Investigation of Strain-Activated Trapping Reactions of 1,2-Cyclohexadiene: Intramolecular Capture by Pendent Furans and Styrenes

by

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Abstract

1,2-Cyclohexadiene is a small carbocyclic allene that as a reactive intermediate can be utilized in a variety of reaction pathways. The chemical literature around this species is largely limited to various methods of generation and simple trapping reactions. Little research exists on methods to control these intermediates and enable their more prominent use in synthesis. One popular method to control a reaction is to move from an intermolecular to intramolecular framework, where more of the factors affecting a reaction can be controlled. In this thesis the development of new intramolecular trapping reactions of 1,2-cyclohexadiene will be discussed with a focus on [4+2] and [2+2] modes of cycloaddition with furans and styrenes respectively.

Chapter 1 will provide a detailed overview of the origins of 1,2-cyclohexadiene including its synthesis, structural investigations, trapping reactions and mechanistic studies; modern synthetic efforts with the intermediate and similar compounds will also be described. This review of the relevant literature will serve as a primer to discuss the new results described in this thesis.

Chapter 2 shows the development of a state-of-the-art intramolecular trapping reaction of 1,2-cyclohexadiene using pendent substituted furans. This [4+2]-cycloaddition reaction was enabled via a modular synthetic sequence that allowed the production of a variety of starting materials and allowed the initial scope of this new methodology to be explored. This mild cycloaddition proceeded in high regio- and diastereoselectivity and allowed access to versatile hetero-tetracycles. Efforts to manipulate these complex hetero-carbocycles were examined and a surprising retro [4+2]-cycloaddition was discovered.

Chapter 3 continues the development of intramolecular trapping reactions of 1,2-cyclohexadiene with new substrates that contain a styrene moiety and undergo [2+2]-cycloaddition. The chemical nature of the double bond on the styrene was shown to be vital to

reaction efficacy and interesting trends were demonstrated through carefully selected substrates. Efforts to synthesize an intermediate in the total synthesis of isocomene are also described.

Chapter 4 will tie the [4+2] and [2+2]-cycloaddition reactions together and discuss exciting future directions for this chemistry. The chemical utility of 1,2-cyclohexadiene, as reported in this thesis, will be discussed and a broad overview of what the future may hold for this reactive intermediate will be evaluated.

Preface

Part of Chapter 2 of this thesis has been published as Lofstrand, V. A.; McIntosh, K. C.; Almehmadi, Y. A.; West, F. G., "Strain-Activated Diels−Alder Trapping of 1,2-Cyclohexadienes: Intramolecular Capture by Pendent Furans," Org. Lett. 2019, 21, 6231-6234. I was responsible for most experimental work, most data collection, and most characterization of compounds as well as some of the manuscript composition. Lofstrand, V. A. was responsible for the concept formation, some preliminary experimental work, some of the manuscript composition, data collection, synthesis and characterization of compounds 48b, 90, 91, 93, 94, 49f/h, 46 h/I, and 48i/j (numbering from Chapter 2). Almehmadi, Y. A. was responsible for some concept formation. West, F. G. was the supervisory author and was involved with concept formation and manuscript composition.

Part of Chapter 3 of this thesis will be published as McIntosh, K. C.; Lofstrand, V.A.; Ochoa, A. S.; Almehmadi, Y. A.; West, F. G. "Strain-Activated Diels−Alder Trapping of 1,2-Cyclohexadienes:Intramolecular Capture by Pendent Styrenes," *manuscript in preparation*. I was responsible for the experimental work, the data collection, and characterization of compounds as well as the manuscript composition. Lofstrand, V. A. was responsible for the concept formation. Ochoa, A. S. was responsible for some experimental work and synthesis and characterization of compounds 87, 88, 89, 91, 92 and 93 (numbering from Chapter 3). Almehmadi, Y. A. was responsible for some concept formation. West, F. G. was the supervisory author and was involved with concept formation and manuscript composition.

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To my family who have supported me all these years. To my mom(Pamela), dad(Timothy) and brothers(Tyler and Chris) who have always been there to support me no matter what. I love you all.

Marius, Yury and Ahmed, thanks for all the insightful discussions we have had over the years and for your good company. Thank you to everyone in the West group.

To anyone I may have missed, thank you.

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List of Symbols and Abbreviations

$\Delta G^{\ddagger}$	Gibbs free energy of activation
π	Pi bond
Δ	Reflux
Ø	Angle
°	Degrees
S_0	Singlet ground state
S_1	Singlet excited state
T_1	Triplet excited state
Ac	Acetyl
app	Apparent
Ar	Aryl
Bn	Benzyl
br	Broad
Bz	Benzoyl
calcd.	Calculated
cat.	Catalyst
CBS	Corey-Bakshi-Shibata
cm^{-1}	Wavenumber
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublets of doublets

dddd	Doublet of doublets of doublets of doublets
DA	Diels-Alder
DCE	Dichloroethane
DCM	Dichloromethane
DDA	Dehydro-Diels-Alder
DIBALH	Diisobutylaluminium hydride
DMAP	4-(Dimethylamino)pyridine
DMS	Doering-Moore-Skattebøl
DMSO	Dimethylsulfoxide
DPIBF	Diphenylisobenzofuran
dr	Diastereomer ratio
dt	Doublet of triplets
ee	Enantiomeric excess
EI	Electron impact
Et_2O	Diethyl ether
EtOAc	Ethyl Acetate
EtOH	Ethanol
equiv.	Equivalents
er	Enantiomer ratio
ESI	Electro spray ionization
EWG	Electron withdrawing group
FMO	Frontier molecular orbital
FVP	Flash vacuum pyrolysis

HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry
hv	Light
IMDAF	Intramolecular Diels-Alder with furan
IR	Infrared Spectroscopy
ISC	Inter-system crossing
K	Kelvin
kcal	Kilocalories
KHMDS	Potassium bis(trimethylsilyl)amide
KO*t*Bu	Potassium *tert*-butoxide
LA	Lewis acid
LAD	Lithium aluminum deuteride
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamine
LG	Leaving group
LSD	Lysergic acid N,N-diethylamide
LUMO	Lowest unoccupied molecular orbital
m `	Multiplet
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
Mhz	Megahertz
mol	Mole

mmol	Millimole
n	Repeating group
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
Nu	Nucleophile
OAc	Acetoxy
OTf	Triflate
OTs	Tosylate
q	Quartet
quint	Quintet
R	Generic group
Rf	Retention factor
rt	Room temperature
s	Singlet
SEM	[2-(Trimethylsilyl)ethoxy]methyl
S_N1	Substitution nucleophilic unimolecular
S_N2	Substitution nucleophilic bimolecular
S_NAr	Substitution nucleophilic aromatic
t	Triplet
TBAF	Tetrabutylammonium fluoride
td	Triplet of doublets
t-BuLi	*Tert*-butyllithium
Tf	Triflyl

THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	Tosyl

1. 1,2-Cyclohexadiene: History, Reactivity and Chemical Utility

1.1 Catalysis

Structurally complex organic compounds and strategies for their assembly receive considerable attention in organic synthesis. The development of new carbon-carbon bond forming reactions are a central strategy to turn simple starting materials into functionalized products.[1] During such transformations a minimum energy cost, the Gibbs free energy of activation ($\Delta G^{\ddagger}$), must be overcome for a reaction to take place. This energy maximum is a transition state between reactants and products and represented as the top of the curve on a standard reaction progress diagram. Transformations with a large $\Delta G^{\ddagger}$ such as direct transformation of **1** to **4** will require the input of energy or a lowering of the activation barrier to proceed.[2] The use of catalysts to effect a lower energy transition state is common; nucleophilic addition reactions to ketone **1** will often employ a Brønsted acid **2** to activate the ketone.[3] Such catalyzed reactions will proceed through a protonated intermediate **3** with a lower $\Delta G^{\ddagger}$ (Figure 1.1).

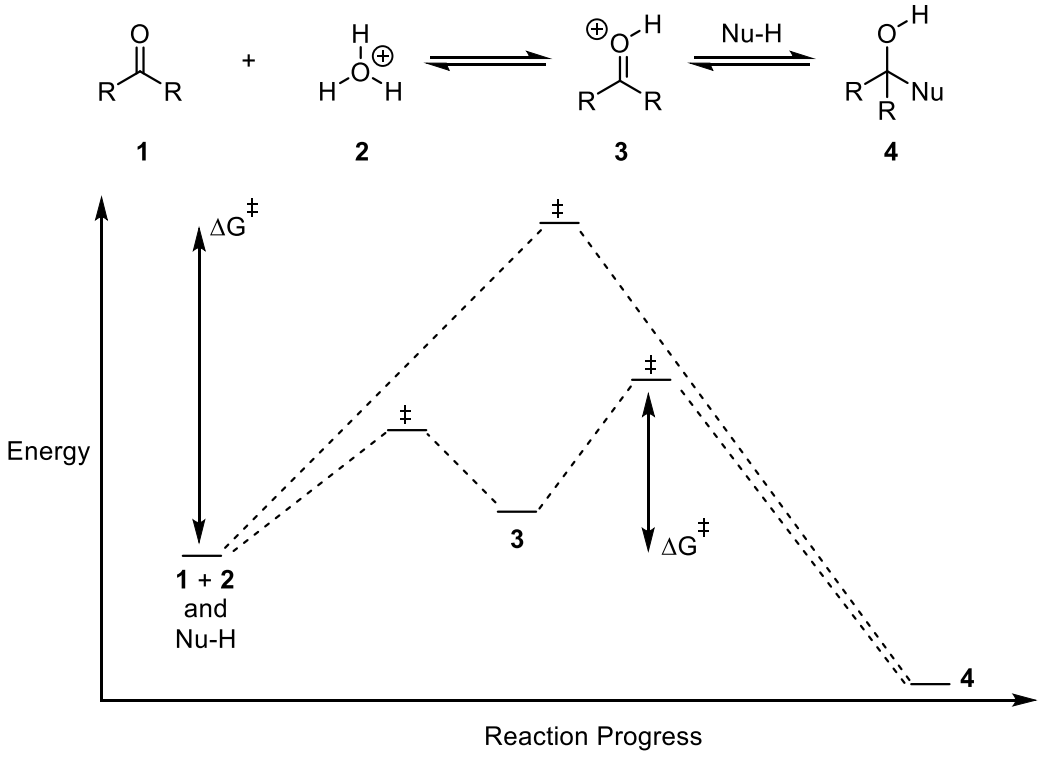
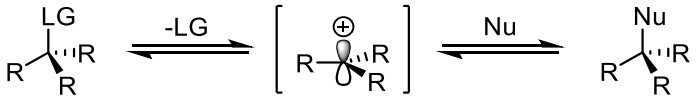


Figure 1.1 - Reaction Progress Diagram of Nucleophilic Addition to Ketone Catalyzed by Brønsted Acid

1.2 Reactive Intermediates

Reactive intermediates are species generated in a reaction that typically have very short lifetimes and will quickly transform into another chemical species. Reactions proceeding through reactive intermediates enable transformations that otherwise might not be possible. The high ground state energy of reactive intermediates leads to a lower $\Delta G^{\ddagger}$ that allows facile reactivity. Nucleophilic substitution reactions can either go through a direct transformation, a substitution nucleophilic bimolecular reaction (S_N2), or through an intermediate carbocation, a substitution nucleophilic unimolecular reaction (S_N1). With bulky substituted systems such as **5** the reaction will proceed through a carbocation intermediate **6** (Scheme 1.1).[4] Many types of reactive intermediates exist, and they are prominent throughout all forms of organic chemistry.[5,6]



Scheme 1.1 - Generic S_N1 Reaction with a Carbocation Intermediate

Two broadly defined types of reactive intermediates are type I and type II intermediates (Figure 1.2).[7] Type I intermediates **8-10** can be viewed as species that have nonbonding electrons or di/trivalent carbon atoms. This incomplete valence shell gives these species their high reactivity and they want to react and form tetravalent carbon. Found in all domains of organic synthesis, type I intermediates include carbocations, radicals and carbenes. Type II intermediates **11-13** differ from type I in that, while they possess complete valence shells, they contain bonds that are deformed away from ideal geometry. These types of intermediate are often found in ring systems where angle strain imparts significant destabilization by raising the ground state energy. These species will react to release the ring strain they contain and adopt a more ideal geometry. Examples of type II intermediates with distorted π bonds (the focus of this thesis) include cycloalkynes, benzynes and cyclic allenes.

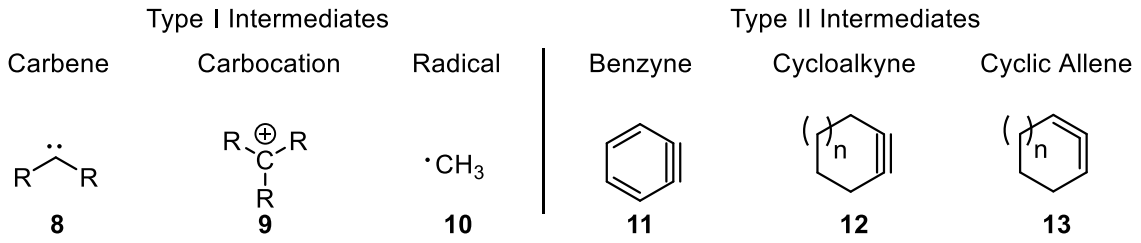


Figure 1.2 - Reactive Intermediates of Type I and Type II

1.3 Type II Reactive Intermediates: Cycloakynes and Arynes

Triple bonds will adopt a bond angle of 180° between the *sp* hybridized carbon atoms in linear systems, resulting in 4 atoms sharing a linear system. When confined within a rigid ring system as in benzyne **11** or cyclohexyne **12a** this ideal geometry is impossible, leading to bond angle distortion to impose an angle of less than 180° (Figure 1.3). Accordingly, these species have large strain energies, with values of 50 kcal/mol and 40 kcal/mol respectively for **11** and **12a**.[8,9] Less effective *p* orbital overlap and consequently a lowering of the LUMO energy level result in weaker π bonds that are susceptible to reaction primarily as electrophiles.[10]

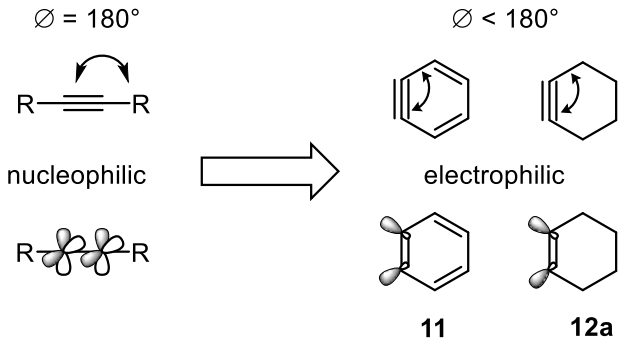
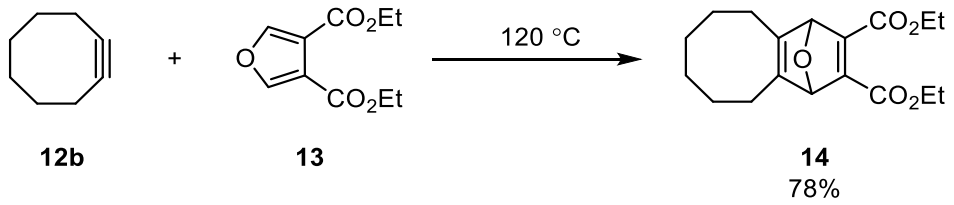


Figure 1.3 - Reduced Orbital Alignment and Increased Reactivity due to Bending of Triple Bonds

Cyclooctyne **12b**, with a strain energy of ~18 kcal/mol,[11] is the smallest cycloalkyne that can be isolated, although it often undergoes oligomerization.[12] Initially fairly harsh conditions with elevated temperatures were required in order to trap **12b**. Tochtermann used diethyl 3,4-furandicarboxylate **13** and generated [4+2]-cycloadduct **14** in 78% yield (Scheme 1.2).[13] From

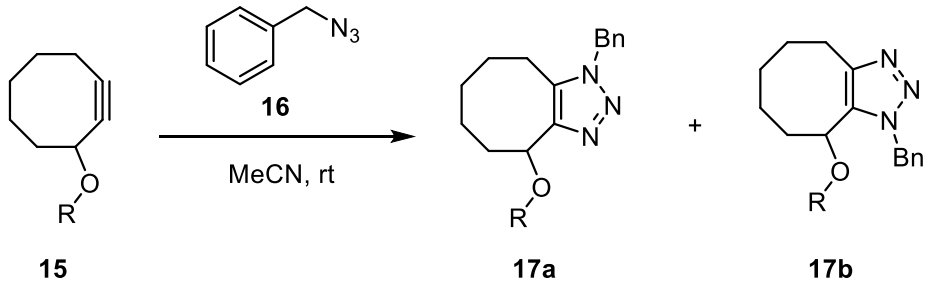
these humble beginnings cyclooctyne has quickly become one of the most important strained intermediates.



12b **13** **14**
78%

Scheme 1.2 - [4+2]-Cycloaddition of Cyclooctyne and Diethyl 3,4-furandicarboxylate

The Huisgen cycloaddition of cyclooctyne derivative **15** with benzyl azide **16** (Scheme 1.3), a copper free [3+2]-cycloaddition demonstrated by Bertozzi, has seen wide uptake in chemical biology where it is used to quickly and efficiently link two fragments in a "bioorthogonal" reaction under conditions compatible with biological systems.[14] This remarkably mild transformation shows the potential of strained intermediates as useful moieties in chemical synthesis. Particularly from a biological standpoint avoiding the use of metals, which can be toxic and hard to remove is advantageous. This application followed Wittig and Krebs original report on the spontaneous cycloaddition of cyclooctyne with azides.[15]

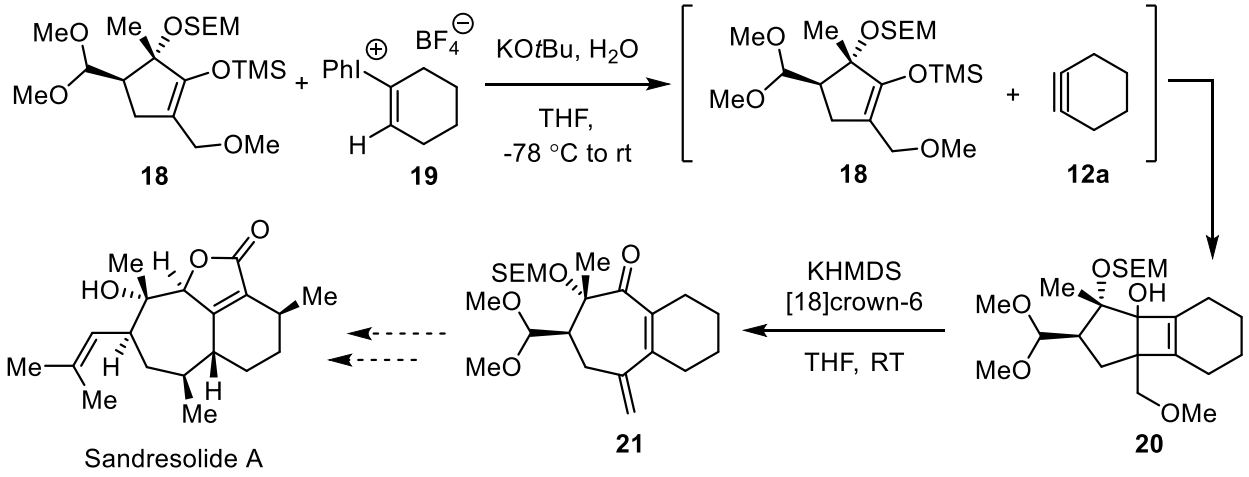


15 **17a** **17b**
R = linker conected to a peptide chain

Scheme 1.3 - Huisgen Cycloaddition with Cyclooctyne and Benzyl Azide

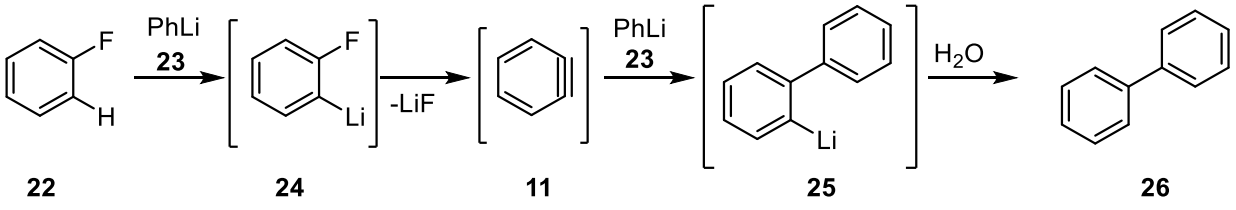
Cyclohexyne **12a** was used in a total synthesis for the first time by Carreira and co-workers, who synthesized sandresolide A (Scheme 1.4).[16] The key step involved a [2+2]-cycloaddition between substituted trimethylsilyl-enol (TMS) ether **18** and cyclohexyne **12a** generated from phenyliodonium salt **19**. The resulting cyclobutene ring in **20** underwent ring expansion via Grob

fragmentation to produce cycloheptenone **21** and was carried forward to sandresolide A. A similar strategy was used to assemble the natural products guanacastepenes N and O.[17]



Scheme 1.4 - [2+2]-Cycloaddition and Ring Expansion Route to Sandresolide A

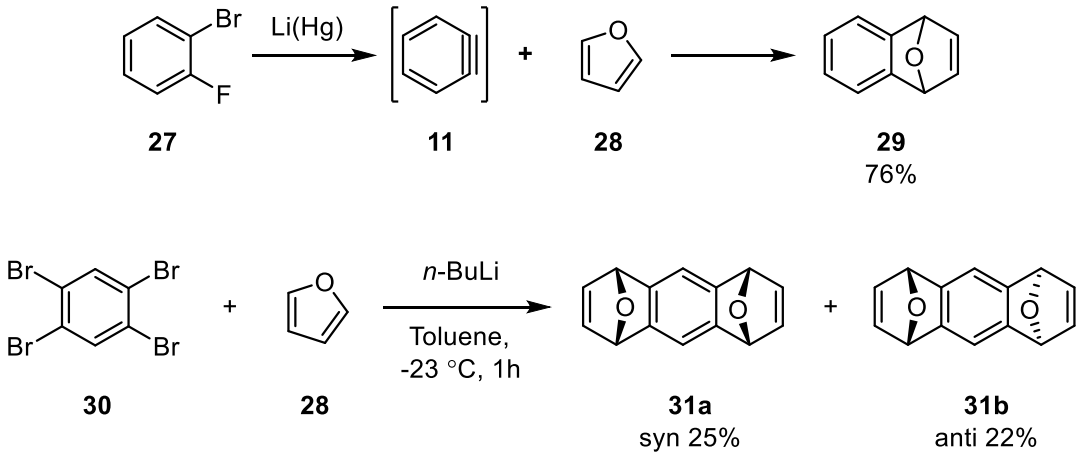
Compared to cycloalkynes, arynes have received much more attention in the literature. Arynes had long been proposed structures in the literature but in 1940 Wittig was able to provide the first experimental evidence of their existence. While investigating the reaction of fluorobenzene **22** with phenyllithium (PhLi) **23** it was noted that biphenyl **26** was obtained. To explain this Wittig proposed a mechanism with deprotonation of the *ortho* position of fluorobenzene **22** to generate lithiated intermediate **24** which would eliminate LiF to produce benzyne **11**. Nucleophilic addition and subsequent quenching of intermediate **25** with water (H_2O) would yield biphenyl **26** (Scheme 1.5).[18]



Scheme 1.5 - Generation of Benzyne and Trapping with Phenyllithium

The first cycloaddition reaction with an aryne was conducted in 1955. Wittig was able to trap benzyne **11**, generated from 2-fluorobromobenzene **27** and lithium amalgam (Li(Hg)), with

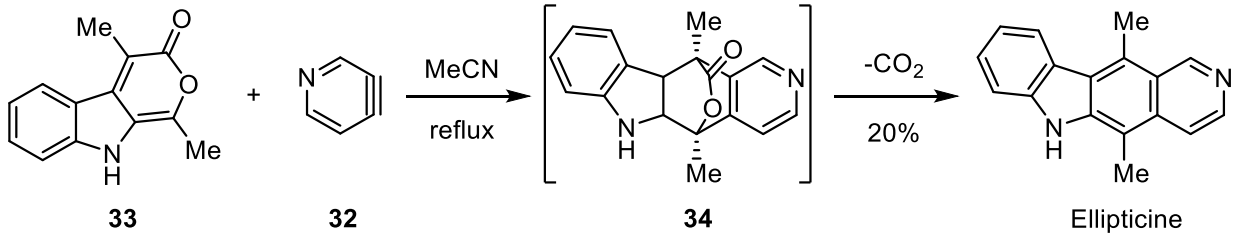
furan **28** to furnish [4+2]-cycloadduct **29** in 76% yield (Scheme 1.6).[19] This result has inspired an extensive body of work in the chemical literature involving Diels-Alder trapping of arynes. The synthesis of tetrahydroanthracenes **31a/b** as a mixture of *syn* and *anti* diastereomers upon reaction of tetrabromobenzene **30** and *n*-butyllithium with furan **28** is a classic example of this reactivity.[20]



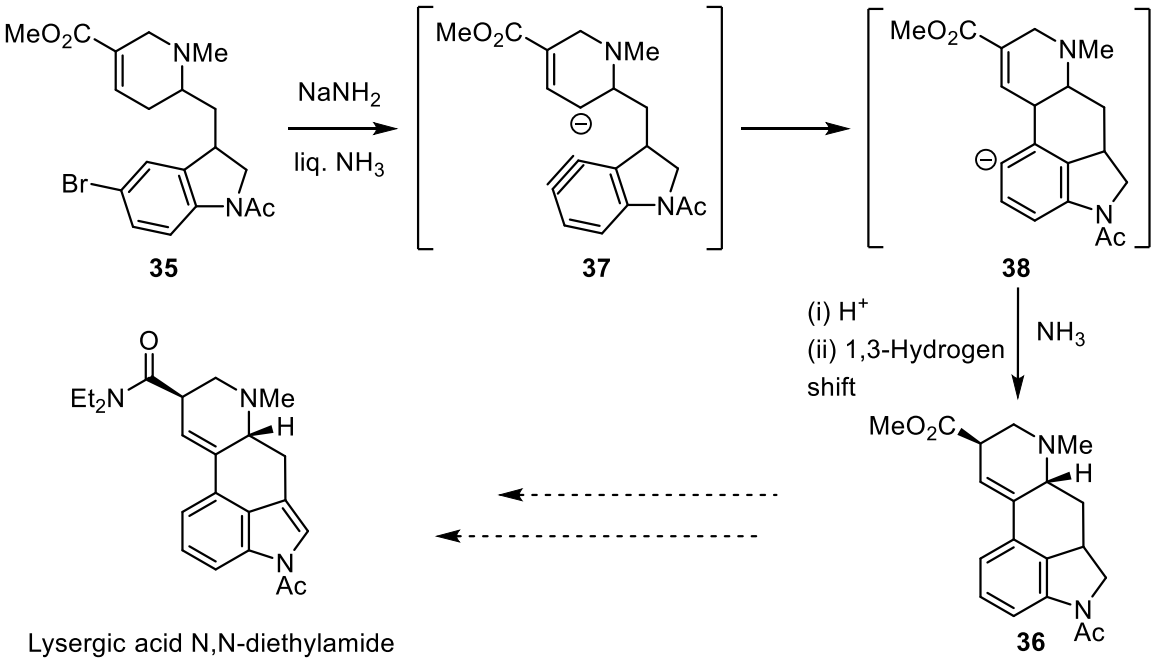
Scheme 1.6 - Diels-Alder Cycloadditions with Furan and Benzyne

Due to their ability to help construct advanced polycyclic systems that contain aromatic moieties, arynes have been used in a variety of total syntheses. Nitrogen-containing arynes such as pyridynes and indolynes are of interest for the synthesis of functionalized heterocycles and natural products.[21] Ellipticine, an antitumor alkaloid that binds to topoisomerase II, has been prepared in 20% yield by Diels-Alder reaction of 3,4-pyridyne **32**.[22] The α-pyrone diene **33** reacted with **32** in acetonitrile (MeCN) under reflux to produce cycloadduct **34,** along with the opposite regioisomer. These intermediates underwent spontaneous aromatization by loss of CO_2 in a Diels-Alder cycloreversion (Scheme 1.7). While an elegant synthesis, unfortunately a high toxicity shown in clinical trials due to intercalative binding to DNA has limited the therapeutic application of ellipticine despite its ability to reduce tumor growth.[23] Nucleophilic addition reactions of arynes have also been utilized in the context of total synthesis. Lysergic acid ester, a precursor to the drug lysergic acid *N*,*N*-diethylamide (LSD), has been prepared using an intramolecular nucleophilic addition reaction of indolinyne as the key step.[24] In this seminal study Julia and co-workers treated 5-bromoindoline **35** with sodium amide ($NaNH_2$) in liquid ammonia (NH_3) and isolated cycloadduct **36**. Compound **36** is assumed to arise from selective nucleophilic attack of vinylogous

enolate **37** onto the C4 position of the indolinyne; subsequent protonation and 1,3-Hydrogen shift of **38** gives the Lysergic acid ester precursor **36** (Scheme 1.8).



Scheme 1.7 - Synthesis of Ellipticine by Diels-Alder Reaction of 3,4-Pyridyne



Scheme 1.8 - Synthesis of LSD Precursor 36

1.4 Cyclic Allenes

1.4.1 Early History of Cyclic Allene Synthesis

Initial studies involving cyclic allenes were closely tied to attempts to synthesize cycloalkynes. In cycloalkene **39** with a vinylic leaving group (Figure 1.4) it would be possible to remove either the alkenyl or allylic protons. The proton that is eliminated will determine whether

cycloalkyne **12** or cyclic allene **13** is generated; removal of the vinylic proton will produce **12** while removal of the allylic proton will produce **13**.

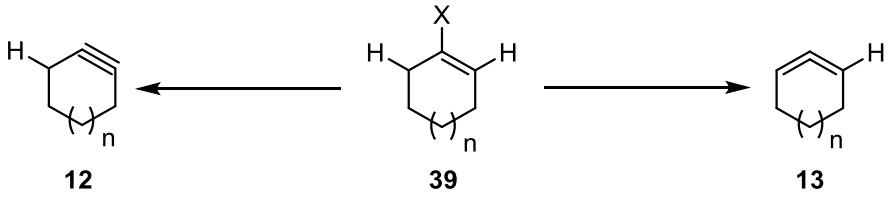
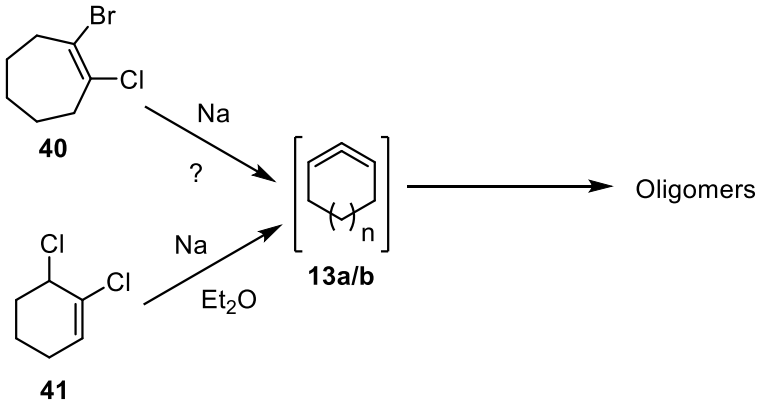


Figure 1.4 - Alkenyl or Allylic Proton Elimination to Synthesize Cycloalkyne or Cyclic Allene

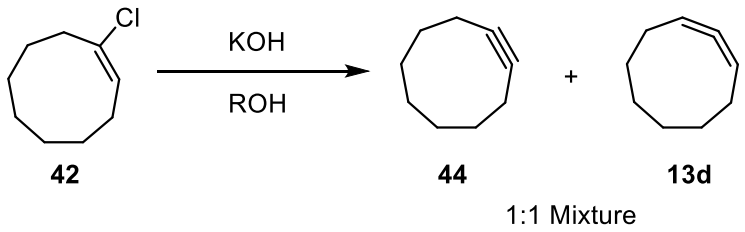
The origins of cyclic allene chemistry date back to the '30s when Favorskii claimed to have isolated 1,2-cycloheptadiene by treating bromo-2-chlorocycloheptene **40** with sodium (Na) in diethyl ether (Et_2O).[25-27] Domnin, a student of Favorskii's, attempted to isolate 1,2-cyclohexadiene **13a** in the '40s by treating dichlorocyclohexene **41** with sodium in Et_2O.[28] In both reactions a distillable hydrocarbon was isolated; Favorskii claimed it was the cyclic allene while Domnin suggested it was an oligomer (Scheme 1.9).



Scheme 1.9 - Initial Studies on Cyclic Allene Synthesis in the Favorskii Laboratory

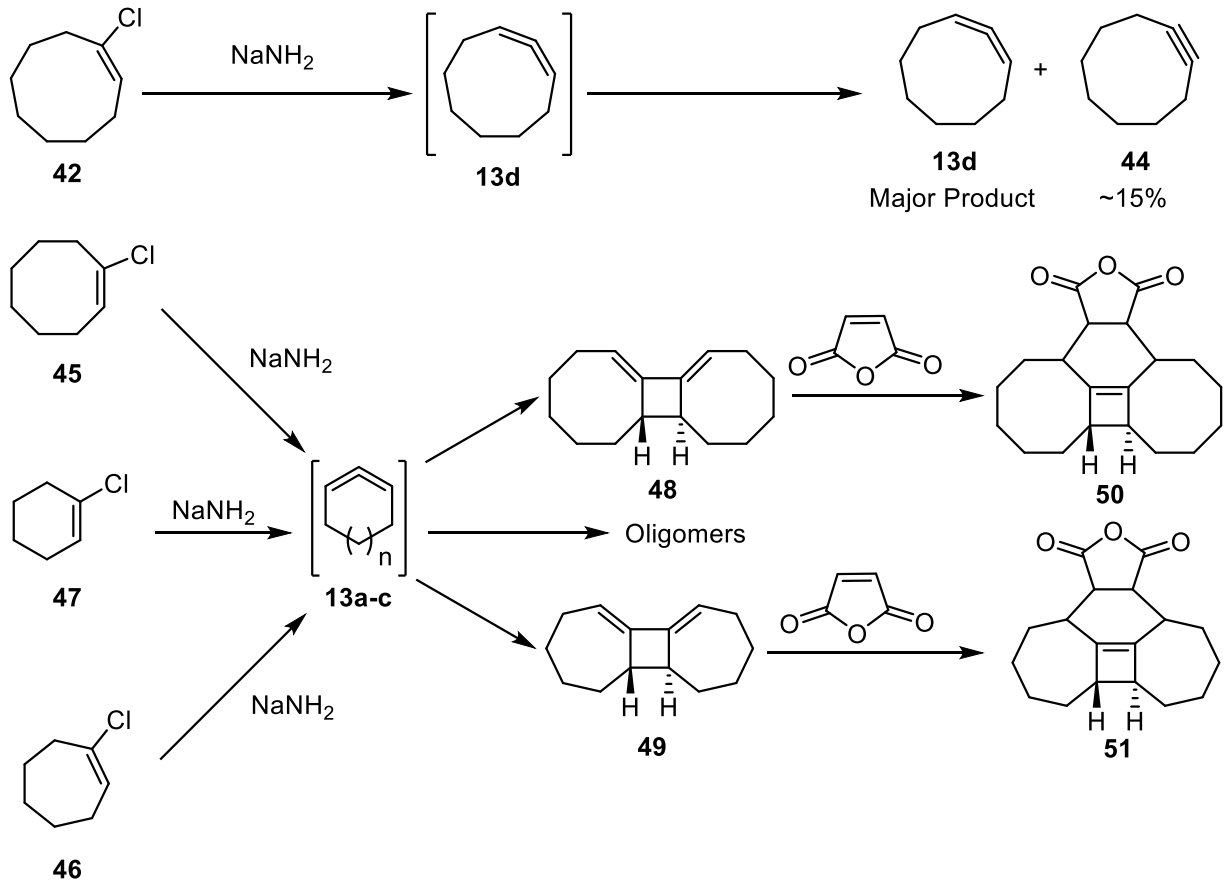
The first definitive synthesis of a cyclic allene with a ring size smaller than ten was accomplished by Blomquist and co-workers in 1951.[29] Using 1-chlorocyclononene **42** and reacting it with alcoholic potassium hydroxide (KOH), Blomquist formed an equal mixture of cyclononyne **44** and 1,2-cyclononadiene **13d** (Scheme 1.10). Because of the large ring size and less deformed

bond angles, 1,2-cyclononadiene only has a strain energy of ~5 kcal/mol and is the smallest cyclic allene to be isolable under standard conditions.[25]



Scheme 1.10 - Synthesis of 1,2-Cyclononadiene by Blomquist

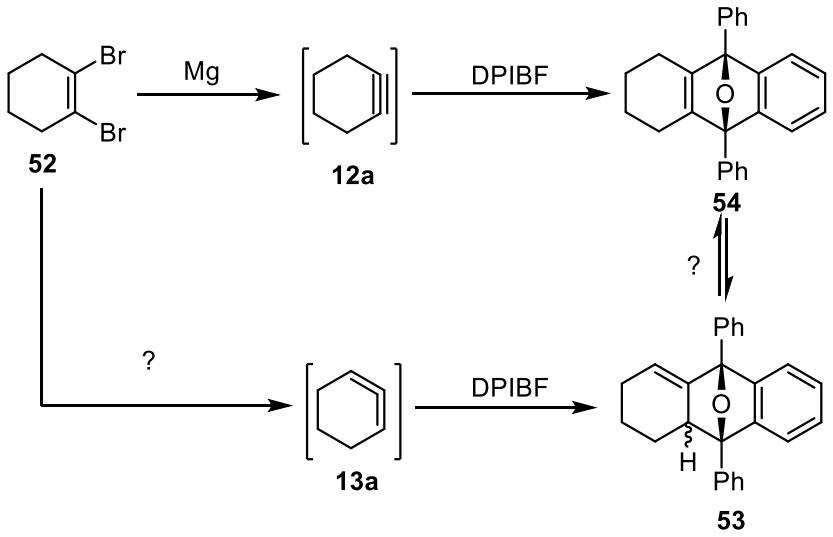
In the 1960's Ball and Landor conducted a series of experiments where they were able to advance the field of cyclic allene chemistry greatly by preparing 1,2-cyclononadiene and smaller size allenes. Through a dehydrohalogenation reaction of 1-chlorocyclononene **42**, 1-chlorocyclooctene **45**, 1-chlorocycloheptene **46** and 1-chlorocyclohexene **47** they were the first to synthesize 1,2-cyclooctadiene **13c**, 1,2-cycloheptadiene **13b** and possibly the first to make 1,2-cyclohexadiene **13a** (Scheme 1.11).[30] Ball and Landor used $NaNH_2$ to effect the dehydrohalogenation and in the case of 1,2-cyclooctadiene **13c** and 1,2-cycloheptadiene **13b** were able to generate the corresponding dimer products **48** and **49**, whose formation is presumed to be driven by the release of the strain resident in the cyclic allene intermediates. Further trapping of the dimers in a [4+2] Diels-Alder cycloaddition with maleic anhydride provided adducts **50** and **51** which can go on to form the diadducts with maleic anhydride. The constant persistence of an unknown impurity in these reactions prevented the accurate reporting of yield. With 1-chlorocyclononene the major product of the reaction was 1,2-cylononadiene and only ~15% of the reaction mixture was cyclononyne. This contrasts with Blomquist's synthesis, where a 1:1 mixture was obtained.[29] In the case of 1,2-cyclohexadiene **13a** they were able to observe oligomers as had been reported by Domnin but could not observe a dimer.



Scheme 1.11 - Experiments by Ball and Landor on Cyclic Allene Synthesis via Dehydrohalogenation

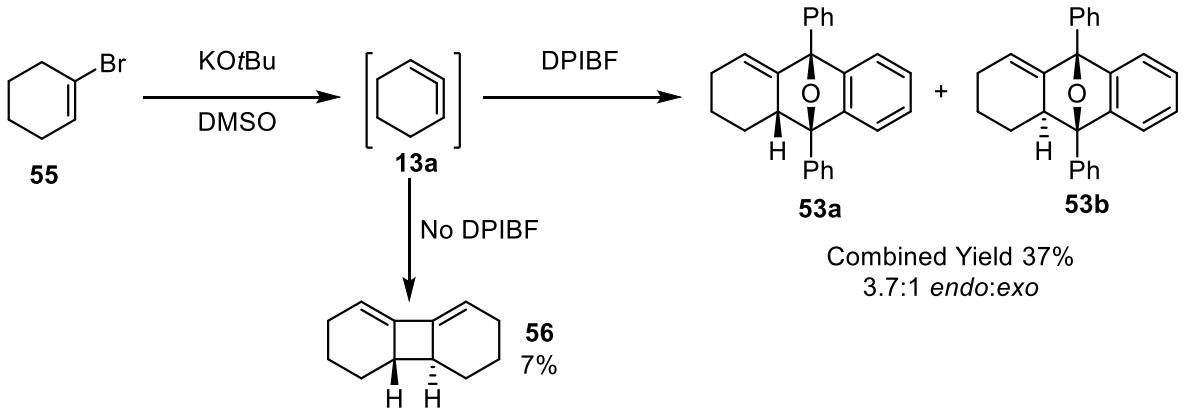
1.4.2 Initial Studies on 1,2-Cylohexadiene: Synthesis, Structure and Dimerization

It was not until 1966 that conclusive evidence was presented by Wittig and Fritze for the synthesis of 1,2-cyclohexadiene.[31] In early experiments with cycloalkynes, 1,3-diphenylisobenzofuran (DPIBF) was often used as a trap to produce [4+2]-cycloadducts.[15] With respect to cyclohexyne **12a** trapping with DPIBF (Scheme 1.12), there was a possibility that 1,2-cylohexadiene **13a** was being generated upon treatment of **52** with magnesium and reacting with DPIBF. This would produce cycloadduct **53** that could theoretically then undergo a rearrangement to **54**.



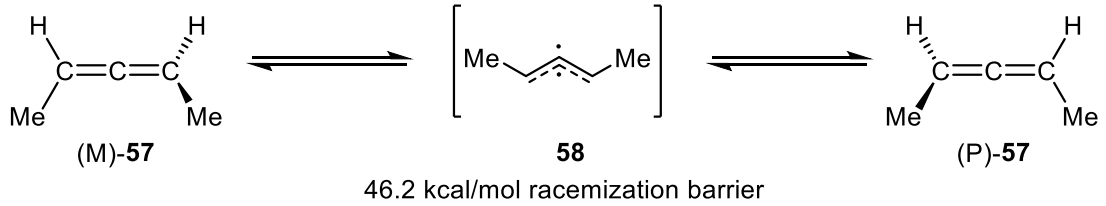
Scheme 1.12 - Trapping of Cyclohexyne with 1,2-Diphenylisobenzofuran and Possible 1,2-Cyclohexadiene Intermediacy

Wittig wanted to disprove the intermediacy of 1,2-cyclohexadiene and went about synthesizing it by a different route so he could compare its reactivity with cyclohexyne. Treating 1-bromocyclohexene **55** with potassium *t*-butoxide (KO*t*Bu) in dimethylsulfoxide (DMSO) and DPIBF resulted in the synthesis of two compounds in a combined yield of 37% (Scheme 1.13). According to Wittig the ^{1}H NMR spectrum of these compounds displayed an olefinic peak at τ 4.3 (δ 5.7), a feature that is not present in cycloadduct **54**. It was determined that the two compounds were the *endo* ***53a*** and *exo* ***53b*** isomers, in a 3.1:1 ratio, resulting from [4+2]-cycloaddition between 1,2-cylohexadiene **13a** and DPIBF. A control experiment where **54**, the alkyne trapping product, was exposed to the same conditions did not result in the formation of any **53**, confirming that the different products cannot isomerize under the reaction conditions. This shows **53** was formed by trapping the allene, not a rearrangement through the alkyne trapping cycloadduct. When **13a** was reacted without the presence of DPIBF the dimer product **56** was obtained in 7% yield. These results demonstrated for the first time the existence (albeit transient) of 1,2-cyclohexadiene.



Scheme 1.13 - Trapping of 1,2-Cyclohexadiene in a [4+2]-Cycloaddition with DPIBF

There was an extensive debate in the early literature about the best structure to represent 1,2-cyclohexadiene. The chiral nature of 1,3-disubstituted allenes had been demonstrated with simple acyclic allenes such as 2,3-pentadiene **57**. The barrier to racemization for **57** has been calculated to be 46.2 kcal/mol with quantum chemical calculations suggesting an allyl diradical intermediate, **58** (Scheme 1.14) .[32,33] As cyclic allenes are also 1,3-disubstituted it holds that they should also be chiral. While going from (M)-**57** to (P)-**57** the orthogonal sets of orbitals must bend and become planar with each other. When an allene is placed within a ring, this bending is present in the ground state due to the geometrical constraints of the ring, and so the question arose whether cyclic allenes are better represented as diradicals (or zwitterions) than as closed-shell 1,2-dienes.



Scheme 1.14 Racemization of 2,3-Pentadiene via Allyl Diradical

The possible structures of 1,2-cyclohexadine are chiral allene **13a**, diradical **59**, and zwitterions **60** and **61** (Figure 1.5). It was suggested by Ball and Landor that the structure was "sp^2 hybridization for carbon atoms 1, 2, and 3 with an unbonded electron on carbon atom 2", implying diradical structure **59**.[30] Moore and Moser suggested zwitterion **60** or a triplet diradical were the ground state configuration and INDO calculations by Dillon and Underwood supported this

assignement.[34] Bottini hypothesized initial formation of a chiral allene that rapidly isomerizes to the diradical, which could then participate in various [2+2] and [4+2] reactions.[35,36] In 1980 evidence for the chirality and therefore closed shell chiral allene (M/P)-**13a** structure of 1,2-cylohexadine was presented by Balci and Jones.[37]

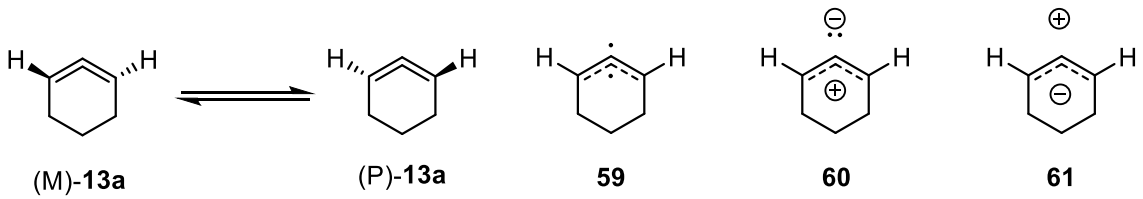
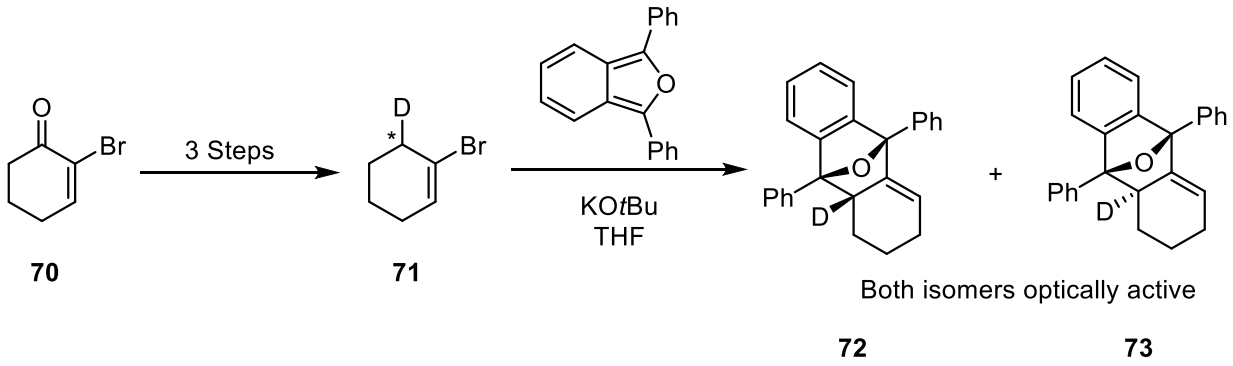


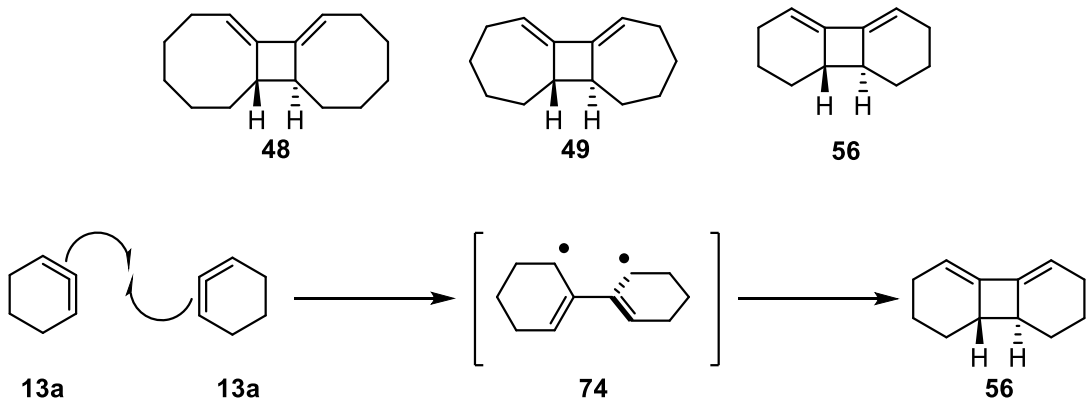
Figure 1.5 - Possible Structures of 1,2-Cyclohexadiene

Starting from 2-bromocyclohexenone **70** a short 3 step sequence involving enantioselective reduction with lithium aluminum hydride (LAH) and quinine, mesylation and displacement with lithium aluminum deuteride (LAD) provided access to enantiomerically enriched vinyl bromide (D)-**71** (Scheme 1.15). The absolute configuration was not determined, and the authors used optical rotation data to confirm one enantiomer was in excess. An enantiomeric enrichment was expected in the cycloadducts generated by elimination with KO*t*Bu as HBr and DBr elimination proceed with different rates and would produce different enantiomers. Trapping with DPIBF indeed confirmed this and cycloadducts **72** and **73** were optically active, though the exact enantiomeric excess was never determined. Interestingly upon heating of the reaction to 80 °C a complete loss of optical activity is noted.



Scheme 1.15 - Optically Active Cycloadducts Resulting from a Chiral Allene

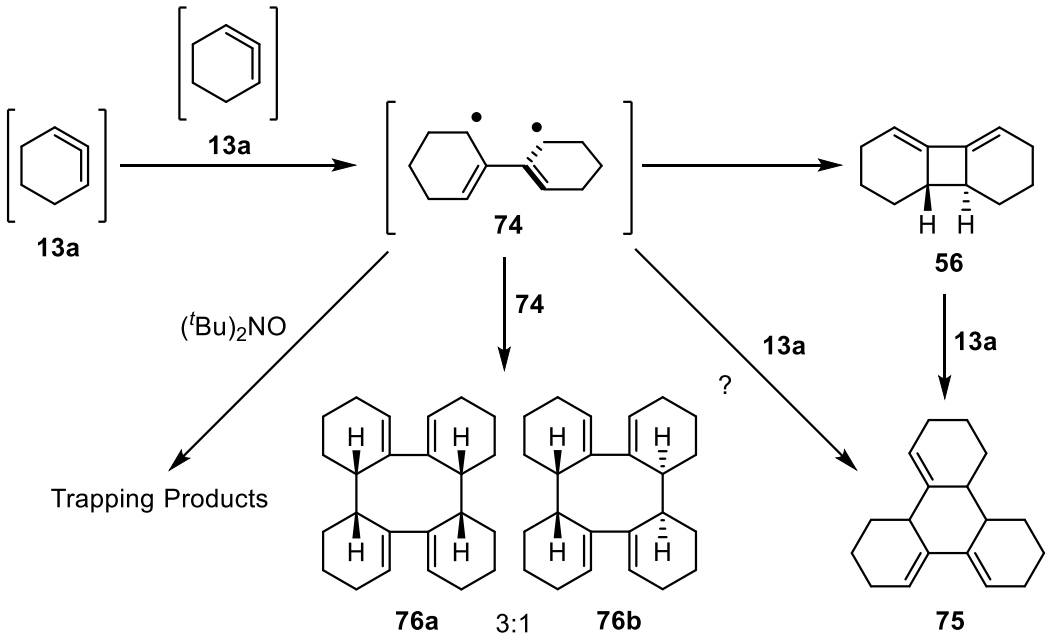
One of the challenges associated with cyclic allene chemistry is the tendency for dimerization and oligomerization. The early syntheses by Ball, Landor, Wittig, and Fritze all generated dimeric compounds or higher-order oligomers.[30,31] Part of the reason for this facile homodimerization process can be explained by the strain energy of these intermediates. Daoust et al. reported a strain energy of 32 kcal/mol for 1,2-cyclohexadiene, which was calculated by examining isodesmic reactions at B3LYP/6-311+G(d,p)+ZPVE level of theory.[38] The most strained position on the allenes is the central *sp* carbon; consequently this is the most reactive site and will rehybridize to sp^2 via dimerization. Through this process ~64 kcal/mol of strain energy is relieved when two molecules of **13a** react to form diradical **74**, which contains two distinct allyl fragments, leading to further stability. Recombination of the diradical to form a cyclobutane ring results in the production of the dimer **56** (Scheme 1.16).



Scheme 1.16 - Observed Dimeric Products in Early Cyclic Allene Experiments and Mechanism of Dimerization for 1,2-Cyclohexadiene

The conditions employed to generate 1,2-cyclohexadiene have a critical influence on the outcome of resulting oligomerization processes. Using KO*t*Bu in DMSO (see section **1.5.4**) leads primarily to dimer **56,** but also the trimer **75**, which it appears to be directly formed from **56** (Scheme 1.17).[35] It should also be possible to form the trimer **75** from the reaction of biradical **74** with 1,2-cyclohexadiene **13a**. Interestingly in the presence of a radical scavenger such as di-*t*-butyl nitroxide ((*t*Bu$_2$)NO) no evidence of **56** or **75** is seen. Instead trapping adducts are observed which indicates it is possible to interrupt the dimerization process and intercept biradical **74**. When Moore

and Moser generated **13a** via a carbene ring opening with methyllithium (MeLi) in Et_2O (see section **1.5.6**) they observed **56** and tetramer **76**.[39] There was an interesting temperature dependence observed: at 35 °C a relatively large amount of **56** was formed (55%), but at -80 °C there were only trace amounts and instead **76** was the major product (61%), formed as a 3:1 *syn* (**76a**) to *anti* (**76b**) mixture. These experiments demonstrated that low temperature dramatically slows cyclobutane ring closure to form the dimer, with the biradical dimerization being consequently considerably favored.



Scheme 1.17 - Dimer, Trimer, and Tetramer Products from 1,2-Cyclohexadiene

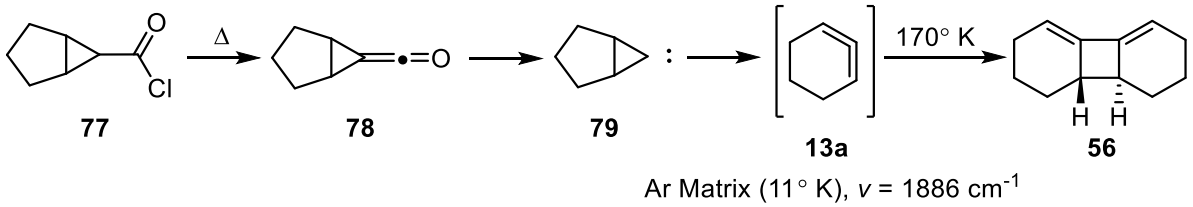
1.5 Methods to Synthesize 1,2-Cylohexadiene

1.5.1 Sodium and Magnesium Metal

Favorskii and Domnin attempted to synthesize cyclic allenes in the '30s and '40s by treatment of bromo-2-chlorocycloheptene or dichlorocyclohexene with sodium in an ether solution. Hydrocarbon liquids were obtained that were most likely the dimer or higher order oligomers, but the intermediacy of an allene could not be proven (see section **1.4.1**).[25-28] Boyden has shown 1,2-cyclohexadiene generation from dibromocyclohexene and magnesium metal while Bottini has shown it from dichlorocyclohexene and magnesium.[36,40]

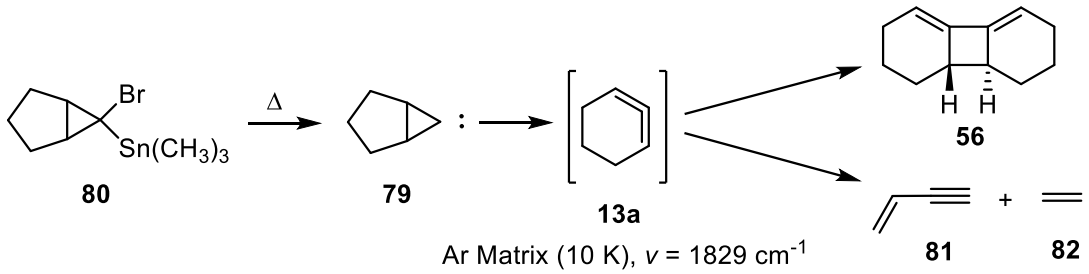
1.5.2 Flash Vacuum Pyrolysis

Wentrup and co-workers generated 1,2-cyclohexadiene by flash vacuum pyrolysis (FVP) of bicyclo[3.1.0]hexane-6-carbonyl chloride **77** at 800 °C/10^{-4} torr.[41] Under these conditions the acid chloride **77** first formed ketene **78** (ν = 2126 cm^{-1}) before decarbonylation gave carbene **79**; this carbene subsequently underwent ring opening to allene **13a**. Preserving **13a** in an argon matrix, an IR absorption at 1886 cm^{-1} was observed that disappeared with increasing temperature and presumed formation of dimer **56** (Scheme 1.18). This experiment provided the first spectroscopic evidence for the existence of 1,2-cyclohexadiene and its chiral allene structure.



Scheme 1.18 - Flash Vacuum Pyrolysis of Bicyclo[3.1.0]hexane-6-carbonyl Chloride

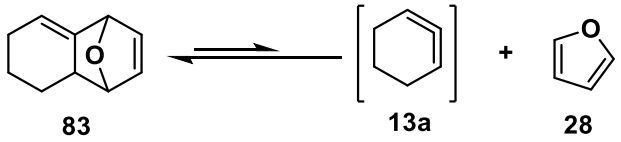
In contrast to the work of Wentrup, Runge and Sandor reported the FVP of 6-bromo-6-(trimethylstannyl)bicyclo[3.1.0]hexane **80** (Scheme 1.19).[42] Interestingly a different IR stretch (ν = 1829 cm^{-1}) was reported for **13a** and **56** was produced only in small amounts, with the retro-Diels-Alder products of **13a**, 1-butene-3-yne **81** and ethylene **82** being the major products. The two different IR stretches reported for 1,2-cyclohexadiene likely indicate one of these experiments had an unidentified source of error.



Scheme 1.19 - Flash Vacuum Pyrolysis of 6-Bromo-6-(trimethylstannyl)bicyclo[3.1.0]hexane

1.5.3 Retro-Diels-Alder Reaction via FVP

1,2-Cyclohexadiene has been shown to react with furan in a [4+2]-cycloaddition reaction (see section **1.6.3**). As Diels-Alder reactions can be reversible, especially when aromatic dienes such as furan are employed, the decomposition of the cycloadduct can yield the cyclic allene. Werstiuk used a carbon dioxide laser and FVP to force the retro-Diels-Alder reaction of cycloadduct **83** into its component building blocks of 1,2-cyclohexadiene **13a** and furan **28** (Scheme 1.20).[43]



Scheme 1.20 - FVP of Furan Cycloadduct and Synthesis of 1,2-Cyclohexadiene

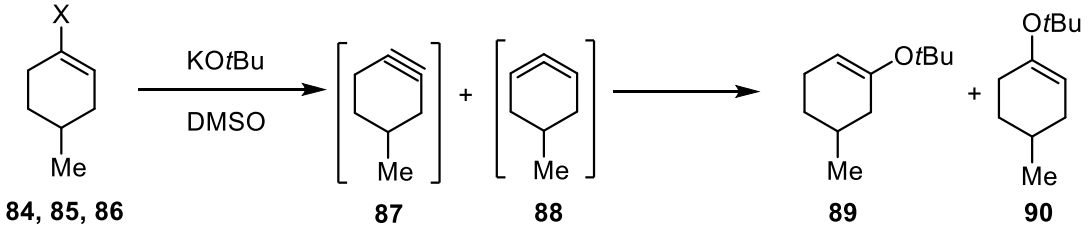
1.5.4 E2 Elimination of Alkenyl Leaving Group

The elimination of an alkenyl leaving group presents certain challenges if 1,2-cyclohexadine is to be the only species generated. For an E2 elimination only the allylic pseudo-equatorial proton next to the leaving group can be deprotonated. If either allylic pseudo-axial proton is eliminated an allylic anion will be generated; meanwhile if the alkenyl proton is eliminated cyclohexyne will be the product. Moderately strong and reversible bases can accomplish the desired transformation as they will not irreversibly deprotonate either allylic pseudo-axial proton.[44]

Ball and Landor's experiments in the 1960's which prepared 1,2-cyclooctadiene, and 1,2-cycloheptadiene used $NaNH_2$ to effect dehydrohalogenation (see section **1.4.1**). Caubère and coworkers also used $NaNH_2$ to prepare 1,2-cyclohexadiene and trap it with enolates (see section **1.6.2**).[45] The first example of 1,2-cyclohexadiene synthesis and trapping by Wittig (see section **1.4.2**) involved the use of KO*t*Bu as a mild base to effect an E2 elimination of a alkenyl bromide.[31] A seminal study by Bottini following Wittig's initial report demonstrated the intricacies of this elimination reaction by examining the base-mediated elimination of 4-methylchlorocyclohexene **84**.[35] Upon elimination with KO*t*Bu an unequal mixture of enol ethers **89** and **90** was formed

(Table 1.1). There was literature precedent at the time for cyclic alkyne trapping by nucleophilic base, such as KO*t*Bu; however, in this case a near 1:1 ratio of enol ethers would be expected if cycloalkyne **87** was formed (non-selective *t*-butoxide anion attack).[45-47] The unequal ratio of products can be explained by the intermediacy of 5-methyl-1,2-cyclohexadiene **88**, which will react preferentially at the electrophilic *sp* carbon of the allene. The choice of solvent and leaving group was shown to affect the ratio of **89** and **90**. Substrates with a poor leaving group and polar solvent favor enol ether **90**, which is most likely to be derived from allene **88**. Meanwhile a good leaving group and less polar solvent produces an almost even ratio of **89** and **90**, suggesting the intermediacy of cycloalkyne **87**. Clearly Bottini demonstrated the ability to generate either allene or alkyne depending on the reaction conditions.

Table 1.1 - Effects of Solvent and Leaving Group on Base Mediated Elimination



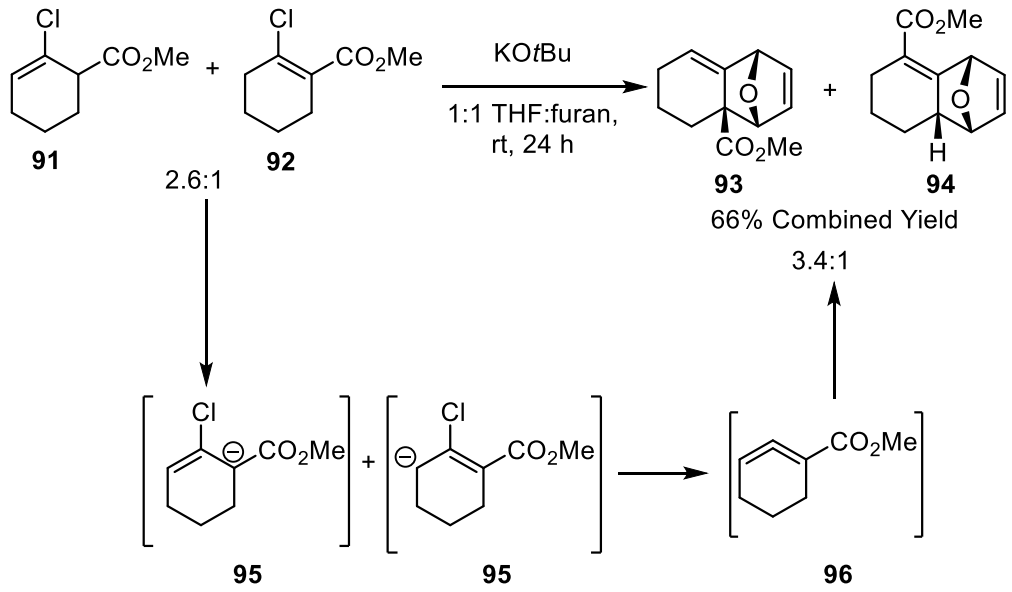
84, 85, 86 **87** **88** **89** **90**

Substrate	Leaving Group (X)	Solvent	Product Ratio of **89**:**90**
84	Cl	DMSO	2:98
84	Cl	Diglyme	10:90
85	Br	DMSO	14:86
86	I	DMSO	25:75
86	I	THF	45:55

1.5.5 E1$_{CB}$ Elimination of Alkenyl Leaving Group

Houk and Tolbert found that in certain cases the allylic anions generated by removing a pseudo-axial proton on a cyclohexene bearing an alkenyl leaving group and a conjugated ester moiety can generate a cyclic allene.[48] A rudimentary analysis would indicate that an elimination should not take place due to improper orbital overlap of the allyl anion and leaving group σ* orbital. Under certain conditions such as extended reaction time, thermal activation or photolysis

the conjugation of the allylic anion system can be broken and a favorable orbital overlap leading to elimination may occur. With a 2.6:1 mixture of methyl 2-chlorocyclohex-2-encarboxylate **91** and methyl 2-chloro-cyclohex-1-encarboxylate **92** in a 1:1 solvent mixture of THF:furan with excess KO*t*Bu, two [4+2] cycloadducts, **93** and **94**, were formed in a combined yield of 66% after 24 h at room temperature (Scheme 1.21). Both cycloadducts were determined to be *endo* diastereomers, with computations finding these adducts to be favored thermodynamically by 0.8 kcal/mol and kinetically by 0.9 kcal/mol.[48] A mixture of regioisomers **93** and **94** in a ratio of 3.4:1 shows a preference for cycloaddition on the more substituted bond of the cyclic allene intermediate. Assuming a concerted reaction, which computations suggest may not be the case,[48] where the allene is a dienophile, it follows that the ester would lower the LUMO energy level and decrease the HOMO-LUMO gap and lead to **93** being favored. Johnson and Tolbert have also shown larger frontier molecular orbital coefficients on the more substituted double bond.[49]

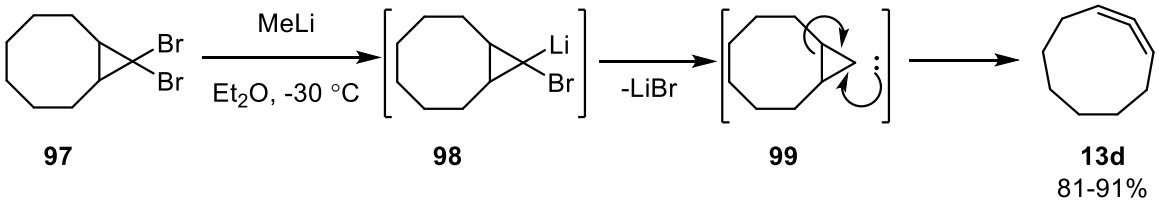


Scheme 1.21 - Synthesis and [4+2] Trapping of Ester-Conjugated 1,2-Cyclohexadiene

1.5.6 Doering-Moore-Skattebøl (DMS) Reaction

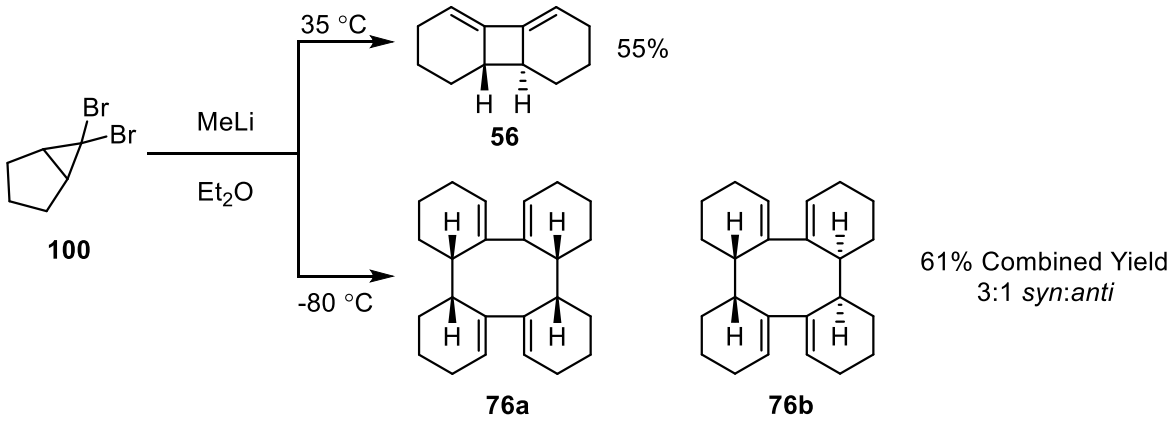
One of the most popular and versatile methods to generate cyclic allenes is the Doering-Moore-Skattebøl (DMS) reaction, named after the researchers who independently reported the rearrangement of dihalocyclopropanes to allenes: Doering,[50] Moore,[51] and Skattebøl.[52] Skattebøl

was the first to use this method to prepare a cyclic allene, 1,2-cyclononadiene **13d**, from dibromocyclopropane **97** and MeLi in 81-91% yield (Scheme 1.22).[53] When this result is compared with the first synthesis of **13d** by Blomquist (see section **1.4.1**) which resulted in a mixture with cyclononyne, the advantages of this method become readily apparent. The interesting mechanism of the DMS reaction proceeds first with a lithium halogen exchange producing metallated compound **98** which can lose an equivalent of lithium-bromide salt resulting in carbene **99**. Subsequent four-electron ring opening of the cyclopropane produces **13d**.[54]



Scheme 1.22 - Synthesis of 1,2-Cylononadiene via DMS Reaction

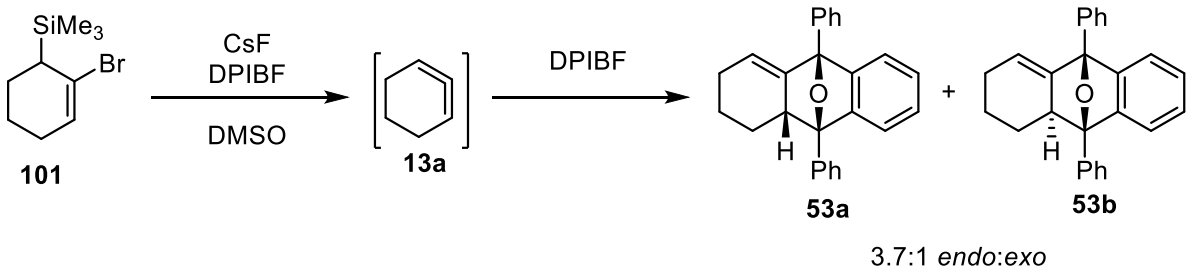
In addition to preparing 1,2-cyclononadiene, the DMS reaction can be used to access 1,2-cyclooctadiene as demonstrated by Marquis and Gardner.[55] Interestingly the DMS reaction cannot be used to synthesize unsubstituted 1,2-cycloheptadiene as a transannular C-H insertion reaction produces a bicyclobutane structure.[25,56] The synthesis of 1,2-cyclohexadiene by the DMS method was reported by Moore and Moser in 1969.[39] Reaction of 6,6-dibromobicyclo[3.1.0]hexane **100** with MeLi led to the formation of either dimer **56** or tetramer **76** depending on the reaction temperature (Scheme 1.23). As discussed in section **1.4.2** there was an interesting temperature dependence observed. At 35 °C a relatively large amount of **56** was formed (55%), but at –80 °C there were only trace amounts of **56** and instead tetramer **76** was the major product (61%), formed as a 3:1 *syn* to *anti* mixture.



