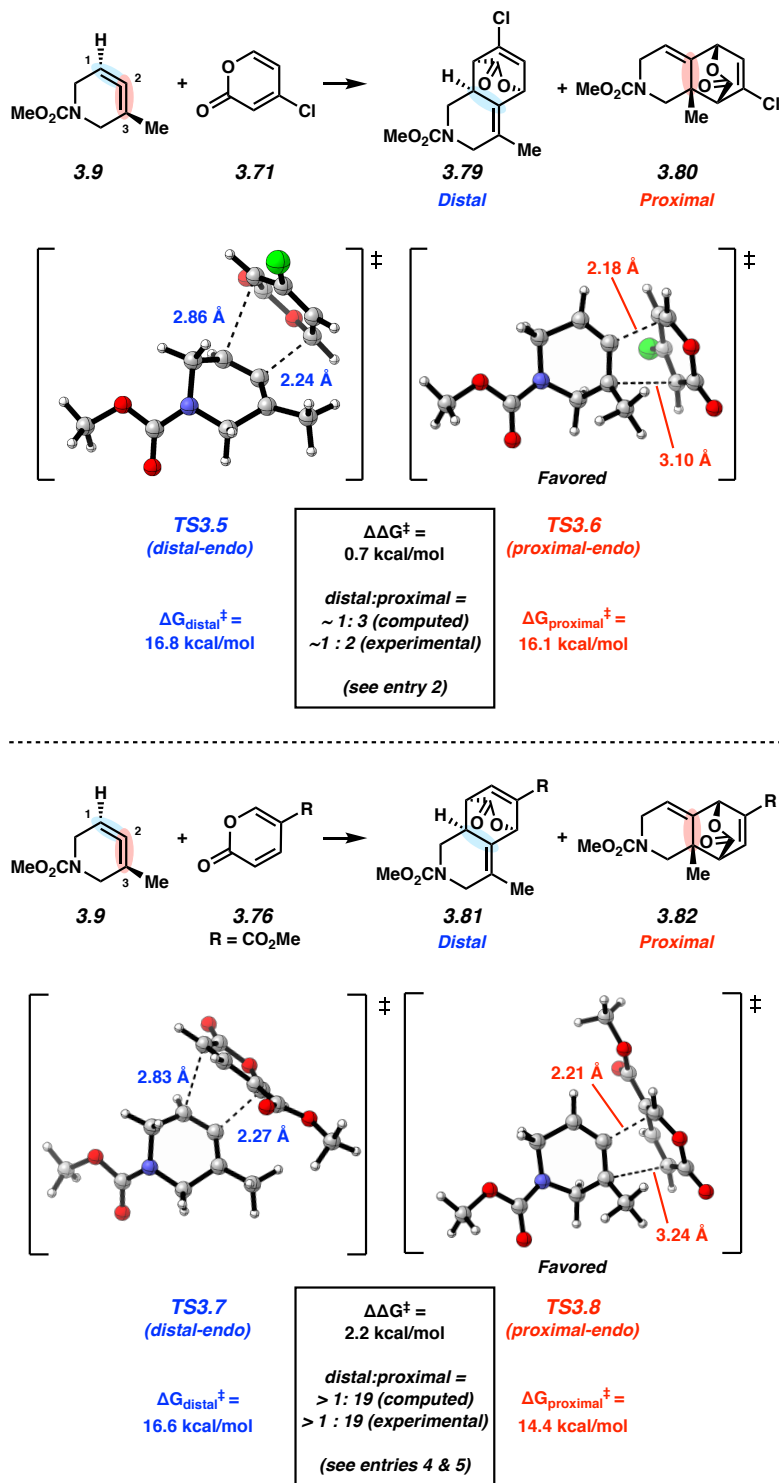


Figure 3.12. Computational study of Diels–Alder trapping of azacyclic allene **3.9** with pyrone **3.71** or **3.76**. Energies in kcal mol⁻¹ obtained at the ω B97X-D/6-311+G(d,p)/SMD(MeCN) level of theory. The energetically favored endo pathways are shown.

3.3.10 Completion of the Racemic Total Synthesis of Lissodendoric Acid A

Having prepared **3.54**, we were optimistic that late-stage manipulations would prove merciful. After optimization, we arrived at the elaboration sequence shown in Figure 3.13A to furnish late-stage intermediate **3.86**. This began with subjection of cycloadduct **3.54** to a redox sequence similar to that we used earlier (see Figure 3.7) to afford cis-decalin **3.83**.^{54,55} Calculations of a model system of **3.83** suggest that the cis isomer is ~15 kcal/mol more stable in energy compared to the corresponding trans isomer (see Section 3.8 for details); we surmise that the kinetic barrier to obtain the trans isomer of **3.83** is prohibitively high. Next, a one-pot protocol allowed for the extrusion of CO₂ in a retro-Diels–Alder reaction⁴² and selective removal of two of the three Boc protecting groups.⁶⁵ This provided diene **3.84**, which was reduced under Rh-catalysis to deliver **3.85** without reducing the ester.⁶⁶ Analogous to our prior route, amine **3.85** was acylated and the corresponding acrylamide was treated with Grubbs' 2nd generation catalyst⁵⁰ to install the macrocycle. We then performed a two-step sequence involving 1,4-reduction⁵⁵ and Rh-catalyzed reduction.⁶⁶ to afford tertiary amine **3.86**.

We questioned if the reductions could be streamlined by reordering the sequence of transformation. As shown in Figure 3.13B, this notion proved fruitful and allowed us to complete the first total synthesis of (±)-**3.15**. From **3.84**, acylation afforded macrocyclization precursor **3.87**. Next, ring-closing metathesis supplied macrocycle **3.88**, analogous to our prior study of related substrates discussed herein.⁵⁰ To complete the synthesis of **3.15**, we performed a Rh-catalyzed reduction⁶⁶ to effect three reduction events in a single operation, followed by trifluoroacetic acid (TFA)-mediated deprotection to deliver lissodendoric acid A (**3.15**), which spectroscopically matched a sample provided by the isolation chemists.^{37,67}

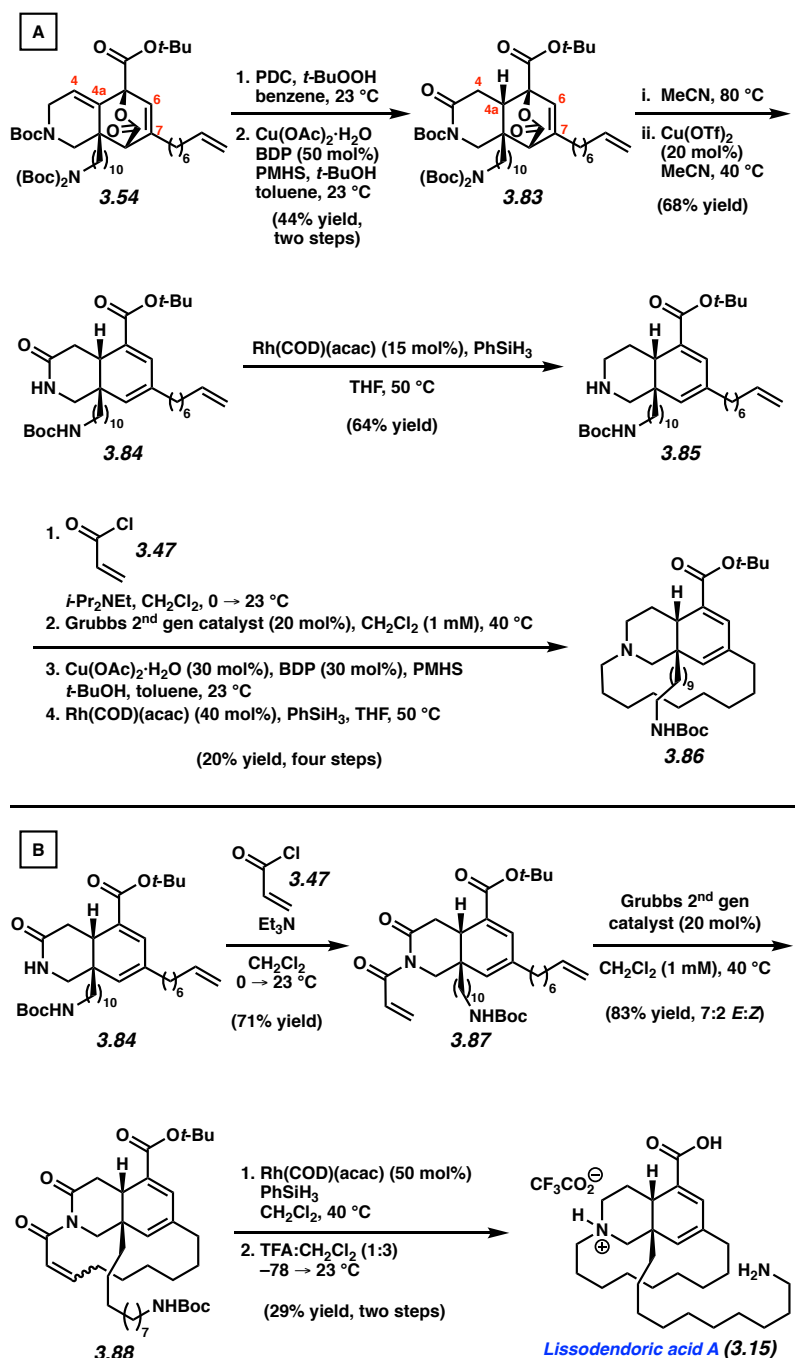


Figure 3.13. (A) Elaboration of cycloadduct **3.54** to tertiary amine **3.86**. (B) Optimization of late-stage reductions and completion of total synthesis of lissodendoric acid A (rac-**3.15**).

3.3.11 Enantioselective Diels–Alder Cycloaddition

To render the total synthesis enantioselective, we sought to prepare a strained cyclic allene precursor in enantioenriched form. We first attempted to synthesize enantioenriched **3.60** using an asymmetric allylic alkylation strategy²⁶. We had previously utilized a similar strategy to generate an enantioenriched oxacyclic allene precursor.²⁶ However, our attempts were unsuccessful in producing allyl ketone **3.38** in higher than 17% ee (Figure 3.14A).

We considered the design of cyclic allene precursors where the silyl substituent would reside on a less substituted 2° carbon. As shown in Figure 3.14B, cyclic allene precursors **3.89** and **3.91** were targeted. Each was prepared in enantioenriched form using chiral SFC in order to perform our scouting studies.³⁰ Unfortunately, when silyl triflate **3.89** (95% ee) was subjected to CsF and pyrone **3.30**, the Diels–Alder reaction proceeded with low stereospecificity, providing cycloadduct **3.90** in only 33% ee. However, when silyl bromide **3.91** (>99% ee) was used, cycloadduct **3.92** was obtained in 84% ee. We were sufficiently encouraged to pursue a non-model system study of **3.91**.

3.3.12 Syntheses of the Silyl Bromide Cyclic Allene Precursor

We envisioned that silyl bromide **3.95** would be a suitable cyclic allene precursor (Figure 3.14). To maximize synthetic efficiency, we first considered the two-step approach shown in Figure 3.14C. Beginning from commercially available bromoenone **3.93**, we performed a 1,4-addition of a silyl cuprate nucleophile, followed by trapping of the resulting enolate with Comins' reagent. Using B-alkyl Suzuki–Miyaura cross-coupling,⁶⁸ the resultant vinyl triflate could be coupled with an alkyl borane, generated in situ from **3.94**, to afford silyl bromide **3.95**. Although

we thought this strategy could be rendered enantioselective (e.g., conjugate addition of the silyl nucleophile),⁶⁹ the low yields led us to pursue an alternative strategy.

Inspired by an elegant strategy reported by West,^{17,70} we developed the route shown in Figure 3.14D. Bromotriflate **3.96** could be obtained from a commercial vendor or prepared in two steps from *tert*-butyl 3,5-dioxopiperidine-1-carboxylate. Treatment of **3.96** with **3.97** furnished ketone **3.98** through Cu-mediated 1,4-addition and ejection of the triflate.⁷¹ Gratifyingly, ketone **3.98** underwent Corey–Bakshi–Shibata (CBS) reduction to afford an enantioenriched alcohol. Subsequent treatment with ethyl chloroformate gave the corresponding carbonate **3.99**,⁷² which was treated with a silyl cuprate nucleophile to generate silyl bromide **3.95** with stereoinversion.^{73,74}

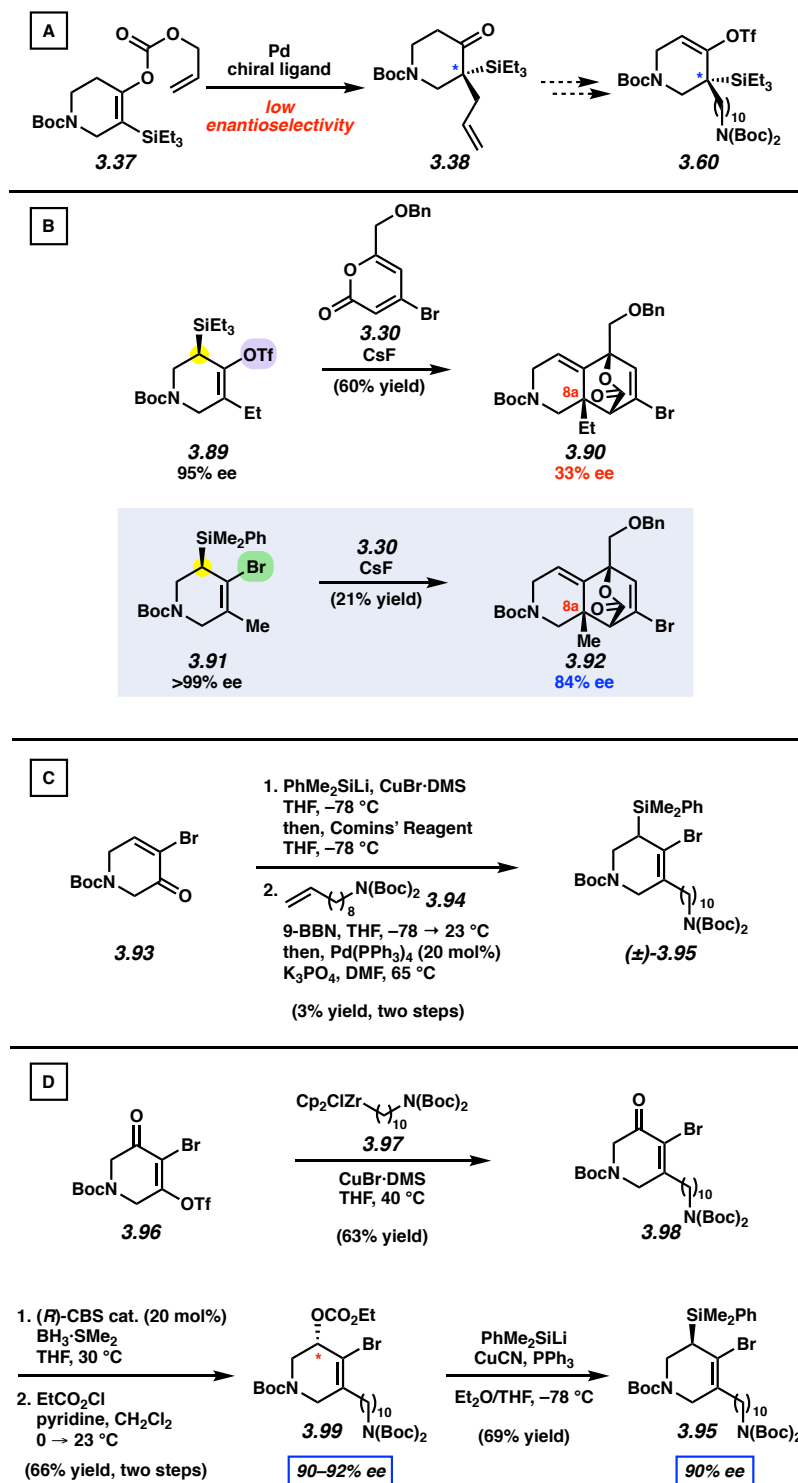


Figure 3.14. A) Unsuccessful approach to enantioenriched silyl triflate **3.60**. (B) Cycloadditions employing newly designed cyclic allene precursors **3.89** and **3.91** in stereospecific trapping

experiments. (C) Initial racemic synthesis of **3.95** via Suzuki–Miyaura cross-coupling. (D) Enantioselective synthesis of **3.95**.

3.3.13 Enantioselective Diels–Alder Cycloaddition

With access to enantioenriched **3.95**, we were poised to attempt the enantiospecific Diels–Alder reaction. Silyl bromide **3.95** was treated with pyrone **3.57** in the presence of CsF (Figure 3.15A). Using acetonitrile as solvent at 23 °C, cycloadduct **3.54** was obtained in 90% yield, thus validating silyl bromide **3.95** as a new cyclic allene precursor. However, the optical yield was 73%, reflecting a significant loss of stereochemical information. Other conditions were examined with select results shown in Figure 3.15A. Most notably, using acetonitrile at 4 °C, which required the use of Bu₄NBr as a phase-transfer catalyst to solubilize the fluoride, led to an improved optical yield of 80%. Finally, decreasing the temperature to –20 °C allowed for an increase in optical yield to 88%.⁷⁵ Because we had already developed a short sequence to convert (±)-**3.54** to (±)-**3.15**, our preparation of enantioenriched **3.54** also provided a means to access the enantioenriched natural product ((–)-**3.15**).

3.3.14 Overview of Total Synthesis and Absolute Stereochemistry

Figure 3.15B provides a summary of our concise enantioselective synthesis of (–)-lissodendoric acid A (**3.15**). Lastly, the topic of absolute stereochemistry also deserves attention, as the absolute chemistry of (–)-**3.15** had not been rigorously established experimentally. The isolation chemists reasonably proposed the configuration based on computational electronic circular dichroism.³⁷ We were delighted to validate this proposal and confirm that the absolute stereochemistry was as proposed and as is shown throughout our manuscript.

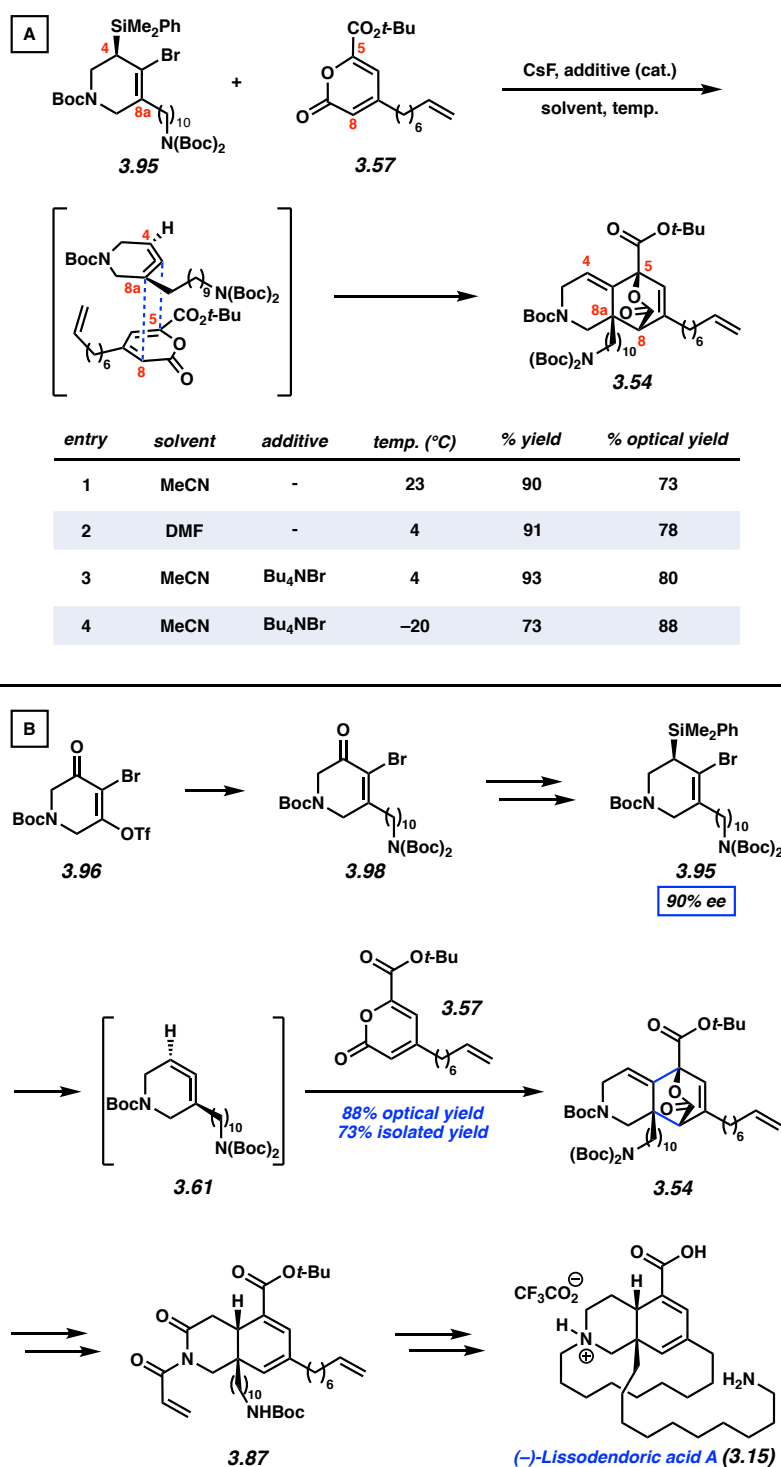


Figure 3.15. (A) Abbreviated optimization of enantiospecific strained cyclic allene Diels–Alder cycloaddition. (B) Overview of asymmetric total synthesis of (–)-**3.15**.

3.4 Conclusion

Our concise enantioselective synthesis of lissodendoric acid A (**3.15**) shows that strained cyclic allenes are versatile tools for the rapid construction of stereo- and structurally-complex scaffolds. Moreover, DFT calculations provide insight into the electronic structure and reactivity of strained cyclic allenes in Diels–Alder trappings with pyrones. We hope this study prompts the further strategic use of unusual strained intermediates in chemical synthesis.

3.5 Experimental Section

3.5.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received unless otherwise specified. Diisopropylethylamine (DIPEA) was purchased from Acros Organics. Anhydrous *t*-BuOH, Grubbs' 2nd generation catalyst, Potassium hexamethyldisilazide (KHMDs), Potassium dichromate (PDC), *t*-BuOOH 70 wt% in H₂O, *N*-methylimidazole, Boc₂O, LiAlH₄ 2.0 M solution in THF, acryloyl chloride (**3.47**), BCl₃ 1.0 M solution in CH₂Cl₂, PhSiH₃, basic alumina, tetrabutylammonium fluoride (TBAF, 1.0 M in THF), and 9-borabicyclo[3.3.1]nonane (9-BBN) 0.5 M solution in THF were obtained from Sigma-Aldrich. AgNO₃, *N*-phenyl-bis(trifluoromethanesulfonimide) (PhNTf₂), PPh₃, Cs₂CO₃, and 9-bromo-1-nonene (**3.100**) were purchased from Oakwood Chemical. CsF, Pd(PPh₃)₄, Cl₂Pd(PPh₃)₂, Cu(OTf)₂, Rh(COD)(acac), Pd/C, 1,2-bis(diphenylphosphino)benzene (BDP), and potassium phosphate (K₃PO₄) were purchased from Strem Chemicals. Copper(II) acetate monohydrate (Cu(OAc)₂·H₂O) and hydrazine monohydrate (N₂H₄·H₂O) were purchased from TCI chemicals.

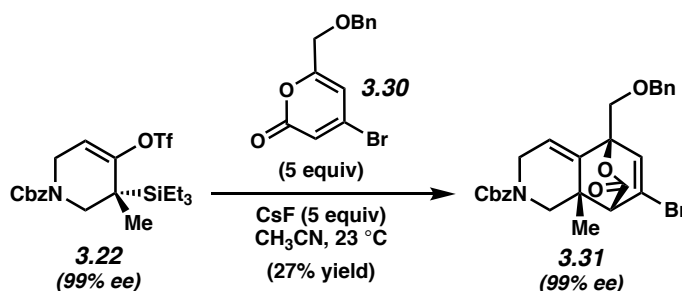
Poly(methylhydrosiloxane) (PMHS) and methyl coumalate (**3.76**) were purchased from Alfa-Aesar. Manganese dioxide (MnO₂) was purchased from Honeywell Fluka. *t*-BuOH, triethylamine (Et₃N), and α -Pyrone (**3.24**) were purchased from Fisher Scientific. Comins' reagent was purchased from Combi-Blocks. 4-chloro-2H-pyran-one (**3.71**) was purchased from Enamine. Potassium phthalimide (**3.102**) was purchased from Chem-Impex. Di-*tert*-butyl iminodicarbonate (NH(Boc)₂) and 4-methoxy-6-methyl-2H-pyran-2H-one (**3.74**) were purchased from Ambeed. Acryloyl chloride (**3.47**) was distilled over CaH₂ prior to use. PMHS and *t*-BuOH were sparged with N₂ prior to use. Unless stated otherwise, reactions were performed at 23 °C. Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV light and anisaldehyde or potassium permanganate staining. Silicycle Siliaflash P60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ¹H-NMR, 2D-NOESY, 2D-HSQC, and 2D-HMBC spectra were recorded on Bruker spectrometers (at 400, 500, or 600 MHz) and are reported relative to the residual solvent signal. Data for ¹H-NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ¹³C-NMR spectra were recorded on Bruker spectrometers (at 100, 125, or 150 MHz) and are reported relative to the residual solvent signal. Data for ¹³C-NMR spectra are reported in terms of chemical shift (δ ppm). IR spectra were obtained on a Perkin-Elmer UATR Two FT-IR spectrometer and are reported in terms of frequency of absorption (cm⁻¹). DART-MS spectra were collected on a Thermo Exactive Plus MSD (Thermo Scientific) equipped with an ID-CUBE ion source, a Vapur Interface (IonSense Inc.), and an Orbitrap mass analyzer. Both the source and MSD were controlled by Excalibur software v. 3.0. The analyte was spotted onto OpenSpot sampling cards (IonSense Inc.) using CDCl₃ as the solvent. Ionization was accomplished using UHP He (Airgas Inc.) plasma with no additional ionization agents. The mass

calibration was carried out using Pierce LTQ Velos ESI (+) and (–) Ion calibration solutions (Thermo Fisher Scientific). ESI-TOF measurements were carried out in positive ionization mode on a Waters LCT-Premier XE Time of Flight Instrument controlled by MassLynx 4.1 software (Waters Corporation, Milford MA). The instrument was equipped with the Multi Mode Ionization source operated in the electrospray mode. A solution of Leucine Enkephalin (Sigma Chemical, L9133) was used in the Lock-Spray to obtain accurate mass measurements. Determination of enantiopurity was carried out on a Mettler Toledo SFC (supercritical fluid chromatography) using a Daicel ChiralPak OD-H column. 3-Bromopropiolic acid (**3.28**),⁴⁵ benzyl propargyl ether (**3.29**),⁷⁶ and bromoenone **3.93**⁷⁷ are known compounds. ¹H NMR spectral data matched those reported in the literature.

3.5.2 Experimental Procedures

Note: Experimental information for compounds **3.15**, **3.28**, **3.30**, **3.54**, **3.56–3.57**, **3.83–3.84**, **3.87–3.88**, **3.89–3.92**, **3.94–3.99**, and **3.102** have been previously reported as part of the original report of the total synthesis of lissodendoric acid A.³⁰ Experimental information for compound **3.22** has been previously reported by our group.²⁵ Experimental information for compounds **3.37–3.38** and **3.103** has been previously reported as part of the progress toward the total synthesis of keramaphidin B.⁵²

3.5.2.1 Model System Studies

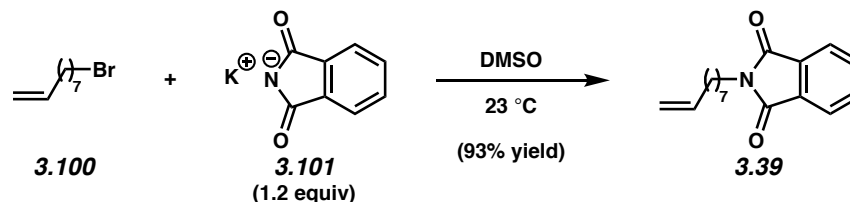


Cycloadduct 3.31. To a solution of silyl triflate **3.22** (16.1 mg, 0.0326 mmol, 1.00 equiv) and pyrone **3.30** (48.1 mg, 0.163 mmol, 5.00 equiv) in acetonitrile (0.32 mL, 0.10 M) was added CsF (24.8 mg, 0.163 mmol, 5.00 equiv). The vial was sealed and the reaction was allowed to stir at 23 °C for 17 h. After 17 h, the reaction was filtered over celite (1 cm) using EtOAc as the eluent and concentrated to a crude oil. The crude oil was purified by preparative thin-layer chromatography (2:1 hexanes:EtOAc) to obtain cycloadduct **3.31** (4.6 mg, 27% yield, unoptimized) as a yellow oil.

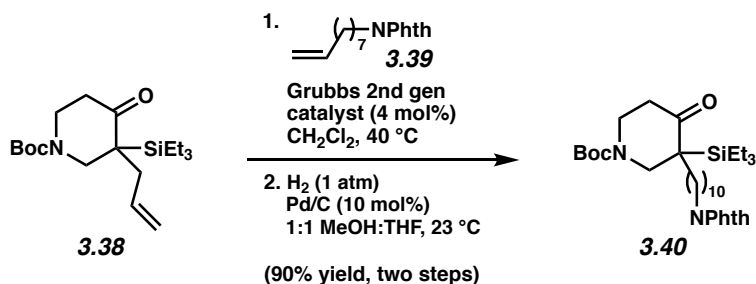
Cycloadduct **3.31**: R_f 0.24 (9:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 7.40–7.28 (m, 10H), 6.54 (dd, $J = 11.7, 1.4$, 1H), 5.73 (dd, $J = 26.5, 3.8$, 1H), 5.23–5.13 (m, 2H), 4.69–4.65 (m, 2H), 4.32–4.19 (m, 1H), 4.17–3.98 (m, 2H), 3.93 (d, $J = 10.7$, 1H), 3.76 (td, $J = 19.6, 5.4$, 1H), 3.52 (dd, $J = 25.5, 1.5$, 1H), 2.55 (dd, $J = 16.5, 11.8$, 1H), 1.14 (d, $J = 16.4$, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 169.2, 156.2, 155.8, 137.9, 137.4, 137.19, 137.16, 136.6, 136.5, 133.1, 132.8, 128.8, 128.7, 128.6, 128.4, 128.33, 128.31, 128.2, 128.15, 128.12, 128.07, 119.3, 118.9, 117.5, 117.1, 85.1, 85.0, 74.2, 67.8, 67.7, 67.6, 60.4, 60.3, 49.7, 49.6, 43.0, 42.7, 37.4, 22.1, 22.0; IR (film): 3036, 2929, 2875, 1765, 1702, 1454, 1417, 1264, 1096 cm^{-1} ; HRMS-APCI (m/z) [$\text{M} - \text{CO}_2$] $^+$ calcd for $\text{C}_{26}\text{H}_{26}\text{BrNO}_3^+$, 479.1091; found 479.1054.

Note: 3.31 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.

3.5.2.2 Synthesis of Silyl Triflate 3.41



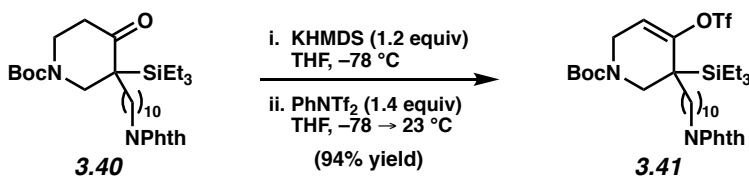
Phthalimide 3.39. To a mixture of 9-bromononene (**3.100**, 10.0 g, 48.7 mmol, 1.00 equiv) and potassium phthalimide (**3.101**, 10.8 g, 58.5 mmol, 1.20 equiv) was added DMSO (60.9 mL, 0.800 M) and the reaction mixture was allowed to stir at 23 °C for 16 h. After 16 h, the mixture was transferred to a separatory funnel with water (100 mL) and CH_2Cl_2 (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (9:1 hexanes:EtOAc) to give phthalimide **3.39** (18.5 g, 93% yield) as a white solid. Phthalimide **3.39**: R_f 0.40 (9:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): 7.82 (dd, $J = 5.5, 3.0$, 2H), 7.69 (dd, $J = 5.5, 3.0$, 2H), 5.78 (ddt, $J = 17.3, 10.1, 6.7$, 1H), 4.99–4.94 (m, 1H), 4.92–4.89 (m, 1H), 3.69–3.64 (m, 2H), 2.04–1.98 (m, 2H), 1.70–1.61 (m, 2H), 1.38–1.24 (m, 8H); ^{13}C NMR (125 MHz, CDCl_3): δ 168.6, 139.2, 133.9, 132.3, 123.3, 114.3, 38.2, 33.8, 29.14, 29.06, 28.9, 28.7, 26.9; IR (film): 3076, 2927, 2855, 1772, 1707, 1394, 1367 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{22}\text{NO}_2^+$, 272.1645; found 272.1654.



Ketone 3.40. A flask in the glove box was charged with Grubbs' 2nd Generation catalyst (235 mg, 0.277 mmol, 4.00 mol%), sealed with a septum, and taken out of the glovebox. To this flask was added a solution of allyl ketone **3.38** (2.45 g, 6.93 mmol, 1.00 equiv) and phthalimide **3.39** (9.41 g, 34.7 mmol, 5.00 equiv) in CH_2Cl_2 (35 mL, 0.20 M). The flask was equipped with a reflux condenser and the reaction mixture was heated to 40 °C and stirred for 16 h at which point it was cooled to 23 °C. The solvent was removed under reduced pressure to give a dark brown tacky oil. The crude oil was purified via flash chromatography (100% benzene $\rightarrow$ 9:1 benzene:EtOAc) and repurified via flash chromatography (9:1 hexanes:EtOAc $\rightarrow$ 5:1 hexanes:EtOAc) to give the cross-metathesis product. To a flask was added the cross-metathesis product (1.31 g, 2.19 mmol, 1.00 equiv), Pd/C (233 mg, 0.219 mmol, 10% w/w, 10 mol%), THF (33 mL), and MeOH (33 mL). The flask was evacuated and backfilled with H_2 from a balloon three times, then left to stir under an atmosphere of H_2 (1 atm) for 45.5 h. Over this time, the flask was evacuated and backfilled with H_2 from a balloon 3 times at 20 h, and 30 h. After 45.5 h, the reaction was filtered over celite (4 cm) with CH_2Cl_2 as the eluent (150 mL). Evaporation under reduced pressure afforded the crude residue. The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc) to afford ketone **3.40** (1.25 g, 90% yield over two steps) as a colorless oil. Ketone **3.40**: R_f 0.35 (5:1 hexanes:EtOAc); ^1H NMR (600 MHz, CDCl_3): δ 7.84 (dd, J = 5.4, 3.0, 2H), 7.70 (dd, J = 5.4, 3.0, 2H), 3.99–3.88 (m, 1H), 3.85–3.72 (m, 1H), 3.72–3.51 (m, 3H), 3.41–3.23 (m, 1H), 2.65–2.48 (m, 1H), 2.45–2.32 (m, 1H), 2.03–1.89 (m, 1H), 1.70–1.63 (m, 2H), 1.46 (s, 9H), 1.35–1.11 (m, 15H),

0.97 (t, $J = 7.7$, 9H), 0.75–0.63 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ 212.3, 211.5, 168.6, 154.7, 133.9, 132.3, 123.3, 80.5, 80.0, 50.9, 50.5, 50.3, 46.5, 45.8, 42.1, 41.6, 40.0, 38.19, 38.18, 34.0, 33.1, 30.69, 30.66, 30.60, 29.6, 29.57, 29.55, 29.53, 29.47, 29.30, 29.27, 28.7, 28.6, 28.5, 27.1, 26.99, 26.97, 26.94, 25.7, 8.0, 2.7, 2.5; IR (film): 2928, 2877, 2855, 1714, 1690, 1396 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{34}\text{H}_{55}\text{N}_2\text{O}_5\text{Si}^+$, 599.3875; found 599.3896.

Note: 3.40 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.

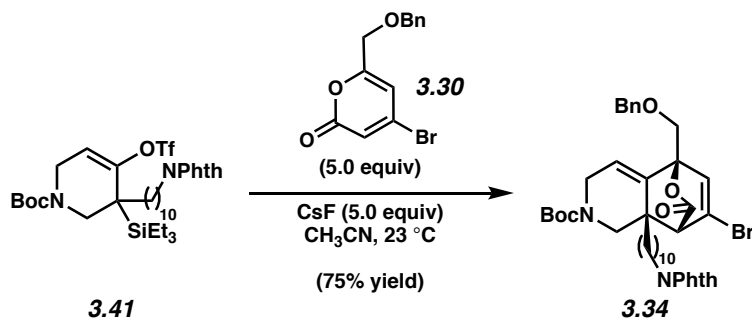


Silyl triflate 3.41. A flask in the glovebox was charged with KHMDS (670 mg, 3.36 mmol, 1.20 equiv), sealed with a septum, and taken out of the glovebox. THF (12.0 mL) was then added to the flask and the reaction mixture was cooled to -78°C . Ketone **3.40** (1.73 g, 2.80 mmol, 1.00 equiv) in THF (6.0 mL) was added to the solution dropwise over 10 min at -78°C . The solution was stirred at -78°C for 1 h. Then, PhNTf_2 (1.40 g, 3.92 mmol, 1.40 equiv) in THF (6.0 mL) was added dropwise over 5 min at -78°C resulting in a final reaction concentration of 0.12 M. The reaction was then warmed to 23°C and stirred for 2 h. After 2 h, the reaction was quenched with a saturated aq. solution of NaHCO_3 (50 mL) and diluted with water (50 mL) and Et_2O (50 mL). The reaction was then transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure to provide the crude residue. The crude residue was purified via flash chromatography (19:1 hexanes: EtOAc $\rightarrow$ 9:1 hexanes: EtOAc) to obtain silyl triflate **3.41** (2.03 g, 94% yield) as a colorless oil. Silyl triflate **3.41**: R_f 0.64 (5:1

hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 7.83 (dd, $J = 5.0, 2.9$, 2H), 7.70 (dd, $J = 5.0, 2.9$, 2H), 5.65 (s, 1H), 4.17 (dd, $J = 18.0, 4.1$, 1H), 3.89–3.64 (m, 4H), 3.48–3.30 (m, 1H), 1.69–1.63 (m, 2H), 1.61–1.52 (m, 2H), 1.46 (s, 9H), 1.43–1.07 (m, 15H), 0.99 (t, $J = 7.9$, 9H), 0.75–0.65 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ 168.60, 168.59, 154.3, 153.5, 133.9, 132.3, 123.3, 122.2, 119.7, 117.1, 114.6, 110.2, 80.5, 47.4, 46.8, 42.3, 41.9, 38.2, 35.6, 35.4, 32.9, 32.6, 30.5, 29.7, 29.60, 29.57, 29.32, 29.29, 28.8, 28.51, 28.48, 27.02, 26.99, 26.96, 25.0, 24.6, 8.1, 2.9, 2.7; IR (film): 2930, 2879, 2856, 1715, 1415, 1396, 1210 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{35}\text{H}_{54}\text{F}_3\text{N}_2\text{O}_7\text{SSi}^+$, 731.3368; found 731.3384.

Note: 3.41 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.

3.5.2.3 First Generation Diels–Alder Cycloaddition

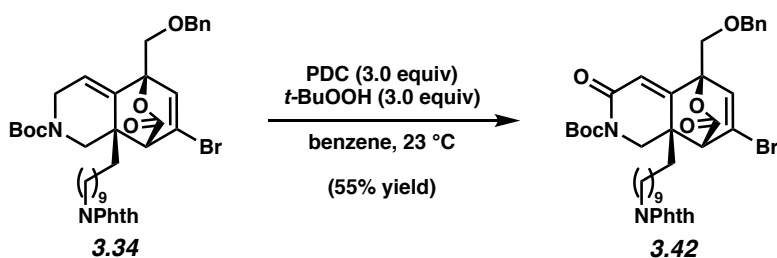


Cycloadduct 3.34. To a solution of silyl triflate **3.41** (555 mg, 0.759 mmol, 1.00 equiv) and pyrone **3.30** (1.12 g, 3.80 mmol, 5.00 equiv) in acetonitrile (7.59 mL) was added CsF (577 mg, 3.80 mmol, 5.00 equiv). The vial was sealed and the reaction was allowed to stir at 23 °C for 16 h. After 16 h, the reaction was filtered over silica (2 cm) using EtOAc (~10 mL) as the eluent and concentrated to a crude oil. The crude oil was purified via flash chromatography (5:1 → 3:1 hexanes:EtOAc) to obtain cycloadduct **3.34** (432 mg, 75% yield) as a yellow foam. Cycloadduct **3.34**: R_f 0.26 (5:1

hexanes:EtOAc); ^1H NMR (600 MHz, CDCl_3): δ 7.83 (dd, $J = 5.4, 3.0$, 2H), 7.69 (dd, $J = 5.4, 3.0$, 2H), 7.40–7.31 (m, 5H), 6.53 (dd, $J = 23.8, 2.4$, 1H), 5.72–5.62 (m, 1H), 4.66 (s, 2H), 4.38–4.10 (m, 2H), 4.05–4.01 (m, 1H), 3.92 (d, $J = 10.7$, 1H), 3.70–3.63 (m, 3H), 3.61–3.55 (m, 1H), 2.30 (dd, $J = 41.3, 11.6$, 1H), 1.69–1.61 (m, 3H), 1.50–1.45 (m, 9H), 1.36–1.16 (m, 15H); ^{13}C NMR (150 MHz, CDCl_3): δ 169.2, 169.1, 168.6, 155.1, 154.9, 138.3, 137.3, 137.2, 133.9, 133.5, 133.0, 132.3, 128.7, 128.3, 128.2, 128.12, 128.09, 123.3, 119.2, 118.8, 117.4, 117.1, 85.2, 85.1, 80.6, 80.4, 74.2, 67.9, 67.8, 57.4, 57.3, 45.6, 44.8, 42.9, 42.5, 40.8, 40.7, 38.2, 34.4, 34.3, 30.0, 29.8, 29.7, 29.60, 29.57, 29.51, 29.3, 29.2, 28.7, 28.6, 28.5, 27.0, 23.5, 23.3; IR (film): 2928, 2855, 1770, 1710, 1395, 1365, 1136 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} - \text{CO}_2]^+$ calcd for $\text{C}_{40}\text{H}_{49}\text{BrN}_2\text{O}_5^+$, 716.2819; found 716.2877.

Note: 3.34 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.

3.5.2.4 Synthesis of Macrocyclization Precursor 3.48

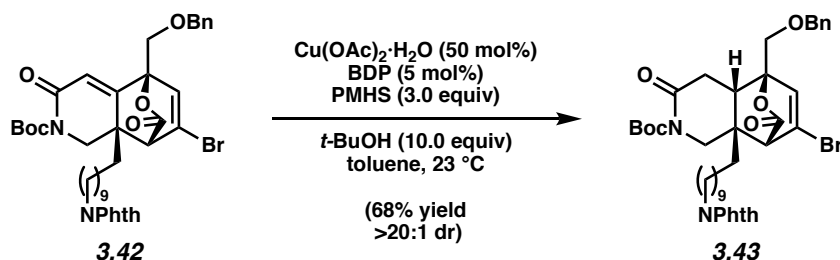


Unsaturated amide 3.42. The oxidation of **3.34** was based on conditions developed by Chandrasekaran and coworkers.⁵⁴ To a solution of cycloadduct **3.34** (50.0 mg, 0.0656 mmol, 1.00 equiv) in benzene (6.56 mL, 0.01 M) was added celite (1.00 g), PDC (74.1 mg, 0.197 mmol, 3.00 equiv), and $t\text{-BuOOH}$ (0.0270 mL, 70 wt% in water, 0.197 mmol, 3.00 equiv). The solution was

stirred at 23 °C for 2.5 h. At this point, the solution was filtered over a pad of celite and rinsed with EtOAc (15 mL). The filtrate was diluted with saturated aq. sodium thiosulfate solution (10 mL) and water (15 mL). The solution was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water (3 x 15 mL) and brine (15 mL), dried over MgSO₄, filtered, and concentrated to a crude yellow oil. The crude oil was purified via preparative TLC (7:3 hexanes:EtOAc) to obtain unsaturated amide **3.42** (28.0 mg, 55% yield) as a yellow foam.

Unsaturated amide **3.42**: *R_f* 0.33 (2:1 hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃): δ 7.83 (dd, *J* = 5.4, 3.0, 2H), 7.70 (dd, *J* = 5.4, 3.0, 2H), 7.40–7.32 (m, 5H), 6.71 (d, *J* = 2.2, 1H), 5.81 (d, *J* = 0.5, 1H), 4.69–4.62 (m, 2H), 4.38 (d, *J* = 12.8, 1H), 4.00 (d, *J* = 10.7, 1H), 3.90 (d, *J* = 10.7, 1H), 3.72 (d, *J* = 2.0, 1H), 3.67 (t, *J* = 7.3, 2H), 3.25 (d, *J* = 12.7, 1H), 1.95–1.87 (m, 1H), 1.69–1.63 (m, 3H), 1.53 (s, 9H), 1.34–1.20 (m, 14H); ¹³C NMR (100 MHz, CDCl₃): δ 168.6, 167.8, 162.6, 156.5, 152.1, 136.7, 134.01, 133.95, 132.3, 128.8, 128.4, 128.2, 123.3, 121.6, 116.8, 84.1, 83.9, 74.3, 67.1, 56.9, 49.8, 40.9, 38.2, 34.2, 29.6, 29.5, 29.3, 28.7, 28.1 (3C), 27.0, 23.5; IR (film): 2933, 2854, 1773, 1712, 1395, 1369, 1151 cm⁻¹; HRMS-APCI (*m/z*) [*M* – CO₂]⁺ calcd for C₄₀H₄₇BrN₂O₆⁺, 731.26903; found 731.26350.

Note: 3.42 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ¹H and ¹³C NMR spectra.

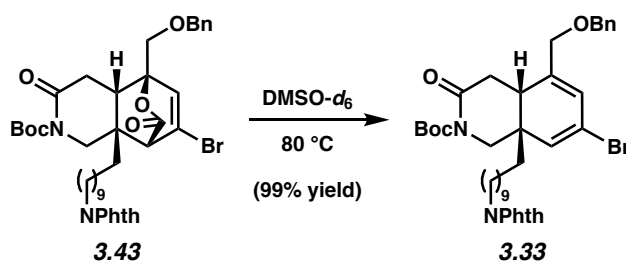


Amide 3.42. The procedure for the reduction of the unsaturated amide **3.42** was inspired by work reported by Lipshutz and coworkers.⁷⁸ A flask was charged with copper(II) acetate monohydrate (54.5 mg, 0.273 mmol, 50.0 mol%) and BDP (24.4 mg, 0.0546 mmol, 10.0 mol%). The solids were dissolved in sparged *t*-BuOH (0.520 mL, 5.46 mmol, 10.0 equiv) and toluene (2.10 mL). The contents of the flask were sonicated for 2 minutes and then stirred for 30 minutes, during which the solution turned blue. PMHS (3.09 mL, 1.64 mmol, 95.0 equiv effective hydride) was added dropwise over 4 minutes, then the solution was allowed to stir for 40 minutes during which it turned yellow/green. A solution of **3.42** (424 mg, 0.546 mmol, 1.00 equiv) in toluene (2.1 mL, 0.26 M) was then added to the modified Stryker reagent dropwise over 3 minutes. The reaction then stirred at 23 °C for 21 h, after which it was diluted with EtOAc (30 mL). The solution was transferred to a separatory funnel and washed with 1N NaOH (10 mL), 1N HCl (10 mL), saturated aq. NaHCO₃ solution (10 mL), and then brine (10 mL). The combined aqueous layers were washed with EtOAc (3 x 10 mL). The organic layers were combined, dried over MgSO₄, and concentrated under reduced pressure. The crude material was purified via flash chromatography (9:1 → 2:1 hexanes:EtOAc) to obtain amide **3.43** (289 mg, 68% yield) as a yellow foam. Amide **3.43**: *R_f* 0.23 (2:1 hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃): δ 7.84 (dd, *J* = 5.4, 3.0, 2H), 7.70 (dd, *J* = 5.4, 3.0, 2H), 7.40–7.30 (m, 5H), 6.46 (d, *J* = 1.9, 1H), 4.65 (d, *J* = 12.0, 1H), 4.57 (d, *J* = 12.0, 1H), 4.24 (d, *J* = 14.0, 1H), 3.82 (d, *J* = 11.2, 1H), 3.69–3.64 (m, 3H), 3.59 (d, *J* = 2.0, 1H), 3.20 (d, *J* = 14.0, 1H), 2.59 (dd, *J* = 14.6, 5.8, 1H), 2.28 (dd, *J* = 11.8, 5.8, 1H), 2.10–2.00 (m, 1H), 1.69–1.62 (m, 3H), 1.52 (s, 9H), 1.34–1.21 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 169.2, 169.0, 168.6, 151.2, 137.0, 134.0, 132.3, 131.0, 128.8, 128.3, 128.1, 123.3, 122.5, 86.6, 84.1, 74.2, 69.1, 56.8, 45.9, 44.7, 43.5, 38.4, 38.2, 37.5, 29.8, 29.6, 29.5, 29.4, 29.3, 28.7, 28.1, 27.0, 23.2; IR (film):

2928, 2855, 1770, 1713, 1396, 1368, 1153 cm^{-1} ; HRMS-APCI (m/z) [$M - \text{CO}_2$] $^+$ calcd for $\text{C}_{40}\text{H}_{49}\text{BrN}_2\text{O}_6^+$, 733.28468; found 733.27974.

Note: 3.43 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.

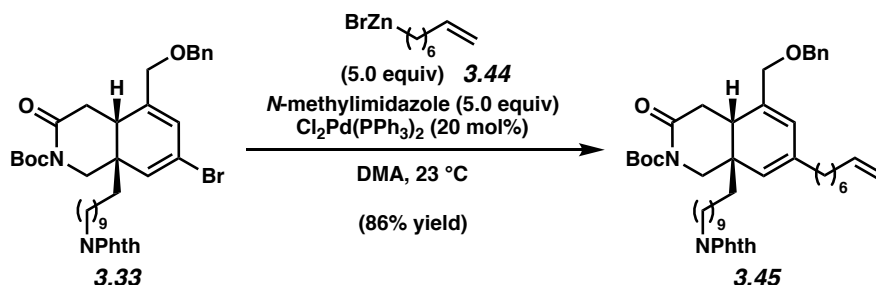
The equivalency of PMHS added was 3.0 equiv based on the mass of the polymer (1900 g/mol) and 95 equiv based on the effective mass per hydride (60 g/mol).



Diene 3.33. A vial was charged with amide **3.43** (129 mg, 0.166 mmol, 1.00 equiv) and $\text{DMSO-}d_6$ (2.10 mL, 0.0800 M). The vial was heated to 80 $^\circ\text{C}$ for 2.5 h, after which it was allowed to cool to 23 $^\circ\text{C}$. The reaction mixture diluted with Et_2O (2 mL) and transferred to a separatory funnel and washed with water (3 x 1 mL). The combined aqueous layers were extracted with Et_2O (2 x 2 mL) and the organic layers were combined, washed with brine (2 mL), and dried over MgSO_4 to obtain diene **3.33** (120 mg, 99% yield) as a pale-yellow oil. Diene **3.33**: R_f 0.37 (2:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 7.84 (dd, $J = 5.4, 3.0, 2\text{H}$), 7.71 (dd, $J = 5.4, 3.0, 2\text{H}$), 7.37–7.29 (m, 5H), 5.95 (s, 1H), 5.60 (s, 1H), 4.55–4.45 (m, 2H), 4.04 (d, $J = 13.0, 1\text{H}$), 3.90 (d, $J = 13.8, 1\text{H}$), 3.72–3.64 (m, 3H), 3.59 (d, $J = 13.8, 1\text{H}$), 2.58 (dd, $J = 14.2, 4.6, 1\text{H}$), 2.54–2.41 (m, 2H), 1.69–1.62 (m, 3H), 1.53 (s, 9H), 1.33–1.19 (m, 15H); ^{13}C NMR (100 MHz, CDCl_3): δ 171.3, 168.6, 151.9, 138.5, 137.8, 134.0, 132.3, 129.3, 128.6, 128.0, 127.8, 124.5, 123.3, 116.8, 83.5, 72.7, 71.0, 51.7, 43.2, 39.6, 38.2, 37.0, 36.8, 30.3, 29.6, 29.5, 29.3, 28.7, 28.1 (2C), 27.0, 23.6; IR (film):

2928, 2854, 1773, 1711, 1396, 1367, 1152 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{40}\text{H}_{50}\text{BrN}_2\text{O}_6^+$, 733.28468; found 733.27959.

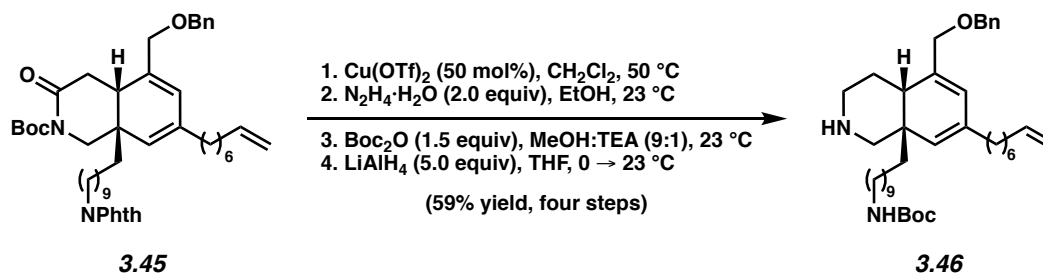
Note: 3.33 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.



Diene 3.45. A flask was charged with vinyl bromide **3.33** (986 mg, 1.34 mmol, 1.00 equiv). To the flask was added bis(triphenylphosphine)palladium(II) chloride (189 mg, 0.269 mmol, 20.0 mol%), 1-methylimidazole (552 mg, 0.536 mL, 6.72 mmol, 5.00 equiv), and a solution of alkylzinc bromide⁷⁹ **3.44** in DMA (1.7 g, 13 mL, 0.52 M, 6.7 mmol, 5.0 equiv). The reaction mixture was stirred at 23 °C for 19 h. After 19 h, the reaction was quenched with saturated aq. NH_4Cl (10 mL) and diluted with EtOAc (10 mL). The aqueous layer was then diluted with H_2O (10 mL) and extracted with EtOAc (7 x 10 mL). The organic layers were combined, dried over MgSO_4 , filtered, and concentrated to a crude residue under reduced pressure. The crude residue was purified via flash chromatography (100% benzene $\rightarrow$ 9:1 benzene:EtOAc) to obtain diene **3.45** (886 mg, 86% yield) as a yellow oil. Diene **3.45**: R_f 0.59 (2:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 7.84 (dd, $J = 5.3, 2.9$, 2H), 7.70 (dd, $J = 5.3, 2.9$, 2H), 7.35–7.32 (m, 5H), 5.87–5.72 (m, 2H), 5.02–4.89 (m, 3H), 4.52 (d, $J = 11.8$, 1H), 4.45 (d, $J = 11.8$, 1H), 4.05 (d, $J = 12.3$, 1H), 3.90 (d, $J = 12.3$, 1H), 3.69–3.63 (m, 3H), 3.61–3.51 (m, 1H), 2.56 (dd, $J = 15.0, 5.9$, 1H), 2.49–2.43 (m, 1H), 2.42–2.32 (m, 1H), 2.08–2.00 (m, 5H), 1.52 (s, 9H), 1.41–1.29 (m, 17H), 1.21–1.17 (m, 8H);

^{13}C NMR (125 MHz, CDCl_3): δ 172.2, 168.6, 152.2, 139.2, 138.2, 135.5, 135.4, 134.0, 132.3, 128.6, 127.80, 127.75, 124.3, 124.0, 123.3, 114.4, 83.1, 72.3, 72.2, 52.6, 40.0, 38.2, 37.6, 37.3, 35.5, 33.9, 30.5, 29.8, 29.71, 29.68, 29.6, 29.3, 29.1, 29.0, 28.8, 28.3, 28.2, 27.0, 23.7, 14.3; IR (film): 2917, 2851, 1773, 1715, 1395 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{48}\text{H}_{65}\text{N}_2\text{O}_6^+$, 765.48371; found 765.48541.

Note: 3.45 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.

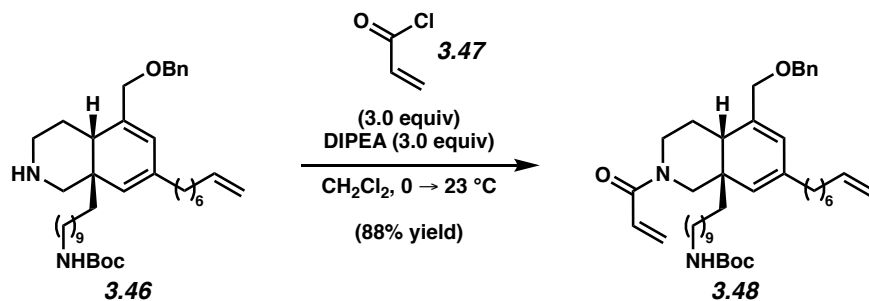


Secondary amine 3.46. To a solution of diene **3.45** (886 mg, 1.16 mmol, 1.00 equiv) in CH_2Cl_2 (11.6 mL, 0.10 M) was added $\text{Cu}(\text{OTf})_2$ (209 mg, 0.579 mmol, 50.0 mol%). The vial was sealed and the reaction mixture was heated to 50 °C and stirred for 1.5 h. At this point, the reaction mixture was cooled to 23 °C and quenched with saturated aq. NaHCO_3 (10 mL). The organic layer was diluted with CH_2Cl_2 (10 mL) and the layers were separated. The organic layer was washed with saturated aq. NaHCO_3 (1 x 10 mL) and water (1 x 10 mL). The combined aqueous layers were washed with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (3:1 benzene:EtOAc $\rightarrow$ 1:2 benzene:EtOAc) to obtain the secondary amide as a colorless oil. To a solution of the secondary amine (457 mg, 0.688 mmol, 1.00 equiv) in ethanol (6.9 mL, 0.10 M) was added hydrazine monohydrate (108 mg, 0.104 mL, 64% wt, 1.38 mmol,

2.00 equiv) over 1 min. The reaction was heated to 40 °C and stirred. After 3 h, additional hydrazine monohydrate (0.104 mL, 64 wt%, 1.38 mmol, 2.00 equiv) was added dropwise to the reaction mixture over 1 min. After 4 h total, the solvent was removed under vacuum. The reaction was diluted with EtOAc (5 mL) and quenched with saturated aq. NaHCO₃ (5 mL). The layers were separated and the aqueous layer was diluted with H₂O (3 mL) and extracted with EtOAc (3 x 5 mL) and CH₂Cl₂ (2 x 5 mL). The organic layers were combined, dried over sodium sulfate and was concentrated under reduced pressure. The crude residue was purified via flash chromatography (9:1 CH₂Cl₂:MeOH → 1:1 CH₂Cl₂:MeOH w/ 5% Et₃N) to obtain the primary amine as a colorless oil. To a solution of the primary amine (197 mg, 0.369 mmol, 1.00 equiv) dissolved in methanol (3.7 mL, 0.10 M) was added triethylamine (0.41 mL) dropwise over 1 min and Boc₂O (121 mg, 0.554 mmol, 1.50 equiv). The reaction was stirred at 23 °C for 13 h. After 13 h, the reaction mixture was concentrated to a crude oil. The crude oil was dissolved in EtOAc (5 mL) and quenched with saturated aq. NaHCO₃ (5 mL). The layers were separated and the aqueous layer was washed with EtOAc (3 x 5 mL). The organic layers were combined and washed with brine (1 x 5 mL). The combined organic layers were dried over sodium sulfate, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (100% DCM → 19:1 CH₂Cl₂:MeOH) to obtain the Boc-protected amine. A solution of the Boc-protected amine (199 mg, 0.313 mmol, 1.00 equiv) in THF (3.1 mL, 0.10 M) was cooled to 0 °C. To this solution was added LiAlH₄ in THF (2.0 M) (0.784 mL, 2.0 M, 1.57 mmol, 5.00 equiv) dropwise over 1 min. The reaction was then warmed to 23 °C and stirred for 4 h. After 4 h, the reaction mixture was cooled to 0 °C and diluted with Et₂O (2 mL). The reaction mixture was then quenched with water (0.150 mL), 3 M aqueous NaOH (0.150 mL), and water (0.300 mL) and was stirred for 5 min. The mixture was warmed to 23 °C, dried over MgSO₄, filtered over a pad of celite, rinsed

with EtOAc (10 mL), and concentrated under reduced pressure. The crude residue was purified via flash chromatography (19:1 CH₂Cl₂:MeOH → 9:1 CH₂Cl₂:MeOH w/ 5% Et₃N) to obtain secondary amine **3.46** (179 mg, 59% yield over 4 steps). Secondary amine **3.46**: R_f 0.14 (19:1 CH₂Cl₂:MeOH); ¹H NMR (500 MHz, CDCl₃): δ 7.39–7.31 (m, 5H), 5.85–5.69 (m, 2H), 5.44–5.32 (m, 1H), 5.25 (s, 1H), 5.02–4.88 (m, 1H), 4.60–4.54 (m, 1H), 4.52–4.42 (m, 2H), 4.13–4.09 (m, 1H), 3.92 (d, *J* = 13.0, 1H), 3.78–3.69 (m, 1H), 3.68–3.61 (m, 1H), 3.13–3.05 (m, 3H), 3.05–2.94 (m, 2H), 2.46–2.40 (m, 1H), 2.29–2.19 (m, 1H), 2.10–1.85 (m, 17H), 1.67–1.51 (m, 5H), 1.48–1.42 (m, 17H), 1.36–1.06 (m, 67H); ¹³C NMR (125 MHz, CDCl₃): δ 156.1, 139.3, 138.84, 138.79, 138.5, 136.64, 136.57, 131.7, 129.9, 128.5, 127.8, 127.7, 124.8, 122.7, 122.6, 114.3, 79.1, 72.3, 72.0, 68.1, 63.3, 60.5, 58.6, 56.1, 54.4, 44.9, 40.8, 38.5, 37.6, 36.1, 35.5, 33.9, 33.0, 32.7, 32.07, 32.05, 30.8, 30.2, 29.84, 29.81, 29.75, 29.7, 29.64, 29.58, 29.51, 29.49, 29.45, 29.37, 29.2, 29.14, 29.06, 28.9, 28.72, 28.66, 28.6, 27.4, 27.0, 25.9, 25.8, 25.6, 23.8, 22.84, 22.83, 21.2, 18.6, 18.1, 14.34, 14.27; IR (film): 2925, 2853, 1707, 1455, 1173 cm⁻¹; HRMS-APCI (*m/z*) [*M* + *H*]⁺ calcd for C₄₀H₆₅N₂O₃⁺, 621.49897; found 621.49822.

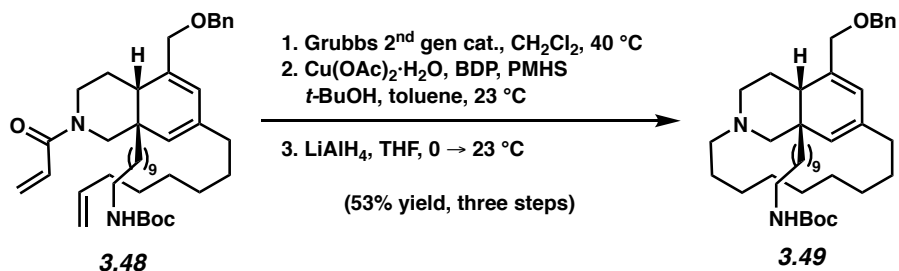
Note: 3.46 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ¹H and ¹³C NMR spectra. Integration in the alkyl region is inflated due to small amounts of material and overlap with grease and water.



Acrylamide 3.48. To a solution of secondary amine **3.46** (163 mg, 0.262 mmol, 1.00 equiv) in CH₂Cl₂ (2.6 mL, 0.10 M) was added *N,N*-diisopropylethylamine (0.137 mL, 0.785 mmol, 3.00 equiv) dropwise over 1 min. The solution was cooled to 0 °C. To the stirring solution, acryloyl chloride (**3.47**, 0.0640 mL, 0.785 mmol, 3.00 equiv) was added dropwise over 1 min at 0 °C. The reaction was warmed to 23 °C and allowed to stir for 1 h. The reaction mixture was quenched with water (3 mL) and diluted with EtOAc (5 mL). The organic layer was washed with saturated aq. NaHCO₃ (1 x 5 mL). The aqueous layers were extracted with EtOAc (4 x 5 mL) and CH₂Cl₂ (1 x 5 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (3:1 hexanes:EtOAc → 1:1 hexanes:EtOAc) to obtain acrylamide **3.48** (155 mg, 88% yield) as a colorless oil. Acrylamide **3.48**: *R*_f 0.41 (19:1 NH₃ saturated CH₂Cl₂:MeOH); ¹H NMR (500 MHz, CDCl₃): δ 7.42–7.31 (m, 5H), 6.63 (ddd, *J* = 90.5, 16.6, 10.7, 1H), 6.28 (dd, *J* = 36.6, 16.6, 1H), 5.87–5.60 (m, 3H), 5.36–5.07 (m, 1H), 4.98 (d, *J* = 17.0, 1H), 4.92 (d, *J* = 10.2, 1H), 4.61–4.44 (m, 3H), 4.11 (d, *J* = 12.6, 1H), 3.95 (d, *J* = 12.6, 1H), 3.91–3.84 (m, 1H), 3.16–3.03 (m, 2H), 2.98–2.84 (m, 1H), 2.55–2.39 (m, 1H), 2.11–1.94 (m, 5H), 1.68–1.61 (m, 2H), 1.44 (s, 13H), 1.40–0.83 (m, 37H); ¹³C NMR (125 MHz, CDCl₃): δ 165.7, 165.4, 156.1, 139.3, 139.2, 138.7, 138.4, 137.9, 136.6, 135.9, 128.7, 128.5, 128.3, 128.03, 127.96, 127.8, 127.3, 125.6, 123.4, 123.0, 114.3, 79.2, 72.5, 72.3, 72.1, 72.0, 53.6, 49.7, 45.9, 42.2, 41.1, 40.8, 40.3, 40.1, 37.1, 37.0, 35.3, 35.2, 33.9, 33.3, 32.1, 30.7, 30.6, 30.2, 29.8, 29.7, 29.6, 29.4, 29.2, 29.1, 29.0, 28.6, 28.4, 27.5, 27.0, 26.3, 24.9, 23.9, 22.8, 14.3; IR (film): 2927, 2854, 1701, 1642, 1453 cm⁻¹; HRMS-APCI (*m/z*) [*M* + *H*]⁺ calcd for C₄₃H₆₇N₂O₄⁺, 675.50954; found 675.50822.

Note: 3.48 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra. Integration in the alkyl region is inflated due to small amounts of material and overlap with grease and water.