Scheme 1.23 - Dimer and Tetramer Products from 1,2-Cyclohexadiene synthesis via DMS Reaction

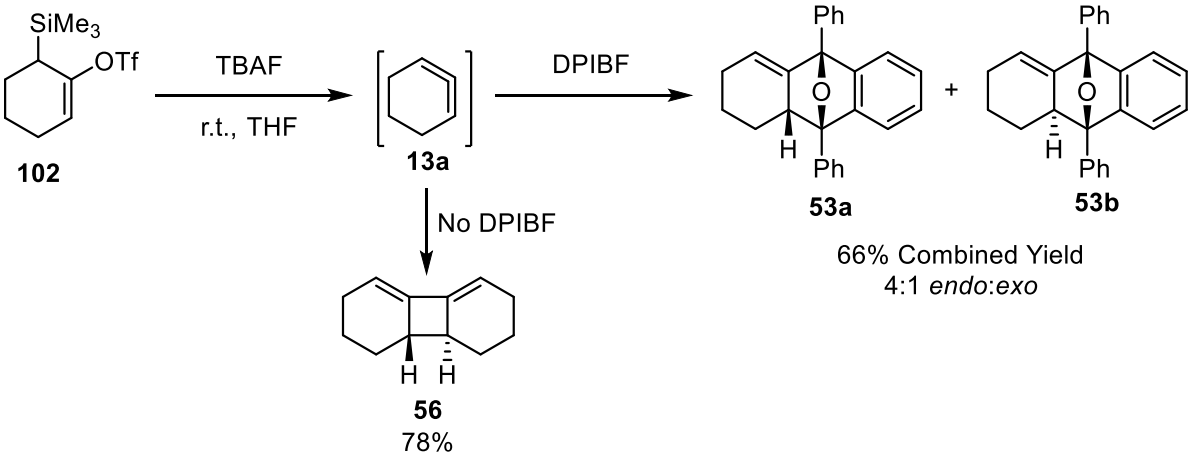
1.5.7 Fluoride-Mediated Elimination of an Allylic Silane

The use of mild or strong bases to effect an elimination has some inherent drawbacks. Bases like KO*t*Bu can present a challenge in terms of selectivity when eliminating a proton and the butoxide anion generated can also act as a nucleophile, reacting with the electrophilic *sp* center of a cyclic allene. Meanwhile the use of a strong base such as MeLi is limited substrates without acidic protons and has a low chemoselectivity with other functional groups. A milder allene generation method utilizing a large allylic silane group was first introduced by Johnson and Shakespeare.[57] A bulky silane will naturally adopt a pseudo-equatorial position, setting it up for elimination, and a fluoride anion source (tetrabutylammonium fluoride (TBAF) or cesium fluoride (CsF)) will chemoselevtively eliminate the silane. Using CsF and 1-bromo-6-trimethylsilylcyclohexene **101** in DMSO the first fluoride mediated elimination en route to a cyclic allene reaction produced 1,2-cyclohexadiene **13a**, which was trapped in situ by DPIBF, resulting in a 3.7:1 mixture of the *endo* **53a** and *exo* **53b** adducts (Scheme 1.24). A yield was not reported for this reaction, but it is interesting to note that the ratio of *endo* to *exo* was the same as reported by Wittig in his synthesis with KO*t*Bu.[31]



Scheme 1.24 - Fluoride-Mediated Elimination and Trapping with DPIBF

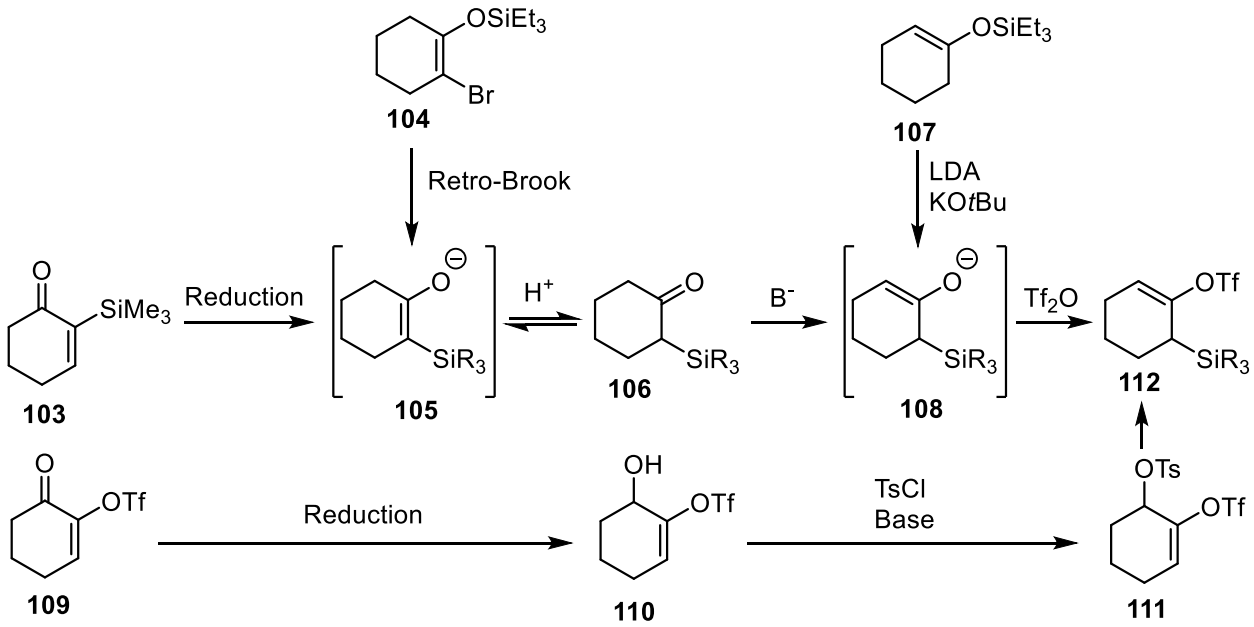
More recently Peña and Guitián replaced the bromide used by Johnson with a triflate group, which was expected to be a superior leaving group for the E2 elimination.[58] With this simple change they could use alkenyl triflate **102** to generate **13a** under very mild conditions and either isolate the dimer **56** in 78% yield or DPIBF cycloadducts **53a/b** in a combined yield of 66% as a 4:1 *endo*:*exo* mixture (Scheme 1.25).



Scheme 1.25 - Fluoride-Mediated Elimination with Triflate Instead of Halide

Because of its mild conditions, fluoride-mediated desilyative elimination has become one of the preferred methods with which to generate cyclic allenes; as such a variety of approaches have been developed to make the generic starting allylic silane **112**. Guitián's original approach involves 1,4-reduction of α-silyl enone **103** followed by protonation to ketone **106** and triflation.[58] Mori's approach uses lithium diisopyropylamine (LDA) and KO*t*Bu to perform an allylic deprotonation on silyl ether **107** followed by in situ migration and triflation,[59] and Garg's approach relies on a retro-Brook rearrangement of silyl ether **104** (Scheme 1.26).[60] A related approach by

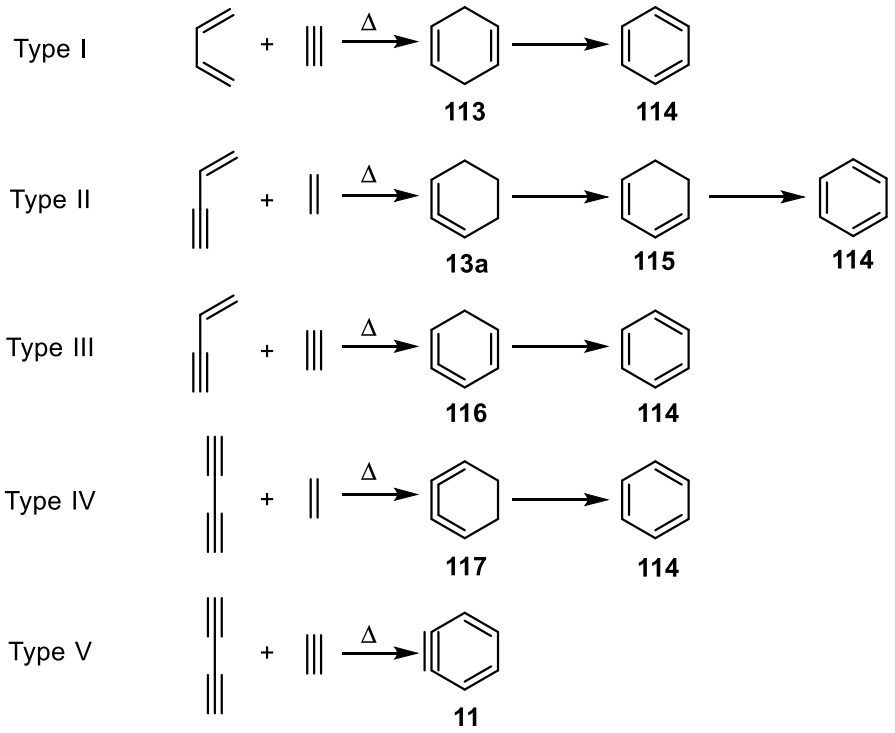
Lofstrand starts with reduction of enone **109,** followed by tosylation of allylic alcohol **110** and conjugate displacement of **111** with dimethylphenyl silane to accesses **112**.[61]



Scheme 1.26 - Different Approaches to Access Vinyl Triflate Starting Material

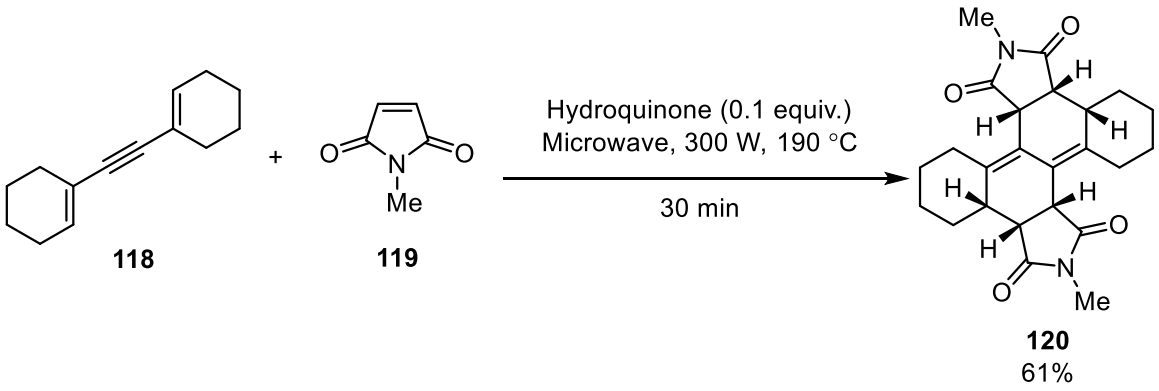
1.5.8 Dehydro-Diels-Alder Reaction

Pericyclic reactions offer a powerful method to assemble carbocycles and the Diels-Alder reaction has been extensively used in organic synthesis.[62] A typical Diels-Alder reaction will bring together two fragments, the diene and dienophile, and create a six membered ring with a residual double bond. If the degree of unsaturation of the reacting components is increased the reaction is called a dehydro-Diels-Alder, which in certain cases can be used to access cyclic allenes. Depending on the degree of unsaturation there are various types of dehydro-Diels-Alder, type II (enyne-ene) and type III (enyene-yne) enable accesses to 1,2-cyclohexadiene and 1,2,4-cyclohexatriene respectively (Scheme 1.27).[63]



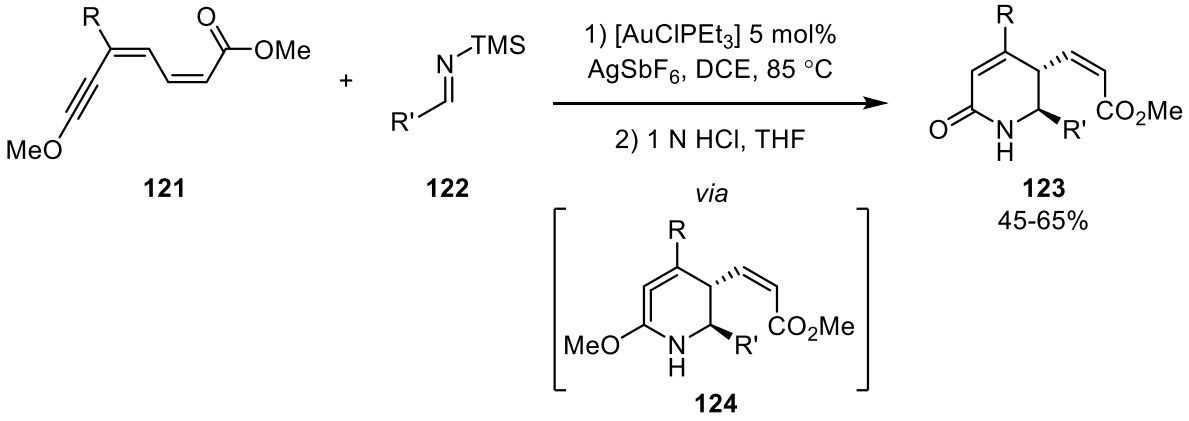
Scheme 1.27 - Types of Dehydro-Diels-Alder Reactions

Dehydro-Diels-Alder (DDA) reactions of type II are [4+2]-cycloadditions between a 4π enyne and a 2π ene component that produce 1,2-cyclohexadiene **13a** as an intermediate. The construction of polycyclic, steroid like carbocycles has been accomplished using this methodology.[64,65] More recently in 2010 Sherburn and co-workers were able to dramatically improve the efficiency of these reactions by performing a DDA reaction with 1,5-dien-3-yne **118** and N-methyl-maleimide **119** under microwave conditions (Scheme 1.28). They obtained polycyclic scaffold **120**, a double DDA reaction product, in 61% yield; a large improvement with respect to the previously reported 15-17%.[66]



Scheme 1.28 - Synthesis of Polycyclic, Steroid Like Scaffold via Double DDA Reaction

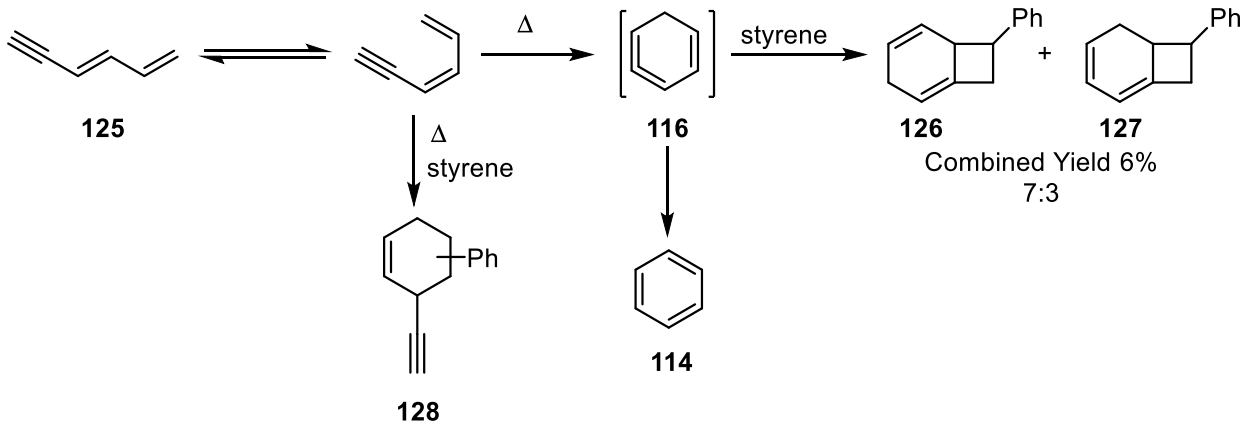
In principal DDA reactions of type II should be able to proceed between enynes and any simple olefin type structure. Extending this chemistry to include heteroatom moieties such as imines would be desirable from the standpoint of medicinal chemistry where nitrogen-containing compounds are ubiquitous.[67] Fernández-García and co-workers have demonstrated this with a novel gold-catalyzed intermolecular [4+2] DDA reaction with dienynes **121** and imines **122** (Scheme 1.29). This aza-DDA reaction provides access to 5,6-dihydropyridin-2-one **123**, in 45-65% yield, via the intermediacy of an aza-1,2-cyclohexadiene **124**.[68] It is interesting to see how in this example the methoxy acts as a latent carbonyl group. DDA reactions of type III, which produce 1,2,4-cyclohexatriene, a close analogue of 1,2-cyclohexadiene, are much more common in the literature and have been the subject of reviews.[69,70]



Scheme 1.29 - Aza-DDA Reaction via Aza-1,2-Cyclohexadiene Intermediate

1.5.9 Dehydro-Electrocyclization Reactions

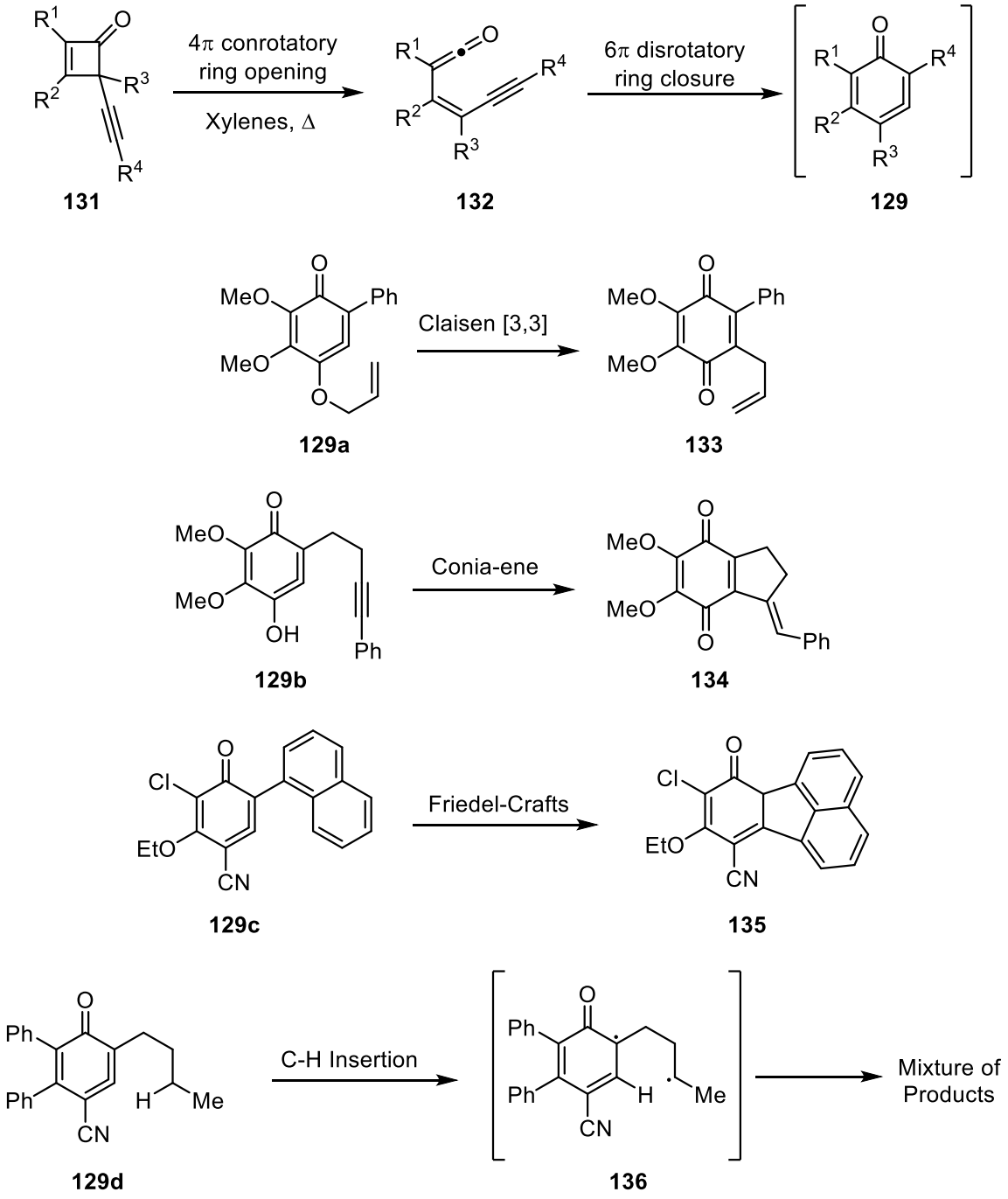
Analogous to how the DDA cycloaddition enables access to cyclic allene derivatives, a 6π dehydro-electrocyclization of dienyne **125**, the Hopf cyclization, produces 1,2,4-cyclohexatriene **116** which will undergo a [1,3]-hydrogen shift to benzene **114**.[71] In the presence of styrene as a trap [2+2] cycloadducts **126** and **127** are generated, in a 7:3 ratio, with benzene **114** and [4+2] styrene cycloadduct **128** as the major side-products (Scheme 1.30).[72] Christl later reported a much higher regioselectivity of 19:1 for **126**:**127** when 1,2,4-cyclohexadtriene was synthesized by the DMS method.[73] This discrepancy shows how with milder generation conditions there is more control over these reactions.



Scheme 1.30 - Hopf Cyclization via 1,2,4-Cyclohexatriene Intermediate and Trapping with Styrene

Related to the Hopf cyclization, the Moore cyclization generates highly substituted 1,2,4-cyclohexatriene intermediates.[74] Cyclobutenone **131** can undergo a 4π conrotatory ring opening to ene-yne-ketene **132**, and subsequent 6π disrotatory ring closure generates substituted 1,2,4-cyclohexadtriene **129**. Depending on the substituents the Moore intermediate can be trapped by a variety of groups: enol ether **129a** can undergo a [3,3] Claisen rearrangement to **133**,[75] alkyne **129b** can undergo a Conia-ene reaction to **134**,[76,77] arene **129c** can undergo a Friedel-Crafts reaction to **135**,[74] and alkyl **129d** can undergo a C-H insertion and generate a variety of products (Scheme 1.31).[74] These represent the first examples of the intramolecular trapping of a cyclic allene derivative. Moore originally proposed the species generated in this reaction to be diradical **130**,

however Fernández has calculated that the closed-shell allene **129** is 19 kcal/mol more stable (Figure 1.6).[78,79] The yields for these reactions are generally high as the degree of substitution on the intermediate prevents aggregation that would lead to dimerization.



Scheme 1.31 - Moore Cyclization and Trapping Reactions of Substituted 1,2,4-Cyclohexatriene Intermediate

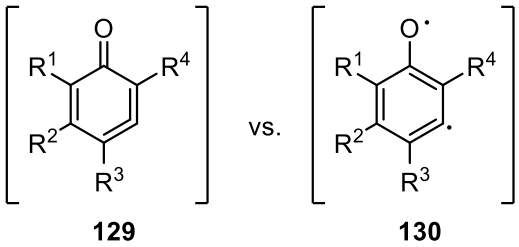
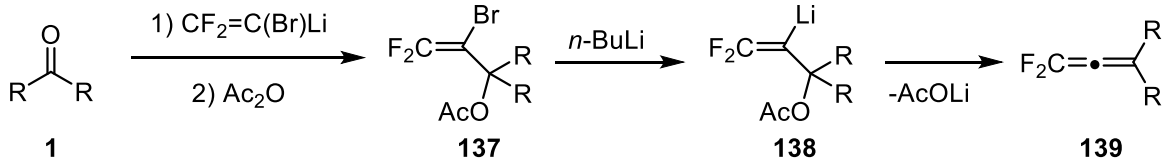


Figure 1.6 - Structure of Possible Intermediates in the Moore Cyclization

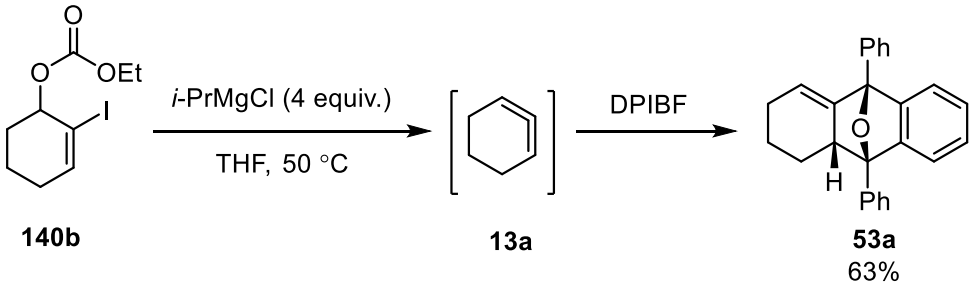
1.5.10 Elimination of an Allylic Carbonate with Organometallic Reagents

The eliminative methods discussed so far all rely on elimination of an alkenyl leaving group; however, eliminating an allylic leaving group is also possible. Yokota and co-workers have elegantly demonstrated this with acyclic allenes in 2009.[80] In this methodology carbonyl compounds were reacted with 1-bromo-2,2-difluorovinyllithium and acetylated. Compound **137** could then undergo lithium halogen exchange, generating **138** which upon allylic elimination produced allene **139** (Scheme 1.32).



Scheme 1.32 - Allylic Elimination Route to Acyclic Allenes

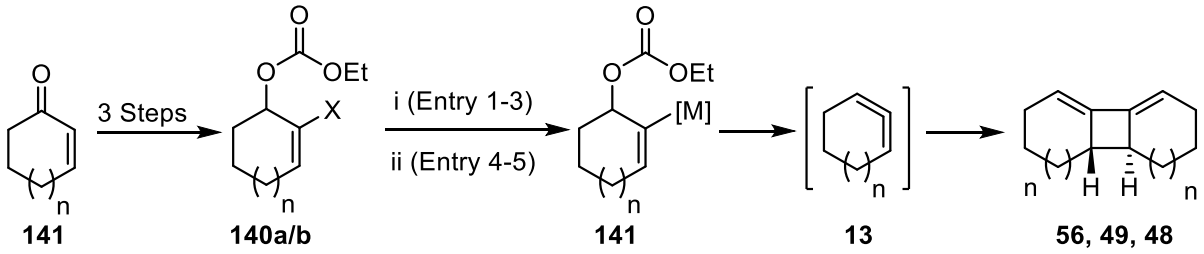
Constantin and Almehmadi have successfully extended this methodology to generate cyclic allenes using organometallic reagents.[81] Allylic carbonate **140** can easily be assembled from cyclohexenone **141** in 3 steps: α-halogenation, reduction, and reaction with ethyl chloroformate (Table 1.2). With either *tert*-butyllithium (*t*-BuLi) or *iso*-propylmagnesiumchloride (*i*-PrMgCl) a metal halogen exchange leads to intermediate **141** which will eliminate to form allene **13**. In the absence of a trap the dimer product is obtained, with increasing yield for a seven membered ring, iodide as the halogen, and *i*-PrMgCl as the organometallic reagent. When DPIBF is used with iodide **140b** the *endo* cycloadduct **53a** is obtained in 63% yield (Scheme 1.33).



140b **13a** **53a**
63%

Scheme 1.33 - Metal-Halogen Exchange Promoted Elimination: Trapping of 1,2-Cyclohexadiene with DPIBF

Table 1.2 - Generating Cyclic Allenes Through Metal-Halogen Exchange Promoted Elimination



141 **140a/b** **141** **13** **56, 49, 48**

i) *t*-BuLi (2 equiv.) 0.5 M in hexane, 0.3 M, rt; ii) *i*-PrMgCl (4 equiv.), THF, 0.1 M, 0 °C

Entry	n	Halogen (X)	Starting Material	Product	Yield (%)
1	1	Br	**140a**	**56**	23
2	2	Br	**140a**	**49**	70
3	3	Br	**140a**	**48**	35
4	1	I	**140b**	**56**	32
5	2	I	**140b**	**49**	86

1.6 Trapping of 1,2-Cyclohexadiene

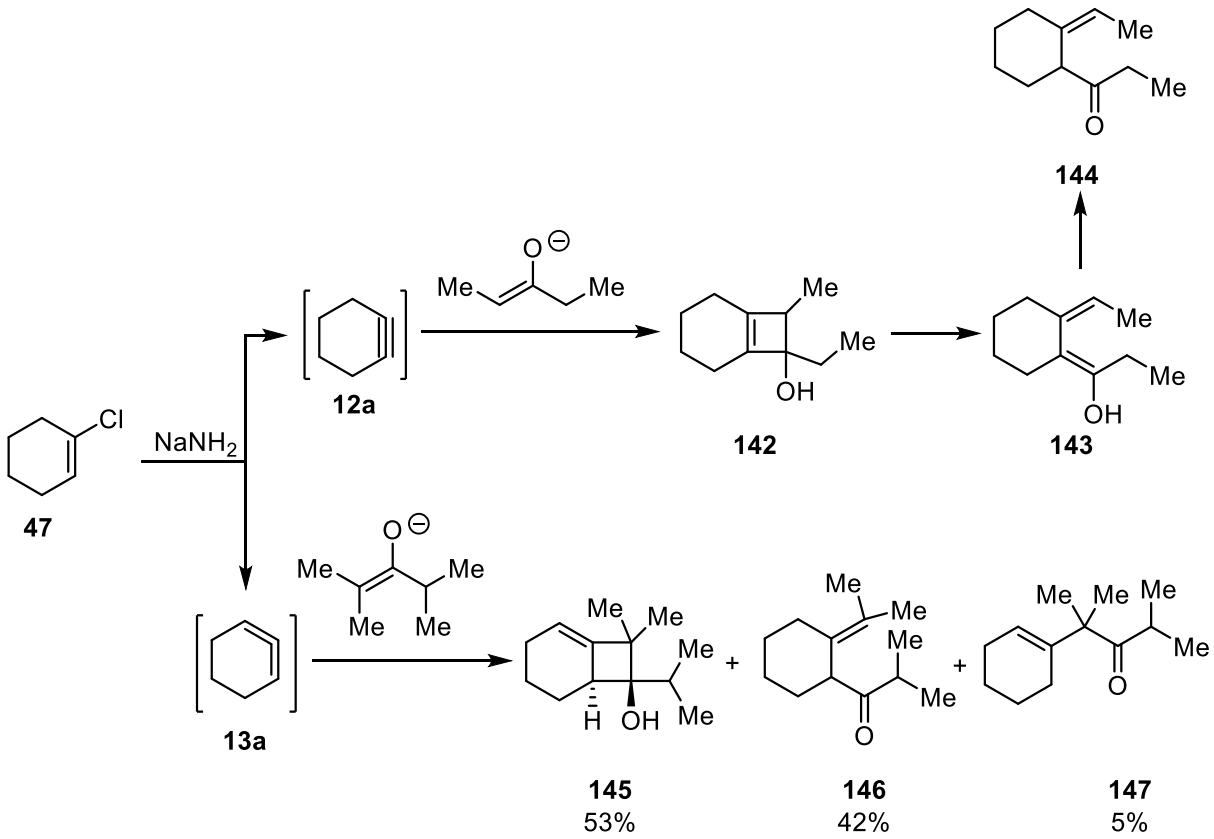
1.6.1 Nucleophilic Bases

The first method used to synthesize 1,2-cyclohexadiene was a base mediated E_2 elimination with KO*t*Bu.[31] As previously discussed (see section **1.4.2**), 1,2-cyclohexadiene is electrophilic at

the *sp* carbon and is susceptible to nucleophilic attack. Trapping can occur with the butoxide anion present in the reaction mixture.[35]

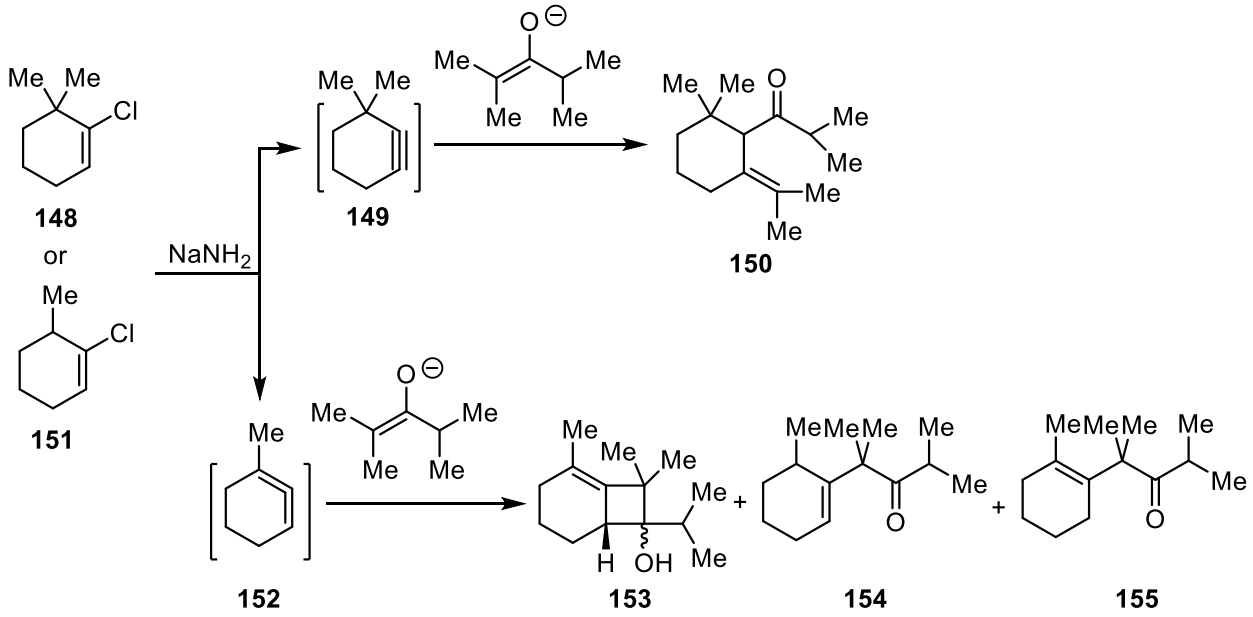
1.6.2 Ketone Enolates

Caubère and coworkers noticed in 1969 that the elimination product of $NaNH_2$ and 1-chlorocyclohexene **47**, originally assumed as cyclohexyne **12a**, could be trapped by a ketone enolate producing **144**.[45] The reaction was proposed to go through a [2+2]-cycloaddition to cyclobutenol **142** followed by a 4π ring opening to **143** and tautomerization. With later experiments they observed cyclohexene-fused cyclobutanol **145** which should not be formed from the proposed cyclohexyne intermediate. Instead **145** must be formed through the intermediacy of 1,2-cyclohexadiene **13a**. A cyclobutanol with the double bond exocyclic to the ring, as with **145**, cannot undergo a 4π ring opening reaction as **142** can (Scheme 1.34).



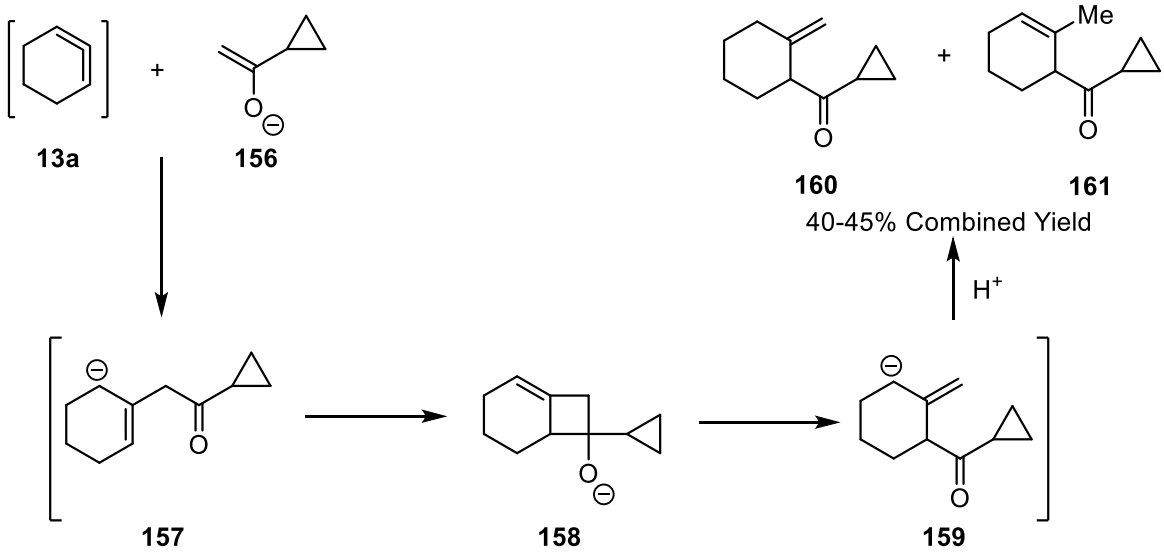
Scheme 1.34 - Original Proposed Trapping with Cyclohexyne and Products Consistent with 1,2-Cyclohexadiene Trapping

Using gem-dimethyl derivative **148**, which cannot eliminate to 1,2-cyclohexadiene, the expected product from cyclohexyne **149**, **150**, was obtained. However, when **151** was used, which can form 1-methyl-1,2-cyclohexadiene **152**, the cyclobutanol product **153** was obtained along with **154** and **155** (Scheme 1.35). These results strongly suggest that the reaction proceeds from 1-methyl-1,2-cyclohexadiene intermediate **152**. These reactions are proposed to go through a stepwise mechanism involving initial nucleophilic attack of the enolate on the *sp* carbon of the allene followed by subsequent ring closure onto the ketone and protonation.



Scheme 1.35 - 1,2-Cyclohexadiene Intermediacy in Trapping with Ketone Enolates

An interesting example involving cyclopropyl methyl ketone derived enolate **156** led to β,γ-unsaturated ketones **166** and **161** in a combined yield of 40-45% (Scheme 1.36).[82] The mechanism for this reaction is proposed to start with nucleophilic attack on the *sp* carbon of the allene followed by ring closure on the carbonyl; collapse of the tetrahedral intermediate **158** generates new allyl anion **159** which gets protonated.



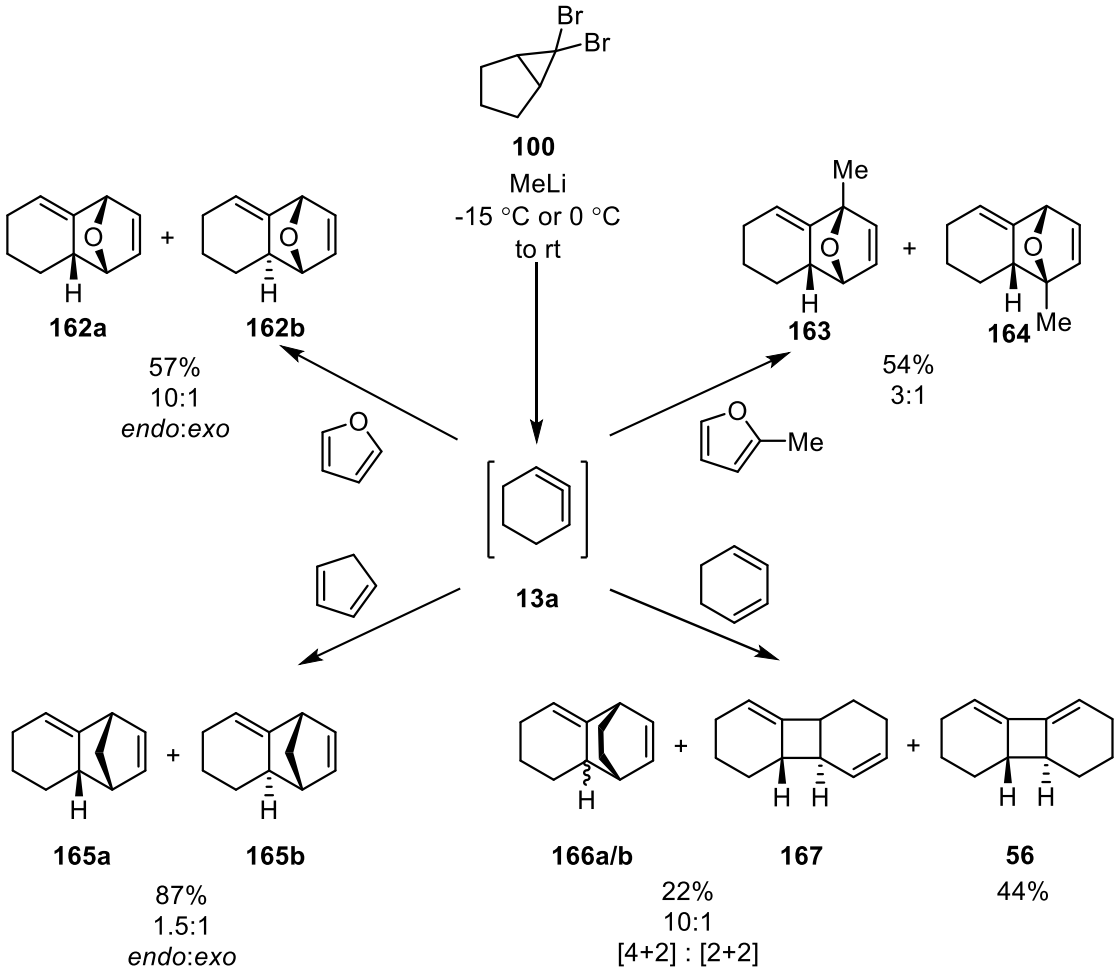
Scheme 1.36 - 1,2-Cyclohexadiene Trapping with the Enolate of Cyclopropyl Methyl Ketone

1.6.3 [4+2]-Cycloadditions

A popular way to intercept 1,2-cyclohexadiene before it can dimerize or oligomerize is to trap with a reactive 4π electron moiety, resulting in a [4+2]-cycloaddition. The use of DPIBF as a trap has already been extensively discussed in sections **1.4** and **1.5** and will only be discussed briefly here. In section **1.5.6** furan was shown to be a trap for ester substituted 1,2-cyclohexadiene.[48]

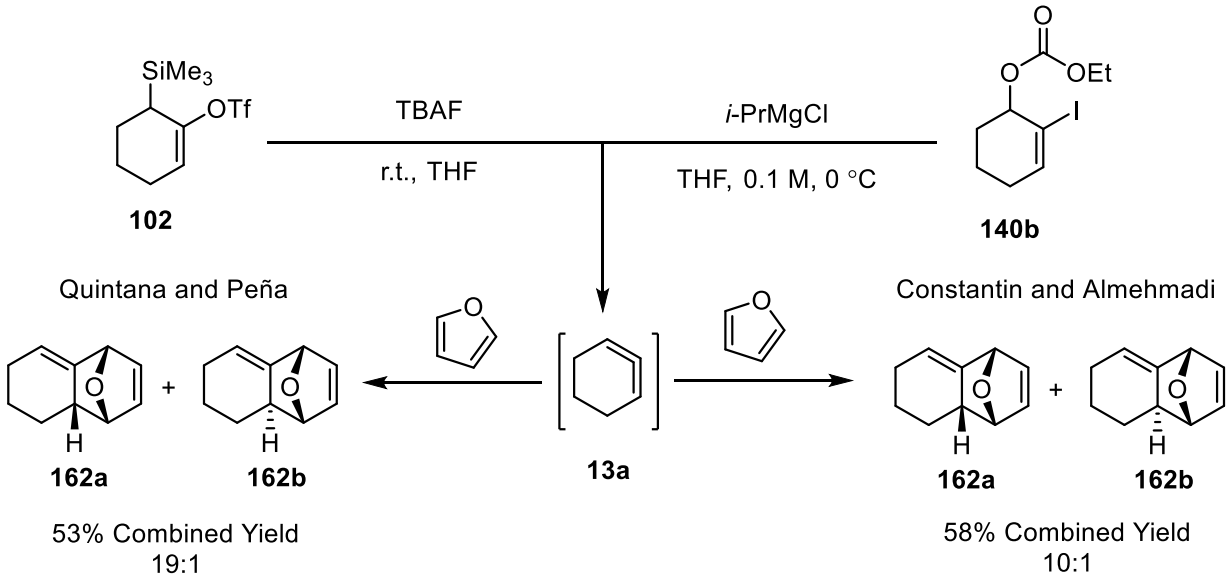
Bottini was the first to show that a variety of other molecules besides DPIBF can be used in a [4+2]-cycloaddition reaction with 1,2-cyclohexadiene: 1,3-cyclohexadiene, furan, 2-methylfuran, and 1,3-cyclopentadiene all gave cycloadducts (Scheme 1.37).[35,36] Unfortunately the dimer product was still observed in these reactions, sometimes being the major product. As a result of this persistent side reaction, when feasible these reactions were run with the trap as solvent. Cycloaddition with furan resulted in a 10:1 mixture of the *endo* and *exo* adducts **162a** and **162b** in a combined 57% yield. Interestingly the reaction with 2-methylfuran gave only the *endo* product; however, a 3:1 mixture of regioisomers **163** and **164** was afforded in a combined yield of 54%. Trapping with 1,3-cyclopentadiene gave a 1.5:1 mixture of *endo* and *exo* adducts **165a** and **165b** in a combined yield of 87% while 1,3-cyclohexadiene gave two diastereomeric [4+2] adducts

166a/b and [2+2] adduct **167** in a 10:1 ratio and combined yield of 22%. Dimer **56** was isolated in 44% yield under these conditions.



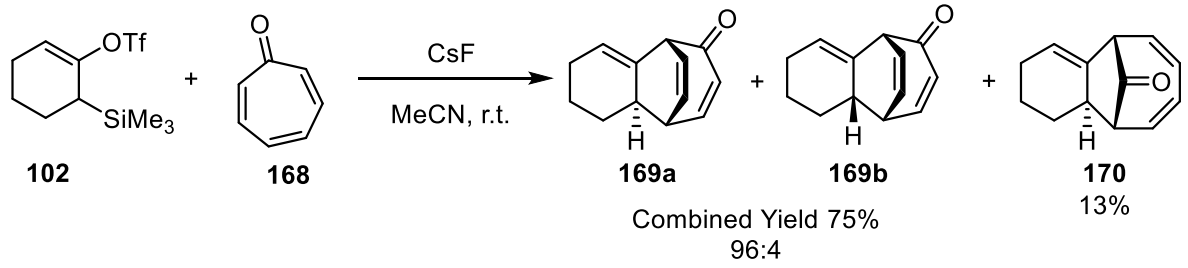
Scheme 1.37 - 1,2-Cyclohexadiene Trapping via [4+2]-Cycloaddition

Other research groups have used furan as a benchmark for trapping 1,2-cyclohexadiene generated by various methods. Quintana and Peña, who generated **13a** via fluoride mediated elimination of alkenyl triflate (see section **1.5.7**), obtained a combined yield of 53% for cycloadduct **162**, with a 19:1 ratio favoring the *endo* isomer.[58] Constantin and Almehmadi, who generated **13a** via elimination of an allylic carbonate with organometallic reagents (see section **1.5.10**) obtained a combined yield of 58% for cycloadduct **162**, with a 10:1 ratio favoring the *endo* isomer (Scheme 1.38).[81]



Scheme 1.38 - Additional 1,2-Cyclohexadiene Trapping via [4+2]-Cycloaddition with Furan

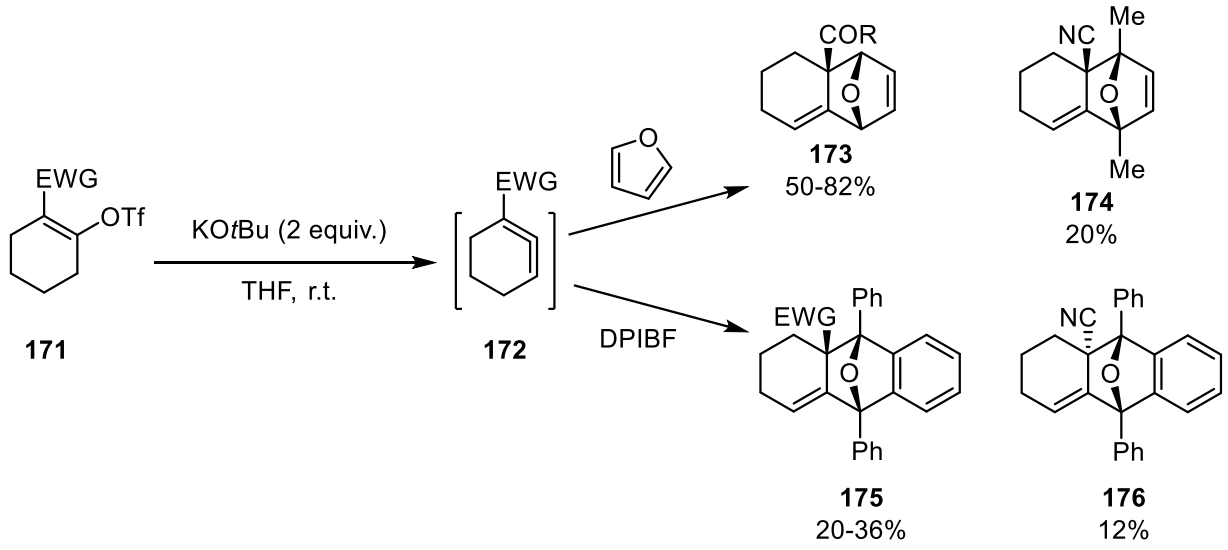
The reaction of tropone with benzyne, a closely related reactive intermediate to 1,2-cyclohexadiene, is known to afford the [4+2] cycloadduct as the major product.[83,84] Acyclic allenes however usually result in mixtures of [8+2] and [4+2] adducts.[85,86] When triflate **102** and tropone **168** were treated with CsF the [4+2] adducts **169a** and **169b** were obtained as the major products in a combined yield of 75% with the *endo* diastereomer **169a** being favored (**169a**:**169b** = 96:4) (Scheme 1.39).[58] A small amount, 13%, of the [6+2] cycloadduct **170** was also obtained.



Scheme 1.39 - 1,2-Cyclohexadiene Trapping via Cycloaddition with Tropone

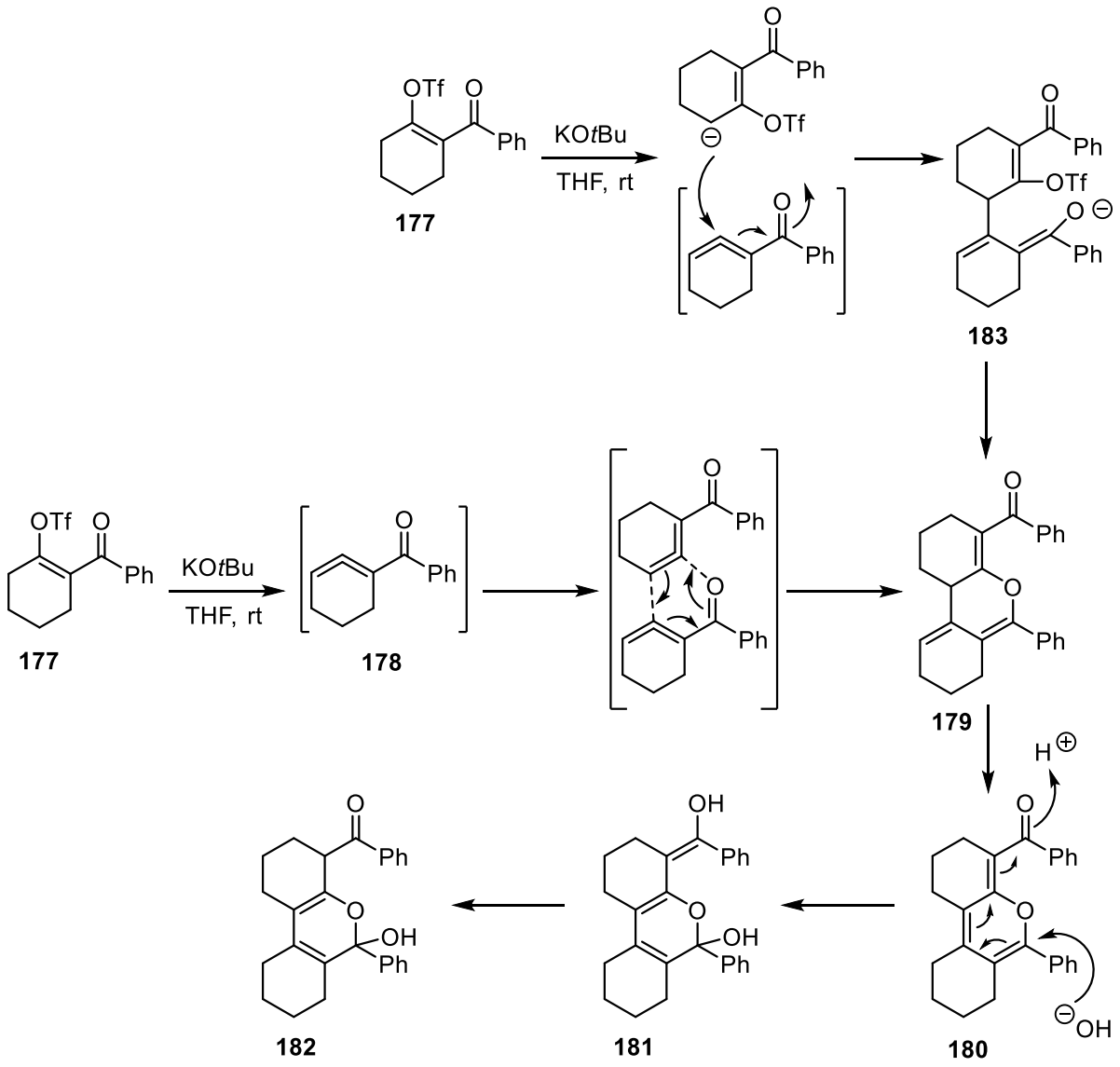
Wang et al. have trapped electron deficient keto- and cyano- substituted 1,2-cyclohexadienes **171** via [4+2]-cycloaddition with furan and DPIBF (Scheme 1.40).[87] Interestingly, complete regioselectivity was observed with the reaction only taking place upon the more electron-deficient allene π bond. This contrasts with reports of trapping with ester substituted

1,2-cyclohexadiene, where a mixture of regioisomers was obtained (see section **1.5.6**).[48] One explanation for this is a stronger electron withdrawing group (EWG) effect of ketones vs. esters. With furan trapping products **173** and **174** complete diastereoselectivity was also observed with only the *endo* isomers present in a range of yields depending on the substituent. To avoid a major amount of [2+2] dimerization products the reactions were run with a large excess of furan, between 92 and 137 equivalents. When the more reactive DPIBF is used as a trap this loading can be reduced to 2-3 equivalents. Once again complete regioselectivity is observed for the proximal double bond with adducts **175** and **176**; complete diastereoselectivity is observed in all cases except for when a cyano EWG group is used, then 12% of the exo isomer **176** is isolated.



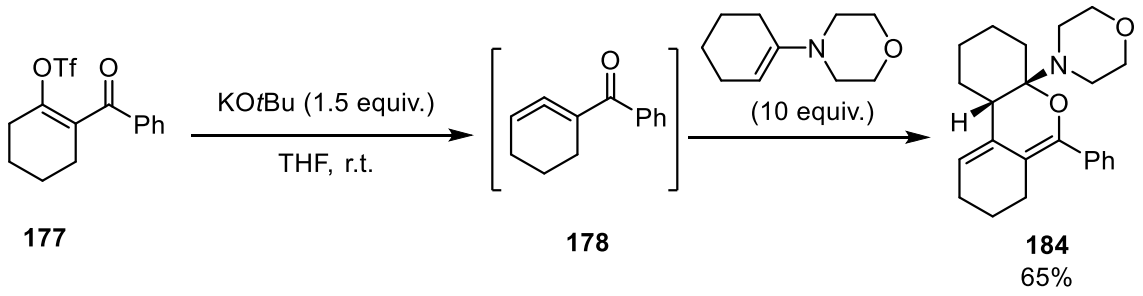
Scheme 1.40 - Trapping of Electron Deficient 1,2-Cyclohexadienes via [4+2]-Cycloaddition

Wang et al. also discovered an unprecedented mode of [4+2] dimerization for their electron deficient keto-1,2-cyclohexadienes (Scheme 1.41).[87] In the course of their studies a small amount of hydrated dimer **182**, with a tricyclic pyranol structure, was isolated from reaction mixtures. This unusual product may arise from a [4+2] hetero-Diels-Alder dimerization reaction between two units of **178** to generate **179**. Isomerization to **180** and hydration upon workup would provide **181** which can tautomerize to **182**. An ionic pathway involving nucleophilic attack of the anion of **177** upon **178** to generate anion **183** and subsequent Michael addition to **179** was not ruled out by the authors.



Scheme 1.41 - Unusual [4+2] Dimer of Electron Deficient 1,2-Cyclohexadienes

In a further application, crossed hetero-Diels-Alder reactions of keto-substituted 1,2-cyclohexadienes was explored, using electron-rich π traps.[87] The use of enamines has been found to be effective as the 2π electron moiety in this inverse electron demand [4+2] Diels-Alder reaction, with cycloadduct **184** being isolated in 65% yield (Scheme 1.42). This process offers a rapid and selective entry into rigid polycyclic scaffolds bearing multiple heteroatoms, and may lead to a new class of bioactive skeletons as potential drug-like molecules.



177 **178** **184**
65%

Scheme 1.42 - [4+2] Trapping of Electron Deficient 1,2-Cyclohexadiene with Enamine

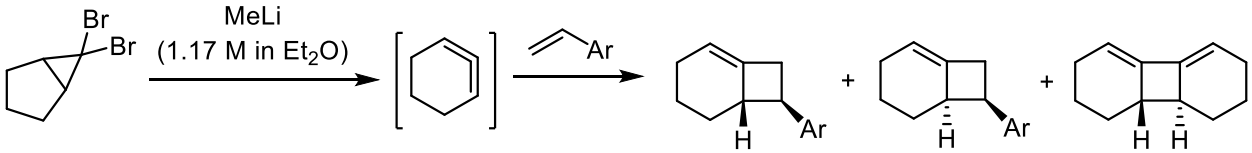
1.6.4 [2+2]-Cycloadditions

In addition to [4+2]-cycloadditions another major trapping mode for 1,2-cyclohexadiene is [2+2]-cycloaddition, with styrene serving as preferred trapping reagents. 1,2-Cyclohexadiene **13a**, generated by Moore and Moser, can react with styrene in a yield of 76% with a 2.2:1 ratio favoring the exo isomer (Table 1.3, Entry 2).[39, 88] A small amount of the dimer, 5%, was also isolated in this cycloaddition. Christl and Schreck, in a more in-depth study, examined the effect that temperature had on the diastereomer ratio of **185/186**.[89,90] At -45 °C (Entry 1) a 4.1:1 ratio of *exo*:*endo* for **185**:**186** was obtained; when the temperature was increased to 42 °C (Entry 3) a lower ratio of 2.7:1 resulted. At 140 °C (Entry 4) the reaction switches from kinetic to thermodynamic control and an equilibrium is established between **185** and **186**, with the *exo* isomer favored by 13:1. When 4-methoxystyrene is used to trap **13a** (Entry 5) a 23% yield is obtained with a diastereomer ratio of 9:1 of **185** and **186**.

In sections **1.4.1** it was discussed how 1,2-cyclohexadiene can act as an electrophile; this would lead one to think trapping with 4-methoxystyrene should result in a higher yield due to its greater electron availability. To explain this discrepancy a Hammett study was conducted with **13a** and different styrenes, the resultant ρ value of +0.79 indicates a slightly nucleophilic 1,2-cyclohexadiene with a small amount of charge separation.[91] Interestingly this result stands in direct contradiction to work presented in this thesis (see chapter **3**) which shows increased yields in intramolecular [2+2] trappings of styrene with greater electron availability. 1,2-Cyclohexadiene appears to have the unique ability to act as either electrophile or nucleophile depending on the reaction conditions.

Constantin and Almehmadi, who generated **13a** via elimination of an allylic carbonate with a Grignard reagent at 0 °C (see section **1.5.10**) were also able to trap with styrene and obtained a combined yield of 76% for cycloadduct **185** and **186** with a 2.5:1 ratio favoring the *exo* isomer.[81]

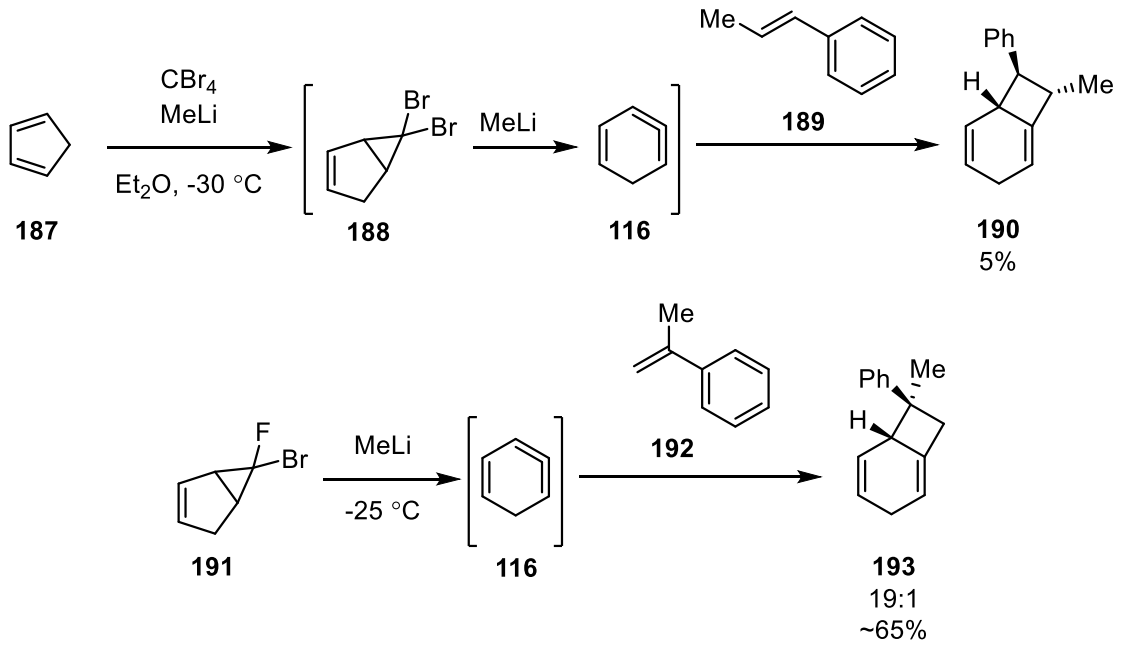
Table 1.3 - 1,2-Cyclohexadiene [2+2]-Cycloaddition with Styrene and Temperature Dependence of Diastereomer Ratio



100 **13a** **185** **186** **56**

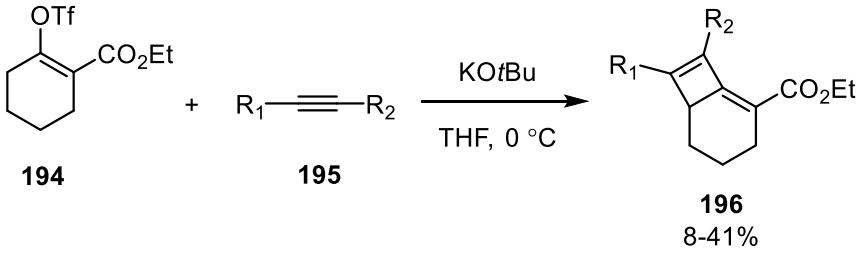
Entry	Ar	Temp (°C)	Yield **185** + **186** (%)	Ratio **185** (*exo*):**186** (*endo*)	Yield **56** (%)
1	Ph	-45	N.A.	4.1:1	N.A.
2	Ph	-15	76	2.2:1	5
3	Ph	42	N.A.	2.7:1	N.A.
4	Ph	140	N.A.	13:1	N.A.
5	4-OMe-C_6H_4	-10	23	9:1	N.A.

1,2,4-Cyclohexadtriene **116** is closely related to 1,2-cyclohexadiene, since both compounds contain an allene installed within a six-membered ring. Over the course of intercepting this allene in a [2+2]-cycloaddition valuable insight into the role of sterics on the electrophilic reaction partner was learned.[73] β-Methylstyrene **189** reacted with **116** to produce the cyclobutane-containing cycloadduct **190** in only 5% yield. Reaction with α-methylstyrene **192,** however, will proceed in ~65% yield (Scheme 1.43). One hypothesis for the lower yield of **190** vs. **192** is that α-methylstyrene provides easier accesses to the reactive double bond and the generated radical intermediate will be more stable compared to β-methylstyrene. While these experiments are informative on the different reactivities of styrenes they do come with a major caveat; the method for generating **116** for cycloadduct **190** involves the use of ether as solvent which would likely have lowered the yield as a result of dilution. To demonstrate that the method of allene generation is not solely responsible for the low yield of **190** styrene was trapped in 49% yield under these conditions.



Scheme 1.43 - [2+2] Trapping of 1,2,4-Cyclohexatriene with Styrenes

While styrene is the most commonly used reagent to trap 1,2-cyclohexadiene via a [2+2] reaction, it is not the only one. Recent work by Zhou has shown terminal alkynes can be used in place of styrene to generate products containing a butene ring (Scheme 1.44).[7] With ester substituted triflate **194** the allene can be generated via base mediated elimination and trapped to provide **196**. The yields for this cycloaddition are modest, ranging from 8-41%, and are higher with aryl groups attached to the alkyne. Attempted trapping using terminal alkynes with aliphatic substituents or disubstituted (internal) alkynes results in decomposition or complex mixtures.



Scheme 1.44 - [2+2] Trapping of Ester Substituted 1,2-Cyclohexadiene with Alkynes

1.6.5 [4+2] and [2+2] Trapping with 1,3-Dienes

Several conjugated dienes can be used to trap 1,2-cyclohexadiene in either [2+2] or [4+2]-cycloadditions (Figure 1.7).[89] With 1,3-butadiene an 8:1:4 mixture of [2+2] adducts **197a** and **197b** along with [4+2] thermal isomerization adduct **198** was obtained in a combined yield of 68%.[92] (*Z*)-1,3-Pentadiene trapped only by [2+2]-cycloaddition, giving **199a** and **199b** in a ratio of 15:1 and 26% yield.[36] Meanwhile (*E*)-1,3-pentadiene formed exclusively **199c** in 17% yield.[92] Five products, **200a**, **200b**, **201**, **202**, and **203** were formed via reaction with isoprene in a 9:2:2:1:1 ratio.[92] 2,3-Dimethyl-1,3-butadiene however gave only a single [2+2] adduct, **204** in 46% yield.[36,92] Lastly, 2,4-hexadiene resulted in a mixture of diastereomers of the [2+2] adduct **205**.[93] All these reactions were performed at low temperature and it is interesting to note that when heated above 130 °C all [2+2] adducts except **205** rearranged to their corresponding [4+2] adducts.[92]

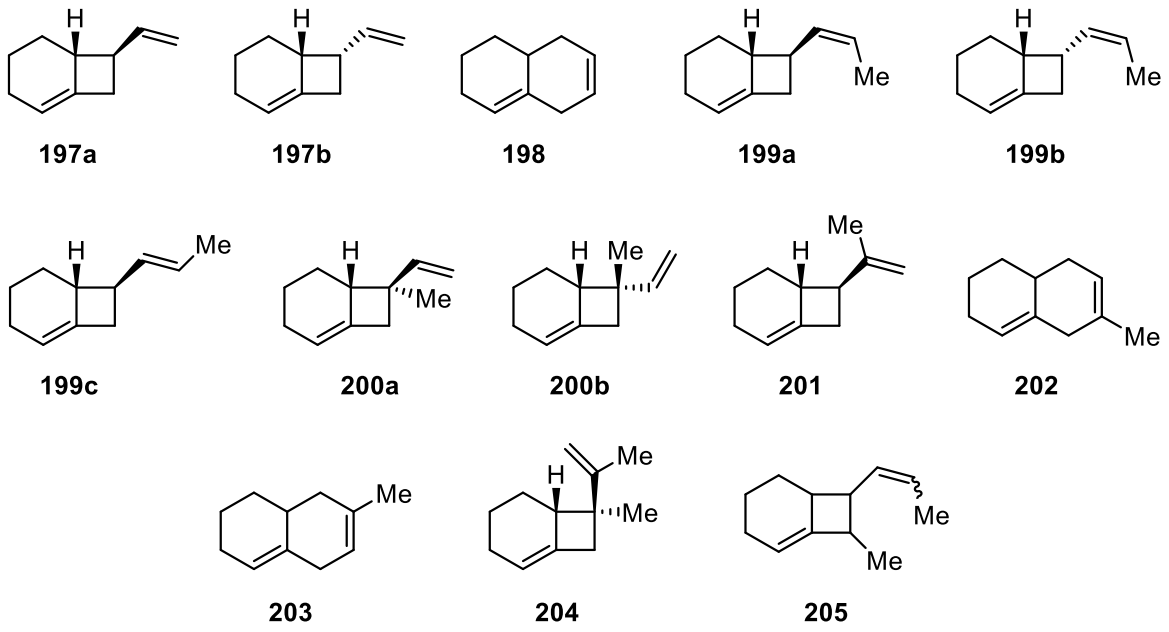
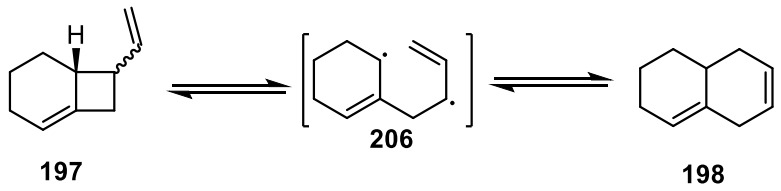


Figure 1.7 - 1,2-Cyclohexadiene Cycloadducts with 1,3-Butadiene, 1,3-Pentadiene, Isoprene, 2,3-Dimethyl-1,3-butadiene, and 2,4-Hexadiene

Given the known preference of acyclic 1,3-dienes to exist in the s-*trans* conformation rather than the s-*cis*, it is not surprising that in most cases their trapping occurs via the [2+2]

pathway. The formation of hexahydronaphthalene **198** via thermal isomerization of **197** is assumed to take place through diradical intermediate **206** (Scheme 1.45).[92]



Scheme 1.45 - Formation of Hexahydronaphthalene from [2+2] Cycloadducts

1.6.6 [3+2]-Cycloadditions

Trapping of 1,2-cyclohexadiene via [3+2]-cycloaddition was not realized until very recently. In 2016 two near simultaneous reports were published by the Garg group and the West group on intercepting 1,2-cyclohexadiene with 1,3-dipoles.[61,94]

Garg and co-workers were the first to report on this transformation, using 1,2-cyclohexadiene and nitrones to access stereochemically rich isoxazolidine products.[94] Allylic silane **207** bearing an sp^2 triflate leaving group was used to generate 1,2-cyclohexadiene via the fluoride mediated elimination method popularized by Guitián (see section **1.5.8**).[58] The allene was trapped with nitrone **208** to give isoxazolidine cycloadduct **209** (Figure 1.8). The cycloaddition was found to proceed best under a high dilution of 0.025 M, to minimize the chance of dimerization; remarkably only 1 or 2 equivalents of nitrone was required for effective trapping, a dramatic decrease when compared to [4+2] or [2+2] reactions (see sections **1.6.3** and **1.6.4**) .[35,36,39] Complete regioselectivity was observed in this reaction as well as a strong preference for the *endo* diastereomer. Nitrones with a variety of substituents formed cycloadducts in this reaction: **209a-c** with simple alkyl substituents, **209d-e** with five-membered heterocycles, **209g** with quinoline, **209h** with indole, **209i** with a ring and **209j-k** with quaternary carbon (Figure 1.8).

Both observed experimental preferences for regio and stereochemistry were supported by calculations; the preferred regioisomer was found to have a transition state 3.7 kcal/mol lower in energy assuming a concerted mechanism. A concerted transition state for the major *endo* isomer was found to have an energy barrier of 14.5 kcal/mol. A concerted transition state for the minor *exo* product could not be found, prompting examination of a possible radical pathway. The

resulting calculations showed an energy barrier of 14.4 kcal/mol for formation of the initial bond on the *sp* carbon of the allene. The subsequent stereochemistry forming step showed a lower energy barrier of 1.2 kcal/mol for the *endo* isomer over an *exo* isomer. As Diels-Alder reactions with allenes are known to have competition between concerted and radical pathways, and the calculated energy barrier for this reaction were nearly identical, it was proposed that the same competing pathways may be at work with the nitrone cycloadditions.[95,96]

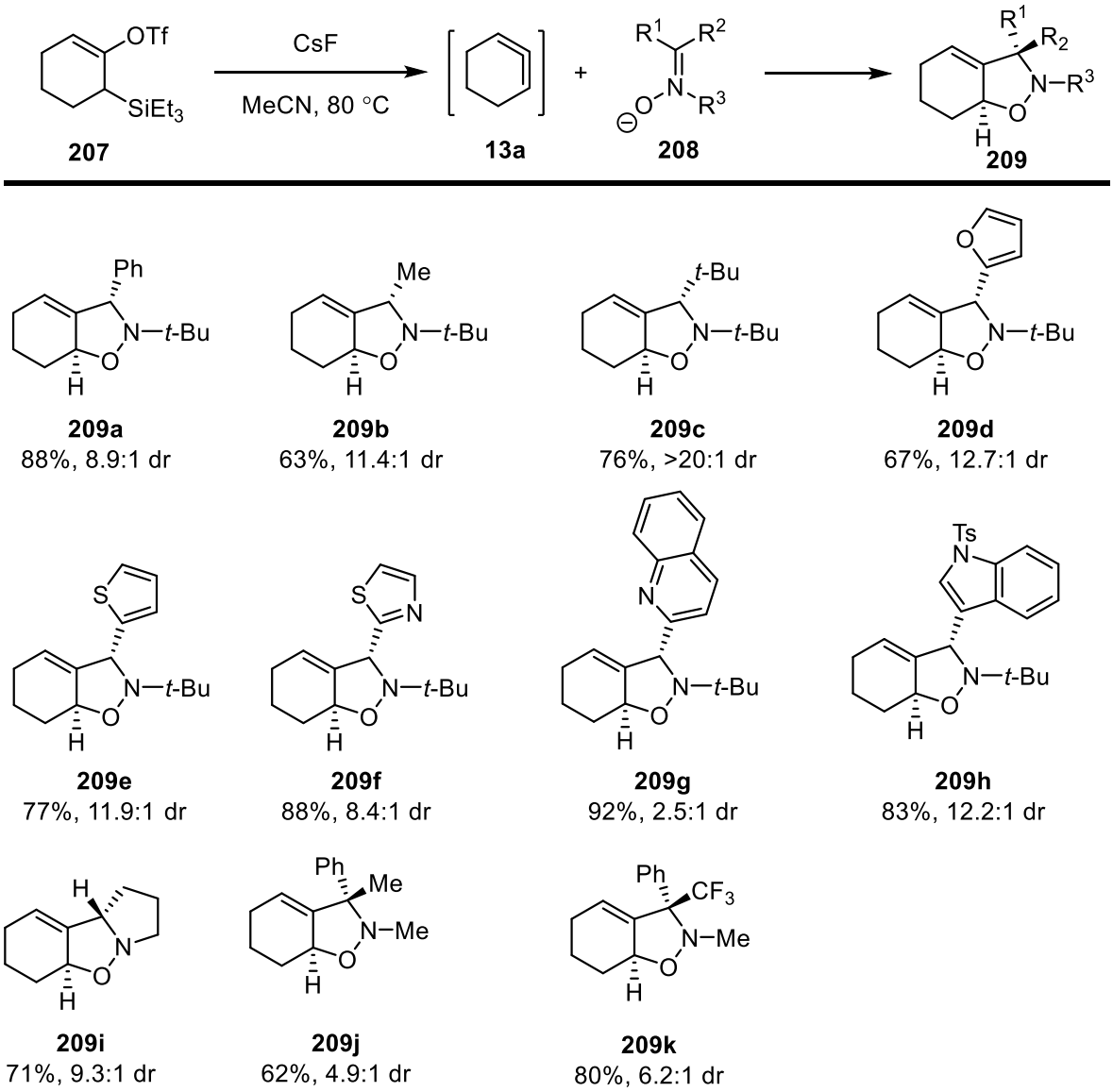
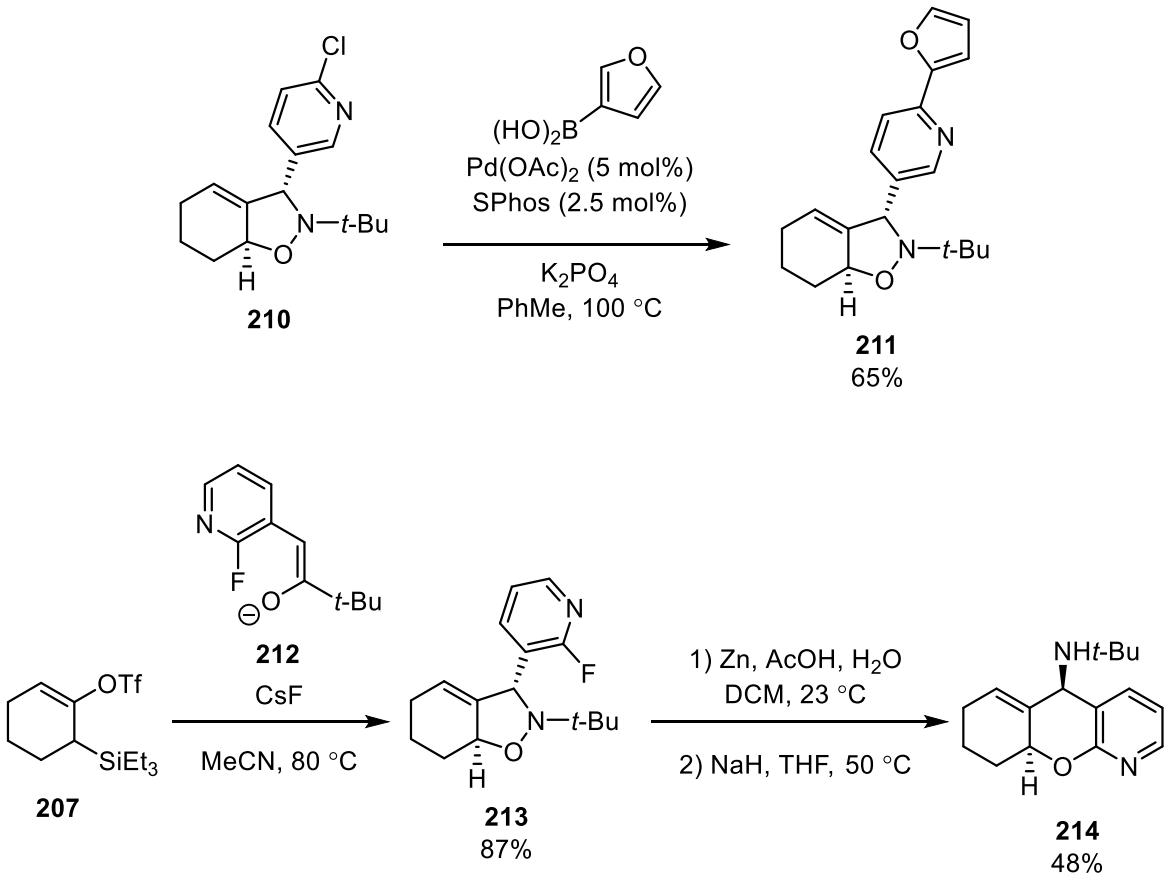


Figure 1.8 - [3+2]-Cycloaddition of 1,2-Cyclohexadiene and Nitrones Reported by Garg Group

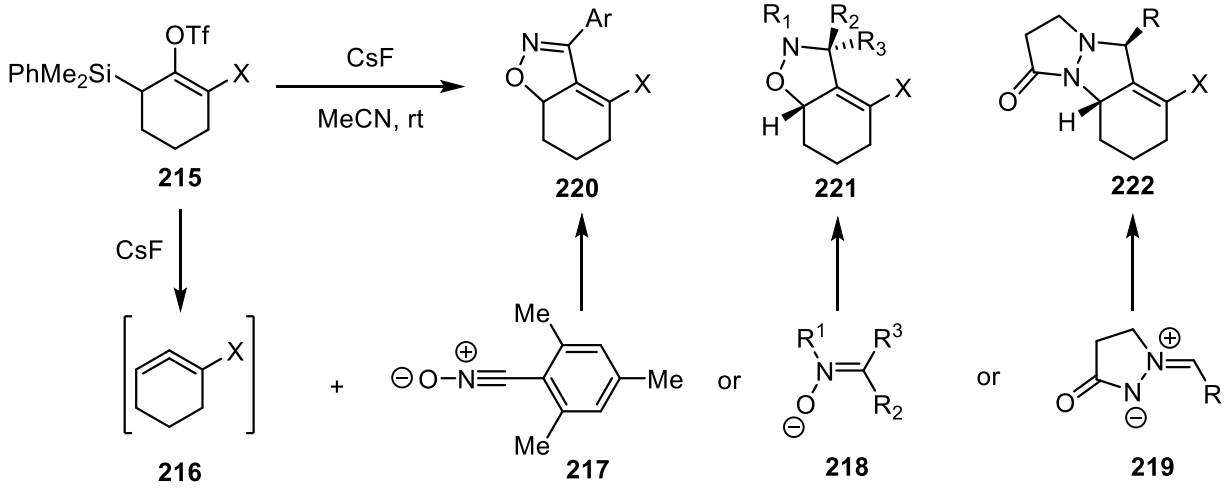
The utility of these transformations was demonstrated with sequential cycloaddition and cross-coupling reactions (Scheme 1.46). Isoxazolidine **210**, synthesized via nitrone allene [3+2]-cycloaddition, was shown to undergo Suzuki-Miyaura cross coupling with 2-furanylboronic acid to produce **211**. The ability to construct a molecule comprised of three different heterocycles will be of great interest to medicinal chemists. Polycyclic heterocyclic scaffold **214**, synthesized by N-O bond cleavage and substitution nucleophilic aromatic (S_NAr) reaction of nitrone cycloadduct **213**, shows the ease with which complex heteroatom moieties can be manipulated with this methodology.



Scheme 1.46 - Synthetic Elaboration of Nitrone Cycloadducts by Garg Group

Lofstrand and West also reported the [3+2]-cycloaddition of 1,3-dipoles with 1,2-cyclohexadiene.[61] Analogous to Garg, Lofstrand also generated 1,2-cyclohexadiene **216** via fluoride mediated elimination of allylic silane **215** bearing an sp^2 triflate leaving group. Lofstrand elaborated on nitrone **218** trapping by also demonstrating cycloadditions with nitrile oxide **217** and

azomethine imine **219** dipoles (Scheme 1.47). Nitrones produced alkylidene isoxazolidines **221** as a single regioisomer and with diastereoselectivity of >20:1 for the *endo* adduct, as previously seen by Garg and co-workers.[94] Nitrile oxide produced isoxazoline **220** while azomethinie imines afforded tricyclic products **222** with complete regioselectivity and a high diastereoselectivity of >20:1. An X-ray crystal structure of **222** confirmed the stereochemistry as the *endo* diastereomer.

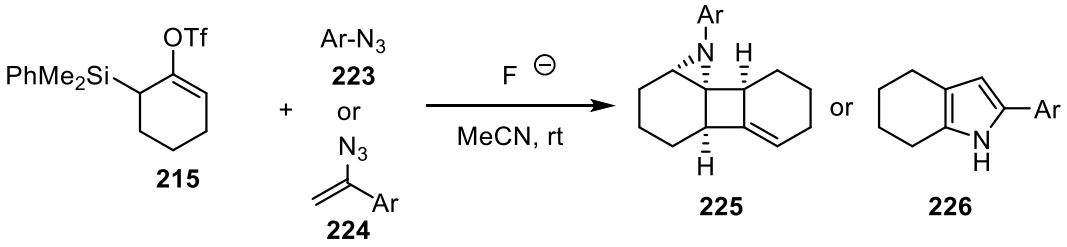


Scheme 1.47 - [3+2]-Cycloaddition of 1,2-Cyclohexadiene and 1,3-Dipoles Reported by West Group

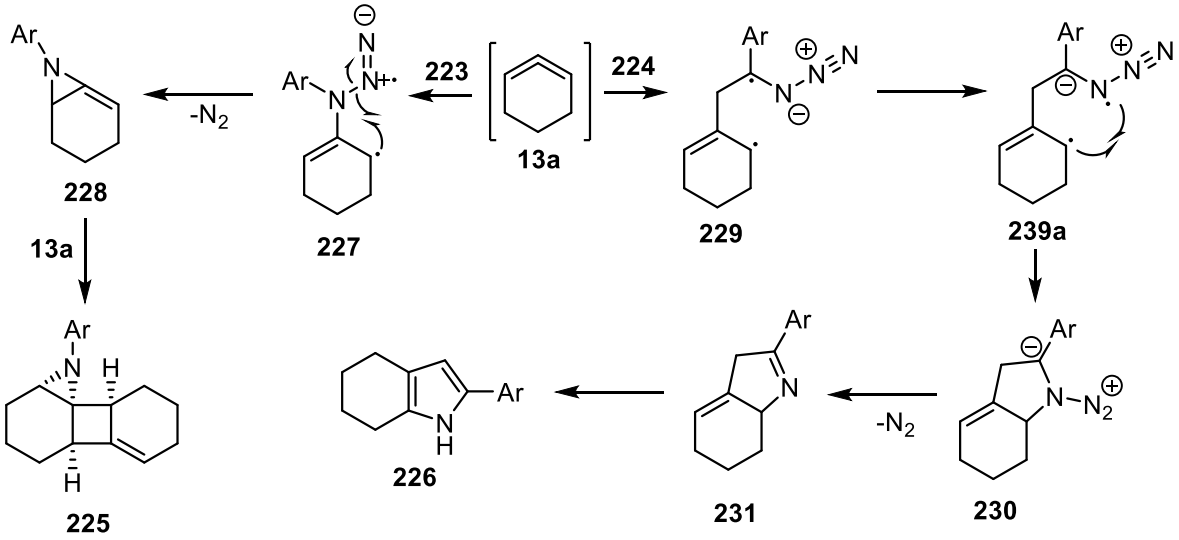
Interestingly 1,2-cyclohexadiene was also shown to react with azides as a 1,3-dipole. Electron deficient aromatic azides **223** gave an unexpected 2:1/cyclic allene/azide [2+1]/[2+2] cycloadduct **225** (Table 1.4, entry 1-2). Electronics did not seem to affect the reaction of azide **224**, which afforded pyrrole products rather than 2:1 adducts, with yields of **226** being similar between entries 3-5. A 2-pyridyl group however, as in entry 6, resulted in a very low yield of product.

The proposed mechanism from which products **225** and **226** form is based on similar observations by Feldman and coworkers working with acyclic allenes and azides (Scheme 1.48).[97,98] 1,2-Cyclohexadiene **13a** and azide **223** formed intermediate **227** which will lose N_2 to give **228**. A [2+2]-cycloaddition of **228** with another unit of **13a** resulted in **225**. Alternatively, **13a** reacted with the olefin on **224** producing diradical **229**. This diradical can undergo ring closure to **230** and extrude N_2 to give **231**. A simple isomerization resulted in the final product **226**.

Table 1.4 - Cycloaddition of 1,2-Cyclohexadiene and Azides by West Group



Entry	Azide	Ar	Product	Yield (%)
1	**223**	4-NO_2-C_6H_4	**225**	52
2	**223**	4-EtO_2C-C_6H_4	**225**	51
3	**224**	Ph	**226**	47
4	**224**	4-MeO-C_6H_4	**226**	66
5	**224**	3-NO_2-C_6H_4	**226**	43
6	**224**	2-pyridyl	**226**	15



Scheme 1.48 - Proposed Mechanism for Formation of Azide Cycloadducts

1.7 Conclusions and Thesis Objective

As with other strained intermediates, cyclic allenes display a rich array of novel reactivity that can form the basis of powerful bond-forming strategies. However, in comparison to other classes of strained cyclic intermediates such as benzynes or cycloalkynes, comparatively little work has been done with cyclic allenes, offering a ripe field for study. A variety of methods now exist for the synthesis of 1,2-cyclohexadine and related cyclic allenes and we can interrupt unwanted dimerization pathways with useful cycloadditions. While great progress has been made there are still many areas of this chemistry that would benefit from refinement. Trapping reactions of 1,2-cyclohexadiene, particularly [4+2] and [2+2] modes, require huge excesses of reagent in order to produce synthetically useful amounts of cycloadduct. Running reactions in furan or styrene is not practical or atom economical. These reactions still generally have modest yields and significant amounts of dimer are often seen. If cyclic allene chemistry is to see the same widespread adoption as cycloalkynes and benzynes these issues must be addressed. One strategy that can be employed to overcome these limitations is going to an intramolecular reaction.

In chapter 2 of this thesis a novel intramolecular [4+2] trapping reaction of 1,2-cyclohexadiene using pendent substituted furans will be described. The ways in which this reaction can overcome the deficiencies discussed previously will be examined. Efforts to manipulate these complex hetero-carbocycles and a surprising retro-[4+2]-cycloaddition will also be discussed. Chapter 3 continues the development of intramolecular trapping reactions of 1,2-cyclohexadiene with new substrates that contain a styrene moiety and undergo [2+2]-cycloaddition. Chapter 4 will tie the [4+2] and [2+2]-cycloaddition reactions together and discuss exciting future directions for this chemistry. The appendices contain some supporting experiments relevant to ideas discussed in this thesis, crystallographic information for x-ray crystal structures and selected ^{1}H and ^{13}C NMR spectrums.

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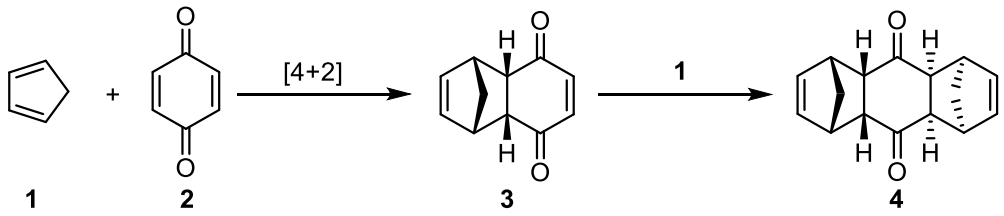
2. Strain-Activated Trapping Reactions of 1,2-Cyclohexadiene: Intramolecular Capture by Pendent Furans[1-2]

2.1 Diels-Alder Cycloaddition

The Diels-Alder cycloaddition reaction is one of the most versatile ways to assemble a six membered ring. In 1928 Professor Otto Diels and his student Kurt Alder published a paper detailing a [4+2]-cycloaddition reaction between cyclopentadiene **1** and quinone **2**. From this reaction they were able to isolate mono-Diels-Alder adduct **3** and di-Diels-Alder adduct **4** (Scheme 2.1).[1] The enormous impact of this discovery upon the field of chemistry and natural product synthesis was summed up by the authors, "Thus it appears to us that the possibility of synthesis of complex compounds related to or identical with natural products such as terpenes, sesquiterpenes, perhaps even alkaloids, has been moved to the near prospect."[2] Indeed such was the importance of their discovery that in 1950 Diels and Alder were awarded the Nobel prize.[3]



Scheme 2.1 - Discovery of the Diels-Alder Reaction

The mechanism of this transformation has received extensive study in the literature and is well understood as a concerted pericyclic process between a diene and dienophile.[4] The concerted nature of the Diels-Alder (DA) reaction has allowed the development of sets of rules to predict stereochemistry; the Alder *endo* rule being the most prominent.[5] An experimental preference for *endo* cycloadducts, where the dienophile is directed inwards toward the former diene, had been noted by Alder and Stein in 1934 but it was not until the groundbreaking work of Woodward and

[1] Note: some of the work presented in this chapter was performed by Dr. Verner Lofstrand.
[2] Lofstrand, V. A.; McIntosh, K. C.; Almehmadi, Y. A.; West, F. G. *Org. Lett.* **2019**, *21*, 6231-6234.

Hoffmann that a suitable explanation involving secondary orbital overlap was proposed (Figure 2.1).[6]

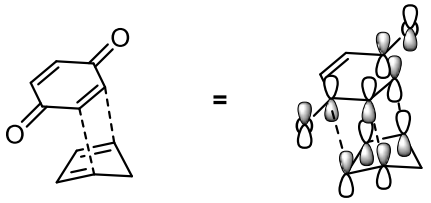
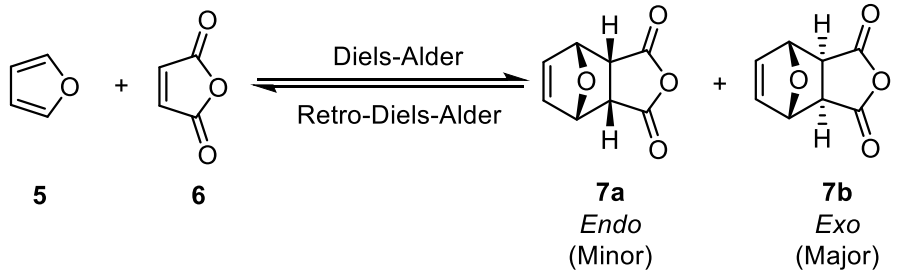


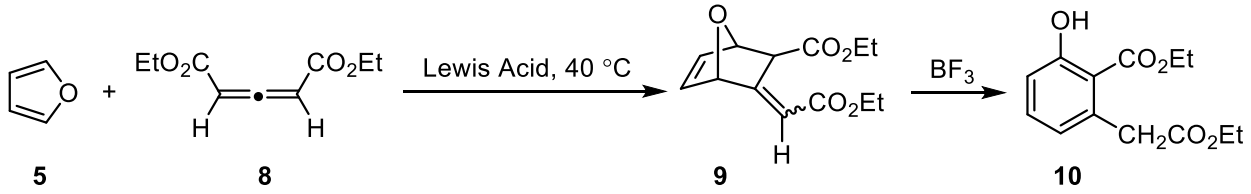
Figure 2.1 - Alder *endo* Rule Stereochemical Preference

The use of a diene component that is confined within a rigid ring system allows for the generation of bridging systems while also accelerating the cycloaddition, a consequence of being locked in the reactive s-*cis* reactive conformation.[7] A popular choice of such 1,3-dienes is furan, whose use in the Diels-Alder reaction allows the synthesis of synthetically versatile oxabicycloheptene scaffolds. The aromaticity of furan brings interesting consequences into effect for the cycloaddition. Breaking aromaticity in a furan cycloaddition often means these reactions must be heated or conducted in the presence of a Lewis acid; retrograde Diels-Alder reaction can be energetically favorable due to the recovery of the aromatic stabilization of the starting furan ring, rendering this reaction a rare example of reversible Diels-Alder cycloaddition. These factors can be seen clearly in the reaction of furan **5** with maleic anhydride **6**, which has an activated double bond (Scheme 2.2).[8] In the reaction the major product is the *exo* isomer **7b**, a contradiction of the Alder *endo* rule previously discussed. The *endo* cycloadduct **7a** only has a small kinetic preference (0.8 kJ/mol) and can undergo a retro-Diels-Alder enabling the thermodynamically stable *exo* adduct **7b** to be formed preferentially.[8]



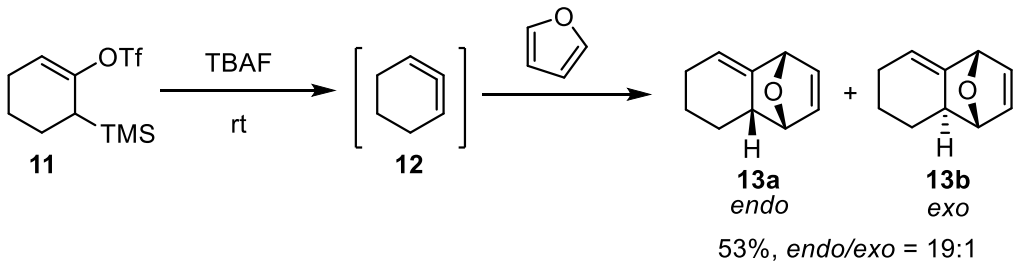
Scheme 2.2 - Retro-Diels-Alder Reaction Leading to Major *Exo* Isomer 7b

Allenic esters have been shown to be suitable dienophile partners for cycloadditions with furan.[9,10] With the use of a Lewis acid the [4+2]-cycloaddition between furan **5** and allenic ester **8** can proceed at 40 °C (Scheme 2.3). Interestingly cycloadduct **9** can be further treated with boron trifluoride to generate phenol **10** through a ring opening of the ether bridge, a transformation important to this thesis which is discussed further in section **2.4.8**.[11]



Scheme 2.3 - Diels-Alder Reaction of Furan with an Allenic Ester

In addition to cycloadditions with acyclic allenes, furan is an excellent trap for cyclic allenes (see chapter **1**, section **1.6.3**). One such example is the cycloaddition reaction of 1,2-cyclohexadiene **12**, generated from alkenyl triflate **11** with furan. This dienophile lacking any traditional activating groups reacts efficiently at room temperature due to strain release. Cycloadduct **13a** was isolated in a combined yield of 53% with the major isomer in this case is the *endo* cycloadduct, following the Alder-*endo* rule as the kinetic product (Scheme 2.4).[14]

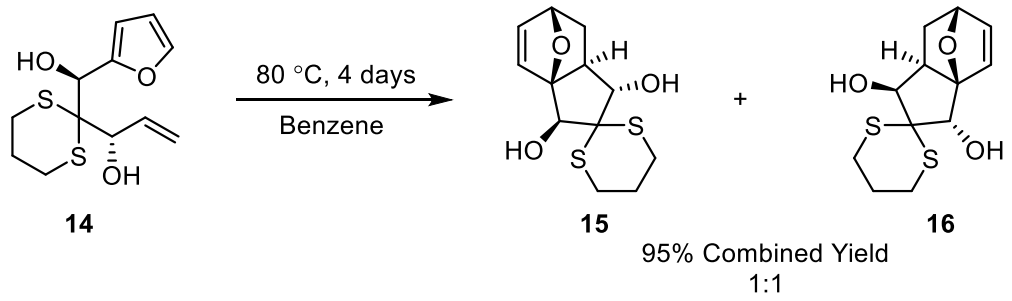


Scheme 2.4 - Diels-Alder Reaction of Furan and 1,2-Cyclohexadiene

2.2 Intramolecular Diels-Alder Cycloaddition with Furan

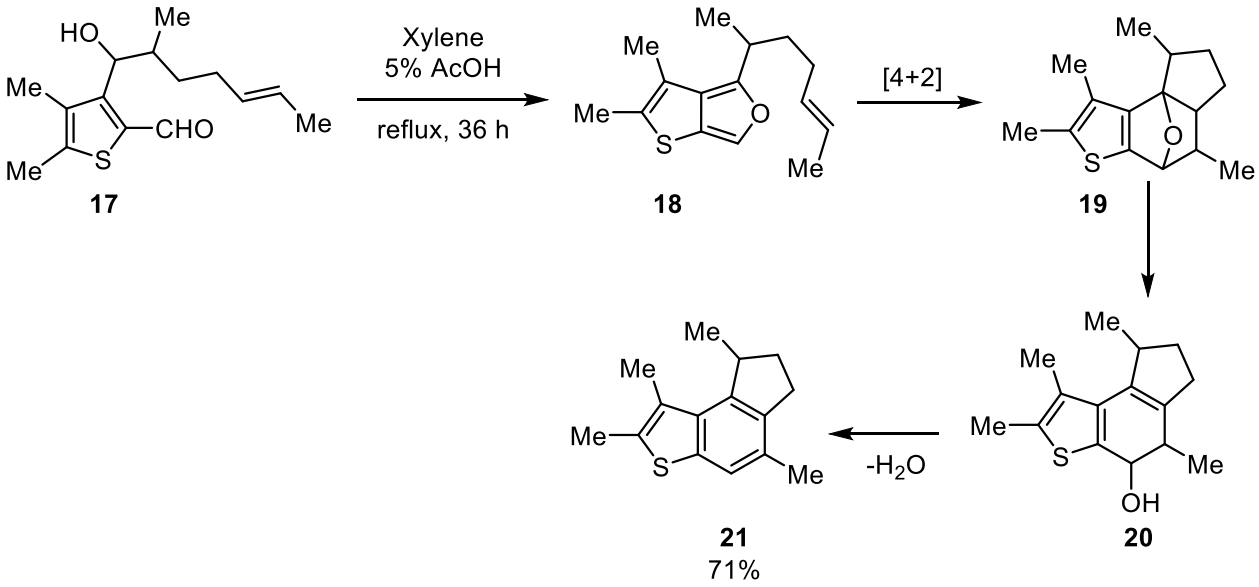
Another strategy to address the loss of aromaticity that occurs in a furan Diels-Alder reaction is to move into an intramolecular framework. Intramolecular Diels-Alder reactions with furan (IMDAF) have the diene and dienophile tethered together in close proximity. The scope of

the IMDAF is broad with respect to both the furan and dienophile components. A simple 2-alkyl substituted furan such as **14** will undergo an intramolecular cycloaddition with its tethered terminal olefin upon heating, generating a 1:1 mixture of diastereomers **15** and **16** in a combined yield of 95% (Scheme 2.5).[12] The dithiane moiety present in **14** provides an enhanced reaction rate by forcing the furan and olefin into closer proximity for the cycloaddition, an example of the Thorpe-Ingold effect.[13]



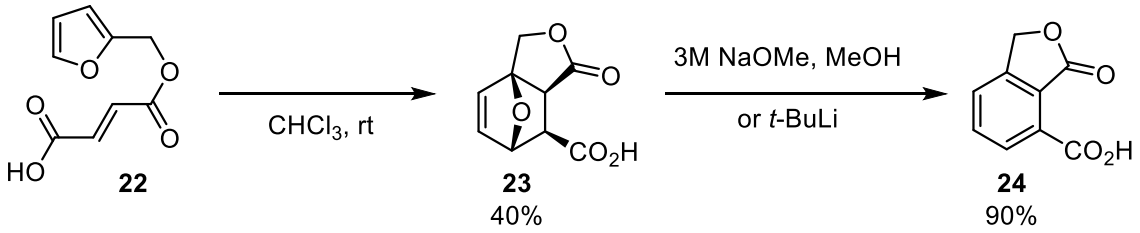
Scheme 2.5 - 2-Alkyl Furan IMDAF Accelerated by a Thorpe-Ingold Effect

In addition to simple substitution on furan, more complex starting materials such as fused polycycles can be utilized in the IMDAF, resulting in correspondingly more complex polycyclic products. Friedrichsen prepared thiamarmelerin **21**, a synthetic analogue of the natural product marmelerin, via [4+2]-cycloaddition of 3,4-fused furan **18** (Scheme 2.6).[15] Thiophene **17** served as a latent furan to generate **18** upon acid-catalyzed ring closure. After the [4+2]-cycloaddition to produce **19**, where the aromaticity of furan is lost but the aromaticity of thiophene is gained, and opening of the ether bridge in **19**, alcohol **20** would lose water to form thiamarmelerin **21**.



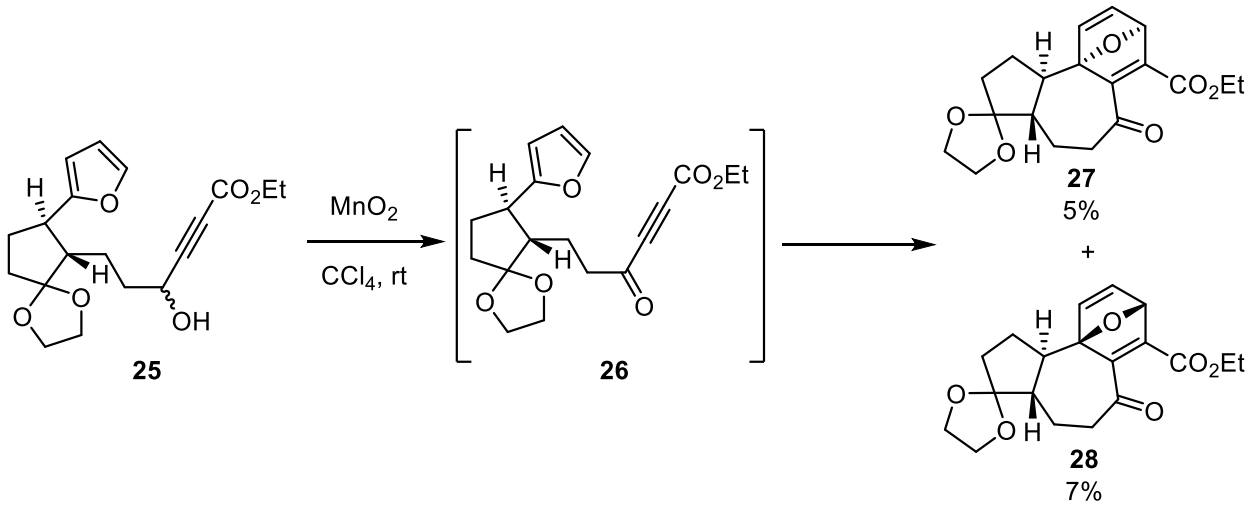
Scheme 2.6 - Synthesis of Thiamarmelerin via Latent 3,4-Fused Furan IMDAF

The 2π dienophile component of the IMDAF can be even more varied than the diene. Almost any electron-deficient π-system that possesses at least two electrons can be utilized in the cycloaddition. The simplest of these dienophiles is an olefin, which can range from a mono-substituted terminal double bond to a highly functionalized internal double bond. When the dienophile is attached to an electron withdrawing moiety the IMDAF proceeds faster, a consequence of a lowering of the dienophile LUMO energy level and a resulting smaller HOMO-LUMO gap. This effect can be seen with the spontaneous room temperature cycloaddition of fumaric ester **22** with a tethered furan to give IMDAFD cycloadduct **23** in 40% yield (Scheme 2.7).[16] Analogous to the example in scheme 2.6 an opening of the ether bridge and subsequent dehydration can lead to the aromatic product **24** in 90% yield.



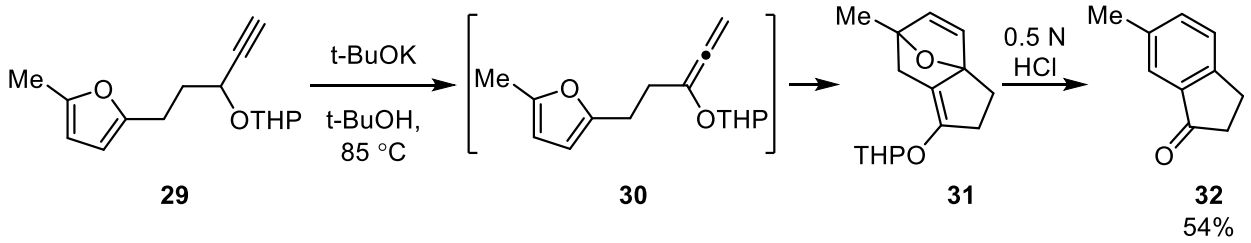
Scheme 2.7 - IMDAF of Fumarate Ester 22 Accelerated by EWG

In addition to alkenes another major class of 2π dienophiles is alkynes. Like the example in Scheme 2.7, electronic activation with an EWG attached to the alkyne is common. Harwood and co-workers used an alkyne IMDAF dienophile during their attempted synthesis of the natural product phorbol.[17] Originally attempting to convert propargylic alcohol **25** into ketone **26,** they noticed the formation of two cycloadducts, **27** and **28** in 5% and 7% yield respectively (Scheme 2.8).



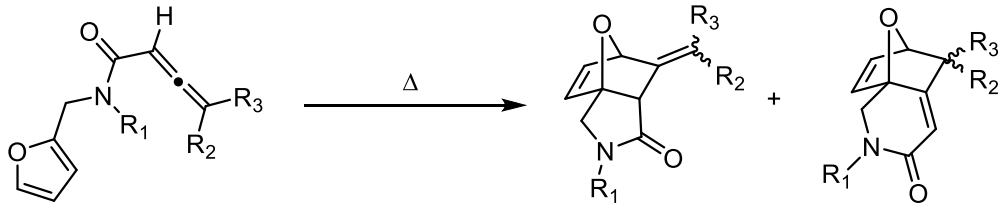
Scheme 2.8 - IMDAF with Pendent Alkyne en route to Phorbol

Alkynes as dienophiles are of note for being isomeric with an allene moiety. When base is present with a terminal unactivated alkyne, a rearrangement to the isomeric allene species is possible. Wu was able to utilize this isomerization in the synthesis of methylated indanone **32** (Scheme 2.9).[18] Propargyl ether **29** under basic conditions rearranged to allenyl ether **30** which underwent a [4+2]-cycloaddition between the furan and allene. The resulting cycloadduct **31** can further aromatize to indanone **32** in 54% yield under acidic conditions by dehydration of the ether bridge.



Scheme 2.9 - IMDAF with Pendent Alkyne Isomerized to Allene

A very interesting example of an IMDAF with an allene moiety was published by Himbert in 1989.[19] Using allenyl amide **33** Himbert was able to perform an IMDAF cycloaddition on either of the double bonds of the allene (Scheme 2.10). Cycloaddition across the doubly substituted bond provided cycloadduct **34** and cycloaddition across the terminal double bond provided cycloadduct **35**. The inclusion of the amide moiety is attractive as it provides easy access to a nitrogen heterocycle, a feature relevant in medicinal chemistry.

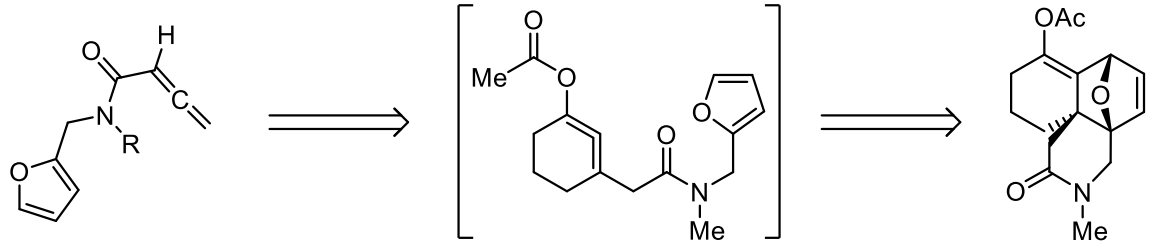


33 **34** **35**

Scheme 2.10 - Himbert IMDAF Cycloaddition with Allene

2.3 Intramolecular Cycloadditions of Cyclic Allenes with Furan

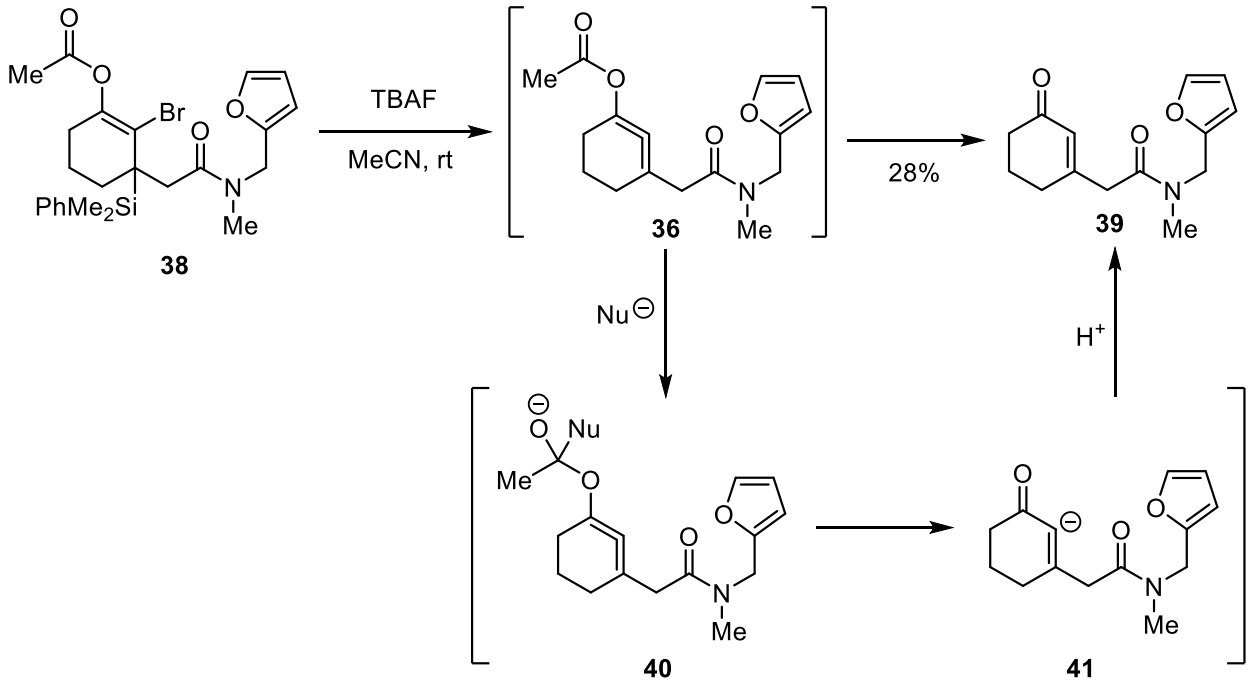
The Himbert cycloaddition served as a source of inspiration for the initial work of Lofstrand on intramolecular cycloadditions of cyclic allenes.[20] It was proposed that if the acyclic allene on **33** was confined to a small ring, such as with compound **36**, the corresponding [4+2]-cycloaddition may proceed spontaneously upon allene generation to produce cycloadduct **37** (Figure 2.2).



33 **36** **37**

Figure 2.2 - Proposed Intramolecular Cycloaddition of 1,2-Cyclohexadiene Inspired by Himbert

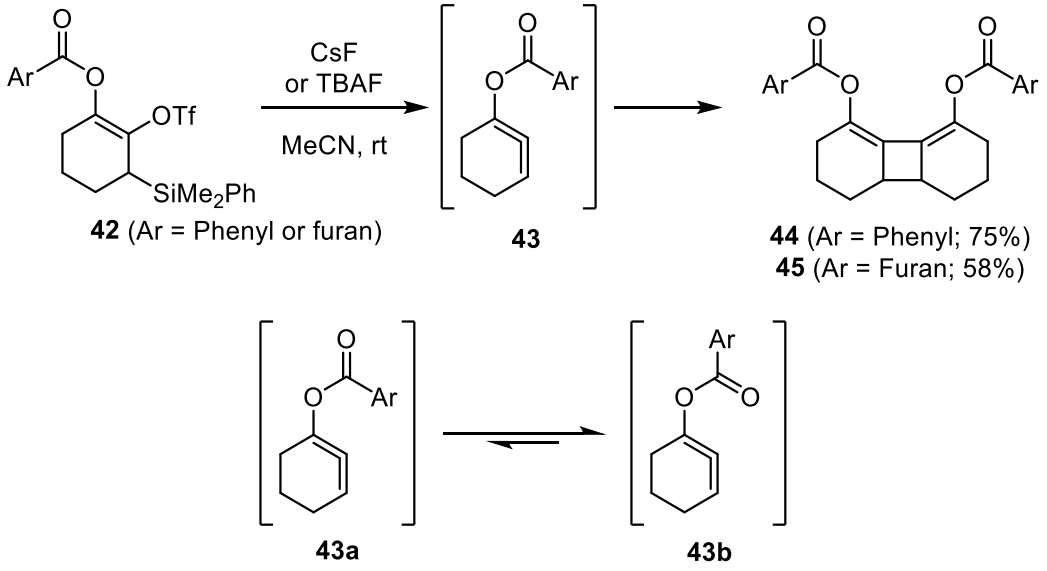
Lofstrand synthesized silyl precursor **38** to test the idea of an intramolecular cycloaddition with an amide tether.[20] Upon exposure to TBAF and subsequent fluoride mediated elimination to (presumably) generate 1,2-cyclohexadiene **36**, no desired cycloadduct **37** was found in the reaction mixture. Instead enone **39** was isolated in 28% yield as the major product (Scheme 2.11). To explain the generation of **39** it was proposed that the basic TBAF solution which contains ~5% water would have small amounts of hydroxide to act as a nucleophile and attack to carbonyl ester attached to allene of **36**. The resulting tetrahedral intermediate **40** would collapse to alkenyl anion **41** and subsequent protonation would generate the isolated product **39**.



Scheme 2.11 - Enone Product Obtained after 1,2-Cyclohexadiene Generation

One potential workaround proposed for the failed cycloaddition was to tether the diene trap through the enol ester oxygen atom (Scheme 2.12).[20] In addition to a furan trap, a phenyl trap was chosen due to the fact that Himbert cycloadditions can employ substituted benzene rings as traps of acyclic allenes.[20] Facile access to the desired starting material **42** was achieved by quenching a conjugate addition of the corresponding enone with various acyl chlorides. Unfortunately, neither the phenyl or furan moiety trapped the allene and no desired cycloadduct was observed. Instead the major products isolated from these reactions were the [2+2] dimers **44**

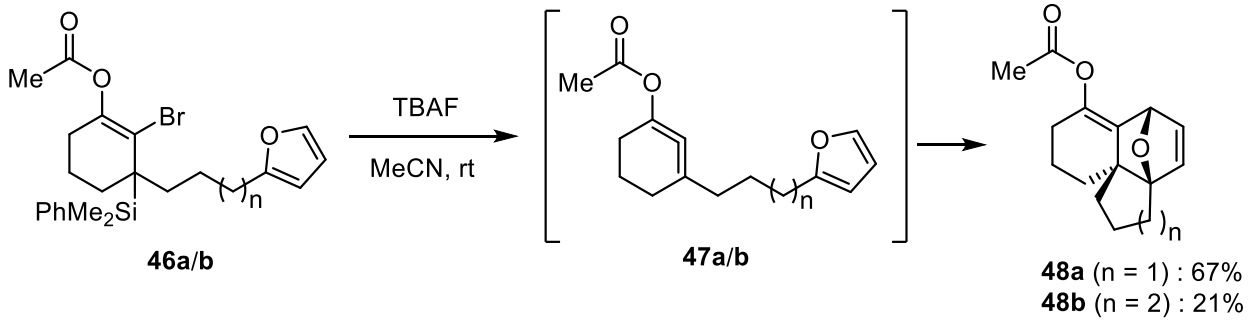
and **45** in yields of 75% and 58% respectively. It has been previously observed in intermolecular trapping of allenes with 1,3-dipoles that the reaction takes place exclusively on the unsubstituted double bond of the allene, suggesting that intramolecular delivery of furan to the oxygenated alkene of the allene intermediate may be disfavored.[21,22] Moreover, inclusion of an ester linker in the tether may disadvantage the cycloaddition due to preference for the s-*cis* conformer **43b** which holds the allene and furan out of bonding proximity (Scheme 2.12).[23]



Scheme 2.12 - Proposed Tether via Ester Moiety and Unfavorable Conformer

As with **43,** one possible reason why amide **36** failed to produce any cycloadduct was an unfavorable rotamer population. Preferential s-*cis* conformation and rigidity due to partial double bond character in the amide linker could inhibit close approach by the furan to the short-lived allene, allowing non-productive processes to predominate over the desired cycloaddition pathway. To overcome this compounds **46a** and **46b** containing all carbon tethers were synthesized by Lofstrand and exposed to TBAF. This generated transient allenes **47a** and **47b**, differing only be their tether length (Scheme 2.13).[20] Gratifyingly, these compounds underwent the desired [4+2]-cycloaddition at room temperature without the need for any Lewis acid activator and provided cycloadducts **48a** and **48b** in 67% and 21% yield respectively. The decreased yield in the case of **48b** highlights the sensitivity of this system; the tether must be flexible enough to enable proper

alignment but cannot have too many degrees of freedom or the yield diminishes. Importantly the cycloadducts were obtained as single regioisomers and as single diastereomers (see section **2.4.3**).



Scheme 2.13 - First Successful Intramolecular Cycloaddition of 1,2-Cyclohexadiene with Pendent Furan

2.4 Results and Discussion

2.4.1 Project Development

In light of the two successful intramolecular trapping examples accomplished by Lofstrand, we sought to explore the scope of this fascinating process. In particular, we wanted to determine the generality of the reaction with respect to furan substitution and tether. We envisioned a variety of potential substrates via modular construction using simple starting materials (Figure 2.3). A retrosynthetic analysis of cycloadduct **48** indicates it can be formed via fluoride mediated elimination of allylic silane **46** bearing an alkenyl leaving group. Compound **46** should be available by silyl anion conjugate addition to **49**, followed by trapping of the enolate oxygen atom with an appropriate acylating agent. A Stork-Danheiser alkylation would provide **49** from 2-bromo-3-ethoxycyclohexenone **50** and alkyl iodide **51**.[24] Finally the furan containing alkyl iodide subunits could be synthesized from simple furfurals **52**.

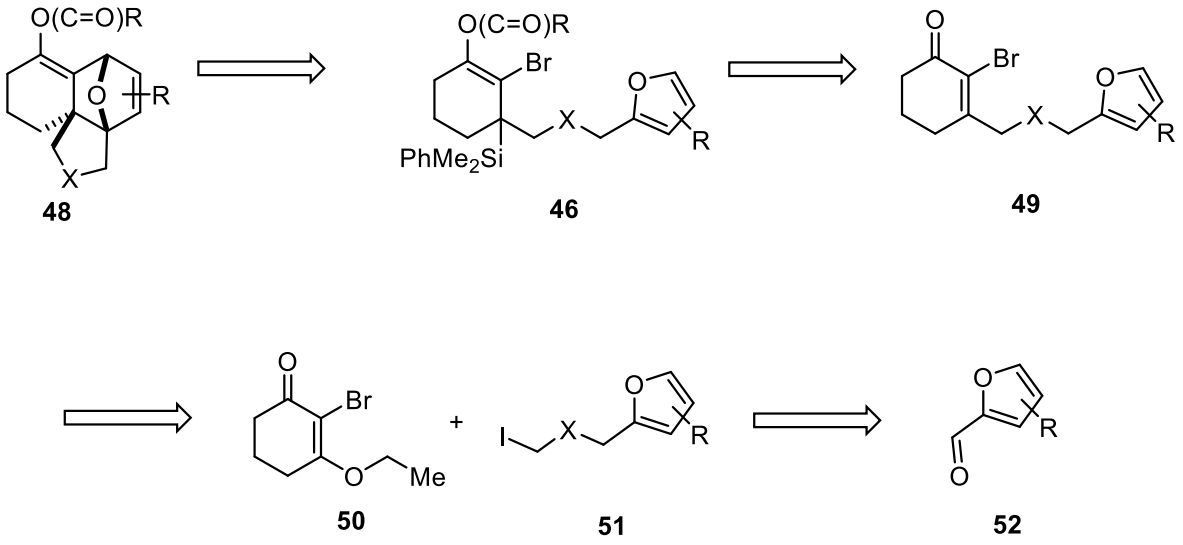
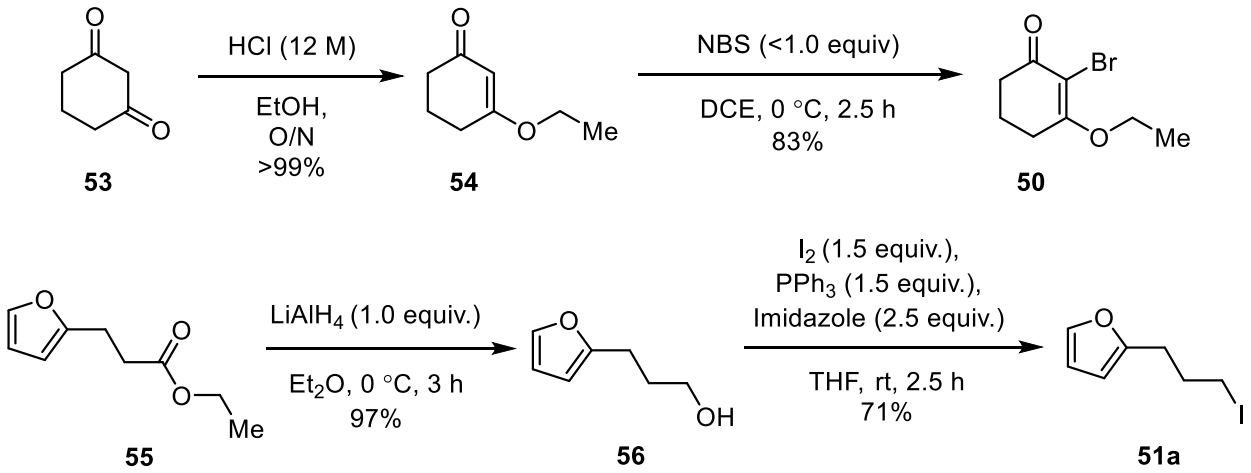


Figure 2.3 - Modular Assembly of Substrates for [4+2]-Cycloaddition Reaction

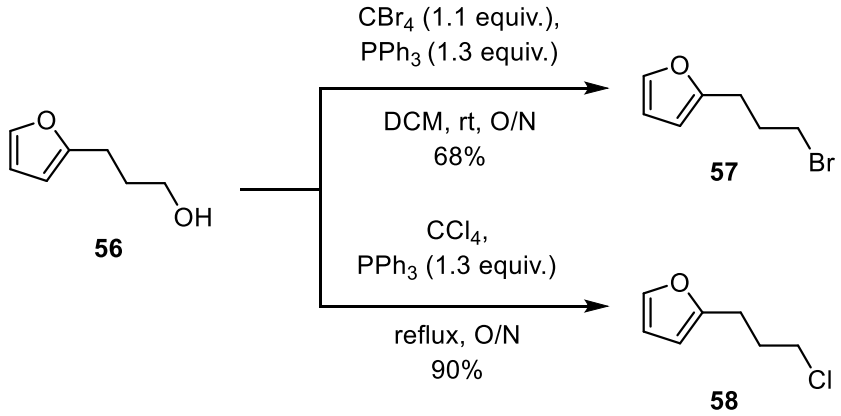
2.4.2 Synthesis of Initial Substrates and Their Diels-Alder Cycloaddition Reactions

The first example targeted was **48a**, which had already been synthesized by Lofstrand and would serve as a benchmark to compare with the results of this thesis.[20] 2-Bromo-3-ethoxycyclohexenone **50**, one of two fragments required for the key Stork-Danheiser step, was synthesized according to the literature starting from 1,3-cyclohexadione **53** and ethanol under acidic conditions, resulting in quantitative yield of **54** (Scheme 2.14).[25]. The α-bromination of **54** required strict control of stoichiometry and reaction time as even a slight excess of *n*-bromosuccinimide (NBS) or an extended stirring period resulted in negligible yields of **50**. The best result was obtained using just under 1.0 equivalent of NBS, providing **50** in a yield of 83%. Iodide **51a**, the other Stork-Danheiser fragment, was also prepared from a literature procedure involving the reduction of ethyl-ester **55** with LAH in 97% yield. Subsequent iodination via an Appel reaction furnished iodide **51a** in 71% yield.[26]



Scheme 2.14 - Assembly of Initial Stork-Danheiser Fragments

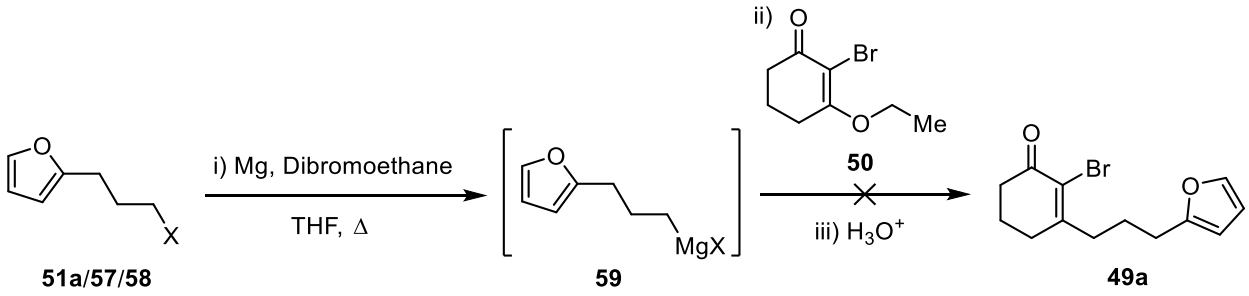
In order to examine the effect of different halides on the key Stork-Danheiser step, bromo and chloro substituted alkyl furans **57** and **58** were also synthesized. Using carbon tetrabromide (CBr_4) dissolved in dichloromethane (DCM) with triphenylphosphine and alcohol **56**, bromide **57** was synthesized in 68% yield. The corresponding chloride **58** was synthesized with triphenylphosphine neat in carbon tetrachloride (CCl_4) for a yield of 90%. (Scheme 2.15).



Scheme 2.15 - Bromo- and Chloroalkylfurans Synthesized for Stork-Danheiser Step

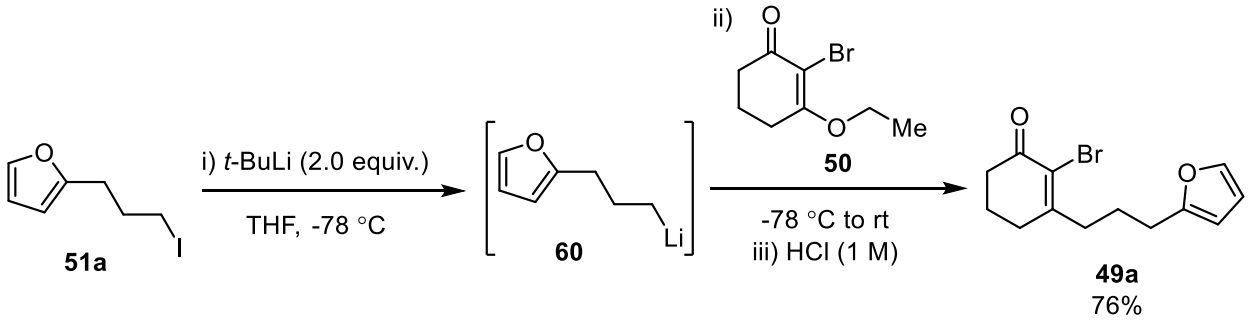
The Stork-Danheiser transposition was the key step to combine the enone and furan fragments en route to the desired starting materials.[24] The initial synthesis by Lofstrand of tethered enone **49a** relied upon formation of Grignard reagent **59** with alkyl chloride **58**.[20] Upon replication of this procedure no desired product was obtained (Scheme 2.16). After an extended attempt at

optimizing this transformation during which the main outcomes were the Grignard-Wurtz coupling product or a complex mixture it was decided that a new approach would have to be undertaken that did not use a Grignard reagent (see section **A.1.1** for some attempted optimization details).



Scheme 2.16 - Attempted Stork-Danheiser Alkylation via Grignard Reagent

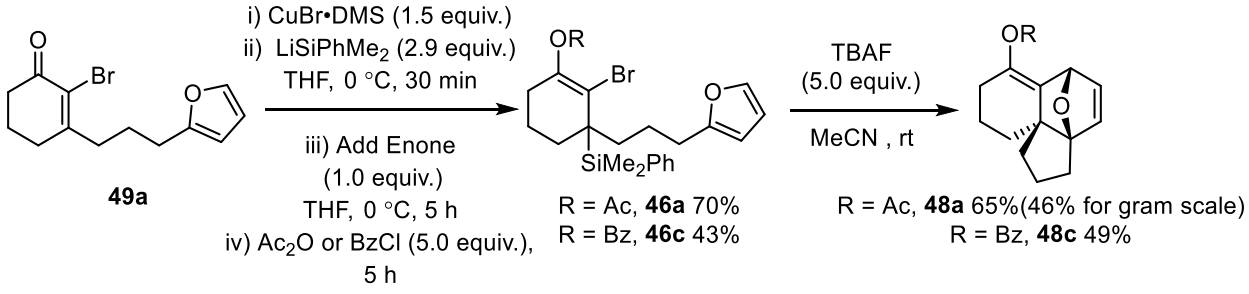
Organolithium reagents, being carbon-based nucleophiles with similar reactivity to Grignard reagents, were envisioned as a workaround to the unproductive attempts at a Stork-Danheiser reaction with Grignard reagents. Alkyl iodide **51a** was chosen as the optimal halide for this transformation due to its fast rate of lithium-halogen exchange with *t*-BuLi. Gratifyingly, when two equivalents of *t*-BuLi were used in the presence of iodide **51a** lithium-halogen exchange led to the formation of lithiated species **60** which attacked the carbonyl of enone **50.** After aqueous workup an acid catalyzed rearrangement furnished **49a** in 76% yield (Scheme 2.17).



Scheme 2.17 - Stork-Danheiser Transposition via Organolithium Reagent

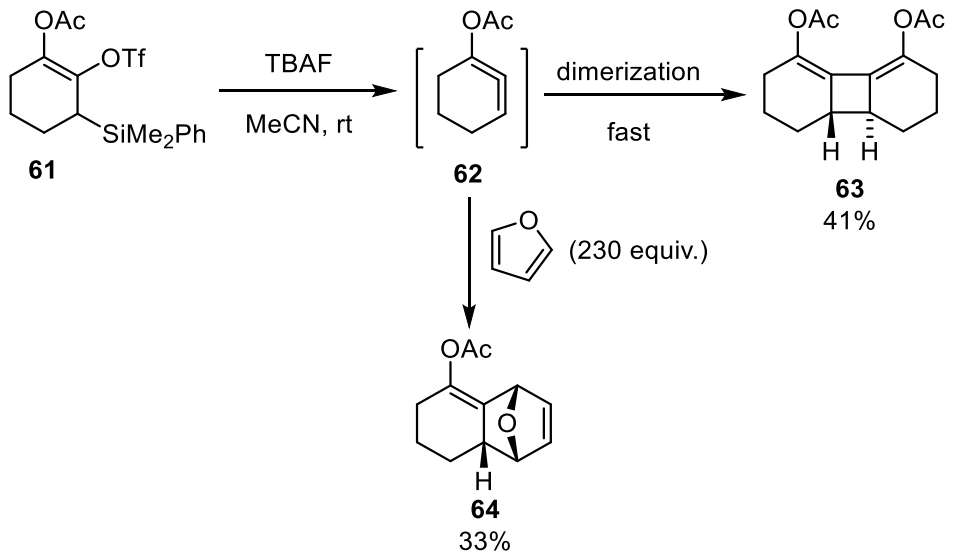
With furan-tethered enone **49a** in hand, allylic silane **46a** was synthesized via silyl anion conjugate addition. Following the work of Gilman and coworkers, a Gilman reagent was prepared from copper (I) and a previously prepared solution of phenyldimethylsilyllithium (Scheme 2.18).[27]

After initial conjugate addition of the silyl group the resulting enolate anion was trapped with acetic anhydride to provide **46a** in 70% yield. The enolate was also trapped with benzoyl chloride affording **46c** in 43% yield. This precursor provides a probe for understanding the effect of the allenyl carboxy group on the efficiency of the [4 + 2] cycloaddition reaction. The final cycloaddition reaction was accomplished with TBAF and resulted in a yield of 65% for **48a** and 49% for **48c**. The isolated yield of 65% for **48a** compared well with the yield obtained by Lofstrand of 67% and served as a validation for the rest of the results to be presented in this thesis. Additionally, a gram-scale cycloaddition was performed and resulted in a 46% yield of **48a**, a slight decrease vs the standard 100-200 mg scale. The lack of alternative regioisomers in the cycloaddition indicates that the length of the tether is an important factor in determining the viability and regiochemical outcome of the reaction. Changing the allenyl carboxy group as in example **48c** had a small negative effect on cycloaddition efficiency but did not alter the regiochemical or steriochemical outcome of the cycloaddition.



Scheme 2.18 - Silyl Anion Conjugate Addition and [4+2]-Cycloaddition

The advantages of the intramolecular methodology for trapping 1,2-cyclohexadiene is readily apparent when compared to intermolecular trapping work on similar acetoxy substituted cyclic allenes (Scheme 2.19).[20] Using one equivalent of furan in **46a** vs. 230 equivalents with silane **61**, the intramolecular reaction still proceeded with a higher yield of desired cycloadduct (65% vs 33%). Furthermore, no dimer was observed in the intramolecular reaction while the major product of the intermolecular reaction was dimer **63**. These results clearly show the superior reaction efficiency of the newly developed methodology.



Scheme 2.19 - Intermolecular Cycloaddition of Acetoxy Substituted 1,2-Cyclohexadiene

2.4.3 Initial Stereochemical Assignment of Diels-Alder Cycloadducts

For most Diels-Alder cycloadditions, two possible diastereomeric products (*endo* and *exo*) can be formed. The Alder endo rule predicts that the *endo* isomer is often favoured,[14] though typically both diastereomers are observed. Thus, it is notable that for **48a-c**, only the *endo* isomer was obtained (see previous section). The intermolecular reaction of 1,2-cyclohexadiene, generated via fluoride-mediated elimination, with furan leads to a 19:1 *endo*/*exo* ratio (see section **2.1** and scheme 2.4), and the additional constraints of a short tether in the intramolecular cases may amplify this selectivity. Garg and co-workers have performed calculations on [4+2]-cycloadditions of furan with 1,2-cyclohexadiene derivatives and have found a preference for the *endo* cycloadduct, with the structural distortion of the allene in the transition state playing a key role in *endo* selectivity.[28] With only one diastereomer in hand, it was necessary to find a clear spectral signature to confirm the *endo* assignment. Intermolecular adducts **65** and **66** demonstrate how this can be accomplished (Figure 2.4). *Endo* isomer **66** displays a distinctive upfield resonance for one cyclohexene proton, due to its position in the shielding cone of the dihydrofuran C=C bond, and this unique anisotropy is not seen in the case of *exo* adduct **65**.[21,29] This spectral feature is clearly present in the ^{1}H NMR spectra of intramolecular cycloadducts **48a** and **48c** in the form of upfield signals at ~0.5 ppm. In the absence of definitive x-ray crystallographic evidence, this observation was used for a tentative *endo* stereochemical assignment of these products.

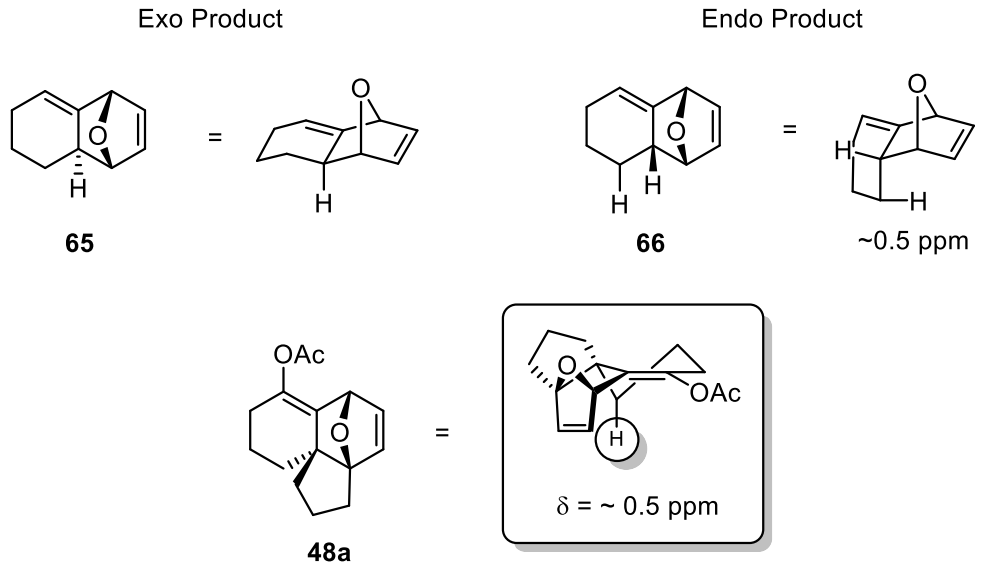
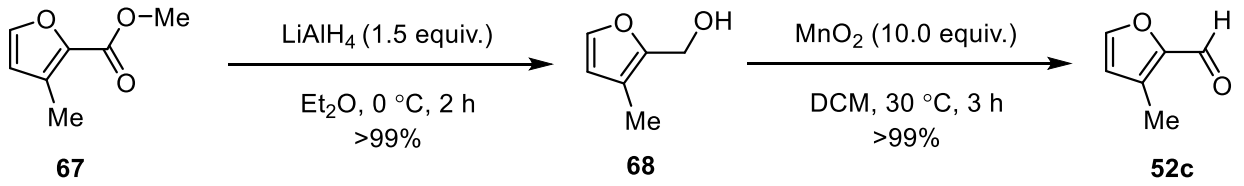


Figure 2.4 - Stereochemical Assignment due to Proton Shift from Magnetic Anisotropy

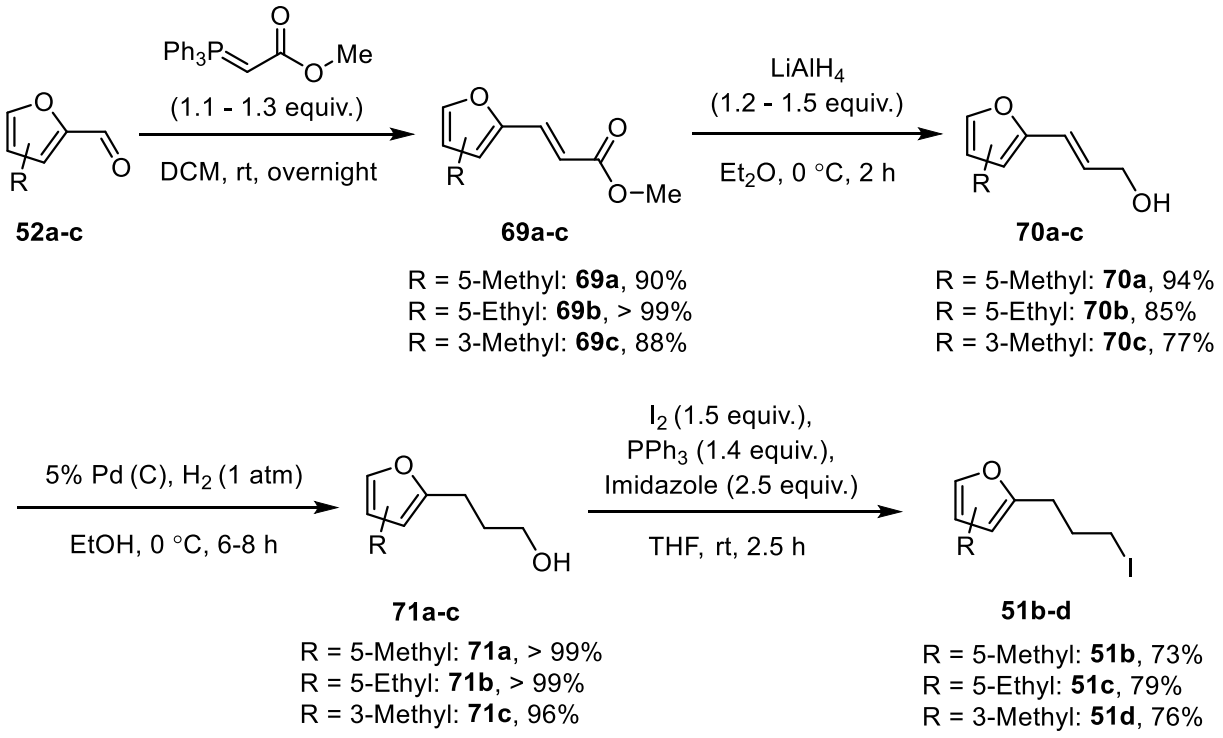
2.4.4 Synthesis of Mono-Alkylfuran Tethered Diels-Alder Cycloadducts

With validation that an intramolecular [4+2]-cycloaddition of 1,2-cyclohexadiene and pendent furan was possible the scope of this methodology was then further examined. A second round of targets with simple methyl or ethyl substitution on the various positions around the furan ring allowed a probe on the effect of substitution patterns on the efficiency of the cycloaddition reaction. As depicted in section **2.4.1**, the initial compound required for these syntheses was the corresponding furfural. While 5-methyl furfural **52a** and 5-ethyl furfural **52b** are available commercially, the synthesis of 3-methyl furfural **52c** was required. Starting from methyl 3-methyl-2-furoate **67**, reduction with LAH provided 3-methyl-furfuryl alcohol **68** in quantitative yield (Scheme 2.20). Subsequent allylic oxidation with an excess of activated manganese dioxide produced 3-methylfurfural **52c** quantitatively. Attempts at a one-step conversion of **67** directly to **51c** with diisobutylaluminium hydride (DIBALH) were low yielding and the reduction/oxidation procedure was more efficient despite the increased step count.



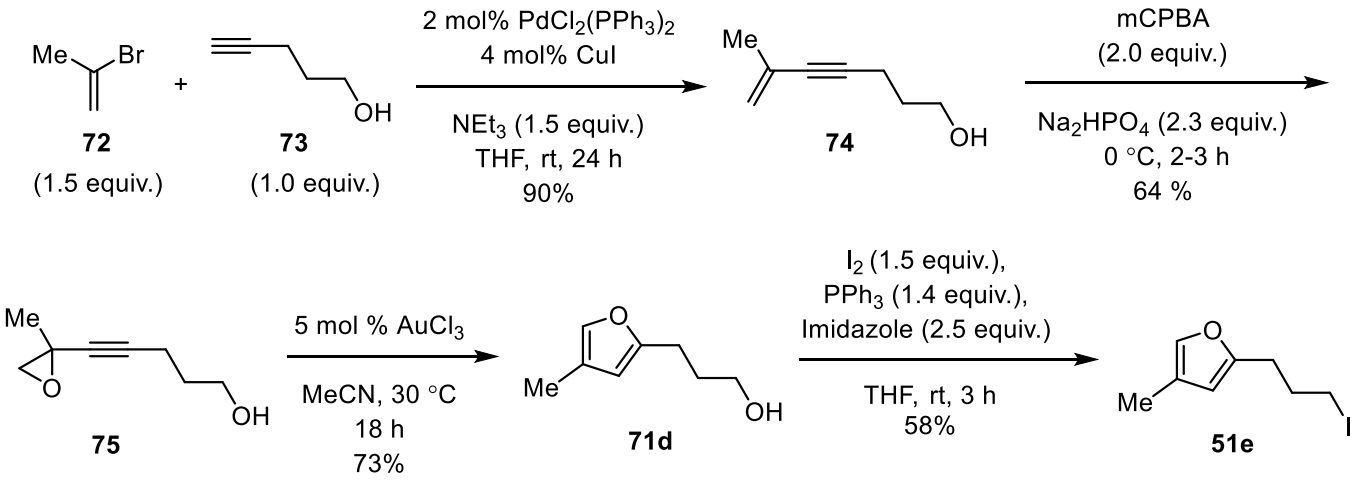
Scheme 2.20 - Synthesis of 3-Methylfurfural

The task of converting furfurals **52a-c** into the corresponding alkyl iodides **51b-d** was accomplished using a modified version of a published procedure (Scheme 2.21).[30] An initial Wittig reaction with an ester-stabilized phosphorus ylide enabled exclusive synthesis of *E* alkenes **69a-c** in excellent yields. Attempts at a hydroalumination reaction to directly convert **69a-c** into **71a-c** failed and therefore a stepwise procedure involving reduction with LAH to **70a-c** and subsequent hydrogenation with palladium on carbon (Pd/C) furnished saturated alkyl alcohols **71a-c**. An Appel reaction then converted **71a-c** into the desired iodides **51b-d**. This simple, modular, and high yielding pathway to iodides **51b-d** enabled their syntheses on the gram scale.



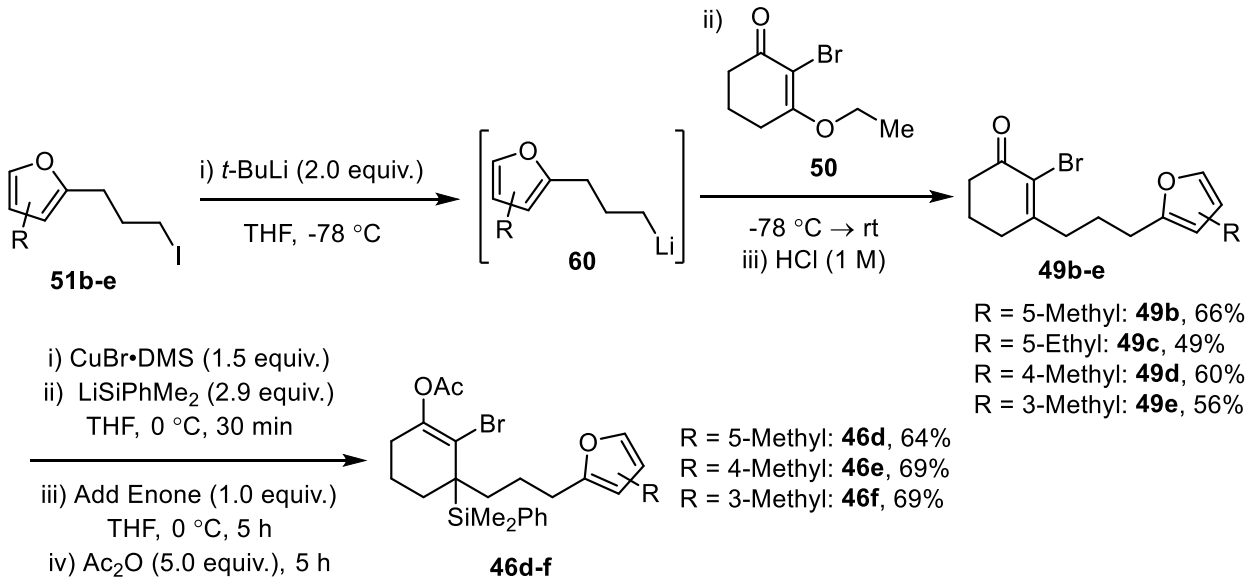
Scheme 2.21 - Synthesis of Alkyl Iodide Compounds

The routes outlined in Scheme 2.21 afforded 3- and 5-substituted furan derivatives, but an alternative approach was required for the 4-substituted example. Starting with 2-bromopropene **72** and pent-4-yne-1-ol **73** a three reaction sequence provided a way to directly accesses 2-(3-iodopropyl)-4-methylfuran **51e** (Scheme 2.22).[31] A Sonogashira coupling provided enyne **74** in 90% yield and subsequent use of *meta*-chloroperbenzoicacid (mCPBA) and disodium phosphate Na_2HPO_4) as a base resulted in the epoxidation of the 1,1-disubstituted olefin and synthesis of **75** in 64% yield. Exposing epoxide **75** to gold (III) chloride ($AuCl_3$) and mild heat initiated a rearrangement that provided furan **71d** in 73% yield which was converted to iodide **51e** via an Appel reaction in 58%.