3.5.2.5 Macrocyclization and Manipulations of Macrocycles 3.49 and 3.52



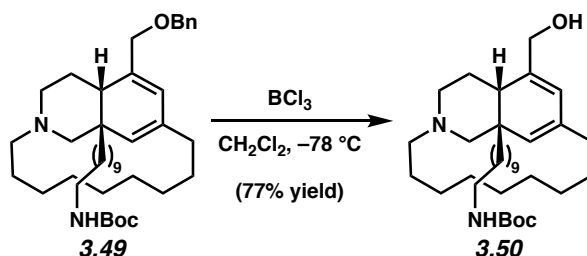
Tertiary amine 3.49.⁷⁸ A flask in the glovebox was charged with a stir bar and Grubbs' 2nd generation catalyst (67.4 mg, 0.0793 mmol, 30.0 mol%). The flask was then removed from the glovebox and acrylamide **3.48** (179 mg, 0.264 mmol, 1.00 equiv) dissolved in CH_2Cl_2 (265 mL, 0.001 M) was added. The flask was equipped with a condenser and heated to 40 °C for 20 h. After 20 h, the reaction was removed from heat and the solvent was removed under reduced pressure. The crude residue was purified via flash chromatography (2:1 hexanes:EtOAc $\rightarrow$ 1:1 hexanes:EtOAc) to obtain the macrocycle as a brown oil. The macrocycle was obtained as a mixture of *E* and *Z* isomers, which were carried forward as a mixture. To a vial was added copper(II)acetate monohydrate (19.7 mg, 0.0988 mmol, 1.00 equiv) and 1,2-bis(diphenylphosphaneyl)benzene (BDP) (22.0 mg, 0.0494 mmol, 50.0 mol%). These were dissolved in sparged $t\text{BuOH}$ (0.190 mL, 1.98 mmol, 20.0 equiv) and toluene (0.38 mL, 0.26 M) and the reaction was stirred at 23 °C for 25 minutes to give a blue solution. At this point PMHS (0.560 mL, 0.296 mmol, 95.0 equiv effective hydride) was added dropwise over 3 min and the solution gradually turned from blue to a yellow/green color over 15 min. A separate vial was

charged with the macrocycle (63.9 mg, 0.0988 mmol, 1.00 equiv), which was dissolved in toluene (0.38 mL). The macrocycle solution was then added to the modified Stryker's reagent solution dropwise over 3 min. The reaction was stirred at 23 °C for 19 h at which point it was diluted with EtOAc (2 mL). The organic layer was washed with 1 N NaOH (2 mL) followed by 1N HCl (2 mL), and saturated aq. NaHCO₃ (2 mL). The aqueous layers were combined and washed with EtOAc (2 x 2 mL). The organic layers were combined, washed with brine (2 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (9:1 hexanes:EtOAc → 1:1 hexanes:EtOAc) to obtain the amide. A solution of the amide (50.9 mg, 1.00 equiv, 0.0784 mmol) dissolved in THF (0.78 mL, 0.10 M) was cooled to 0 °C. To this solution was added LiAlH₄ in THF (14.9 mg, 0.196 mL, 2.0 M, 5.00 equiv, 0.392 mmol) dropwise over 1 min. The reaction was then warmed to 23 °C and stirred for 40 min. After 40 min, the reaction mixture was cooled to 0 °C and diluted with Et₂O (1 mL). The reaction mixture was then quenched with water (0.040 mL), 2 M aqueous NaOH (0.040 mL), and water (0.120 mL) and was stirred for 5 min. The mixture was warmed to 23 °C, dried over magnesium sulfate, filtered over a pad of celite, rinsed with EtOAc (10 mL), and concentrated under reduced pressure to obtain tertiary amine **3.49** (38.9 mg, 72% yield over three steps) as a colorless oil that was used without further purification. Tertiary amine **3.49**: R_f 0.58 (3:1 Hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃): δ 7.40–7.31 (m, 5H), 5.64 (s, 1H), 5.28 (s, 1H), 4.59–4.42 (m, 4H), 4.15–4.10 (m, 1H), 3.96–3.91 (m, 1H), 3.14–3.02 (m, 4H), 2.76–2.62 (m, 3H), 2.42–2.33 (m, 2H), 2.31–2.23 (m, 2H), 2.23–2.13 (m, 2H), 2.06–1.96 (m, 2H), 1.82–1.73 (m, 4H), 1.73–1.63 (m, 5H), 1.63–1.53 (m, 6H), 1.44 (m, 28H), 1.37–0.79 (m, 49H); ¹³C NMR (125 MHz, CDCl₃): δ 156.1, 139.6, 138.7, 132.7, 131.1, 128.7, 128.5, 127.8, 127.6, 127.1, 123.3, 79.1, 72.7, 71.7, 65.6, 65.5, 63.1, 63.0, 62.9, 55.9, 52.0, 40.9, 40.8, 39.2, 37.0, 32.7, 30.9, 30.3, 30.2, 29.8, 29.73, 29.70, 29.66, 29.4, 28.6, 28.4, 27.0,

26.8, 25.7, 25.62, 25.57, 25.1, 24.2, 23.9; IR (film): 2925, 2853, 1694, 1365, 1172 cm^{-1} ; HRMS-APCI (m/z) [$M + H$] $^{+}$ calcd for $\text{C}_{41}\text{H}_{67}\text{N}_2\text{O}_3^{+}$, 635.51462; found 635.51459.

Note: 3.49 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra. Integration in the alkyl region is inflated due to small amounts of material and overlap with grease and water.

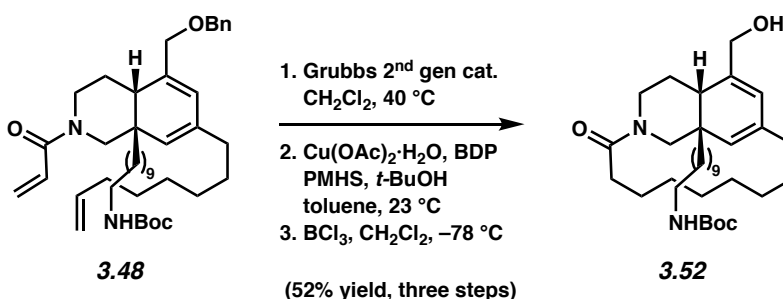
The equivalency of PMHS added was 3.0 equiv based on the mass of the polymer (1900 g/mol) and 95 equiv based on the effective mass per hydride (60 g/mol).



Alcohol 3.50. A solution of tertiary amine **3.49** (3.8 mg, 0.0060 mmol, 1.0 equiv) dissolved in CH_2Cl_2 (0.20 mL, 0.030 M) was cooled to $-78\text{ }^\circ\text{C}$. To the solution was added boron trichloride in CH_2Cl_2 (30 μL , 1.0 M, 0.030 mmol, 5.0 equiv) dropwise over 1 min. The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 25 min. The reaction mixture was quenched with saturated aq. NaHCO_3 (1 mL) and the reaction was allowed to warm to $23\text{ }^\circ\text{C}$. The reaction mixture was diluted with CH_2Cl_2 (1 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified via silica plug (2:1 hexanes:EtOAc) to obtain alcohol **3.50** (2.5 mg, 77% yield) as a colorless oil. Alcohol **3.50**: R_f 0.65 (3:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 5.70 (s, 1H), 5.32 (s, 1H), 4.48 (s, 1H), 4.21–4.15 (m, 1H), 4.11 (d, $J = 11.2$, 1H), 3.14–3.03 (m, 2H), 2.75–2.63 (m, 2H), 2.43–2.34 (m, 1H), 2.29–2.22 (m, 1H),

2.22–2.14 (m, 1H), 2.02–1.94 (m, 1H), 1.86 (dd, $J = 12.3, 4.9$, 1H), 1.81–1.76 (m, 1H), 1.72–1.64 (m, 3H), 1.64–1.52 (m, 7H), 1.49–1.39 (m, 18H), 1.38–0.91 (m, 31H); ^{13}C NMR (125 MHz, CDCl_3): δ 156.1, 138.2, 134.0, 130.9, 125.5, 79.1, 62.7, 55.8, 51.8, 48.9, 40.9, 40.8, 39.4, 36.7, 32.6, 30.8, 30.7, 30.2, 30.1, 29.8, 29.7, 29.4, 28.6, 28.4, 27.0, 26.8, 25.64, 25.59, 25.5, 25.1, 24.1, 23.7; IR (film): 2927, 2854, 1702, 1249, 1173 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{34}\text{H}_{61}\text{N}_2\text{O}_3^+$, 545.46767; found 545.46665.

Note: 3.50 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra. Integration in the alkyl region is inflated due to small amounts of material and overlap with grease and water.



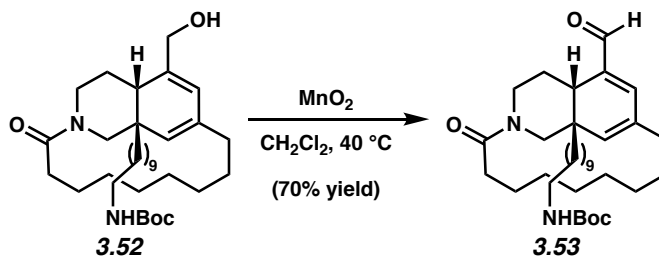
Alcohol 3.52.⁷⁸ To a flask in the glovebox was added a stir bar and Grubbs' 2nd generation catalyst (67.4 mg, 0.0793 mmol, 30.0 mol%). The flask was then removed from the glovebox and acrylamide **3.48** (179 mg, 0.264 mmol, 1.00 equiv) was added as a solution in CH_2Cl_2 (265 mL, 0.001 M). The flask was equipped with a condenser and heated to 40 $^\circ\text{C}$ for 20 h. After 20 h, the reaction was removed from heat and the solvent evaporated under reduced pressure. The crude residue was purified via flash chromatography (2:1 hexanes:EtOAc $\rightarrow$ 1:1 hexanes:EtOAc) to obtain the macrocycle as a brown oil. The macrocycle was obtained as a mixture of *E* and *Z* isomers, which were carried forward as a mixture. To a vial was added copper(II)acetate monohydrate (19.7 mg, 0.0988 mmol, 1.00 equiv) and 1,2-bis(diphenylphosphanyl)benzene

(BDP) (22.0 mg, 0.0494 mmol, 50.0 mol%). These were dissolved in sparged *t*BuOH (0.190 mL, 1.98 mmol, 20.0 equiv) and toluene (0.38 mL, 0.26 M) and the reaction was stirred for 25 minutes to give a blue solution. At this point PMHS (0.560 mL, 0.296 mmol, 95.0 equiv effective hydride) was added dropwise over 3 min and the solution gradually turned from blue to a yellow/green color (~15 min). A separate vial was charged with the macrocycle (63.9 mg, 0.0988 mmol, 1.00 equiv) dissolved in toluene (0.38 mL). The macrocycle solution was then added to the modified Stryker's reagent solution dropwise over 3 min. The reaction was stirred at 23 °C for 19 h at which point it was diluted with EtOAc (2 mL). The organic layer was washed with 1 N NaOH (2 mL) followed by 1N HCl (2 mL), and saturated aq. NaHCO₃ (2 mL). The aqueous layers were combined and washed with EtOAc (2 x 2 mL). The organic layers were combined, washed with brine (2 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (9:1 hexanes:EtOAc → 1:1 hexanes:EtOAc) to obtain the amide. A solution of the amide (15.9 mg, 0.0245 mmol, 1.00 equiv) dissolved in CH₂Cl₂ (0.40 mL, 0.050 M) was cooled to -78 °C. To the solution was added boron trichloride in CH₂Cl₂ (0.123 mL, 1.0 molar, 0.123 mmol, 5.00 equiv) dropwise over 1 min. The reaction mixture was stirred for 30 min. The reaction mixture was quenched with saturated aq. NaHCO₃ (1 mL) and the reaction was allowed to warm to 23 °C. The reaction mixture was diluted with CH₂Cl₂ (1 mL), the layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 1 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified via silica plug (1:1 hexanes:EtOAc) to obtain alcohol **3.52** (10.4 mg, 71% yield over two steps) as a colorless oil. Alcohol **3.52**: R_f 0.36 (1:1 hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃): δ 5.77 (s, 1H), 5.36 (s, 1H), 4.83 (d, *J* = 13.6, 1H), 4.50 (s, 1H), 4.19–4.10 (m, 2H), 3.83 (d, *J* = 14.2, 1H), 3.15–3.04 (m, 3H), 2.92 (t, *J* = 14.1, 1H),

2.72–2.63 (m, 1H), 2.30 (d, $J = 13.2$, 1H), 2.16–2.05 (m, 3H), 2.05–2.00 (m, 2H), 1.82–1.71 (m, 2H), 1.50–1.35 (m, 28H), 1.35–0.83 (m, 39H); ^{13}C NMR (125 MHz, CDCl_3): δ 172.3, 156.1, 137.1, 135.1, 130.7, 126.3, 79.1, 49.1, 48.3, 46.2, 40.9, 40.8, 40.1, 36.8, 34.0, 33.4, 30.6, 30.2, 29.64, 29.62, 29.60, 29.4, 28.6, 28.3, 27.0, 26.9, 26.7, 26.5, 26.4, 25.4, 25.1, 23.6; IR (film): 3339, 2927, 2855, 1706, 1628, 1173 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{34}\text{H}_{59}\text{N}_2\text{O}_4^+$, 559.44693; found 559.44658.

Note: 3.52 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra. Integration in the alkyl region is inflated due to small amounts of material and overlap with grease and water.

The equivalency of PMHS added was 3.0 equiv based on the mass of the polymer (1900 g/mol) and 95 equiv based on the effective mass per hydride (60 g/mol).

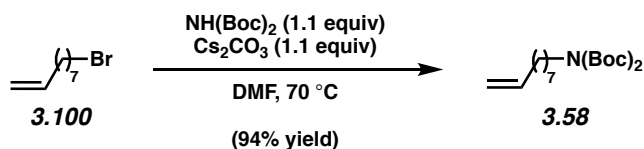


Aldehyde 3.53. To a solution of alcohol **3.52** (1.0 mg, 0.0018 mmol, 1.0 equiv) in CH_2Cl_2 (0.3 mL, 0.006 M) was added manganese dioxide (16 mg, 0.18 mmol, 100 equiv) in one portion. The vial was sealed with a Teflon-coated cap and the reaction mixture was heated to 40 $^\circ\text{C}$ and stirred for 19 h. After 19 h the reaction mixture was cooled to room temperature, filtered over celite, rinsed with CH_2Cl_2 (10 mL), and concentrated under reduced pressure to yield aldehyde **3.53** (0.7 mg, 70% yield) as a colorless oil. Aldehyde **3.53**: R_f 0.59 (1:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 9.53 (s, 1H), 6.58 (s, 1H), 5.90 (s, 1H), 4.90 (d, $J = 13.4$, 1H), 4.50 (s, 1H), 3.80

(d, $J = 14.1$, 1H), 3.17–3.05 (m, 2H), 2.99 (td, $J = 13.3$, 2.5, 1H), 2.72–2.62 (m, 2H), 2.40–2.31 (m, 2H), 2.22–2.16 (m, 2H), 2.16–2.09 (m, 1H), 1.73–1.65 (m, 2H), 1.50–1.41 (m, 20H), 1.40–0.82 (m, 55H); ^{13}C NMR (125 MHz, CDCl_3): δ 192.7, 172.4, 145.3, 140.6, 136.0, 79.1, 49.0, 46.0, 40.8, 40.4, 37.3, 35.7, 33.9, 33.2, 30.5, 30.2, 29.9, 29.6, 29.5, 29.4, 28.6, 28.4, 27.0, 26.7, 26.3, 26.2, 25.3, 24.8, 23.8, 22.8, 14.3 (2 of 3 carbonyl peaks and 3 of 4 olefin peaks observed); IR (film): 2926, 2855, 1712, 1672, 1172 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{34}\text{H}_{57}\text{N}_2\text{O}_4^+$, 557.43128; found 557.43115.

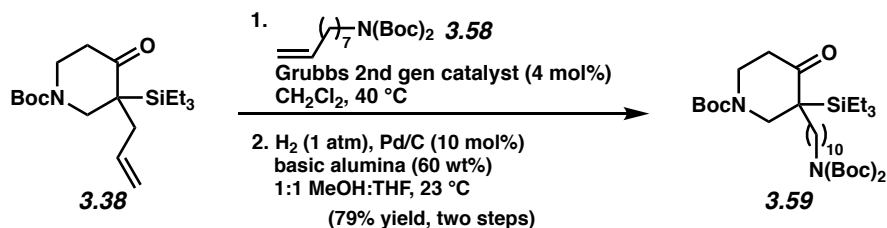
Note: 3.53 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra. Integration in the alkyl region is inflated due to small amounts of material and overlap with grease and water.

3.5.2.6 Synthesis of Silyl Triflate 3.60 and Diels–Alder Cycloaddition



Alkene 3.58. To a solution of bromide **3.100** (15.0 g, 73.2 mmol, 1.00 equiv) in DMF (360 mL, 0.20 M) was added di-tert-butyl iminodicarbonate (17.5 g, 80.6 mmol, 1.10 equiv) and cesium carbonate (26.2 g, 80.4 mmol, 1.10 equiv). The reaction mixture was heated to 70 °C for 2 h. After this time, the mixture was allowed to cool to 23 °C and then was transferred to a separatory funnel with water (500 mL) and Et_2O (200 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 200 mL). The combined organic layers were washed with water (3 x 200 mL) and brine (100 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (20:1 hexanes:EtOAc) to afford alkene

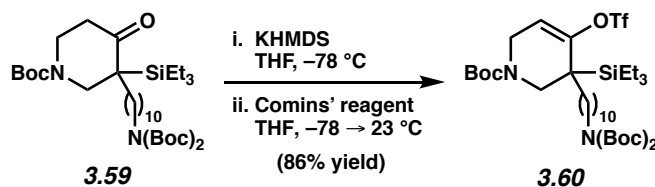
3.58 (23.4 g, 94% yield) as a colorless oil. Alkene **3.58**: R_f 0.47 (9:1 Hexanes:EtOAc); ^1H NMR (400 MHz, CDCl_3): δ 5.78 (ddt, $J = 17.1, 10.2, 6.7$, 1H), 5.01–4.87 (m, 2H), 3.56–3.48 (m, 2H), 2.05–1.97 (m, 2H), 1.58–1.51 (m, 2H), 1.48 (s, 18H), 1.39–1.31 (m, 2H), 1.31–1.23 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 152.8, 139.2, 114.3, 82.0, 46.6, 33.9, 29.3, 29.14, 29.12, 28.9, 28.2, 26.9; IR (film): cm^{-1} ; IR (film): 3078, 2930, 1697, 1367, 1128 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{36}\text{NO}_4^+$, 342.26389; found 342.25999.



Ketone 3.59. To a flask in the glovebox was added Grubbs' 2nd generation catalyst (50.1 mg, 0.0591 mmol, 4.00 mol%). The flask was then removed from the glovebox and silyl ketone **3.38** (522 mg, 1.48 mmol, 1.00 equiv) and alkene **3.58** (2.52 g, 7.38 mmol, 5.00 equiv) dissolved in CH_2Cl_2 (7.0 mL, 0.20 M) were added. The flask was fitted with a reflux condenser and heated to 40 °C for 21 h. After this time, the reaction was removed from heat and the solvent was removed under reduced pressure. The crude residue was purified via flash chromatography (19:1 hexanes:EtOAc $\rightarrow$ 9:1 hexanes:EtOAc) to afford the cross-metathesis product. To a solution of the cross-metathesis product (1.28 g, 1.84 mmol, 1.00 equiv) in THF (28 mL, 0.033 M) and methanol (28 mL) was added basic alumina (1.30 g) and palladium on carbon (203 mg, 10.0 wt%, 0.191 mmol, 10.0 mol%). The flask was then sparged with H_2 from a balloon and then left to stir under an atmosphere of H_2 (1 atm) for 7 h. The reaction was then filtered over celite (3 cm, monster pipette) with CH_2Cl_2 as the eluent (50 mL) and the solvent was removed under reduced pressure. The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc) to afford ketone

3.59 (1.26 g, 79% yield over two steps) as a colorless oil. Ketone **3.59**: R_f 0.56 (4:1 hexanes:EtOAc); ^1H NMR (400 MHz, CDCl_3): δ 4.02–3.60 (m, 3H), 3.56–3.49 (m, 2H), 3.41–3.22 (m, 1H), 2.57 (br s, 1H), 2.45–2.29 (m, 1H), 2.07–1.95 (m, 1H), 1.70–1.61 (m, 1H), 1.53–1.43 (m, 29H), 1.31–1.14 (m, 14H), 0.97 (t, $J = 7.9$, 9H), 0.79–0.60 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 152.9, 82.1, 46.7, 40.0, 30.7, 29.7, 29.6, 29.4, 29.2, 28.6, 28.2, 27.0, 25.7, 8.0, 2.5 (15 out of 23 signals observed); IR (film): 2928, 2857, 1746, 1694, 1366, 1127 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{36}\text{H}_{69}\text{N}_2\text{O}_7\text{Si}^+$, 669.48686; found 669.48074.

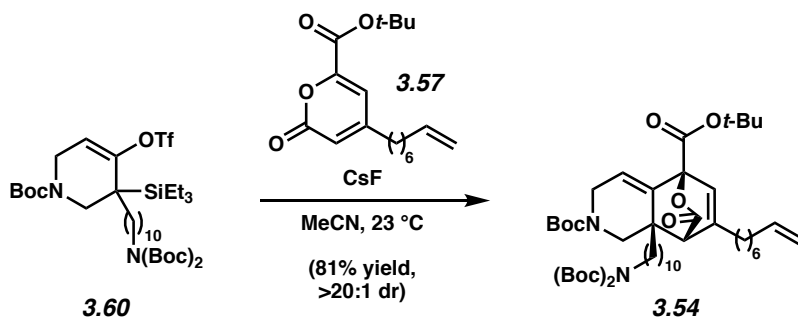
Note: 3.59 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.



Silyl Triflate 3.60. To a flask in the glovebox was added potassium hexamethyldisilazide (697 mg, 3.32 mmol, 1.21 equiv). The flask was then removed from the glovebox, THF (10 mL) was added, and it was cooled to $-78 \text{ }^\circ\text{C}$. To another flask was added silyl ketone **3.59** (1.93 g, 2.75 mmol, 1.00 equiv) and THF (9 mL). The ketone solution was then added dropwise over 10 min to the KHMDS solution at $-78 \text{ }^\circ\text{C}$. After stirring for 1 h at $-78 \text{ }^\circ\text{C}$, a third solution of Comins' Reagent (1.29 g, 3.29 mmol, 1.20 equiv) in THF (9 mL) was added dropwise over 5 min at $-78 \text{ }^\circ\text{C}$. The reaction was then warmed to $23 \text{ }^\circ\text{C}$ and stirred at this temperature for 2 h. After this time, the reaction was quenched with saturated aq. NaHCO_3 (50 mL) and diluted with water (50 mL) and Et_2O (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under

reduced pressure to provide the crude residue. The crude residue was purified via flash chromatography (97:3 → 93:7 hexanes:EtOAc) to afford silyl triflate **3.60** (1.92 g, 86% yield) as a colorless oil. Silyl triflate **3.60**: R_f 0.21 (9:1 Hexanes:EtOAc); ^1H NMR (400 MHz, CDCl_3): δ 5.66 (br s, 1H), 4.17 (dd, $J = 17.9, 4.1$, 1H), 3.92–3.63 (m, 2H), 3.56–3.49 (m, 1H), 3.48–3.31 (m, 1H), 1.65–1.52 (m, 4H), 1.51–1.40 (m, 27H), 1.33–1.15 (m, 15H), 0.99 (t, $J = 7.9$, 9H), 0.76–0.65 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 154.3, 152.9, 110.3, 82.1, 80.5, 46.7, 30.6, 30.2, 29.7, 29.6, 29.5, 29.4, 29.2, 28.6, 28.5, 28.2, 27.0, 24.3, 8.1, 2.8 (20 out of 24 signals observed); IR (film): 2931, 2856, 1699, 1366, 1127 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{37}\text{H}_{68}\text{F}_3\text{N}_2\text{O}_9\text{SSi}^+$, 801.43614; found 801.42924.

*Note: **3.60** was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra.*



Cycloadduct 3.54. To a vial in the glovebox was added CsF (584 mg, 3.84 mmol, 7.38 equiv). This vial was removed from the glovebox and then a separate solution of silyl triflate **3.60** (426 mg, 521 μmol , 1.00 equiv) and pyrone **3.57** (804 mg, 2.62 mmol, 5.00 equiv) in MeCN (5.2 mL) was added to the vial containing cesium fluoride. The reaction mixture was allowed to stir vigorously at 23 °C for 20 h. After this time, the reaction mixture was filtered through a short plug of silica gel (3 cm silica) eluting with 1:1 hexanes:EtOAc (~30 mL) and the concentrated under reduced pressure. The crude residue was purified via flash chromatography (8:1:1

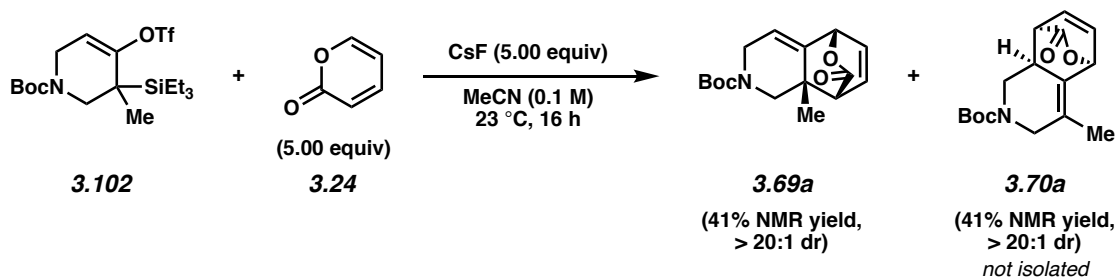
hexanes:CH₂Cl₂:Et₂O → 3:1:1 hexanes:CH₂Cl₂:Et₂O) to afford the cycloadduct **3.54** (369 mg, 81% yield) as yellow oil. Spectral data match those previously reported.³⁰

3.5.2.7 Study of Pyrone Cycloadditions

General Procedure for Cycloadducts 3.69a–3.70b, 3.72–3.73, 3.75, and 3.77: To a solution of silyl triflate **3.102** (0.10 mmol, 1.00 equiv) and pyrone (5.00 equiv) in MeCN (1.00 mL, 0.10 M) was added CsF (5.00 equiv). The reaction mixture was allowed to stir at 1000 RPM at 23 °C. After the allotted time, the reaction mixture was filtered through a short plug of silica gel (3 cm silica) eluting with EtOAc (~10 mL) and then concentrated under reduced pressure. Yields were determined as an average of two experiments via ¹H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.

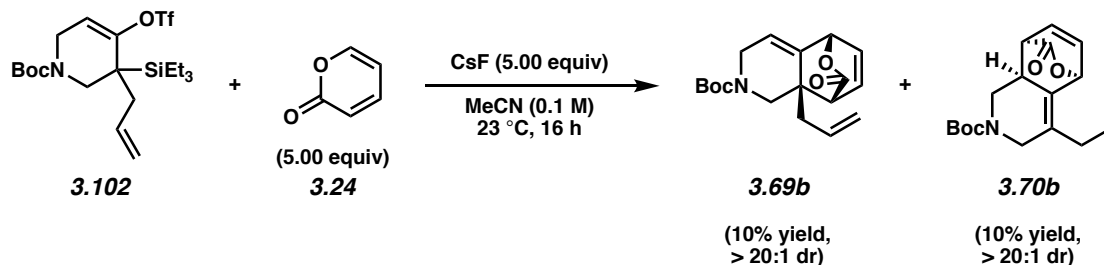
Any deviations from the General Procedure are detailed below. For all compounds in which the diastereomeric ratio was >20:1, the minor diastereomer was not observed in the ¹H NMR of the crude reaction mixture.

Note: Cycloadducts 3.69a–3.70b, 3.69b–3.70b, 3.72–3.73, 3.75, and 3.77 are isolated as a mixture of N-epimers. These data represent empirically observed chemical shifts from the ¹H and ¹³C NMR spectra. Protons in the ¹H NMR spectra are integrated together for each N-epimer. J-coupling values are provided for a single epimer. With regard to the ¹³C NMR spectra, some peaks overlap, leading to fewer peaks than expected for the two N-epimers.



Cycloadduct 3.69a: An analytical sample of **3.69a** was obtained via preparative TLC (9:1 benzene:acetone). Cycloadduct **3.69a**: R_f 0.42 (9:1 benzene:acetone); ^1H NMR (500 MHz, CDCl_3): δ 6.49–6.41 (m, 1H), 6.39–6.30 (m, 1H), 5.68 (dd, $J = 28.9, 3.3$ 1H), 5.43 (d, $J = 4.9$, 1H), 4.25 (dd, $J = 54.6, 19.6$, 1H), 3.93 (dd, $J = 87.1, 11.4$, 1H), 3.69–3.55 (m, 1H), 3.37 (t, $J = 6.5$, 1H), 2.21 (dd, $J = 39.7, 11.6$, 1H), 1.48 (s, 9H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 171.7, 155.6, 155.3, 137.7, 137.3, 132.8, 132.5, 128.4, 128.1, 117.7, 117.2, 80.44, 80.39, 51.5, 51.3, 50.1, 43.2, 42.7, 35.6, 35.5, 28.6, 22.3, 22.1; IR (film): 2979, 2928, 1761, 1696, 1399 cm^{-1} ; HRMS–APCI (m/z) [$M + H$] $^+$ calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_4^+$, 292.1543; found 292.1526.

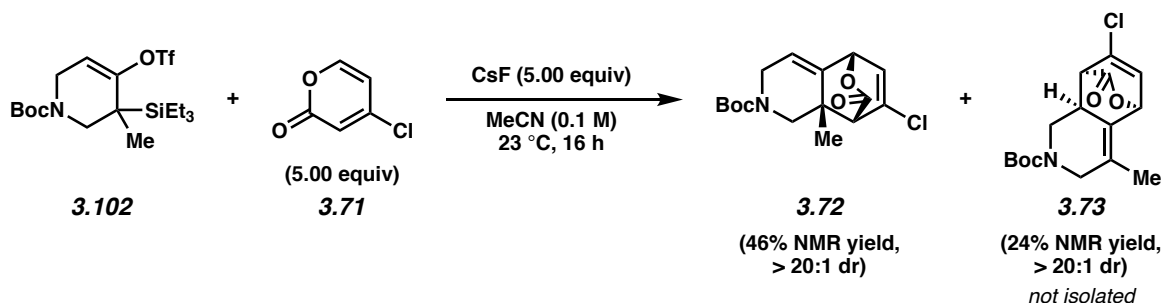
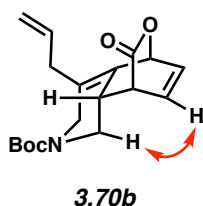
Note: The endo stereochemistry of 3.69a was assigned in analogy to cycloadduct 3.77. Regioisomeric cycloadduct 3.70a was observed in the ^1H NMR spectrum of the crude material, but an analytical sample could not be obtained due to decomposition; the structure of 3.70a was assigned based on integration of peaks analogous to those observed for isolable cycloadduct 3.70b.



Cycloadducts 3.69b and 3.70b: To a solution of silyl triflate **3.102** (46.8 mg, 0.0964 mmol, 1.00 equiv) and pyrone **3.24** (46.3 mg, 0.482 mmol, 5.00 equiv) in THF (0.960 mL, 0.10 M) was added CsF (73.2 mg, 0.482 mmol, 5.00 equiv). The reaction mixture was allowed to stir at 1000 RPM at 23 °C for 16 h. After this time, the reaction mixture was filtered through a short plug of silica gel (3 cm silica) eluting with EtOAc (10 mL) and then concentrated under reduced pressure. The crude material was purified by column chromatography (5:1:1 hexanes:CH₂Cl₂:Et₂O → 1:1 CH₂Cl₂:Et₂O, then 5:1 → 1:1 hexanes:EtOAc) to provide **3.70b** (3.00 mg, 10% yield) as a yellow oil. Further purification of the reaction mixture by preparative TLC (4:1 benzene:EtOAc) was performed to afford **3.69b** (3.10 mg, 10% yield) as a yellow oil. Cycloadduct **3.69b**: *R_f* 0.30 (2:1 hexanes:EtOAc); ¹H NMR (600 MHz, CDCl₃): δ 6.53–6.46 (m, 1H), 6.33 (q, *J* = 6.95, 1H), 5.93–5.84 (m, 1H), 5.74 (dd, *J* = 45.2, 3.5, 1H), 5.47 (d, *J* = 4.7, 1H), 5.28–5.17 (m, 2H), 4.31–4.09 (m, 2H), 3.65 (dd, *J* = 19.6, 4.3, 1H), 3.59–3.52 (m, 1H), 2.39–2.27 (m, 1H), 2.10 (dd, *J* = 52.1, 11.7, 1H), 1.98 (dd, *J* = 14.3, 7.4, 1H), 1.50 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 171.5, 155.14, 155.08, 137.9, 137.4, 133.3, 133.0, 131.7, 131.5, 131.0, 128.0, 127.7, 121.1, 120.9, 120.7, 118.0, 117.6, 116.8, 80.5, 80.4, 66.0, 48.1, 47.6, 47.1, 46.1, 43.3, 42.8, 39.3, 39.2, 38.6, 38.4, 30.4, 29.8, 28.6, 28.4, 28.3; IR (film): 3240, 2980, 1760, 1701, 1396 cm⁻¹; Cycloadduct **3.70b**: *R_f* 0.37 (2:1 hexanes:EtOAc); ¹H NMR (600 MHz, CDCl₃): δ 6.52–6.43 (m, 1H), 6.30–6.22 (m, 1H), 5.79–5.67 (m, 1H), 5.12–5.02 (m, 2H), 4.33–4.03 (m, 2H, overlap with residual solvent), 3.63–3.59 (m,

1H), 3.54 (dd, $J = 18.5, 1.9$, 1H), 3.04–2.93 (m, 1H), 2.86–2.75 (m, 1H), 2.51 (app. d, $J = 9.7$, 1H), 2.05 (dt, $J = 54.4, 11.5$, 1H, overlap with residual solvent), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $(\text{CD}_3)_2\text{CO}$): δ 172.6, 155.1, 154.8, 136.6, 133.4, 133.2, 130.1, 129.9, 128.4, 128.1, 116.7, 116.6, 80.0, 74.9, 46.8, 46.4, 46.3, 45.5, 45.3, 35.1, 35.0, 34.0, 33.8, 28.5; IR (film): 2981, 2932, 1760, 1694, 1403 cm^{-1} .

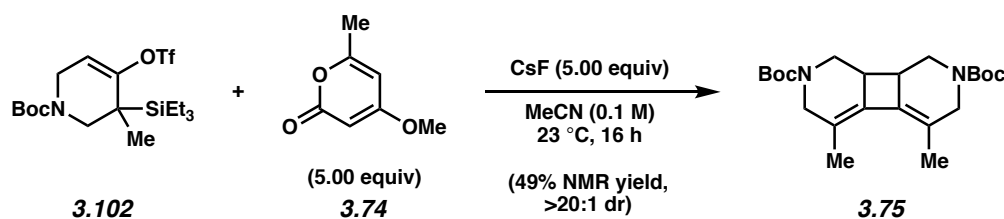
Whereas methyl-substituted distal cycloadducts **3.70a** and **3.73** were not isolable in our hands, allyl-substituted distal cycloadduct **3.70b** could be isolated. The structural assignment of **3.70b** was used to identify distal cycloadducts **3.70a** and **3.73** by analogy. The structure of **3.70b** was verified by 2D-NOESY, as the following interaction was observed.



Cycloadduct 3.72: An analytical sample of **3.72** was obtained via preparative TLC (1:1:1 hexanes: CH_2Cl_2 : Et_2O). Cycloadduct **3.72**: R_f 0.46 (1:1:1 hexanes: CH_2Cl_2 : Et_2O); ^1H NMR (500 MHz, CDCl_3): δ 6.39 (ddd, $J = 13.9, 5.6, 2.3$, 1H), 5.76–5.64 (m, 1H), 5.42, (d, $J = 5.7$, 1H), 4.38–4.17 (m, 1H), 4.03 (dd, $J = 89.2, 11.6$, 1H), 3.65 (td, $J = 20.0, 4.5$, 1H), 3.49–3.41 (m, 1H), 2.41 (dd, $J = 31.3, 11.7$, 1H), 1.49 (s, 9H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 169.4, 155.6, 155.3, 137.3, 136.7, 133.0, 132.6, 127.6, 127.2, 118.3, 117.9, 80.7, 80.6, 59.2, 59.1, 50.2, 49.1,

43.1, 42.6, 36.0, 35.9, 28.6, 22.0, 21.9; IR (film): 2975, 2936, 2876, 1768, 1697 cm^{-1} ; HRMS–APCI (m/z) [$M + H$] $^+$ calcd for $\text{C}_{16}\text{H}_{21}\text{ClNO}_4^+$, 326.1154; found 326.1137.

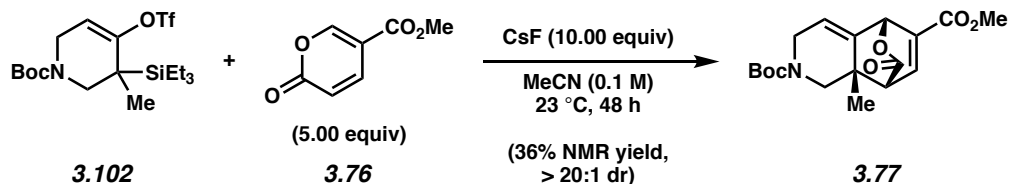
Note: The endo stereochemistry of 3.72 was assigned in analogy to cycloadduct 3.77. Regioisomeric cycloadduct 3.73 was observed in the ^1H NMR spectrum of the crude material, but an analytical sample could not be obtained due to decomposition; the structure of 3.73 was assigned based on integration of peaks analogous to those observed for isolable cycloadduct 3.70b.



Dimer 3.75: An analytical sample of **3.75** was obtained via preparative TLC (2:1 hexanes:EtOAc).

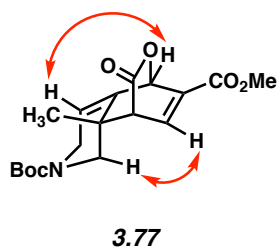
Dimer 3.75: R_f 0.41 (5:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 4.49–4.11 (m, 4H), 3.38 (t, $J = 18.5$, 2H), 2.62–2.34 (m, 4H), 1.76 (s, 6H), 1.46 (s, 18H); ^{13}C NMR (125 MHz, CDCl_3): δ 155.1, 134.4, 133.8, 118.2, 117.6, 79.9, 47.7, 47.1, 45.6, 44.4, 42.9, 28.6, 16.9; IR (film): 2975, 2926, 2857, 1695, 1404 cm^{-1} ; HRMS–APCI (m/z) [$M + H$] $^+$ calcd for $\text{C}_{22}\text{H}_{35}\text{N}_2\text{O}_4^+$, 391.2591; found 391.2567.

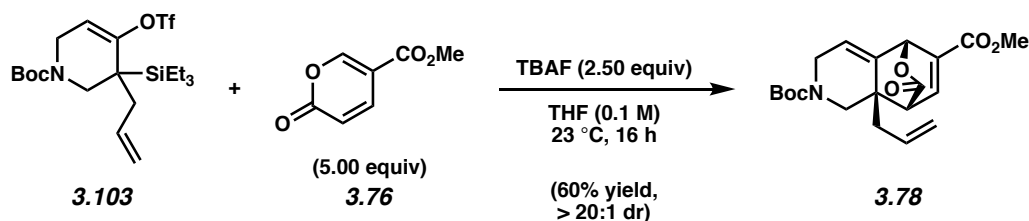
Note: 3.75 was isolated as a single isomer, but as an unassigned diastereomer due to the dimeric nature of the product.



Cycloadduct 3.77: 10.0 equivalents of CsF were added to this reaction mixture and the reaction was allowed to stir for 48 h. An analytical sample of **3.77** was obtained via preparative TLC (1:1:1 hexanes:CH₂Cl₂:Et₂O). Cycloadduct **3.77**: *R_f* 0.36 (1:1:1 hexanes:CH₂Cl₂:Et₂O); ¹H NMR (500 MHz, CDCl₃): δ 7.19–7.14 (m, 1H), 5.91 (s, 1H), 5.81 (d, *J* = 29.4, 1H), 4.26 (dd, *J* = 53.7, 19.7, 1H), 3.98 (dd, *J* = 90.5, 11.5, 1H), 3.81 (s, 3H), 3.67–3.57 (m, 1H), 3.53 (t, *J* = 5.6, 1H), 2.15 (dd, *J* = 46.1, 11.4, 1H), 1.47 (s, 9H), 1.19 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 170.1, 162.1, 162.0, 155.5, 155.1, 137.1, 136.9, 136.7, 136.6, 136.5, 136.0, 119.1, 118.7, 80.64, 80.60, 52.61, 52.58, 51.9, 51.4, 50.1, 43.2, 42.7, 36.3, 36.2, 28.6, 22.3, 22.2; IR (film): 2974, 2860, 1769, 1723, 1697 cm⁻¹; HRMS–APCI (*m/z*) [*M* + *H*]⁺ calcd for C₁₈H₂₄NO₆⁺, 350.1598; found 350.1577.

The structure of **3.77** was verified by 2D-NOESY, as the following interactions were observed.

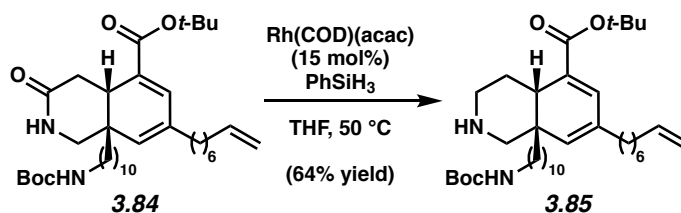




Cycloadduct 3.78: To a solution of silyl triflate **3.103** (486 mg, 1.00 mmol, 1.00 equiv) and pyrone **3.76** (771 mg, 5.00 mmol, 5.00 equiv) in THF (10.0 mL, 0.10 M) was added TBAF (2.50 mL, 2.50 mmol, 2.50 equiv). The reaction mixture was allowed to stir at 1000 RPM at 23 °C for 16 h. After this time, the reaction mixture was filtered through a short plug of silica gel (3 cm silica) eluting with EtOAc (75 mL) and then concentrated under reduced pressure. The crude material was purified by column chromatography (9:1 → 1:1 hexanes:EtOAc) to afford **3.78** (227 mg, 60% yield) as an amorphous white foam. Cycloadduct **3.78**: R_f 0.54 (1:1 hexanes:EtOAc); ^1H NMR (500 MHz, DMSO- d_6): δ 7.28 (td, J = 6.4, 2.0, 1H), 6.00 (s, 1H), 5.95 (dd, J = 19.3, 3.3, 1H), 5.88–5.71 (m, 1H), 5.22 (dd, J = 27.2, 10.2, 1H), 5.08 (t, J = 18.0, 1H), 4.19–3.99 (m, 2H), 3.79 (dd, J = 9.9, 6.4, 1H), 3.74 (s, 3H), 3.57 (qd, J = 19.4, 4.8, 1H), 2.31–2.16 (m, 1H), 1.93 (dd, J = 63.0, 12.1, 1H), 1.82–1.71 (m, 1H), 1.41 (d, J = 4.6, 9H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 170.3, 162.0, 154.7, 154.3, 138.23, 138.16, 136.7, 136.5, 135.9, 135.8, 131.9, 131.8, 120.8, 120.7, 120.2, 120.1, 79.8, 76.5, 76.4, 55.4, 52.8, 48.30, 48.26, 47.1, 46.1, 43.2, 42.9, 38.6, 38.5, 28.5; IR (film): 3082, 2872, 1767, 170, 1698 cm^{-1} ; HRMS–APCI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_6^+$, 376.1755; found 376.1753.

*Note: The endo stereochemistry of **3.78** was assigned in analogy to cycloadduct **3.77**.*

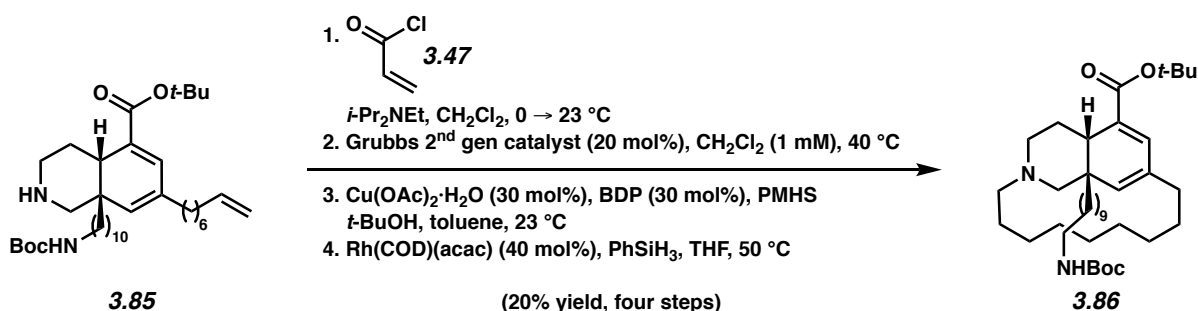
3.5.2.8 Elaboration of 3.84 to Macrocycle 3.86



Secondary amine 3.85.⁶⁶ To a vial was added diene **3.84** (65.0 mg, 0.106 mmol, 1.00 equiv). The vial was then brought into the glovebox and charged with $[\text{Rh(COD)(acac)}]$ (4.92 mg, 0.0159 mmol, 15.0 mol%). The vial was then removed from the glovebox, the mixture was dissolved in THF (1.27 mL, 0.0800 M), and phenylsilane (0.0522 mL, 0.423 mmol, 4.00 equiv) was added. The reaction mixture was then allowed to stir at 50 °C for 12.5 h. After 12.5 h, the reaction mixture was cooled to 23 °C and quenched slowly with saturated aq. ammonium fluoride (1.0 mL). The reaction mixture stirred for 2.5 h at 23 °C and then was diluted with Et₂O (5 mL), water (5 mL), and 1 M aq NaOH (5 mL). The layers were separated and the aqueous layer was washed with Et₂O (3 x 5 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography (100% EtOAc → 100% CH₂Cl₂ saturated with NH₃) to afford secondary amine **3.85** (40.8 mg, 64% yield) as a pale yellow oil. Secondary amine **3.85**: *R_f* 0.26 (9:1 CH₂Cl₂:MeOH); ¹H NMR (500 MHz, CDCl₃): δ 6.76 (s, 1H), 5.86–5.74 (m, 1H), 5.58 (s, 1H), 5.04–4.88 (m, 2H), 4.51 (br s, 1H), 3.15–3.04 (m, 2H), 2.99 (d, *J* = 12.3, 1H), 2.92–2.82 (m, 1H), 2.46–2.34 (m, 3H), 2.17–2.07 (m, 2H), 2.06–1.99 (m, 3H), 1.65–1.55 (m, 2H), 1.50 (s, 10H), 1.43 (s, 14H), 1.39–1.04 (m, 48H), 0.95–0.78 (m, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 166.8, 156.1, 139.4, 139.2, 136.1, 135.5, 134.2, 133.41, 133.38, 133.03, 133.00, 127.8, 114.3, 114.2, 80.3, 79.1, 55.1, 45.2, 40.8, 39.0, 37.8, 35.2, 34.0, 33.9, 33.6, 33.3, 32.1, 32.0, 30.7, 30.3, 30.2, 29.83, 29.79, 29.75, 29.7, 29.60, 29.56, 29.5, 29.43, 29.41, 29.29,

29.27, 29.2, 29.11, 29.07, 29.0, 28.82, 28.78, 28.7, 28.6, 28.3, 28.21, 28.16, 26.94, 26.86, 26.6, 26.0, 24.0, 23.9, 22.8, 14.3, 11.0; IR (film): 2925, 2854, 1699, 1161, 1135 cm^{-1} ; HRMS-APCI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{37}\text{H}_{65}\text{N}_2\text{O}_4^+$, 691.49388; found 601.49212.

Note: 3.85 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^1H and ^{13}C NMR spectra. Integration in the alkyl region is inflated due to small amounts of material and overlap with grease and water.



Tertiary amine 3.86.⁷⁸ A solution of secondary amine **3.85** (5.0 mg, 0.0083 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 mL) was cooled to 0°C . To the solution were added *N,N*-diisopropylethylamine (3.2 mg, 0.0043 mL, 0.025 mmol, 3.0 equiv) and acryloyl chloride (**3.47**, 2.3 mg, 0.0020 mL, 0.025 mmol, 3.0 equiv). The reaction was allowed to warm to 23°C and stirred for 2 h, then quenched with water (2 mL) and saturated aq. NaHCO_3 (2 mL) and diluted with Et_2O (5 mL). The aqueous layer was separated from the organics and washed with Et_2O (2 x 5 mL). The combined organic fractions were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified via preparative TLC (7:3 hexanes: EtOAc) to afford the acrylamide. To a vial in the glovebox was added Grubbs' 2nd generation catalyst (0.8 mg, 20 mol%, 0.0009 mmol). The vial was then removed from the glovebox and then a solution of the acrylamide (3.0 mg, 1.0 equiv, 0.0046 mmol) in sparged CH_2Cl_2 (4.6 mL) was added to the vial containing Grubbs' catalyst. The reaction vial was sealed and allowed to stir at 40°C for 14 h. After this time, the reaction mixture

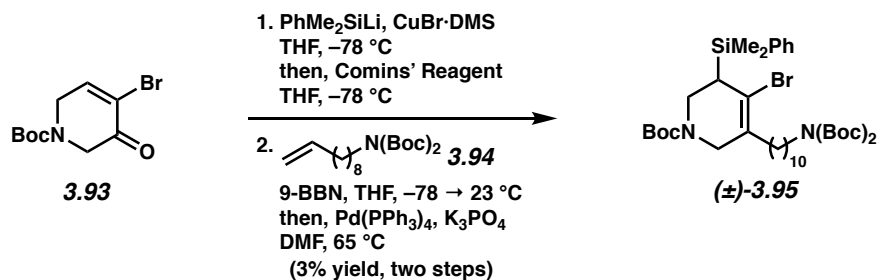
was concentrated under reduced pressure. The crude residue was purified via preparative TLC (7:3 hexanes:EtOAc) to afford the macrocycle as a yellow oil. The macrocycle was obtained as a mixture of *E* and *Z* isomers, which were carried forward as a mixture. To a vial was added copper(II) acetate monohydrate (0.78 mg, 0.0039 mmol, 30 mol%) and 1,2-bis(diphenylphosphino)benzene (BDP) (1.8 mg, 0.0039 mmol, 30 mol%). These were dissolved in toluene (1.5 mL, sparged with nitrogen) and *t*-BuOH (0.025 mL, 0.26 mmol, 20 equiv) the reaction mixture was allowed to stir for 30 min to give a blue solution. At this point PMHS (75 mg, 0.074 mL, 0.039 mmol, 95.0 equiv effective hydride) was added dropwise over 1 min and the solution gradually turned from blue to a yellow/green color (30 min). A separate vial was charged with the macrocycle (8.2 mg, 0.013 mmol, 1.00 equiv), which was dissolved in toluene (1.5 mL). The macrocycle solution was then added to the modified Stryker's reagent dropwise over 3 min. The reaction mixture was allowed to stir at 23 °C for 19.5 h. After this time, the reaction mixture was passed through a plug of silica gel (1 x 3 cm) eluting with EtOAc (50 mL). The crude residue was purified via preparative TLC (65:35 hexanes:EtOAc) to afford the amide. The procedure for the Rh-catalyzed reduction of the amide is derived from the work of Beller and coworkers.⁶⁶ To a vial was added the amide (3.0 mg, 1.0 equiv, 0.0048 mmol). The vial was then brought into the glovebox and Rh(COD)(acac) (0.6 mg, 40 mol%, 0.002 mmol) was added. The vial was then removed from the glovebox and the mixture was dissolved in THF (0.3 mL) and to this solution was added phenylsilane (2.6 mg, 0.0030 mL, 5.0 equiv, 0.024 mmol). The vial was sealed with a Teflon-lined cap and the reaction mixture was then heated to 50 °C and stirred for 14.5 h. After this time, the reaction mixture was allowed to cool to 23 °C and was then quenched slowly with saturated aq. ammonium fluoride (0.5 mL). The reaction mixture was allowed to stir for 30 min at 23 °C and then diluted with Et₂O (5 mL), water (5 mL), and 1 M aq NaOH (5 mL). The layers

were separated and the aqueous layer was washed with Et₂O (2 x 5 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified via preparative TLC (9:1 hexanes:EtOAc) to afford tertiary amine **3.86** (1.2 mg, 34% yield over four steps) as a colorless oil. Tertiary amine **3.86**: *R_f* 0.80 (4:1 Hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃): δ 6.69 (s, 1H), 5.59 (s, 1H), 4.48 (br s, 1H), 3.16–3.01 (m, 2H), 2.73 (dd, *J* = 10.9, 1.2, 1H), 2.69–2.61 (m, 1H), 2.41–2.05 (m, 6H), 1.80 (d, *J* = 11.0, 1H), 1.75–1.66 (m, 3H), 1.50 (s, 9H), 1.44 (s, 9H), 1.34–1.02 (m, 31H); ¹³C NMR (125 MHz, CDCl₃): δ 167.0, 156.1, 139.4, 134.5, 134.0, 131.6, 80.0, 79.1, 62.9, 55.8, 51.7, 40.8, 39.7, 38.6, 36.8, 32.6, 30.8, 30.5, 30.2, 29.9, 29.71, 29.69, 29.5, 29.4, 28.6, 28.4, 28.3, 27.03, 26.96, 25.6, 25.54, 29.50, 25.1, 24.03, 24.00; IR (film): 2926, 2853, 1697, 1249, 1164 cm⁻¹; HRMS-APCI (*m/z*) [*M* + *H*]⁺ calcd for C₃₈H₆₇N₂O₄⁺, 615.50954; found 615.50877.

Note: 3.86 was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ¹H and ¹³C NMR spectra.

The equivalency of PMHS added was 3.0 equiv based on the mass of the polymer (1900 g/mol) and 95 equiv based on the effective mass per hydride (60 g/mol).

3.5.2.9 Synthesis of Silyl Bromide (±)-3.95

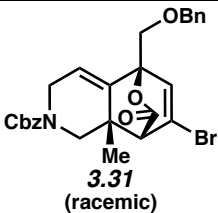
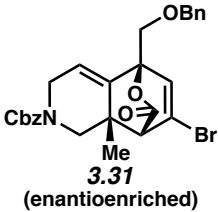


Silyl bromide (±)-3.95. A solution of copper bromide-dimethylsulfide complex (70.5 mg, 0.343 mmol, 1.25 equiv) in THF (1.90 mL) was cooled to 0 °C. Then, (dimethyl(phenyl)silyl)lithium⁸⁰ (2.21 mL, 0.310 M, 0.686 mmol, 2.50 equiv) was added dropwise over 1 min and the mixture was stirred at 0 °C for 30 min. The reaction mixture was cooled to –78 °C and a cooled (–78 °C) solution of enone **3.93** (75.8 mg, 0.275 mmol, 1.00 equiv) in THF (0.9 mL) was added dropwise over 2 minutes. The reaction was allowed to stir at –78 °C for 1 h. Then, a solution of Comins' reagent (431 mg, 1.10 mmol, 4.00 equiv) in THF (0.4 mL) was added dropwise over 3 min and the reaction was allowed to stir at –78 °C for 4 h. After this time, the reaction was diluted with Et₂O (3 mL), quenched with water (3 mL), and allowed to warm to 23 °C. The reaction mixture was then transferred to a separatory funnel containing Et₂O (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (three iterations: 9:1 hexanes:EtOAc → 3:1 hexanes:EtOAc, 9:1 hexanes:benzene → 1:3 hexanes:benzene, 1:1 hexanes:benzene → 100% benzene) to afford the allyl silane bromide as a light yellow oil. A solution of the olefin **3.94**³⁰ (31.0 mg, 0.0871 mmol, 2.00 equiv) in THF (0.2 mL) was cooled to –78 °C. Then, a solution of 9-BBN (0.200 mL, 0.500 M, 0.100 mmol, 2.30 equiv) was added at –78 °C dropwise over 1 min. The solution was allowed to warm to 23 °C and stir for 5 h. Meanwhile, a vial was brought into a glovebox and charged with Pd(PPh₃)₄ (10.1 mg, 0.00871 mmol, 0.200 equiv). The vial was brought out of the glovebox. To the flask was added DMF (0.2 mL) and the solution was sparged with nitrogen for 20 min. K₃PO₄ (13.9 mg, 0.0653 mmol, 1.50 equiv) and the allyl silane (23.7 mg, 0.0453 mmol, 1.00 equiv) were quickly added to the flask. The solution was allowed to stir for 2 min at 23 °C, and then the solution of alkyl borane

in THF was added in a single portion. The solution was placed in a pre-heated 65 °C aluminum block and stirred for 19.5 h. After this time, the solution was cooled to 23 °C and quenched with brine (1 mL) and EtOAc (1 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with water (3 x 1 mL) and brine (2 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified via preparative TLC (three iterations: 9:1 hexanes:EtOAc, 100% benzene, 10:10:1 hexanes:CH₂Cl₂:Et₂O) to obtain silyl bromide (**±**)-**3.95** as a colorless oil (3.6 mg, 11% yield). Spectral data match those previously reported.³⁰

3.6 Chiral SFC Data

Table 3.1. Chiral SFC data.

Compound	Method Column/Temp.	Solvent	Method Flow Rate	Retention Times (min)	Enantiomeric Ratio (er)
 3.31 (racemic)	Diacel ChiralPak OD-H / 35 °C	15% isopropanol in CO ₂	2 mL/min	16.29/18.47	~50.5:49.5
 3.31 (enantioenriched)	Diacel ChiralPak OD-H / 35 °C	15% isopropanol in CO ₂	2 mL/min	16.29/18.40	~99.4:0.6

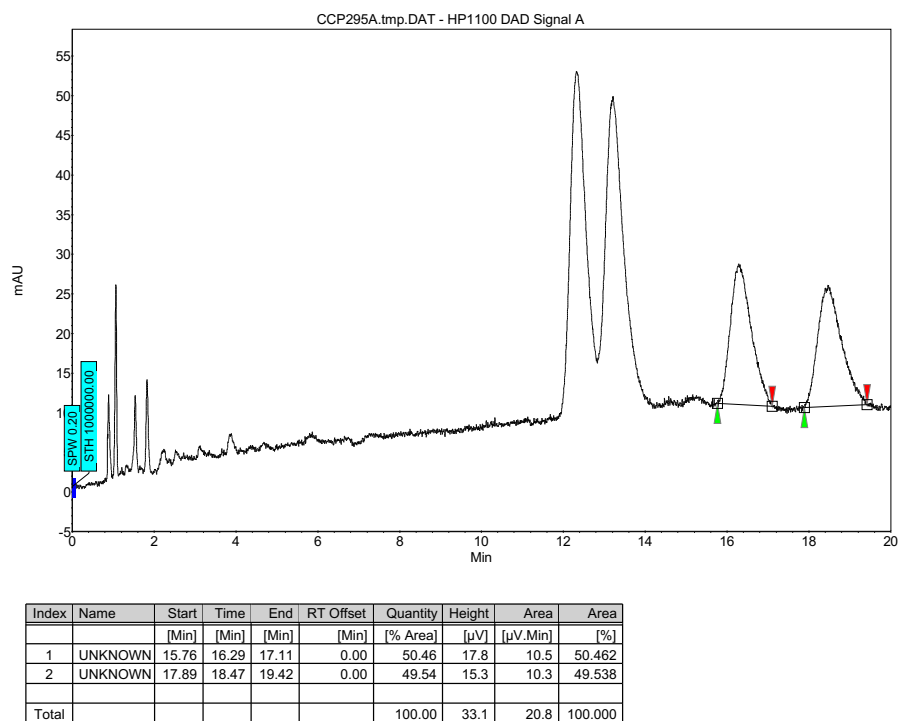


Figure 3.16. SFC trace of racemic **3.31**. Cycloadduct **3.31** undergoes decarboxylation, resulting in inconsequential peaks from 12–14 min.

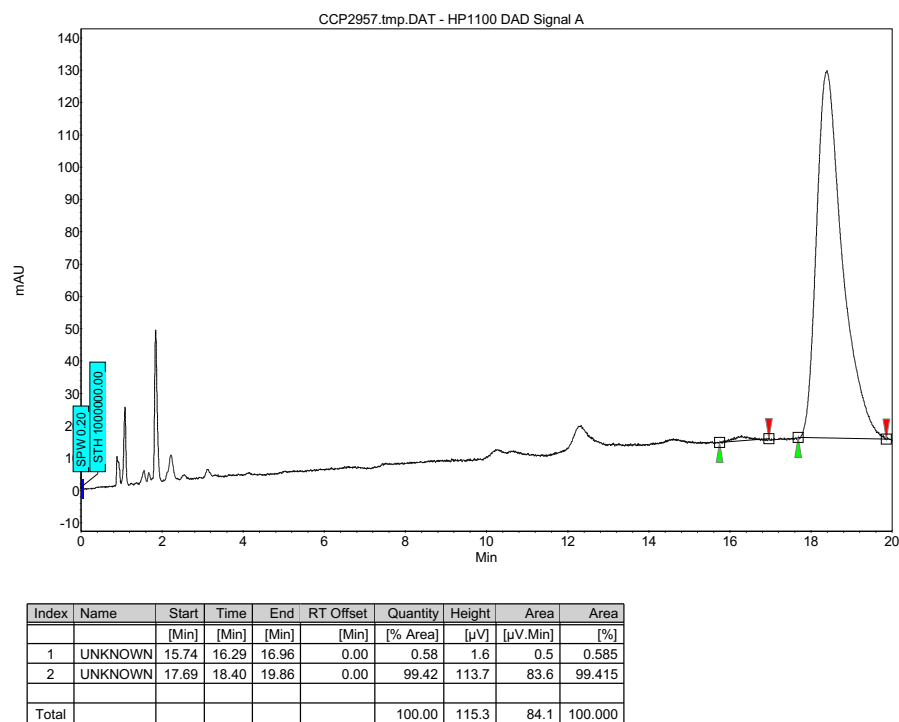


Figure 3.17. SFC trace of enantioenriched **3.31**.

3.7 Spectra Relevant to Chapter Three:

Total Synthesis of Lissodendoric Acid A

Francesca M. Ippoliti,[†] Laura G. Wonilowicz,[†] Nathan J. Adamson, Evan R. Darzi, Joyann S. Donaldson, Daniel J. Nasrallah, Milauni M. Mehta, Andrew V. Kelleghan, K. N. Houk,
and Neil K. Garg.

Angew. Chem., Int. Ed. **2024**, doi: 10.1002/anie.202406676.

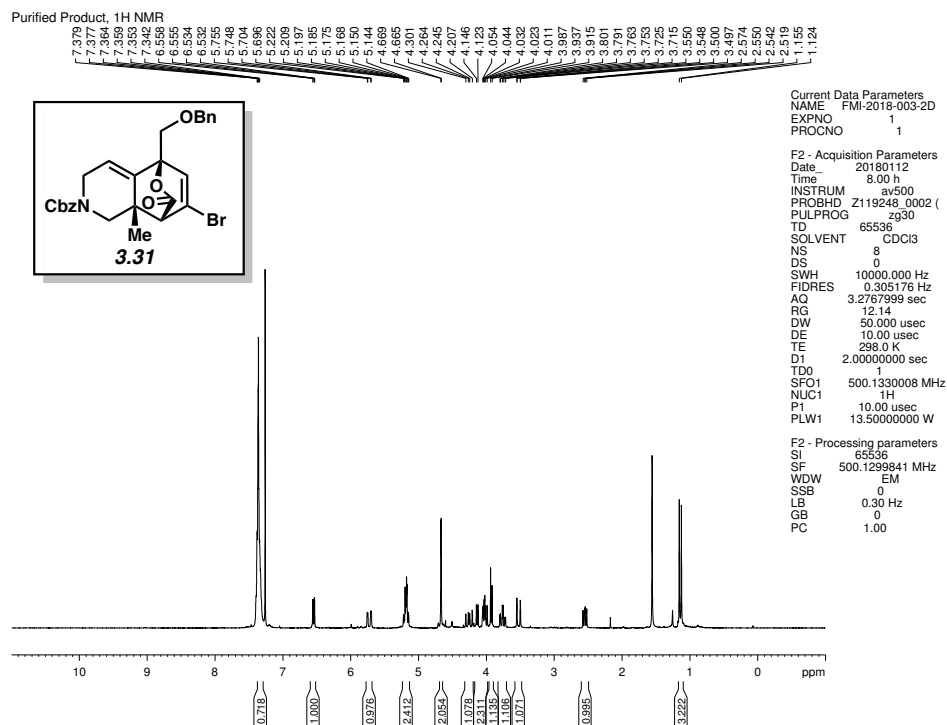


Figure 3.18. ^1H NMR (500 MHz, CDCl_3) of compound **3.31**.

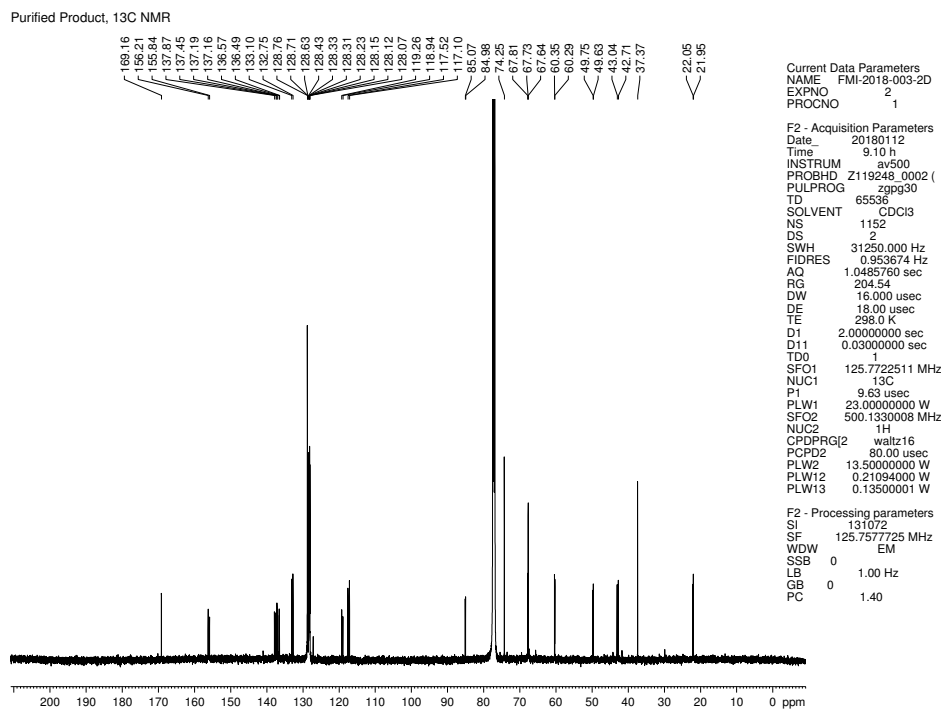


Figure 3.19. ^{13}C NMR (125 MHz, CDCl_3) of compound **3.31**.