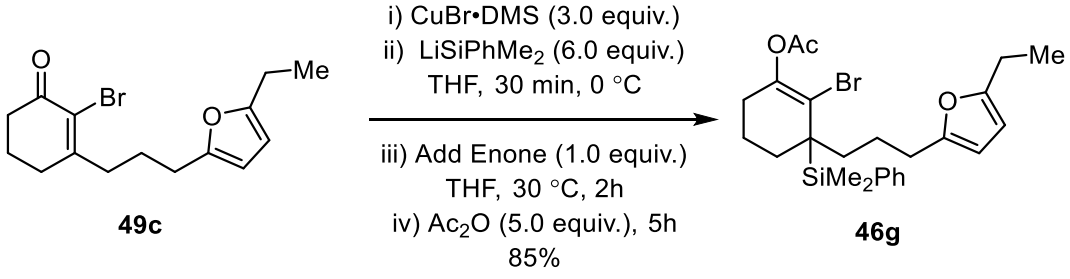
Scheme 2.22 - Synthesis of 2-(3-iodopropyl)-4-methylfuran

With alkyl iodide compounds **51b-e** synthesized, derivatives of furan with a substituent group at the 5, 4, and 3 position were available. To combine these furan-containing fragments with enone **50**, a Stork-Danheiser transposition was again employed via lithium-halogen exchange using *t*-BuLi (Scheme 2.23). The Stork-Danheiser products **49b-e** were obtained in acceptable yields ranging from 49-66% depending on the substituent position on the furan moiety. Silyl anion conjugate addition and enolate anion trapping with acetic anhydride also proceeded in good yields with the starting allylic silanes **46d-f** required or the cycloaddition obtained in yields of 64-69%.



Scheme 2.23 - Synthesis of Diels-Alder Starting Materials with Different Substitution Patterns on Pendent Furan

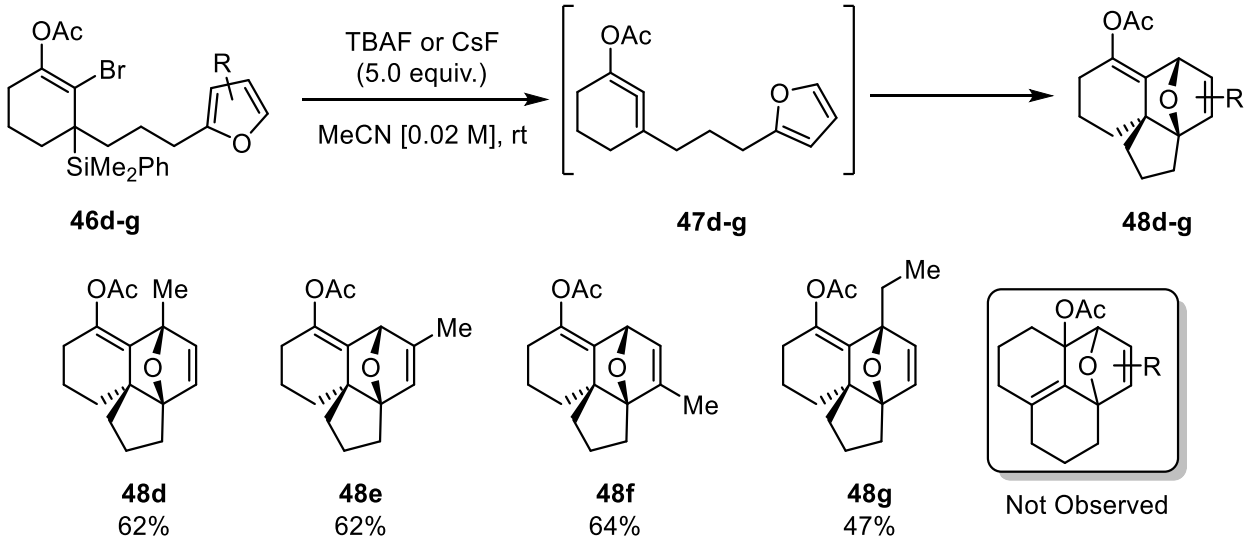
5-Ethyl substituted compound **49c** required special conditions in order to obtain product from the conjugate addition (Scheme 2.24). Standard conditions and increased equivalents of reagents resulted in starting material **49c** being isolated. Only when gentle heating was applied did the allylic silane **46g** form in a yield of 85%.



Scheme 2.24 - Conjugate Addition to 5-Ethyl Furan Compound 49c

When **46d-f** and **46g** were subjected to TBAF and CsF respectively they formed transient cyclic allenes **47d-g** which subsequently underwent the desired intramolecular [4+2]-cycloaddition reaction to give tetracyclic products **48d-g** (Scheme 2.25). As in the case of **46a-c**, all cycloadducts were obtained as single diastereomers assigned as the *endo* isomers with no *exo* diastereomers being generated. Assignment relied on the diagnostic proton at ~0.5 ppm (see

section **2.4.3**). No dimer or regioisomer resulting from reaction via the acetoxy-substituted C=C bond were observed. The position of methyl substituents on the furan moiety did not appear to influence the cycloaddition efficiency as yields between **48d-f** are all similar (62-64%). Surprisingly, changing to an ethyl group in the case of **48g** did decrease the yield slightly to 47%. With cycloadduct **48g** it was also found that using CsF as the source of fluoride anion was more efficient than TBAF as it limited acetoxy cleavage and enone protonation which was noticeable when using TBAF (see section **2.3**).



Scheme 2.25 - Intramolecular [4+2]-Cycloaddition Reactions of 1,2-Cyclohexadienes Bearing Pendent Alkyl-Susbstituted Furan Traps with Methyl and Ethyl Substituents

Although the well-established ^{1}H NMR chemical shift trends had allowed us to assign the *endo* stereochemistry to all intramolecular Diels-Alder adducts,[21,29] we wished to obtain additional compelling evidence for this configuration. Accordingly, we set out to obtain diffraction-quality crystals for several of the cycloadducts, and found that product **48f** formed suitable crystals (see section **A.1.3**).[32]As shown in Figure 2.5, the *endo* configuration was confirmed for this compound, in agreement with the NMR trends noted previously. The measured distance from the shielded proton on C12 to C5 is 2.7 Å.

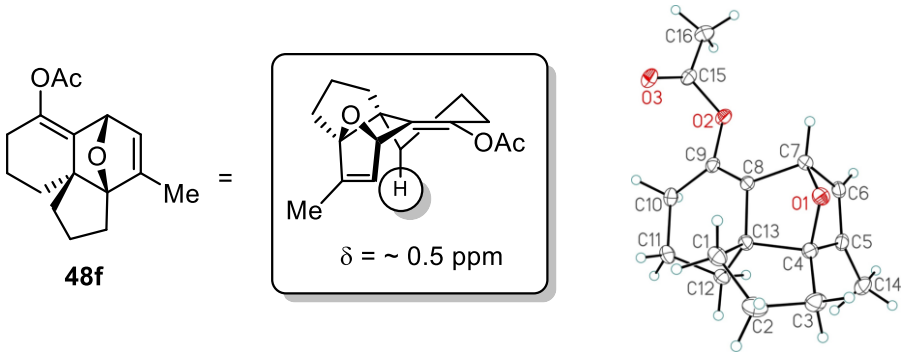
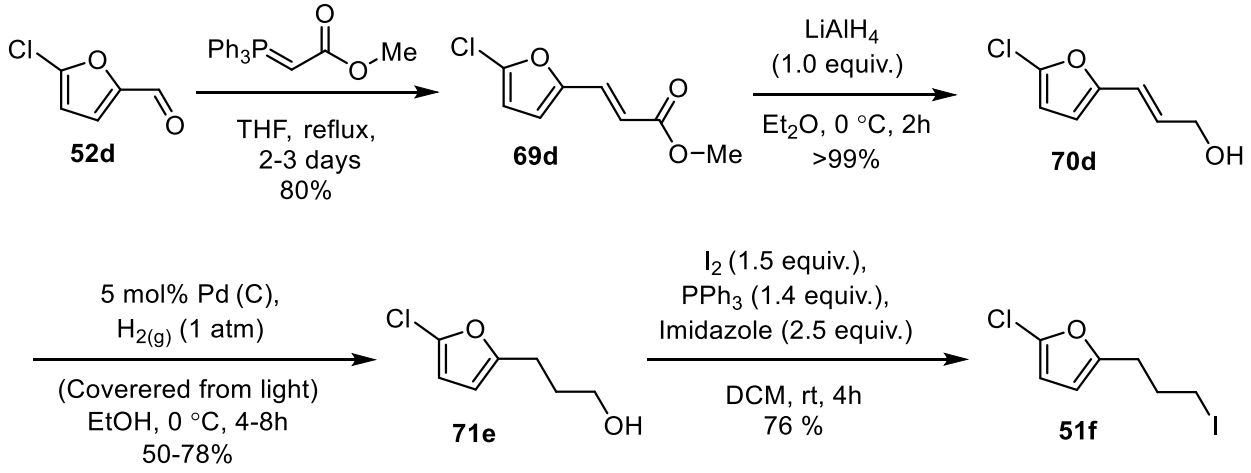


Figure 2.5 - ORTEP Structure of Compound 48f Confirming NMR Assignment of Stereochemistry

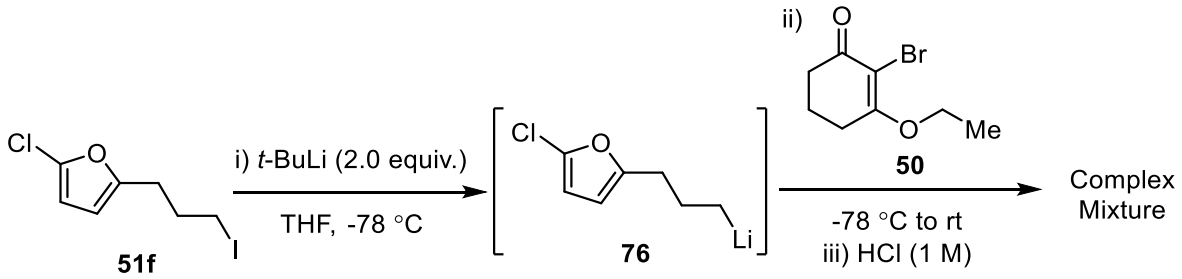
2.4.5 Attempted 5-Chlorofuran and 3,5-Dimethylfuran Derivative Synthesis

We were also interested in examining substrates with additional functionality. One starting material that interested us was furan **52d** with a chloride at the 5 position (Scheme 2.26). With this substrate we hoped to demonstrate compatibility with other functionality on the furan besides alkyl groups. Further, a halide in the final cycloadduct would serve as an important reactive handle potentially allowing for further synthetic elaboration. In order to synthesize the corresponding substrate, we first started with a Wittig reaction to produce **69d** (Scheme 2.26). After a small optimization **69d** was isolated in 80% yield. With the ester product **69d** in hand a reduction with LAH cleanly provided unsaturated alcohol **70d** in quantitative yield. Upon attempted hydrogenation of **70d** a complex mixture was obtained; it was eventually found that on exposure to light **70d** will spontaneously decompose. The exact decomposition pathway is unknown as no decomposition products could be fully characterized. To overcome this limitation the hydrogenation was performed immediately following the reduction. Furthermore, the reaction flask was covered in aluminum foil to minimize light penetration and decomposition. Under these conditions varying amounts of impure **71e** could be formed (some decomposition was unavoidable). An Appel reaction then provided iodide **51f** in 76% yield. This compound appeared to be stable on the order of days when stored in a freezer. Unfortunately, the key Stork-Danheiser step resulted in a complex mixture and this substrate could not be carried forward to the final starting material (Scheme 2.27). It is possible that there was competing lithium halogen exchange with the chloride on furan instead of the iodide, resulting in unwanted side reactions and a complex

mixture. Perhaps at a lower temperature, such as is available with the Trapp solvent mixture (4:1:1 THF:Et_2O:pentane),[33] only the desired and faster iodide-lithium exchange would take place; regrettably this idea was not tested with this compound.



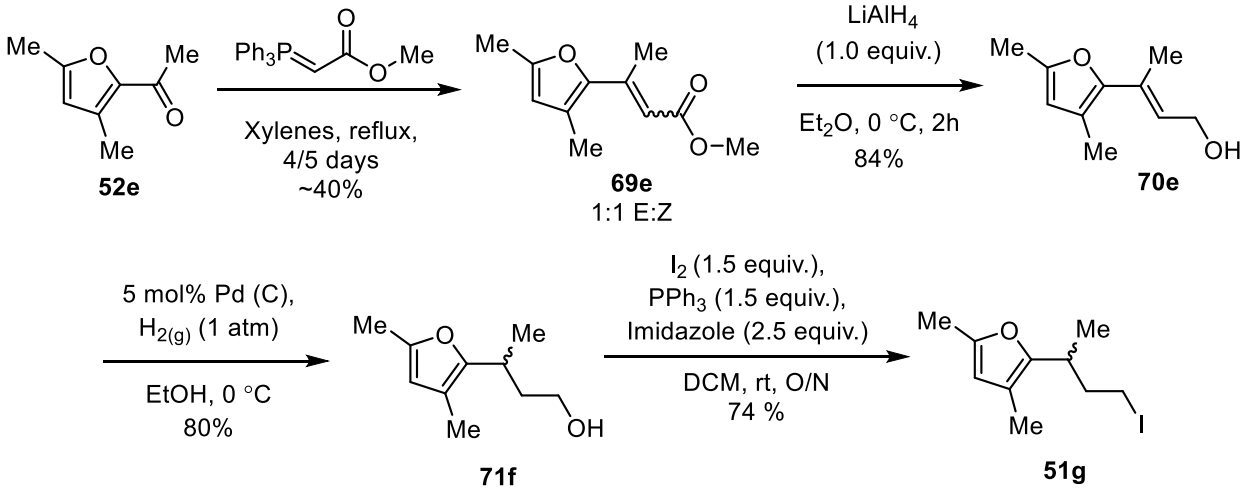
Scheme 2.26 - Synthesis of 2-(3-iodopropyl)-5-chlorofuran



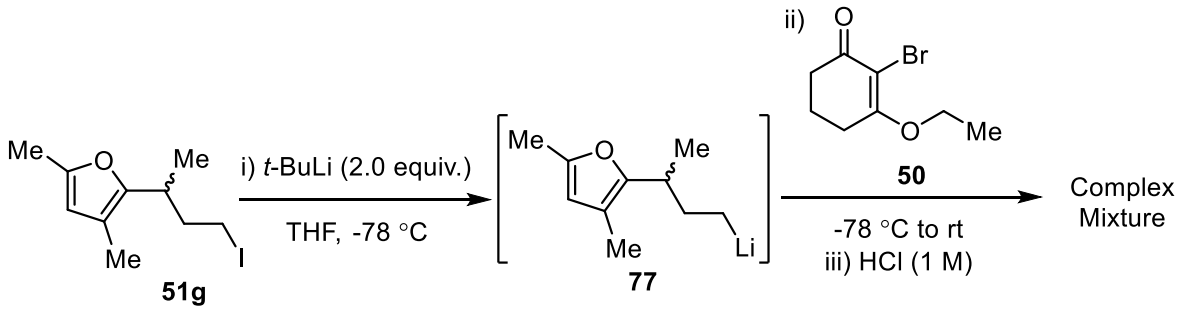
Scheme 2.27 - Attempted Stork-Danheiser Transposition with 2-(3-iodopropyl)-5-chlorofuran

Another interesting example we wanted to synthesize was a furan with multiple alkyl substituents, including one on the tether. This compound was envisioned to serve three purposes: to show the effect of multiple substitutions on the cycloaddition efficacy, to probe a Thorpe-Ingold effect, and to provide additional complexity through the introduction of a new stereocenter on the carbon tether. Instead of starting with a furfural, ketone **52e** which was previously synthesized in-house for an unrelated project, was employed as a starting material to probe these questions. The initial Wittig reaction to produce ester **69e** only produced significant amount of product, as a 1:1 mixture of *E* and *Z* isomers, when refluxing in xylenes for 4 or 5 days (Scheme 2.28).

Optimizations were attempted for both the Wittig reaction and a Horner-Emmons-Wadsworth reaction but the yield could not be improved. A LAH reduction of **69e** to **70e** and subsequent hydrogenation produced **71f** in good yields. The 1:1 mixture of *E* and *Z* isomers obtained from the Wittig reaction were not separated as there was a hydrogenation in the subsequent steps that that established a stereogenic centre at the branched carbon on the alkyl chain. Using an Appel reaction that went overnight iodide **51g** was synthesized in 74% yield. Unfortunately, when the Stork-Danheiser reaction was attempted (Scheme 2.29) a complex mixture was obtained and the forward synthesis to the desired final starting material could not be completed. Clearly the data from both the 5-chlorofuran derivative and 5,3-dimethyl derivative show that the most sensitive and limiting step in our attempted preparations is the Stork-Danheiser transposition.



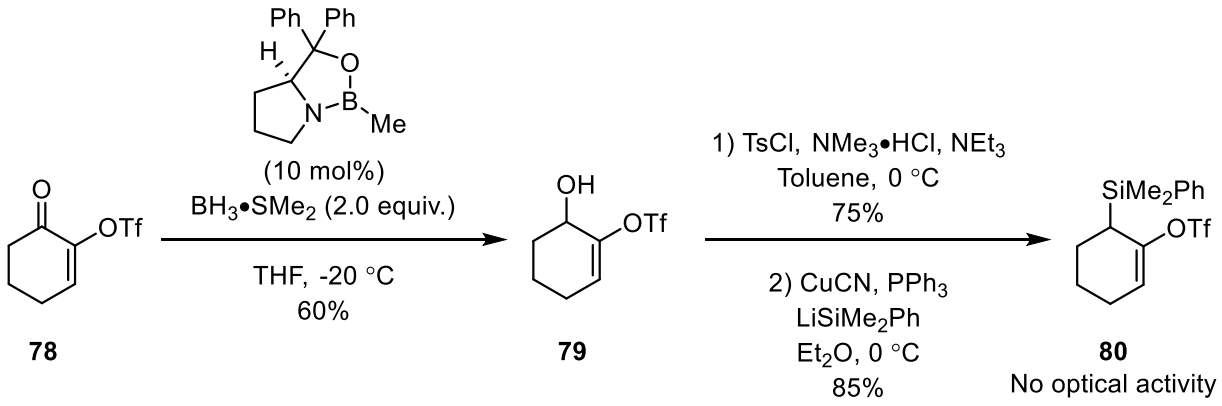
Scheme 2.28 - Synthesis of Iodide 51g



Scheme 2.29 - Attempted Stork-Danheiser Transposition with Iodide 51g

2.4.6 Synthesis of Non-Oxygenated 1,2-Cyclohexadiene Derivative

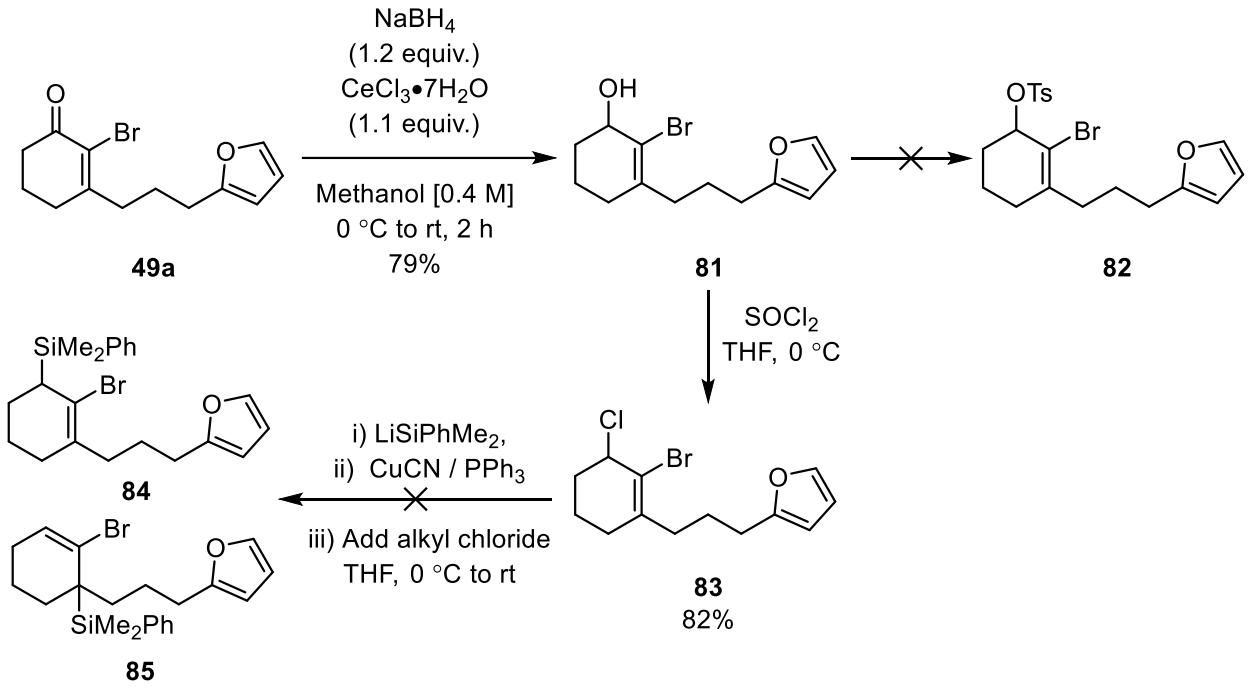
During his studies on enantiomerically enriched cyclic allenes Lofstrand devised a synthesis for an alkenyl triflate to accesses non-oxygenated cyclic allenes.[20] Lofstrand was interested in producing enantiomerically enriched alkenyl silyl triflate **80** from 2-trifluoromethanesulfonyloxycyclohexenone **78** via Corey-Bakshi-Shibata (CBS) reduction, tosylation, and displacement with a cyano-Gilman reagent (Scheme 2.30). We envisioned this synthetic route as being easily adaptable to the intramolecular intermediates from the Stork-Danheiser reaction, enabling accesses to a non-oxygenated 1,2-cyclohexadiene derivative.



Scheme 2.30 - Attempted Enantiomerically Enriched Allene Precursor Synthesis by Dr. Lofstrand

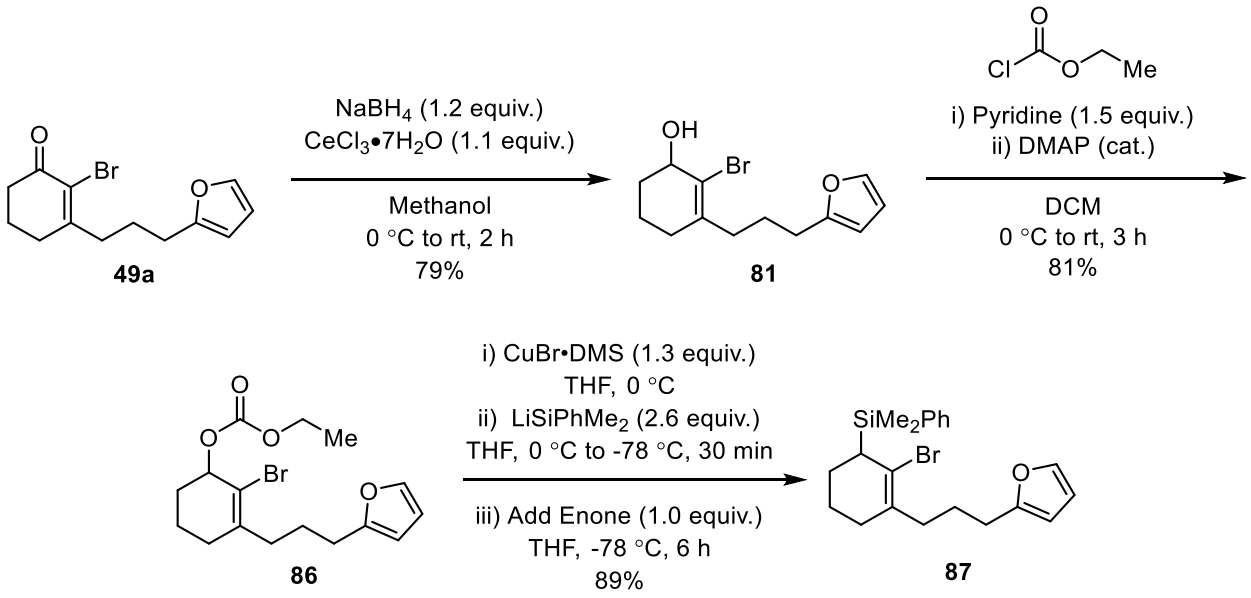
Adapting the route of Lofstrand, Stork-Danheiser product **49a** was reduced under Luche reduction conditions to accesses allylic alcohol **81** in 79% yield (Scheme 2.31). An enantiocontrolled reduction such as with CBS reagent was not performed as Lofstrand found allylic silane **80** was not formed with any enantioselectivity. Furthermore, for this study production of enantiomerically enriched substrates was not the goal here, just formation of a substrate lacking acetoxy substitution on the allene precursor; however, the prospect of an enantioenriched starting material remains a promising avenue for future plans. A variety of conditions were explored to convert alcohol **81** to tosylate **82** (see section **A.1.2**) without success. In addition to these results Constantine attempted similar tosylation conditions on a non-tethered allylic alcohol with an alkenyl bromide and did not observe any tosylate product.[34] Recanvasing

the work of Lofstrand it was found that if compound **78** had its triflate replaced with a bromide the tosylation would not work. It would appear the alkenyl leaving group has a strong modulating effect on the nucleophilic reactivity of the neighboring allylic alcohol. One attempted workaround for the failure of the tosylation was to try a displacement reaction with a simple halide leaving group (Scheme 2.31). To this end chloride **83** was synthesized and subjected to the cyano-Gillman conditions. Unfortunately, neither S_N2 product **84** nor S_N2' product **85** was observed in the corresponding reaction mixture.



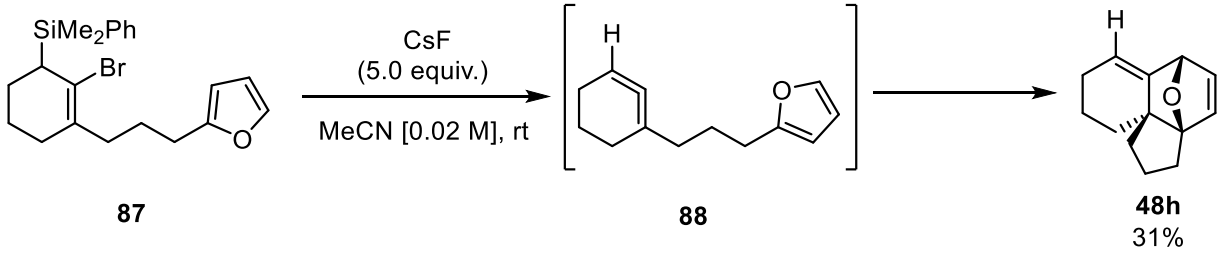
Scheme 2.31 - Attempted Tosylation and Synthesis of Allylic Chloride and Attempted Displacement by Cyano-Gillman Reagent

A paper from Sawamura and co-workers on the syntheses of silanes from allylic carbonates revealed an alternative way to generate the desired allylic silane.[35] Using a conceptually similar approach to Sawamura allylic alcohol **81** was reacted with ethyl chloroformate to produce allylic carbonate **86** in 81% yield (Scheme 2.32). Carbonate **86** was then cleanly converted to allylic silane **87** in 89% yield. Interestingly the product obtained arises only from an S_N2 displacement of the carbonate, with no evidence for competing S_N2' reactivity.



Scheme 2.32 - Synthesis of Allylic Silane via Carbonate Intermediate

The final cycloaddition reaction of allylic silane **87** resulted in the formation of [4+2] cycloadduct **48h** in 31% yield as the *endo* isomer (Scheme 2.33). Interestingly the yield is much lower than when an acetoxy group is attached to the allene. Assuming normal electron-demand Diels-Alder reactivity, replacement of the mildly electron-releasing acetoxy moiety with a hydrogen atom would be expected to improve reactivity via reduction of the HOMO-LUMO gap, although it is difficult to generalize with only one non-oxygenated example. In considering other possible explanations for the reduced efficiency of the Diels-Alder reaction to product **48h**, an argument based on accessibility of the allene moiety may provide more valuable insight. During work on the Moore cyclization (see chapter **1**, section **1.5.10**) it was noted that a high degree of substitution around the allene was vital in order to prevent dimerization and oligomerization of the allene moiety.[36] It may be the case with allene **88** that a lack of steric bulk around the allene, which would be provided by acetoxy substitution, is enabling closer approach and therefore corresponding oligomerization reactions to take over. While no dimeric product was seen in the crude NMR spectra or could be isolated from the reaction mixture of **48h**, that does not rule out the possible formation of dimers or higher oligomers that may have resisted isolation or characterization due to low solubility and/or complex spectral properties.

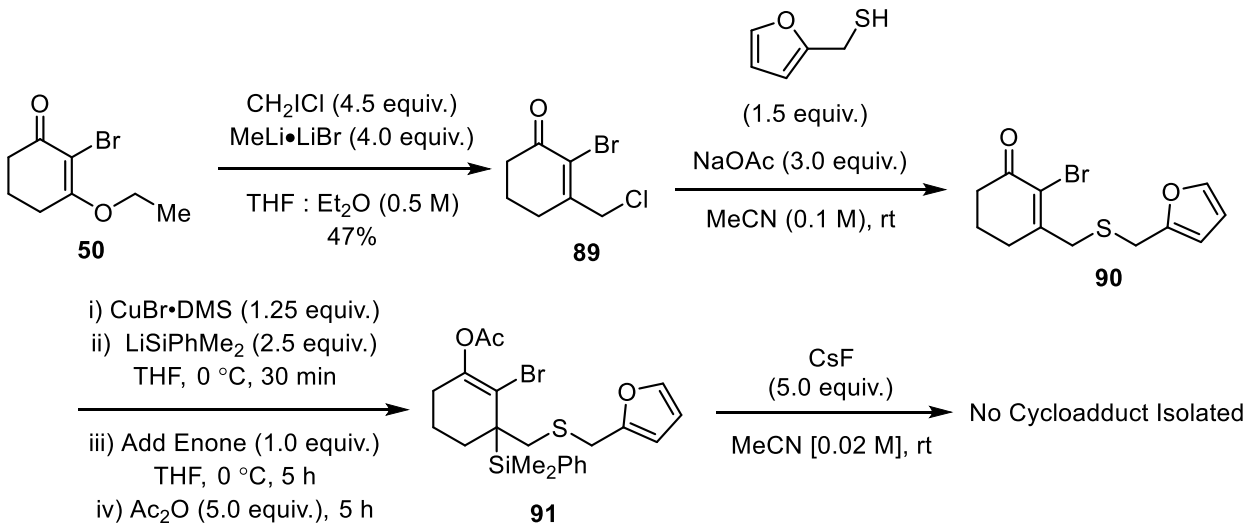


Scheme 2.33 - [4+2]-Cycloaddition of Allylic Silane 87

2.4.7 Synthesis of Substrates with Heteroatom Containing Tethers

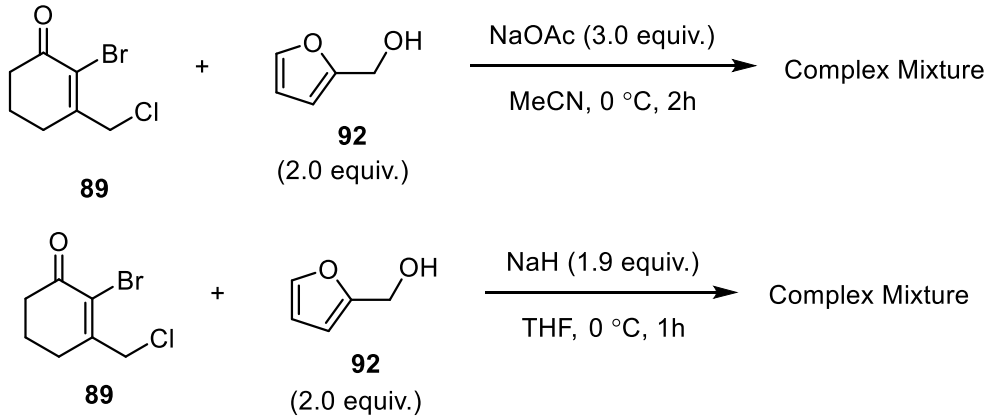
Compounds containing heteroatoms in the tether were also of great interest during the examination of the scope of this new methodology. The inclusion of oxygen, nitrogen, and sulfur atoms would increase the complexity of the polycyclic products obtained and provide further probing of the effects of modifying the tether on reaction efficiency. In addition, successful intramolecular trapping of a substrate with a nitrogen atom in the tether would result in an azacyclic product, with potential relevance to the preparation of natural products or other bioactive targets. Oxygen in the tether was also valuable way to further probe the effect of a bond angle change in the tether.

The first heteroatom targeted for inclusion in the tether was sulfur.[37] Starting with enone **50** a Stork-Danheiser alkylation with chloroiodomethane enabled the synthesis of chloro-methyl substituted enone **89** (Scheme 2.34). Upon reaction of furfuryl mercaptan with **89** in the presence of sodium acetate as a base, enone **90** with a sulfur atom in the tether was synthesized in unreported yield. Using the standard silyl anion conjugate addition procedure, the cycloaddition precursor, silane **91** could be generated unreported yield. Upon exposure of starting material **91** to CsF two unidentified products were produced; however, neither of these were the desired cycloadduct and they were not characterized.



Scheme 2.34 - Attempted Synthesis of Sulfur Containing Cycloadduct by Dr. Lofstrand

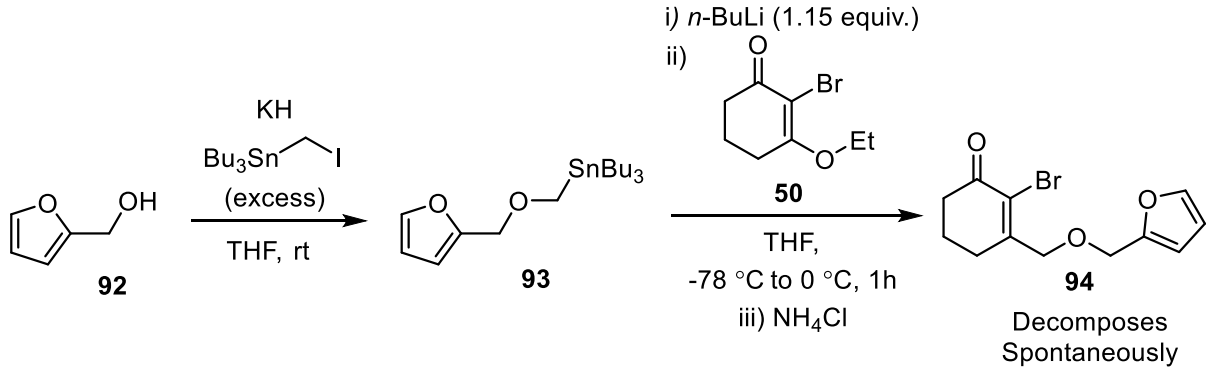
After the failure of the sulfur containing derivative the next target was an oxygen containing example. Using sodium acetate as a base, as with the previous example, furfuryl alcohol **92** was reacted with enone **89** but a complex mixture was obtained and no evidence of the desired product was seen (Scheme 2.35). Changing the base employed to sodium hydride also resulted in a complex mixture and after attempts at troubleshooting this reaction were unsuccessful an alternative way to assemble the substrate had to be devised.



Scheme 2.35 - Attempted Synthesis of Oxygen Containing Tether

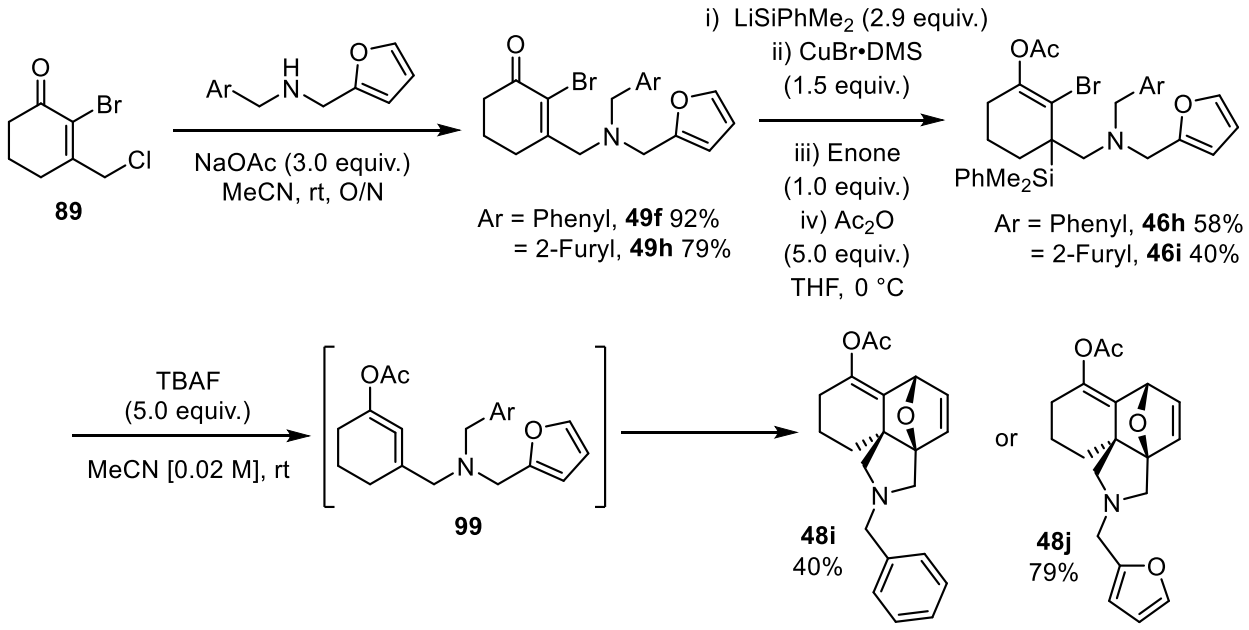
Eventually a workaround was discovered by Lofstrand that enabled the synthesis of oxygen containing tethered enone **94** (Scheme 2.36).[37] This strategy involved the formation of stannane

93 followed by lithium-tin exchange and subsequent Stork-Danheiser transposition onto enone **50**. While **94** was formed under these conditions the yield was not quantified as it was found that it quickly and spontaneously decomposed. This apparent spontaneous decomposition may help explain the complex mixtures obtained when attempting to make **94** by nucleophilic substitution; it is possible the product was being formed and decomposing.



Scheme 2.36 - Synthesis of Oxygen Containing Tether via Stannane 93 by Dr. Lofstrand

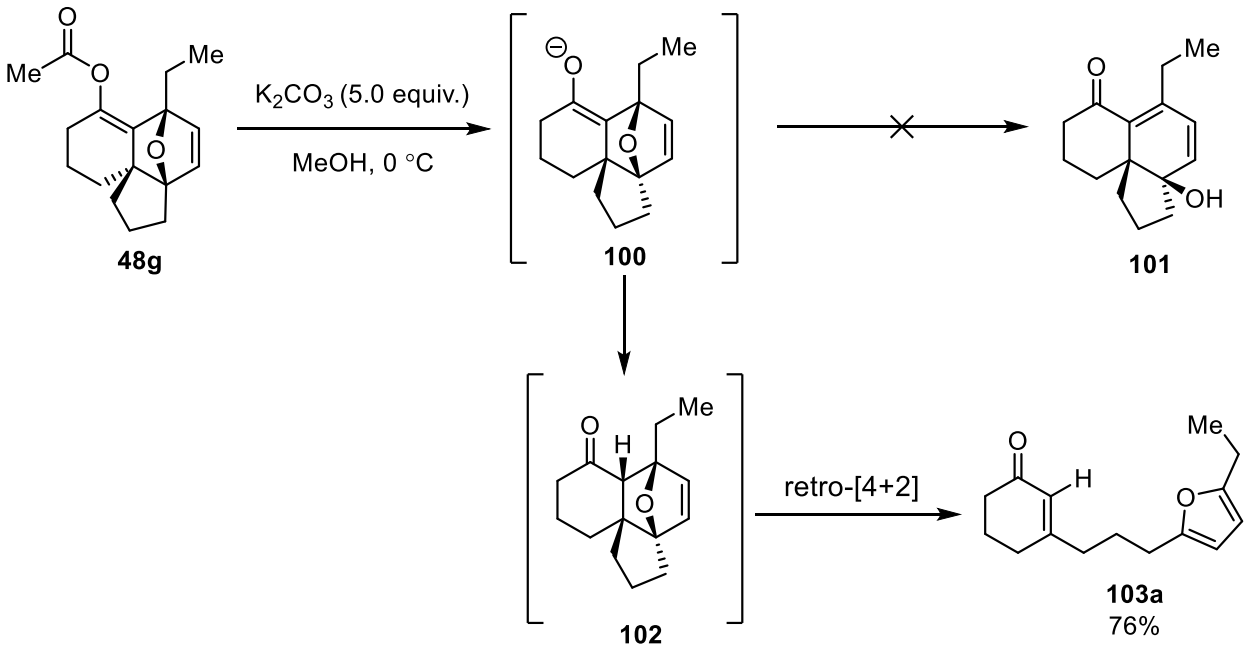
With the failure of both sulfur and oxygen containing tethers we were pessimistic about the nitrogen containing compounds, but thankfully we still decided to synthesize them. Using different secondary amines and enone **89** under basic conditions with sodium acetate compounds **49f** and **49h** with a nitrogen atom in the tether were synthesized (Scheme 2.37). Silyl anion conjugate addition then provided the starting materials for the cycloaddition, **46h** and **46i**. Gratifyingly, both nitrogen containing starting materials underwent the [4+2]-cycloaddition and generated cycloadducts **48i** and **48j** in yields of 40% and 79% respectively with complete regio and diastereoselectivity. Cycloadduct **48j** with two furyl groups provided the highest yield, which is logical as there is a much higher probability that the reactive allene will encounter a diene trap in intermediate **99**.



Scheme 2.37 - Synthesis of Nitrogen Containing Polycyclic Compounds by Dr. Lofstrand

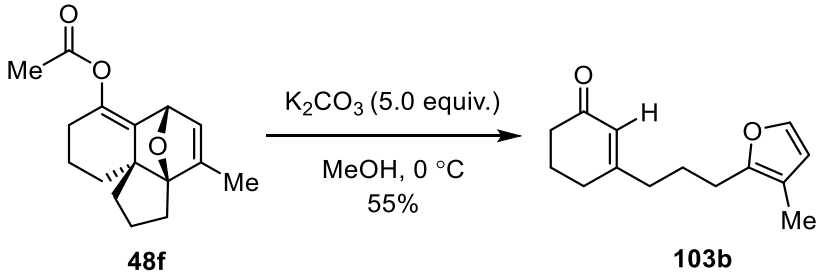
2.4.8 Unexpected Retro Diels-Alder Reaction

The Diels-Alder cycloadducts produced via our new methodology have a masked enolate moiety adjacent to a bridged dihydrofuran C–O bond. This ether bridge is part of a strained tetracyclic core, and we hoped to open it via an elimination process. Looking back at the literature regarding IMDAF (see section **2.2**) there was a precedent for being able to open the ether bridge of the generated cycloadducts.[15-16,18] We hoped to apply this to our cycloadducts and generate a tertiary alcohol (Scheme 2.38). When we subjected cycloadduct **48g** to treatment with potassium carbonate in methanol we saw clean formation of furan tethered cyclohexanone **103a** in 76% yield, not the desired alcohol **101**. This unexpected result appeared to come from a retro-Diels-Alder reaction of **102**, which could arise from protonation of intermediate **100**. We cannot at this time rule out a cycloreversion directly from **100**.



Scheme 2.38 - Attempted Opening of Ether Bridge and Unexpected Retro Diels-Alder Reaction

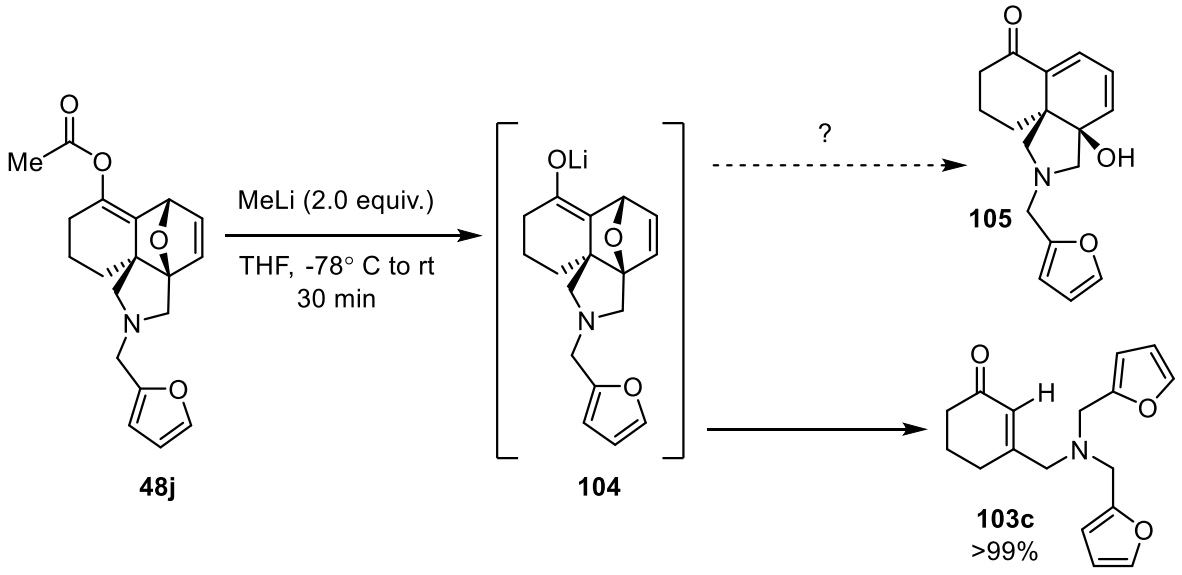
We wished to determine whether this cycloreversion pathway was general, or unique to **48g**. To test this, we subjected cycloadduct **48f** to the same conditions and observed the formation of cyclohexenone **103b** in 55% yield (Scheme 2.39). While a lower yield of product was found in this case it still showed that our tetracyclic cycloadducts appeared to be facile substrates for this retro [4+2] reaction.



Scheme 2.39 - Retro-Diels-Alder Reaction of Enol Acetate Cleavage Product

As we hypothesized that the retro-Diels-Alder reaction was proceeding through a protonated intermediate after enol acetate cleavage we wondered if we could observe the desired ether bridge opening under anhydrous conditions. Therefore, we subjected cycloadduct **48j** to

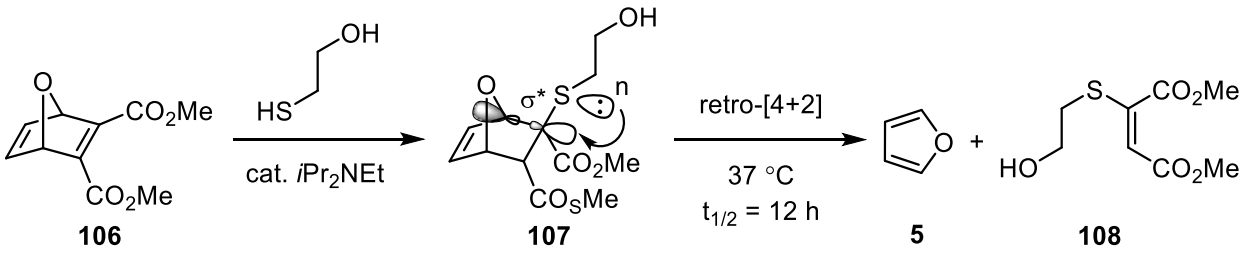
MeLi in THF, hoping to generate intermediate **104** under aprotic conditions, which would permit ether opening **105** as there would be no proton source available to protonate the lithium enolate. Instead we observed quantitative conversion to **103c**, presumably via protonation upon aqueous workup and rapid cycloreversion (Scheme 2.40). To rule out a cycloreversion directly from **104** it would be worthwhile to attempt to intercept the enolate oxygen with an electrophile such as a silyl chloride. Unfortunately, this idea was not tested but presents an avenue for future investigations.



Scheme 2.40 - Retro-Diels-Alder Reaction Under Anhydrous Conditions

While we did not obtain our desired outcome with these reactions the fact that the cycloreversion is incredibly facile does provide valuable insight into our methodology. The generality suggests a Diels-Alder equilibrium that strongly favors the diene and dienophile reactants over the cycloadduct. Indeed, if would appear that the strain inherent to the generated 1,2-cyclohexadiene is critical in forcing the [4+2] reaction to completion. If the allene moiety was not present and tethered enones **103a-c** were simply heated in a thermal Diels-Alder reaction the equilibrium would be expected to lie entirely on the side of reactants, with no IMDAF products formed. There is also literature precedent for the cycloreversion of furan cycloadducts such as we observed. Houk and co-workers studied the concerted cycloreversion of oxanorbornadienes to furan under mild conditions (Scheme 2.41).[38] With oxanorbornadiene **106** the driving force for cycloreversion appeared to be a n to σ* hyperconjugation of the lone pair on sulfur to the anti-

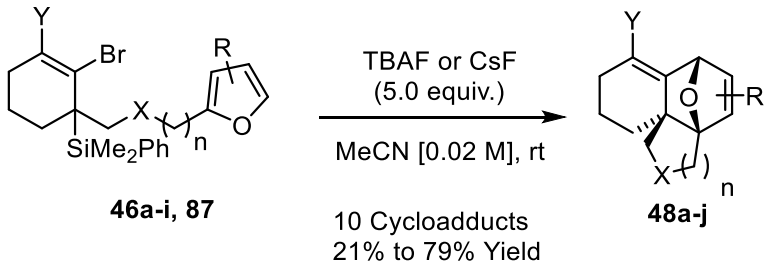
bonding orbital of a carbon-carbon bond, resulting in the synthesis of furan and thiomaleate **108**. In our case the strain present in the tetracyclic product may lower the activation barrier for cycloreversion sufficiently that it proceeds even at room temperature. Additionally, the generation of an aromatic furan moiety may be a driving force for this reaction.



Scheme 2.41 - Retro-Diels-Alder Reaction of Oxanorborenes

2.5 Conclusion

In conclusion we have developed the first intramolecular Diels-Alder reaction of 1,2-cyclohexadiene and pendent furans.[39] Our general substrates and modular synthesis approach have enabled the synthesis of 10 cycloadducts that range in yield from 21% to 79%. Importantly all our cycloadducts were produced as single regioisomers and we only observe the *endo* diastereomer (Scheme 2.42) which we confirmed by X-ray crystallography. These tetracyclic products were produced under mild conditions and in a single step from their starting materials. We have also demonstrated the remarkable improvement to atom economy offered by an intramolecular vs. intermolecular approach to reactions with 1,2-cyclohexadiene. We have gained valuable insight into the factors that affect the efficiency of this cycloaddition such as tether length and relative equivalents of tethered trapping moieties. Importantly we have shown the requirement for a high energy allene species in order to drive the Diels-Alder equilibrium towards cycloadducts. Overall this new methodology represents a seminal study in the area of intramolecular reactions of cyclic allenes.



Scheme 2.42 - Strain-Activated Trapping Reactions of 1,2-Cyclohexadiene: Intramolecular Capture by Pendent Furans

2.6 Experimental Data

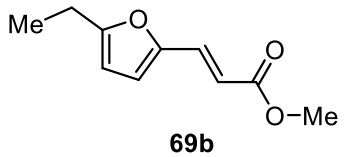
2.6.1 General Information

Unless otherwise noted, all reactions were performed in glassware that was dried in an oven (200 °C) overnight or flame-dried immediately prior to use under a positive nitrogen atmosphere. Reagents were transferred with oven-dried syringes or cannulas. All solvents, unless otherwise noted, were dried using either a solvent purification system or by distillation. MeCN, NEt_3, and DCM were distilled from calcium hydride; Et_2O, and THF were distilled from sodium/benzophenone and toluene was distilled from sodium metal. Reagents were used as purchased from the Sigma-Aldrich, Oakwood, and Alfa Aesar corporation unless otherwise noted. Glass plates with 0.25 mm Kieselgel 60 F254 Silica (Merck) were used for all thin layer chromatography; column chromatography was performed with 230-400 mesh silica gel (Silicycle). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz, 500 MHz or 700 MHz and coupling constants (*J*) are reported in Hertz (Hz). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100MHz, 125 MHz or 175 MHz. All chemical shifts are referenced to residual solvent peaks ($CDCl_3$: s, 7.26 ppm, ^{1}H; t, 77.06 ppm, ^{13}C) as internal standards and reported in δ (ppm). Standard notation is used to describe all observed ^{1}H NMR signal multiplicity: broad (br), apparent (app), multiplet (m), singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), etc. Infrared spectra were measured with a Mattson Galaxy Series FT-IR 3000 spectrophotometer. HRMS data (EI technique) were recorded using a Kratos MS50 instrument and HRMS (ESI/APPI technique) were recorded using an Agilent 6220 oaTOF instrument.

2.6.2 Physical Data

Compounds **50**, **51a-b**, **52c**, **54**, **56-58**, **63-64**, **68**, **69a**, **69c**, **70c** and **71a** are known literature compounds whose spectral data matches those reported in prior publications.[20, 40-49]

Methyl (*E*)-3-(5-ethylfuran-2-yl)acrylate (69b)



69b

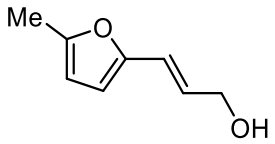
To a solution of methyl (triphenylphosphoranylidene) acetate (1.2 equiv., 3.23 g, 9.67 mmol) in DCM [0.4 M], 5-ethylfurfural (1.0 equiv., 1.00 g, 8.06 mmol) was added and the reaction was stirred at rt until complete as observed by TLC. After evaporation of the solvent, Et_2O (30 mL) was added and the solution was filtered to separate off triphenyl phosphine oxide (multiple filtrations may be required to remove most triphenyl phosphine oxide); after passing through a silica plug (1:1 hexane /Et_2O) the virtually pure product methyl (*E*)-3-(5-ethylfuran-2-yl)acrylate (**69b**) (1.45 g, >99%) was obtained as a yellow oil.

R_f 0.76 (1:2 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 15.6 Hz, 1H), 6.48 (d, *J* = 4 Hz, 1H), 6.19 (d, *J* = 15.6 Hz, 1H), 6.04 (app d, *J* = 3.6 Hz, 1H), 3.74 (s, 3H), 2.65 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 161.1, 149.4, 131.4, 116.4, 113.6, 107.3, 51.6, 21.7, 11.9; IR (cast film, cm^{-1}) 3120, 2977, 1717, 1639, 1020; HRMS (EI) calcd for $C_{10}H_{12}O_2[M]^+$ 180.0786, found 180.0783.

General Procedure for Reduction Reaction

A suspension of LAH (1.2 equiv.) in Et_2O was cooled to 0 °C and a solution of α, β-unsaturated ester (1.0 equiv.) in Et_2O was added dropwise. After addition, the flask was stirred at 0 °C for one hour and then warmed to room temperature with stirring continued until the reaction was complete as observed by TLC. The reaction was quenched at 0 °C by careful dropwise addition of H_2O. A saturated solution of Rochelle salt was added and upon formation of two clear layers the aqueous phase was extracted with Et_2O (3 x 30mL). The combined organic phases were washed with $NaHCO_3$ (sat), H_2O, brine, and dried with $MgSO_4$. After evaporation of the solvent, the crude mixture was subjected to column chromatography to afford the pure product.

(*E*)-3-(5-methylfuran-2-yl)prop-2-en-1-ol (70a)

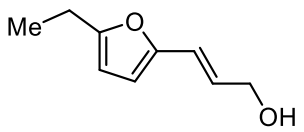


70a

Using $LiAlH_4$ (0.400 g, 10.5 mmol) and methyl (*E*)-3-(5-methylfuran-2-yl)acrylate (**69a**)[40] (1.45 g, 8.73 mmol) furnished (E)-3-(5-methylfuran-2-yl)prop-2-en-1-ol (**70a**) (1.3 g, 94%) as a yellow oil after column chromatography with 1:4 EtOAc/hexane.

R_f 0.33 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (d, J = 15.6 Hz, 1H), 6.23 (dt, J = 16 Hz, 5.6 Hz, 1H), 6.12 (d, J = 3.2 Hz, 1H), 5.95 (d, J = 3.2 Hz, 1H), 4.27 (d, J = 5.6 Hz, 2H), 2.30 (s, 3H), 1.43 (br s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 150.8, 125.5, 119.7, 109.3, 107.4, 63.5, 13.7; IR (cast film, cm^{-1}) 3341, 3015, 2923, 1535; HRMS (EI) calcd for $C_8H_{10}O_2[M]^+$ 138.0681, found 138.0684.

(*E*)-3-(5-ethylfuran-2-yl)prop-2-en-1-ol (70b)



70b

Using $LiAlH_4$ (0.40g, 10.4 mmol) and methyl (*E*)-3-(5-ethylfuran-2-yl)acrylate (**69b**) (1.25 g, 6.96 mmol) furnished (*E*)-3-(5-ethyllfuran-2-yl)prop-2-en-1-ol (**70b**) (0.90 g, 85%) as a clear oil after column chromatography with 1:4 EtOAc/hexane.

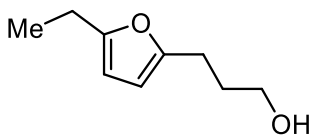
Note: always obtained small amount of 3-(5-ethylfuran-2-yl)propan-1-ol; from hydroalumination side reaction.

R_f 0.49 (1:2 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.39 (app dt, *J* = 15.7 Hz, 1.47 Hz, 1H), 6.22 (dt, *J* = 15.8 Hz, 5.8 Hz, 1H), 6.14 (d, *J* = 3.5 Hz, 1H), 5.96 (app dt, *J* = 3.0 Hz, 1.0 Hz, 1H), 4.29 (app dd, *J* = 6 Hz, 1.5 Hz, 2H), 2.66 (q, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.5Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 150.7, 125.5, 119.8, 109.1, 105.8, 63.5, 21.5, 12.2; IR (cast film, cm^{-1}) 3356, 2973, 2973, 1661; HRMS (EI) calcd for $C_9H_{12}O_2[M]^+$ 152.0837, found 152.0836.

General Procedure for Hydrogenation Reaction

A suspension of 5% Pd/C (5.0 mol%) in EtOH was cooled to 0 °C and a solution of the allylic alcohol (1.0 equiv.) in EtOH was added. The nitrogen inside the flask was evacuated and replaced with hydrogen (1 atm.). The mixture was stirred at 0 °C until the reaction was complete as observed by TLC. The mixture was then passed through a Celite plug and flushed with EtOH. After evaporation of the solvent, the crude mixture was subjected to column chromatography to afford the pure product.

3-(5-Ethylfuran-2-yl)propan-1-ol (71b)

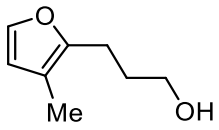


71b

Using 5% Pd/C (24 mg, 0.22 mmol) and (*E*)-3-(3-ethylfuran-2-yl)prop-2-en-1-ol (**70b**) (0.67 g, 4.4 mmol) furnished 3-(3-ethylfuran-2-yl)propan-1-ol (**71b**) (0.70 g, 99%) as a yellow oil after column chromatography with 1:4 EtOAc/hexane.

R_f 0.37 (1:2 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (d, J = 3 Hz, 1H), 5.85 (d, J = 3 Hz, 1H), 3.70 (q, J = 6 Hz, 2H), 2.68 (t, J = 7.5 Hz, 2H), 2.60 (q, J = 7.5 Hz, 2H), 1.89 (quint, J = 6.5 Hz, 2H), 1.38 (app t, J = 5.5 Hz, 1H), 1.21 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 153.6, 105.4, 104.3, 62.3, 31.2, 24.5, 21.4, 12.3; IR (cast film, cm^{-1}) 3340, 3105, 2971, 2939, 1567, 1058; HRMS (EI) calcd for $C_9H_{14}O_2[M]^+$ 154.0994, found 154.0991.

3-(3-Methylfuran-2-yl)propan-1-ol (71c)



71c

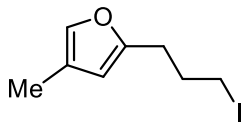
Using 5% Pd/C (17 mg, 0.16 mmol) and (*E*)-3-(3-methylfuran-2-yl)prop-2-en-1-ol (**70c**)[41] (0.43 g, 3.1 mmol) furnished 3-(3-methylfuran-2-yl)propan-1-ol (**71c**) (0.42 g, 96%) as a yellow oil after column chromatography with 1:4 EtOAc/hexane.

R_f 0.20 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 1.2 Hz, 1H), 6.16 (d, *J* = 1.2 Hz, 1H), 3.64 (app q, *J* = 6 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 1H), 1.97 (s, 3H), 1.86 (quint, *J* = 6.8 Hz, 2H), 1.58 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 139.9, 114.1, 112.8, 62.2, 31.3, 22.2, 9.8; IR (cast film, cm^{-1}) 3339, 2972, 2873, 1511, 1062; HRMS (EI) calcd for $C_8H_{12}O_2[M]^+$ 140.0837, found 140.0834.

General Procedure for Appel Reaction

Iodine (1.5 equiv.) was added to a solution of triphenylphosphine (1.5 equiv.) and imidazole (2.5 equiv.) dissolved in THF [0.4 M] at -20°C. A solution of the saturated alcohol (1.0 equiv.) in THF (2.0-3.0 mL) was added over 2-3 min and the reaction stirred for 30 min before warming to rt. The solution was further stirred until the reaction was complete as determined by TLC. $NaHCO_3$ (sat) (30 mL) was added and the resulting precipitates removed by filtration. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with 10% Na_2SO_3, H_2O, brine, and dried with $MgSO_4$. Evaporation of the solvent gave a crude mixture which was purified by column chromatography.

2-(3-Iodopropyl)-4-methylfuran (51e)

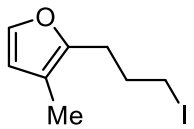


51e

Using PPh_3 (0.780 g, 2.85 mmol), imidazole (0.300 g, 4.38 mmol), iodine (0.720 g, 2.85 mmol), and 3-(4-methylfuran-2-yl)propan-1-ol (**71d**) (0.310 g, 2.19 mmol) furnished 2-(3-iodopropyl)-4-methylfuran (**51e**) (0.32 g, 58%) as a yellow oil after column chromatography with 1:4 EtOAc/hexane.

R_f 0.88 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (app t, J = 1.2 Hz, 1H), 5.91 (s, 1H), 3.19 (t, J = 6.8 Hz, 2H), 2.70 (t, J = 7.2 Hz, 2H), 2.12 (quint, J = 6.8 Hz, 2H), 1.98 (d, J = 1.2 Hz, 3H).

2-(3-Iodopropyl)-3-methylfuran (51d)



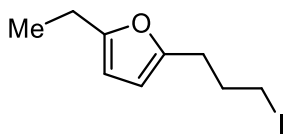
51d

Using PPh_3 (1.02 g, 3.90 mmol), imidazole (0.408 g, 6.00 mmol), iodine (0.980 g, 3.90 mmol), and 3-(3-methylfuran-2-yl)propan-1-ol (**71c**) (0.421 g, 3.00 mmol) furnished 2-(3-iodopropyl)-3-methylfuran (**51d**) (0.57 g, 76%) as a yellow oil after column chromatography with 1:4 EtOAc/hexane.

Note: product contained a minor impurity identified as triphenylphosphine. The presence of this impurity did not affect full characterization, all product signals are clearly identifiable. The impurity is apparent from the peaks in the in the aromatic region of the ^{1}H and ^{13}C NMR spectrums.

R_f 0.88 (1:4 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, J = 2 Hz, 1H), 6.16 (d, J = 2 Hz, 1H), 3.16 (t, J = 7 Hz, 2H), 2.69 (t, J = 7 Hz, 2H), 2.13 (quint, J = 7 Hz, 2H), 2.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1, 140.2, 114.9, 112.8, 32.1, 26.4, 9.9, 6.1; IR (cast film, cm^{-1}) 3052, 2925, 2867, 1511, 737; HRMS (EI) calcd for $C_8H_{11}OI[M]^+$ 249.9855, found 249.9852.

2-(3-Iodopropyl)-5-ethylfuran (51c)



51c

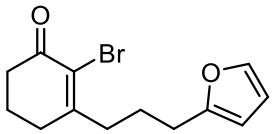
Using PPh_3 (2.20g, 8.41 mmol), imidazole (0.880 g, 12.9 mmol), iodine (2.13 g, 8.41 mmol), and 3-(5-ethylfuran-2-yl)propan-1-ol (**71b**) (1.00 g, 6.47 mmol) furnished 2-(3-iodopropyl)-5-ethylfuran (**51c**) (1.36 g, 79%) as a yellow oil after column chromatography with 1:4 EtOAc/hexane.

R_f 0.84 (1:2 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (d, *J* = 3 Hz, 1H), 5.85 (d, *J* = 3 Hz, 1H), 3.20 (t, *J* = 6.8 Hz, 2H), 2.71 (t, *J* = 7.1 Hz, 2H), 2.59 (q, *J* = 7.5 Hz, 2H), 2.13 (quint, *J* = 6.9 Hz, 2H), 1.20 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 152.0, 106.1, 104.2, 31.9, 28.8, 21.4, 12.2, 6.0; IR (cast film, cm^{-1}) 3103, 2970, 2846, 1567, 1429, 778; HRMS (EI) calcd for $C_9H_{13}OI[M]^+$ 264.0011, found 264.0014.

General Procedure for Stork-Danheiser Transposition

A solution containing the primary iodide (1.0 equiv.) dissolved in THF (0.1 M) was cooled to -78°C and *t*-BuLi (1.7 M in pentane; 2.0 equiv.) was added dropwise over 5 min. The mixture was stirred at -78°C for 30 min and added via cannula to a solution of cyclohexenone (1.0 equiv.) in THF (0.2 M) at -78°C with oven dried 4Å MS. This mixture was stirred at -78°C for 1 h before warming to 0°C and stirring for a further 30 min before addition of HCl (1 M). After stirring for 1 h Et_2O was added and the aqueous phase was extracted with Et_2O (4 x 30 mL). The combined organic phases washed with $NaHCO_3$ (sat), Na_2SO_3 (10 %), H_2O, brine, and dried over $MgSO_4$. Evaporation of solvent gave a crude mixture that was purified by column chromatography.

2-Bromo-3-(3-(furan-2-yl)propyl)cyclohex-2-en-1-one (49a)

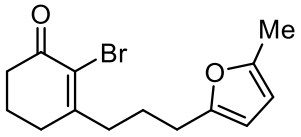


49a

Using 2-(3-iodopropyl)furan (**51a**)[42] (0.250 g, 1.06 mmol), *t*-BuLi (1.7 M in pentanes; 1.25 mL, 2.12 mmol), and cyclohexenone (**50**)[43-44] (0.186 g, 0.851 mmol) furnished 2-bromo-3-(3-(furan-2-yl)propyl)cyclohex-2-en-1-one (**49a**) (0.18 g, 76%) as a colorless oil after column chromatography with 1% MeOH in DCM.

R_f 0.44 (1% MeOH in DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 1.8 Hz, 1.0 Hz, 1H), 6.29 (dd, *J* = 3.0 Hz, 2.0 Hz, 1H), 6.03 (dd, *J* = 3.2 Hz, 1.0 Hz, 1H), 2.72 (t, *J* = 7.5 Hz, 2H), 2.59 - 2.52 (m, 4H), 2.49 (t, *J* = 6.0 Hz, 2H), 1.98 (app quint, *J* = 6.0 Hz, 2H), 1.89 (app quint, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.1, 163.1, 154.9, 141.1, 123.0, 110.2, 105.4, 38.7, 37.8, 32.4, 27.9, 25.2, 22.0; IR (cast film, cm^{-1}) 3115, 2936, 2867, 1682, 1595, 1457, 731; HRMS (EI) calcd for $C_{13}H_{15}O_2{}^{79}Br[M]^+$ 282.0255, found 282.0254.

2-Bromo-3-(3-(5-methylfuran-2-yl)propyl)cyclohex-2-en-1-one (49b)

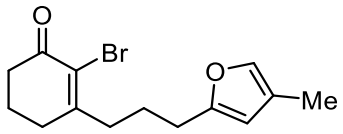


49b

Using 2-(3-iodopropyl)-5-methylfuran (**51b**)[45] (0.400 g, 1.60 mmol), *t*-BuLi (1.7 M in pentanes; 1.88 mL, 3.20 mmol), and cyclohexenone (**50**)[43-44] (0.350 g, 1.60 mmol) furnished 2-bromo-3-(3-(5-methylfuran-2-yl)propyl)cyclohex-2-en-1-one (**49b**) (0.31 g, 66%) as a colorless oil after column chromatography with 1% MeOH in DCM.

R_f 0.69 (1% MeOH in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (d, *J* = 2.8 Hz, 1H), 5.80 (d, *J* = 2.8 Hz, 1H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.59 – 2.51 (m, 4H), 2.48 (t, *J* = 6.0 Hz, 2H), 2.21 (s, 3H), 2.01 - 1.93 (m, 2H), 1.90 - 1.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.1, 163.3, 153.1, 150.5, 122.9, 106.0, 105.9, 38.7, 37.8, 32.4, 28.0, 25.4, 22.0, 13.5; IR (cast film, cm^{-1}) 3102, 2950, 2869, 1683, 1595, 1462, 784; HRMS (EI) calcd for $C_{14}H_{17}O_2{}^{79}Br[M]^+$ 296.0412, found 296.0408.

2-Bromo-3-(3-(4-methylfuran-2-yl)propyl)cyclohex-2-en-1-one (49d)

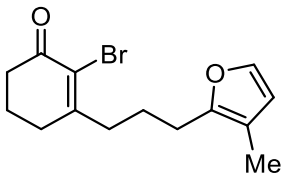


49d

Using 2-(3-iodopropyl)-4-methylfuran (**51d**) (0.195 g, 0.780 mmol), *t*-BuLi (1.7 M in pentanes; 0.910 mL, 1.56 mmol), and cyclohexenone (**50**)[43-44] (0.170 g, 0.780 mmol) furnished 2-bromo-3-(3-(4-methylfuran-2-yl)propyl)cyclohex-2-en-1-one (**49d**) (0.14 g, 60%) as a colorless oil after column chromatography with 1% MeOH in DCM.

R_f 0.62 (1% MeOH in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H), 5.89 (s, 1H), 2.66 (t, *J* = 7.2 Hz, 2H), 2.59 - 2.51 (m, 4H), 2.48 (t, *J* = 6.0 Hz, 2H), 2.01-1.94 (m, 2H), 1.98 (s, 3H), 1.91 - 1.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 163.3, 155.0, 137.6, 122.9, 120.6, 108.3, 38.7, 37.8, 32.4, 28.0, 25.2, 22.0, 9.8; IR (cast film, cm^{-1}) 2953, 2889, 1683, 1595, 1461, 810; HRMS (EI) calcd for $C_{14}H_{17}O_2{}^{79}Br[M]^+$ 296.0412, found 296.0404.

2-Bromo-3-(3-(3-methylfuran-2-yl)propyl)cyclohex-2-en-1-one (49e)

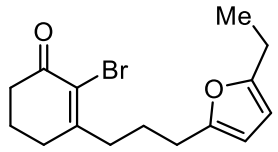


49e

Using 2-(3-iodopropyl)-3-methylfuran (**51e**) (0.431 g, 1.97 mmol), *t*-BuLi (1.7 M in pentanes; 2.57 mL, 4.38 mmol), and cyclohexenone (**50**)[43-44] (0.550 g, 1.97 mmol) furnished 2-bromo-3-(3-(3-methylfuran-2-yl)propyl)cyclohex-2-en-1-one (**49e**) (0.33 g, 56%) as a yellow oil after column chromatography with 2:1 pentane/Et_2O.

R_f 0.44 (2:1 pentane /Et_2O); ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 2.0 Hz, 1H), 6.16 (d, *J* = 2.0 Hz, 1H), 2.65 (t, *J* = 7.0 Hz, 2H), 2.58 - 2.55 (m, 2H), 2.52 - 2.45 (m, 4H), 2.00-1.85 (m, 2H), 1.97 (s, 3H), 1.90 - 1.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.1, 163.4, 149.9, 140.0, 122.8, 114.5, 112.8, 38.7, 37.8, 32.3, 25.8, 25.5, 22.0, 9.8; IR (cast film, cm^{-1}) 2944, 2867, 1683, 1596, 1510, 1175, 732; HRMS (EI) calcd for $C_{14}H_{17}O_2{}^{79}Br[M]^+$ 296.0412, found 296.0410.

2-Bromo-3-(3-(5-ethylfuran-2-yl)propyl)cyclohex-2-en-1-one (49c)



49c

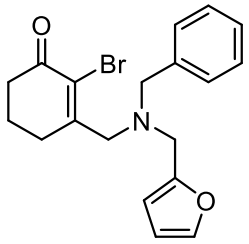
Using 2-(3-iodopropyl)-5-ethylfuran (**51c**) (0.669 g, 2.53 mmol), *t*-BuLi (1.7 M in pentanes; 2.97 mL, 5.06 mmol), and cyclohexenone (**50**)[43-44] (0.500 g, 2.28 mmol) furnished 2-bromo-3-(3-(5-ethylfuran-2-yl)propyl)cyclohex-2-en-1-one (**49c**) (0.34 g, 49%) as a yellow oil after column chromatography with 1% MeOH in DCM.

R_f 0.70 (1% MeOH in DCM); ^1H NMR (500 MHz, $CDCl_3$) δ 5.91 (d, *J* = 2.7 Hz, 1H), 5.85 (d, *J* = 2.7 Hz, 1H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.62 - 2.53 (m, 6H), 2.49 (t, *J* = 6.0 Hz, 2H), 1.98 (app quint, *J* = 6.7 Hz, 2H), 1.87 (app quint, *J* = 7.8 Hz, 2H), 1.21 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.1, 163.4, 156.4, 153.0, 122.9, 105.7, 104.3, 38.7, 37.8, 32.4, 28.0, 25.3, 22.0, 21.4, 12.2; IR (cast film, cm^{-1}) 3103, 2937, 1684, 1596, 1174, 796; HRMS (EI) calcd for $C_{15}H_{19}O_2{}^{79}Br[M]^+$ 310.0569, found 310.0569.

General Procedure for S_N2 Alkylation

To a solution of 2-bromo-3-(chloromethyl)cyclohex-2-en-one (**89**) (1.0 equiv.) in MeCN [0.2 M] was added the corresponding amine (3.0 equiv.) and NaOAc (3.0 equiv.). The reaction was stirred overnight and then diluted with DCM before solids were removed by filtration through Celite. Evaporation of solvent gave a crude mixture that was purified by column chromatography.

3-((Benzyl(furan-2-ylmethyl)amino)methyl)-2-bromocyclohex-2-en-1-one (49f)



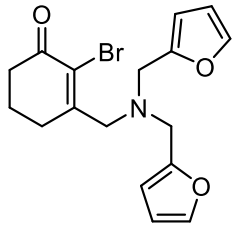
49f

Using 2-bromo-3-(chloromethyl)cyclohex-2-en-1-one **(89)** (0.143 g, 0.640 mmol), N-benzylfurfurylamine (0.359 g, 1.92 mmol), and NaOAc (0.261 g, 1.92 mmol) furnished 3-((benzyl(furan-2-ylmethyl)amino)methyl)-2-bromocyclohex-2-en-1-one (**49f**) (0.220 g, 92%) as a brown oil after column chromatography with 1:9 EtOAc/hexane.

Note: Synthesis by Dr. Lofstrand.

R_f 0.70 (3:7 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 1.8, 0.5 Hz, 1H), 7.40 – 7.32 (m, 4H), 7.30 – 7.25 (m, 1H), 6.34 (dd, *J* = 3.0, 2.0 Hz, 1H), 6.25 (dd, *J* = 2.5, 1.0 Hz, 1H), 3.65 (s, 2H), 3.64 (s, 2H), 3.53 (s, 2H), 2.59 (t, *J* = 6.0 Hz, 2H), 2.57 – 2.53 (m, 2H), 1.92 (app quint, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.2, 161.6, 152.1, 142.2, 138.7, 128.9, 128.4, 127.3, 123.2, 110.2, 109.0, 60.0, 59.1, 51.3, 38.3, 30.7, 21.9; IR (cast film, cm^{-1}) 3118, 3026, 2931, 2888, 1685, 1597, 1453, 1147, 736; HRMS (EI) calcd for $C_{19}H_{20}O_2{}^{79}BrN[M]^+$ 373.0677, found 373.0678.

3-((Bis(furan-2-ylmethyl)amino)methyl)-2-bromocyclohex-2-en-1-one (49h)



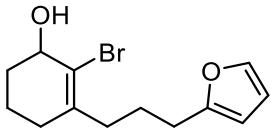
49h

Using 2-bromo-3-(chloromethyl)cyclohex-2-en-1-one (**89**) (0.445 g, 1.99 mmol), bis((furan-2-yl)methyl)amine (1.06 g, 5.97 mmol), and NaOAc (0.812 g, 5.97 mmol) furnished 3-((bis(furan-2-ylmethyl)amino)methyl)-2-bromocyclohex-2-en-1-one (**49h**) (0.574 g, 79%) as a brown oil after column chromatography with 1:9 EtOAc/hexane.

Note: Synthesis by Dr. Lofstrand. In the ^{13}C NMR spectrum an artifact (from v700 NMR machine) is visible at 206.3 ppm.

R_f 0.58 (3:7 EtOAc/hexane); ^1H NMR (500 MHz, CD_2Cl_2) δ 7.43 – 7.40 (m, 2H), 6.37 – 6.33 (m, 2H), 6.30 – 6.26 (m, 2H), 3.66 (s, 4H), 3.53 (s, 2H), 2.60 – 2.48 (m, 4H), 1.95 – 1.88 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 191.3, 161.6, 151.8, 142.3, 122.8, 110.3, 109.2, 59.7, 51.1, 38.3, 30.6, 22.0; IR (cast film, cm^{-1}) 3117, 2924, 2869, 1685, 1597, 1504, 1148, 738; HRMS (ESI) calcd for $C_{17}H_{19}BrNO_3[M+H]^+$ 364.0543, found 364.0546.

2-Bromo-3-(3-(furan-2-yl)propyl)cyclohex-2-en-1-ol (81)



81

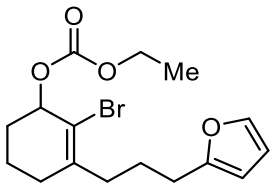
To a solution of 2-bromo-3-(3-(furan-2-yl)propyl)cyclohex-2-en-1-one (**49a**) (1.0 equiv., 1.00 g, 3.53 mmol) and $CeCl_3 \cdot 7H_2O$ (1.1 equiv., 1.45 g, 3.88 mmol) in MeOH [0.4 M] at 0 °C was

portion-wise added $NaBH_4$ (1.2 equiv., 0.160 g, 4.24 mmol) over 5 min. The reaction was stirred at 0 °C for 1 h before warming to rt with stirring continued for 1 h. The reaction was quenched with the addition of HCl (1 M) and the aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with $NaHCO_3$ (sat), H_2O, brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude mixture that was purified to furnish 2-bromo-3-(3-(furan-2-yl)propyl)cyclohex-2-en-1-ol (**81**) (0.785 g, 79%) as a yellow oil after column chromatography with 1:2 EtOAc/hexane.

Note: alcohol proton was not detected in ^1H NMR spectrum.

R_f 0.57 (2:1 hexane/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 2.0 Hz, 1H), 6.28 (dd, J = 3.0, 2.0 Hz, 1H), 6.01 (d, J = 3.0 Hz, 1H), 4.25 (app t, J = 4.5 Hz, 1H), 2.66 (t, J = 7.5 Hz, 2H), 2.27 – 2.24 (m, 2H), 2.19 – 2.14 (m, 1H), 2.11 - 2.05 (m, 1H), 1.90 – 1.84 (m, 2H), 1.83 - 1.72 (m, 3H), 1.75 - 1.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 140.9, 140.3, 123.3, 110.1, 105.0, 71.2, 36.8, 32.0, 31.5, 27.8, 25.4, 18.4; IR (neat, cm^{-1}) 3405, 3116, 2938, 2865, 1077, 728; HRMS (EI) calcd for $C_{13}H_{15}OBr$ $[M-H_2O]^+$ 266.0306, found 266.0308.

2-Bromo-3-(3-(furan-2-yl)propyl)cyclohex-2-en-1-yl ethyl carbonate (86)



86

To a solution of 2-bromo-3-(3-(furan-2-yl)propyl)cyclohex-2-en-1-ol (**81**) (1.0 equiv., 0.330 g, 1.16 mmol) in DCM [0.1 M] at 0 °C was added pyridine (1.5 equiv., 0.140 mL, 1.74 mmol) and then dropwise ethyl chloroformate (1.2 equiv., 0.132 mL, 1.39 mmol) over 1-2 min. The mixture was warmed to rt and stirred 1 h before ~ 5mg of DMAP was added. Upon completion of the reaction, as determined by TLC, the mixture was cooled to 0 °C and quenched by addition of HCl (1 M). The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers

were washed with $NaHCO_3$ (sat), H_2O, brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude mixture that was purified to furnish 2-bromo-3-(3-(furan-2-yl)propyl)cyclohex-2-en-1-yl ethyl carbonate (**86**) (0.337 g, 81%) as a colorless oil after column chromatography with 1:4 EtOAc/hexane.

R_f 0.62 (1:4 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 2.0 Hz, 1H), 6.27 (dd, *J* = 3.0, 2.0 Hz, 1H), 6.00 (d, *J* = 3.0 Hz, 1H), 5.30 (t, *J* = 3.5 Hz, 1H), 4.26 – 4.19 (m, 2H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.34-2.16 (m, 3H), 2.09 (m, 1H), 2.00 – 1.96 (m, 1H), 1.90-1.64 (m, 5H), 1.33 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 155.6, 154.8, 143.8, 140.9, 116.5, 110.1, 105.0, 76.8, 64.1, 36.8, 31.2, 30.1, 27.9, 25.4, 18.0, 14.3; IR (neat, cm^{-1}) 3115, 2940, 2868, 1740, 1248, 732; HRMS (EI) calcd for $C_{16}H_{21}O_4Br$ $[M]^+$ 356.0623, found 356.0621.

General Procedures for Silyl Anion Conjugate Addition

Note: Method A was our "standard" procedure and was always employed first with a substrate. If conversion or isolated yield was not satisfactory method B was then utilized. Method C was only used for displacement of a carbonate.

Method A

To a suspension of CuBr·DMS complex (1.5 equiv.) in THF [0.15 M] cooled to 0 °C was added a previously prepared solution of $LiSiMe_2Ph$[50] (2.9 equiv.) in THF [0.4 M] via cannula. The mixture was stirred at 0 °C for 30 min before a solution of the corresponding enone (1.0 equiv.) in THF [0.1 M] at 0 °C was added via cannula. This mixture was stirred at 0°C for 5 h before addition of acetic anhydride or benzoyl chloride (5.0 equiv.) and further stirring for 5 h. Et_2O (20 mL) and H_2O (15 mL) were added and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with H_2O, brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude mixture that was purified by column chromatography.

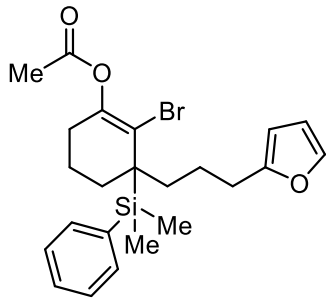
Method B

To a suspension of CuBr·DMS complex (3.0 equiv.) in THF [0.15 M] cooled to 0 °C was added a previously prepared solution of $LiSiMe_2Ph$[50] (6.0 equiv.) in THF [0.4 M] via cannula. The mixture was stirred at 0 °C for 30 min before a solution of the corresponding enone (1.0 equiv.) in THF [0.1 M] at 0 °C was added via cannula. This mixture was stirred at 30°C for 5 h before addition of acetic anhydride or benzoyl chloride (5.0 equiv.) and further stirring for 5 h. Et_2O (20 mL) and H_2O (15 mL) were added and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with H_2O, brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude mixture that was purified by column chromatography.

Method C

To a suspension of CuBr·DMS complex (1.3 equiv.) in THF [0.15 M] cooled to 0 °C was added a previously prepared solution of $LiSiMe_2Ph$[50] (2.6 equiv.) in THF [0.4 M] via cannula. The mixture was stirred at 0 °C for 30 min before being cooled to -78 °C. A solution of the corresponding carbonate (1.0 equiv.) in THF [0.1 M] at 0 °C was added via cannula. This mixture was stirred at -78 °C for 5 h. Et_2O (20 mL) and H_2O (15 mL) were added and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with H_2O, brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude mixture that was purified by column chromatography.

2-Bromo-3-(dimethyl(phenyl)silyl)-3-(3-(furan-2-yl)propyl)cyclohex-1-en-1-yl acetate (46a)



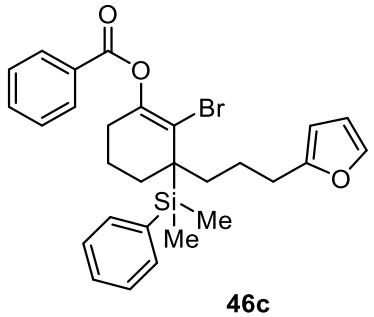
46a

Method A

Using 2-bromo-3-(3-(furan-2-yl)propyl)cyclohex-2-en-1-one (**49a**) (0.150 g, 0.530 mmol), $LiSiPhMe_2$[50] (0.218 g, 1.54 mmol), and CuBr·DMS complex (0.163 g, 0.798 mmol) furnished 2-bromo-3-(dimethyl(phenyl)silyl)-3-(3-(furan-2-yl)propyl)cyclohex-1-en-1-yl acetate (**46a**) (0.17 g, 70%) as a colorless oil after column chromatography with 3:1 hexane/DCM.

R_f 0.66 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 - 7.55 (m, 2H), 7.38 - 7.31 (m, 3H), 7.30 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.26 (dd, *J* = 3.2, 2.0 Hz, 1H), 5.97 (dd, *J* = 3.2, 0.9 Hz, 1H), 2.64 - 2.58 (m, 2H), 2.12 - 1.93 (m, 3H), 2.17 (s, 3H), 1.70-1.57 (m, 7H), 0.48 (s, 3H), 0.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 156.1, 144.7, 140.7, 137.5, 134.7, 129.0, 127.6, 120.5, 110.0, 104.8, 35.8, 35.7, 31.5, 28.8, 28.6, 23.2, 20.8, 20.8, -2.7, -3.2; IR (cast film, cm^{-1}) 3069, 3014, 2951, 2867, 1761; HRMS (EI) calcd for $C_{23}H_{29}O_3{}^{79}BrSi[M]^+$ 460.1069, found 460.1066.

2-Bromo-3-(dimethyl(phenyl)silyl)-3-(3-(furan-2-yl)propyl)cyclohex-1-en-1-yl benzoate (46c)



46c

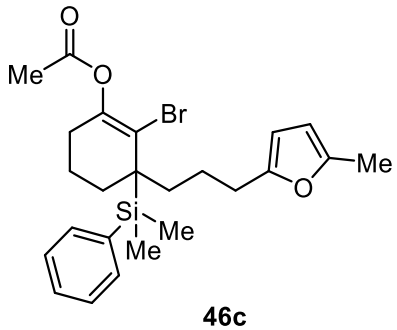
Method A

Using 2-bromo-3-(3-(furan-2-yl)propyl)cyclohex-2-en-1-one (**49a**) (0.100 g, 0.350 mmol), $LiSiPhMe_2$[50] (0.164 g, 1.05 mmol), and CuBr·DMS complex (0.107 g, 0.525 mmol) furnished 2-bromo-3-(dimethyl(phenyl)silyl)-3-(3-(furan-2-yl)propyl)cyclohex-1-en-1-yl benzoate (**46c**) (0.110 g, 43%) as a colorless oil after column chromatography with 1:3 DCM/hexane.

R_f 0.67 (1:4 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 – 8.12 (m, 2H), 7.63 – 7.55 (m, 3H), 7.51 – 7.45 (m, 2H), 7.40 – 7.33 (m, 3H), 7.29 (dd, *J* = 2.0, 1.0 Hz, 1H), 6.27 (dd, *J* = 2.0, 3.0 Hz, 1H), 5.99 (dd, *J* = 3.0, 1.0 Hz, 1H), 2.69 – 2.53 (m, 2H), 2.36 – 2.17 (m, 2H), 2.04 – 1.95

(m, 1H), 1.77 – 1.57 (m, 7H), 0.51 (s, 3H), 0.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 156.2, 144.9, 140.7, 137.5, 134.8, 133.4, 130.1, 129.6, 129.1, 128.5, 127.6, 120.6, 110.1, 104.8, 35.8, 35.8, 31.6, 29.0, 28.6, 23.3, 20.3, -2.5, -3.1; IR (cast film, cm^{-1}) 3069, 3041, 2950, 2868, 1736, 1266, 705; HRMS (ESI) calcd for $C_{28}H_{31}BrNaO_3Si[M+Na]^+$ 545.112, found 545.111.

2-Bromo-3-(dimethyl(phenyl)silyl)-3-(3-(5-methylfuran-2-yl)propyl)cyclohex-1-en-1-yl acetate (46c)



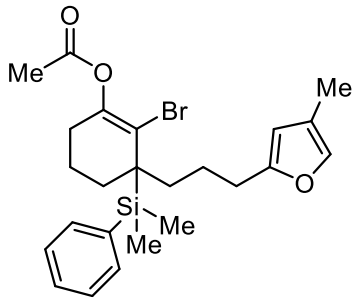
46c

Method A

Using 2-bromo-3-(3-(5-methylfuran-2-yl)propyl)cyclohex-2-en-1-one (**49b**) (0.150 g, 0.508 mmol), $LiSiPhMe_2$[50] (0.208 g, 1.47 mmol), and CuBr·DMS complex (0.156 g, 0.760 mmol) furnished 2-bromo-3-(dimethyl(phenyl)silyl)-3-(3-(5-methylfuran-2-yl)propyl)cyclohex-1-en-1-yl acetate (**46c**) (0.154 g, 64%) as a colorless oil after column chromatography with 1:3 DCM/hexane.

R_f 0.64 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 2H), 7.40 - 7.29 (m, 3H), 5.83 – 5.80 (m, 2H), 2.63 – 2.45 (m, 2H), 2.25 (s, 3H), 2.24 – 2.13 (m, 1H), 2.17 (s, 3H), 2.13 – 1.89 (m, 2H), 1.71 – 1.60 (m, 7H), 0.48 (s, 3H), 0.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 154.3, 150.0, 144.7, 137.5, 134.7, 129.0, 127.6, 120.5, 105.7, 105.4, 35.8, 35.8, 31.5, 28.8, 28.6, 23.4, 20.8, 20.2, 13.5, -2.6, -3.1; IR (cast film, cm^{-1}) 3069, 3014, 2949, 1761, 1204; HRMS (EI) calcd for $C_{24}H_{31}O_3Si^{79}Br[M]^+$ 474.1226, found 474.1226.

2-Bromo-3-(dimethyl(phenyl)silyl)-3-(3-(4-methylfuran-2-yl)propyl)cyclohex-1-en-1-yl acetate (46d)



46d

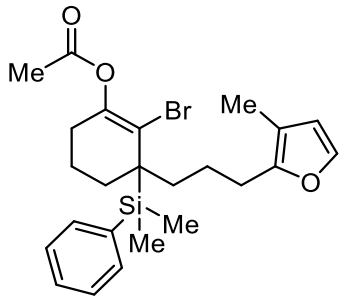
Method A

Using 2-bromo-3-(3-(4-methylfuran-2-yl)propyl)cyclohex-2-en-1-one (**49d**) (0.150 g, 0.508 mmol), $LiSiPhMe_2$[50] (0.218 g, 1.54 mmol), and CuBr·DMS complex (0.163 g, 0.795 mmol) furnished 2-bromo-3-(dimethyl(phenyl)silyl)-3-(3-(4-methylfuran-2-yl)propyl)cyclohex-1-en-1-yl acetate (**46d**) (0.171 g, 69%) as a colorless oil after column chromatography with 1:4 EtOAc/hexane.

Note: Impurity of less than 10% always co-elutes with desired product, even with alternative solvent systems. Spots overlap on TLC but product signals all clearly identifiable in NMR. Impurity identified as starting material **49d**.

R_f 0.48 (1:4 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, J = 7.8, 1.5 Hz, 2H), 7.37 – 7.32 (m, 3H), 7.04 (s, 1H), 5.83 (s, 1H), 2.62 – 2.46 (m, 2H), 2.22 – 2.14 (m, 1H), 2.17 (s, 3H), 2.12 – 2.03 (m, 1H), 1.98 (s, 3H), 1.97 – 1.92 (m, 1H), 1.70 – 1.55 (m, 7H), 0.48 (s, 3H), 0.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 156.2, 144.7, 137.5, 134.7, 134.7, 129.0, 127.6, 120.5, 120.4, 107.7, 35.8. 35.7, 31.5, 28.8, 28.7, 23.2, 20.8, 20.2, 9.8, -2.6, -3.1; IR (cast film, cm^{-1}) 3069, 2947, 2870, 1761, 1203; HRMS (EI) calcd for $C_{24}H_{31}O_3Si^{79}Br[M]^+$ 474.1226, found 474.1232.

2-Bromo-3-(dimethyl(phenyl)silyl)-3-(3-(3-methylfuran-2-yl)propyl)cyclohex-1-en-1-yl acetate (46e)



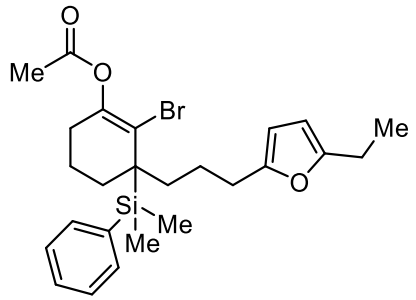
46e

Method A

Using 0.100 g (0.350 mmol) of 2-bromo-3-(3-(3-methylfuran-2-yl)propyl)cyclohex-2-en-1-one (**49e**) (0.100 g, 0.320 mmol), $LiSiPhMe_2$[50] (0.131 g, 0.930 mmol), and CuBr·DMS complex (0.0980 g, 0.480 mmol) furnished 2-bromo-3-(dimethyl(phenyl)silyl)-3-(3-(3-methylfuran-2-yl)propyl)cyclohex-1-en-1-yl acetate (**46e**) (0.111 g, 69%) as a colorless oil after column chromatography with 1:9 EtOAc/hexane.

R_f 0.44 (1:9 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.37 – 7.31 (m, 3H), 7.19 (d, *J* = 2.0 Hz, 1H), 6.14 (d, *J* = 2.0 Hz, 1H), 2.59 – 2.43 (m, 2H), 2.21 – 2.12 (m, 1H), 2.16 (s, 3H), 2.10 – 2.02 (m, 1H), 1.94 (s, 3H), 1.93 – 1.86 (m, 1H), 1.68 – 1.52 (m, 7H), 0.46 (s, 3H), 0.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 151.1, 144.7, 137.5, 134.7, 134.7, 129.0, 127.5, 120.6, 113.8, 112.6, 35.8, 35.7, 31.5, 28.8, 26.4, 23.6, 20.8, 20.2, 9.8, -2.6, -3.1; IR (cast film, cm^{-1}) 3069, 2945, 2868, 1761, 1203; HRMS (EI) calcd for $C_{24}H_{31}O_3Si^{79}Br[M]^+$ 474.1226, found 474.1231 .

2-Bromo-3-(dimethyl(phenyl)silyl)-3-(3-(5-ethylfuran-2-yl)propyl)cyclohex-1-en-1-yl acetate (46f)



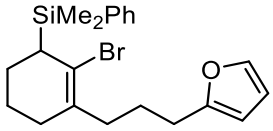
46f

Method B

Using 0.100 g (0.32 mmol) of 2-bromo-3-(3-(5-ethylfuran-2-yl)propyl)cyclohex-2-en-1-one (**49c**) (0.100 g, 0.320 mmol), $LiSiPhMe_2$[50] (0.131 g, 0.930 mmol), and CuBr·DMS complex (0.0980 g, 0.480 mmol) furnished 2-bromo-3-(dimethyl(phenyl)silyl)-3-(3-(5-ethylfuran-2-yl)propyl)cyclohex-1-en-1-yl acetate (**46f**) (0.132 g, 85%) as a light-yellow oil after column chromatography with 1:4 EtOAc/hexane.

R_f 0.62 (1:4 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, J = 7.8 Hz, 1.5 Hz, 2H), 7.37 – 7.32 (m, 3H), 5.84 (d, *J* = 3.0 Hz, 1H), 5.83 (dt, *J* = 3.0, 1.0 Hz, 1H), 2.59 (q, *J* = 7.5, 2H), 2.57 – 2.46 (m, 2H), 2.17 (s, 3H), 2.12 – 1.92 (m, 3H), 1.69 - 1.55 (m, 7H), 1.20 (t, *J* = 7.5 Hz, 3H), 0.48 (s, 3H), 0.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 155.9, 154.2, 144.7, 137.5, 134.7, 129.0, 127.6, 120.6, 105.2, 104.1, 35.8, 35.8, 31.5, 28.8, 28.6, 23.4, 21.4, 20.8, 20.2, 12.3, -2.6, -3.1 ; IR (neat, cm^{-1}) 3068, 3007, 2998, 2953, 1760, 1248; HRMS (EI) calcd for $C_{25}H_{33}O_3{}^{79}BrSi[M]^+$ 488.1382, found 488.1388.

(2-Bromo-3-(3-(furan-2-yl)propyl)cyclohex-2-en-1-yl)dimethyl(phenyl)silane (87)



87

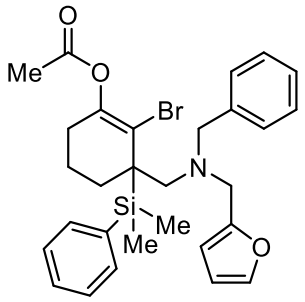
Method C

Using 2-bromo-3-(3-(furan-2-yl)propyl)cyclohex-2-en-1-yl ethyl carbonate (**86**) (0.250 g, 0.700 mmol), $LiSiPhMe_2$[50] (0.250 g, 1.82 mmol), and CuBr·DMS complex (0.187 g, 0.910 mmol) furnished (2-bromo-3-(3-(furan-2-yl)propyl)cyclohex-2-en-1-yl)dimethyl(phenyl)silane (**87**) (0.250 g, 89%) as a light yellow oil after column chromatography with 1:9 EtOAc/hexane.

Note: reaction scale is limited to ≤400 mg of starting material. Significant erosion of yield is seen on larger scale. In the ^{13}C NMR spectrum an artifact (from v700 NMR machine) is visible at 206.3 ppm.

R_f 0.54 (1:9 EtOAc/hexane); ^1H NMR (700 MHz, $CDCl_3$) δ 7.54 – 7.52 (m, 2H), 7.35 – 7.24 (m, 4H), 6.27 (dd, *J* = 2.8, 2.1 Hz, 1H), 5.98 (d, *J* = 3.5 Hz, 1H), 2.59 (app t, *J* = 7.7 Hz, 2H), 2.35 – 2.30 (m, 2H), 2.10-1.94 (m, 3H), 1.76-1.66 (m, 3H), 1.63 – 1.59 (m, 1H), 1.53-1.49 (m, 2H), 0.45 (s, 3H), 0.41 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.2, 138.6, 135.0, 134.0, 133.0, 128.9, 127.6, 121.9, 110.0, 104.7, 37.1, 36.5, 30.9, 27.9, 27.8, 25.8, 21.9, -1.6, -2.3. IR (cast film, cm^{-1}) 3080, 2954, 2860, 1234, 740; HRMS (EI) calcd for $C_{21}H_{26}OSiBr$ $[M]^+$ 401.0936, found 401.0939.

3-((Benzyl(furan-2-ylmethyl)amino)methyl)-2-bromo-3(dimethyl(phenyl)silyl)cyclohex-1-en-1-yl acetate (46g)



46g

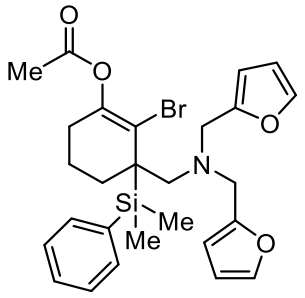
Method A

Using 3-((benzyl(furan-2-ylmethyl)amino)methyl)-2-bromocyclohex-2-en-1-one (**49f**) (0.637 g, 1.70 mmol), $LiSiPhMe_2$[50] (0.601 g, 4.26 mmol), and CuBr·DMS complex (0.438 g, 2.13 mmol) furnished 3-((benzyl(furan-2-ylmethyl)amino)methyl)-2-bromo-3(dimethyl(phenyl)silyl)cyclohex-1-en-1-yl acetate (**46g**) (0.533 g, 58%) as a light-yellow oil after column chromatography with 1:9 EtOAc/hexane.

Note: synthesis by Dr. Lofstrand.

R_f 0.61 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.10 (m, 11H), 6.30 (dd, *J* = 3.2, 2.0 Hz, 1H), 6.18 (d, *J* = 3.2 Hz, 1H), 3.98 (d, *J* = 13.2 Hz, 1H), 3.81 (d, *J* = 14.8 Hz, 1H), 3.37 (d, *J* = 14.8 Hz, 1H), 3.21 (d, *J* = 13.2 Hz, 1H), 3.11 (d, *J* = 14.0 Hz, 1H), 2.80 (d, *J* = 14.0 Hz, 1H) 2.26 – 1.98 (m, 3H), 2.12 (s, 3H), 1.67 – 1.56 (m, 3H), 0.40 (s, 3H), 0.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 153.5, 145.4, 139.8, 137.1, 134.7, 134.7, 129.2, 128.9, 128.1, 127.5, 126.8, 121.0, 110.0, 108.4, 59.6, 57.2, 50.7, 37.3, 31.3, 29.1, 20.8, 20.3, -2.9, -4.3; IR (cast film, cm^{-1}) 3068, 2952, 2835, 1761, 1202; HRMS (ESI) calcd for $C_{29}H_{35}BrNO_3Si[M+H]^+$ 552.1564, found 552.1571.

3-((Bis(furan-2-ylmethyl)amino)methyl)-2-bromo-3-(dimethyl(phenyl)silyl)cyclohex-1-en-1-yl acetate (46h)



46h

Method A

Using 3-((bis(furan-2-ylmethyl)amino)methyl)-2-bromocyclohex-2-en-1-one (**49h**) (0.120 g, 0.329 mmol), $LiSiPhMe_2$[50] (0.112 g, 0.789 mmol), and CuBr·DMS complex (0.102 g, 0.495 mmol) furnished 3-((bis(furan-2-ylmethyl)amino)methyl)-2-bromo-3-(dimethyl(phenyl)silyl)cyclohex-1-en-1-yl acetate (**46h**) (0.0709 g, 40%) as a dark-yellow oil after column chromatography with 1:1:19 EtOAc/DCM/hexane.

Note: synthesis by Dr. Lofstrand

R_f 0.63 (1:4 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.47 (m, 2H), 7.37 – 7.29 (m, 5H), 6.27 (dd, *J* = 3.0, 1.5 Hz, 2H), 6.17 (d, *J* = 3.0 Hz, 2H), 3.80 (d, *J* = 15.0 Hz, 2H), 3.47 (d, *J* = 14.5 Hz, 2H), 3.19 (d, *J* = 14.0 Hz, 1H), 2.79 (d, *J* = 14.0 Hz, 1H), 2.26 – 2.07 (m, 4H), 2.15 (s, 3H), 1.65 – 1.55 (m, 2H), 0.44 (s, 3H), 0.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 153.3, 145.7, 141.7, 137.2, 134.8, 128.9, 127.5, 120.6, 110.0, 108.6, 56.8, 51.0, 37.4, 31.4, 29.1, 20.8, 20.3, -2.9, -4.3; IR (cast film, cm^{-1}) 3069, 2935, 2899, 1760, 1203; HRMS (ESI) calcd for $C_{27}H_{33}BrNO_4Si[M+H]^+$ 542.1357, found 542.351.

General Procedures for [4+2]-Cycloaddition

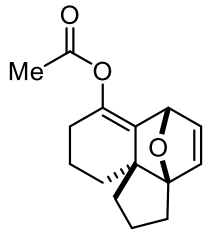
Method A

To a solution of the substrate (1.0 equiv.) in MeCN [0.02 M] at rt was added a TBAF solution (1.0 M in THF, 5 equiv.) which had been diluted with THF to approximately twice the original volume, via syringe pump at a rate of 1.0 mL/h. The needle tip was bent to allow contact with the flask and a steady stream of TBAF into solution; dropwise addition negatively affected reaction yield. After the addition, the mixture was stirred at rt for 1 h before evaporation of most of the solvent gave a crude mixture that was flushed with DCM through a pipet packed with silica to remove any excess fluoride. This was followed by purification via column chromatography or preparative TLC.

Method B

To a suspension of CsF (5.0 equiv.) in MeCN [0.02 M] at rt was added a solution of the substrate dissolved in MeCN. After the addition, the mixture was stirred at rt until the reaction was complete, typically within 24 h (up to 72 h for gram-scale), as observed by TLC. Evaporation of most of the solvent gave a crude mixture that was flushed with DCM through a pipet packed with silica to remove any excess fluoride. This was followed by purification via column chromatography.

***Endo*-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-9-yl acetate (48a)**



48a

Method A

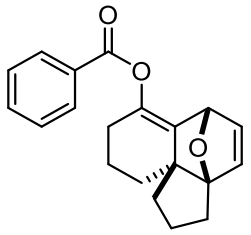
Using 2-bromo-3-(dimethyl(phenyl)silyl)-3-(3-(furan-2-yl)propyl)cyclohex-1-en-1-yl acetate (**46a**) (0.080 g, 0.174 mmol) and TBAF (0.871 µl, 0.871 mmol) furnished *endo*-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-9-yl acetate (**48a**) (0.028 g, 65%) as a colorless oil after column chromatography with 1:30 EtOAc/DCM.

Method B

Using 2-bromo-3-(dimethyl(phenyl)silyl)-3-(3-(furan-2-yl)propyl)cyclohex-1-en-1-yl acetate (**46a**) (1.00 g, 2.17 mmol) and CsF(1.65 g, 10.8 mmol) furnished *endo*-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-9-yl acetate (**48a**) (0.245 g, 46%) as a colorless oil after column chromatography with 1:30 EtOAc/DCM.

R_f 0.50 (1:3 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (dd, *J* = 5.6, 1.6 Hz, 1H), 6.17 (d, *J* = 5.6 Hz, 1H), 5.18 (d, *J* = 1.6 Hz, 1H), 2.30 (ddd, *J* = 17.2, 4.8, 2.4 Hz, 1H), 2.14 (s, 3H), 2.12 – 1.80 (m, 8H), 1.70 (ddd, *J* = 12.4, 7.8, 3.6 Hz, 1H), 1.55 (dt, *J* = 12.0, 3.2 Hz, 1H), 0.47 (app dddd, *J* = 17.3, 11.6, 7.8, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 141.4, 136.7, 132.5, 131.5, 101.3, 77.9, 53.6, 33.4, 30.6, 26.4, 25.8, 23.4, 20.9, 20.8; IR (cast film, cm^{-1}) 2936, 2851, 1760, 1219; HRMS (EI) calcd for $C_{15}H_{18}O_3[M]^+$ 246.1256, found 246.1251.

***Endo*-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-9-yl benzoate (48c)**



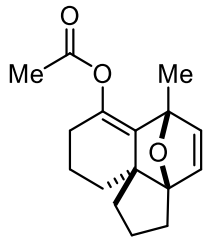
48c

Method A

Using 2-bromo-3-(dimethyl(phenyl)silyl)-3-(3-(furan-2-yl)propyl)cyclohex-1-en-1-yl benzoate (**46c**) (0.083 g, 0.160 mmol) and TBAF (0.800 µl, 0.800 mmol) furnished *endo*-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-9-yl benzoyl (**48c**) (0.024 g, 49%) as a colorless oil after column chromatography with 1:30 EtOAc/DCM.

R_f 0.70 (1:19 EtOAc/DCM); ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.11 – 8.04 (m, 2H), 7.64 – 7.57 (m, 1H), 7.51 – 7.44 (m, 2H), 6.48 (dd, *J* = 5.5, 1.5 Hz, 1H), 6.22 (d, *J* = 5.5 Hz, 1H), 5.23 (d, *J* = 1.5 Hz, 1H), 2.42 (ddd, *J* = 17.8, 5.5, 2.0 Hz, 1H), 2.19 – 1.86 (m, 8H), 1.75 (ddd, *J* = 12.5, 8.3, 3.5 Hz, 1H), 1.60 (dt, *J* = 12.0, 3.5 Hz, 1H), 0.56 (app dddd, *J* = 15.5, 10.5, 7.0, 1.5 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 164.8, 141.6, 136.8, 133.3, 132.5, 132.0, 129.9, 129.8, 128.5, 101.4, 78.0, 53.8, 33.4, 30.7, 26.5, 25.9, 23.5, 20.9; IR (cast film, cm^{-1}) 3068, 3032, 2941, 2870, 1734, 1267; HRMS (EI) calcd for $C_{20}H_{20}O_3[M]^+$ 308.1412, found 308.1410.

***Endo*-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-11-methyl-9-yl acetate (48c)**



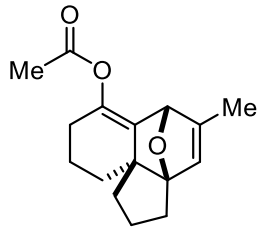
48c

Method A

Using 2-bromo-3-(dimethyl(phenyl)silyl)-3-(3-(5-methylfuran-2-yl)propyl)cyclohex-1-en-1-yl acetate (**46c**) (0.230 g, 0.486 mmol) and TBAF (2.40 mL, 2.43 mmol) furnished *endo*-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-11-methyl-9-yl acetate (**48c**) (0.079 g, 62%) as a yellow oil after column chromatography with 1:30 EtOAc/DCM.

R_f 0.62 (1:3 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25 (d, *J* = 5.6 Hz, 1H), 6.15 (d, *J* = 5.6 Hz, 1H), 2.30 (ddd, *J* = 17.2, 6.0, 2.1 Hz, 1H), 2.14 (s, 3H), 2.12 – 1.81 (m, 8H), 1.71 (ddd, *J* = 12.6, 8.4, 2.8 Hz, 1H), 1.66 (s, 3H), 1.51 (dt, *J* = 11.9, 2.8 Hz, 1H), 0.49 (app dddd, *J* = 18.1, 11.9, 6.3, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 141.7, 140.2, 133.8, 133.1, 100.0, 86.5, 55.9, 33.6, 30.2, 26.5, 26.2, 23.3, 20.9, 20.8, 17.4; IR (cast film, cm^{-1}) 2925, 2851, 1761, 1248; HRMS (EI) calcd for $C_{16}H_{20}O_3[M]^+$ 260.1412, found 260.1411.

***Endo*-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-12-methyl-9-yl acetate (48d)**



48d

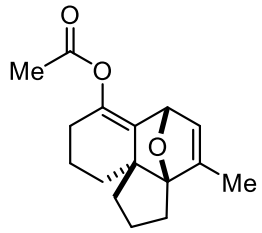
Method A

Using 2-bromo-3-(dimethyl(phenyl)silyl)-3-(3-(4-methylfuran-2-yl)propyl)cyclohex-1-en-1-yl acetate (**46d**) (0.080 g, 0.170 mmol) and TBAF (0.850 µl, 0.850 mmol) furnished *endo*-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-12-methyl-9-yl acetate (**48d**) (0.0275 g, 62%) as a colorless oil after column chromatography with 1:30 EtOAc/DCM.

Note: product contained an apparent minor impurity after both column chromatography and preparative TLC. However, the presence of this impurity did not affect full characterization. Impurity identified as starting material **46d.**

R_f 0.58 (1:3 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (br q, *J* = 2.0 Hz, 1H), 4.93 (s, 1H), 2.38 (m, 1H), 2.13 (s, 3H), 2.10 – 1.77 (m, 8H), 1.88 (br d, *J* = 1.5 Hz, 3H), 1.70 – 1.63 (m, 1H), 1.53 (dt, *J* = 12.0, 3.5 Hz, 1H), 0.50 – 0.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 148.3, 141.3, 131.9, 125.5, 101.9, 81.4, 54.9, 33.4, 30.8, 26.5, 25.8, 23.3, 21.0, 20.8, 13.3; IR (cast film, cm^{-1}) 2941, 2870, 1751, 1222; HRMS (EI) calcd for $C_{16}H_{20}O_3[M]^+$ 260.1412, found 260.1407.

***Endo*-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-13-methyl-9-yl acetate (48e)**



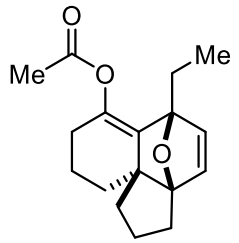
48e

Method A

Using 2-bromo-3-(dimethyl(phenyl)silyl)-3-(3-(3-methylfuran-2-yl)propyl)cyclohex-1-en-1-yl acetate (**46e**) (0.111 g, 0.230 mmol) and TBAF (1.16 mL, 1.15 mmol) furnished *endo*-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-13-methyl-9-yl acetate (**48e**) (0.038 g, 64%) as a low melting white solid after column chromatography with 1:30 EtOAc/DCM.

R_f 0.33 (1:30 EtOAc/DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (app quint, J = 1.5 Hz, 1H), 5.05 (d, J = 1.0 Hz, 1H), 2.31 (ddd, J = 15.0, 6.3, 1.8 Hz, 1H), 2.13 (s, 3H), 2.08 – 1.81 (m, 8H), 1.80 (app d J = 1.5 Hz, 3H), 1.72 (ddd, J = 12.7, 8.0, 3.0 Hz, 1H), 1.53 (dt, J = 11.5, 3.5 Hz, 1H), 0.57 (app dddd, J = 20.0, 11.7, 5.5, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 142.7, 139.8, 133.1, 130.1, 102.6, 77.1, 53.6, 33.5, 29.4, 25.6, 24.7, 23.3, 20.9, 20.6, 14.0; IR (cast film, cm^{-1}) 2937, 2853, 1760, 1219; HRMS (EI) calcd for $C_{16}H_{20}O_3[M]^+$ 260.1412, found 260.1412.

***Endo*-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-11-ethyl-9-yl acetate (48f)**



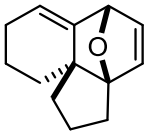
48f

Method B

Using 2-bromo-3-(dimethyl(phenyl)silyl)-3-(3-(5-ethylfuran-2-yl)propyl)cyclohex-1-en-1-yl acetate (**46f**) (0.132 g, 0.270 mmol) and CsF (0.205 g, 1.35 mmol) furnished *endo*-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-11-ethyl-9-yl acetate (**48f**) (0.035 g, 47%) as a colorless oil after column chromatography with 1:30 EtOAc/DCM.

R_f 0.42 (1:30 EtOAc/DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.24 (d, *J* = 5.5 Hz, 1H), 6.15 (d, *J* = 5.5 Hz, 1H), 2.32 (ddd, *J* = 16.5, 5.5, 3.0 Hz, 1H), 2.13 (s, 3H), 2.11 – 1.76 (m, 10H), 1.68 (ddd, *J* = 12.3, 8.3, 2.5 Hz, 1H), 1.51 (dt, *J* = 12.0, 3.5 Hz, 1H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.50 (app dddd, *J* = 14.0, 11.0, 9.0, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 141.5, 139.5, 133.1, 132.2, 99.7, 91.2, 55.9, 33.3, 30.1, 26.4, 26.2, 24.0, 23.2, 20.9, 20.7, 8.8; IR (cast film, cm^{-1}) 2966, 2874, 1759, 1220; HRMS (ESI) calcd for $C_{17}H_{22}NaO_3$[M+Na]$^+$ 297.146, found 297.146.

***Endo*-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dienyl (48g)**



48g

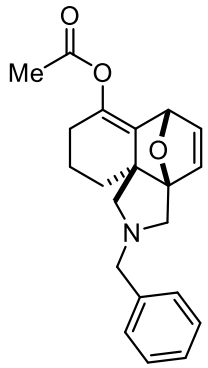
Method B

Using (2-bromo-3-(3-(furan-2-yl)propyl)cyclohex-2-en-1-yl)dimethyl(phenyl)silane (**87**) (200 mg, 0.50 mmol), and CsF (0.42 g, 2.79 mmol) furnished *endo*-14-oxatetracyclo[9.2.1.01,5.05,10]tetradeca-9,12-dienyl (**48g**) (29 mg, 31%) as a colorless oil after column chromatography with 5:95 EtOAc/hexane.

Note: In the ^{13}C NMR spectrum there is a noticeable artifact at 206.3 ppm (this is a known problem with the v700 NMR machine).

R_f 0.51 (1:9 EtOAc/hexane); ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.36 (dd, J = 5.3, 1.4 Hz, 1H), 6.08 (dd, J = 5.6, 1.4 Hz, 1H), 5.59, (dd, J = 4.9, 2.8 Hz, 1H), 4.99 (app s, 1H), 2.15-2.07 (m, 3H), 2.01-1.86 (m, 3H), 1.78-1.69 (m, 4H), 1.57 (dt, J = 10.5, 3.5 Hz, 1H), 0.41 – 0.36 (m, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 145.1, 137.2, 131.3, 118.9, 101.6, 80.2, 51.7, 33.4, 30.9, 26.7, 24.2, 23.4, 19.6; IR (direct deposit, cm^{-1}) 2936, 2868, 2850, 1443, 956; HRMS (EI) calcd for $C_{13}H_{16}O[M]^+$ 188.1201, found 188.1203.

***Endo*-3-aza-14-oxotetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-3-benzyl-9-yl acetate (48h)**



48h

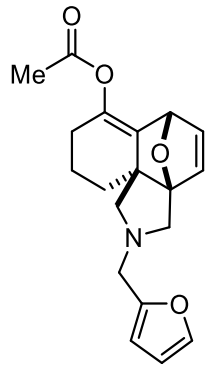
Method A

Using 3-((benzyl(furan-2-ylmethyl)amino)methyl)-2-bromo-3(dimethyl(phenyl)silyl)cyclohex-1-en-1-yl acetate (**46g**) (0.0488 g, 0.0900 mmol) and TBAF (0.270 µl, 0.270 mmol) furnished *endo*-3-aza-14-oxotetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-3-benzyl-9-yl acetate (**48h**) (0.0124 g, 40%) as a yellow oil after preparative TLC with 1:10:10 DCM/EtOAc/hexane.

Note: Synthesis by Dr. Lofstrand.

R_f 0.13 (1:4 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 4H), 7.25 – 7.24 (m, 1H), 6.39 (dd, *J* = 5.5, 1.5 Hz, 1H), 6.20 (d, *J* = 5.5 Hz, 1H), 5.18 (d, *J* = 1.5 Hz, 1H), 3.85 (d, *J* = 13.5 Hz, 1H), 3.75 (d, *J* = 13.5 Hz, 1H), 3.51 (d, *J* = 11.5 Hz, 1H), 2.93 (d, *J* = 8.0 Hz, 1H), 2.80 (d, *J* = 12.0 Hz, 1H), 2.63 (dd, *J* = 8.3, 1.5 Hz, 1H), 2.27 (dd, *J* = 16.5, 7.0 Hz, 1H), 2.12 (s, 3H), 2.06 – 1.76 (m, 4H), 0.49 – 0.46 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 143.0, 139.8, 136.5, 131.0, 128.4, 128.2, 128.2, 126.8, 99.6, 78.1, 60.3, 60.2, 53.9, 53.9, 29.8, 26.1, 21.3, 20.9; IR (cast film, cm^{-1}) 3360, 3024, 2950, 2827, 1749, 1238; HRMS (ESI) calcd for $C_{21}H_{24}NO_3[M+H]^+$ 338.1751, found 338.1746.

***Endo*-3-aza-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-3-furfuryl-9-yl acetate (48i)**



48i

Method A

Using 3-((bis(furan-2-ylmethyl)amino)methyl)-2-bromo-3-(dimethyl(phenyl)silyl) cyclohex-1-en-1-yl acetate (**46h**) (0.041 g, 0.076 mmol) and TBAF (0.226 µl, 0.226 mmol) furnished *endo*-3-aza-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-3-furfuryl-9-yl acetate (**48i**) (0.0196 g, 79%) as a yellow oil after preparative TLC with 1:10:10 DCM/EtOAc/hexane.

Note: Synthesis by Dr. Lofstrand.

R_f 0.19 (1:4 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 1.5 Hz, 1H), 6.38 (dd, *J*= 5.6, 1.5 Hz, 1H), 6.32 (dd, *J* = 3.2, 2.0 Hz, 1H), 6.20 (d, *J*= 0.8 Hz, 1H), 6.18 (d, *J*= 5.6 Hz, 1H) 5.17 (d, *J* = 1.6 Hz, 1H), 3.77 (q, *J* = 14.5 2H), 3.51 (d, *J* = 12.4 Hz, 1H), 2.94 (s, 1H), 2.96 (d, *J* = 8.8 Hz, 1H), 2.67 (dd, *J* = 8.8, 2.0 Hz, 1H), 2.27 (dd, *J* = 16.2, 7.6 Hz, 1H), 2.11 (s, 3H), 2.00 – 1.74 (m, 4H), 0.45 (app dddd, *J* = 13.6, 10.4, 4.2, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 152.8, 143.0, 142.0, 136.7, 130.7, 128.2, 110.1, 107.9, 99.5, 78.2, 59.8, 53.9, 53.2, 52.2, 29.7, 26.0, 21.1, 20.9; IR (cast film, cm^{-1}) 3009, 2937, 2851, 1760, 1200; HRMS (ESI) calcd for $C_{19}H_{22}NO_4[M+H]^+$ 328.1543, found 328.1540.

General Procedures for Retro Diels-Alder Cycloaddition

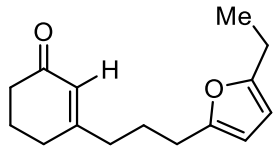
Method A

To a solution of the tetracycle (1.0 equiv.) in MeOH was added K_2CO_3 (5 equiv.). The mixture was stirred at 0 ℃ until the reaction was complete as observed by TLC analysis. Excess base was filtered off and the solvent was mostly evaporated. The compound was immediately purified by column chromatography or preparative TLC.

Method B

To a solution of the tetracycle (1.0 equiv.) in THF at -78 °C was added MeLi (2.0 equiv.). The mixture was stirred at -78 ℃ for 30 min before the reaction was quenched with NH_4Cl (sat). The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with $NaHCO_3$ (sat), H_2O, brine, and dried over $MgSO_4$. Evaporation of the solvent gave a virtually pure product.

3-(3-(5-Ethylfuran-2-yl)propyl)cyclohex-2-en-1-one (103)



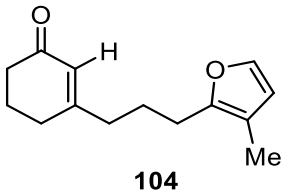
103

Method A

Using *endo*-14-oxatetracyclo[9.2.1.$0^{1,5}$.$0^{5,10}$]tetradeca-9,12-dien-11-ethyl-9-yl acetate (**48f**) (30 mg, 0.11 mmol) and K_2CO_3 (75 mg, 0.56 mmol) furnished 3-(3-(5-ethylfuran-2-yl)propyl)cyclohex-2-en-1-one (**103**) (19 mg, 76%) as a clear colorless oil after column chromatography with 1:30 EtOAc/DCM.

R_f = 0.44 (1:30 EtOAc/DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (br s, 1H), 5.87 (d, *J* = 3.0 Hz, 1H), 5.85 (d, *J* = 3.0 Hz, 1H), 2.62 – 2.56 (m, 4H), 2.37 – 2.34 (m, 2H), 2.29 – 2.24 (m, 4H), 1.97 (app quint, *J* = 6.5 Hz, 2H), 1.84 (app quint, *J* = 7.5 Hz, 2H), 1.21 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 165.8, 156.3, 153.2, 125.9, 105.6, 104.2, 37.4, 37.4, 29.7, 27.5, 25.4, 22.7, 21.3, 12.2; HRMS (EI) calcd for $[M]^+C_{15}H_{20}O_2$: 232.1463, found: 232.1463.

3-(3-(3-Methylfuran-2-yl)propyl)cyclohex-2-en-1-one (104)



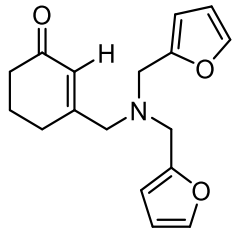
104

Method A

Using *endo*-14-oxatetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-13-methyl-9-yl acetate (**48e**) (9.4 mg, 3.6x10^{-2} mmol) and K_2CO_3 (25 mg, 0.18 mmol) furnished 3-(3-(3-methylfuran-2-yl)propyl)cyclohex-2-en-1-one (**104**) (4.3 mg, 55%) as a clear colorless oil after column chromatography with 1:30 EtOAc/DCM.

R_f = 0.33 (1:30 EtOAc/DCM); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.21 (d, *J* = 1.4 Hz, 1H), 6.15 (d, *J* = 1.4 Hz, 1H), 5.87 (s, 1H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.34 (t, *J* = 6.3 Hz, 2H), 2.26 (t, *J* = 6.3 Hz, 2H), 2.21 (t, *J* = 7.7 Hz, 2H), 1.97 (quint, *J* = 6.3 Hz, 2H), 1.94 (s, 3H), 1.83 (quint, *J* = 7.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 165.8, 150.1, 140.0, 125.9, 114.3, 112.8, 37.4, 29.7, 29.6, 25.6, 25.3, 22.7, 9.8**;** IR (cast film, cm^{-1}) 2926, 2868, 1670, 1455; HRMS (EI) calcd for $[M]^+C_{14}H_{18}O_2$: 218.1307, found: 218.1305.

3-((Bis(furan-2-ylmethyl)amino)methyl)cyclohex-2-en-1-one (107)



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Method B

Using *endo*-3-aza-14-oxatetracyclo[9.2.1.$0^{1,5}$.$0^{5,10}$]tetradeca-9,12-dien-3-N-furfuryl-9-yl acetate (**48i**) (7.5 mg, 2.3x10^{-2} mmol) and MeLi (2.9 uL, 4.5x10^{-2} mmol) furnished 3-((bis(furan-2-ylmethyl)amino)methyl)cyclohex-2-en-1-one (**107**) (6.5 mg, >99%) as a yellow oil after column chromatography with 1:30 EtOAc/DCM.

R_f = 0.21 (1:4 EtOAc/hexane); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38 (d, *J* = 1.4 Hz, 2H), 6.32 (dd, *J* = 3.5, 1.4 Hz, 2H), 6.21 (d, *J* = 3.5 Hz, 2H), 6.08 (s, 1H), 3.64 (s, 4H) 3.12 (s, 2H), 2.37 (t, *J* = 6.3 Hz, 2H), 2.33 (t, *J* = 5.6 Hz, 2H), 1.97 (quint, *J* = 6.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 163.4, 151.9, 142.2, 126.9, 110.1, 109.0, 59.0, 50.1, 37.8, 27.7, 22.6; IR (cast film, cm^{-1}) 3116, 2926, 2868, 1670, 1427; HRMS (EI) calcd for $[M]^+C_{17}H_{19}O_3N$: 285.1365, found: 285.1365.

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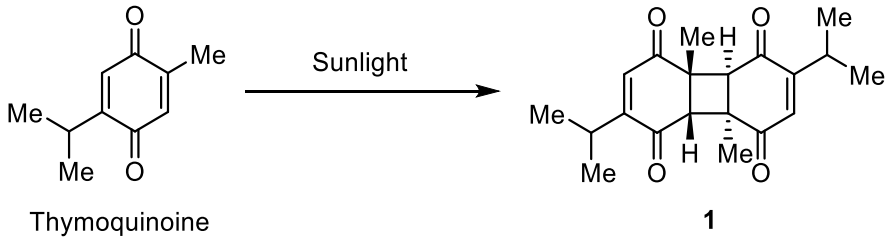
3. Strain-Activated Trapping Reactions of 1,2-Cyclohexadiene: Intramolecular Capture by Pendent Styrenes

3.1 Cyclobutane Synthesis via [2+2]-Cycloaddition

Cycloaddition reactions enable facile synthesis of complex carbocyclic and heterocyclic products. The Diels-Alder reaction (see Chapter **2**) and [2+2]-cycloadditions are common ways in which carbocyclic products are assembled.[1] The first examples of [2+2]-cycloadditions in the chemical literature were photodimerization reactions between two identical olefin units which would form a cyclobutane ring. In 1877 Liebermann discovered the first such dimerization reaction with thymoquinoine.[2] Thymoquinone upon exposure to sunlight formed its respective dimer product **1** in the first described [2+2]-cycloaddition (Scheme 3.1).



Thymoquinoine **1**

Scheme 3.1 - Photodimerization of Thymoquinone

Concerted [2+2]-cycloadditions are understood mechanistically to be suprafacial and allowed photochemically but thermally forbidden.[3] Frontier molecular orbital (FMO) analysis indicates that thermal [2+2]-cycloadditions are symmetry forbidden due to improper orbital overlap. However, upon photoexcitation to a singlet excited state S_1 a [2+2]-cycloaddition is symmetry allowed (Figure 3.1).

For reactions in which a long-lived excited state is desirable, olefins conjugated to carbonyls such as α,β-unsaturated ketones are often employed as their excited states are lower in energy and more easily accessible. Mechanistically this long-lived excited state is achieved through intersystem crossing of the singlet excited state to a triplet excited state through which the photochemical reaction proceeds in a stepwise manner.[4]

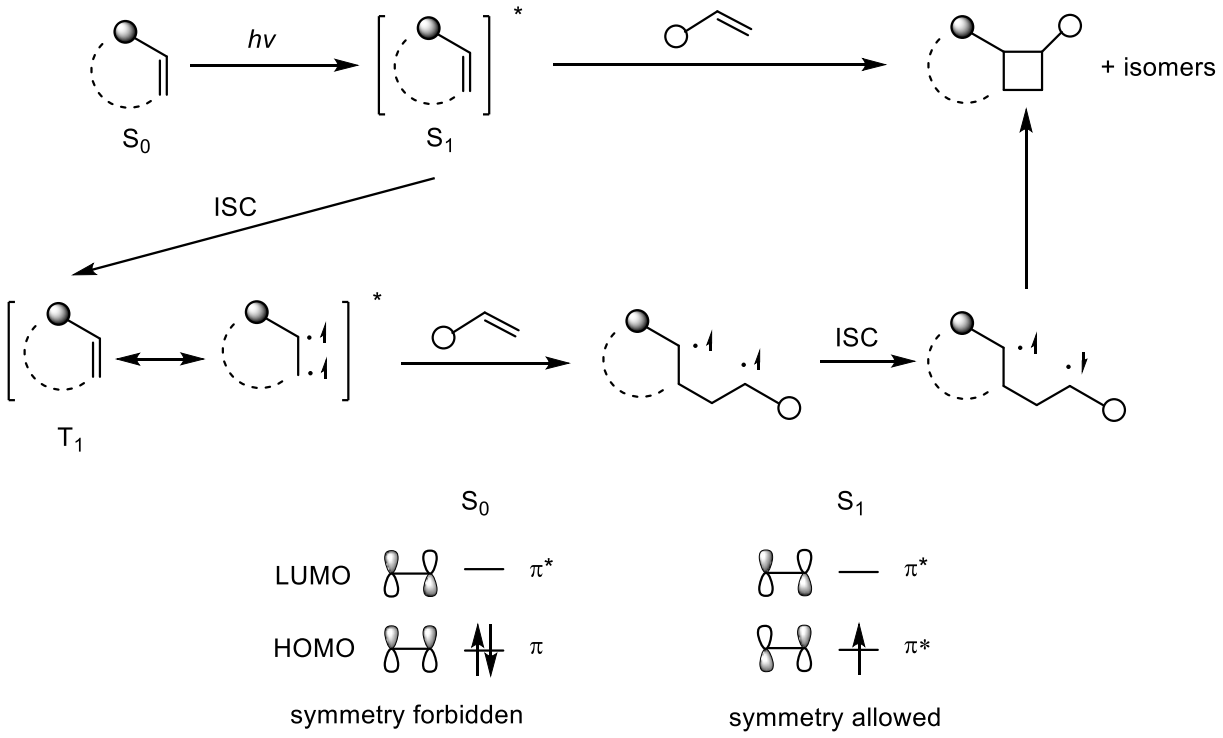
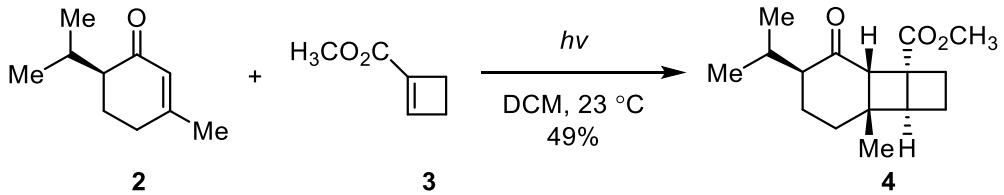


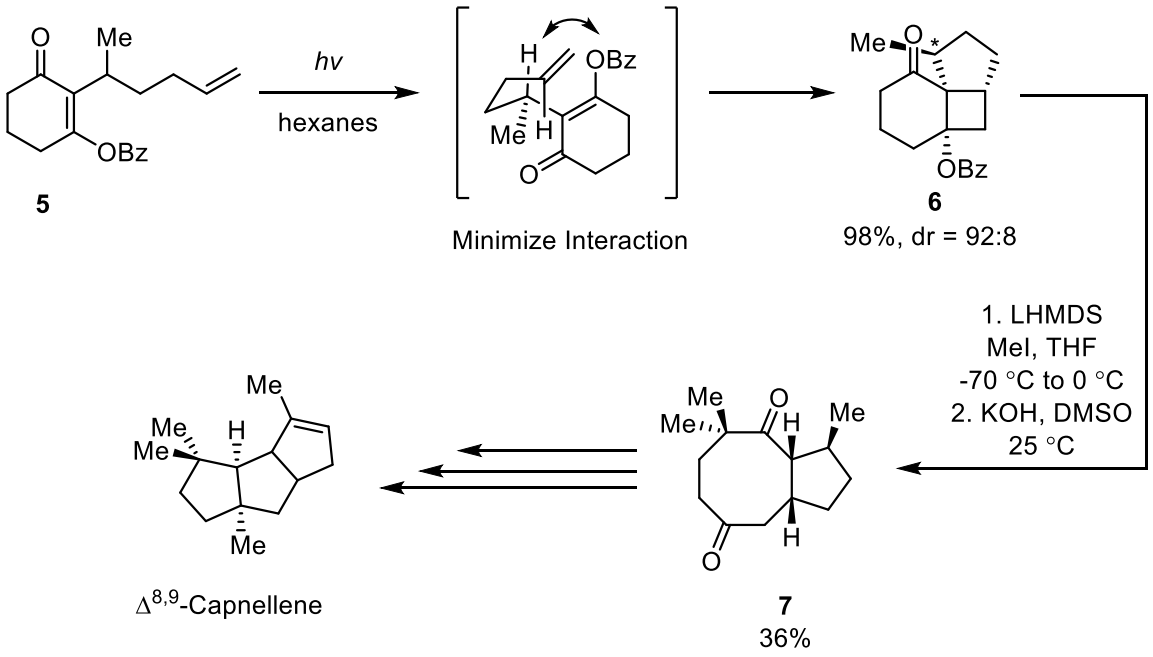
Figure 3.1 - Mechanism and FMO Analysis of [2+2]-Cycloaddition

As previously mentioned, enones are a popular choice of olefins to participate in a photochemical [2+2]-cycloaddition. Incorporation of a cyclobutene as one of the participants in a [2+2]-cycloaddition offers a versatile way to access bicylo[2.2.0]hexane cores that are important motifs in the synthesis of terpenes.[5] Huffman and co-workers synthesized the skeleton of germacrene, a sesquiterpene natural product.[6] The key step involved a [2+2]-cycloaddition between piperitone **2** and cyclobutene **3** to produce a bicyclo[2.2.0]hexane **4** core that was further modified to access a germacrene skeleton (Scheme 3.2). Importantly there is no "endo" effect, such as is found in Diels-Alder cycloadditions and the stereoselectivity appears to be dominated by the least hindered transition state.



Scheme 3.2 - Synthesis of Bicyclo[2.2.0]hexane Skeleton via [2+2]-Cycloaddition

Intramolecular versions of [2+2]-cycloadditions with enones are also utilized in the context of total synthesis. Importantly, the tethering of an enone and olefin helps control regioselectivity issues such as head to tail or head to head isomers. Birch and Pattenden were able to synthesize the natural product $\Delta^{8,9}$-capnellene with a key step involving an intramolecular [2+2]-cycloaddition with enone **5**, containing a tethered terminal olefin (Scheme 3.3).[7,8] Importantly this reaction also demonstrated the importance of the least hindered transition state in determining stereoselectivity.



Scheme 3.3 - Synthesis of $\Delta^{8,9}$-Capnellene Key Intermediate via Intramolecular [2+2]-Cycloaddition

In addition to enones, ketenes are another popular choice of compounds for [2+2]-cycloadditions. In contrast to simple olefins, ketenes are capable of undergoing antarafacial [2+2]-cycloadditions that are thermally allowed (Figure 3.2).[9] While the thermal (π2s + π2a) cycloaddition is allowed there is still the issue of proper geometrical alignment between the reacting orbitals, which leads to the reaction being disfavored for most substrates. While mild heat may be required to promote these cycloadditions the lack of requirement for visible light input is a major advantage.

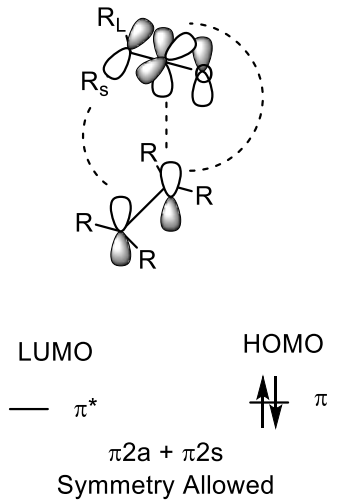
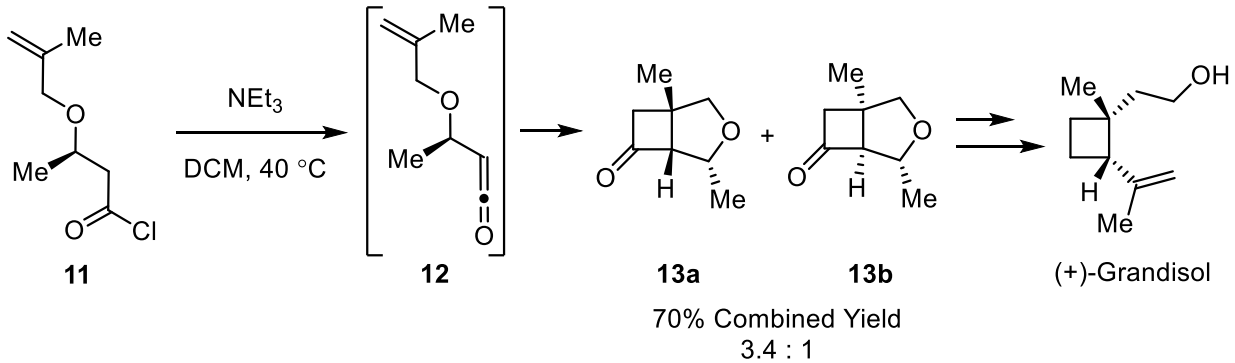


Figure 3.2 - Orbital Overlap for Thermally Allowed Antarafacial [2+2]-Cycloaddition Between Ketenes and Olefins

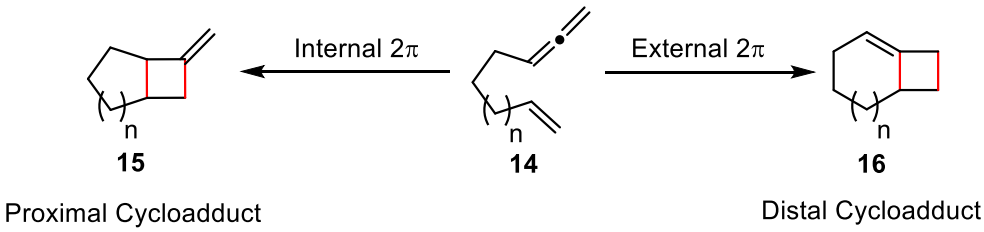
One additional advantage of ketene [2+2]-cycloadditions is the relative ease with which the corresponding substrates can be synthesized. Acid chlorides provide a fast and simple way to generate ketenes in situ. This transformation was utilized by Mori and Miyake in the total synthesis of (+)-grandisol.[10] Acid chloride **11** in the presence of base and under mild heating generated ketene **12** which underwent a [2+2] cycloaddition with its tethered terminal disubstituted olefin (Scheme 3.4). Cycloadducts **13a** and **13b** were formed in a combined yield of 70% and in a 3.4:1 ratio. After separation via reduction, chromatography, and oxidation **13a** was carried on to access (+)-grandisol.



Scheme 3.4 - Total Synthesis of (+)-Grandisol via [2+2]-Cycloaddition with Ketene and Tethered Olefin

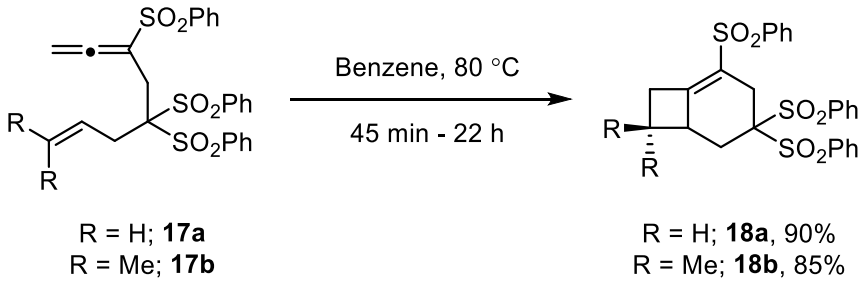
3.2 Intramolecular [2+2]-Cycloadditions of Allenes

Allenes, like ketenes, can undergo antarafacial [2+2]-cycloadditions that are thermally allowed due to the presence of an sp-hybridized central carbon (see section **3.1**).[9] In the case of intramolecular [2+2]-cycloadditions of allenes with olefins, two possible regioisomers can be formed.[11] If the tethered olefin reacts with allene **14** via its internal 2π component the product obtained will be proximal cycloadduct **15** (Scheme 3.5). However, if **14** reacts with its external 2π component the product obtained is the distal cycloadduct **16**.



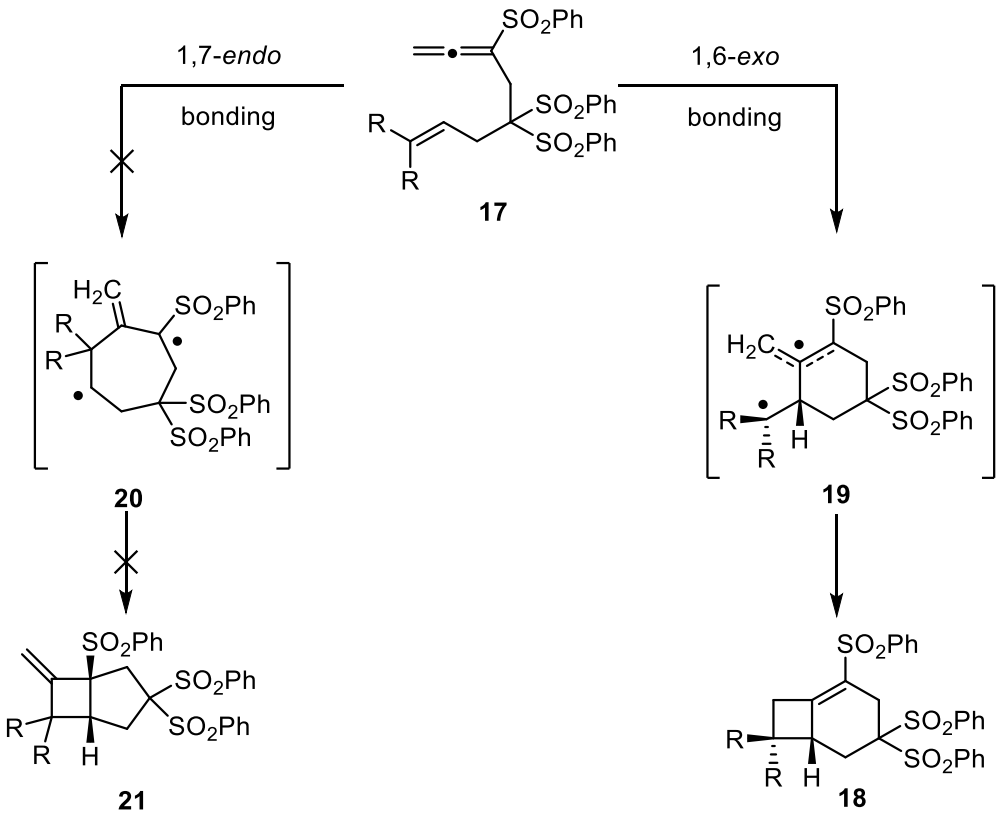
Scheme 3.5 - Proximal vs. Distal Cycloadducts of Intramolecular [2+2]-Cycloadditions of Allenes

Pioneering work by Padwa on selectivity in intramolecular [2+2]-cycloaddition reactions of phenylsulfonyl-substituted allenes clearly demonstrated that the preference for an allene to form a proximal or distal cycloadduct can be modulated by the substituents on either the allene or olefin moiety.[12,13] Thermal reactions of phenylsulfonyl allenes **17a** and **17b** happened only across the non-activated π system of the allene resulting in complete regioselectivity for the formation of distal cycloadducts **18a** and **18b** in yields of 90% and 85% respectively (Scheme 3.6). This result would come as a surprise if this cycloaddition proceeded via a concerted antarafacial [2+2] pathway as the phenylsulfonyl group would activate one double bond of the allene π system. Calculations have shown that the attached phenylsulfonyl group lowers the LUMO energy level of the proximal double bond by 1.3 eV and that the largest orbital coefficients are on the allene sp carbon and the carbon with the phenylsulfonyl group.[14-16] This would all indicate that reaction with the internal π system and formation of the proximal cycloadduct should be favored, however this is not the case.