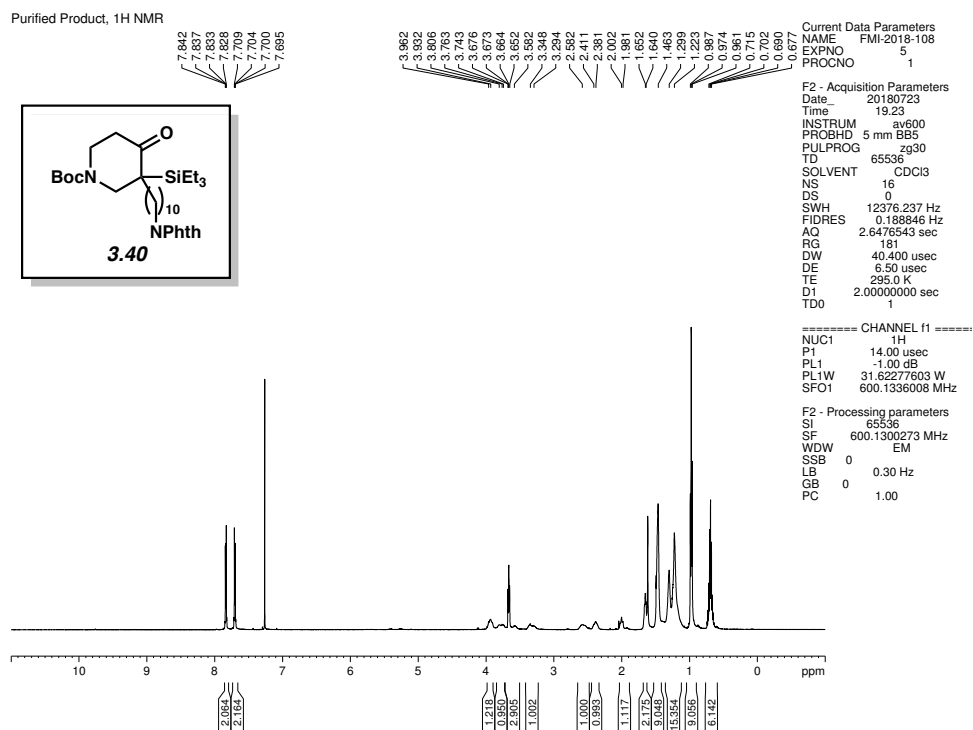


Figure 3.22. ¹H NMR (600 MHz, CDCl₃) of compound **3.40**.

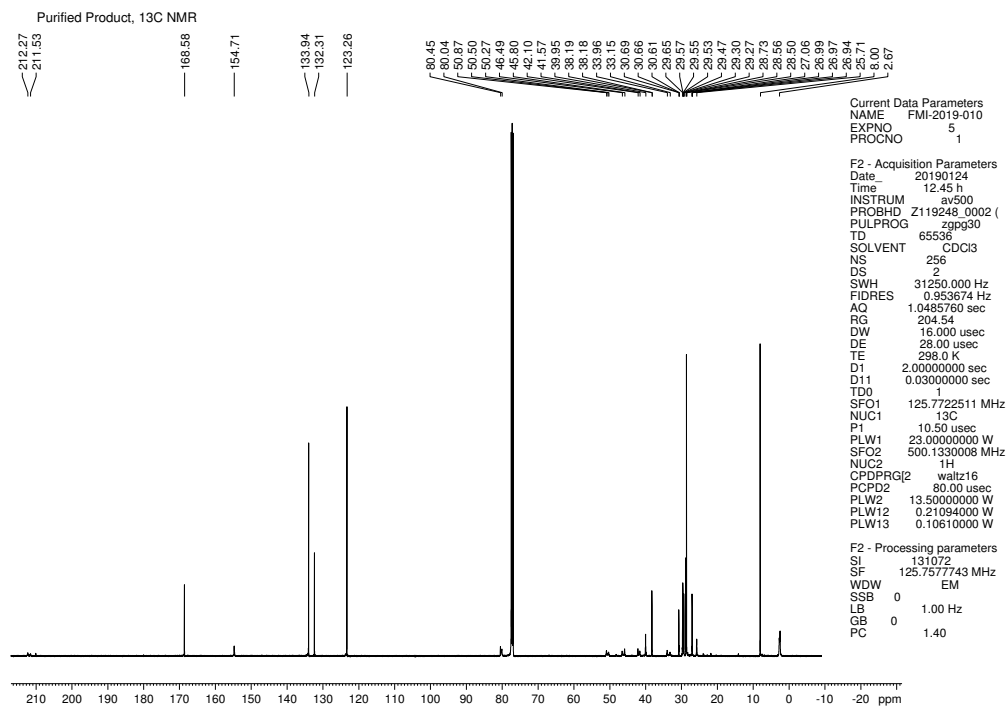


Figure 3.23. ¹³C NMR (125 MHz, CDCl₃) of compound **3.40**.

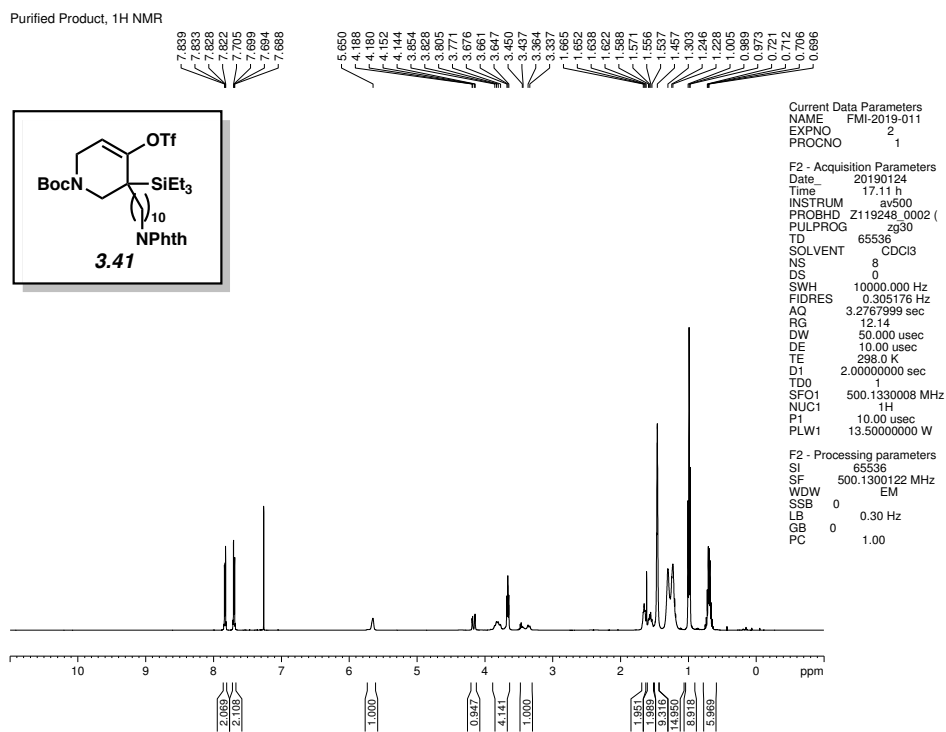


Figure 3.24. ^1H NMR (500 MHz, CDCl_3) of compound **3.41**.

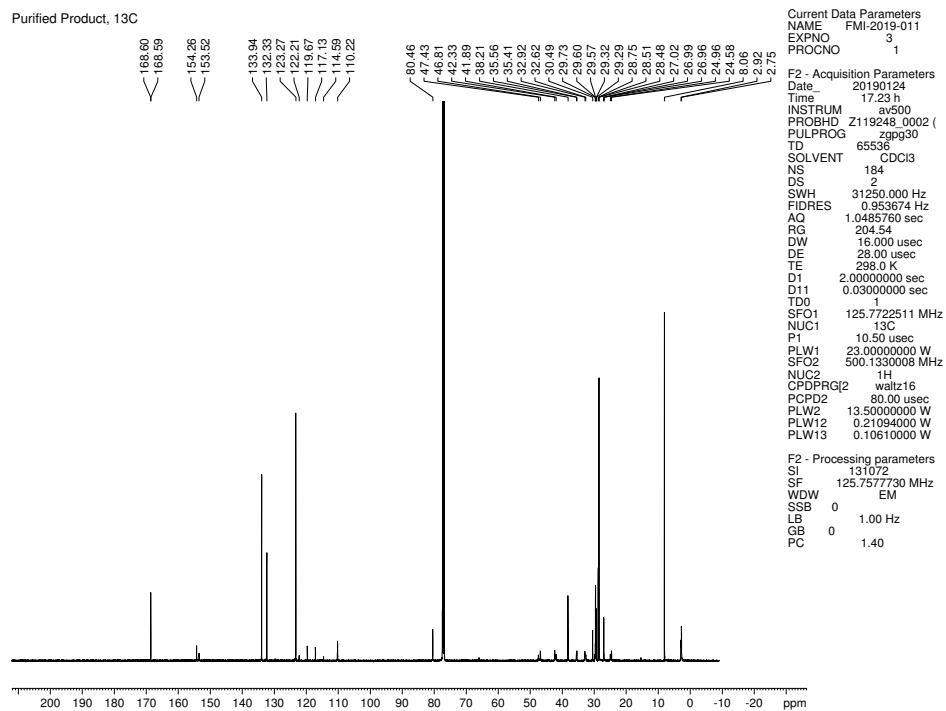


Figure 3.25. ^{13}C NMR (125 MHz, CDCl_3) of compound **3.41**.

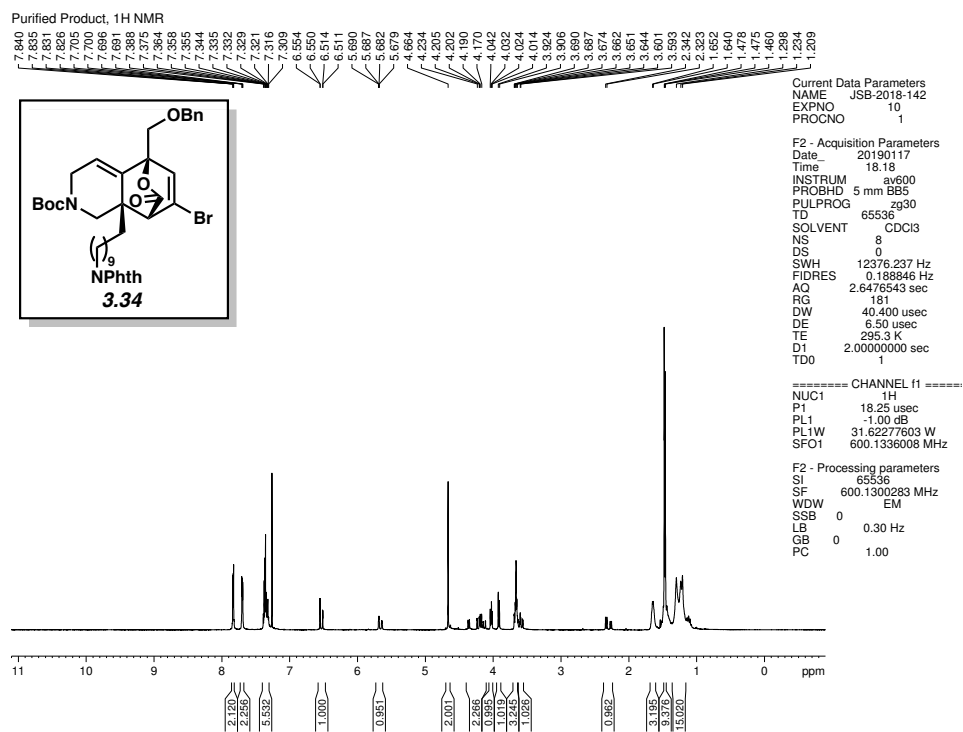


Figure 3.26. ¹H NMR (600 MHz, CDCl₃) of compound 3.34.

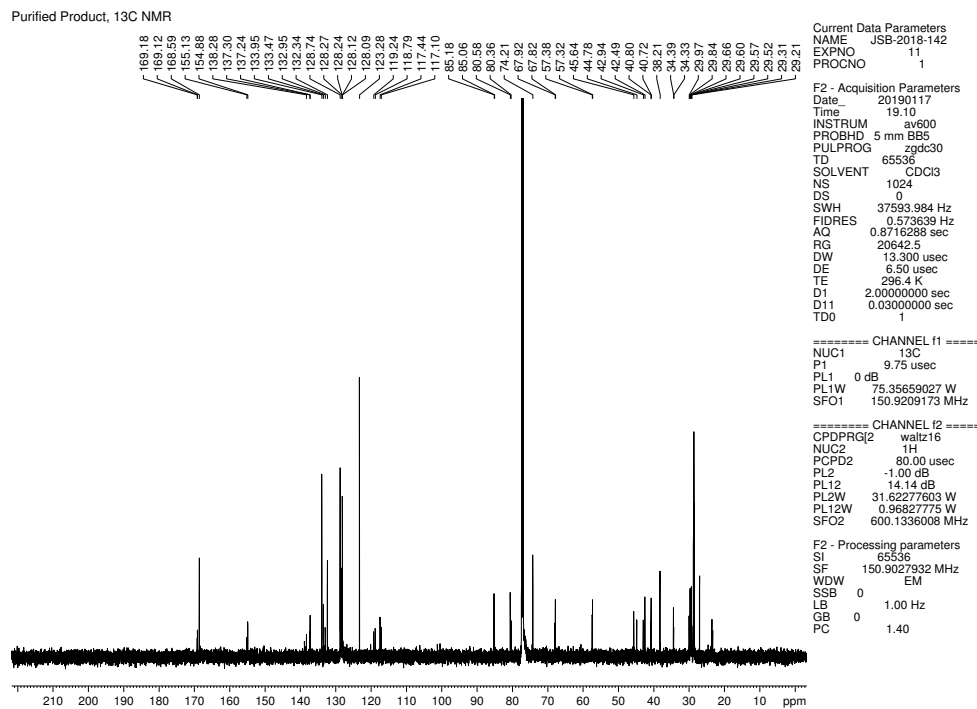


Figure 3.27. ¹³C NMR (150 MHz, CDCl₃) of compound 3.34.

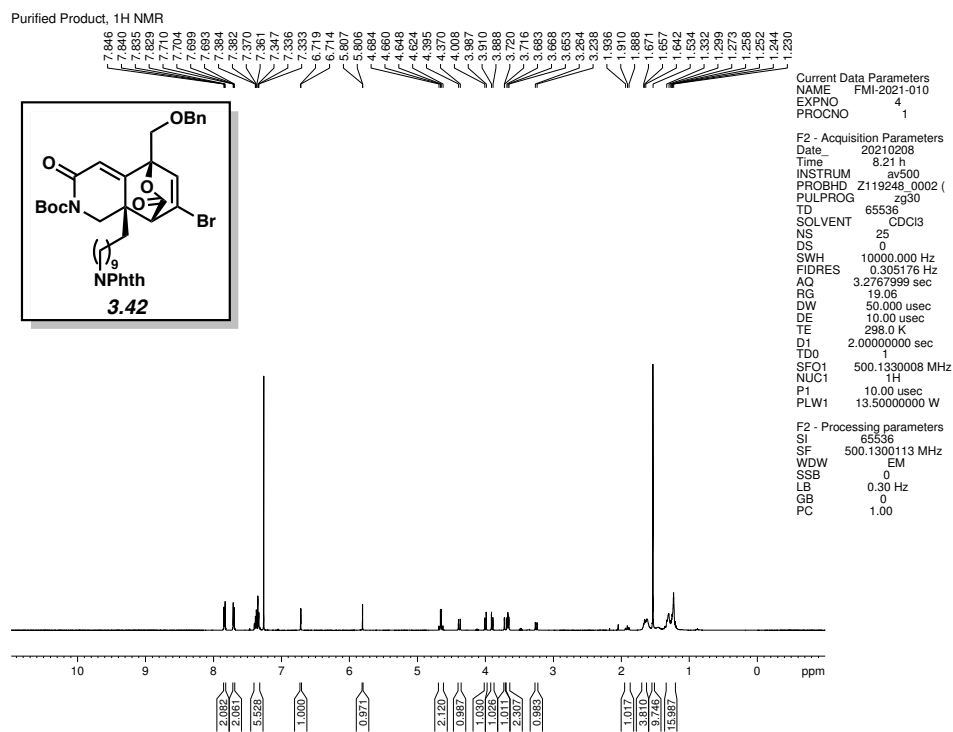


Figure 3.28. ¹H NMR (500 MHz, CDCl₃) of compound 3.42.

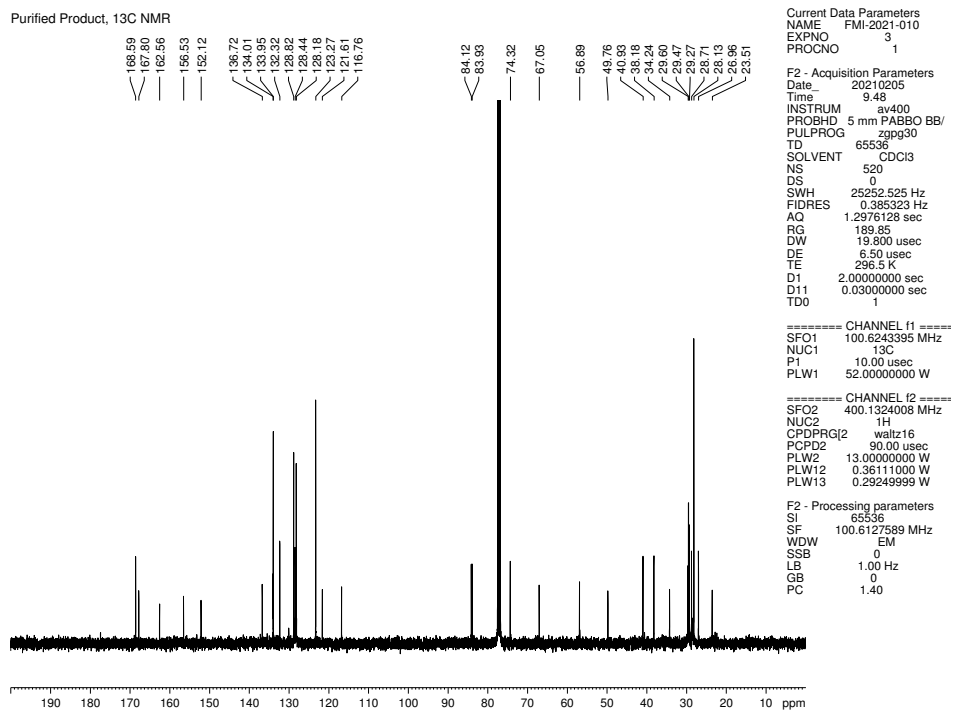


Figure 3.29. ¹³C NMR (100 MHz, CDCl₃) of compound 3.42.

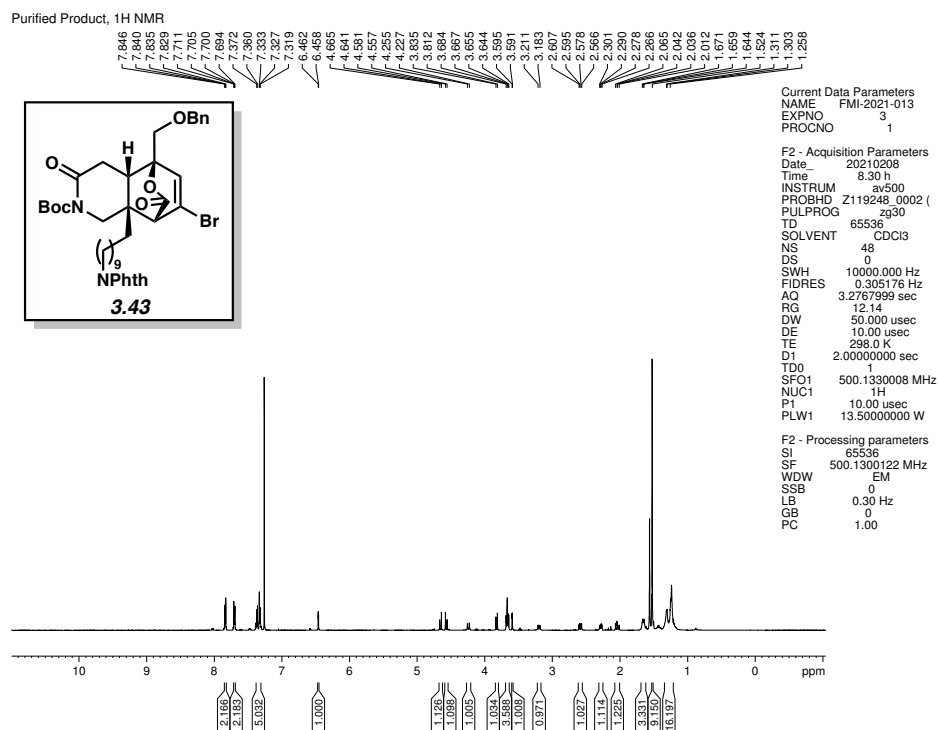


Figure 3.30. ¹H NMR (500 MHz, CDCl₃) of compound **3.43**.

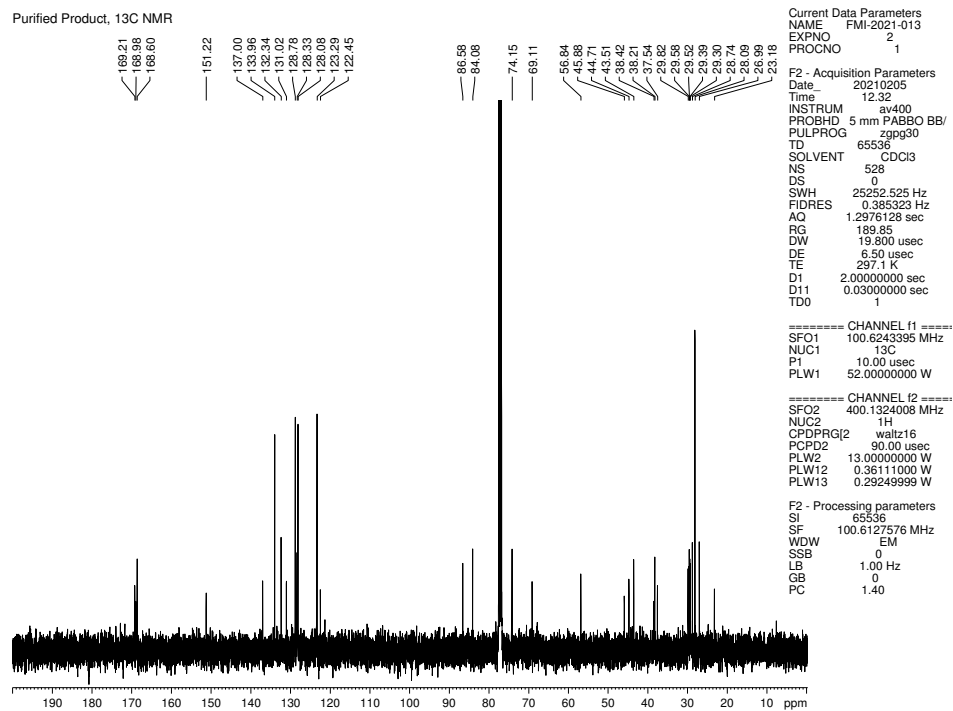


Figure 3.31. ¹³C NMR (100 MHz, CDCl₃) of compound **3.43**.

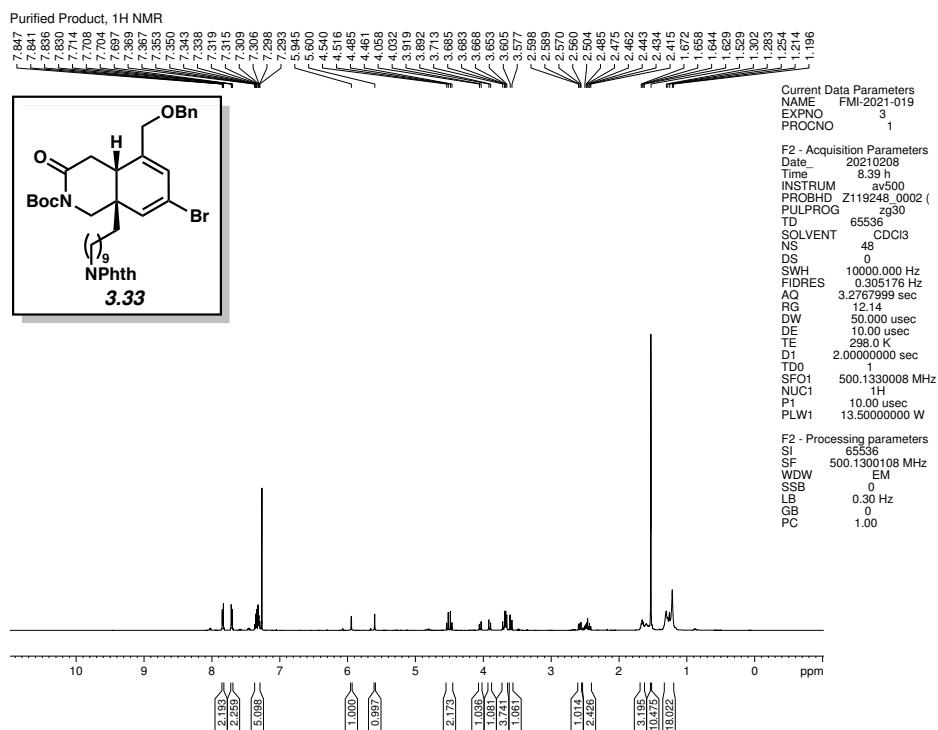


Figure 3.32. ¹H NMR (500 MHz, CDCl₃) of compound **3.33**.

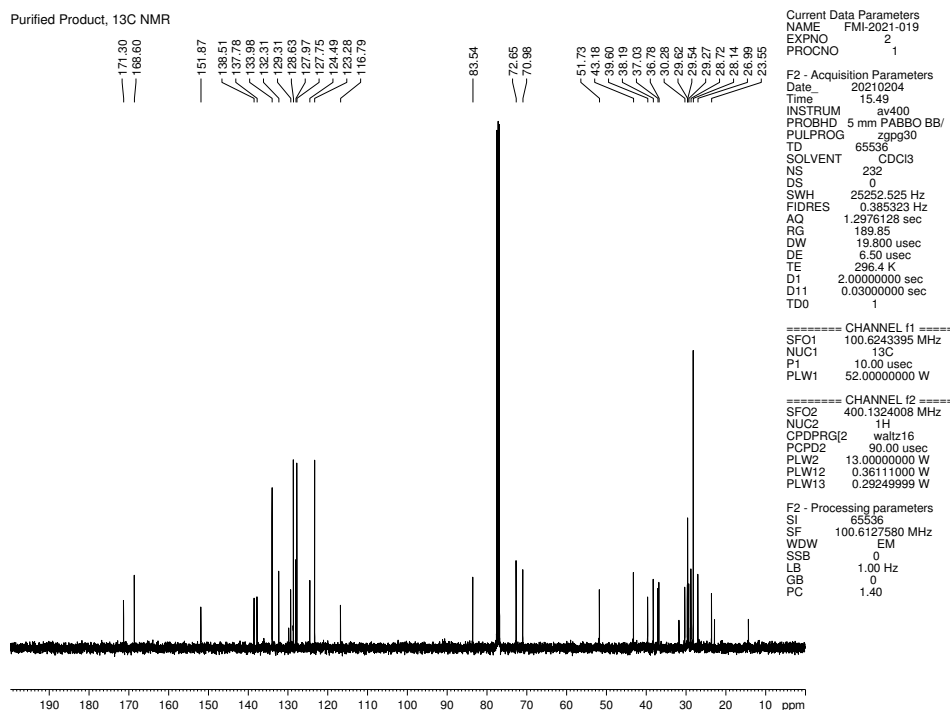


Figure 3.33. ¹³C NMR (100 MHz, CDCl₃) of compound **3.33**.

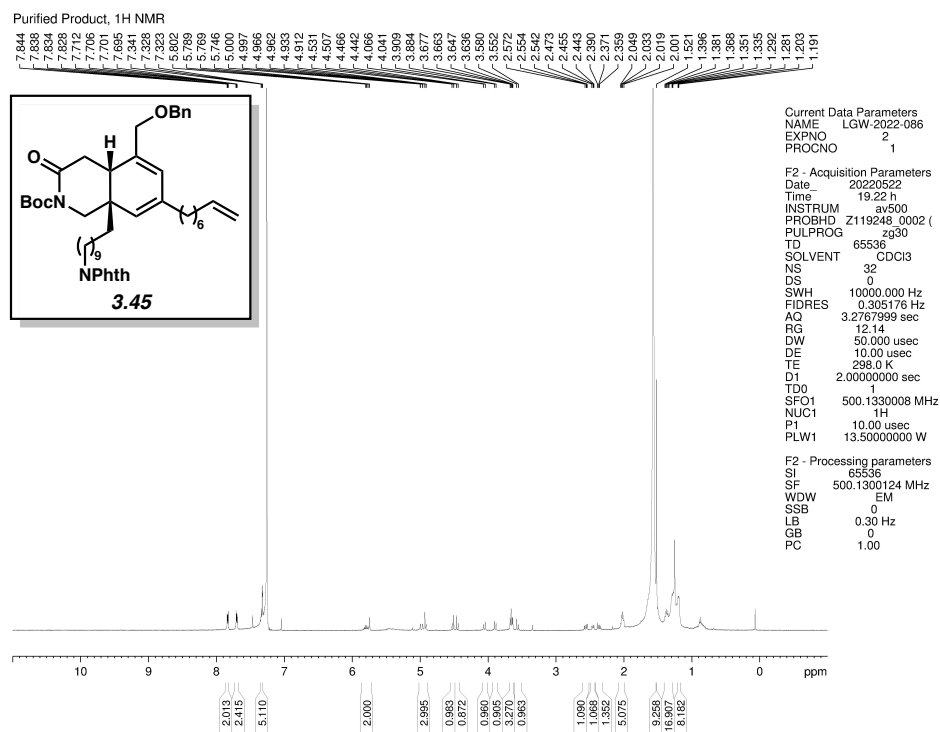


Figure 3.34. ¹H NMR (500 MHz, CDCl₃) of compound **3.45**.

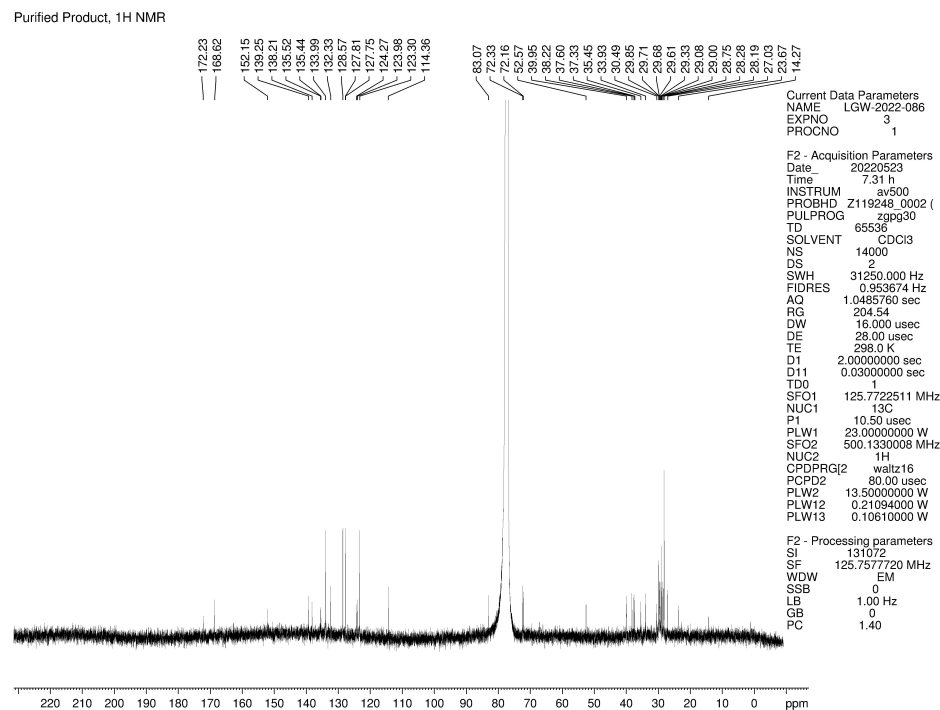


Figure 3.35. ¹³C NMR (125 MHz, CDCl₃) of compound **3.45**.

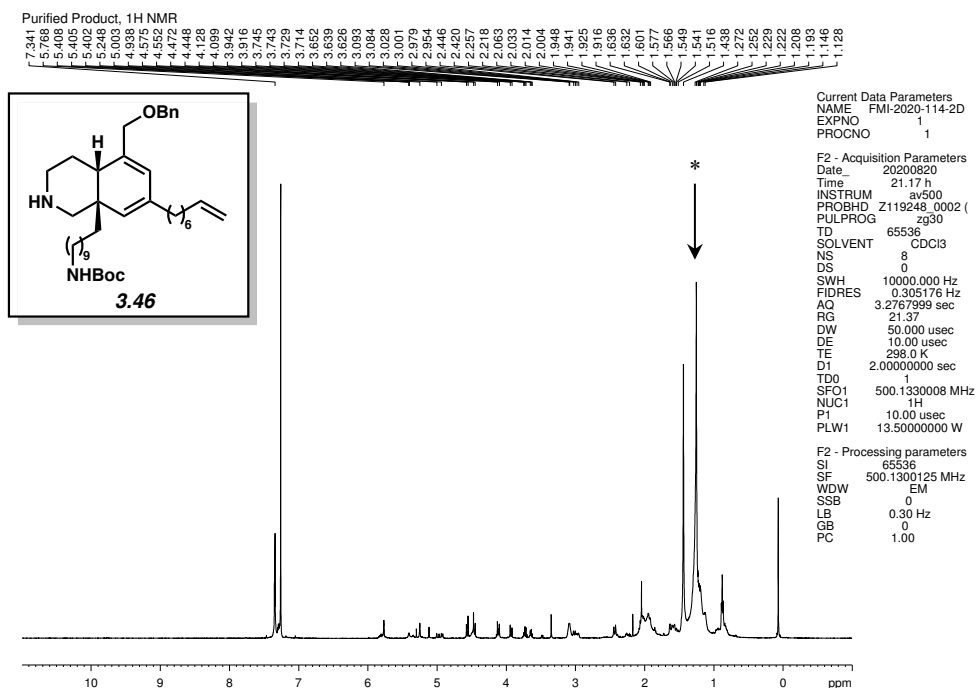


Figure 3.36. ¹H NMR (500 MHz, CDCl₃) of compound 3.46.

*Residual grease. Inconsequential minor impurities are present, which are an artifact of small scale and challenging purification.

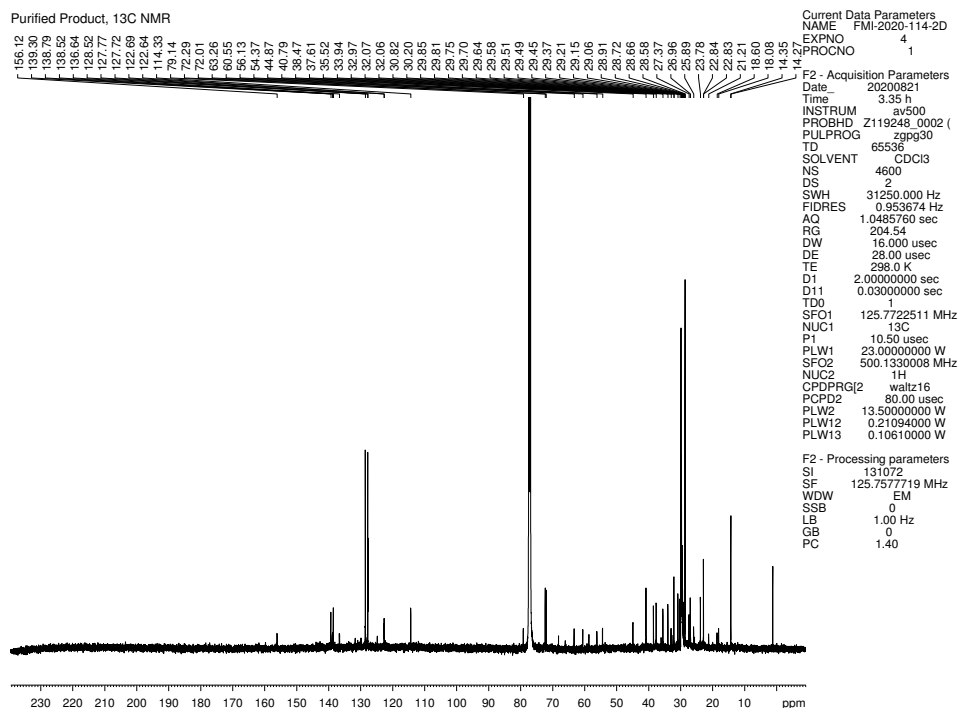


Figure 3.37. ¹³C NMR (125 MHz, CDCl₃) of compound 3.46.

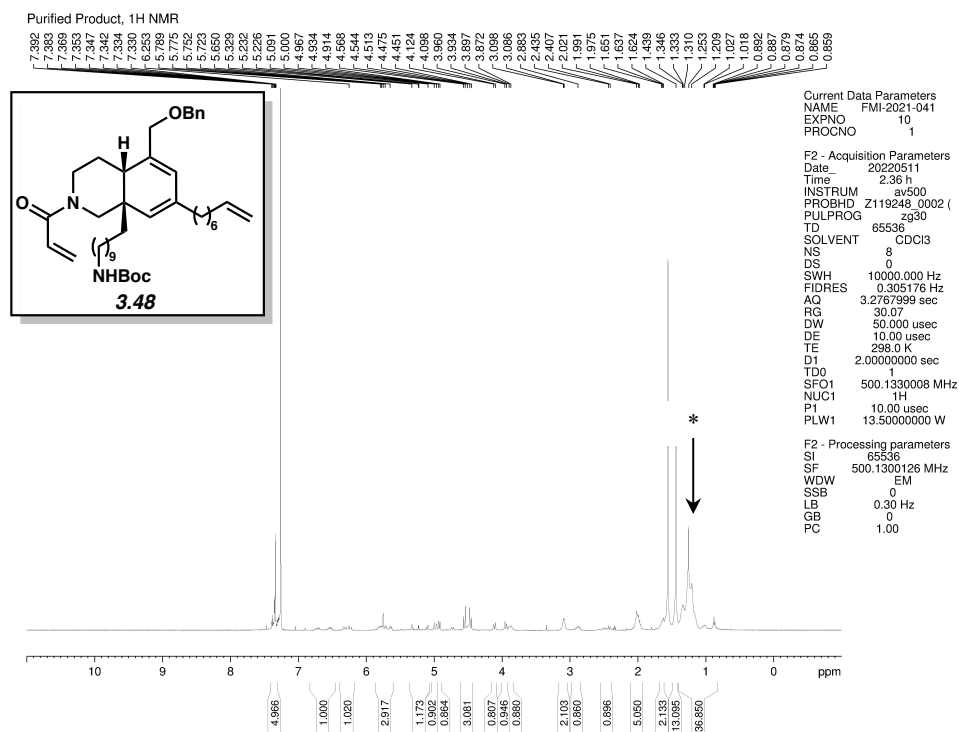


Figure 3.38. ^1H NMR (500 MHz, CDCl_3) of compound 3.48.

*Residual grease. Inconsequential minor impurities are present, which are an artifact of small scale and challenging purification.

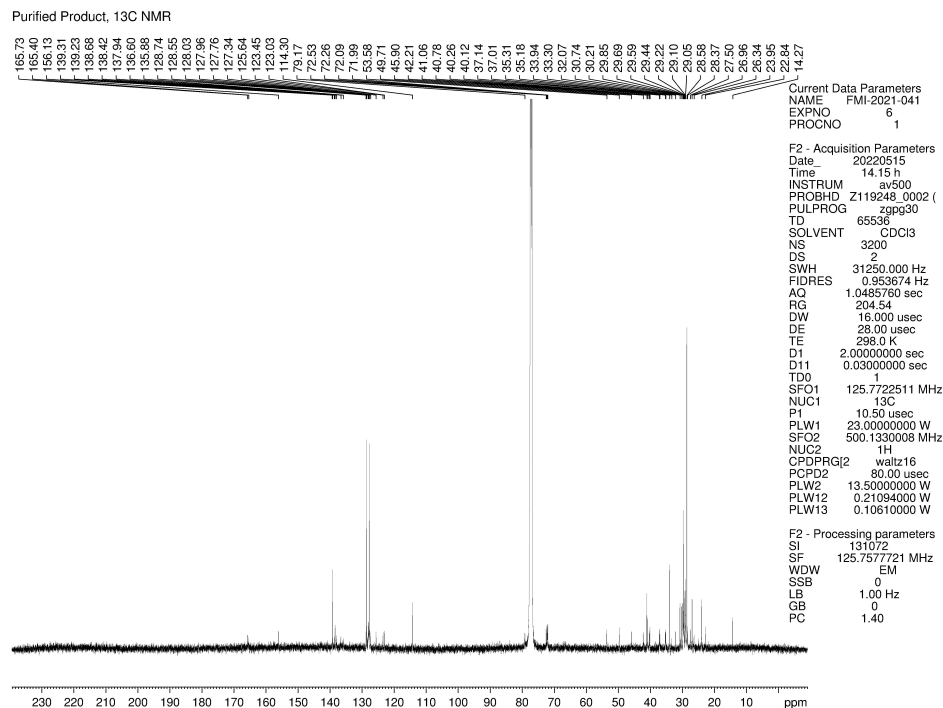


Figure 3.39. ^{13}C NMR (125 MHz, CDCl_3) of compound 3.48.

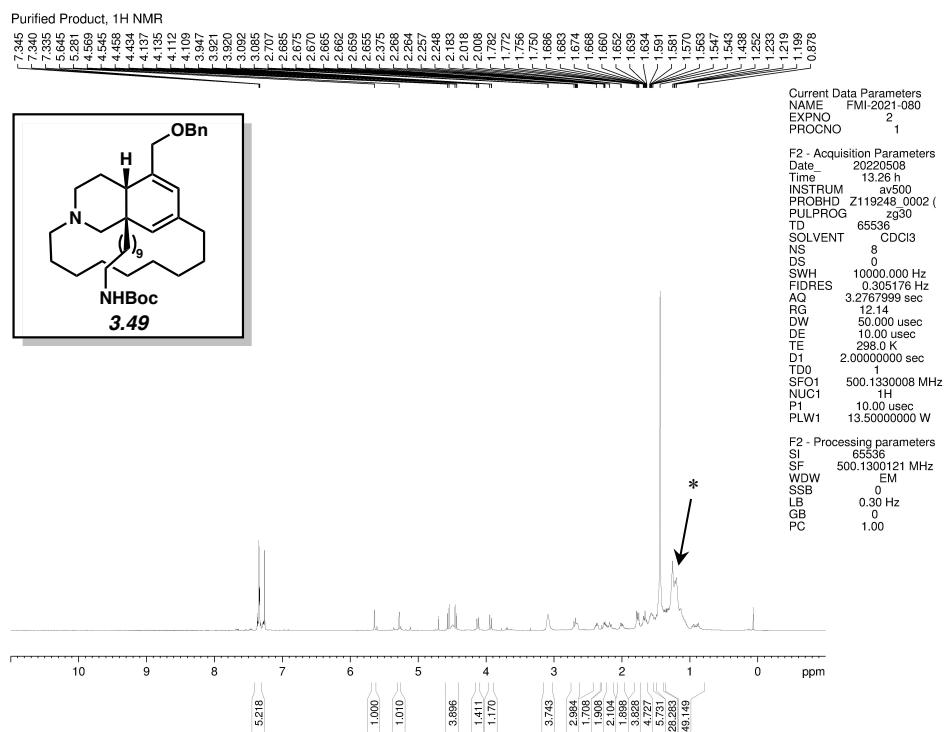


Figure 3.40. ^1H NMR (500 MHz, CDCl_3) of compound **3.49**.
 *Residual grease. Inconsequential minor impurities are present, which are an artifact of small scale and challenging purification.

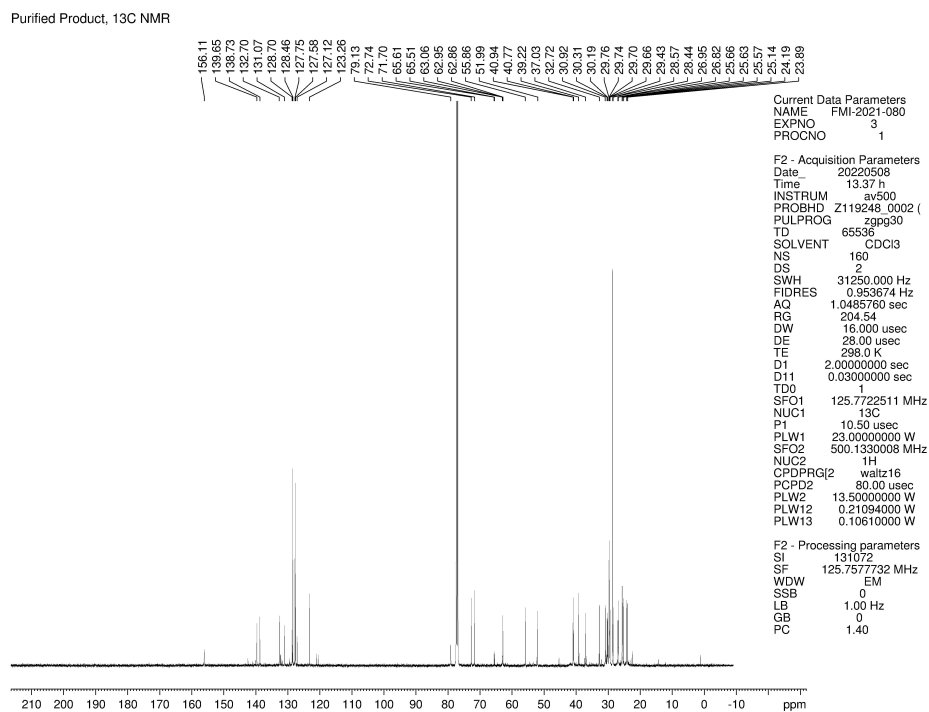


Figure 3.41. ^{13}C NMR (125 MHz, CDCl_3) of compound **3.49**.

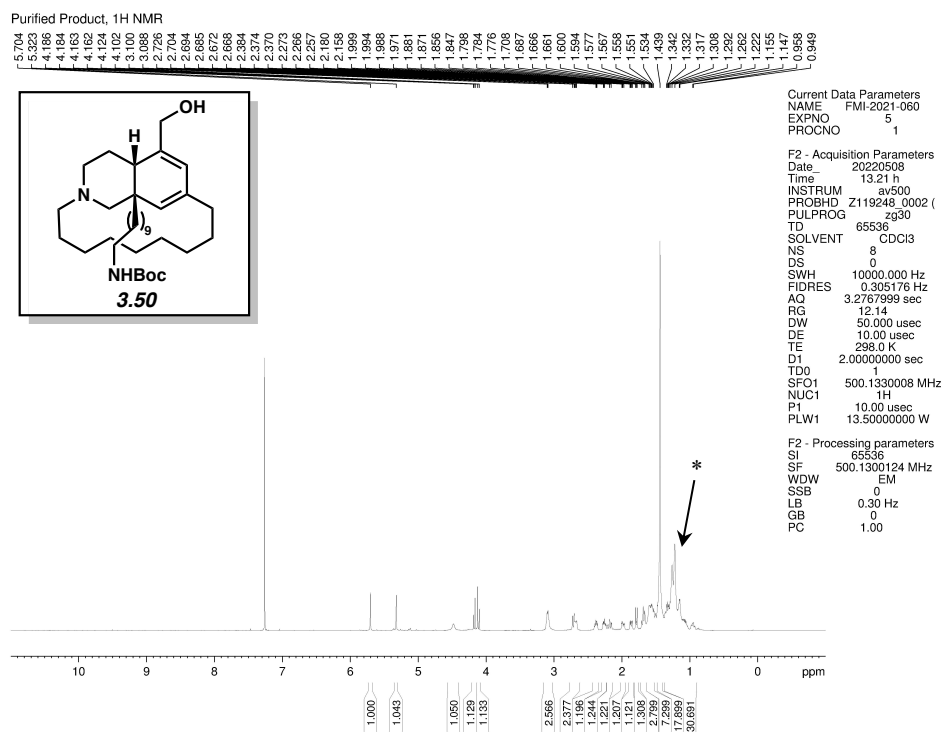


Figure 3.42. ¹H NMR (500 MHz, CDCl₃) of compound **3.50**.
 *Residual grease. Inconsequential minor impurities are present, which are an artifact of small scale and challenging purification.

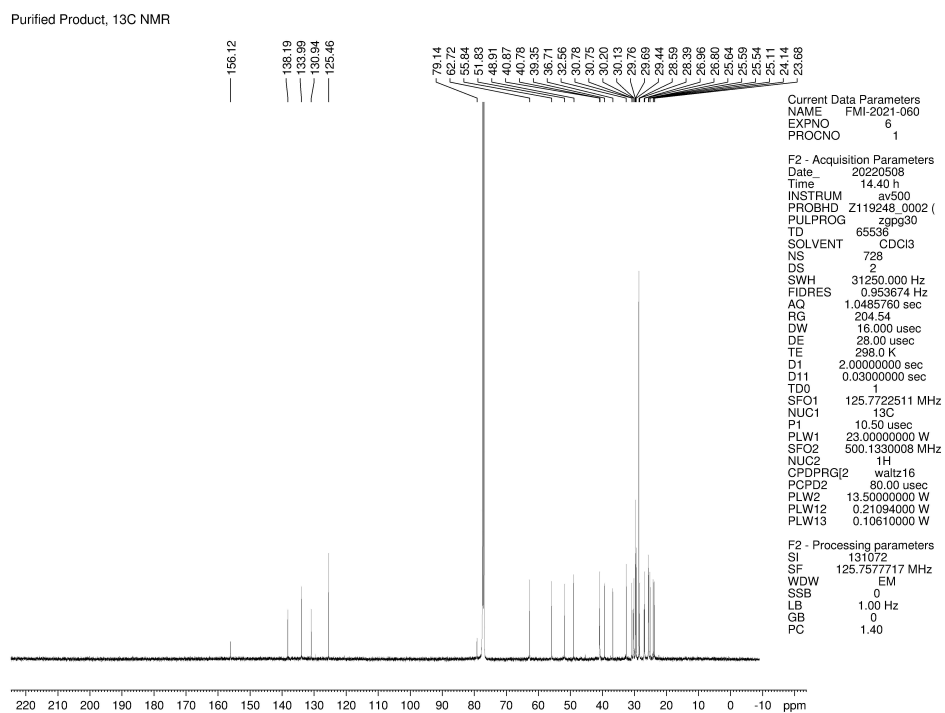


Figure 3.43. ¹³C NMR (125 MHz, CDCl₃) of compound **3.50**.

Purified Product, ¹H NMR

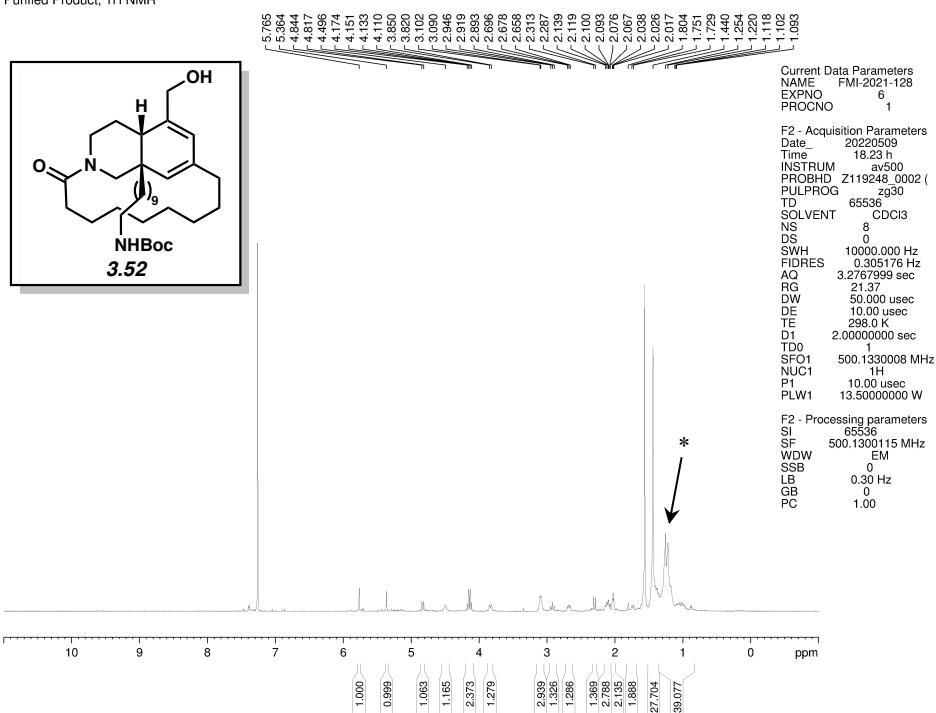


Figure 3.44. ¹H NMR (500 MHz, CDCl₃) of compound 3.52.

*Residual grease. Inconsequential minor impurities are present, which are an artifact of small scale and challenging purification.

Purified Product, ¹³C NMR

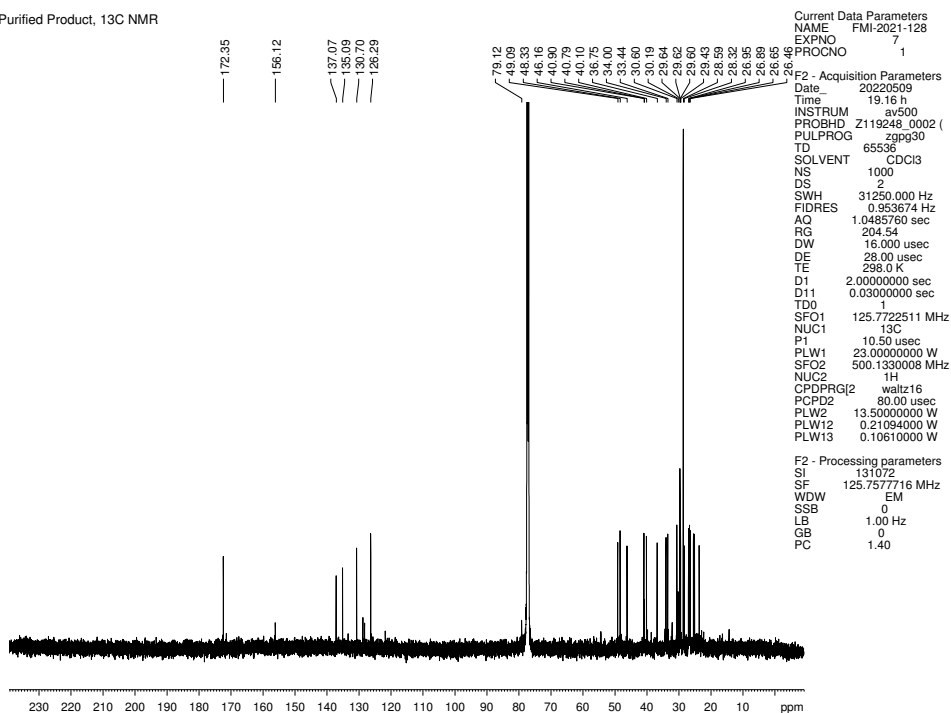


Figure 3.45. ¹³C NMR (125 MHz, CDCl₃) of compound 3.52.

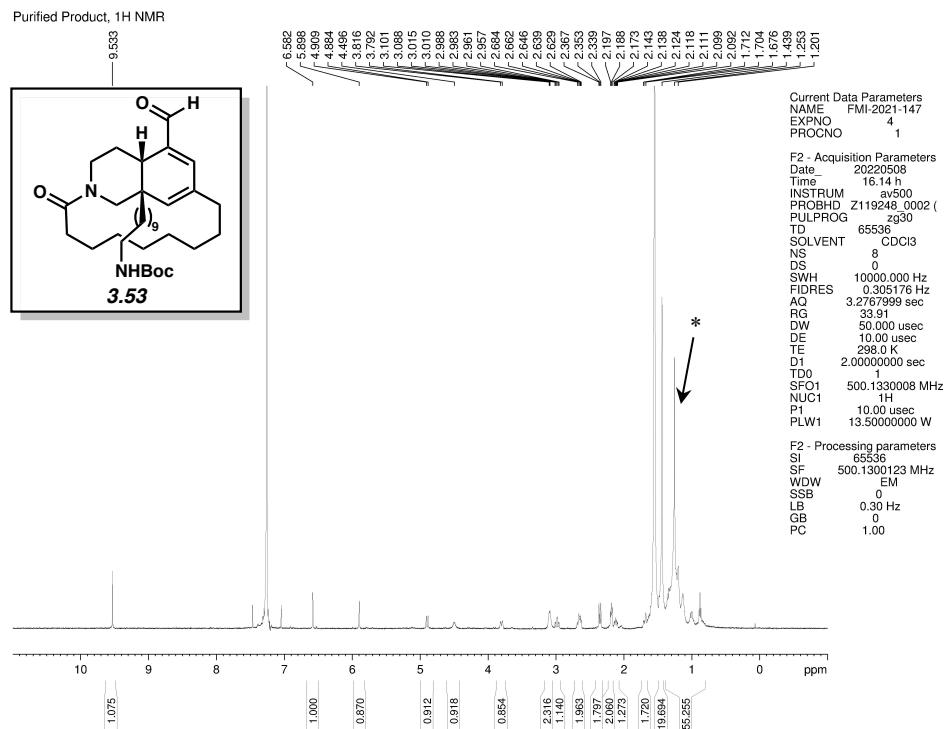


Figure 3.46. ^1H NMR (500 MHz, CDCl_3) of compound **3.53**.
*Residual grease. Inconsequential minor impurities are present, which are an artifact of small scale and challenging purification.

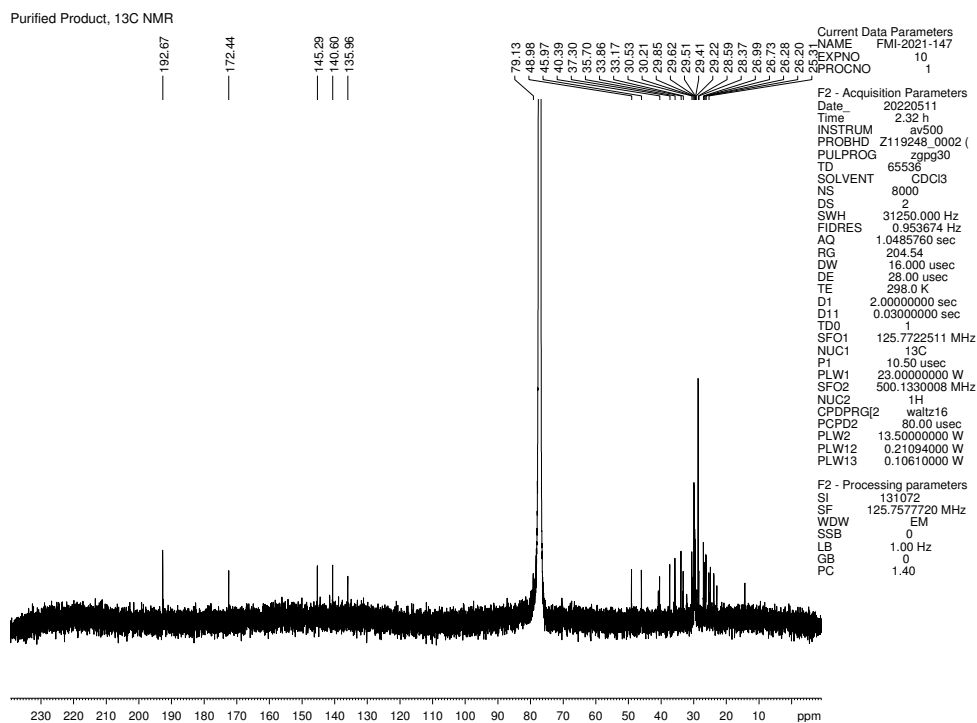


Figure 3.47. ^{13}C NMR (125 MHz, CDCl_3) of compound **3.53**.

Purified Product, ¹H NMR

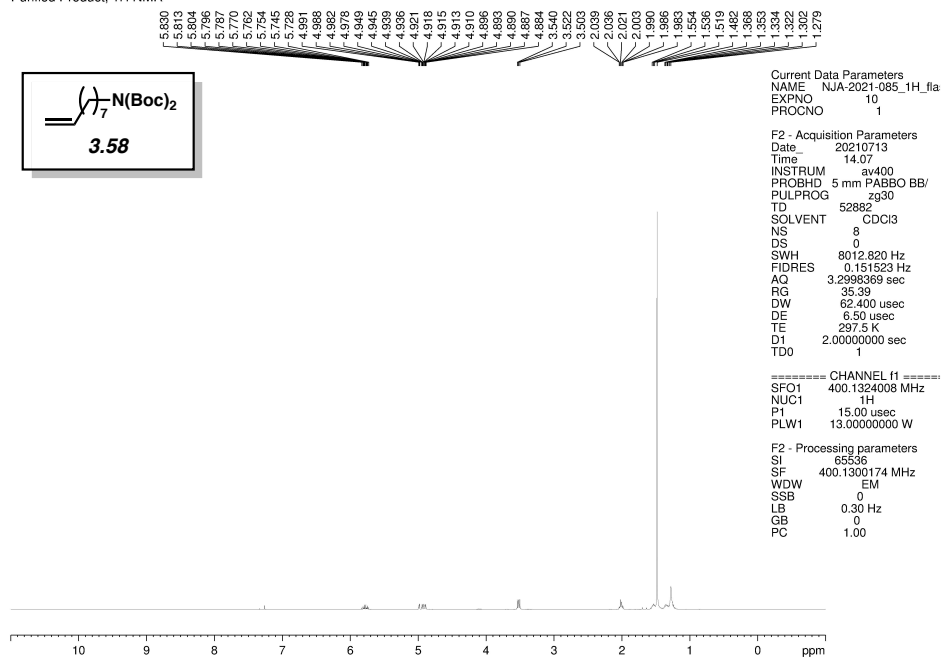


Figure 3.48. ¹H NMR (400 MHz, CDCl₃) of compound 3.58.

Purified Product, ¹³C NMR

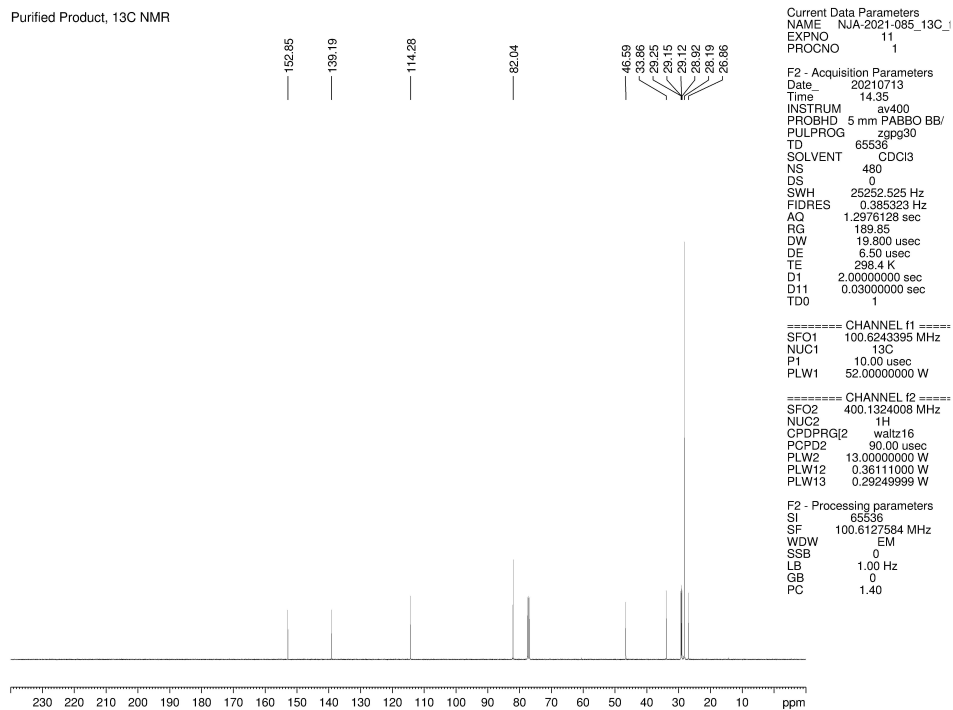


Figure 3.49. ¹³C NMR (100 MHz, CDCl₃) of compound 3.58.

Purified Product, ¹H NMR

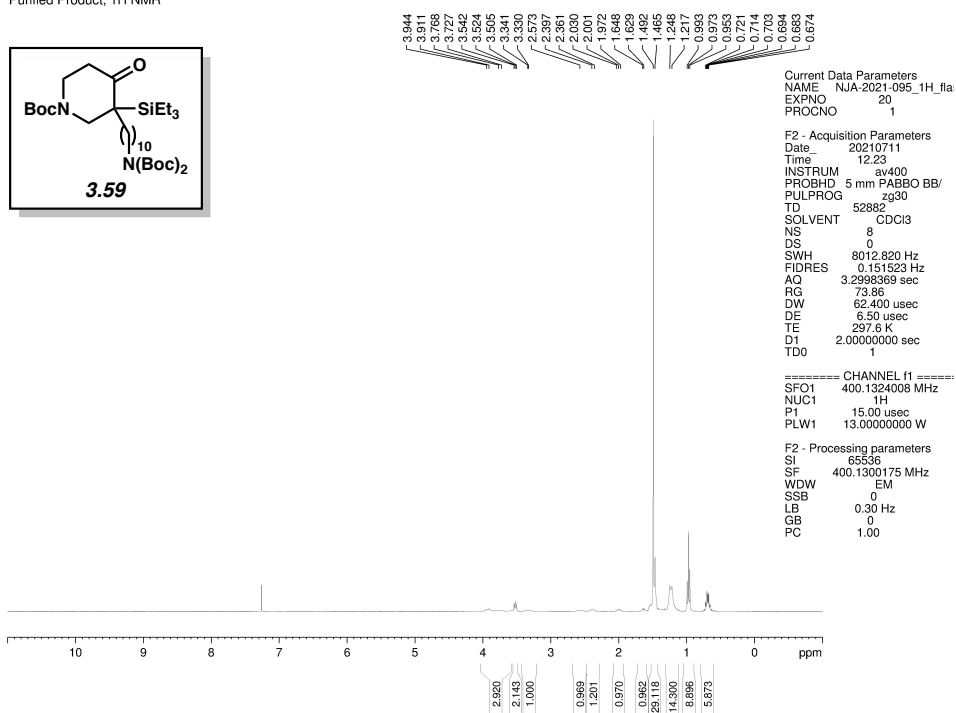


Figure 3.50. ¹H NMR (400 MHz, CDCl₃) of compound **3.59**.