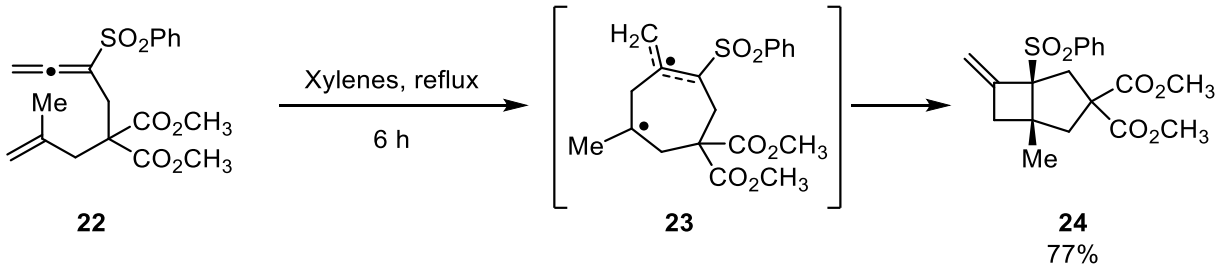
Scheme 3.6 - [2+2]-Cycloaddition of Phenylsulfonyl Allene Tethered with Olefin

The selectivity for a distal cycloadduct observed by Padwa can be partially explained if a two-step radical reaction is considered in place of a concerted cycloaddition (Scheme 3.7). An initial carbon-carbon bond forming reaction can occur between the terminus or internal carbon of the pendent olefin and the central carbon of the allene. If the central carbon of the allene reacts with the terminus of the pendent olefin in a 1,7-*endo* manner, diradical intermediate **20** would be generated; however, if the reaction proceeds on the internal carbon in a 1,6-exo manner diradical intermediate **19** is generated instead. Diradical **19** with an allyl radical would be more stable than **20**, leading to its preferential generation. When R = Me as with **17a** a stable tertiary radical is also generated and reaction proceeds with a much faster rate and id done within one hour. Without this stable radical the reaction takes almost a whole day as with **17b**.



Scheme 3.7 - Regioselectivity of [2+2]-Cycloaddition of Allenyl Sulfones and Tethered Olefins

An interesting observation is noted when a small change is made to the structure of the tethered olefin. With allene **22** the cycloaddition occurs across the terminus of the pendent olefin leading to proximal cycloadduct **24** in a yield of 77% (Scheme 3.8). The initial carbon-carbon bond formation produces allyl radical **23** that in the subsequent ring closure forms bicyclo[3.2.0]heptane **24**. A likely reason for this complete switch in regioselectivity is the use of a 1,1-disubstituted olefin partner, since this now greatly favors stepwise cycloaddition to produce a tertiary radical center on the former internal carbon of the olefin. These results clearly show the importance of producing a stabilized radical during an intramolecular [2+2]-cycloaddition of an allene and tethered olefin. Since this early work intramolecular [2+2] allenic cycloadditions have been utilized to prepare a variety of different carbocycles.[17-18]



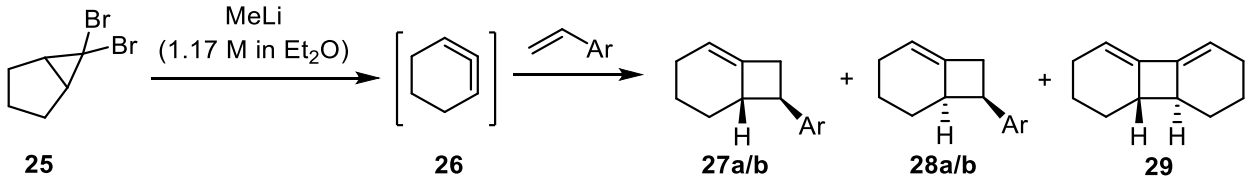
22 **23** **24** 77%

Scheme 3.8 - Change of Regiochemistry in Phenylsulfonyl Allene [2+2]-Cycloaddition with a Tethered Olefin

3.3 [2+2]-Cycloadditions of Cyclic Allenes

In Chapter **1** section **1.6.4** the [2+2] cycloaddition of 1,2-cyclohexadiene **26** with styrene and other π systems is discussed in detail. When styrene is used as a trap for 1,2-cyclohexadiene generated by the method of Moore and Moser (see chapter **1**, section **1.5.7**) a combined yield of 76% with a 2.2:1 ratio favoring the exo isomer is obtained (Table 3.1, Entry 1).[19, 20] A small amount of the dimer, 5%, was also isolated in this cycloaddition. When 4-methoxystyrene was used to trap **26** (Entry 2) a combined yield of 23% was obtained with a diastereomer ratio of 9:1.

Table 3.1 - 1,2-Cyclohexadiene [2+2]-Cycloaddition with Styrene

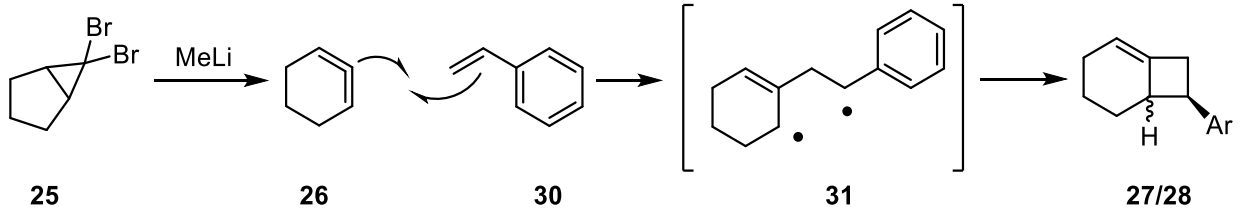


25 **26** **27a/b** **28a/b** **29**

Entry	Ar	Temp (°C)	Yield **27** + **28** (%)	Product	Ratio **27** (*exo*):**28** (*endo*)	Yield **29** (%)
1	Ph	-15	76	**a**	2.2:1	5
2	4-OMe-C_6H_4	-10	23	**b**	9:1	N.A.

The mechanism for the [2+2]-cycloaddition of 1,2-cyclohexadiene and styrene is believed to proceed analogously to the acyclic examples discussed in section **3.2**. An initial carbon-carbon bond forming reaction between the sp carbon of 1,2-cyclohexadiene **26** and the terminal olefin

carbon generates diradical intermediate **31** (Scheme 3.9). Recombination of the diradical then leads to cycloadducts **27** and **28**. Importantly the diradical intermediate **31** produced in this reaction has two stable radicals, an allyl radical and a benzylic radical, and the lower energy of this intermediate helps drive the overall efficiency of the transformation. Described herein are our efforts to generalize and optimize intramolecular [2+2] trapping of cyclic allenes.



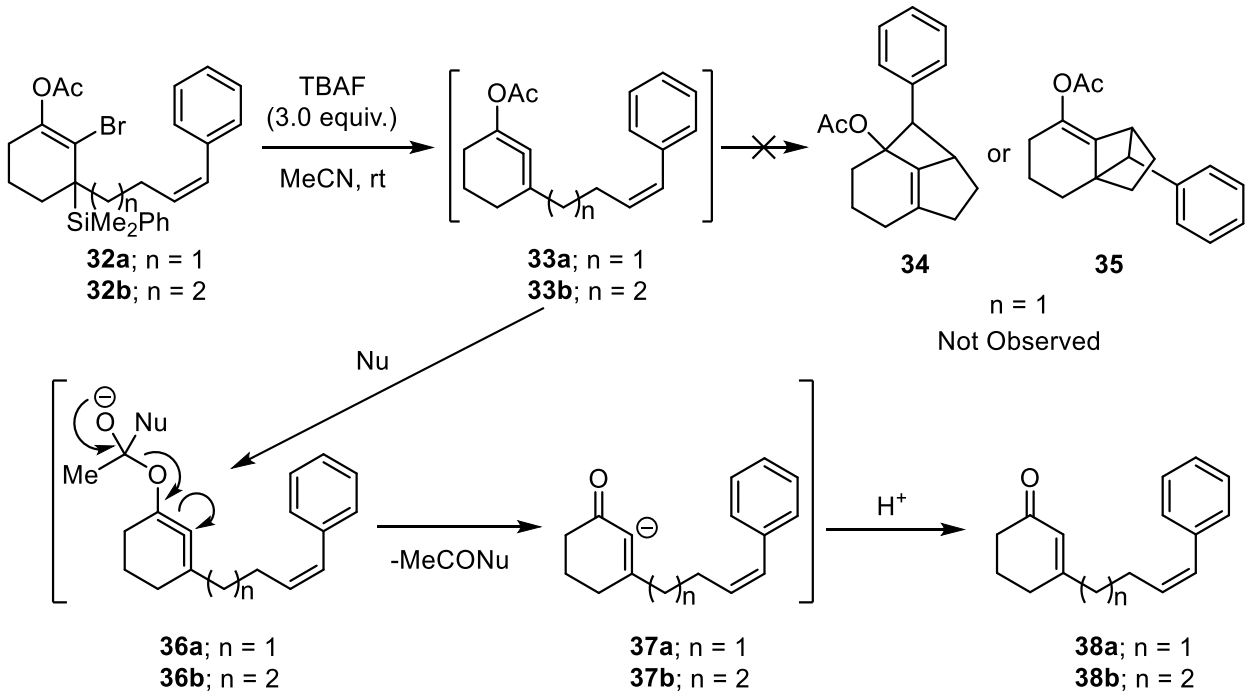
Scheme 3.9 - Mechanism of [2+2]-Cycloaddition of 1,2-Cyclohexadine and Styrene

3.4 Results and Discussion

3.4.1 Project Development and Initial [2+2]-Cycloaddition

Having demonstrated the ability of furans to effectively trap 1,2-cyclohexadienes when attached to a tether (see Chapter **2**) we wondered it a similar approach could be applied to styrenes.[21] The ability to trap a pendent styrene in an intramolecular [2+2]-cycloaddition with 1,2-cyclohexadiene would complement the methodology described in Chapter 2 and allow the probing of interesting synthetic questions. The expected diradical nature of the cycloaddition (see section **3.3**) could lead to interesting bridged products and from cycloaddition across either double bond of the 1,2-cyclohexadiene moiety. To test these questions allylic silanes **32a/b** with alkenyl leaving groups and different carbon tether lengths were synthesized and subjected to desilyative elimination conditions with fluoride (Scheme 3.10).[22] We envisioned two cycloadducts to be possible from **33a** where n = 1, cycloadduct **34** where the [2+2] reaction has taken place across the distal-oxygen substituted double bond or **35** where the reaction has taken place across the proximal carbon-substituted double bond. Neither of these adducts was observed in the reaction mixture and no cycloadducts were observed in the case of n = 2 either; instead cyclohexenone products **38a/b** were the only characterizable materials from the reaction mixture. As we have occasionally observed in furan trapping reactions (see Chapter **2**, section **2.3**), enone formation rather than the

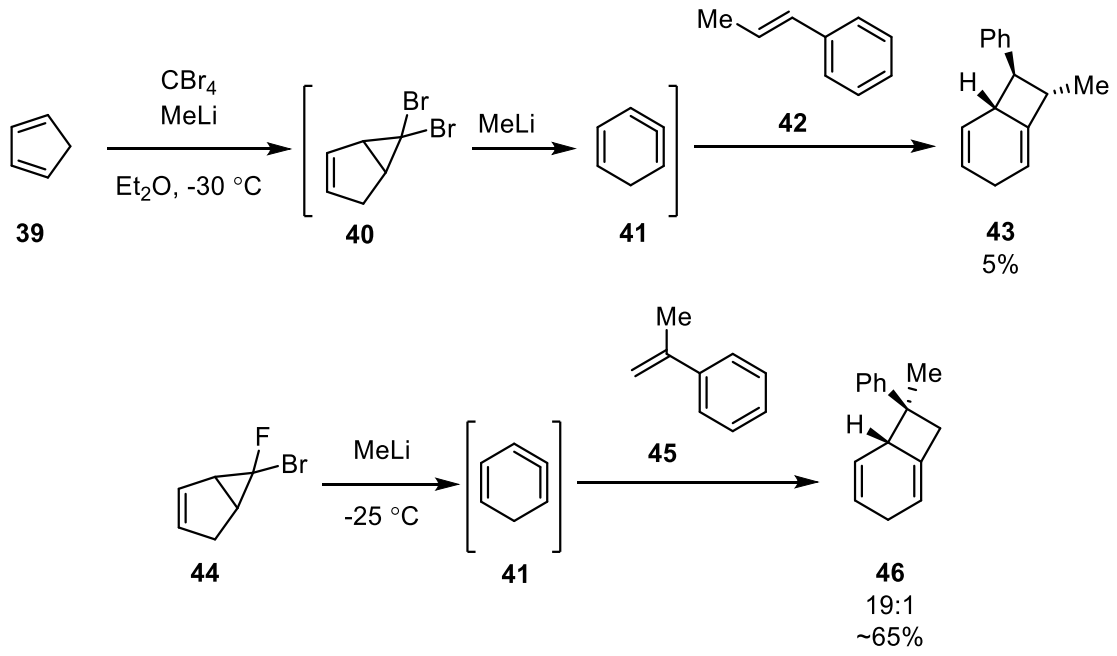
expected allene cycloadducts is believed to occur via hydroxide cleavage of the enol acetate. The presence of traces of water in commercial TBAF and the intrinsic basicity of fluoride explains the source of this nucleophile. The resulting tetrahedral intermediates **36a/b** would collapse to cyclohexenone α anions **37a/b** and subsequent protonation would generate the isolated products **38a/b**.



Scheme 3.10 - Attempted Intramolecular Trapping of Styrene-Tethered 1,2-Cyclohexadiene

The role of styrene substitution patterns in the efficiency of trapping reactions is crucially important, a phenomenon attributed to steric interactions in the initial bonding event to the central allene carbon,[23] and this may explain the failure to observe [2+2] reactivity in the case of β-styrenes **33a/b**. Outcomes from reaction of 1,2,4-cyclohexatriene **41** with various styrenes proceeded differently depending on the styrene employed: β-methylstyrene **42** reacted with **41** to produce cyclobutane product **43** in only 5% yield while α-methylstyrene **45** afforded cycloadduct **46** in ~65% yield (Scheme 3.11). One hypothesis for the lower yield of **43** vs. **46** is that the unsubstituted reactive terminus of α-methylstyrene is much more accessible in the transition state leading to bond formation with the central allene carbon. With this information it was possible to devise a

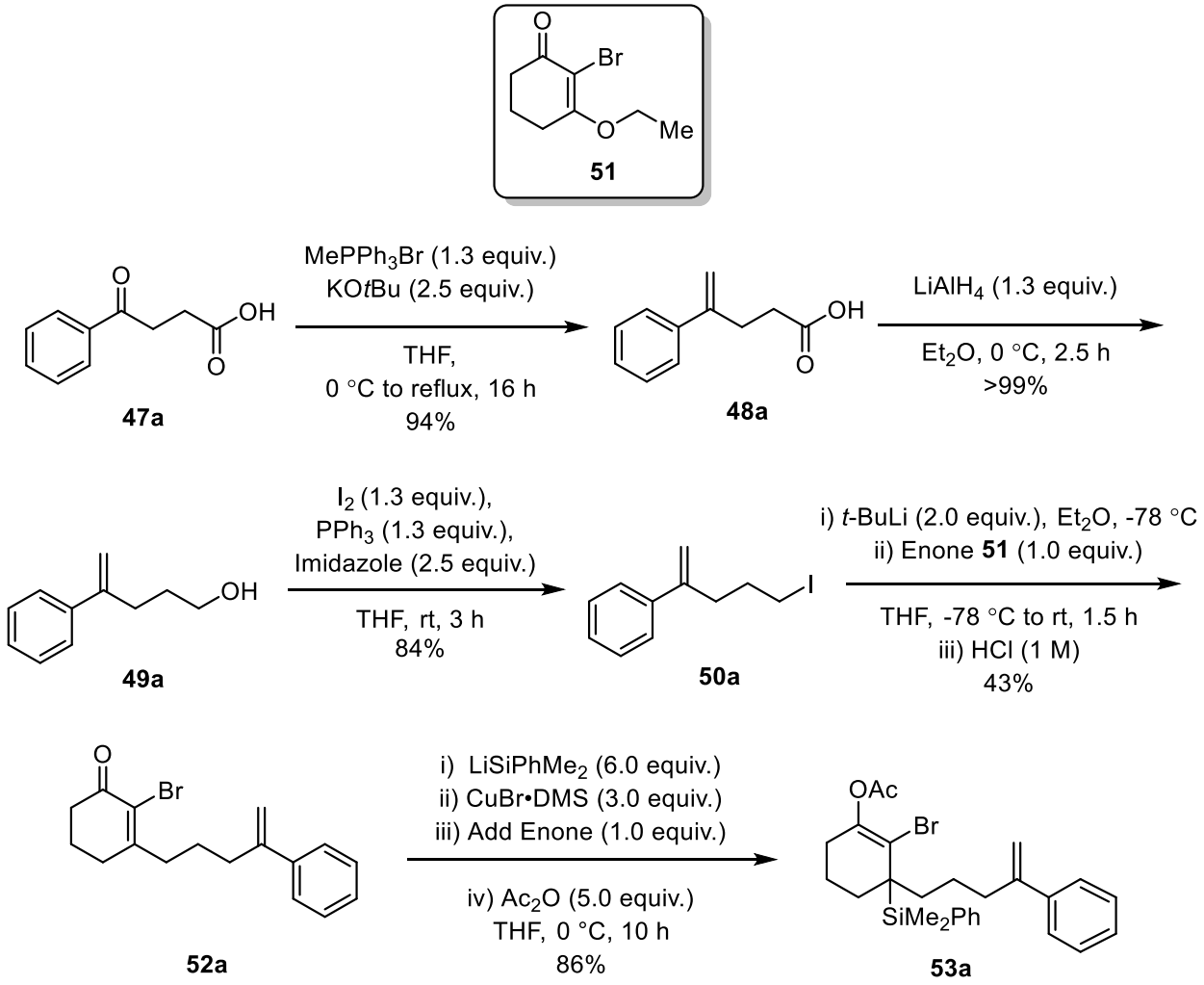
class of substrates with an alternative substitution pattern that would be expected to undergo efficient intramolecular [2+2]-cycloaddition between a transient 1,2-cyclohexadiene and a pendent styrene trap.



Scheme 3.11 - [2+2] Trapping of 1,2,4-Cyclohexatriene with α- and β-Methylstyrene

With the literature examples previously described we were confident that a substrate bearing a pendent styrene trap tethered via the α-carbon group (i.e., 1,1-disubstitution) would have a much greater chance at undergoing an intramolecular [2+2]-cycloaddition than a substrate tethered via the β-carbon. To access such a substrate, we envisioned a pathway similar to how our [4+2]-cycloaddition starting materials were assembled (see Chapter **2**, section **2.4.1**). Starting with 3-benzoylpropanoic acid **47a**, a Wittig methylenation (using $MePPh_3Br$ and KO*t*Bu in THF) provided 4-phenyl-4-pentenoic acid **48a** cleanly in 94% yield (Scheme 3.12). Subsequent reduction with LAH provided 4-phenyl-4-penten-1-ol **49a** in quantitative yield. The Appel reaction to generate the required iodide fragment **50a** for the Stork-Danheiser transposition also proceeded in an excellent yield of 84%. For the Stork-Danheiser transposition to combine enone **51** and iodide **50a** a slightly modified procedure was used as compared to the procedure for introduction of pendent furans (see Chapter **2**). The initial lithium-halogen exchange process was conducted in diethyl ether in order to limit the observation of Wurtz coupling side products.[24]

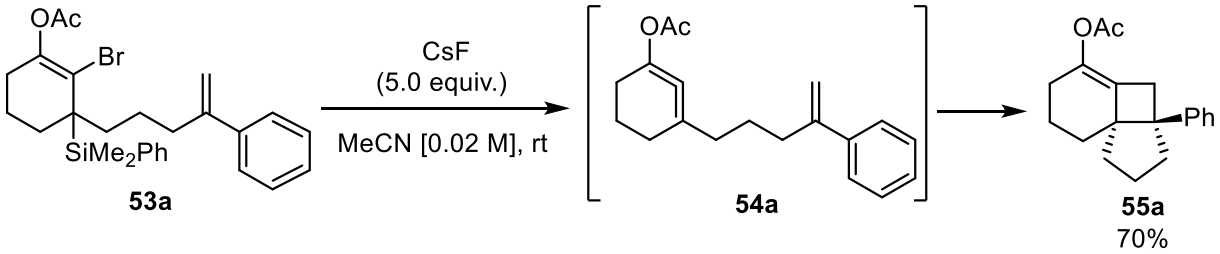
Another advantage of using Et_2O vs. THF is there is less of a chance for background reactions of *t*-BuLi and THF.[25] Although ether is the preferred solvent for the metalation step, the addition of the resulting organolithium reagent to enone **51** must be conducted in THF due to its limited solubility in ether. Using these new conditions, the Stork-Danheiser product **52a** was obtained in a yield of 43%. Finally, a silyl anion conjugate addition enabled conversion in 86% yield to the desired allylic silane starting material **53a** with a styrene trap tethered via the α-carbon moiety.



Scheme 3.12 - Synthesis of Pendent α-Carbon Moiety Starting Material for Intramolecular [2+2]-Cycloaddition

With allylic silane **53a** in hand we next exposed it to CsF to effect a desilyative elimination reaction (Scheme 3.13). Gratifyingly, when allene **54a** was generated it did not undergo acetoxy

cleavage as observed with β-styrene examples (see Scheme **3.10**) but instead underwent the desired [2+2]-cycloaddition reaction resulting in the synthesis of cycloadduct **55a** in 70% yield. This example represented the first time 1,2-cyclohexadiene had been trapped by styrene in an intramolecular [2+2]-cycloaddition reaction. The yield was comparable to those obtained in Table **3.1** where styrene is used as a solvent, demonstrating the greater reaction efficiency of this new methodology. The allene generation conditions are also much more operationally convenient and compatible with more functional groups than other common conditions such as the DMS reaction. This methodology now offered a rapid way to assemble tricyclic cyclobutane containing products.



Scheme 3.13 - Intramolecular [2+2]-Cycloaddition of 1,2-Cyclohexadiene with Pendent α-Carbon Moiety

3.4.2 Structural Assignment and Initial Stereochemical Determination

The structure of cycloadduct **55a** has a strong resemblance to the proximal cycloadduct products obtained from an intramolecular reaction of acyclic allenes and olefins (see section **3.2**). The products synthesized from 1,2-cyclohexadiene contain an extra carbocyclic ring fused to the cyclobutane. One of the key features that is observable in the ^{1}H NMR spectral data that supports the assigned structure is the observation of a long range 5-bond coupling between allylic methylenes on either side of the enol acetate π-system (Figure 3.3).[26] This feature would not be observable in the ^{1}H NMR spectrum of other regioisomers due to a lack of a methylene on one side of the enol acetate π-system. Further support for the assigned structure comes in the form of an nOe correlation between the hydrogens on the cyclobutane ring and the ortho hydrogens on the aromatic phenyl ring. The initial assignment of the stereochemistry as a cis-bicyclo[3.2.0]heptane core was based on the trans isomer being much more strained and less likely to form in the reaction.[27] If the trans isomer were to form it would likely be a minor component and we were

only able to isolate one diastereomer from the reaction. No evidence was observed of a second diastereomer.

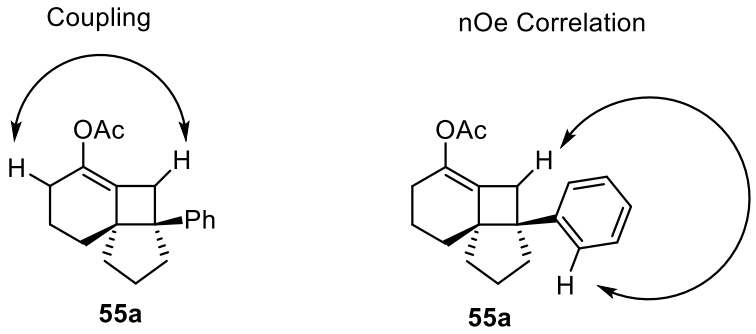


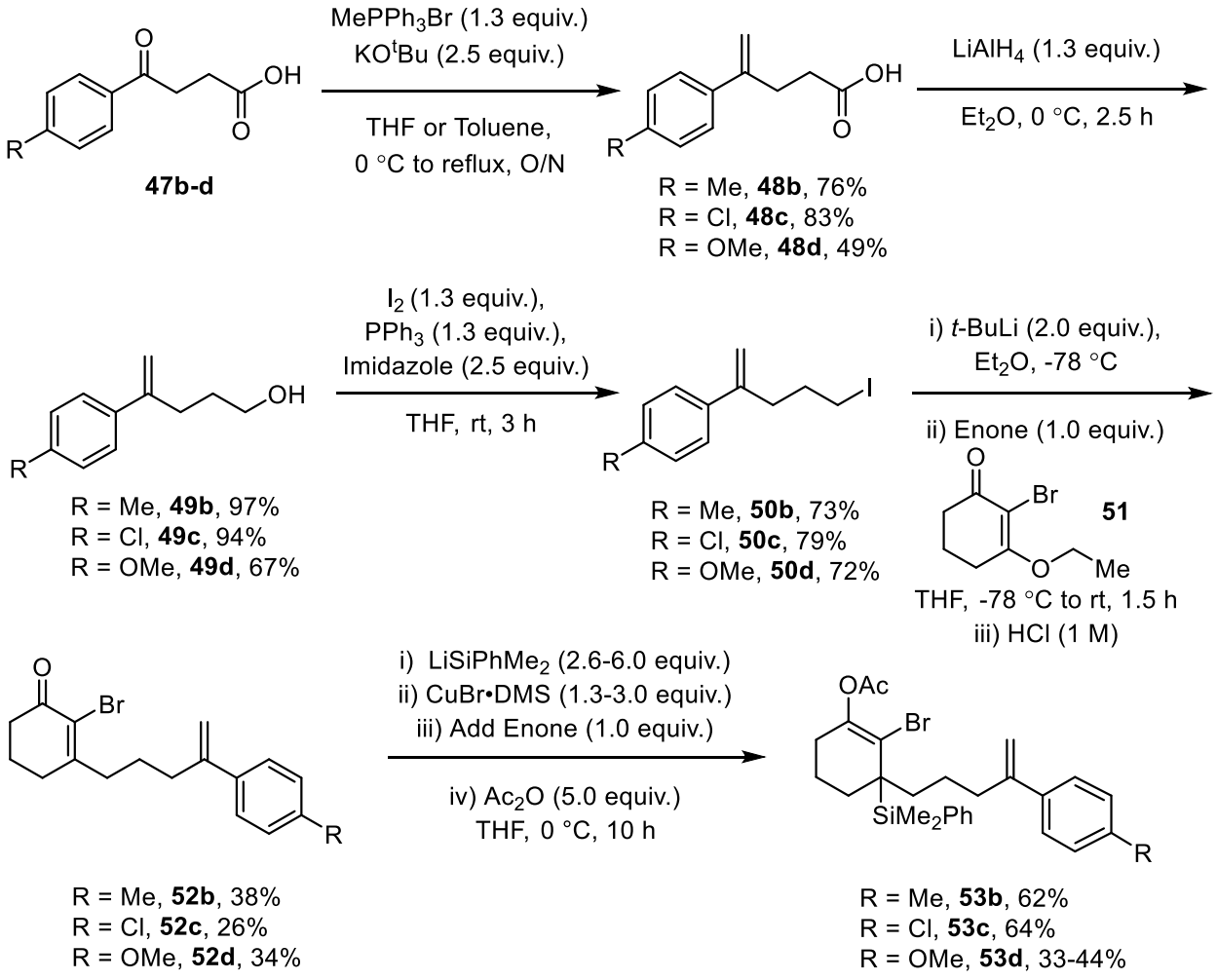
Figure 3.3 - Cyclobutane Hydrogens Coupling Through Enol Acetate π-system and nOe Interaction with Phenyl Ring

3.4.3 Probe of [2+2]-Cycloaddition Reaction with Different Phenyl Moieties

To examine the scope of this novel reaction and learn more about its mechanistic pathway we decided to synthesize a variety of derivatives where the phenyl ring was modified with different functional groups. Using *p*-methyl, *p*-chloro, and *p*-methoxy groups allowed a probe of the cycloaddition reaction with electron neutral, electron withdrawing, and electron donating substituents. A *p*-chlorophenyl derivative also opened the door to further synthetic modifications making use of cross-coupling methodology.

Starting with *p*-substituted 3-benzoylproponoic acids **47b-c** a Wittig methylenation (using $MePPh_3Br$ and KO*t*Bu in THF or toluene) provided **48b-c** in good yields (Scheme 3.14). For compound **47d** refluxing toluene was required to provide a moderate yield of 49%; under refluxing THF an inseparable mixture of starting material and product was always obtained. Subsequent reduction with LAH and an Appel reaction produced iodide fragments **50b-d** in good yields. With new conditions for the Stork-Danheiser transposition (see section **3.4.1**) intermediates **52b-d** were obtained in low yields. Unfortunately yields for the Stork-Danheiser were always lower with pendent styryl moieties than with furan (see Chapter **2**). One possible explanation for this is the ease with which styrene and related compounds can undergo anionic polymerization in the presence of organolithium reagents.[28] Silyl anion conjugate addition proceeded in moderate yields for compounds **52b-c** but only low and variable yield for **52d**. It is possible that the methoxy group

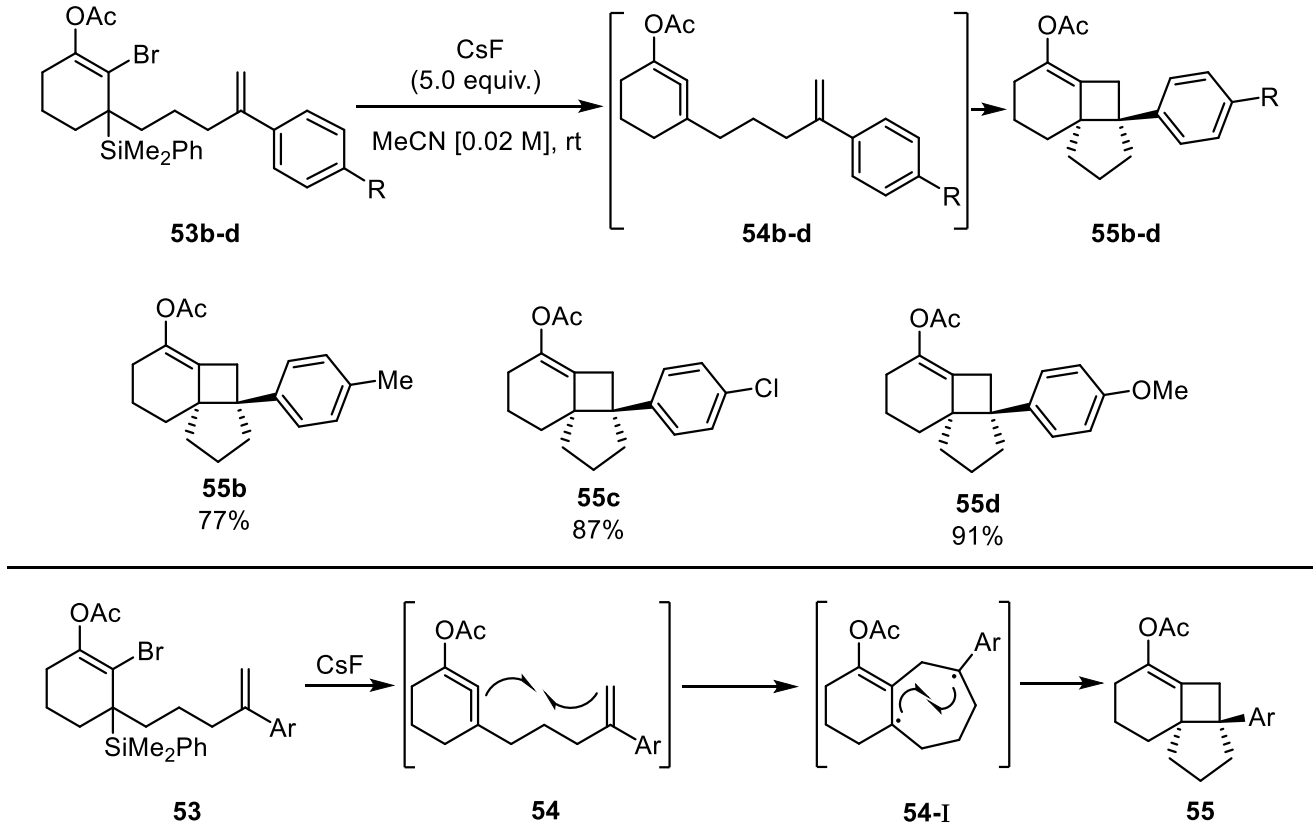
on **52d** is coordinating to the Gilman reagent and reducing the effectiveness of the conjugate addition.



Scheme 3.14 - Synthesis of Electronically Varied Pendent α-Carbon Moiety Substrates for Intramolecular [2+2]-Cycloaddition

Upon exposure to CsF allylic silanes **53b-d** generated 1,2-cyclohexadienes **54b-d** which underwent intramolecular [2+2]-cycloadditions with their tethered styryl moieties (Scheme 3.15). All cycloadducts were obtained in high yield as single products with no additional diastereomers or regioisomers visible in the crude ^{1}H NMR spectrum. Gratifyingly, an X-ray crystal structure of cycloadduct **55d** was obtained and confirmed the structural and stereochemical assignment (Figure

3.4).[29] Cycloadduct **55b**, with a *p*-methyl group, was isolated in 77% yield; this electron neutral (or slightly electron donating) group resulted in a small increase in yield vs unsubstituted **55a** (70%). Interestingly cycloadducts **55c** and **55d** were isolated in an even higher yield of 87% and 91% respectively. In section **3.2** it was shown that [2+2]-cycloadditions with acyclic allenes depend on the formation of a stable radical species. With the present intramolecular methodology, if the reaction proceeds through a stepwise mechanism involving initial 7-endo cyclization (Scheme 3.15) to form benzylic and allylic radical **54-I**, followed by transannular radical-radical coupling, the increased yields observed for species with more electron density in the aromatic ring may be due to additional stabilization of proposed diradical intermediates.



Scheme 3.15 - Intramolecular [2+2]-Cycloaddition of 1,2-Cyclohexadiene with Different Pendent Phenyl Groups and Proposed Stepwise Mechanism

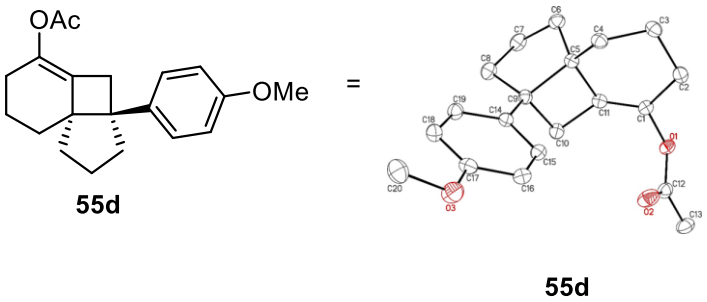
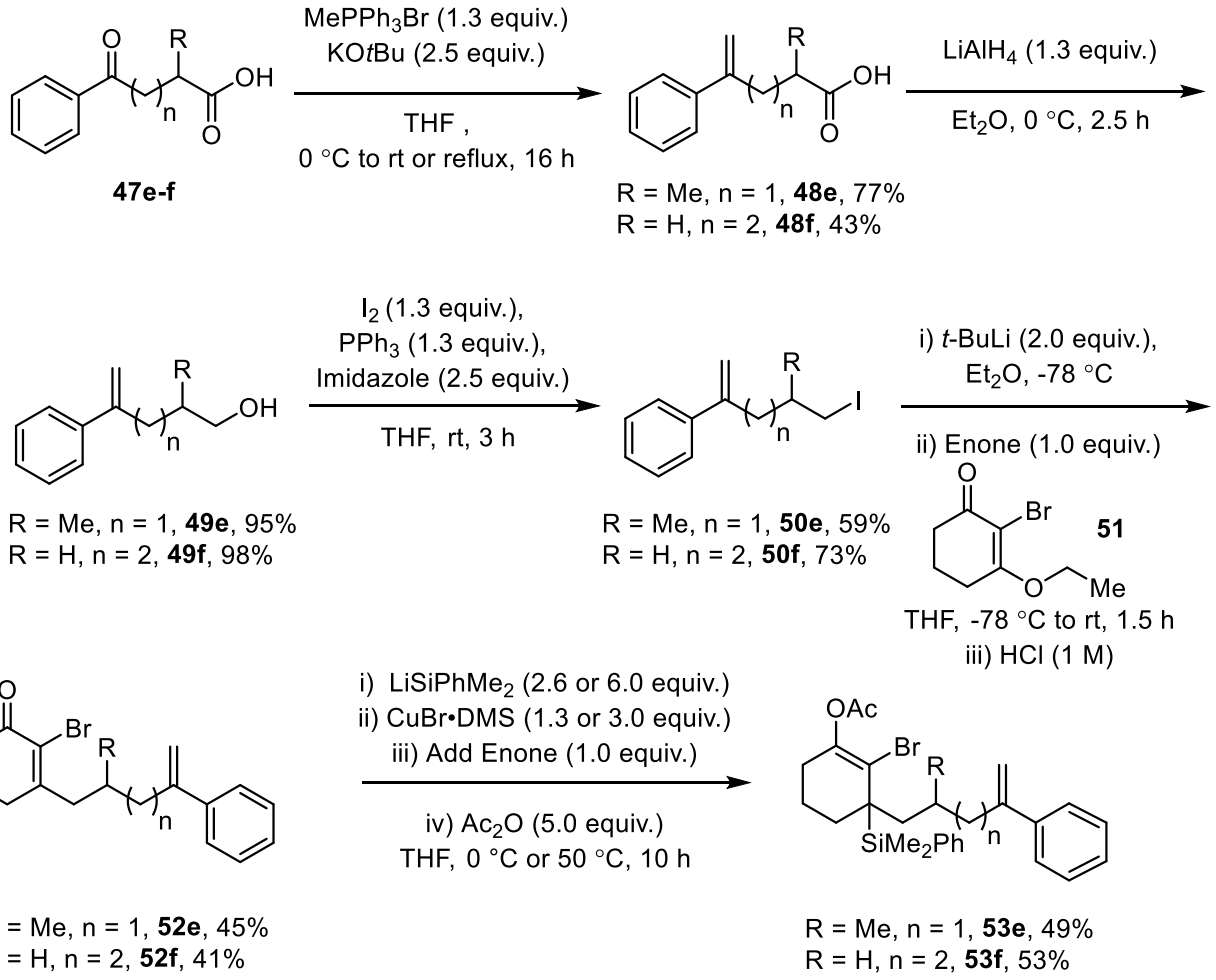


Figure 3.4 - X-Ray Crystal Structure for Cycloadduct 55d

3.4.4 Steric Probe of [2+2]-Cycloaddition Reaction

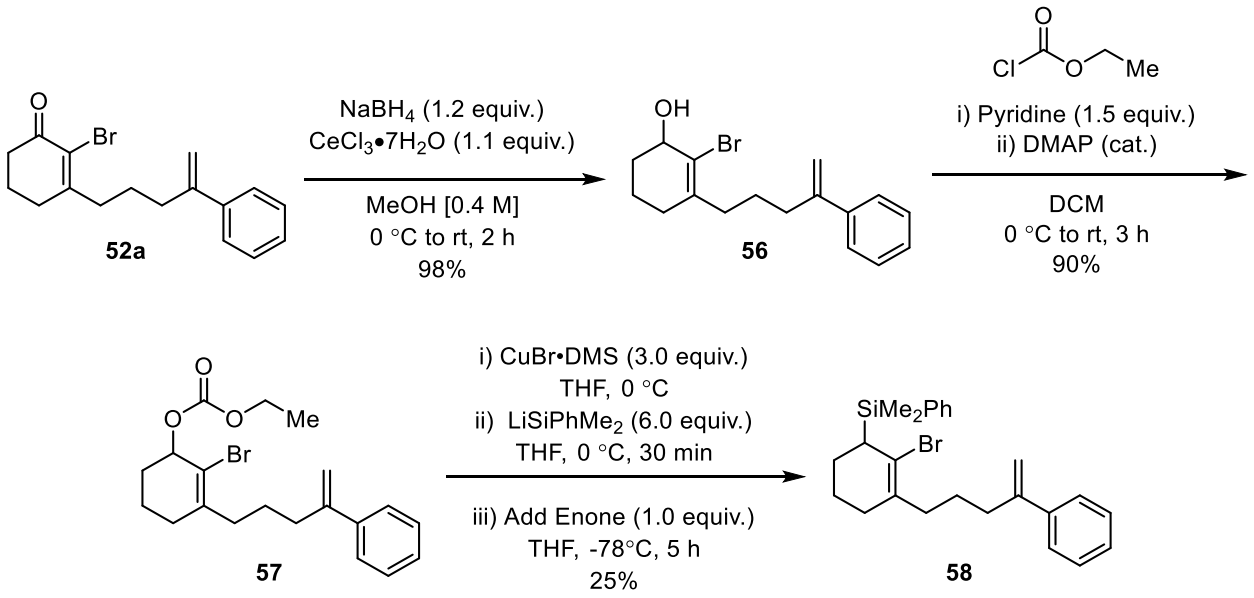
With the viability of the [2+2]-cycloaddition established (see section **3.4.3**), the next round of targets was designed to probe steric aspects of the cycloaddition. A substrate with an extended carbon tether allowed a probe into the effect of increasing the degrees of freedom of the tether; a similar substrate in the [4+2] methodology described in Chapter **2** afforded the trapping products in drastically reduced yield. Incorporation of a methyl branch on the 3-carbon tether would provide valuable information on the steric cost of additional substitution, as well as the possible benefit through either Thorpe-Ingold steric compression or reactive rotamer effects. Additionally, a substrate lacking acetoxy substitution on the allene was targeted to probe whether reduced allene substitution would lead to diminished trapping yields due to competing dimerization side-reactions (see Chapter **2**, section **2.4.6**).

Starting with **47e** a Wittig reaction provided **48e** in a good yield of 77% (Scheme 3.16). For compound **47f** refluxing THF provided a moderate yield of 43%. Subsequent reduction with LAH, Appel reaction, Stork-Danheiser transposition and silyl anion conjugate addition proceeded in moderate yields to eventually generate allylic silane starting materials **53e-f**.



Scheme 3.16 - Synthesis of Extended and Methyl Substituted Carbon Tether Substrates for Intramolecular [2+2]-Cycloaddition

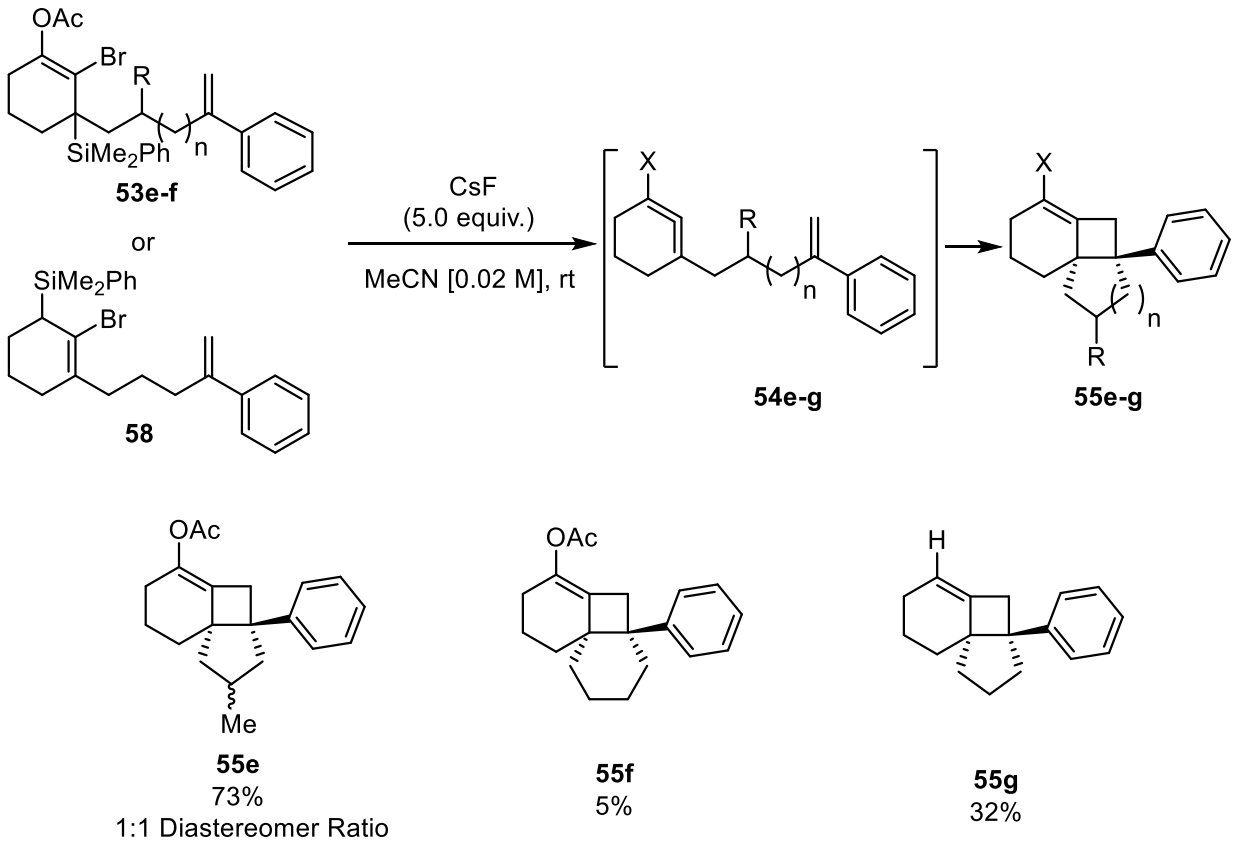
Using a variation on the methodology of Sawamura and co-workers to generate allylic silanes from the corresponding carbonates (see Chapter **2**, section **2.4.6**)[30] allylic alcohol **56** was reacted with ethyl chloroformate to produce allylic carbonate **57** in 90% yield (Scheme 3.17). Carbonate **57** was then converted to allylic silane **58** in 25% yield. While the yield for the last transformation was low it still enabled access to enough of the desired starting material to test the [2+2]-cycloaddition.



Scheme 3.17 - Synthesis of Allylic Silane Lacking Acetoxy Substituent via Allylic Carbonate Intermediate

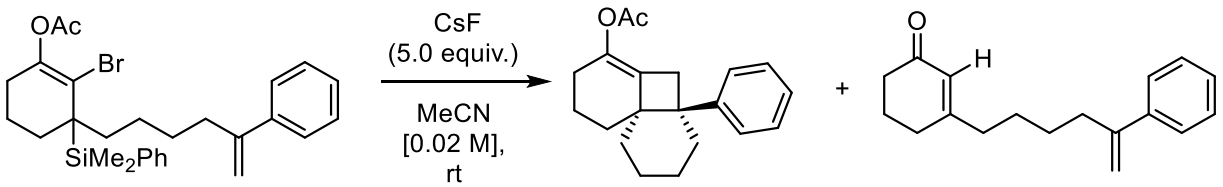
Upon exposure to CsF allylic silanes **53e-f** and **58** generated 1,2-cyclohexadienes **54e-g** which underwent intramolecular [2+2]-cycloadditions with their tethered styrene moieties (Scheme 3.18). All cycloadducts were obtained as single regioisomers and **55f-g** were further obtained as single diastereomers. With cycloadduct **55e** containing a methyl group on the carbon tether a 1:1 mixture of inseparable diastereomers was obtained in a combined yield of 73%. The small increase in yield vs the parent example (70%) suggests that any benefit derived from the Thorpe-Ingold effect of a single methyl branch is negligible; an example with a geminal dimethyl group would allow a more robust look into this question and is a potential avenue for future work. The added spectral complexity caused by the presence of a stereocenter in the tether was exacerbated by the inability to successfully separate the diastereomers, requiring characterization as a mixture. With cycloadduct **55f** a dramatic drop in yield was evident; this example once again demonstrates the importance of having a tether that can properly align itself for the cycloaddition but does not have too many degrees of freedom (see Chapter **2**, section **2.3**). For cycloadduct **55g** the yield obtained is remarkably close to the analogous [4+2] trapping with furan (see Chapter **2**, section **2.4.6**). One explanation for the diminished yield without acetoxy substitution is that

increased oligomerization side-reactions are taking place due to less steric bulk around the 1,2-cyclohexadiene.



Scheme 3.18 - Effect of Tether Length, Substitution, and Absence of Allene Acetoxy Substituent on Intramolecular [2+2]-Cycloaddition

In the case of substrate **53f** with a 4-carbon tether, the desired cycloadduct **55f** was isolated in only 5% yield, along with a second product (Scheme 3.19). This was found to be cyclohexenone **59**, which was the major project, albeit in only 24% yield. This type of side-product was seen previously in attempted [4+2]-trapping reactions (see Chapter **2**, section **2.3**) and using β-tethered styrene traps (see section **3.4.1** of this chapter). It is likely that **59** is generated through nucleophilic cleavage of the acetoxy moiety of allene **55g** and subsequent protonation. It is proposed that the longer tether reduced the efficiency of the initial cyclization, since that would require an 8-endo cyclization to form the diradical.



53f **55f** 5% **59** 24%

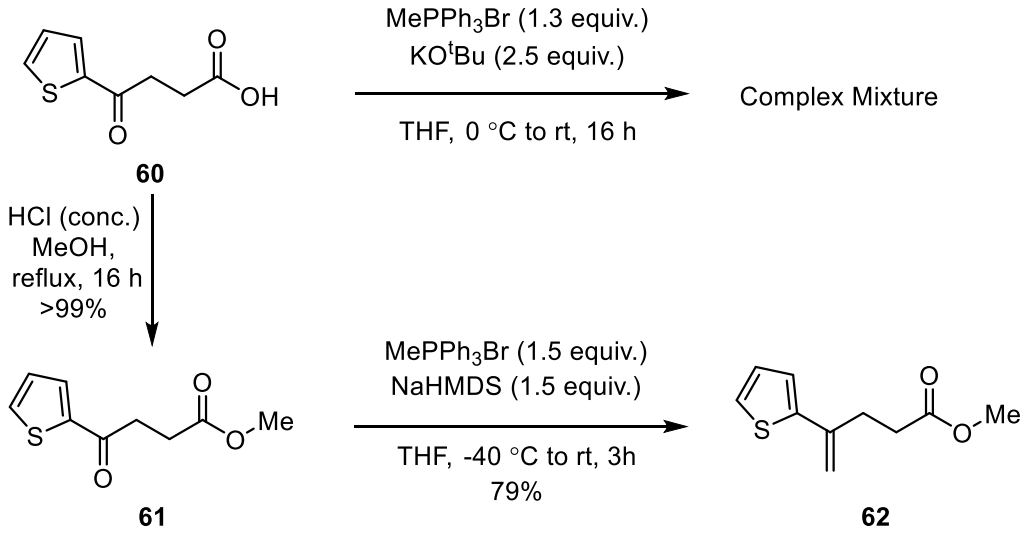
Scheme 3.19 - Intramolecular [2+2]-Cycloaddition of 53f and Major Cyclohexenone Product

3.4.5 Attempted Preparation of Thiophene Containing Tether

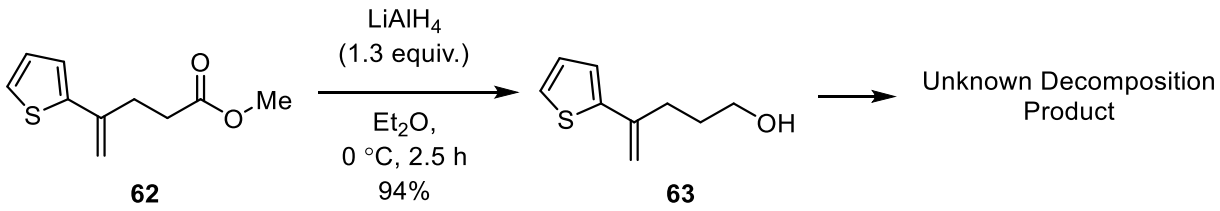
Through the cycloadducts previously discussed in section **3.4.3** we demonstrated that a stabilized tertiary benzylic radical enabled the [2+2]-cycloaddition to proceed in high yields. The question of whether other aromatic rings could be used in place of the phenyl group and still achieve effective [2+2]-cycloaddition was an appealing prospect. In place of a phenyl group we imagined a thiophene moiety might enable the desired transformation to be realized. We were also interested in the question of possible alternative [4+2] reactivity involving the heteroaromatic ring, which could potentially compete with the stepwise [2+2] process. However, we deemed this outcome to be unlikely, given the high aromatic character of thiophene, which should disfavor Diels-Alder reactivity.

To test this idea, we began synthesizing a thiophene containing tether. Starting with carboxylic acid **60** a Wittig reaction under our standard conditions resulted in a complex mixture (Scheme 3.20). To avoid any complications potentially caused by the carboxylic acid moiety a Fischer esterification with methanol was performed to accesses methoxy ester **61** in quantitative yield. Use of sodium bis(trimethylsilyl)amide as a replacement base for KO*t*Bu at 0 °C resulted in the synthesis of Wittig product **62** in 22% yield; when the reaction was cooled to -40 °C for 3 h an increased yield of 79% was obtained. Subsequent reduction of the ester moiety with LAH provided alcohol **63** in 94% yield (Scheme 3.21). While the initial reduction appeared clean, after storage overnight in a freezer intermediate **63** would start to decompose into an unknown product. To overcome this the Appel reaction to access **64** in 56% yield was performed immediately after the synthesis of **63** (Scheme 3.22). Unfortunately, the Stork-Danheiser transposition gave a complex

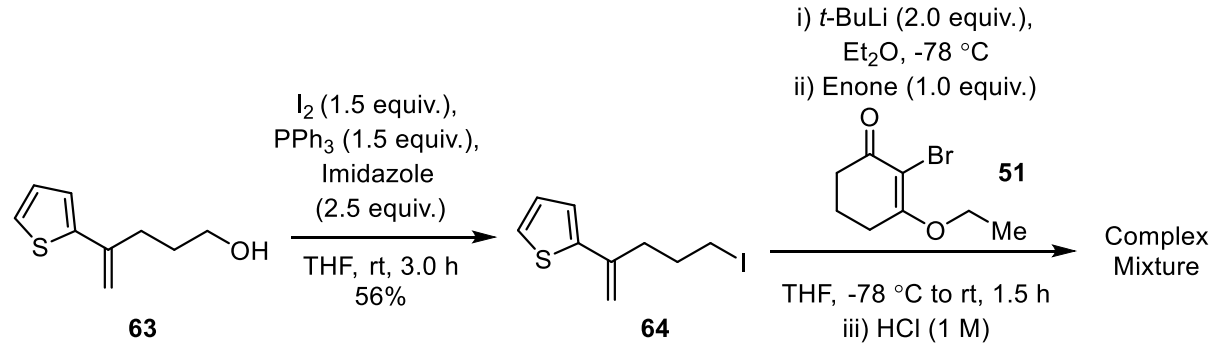
mixture from which no products could be characterized, and this substrate could not be developed further.



Scheme 3.20 - Synthesis of Methyl 4-(2-Thienyl)-4-pentenoate 62



Scheme 3.21 - Spontaneous Decomposition of Alcohol Intermediate 63

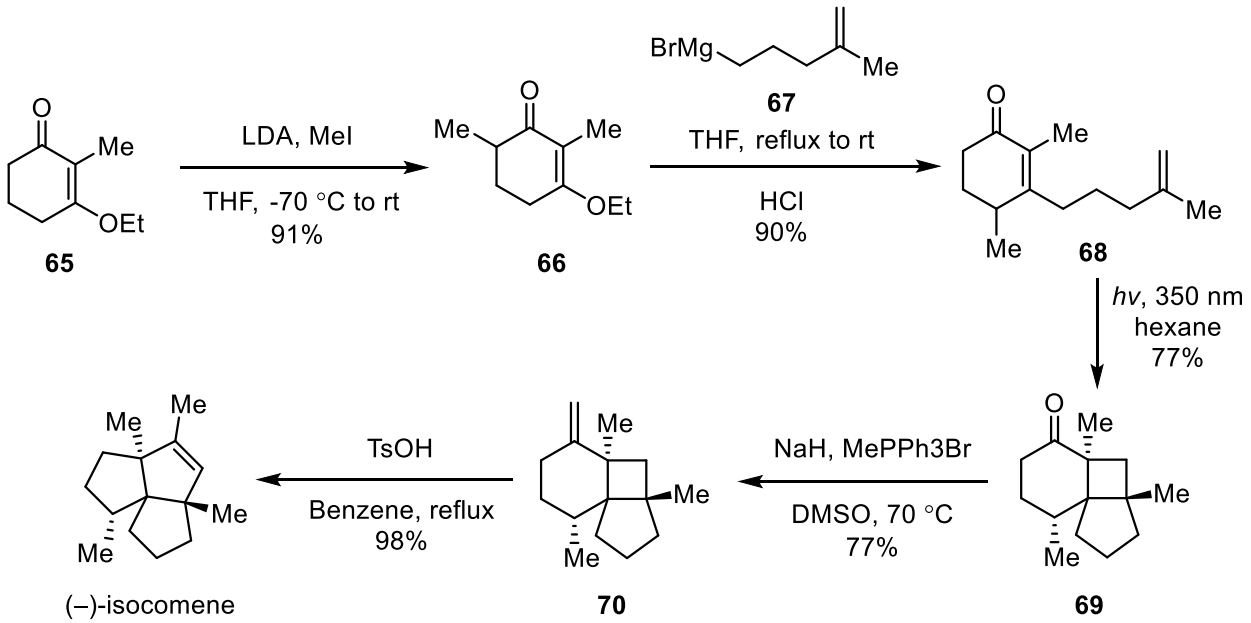


Scheme 3.22 - Attempted Stork-Danheiser Transposition of Thiophene Containing Compound

3.4.6 A Preliminary Approach to Isocomene

The results described above show that a general route is accessible to form highly strained tricyclo[6.3.0.$0^{1,6}$]undecene skeletons via [2+2]-cycloaddition trapping of 1,2-cyclohexadienes with pendent styrenes. Although the methodology we have developed is unique with regard to harnessing the strain energy resident in cyclic allenes, it is not the only route to these core structures. Intramolecular [2+2]-photocycloadditions of cyclohexenones with pendent alkenes have also been used to access similar structures containing the tricyclo[6.3.0.$0^{1,6}$]undecane core (see section **3.1**).[31]

This tricyclo[6.3.0.$0^{1,6}$]undecanone structural motif was key for the synthesis of the natural product (–)-isocomene by Pirrung.[26,32] Starting from β-ethoxy enone **65** Pirrung obtained α-methyl enone **66** with LDA and MeI in 91% yield (Scheme 3.23). A Stork-Danheiser transposition with Grignard regent **67** then produced enone **68** containing a tethered olefin moiety. The subsequent key step involved a photochemical [2+2] cycloaddition between the enone and olefin to produce **69** in 77% yield with a tricyclo[6.3.0.$0^{1,6}$]undecanone core. This cycloaddition produced cycloadduct **69** as a single diastereomer, which Pirrung rationalized based on preferential approach of the pendent alkene from the opposite face to the γ-methyl substituent of enone **68**.[33] A Wittig reaction to afford alkene **70** in 77% yield followed by an acid catalyzed rearrangement provided (–)-isocomene in 98% yield. In total Pirrung obtained (–)-isocomene in 34% yield over 7 steps.



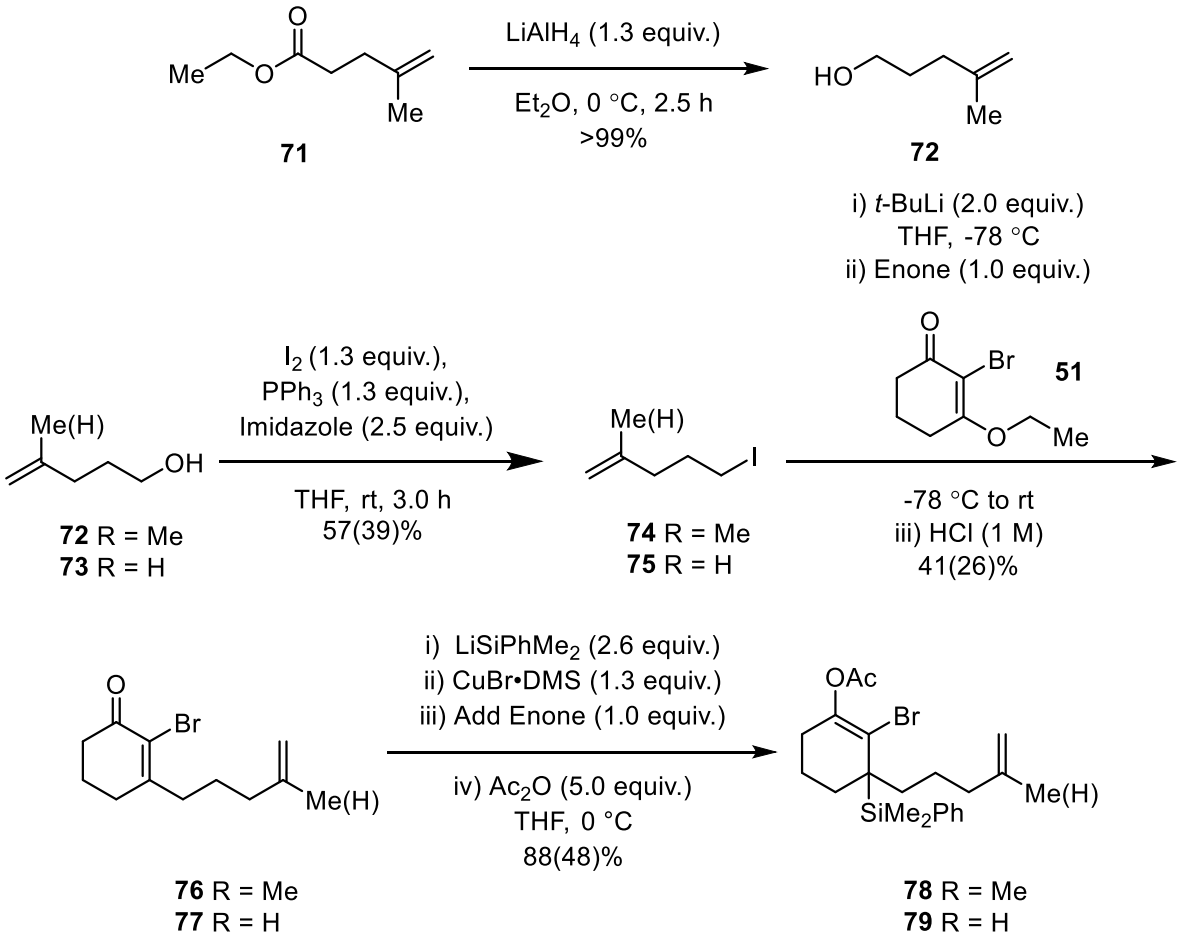
Scheme 3.23 - Synthesis of Isocomene by Pirrung

3.4.7 Attempted [2+2]-Cycloaddition with Simple Olefins

The notable resemblance of Pirrung's photochemical [2+2]-cycloaddition product to the products of intramolecular styrene trapping of cyclic allenes causes us to consider whether isocomene or one of Pirrung's intermediates could be obtained via cyclic allene [2+2]-cycloaddition. In particular, the presence of an enol acetate in the product corresponded to the location of the ketone in **69**, with the potential for bridgehead methylation via unmasking of an enolate. However, our process is presumed to involve a strained ground state reactant, which although highly reactive, is probably less energetic than the photoexcited enone used in Pirrung's synthesis. Therefore, we wondered whether a less stabilizing methyl group on the olefin trap would be tolerated in the desired [2+2] process.

To evaluate the feasibility of this approach, a tether with a terminal mono or di-substituted olefin was synthesized (Scheme 3.24). In the case of the di-substituted olefin the synthesis commenced with the reduction of ester **71** to alcohol **72** with LAH in quantitative yield. The corresponding monosubstituted 4-penten-1-ol **73** was obtained from commercial sources. Alcohols **72** and **73** were then converted to their corresponding iodides via an Appel reaction in 57 and 39% yield respectively; the lower yield for these transformations was due in part to the low molecular

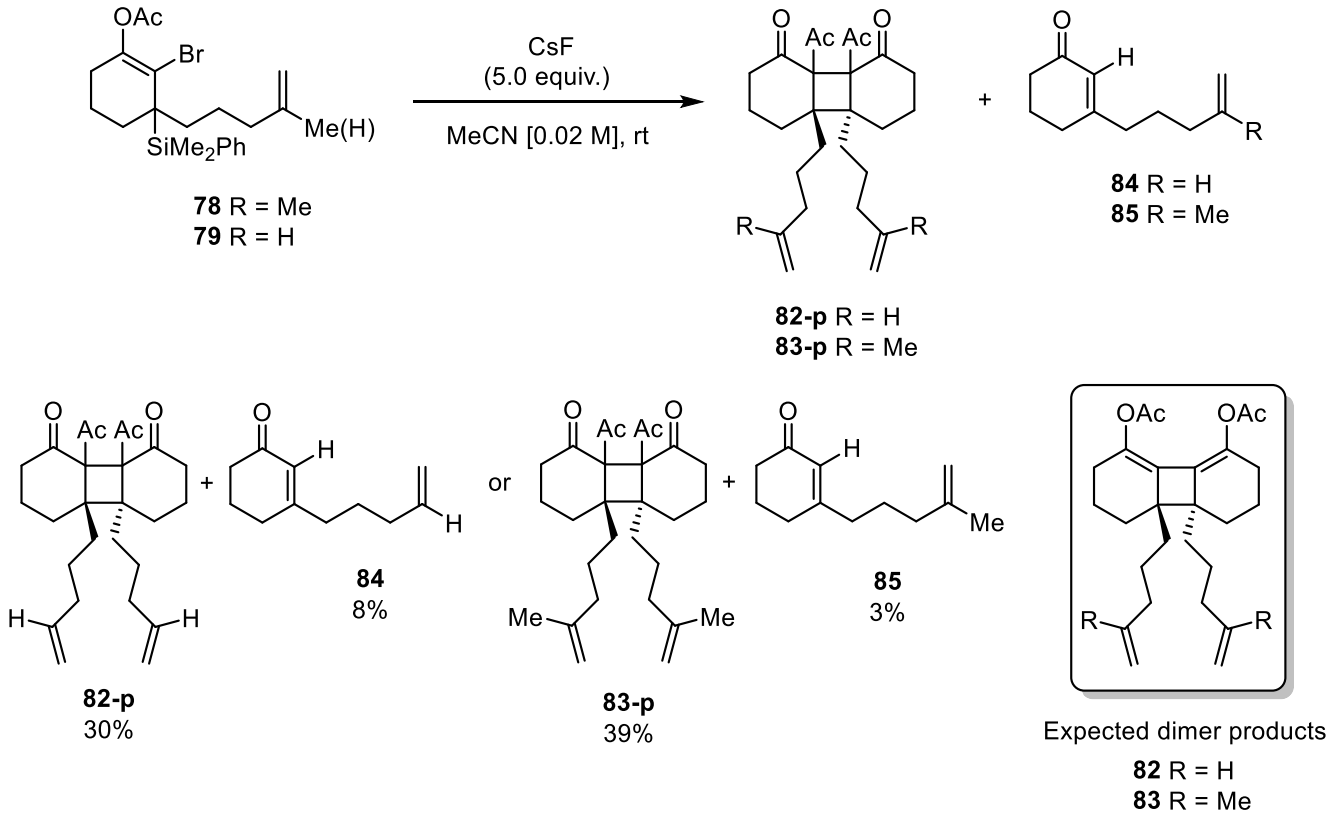
weight and volatility of the products. After a Stork-Danheiser transposition that proceeded in moderate yield and efficient silyl anion conjugate addition, the desired starting materials for the cycloaddition reaction, olefins **78** and **79** were obtained.



Scheme 3.24 - Synthesis of Simple Olefin Containing Starting Materials

Upon exposure to CsF allylic silanes **78** and **79** were expected to generated the corresponding 1,2-cyclohexadienes intermediates which we hoped would undergo intramolecular [2+2]-cycloadditions with their tethered olefin moieties. The successful intermolecular cycloaddition of phenylsulfonyl allenes tethered with di-substituted olefins to generate a bicyclo[3.2.0]heptane core demonstrated by the Padwa group (see Scheme 3.8) made us optimistic about the possibility of this transformation.[12,13] Unfortunately, no trace of the desired cycloadducts was seen in the crude reaction mixture. Instead protonated cyclohexenone products **84**/**85** were formed under the reaction conditions (Scheme 3.25). With mono-substituted olefin substrate **79**

cyclohexenone product **84** was obtained in 8% yield while with di-substituted olefin **78** cyclohexenone product **85** was isolated in 3% yield. In addition to the cyclohexenone products isolated another set of compounds, 1,3-diketone structures **82-p/83-p** were isolated from the reaction mixtures. With compound **83-p** obtained in 39% yield the obtained HRMS data shows a (M+Na)+ peak for $C_{28}H_{40}NaO_4$ at 463.2815 m/z+. This in conjunction with the ^1H NMR spectrum data which clearly shows two alkenyl resonances at 4.73 and 4.67 ppm, two singlet methyl peaks at 2.32 and 1.71 ppm, and 12 other aliphatic protons between 2.5 and 1.5 ppm originally led us to believe that the dimer product **83** had been formed. The formation of this dimer product would not be unexpected one as in section **3.4.3** all the formed cycloadducts had an aromatic ring conjugated to the reacting olefin. In the present examples however, no aromatic ring is conjugated to the olefin and the resulting stabilized benzylic radical seen in previous examples cannot be generated. The absence of a stabilizing aryl substituent apparently raises the transition state energy for the initial cyclization to the diradical sufficiently that the competing dimerization process predominates. The ^{13}C NMR spectrum and IR data however tell a different story and suggest the actual structure is **83-p**. In all our acetoxy substituted cycloadducts a clear peak around ~170 ppm is visible in the ^{13}C NMR spectrum. In the present example however, this is replaced by two peaks at 204.5 and 197.3 ppm which suggests the presence of two ketone carbons. The presence of two distinct ketone stretches in the obtained IR spectrum at 1703 and 1666 cm^{-1} respectively, being well below the frequency observed for our acetoxy substituted examples, also supports the notion of structure **83-p**. The same analysis holds true for expected dimer **82** and isolated product **82-p**. One possible explanation for the formation of these unexpected products could be a 1,3-acyl shift after formation of dimer products 82 and 83. This shift however has not been observed in any other dimers of acetoxy substituted 1,2-cyclohexadiene and warrants further investigation.

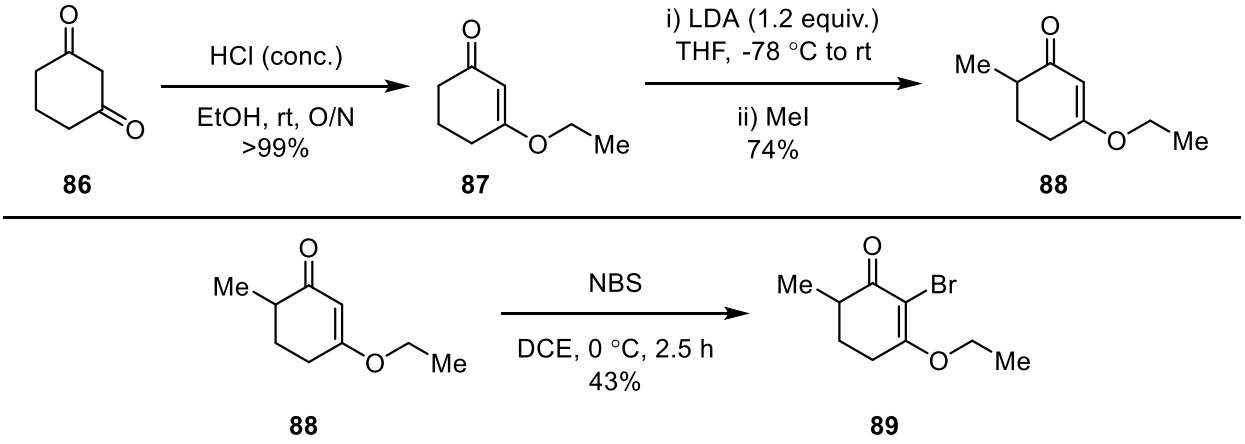


Scheme 3.25- Attempted [2+2]-Cycloaddition with Non-Styrene Olefin Containing Starting Materials

3.4.8 Attempted Incorporation of a Methyl Branch Allylic to the Allene

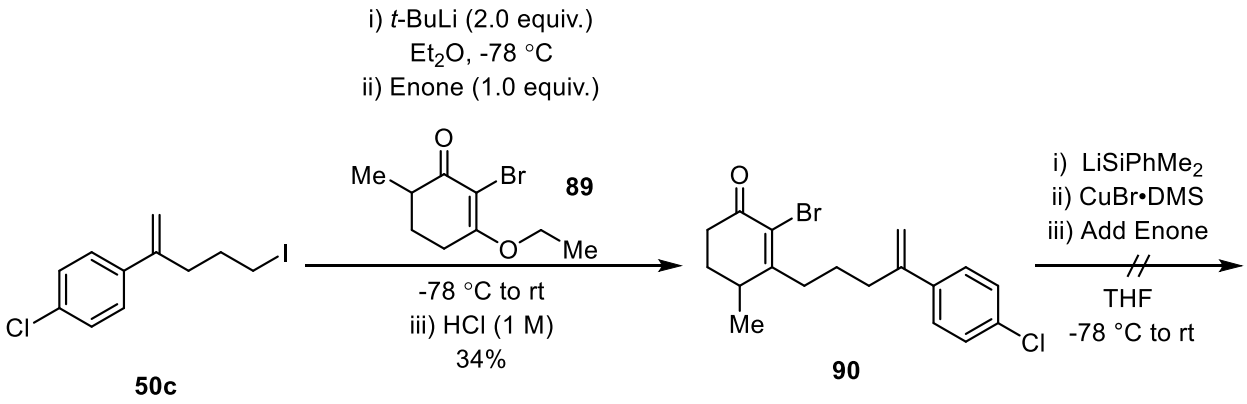
For the synthesis of the natural product (–)-isocomene by Pirrung a γ-methyl enone was required (see Scheme 3.23).[26,32] Despite the failure of tethered olefins to react in our methodology (see section **3.4.7**) we were intrigued by the possibility of incorporating a methyl branch allylic to the allene into our reaction scope. The incorporation of a methyl branch on our 1,2-cyclohexadiene substrates would serve as a probe of how a group on the allylic position would affect the cycloaddition reaction while at the same time generating a more complex structure through the introduction of a new stereocenter. Additionally, the pathway through which the methyl branch would be introduced, α-alkylation of a cyclohexenone, would allow for the introduction of a variety of other groups on the allene moiety and greatly expand the scope of this new methodology. To test these ideas α-methyl cyclohexenone **88** was synthesized from cyclohexenone **87** (Scheme

3.26). Deprotonation with LDA and subsequent alkylation with methyl iodide enabled the synthesis of **88** in 74% yield. Replacement of the methyl iodide with other electrophiles would enable the aforementioned expanded scope. Subsequent bromination with NBS provided bromo-enone **89**, required for the Stork-Danheiser transposition, in 42% yield.