Purified Product, ¹³C NMR

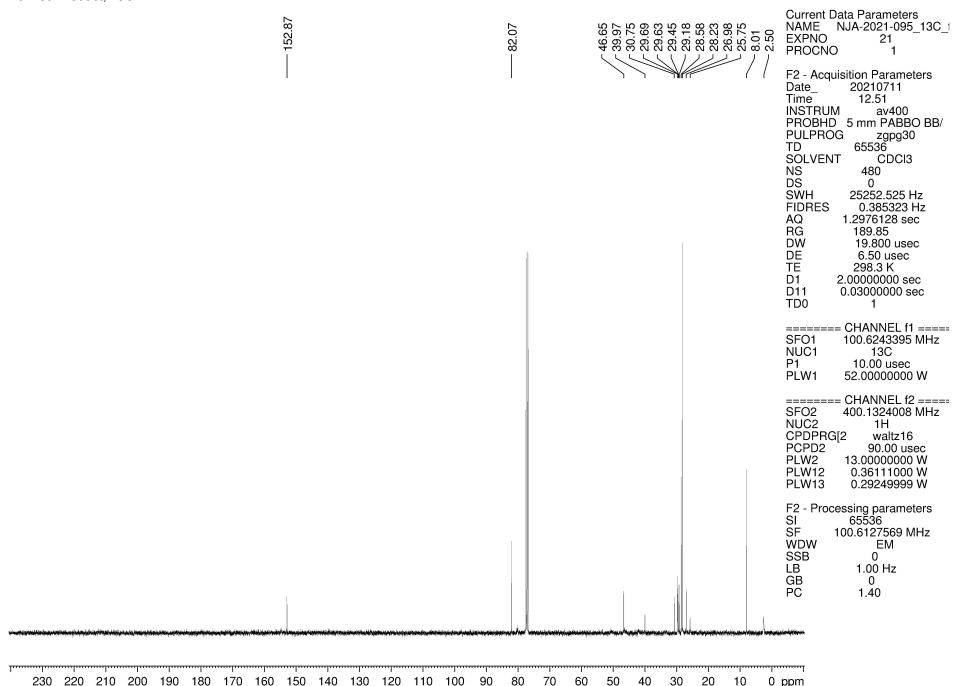


Figure 3.51. ¹³C NMR (100 MHz, CDCl₃) of compound **3.59**.

Purified Product, ¹H NMR

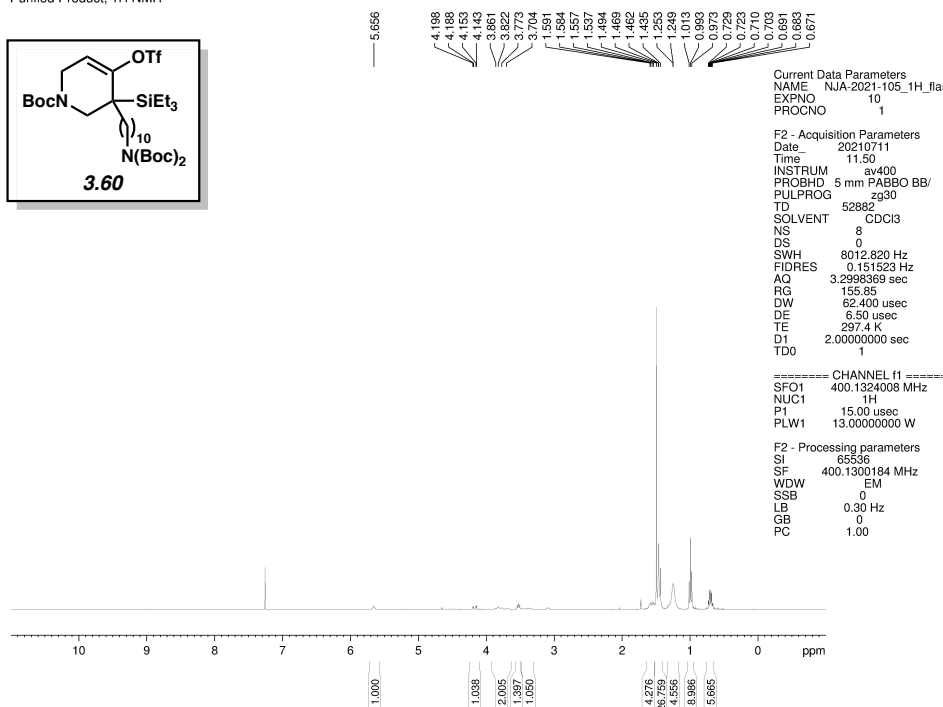
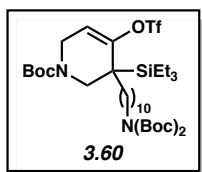


Figure 3.52. ¹H NMR (400 MHz, CDCl₃) of compound **3.60**.

Purified Product, ¹³C NMR

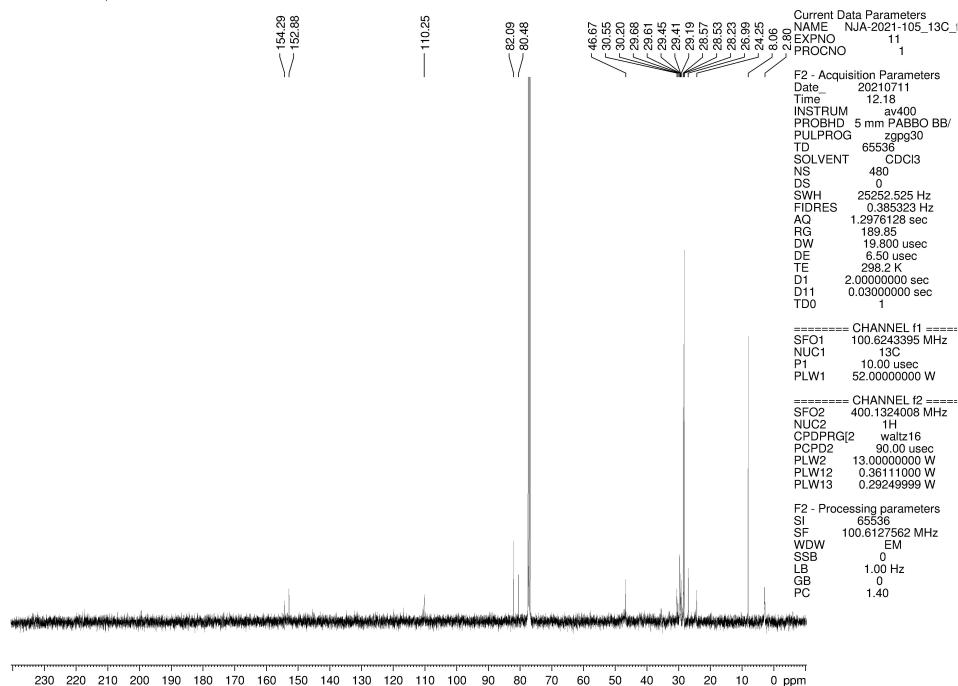


Figure 3.53. ¹³C NMR (100 MHz, CDCl₃) of compound **3.60**.

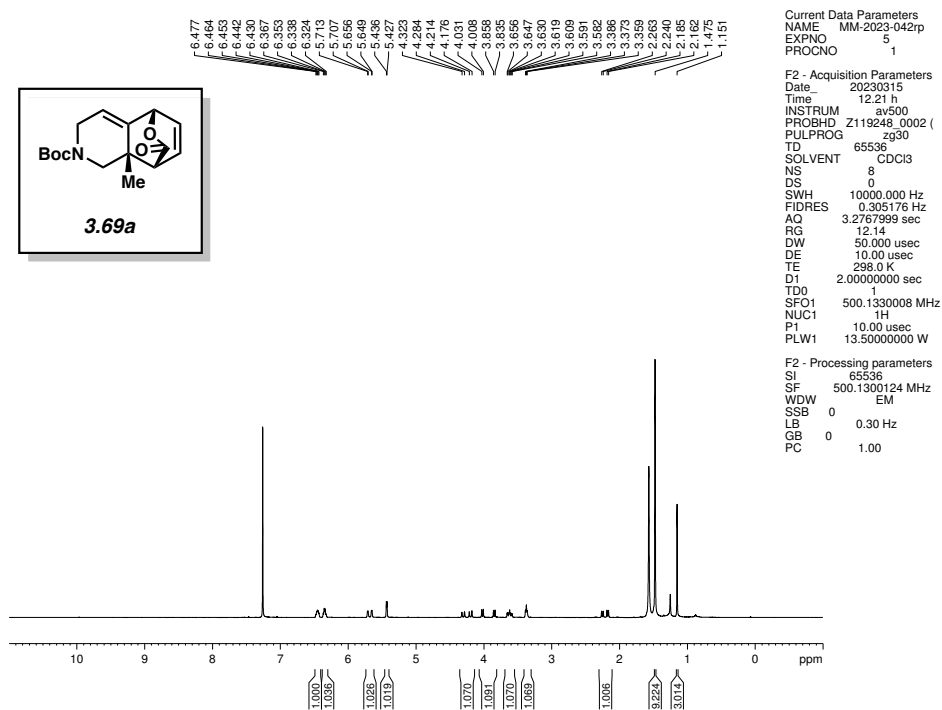


Figure 3.54. ^1H NMR (500 MHz, CDCl_3) of compound **3.69a**.

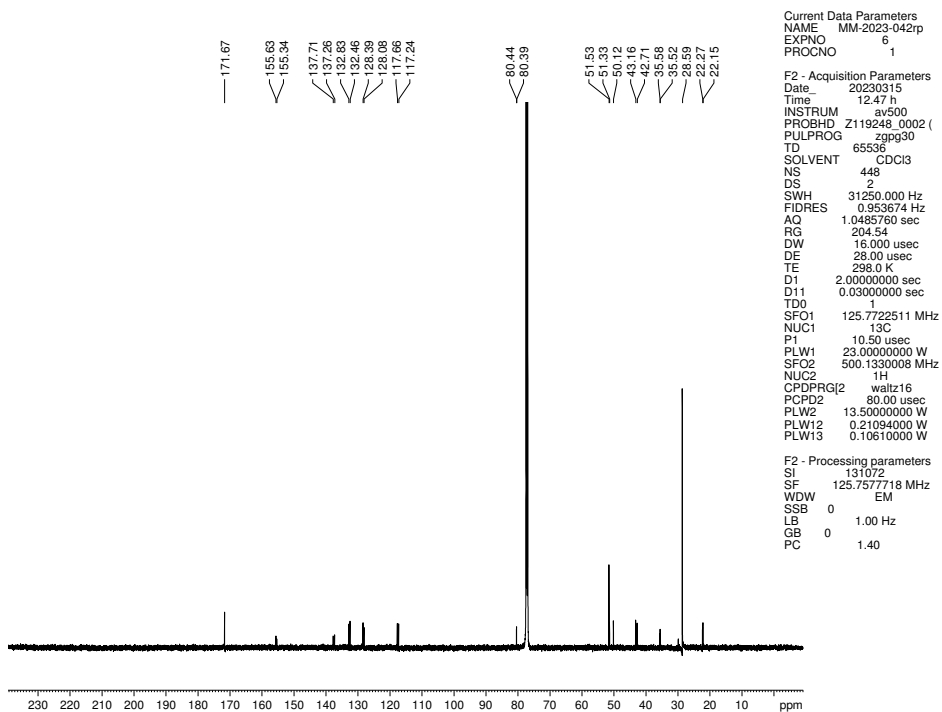


Figure 3.55. ^{13}C NMR (125 MHz, CDCl_3) of compound **3.69a**.

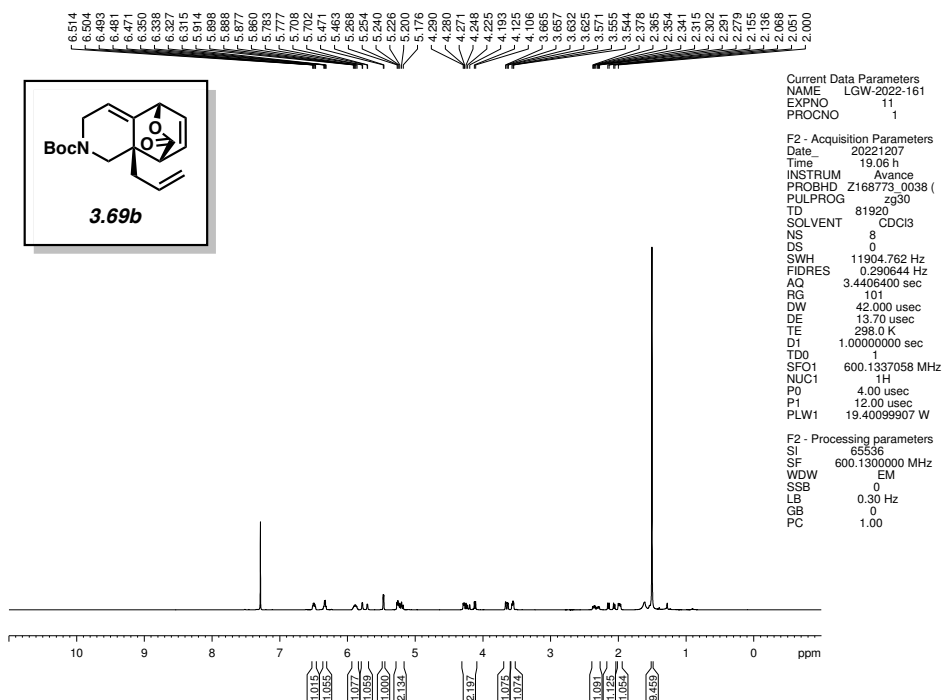


Figure 3.56. ^1H NMR (600 MHz, CDCl_3) of compound **3.69b**.

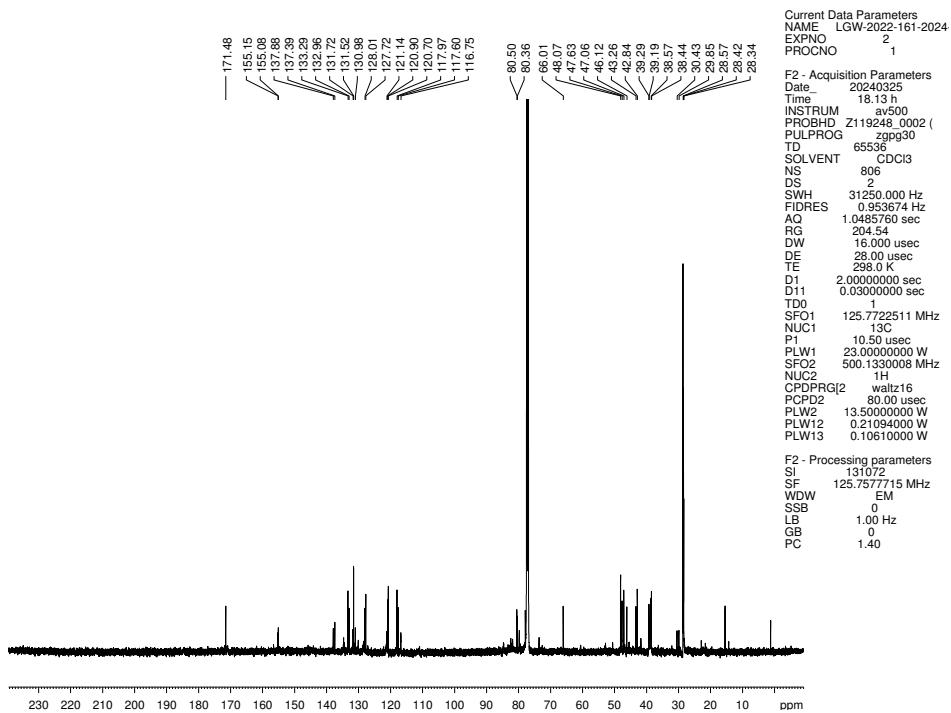


Figure 3.57. ^{13}C NMR (125 MHz, CDCl_3) of compound **3.69b**.

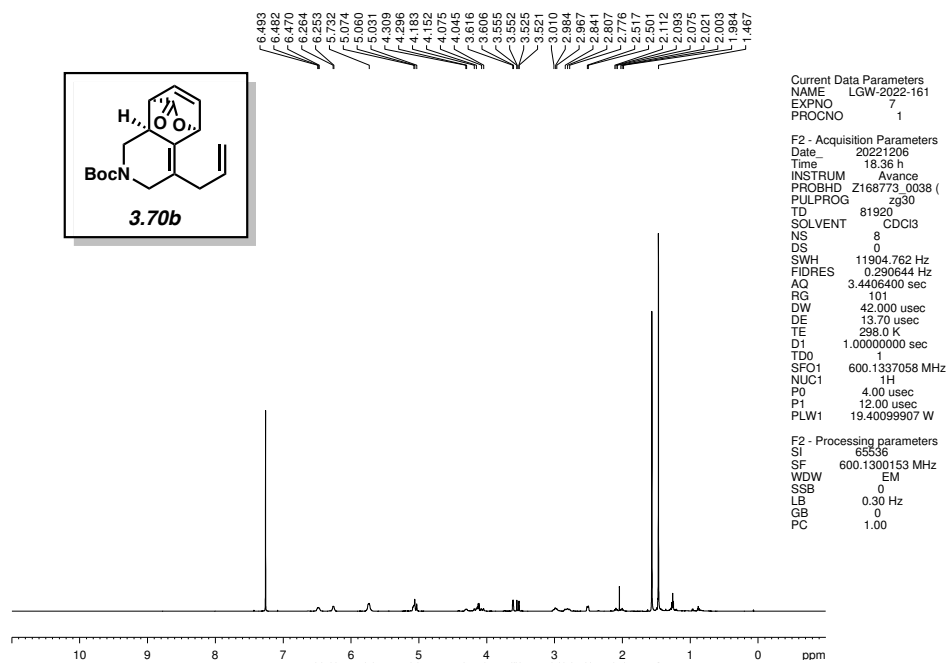


Figure 3.58. ^1H NMR (600 MHz, CDCl_3) of compound **3.70b**.

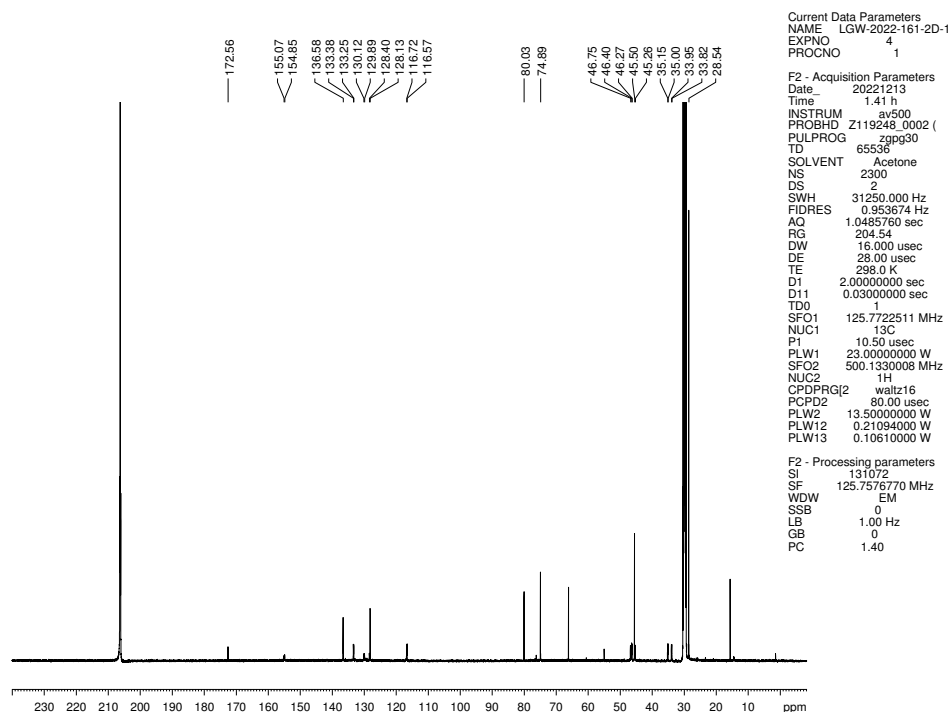


Figure 3.59. ^{13}C NMR (125 MHz, CDCl_3) of compound **3.70b**.

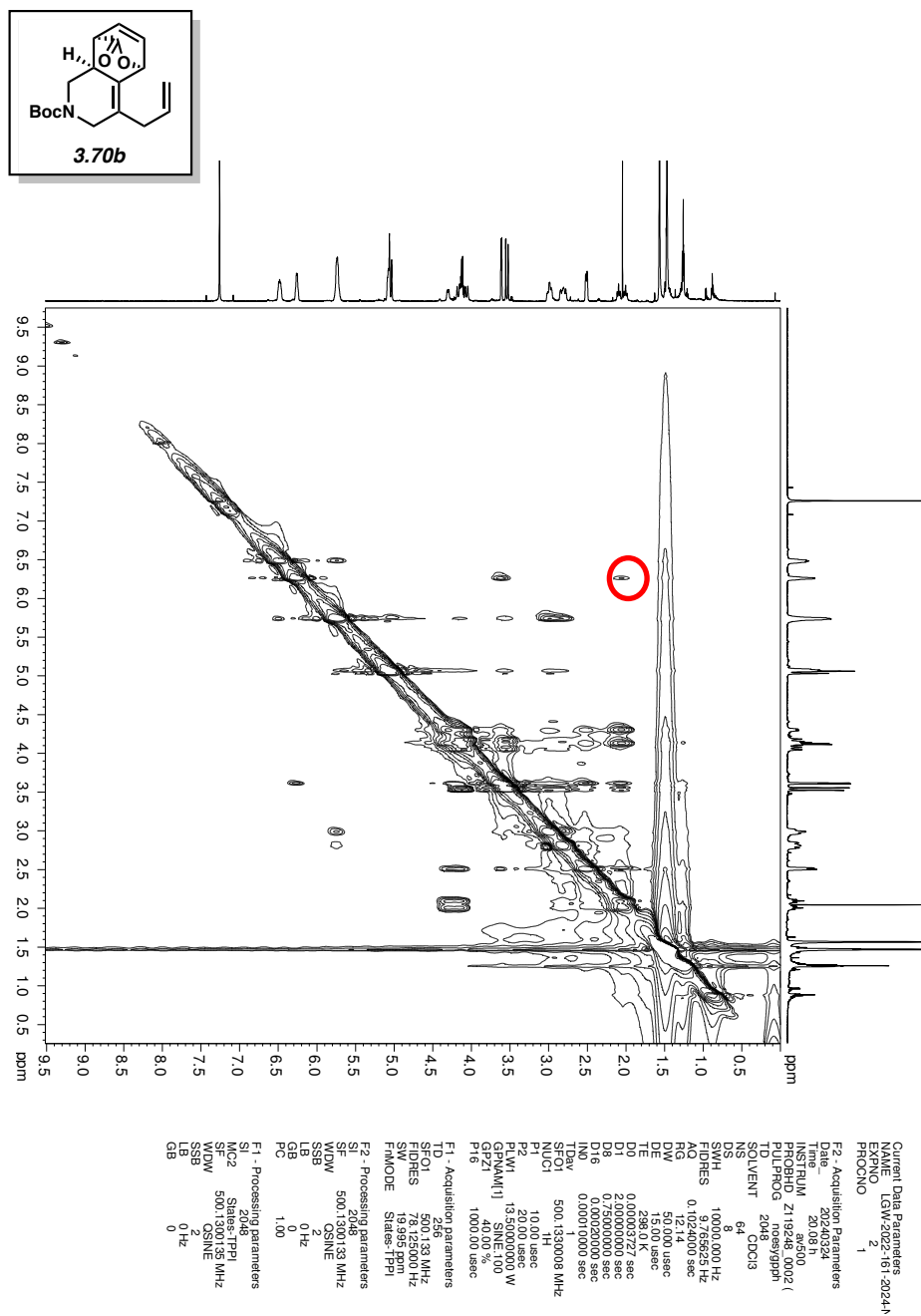


Figure 3.60. NOESY (500 MHz, CDCl₃) of compound **3.70b**.

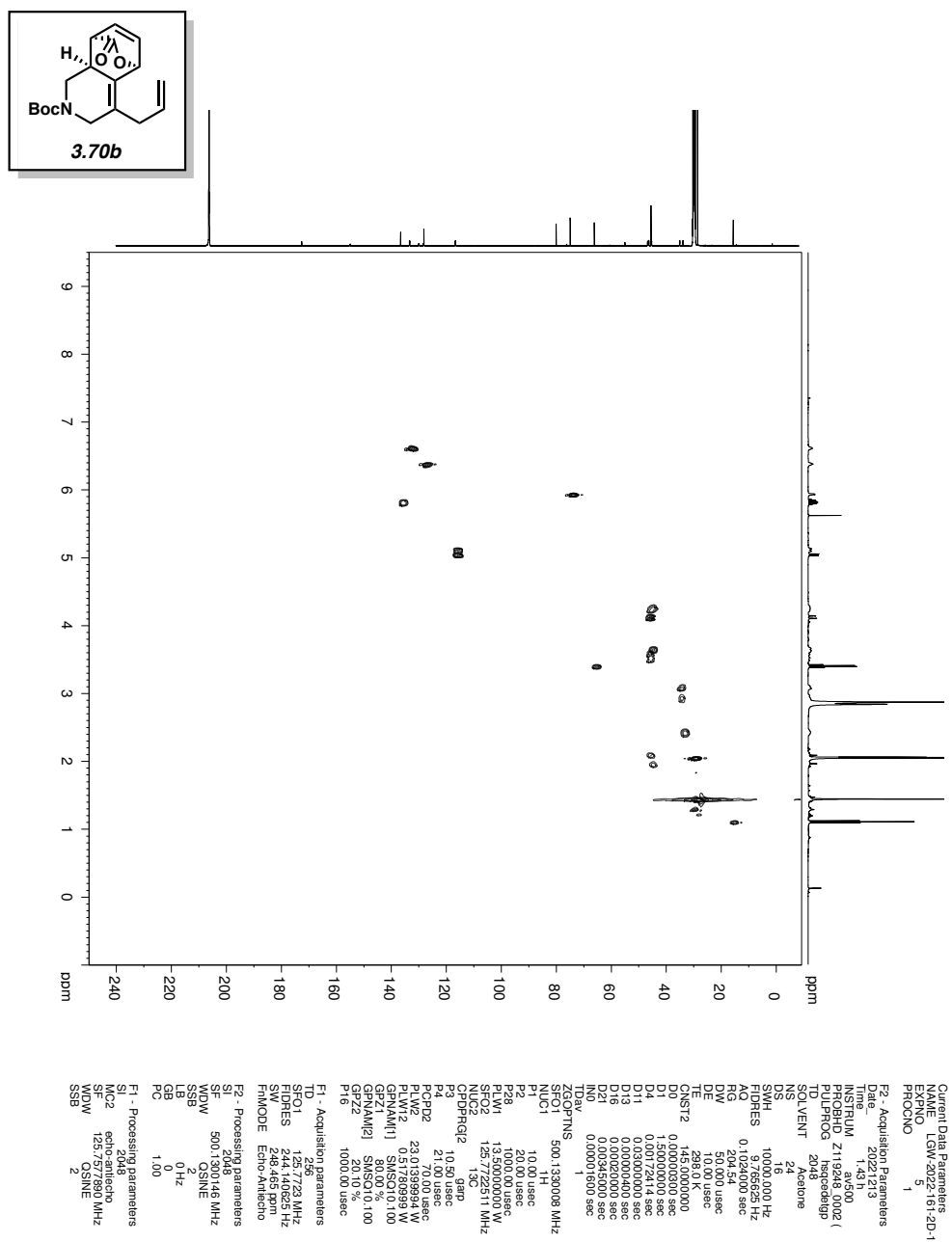


Figure 3.61. HSQC (500 MHz, $(\text{CD}_3)_2\text{CO}$) of compound **3.70b**.

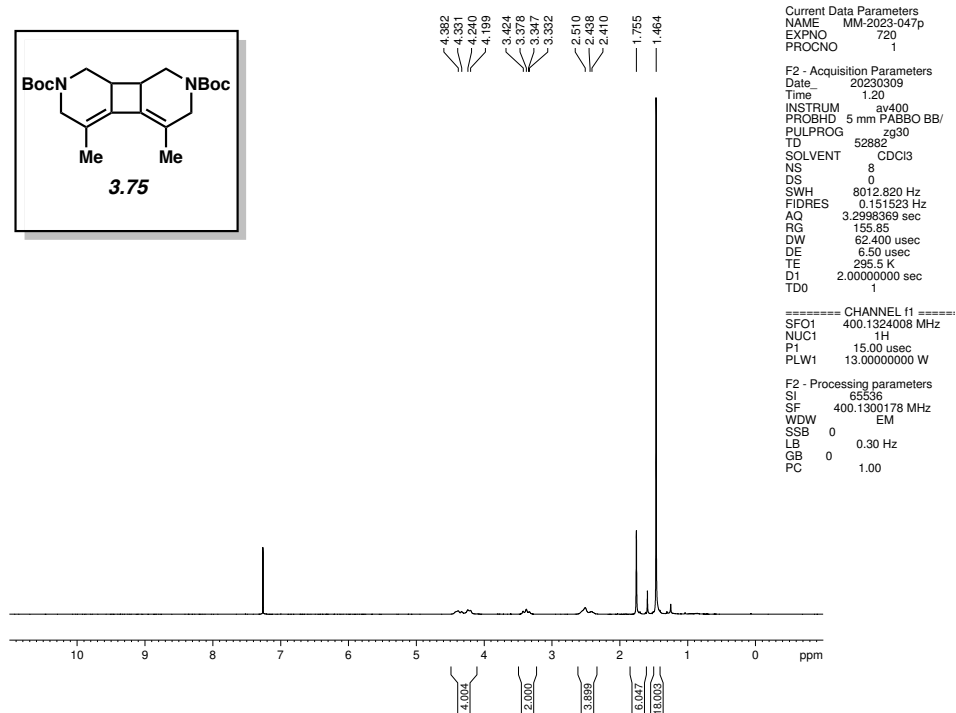


Figure 3.65. ¹H NMR (500 MHz, CDCl₃) of compound **3.75**.

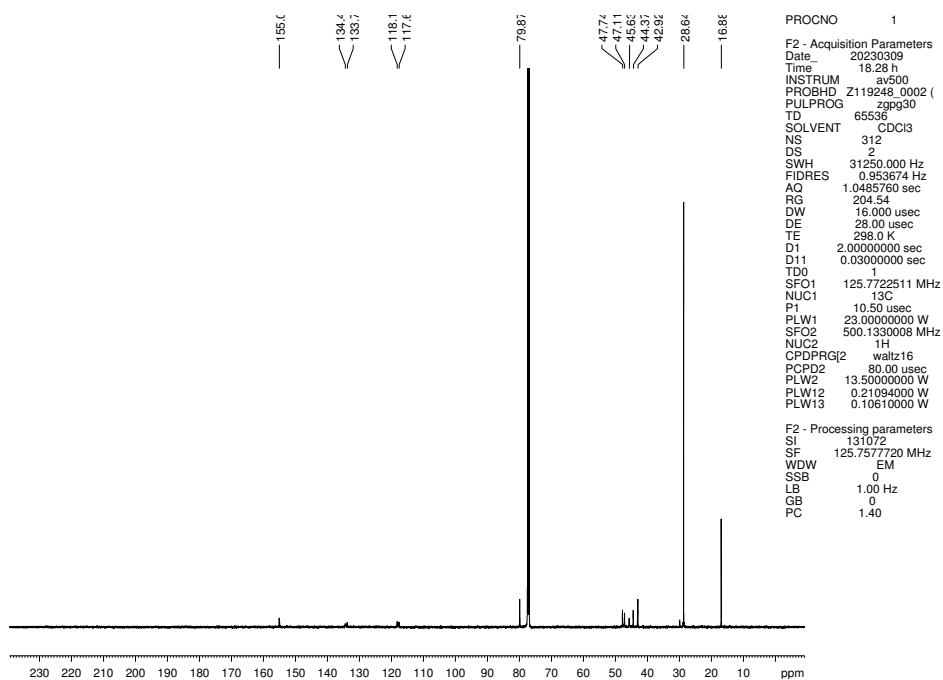


Figure 3.66. ¹³C NMR (125 MHz, CDCl₃) of compound **3.75**.

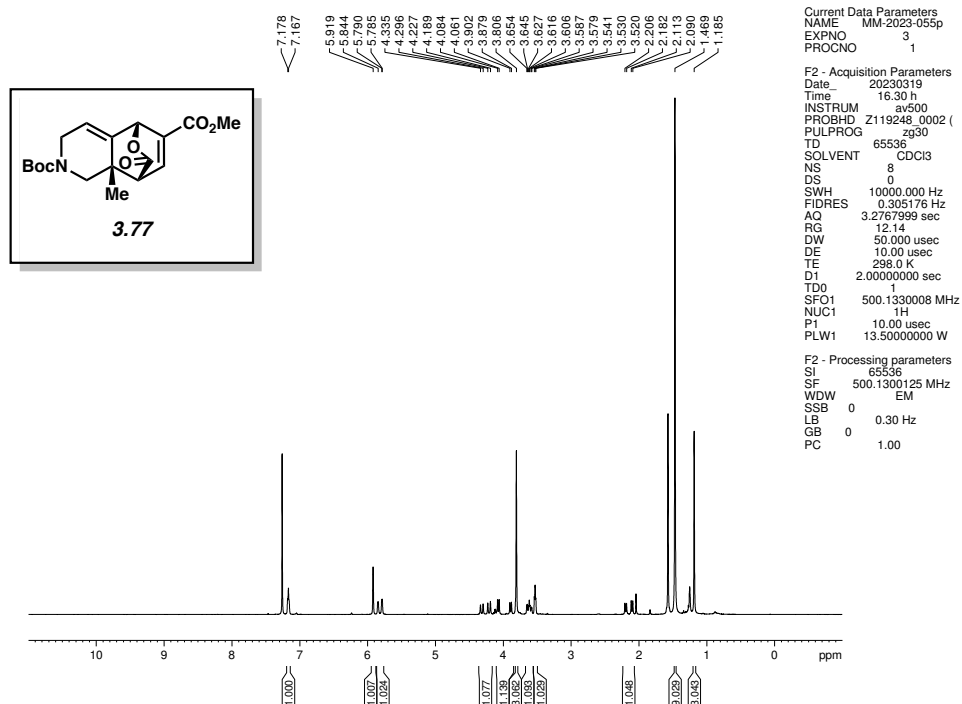


Figure 3.67. ¹H NMR (500 MHz, CDCl₃) of compound **3.77**.

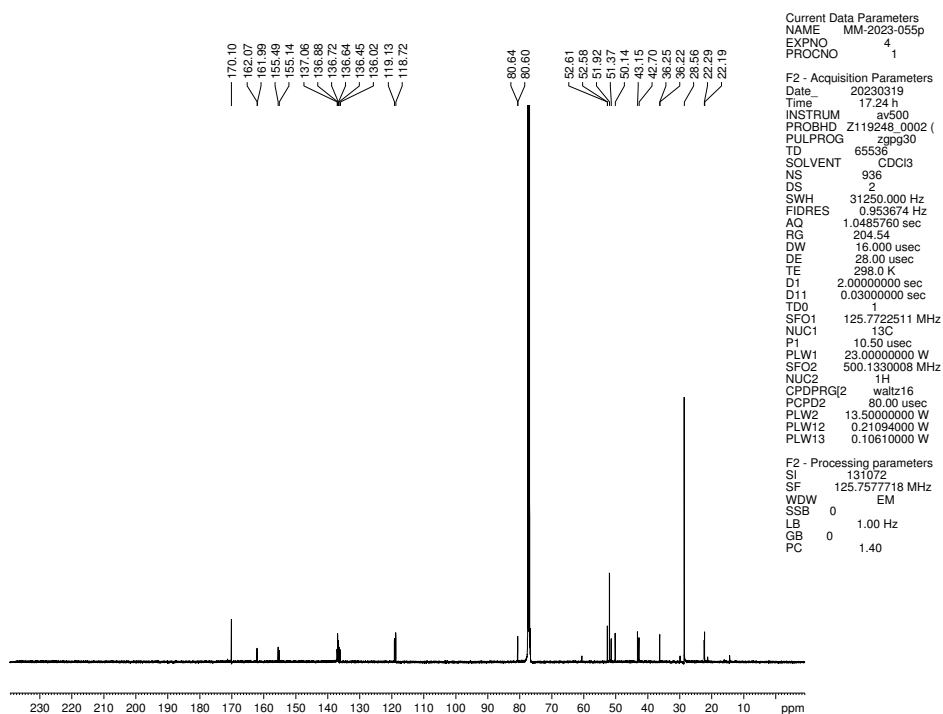


Figure 3.68. ¹³C NMR (125 MHz, CDCl₃) of compound **3.77**.

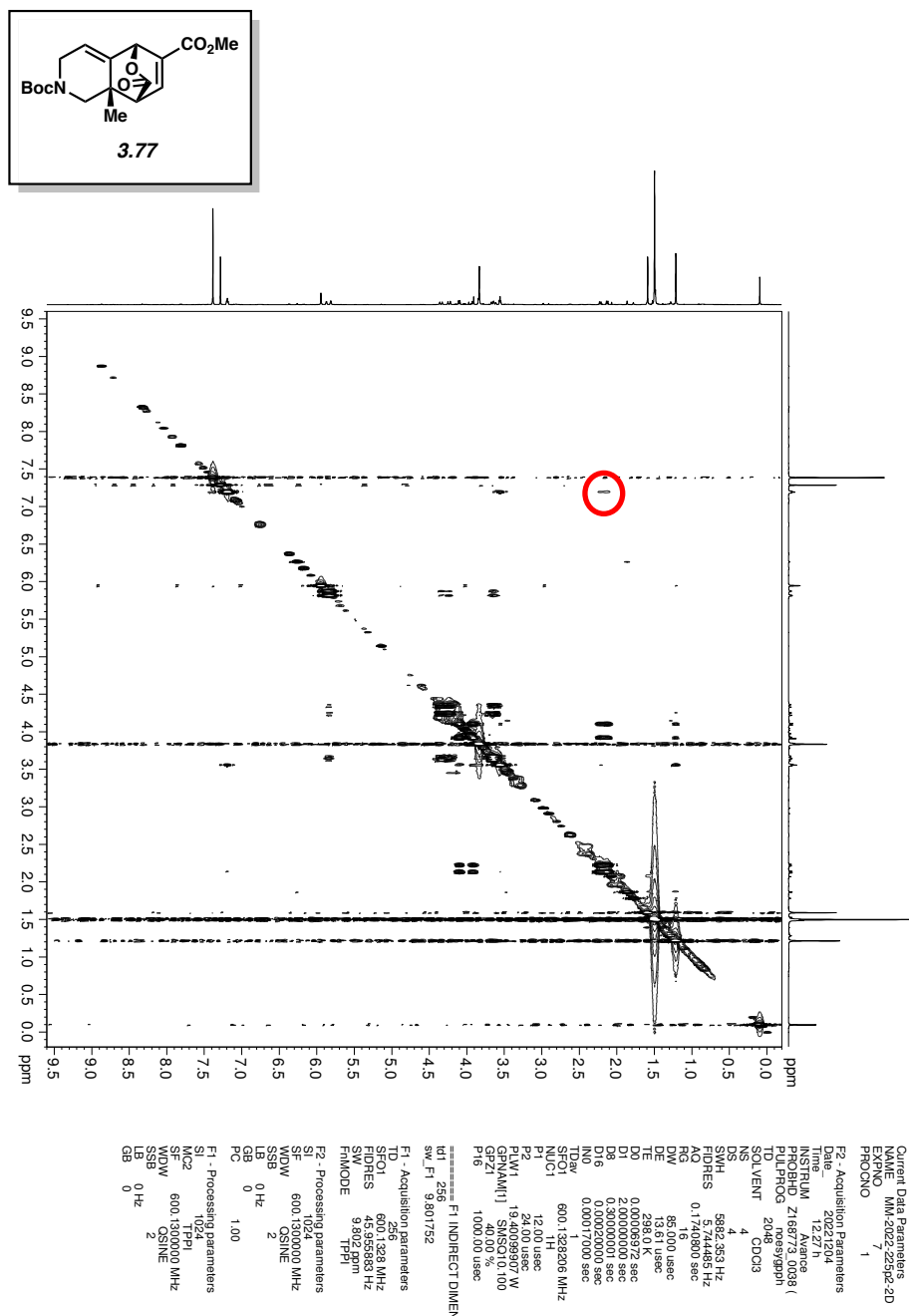


Figure 3.69. NOESY (600 MHz, CDCl₃) of compound **3.77**.

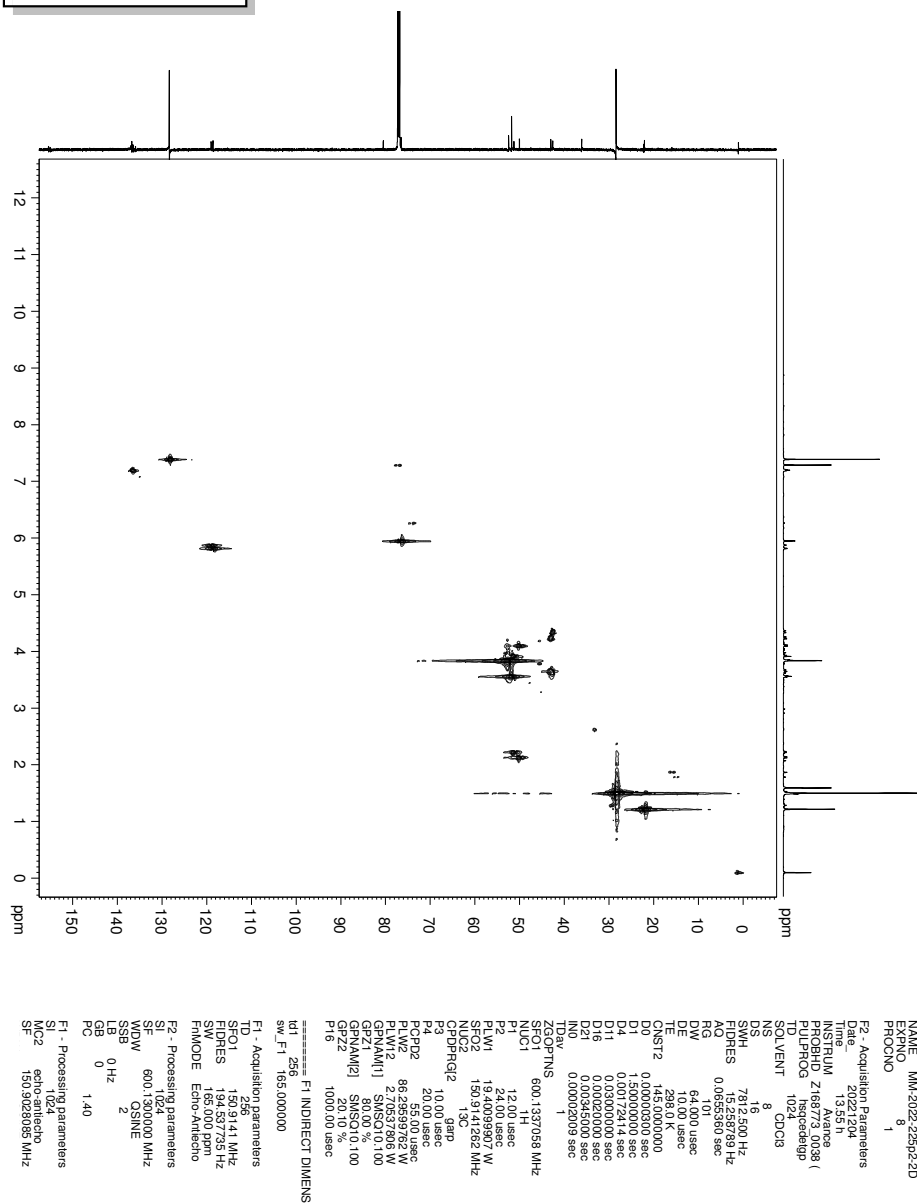
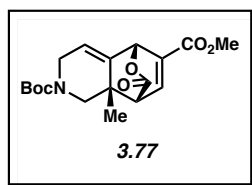


Figure 3.70. HSQC (600 MHz, CDCl_3) of compound 3.77.

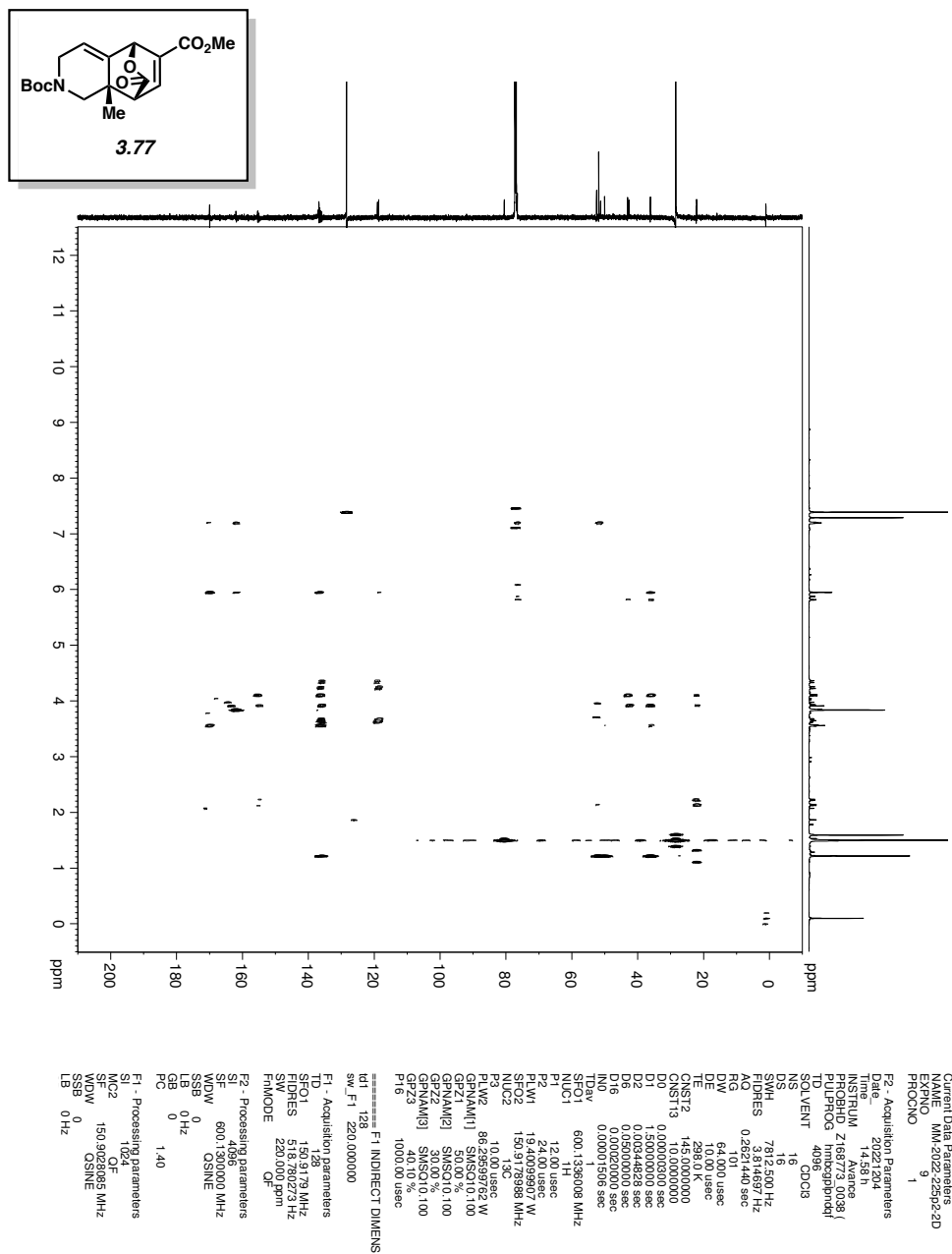


Figure 3.71. HMBC (600 MHz, CDCl₃) of compound **3.77**.

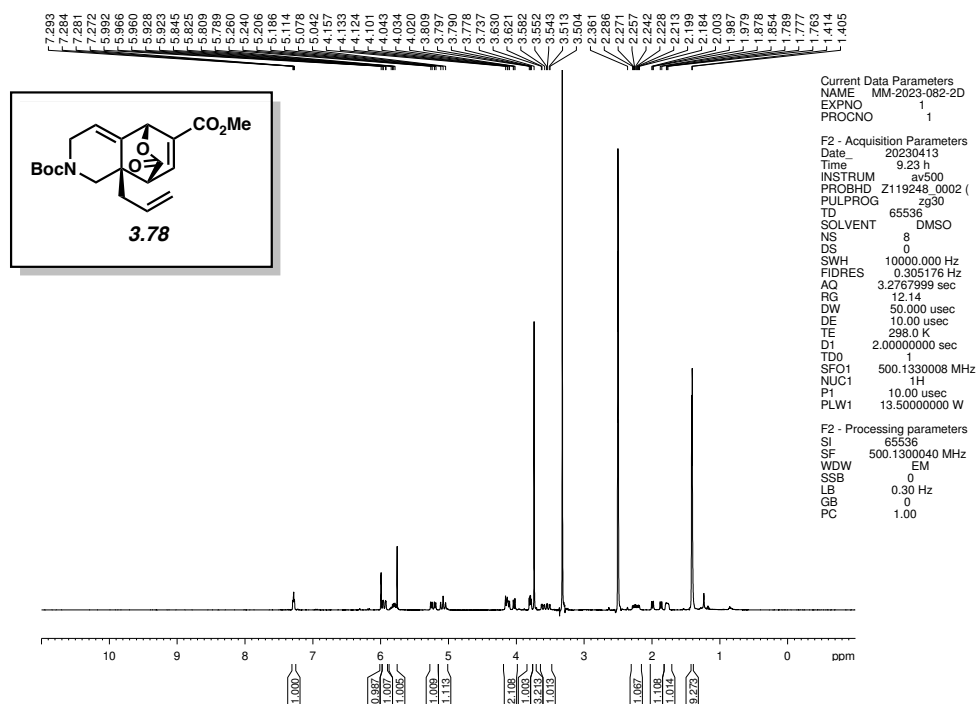


Figure 3.72. ¹H NMR (500 MHz, DMSO-d₆) of compound 3.78.

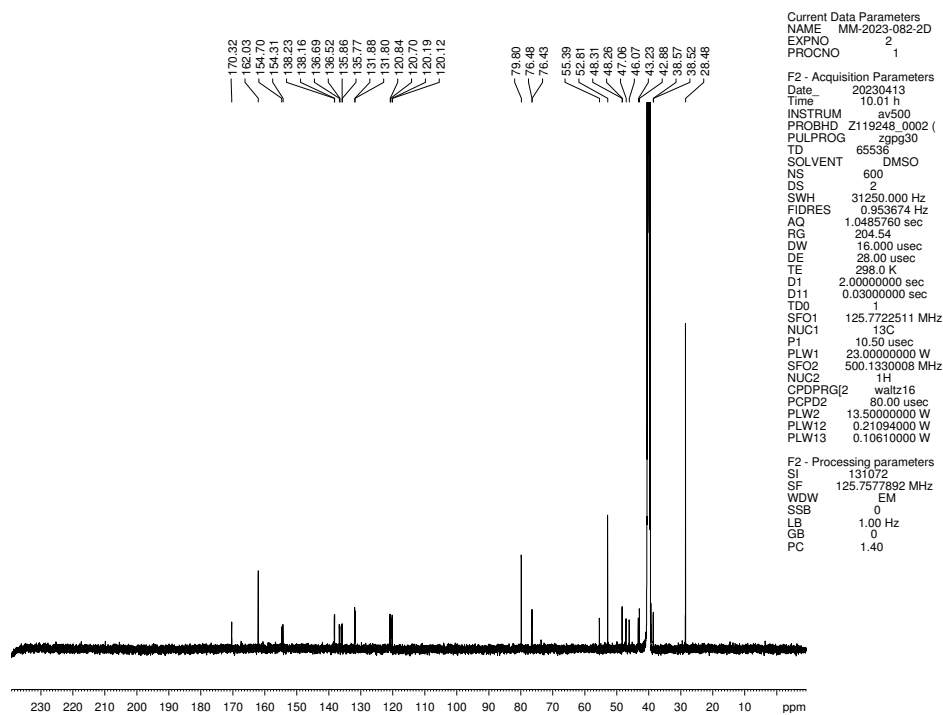


Figure 3.73. ¹³C NMR (125 MHz, DMSO-d₆) of compound 3.78.

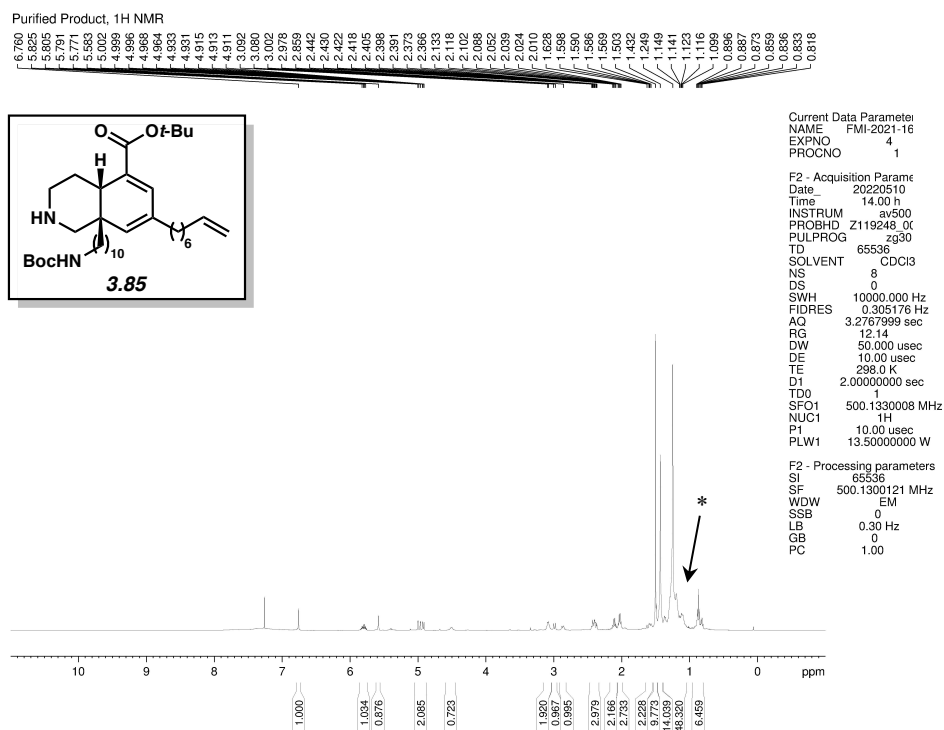


Figure 3.74. ^1H NMR (500 MHz, CDCl_3) of compound **3.85**.
*Residual grease

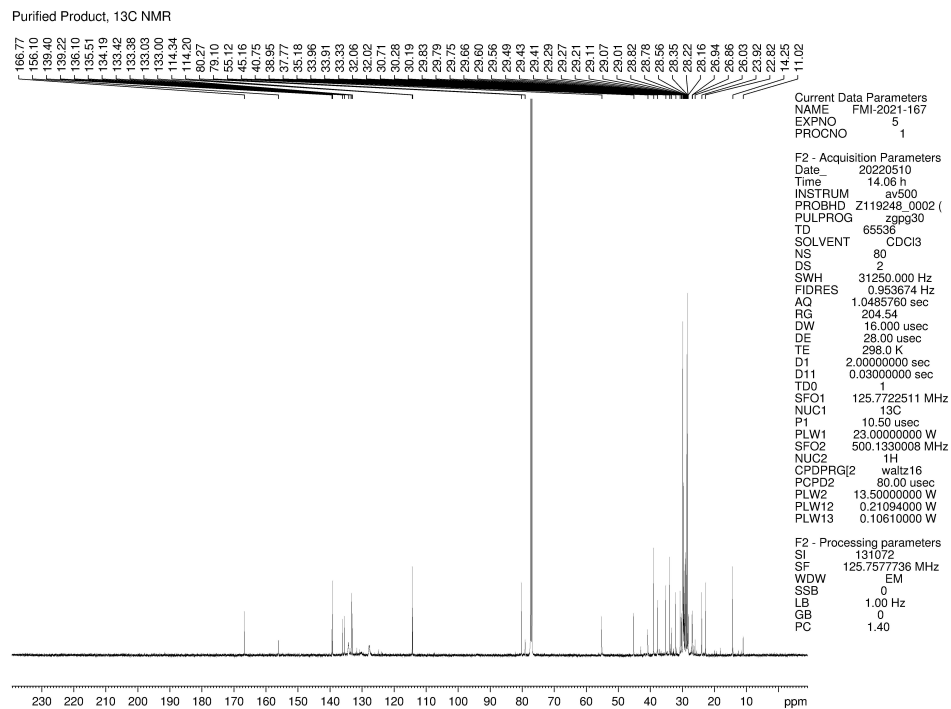


Figure 3.75. ^{13}C NMR (125 MHz, CDCl_3) of compound **3.85**.

Purified Product, ¹H NMR

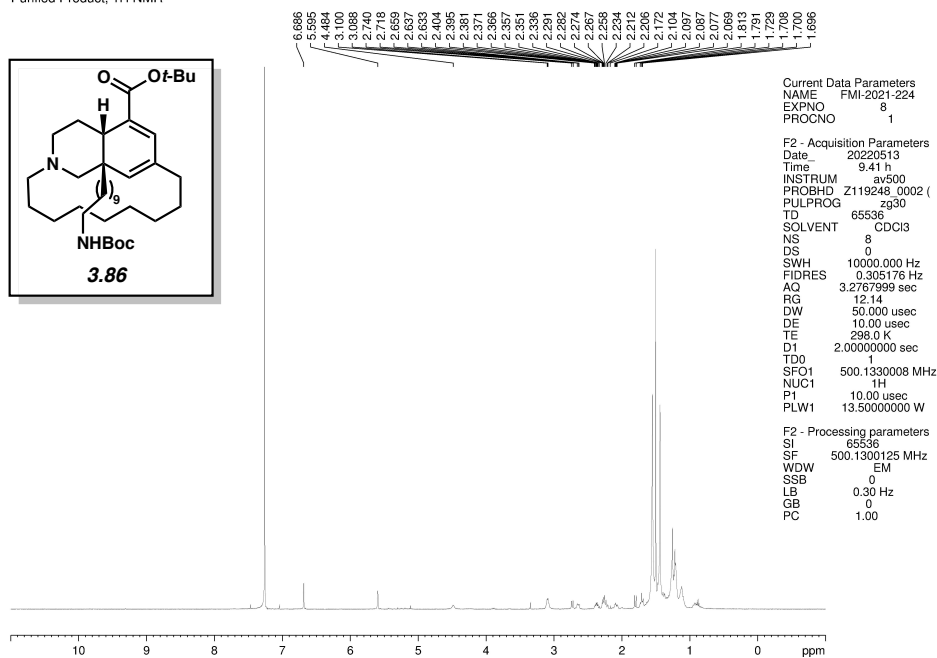


Figure 3.76. ¹H NMR (500 MHz, CDCl₃) of compound **3.86**.

Purified Product, ¹³C NMR

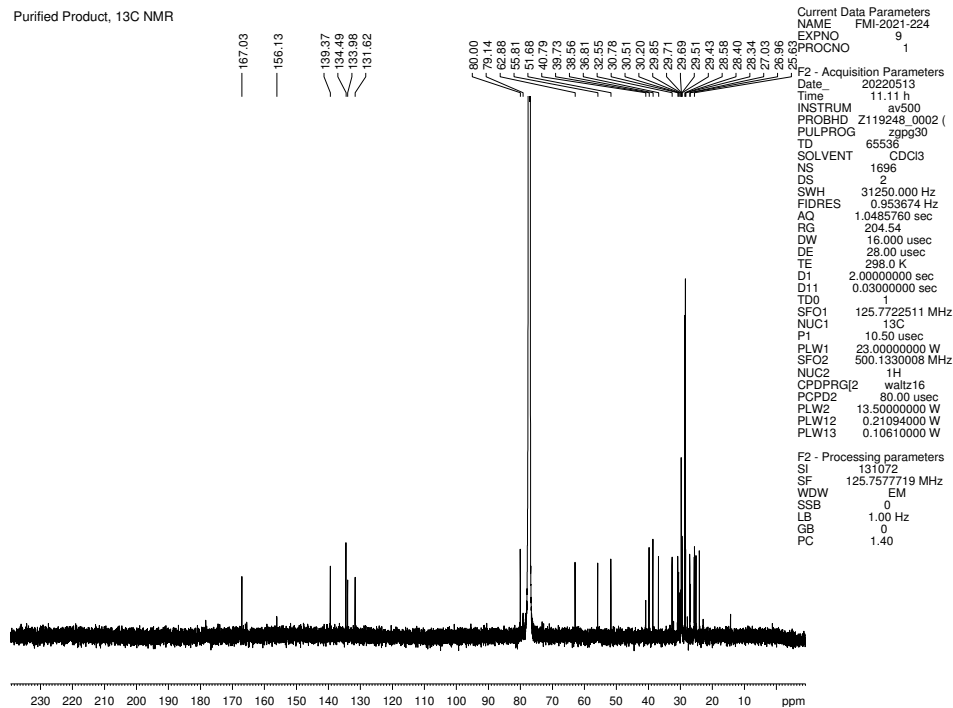


Figure 3.77. ¹³C NMR (125 MHz, CDCl₃) of compound **3.86**.

3.8 Computational Section:

Total Synthesis of Lissodendoric Acid A

Francesca M. Ippoliti,[†] Laura G. Wonilowicz,[†] Nathan J. Adamson, Evan R. Darzi, Joyann S. Donaldson, Daniel J. Nasrallah, Milauni M. Mehta, Andrew V. Kelleghan, K. N. Houk,
and Neil K. Garg.

Angew. Chem., Int. Ed. **2024**, doi: 10.1002/anie.202406676.

3.8.1 Computational Methods

Conformational searches were performed with Spartan '20 V1.1.4⁸¹ using Molecular Mechanics. Conformers were then optimized in Gaussian 16 A.03⁸² at the ω B97XD/6-311+G(d,p)/SMD(MeCN) level of theory.⁸³ All geometries were verified as stationary points on the potential energy surface and characterized as minima by frequency calculations. GoodVibes⁸⁴ (v. 3.2) with quasi-harmonic entropy⁸⁵ and enthalpy⁸⁶ treatment (frequency cut-off value: 100 cm⁻¹) was used to obtain corrected Gibbs free energies and enthalpies at 298.15 K and 1 atm. The frontier molecular orbitals in **3.9** were obtained at the HF/6-31G(d) level of theory.⁴³ The HOMO of allene **3.9** and LUMO of pyrone **3.62** in Figure 16B were obtained from the transition state geometry at the HF/6-31G(d) level of theory. Optimized structures are presented using vrchem.net/vr/export.html or CYLview.⁸⁷

3.8.2 Transition State Analyses

The transition states leading to distal/endo, proximal/endo, distal/exo, and proximal/exo cycloadducts from the reaction of allene **3.9** and pyrones **3.24**, **3.62**, **3.71**, and **3.76** were calculated. The $\Delta G^\ddagger$ values for the transition states leading to each of the products are shown in Figure 3.78. In nearly all cases, endo pathways were found to be most favorable. One exception lies in the calculations for pyrone **3.76**, where the exo pathway leading to distal product **3.111** was found to be energetically more favorable compared to the corresponding endo pathway that would lead to distal product **3.81**. However, neither **3.111** or **3.81** were observed experimentally, and the calculations correctly predict cycloadduct **3.82** (proximal, endo) as the major product.

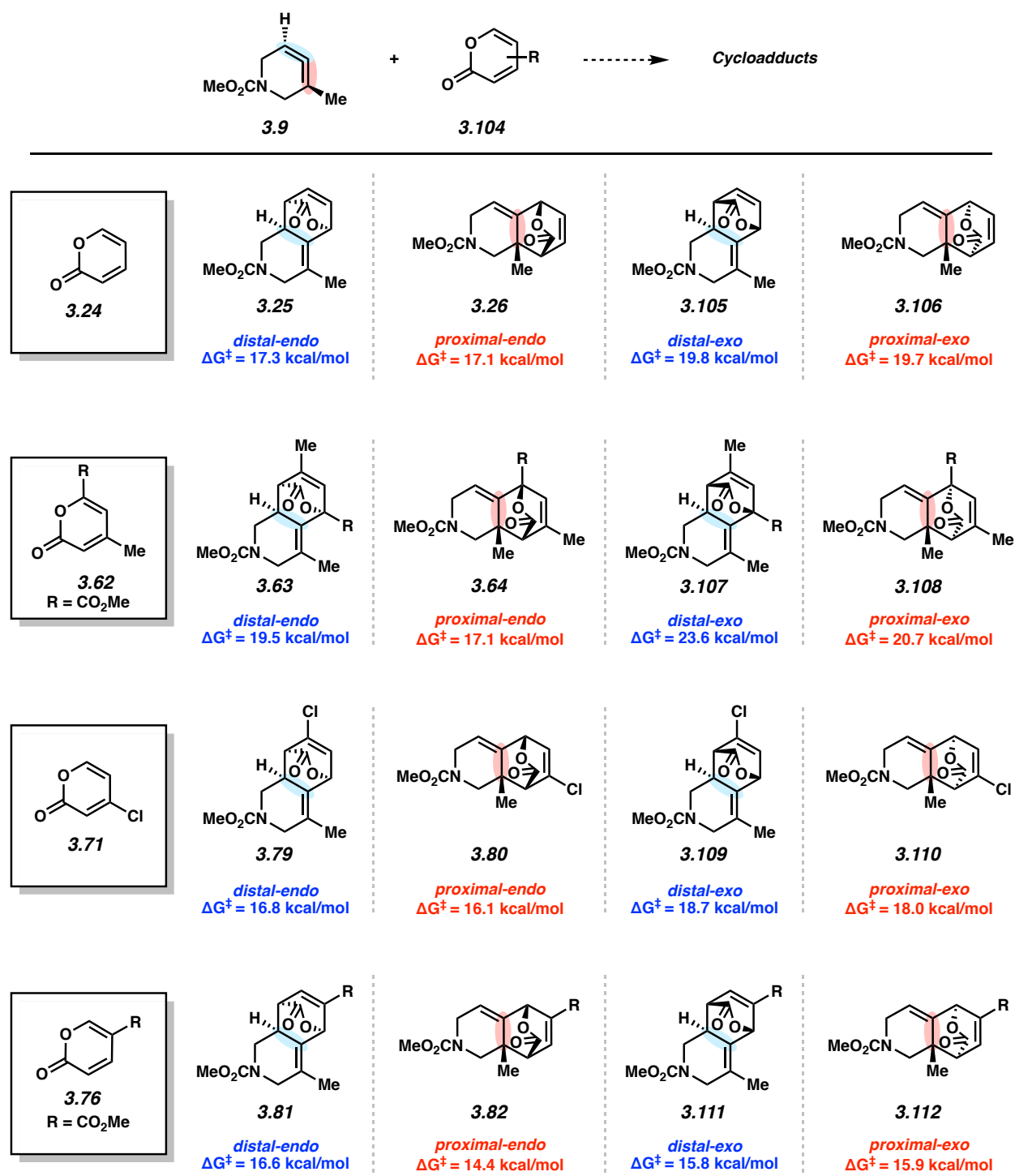


Figure 3.78. Transition state energies for Diels–Alder cycloadditions of allene **3.9** and pyrones **3.104** leading to the corresponding cycloadducts **3.25–3.26**, **3.63–3.64**, **3.79–3.82**, and **3.105–3.112**. Geometry optimizations were performed at the ω B97XD/6-311+G(d,p)/SMD(MeCN) level of theory.

3.8.3 Ground State Energies of Computational Models of 3.83 and 3.113

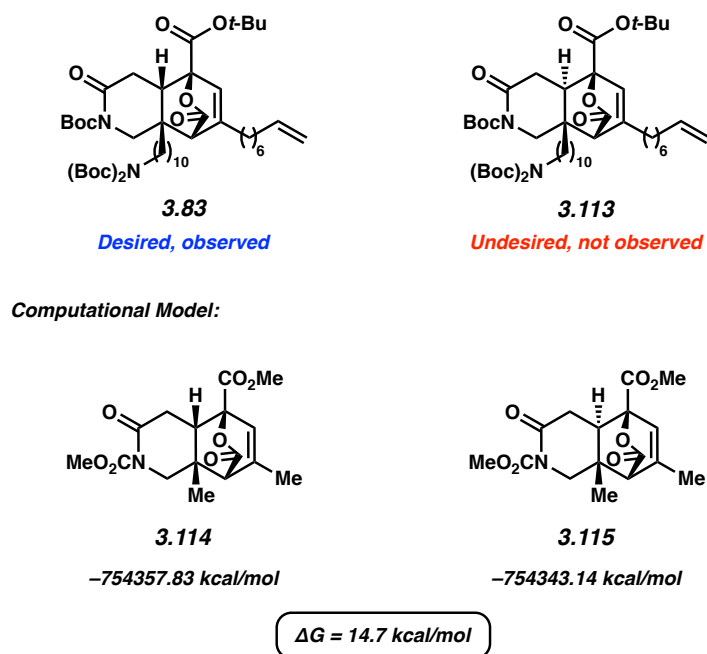


Figure 3.79. Comparison of ground state energies of computational models for azadecalin **3.83** (observed) and **3.113** (not observed). Geometry optimizations were performed at the ω B97XD/6-311+G(d,p) level of theory.