Scheme 3.26 - Synthesis of α'-Methyl-Bromo-Cyclohexenone

For the Stork-Danheiser transposition of enone **89**, *p*-chlorostyrene compound **50c** would provide accesses to an assumed final target with added complexity via substitution in the cyclohexene ring. While the Stork-Danheiser transposition proceeded in 34% yield the subsequent conjugate addition reaction would not proceed under all conditions tested. In all cases large amounts of starting material were recovered, along with some apparent decomposition products that were not characterized. The methyl group in the γ-position of **90** was assumed to be preventing the addition of the Gilman reagent through steric hindrance by blocking approach of the reagent (Figure 3.5). In Chapter **2** section **2.4.6** and Chapter **3** section **3.4.4** it was described how there are multiple ways to access allylic silanes, including a paper from Sawamura and co-workers on the syntheses of silanes from allylic carbonates.[30] The corresponding carbonate intermediates that were synthesized for the [4+2] methodology appeared to react in an S_N2 like substitution reaction. This alternative pathway to a silane should avoid the problems in the present conjugate addition as the delivery of silicon would no longer take place adjacent to the methyl-branched methine carbon.



Scheme 3.27 - Attempted Conjugate Addition with γ-Methyl Substrate

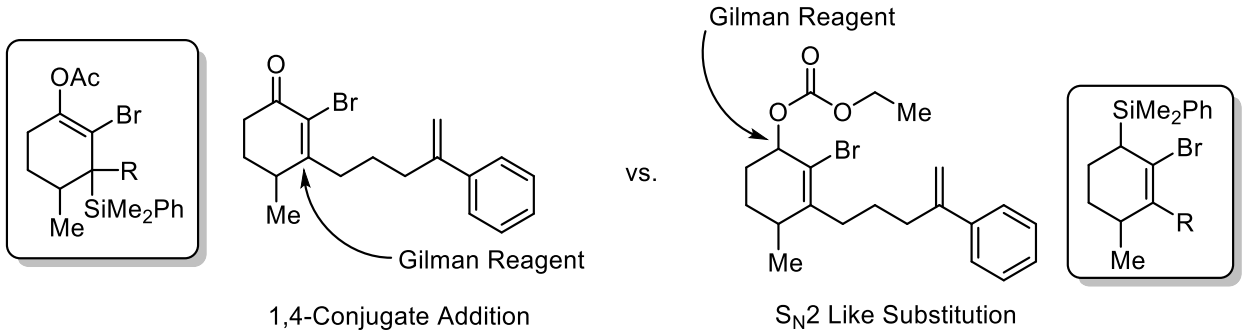
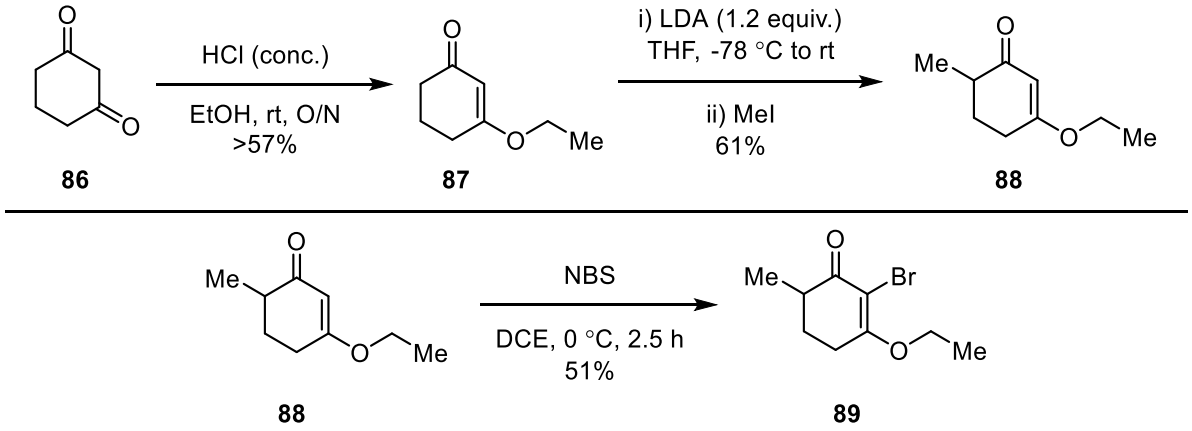
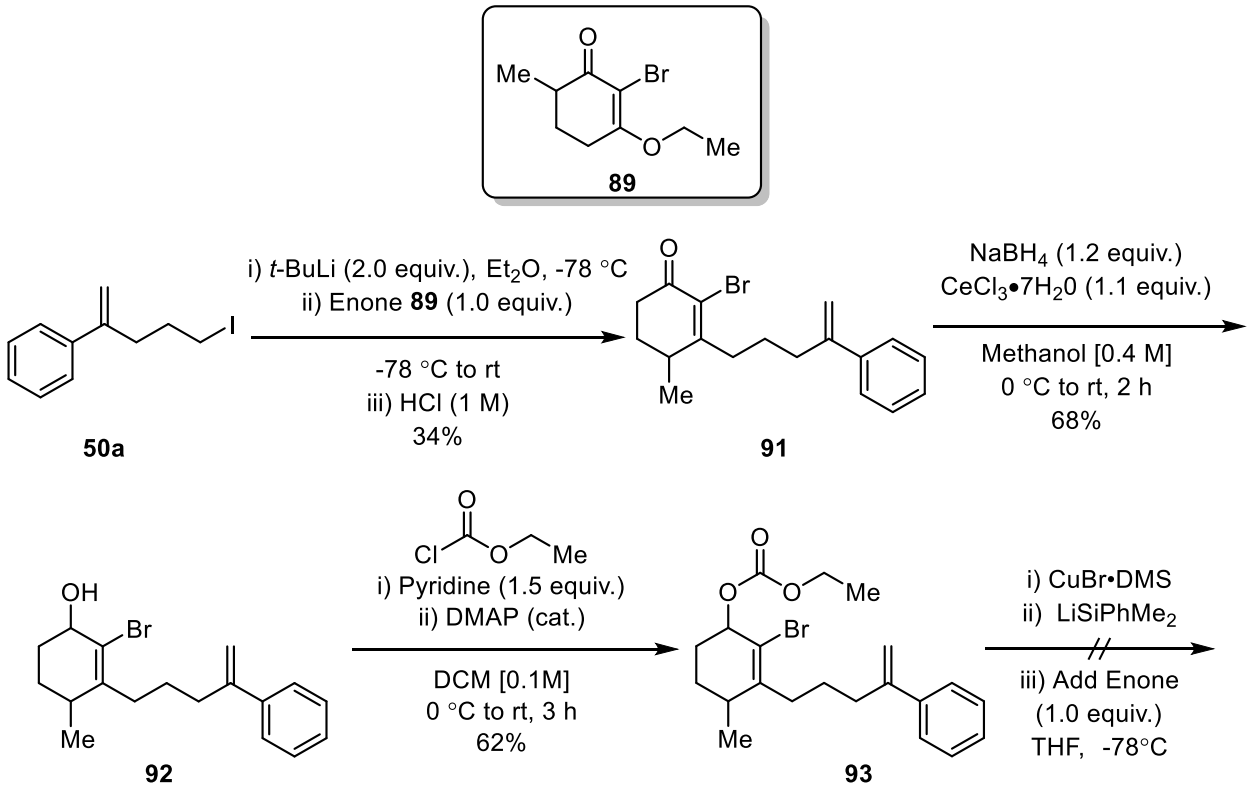


Figure 3.5 - Alternative Reaction Pathway to Access Desired Substrate

The idea for the incorporation of a methyl branch allylic to the allene was developed into a project for undergraduate researcher Alexis Ochoa (Scheme 3.28). Starting from 1,3-cyclohexanone **86**, Alexis was able to synthesize α-methyl-bromo-cyclohexenone **89** and react it with styrene **50a** to produce Stork-Danheiser transposition product **91**. Reduction of the ketone in **91** and acylation of **92** with ethyl chloroformate enabled accesses to carbonate **93**. Unfortunately carbonate **93** did not appear to undergo the expected S_N2-like substitution reaction. As with cyclohexenone **90** (Scheme 3.27) in all attempted reactions the major product isolated was starting material.



Scheme 3.28 - Synthesis of α-Methyl-Bromo-Cyclohexenone by Alexis Ochoa



Scheme 3.29 - Attempted S_N2 Reaction with Methyl Substrate by Alexis Ochoa

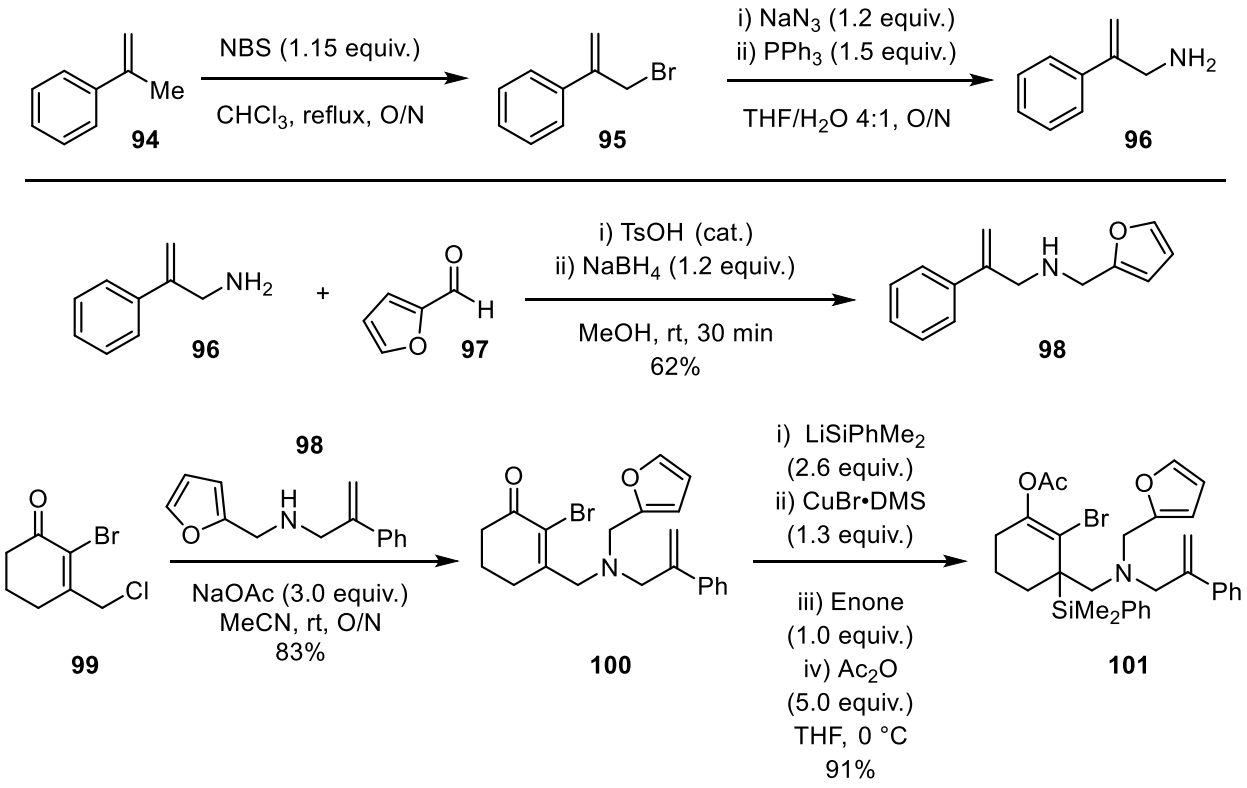
3.4.9 Incorporation of Heteroatoms into Tether

As with our [4+2] methodology compounds containing heteroatoms in the tether were of great interest during the examination of the scope of the [2+2] methodology. In our examination of the scope in the [4+2] methodology the only heteroatom we could successfully incorporate into

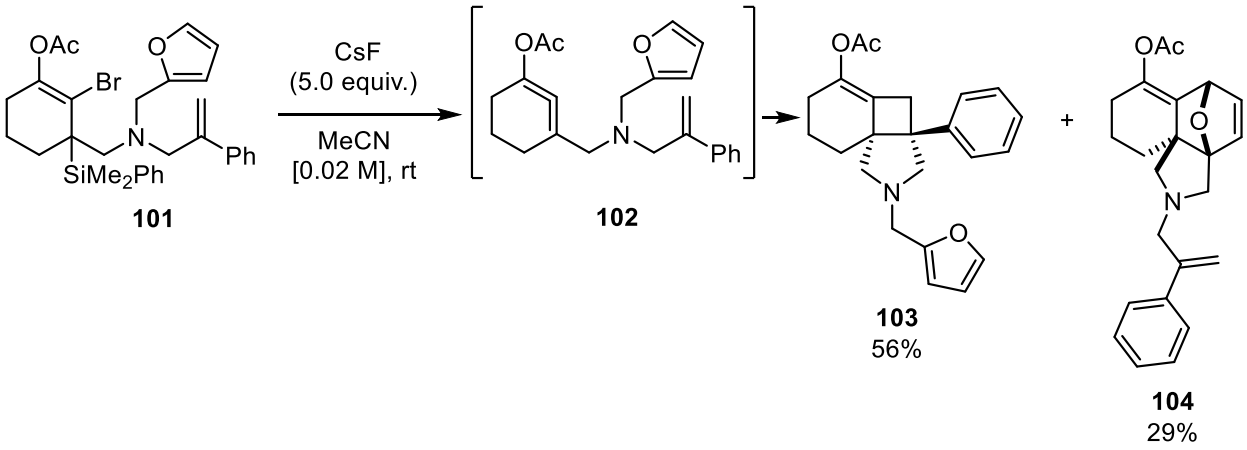
the tether was a nitrogen atom in the form of a tertiary amine. Given this prior experience, examination of heteroatom-containing tethers in the [2+2] substrates focused only on nitrogen. The secondary amine tether used to synthesize analogous substrates also presented the ability to have both a styrene moiety and a furan moiety present in our substrate. Interestingly would permit the examination of competing [2+2] and [4+2]-cycloaddition pathways for the intermediate allene, and we were interested in seeing if one pathway takes precedence over the other.

The synthesis of a nitrogen-tethered substrate commenced with α-methylstyrene **94**, whose treatment with NBS furnished allylic bromide **95** (Scheme 3.30).This volatile intermediate was used as a crude mixture in the subsequent azide displacement and Staudinger reduction to access primary amine **96**. With the amine compound in hand a reductive amination with furfural **97** gave secondary amine **98** in 62% yield which contained both a styrene and furan moiety, either of which could potentially react in an intramolecular cycloaddition reaction with the transient 1,2-cyclohexadiene. Using previously synthesized enone **99** and the secondary amine an S_N2 reaction generated compound **100** in 83% yield which now had the nitrogen tether incorporated into the allene precursor. Silyl anion conjugate addition then enabled access to the desired substrate **101** in 91% yield. With this compound in hand we were able to test the [2+2]-cycloaddition with a nitrogen in the tether and see if any [4+2] cycloadduct was produced.

Generation of allene **102** under the standard conditions afforded two main products, [2+2]-cycloadduct **103** in 56% yield, and [4+2]-cycloadduct **104** in 29% yield (Scheme 3.31). Importantly this example demonstrated the tolerance of the methodology to the presence of an amino group in the tether. The apparent preference for reaction via the [2+2] manifold, as evidenced by the ca. 2:1 ratio of **103** to **104**, was also interesting. The fact that [2+2]-cycloaddition seems to be more facile is consistent with the generally higher yields observed in the styrene trapping reactions as compared with the furan trapping.



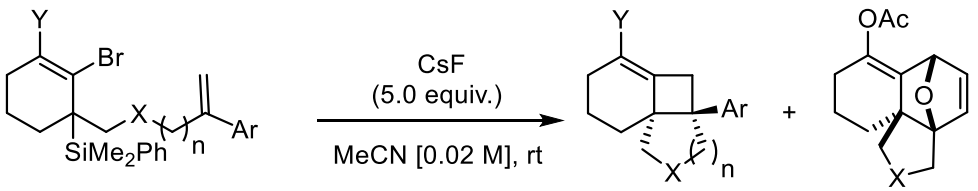
Scheme 3.30 - Synthesis of Starting Material Containing Nitrogen and Potential [2+2] and [4+2] Trapping Moieties



Scheme 3.31 - Competitive Cyclic Allene Trapping By [2+2]- and [4+2]- Cycloaddition

3.5 Conclusion

In conclusion we have expanded upon the first intramolecular Diels-Alder reaction of 1,2-cyclohexadiene and pendent furans presented in Chapter **2** by introducing styrene as an alternative intramolecular trapping moiety for [2+2]-cycloaddition reactions. Our general substrates and modular synthesis approach have enabled the synthesis of 9 cycloadducts obtained as racemic mixtures apart from cycloadduct **55e** which was also obtained as a 1:1 mixture of diastereomers. The relative configuration of the cycloadducts was determined by a combination of X-ray crystallographic analysis and characteristic NMR spectral features. These tricyclic products were produced under mild conditions and in a single step from their starting materials. We have also demonstrated the remarkable improvement to atom economy offered by an intramolecular vs. intermolecular approach to reactions with 1,2-cyclohexadiene. We have gained valuable insight into the factors that affect the efficiency of this cycloaddition such as tether length and electron availability in the pendent aryl ring. Importantly we have shown that substrates bearing both a [4+2] and [2+2] trapping moiety can both undergo the desired cycloadditions with the [2+2] pathway being the favored outcome. Overall, this new methodology represents an important extension of the seminal work presented in Chapter **2**.



Scheme 3.32 Competing Intramolecular Capture of a 1,2-Cyclohexadiene by Pendent Styrene and Furan Traps

3.6 Experimental Data

3.6.1 General Information

Unless otherwise noted, all reactions were performed in glassware that was dried in an oven (200 °C) overnight or flame-dried immediately prior to use under a positive nitrogen

atmosphere. Reagents were transferred with oven-dried syringes or cannulas. All solvents, unless otherwise noted, were dried using either a solvent purification system or by distillation. MeCN, NEt_3, and DCM were distilled from calcium hydride; Et_2O, and THF were distilled from sodium/benzophenone and toluene was distilled from sodium metal. Reagents were used as purchased from the Sigma-Aldrich, Oakwood, and Alfa Aesar corporation unless otherwise noted. Glass plates with 0.25 mm Kieselgel 60 F254 Silica (Merck) were used for all thin layer chromatography; column chromatography was performed with 230-400 mesh silica gel (Silicycle). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz, 500 MHz or 700 MHz and coupling constants (*J*) are reported in Hertz (Hz). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100MHz, 125 MHz or 175 MHz. All chemical shifts are referenced to residual solvent peaks ($CDCl_3$: s, 7.26 ppm, ^{1}H; t, 77.06 ppm, ^{13}C) as internal standards and reported in δ (ppm). Standard notation is used to describe all observed ^{1}H NMR signal multiplicity: broad (br), apparent (app), multiplet (m), singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), etc. Infrared spectra were measured with a Mattson Galaxy Series FT-IR 3000 spectrophotometer. HRMS data (EI technique) were recorded using a Kratos MS50 instrument and HRMS (ESI/APPI technique) were recorded using an Agilent 6220 oaTOF instrument.

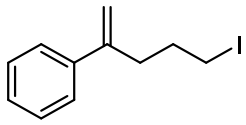
3.6.2 Physical Data

Compounds **48a-f**, **49a-f**, **50f**, **74**, and **75** are known literature compounds whose spectral data matches those reported in prior publications.[34-41]

General Procedure for Appel Reaction

Iodine (1.3-1.5 equiv.) was added to a solution of triphenylphosphine (1.3-1.5 equiv.) and imidazole (2.5 equiv.) dissolved in THF [0.4 M] at -20°C. A solution of the alcohol (1.0 equiv.) dissolved in a minimum amount of THF (~1.0 – 2.0 mL) was added over 2-3 min and the reaction stirred for 30 min before warming to rt. The solution was further stirred until the reaction was complete as determined by TLC. $NaHCO_3$ (sat) (30 mL) was added and the resulting precipitates were removed by filtration. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with 10% Na_2SO_3, H_2O, brine, and dried with $MgSO_4$. Evaporation of the solvent gave a crude mixture which was purified by column chromatography.

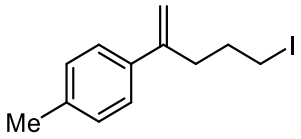
2-Phenyl-5-iodopent-1-ene (50a)



Using PPh_3 (1.70 g, 6.47 mmol), imidazole (0.787 g, 11.6 mmol), iodine (1.64 g, 6.47 mmol), and 2-phenylpent-1-en-5-ol[34] (**49a**) (0.750 g, 4.62 mmol) furnished 2-phenyl-5-iodopent-1-ene (**50a**) (1.05 g, 84%) as a clear oil after column chromatography with 1:9 EtOAc/hexane.

R_f 0.64 (1:9 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 2H), 7.36 – 7.31 (m, 2H), 7.30 – 7.26 (m, 1H), 5.33 (app q, *J* = 1.4 Hz, 1H), 5.13 (d, *J* = 1.3 Hz, 1H), 3.19 (t, *J* = 6.8 Hz, 2H), 2.64 (td, *J* = 7.2, 1.2 Hz, 2H), 1.95 (quint, *J* = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 146.6, 140.7, 128.5, 127.7, 126.2, 113.6, 35.9, 31.7, 6.6.

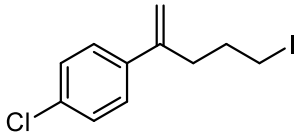
2-(*p*-Tolyl)-5-iodopent-1-ene (50b)



Using PPh_3 (3.65 g, 13.90 mmol), imidazole (1.69 g, 24.8 mmol), iodine (3.53 g, 13.9 mmol), and 2-(*p*-tolyl)pent-1-en-5-ol[34] (**49b**) (1.75 g, 9.93 mmol) furnished 2-(*p*-tolyl)-5-iodopent-1-ene (**50b**) (2.06 g, 73%) as a clear oil after column chromatography with 1:9 EtOAc/hexane.

R_f 0.78 (1:9 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 5.30 (d, *J* = 1.4 Hz, 1H), 5.09 (app q, *J* = 1.4 Hz, 1H), 3.18 (t, *J* = 6.8 Hz, 2H), 2.62 (td, *J* = 7.3, 1.2 Hz, 2H), 2.35 (s, 3H), 1.95 (quint, *J* = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 146.4, 137.7, 137.5, 129.2, 126.1, 112.8, 35.9, 31.7, 21.2, 6.7, IR (cast film, cm^{-1}) 3082, 2938, 2865, 1513, 825; HRMS (EI) calcd for $C_{12}H_{15}I[M]^+$ 286.0219, found 286.0222.

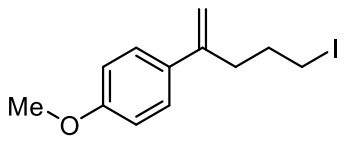
2-(4-Chlorophenyl)-5-iodopent-1-ene (50c)



Using PPh_3 (4.51 g, 17.2 mmol), imidazole (2.25 g, 33.0 mmol), iodine (4.36 g, 17.2 mmol), and 2-(4-chlorophenyl)pent-1-en-5-ol[34] (**49c**) (2.60 g, 13.2 mmol) furnished 2-(4-chlorophenyl)-5-iodopent-1-ene (**50c**) (3.20 g, 79%) as a clear oil after column chromatography with 1:9 EtOAc/hexane.

R_f 0.81 (1:9 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 4H), 5.31 (d, *J* = 1.1 Hz, 1H), 5.14 (app q, *J* = 1.3 Hz, 1H), 3.18 (t, *J* = 6.7 Hz, 2H), 2.61 (td, *J* = 7.3, 1.2 Hz, 2H), 1.93 (p, *J* = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 145.5, 139.1, 133.5, 128.7, 127.5, 114.1, 35.8, 31.6, 6.4, IR (cast film, cm^{-1}) 3083, 2939, 1492, 835.

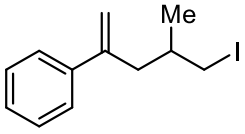
2-(4-Methoxyphenyl)-5-iodopent-1-ene (50d)



Using PPh_3 (1.33 g, 5.07 mmol), imidazole (0.664 g, 9.75 mmol), iodine (1.29 g, 5.07 mmol), and 2-(4-methoxyphenyl)pent-1-en-5-ol (**49d**) (0.750 g, 3.90 mmol) furnished 2-(4-methoxyphenyl)-5-iodopent-1-ene (**50d**) (0.85 g, 72%) as a clear oil after column chromatography with 1:9 EtOAc/hexane.

R_f 0.65 (1:9 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.26 (d, J = 1.4 Hz, 1H), 5.04 (app q, J = 1.4 Hz, 1H), 3.82 (s, 3H), 3.18 (t, J = 6.8 Hz, 2H), 2.61 (td, J = 7.2, 1.1 Hz, 2H), 1.95 (p, J = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 159.3, 145.9, 133.0, 127.3, 113.9, 112.0, 55.4, 36.0, 31.8, 6.7, IR (cast film, cm^{-1}) 3036, 2954, 2834, 1607, 1512, 1248, 835, HRMS (EI) calcd for $C_{12}H_{15}OI[M]^+$ 302.0168, found 302.063.

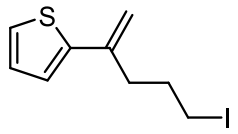
(5-Iodo-4-methylpent-1-en-2-yl)benzene (50e)



Using PPh_3 (1.16 g, 4.43 mmol), imidazole (0.579 g, 8.50 mmol), iodine (1.12 g, 4.43 mmol), and 2-methyl-4-phenylpent-4-en-1-ol (**49e**) (0.600 g, 3.10 mmol) furnished (5-iodo-4-methylpent-1-en-2-yl)benzene (**50e**) (0.97 g, 59%) as a clear oil after column chromatography with 1:9 EtOAc/hexane.

R_f 0.64 (1:9 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, 2H), 7.36 – 7.31 (m, 2H), 7.30 – 7.26 (m, 1H), 5.33 (d, *J* = 1.6 Hz, 1H), 5.14 (d, *J* = 1.4 Hz, 1H), 3.21 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.16 (dd, *J* = 9.6, 5.3 Hz, 1H), 2.64 (ddd, *J* = 14.2, 7.0, 1.2 Hz, 1H), 2.40 (ddd, *J* = 14.1, 7.1, 1.1 Hz, 1H), 1.57 – 1.46 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 146.4, 140.7, 128.5, 127.7, 126.4, 114.8, 42.5, 32.6, 20.7, 17.75, IR (cast film, cm^{-1}) 3081, 2959, 2867, 1626, 1494, 778.

2-(5-Iodopent-1-en-2-yl)thiophene (64)



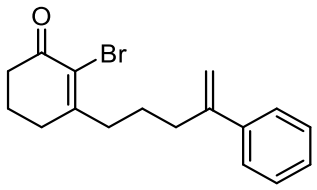
Using PPh_3 (1.96 g, 7.49 mmol), imidazole (0.980 g, 14.4 mmol), iodine (1.90 g, 7.49 mmol), and 4-(thiophen-2-yl)pent-4-en-1-ol (**63**) (0.970 g, 5.77 mmol) furnished 2-(5-Iodopent-1-en-2-yl)thiophene (**64**) (0.90 g, 56%) as a yellow oil after column chromatography with 1:4 EtOAc/hexane.

R_f 0.77 (1:4 EtOAc/hexane); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.05 (dd, *J* = 3.6, 1.1 Hz, 1H), 6.99 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.44 (s, 1H), 5.02 (s, 1H), 3.23 (t, *J* = 6.8 Hz, 2H), 2.65 – 2.56 (m, 2H), 2.13 – 2.03 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) 144.7, 139.9, 127.5, 124.5, 123.7, 112.1, 36.2, 32.0, 6.5, IR (cast film, cm^{-1}) 3082, 2932, 1617, 1438, 886, HRMS (EI) calcd for $C_9H_{11}SI[M]^+$ 277.9626, found 277.9626.

General Procedure for Stork-Danheiser Transposition

A solution containing the primary iodide (1.0 equiv.) dissolved in Et_2O (0.1 M) with solid 4Å MS preactivated in an oven was cooled to -78°C and *t*-BuLi (1.7 M in pentane; 1.5-2.0 equiv.) was added dropwise over 5 min. The mixture was stirred at -78°C for 30 min and a solution of enone **51** (1.0 equiv.) in THF (0.2 M) was added via cannula. This mixture was stirred at -78°C for 1 h before warming to 0°C and stirring for a further 30 min, followed by addition of HCl (1 M). After stirring for 1 h the mixture was diluted with Et_2O and the aqueous phase was extracted with Et_2O (4 x 30 mL). The combined organic phases washed with $NaHCO_3$ (sat), Na_2SO_3 (10 %), H_2O, brine, and dried over $MgSO_4$. Evaporation of solvent gave a crude mixture that was purified by column chromatography.

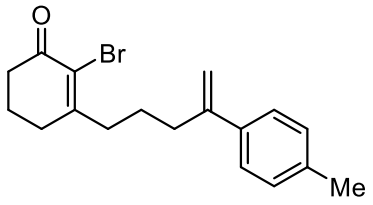
2-Bromo-3-(4-phenylpent-4-en-1-yl)cyclohex-2-enone (52a)



Using 2-phenyl-5-iodopent-1-ene (**50a**) (0.325 g, 1.19 mmol), *t*-BuLi (1.70 M in pentanes; 1.40 mL, 2.39 mmol), and enone **51** (0.235 g, 1.07 mmol) furnished 2-bromo-3-(4-phenylpent-4-en-1-yl)cyclohex-2-enone (**52a**) (0.15 g, 43%) as an off-white (beige) oil after column chromatography with 1:2 Et_2O:pentane.

R_f 0.37 (1:2 Et_2O:pentane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.38 (m, 2H), 7.36 – 7.31 (m, 2H), 7.30 – 7.26 (m, 1H), 5.31 (d, J = 1.3 Hz, 1H), 5.10 (d, J = 1.4 Hz, 1H), 2.61 (t, J = 7.5 Hz, 2H), 2.57 – 2.48 (m, 4H), 2.42 (t, J = 6.0 Hz, 2H), 1.99 – 1.91 (m, 2H), 1.73 – 1.64 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 191.2, 163.7, 147.7, 140.9, 128.5, 127.6, 126.2, 122.9, 113.1, 38.9, 37.9, 35.3, 32.5, 25.4, 22.1, IR (cast film, cm^{-1}) 3080, 2933, 2866, 1684, 1596, HRMS (EI) calcd for $C_{17}H_{19}OBr[M]^+$ 318.0619, found 318.0611.

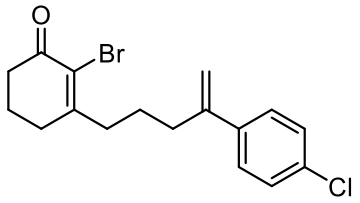
2-Bromo-3-(4-(*p*-tolyl)pent-4-en-1-yl)cyclohex-2-enone (52b)



Using 2-(*p*-tolyl)-5-iodopent-1-ene (**50b**) (0.750 g, 2.62 mmol), *t*-BuLi (1.70 M in pentanes; 2.94 mL, 5.00 mmol), and enone **51** (0.517 g, 2.36 mmol) furnished 2-bromo-3-(4-(*p*-tolyl)pent-4-en-1-yl)cyclohex-2-enone (**52b**) (0.24 g, 38%) as a yellow oil after column chromatography with 1:2 Et_2O:pentane.

R_f 0.44 (1:2 Et_2O:pentane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 5.28 (d, J = 1.4 Hz, 1H), 5.05 (d, J = 1.4 Hz, 1H), 2.61 – 2.50 (m, 6H), 2.42 (t, J = 6.0 Hz, 2H), 2.35 (s, 3H), 1.98 – 1.92 (m, 2H), 1.72 – 1.65 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 191.2, 163.7, 147.5, 137.9, 137.4, 129.2, 126.1, 122.8, 112.4, 39.0, 37.9, 35.3, 32.5, 25.4, 22.1, 21.2, IR (cast film, cm^{-1}) 3081, 2939, 2867, 1684, 1596, HRMS (EI) calcd for $C_{18}H_{21}OBr$ $[M]^+$ 332.0776, found 332.0775.

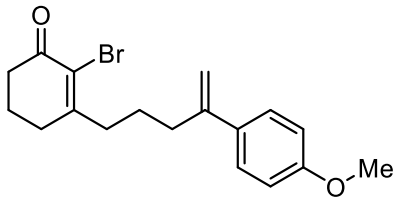
2-Bromo-3-(4-(4-chlorophenyl)pent-4-en-1-yl)cyclohex-2-enone (52c)



Using 2-(4-chlorophenyl)-5-iodopent-1-ene (**50c**) (1.00 g, 3.26 mmol), *t*-BuLi (1.70 M in pentanes; 3.64 mL, 6.19 mmol), and enone **51** (0.642 g, 2.93 mmol) furnished 2-bromo-3-(4-(4-chlorophenyl)pent-4-en-1-yl)cyclohex-2-enone (**52c**) (0.38 g, 26%) as a white solid after column chromatography with 1:2 Et_2O:pentane.

R_f 0.32 (1:2 Et_2O:pentane); ^1H NMR (700 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 4H), 5.30 (s, 1H), 5.11 (s, 1H), 2.60 – 2.53 (m, 4H), 2.52 – 2.47 (m, 2H), 2.42 (t, J = 6.0 Hz, 2H), 1.96 (quint, J = 6.2 Hz, 2H), 1.70 – 1.63 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) 191.1, 163.4, 146.5, 139.3, 133.4, 128.6, 127.5, 123.0, 113.7, 38.9, 37.9, 35.2, 32.5, 25.3, 22.1, IR (cast film, cm^{-1}) 3082, 2940, 2887, 684, 1596, HRMS (EI) calcd for $C_{17}H_{18}OBrCl[M]^+$ 353.0302, found 352.0264.

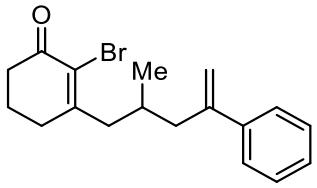
2-Bromo-3-(4-(4-methoxyphenyl)pent-4-en-1-yl)cyclohex-2-enone (52d)



Using 2-(4-methoxyphenyl)-5-iodopent-1-ene (**50d**) (0.850 g, 2.81 mmol), *t*-BuLi (1.70 M in pentanes; 3.31 mL, 5.62 mmol), and enone **51** (0.615 g, 2.81 mmol) furnished 2-bromo-3-(4-(4-methoxyphenyl)pent-4-en-1-yl)cyclohex-2-enone (**52d**) (0.34 g, 34%) as a yellow oil after column chromatography with 1:2 EtOAc:hexane.

R_f 0.47 (1:2 EtOAc:hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 2H), 6.89 – 6.85 (m, 2H), 5.24 (d, J = 1.4 Hz, 1H), 5.01 (d, J = 1.4 Hz, 1H), 3.81 (s, 3H), 2.59 – 2.54 (m, 4H), 2.52 – 2.48 (m, 2H), 2.42 (t, J = 6.0 Hz, 2H), 1.98 – 1.92 (m, 2H), 1.72 – 1.65 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 191.2, 163.7, 159.2, 146.9, 133.3, 127.3, 122.8, 113.8, 111.6, 55.4, 38.9, 37.9, 35.4, 32.5, 25.4, 22.1, IR (cast film, cm^{-1}) 3041, 2935, 2866, 1683, 1511, 1248, HRMS (EI) calcd for $C_{18}H_{21}O_2Br$ $[M]^+$ 348.0725, found 348.0720.

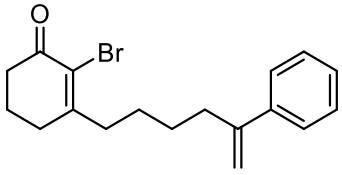
2-Bromo-3-(2-methyl-4-phenylpent-4-en-1-yl)cyclohex-2-enone (52e)



Using (5-iodo-4-methylpent-1-en-2-yl)benzene (**50e**) (0.550 g, 1.92 mmol), *t*-BuLi (1.70 M in pentanes; 2.26 mL, 3.84 mmol), and enone **51** (0.504 g, 2.36 mmol) furnished 2-bromo-3-(2-methyl-4-phenylpent-4-en-1-yl)cyclohex-2-enone (**52e**) (0.29 g, 45%) as a white solid after column chromatography with 1:4 EtOAc:hexane.

R_f 0.46 (1:4 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 4H), 7.29 – 7.26 (m, 1H), 5.31 (d, *J* = 1.6 Hz, 1H), 5.09 (d, *J* = 1.4 Hz, 1H), 2.61 – 2.52 (m, 4H), 2.46 (ddd, *J* = 14.1, 7.8, 1.1 Hz, 1H), 2.40 (dd, *J* = 12.7, 9.0 Hz, 1H), 2.32 – 2.23 (m, 2H), 1.98 – 1.89 (m, 3H), 0.91 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 191.4, 163.4, 147.2, 141.2, 128.7, 127.9, 126.6, 124.3, 114.9, 46.3, 43.8, 38.3, 33.2, 30.8, 22.4, 19.9, IR (cast film, cm^{-1}) 3081, 2956, 2927, 1684, 1593, HRMS (EI) calcd for $C_{18}H_{21}O[M\text{-}Br]^+$ 253.1592, found 253.1593.

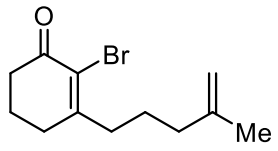
2-Bromo-3-(5-phenylhex-5-en-1-yl)cyclohex-2-enone (52f)



Using (6-iodohex-1-en-2-yl)benzene[36] (**50f**) (1.40 g, 4.89 mmol), *t*-BuLi (1.70 M in pentanes; 5.76 mL, 9.79 mmol), and enone **51** (0.860 g, 3.91 mmol) furnished 2-bromo-3-(5-phenylhex-5-en-1-yl)cyclohex-2-enone (**52f**) (0.54 g, 41%) as a yellow oil after column chromatography with 1:4 EtOAc:hexane.

R_f 0.55 (1:4 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H), 7.35 – 7.31 (m, 2H), 7.29 – 7.26 (m, 1H), 5.28 (d, *J* = 1.5 Hz, 1H), 5.07 (d, *J* = 1.4 Hz, 1H), 2.59 – 2.51 (m, 4H), 2.50 – 2.45 (m, 2H), 2.43 (t, *J* = 6.0 Hz, 2H), 1.97 – 1.91 (m, 2H), 1.59 – 1.50 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) 191.3, 163.9, 148.2, 141.2, 128.4, 127.5, 126.3, 122.8, 112.8, 39.1, 37.9, 35.1, 32.5, 27.9, 26.3, 22.1, IR (cast film, cm^{-1}) 3080, 2934, 2863, 1683, 1596, HRMS (EI) calcd for $C_{18}H_{21}O$ $[M\text{-}Br]^+$ 253.1592, found 253.1591.

2-Bromo-3-(4-methylpent-4-en-1-yl)cyclohex-2-enone (76)

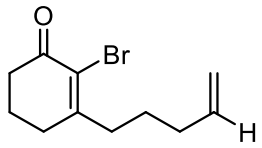


Using 5-iodo-2-methyl-1-pentene[40] (**74**) (1.00 g, 4.76 mmol), *t*-BuLi (1.70 M in pentanes; 5.60 mL, 9.52 mmol), and enone **51** (0.930 g, 4.28 mmol) furnished 2-bromo-3-(4-methylpent-4-en-1-yl)cyclohex-2-enone (**76**) (0.46 g, 41%) as a clear oil after column chromatography with 1:9 EtOAc:hexane.

Note: there is a small amount of side product from *t*-BuLi addition into cyclohexenone **51** that could not be removed from product **76** and is visible in the ^{1}H and ^{13}C NMR spectrums.

R_f 0.24 (1:9 EtOAc:hexane); ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.76 (s, 1H), 4.71 (s, 1H), 2.61 – 2.56 (m, 2H), 2.51 (t, *J* = 6.0 Hz, 2H), 2.50 – 2.44 (m, 2H), 2.10 (t, *J* = 7.5 Hz, 2H), 2.00 (quint, *J* = 6.2 Hz, 2H), 1.74 (s, 3H), 1.72 – 1.64 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) 191.2, 163.9, 144.8, 122.8, 110.8, 39.0, 37.9, 37.7, 32.6, 24.7, 22.4, 22.2, IR (cast film, cm^{-1}) 3078, 2937, 2889, 1684, 1597, HRMS (EI) calcd for $C_{12}H_{17}OBr[M]^+$ 256.0463, found 256.0460.

2-Bromo-3-(pent-4-en-1-yl)cyclohex-2-enone (77)

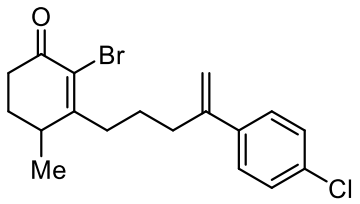


Using 5-iodo-1-pentene (**75**) (0.385 g, 1.96 mmol), *t*-BuLi (1.70 M in pentanes; 1.73 mL, 2.94 mmol), and enone **51** (0.219 g, 1.76 mmol) furnished 2-bromo-3-(pent-4-en-1-yl)cyclohex-2-enone (**77**) (0.23 g, 26%) as an oil after column chromatography with 1:9 EtOAc:hexane.

Note: there is a small amount of side product from *t*-BuLi addition into cyclohexenone **51** that could not be removed from product **77** and is visible in the ^{1}H and ^{13}C NMR spectrums.

R_f 0.30 (1:9 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.05 (app dq, J = 17.1, 1.7 Hz, 1H), 5.01 (app dq, J = 10.2, 1.4 Hz, 1H), 2.58 (m, 2H), 2.53 – 2.46 (m, 4H), 2.14 (app q, J = 7.1 Hz, 2H), 1.99 (quint, J = 6.3 Hz, 2H), 1.69 – 1.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 191.2, 163.8, 137.7, 122.8, 115.5, 38.8, 37.9, 33.7, 32.6, 26.1, 22.1, IR (cast film, cm^{-1}) 3076, 2931, 2866, 1685, 1596, HRMS (APPI) calcd for $C_{11}H_{15}BrO[M+H]^{+}$ 243.0379, found 243.0377.

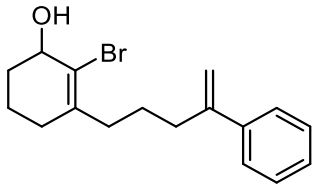
2-Bromo-3-(4-(4-chlorophenyl)pent-4-en-1-yl)-4-methylcyclohex-2-enone (90)



Using 1-chloro-4-(5-iodopent-1-en-2-yl)benzene (**50c**) (0.725 g, 2.36 mmol), *t*-BuLi (1.70 M in pentanes; 2.78 mL, 4.72 mmol), and enone **89** (0.551 g, 2.36 mmol) furnished 2-bromo-3-(4-(4-chlorophenyl)pent-4-en-1-yl)-4-methylcyclohex-2-enone (**90**) (0.28 g, 33%) as a yellow oil after column chromatography with 1:2 Et_2O:pentane.

R_f 0.43 (1:2 Et_2O:pentane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 4H), 5.30 (s, 1H), 5.12 (s, 1H), 2.74 – 2.48 (m, 6H), 2.33 – 2.23 (m, 1H), 2.15 – 2.03 (m, 1H), 1.76 (dq, *J* = 14.0, 4.9 Hz, 1H), 1.67 (app quint, *J* = 7.6 Hz, 2H), 1.19 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) 190.8, 167.5, 146.6, 139.3, 133.5, 128.6, 127.6, 123.4, 113.7, 37.0, 36.0, 35.4, 34.0, 29.2, 25.5, 17.8 IR (cast film, cm^{-1}) 3083, 2961, 2868, 1684, 1593, HRMS (EI) calcd for $C_{18}H_{20}OCl[M\text{-}Br]^+$ 287.203, found 287.1206.

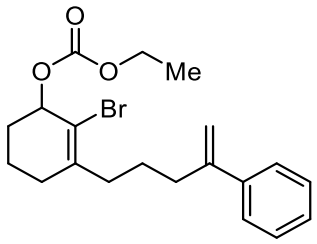
2-Bromo-3-(4-phenylpent-4-en-1-yl)cyclohex-2-enol (56)



To a solution of 2-bromo-3-(4-phenylpent-4-en—yl)cyclohex-2-enone (**52a**) (0.360 g, 1.13 mmol, 1.00 equiv.) and $CeCl_3 \cdot 7H_2O$ (0.447 g, 1.20 mmol, 1.10 equiv.) in MeOH [0.4 M] at 0°C was portion-wise added $NaBH_4$ (50.0 mg, 1.31 mmol, 1.20 equiv.) over 5 min. The reaction was stirred at 0°C for 1 h before warming to rt with stirring continued for 1 h. The reaction was quenched with the addition of HCl (1 M) and the aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with $NaHCO_3$ (sat), H_2O, brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude mixture that was purified by column chromatography with 1:2 EtOAc:hexane to furnish 2-bromo-3-(4-phenylpent-4-en-1-yl)cyclohex-2-enol (**56**) (0.36 g, 98%) as a yellow oil.

R_f 0.55 (1:2 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.39 (m, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.26 (m, 1H), 5.29 (d, *J* = 1.4 Hz, 1H), 5.08 (d, *J* = 1.5 Hz, 1H), 4.24 (d, *J* = 4.0 Hz, 1H), 2.54 (t, *J* = 7.6 Hz, 2H), 2.23 (dd, *J* = 9.2, 6.8 Hz, 2H), 2.18 (d, *J* = 3.9 Hz, 1H), 2.10 (dt, *J* = 17.3, 5.2 Hz, 1H), 2.03 (ddd, *J* = 17.3, 8.5, 5.3 Hz, 1H), 1.88 – 1.83 (m, 2H), 1.78 – 1.69 (m, 1H), 1.63 – 1.55 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 141.1, 140.5, 128.3, 127.3, 126.1, 123.0, 112.5, 71.1, 36.9, 35.1, 31.9, 31.4, 25.6, 18.3; IR (neat, cm^{-1}) 3390, 3080, 2937, 2864,1627, 704; HRMS (EI) calcd for $C_{17}H_{21}OBr$ $[M-H_2O]^+$ 320.0776, found 320.0771.

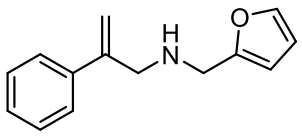
2-Bromo-3-(4-phenylpent-4-en-1-yl)cyclohex-2-en-1-yl ethyl carbonate (57)



To a solution of 2-bromo-3-(4-phenylpent-4-en-1-yl)cyclohex-2-enol (**56**) (0.30 g, 0.93 mmol, 1.0 equiv.) in DCM [0.1 M] at 0°C was added pyridine (0.113 mL, 1.40 mmol, 1.50 equiv.) and then dropwise ethyl chloroformate (0.107 mL, 1.12 mmol, 1.20 equiv.) over 1-2 min. The mixture was warmed to rt and stirred 1 h before ~ 5mg of DMAP was added. Upon completion of the reaction, as determined by TLC, the mixture was cooled to 0°C and quenched by addition of HCl (1 M). The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with $NaHCO_3$ (sat), H_2O, brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude mixture that was purified by column chromatography with with 1:4 EtOAc:hexane to furnish 2-bromo-3-(4-phenylpent-4-en-1-yl)cyclohex-2-en-1-yl ethyl carbonate (**57**) (0.33 g, 90%) as a clear oil.

R_f 0.64 (1:4 EtOAc:hexane); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.32 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.29 – 7.25 (m, 1H), 5.30 – 5.27 (m, 1H), 5.28 (d, *J* = 1.6 Hz, 1H), 5.08 (d, *J* = 1.5 Hz, 1H), 4.22 (m, 2H), 2.54 (t, *J* = 7.6 Hz, 2H), 2.27 (ddd, *J* = 13.0, 10.2, 5.8 Hz, 1H), 2.22 (ddd, *J* = 13.0, 10.2, 5.9 Hz, 1H), 2.14 (dt, *J* = 17.6, 4.4 Hz, 1H), 2.08 – 1.94 (m, 2H), 1.88 – 1.81 (m, 1H), 1.72 (tddd, *J* = 13.2, 10.4, 5.2, 3.1 Hz, 1H), 1.67 – 1.53 (m, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 154.6, 148.0, 144.0, 141.0, 128.2, 127.3, 126.1, 116.1, 112.5, 76.7, 64.0, 36.8, 35.1, 31.1, 30.0, 25.4, 17.9, 14.2; IR (neat, cm^{-1}) 3082, 2940, 2867, 1742, 1371, 705; HRMS (EI) calcd for $C_{20}H_{25}O_3Br$ $[M]^+$ 392.0987, found 392.0980.

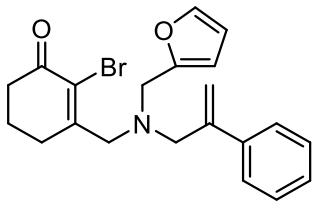
_N_-(furan-2-ylmethyl)-2-phenylprop-2-en-1-amine (98)



A mixture of amine (**96**) (0.600 g, 4.08 mmol, 1.00 equiv.), furaldehyde (0.392 g, 4.08 mmol, 1.00 equiv.), and TsOH (~ 10 mg) were mixed with a glass stir rod neat for 10 min. MeOH [0.4 M] was added and the mixture was cooled to 0°C. $NaBH_4$ (0.185 g, 4.90 mmol, 1.20 equiv.) was then added portion wise to the cooled mixture over 10 min. The mixture was stirred for 30 min before being warmed to rt and stirred a further 30 min. Upon completion of the reaction, as determined by TLC, the mixture was cooled to 0°C and quenched by addition of HCl (1 M). The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with $NaHCO_3$ (sat), H_2O, brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude mixture that was purified by column chromatography with with 1:1 EtOAc:hexane to furnish *N*-(furan-2-ylmethyl)-2-phenylprop-2-en-1-amine (**98**) (0.54 g, 62%) as a yellow oil.

R_f 0.54 (1:1 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.41 (m, 2H), 7.37 – 7.32 (m, 3H), 7.31 – 7.27 (m, 1H), 6.31 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.17 (dd, *J* = 3.2, 0.9 Hz, 1H), 5.43 – 5.42 (m, 1H), 5.26 (d, *J* = 1.4 Hz, 1H), 3.80 (s, 2H), 3.67 (s, 2H), 1.58 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 146.1, 141.9, 139.9, 128.5, 127.8, 126.3, 113.7, 110.2, 107.1, 52.4, 45.3.

2-Bromo-3-(((furan-2-ylmethyl)(2-phenylallyl)amino)methyl)cyclohex-2-enone (100)



To a solution of 2-bromo-3-(chloromethyl)cyclohex-2-enone (**99**) (0.210 g, 0.94 mmol, 1.00 equiv.) in MeCN [0.1 M] was added *N*-(furan-2-ylmethyl)-2-phenylprop-2-en-1-amine (**98**) (0.400 g, 1.87 mmol, 2.00 equiv.) and then NaOAc (0.254 g, 1.87 mmol, 2.00 equiv.). The mixture was stirred for 16 h upon which the reaction was complete as determined by TLC. Water (30 mL) and Et_2O (30 mL) was added and the aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with $NaHCO_3$ (sat), H_2O, brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude mixture that was purified by column chromatography with 1:4 EtOAc:hexane to furnish 2-bromo-3-(((furan-2-ylmethyl)(2-phenylallyl)amino)methyl)cyclohex-2-enone (**100**) (0.31 g, 83%) as a yellow oil.

R_f 0.40 (1:4 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.38 – 7.35 (m, 2H), 7.33 – 7.26 (m, 3H), 6.33 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.21 (dd, *J* = 3.2, 0.8 Hz, 1H), 5.48 (d, *J* = 1.5 Hz, 1H), 5.33 (d, *J* = 1.4 Hz, 1H), 3.60 (s, 2H), 3.52 (s, 2H), 3.50 (s, 2H), 2.51 – 2.47 (m, 2H), 2.17 (t, *J* = 6.0 Hz, 2H), 1.75 (quint, *J* = 6.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.3, 162.0, 152.0, 145.1, 142.2, 139.7, 128.0, 127.6, 126.5, 122.9, 116.0, 110.2, 109.1, 59.4, 59.1, 51.1, 38.3, 30.3, 21.8; HRMS (EI) calcd for $C_{21}H_{22}BrNO_2[M]^+$ 399.0756, found 399.0760.

General Procedures for Silyl Anion Conjugate Addition

Method A

To a suspension of CuBr·DMS complex (1.3-1.5 equiv.) in THF [0.15 M] cooled to 0°C was added a previously prepared solution of $LiSiMe_2Ph$[41] (2.6-2.9 equiv.) in THF [0.4 M] via cannula. The mixture was stirred at 0°C for 30 min before a solution of the corresponding enone (1.0 equiv.) in THF [0.1 M] at 0°C was added via cannula. This mixture was stirred at 0°C for 5 h before addition of acetic anhydride (5.0 equiv.) and further stirring for 5 h. Et_2O (20 mL) and H_2O (15 mL) were added and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with H_2O, brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude mixture that was purified by column chromatography.

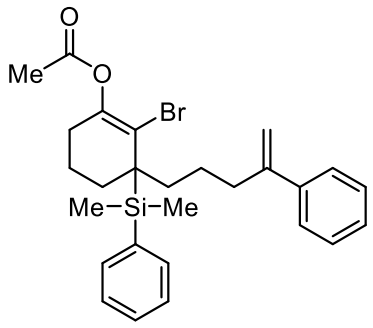
Method B

To a suspension of CuBr·DMS complex (3.0 equiv.) in THF [0.15 M] cooled to 0°C was added a previously prepared solution of $LiSiMe_2Ph$[41] (6.0 equiv.) in THF [0.4 M] via cannula. The mixture was stirred at 0°C for 30 min before a solution of the corresponding enone (1.0 equiv.) in THF [0.1 M] at 0°C was added via cannula. This mixture was stirred at 0°C for 1 h before warming to 30°C and further stirring for 4 h. Acetic anhydride (5.0 equiv.) was added and the mixture was further stirred for 5 h. Et_2O (20 mL) and H_2O (15 mL) were added and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with H_2O, brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude mixture that was purified by column chromatography.

Method C

To a suspension of CuBr·DMS complex (3.0 equiv.) in THF [0.15 M] cooled to 0°C was added a previously prepared solution of $LiSiMe_2Ph$[41] (6.0 equiv.) in THF [0.4 M] via cannula. The mixture was stirred at 0°C for 30 min before being cooled to -78°C. A solution of the corresponding carbonate (1.0 equiv.) in THF [0.1 M] at 0°C was added via cannula. This mixture was stirred at -78°C for 5 h. Et_2O (20 mL) and H_2O (15 mL) were added and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with H_2O, brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude mixture that was purified by column chromatography.

2-Bromo-3-(dimethyl(phenyl)silyl)-3-(4-phenylpent-4-en-1-yl)cyclohex-1-en-yl acetate (53a)

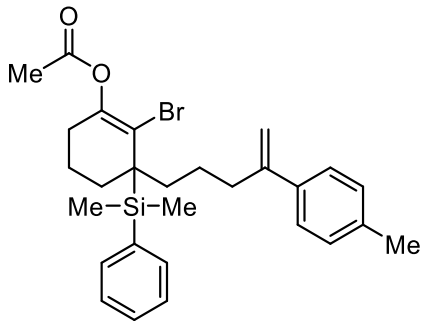


Method B

Using 2-bromo-3-(4-phenylpent-4-en-1-yl)cyclohex-2-enone (**52a**) (0.15 g, 0.47 mmol), $ClSiPhMe_2$ (0.464 g, 2.73 mmol), Li (0.114 g, 16.4 mmol), CuBr·DMS complex (0.290 g, 1.41 mmol), and Ac_2O (0.240 g, 2.35 mmol) furnished 2-bromo-3-(dimethyl(phenyl)silyl)-3-(4-phenylpent-4-en-1-yl)cyclohex-1-en-yl acetate (**53a**) (0.080 g, 86%) as a yellow oil after column chromatography with 1:1 DCM:hexane.

R_f 0.47 (1:1 DCM:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.48 (m, 2H), 7.40 – 7.30 (m, 7H), 7.28 – 7.23 (m, 1H), 5.27 (d, *J* = 1.5 Hz, 1H), 5.05 (d, *J* = 1.4 Hz, 1H), 2.56 – 2.38 (m, 2H), 2.16 (s, 3H), 2.24 – 2.00 (m, 2H), 1.90 (ddd, *J* = 13.7, 11.4, 4.7 Hz, 1H), 1.69 – 1.41 (m, 7H), 0.46 (s, 3H), 0.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 168.1, 148.5, 144.6, 141.5, 137.7, 134.8, 129.1, 128.3, 127.6, 127.3, 126.2, 120.8, 112.4, 36.1, 36.0, 35.9, 31.6, 28.9, 23.4, 20.9, 20.2, -2.5, -3.0, IR (cast film, cm^{-1}) 3069, 2946, 2867, 1761, 1626, 1204, HRMS (EI) calcd for $C_{27}H_{33}O_2BrSi[M]^+$ 496.1433, found 496.1438.

2-Bromo-3-(dimethyl(phenyl)silyl)-3-(4-(*p*-tolyl)pent-4-en-1-yl)cyclohex-1-en-yl acetate (53b)

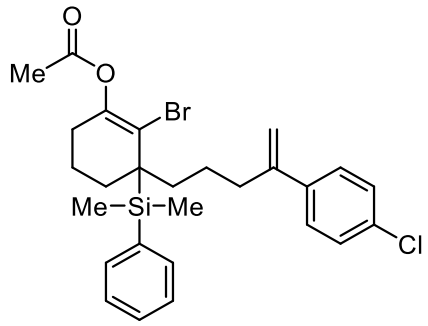


Method A

Using 2-bromo-3-(4-(*p*-tolyl)pent-4-en-1-yl)cyclohex-2-enone (**52b**) (0.23 g, 0.67 mmol), $ClSiPhMe_2$ (0.296 g, 1.74 mmol), Li (73.0 mg, 10.5 mmol), CuBr·DMS complex (0.18 g, 0.87 mmol), and Ac_2O (0.342 g, 3.35 mmol) furnished 2-bromo-3-(dimethyl(phenyl)silyl)-3-(4-(*p*-tolyl)pent-4-en-1-yl)cyclohex-1-en-yl acetate (**53b**) (0.093 g, 62%) as a clear oil after column chromatography with 1:9 EtOAc:hexane.

R_f 0.58 (1:9 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.37 – 7.25 (m, 5H), 7.15 – 7.08 (m, 2H), 5.24 (d, *J* = 1.5 Hz, 1H), 5.00 (d, *J* = 1.4 Hz, 1H), 2.53 – 2.45 (m, 1H), 2.45 – 2.37 (m, 1H), 2.34 (s, 3H), 2.16 (s, 3H), 2.19 – 2.01 (m, 2H), 1.90 (ddd, *J* = 13.6, 11.4, 4.6 Hz, 1H), 1.67 – 1.37 (m, 7H), 0.45 (s, 3H), 0.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 168.2, 148.2, 144.6, 138.6, 137.7, 137.0, 134.8, 129.1, 129.0, 127.6, 126.1, 120.8, 111.6, 36.1, 36.0, 35.9, 31.6, 28.9, 23.4, 21.2, 20.9, 20.2, -2.4, -3.0, IR (cast film, cm^{-1}) 3069, 2946, 2868, 1762, 1513, 1204, HRMS (APPI) calcd for $C_{28}H_{36}BrO_2Si[M+H]^+$ 511.1662, found 511.1669.

2-Bromo-3-(4-(4-chlorophenyl)pent-4-en-1-yl)-3-(dimethyl(phenyl)silyl)cyclohex-1-en-yl acetate (53c)

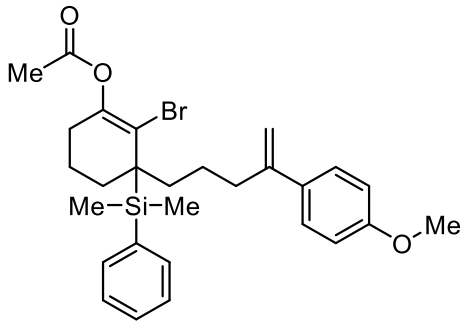


Method B

Using 2-bromo-3-(4-(4-chlorophenyl)pent-4-en-1-yl)cyclohex-2-enone (**52c**) (0.35 g, 0.99 mmol), $ClSiPhMe_2$ (0.750 g, 4.41 mmol), Li (0.186 g, 26.5 mmol), CuBr·DMS complex (0.454 g, 2.21 mmol), and Ac_2O (0.505 g, 4.95 mmol) furnished 2-bromo-3-(4-(4-chlorophenyl)pent-4-en-1-yl)-3-(dimethyl(phenyl)silyl)cyclohex-1-en-yl acetate (**53c**) (0.34 g, 64%) as a clear oil after column chromatography with 1:1 DCM:hexane.

R_f 0.44 (1:1 DCM:hexane); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.51 (d, *J* = 6.9 Hz, 2H), 7.39 – 7.26 (m, 7H), 5.25 (s, 1H), 5.06 (s, 1H), 2.48 (dt, *J* = 14.6, 7.3 Hz, 1H), 2.42 (dt, *J* = 14.8, 7.5 Hz, 1H), 2.17 (s, 3H), 2.18 – 2.15 (m, 1H), 2.06 (dt, *J* = 16.7, 5.4 Hz, 1H), 1.90 (ddd, *J* = 13.8, 11.4, 4.7 Hz, 1H), 1.68 – 1.38 (m, 7H), 0.47 (s, 3H), 0.43 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) 168.1, 147.3, 144.7, 139.9, 137.6, 134.8, 133.1, 129.1, 128.4, 127.6, 127.6, 120.7, 113.0, 36.0, 35.9, 35.8, 31.6, 28.9, 23.2, 20.9, 20.2, -2.5, -3.0, IR (cast film, cm^{-1}) 3070, 2946, 2868, 1761, 1492, 1204, HRMS (MALDI) calcd for $C_{27}H_{32}BrClNaO_2Si[M+Na]^+$ 553.0636, found 553.0935.

2-Bromo-3-(dimethyl(phenyl)silyl)-3-(4-(4-methoxyphenyl)pent-4-en-1-yl)cyclohex-1-en-yl acetate (55d)

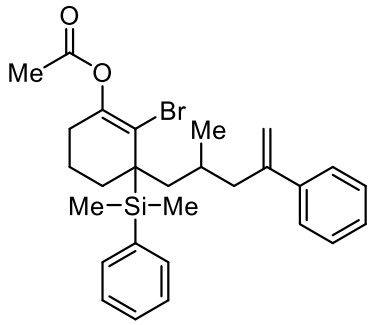


Method B

Using 2-bromo-3-(4-(4-methoxyphenyl)pent-4-en-1-yl)cyclohex-2-enone (**52d**) (0.20 g, 0.57 mmol), $ClSiPhMe_2$ (0.507 g, 2.98 mmol), Li (0.125 g, 17.9 mmol), CuBr·DMS complex (0.304 g, 1.48 mmol), and Ac_2O (0.291 g, 2.85 mmol) furnished 2-bromo-3-(dimethyl(phenyl)silyl)-3-(4-(4-methoxyphenyl)pent-4-en-1-yl)cyclohex-1-en-yl acetate (**55d**) (0.098 g, 33%) as a clear oil after column chromatography with 1:9 EtOAc:hexane.

R_f 0.49 (1:9 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.36 – 7.29 (m, 5H), 6.89 – 6.80 (m, 2H), 5.19 (d, *J* = 1.6 Hz, 1H), 4.96 (d, *J* = 1.4 Hz, 1H), 3.81 (s, 3H), 2.52 – 2.44 (m, 1H), 2.44 – 2.37 (m, 1H), 2.16 (s, 3H), 2.15 – 2.11 (m, 1H), 2.10 – 2.03 (m, 1H), 1.89 (ddd, *J* = 13.5, 11.3, 4.6 Hz, 1H), 1.65 – 1.55 (m, 4H), 1.49 – 1.38 (m, 3H), 0.46 (s, 3H), 0.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 168.1, 159.1, 147.7, 144.6, 137.7, 134.8, 133.9, 129.1, 127.6, 127.3, 120.8, 113.7, 110.9, 55.4, 36.1, 36.0, 35.9, 31.6, 28.9, 23.4, 20.9, 20.2, -2.4, -3.0, IR (cast film, cm^{-1}) 3070, 2948, 2837, 1761, 1607, 1511, 1249, HRMS (ESI) for $C_{28}H_{35}BrNaO_3Si[M+Na]^+$, found 549.1000.

2-Bromo-3-(dimethyl(phenyl)silyl)-3-(2-methyl-4-phenylpent-4-en-1-yl)cyclohex-1-en-yl acetate (53e)



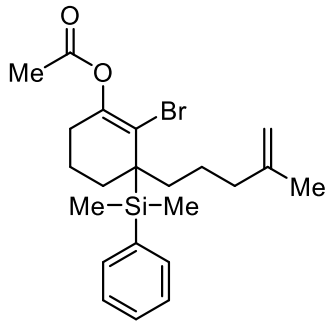
Method B

Using 2-bromo-3-(2-methyl-4-yphenylpent-4-en-1-yl)cyclohex-2-enone (**52e**) (0.18 g, 0.52 mmol), $ClSiPhMe_2$ (0.464 g, 2.73 mmol), Li (0.114 g, 16.2 mmol), CuBr·DMS complex (0.278 g, 1.35 mmol), and Ac_2O (0.265 g, 2.60 mmol) furnished 2-bromo-3-(dimethyl(phenyl)silyl)-3-(2-methyl-4-phenylpent-4-en-1-yl)cyclohex-1-en-yl acetate (**53e**) (0.13 g, 49%, inseparable 1:1 mixture of diastereomers) as an oil after column chromatography with 1:9 EtOAc:hexane.

Mixture of diastereomers as determined by relative integration.

R_f 0.33 (1:9 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.7, 1.8 Hz, 2H), 7.51 – 7.49 (m, 2H), 7.42 – 7.38 (m, 3H), 7.37 – 7.33 (m, 5H), 7.29 (s, 1H), 7.30 – 7.24 (m, 7H), 5.26 (d, *J* = 1.8 Hz, 1H), 5.20 (d, *J* = 1.9 Hz, 1H), 5.05 (d, *J* = 1.6 Hz, 1H), 5.00 (s, 1H), 3.13 (dd, *J* = 14.1, 3.5 Hz, 1H), 2.48 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.34 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.22 (s, 3H), 2.26 – 2.17 (m, 1H), 2.16 (s, 3H), 2.13 – 2.03 (m, 4H), 1.86 – 1.64 (m, 2H), 1.49 – 1.39 (m, 2H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.48 (s, 3H), 0.45 (s, 3H), 0.44 (s, 3H), 0.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 168.3, 168.2, 148.4, 148.0, 144.6, 144.0, 141.6, 141.6, 137.6, 135.0, 134.8, 129.1, 129.1, 128.3, 128.2, 127.6, 127.6, 127.3, 127.2, 126.8, 126.5, 122.3, 121.6, 114.1, 113.8, 45.7, 43.6, 42.9, 40.6, 36.6, 35.4, 31.7, 31.5, 28.9, 28.7, 28.0, 22.0, 20.9, 20.9, 20.5, 20.2, 20.1, -2.5, -2.7, -3.3, -3.8, IR (cast film, cm^{-1}) 3070, 2953, 2871, 1762, 1600, 1427, 1205, HRMS (EI) calcd for $C_{28}H_{35}O_2BrSi[M]^+$ 510.1590, found 510.1580. 1:9 EtOAc:hexane

2-Bromo-3-(dimethyl(phenyl)silyl)-3-(4-methylpent-4-en-1-yl)cyclohex-1-en-1-yl acetate (78)

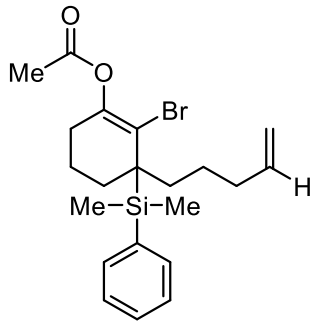


Method A

Using 2-bromo-3-(4-methylpent-4-en-1-yl)cyclohex-2-enone (**76**) (0.400 g, 1.56 mmol), $ClSiPhMe_2$ (0.687 g, 4.04 mmol), Li (0.170 g, 24.2 mmol), CuBr·DMS complex (0.415 g, 2.02 mmol), and Ac_2O (0.796 g, 7.80 mmol) furnished 2-bromo-3-(dimethyl(phenyl)silyl)-3-(4-methylpent-4-en-1-yl)cyclohex-1-en-1-yl acetate (**78**) (0.60 g, 88%) as a clear oil after column chromatography with 1:9 EtOAc:hexane.

R_f 0.58 (1:9 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.5, 2.0 Hz, 2H), 7.38 – 7.31 (m, 3H), 4.69 (s, 1H), 4.66 (s, 1H), 2.24 – 2.20 (m, 1H), 2.17 (s, 3H), 2.08 (dt, *J* = 16.7, 5.6 Hz, 1H), 1.98 (t, *J* = 7.5 Hz, 2H), 1.90 (ddd, *J* = 13.3, 11.4, 4.4 Hz, 1H), 1.70 (s, 3H), 1.68 – 1.60 (m, 4H), 1.53 – 1.34 (m, 3H), 0.49 (s, 3H), 0.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 168.2, 146.0, 144.7, 137.7, 134.8, 129.1, 127.6, 120.8, 110.0, 38.6, 36.0, 35.9, 31.7, 29.0, 22.6, 22.5, 20.9, 20.3, -2.5, -3.0, IR (cast film, cm^{-1}) 3070, 2944, 1762, 1650, 1428, 1203, HRMS (ESI) calcd for $C_{22}H_{31}BrNaO_2Si[M+Na]^+$ 457.1169, found 457.1176.

2-Bromo-3-(dimethyl(phenyl)silyl)-3-(pent-4-en-1-yl)cyclohex-1-en-1-yl acetate (79)

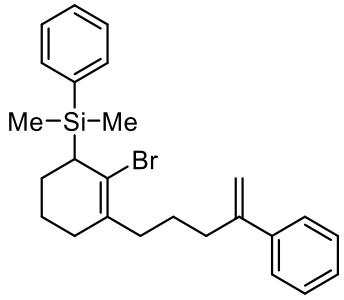


Method A

Using 2-bromo-3-(pent-4-en-1-yl)cyclohex-2-enone (**77**) (0.20 g, 0.82 mmol), $ClSiPhMe_2$ (0.364 g, 2.14 mmol), Li (90.0 mg, 12.8 mmol), CuBr·DMS complex (0.219 g, 1.07 mmol), and Ac_2O (0.419 g, 4.10 mmol) furnished 2-bromo-3-(dimethyl(phenyl)silyl)-3-(pent-4-en-1-yl)cyclohex-1-en-1-yl acetate (**79**) (0.17 g, 48%) as a clear oil after column chromatography with 1:9 EtOAc:hexane.

R_f 0.59 (1:9 EtOAc:hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.3, 2.2 Hz, 2H), 7.40 – 7.30 (m, 3H), 5.79 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 4.99 (dd, *J* = 17.1, 1.9 Hz, 1H), 4.93 (d, *J* = 10.3 Hz, 1H), 2.23 – 2.20 (m, 1H), 2.17 (s, 3H), 2.11 – 1.99 (m, 3H), 1.91 (ddd, *J* = 13.6, 11.1, 4.8 Hz, 1H), 1.68 – 1.58 (m, 4H), 1.58 – 1.46 (m, 1H), 1.43 – 1.32 (m, 2H), 0.49 (s, 3H), 0.45 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) 168.2, 144.7, 138.9, 137.7, 134.8, 129.1, 127.6, 120.7, 114.6, 35.9, 35.8, 34.5, 31.7, 28.9, 23.9, 20.9, 20.3, -2.5, -3.0, IR (cast film, cm^{-1}) 3070, 2955, 1759, 1428, 1215, HRMS (EI) calcd for $C_{21}H_{29}O_2SiBr[M]^+$ 420.1120, found 420.1124.