3.8.4 Cartesian Coordinates of Optimized Geometries

Azacyclic allene **3.9**

C	-0.7009800	0.5063970	1.1404000
C	-1.6369260	1.0452710	0.0606560
C	-2.4792970	0.0763510	-0.2719610
C	-2.3480190	-1.2359110	-0.1883860
C	-0.9103140	-1.7164850	-0.0431750
N	-0.0518780	-0.6375220	0.4611060
C	1.2193550	-0.5621080	-0.0311810
O	1.7326920	-1.4051220	-0.7432680
O	1.8674860	0.5362620	0.3848870
C	3.2168030	0.6794120	-0.0677640
C	-1.3132180	2.3000870	-0.6747550
H	-1.2383260	0.1473270	2.0181750
H	0.0591270	1.2182510	1.4468780
H	-0.9386430	-2.5340490	0.6862820

H	-0.4725710	-2.1067690	-0.9618090
H	-3.1465140	-1.9489250	-0.0169010
H	3.2562420	0.7339470	-1.1569160
H	3.8333600	-0.1493160	0.2842350
H	-1.4593740	3.1767560	-0.0346590
H	-0.2563680	2.2910750	-0.9639670
H	-1.9275220	2.4124460	-1.5695920
H	3.5678820	1.6147070	0.3645800

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -516.574661 Hartrees

Thermal correction to Gibbs free energy = 0.144035 Hartrees

Imaginary frequencies = 0

Pyrone **3.24**

O	2.2494570	-0.0445440	0.0000130
C	1.0428710	0.0420420	0.0000230
O	0.3285620	-1.1415210	-0.0000780
C	0.2558480	1.2511410	0.0000850
C	-1.0173510	-1.1758080	-0.0000920
C	-1.7690190	-0.0628440	-0.0000140
C	-1.0965600	1.1981590	0.0000700
H	0.8013140	2.1856660	0.0001490
H	-2.8471890	-0.1382010	-0.0000210
H	-1.3963880	-2.1893530	-0.0001630
H	-1.6766220	2.1142800	0.0001270

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -343.356874 Hartrees

Thermal correction to Gibbs free energy = 0.052038 Hartrees

Imaginary frequencies = 0

Pyrone **3.62**

O	-1.4959380	2.7375250	-0.0001140
C	-1.3426890	1.5391200	-0.0000370
O	-0.0408840	1.0752300	0.0000280
C	-2.3766500	0.5331640	0.0000230
C	0.2441470	-0.2399000	-0.0000220
C	1.7018000	-0.5737290	-0.0000360
O	2.4681400	0.5016030	0.0001720
C	3.8877980	0.2731280	0.0000750
O	2.1016310	-1.7127640	-0.0002110
C	-0.7058790	-1.1881270	-0.0000430
C	-2.0887770	-0.7916700	0.0000110

C	-3.1435710	-1.8496500	0.0001020
H	-3.3968160	0.8962190	0.0000760
H	4.1811460	-0.2787560	-0.8939500
H	4.1813050	-0.2783040	0.8943320
H	4.3389900	1.2624610	-0.0002100
H	-0.4218740	-2.2316740	-0.0000900
H	-4.1448470	-1.4182690	0.0001600
H	-3.0292200	-2.4891980	0.8803910
H	-3.0293460	-2.4892580	-0.8801570

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -610.548842 Hartrees

Thermal correction to Gibbs free energy = 0.113179 Hartrees

Imaginary frequencies = 0

Pyrene 3.71

O	-2.4706510	-1.3797650	0.0000330
C	-1.5376710	-0.6145150	0.0000020
O	-1.8285750	0.7385640	0.0000330
C	-0.1378920	-0.9637530	-0.0000520
C	-0.8719060	1.6798920	0.0000220
C	0.4400710	1.3931970	0.0000080
C	0.7970450	0.0116590	-0.0000880
H	0.1094190	-2.0161570	-0.0000400
H	1.1766840	2.1833490	0.0000610
H	-1.2801630	2.6816180	0.0000860
Cl	2.4852930	-0.3975340	0.0000010

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -802.962896 Hartrees

Thermal correction to Gibbs free energy = 0.040230 Hartrees

Imaginary frequencies = 0

Pyrene 3.76

O	-3.7909300	-0.4378990	0.0000080
C	-2.6216780	-0.1495550	-0.0000230
O	-1.7163480	-1.2100720	-0.0000660
C	-2.0364560	1.1690650	0.0000200
C	-0.3949860	-1.0321540	-0.0000160
C	0.1721910	0.1937000	0.0000460
C	-0.6970830	1.3327970	0.0000450
H	-2.7227790	2.0053500	0.0000350
H	0.1469190	-1.9684530	-0.0000680
H	-0.2609580	2.3250810	0.0000710

C	1.6415180	0.3829140	0.0000440
O	2.1699390	1.4701350	-0.0001080
O	2.3061450	-0.7687480	0.0001220
C	3.7392930	-0.6861650	-0.0000310
H	4.0905850	-0.1682810	0.8935620
H	4.0885830	-1.7162050	0.0000180
H	4.0904050	-0.1684250	-0.8937780

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -571.231679 Hartrees

Thermal correction to Gibbs free energy = 0.087629 Hartrees

Imaginary frequencies = 0

Cis-azadecalin **3.114**

O	-2.3511540	-2.5980690	-1.9656600
C	-1.9631320	-1.8430800	-1.1240790
O	-2.5591170	-0.6461120	-0.9228040
C	-0.7828560	-2.0503130	-0.1909430
C	0.2196730	-0.8879730	-0.4892680
C	0.7294620	-0.9874880	-1.9303010
C	1.4027400	-0.9821870	0.4820270
N	2.2723680	0.1913460	0.3496610
C	1.6709650	1.4533330	0.5078220
C	-1.9874630	0.1056410	0.1734950
C	-2.8157380	1.3712670	0.3528530
O	-3.0847150	1.9520150	-0.8074370
C	-3.8356120	3.1693380	-0.7421950
O	-3.1224360	1.8111430	1.4295080
C	-1.9591110	-0.7576670	1.4064920
C	-1.3257840	-1.9119030	1.2184500
C	-1.1331040	-3.0071480	2.2134260
C	3.6164550	-0.0571790	0.0376670
O	4.3250870	1.0456960	-0.1223200
C	5.7038980	0.8470020	-0.4432280
O	4.0549890	-1.1764120	-0.0760870
H	-0.3339080	-3.0228270	-0.3906910
H	-0.0889290	-0.9025350	-2.6490470
H	1.4420740	-0.1865350	-2.1425030
H	1.2333870	-1.9430260	-2.0981910
H	2.0075660	-1.8605510	0.2667760
H	1.0555370	-1.0545770	1.5156940
H	-3.2905300	3.9211820	-0.1696460
H	-3.9620080	3.4873670	-1.7739350
H	-4.8042160	2.9900230	-0.2740990
H	-2.4226140	-0.4262960	2.3259520

H	-1.5990760	-3.9317200	1.8590010
H	-0.0676560	-3.2195630	2.3522740
H	-1.5667000	-2.7466920	3.1801300
H	6.1200310	1.8476330	-0.5310650
H	5.8038640	0.3042470	-1.3841430
H	6.2048170	0.2902980	0.3497980
C	-0.5355500	0.4543670	-0.2570770
H	-0.6165820	0.9873830	-1.2076080
O	2.2474230	2.5067170	0.4625950
C	0.1759660	1.3548630	0.7572980
H	-0.2099200	2.3734610	0.7355270
H	0.0228230	0.9682370	1.7711570

Electronic energy (ω B97XD/6-311+G(d,p)) = -1202.461553 Hartrees

Thermal correction to Gibbs free energy = 0.293876 Hartrees

Imaginary frequencies = 0

Trans-azadecalin **3.115**

O	2.8269190	-2.2120510	1.9268500
C	2.2337030	-1.6002230	1.0905810
O	2.5918850	-0.3343440	0.7568400
C	1.0075910	-2.0608920	0.3114970
C	-0.0576790	-0.9631060	0.6355520
C	-0.1233230	-0.8049000	2.1720780
C	-1.4611750	-1.2435330	0.1264710
N	-2.2586910	0.0112450	0.1587890
C	-1.7708690	1.2565770	0.6430180
C	1.9065210	0.1684010	-0.4064660
C	2.4949120	1.5094980	-0.8007560
O	2.9376810	2.1956100	0.2415000
C	3.4480030	3.5035300	-0.0402660
O	2.4726750	1.9129330	-1.9344700
C	1.9761490	-0.8738670	-1.5031380
C	1.4550180	-2.0440560	-1.1411400
C	1.3301970	-3.2715540	-1.9813030
C	-3.6059650	-0.1918320	-0.1689530
O	-4.2377630	0.9283110	-0.4809030
C	-5.6246250	0.7873370	-0.7917410
O	-4.0922960	-1.2944800	-0.2271930
H	0.7061900	-3.0470130	0.6631120
H	0.7580980	-0.3140370	2.5865290
H	-1.0001540	-0.2398700	2.4926150
H	-0.1975010	-1.7958140	2.6270590
H	-1.9732360	-1.9865680	0.7408680

H	-1.4383980	-1.6126460	-0.9033820
H	2.6675320	4.1295240	-0.4754910
H	3.7703200	3.9010380	0.9187150
H	4.2882920	3.4403680	-0.7325340
H	2.3525450	-0.6183440	-2.4849530
H	1.7074060	-3.1014420	-2.9908290
H	1.8872370	-4.1016390	-1.5359280
H	0.2834480	-3.5861260	-2.0483930
H	-5.7583130	0.1591840	-1.6737480
H	-5.9782360	1.7977750	-0.9821720
H	-6.1611950	0.3477710	0.0500450
C	0.3797950	0.2997680	-0.1295240
H	-0.0563060	0.2423100	-1.1297570
O	-2.4922520	2.0944800	1.1122230
C	-0.2654930	1.5024710	0.5163770
H	-0.1627370	2.4042270	-0.0937670
H	0.1244970	1.7372010	1.5079760

Electronic energy (ω B97XD/6-311+G(d,p)) = -1202.438260 Hartrees

Thermal correction to Gibbs free energy = 0.294491 Hartrees

Imaginary frequencies = 0

TS 3.1

O	-2.8529440	-2.7105990	-0.8718490
C	-2.7859070	-1.6190710	-0.3453420
O	-3.0029100	-0.5205950	-1.1440730
C	-2.5562620	-1.3412600	1.0510130
C	-0.1739410	-0.5356170	-0.2929060
C	0.8304670	-0.5153270	0.8346840
N	1.8863820	0.4074870	0.3623720
C	1.4854750	1.7600020	-0.0208350
C	-0.0074780	1.8676610	-0.2939670
C	-0.6111760	3.2256510	-0.1406710
C	-0.6024600	0.7087490	-0.5726570
C	-2.8312370	0.7308880	-0.6516080
C	-2.9541780	0.9874510	0.6971010
C	-2.7987360	-0.0948440	1.5696280
C	3.1248430	-0.0131820	-0.0126210
O	3.3418520	-1.3045130	0.2832120
C	4.6332580	-1.8175000	-0.0547570
O	3.9641820	0.6980480	-0.5362480
H	-2.3557980	-2.1977780	1.6816620
H	-0.2093820	-1.3702630	-0.9840660
H	1.2727840	-1.4837320	1.0428380

H	0.3936460	-0.1122140	1.7518020
H	1.6921980	2.4546920	0.8028160
H	2.0850670	2.0825070	-0.8736000
H	-0.6304960	3.5161480	0.9151100
H	-1.6282250	3.2660120	-0.5300140
H	-0.0062800	3.9708300	-0.6676940
H	-3.0327020	2.0084280	1.0432300
H	4.8066910	-1.7544760	-1.1303040
H	5.4172180	-1.2768860	0.4782410
H	4.6204910	-2.8597590	0.2592170
H	-2.9660920	1.4818210	-1.4186030
H	-2.7812470	0.0619130	2.6420610

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -859.927813 Hartrees

Thermal correction to Gibbs free energy = 0.218594 Hartrees

Imaginary frequencies = 1, -344.00 cm^{-1}

TS 3.2

O	-3.5397990	-2.0977090	-0.2194820
C	-3.2010550	-0.9553850	0.0184120
O	-3.1446820	-0.0828830	-1.0451120
C	-2.9085730	-0.3914960	1.3085660
C	-0.2623260	-0.5234800	-0.2768170
C	-0.4020140	-1.7891610	-1.0535310
C	0.6832820	-0.4510350	0.9087270
N	1.8558580	0.2814610	0.3980920
C	1.6483460	1.6073980	-0.1949410
C	0.1972690	1.8144550	-0.5522160
C	-0.5485230	0.7248390	-0.6977830
C	-2.6561890	1.1736670	-0.8768870
C	-2.7234980	1.7967760	0.3562980
C	-2.8224150	0.9673270	1.4786030
C	3.0546600	-0.3567870	0.3392280
O	4.0057190	0.4195980	-0.2061190
C	5.3081720	-0.1620240	-0.3103280
O	3.2699080	-1.4851220	0.7448720
H	-2.9252880	-1.0756390	2.1471210
H	-1.0057870	-1.6508650	-1.9509260
H	0.5980040	-2.1260650	-1.3550200
H	-0.8421940	-2.5895340	-0.4514500
H	1.0176970	-1.4289810	1.2463510
H	0.2422120	0.0948220	1.7456520
H	2.3065860	1.7274860	-1.0559760
H	1.9122500	2.3872670	0.5292790

H	-0.1834870	2.8298870	-0.5794440
H	-2.5615080	2.8626030	0.4304430
H	5.7000010	-0.4135470	0.6766500
H	5.9296020	0.6025550	-0.7733710
H	5.2857030	-1.0546100	-0.9376950
H	-2.7632340	1.3864410	2.4768740
H	-2.6335460	1.7163110	-1.8123960

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -859.927726 Hartrees

Thermal correction to Gibbs free energy = 0.218111 Hartrees

Imaginary frequencies = 1, -377.61 cm^{-1}

TS 3.3

O	1.3669800	2.4173480	-2.5268620
C	1.5099560	1.9449620	-1.4187420
O	2.0560330	0.6853360	-1.3395250
C	1.2150970	2.5767380	-0.1596900
C	-0.6581190	0.5121070	-0.5357590
C	-1.8284850	1.0537090	0.2494160
N	-2.5812030	-0.1509650	0.6480750
C	-1.8575080	-1.1372040	1.4381110
C	-0.3473030	-1.0335320	1.2762660
C	0.4435780	-1.6113010	2.4032510
C	0.0576710	-0.3830870	0.1791940
C	2.1567560	0.0657850	-0.1348590
C	2.7374690	-1.3164210	-0.2409180
O	2.6231410	-1.8186350	-1.4557800
C	3.1343750	-3.1483060	-1.6447880
O	3.2432690	-1.8841690	0.6971890
C	2.2766160	0.8117560	1.0269110
C	1.7419430	2.1069470	1.0239340
C	1.6394740	2.8866810	2.3007050
C	-3.7350050	-0.5411760	0.0367270
O	-4.2260310	0.4039280	-0.7780480
C	-5.4579860	0.0896340	-1.4338800
O	-4.2838850	-1.6119350	0.2230100
H	0.7247070	3.5408260	-0.2161650
H	-0.6556230	0.5702190	-1.6184110
H	-2.4724030	1.7074060	-0.3291070
H	-1.5014240	1.5747100	1.1521130
H	-2.0553160	-0.9741660	2.5048630
H	-2.2206890	-2.1358350	1.1903290
H	0.3268560	-0.9810010	3.2915110
H	1.5029470	-1.6943530	2.1742730

H	0.0580370	-2.6029260	2.6623250
H	2.6074400	-3.8507260	-0.9973770
H	4.2045120	-3.1762430	-1.4350180
H	2.9477440	-3.3835810	-2.6900760
H	2.6329470	0.3391500	1.9318700
H	1.2181040	3.8780800	2.1288840
H	2.6259250	3.0000000	2.7585000
H	1.0056930	2.3549560	3.0169400
H	-5.3443490	-0.7891300	-2.0707590
H	-6.2519180	-0.0814260	-0.7049840
H	-5.6919970	0.9620520	-2.0413750

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -1127.117446 Hartrees

Thermal correction to Gibbs free energy = 0.280227 Hartrees

Imaginary frequencies = 1, -377.35 cm^{-1}

TS 3.4

O	2.3181470	-2.0624970	2.3364330
C	2.1404870	-1.6604670	1.2049220
O	2.4844900	-0.3556000	0.9416550
C	1.6546940	-2.4210050	0.0860010
C	-0.4996400	-0.4475580	0.7897290
C	-0.4389020	-0.3518290	2.2760550
C	-1.6218080	-1.2166950	0.1137740
N	-2.5228900	-0.1749240	-0.4035490
C	-1.9671630	0.8210700	-1.3213230
C	-0.4672590	0.8872860	-1.2025420
C	0.0830240	0.3869310	-0.0999630
C	2.1977510	0.1814630	-0.2740660
C	2.5493800	1.6333410	-0.4020600
O	2.8145000	2.1990420	0.7616050
C	3.1166390	3.6031900	0.7313080
O	2.5616520	2.2003650	-1.4685100
C	2.1391940	-0.6266210	-1.3993730
C	1.8044720	-1.9764120	-1.2078220
C	1.5153690	-2.8582580	-2.3853360
C	-3.7726910	-0.0630670	0.1221460
O	-4.4426470	0.9746670	-0.4038740
C	-5.7715350	1.1775100	0.0856740
O	-4.2529210	-0.8144710	0.9511780
H	1.3337960	-3.4326170	0.3023760
H	0.3384700	0.3368700	2.6080860
H	-1.4077660	0.0131100	2.6398940
H	-0.2700100	-1.3283180	2.7394650

H	-2.1832240	-1.8397120	0.8056940
H	-1.2522410	-1.8268600	-0.7130070
H	-2.4364120	1.7884330	-1.1403340
H	-2.1879060	0.5409290	-2.3588050
H	0.0952290	1.2684220	-2.0486570
H	2.2697340	4.1631860	0.3317840
H	3.2995260	3.8816550	1.7665990
H	4.0056370	3.7876620	0.1265790
H	2.1949600	-0.1794530	-2.3821180
H	2.3880710	-2.9117780	-3.0423020
H	1.2527610	-3.8693160	-2.0712800
H	0.6898370	-2.4458000	-2.9727490
H	-6.3998700	0.3120960	-0.1310300
H	-6.1446460	2.0511530	-0.4458810
H	-5.7635580	1.3694820	1.1598820

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -1127.120672 Hartrees

Thermal correction to Gibbs free energy = 0.279748 Hartrees

Imaginary frequencies = 1, -376.31 cm^{-1}

TS 3.5

O	-2.2833870	-2.9217270	-1.3101950
C	-2.3184100	-1.7800720	-0.9083310
O	-2.4063580	-0.7787670	-1.8483560
C	-2.3154520	-1.3531340	0.4693050
C	0.2513710	-0.6065340	-0.5411300
C	1.0479940	-0.4427160	0.7325570
N	2.1523630	0.4601320	0.3436810
C	1.7921420	1.7602760	-0.2150790
C	0.3691170	1.7878800	-0.7534230
C	-0.2795270	3.1307310	-0.8369240
C	-0.1451370	0.5867060	-1.0189310
C	-2.3365070	0.5192210	-1.4748090
C	-2.6881100	0.9235710	-0.2048160
C	-2.6529810	-0.0637430	0.7802430
C	3.4328490	0.0283740	0.1686720
O	3.6125550	-1.2313040	0.5930870
C	4.9412280	-1.7488190	0.4789400
O	4.3303740	0.7088520	-0.2942750
H	-2.2088290	-2.1243660	1.2197530
H	0.3364350	-1.5110650	-1.1331610
H	1.4609670	-1.3708320	1.1125290
H	0.4591430	0.0392980	1.5161670
H	1.8271720	2.5235780	0.5724980

H	2.5264160	2.0413580	-0.9713360
H	-0.5054150	3.5047970	0.1673730
H	-1.2042290	3.1019200	-1.4128840
H	0.4000710	3.8514170	-1.3031130
H	-2.8365390	1.9706690	0.0138710
H	5.2636640	-1.7624210	-0.5634170
H	5.6393750	-1.1581680	1.0744880
H	4.8888650	-2.7650230	0.8656920
H	-2.3524090	1.1852580	-2.3268270
Cl	-2.9045980	0.3873990	2.4460510

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -1319.535610 Hartrees

Thermal correction to Gibbs free energy = 0.207261 Hartrees

Imaginary frequencies = 1, -339.01 cm^{-1}

TS 3.6

O	-2.9712490	2.5668070	-0.8223840
C	-2.7548480	1.4908890	-0.3076760
O	-2.6239970	1.4603430	1.0631320
C	-2.6614310	0.2231680	-0.9802900
C	0.1811600	0.9177800	0.0378750
C	0.2379190	2.3952500	-0.1469610
C	0.9341610	-0.0061340	-0.9036900
N	2.0990570	-0.4443980	-0.1169570
C	1.8592460	-1.1030850	1.1704460
C	0.4661990	-0.8127390	1.6704700
C	-0.1503810	0.2484940	1.1600330
C	-2.2617560	0.3156810	1.6918930
C	-2.5311950	-0.9214110	1.1355060
C	-2.6942840	-0.9344630	-0.2503730
C	3.3418540	-0.0560130	-0.5130090
O	4.2890710	-0.4707260	0.3431550
C	5.6346550	-0.1159830	0.0112560
O	3.5896790	0.5697910	-1.5276640
H	-2.7265200	0.2327390	-2.0595930
H	-0.2427720	2.9276310	0.6741850
H	1.2913260	2.6992270	-0.1916390
H	-0.2230430	2.7031660	-1.0901540
H	1.2961660	0.4992400	-1.7955410
H	0.3339390	-0.8721530	-1.1897870
H	2.6278600	-0.8027730	1.8827930
H	1.9298960	-2.1912520	1.0525520
H	0.0041640	-1.5288080	2.3417590
H	-2.4643980	-1.8188000	1.7319330

H	5.9231460	-0.5480480	-0.9483120
H	6.2481140	-0.5340830	0.8073900
H	5.7530310	0.9683230	-0.0205010
H	-2.1607060	0.4612410	2.7586090
Cl	-2.8329070	-2.4672450	-1.0728110

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -1319.535950 Hartrees

Thermal correction to Gibbs free energy = 0.206459 Hartrees

Imaginary frequencies = 1, -375.44 cm^{-1}

TS 3.7

O	0.6193830	3.9908580	-0.8017070
C	1.0344460	2.9287670	-0.3983830
O	1.5785460	2.0703040	-1.3314760
C	1.0600170	2.4631960	0.9680900
C	-0.9113330	0.8518210	-0.2686950
C	-1.6803250	0.3124180	0.9131940
N	-2.3924760	-0.8492540	0.3429370
C	-1.5815350	-1.8940130	-0.2714240
C	-0.2017820	-1.4019140	-0.6847720
C	0.8434090	-2.4565970	-0.8452280
C	-0.0880490	-0.0769370	-0.7908870
C	1.9821610	0.8321380	-0.9789450
C	2.3531080	0.5549920	0.3268070
C	1.8299760	1.3931620	1.3252190
C	-3.7256990	-0.8257990	0.0529110
O	-4.3377780	0.2595520	0.5466270
C	-5.7480450	0.3432060	0.3198320
O	-4.3101690	-1.7006230	-0.5588970
H	0.5914930	3.1048870	1.7024840
H	-1.2676360	1.7270850	-0.8009820
H	-2.4004250	1.0106380	1.3258890
H	-1.0116600	-0.0336670	1.7043910
H	-1.3990900	-2.6951300	0.4563320
H	-2.1324130	-2.3319080	-1.1047790
H	1.1813540	-2.8109050	0.1353550
H	1.7036890	-2.0896530	-1.4022660
H	0.4300760	-3.3220520	-1.3724590
H	-5.9670940	0.3694730	-0.7487340
H	-6.2647710	-0.4985750	0.7837150
H	-6.0600690	1.2754750	0.7870980
H	2.3233930	0.2614360	-1.8314610
H	1.9858560	1.1477450	2.3692820
C	3.1372940	-0.6415100	0.6900470

O	3.2221850	-1.0791980	1.8153940
O	3.7664910	-1.1720280	-0.3588190
C	4.4847820	-2.3911040	-0.1285180
H	4.8830080	-2.6817660	-1.0983290
H	5.2987840	-2.2269580	0.5790760
H	3.8130260	-3.1632260	0.2503640

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -1087.805482 Hartrees

Thermal correction to Gibbs free energy = 0.255755 Hartrees

Imaginary frequencies = 1, -339.63 cm^{-1}

TS 3.8

O	1.8137510	3.8162150	-0.3354660
C	1.9414170	2.6416120	-0.0738530
O	2.1160290	1.7787620	-1.1415660
C	1.9844550	2.0393990	1.2329670
C	-0.7261270	1.0905950	-0.2632730
C	-1.0531080	2.3156160	-1.0420250
C	-1.5408610	0.7158450	0.9626190
N	-2.3666660	-0.4065820	0.4896070
C	-1.6831490	-1.5854150	-0.0453550
C	-0.2726860	-1.2482300	-0.4622650
C	0.0085640	0.0356560	-0.6660990
C	2.1584540	0.4430690	-0.9557350
C	2.5465130	-0.0854370	0.2678240
C	2.3974480	0.7499570	1.3924270
C	-3.7092210	-0.2150600	0.3490960
O	-4.3127970	-1.2901860	-0.1787880
C	-5.7295900	-1.1919210	-0.3549350
O	-4.3088400	0.7902550	0.6816010
H	1.8153650	2.6978430	2.0745880
H	-0.4788710	2.3798130	-1.9661590
H	-2.1212170	2.2880530	-1.2916900
H	-0.8900530	3.2226320	-0.4522700
H	-2.2016740	1.5121420	1.2952120
H	-0.9085690	0.3896540	1.7902720
H	-2.2688660	-2.0113080	-0.8595590
H	-1.5980020	-2.3527860	0.7341160
H	0.4500480	-2.0560370	-0.4833250
H	-6.2288130	-1.0472950	0.6044800
H	-6.0322340	-2.1412770	-0.7929920
H	-5.9797770	-0.3720500	-1.0300590
H	2.2675460	-0.0876330	-1.8907820
H	2.5694150	0.3449460	2.3831810

C	2.9480030	-1.4915550	0.4240740
O	3.2138970	-2.0099930	1.4862170
O	3.0017820	-2.1379400	-0.7451480
C	3.3459200	-3.5283300	-0.6947520
H	2.6198950	-4.0802250	-0.0951240
H	3.3194940	-3.8717760	-1.7267730
H	4.3461960	-3.6603320	-0.2794660

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -1087.807584 Hartrees

Thermal correction to Gibbs free energy = 0.253982 Hartrees

Imaginary frequencies = 1, -350.05 cm^{-1}

TS leading to **3.105**

O	3.1630850	-0.5714480	2.1426260
C	2.9700160	-0.6497230	0.9454460
O	3.0457740	0.5164830	0.2197180
C	2.7323180	-1.8442730	0.1798110
C	0.0698740	-0.6093950	-0.1549720
C	-0.9106500	-0.5291150	0.9896280
N	-1.9335900	0.4258090	0.5115470
C	-1.4707760	1.7661450	0.1687380
C	0.0159870	1.7946020	-0.1685750
C	0.7109050	3.1023150	0.0242330
C	0.5340060	0.6081690	-0.4871590
C	2.6091110	0.5418830	-1.0713240
C	2.6772940	-0.5919060	-1.8593470
C	2.7330520	-1.8178660	-1.1957670
C	-3.1399600	0.0203290	0.0206300
O	-3.3734300	-1.2805950	0.2478240
C	-4.6395990	-1.7782130	-0.1946540
O	-3.9374820	0.7522070	-0.5363750
H	2.6994690	-2.7727010	0.7351400
H	0.1031200	-1.4800830	-0.7989640
H	-0.4488150	-0.1237730	1.8922950
H	-1.3842920	-1.4765090	1.2234220
H	-1.5938910	2.4305670	1.0328280
H	-2.0895280	2.1607600	-0.6381120
H	0.1612520	3.9097990	-0.4706140
H	0.7485430	3.3463890	1.0917520
H	1.7318360	3.0926440	-0.3554880
H	2.5528730	-0.5078440	-2.9301010
H	-4.7433380	-1.6670450	-1.2752090
H	-4.6441640	-2.8332260	0.0732420
H	-5.4568090	-1.2609770	0.3108410

H	2.6989970	-2.7472280	-1.7534810
H	2.6668120	1.5376640	-1.4888580

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -859.922996 Hartrees

Thermal correction to Gibbs free energy = 0.217233 Hartrees

Imaginary frequencies = 1, -391.95 cm^{-1}

TS leading to **3.106**

O	2.5986400	-0.0365550	2.4408560
C	2.6956470	-0.1766210	1.2371260
O	2.8979540	0.9571360	0.4863370
C	2.6795570	-1.4103870	0.5000750
C	0.1356290	-0.3998210	-0.3642950
C	-0.0686540	-1.5766310	-1.2582980
C	-0.7233320	-0.2146570	0.8715900
N	-1.7786320	0.7144290	0.4140080
C	-1.3511240	2.0257350	-0.0750220
C	0.0924120	1.9975190	-0.5400000
C	0.6239790	0.8027270	-0.7494190
C	2.7819630	0.8949880	-0.8698260
C	3.1281200	-0.2601560	-1.5471890
C	3.0654060	-1.4482180	-0.8221400
C	-3.0324920	0.2884760	0.0852830
O	-3.2536780	-0.9823280	0.4527450
C	-4.5543200	-1.5028470	0.1643670
O	-3.8757590	0.9806020	-0.4546900
H	2.5275920	-2.3131750	1.0774850
H	0.6844030	-1.6137000	-2.0474450
H	-1.0462090	-1.4800810	-1.7491050
H	-0.0644590	-2.5174450	-0.7035880
H	-1.1796960	-1.1354330	1.2206400
H	-0.1706460	0.2515420	1.6885370
H	-2.0486900	2.3523750	-0.8464920
H	-1.3962020	2.7568650	0.7412790
H	0.6446710	2.9314510	-0.5327460
H	3.2768440	-0.2313310	-2.6178290
H	-4.7470410	-1.4897890	-0.9096070
H	-4.5409950	-2.5288510	0.5277250
H	-5.3245220	-0.9319940	0.6855890
H	2.8427580	1.8796070	-1.3146860
H	3.2186250	-2.4025210	-1.3133000

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -859.924505 Hartrees

Thermal correction to Gibbs free energy = 0.219001 Hartrees

Imaginary frequencies = 1, -406.83 cm⁻¹

TS leading to **3.107**

O	-0.9823000	1.5799470	2.7878140
C	-1.1760610	1.5743260	1.5914460
O	-2.0257780	0.6292320	1.0880440
C	-0.6116600	2.4781020	0.6172890
C	0.8401220	0.6347100	-0.1160010
C	1.8317220	0.3331630	0.9827530
N	2.5115600	-0.8805520	0.4900270
C	1.6716210	-2.0493350	0.2762640
C	0.2154330	-1.6917720	-0.0341330
C	-0.7733350	-2.8070840	0.1383910
C	0.0001490	-0.4139520	-0.3227460
C	-2.1417700	0.4903090	-0.2604310
C	-3.0163220	-0.6460950	-0.6925910
O	-3.5830980	-1.2670720	0.3261880
C	-4.4162640	-2.3914040	0.0050300
O	-3.1805770	-0.9259160	-1.8555460
C	-1.9740870	1.5782830	-1.0955140
C	-1.1839460	2.6295080	-0.6385640
C	-0.7916720	3.7619190	-1.5376280
C	3.7251610	-0.8328410	-0.1344140
O	4.3082800	0.3689500	-0.0208930
C	5.6079860	0.4947840	-0.6056050
O	4.2437890	-1.7732880	-0.7063430
H	0.0841540	3.2114050	1.0070190
H	1.1342190	1.3197000	-0.9033110
H	1.3320700	0.0953160	1.9236780
H	2.5600380	1.1199530	1.1470140
H	1.6321930	-2.6447840	1.1976220
H	2.1185580	-2.6716580	-0.4994030
H	-1.4794360	-2.8390810	-0.6928480
H	-0.2615530	-3.7720090	0.1698580
H	-1.3415630	-2.6969080	1.0670110
H	-3.8422810	-3.1475580	-0.5330260
H	-4.7547070	-2.7831350	0.9614200
H	-5.2681140	-2.0721910	-0.5972030
H	-2.3289070	1.5228290	-2.1160810
H	0.1254290	3.5007650	-2.0775970
H	-1.5688610	3.9598500	-2.2779730
H	-0.5983670	4.6734640	-0.9696320
H	5.5673720	0.3156170	-1.6812150
H	5.9137910	1.5210430	-0.4101760

H 6.3100580 -0.1992980 -0.1407380

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -1127.111893 Hartrees

Thermal correction to Gibbs free energy = 0.281412 Hartrees

Imaginary frequencies = 1, -393.19 cm^{-1}

TS leading to **3.108**

O	1.4355470	-1.2241610	2.8660410
C	1.6728090	-1.1882230	1.6761960
O	2.1943740	-0.0261060	1.1701990
C	1.5028730	-2.2564620	0.7259530
C	-0.5691940	-0.8336370	-0.2466640
C	-0.7516590	-1.6964750	-1.4500210
C	-1.5906120	-0.8666740	0.8722880
N	-2.4818700	0.2617530	0.5529620
C	-1.8894410	1.5977120	0.4705300
C	-0.3999480	1.5197210	0.2009310
C	0.0720690	0.3653900	-0.2451350
C	2.2470740	0.1267230	-0.1857280
C	2.6459970	1.4975640	-0.6449430
O	2.7516020	2.3585540	0.3524510
C	3.0854310	3.7097780	-0.0062550
O	2.8312040	1.7590660	-1.8083990
C	2.5124170	-0.9695250	-0.9911190
C	2.1245550	-2.2210600	-0.5117690
C	2.2565440	-3.4547320	-1.3530330
C	-3.7393190	-0.0117510	0.1048340
O	-4.4047360	1.1037850	-0.2307520
C	-5.7421230	0.9186500	-0.7045470
O	-4.2279130	-1.1246140	0.0358410
H	1.0779700	-3.1736220	1.1155430
H	0.0790190	-1.5939860	-2.1500850
H	-1.6577840	-1.3633890	-1.9730720
H	-0.8861470	-2.7473410	-1.1859170
H	-2.1804150	-1.7794610	0.8835670
H	-1.1342960	-0.7071090	1.8504510
H	-2.4161200	2.1810750	-0.2836240
H	-2.0052810	2.1160600	1.4299490
H	0.2031910	2.3707760	0.4981610
H	2.3258840	4.1227030	-0.6717330
H	4.0630680	3.7427390	-0.4889070
H	3.1074270	4.2605280	0.9312460
H	2.8464010	-0.8164390	-2.0082870
H	1.5566460	-4.2274210	-1.0302350

H	2.0839000	-3.2323720	-2.4081890
H	3.2693780	-3.8594690	-1.2598010
H	-6.3623750	0.4513870	0.0620550
H	-6.1113250	1.9189280	-0.9238460
H	-5.7515110	0.3099670	-1.6101620

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -1127.116088 Hartrees

Thermal correction to Gibbs free energy = 0.280946 Hartrees

Imaginary frequencies = 1, -414.15 cm^{-1}

TS leading to **3.109**

O	2.9955440	1.3406950	2.1905610
C	2.7881900	0.7684710	1.1417750
O	2.5390340	1.5519340	0.0351880
C	2.8278210	-0.6495120	0.9133600
C	-0.2241690	-0.2085090	0.3014190
C	-1.3523540	0.0205620	1.2797680
N	-2.4609750	0.4961120	0.4260260
C	-2.2238810	1.7215160	-0.3275980
C	-0.7402850	1.9709000	-0.5628950
C	-0.3225600	3.3829820	-0.7980860
C	0.0317710	0.8896530	-0.4234350
C	2.0692470	0.9901540	-1.1099880
C	2.3584580	-0.3234630	-1.4317070
C	2.7285000	-1.1388220	-0.3634720
C	-3.4589040	-0.3336250	-0.0016030
O	-3.4573450	-1.5077120	0.6435090
C	-4.5014880	-2.4205200	0.2907190
O	-4.2813730	-0.0382680	-0.8480530
H	3.0545570	-1.2810010	1.7611050
H	0.1023430	-1.2102870	0.0459160
H	-1.1119890	0.7986680	2.0066740
H	-1.6580280	-0.8778700	1.8048530
H	-2.5809680	2.5834050	0.2495680
H	-2.7969770	1.6875900	-1.2548360
H	0.7387800	3.4687260	-1.0285980
H	-0.9008640	3.8278800	-1.6147950
H	-0.5252240	3.9786130	0.0988500
H	2.1783900	-0.6949270	-2.4298130
H	-4.4387450	-2.6902040	-0.7646670
H	-4.3366840	-3.2998370	0.9106920
H	-5.4806390	-1.9896020	0.5058870
H	1.8968070	1.7322830	-1.8768460
Cl	2.9904190	-2.8410670	-0.6479610

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -1319.531036 Hartrees

Thermal correction to Gibbs free energy = 0.204861 Hartrees

Imaginary frequencies = 1, -395.66 cm^{-1}

TS leading to **3.110**

O	-1.9859440	-1.6938190	2.3410110
C	-2.1890820	-1.1422320	1.2797620
O	-2.1909670	-1.9265810	0.1487410
C	-2.4826480	0.2491470	1.0739990
C	0.2339270	0.1910400	-0.1473190
C	0.0981130	1.6123740	-0.5705380
C	1.2109560	-0.2007360	0.9451200
N	2.3705100	-0.7035080	0.1808560
C	2.1473340	-1.8557120	-0.6906990
C	0.6907290	-1.9667620	-1.0927400
C	-0.0627920	-0.8933070	-0.8992710
C	-2.1668370	-1.3385370	-1.0772320
C	-2.7864610	-0.1183610	-1.2862760
C	-2.9284430	0.6761380	-0.1542640
C	3.4830410	0.0591250	-0.0375070
O	3.4948380	1.1691880	0.7131660
C	4.6386350	2.0161480	0.5651990
O	4.3818590	-0.2390850	-0.8010630
H	-2.5052390	0.8828250	1.9499060
H	-0.6685600	1.7334910	-1.3372530
H	1.0501200	1.9318630	-1.0150360
H	-0.1092700	2.2734120	0.2736630
H	1.5203610	0.6341840	1.5657130
H	0.8237170	-1.0028490	1.5747700
H	2.8284210	-1.7896620	-1.5391220
H	2.3835820	-2.7795870	-0.1486380
H	0.3174220	-2.9438680	-1.3809860
H	-2.9913720	0.2283980	-2.2885960
H	4.7187720	2.3814450	-0.4599000
H	4.4700680	2.8487770	1.2455910
H	5.5509530	1.4855870	0.8422840
H	-2.0627710	-2.0706540	-1.8670330
Cl	-3.5786410	2.2884480	-0.3144470

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -1319.532702 Hartrees

Thermal correction to Gibbs free energy = 0.205916 Hartrees

Imaginary frequencies = 1, -409.53 cm^{-1}

TS leading to **3.111**

O	-4.3632110	1.7438430	-1.0684870
C	-3.6093650	0.8196250	-0.8645550
O	-3.1207470	0.6929420	0.4275330
C	-3.2004420	-0.1985190	-1.7934490
C	0.0995590	0.9510030	-0.9258450
C	1.2947590	1.8471530	-1.1611510
N	2.2290660	1.4446080	-0.0878330
C	1.7620840	1.6512420	1.2769080
C	0.2442190	1.6183960	1.3704070
C	-0.4025990	2.2624630	2.5458390
C	-0.3657850	1.0545850	0.3206540
C	-2.1287220	-0.1693990	0.7327560
C	-1.8471100	-1.2475300	-0.0952190
C	-2.3926910	-1.2201380	-1.3985150
C	3.1784280	0.4776970	-0.2931370
O	3.3565150	0.2099400	-1.5920880
C	4.3606790	-0.7621760	-1.9017840
O	3.8170410	-0.0556330	0.5932740
H	-3.6074240	-0.1386520	-2.7938700
H	-0.1529400	0.1513500	-1.6147890
H	1.0569690	2.9046270	-1.0368910
H	1.7639210	1.6962840	-2.1274430
H	2.0553180	2.6530430	1.6147880
H	2.2424460	0.9269070	1.9354930
H	-0.0993370	1.7620080	3.4730080
H	-0.0795500	3.3054120	2.6276870
H	-1.4899860	2.2380420	2.4707520
H	4.1158880	-1.7254960	-1.4515640
H	4.3560460	-0.8452110	-2.9869900
H	5.3403620	-0.4286150	-1.5561050
H	-1.9228430	-0.1773230	1.7924950
H	-2.1378750	-2.0155120	-2.0903650
C	-0.8841870	-2.2832560	0.2923840
O	-0.5668450	-3.2216320	-0.4084200
O	-0.3775300	-2.0722580	1.5115330
C	0.6217070	-2.9946560	1.9602310
H	0.9101730	-2.6523270	2.9520740
H	0.2159110	-4.0061850	2.0147710
H	1.4844880	-2.9771680	1.2918930

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -1087.804734 Hartrees

Thermal correction to Gibbs free energy = 0.252777 Hartrees

Imaginary frequencies = 1, -360.06 cm^{-1}

TS leading to **3.112**

O	-1.1225300	3.7853120	0.1734160
C	-1.5325330	2.6687890	-0.0537050
O	-1.8423900	1.8826090	1.0427360
C	-1.7969220	2.0755870	-1.3364940
C	0.6340750	0.2242020	-0.4152300
C	0.4304460	-0.6168780	-1.6239890
C	1.8809710	1.0775700	-0.2706310
N	2.6953520	0.2885440	0.6742970
C	2.1318520	0.0510630	2.0013920
C	0.6210280	0.1429080	1.9780670
C	0.0381060	0.0795040	0.7868900
C	-2.0790190	0.5598630	0.8915130
C	-2.6258940	0.0783540	-0.2910800
C	-2.4387250	0.8735070	-1.4350940
C	3.7081860	-0.5291820	0.2531620
O	4.0214420	-0.3293320	-1.0333350
C	5.0946940	-1.1226150	-1.5505860
O	4.2854010	-1.3278650	0.9653700
H	-1.5775050	2.6813320	-2.2056650
H	-0.4972640	-1.1869440	-1.5784160
H	1.2577760	-1.3367900	-1.6806150
H	0.4585030	-0.0216260	-2.5399650
H	2.4245330	1.2073840	-1.2010120
H	1.6648400	2.0521200	0.1683860
H	2.5070740	-0.9009460	2.3768200
H	2.4697080	0.8348530	2.6905710
H	0.1122900	0.3893160	2.9043000
H	4.8571450	-2.1852900	-1.4818590
H	5.1927420	-0.8286650	-2.5939590
H	6.0219100	-0.9138600	-1.0145350
H	-2.2230680	0.0702190	1.8444790
H	-2.7490200	0.4960090	-2.4029240
C	-3.1791620	-1.2776910	-0.3964170
O	-3.6669120	-1.7387320	-1.4062240
O	-3.0859870	-1.9561360	0.7509650
C	-3.6058520	-3.2914450	0.7521970
H	-3.4364410	-3.6685160	1.7587140
H	-4.6736850	-3.2868810	0.5270640
H	-3.0767060	-3.9095900	0.0251460

Electronic energy (ω B97XD/6-311+G(d,p)/SMD(MeCN)) = -1087.805363 Hartrees

Thermal correction to Gibbs free energy = 0.254031 Hartrees

Imaginary frequencies = 1, -381.53 cm^{-1}

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- (63) The use of basic alumina in the hydrogenation of the allyl ketone was found to minimize undesired protodesilylation.
- (64) The calculated HOMO–LUMO energy gaps using allene **3.9** and pyrone **3.62** in their ground state geometries are consistent with an inverse-electron-demand Diels–Alder reaction pathway (i.e., DE LUMOPyrone–HOMOallene = 10.0 eV versus DE LUMOallene–HOMOPyrone = 11.0 eV). FMO energies were calculated at the HF/6-

311+G(d,p)// ω B97XD/6-311+G(d,p)/SMD(MeCN) level of theory. Partial atomic charges (calculated at ω B97X-D/6-311+G(d,p)/SMD(MeCN) are also consistent with an inverse-electron-demand Diels–Alder reaction pathway and are as follows: C4 of **3.9**, 0.15; C4a of **3.9**, 0.17; C8a of **3.9**, 1.09; C5 of **3.62**, –0.05; C6 of **3.62**, –0.12; C7 of **3.62**, 0.51; C8 of **3.62**, –0.41.

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CHAPTER FOUR

Diels–Alder Cycloadditions of Oxacyclic Allenes and α -Pyrones

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Manuscript in Preparation

4.1 Abstract

The reaction of α -pyrones with oxacyclic allenes in Diels–Alder trappings is described. We investigate regioselectivity trends with respect to both coupling partners and perform competition experiments to assess the influence of structural features on relative reaction rates. Additionally, the first ester-substituted oxacyclic allene is accessed and evaluated in a Diels–Alder reaction with α -pyrone. We also demonstrate the stereospecific trapping of an oxacyclic allene, which proceeds in high optical yield. This study provides insight into strained cyclic allene reactivity, as well as new synthetic tools for the rapid construction of complex, heterocyclic scaffolds.

4.2 Introduction

Intermediates containing a functional group with preferred linear geometry constrained within a six-membered ring can be leveraged to build structural complexity. Cycloadditions of strained intermediates are particularly useful as they typically generate two new bonds and multiple stereocenters.^{1,2,3,4,5,6,7,8,9,10} In the 1950s–1960s, furans (**4.2**, where X = O, Figure 4.1), which are commonly employed as electron-rich dienes in Diels–Alder cycloadditions, were used to validate the existence of strained alkynes, such as benzyne^{11,12,13,14} and cyclohexyne^{15,16} (**4.3**, Figure 4.1). In contrast to furans, pyrones (**4.4**)¹⁷ are relatively understudied dienes in Diels–Alder reactions with strained cyclic alkynes (**4.3**). The first examples of benzyne^{18,19} and cyclohexyne²⁰

undergoing the Diels–Alder cycloaddition with α -pyrone were published in 1997 and 1998, respectively, three decades after furans had been deemed competent reaction partners in the Diels–Alder cycloadditions with strained cyclic alkynes.^{1,2,3,4} Notably, cycloadducts **4.5** are often unstable due to facile extrusion of CO₂ and subsequent aromatization; thus, although this method is useful for initially generating interesting bridged bicyclic structures, much of the structural and stereochemical complexity built in the Diels–Alder reaction of strained cyclic alkynes is typically ablated.^{21,22,23,24,25}

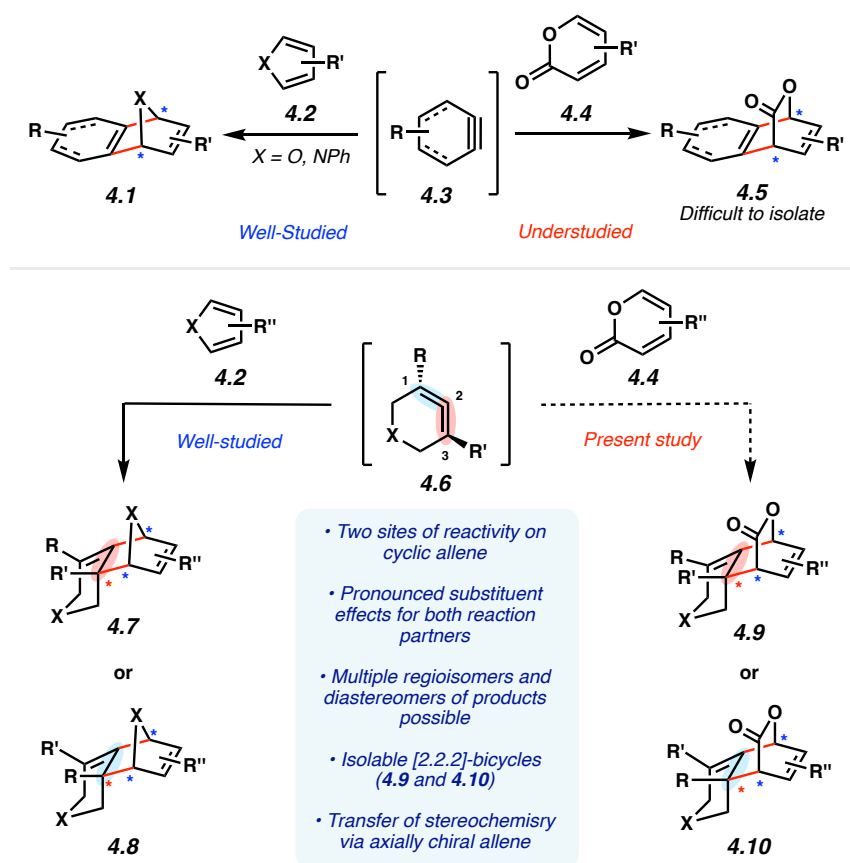


Figure 4.1. Overview of scaffolds accessible from strain-promoted Diels–Alder cycloadditions of intermediates **4.3** or **4.6** with furans **4.2** or pyrones **4.4**.

We were interested in evaluating a related class of strained intermediates, cyclic allenes (**4.6**, Figure 4.1),²⁶ in Diels–Alder cycloadditions with α -pyrones (**4.4**). Several factors motivated these studies: a) Similar to cyclic alkynes **4.3**, cyclic allenes **4.6** can be generated under mild reaction conditions and exhibit strain-promoted reactivity.^{5,6,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50 51,52} b) cyclic allenes **4.6** have two sites of reactivity that can be differentiated based on substituent effects, potentially allowing for the controlled formation of isomeric products; c) like linear allenes, cyclic allenes are chiral, providing long-term opportunities to control stereochemistry; d) although Diels–Alder trappings of cyclic allenes **4.6** have been known for decades, nearly all studies focus on the use of electron-rich dienes **4.2** to provide cycloadducts **4.7** or **4.8**.^{20,28,29,30,31,32,33,34,35,36,37,41,44,45,46,47,48,49,51,52} The use of ambiphilic pyrones, which relies on the influence of substituents on each reaction partner to guide selectivity parameters of the cycloaddition,⁵³ are not well explored, but can deliver structurally complex and isolable⁵⁴ cycloadducts **4.9** or **4.10**. There are limited reports describing Diels–Alder cycloadditions between strained cyclic allenes and pyrones as shown by our laboratory in the context of total synthesis studies using azacyclic allenes.^{55,56,57}

In this study, we evaluate Diels–Alder reactions of strained oxacyclic allenes and α -pyrones. We describe the scope of the oxacyclic allene and pyrone components with a focus on electronic perturbations and principles that guide regioselectivity. In addition, we perform competition experiments to gauge relative reaction rates when employing different cyclic allene / pyrone combinations. We also demonstrate that the use of an enantioenriched oxacyclic allene precursor in the cycloaddition allows for a stereoselective cycloaddition and access to an enantioenriched cycloadduct. Overall, this study advances the field of cyclic allene chemistry, while providing new synthetic tools for the synthesis of functionalized heterocycles.

4.3 Results and Discussion

4.3.1. Scope of Cycloadditions with Methyl-Substituted Heterocyclic Allenes

We initiated our studies by investigating cycloadditions with allenes bearing either electron-donating or electron-withdrawing groups, beginning with methyl-substituted heterocyclic allene precursors **4.11a/b** (Figure 4.2).⁵⁸ The use of Kobayashi-type silyl triflate precursors² **4.11a/b** allows for cyclic allene generation under mild fluoride-based conditions. Whereas the focus of this study was the cycloadditions of oxacyclic allenes with pyrones, the analogous cycloadditions of azacyclic allenes that we reported recently⁵⁷ are shown for comparison. For the scope of the pyrone trapping partners, we evaluated unsubstituted pyrone **4.15**, 4-chloro pyrone **4.16**, pyrone **4.17** with electron-donating groups, and pyrone **4.18** with an electron-withdrawing substituent. We observed that the combination of the ambiphilic nature of pyrones **4.15** and **4.16** with allenes **4.12** leads to a mixture of isomers **4.19a/b**, **4.20a/b**, **4.21a/b**, and **4.22a/b** (entries 1a/b and 2a/b).⁵⁹ It is inferred that the C1–C2 and C2–C3 olefins lack the electronic distinction required for a highly selective cycloaddition of one olefin over the other. Pyrone **4.17** did not undergo the cycloaddition with either oxa- or azacyclic allene **4.12a/b**; instead, only dimers **4.23** and **4.24** were observed in moderate yields (entry 3a/b). We were pleased to find that ester-substituted pyrone **4.18** underwent the Diels–Alder cycloaddition with allenes **4.12** to give cycloadducts with high regioselectivity. More specifically, cycloadducts **4.25** and **4.26** were isolated in 39% and 36% yield, respectively, as single observed isomers with >20:1 dr (Entry 4a/b, Figure 4.2). These studies suggest that methyl-substituted cyclic allenes generally behave as relatively electron-rich dienophiles due to the electron-donating effect of the methyl group; as such, strongly electron-withdrawing substituents are required on the pyrone for the cycloadditions to proceed with high

regioselectivity. It is also worth noting that all major Diels–Alder cycloadducts obtained reflect endo-selectivity, which is consistent with prior studies.^{55,56,57,60,61}

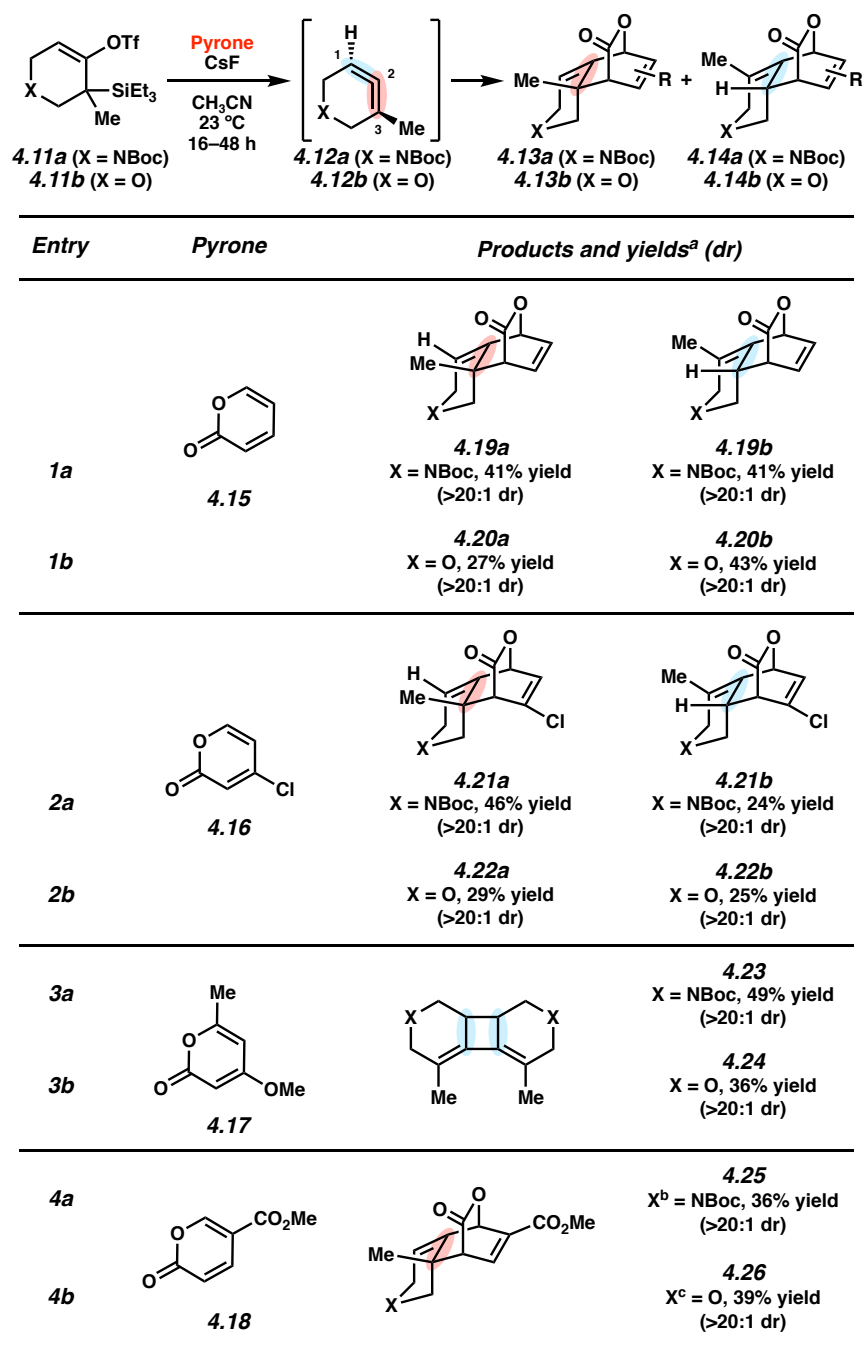


Figure 4.2. Scope of the Diels–Alder cycloaddition with methyl-substituted oxa and azacyclic allenes (4.12) and pyrones 4.15–4.18. Conditions unless otherwise stated: silyl triflate substrate (1.0 equiv), pyrone (5.0 equiv), CsF (5.0 equiv), acetonitrile (0.1 M) at 23 °C. Yields reflect the

average of two experiments. ^aYield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an external standard. ^bSee reference 57 for conditions. ^cReaction performed with 2.5 equiv TBAF in THF for 16 h.

4.3.2 Cycloadditions with Ester-Substituted Oxacyclic Allenes

We also investigated cycloadditions of ester-substituted cyclic allenes **4.27** and **4.31** with both α -pyrone (**4.15**) and 2,5-dimethylfuran (**4.29**) as trapping partners (Figure 4.3). Cyclic allenes **4.27** and **4.31** are new compounds and were accessed from their corresponding silyl triflate precursors, whose syntheses are described in Section 4.5.2.1. We first evaluated the reaction of ester-substituted allene **4.27** with pyrone **4.15** and observed a 33% yield of cycloadduct **4.28** (4:1 dr). To further perturb the electronics of the system, we evaluated the corresponding cyclic allene bearing an additional methyl group (i.e., **4.31**). The Diels–Alder trapping using pyrone **4.15** proceeded with similar regioselectivity, giving cycloadduct **4.32** as the major product in 55% yield and 9:1 dr. Recognizing the strong influence of the ester substituents in determining the electronic nature of cyclic allenes **4.27** and **4.31**, we explored the use of 2,5-dimethylfuran (**4.29**) as an electron-rich trapping partner. In both cases, the cycloaddition proceeded with excellent yield and dr to provide cycloadducts **4.30** and **4.33**, which arose from cycloaddition on the C2–C3 olefins positioned proximal to the ester of **4.27** and **4.31**, respectively. Our results suggest that the greater electronic matching between ester-substituted allenes and electron-rich trapping partners leads to more efficient and selective reactions in comparison to the use of ambiphilic pyrone trapping partners.

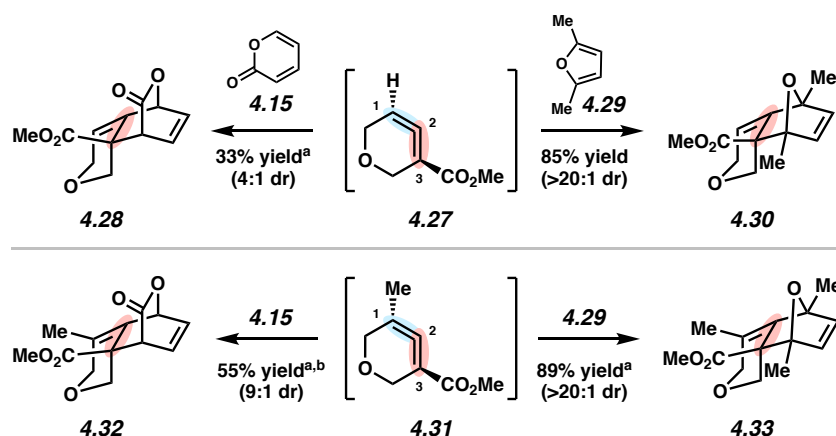


Figure 4.3. Cycloaddition reactions with α -pyrone (**4.15**) and 2,5-dimethylfuran (**4.29**) with ester-substituted oxacyclic allene **4.27** and disubstituted oxacyclic allene **4.31**. Conditions: silyl triflate substrate (1.0 equiv), pyrone (5.0 equiv), CsF (5.0 equiv), acetonitrile (0.1 M) at 23 °C. ^aYield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an external standard. ^bA constitutional isomer of **4.32** was also observed in ~20% yield, see Section 4.5.2.3 for further details.

Several aspects of the Diels–Alder cycloadditions of strained cyclic allenes and pyrones should be noted. In particular, the reactions occur at ambient temperature and are enabled by the high ring strain of the cyclic allene as compared to the typically elevated temperature required for Diels–Alder cycloadditions with pyrones as dienes.^{27,53} Two new C–C bonds and three new stereocenters are formed in addition to other elements of structural complexity, such as a bicyclic ring system. Additionally, the use of reaction partners with either highly electron-donating or electron-withdrawing substituents resulted in the cycloaddition proceeding with high regioselectivity. Notably, the cycloadducts arising from methyl-substituted allenes (**4.12**) displayed excellent diastereoselectivity, whereas the cycloadducts arising from the allenes with ester substituents (**4.27** and **4.31**) were obtained in slightly lower diastereomeric ratios.

4.3.3 Competition Experiments

Competition experiments were performed to compare the relative reaction efficiency of α -pyrone (**4.15**) and 2,5-dimethylfuran (**4.29**) with cyclic allenes generated from cyclic allene precursors **4.34** and **4.35** (Figure 4.4). In the first experiment, **4.34**, bearing an electron-donating methyl group, was treated with cesium fluoride in acetonitrile at 23 °C for 16 hours in the presence of equimolar amounts of **4.15** and **4.29**. We observed that cycloaddition with pyrone **4.15** occurred preferentially to give the mixture of isomers **4.20a** and **4.20b** in 56% overall yield and >20:1 dr for each constitutional isomer. In the second experiment, allene precursor **4.35**, bearing the electron-withdrawing ester substituent, was subjected to the same reaction conditions with equimolar amounts of **4.15** and **4.29**. In this experiment, we observed almost exclusive cycloaddition between the ester-substituted allene and 2,5-dimethylfuran (**4.29**), which gave rise to cycloadduct **4.30** in 89% yield (>20:1 dr), with cycloadduct **4.28** observed in <5% yield. Whereas the methyl-substituted oxacyclic allene arising from **4.34** can be generally considered electron-rich, thus leading to selective reactivity with electron-deficient pyrone over electron-rich furan, there is insufficient electronic bias between the two cyclic allene olefins to yield one constitutional isomer of the cycloadduct **4.20**. In the case of **4.35**, the electron-deficient cyclic allene generated in situ preferentially reacts with the electron rich diene **4.29**. The observation of the single constitutional isomer of **4.30** also suggests better electronic matching between the Diels–Alder partners. Overall, these findings underscore that electronic matching of the cycloaddition partners is largely influenced by the substituents on both the cyclic allene (i.e., methyl vs ester) and the pyrone.

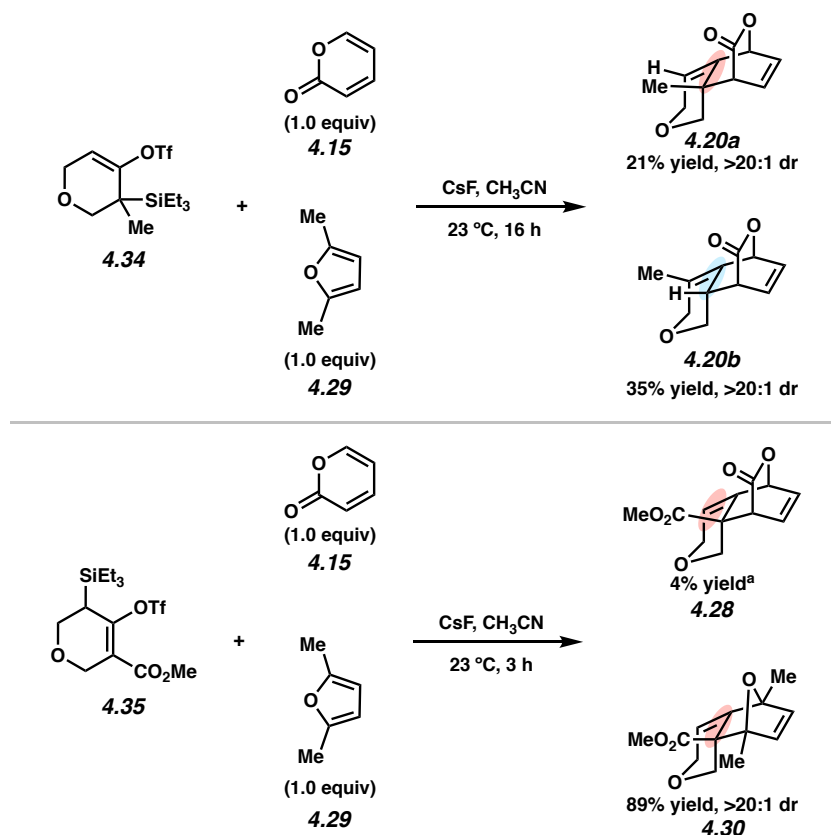


Figure 4.4. Competition experiments with allene precursors **4.34** and **4.35** with 2,5-dimethylfuran (**4.29**) and α -pyrone (**4.15**). Conditions unless otherwise stated: silyl triflate substrate (1.0 equiv), pyrone (5.0 equiv), CsF (5.0 equiv), acetonitrile (0.1 M) at 23 °C. ^aYield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.

4.3.4 Enantiospecific Diels–Alder Reaction

The inherent axial chirality present in strained cyclic allenes provides an opportunity to access structurally complex products with control of absolute stereochemistry. We have previously studied stereoselective trappings in the context of azacyclic allenes,^{45,56,57} as well as one example of a stereoselective Diels–Alder trapping of an oxacyclic allene using 2,5-dimethylfuran.⁴⁹ With the goal of probing stereospecificity in a Diels–Alder reaction between an oxacyclic allene and a pyrone, we aimed to access an oxacyclic allene precursor that could be prepared both racemically

and enantioselectively. Analogous to the azacyclic variant employed in our recent studies^{56,57} and inspired by reports from West and coworkers,^{51,52} methyl-substituted oxacyclic silyl bromide **4.38** was deemed a suitable precursor for accessing the corresponding allene (Figure 4.5). We first developed the racemic synthesis shown in Figure 4.5 to validate the reactivity of silyl bromide (±)-**4.38**. The synthesis began with known enone **4.36**,^{62,63,64,65} which was subjected to bromination and subsequent Luche reduction to afford alcohol (±)-**4.37**. Treatment of alcohol (±)-**4.37** with ethyl chloroformate provided the corresponding carbonate, which underwent displacement by a silyl nucleophile to afford silyl bromide (±)-**4.38**.^{51,66,67,68} Treatment of (±)-**4.38** with pyrone **4.18** and a CsF/Bu₄NBr yielded cycloadduct (±)-**4.26**. We then accessed enantioenriched (+)-**4.38** using an analogous synthetic route featuring an enantioselective CBS reduction (see Section 4.5.2.5 for details). Employing enantioenriched silyl bromide (+)-**4.38** in the same cycloaddition, albeit with a longer reaction time to increase the yield, provided cycloadduct (–)-**4.26** in 94% ee (97% optical yield). Notably, in this transformation, the single stereocenter present in (+)-**4.38** is transmitted to axially chiral allene **4.12b**. In turn, the chirality present in **4.12b** is relayed to establish the three stereocenters present in (–)-**4.26**, including the challenging quaternary stereocenter. It is notable that cycloaddition occurs preferentially over enantiomerization of the cyclic allene.⁶⁹ Overall, this strategy presents a new avenue for the synthesis of complex, enantioenriched oxygen-containing heterocycles.

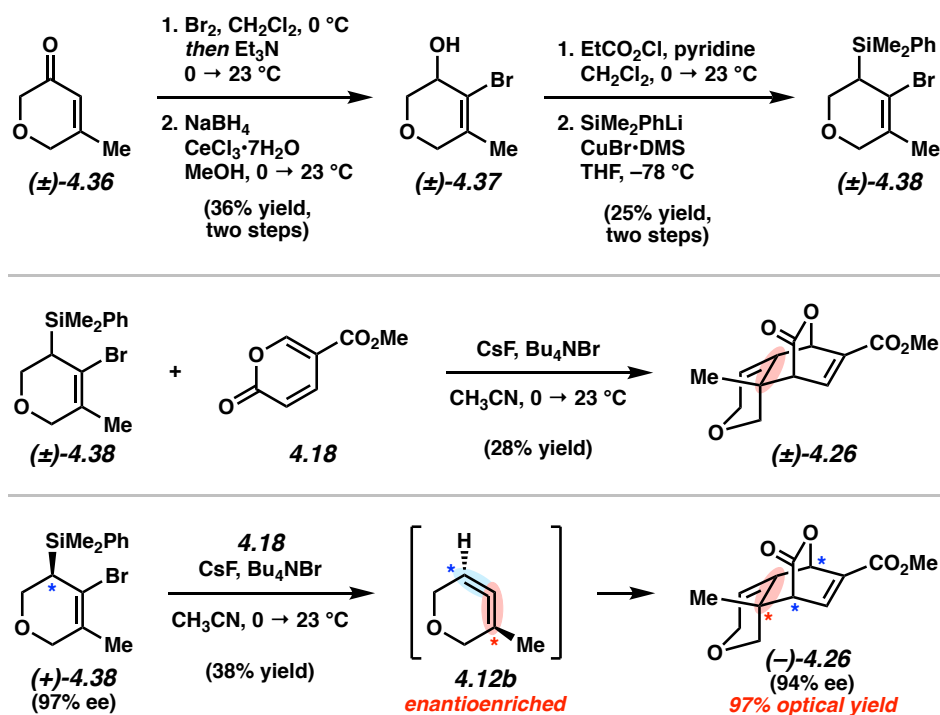


Figure 4.5. Synthesis of silyl bromide (±)-4.38, Diels–Alder cycloaddition employing (±)-4.38 to furnish (±)-4.26, and Diels–Alder cycloaddition employing (+)-4.38 to provide (–)-4.26. See Section 4.5.2.5 for further details in the synthesis of (+)-4.38. Conditions for Diels–Alder cycloaddition: silyl triflate substrate (1.0 equiv), pyrone (5.0 equiv), CsF (5.0 equiv), Bu₄NBr (40 mol%), acetonitrile (0.1 M) at 0 → 23 °C. Yield of cycloadditions determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.

4.4 Conclusions

We have studied reactions between strained oxacyclic allenes and α-pyrone. Substituents on both reactants can be modulated to influence regioselectivity in the Diels–Alder cycloaddition reactions. Based on the competition experiments reported, it is hypothesized that predictable selectivity of the cycloaddition can be observed provided there is significant electronic bias between the two reaction partners. Finally, the Diels–Alder cycloaddition of an enantioenriched

oxacyclic allene and a pyrone demonstrates that the method can be used to access complex bicycles with control of absolute stereochemistry. These studies provide fundamental insight into strained cyclic allene reactivity, new tools for the assembly of complex scaffolds, and the impetus for further studies geared toward the understanding of selectivity-guiding principles in strained cyclic allene trapping reactions.

4.5 Experimental Section

4.5.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received unless otherwise specified. Non-commercially available substrates were synthesized according to known preparations or following protocols specified in the Experimental Procedures. Tetrahydrofuran (THF), diethyl ether (Et₂O), and acetonitrile (MeCN) were passed through an activated alumina column prior to use. Iodomethane (MeI), *n*-butyllithium (*n*-BuLi), potassium bis(trimethylsilyl)amide (KHMDs), diisopropylamine, hexamethylphosphoramide (HMPA), methyl cyanoformate (Mander's reagent), sodium hydride (NaH, 60 wt%), 2,5-dimethylfuran, tetrabutylammonium fluoride (TBAF, 1.0 M in THF), sulfuric acid (H₂SO₄, 95–98%), ethyl chloroformate, methylmagnesium bromide (MeMgBr, 3.0 M in Et₂O), and cerium(III) chloride heptahydrate (CeCl₃•7H₂O) were obtained from Sigma-Aldrich. Sodium hydride was washed with pentane prior to use and stored in a Nitrogen-filled glovebox. Cesium fluoride (CsF) was purchased from Strem Chemicals. Triethylsilylchloride (TESCl), 4-dimethylaminopyridine (DMAP), sodium borohydride (NaBH₄), and were obtained from Oakwood Products, Inc. *N*-(5-chloro-2-

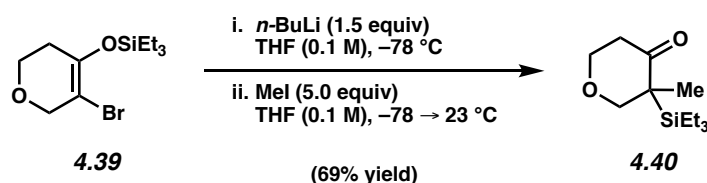
pyridyl)bis(trifluoromethanesulfonimide) (Comins' Reagent), trifluoromethanesulfonic acid (Tf₂O), methyl coumalate (**4.18**), and (*R*)-CBS catalyst were purchased from Combi-Blocks. BH₃·SMe₂ was purchased from Alfa Aesar. α-Pyrone (**4.15**) was purchased from Fischer Scientific. 4-chloro-2H-pyran-one (**4.16**) was purchased from Enamine. 4-methoxy-6-methyl-2H-pyran-2H-one (**4.17**) and 2H-pyran-3,5(4H,6H)-dione (**4.45**) were purchased from Ambeed. Bromocopper methylsulfanylmethane (CuBr·DMS) and ethanol (95.0%) were purchased from Acros Organics. Triflic anhydride (Tf₂O), hexamethylphosphoramide (HMPA), diisopropylamine, and ethyl chloroformate were distilled over CaH₂ prior to use. Reaction temperatures at or above 23 °C were controlled using an IKA Mag temperature modulator. Thin-layer chromatography (TLC) was conducted with EMD gel 60 F₂₅₄ pre-coated plates (0.25 mm for analytical chromatography and 0.50 mm for preparative chromatography) and visualized using a combination of UV light, anisaldehyde and potassium permanganate staining. Silicycle Siliaflash P60 (particle size 0.040–0.063 mm) was used for flash column chromatography and RediSep Gold® Silica (0.020–0.04 mm) was used for automated chromatography unless otherwise specified. ¹H NMR, 2D-NOESY, 2D-HSQC, and 2D-HMBC spectra were recorded on Bruker spectrometers (at 400, 500, and 600 MHz) and are reported relative to the residual solvent signal. Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ¹³C NMR spectra were recorded on Bruker spectrometers (at 100, 125, and 150 MHz) and are reported relative to the residual solvent signal. Data for ¹³C-NMR spectra are reported in terms of chemical shift (δ ppm). ¹⁹F NMR spectra were recorded on Bruker spectrometers (at 376 MHz) and reported in terms of chemical shift (δ ppm). IR spectra were obtained on a Perkin-Elmer UATR Two FT-IR spectrometer and are reported in terms of frequency of absorption (cm⁻¹). DART-MS spectra were collected on a Thermo Exactive Plus MSD (Thermo

Scientific) equipped with an ID-CUBE ion source, a Vapor Interface (IonSense Inc.), and an Orbitrap mass analyzer. Both the source and MSD were controlled by Excalibur software v. 3.0. The analyte was spotted onto OpenSpot sampling cards (IonSense Inc.) using CDCl₃ or CH₂Cl₂ as the solvent. Ionization was accomplished using UHP He (Airgas Inc.) plasma with no additional ionization agents. The mass calibration was carried out using Pierce LTQ Velos ESI (+) and (–) Ion calibration solutions (Thermo Fisher Scientific). Optical rotations were measured with a Rudolf Autopol III Automatic Polarimeter. Determination of enantiopurity was carried out on an Agilent 1260 SFC (supercritical fluid chromatography) using a Diacel ChiralPak IB column or a JASCO SFC using a Diacel ChiralPak IG column.

Silyl enol ether **4.39** and silyl ketone **4.41** are known compounds.⁴⁹ ¹H NMR spectral data match those reported in literature. Experimental information for **4.19a**, **4.19b**, **4.21a**, **4.21b**, **4.23**, **4.25**, **4.46**, and **4.47** is detailed in our recent report.⁵⁷

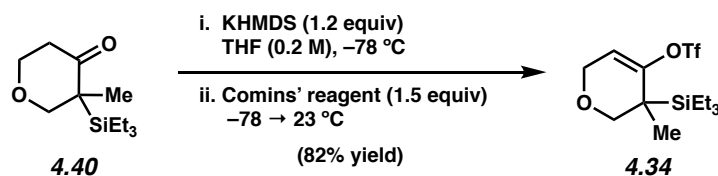
4.5.2 Experimental Procedures

4.5.2.1 Synthesis of Silyl Triflates



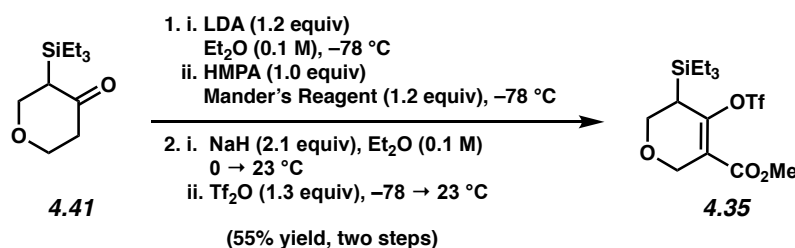
Silyl ketone 4.40: To a solution of silyl enol ether **4.39** (1.00 g, 3.41 mmol, 1.00 equiv) in THF (40 mL) at $-78\text{ }^{\circ}\text{C}$ was added *n*-BuLi (2.09 mL, 2.4 M in hexanes, 5.11 mmol, 1.50 equiv) over 3 min. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. Neat MeI (2.42 g, 1.07 mL, 17.0 mmol, 5.00 equiv) was then added over 4 min at $-78\text{ }^{\circ}\text{C}$ and the reaction was allowed to stir at this temperature for 2 h. The reaction was then warmed to $23\text{ }^{\circ}\text{C}$ and stirred for an additional 5 h, after which it was

quenched by the addition of deionized water (100 mL). The layers were shaken, then separated and the aqueous layer was extracted with EtOAc (4 x 50 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (19:1 hexanes:EtOAc → 4:1 hexanes:EtOAc) to afford silyl ketone **4.40** as a colorless oil (540 mg, 69% yield). Silyl ketone **4.40**: *R_f* 0.29 (9:1 hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃): δ 4.26–4.18 (m, 2H), 3.70 (td, *J* = 3.6, 11.9, 1H), 3.38 (d, *J* = 11.4, 1H), 2.60 (ddd, *J* = 7.8, 12.1, 15.8, 1H), 2.36–2.30 (m, 1H), 1.08 (s, 3H), 0.99 (t, *J* = 7.9, 9H), 0.79–0.65 (m, 6H); ¹³C NMR (150 MHz, CDCl₃): δ 209.9, 75.1, 67.9, 46.9, 41.5, 15.9, 7.8, 2.8; IR (film): 2956, 2878, 1687, 1460 cm⁻¹; HRMS–APCI (*m/z*) [*M* + *H*]⁺ calcd for C₁₂H₂₅O₂Si⁺, 229.1618; found 229.1621.



Silyl triflate 4.34: To a flask in the glovebox was added KHMDS (331 mg, 1.66 mmol, 1.20 equiv). The flask was then removed from the glovebox, charged with THF (2.30 mL), and cooled to -78 °C. To another flask was added the silyl ketone **4.40** (316 mg, 1.38 mmol, 1.00 equiv) and THF (2.30 mL). The ketone solution was then added dropwise over 5 min to the KHMDS solution at -78 °C. After stirring for 1 h at -78 °C, a solution of Comins' Reagent (812 mg, 2.07 mmol, 1.50 equiv) in THF (2.30 mL) was added dropwise over 3 min at -78 °C. The reaction was allowed to gradually warm to 23 °C and stirred for 16 h. After this time, the reaction was quenched with saturated aq. NH₄Cl (15 mL) and diluted with deionized water (10 mL). The layers were shaken, then separated and the aqueous layer was extracted with Et₂O (3 x 15 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to provide the

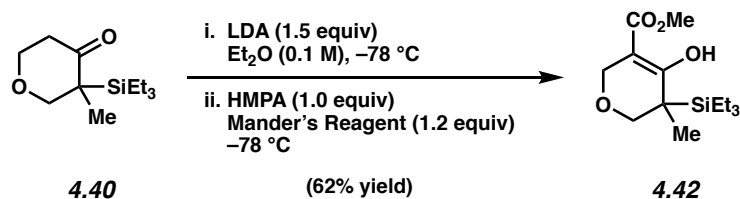
crude residue. The crude residue was purified via flash chromatography (7:1 $\rightarrow$ 1:1 hexanes:benzene) to afford silyl triflate **4.34** (408 mg, 82% yield) as a clear colorless oil. Silyl triflate **4.34**: R_f 0.52 (3:2 hexanes:benzene); ^1H NMR (600 MHz, CDCl_3): δ 5.67 (t, $J = 2.89$, 1H), 4.29 (dd, $J = 3.2, 16.1$, 1H), 4.19 (dd, $J = 2.6, 16.1$, 1H), 3.84 (d, $J = 11.3$, 1H), 3.58 (d, $J = 11.4$, 1H), 1.20 (s, 3H), 1.00 (t, $J = 7.85$, 9H), 0.72–0.66 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ 153.8, 118.5 (q, $J = 319.3$), 111.5, 73.7, 64.8, 31.3, 17.7, 7.8, 2.5; ^{19}F NMR (376 MHz, CDCl_3): δ -74.5; IR (film): 2958, 2880, 2835, 1670, 1416 cm^{-1} . HRMS–APCI (m/z) $[\text{M} - \text{Tf}]^+$ calcd for $\text{C}_{12}\text{H}_{23}\text{O}_2\text{Si}^+$, 227.1462; found 227.1462.



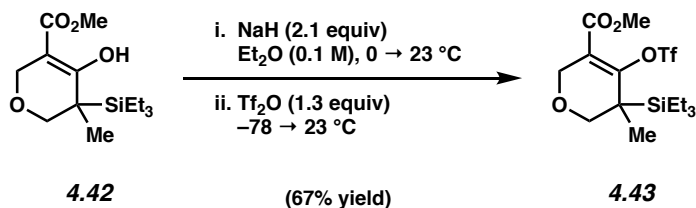
Silyl Triflate 4.35: To a solution of diisopropylamine (0.45 mL, 3.22 mmol, 1.20 equiv) in Et_2O (13 mL) at $-78\text{ }^\circ\text{C}$ was added $n\text{-BuLi}$ (1.34 mL, 2.4 M in hexanes, 3.22 mmol, 1.20 equiv) over 10 min. The reaction was stirred at $-78\text{ }^\circ\text{C}$ for 20 min, then allowed to stir at $23\text{ }^\circ\text{C}$ for 10 min. Then the reaction mixture was cooled to $-78\text{ }^\circ\text{C}$ and a solution of ketone **4.41** (575 mg, 2.68 mmol, 1.00 equiv) in Et_2O (13 mL) was added dropwise over 15 min and stirred at $-78\text{ }^\circ\text{C}$ for 1 h. Then HMPA (467 μL , 2.68 mmol, 1.00 equiv) and Mander's reagent (256 μL , 3.22 mmol, 1.20 equiv) were added dropwise sequentially over 3 min at $-78\text{ }^\circ\text{C}$. The reaction was stirred at $-78\text{ }^\circ\text{C}$ for 1 h, then quenched by the addition of cold deionized water ($0\text{ }^\circ\text{C}$, 15 mL) and allowed to warm to $23\text{ }^\circ\text{C}$. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to provide the crude product, which was purified by flash column chromatography

(hexanes → 9:1 hexanes:EtOAc) to afford the β -keto ester as a colorless oil (605 mg, 2.22 mmol). This material was used directly in the next step.

To a flask in the glovebox was added NaH (68.5 mg, 2.85 mmol, 2.10 equiv). The flask was removed from the glovebox, CH₂Cl₂ (7 mL) was added, and the suspension was cooled to 0 °C. A solution of the β -keto ester (370 mg, 1.36 mmol, 1.00 equiv) in CH₂Cl₂ (7 mL) was added dropwise over 10 min and allowed to warm to 23 °C. After stirring for 1 h, the reaction was cooled to –78 °C and Tf₂O (298 μ L, 1.77 mmol, 1.30 equiv) was added dropwise over 5 min. After stirring for 15 min, the reaction was allowed to warm to 23 °C and stirred for 2 h. The reaction was cooled to 0 °C and was quenched by the addition of deionized water (15 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by flash chromatography (9:1 hexanes:EtOAc) to afford silyl triflate **4.35** (364 mg, 55% yield, two steps) as a clear oil. Silyl triflate **4.35**: *R*_f 0.55 (5:1 hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃): δ 4.55 (dd, *J* = 16.2, 3.0, 1H), 4.36 (dd, *J* = 16.1, 1.8, 1H), 3.93 (d, *J* = 3.8, 2H), 3.78 (s, 3H), 2.12–2.07 (m, 1H), 1.00 (t, *J* = 7.9, 9H), 0.71 (q, *J* = 7.7, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 163.1, 154.6, 118.4 (q, *J* = 320.2), 117.5, 66.5, 65.6, 52.1, 30.2, 7.2, 2.9; ¹⁹F NMR (376 MHz, CDCl₃): δ –74.3; (IR (film): 2957, 2880, 1716, 1655, 1424 cm^{–1}; HRMS–APCI (*m/z*) [M + H]⁺ calcd for C₁₄H₂₄F₃O₆SSi⁺, 405.1010; found 405.1005.



β -Keto Ester 4.42: To a solution of diisopropylamine (0.29 mL, 2.07 mmol, 1.50 equiv) in Et₂O (5.5 mL) at $-78\text{ }^{\circ}\text{C}$ was added *n*-BuLi (863 μL , 2.4 M in hexanes, 2.07 mmol, 1.50 equiv) over 10 min. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 20 min, then allowed to stir at $23\text{ }^{\circ}\text{C}$ for 10 min. Then the reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of ketone **4.40** (315 mg, 1.38 mmol, 1.00 equiv) in Et₂O (8.3 mL) was added dropwise over 7 min and stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. Then HMPA (240 μL , 1.38 mmol, 1.00 equiv) and Mander's reagent (132 μL , 1.656 mmol, 1.20 equiv) were added dropwise sequentially over 5 min at $-78\text{ }^{\circ}\text{C}$. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 3 h, then quenched by the addition of saturated aq. NaHCO₃ (10 mL) and allowed to warm to $23\text{ }^{\circ}\text{C}$. The reaction further diluted with deionized water (25 mL) and Et₂O (25 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by flash column chromatography (40:1 hexanes:EtOAc $\rightarrow$ 5:1 hexanes:EtOAc) to afford β -keto ester **4.42** (243 mg, 62% yield) as a light pink oil. β -keto ester **4.42**: *R*_f 0.60 (9:1 hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃): δ 4.32 (d, *J* = 13.7, 1H), 4.25 (d, *J* = 13.6, 1H), 3.84 (d, *J* = 11.3, 1H), 3.74 (s, 3H), 3.46 (d, *J* = 11.4, 1H), 1.20 (s, 3H), 0.98 (t, *J* = 8.1, 9H), 0.75–0.67 (m, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 177.5, 171.1, 94.5, 73.2, 64.2, 51.4, 32.3, 17.4, 7.9, 2.8; IR (film): 2954, 2877, 1746, 1653, 1607 cm⁻¹; HRMS–APCI (*m/z*) [*M* + *H*]⁺ calcd for C₁₄H₂₇O₄Si⁺, 287.1673; found 287.1682.



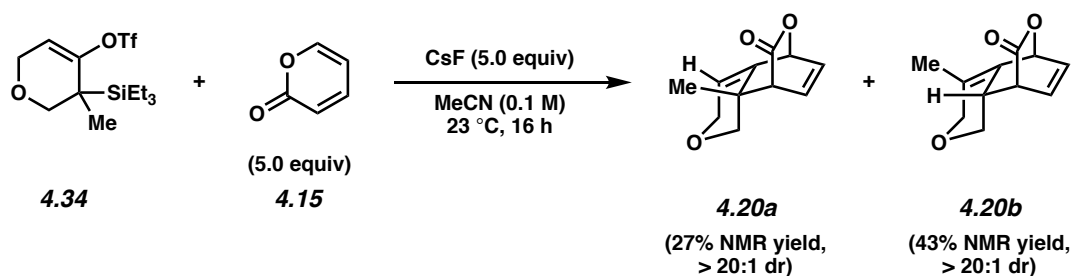
Silyl Triflate 4.43: To a flask in the glovebox was added NaH (17.6 mg, 733 μmol , 2.10 equiv). The flask was removed from the glovebox and Et_2O (1.75 mL) was added at 0 $^\circ\text{C}$. Next, a solution of β -keto ester **4.42** (100 mg, 349 μmol , 1.00 equiv) in Et_2O (1.75 mL) was added dropwise over 3 min and the suspension was allowed to warm to 23 $^\circ\text{C}$. After stirring for 1 h, the reaction was cooled to -78 $^\circ\text{C}$ and Tf_2O (76.7 μL , 454 μmol , 1.30 equiv) was added dropwise over 1 min. After stirring for 2 h at -78 $^\circ\text{C}$, the reaction was allowed to warm to 23 $^\circ\text{C}$ and stirred for 15 h. The reaction was quenched by the addition of deionized water (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure to provide the crude product, which was purified by flash chromatography (19:1 hexanes: EtOAc $\rightarrow$ 5:1 hexanes: EtOAc) to afford silyl triflate **4.43** (98.5 mg, 67% yield) as a clear oil. Silyl triflate **4.43**: R_f 0.47 (9:1 hexanes: EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 4.67 (d, $J = 16.0$, 1H), 4.17 (d, $J = 16.0$, 1H), 3.76 (s, 3H), 3.71 (m, 2H), 1.31 (s, 3H), 1.0 (t, $J = 8.0$, 9H), 0.71 (q, $J = 7.6$, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ 163.8, 156.0, 118.8, 118.5 (q, $J = 320.4$), 74.2, 66.6, 52.3, 33.5, 17.7, 7.7, 2.4; ^{19}F NMR (376 MHz, CDCl_3): δ -72.5 ; IR (film): 2958, 2882, 1724, 1651, 1423 cm^{-1} ; HRMS–APCI (m/z) [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{15}\text{H}_{26}\text{F}_3\text{O}_6\text{SSi}^+$, 419.1166; found 419.1183.

4.5.2.2 Scope of Cycloadditions with Methyl-Substituted Heterocyclic Allenes

General Procedure: To a solution of silyl triflate **4.34** (0.10 mmol, 1.00 equiv) and pyrone (5.00 equiv) in MeCN (1.00 mL, 0.10 M) was added CsF (5.00 equiv). The reaction mixture was allowed to stir at 1000 RPM at 23 $^\circ\text{C}$. After this time, the reaction mixture was filtered through a short plug of silica gel (3 cm silica) eluting with EtOAc ($\sim$ 10 mL) and then concentrated under reduced

pressure. Yields were determined as an average of two experiments via ^1H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.

Any deviations from the General Procedure are detailed below. For all compounds in which the diastereomeric ratio was >20:1, the minor diastereomer was not observed in the ^1H NMR of the crude reaction mixture.



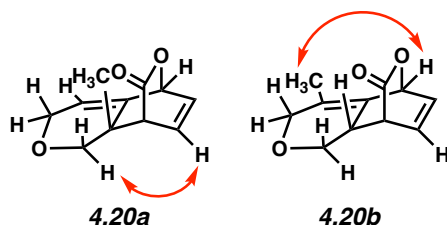
Cycloadducts 4.20a and 4.20b: An analytical sample of 1.4:1 mixture of **4.20a** and **4.20b** was obtained via preparative TLC (9:1 benzene:MeCN followed by 19:1 CH_2Cl_2 : Et_2O). The cycloadducts were characterized as a mixture. Cycloadducts **4.20a** and **4.20b**: R_f 0.17 (2:1 hexanes: EtOAc) ^1H NMR (500 MHz, CDCl_3): **4.20a** (major isomer, proximal cycloadduct): δ 6.48–6.43 (m, 1H), 6.31–6.26 (m, 1H), 5.64 (br s, 1H), 5.45 (d, $J = 5.2$, 1H), 4.44 (d, $J = 17.5$, 1H), 4.08 (dd, $J = 3.3, 17.7$, 1H), 3.64 (d, $J = 9.4$, 1H), 3.30 (d, $J = 5.9$, 1H), 2.77 (d, $J = 9.2$, 1H), 1.29 (s, 3H); **4.20b** (minor isomer, distal cycloadduct): δ 6.55–6.51 (m, 1H), 6.20–6.15 (m, 1H), 5.74 (d, $J = 5.0$, 1H), 4.19 (d, $J = 16.7$, 1H), 4.03 (dd, $J = 4.3, 9.3$, 1H), 3.94–3.88 (m, 1H), 3.57–3.53 (m, 1H), 2.70–2.64 (m, 1H), 2.62–2.57 (m, 1H), 1.69 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 172.5, 171.6, 136.5, 133.1, 132.5, 127.7, 126.5, 126.2, 126.0, 118.7, 77.3, 74.5, 71.7, 68.7, 67.4, 64.6, 50.6, 43.9, 34.3, 32.0, 22.5, 13.8; IR (film): 2981, 2922, 2886, 1759, 1382 cm^{-1} . HRMS–APCI (m/z) [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{11}\text{H}_{13}\text{O}_3^+$, 193.0859; found 193.0865.

*Note: Compounds **4.20a** and **4.20b** were characterized as a mixture of constitutional isomers.*

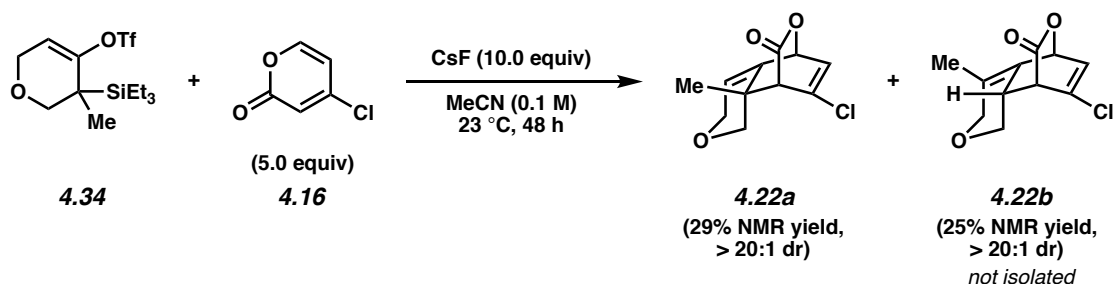
*Due to the selective decomposition of constitutional isomer **4.20b**, the ratio of cycloadducts*

***4.20a:b** changes upon purification of the crude reaction mixture.*

The structure of **4.20a** and **4.20b** were verified by 2D-NOESY, as the following interactions were observed.



The endo stereochemical relationship shown in **4.20b** was also assigned in analogy to similar azacyclic variants recently reported.⁵⁷

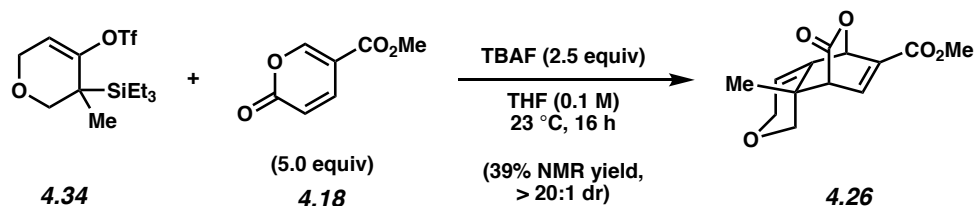
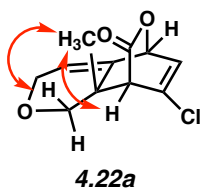


Cycloadduct 4.22a: 10.0 equivalents of CsF were added to this reaction mixture and the reaction was allowed to stir for 48 h. An analytical sample of **4.22a** was obtained via preparative TLC (9:1 benzene:MeCN followed by 19:1 CH₂Cl₂:Et₂O). Cycloadduct **4.22a**: *R_f* 0.40 (2:1 hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃): δ 6.39 (dd, *J* = 2.1, 5.57, 1H), 5.67 (br s, 1H), 5.44 (d, *J* = 5.7, 1H), 4.44 (d, *J* = 17.8, 1H), 4.12 (dd, *J* = 3.2, 17.7, 1H), 3.74 (d, *J* = 9.6, 1H), 3.38 (d, *J* = 1.48, 1H), 2.97 (d, *J* = 9.5, 1H), 1.31 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 169.3, 136.1, 132.4, 127.8,

119.4, 77.1, 70.6, 64.6, 58.2, 34.7, 22.2; IR (film): 2981, 2932, 2862, 1765, 1611 cm^{-1} ; HRMS–APCI (m/z) [$M + H$] $^{+}$ calcd for $\text{C}_{11}\text{H}_{12}\text{ClO}_3^{+}$, 227.0470; found 227.0465.

*Note: Cycloadduct **4.22b** was observed in the ^1H NMR spectrum of the crude material, but an analytical sample could not be obtained due to decomposition. The yield of cycloadduct **4.22b** reported in Figure 4.2 is based on integration of peaks analogous to those observed for cycloadduct **4.20b**.*

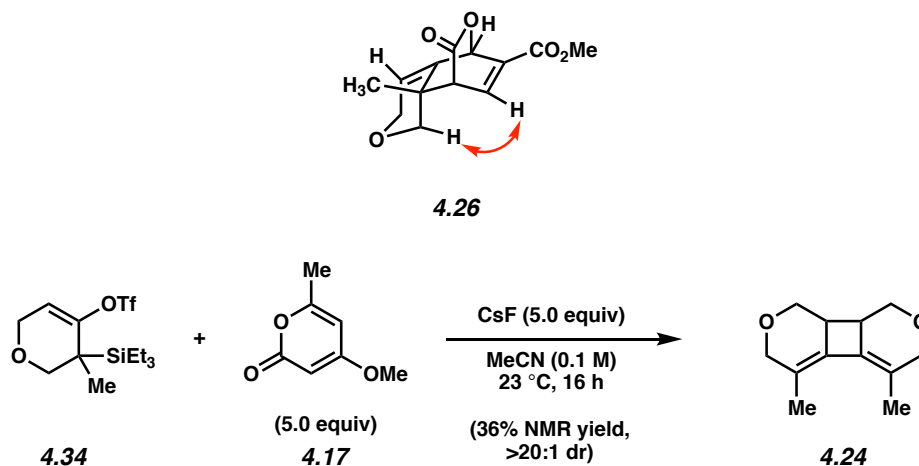
The structure of **4.22a** was verified by 2D-NOESY, as the following interactions were observed.



Cycloadduct 4.26: To a solution of silyl triflate **4.34** (36.0 mg, 0.10 mmol, 1.00 equiv) and pyrone **4.18** (77.1 mg, 0.50 mmol, 5.00 equiv) in THF (10.0 mL, 0.10 M) was added TBAF (0.25 mL, 0.25 mmol, 2.50 equiv). The reaction mixture was allowed to stir at 1000 RPM at 23 $^\circ\text{C}$ for 16 h. After this time, the reaction mixture was filtered through a short plug of silica gel (3 cm silica) eluting with EtOAc (~10 mL) and then concentrated under reduced pressure. The yield was determined as an average of two experiments via ^1H NMR analysis using 1,3,5-trimethoxybenzene as an external standard. An analytical sample of **4.26** was obtained via preparative TLC (3:1 hexanes:EtOAc, followed by 19:1 CH_2Cl_2 :Et₂O, followed by 4:1:1 hexanes: CH_2Cl_2 :Et₂O, followed by 5:1 benzene:acetone). Cycloadduct **4.26**: R_f 0.17 (2:1 hexanes:EtOAc); ^1H NMR (500

MHz, CDCl₃): δ 7.11 (dd, J = 1.7, 6.3, 1H), 5.94 (s, 1H), 5.77 (br s, 1H), 4.44 (d, J = 17.8, 1H), 4.07 (dd, J = 3.2, 18.1, 1H), 3.81 (s, 3H), 3.67 (d, J = 9.5, 1H), 3.46 (d, J = 6.3, 1H), 2.70 (d, J = 9.5, 1H), 1.33 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 169.9, 162.1, 137.4, 136.4, 135.3, 120.1, 76.7, 71.6, 64.7, 52.6, 51.0, 34.8, 22.5; IR (film): 2981, 2882, 1771, 1721, 1354 cm⁻¹; HRMS–APCI (m/z) [$M + H$]⁺ calcd for C₁₃H₁₅O₅⁺, 251.0914; found 251.0909.

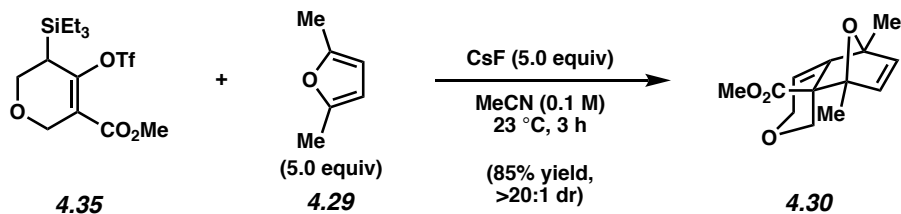
The structure of **4.26** was verified by 2D-NOESY, as the following interactions were observed.



Dimer 4.24: An analytical sample of **4.24** was obtained via preparative TLC (3:1 hexanes:EtOAc, followed by 4:1:1 hexanes:CH₂Cl₂:Et₂O, followed by a short plug of silica gel (3 cm silica) washing with hexanes (10 mL) and eluting with EtOAc (10 mL)). Dimer **4.24**: R_f 0.20 (5:1 hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃): δ 4.18 (d, J = 16.1, 2H), 4.05 (dd, J = 5.6, 10.0, 2H), 3.96 (d, J = 16.1, 2H), 3.15 (t, J = 9.7, 2H), 2.67 (br s, 2H), 1.69 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 133.3, 118.1, 68.6, 67.4, 42.6, 15.1; IR (film): 2981, 2915, 2850, 1374, 1252 cm⁻¹; HRMS–APCI (m/z) [$M + H$]⁺ calcd for C₁₂H₁₆O₂⁺, 193.1223; found 193.1232.

Note: 4.24 was isolated as a single isomer, but as an unassigned due to the dimeric nature of the product.

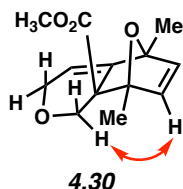
4.5.2.3 Cycloadditions with Ester-Substituted Oxacyclic Allenes

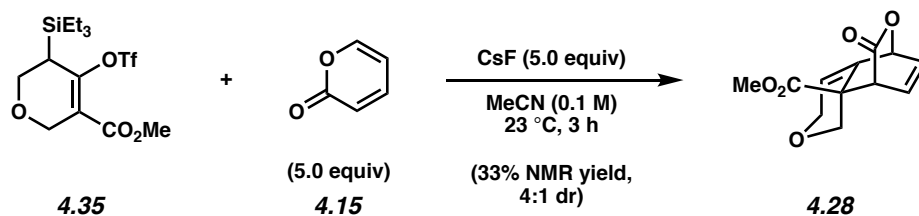


Cycloadduct 4.30: Silyl triflate **4.35** (20 mg, 0.05 mmol, 1.00 equiv) and furan **4.29** (27 μ L, 0.25 mmol, 5.0 equiv) were added to the reaction flask and dissolved in MeCN (0.50 mL, 0.10 M). The solution was purged with nitrogen for 5 min and then CsF (38 mg, 0.25 mmol, 5.00 equiv) was added to the vial. The reaction mixture was then allowed to stir at 1000 RPM at 23 °C for 3 h. After this time, the reaction mixture was filtered through a short plug of silica gel (3 cm silica) eluting with EtOAc (~10 mL) and then concentrated under reduced pressure. Purification by flash chromatography (9:1 $\rightarrow$ 1:1 hexanes:EtOAc) afforded cycloadduct **4.30** as a clear oil (85% yield).

Cycloadduct 4.30: R_f 0.48 (1:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 6.22 (d, $J = 5.3$, 1H), 5.89 (d, $J = 5.3$, 1H), 5.57–5.52 (m, 1H), 4.54 (d, $J = 9.4$, 1H), 4.31 (d, $J = 17.0$, 1H), 4.00–3.92 (m, 1H), 3.76–3.70 (m, 3H), 2.41 (d, $J = 9.4$, 1H), 1.73 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 172.6, 142.7, 142.1, 133.8, 115.4, 88.6, 87.1, 70.7, 64.8, 57.4, 52.5, 16.8, 14.8; IR (film): 3090, 2933, 1722, 1452, 1217 cm^{-1} ; HRMS–APCI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{17}\text{O}_4^+$, 237.1121; found 237.1121.

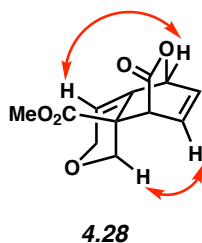
The structure of **4.30** was verified by 2D-NOESY, as the following interactions were observed.

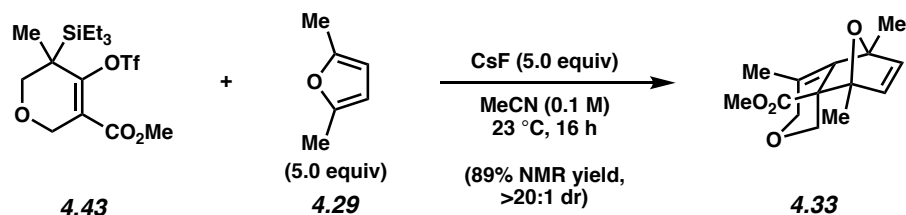




Cycloadduct 4.28: Silyl triflate **4.35** (21 mg, 0.05 mmol, 1.00 equiv) and pyrone **4.15** (21 μL , 0.26 mmol, 1.0 equiv) were added to the reaction flask and dissolved in MeCN (0.52 mL, 0.10 M). The solution was purged with nitrogen for 5 min and then CsF (39 mg, 0.26 mmol, 5.00 equiv) was added to the vial. The reaction mixture was then allowed to stir at 1000 RPM at 23 $^\circ\text{C}$ for 3 h. After this time, the reaction mixture was filtered through a short plug of silica gel (3 cm silica) eluting with EtOAc (~ 10 mL) and then concentrated under reduced pressure. Yields were determined via ^1H NMR analysis using 1,3,5-trimethoxybenzene as an external standard. An analytical sample of **4.28** was obtained via preparative TLC (1:1 hexanes:EtOAc). Cycloadduct **4.28**: R_f 0.21 (1:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 6.57 (t, $J = 6.0$, 1H), 6.34–6.25 (m, 1H), 5.85 (s, 1H), 5.58 (d, $J = 4.5$, 1H), 4.52–4.33 (m, 2H), 4.11 (d, $J = 18.3$, 1H), 3.79 (d, $J = 6.1$, 1H), 3.75 (s, 3H), 2.75 (d, $J = 9.5$, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 171.3, 169.7, 135.4, 134.6, 131.8, 127.7, 126.4, 121.4, 76.4, 69.9, 69.1, 65.5, 65.4, 53.4, 49.0, 47.4, 47.2; IR (film): 3089, 2862, 1758, 1733, 1478 cm^{-1} ; HRMS–APCI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{13}\text{O}_5^+$, 237.0758; found 237.0761.

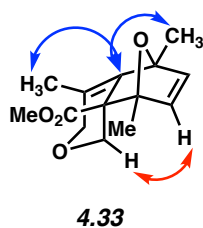
The structure of **4.28** was verified by 2D-NOESY, as the following interaction was observed.

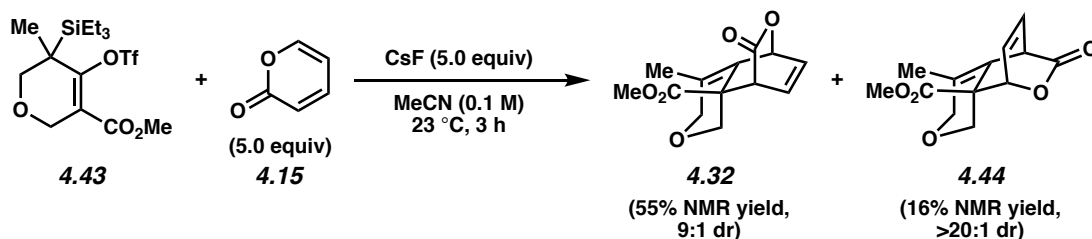




Cycloadduct 4.33: Silyl triflate **4.43** (42 mg, 0.1 mmol, 1.00 equiv) and furan **4.29** (53 μ L, 0.50 mmol, 1.0 equiv) were added to the reaction flask and dissolved in MeCN (1.0 mL, 0.10 M). CsF (76 mg, 0.50 mmol, 5.00 equiv) was added to the vial. The reaction mixture was then allowed to stir at 1000 RPM at 23 °C for 16 h. After this time, the reaction mixture was filtered through a short plug of silica gel (3 cm silica) eluting with EtOAc (~10 mL) and then concentrated under reduced pressure. The yield was determined via ^1H NMR analysis using 1,3,5-trimethoxybenzene as an external standard. An analytical sample of **4.33** was obtained via preparative TLC (2:1 hexanes:EtOAc). Cycloadduct **4.33**: R_f 0.23 (1:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 6.36 (d, $J = 5.3$, 1H), 5.87 (d, $J = 5.3$, 1H), 4.49 (d, $J = 9.4$, 1H), 4.07 (d, $J = 16.4$, 1H), 3.72 (s, 3H), 3.69 (d, 16.4, 1H), 2.38 (d, $J = 9.4$, 1H), 1.88 (s, 3H), 1.68 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 173.0, 141.6, 135.3, 134.4, 123.1, 87.8, 87.6, 70.7, 68.6, 57.0, 52.4, 17.7, 16.8, 13.8; IR (film): 2981, 2867, 1721, 1453, 1384 cm^{-1} . HRMS–APCI (m/z) [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{14}\text{H}_{19}\text{O}_4^+$, 251.1278; found 251.1277.

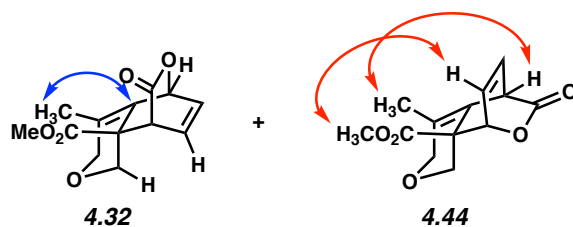
The structure of **4.33** was verified by 2D-NOESY (red) and 2D-HMBC (blue), as the following interactions were observed.



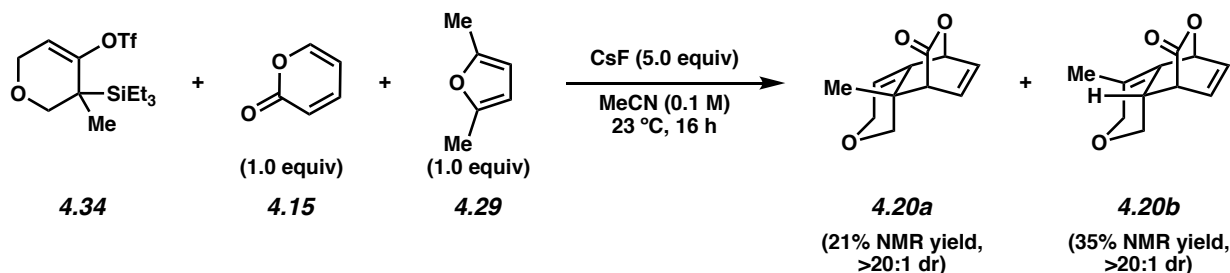


Cycloadducts 4.32 and 4.44: Silyl triflate **4.43** (42 mg, 0.1 mmol, 1.00 equiv) and pyrone **4.15** (48 mg, 0.50 mmol, 1.0 equiv) were added to the reaction flask and dissolved in MeCN (1.0 mL, 0.10 M). CsF (76 mg, 0.50 mmol, 5.00 equiv) was added to the vial. The reaction mixture was then allowed to stir at 1000 RPM at 23 °C for 16 h. After this time, the reaction mixture was filtered through a short plug of silica gel (3 cm silica) eluting with EtOAc (~10 mL) and then concentrated under reduced pressure. Yields were determined via ^1H NMR analysis using 1,3,5-trimethoxybenzene as an external standard. Analytical samples of constitutional isomers **4.32** and **4.44** were obtained via preparative TLC (2:1 hexanes:EtOAc followed by 2:1:1 benzene:CH₂Cl₂:Et₂O). Cycloadduct **4.32** (major product): R_f 0.28 (1:1 hexanes:EtOAc); ^1H NMR (600 MHz, CDCl₃): 6.60–6.56 (m, 1H), 6.29–6.25 (m, 1H), 5.86 (dd, J = 1.5, 5.2, 1H), 4.36 (d, J = 9.4, 1H), 4.25 (d, J = 17.1, 1H), 3.92 (d, J = 17.0, 1H), 3.77 (dd, J = 1.6, 6.2, 1H), 3.74 (s, 3H), 2.76 (d, J = 9.4, 1H), 1.74 (s, 3H); ^{13}C NMR (125 MHz, CDCl₃): 171.8, 170.2, 133.9, 128.4, 126.7, 124.9, 74.0, 70.4, 68.8, 53.3, 47.2, 46.9, 14.1; IR (film): 2981, 2922, 1757, 1737, 1453 cm⁻¹. HRMS–APCI (m/z) [$M + H$]⁺ calcd for C₁₃H₁₅O₅⁺, 251.0914; found 251.0912. Cycloadduct **4.44** (minor product): R_f 0.23 (1:1 hexanes:EtOAc); ^1H NMR (600 MHz, CDCl₃): 6.56–6.52 (m, 1H), 6.50–6.46 (m, 1H), 5.26 (dd, J = 1.7, 4.6, 1H), 4.47 (d, J = 6.0, 1H), 4.34 (d, J = 10.0, 1H), 4.23 (d, J = 16.9, 1H), 4.00 (d, J = 16.9, 1H), 3.67 (s, 3H), 3.38 (d, J = 10.0, 1H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, CDCl₃): 171.1, 169.2, 133.4, 131.5, 130.4, 117.7, 74.6, 69.5, 69.3, 52.8, 52.7, 45.3, 14.4; IR (film): 2981, 2886, 1749, 1728, 1382 cm⁻¹. HRMS–APCI (m/z) [$M + H$]⁺ calcd for C₁₃H₁₅O₅⁺, 251.0914; found 251.0916.

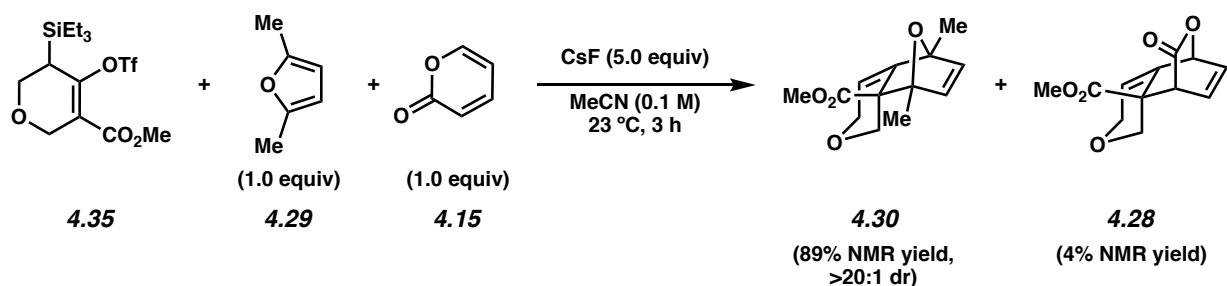
The structure of **4.32** and **4.44** was verified by 2D-NOESY and 2D-HMBC (blue), as the following interactions were observed.



4.5.2.4. Competition Experiments

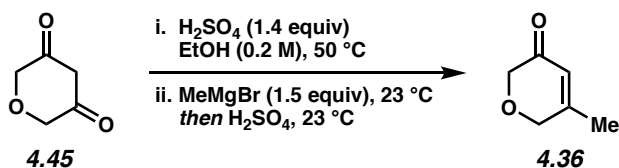


Silyl triflate **4.34** (18.0 mg, 50 μ mol, 1.00 equiv), furan **4.29** (5.3 μ L, 50 μ mol, 1.0 equiv), and pyrone **4.15** (4.8 mg, 50 μ mol, 1.0 equiv) were added to the reaction vial and dissolved in MeCN (500 μ L, 0.10 M). CsF (38.0 mg, 250 μ mol, 5.00 equiv) was added to the vial. The reaction mixture was then allowed to stir at 1000 RPM for 16 h at 23 °C. After this time, the reaction mixture was filtered through a short plug of silica gel (3 cm silica) eluting with EtOAc (~10 mL) and then concentrated under reduced pressure. Yields were determined via ¹H NMR analysis using 1,3,5-trimethoxybenzene as an external standard. Characterization data for **4.20a** and **4.20b** are detailed in Section 4.5.2.2.



Silyl triflate **4.35** (20.0 mg, 49.4 μmol , 1.00 equiv), furan **4.29** (5.3 μL , 49 μmol , 1.0 equiv), and pyrone **4.15** (3.4 μL , 49 μmol , 1.0 equiv) were added to the reaction vial and dissolved in MeCN (494 μL , 0.10 M). The solution was purged with nitrogen for 5 min and then CsF (37.6 mg, 247 μmol , 5.00 equiv) was added swiftly to the vial. The reaction mixture was then allowed to stir at 1000 RPM at 23 $^{\circ}\text{C}$ for 3 h. After this time, the reaction mixture was filtered through a short plug of silica gel (3 cm silica) eluting with EtOAc ($\sim$ 10 mL) and then concentrated under reduced pressure. Yields were determined via ^1H NMR analysis using 1,3,5-trimethoxybenzene as an external standard. Characterization data for **4.30** and **4.28** are detailed in Section 4.5.2.3.

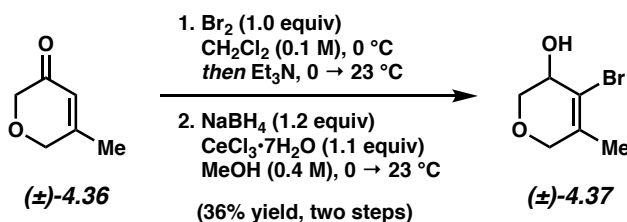
4.5.2.5. Racemic Oxacyclic Silyl Bromide Synthesis and Diels–Alder Cycloaddition



Enone 4.36.^{47,48,65} To a stirring solution of 2H-pyran-3,5(4H,6H)-dione (**4.45**) (1.51 g, 13.2 mmol, 1.00 equiv) in EtOH (75.0 mL, 0.2 M) was added H_2SO_4 (95–98%, 1.17 mL, 1.40 equiv). The flask was fitted with an air condenser and the reaction was stirred at 50 $^{\circ}\text{C}$ for 16 h. After this time, the reaction was quenched with saturated aq. NaHCO_3 (50 mL). The solution was diluted with deionized water (50 mL) and EtOAc (50 mL). The layers were separated and the aqueous layer

was extracted with EtOAc (3 x 75 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to provide the crude product, which was filtered over a pad of silica 1:1 hexanes:EtOAc as the eluent to afford the enol ether as a yellow solid (1.01 g, 7.11 mmol). This material was used directly in the next step.

To a stirring solution of the enol ether (919 mg, 6.46 mmol, 1.00 equiv) in Et₂O (23 mL, 0.3 M) at 23 °C was added methylmagnesium bromide (3.0 M in Et₂O, 3.23 mL, 9.70 mL, 1.50 equiv) dropwise over 8 min. The reaction was stirred at 23 °C for 45 min, after which an aqueous solution of H₂SO₄ (10% w/w, 45 mL) was added dropwise over 10 min at 23 °C, and the solution was stirred vigorously at 900 rpm for an additional 15 min. The biphasic mixture was diluted with deionized water (50 mL) and Et₂O (50 mL), the layers were separated, and the aqueous layer was extracted with Et₂O (3 x 30 mL). The combined organic layers were washed with brine (100 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure (vacuum pressure ≥ 400 mbar). Due to volatility concerns, the product was subjected to the next reaction without further purification, but analytical samples of enone **4.36** matched those reported in the literature.⁷⁰

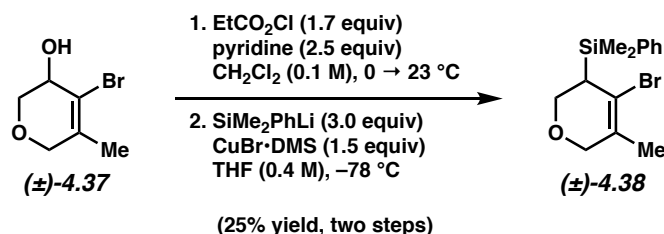


Alcohol (±)-4.37.^{47,48,65} A solution of enone **4.36** (1.03 g, 9.16 mmol, 1.00 equiv) in CH₂Cl₂ (61.0 mL, 0.15 M) was cooled to 0 °C. The hood light was then turned off for the duration of the reaction and workup. To this solution was added a separate solution of bromine (1.46 g, 472 μL, 9.16 mmol, 1.00 equiv) in CH₂Cl₂ (30.0 mL, 0.3 M) dropwise over 20 min. The reaction was covered with aluminum foil and allowed to stir at 0 °C for 25 min. After 25 min, triethylamine (1.85 g, 2.55 mL,

18.3 mmol, 2.00 equiv) was added dropwise over 10 min at 0 °C. The reaction was allowed to warm to 23 °C and stir for 1.5 h. After this time, the reaction was diluted with CH₂Cl₂ (50 mL) and deionized water (100 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with deionized water (200 mL), saturated aqueous sodium thiosulfate (1 x 250 mL, 1 x 100 mL), and brine (200 mL). The organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by automated chromatography (hexanes → 1:4 hexanes:EtOAc) to afford the bromoenone as an orange solid (700 mg, 3.67 mmol). This material was used directly in the next step.

To a solution of the bromoenone (301 mg, 1.57 mmol, 1.00 equiv) in MeOH (3.9 mL, 0.4 M) was added CeCl₃•7H₂O (645 mg, 1.73 mmol, 1.10 equiv). The solution was cooled to 0 °C and NaBH₄ (71.4 mg, 1.89 mmol, 1.20 equiv) was added in 5 portions over 5 min. The solution was allowed to stir at 0 °C for 30 minutes, and then allowed to warm to 23 °C and stirred for an additional 1.25 h. After this time, the reaction was cooled to 0 °C and quenched with 1 M HCl (5 mL) dropwise over 4 min. The mixture was allowed to stir for 10 min at 23 °C and then was transferred to a separatory funnel with water (10 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 15 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was filtered through a pad of celite using Et₂O and concentrated to afford the crude enantioenriched alcohol as a light yellow oil (270 mg, 1.40 mmol, 36% yield, two steps). Alcohol (±)-**4.37** was used in subsequent steps without further purification due to instability upon prolonged exposure to silica gel. The calculated yield reflects the mass of crude alcohol obtained. An analytical sample of (±)-**4.37** was afforded via silica plug (1 x 1 cm silica), eluting with EtOAc (5 mL). Alcohol (±)-**4.37**: R_f 0.28 (2:1

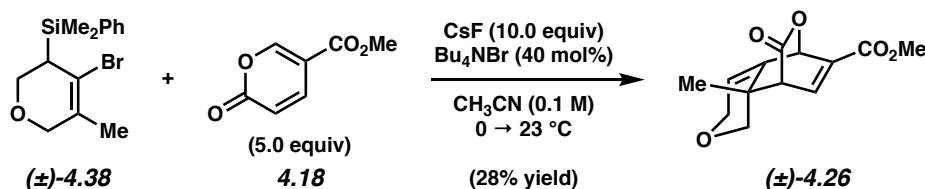
hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): 4.11–4.00 (m, 3H), 3.97 (dd, $J = 11.8, 2.5$, 1H), 3.78 (dd, $J = 11.9, 3.0$, 1H), 2.28 (br s, 1H), 1.76–1.74 (m, 3H); δ ^{13}C NMR (125 MHz, CDCl_3): δ 136.2, 118.5, 71.3, 70.4, 69.5, 18.3; IR (film): 3395, 2926, 2855, 1451, 1050 cm^{-1} .



Silyl Bromide (±)-4.38.^{47,48,65} A solution of alcohol (±)-4.37 (176 mg, 0.914 mmol, 1.00 equiv) in CH_2Cl_2 (9.1 mL, 0.1 M) was cooled to $0\text{ }^\circ\text{C}$. To the solution was added pyridine (0.185 mL, 2.23 mmol, 2.50 equiv) as a single portion, followed by ethyl chloroformate (0.148 mL, 1.55 mmol, 1.70 equiv) dropwise over 2 min. The reaction was stirred at $0\text{ }^\circ\text{C}$ for 10 min and then allowed to warm to $23\text{ }^\circ\text{C}$, stirring for another 1.5 h. After this time, the reaction mixture was diluted with Et_2O (10 mL) quenched with saturated aq. NaHCO_3 (15 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified via automated chromatography (hexanes $\rightarrow$ 1:1 hexanes:EtOAc) to afford the carbonate (167 mg, 0.628 mmol). This material was used directly in the next step.

To a solution of $\text{CuBr}\cdot\text{DMS}$ (69.8 mg, 0.339 mol, 1.50 equiv) in THF (3.4 mL, 0.1 M) at $0\text{ }^\circ\text{C}$ was added (dimethyl(phenyl)silyl)lithium^{47,48,65} (0.87 mL, 0.780 M, 0.679 mmol, 3.00 equiv) dropwise over 2 min. The mixture was stirred at $0\text{ }^\circ\text{C}$ for 30 min and then cooled to $-78\text{ }^\circ\text{C}$. Then, a solution of the carbonate (60.0 mg, 0.226 mmol, 1.00 equiv) in THF (2.4 mL, 0.09 M) was added dropwise over 2 minutes. The reaction was allowed to stir at $-78\text{ }^\circ\text{C}$ for 1.5 h. After this time, the reaction was diluted with Et_2O (5 mL), quenched with water (10 mL), and allowed to warm to $23\text{ }^\circ\text{C}$.

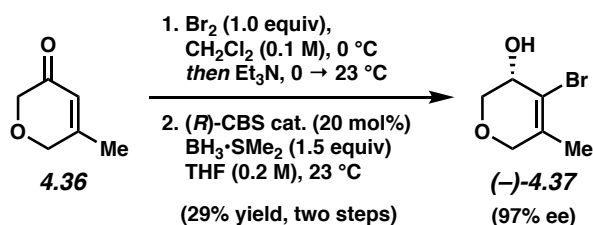
°C. The reaction mixture was then transferred to a separatory funnel containing Et₂O (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with Et₂O (2 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified via automated chromatography (hexanes → 1:1 hexanes:EtOAc) to afford silyl bromide (±)-**4.38** (25 mg, 0.081 mmol, 25% yield, two steps) as a colorless oil. Silyl bromide (±)-**4.38**: R_f: R_f 0.34 (9:1 hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃): 7.58–7.53 (m, 2H), 7.32–7.28 (m, 3H), 4.06 (d, *J* = 15.4, 1H), 3.91 (d, *J* = 15.4, 1H), 3.78 (dd, *J* = 10.9, 2.5, 1H), 3.72 (dd, *J* = 10.7, 3.4, 1H), 2.16 (app br s, 1H), 1.65 (s, 3H), 0.50 (s, 3H), 0.42 (s, 3H); δ ¹³C NMR (125 MHz, CDCl₃): δ 137.7, 134.2, 129.2, 128.1, 127.8, 117.5, 70.4, 68.2, 37.6, 18.3, –2.0, –3.3; IR (film): 2958, 2853, 1428, 1251, 1108 cm^{–1}.



Cycloadduct (±)-4.26. In a vial, silyl bromide (±)-**4.38** (20.0 mg, 0.064 mmol, 1.00 equiv) and pyrone **4.18** (49.3 mg, 0.320 mmol, 5.00 equiv) were dissolved in MeCN (0.64 mL, 0.1 M). CsF (97.1 mg, 0.639 mmol, 10.0 equiv) was added to the vial and the heterogenous solution was cooled to 0 °C. The reaction mixture was allowed to stir 2 min, and then Bu₄NBr (8.2 mg, 0.026 mmol, 40 mol%) was added at 0 °C. The reaction was sealed with a Teflon-lined cap and stirred at 1000 rpm while gradually warming to 23 °C. After stirring at 1000 rpm for 19 h, the reaction mixture was filtered through a short plug of silica gel (1 cm silica) eluting with EtOAc (10 mL) and then concentrated under reduced pressure. The yield was determined via ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an external standard. An analytical sample of

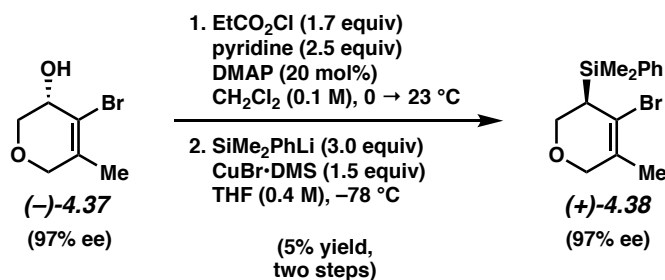
(±)-**4.26** was obtained by automated chromatography (2:1 hexanes:EtOAc → 1:4 hexanes:EtOAc) and preparatory TLC (9:1 benzene:acetone). Characterization data matched those reported in Section 4.5.2.2.

4.5.2.6. Enantioselective Oxacyclic Silyl Bromide Synthesis and Stereospecific Diels–Alder Cycloaddition



Alcohol (-)-4.37.^{47,48,65} A solution of enone **4.36** (1.03 g, 9.16 mmol, 1.00 equiv) in CH₂Cl₂ (61.0 mL, 0.15 M) was cooled to 0 °C. The hood light was then turned off for the duration of the reaction and workup. To this solution was added a separate solution of bromine (1.46 g, 472 μL, 9.16 mmol, 1.00 equiv) in CH₂Cl₂ (30.0 mL, 0.3 M) dropwise over 20 min. The reaction was covered with aluminum foil and allowed to stir at 0 °C for 25 min. After 25 min, triethylamine (1.85 g, 2.55 mL, 18.3 mmol, 2.00 equiv) was added dropwise over 10 min at 0 °C. The reaction was allowed to warm to 23 °C and stir for 1.5 h. After this time, the reaction was diluted with CH₂Cl₂ (50 mL) and deionized water (100 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with deionized water (200 mL), saturated aqueous sodium thiosulfate (1 x 250 mL, 1 x 100 mL), and brine (200 mL). The organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by automated chromatography (hexanes → 1:4 hexanes:EtOAc) to afford the bromoenone as an orange solid (700 mg, 3.67 mmol). This material was used directly in the next step.

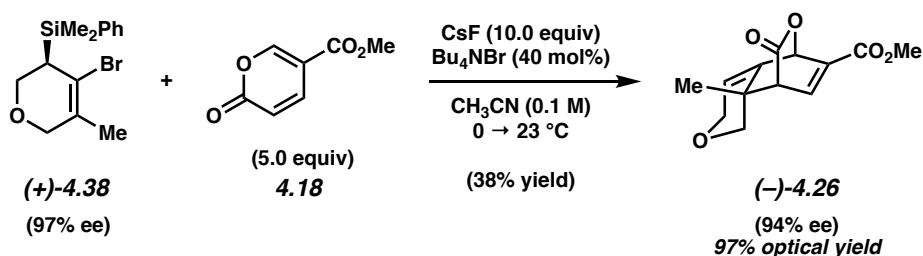
To a vial in the glovebox was added (*R*)-CBS catalyst (61.1 mg, 0.220 mmol, 20.0 mol%). The vial was brought out of the glovebox and the CBS catalyst was dissolved in THF (2.2 mL, 0.1 M). In a separate vial, to a stirring solution of the bromoenone (201 mg, 1.05 mmol, 1.00 equiv) in THF (2.2 mL, 0.5 M) was added the CBS catalyst solution and the reaction mixture was stirred at 23 °C. To this mixture was added borane-methyl sulfide complex (0.78 mL, 2.0 M, 1.60 mmol, 1.50 equiv) dropwise over 5 min at 23 °C. The mixture was allowed to stir at 23 °C for 1.25 h. After this time, the reaction was quenched with methanol (8 mL) dropwise over 15 min at 23 °C and stirred for 1 h at this temperature. The mixture was transferred to a separatory funnel with Et₂O (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 15 mL). The combined organic layers were then washed with water (2 x 50 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure to afford the crude enantioenriched alcohol as a light yellow oil (147 mg, 0.763 mmol, 29% yield, two steps). Alcohol (–)-**4.37** was used in subsequent steps without further purification due to instability upon prolonged exposure to silica gel. The calculated yield reflects the mass of crude alcohol obtained. An analytical sample of the enantioenriched alcohol was afforded via silica plug (1 x 1 cm silica), eluting with EtOAc (5 mL). $[\alpha]_D^{27} -82.8$ ($c = 2.9$ mg/mL, CH₂Cl₂). Characterization data matched those reported in Section 4.5.2.5. Note ee's ranged from 95–97% for this step (see Section 4.6).



Silyl Bromide (+)-4.38.^{47,48,65} A solution of alcohol (-)-4.37 (215 mg, 1.12 mmol, 1.00 equiv) and DMAP (27.2 mg, 0.223 mmol, 20 mol%) in CH_2Cl_2 (11 mL, 0.1 M) was cooled to 0°C . To the solution was added pyridine (0.225 mL, 2.79 mmol, 2.50 equiv) as a single portion and ethyl chloroformate (0.180 mL, 1.90 mmol, 1.70 equiv) dropwise over 2 min. The reaction was stirred and allowed to warm to 23°C , stirring for 2 h. After this time, the reaction mixture was diluted with Et_2O (10 mL) quenched with saturated aq. NaHCO_3 (15 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified via automated chromatography (hexanes $\rightarrow$ 1:1 hexanes: EtOAc) to afford the carbonate (106 mg, 0.398 mmol). This material was used directly in the next step.

To a solution of $\text{CuBr}\cdot\text{DMS}$ (62.2 mg, 0.303 mol, 1.50 equiv) in THF (3.0 mL, 0.1 M) at 0°C was added (dimethyl(phenyl)silyl)lithium^{47,48,65} (2.24 mL, 0.270 M, 0.605 mmol, 3.00 equiv) dropwise over 4 min. The mixture was stirred at 0°C for 30 min and then cooled to -78°C . Then, a solution of the carbonate (53.5 mg, 0.202 mmol, 1.00 equiv) in THF (2.0 mL, 0.1 M) was added dropwise over 4 minutes. The reaction was allowed to stir at -78°C for 1 h. After this time, the reaction was diluted with Et_2O (5 mL), quenched with water (15 mL), and allowed to warm to 23°C . The reaction mixture was then transferred to a separatory funnel containing Et_2O (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under

reduced pressure. The crude residue was purified via automated chromatography (hexanes $\rightarrow$ 3:2 hexanes:EtOAc) and subsequent preparative TLC (two iterations; 3:1 benzene:hexanes, then 1:1:1 hexanes:CH₂Cl₂:benzene) to afford silyl bromide **(+)-4.38** (9.6 mg, 0.031 mmol, 5% yield, two steps). $[\alpha]^{26}_D +48.0$ ($c = 1.0$ mg/mL, CH₂Cl₂). Characterization data matched those reported in Section 4.5.2.5. See Section 4.6 for chiral SFC data. Note: the poor yield is attributed to batch-to-batch variation of the dimethyl(phenyl)silyl)lithium reagent. Since our primary goal was to assess stereoselectivity in the subsequent step, further yield optimization efforts were not undertaken.

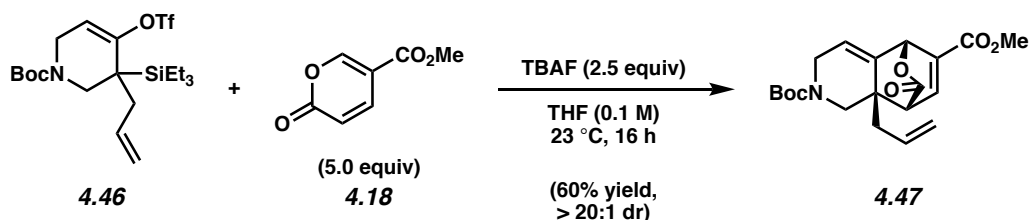


Cycloadduct (-)-4.26. In a vial, silyl bromide **(+)-4.38** (9.6 mg, 0.031 mmol, 1.00 equiv, 97% ee) and pyrone **4.18** (24.0 mg, 0.15 mmol, 5.00 equiv) were dissolved in MeCN (0.31 mL, 0.1 M). CsF (47.0 mg, 0.31 mmol, 10.0 equiv) was added to the vial and the heterogenous solution was cooled to 0 °C. The reaction mixture was allowed to stir 2 min, and then Bu₄NBr (4.0 mg, 0.012 mmol, 40 mol%) was added at 0 °C. The reaction was sealed with a Teflon-lined cap and stirred at 1000 rpm while gradually warming to 23 °C. After stirring at 1000 rpm for 38 h, the reaction mixture was filtered through a short plug of silica gel (1 cm silica) eluting with EtOAc (10 mL) and then concentrated under reduced pressure. The yield was determined via ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an external standard. An analytical sample of **(-)-4.26** was obtained by preparatory TLC (9:1 benzene:acetone) in 94% ee (97% optical

yield). $[\alpha]^{27}_D -77.5$ ($c = 0.8$ mg/mL, CH_2Cl_2). Characterization data matched those reported in Section 4.5.2.2. See Section 4.6 for chiral SFC data.

4.5.2.7. 1 mmol Scale Reaction

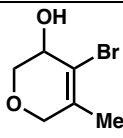
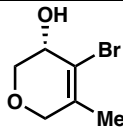
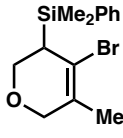
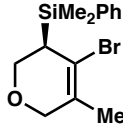
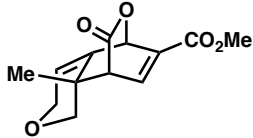
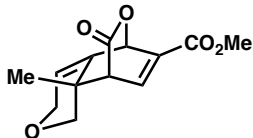
The Diels–Alder cycloaddition of a strained azacyclic allene and pyrone has been performed on a 1 mmol scale⁵⁷ and is detailed below:



Cycloadduct 4.47: To a solution of silyl triflate **4.46** (486 mg, 1.00 mmol, 1.00 equiv) and pyrone **4.18** (771 mg, 5.00 mmol, 5.00 equiv) in THF (10.0 mL, 0.10 M) was added TBAF (2.50 mL, 2.50 mmol, 2.50 equiv). The reaction mixture was allowed to stir at 1000 RPM at 23 °C for 16 h. After this time, the reaction mixture was filtered through a short plug of silica gel (3 cm silica) eluting with EtOAc (75 mL) and then concentrated under reduced pressure. The crude material was purified by column chromatography (9:1 → 1:1 hexanes:EtOAc) to afford **4.47** (227 mg, 60% yield) as an amorphous white foam. Characterization data matched those reported previously.⁵⁷

4.6. Chiral SFC Data

Table 4.1. Chiral SFC information.

Compound	Method Column/Temp.	Solvent	Method Flow Rate	Retention Times (min)	Enantiomeric Ratio (er)
 4.37 (racemic)	Diacel ChiralPak IB / 30 °C	10% isopropanol in CO ₂	1.5 mL/min	5.15/6.12	~50.2:49.8
 4.37 (enantioenriched)	Diacel ChiralPak IB / 30 °C	10% isopropanol in CO ₂	1.5 mL/min	5.21/6.19	~98.3:1.7
 4.38 (racemic)	Diacel ChiralPak IB / 30 °C	5% isopropanol in CO ₂	1.5 mL/min	4.70/5.94	~50.2:49.8
 4.38 (enantioenriched)	Diacel ChiralPak IB / 30 °C	5% isopropanol in CO ₂	1.5 mL/min	4.86/6.11	~98.5:1.5
 4.26 (racemic)	Diacel ChiralPak IG / 30 °C	10% isopropanol in CO ₂	4.0 mL/min	4.16/5.40	~50.1:49.9
 4.26 (enantioenriched)	Diacel ChiralPak IG / 30 °C	10% isopropanol in CO ₂	4.0 mL/min	4.27/5.19	~97.1:2.9

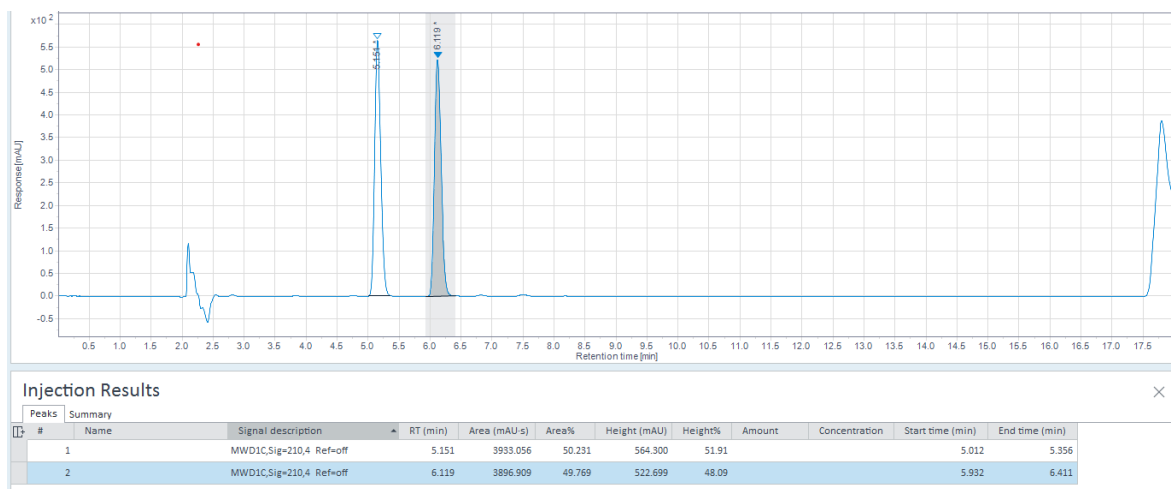


Figure 4.6. SFC trace of racemic **4.37**.

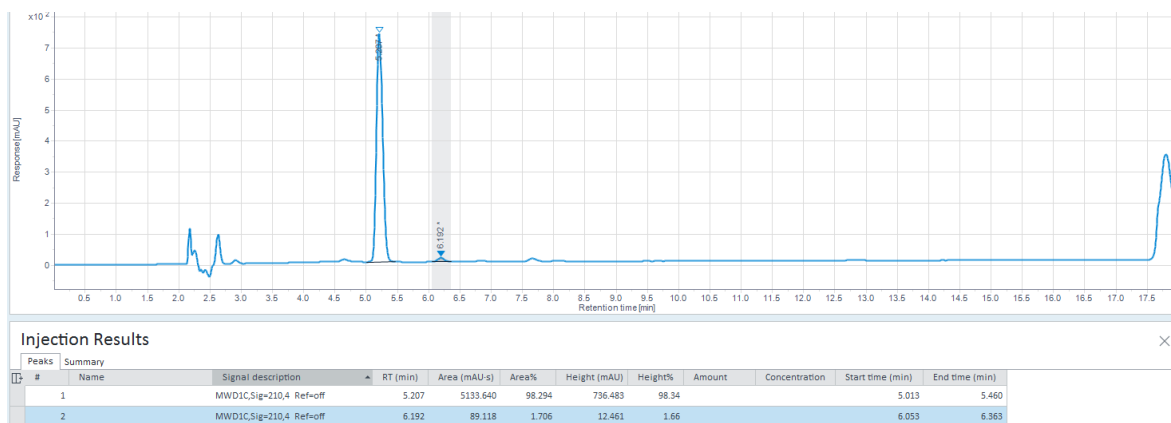


Figure 4.7. SFC trace of enantioenriched **4.37**.

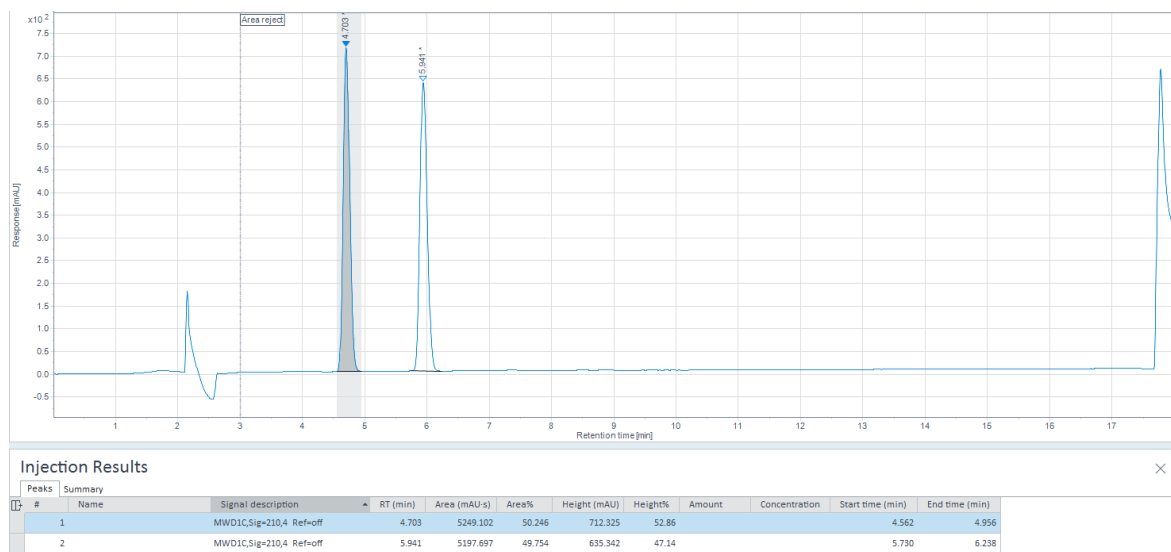


Figure 4.8. SFC trace of racemic **4.38**.

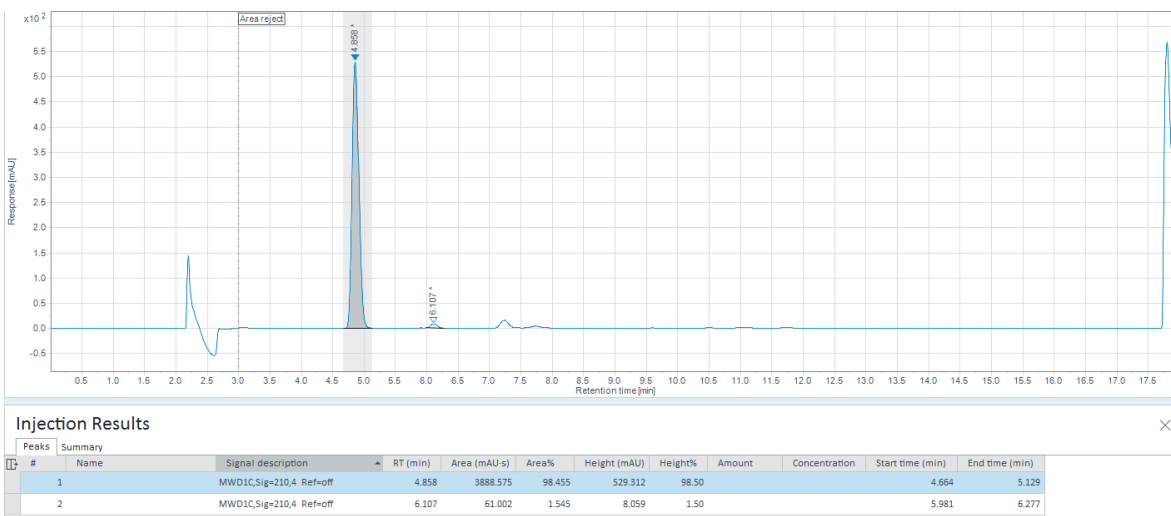
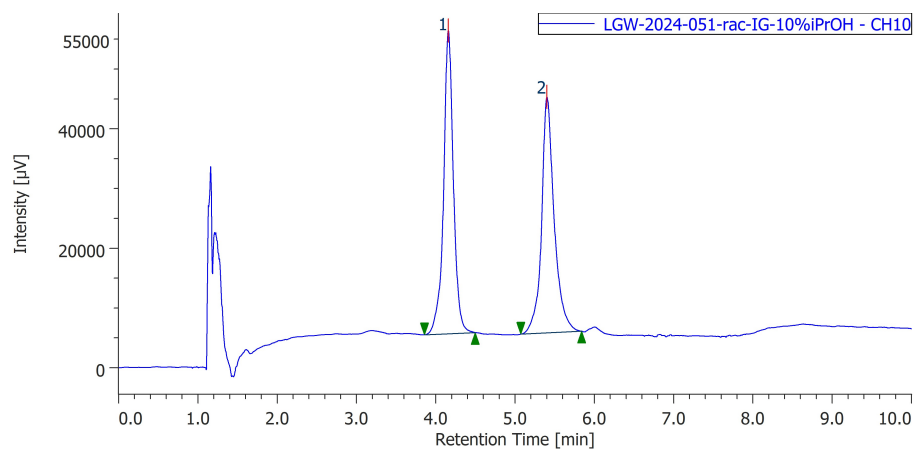
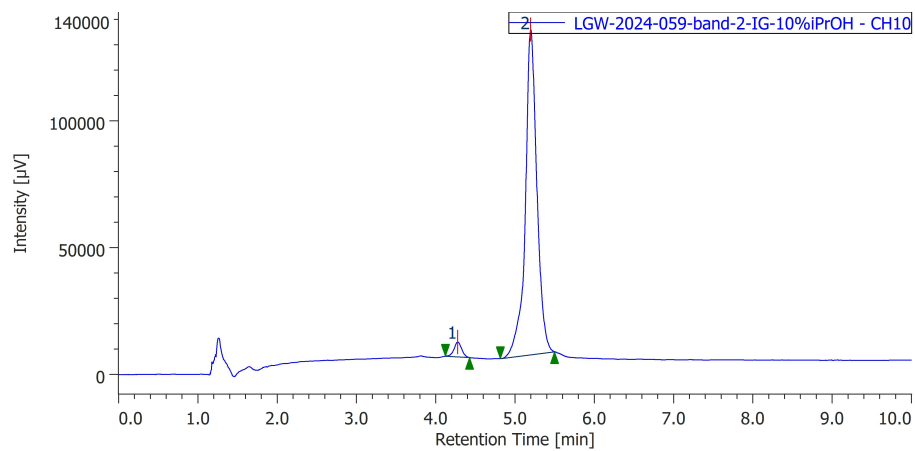


Figure 4.9. SFC trace of enantioenriched **4.38**.



#	Peak Name	CH	tR [min]	Area [$\mu\text{V}\cdot\text{sec}$]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	10	4.157	439344	50760	50.055	56.247	N/A	6449	5.369	0.967	
2	Unknown	10	5.400	438381	39485	49.945	43.753	N/A	7045	N/A	1.155	

Figure 4.10. SFC trace of racemic **4.26**.



#	Peak Name	CH	tR [min]	Area [$\mu\text{V}\cdot\text{sec}$]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	10	4.273	39625	5849	2.949	4.362	N/A	9579	4.436	1.022	
2	Unknown	10	5.193	1304172	128231	97.051	95.638	N/A	7412	N/A	0.964	

Figure 4.11. SFC trace of enantioenriched **4.26**.

4.7 Spectra Relevant to Chapter Four:

Strain-Promoted (4+2) Cycloadditions of Heterocyclic Allenes and α -Pyrones

Laura Wonilowicz,[†] Milauni M. Mehta,[†] Lisa Kamecke, Sarah A. French, and Neil K. Garg*

Manuscript in Preparation

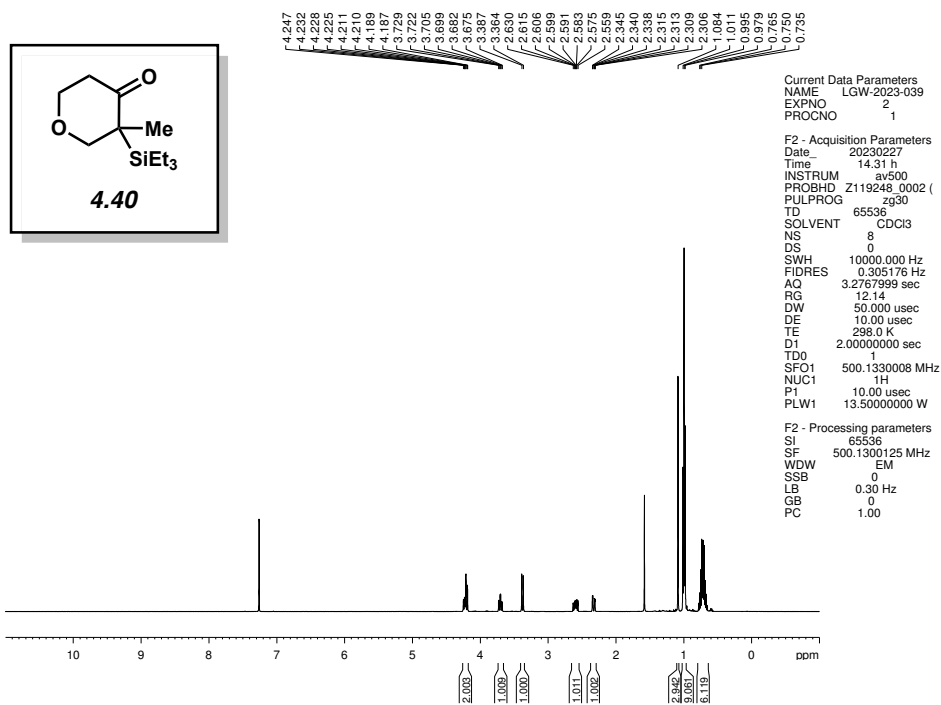


Figure 4.12. ^1H NMR (500 MHz, CDCl_3) of compound **4.40**.

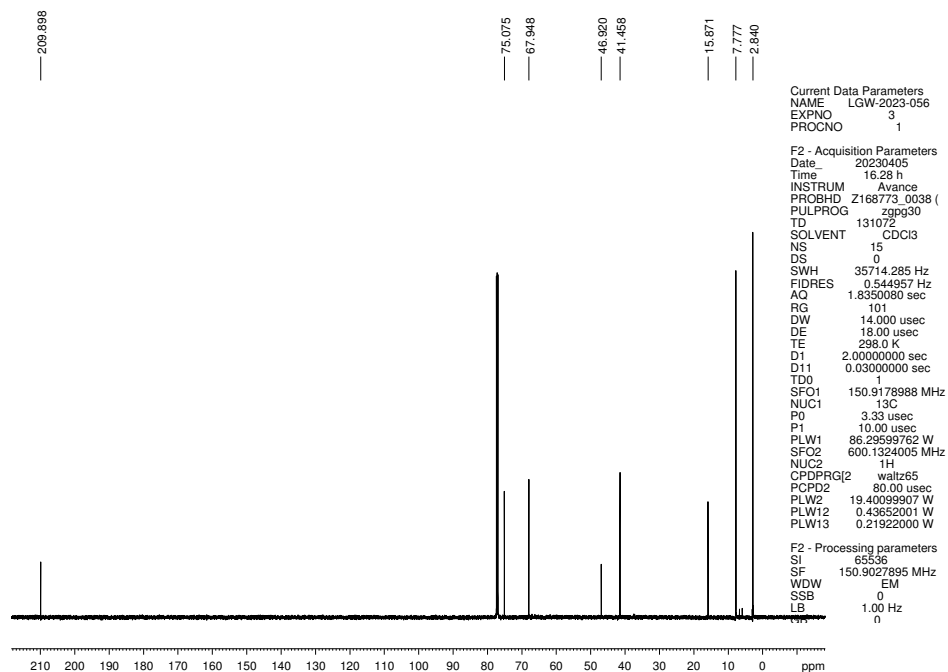


Figure 4.13. ^{13}C NMR (150 MHz, CDCl_3) of compound **4.40**.

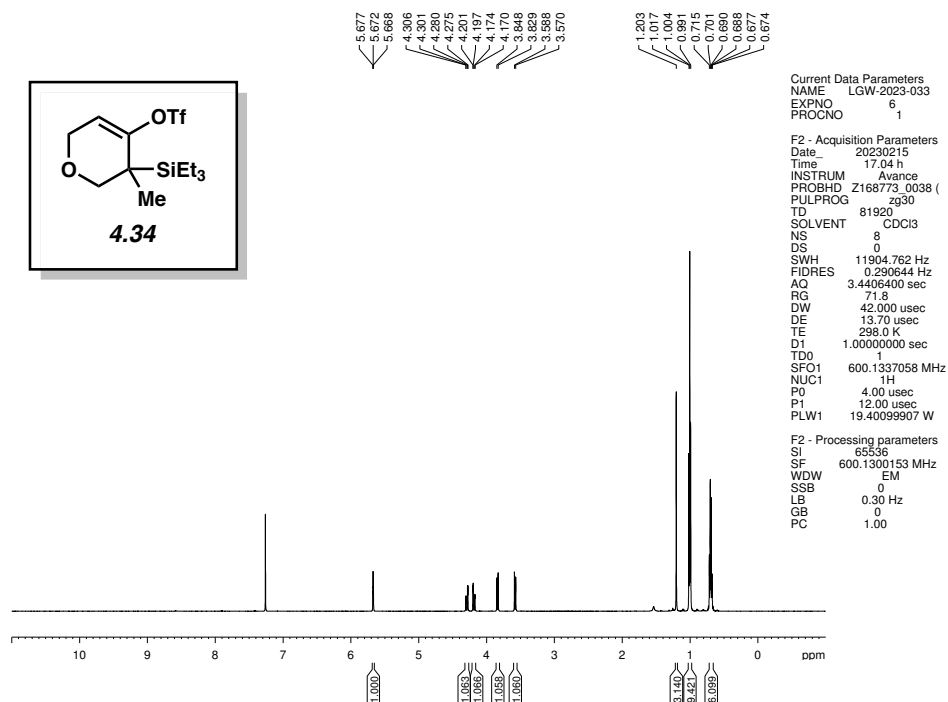


Figure 4.14. ^1H NMR (600 MHz, CDCl_3) of compound **4.34**.

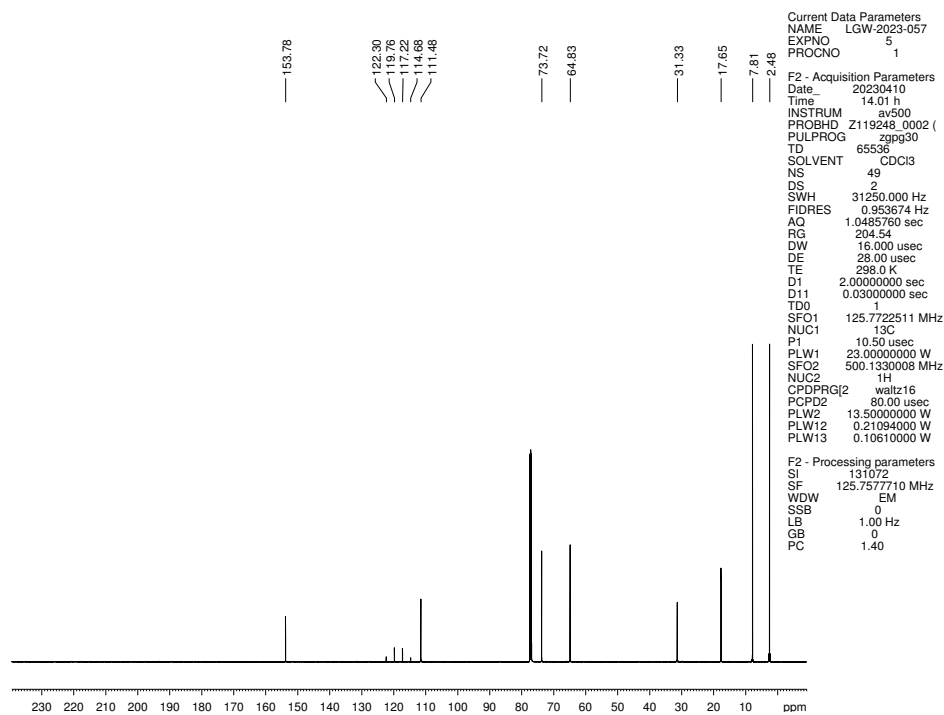


Figure 4.15. ^{13}C NMR (500 MHz, CDCl_3) of compound **4.34**.

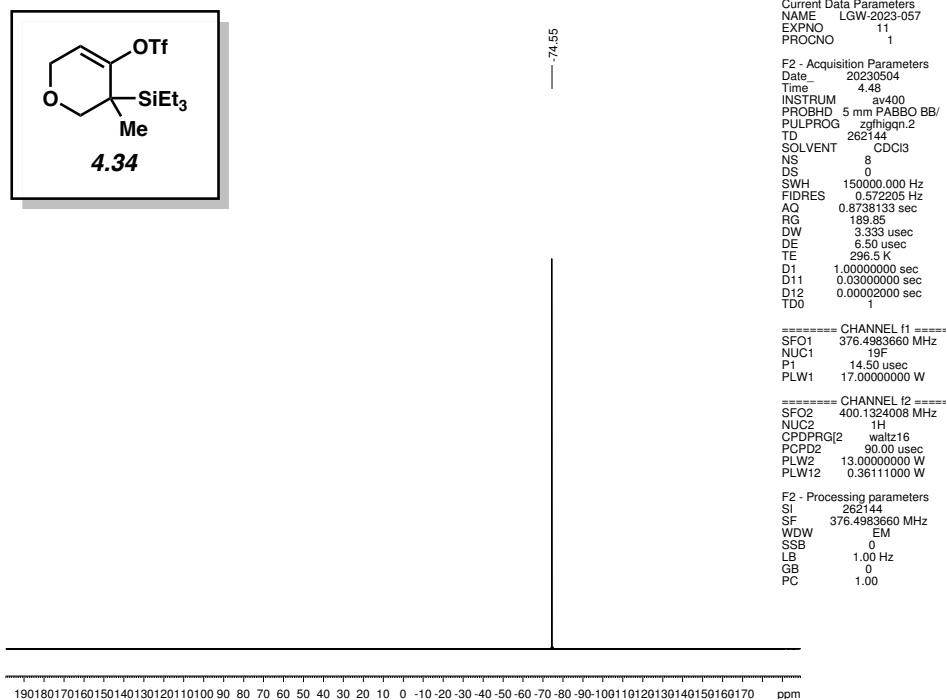


Figure 4.16. ¹⁹F NMR (376 MHz, CDCl₃) of compound **4.34**.

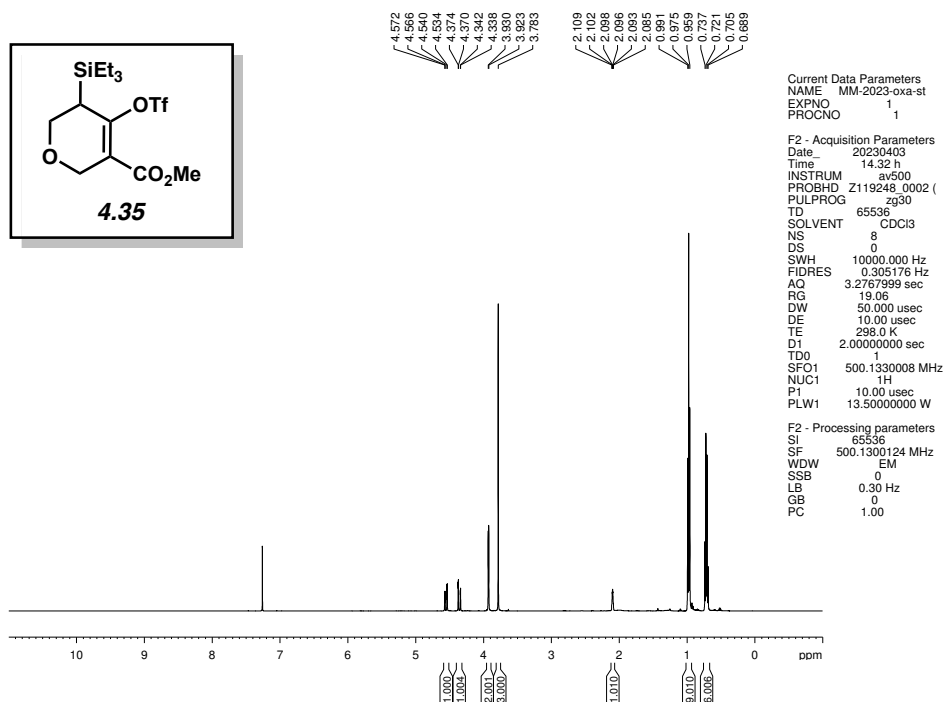


Figure 4.17. ^1H NMR (500 MHz, CDCl_3) of compound 4.35.

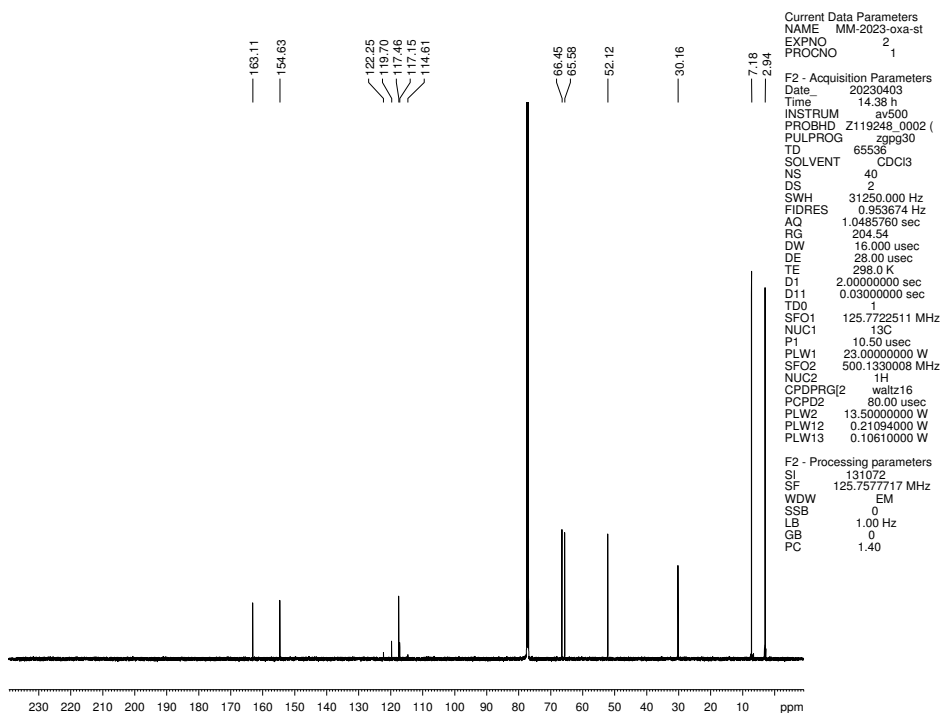


Figure 4.18. ^{13}C NMR (125 MHz, CDCl_3) of compound 4.35.

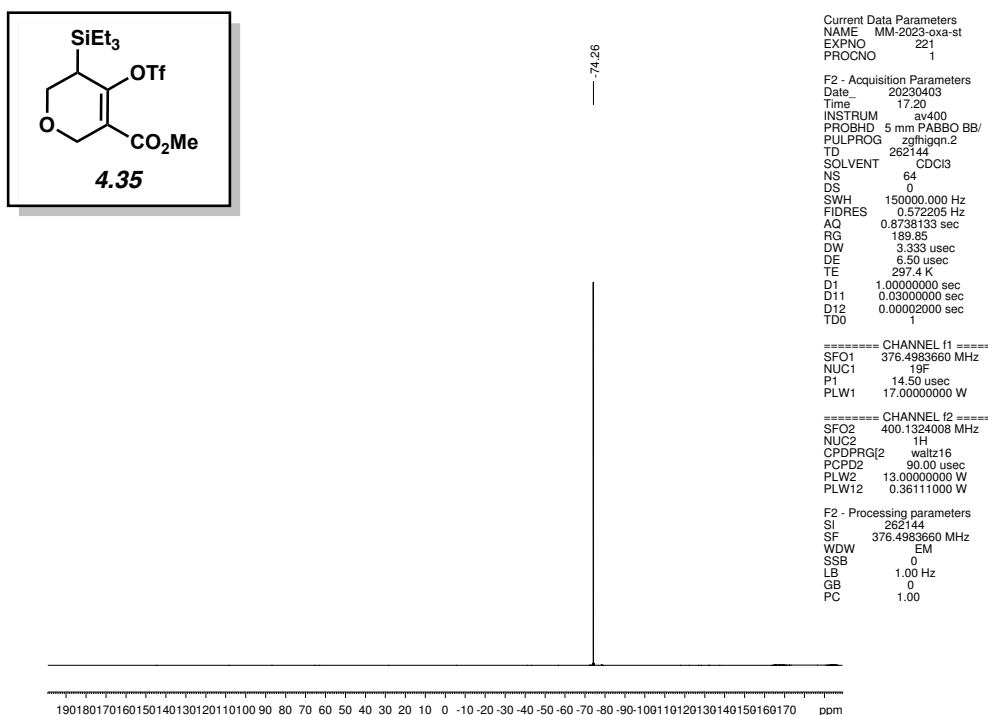


Figure 4.19. ^{19}F NMR (376 MHz, CDCl_3) of compound **4.35**.

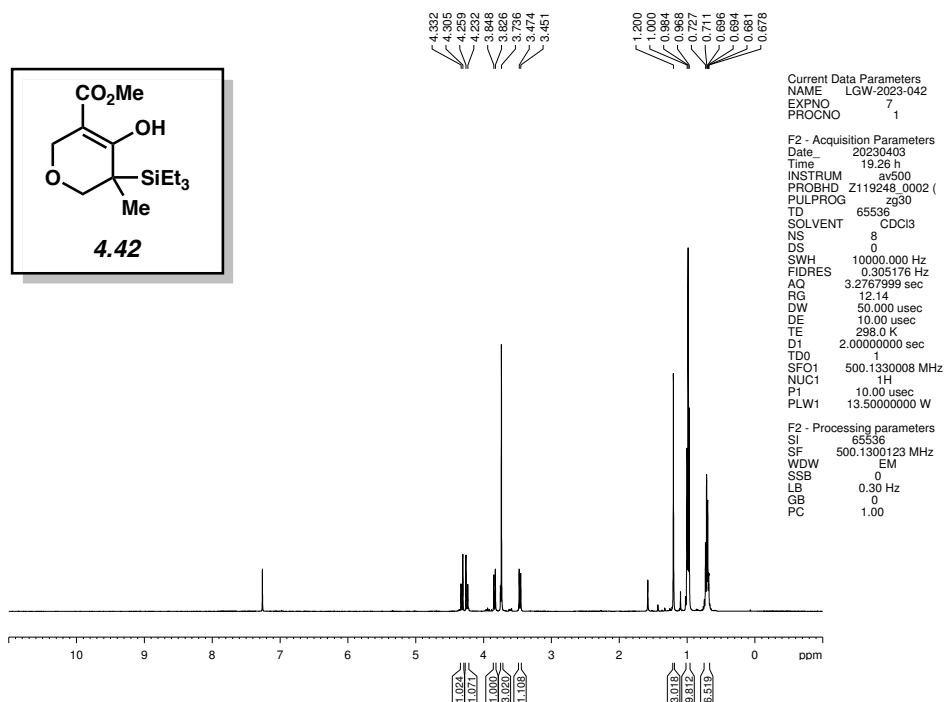


Figure 4.20. ¹H NMR (500 MHz, CDCl₃) of compound 4.42.

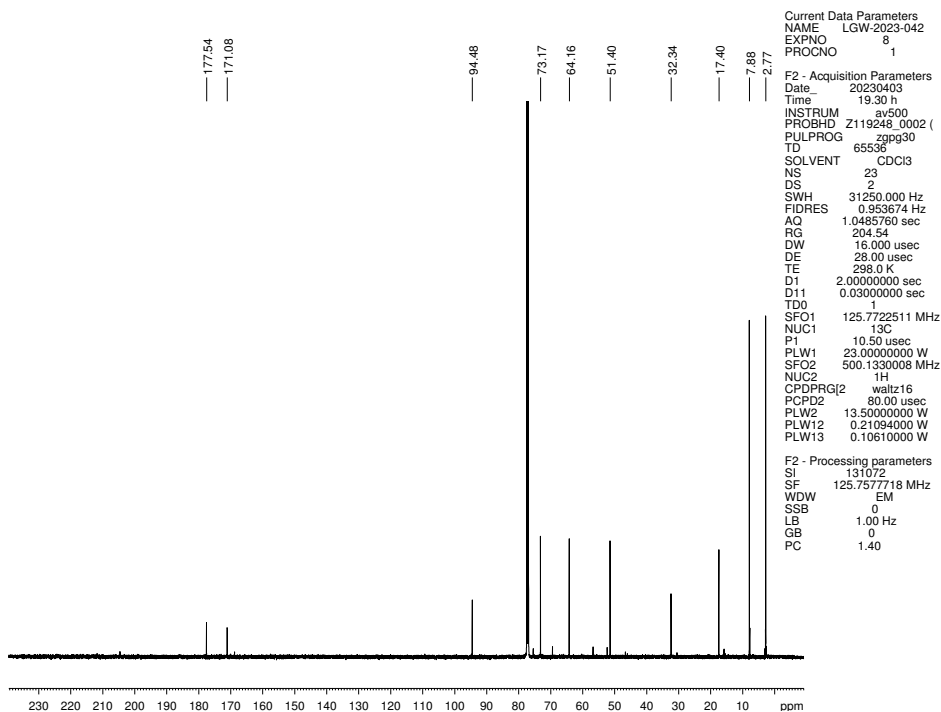


Figure 4.21. ¹³C NMR (125 MHz, CDCl₃) of compound 4.42.

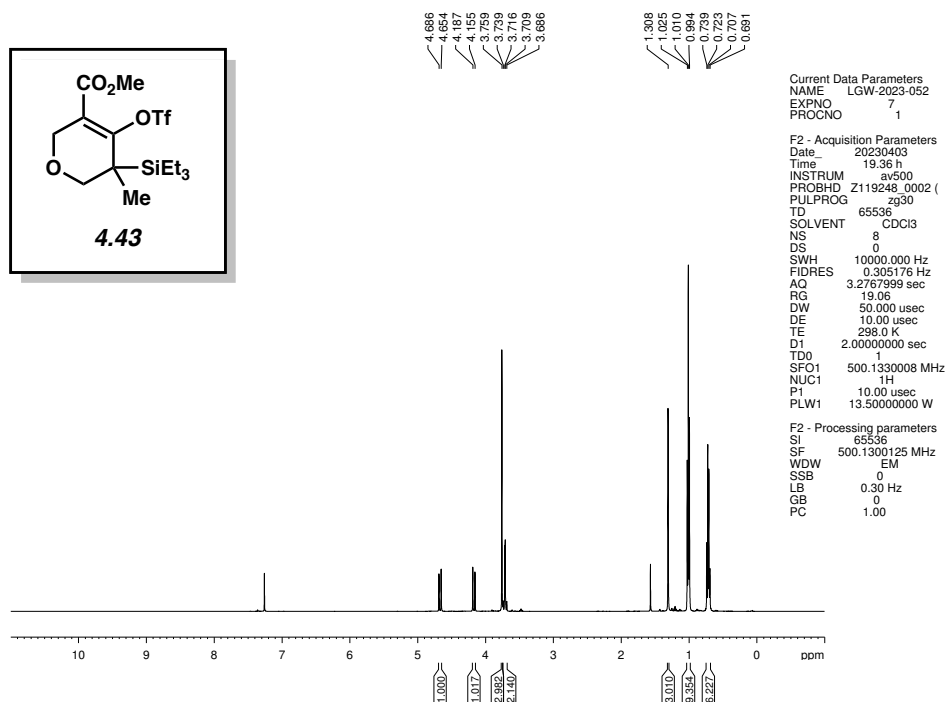


Figure 4.22. ¹H NMR (500 MHz, CDCl₃) of compound **4.43**.

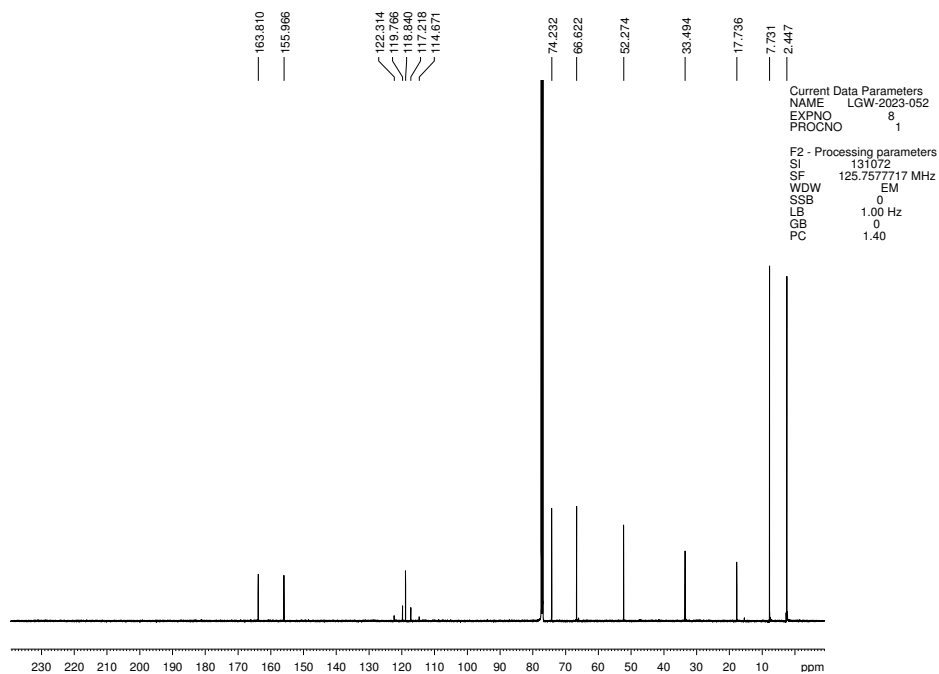


Figure 4.23. ¹³C NMR (125 MHz, CDCl₃) of compound **4.43**.

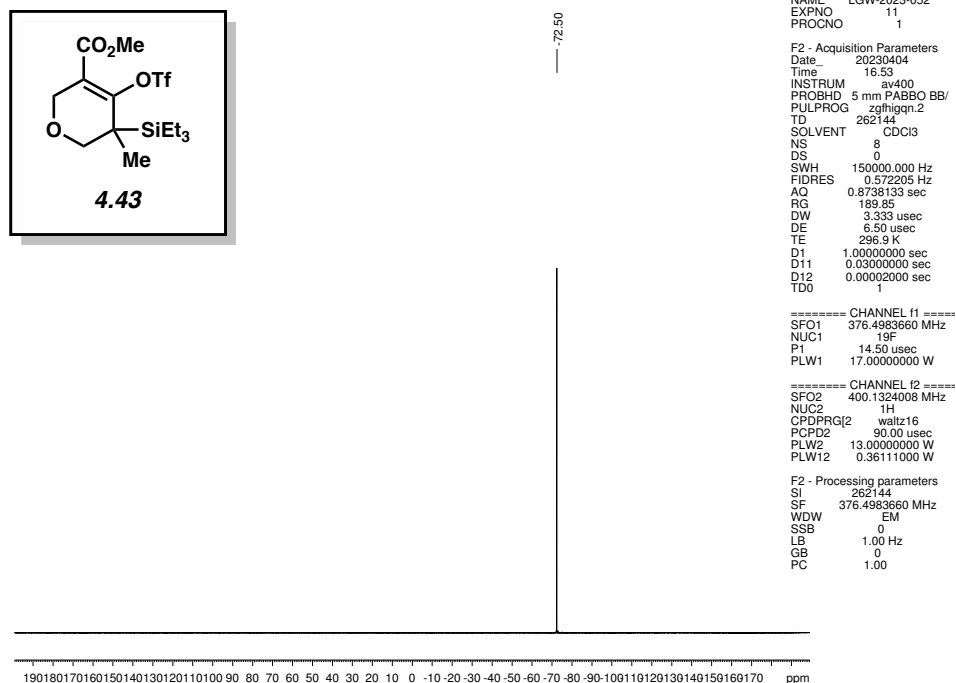


Figure 4.24. ^{19}F NMR (376 MHz, CDCl_3) of compound **4.43**.



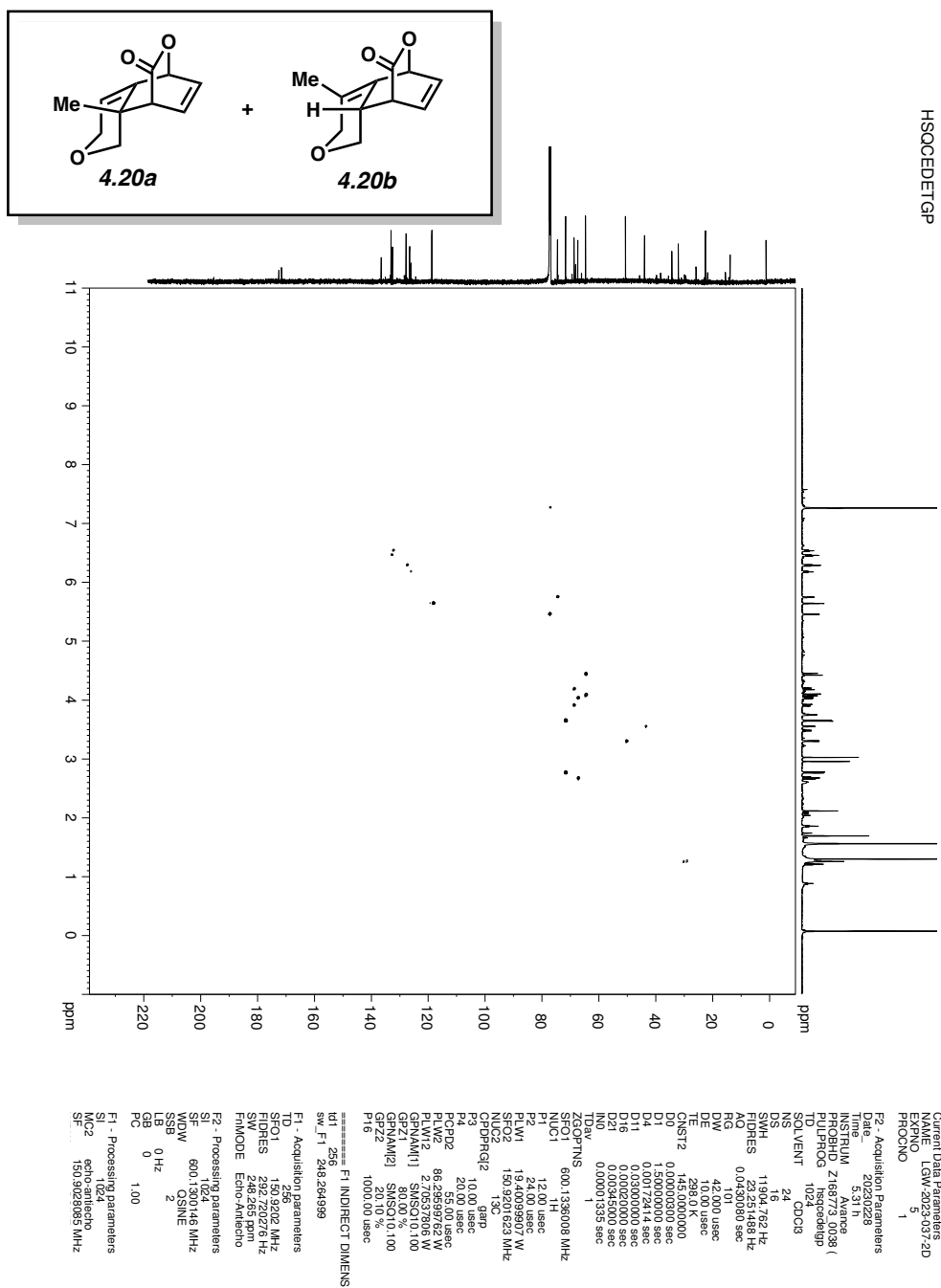


Figure 4.28. HSQC (600 MHz, CDCl₃) of compound **4.20a** and **4.20b**.

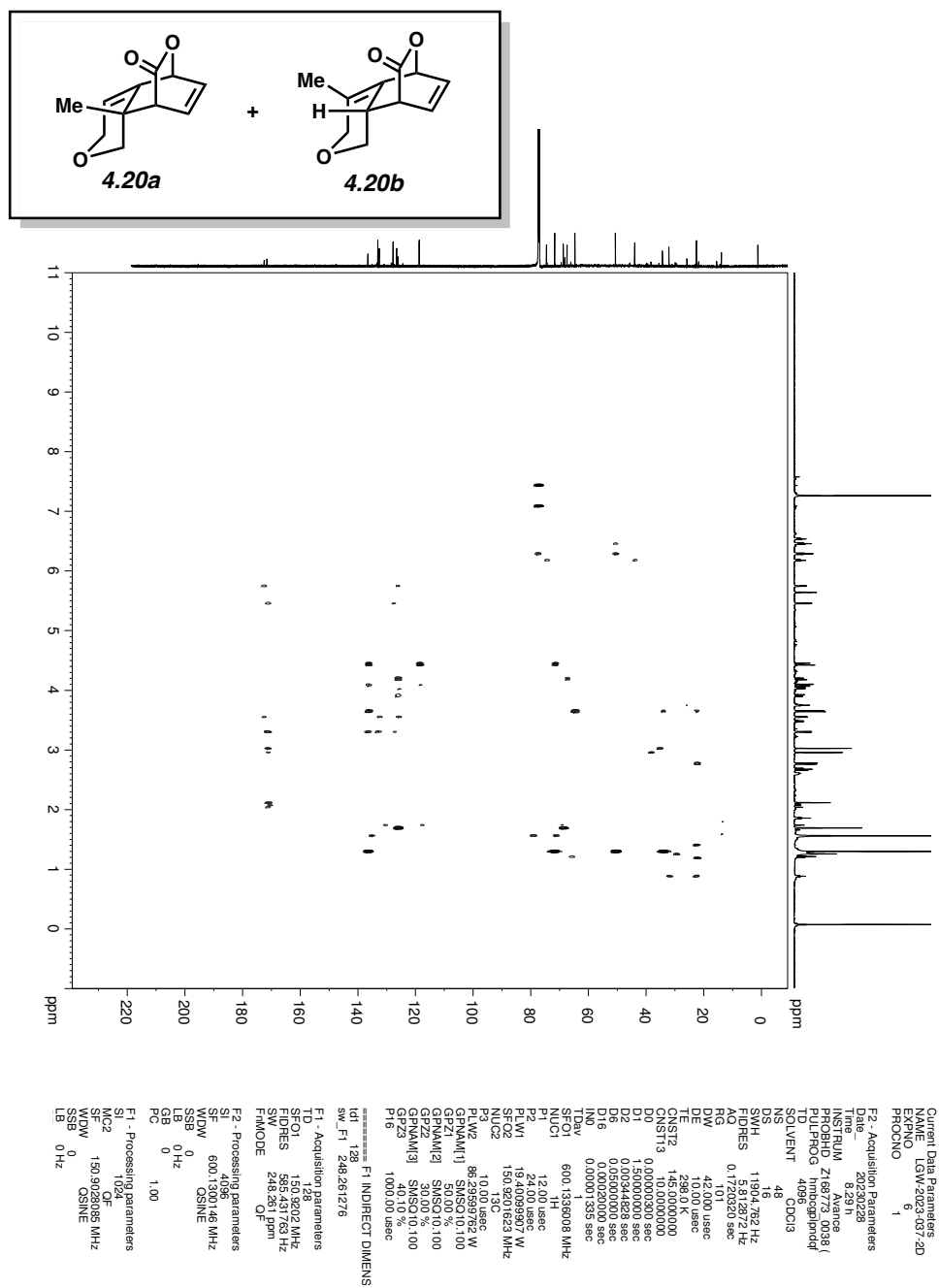


Figure 4.29. HMBC (600 MHz, CDCl₃) of compound **4.20a** and **4.20b**.

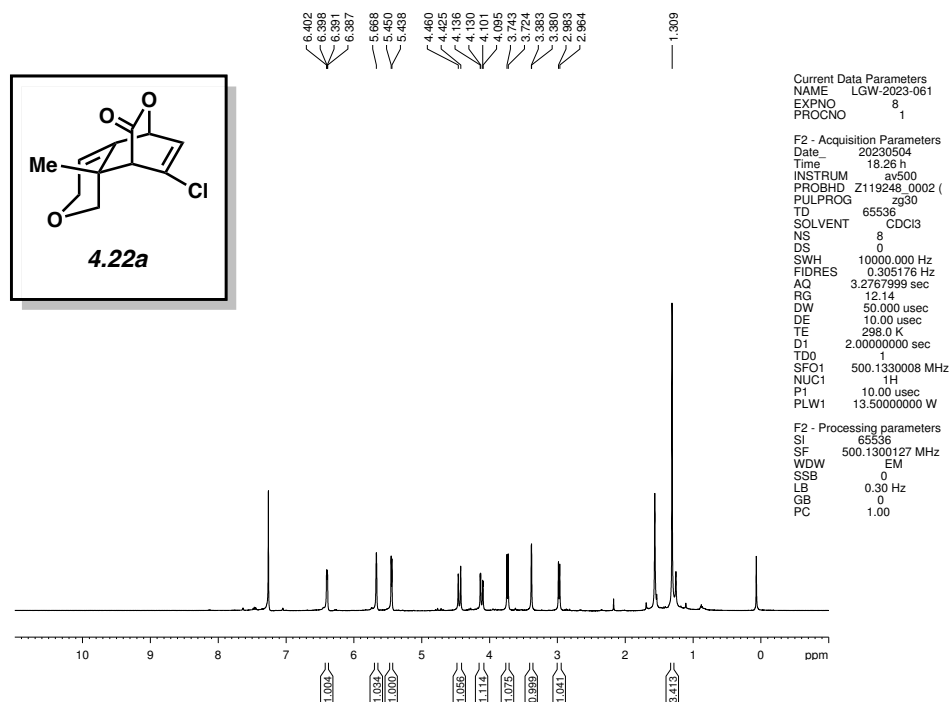


Figure 4.30. ^1H NMR (500 MHz, CDCl_3) of compound **4.22a**.

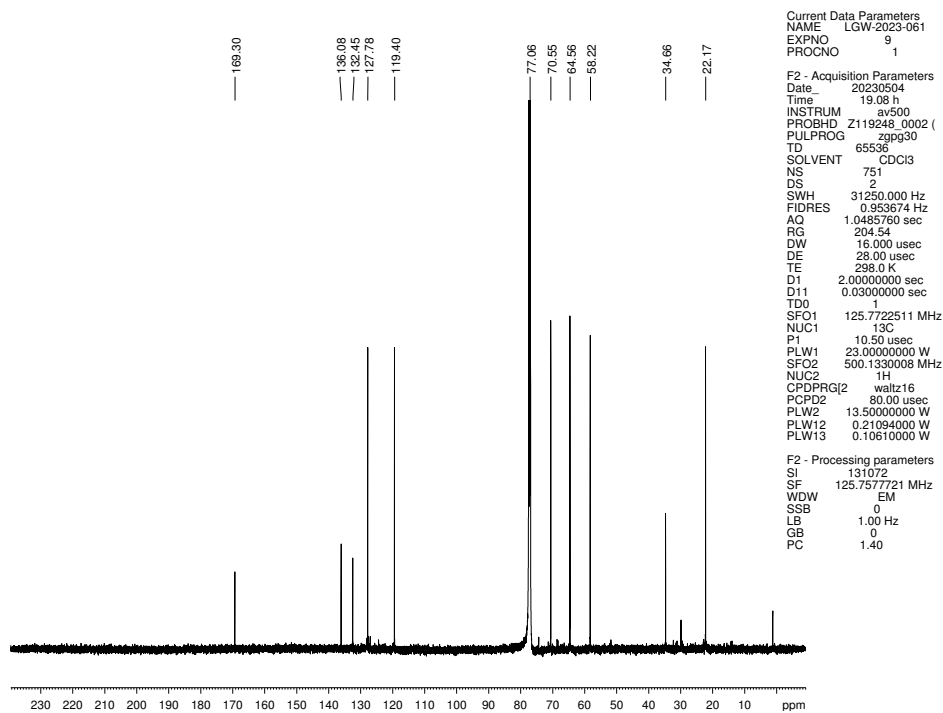


Figure 4.31. ^{13}C NMR (125 MHz, CDCl_3) of compound **4.22a**.

NOESY/GPPH

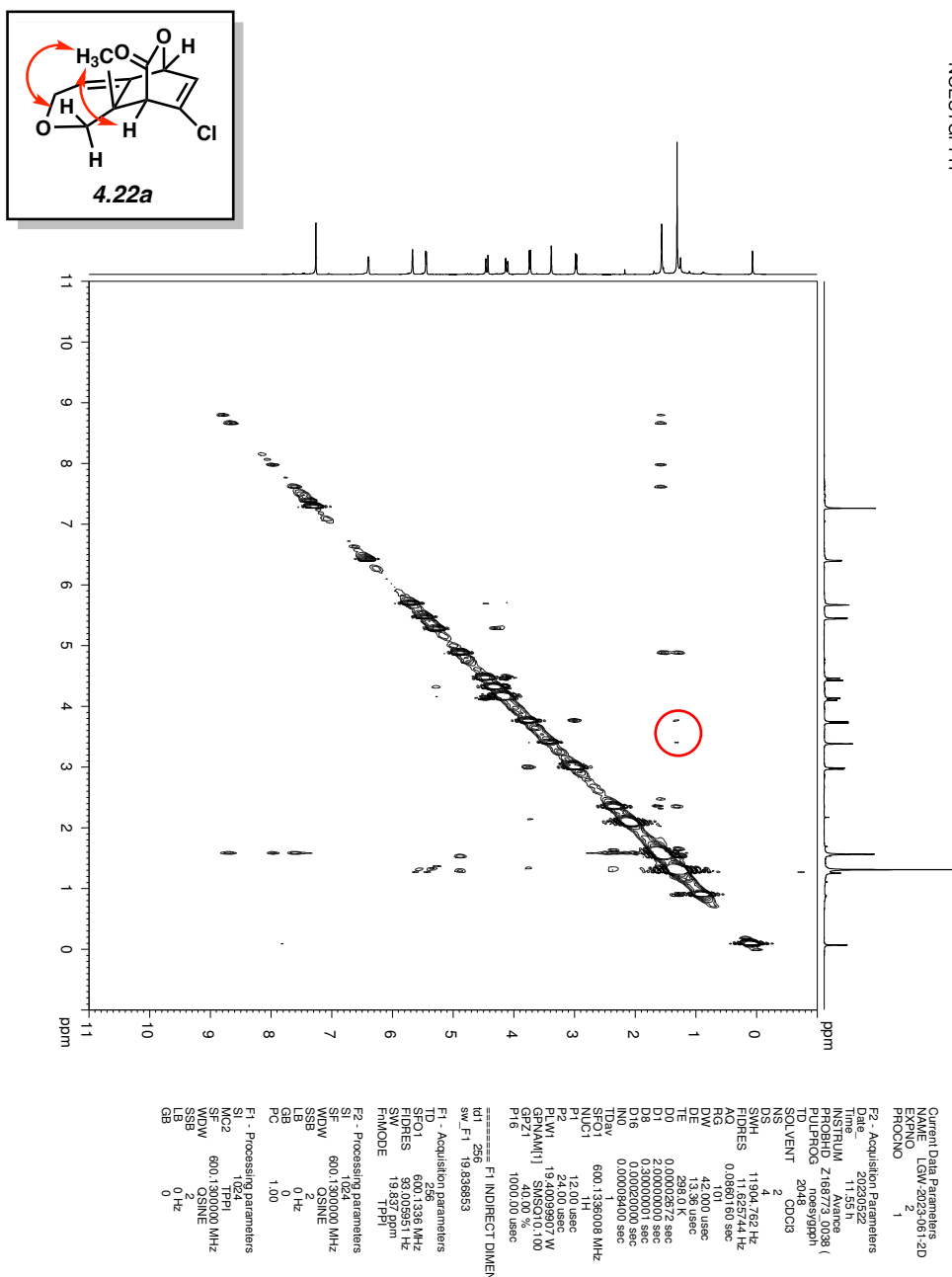


Figure 4.32. NOESY (600 MHz, CDCl₃) of compound **4.22a**.

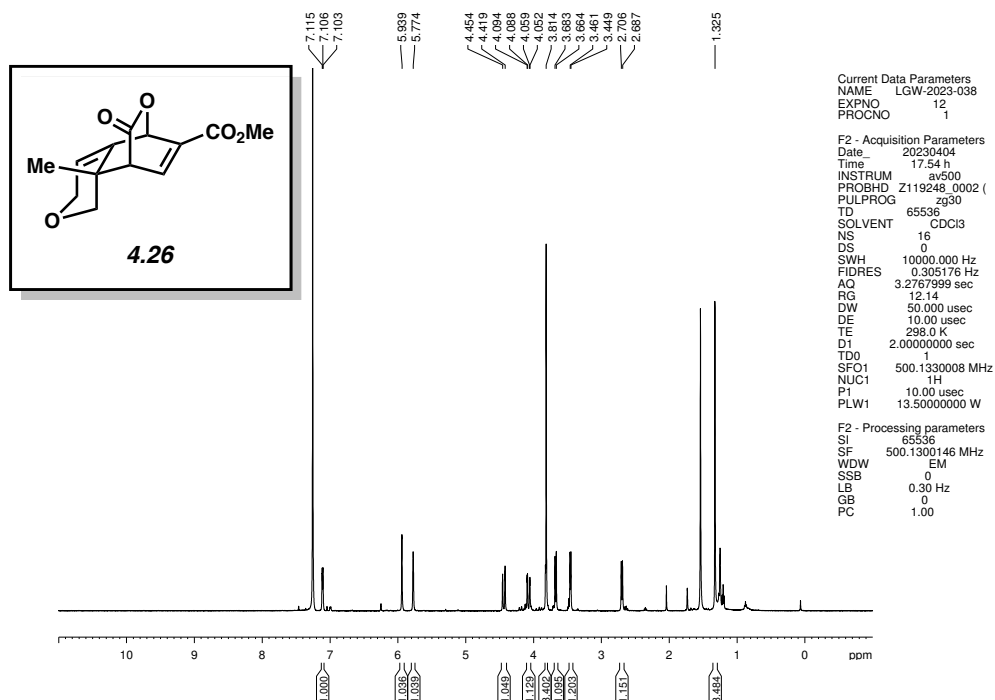


Figure 4.33. ^1H NMR (500 MHz, CDCl_3) of compound 4.26.

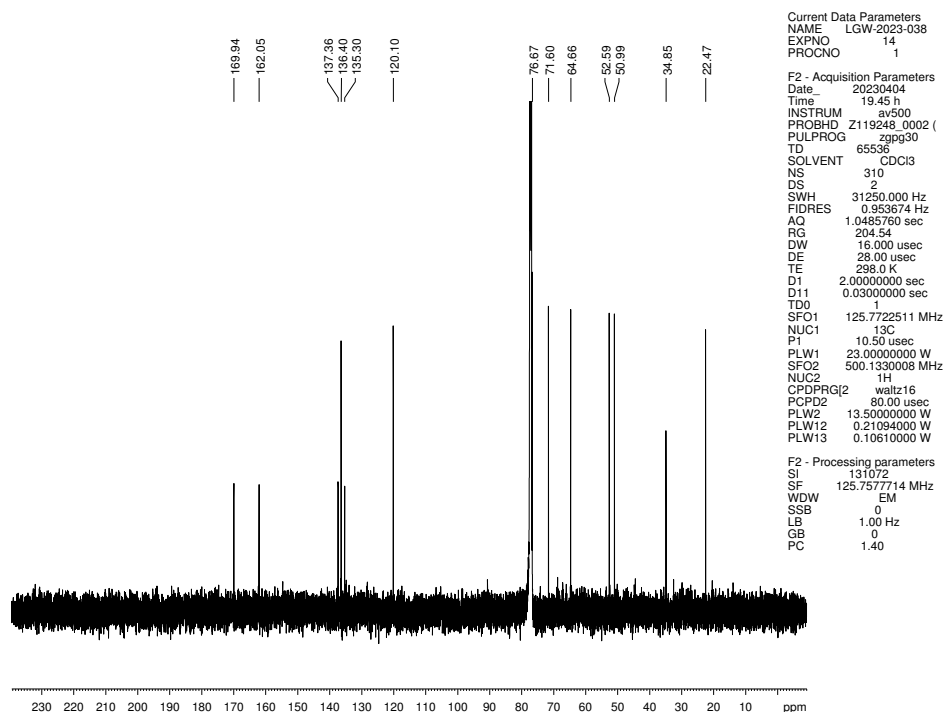


Figure 4.34. ^{13}C NMR (125 MHz, CDCl_3) of compound 4.26.

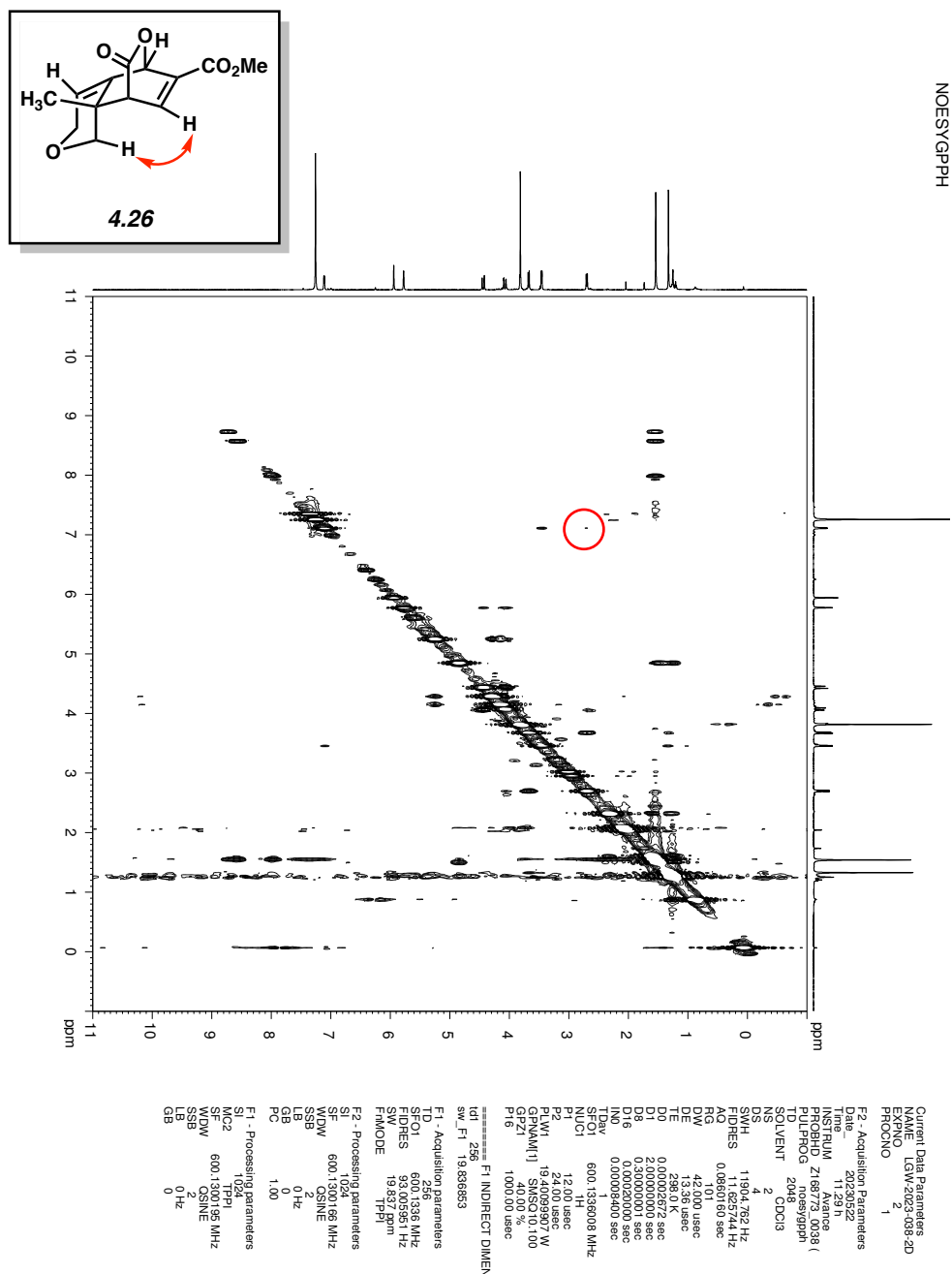


Figure 4.35. NOESY (600 MHz, CDCl₃) of compound **4.26**.

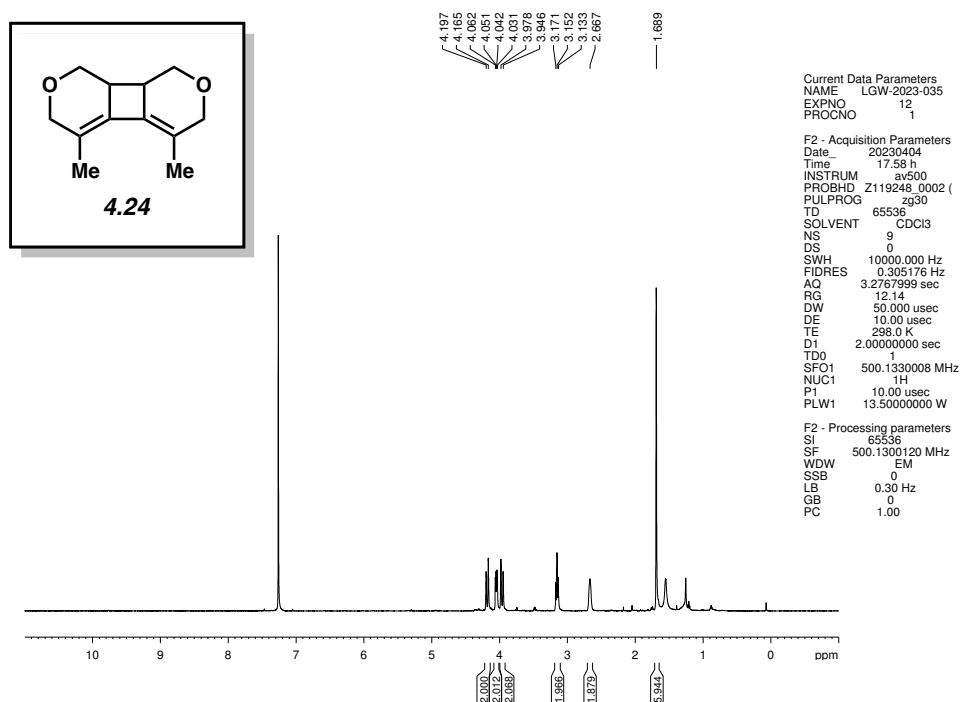


Figure 4.36. ^1H NMR (500 MHz, CDCl_3) of compound **4.24**.

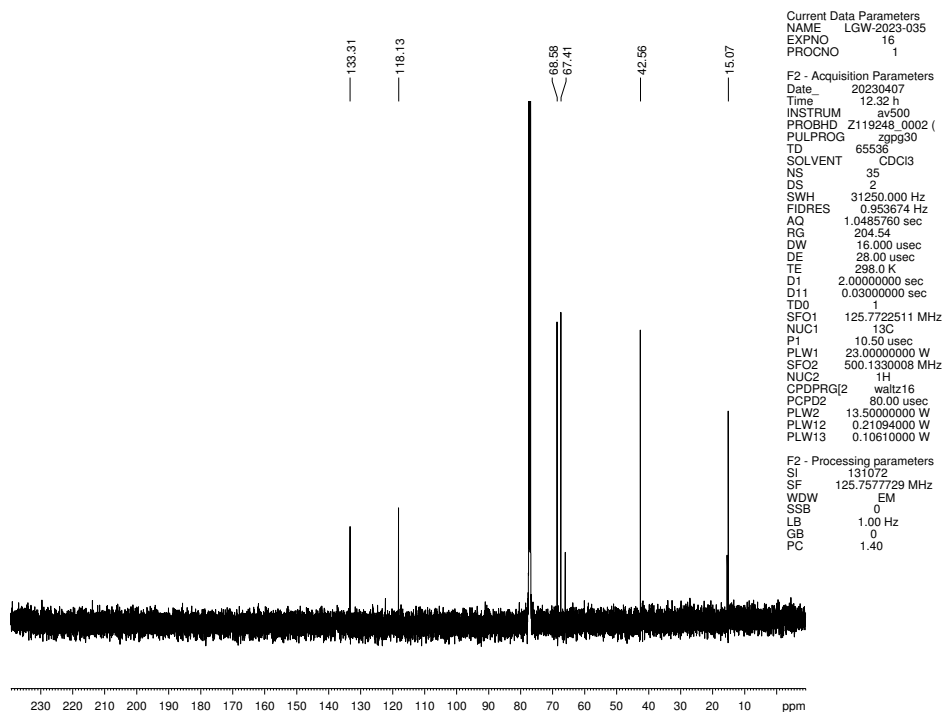


Figure 4.37. ^{13}C NMR (125 MHz, CDCl_3) of compound **4.24**.

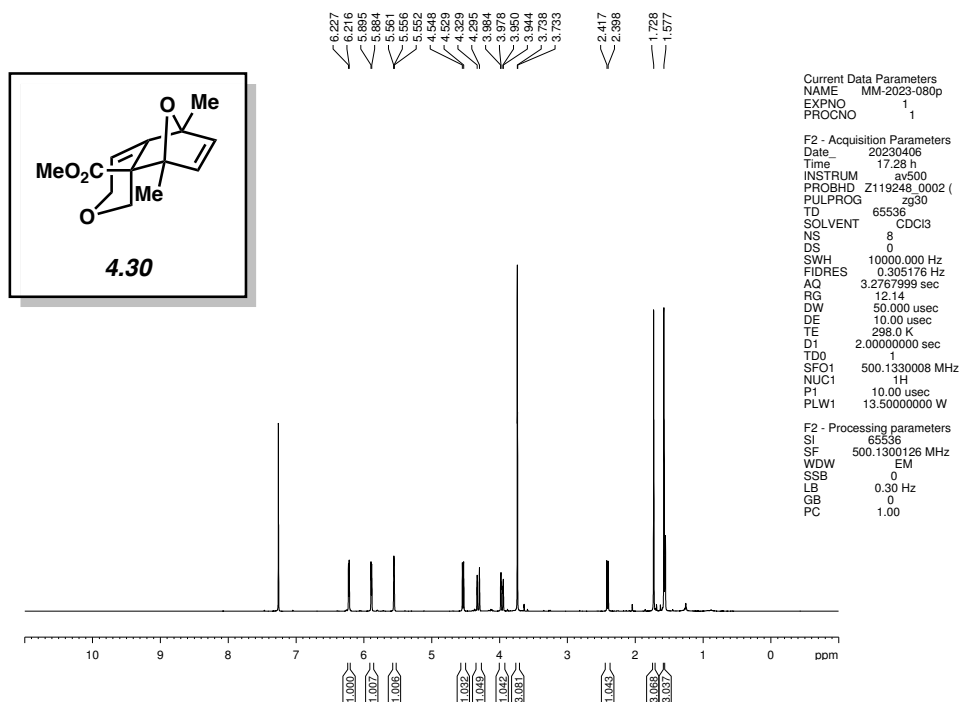


Figure 4.38. ¹H NMR (500 MHz, CDCl₃) of compound 4.30.

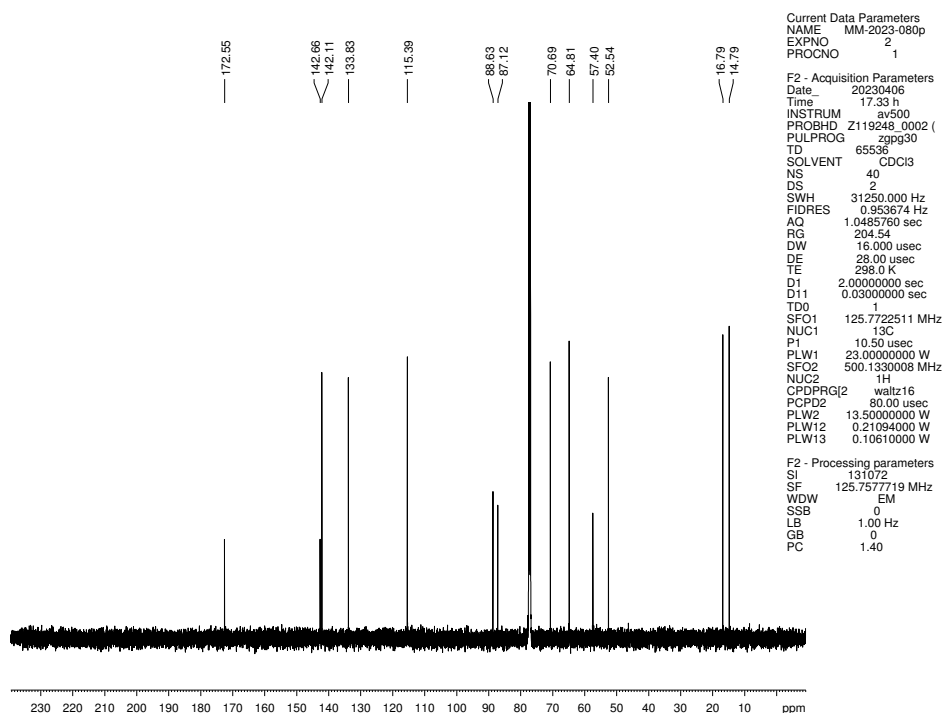


Figure 4.39. ¹³C NMR (125 MHz, CDCl₃) of compound 4.30.

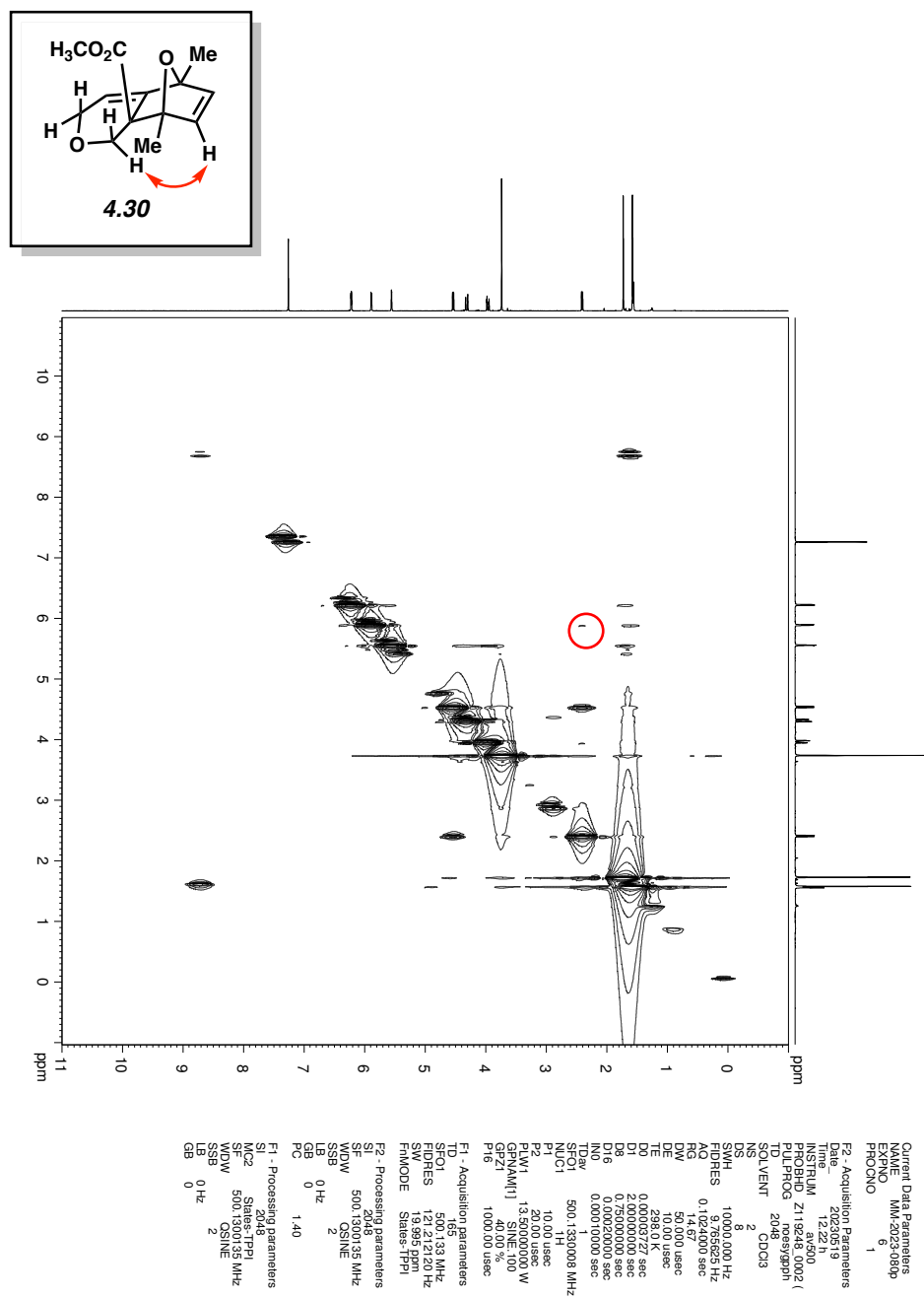


Figure 4.40. NOESY (600 MHz, CDCl_3) of compound **4.30**.

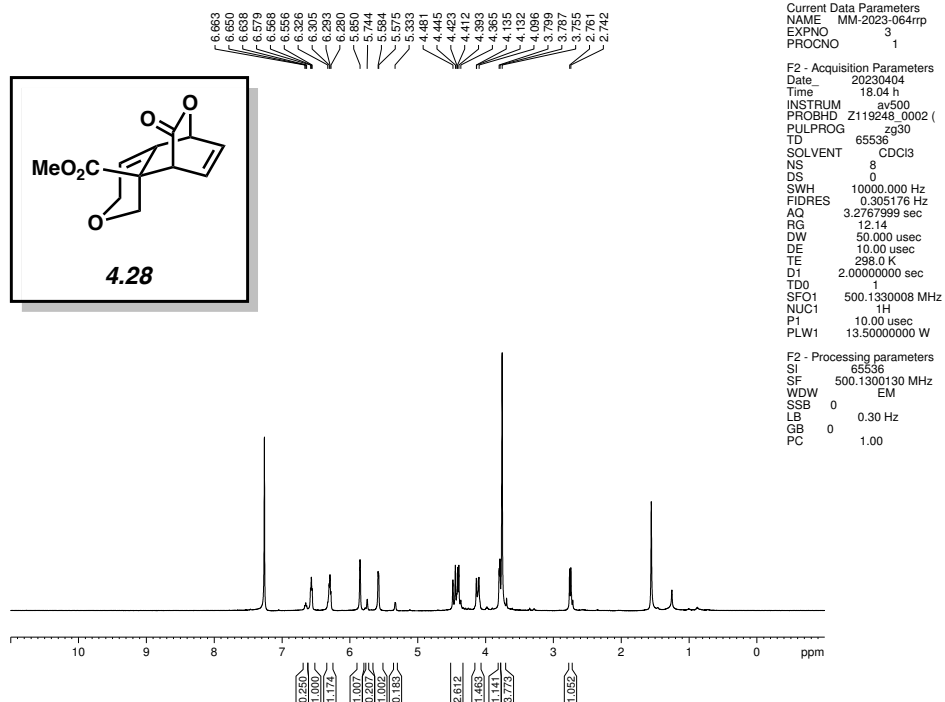


Figure 4.41. ¹H NMR (500 MHz, CDCl₃) of compound 4.28.

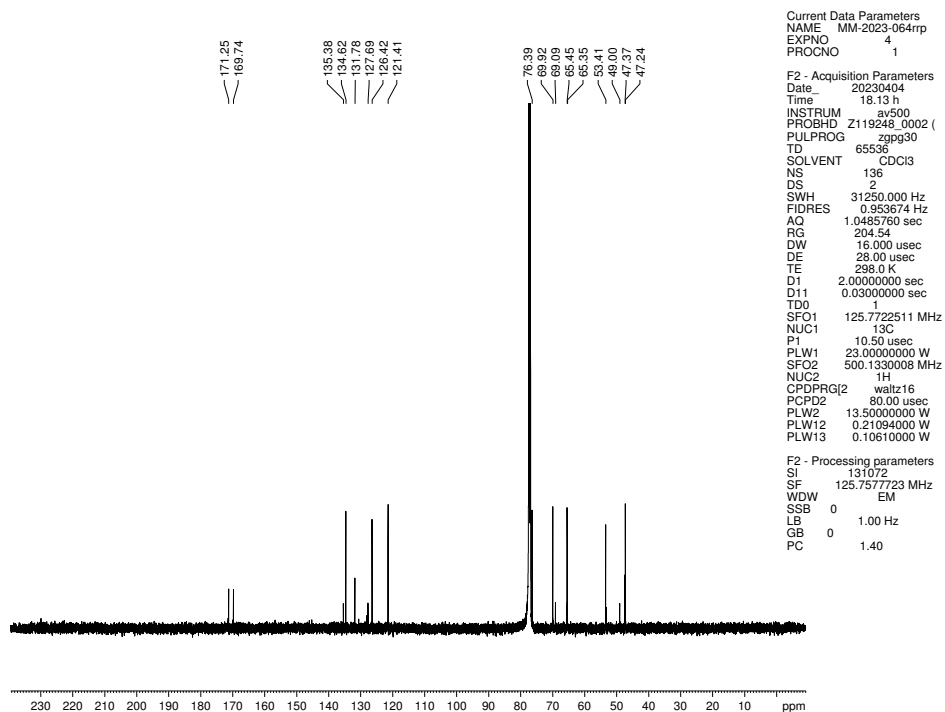


Figure 4.42. ¹³C NMR (125 MHz, CDCl₃) of compound 4.28.

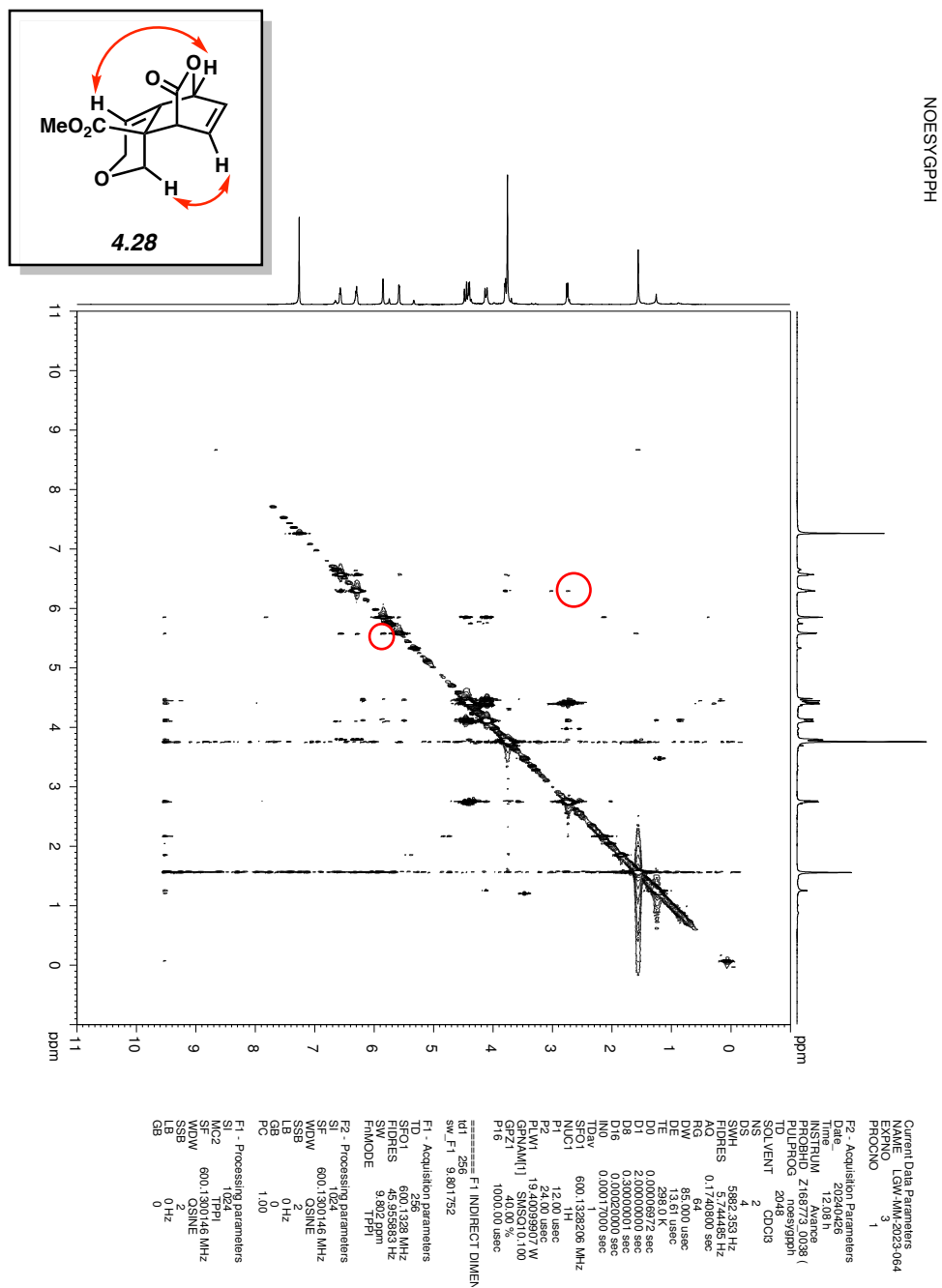


Figure 4.43. NOESY (600 MHz, CDCl_3) of compound **4.28**.

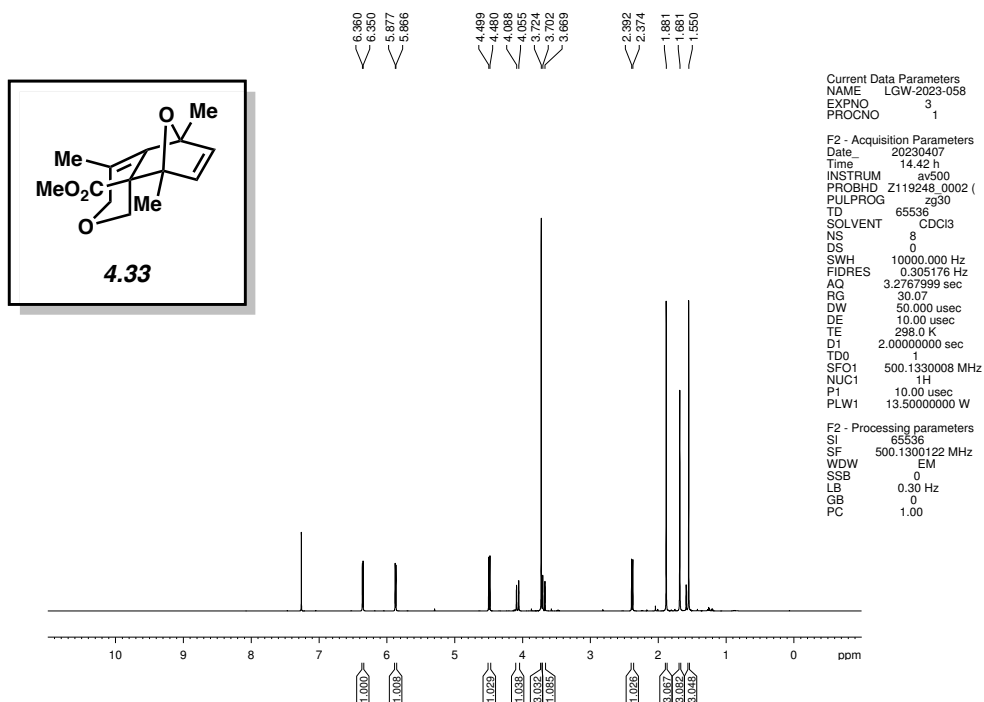


Figure 4.44. ¹H NMR (500 MHz, CDCl₃) of compound 4.33.

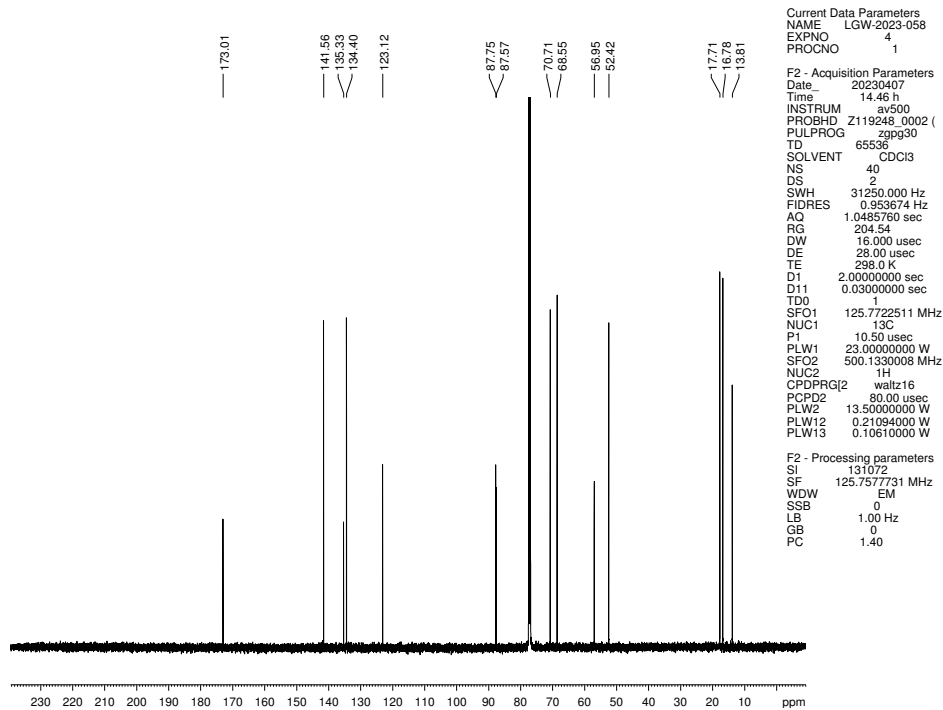


Figure 4.45. ¹³C NMR (125 MHz, CDCl₃) of compound 4.33.

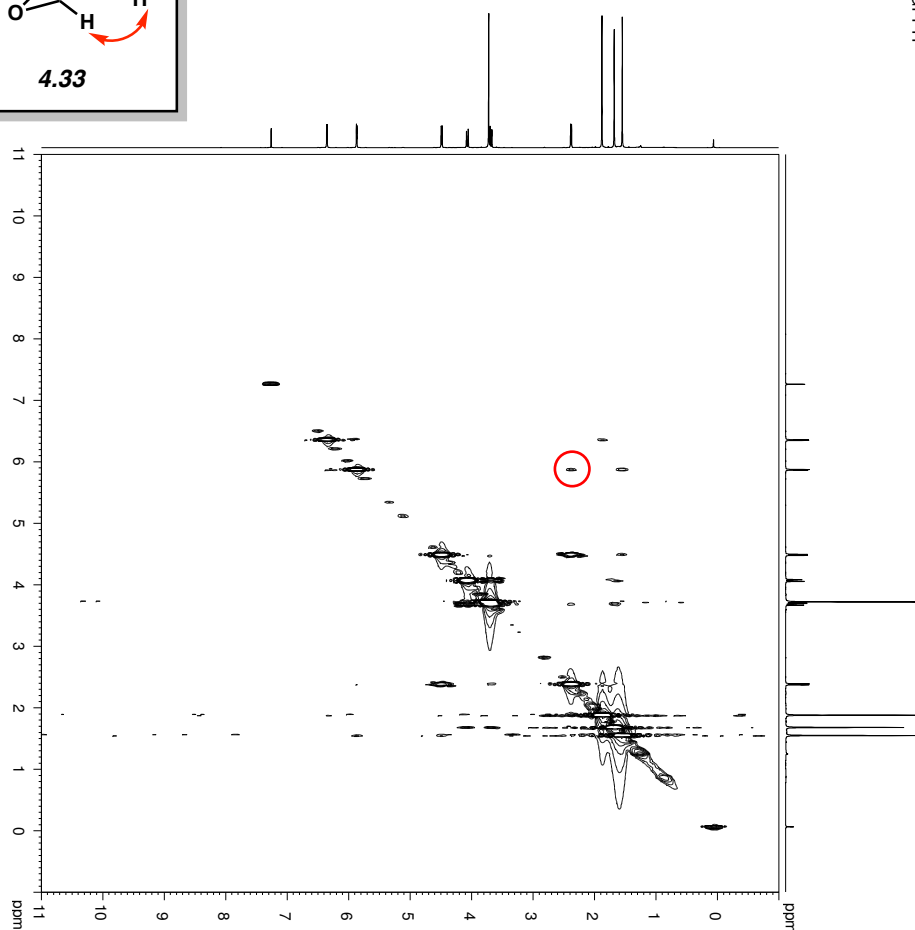
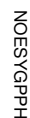
[illegible]

Figure 4.46. NOESY (600 MHz, CDCl₃) of compound **4.33**.

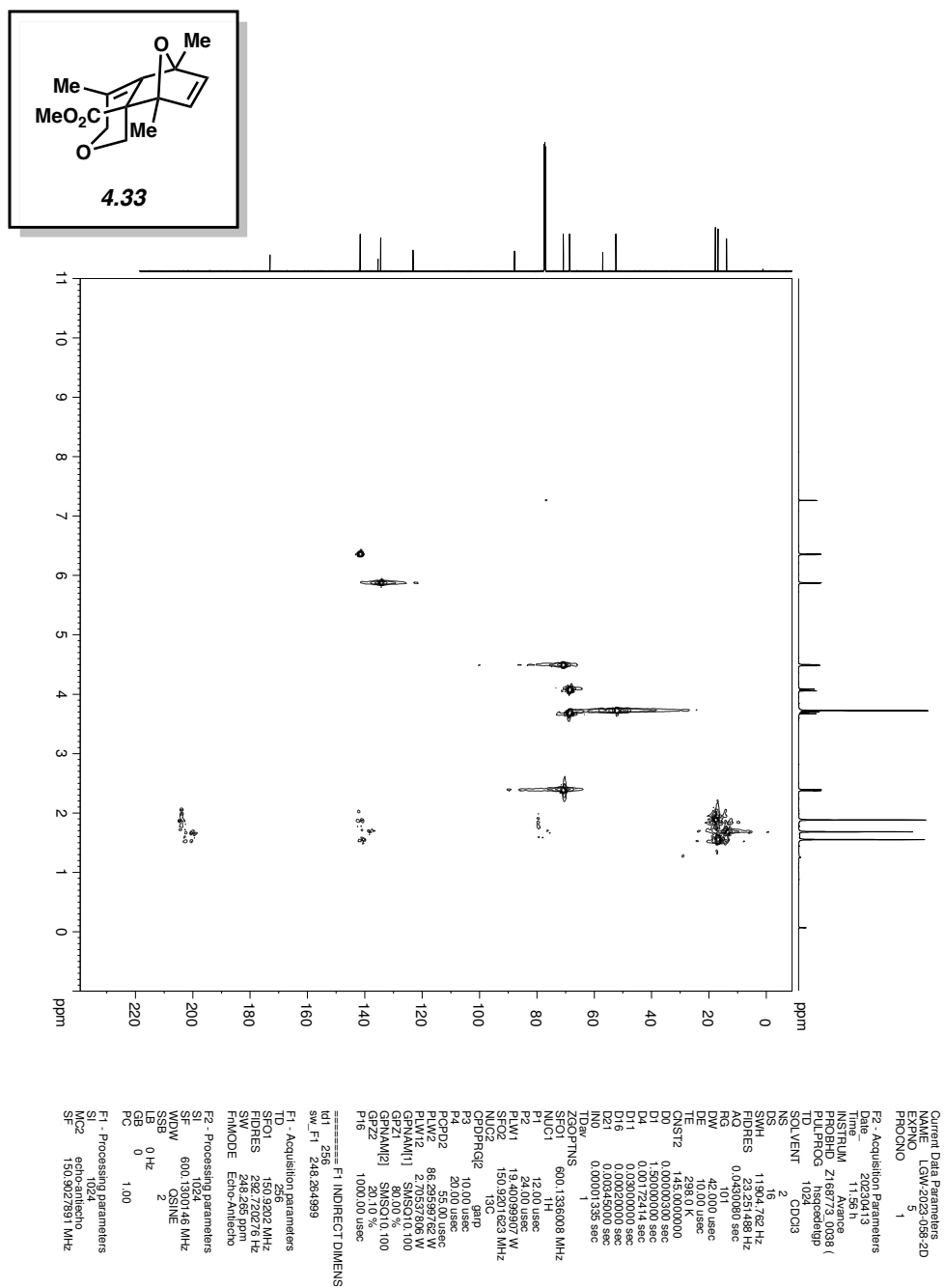


Figure 4.47. HSQC (600 MHz, CDCl₃) of compound 4.33.



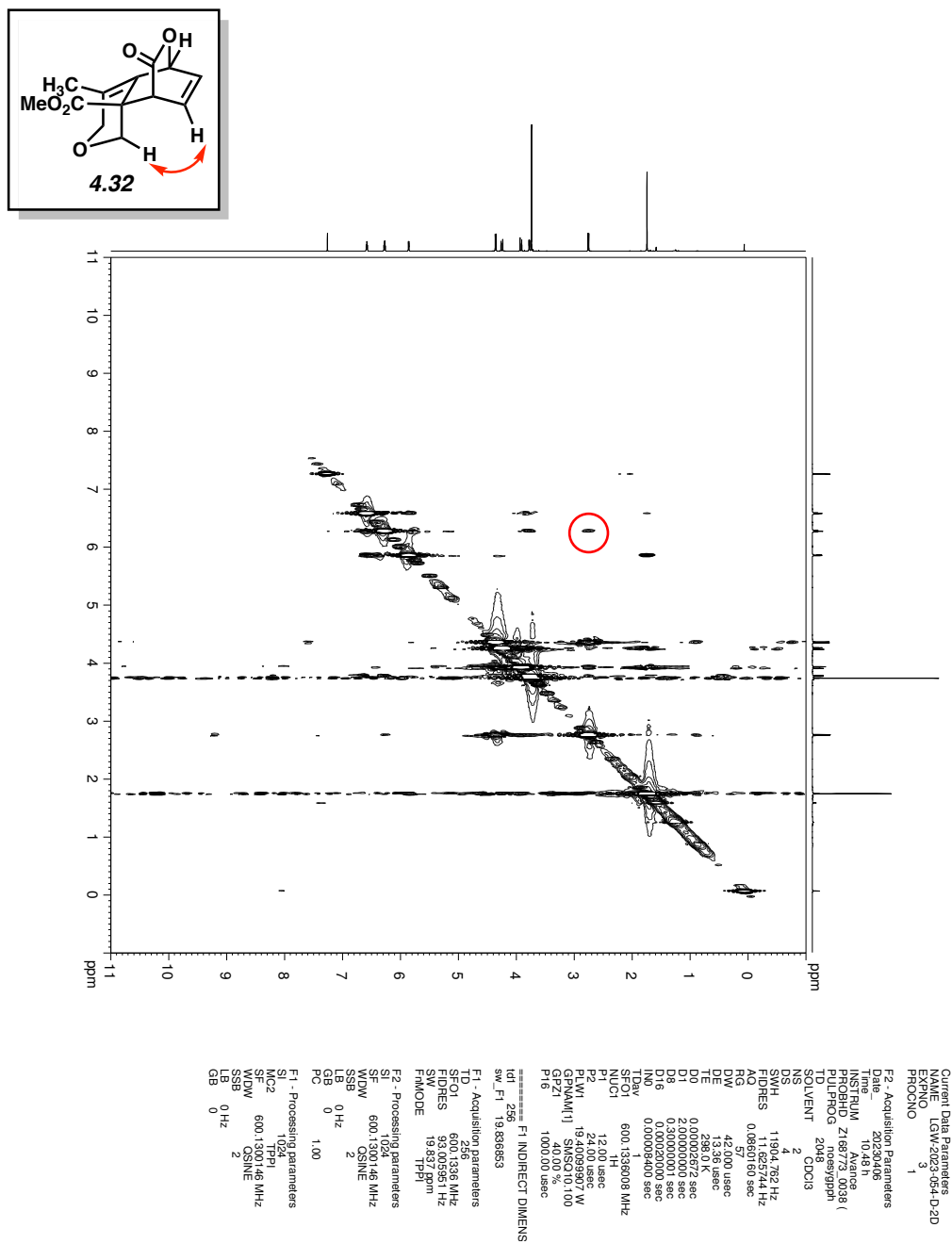


Figure 4.51. NOESY (600 MHz, CDCl₃) of compound 4.32.

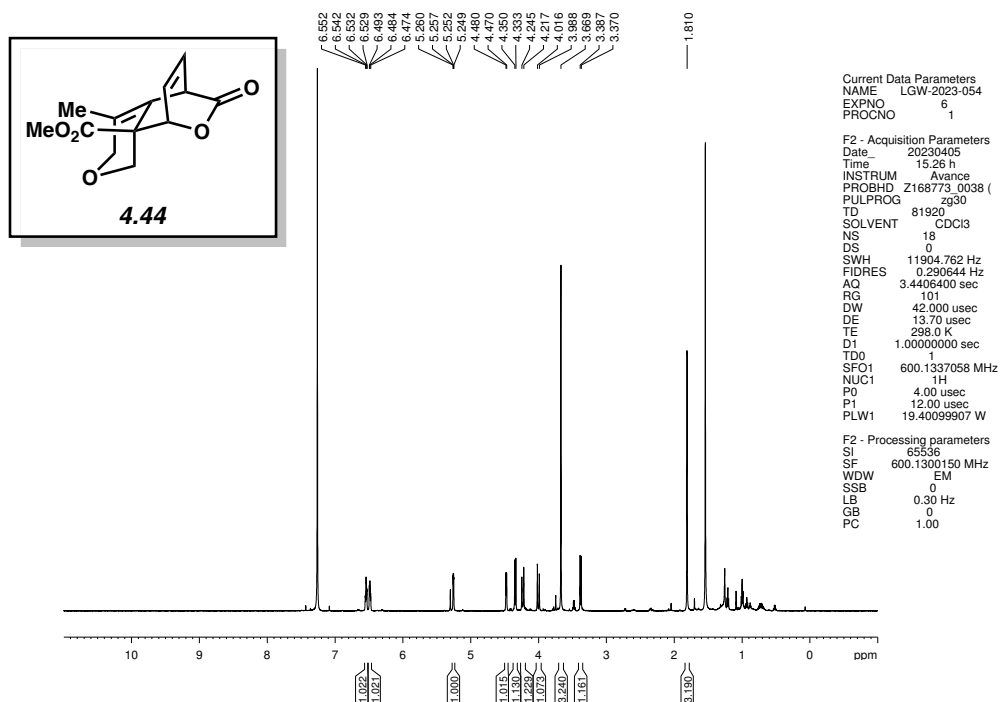


Figure 4.53. ^1H NMR (600 MHz, CDCl_3) of compound 4.44.

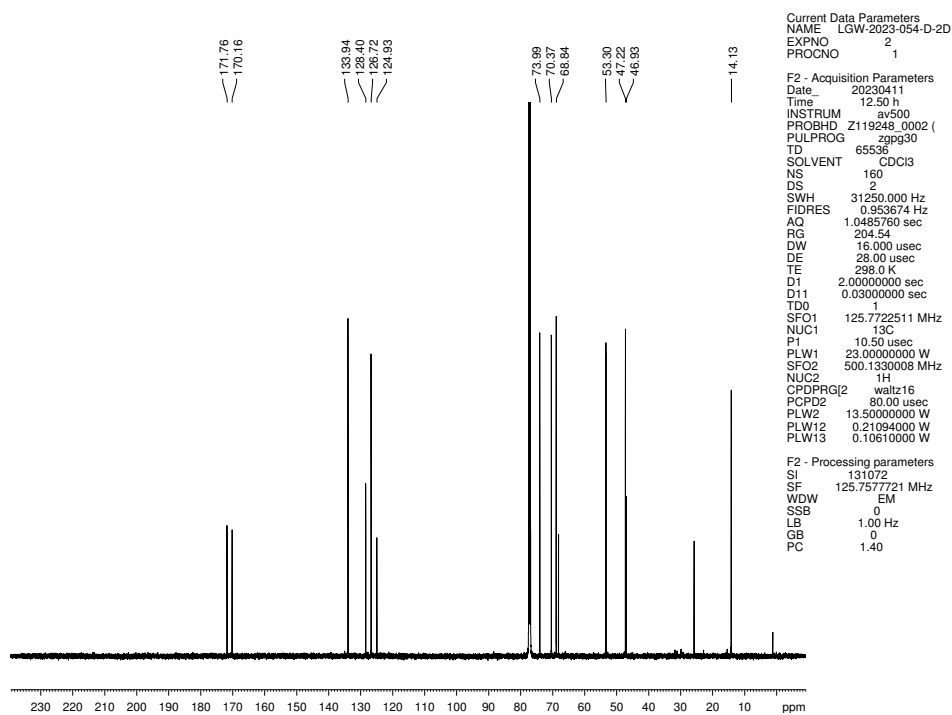


Figure 4.54. ^{13}C NMR (125 MHz, CDCl_3) of compound 4.44.

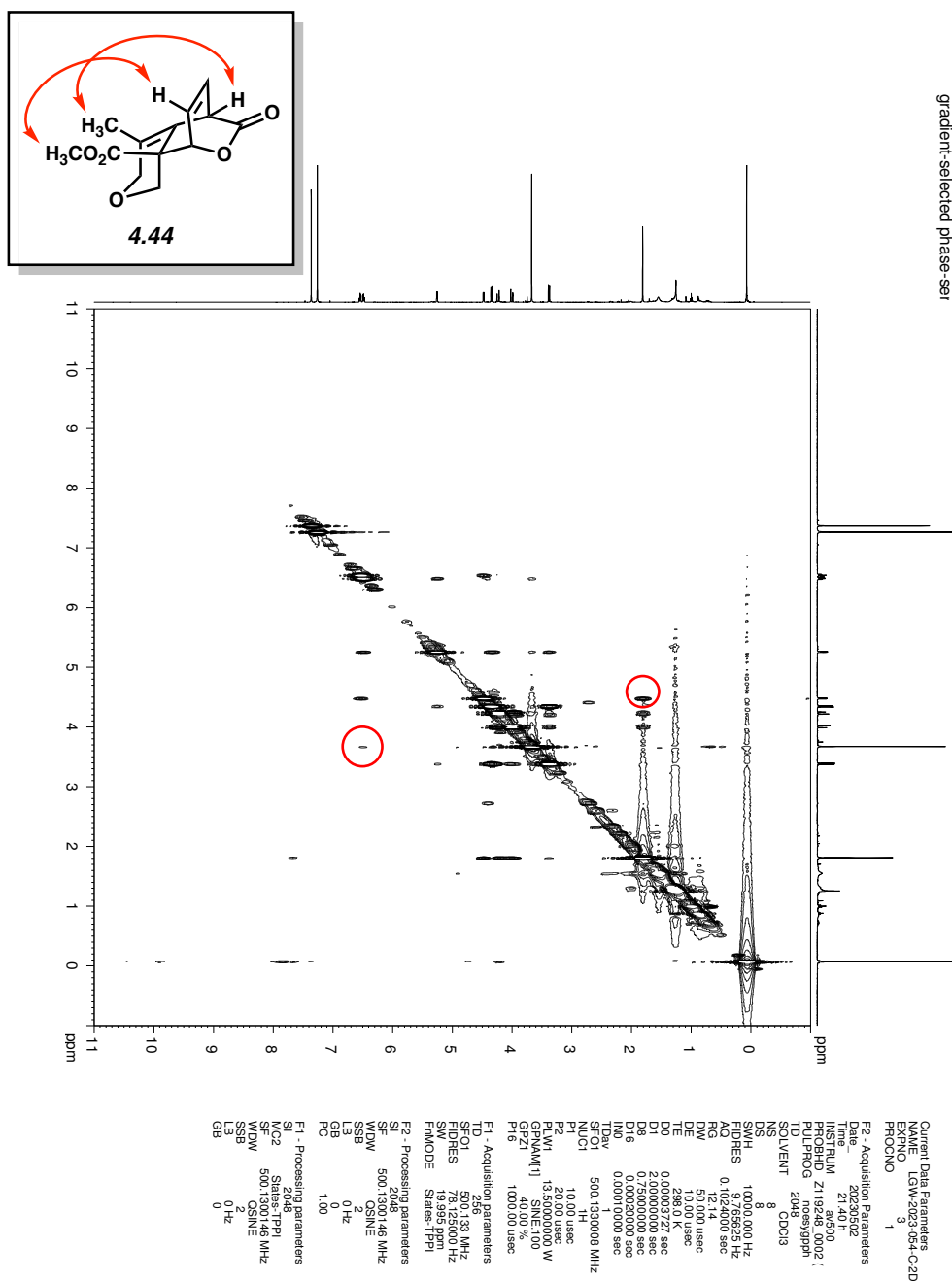


Figure 4.55. NOESY (500 MHz, CDCl₃) of compounds **4.44**.

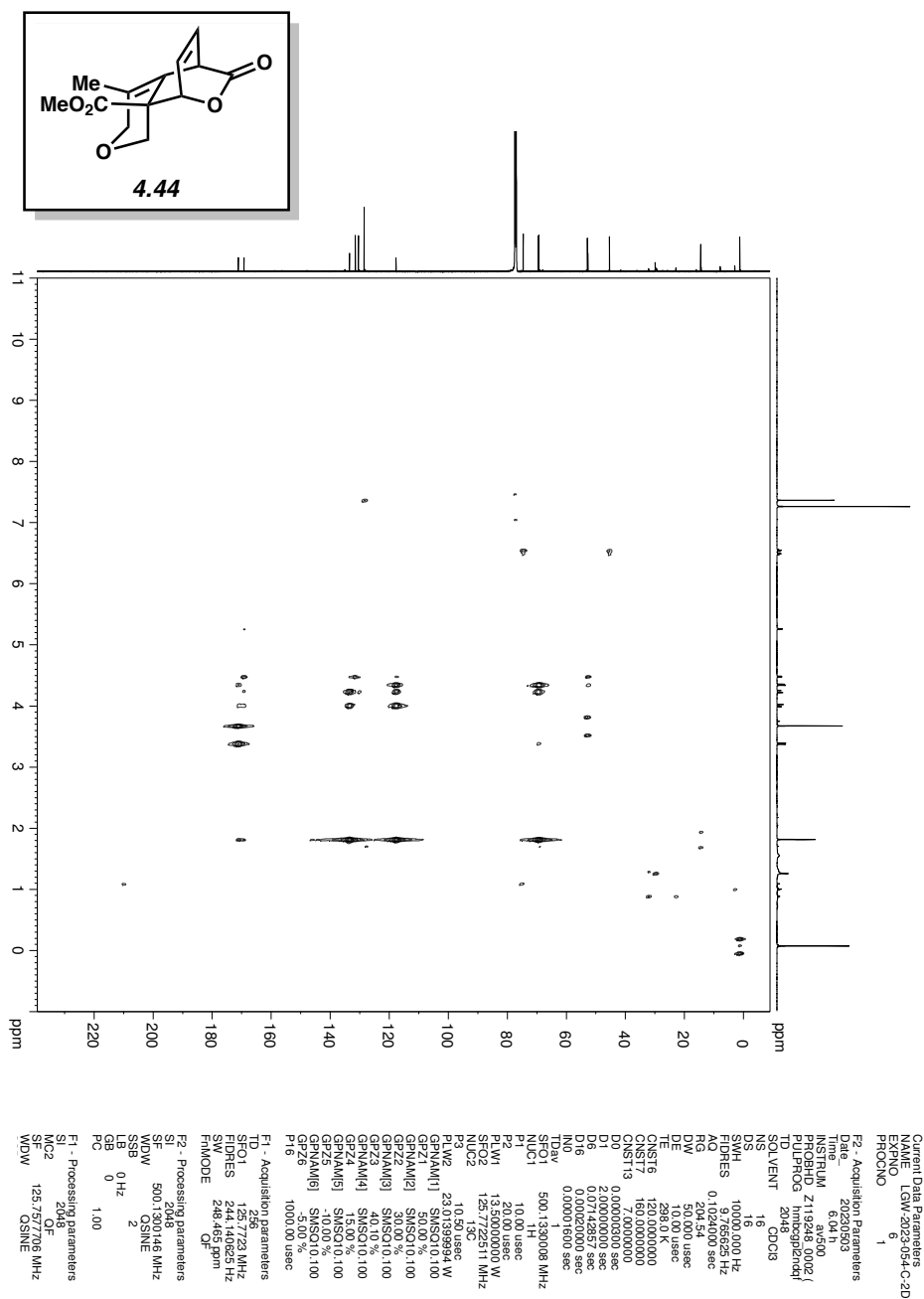


Figure 4.56. HMBC (600 MHz, CDCl₃) of compound **4.44**.

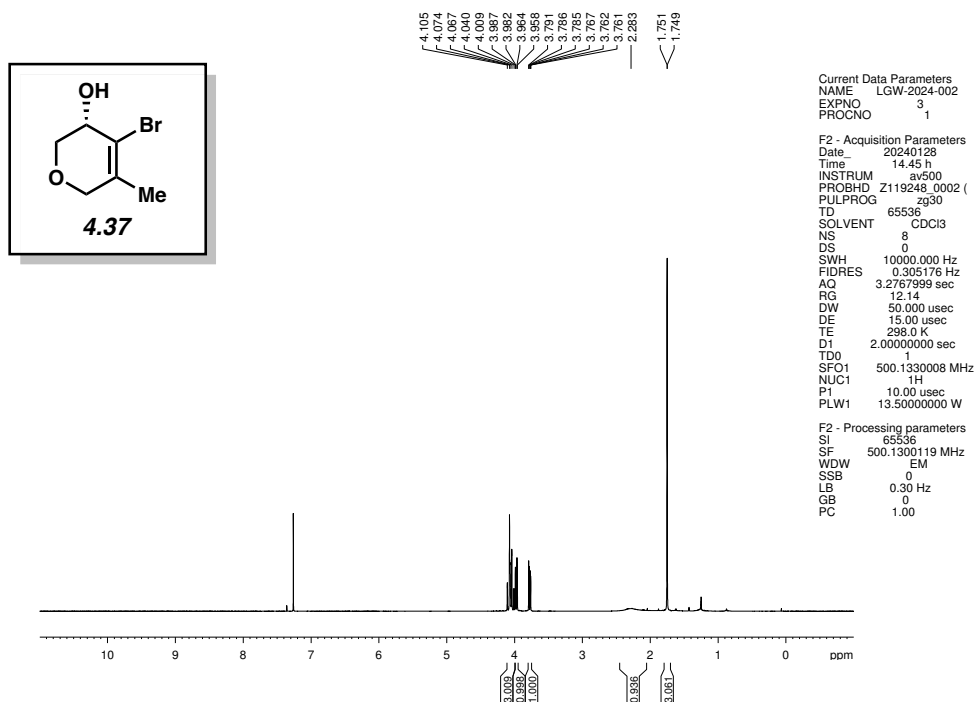


Figure 4.57. ^1H NMR (500 MHz, CDCl_3) of compound 4.37.

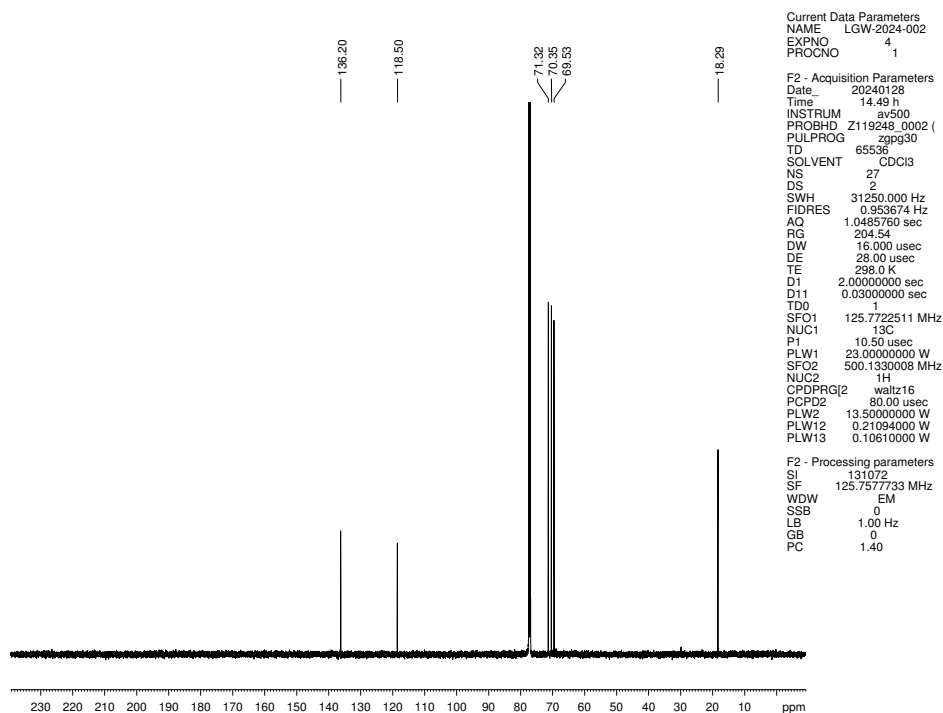


Figure 4.58. ^{13}C NMR (125 MHz, CDCl_3) of compound 4.37.



4.8 Notes and References

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CHAPTER FIVE

Organic Chemistry for Kids

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Manuscript In Preparation

5.1 Abstract

Chem Kids is a summer camp where children ages 10 to 12 years old learn the notorious subject of organic chemistry. The camp features interactive lessons, hands-on activities, connections between organic chemistry and everyday life, interaction with 3D chemical structures, and games that promote the understanding and manipulation of 3D objects.

5.2 Introduction

Organic chemistry is notorious for being a challenging class. Students pursuing science degrees or healthcare careers often hear about the fierce intellectual challenges associated with the subject well before taking organic chemistry coursework. In our own cases, organic chemistry was rumored to require extensive amounts of memorization and exams that verge on impossibility. However, practitioners of organic chemistry will offer that the subject is often misunderstood. Positive experiences in learning organic chemistry result from effective teaching, where the instructor may frame the subject not as an obstacle to overcome, but as an opportunity to learn a new language with applications woven into our daily lives. Moreover, especially as the course materials becomes more advanced, organic chemistry coursework provides excellent opportunities for students to develop their creativity and problem-solving skills.

With the aim of improving organic chemistry education and accessibility, we sought to integrate organic chemistry into a summer camp for children. This effort would complement other

educational efforts we have led,¹ such as the development of classroom and online resources for college-level students^{2,3,4,5} and the creation of organic chemistry coloring and activity books for children.^{6,7,8,9} Teaching organic chemistry to children would be notably different from typical organic chemistry teaching, which usually occurs during undergraduate studies. Moreover, making challenging Science, Technology, Engineering, and Mathematics (STEM) subjects¹⁰ accessible to the younger generation could be valuable for the long-term. Introducing organic chemistry to children could have the potential to help overcome negative perceptions of the subject, spark interest at a young age, and help fuel the STEM pipeline.

5.3. Camp Design

Chem Kids was designed for children ages 10–12, with the goal of integrating introductory organic chemistry concepts into a fun-filled summer camp. Although not a research study, we recognized that the selection of topics and activities would have to be done carefully in order to ensure a successful experience for the camp participants. Several key aspects of the camp design are as follows: a) we sought to convey that organic chemistry is enjoyable, b) an effort was made to relate organic chemistry concepts to everyday life, c) hands-on activities were considered ideal for ensuring high levels of engagement, d) we hoped to encourage students to embrace STEM fields and be proud of their intellect, and e) it was important to create a fun and collaborative environment. Diving further into the details, we deemed it important to help campers visualize things in three dimensions, as the understanding of three-dimensional structures is central to organic chemistry and provides a point of contrast compared to many other STEM fields. Thus, developing ways to teach 3D-related concepts like stereochemistry was a key consideration that

led us to incorporate a variety of “brain games” into the camp, such as solving Rubik’s cube (taught to all campers) and playing Jenga, which were done daily during the camp.

5.4 Camp Programming

Chem Kids was launched in the summer of 2023 at UCLA as a partnership with UCLA Recreation. The capacity for this pilot program was set to fourteen campers ages 10–12 and the camp enrollment filled on the first day of registration. Anecdotally, this may suggest a greater need for STEM-focused camps for children with such interests. The camp met daily over the course of one week and was led by one of us (NKG), with seven organic chemistry graduate students (including two of the authors: ATM and LGW) serving as content creators and camp counselors in a voluntary capacity. We describe here the activities that were undertaken during the Chem Kids camp.

The first day of Chem Kids focused on ice-breaker activities and introductory organic chemistry topics. To begin, the campers played a “Smell the Chemistry” activity that allowed them to associate everyday harmless smells (e.g., cinnamon, spearmint, and banana) with the organic molecules responsible for them. They learned that organic molecules are composed of the element carbon from the period table of elements, which is a fact that perhaps most of the general population may not be aware of. The campers then completed a lesson and worksheet introducing them to concepts such as elements and atoms, the periodic table, valence electrons, Lewis dot structures, and even drawing bond line structures of organic molecules.

On day two, campers visualized organic molecules in three dimensions using interactive educational tools such as QRChem⁸ and our laboratory’s virtual reality (VR) resources that are in development.¹¹ By interacting with molecules – especially through immersive VR – the children

were introduced to three-dimensionality of organic molecules in a fun and engaging way that brought chemistry to life.

Day two, as well as day three, of Chem Kids also included demonstrations and activities that were intended to be safe and engaging. Campers had the chance to see different types of research laboratories and equipment from a safe distance, just to provide them with a sense of what scientists do on a daily basis. Concepts such as states of matter and chemiluminescence were conveyed through demonstration, like shattering frozen gummy bears and explaining the science of luminol, respectively.

Several of the activities helped the campers relate organic chemistry to everyday life. One important organic molecule that was introduced to the students is DNA. Thus, a hands-on strawberry DNA-extraction experiment, coupled with a worksheet that helped campers record and analyze observations, was undertaken by each camper. The lesson on DNA continued with a VR activity,¹¹ which allowed campers to visualize and interact with the remarkable structure of DNA. Other hands-on activities included making ‘slime’ and ‘oobleck’ using household ingredients.

Yet another activity was taken on in day four of Chem Kids, where campers first connected organic chemistry with color through the PHOTONbooth, an interactive experience developed by Professor Ellen Sletten’s research team at UCLA.¹² After exploring the world of fluorescence and capturing memorable photos in the PHOTONbooth, campers were able to use QRChem⁸ to view relevant fluorescent molecules in 3D.

Day four also included lessons on stereochemistry. The campers were taught the concept of chirality and the Cahn–Ingold–Prelog rules. Campers were given periodic tables and were given the challenge of assigning stereocenters as *R* or *S* on relatively simple molecules. This lesson also included the chirality and stereocenters present in more complex molecules the campers had seen

throughout the week, to help relate some of the activities they had performed already to assigning stereocenters. A sample of the ‘Stereocenter Smackdown’ worksheet is shown in Figure 5.1A, which displays the skills of a camper, as well as their sense of joy.

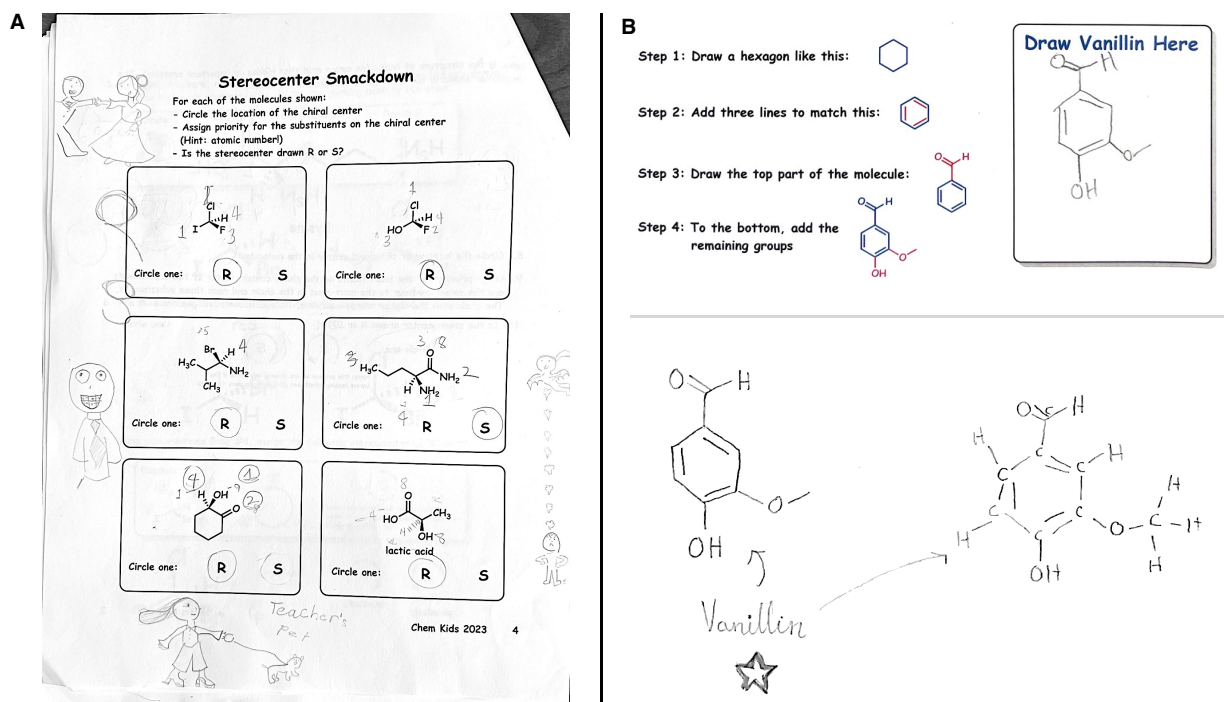


Figure 5.1. (A) Excerpt of “Stereocenter Smackdown” worksheet completed by camper. (B)

Exercise for drawing structures and drawings of vanillin by a camper.

Finally, day five of Chem Kids involved a celebration of the campers’ progress with the chemistry of ice cream. Vanillin, a molecule introduced on day one of the camp, was a central focus of the day. In addition to drawing the structure of vanillin in various forms (Figure 5.1B), campers explored the chemical structures of other chemicals associated with ice cream, such as sweeteners and caffeine found in chocolate.

Chem Kids concluded with campers solving organic chemistry problems on the boards, making their own vanillin molecular model souvenir necklaces, and receiving other

commemorative gifts, such as Chem Kids t-shirts, Rubik's cubes, laminated periodic tables, and organic chemistry coloring books. These memorabilia were intended to help the young campers retain their fun memories of Chem Kids for many years to come. Additionally, the finale of Chem Kids also featured more brain games, including Rubik's cube-solving showdowns, where the youthful campers often performed favorably compared to the graduate student camp counselors and the professor.

Anonymous feedback from the campers on Chem Kids was overwhelming positive and reflected great enjoyment in learning organic chemistry. When asked what was the "coolest" aspect of the camp, responses included "organic chemistry", "valence electrons", "DNA", "the elements", "chemistry", "extracting a strawberry's DNA", "drawing molecules", and "everything here is cool". One camper proudly proclaimed that if they ever take chemistry in college they would "probably ace it." Similarly, the organic chemistry graduate student volunteer counselors and the professor unanimously agreed that creating and offering Chem Kids was a wonderful and efficient way to share their passion for organic chemistry and STEM fields in general with the next generation of scientists.

5.5 Future Directions

Given our successful experience, Chem Kids is being offered again in 2024 and we hope it will continue for the foreseeable future. We suggest several future directions: a) the expansion of Chem Kids, both in terms of capacity of the current camp and the creation of Chem Kids camps at other institutions, b) the creation of resources that help introduce organic chemistry to children, c) the creation of camps and resources that allow youngsters to explore other STEM fields beyond organic chemistry that are typically not taught until a later point in one's educational journey. We

would also welcome experts in pedagogy to help answer the question: *when is the best age for organic chemistry to be taught?* Such efforts should help improve organic chemistry education, foster the STEM education pipeline, and provide an opportunity for us scientists to share our passion for science with others.

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