(2-Bromo-3-(4-phenylpent-4-en-1-yl)cyclohex-2-en-1-yl)dimethyl(phenyl)silane (58)

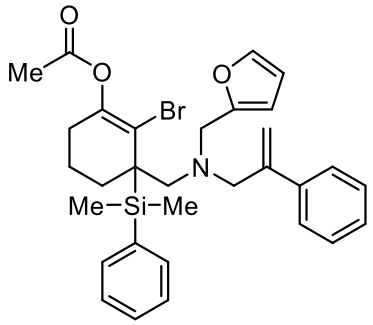


Method C

Using 2-bromo-3-(4-phenylpent-4-en-1-yl)cyclohex-2-en-1-yl ethyl carbonate (**57**) (0.25 g, 0.64 mmol), $ClSiPhMe_2$ (0.566 g, 3.33 mmol), Li (0.140 g, 20.0 mmol), and CuBr·DMS complex (0.341 g, 1.66 mmol) furnished (2-bromo-3-(4-phenylpent-4-en-1-yl)cyclohex-2-en-1-yl)dimethyl(phenyl)silane (**58**) (0.072 g, 25%) as a clear oil after column chromatography with 5:95 EtOAc:hexnae.

R_f 0.46 (5:95 EtOAc:hexnae); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53 – 7.50 (m, 2H), 7.41 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.35 – 7.27 (m, 6H), 5.28 (d, *J* = 1.5 Hz, 1H), 5.07 (d, *J* = 1.4 Hz, 1H), 2.49 (td, *J* = 7.4, 4.2 Hz, 2H), 2.35 – 2.27 (m, 2H), 2.10 – 2.03 (m, 1H), 2.00 (dtd, *J* = 16.6, 7.2, 2.0 Hz, 1H), 1.92 (dtd, *J* = 17.0, 5.5, 1.8 Hz, 1H), 1.77 – 1.69 (m, 1H), 1.64 – 1.58 (m, 1H), 1.55 – 1.45 (m, 4H), 0.45 (s, 3H), 0.40 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) 148.6, 141.6, 138.8, 134.1, 133.5, 129.0, 128.4, 127.7, 127.4, 126.3, 121.8, 112.3, 37.5, 36.6, 35.3, 31.0, 28.1, 26.2, 22.0, -1.5, -2.2, IR (cast film, cm^{-1}) 3068, 2931, 2859, 1627, HRMS (EI) calcd for $C_{25}H_{31}SiBr[M]^+$ 438.1379, found 438.1371.

2-Bromo-3-(dimethyl(phenyl)silyl)-3-(((furan-2-ylmethyl)(2-phenylallyl)amino)methyl)cyclohex-1-en-1-yl acetate (101)



Method A

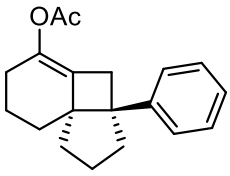
Using 2-bromo-3-(((furan-2-ylmethyl)(2-phenylallyl)amino)methyl)cyclohex-2-enone (**100**) (0.30 g, 0.75 mmol), $ClSiPhMe_2$ (0.332 g, 1.95 mmol), Li (81.0 mg, 11.7 mmol), CuBr·DMS complex (0.20 g, 0.97 mmol) and Ac_2O (0.382 g, 3.75 mmol) gave 2-bromo-3-(dimethyl(phenyl)silyl)-3-(((furan-2-ylmethyl)(2-phenylallyl)amino)methyl) cyclohex-1-en-1-yl acetate (**101**) (0.38 g, 91%) as a yellow oil after column chromatography with 1:9 EtOAc:hexane followed by column chromatography with 5:95 MeCN:toluene.

R_f 0.38 (1:9 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) 7.48 – 7.45 (m, 2H), 7.39 – 7.29 (m, 4H), 7.21 – 7.13 (m, 3H), 7.12 – 7.07 (m, 2H), 6.31 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.17 (d, *J* = 3.1 Hz, 1H), 5.33 (s, 1H), 5.22 (s, 1H), 3.91 (app t, *J* = 14.9 Hz, 2H), 3.36 (d, *J* = 14.5 Hz, 1H), 3.01 (d, *J* = 9.4 Hz, 1H), 2.99 (d, *J* = 9.5 Hz, 1H), 2.80 (d, *J* = 13.9 Hz, 1H), 2.14 (s, 3H), 2.02 – 1.96 (m, 2H), 1.88 – 1.70 (m, 1H), 1.23 – 1.18 (m, 1H), 0.44 (s, 3H), 0.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 168.2, 153.6, 146.4, 145.7, 141.7, 140.1, 137.3, 135.0, 129.1, 127.8, 127.5, 127.2, 126.9, 121.1, 115.6, 110.2, 108.8, 59.8, 56.6, 51.0, 37.1, 31.4, 29.2, 20.9, 20.1, -2.7, -4.5; HRMS (APPI) calcd for $C_{31}H_{37}BrNO_2Si[M+H]^+$ 499.2480, found 499.2482.

General Procedure for [2+2]-Cycloaddition Reaction

To a suspension of CsF (5.0 equiv.) in MeCN [0.02 M] at rt was added a solution of the substrate dissolved MeCN [0.5 M]. After the addition, the mixture was stirred at rt until the reaction was complete, typically within 24-48 h, as observed by TLC. Evaporation of most of the solvent gave a crude mixture that was flushed with DCM through a pipete packed with silica to remove any excess fluoride. This was followed by purification via column chromatography or preparative TLC.

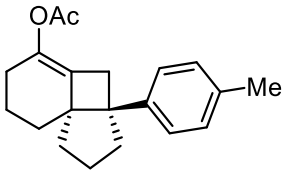
(1*R,8*S**)-8-Phenyltricyclo[6.3.0.0^{1,6}]undeca-5-ene-5-yl acetate (55a)**



Using 2-bromo-3-(dimethyl(phenyl)silyl)-3-(4-phenylpent-4-en-1-yl)cyclohex-1-en-1-yl acetate (**53a**) (0.060 g, 0.12 mmol) and CsF (0.091 g, 0.60 mmol) furnished (1*R**,8*S**)-8-phenyltricyclo[6.3.0.0^{1,6}]undeca-5-ene-5-yl acetate (**55a**) (0.023 g, 70%) as a clear oil after column chromatography with 1:30 EtOAc:DCM.

R_f 0.65 (1:30 EtOAc:DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 7.27 – 7.26 (m, 1H), 7.25 – 7.24 (m, 1H), 7.22 – 7.17 (m, 1H), 3.03 (dt, *J* = 15.6, 2.2 Hz, 1H), 2.66 (ddd, *J* = 15.6, 4.1, 2.7 Hz, 1H), 2.30 – 2.22 (m, 2H), 2.12 (s, 3H), 2.07 – 1.92 (m, 5H), 1.87 – 1.79 (m, 1H), 1.76 – 1.67 (m, 1H), 1.63 (td, *J* = 12.4, 7.1 Hz, 1H), 1.27 (dt, *J* = 12.2, 3.3 Hz, 1H), 1.13 (ddd, *J* = 13.8, 12.0, 3.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 144.1, 138.6, 128.1, 127.1, 126.5, 125.8, 59.4, 56.2, 42.8, 39.7, 36.3, 31.7, 26.7, 25.1, 21.3, 21.1, IR (cast film, cm^{-1}) 3083, 2941, 2852, 1759, 1447, 1216, HRMS (ESI) calcd for $C_{19}H_{23}O_2[M+H]^+$, 283.1693 found 283.1695.

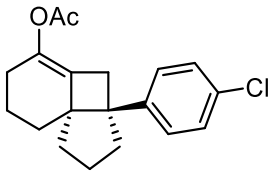
(1*R,8*S**)-8-(*p*-Tolyl)tricyclo[6.3.0.0^{1,6}]undeca-5-ene-5-yl acetate (55b)**



Using 2-bromo-3-(dimethyl(phenyl)silyl)-3-(4-(*p*-tolyl)pent-4-en-1-yl)cyclohex-1-en-1-yl acetate (**53b**) (0.075 g, 0.15 mmol) and CsF (0.115 g, 0.75 mmol) furnished (1*R**,8*S**)-8-(*p*-tolyl)tricyclo[6.3.0.0^{1,6}]undeca-5-ene-5-yl acetate (**55b**) (0.034 g, 77%) as a clear oil after column chromatography with 1:30 EtOAc:DCM.

R_f 0.68 (1:30 EtOAc:DCM); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.15 (s, 4H), 3.00 (d, *J* = 15.6 Hz, 1H), 2.64 (dt, *J* = 15.5, 3.4 Hz, 1H), 2.33 (s, 3H), 2.27 – 2.24(m, 2H), 2.12 (s, 3H), 2.03 – 1.90 (m, 5H), 1.85 – 1.80 (m, 1H), 1.73 – 1.68 (m, 1H), 1.62 (td, *J* = 12.4, 7.0 Hz, 1H), 1.26 (dt, *J* = 11.9, 3.2 Hz, 1H), 1.13 (ddd, *J* = 15.2, 12.1, 3.5 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 168.9, 140.9, 138.6, 135.2, 128.9, 127.0, 126.6, 59.2, 55.9, 42.8, 39.7, 36.3, 31.8, 26.8, 25.1, 21.3, 21.1, 21.0, IR (cast film, cm^{-1}), 3022, 2841, 2853, 1759, 1514, 1217, HRMS (ESI) calcd for $C_{20}H_{24}NaO_2$[M+Na]$^+$, 319.1669 found 319.1670.

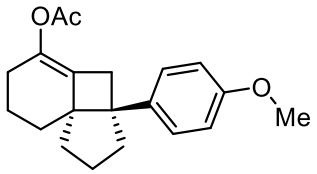
(1*R,8*S**)-8-(4-Chlorophenyl)tricyclo[6.3.0.0^{1,6}]undeca-5-ene-5-yl acetate (55c)**



Using 2-bromo-3-(4-(4-chlorophenyl)pent-4-en-1-yl)-3-(dimethyl(phenyl)silyl)cyclohex-1-en-1-yl acetate (**53c**) (0.25 g, 0.47 mmol) and CsF (0.358 g, 2.36 mmol) furnished (1*R**,8*S**)-8-(4-chlorophenyl)tricyclo[6.3.0.0^{1,6}]undeca-5-ene-5-yl acetate (**55c**) (0.13 g, 87%) as a white solid after column chromatography with 1:9 EtOAc:hexane.

R_f 0.33 (1:9 EtOAc:hexane); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.30 – 7.28 (m, 2H), 7.21 – 7.18 (m, 2H), 2.95 (dt, *J* = 15.6, 2.2 Hz, 1H), 2.67 (ddd, *J* = 15.5, 4.0, 2.7 Hz, 1H), 2.28 – 2.20 (m, 2H), 2.12 (s, 3H), 2.09 – 1.89 (m, 5H), 1.83 (ddt, *J* = 14.1, 7.2, 3.5 Hz, 1H), 1.70 (tddd, *J* = 13.9, 10.4, 7.0, 3.2 Hz, 1H), 1.61 (td, *J* = 12.3, 6.4 Hz, 1H), 1.23 (dt, *J* = 12.0, 3.3 Hz, 1H), 1.10 (ddd, *J* = 14.0, 12.0, 3.5 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 168.8, 142.5, 138.8, 131.5, 128.5, 128.2, 126.1, 59.4, 55.8, 42.4, 39.6, 36.5, 31.6, 26.7, 25.1, 21.2, 21.1, IR (cast film, cm^{-1}) 3020, 2867, 2844, 1763, 1202, HRMS (ESI) calcd for $C_{19}H_{21}ClNaO_2[M+Na]^+$, 339.1122 found 339.1123.

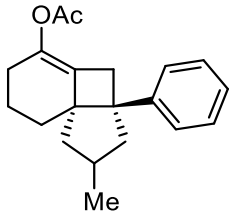
(1*R,8*S**)-8-(4-Methoxyphenyl)tricyclo[6.3.0.0^{1,6}]undeca-5-ene-5-yl acetate (55d)**



Using 2-bromo-3-(dimethyl(phenyl)silyl)-3-(4-(4-methoxyphenyl)pent-4-en-1-yl)cyclohex-1-en-1-yl acetate (**53d**) (0.050 g, 0.090 mmol) and CsF (0.068 g, 0.45 mmol) furnished (1*R**,8*S**)-8-(4-methoxyphenyl)tricyclo[6.3.0.0^{1,6}]undeca-5-ene-5-yl acetate (**55d**) (0.026 g, 91%) as a white solid after column chromatography with 1:9 EtOAc:hexane.

R_f 0.42 (1:9 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.17 (m, 2H), 6.90 – 6.86 (m, 2H), 3.80 (s, 3H), 2.96 (dt, *J* = 15.5, 2.2 Hz, 1H), 2.65 (ddd, *J* = 15.5, 4.0, 2.7 Hz, 1H), 2.28 – 2.20 (m, 2H), 2.12 (s, 3H), 2.08 – 1.88 (m, 5H), 1.86 – 1.79 (m, 1H), 1.70 (tddd, *J* = 13.9, 10.5, 7.0, 3.4 Hz, 1H), 1.64 – 1.56 (m, 1H), 1.23 (dt, *J* = 12.0, 3.3 Hz, 1H), 1.13 (ddd, *J* = 13.8, 12.0, 3.6 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 168.9, 157.7, 138.6, 136.0, 128.0, 126.6, 113.5, 59.1, 55.5, 55.3, 42.4, 39.6, 36.6, 31.7, 26.8, 25.0, 21.3, 21.1, IR (cast film, cm^{-1}), 3065, 2941, 2862, 1746, 1514, 1244, HRMS (ESI) calcd for $C_{20}H_{25}O_3[M+H]^+$, 313.1798 found 313.1786.

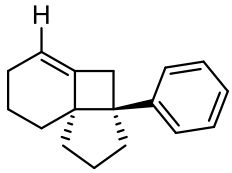
(1*R,8*S**)-2-Methyl-8-phenyltricyclo[6.3.0.0^{1,6}]undeca-5-ene-5-yl acetate (55e)**



Using 2-bromo-3-(dimethyl(phenyl)silyl)-3-(2-methyl-4-phenylpent-4-en-1-yl)cyclohex-1-en-1-yl acetate (**53e**) (0.10 g, 0.20 mmol) and CsF (0.15 g, 0.98 mmol) furnished (1*R**,8*S**)-2-methyl-8-phenyltricyclo[6.3.0.0^{1,6}]undeca-5-ene-5-yl acetate (**55e**) (0.043 g, 73%, 1:1 mixture of diastereomers) as a clear oil after column chromatography with 1:9 EtOAc:hexane followed by preparative TLC with 5:40:55 Et_2O:DCM:hexane.

Mixture of diastereomers as determined by relative integration.
R_f 0.46 (1:9 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 4H), 7.27 – 7.23 (m, 2H), 7.23 – 7.15 (m, 4H), 3.36 (dt, *J* = 15.1, 1.7 Hz, 1H), 3.03 (dt, *J* = 15.6, 2.2 Hz, 1H), 2.82 (dt, *J* = 15.0, 3.3 Hz, 1H), 2.72 (ddd, *J* = 15.6, 4.1, 2.6 Hz, 1H), 2.53 (tq, *J* = 12.0, 6.0 Hz, 1H), 2.46 – 2.31 (m, 3H), 2.29 – 2.21 (m, 1H), 2.15 (s, 3H), 2.12 (s, 3H), 2.11 – 2.08 (m, 1H), 2.05 – 1.62 (m, 12H), 1.32 – 1.24 (m, 2H), 1.15 (d, *J* = 6.3 Hz, 3H), 1.12 (d, *J* = 6.3 Hz, 3H), 1.16-1.14 (m, 1H), 0.54 (td, *J* = 12.9, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 169.1, 144.3, 143.9, 139.0, 138.4, 128.5, 128.4, 127.3, 127.0, 126.6, 126.0, 125.9, 125.5, 62.3, 60.2, 57.7, 56.9, 54.4, 51.6, 48.6, 48.1, 42.1, 39.5, 37.2, 32.8, 32.1, 30.1, 27.0, 26.5, 21.5, 21.4, 21.4, 21.4, 19.8, 19.6, IR (cast film, cm^{-1}), 3089, 2933, 2868, 1757, 1445, 1215, HRMS (EI) calcd for $C_{20}H_{22}O_2[M]^+$, 296.1776 found 296.1773.

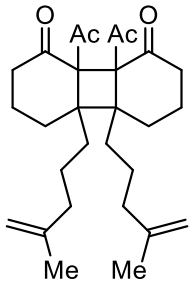
(1*R,8*S**)-8-Phenyltricyclo[6.3.0.0^{1,6}]undeca-5-ene (55g)**



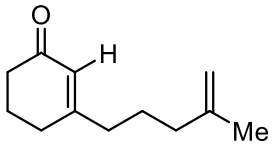
Using 2-bromo-3-(4-phenylpent-4-en-1-yl)cyclohex-2-en-1-yl ethyl carbonate (**57**) (0.060 g, 0.14 mmol) and CsF (0.10 g, 0.68 mmol) furnished (1*R**,8*S**)-8-phenyltricyclo[6.3.0.0^{1,6}]undeca-5-ene (**55g**) (0.010 g, 32%) as a clear oil after column chromatography with 5:95 EtOAc:hexane followed by preparative TLC with hexane.

R_f 0.31 (hexane); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.27 – 7.24 (m, 2H), 7.18 (tt, *J* = 7.2, 1.3 Hz, 1H), 5.27 (d, *J* = 2.5 Hz, 1H), 3.07 (dd, *J* = 15.2, 2.0 Hz, 1H), 2.78 (ddt, *J* = 15.2, 4.7, 2.7 Hz, 1H), 2.22 (dd, *J* = 12.6, 6.5 Hz, 1H), 2.11 – 1.90 (m, 6H), 1.69 (ddt, *J* = 14.1, 7.2, 3.5 Hz, 1H), 1.64 (td, *J* = 12.4, 7.0 Hz, 1H), 1.58 (dddq, *J* = 13.8, 10.2, 6.8, 3.4 Hz, 1H), 1.33 (dt, *J* = 11.8, 3.4 Hz, 1H), 1.06 (ddd, *J* = 14.8, 11.7, 3.5 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 144.8, 141.4, 128.0, 127.2, 125.6, 116.0, 59.7, 56.2, 43.5, 39.9, 39.1, 32.5, 25.3, 25.0, 20.2, IR (cast film, cm^{-1}), 3084, 2934, 2852, 1497, 1446, HRMS (EI) calcd for $C_{17}H_{20}[M]^+$, 224.1565 found 224.1564.

(4a,4b)-8a,8b-diacetyl-4a,4b-bis(4-methylpent-4-en-1-yl)octahydrobiphenylene-1,8(8aH,8bH)-dione (83-p)



3-(4-Methylpent-4-en-1-yl)cyclohex-2-enone (85)



Using 2-bromo-3-(dimethyl(phenyl)silyl)-3-(4-methylpent-4-en-1-yl)cyclohex-2-en-1-yl acetate (**78**) (0.30 g, 0.69 mmol) and CsF (0.523 g, 3.44 mmol) furnished (4a,4b)-8a,8b-diacetyl-4a,4b-bis(4-methylpent-4-en-1-yl)octahydrobiphenylene-1,8(8aH,8bH)-dione (**83-p**) (0.060 g, 39%) as a yellow oil and 3-(4-methylpent-4-en-1-yl)cyclohex-2-enone (**85**) (0.0050 g, 3%) as a clear oil after column chromatography with 1:9 EtOAc:hexane.

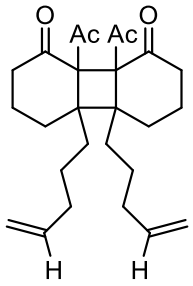
(4a,4b)-8a,8b-diacetyl-4a,4b-bis(4-methylpent-4-en-1-yl)octahydrobiphenylene-1,8(8aH,8bH)-dione (**83-p**)

R_f 0.22 (1:9 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 – 4.71 (m, 1H), 4.68 – 4.64 (m, 1H), 2.45 – 2.36 (m, 4H), 2.32 (s, 3H), 2.21 – 2.12 (m, 2H), 2.08 – 1.92 (m, 4H), 1.71 (s, 3H), 1.68 – 1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 197.3, 163.2, 144.8, 139.9, 110.8, 37.8, 37.7, 35.2, 32.1, 30.1, 26.1, 22.3, 22.1, IR (cast film, cm^{-1}), 3074, 2939, 2866, 1703, 1666, 1360, HRMS (ESI) calcd for $C_{28}H_{40}NaO_4[M+Na]^+$, 463.2819 found 463.2815.

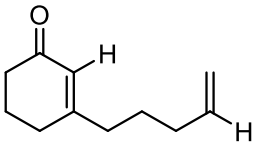
3-(4-Methylpent-4-en-1-yl)cyclohex-2-enone (85)

R_f 0.29 (1:9 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (s, 1H), 4.74 (s, 1H), 4.68 (s, 1H), 2.39 – 2.33 (m, 2H), 2.29 (t, *J* = 6.1 Hz, 2H), 2.20 (t, *J* = 7.8 Hz, 2H), 2.07 – 1.96 (m, 4H), 1.71 (s, 3H), 1.65 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 166.4, 145.0, 125.9, 110.6, 37.6, 37.5, 37.3, 29.8, 24.8, 22.9, 22.4.

(4a,4b)-8a,8b-diacetyl-4a,4b-di(pent-4-en-1-yl)octahydrobiphenylene-1,8(8aH,8bH)-dione (82-p)



3-(Pent-4-en-1-yl)cyclohex-2-enone (84)



Using 2-bromo-3-(dimethyl(phenyl)silyl)-3-(pent-4-en-1-yl)cyclohex-2-en-1-yl acetate (**79**) (0.025 g, 0.059 mmol) and CsF (0.045 g, 0.29 mmol) furnished (4a,4b)-8a,8b-diacetyl-4a,4b-di(pent-4-en-1-yl)octahydrobiphenylene-1,8(8aH,8bH)-dione (**82-p**) (0.0037 g, 30%) as a yellow oil and 3-(pent-4-en-1-yl)cyclohex-2-enone (**84**) (0.0010 g, 8%) as a clear oil after preparative TLC with 1:9 EtOAc:hexane.

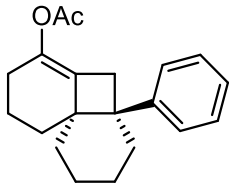
(4a,4b)-8a,8b-diacetyl-4a,4b-di(pent-4-en-1-yl)octahydrobiphenylene-1,8(8aH,8bH)-dione (82-p)

R_f 0.21 (1:9 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.05 – 4.95 (m, 2H), 2.40 (app dt, *J* = 12.3, 6.3 Hz, 3H), 2.32 (s, 3H), 2.22 – 2.15 (m, 2H), 2.11 – 2.04 (m, 2H), 2.02 – 1.95 (m, 2H), 1.64 – 1.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 197.3, 163.1, 139.9, 137.7, 115.5, 37.7, 35.1, 33.7, 32.1, 30.0, 27.4, 22.1, IR (cast film, cm^{-1}), 3077, 2933, 2867, 1704, 1667, 1363, HRMS (ESI) calcd for $C_{26}H_{36}NaO_4[M]^+$, 435.2506 found 435.2506.

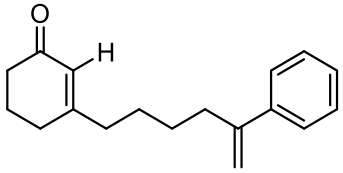
3-(Pent-4-en-1-yl)cyclohex-2-enone (84)

R_f 0.24 (1:9 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 – 5.86 (m, 1H), 5.79 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.06 – 4.95 (m, 2H), 2.39 – 2.33 (m, 2H), 2.28 (t, *J* = 6.1 Hz, 2H), 2.22 (t, *J* = 7.7 Hz, 2H), 2.08 (q, *J* = 7.1 Hz, 2H), 1.99 (quint, *J* = 6.3 Hz, 2H), 1.62 (q, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 166.3, 138.0, 125.9, 115.4, 37.5, 37.5, 33.3, 29.8, 26.2, 22.8, IR (cast film, cm^{-1}), 3077, 2933, 2866, 1671, HRMS (EI) calcd for $C_{11}H_{16}O[M]^+$, 164.1201 found 164.1199.

(1*R,8*S**)-8-Phenyltricyclo[6.4.0.0^{1,6}]dodeca-5-ene-5-yl acetate (55f)**



3-(5-Phenylhex-5-en-1-yl)cyclohex-2-enone (59)



Using 2-bromo-3-(dimethyl(phenyl)silyl)-3-(5-phenylhex-5-en-1-yl)cyclohex-2-en-1-yl acetate (**53f**) (0.10 g, 0.20 mmol) and CsF (0.152 g, 1.00 mmol) furnished (1*R**,8*S**)-8-phenyltricyclo[6.4.0.0^{1,6}]dodeca-5-ene-5-yl acetate (**55f**) (0.0027 g, 5%) as a clear oil and 3-(5-phenylhex-5-en-1-yl)cyclohex-2-enone (**59**) (0.012 g, 24%) as a clear oil after preparative TLC with 1:9 EtOAc:hexane.

Note: due to insufficient sample full characterization of this compound was not possible but the obtained ^{1}H NMR spectrum matches with, and has the characteristic peaks associated with, previous examples of [2+2] cycloadducts described in this thesis.

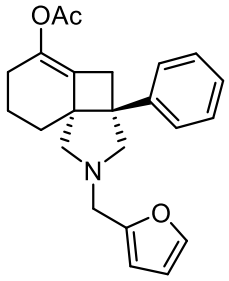
(1*R,8*S**)-8-Phenyltricyclo[6.4.0.0^{1,6}]dodeca-5-ene-5-yl acetate (55f)**

R_f 0.42 (1:9 EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 4H), 7.21 – 7.16 (m, 1H), 3.02 – 3.00 (m, 2H), 2.15 (s, 3H), 2.08 – 1.91 (m, 2H), 1.88 – 1.61 (m, 8H), 1.61 – 1.55 (m, 1H), 1.43 – 1.35 (m, 1H), 1.14 (dt, *J* = 12.2, 3.1 Hz, 1H), 0.56 (td, *J* = 12.8, 3.5 Hz, 1H).

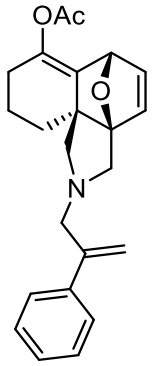
3-(5-Phenylhex-5-en-1-yl)cyclohex-2-enone (59)

R_f 0.16 (1:9 EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 5.85 (s, 1H), 5.27 (d, *J* = 1.5 Hz, 1H), 5.05 (d, *J* = 1.5 Hz, 1H), 2.53 (t, *J* = 7.0 Hz, 2H), 2.36 – 2.30 (m, 2H), 2.21 (dt, *J* = 13.6, 6.9 Hz, 4H), 1.94 (quint, *J* = 6.3 Hz, 2H), 1.53 – 1.42 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 166.4, 148.2, 141.2, 128.4, 127.5, 126.2, 125.9, 112.7, 37.9, 37.4, 35.1, 29.7, 27.7, 26.5, 22.8, IR (cast film, cm^{-1}) 3080, 2935, 2863, 1669, 1625, HRMS (EI) calcd for $C_{18}H_{22}O[M]^+$, 254.1671 found 254.1667.

(1*R,8*R**)-10-Azatricyclo[6.3.0.0^{1,6}]undeca-5-ene-8-phenyl-3-furfuryl-5-yl acetate (103)**



***Endo*-3-aza-14-oxotetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-3-homo(α-methylstyrene)-9-yl acetate (104)**



Using 2-bromo-3-(dimethyl(phenyl)silyl)-3-(((furan-2-ylmethyl)(2-phenylallyl)amino)methyl) cyclohex-2-en-1-yl acetate (**101**) (0.38 g, 0.68 mmol) and CsF (0.513 g, 3.38 mmol) furnished (1*R**,8*R**)-10-azatricyclo[6.3.0.0^{1,6}]undeca-5-ene-8-phenyl-3-furfuryl-5-yl acetate (**103**) (0.14 g, 56%) as a clear oil and *Endo*-3-aza-14-oxotetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-3-homo(α-methylstyrene)-9-yl acetate (**104**) (0.071 g, 29%) as a clear oil after column chromatography with 1:3 EtOAc:hexane.

(1*R,8*R**)-10-Azatricyclo[6.3.0.0^{1,6}]undeca-5-ene-8-phenyl-3-furfuryl-5-yl acetate (103)**

R_f 0.46 (1:3 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.37 (m, 1H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.27 – 7.24 (m, 2H), 7.23 – 7.19 (m, 1H), 6.33 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.22 (d, *J* = 3.2 Hz, 1H), 3.80 (d, *J* = 14.0 Hz, 1H), 3.71 (d, *J* = 14.1 Hz, 1H), 3.48 (d, *J* = 9.1 Hz, 1H), 3.17 (ddd, *J* = 14.7, 3.9, 2.7 Hz, 1H), 3.09 (d, *J* = 9.2 Hz, 1H), 3.04 – 2.97 (m, 1H), 2.60 (d, *J* = 9.2 Hz, 1H), 2.35 (d, *J* = 9.1 Hz, 1H), 2.31 – 2.23 (m, 1H), 2.12 (s, 3H), 2.07 – 1.96 (m, 1H), 1.89 – 1.79 (m, 1H), 1.60 (tddd, *J* = 13.9, 10.3, 6.8, 3.2 Hz, 1H), 1.37 (dt, *J* = 12.2, 3.2 Hz, 1H), 1.20 (ddd, *J* = 14.0, 12.2, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 152.8, 141.8, 141.0, 138.5, 128.2, 127.4, 126.3, 126.1, 110.2, 108.0, 67.5, 65.9, 58.8, 55.4, 51.5, 37.5, 29.5, 26.8, 21.5, 21.1, HRMS (EI) calcd for $C_{23}H_{25}NO_3[M]^+$, 363.1872 found 363.1870.

***Endo*-3-aza-14-oxotetracyclo[9.2.1.0^{1,5}.0^{5,10}]tetradeca-9,12-dien-3-homo(α-methylstyrene)-9-yl acetate (104)**

R_f 0.32 (1:3 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 2H), 7.34 – 7.29 (m, 2H), 7.28 – 7.24 (m, 1H), 6.39 (dd, *J* = 5.6, 1.7 Hz, 1H), 6.17 (d, *J* = 5.5 Hz, 1H), 5.43 (s, 1H), 5.28 (s, 1H), 5.20 (s, 1H), 3.67 (d, *J* = 13.9 Hz, 1H), 3.60 (d, *J* = 13.9 Hz, 1H), 3.56 (d, *J* = 11.9 Hz, 1H), 2.95 (d, *J* = 8.4 Hz, 1H), 2.86 (d, *J* = 11.9 Hz, 1H), 2.66 (dd, *J* = 8.5, 1.7 Hz, 1H), 2.29 (dd, *J* = 17.6, 7.2 Hz, 1H), 2.14 (s, 3H), 1.97 – 1.70 (m, 5H), 0.43 (td, *J* = 12.5, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 145.7, 143.1, 140.4, 136.5, 131.1, 128.2, 128.1, 127.5, 126.3, 114.2, 99.6, 78.2, 60.4, 60.0, 53.9, 53.7, 29.8, 26.2, 21.4, 21.0, HRMS (EI) calcd for $C_{23}H_{25}NO_3[M]^+$, 363.1864 found 363.1869.

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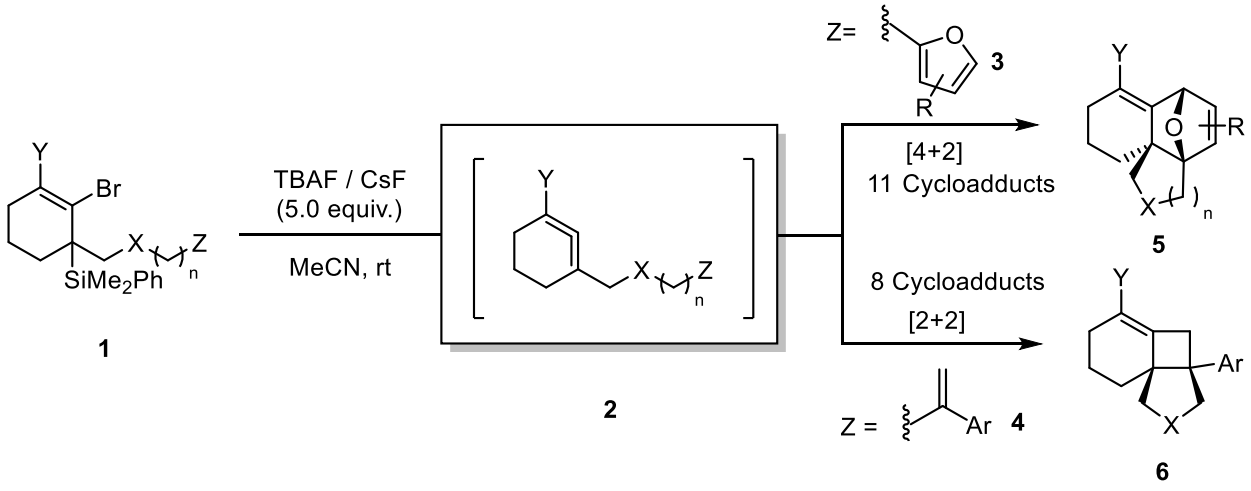
4. 1,2-Cyclohexadiene: How far have we come, and where do we go from here?

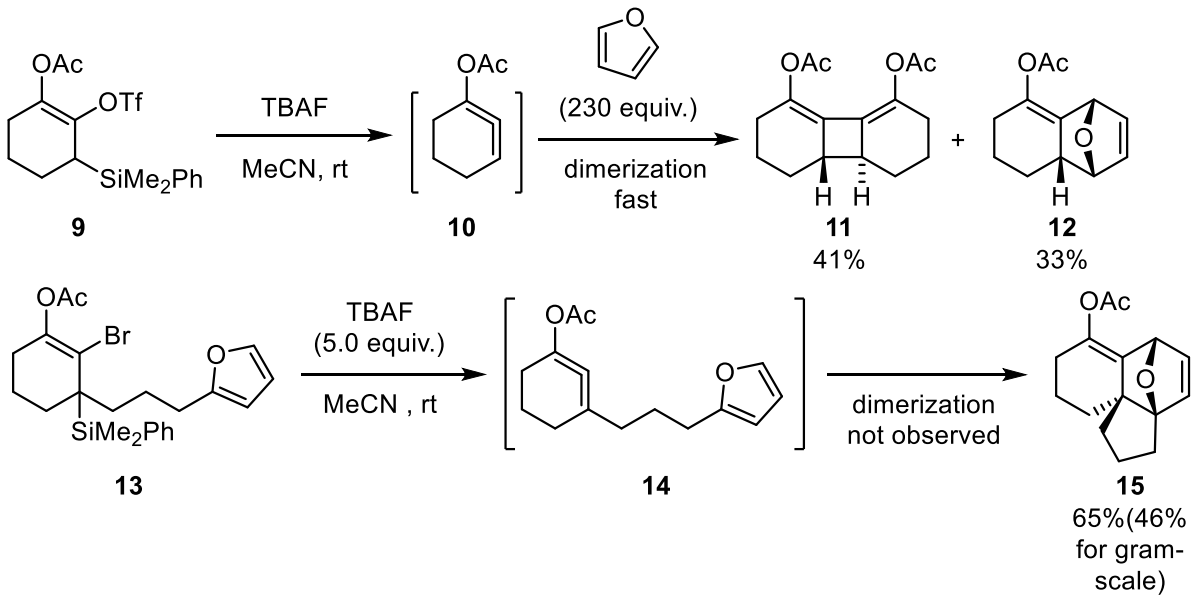
4.1 Summary of [4+2] and [2+2]-Cycloaddition

In Chapters **2** and **3** of this thesis new methodologies for [4+2] and [2+2]-cycloadditions of substituted 1,2-cyclohexadiene have been described. In contrast to the bulk of the literature on 1,2-cyclohexadiene, the presented work features intramolecular cycloadditions enabled by the inclusion of a tethered trapping moiety.[1-5] These seminal works have demonstrated for the first time the ability to use high energy allene intermediate **2**, generated from **1** via fluoride mediated elimination, in conjunction with tethered furan **3** and styrene **4** moieties to produce complex carbocyclic products **5** and **6** through [4+2] and [2+2] cycloadditions respectively. In total 19 successful cycloadducts between two core structural motifs have been successfully synthesized (Scheme 4.1). Each of these core structures has multiple points of variation: the group on 1,2-cyclohexadiene (Y), the group/atom in the tether chain (X) and the substituents on the trapping moiety (R/Ar).



Scheme 4.1 - Synthesis of [4+2] and [2+2]-Cycloadducts via Methodology Presented in this Thesis

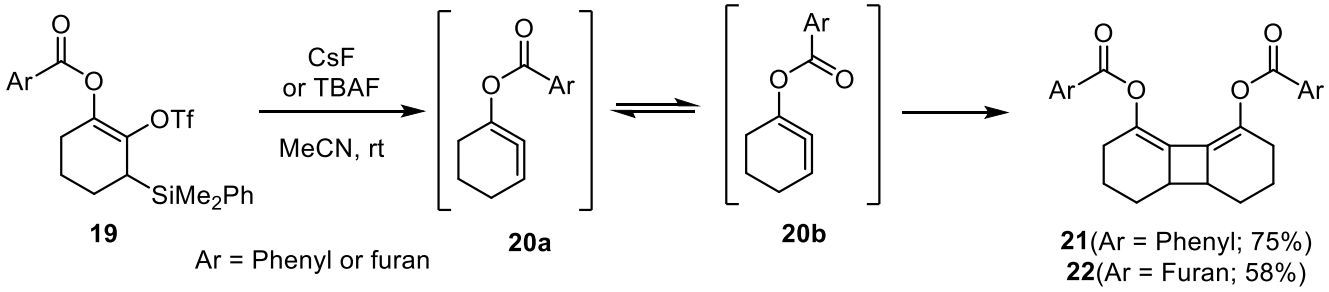
At the onset of these investigations we set out to answer several important questions about the proposed methodology. At the most basic level a demonstration, for the first time, of a generalized intramolecular [4+2] and [2+2] cycloaddition of 1,2-cyclohexadiene was desired; with a number of successful examples for both types of cycloaddition in hand, clearly the feasibility of this reactivity has been demonstrated. The design of the presented methodology also demonstrated how to overcome many of the traditional problems associated with cyclic allenes.[1,6-8] Low yields and propensity for dimerization in the trapping chemistry of strained cyclic allenes are common challenges; a methodology with improved yields and atom economy would be highly desirable. Remarkably, we do not observe dimerization with our [4+2] examples and only in specific conditions do we see dimers with [2+2] substrates (see section **3.4.7** in chapter **3**). In general, the yields we have obtained are superior to analogous intermolecular reactions (Scheme 4.2). Acetoxy substituted 1,2-cyclohexadiene **10** requires 230 equivalents of furan in order to produce cycloadduct **12** in 33% yield, with the dimer **11** being the major product formed in 41% yield.[9] Comparatively substrate **14** with a tethered furan generates the desired cycloadduct in a yield of 65% (46% on the gram scale) with no evidence of dimerization observed.



Scheme 4.2 - Improved Yield and Atom Economy for Intramolecular Methodology vs. Intermolecular Methodology

The net result of reduced dimerization is an increase in yield of desired cycloadduct in comparison to the corresponding intermolecular cycloadditions. One of the most drastic improvements vs. other methodologies reported is the vastly improved atom economy; with a trap to allene ratio of just 1:1 or 2:1. By utilizing the strain energy inherent to cyclic allenes (e.g., ~32 kcal/mol for 1,2-cyclohexadiene itself), these cycloadditions can proceed at room temperature, a great advantage compared to the requirement for heat or Lewis acid activation with many Diels-Alder reactions.[10]

Chapter **2** of this thesis described how the first intramolecular Diels-Alder reaction of 1,2-cyclohexadiene and pendent furans was developed and the preliminary scope of the reaction. As the methodology developed, a great deal about the structural requirements for an intramolecular cycloaddition was discovered. A flexible tether was key to enabling the cycloaddition; if a tether is too rigid or has too many unreactive rotamers, such as with amide **17** and ester **20a** which can exist in the s-cis conformation of **20b**, the desired cycloaddition does not take place (Scheme 4.3). Additionally, it was discovered that the substitution pattern around the furan moiety does not appear to have a great effect on cycloaddition efficacy with yields ranging from 47-64% for different furans (Figure 4.1). Importantly these cycloadditions produced only a single diastereomer, the endo isomer. This configuration was initially assigned based on the presence of an upfield proton at ~0.5 ppm in the ^{1}H NMR spectrum which has a literature precedent.[11-12] This assignment was later confirmed with an X-Ray crystal structure of **15d** (Figure 4.2).[13]



Scheme 4.3 - Unsuccessful Cycloaddition Reactions due to Tether Constraints

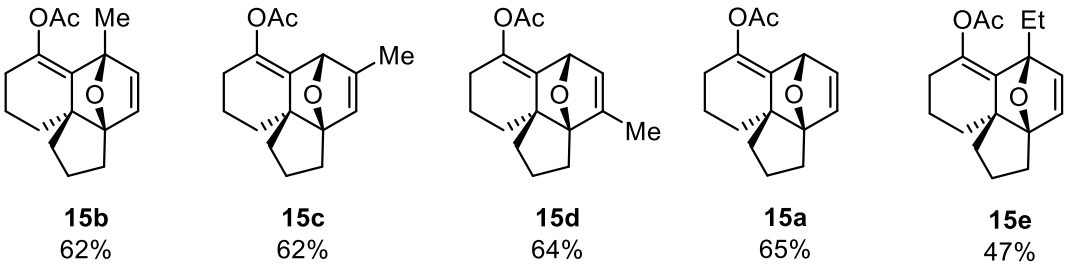


Figure 4.1 - Variation of Furan Substitution Pattern

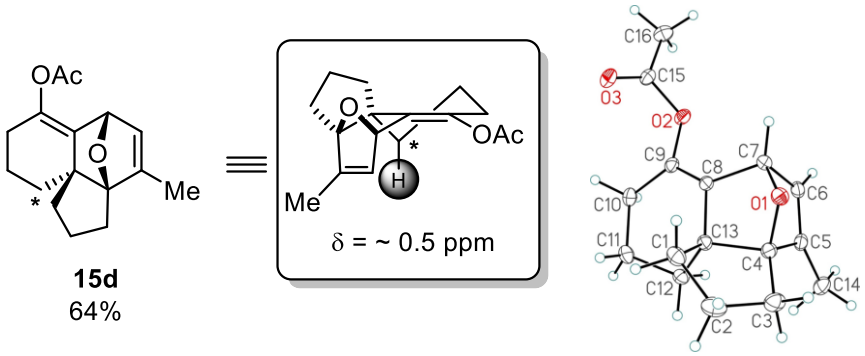
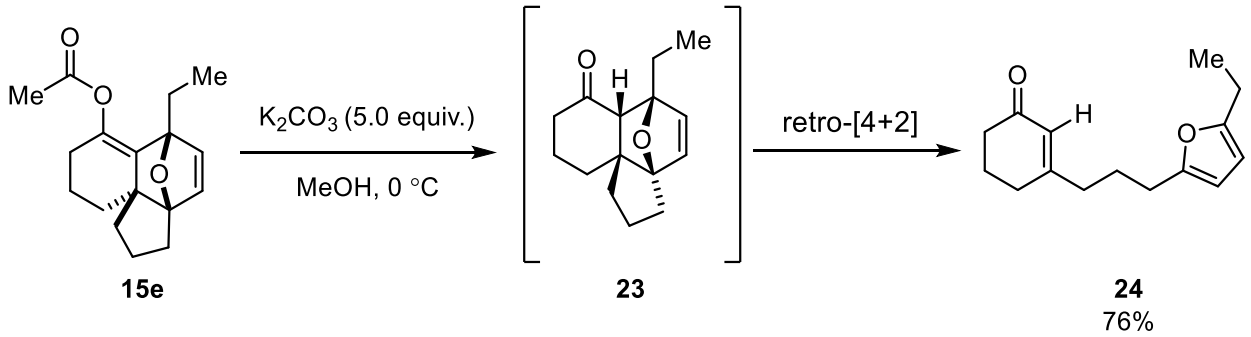


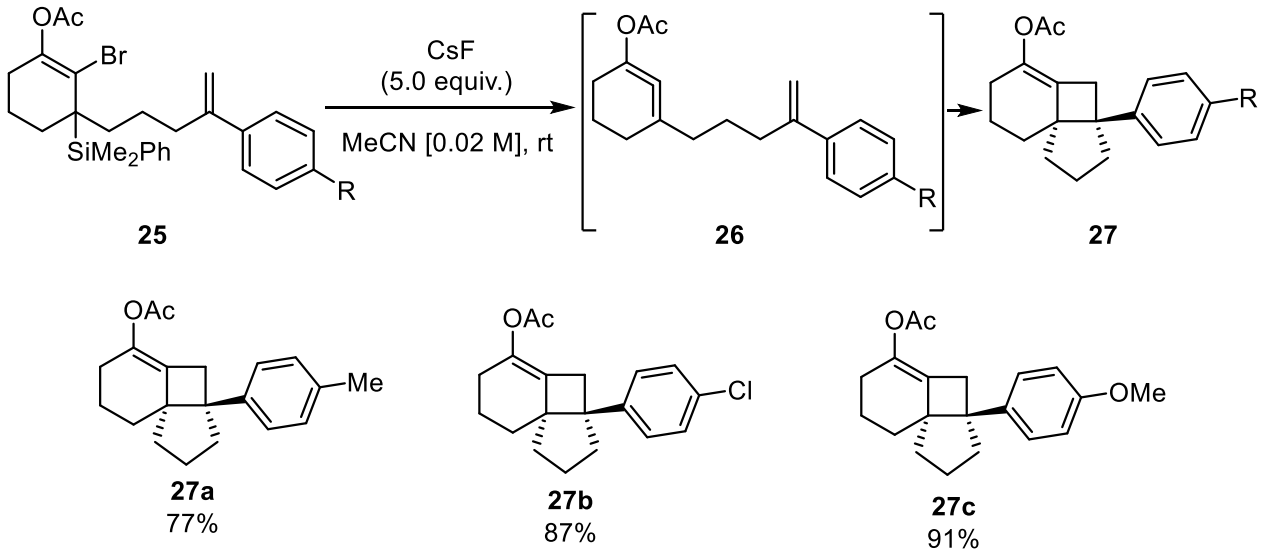
Figure 4.2 - Obtained Crystal Structure for Compound 15d

Interestingly, we found that that these [4+2] cycloadducts can be prone to retro Diels-Alder reaction. Originally attempting to open the ether bridge of cycloadduct **15e** (see section **2.4.8** in Chapter **2**) instead the formation of cyclohexenone **24** in 76% yield was observed (Scheme 4.4). We propose that after base promoted acetoxy cleavage of **15e** compound **23** is formed, which will undergo a rapid cycloreversion to **24**.

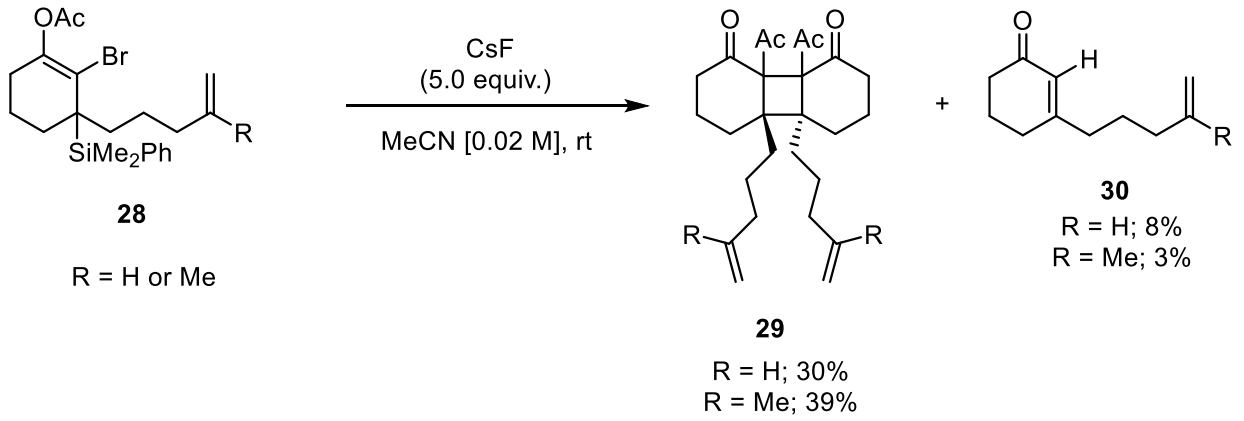


Scheme 4.4 - Example of Retro Diels-Alder Reaction of Cycloadduct 15e

Chapter **3** of this thesis advanced the seminal work of Chapter **2** by introducing an alternate cycloaddition partner, a substituted styrene capable of [2+2]-cycloaddition. Yields are consistently higher with the [2+2] process (up to 91%) than the corresponding [4+2] cases, where the yields range from 21-79%. Increased electron availability on the styrene moiety appeared to correlate with increased yields of the desired cycloadducts (Scheme 4.5). Compounds with available lone pairs and electron donating capability, such as **27b** and **27c** were formed in some of the highest yields observed for cycloadditions of 1,2-cyclohexadiene. The type of double bond utilized in the cycloaddition was found to be vital; with simple unconjugated olefins not producing the desired cycloadduct (Scheme 4.6). With either mono or disubstituted terminal olefin **28** dimeric ketone product **29** and cyclohexenone product **30** are obtained. Dimerization is faster than the desired [2+2] cycloaddition in these substrates because the intermediate diradical in the presumably stepwise mechanism lacks benzylic stabilization.

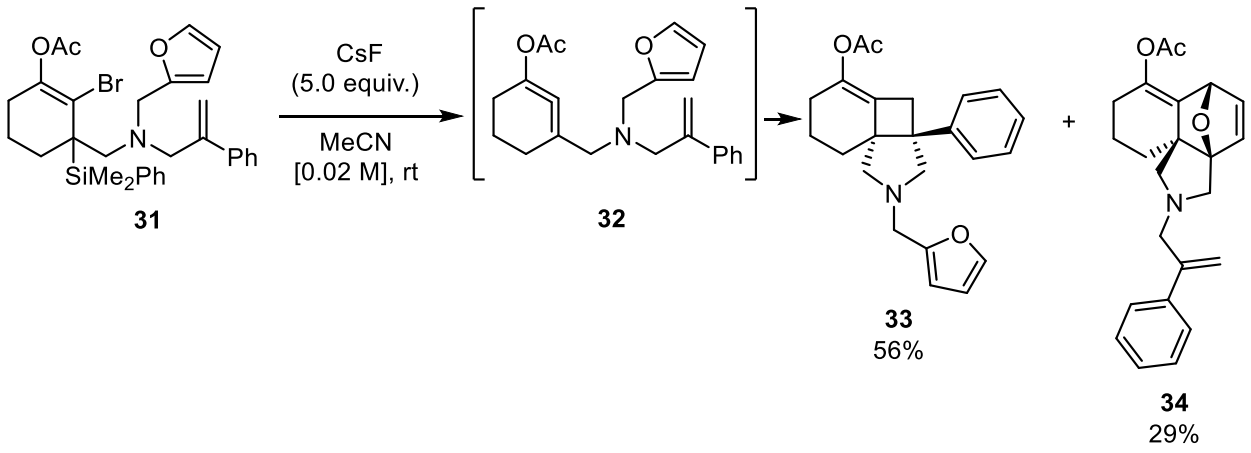


Scheme 4.5 - Apparent Correlation Between Cycloaddition Yield and Electron Availability of Styrene Moiety



Scheme 4.6 – Ketone Dimer and Cyclohexenone Products Observed with Attempted Cycloadditions of Olefins

Finally, an experiment with both [4+2] and [2+2] trapping moieties present showed that both cycloadditions are possible simultaneously with the [2+2] being favored in an approximate ratio of 2:1 (Scheme 4.7). Compound **31** which has both a styrene and furan component in the tether underwent the desired cycloaddition in a combined yield of 85% to produce **33** and **34**. While we were able to demonstrate a great deal of chemistry for these new methodologies there are countless ways we envision being able to expand upon this initial work.



Scheme 4.7 - [4+2] and [2+2]-Cycloadducts Produced from a Single Starting Material

4.2 Future Plans for [4+2]

In Chapter **2** of this thesis a new methodology was described whereby high energy 1,2-cyclohexadiene intermediates were trapped by pendent furan moieties in an intramolecular [4+2]-cycloaddition reaction.[14] So far all of the reported cycloadditions have utilized furan as the 4π electron partner in the cycloaddition. In addition to being locked in s-cis reactive conformation, furan was chosen specifically for this methodology as it has less aromatic stabilization than either thiophene or pyrrole and as such the cycloaddition reaction, wherein aromaticity must be broken, should have less of an energetic cost. Naturally this raises the question if other 4π diene components can be used in place of furan (Figure 4.3). Thiophene **35** and pyrrole **36** containing substrates would be natural choices to extend this methodology to other heterocycles as they are known to participate in cycloaddition reactions, and reactions with 1,2-cyclohexadiene.[15-16] More interesting would be heterocycles with multiple heteroatoms such as imidazole and thiazole. If species such as **37** and **38** could be induced to undergo the desired transformation very interesting heterocycles **42** and **43** would be generated. There are very limited reports using imidazole as a diene in an inverse electron demand Diels-Alder reaction; however, these proposed transformations could prove very challenging due to the high degree of aromatic stability of these heterocycles.[19] On the other hand, the high strain energy of the cyclic allene partner may overcome the aromatic stabilization problem. In addition to cyclic aromatic species, other cyclic 4π diene molecules such as cyclopentadiene **39** could also be examined with this methodology. While acyclic 4π diene species may also be examined with this methodology, cyclic examples are seen as more promising substrates due being locked in the required s-cis reactive conformation.

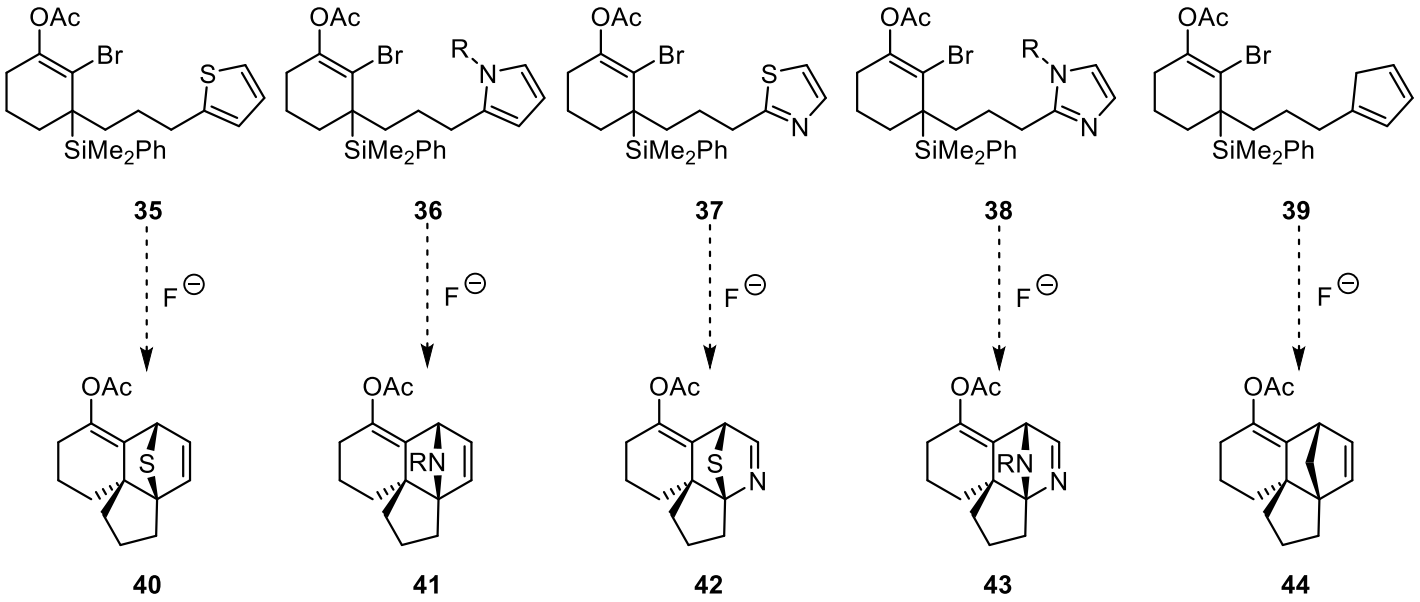
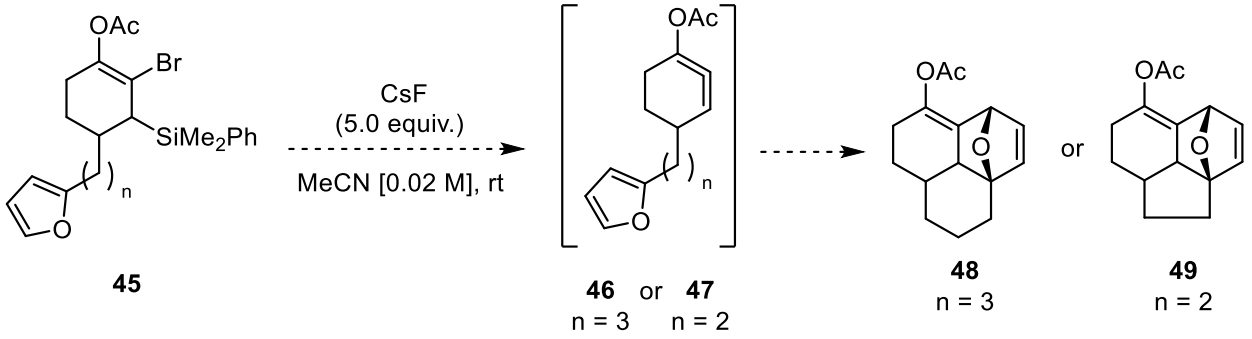


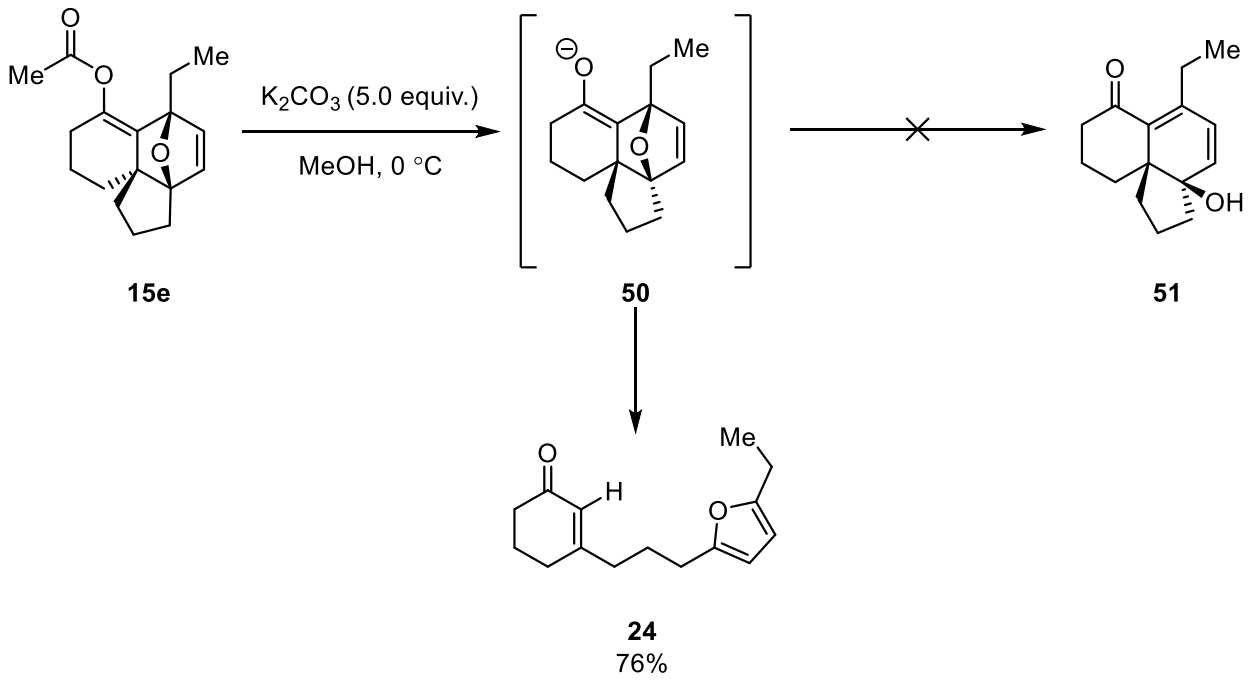
Figure 4.3 - 4 π Electron Moieties Besides Furan in a [4+2]-Cycloaddition Reaction

In all the reported [4+2] examples in this thesis the tether has been attached to the 1,2-cyclohexadiene in a β-position relative to the precursor ketone. This opens the possibility of attaching the tether in a different location on 1,2-cyclohexadiene. One possibility that has not yet been explored would be incorporating a trap in the γ-position as with compound **45** (Scheme 4.8). This would produce an interesting and different skeleton in the cycloadduct, compound **48**, than our current examples. One drawback to this would be having the tether and trapping moiety farther away from the generated allene; and as shown in Chapter **2** and **3** the constraints of the tether have a large effect on cycloaddition efficiency. One way to overcome this would be to shorten the tether as with **47** and see if **49** could be generated.

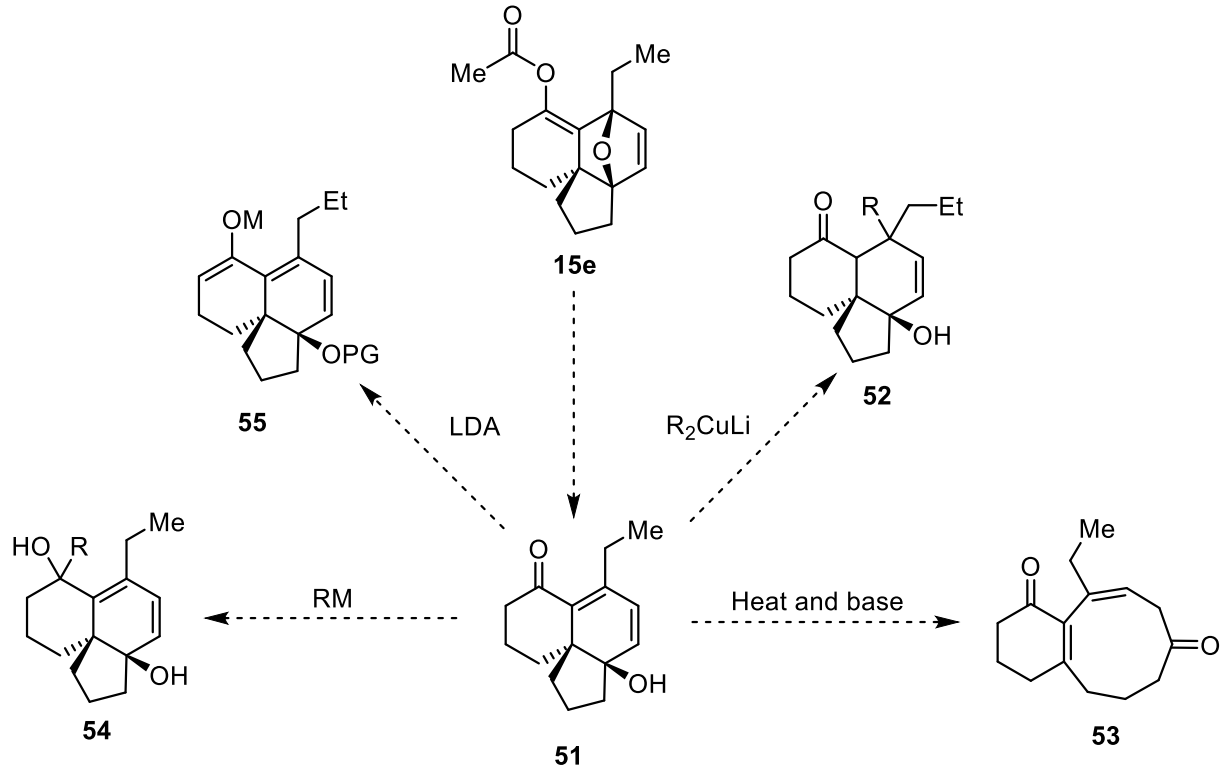


Scheme 4.8 - Incorporation of a γ-Tethered Trapping Moiety on 1,2-Cyclohexadiene

The most interesting prospect for future work with this methodology may lie in revisiting the unexpected retro-Diels-Alder reaction observed upon cleavage of the ester moiety of compounds such as **15e** (Scheme 4.9). Although the cycloreversion process is a surprising and interesting observation, if conditions could be found to enable opening of the oxo-bridge ether to proposed tertiary alcohol **51** a variety of further transformations would become available (Scheme 4.10). Access to tertiary alcohol **51** leaves several hypothetical transformations available such as organocuprate addition to **52**, oxy-cope rearrangement to **53**, organometallic addition to **54**, and alkylation to **55**.

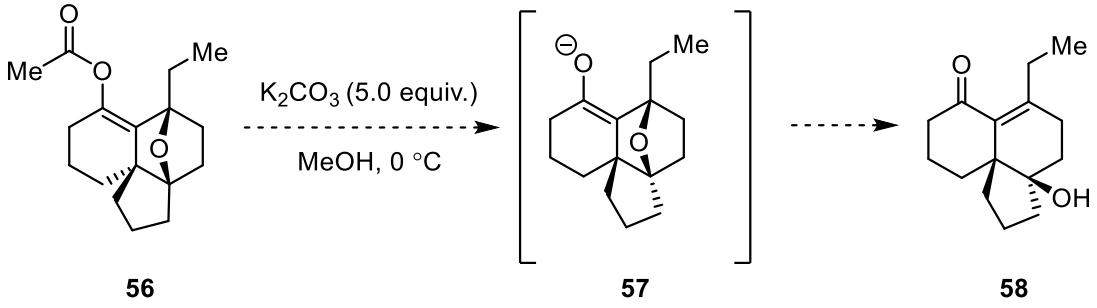


Scheme 4.9 - Retro-Diels-Alder Reaction and Hypothesized Oxo-Bridge Opening



Scheme 4.10 - Hypothetical Transformations of Tertiary Alcohol 51

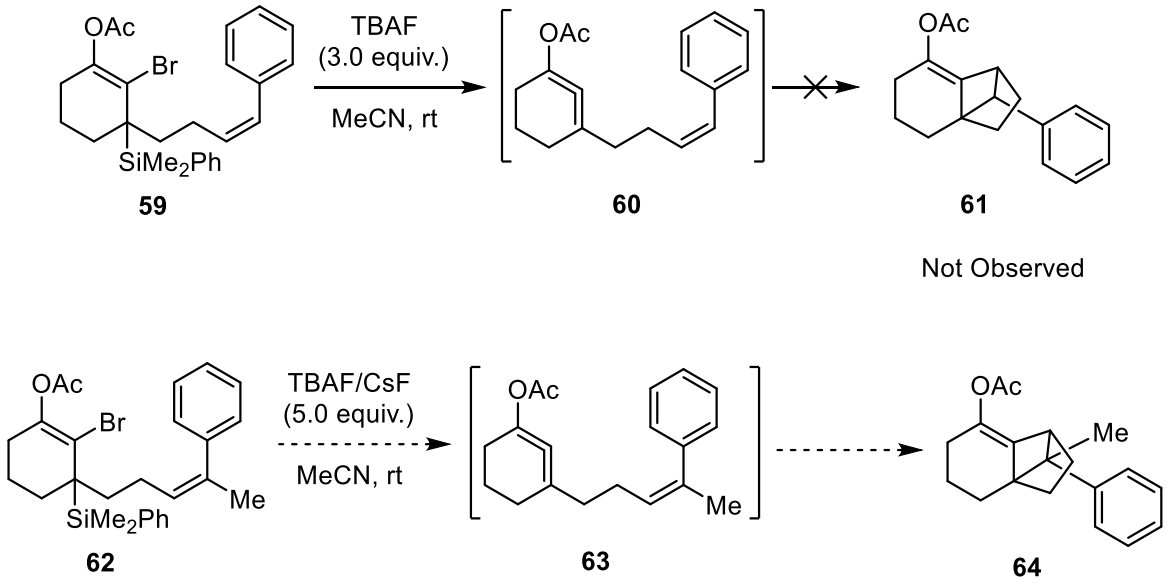
One of the suspected reasons for the difficulty associated with the proposed oxo-bridge opening is the formation of a stable aromatic species after retro-DA reaction. The generation of aromatic furan may drive this reaction pathway over oxo-bridge opening. If the residual double bond from furan in cycloadduct **15e** is hydrogenated to **56** a retro-DA reaction is no longer possible because a cyclohexene is not present, and the desired transformation may be enabled (Scheme 4.11).



Scheme 4.11 - Proposed Oxo-Bridge Opening to Tertiary Alcohol 58

4.3 Future Plans for [2+2]

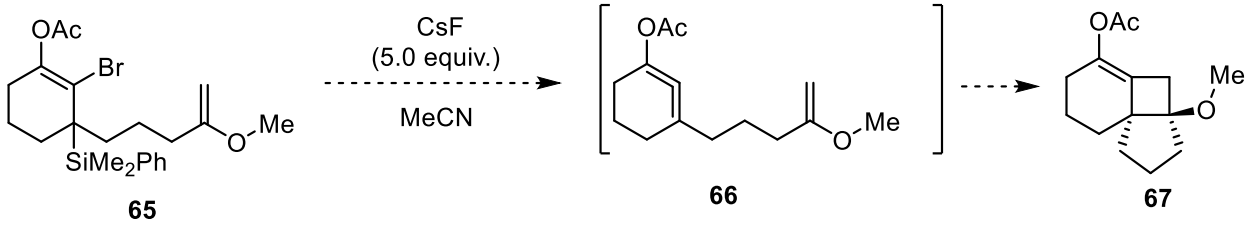
During the development of the [2+2] cycloaddition methodology presented in Chapter **3** β-styrene compounds such as **59** would not undergo the desired cycloaddition to **61** (Scheme 4.12). Only compounds presumably able to form a stable tertiary benzylic radical intermediate *en* route to the final cycloadduct underwent the cycloaddition. It should be noted that steric interactions due to substitution at the reactive end of the allene may also contribute to its failure to undergo the desired cycloaddition. This raises the interesting possibility of using a substituted β-styrene as in **62** that would also be able to generate a stable tertiary benzylic radical. This transformation, if successful, would further support the mechanistic hypothesis we have proposed to explain observed trends in these [2+2] cycloadditions. The proposed structure to be generated from this cycloaddition, **64**, is also a new core motif, allowing potential access to a new series of structures.



Scheme - 4.12 Proposed New Styrene [2+2]-Cycloaddition

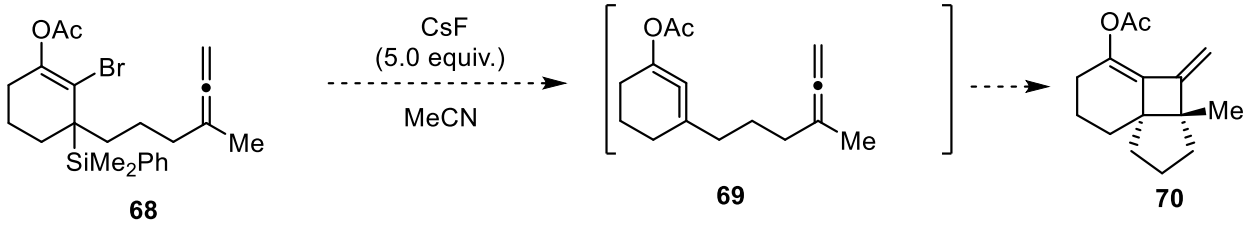
In addition to the substituted β-styrene previously mentioned there are a variety of other structural moieties would be interesting to examine. To enable a non-conjugated double bond to undergo the [2+2]-cycloaddition, a simple strategy based on our mechanistic understanding would be to increase the electron availability at the double bond. While a disubstituted terminal olefin

has been attempted as a substrate in this methodology we have not yet tested a species that has a strong electron donating group, such as enol ether **65** (Scheme 4.13).



Scheme 4.13 - Proposed Use of a Enol Ether in a [2+2]-Cycloaddition

In addition to the molecules already discussed it would be interesting to have cycloaddition examples with cumulated species. An obvious candidate for this would be to use allenes (Scheme 4.14).



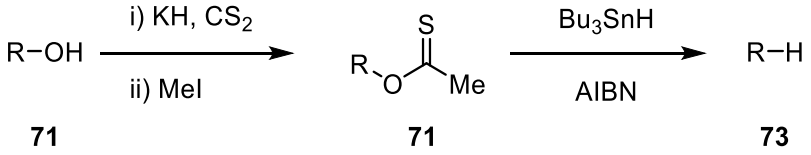
Scheme 4.14 - Proposed Use of Allenes in a [2+2]-Cycloaddition

4.4 Alternative Generation Modes of 1,2-Cyclohexadiene

So far, all the results and proposed reactions in this thesis have used a fluoride mediated elimination pathway to generate reactive 1,2-cyclohexadiene species. The reason for this method of generation, as discussed in Chapter **1**, is the relatively mild conditions employed and the operation simplicity. A natural extension of this work would therefore be to try to generate our 1,2-cylohexadiene species under different conditions.

4.4.1 Barton-McCombie Radical Deoxygenation

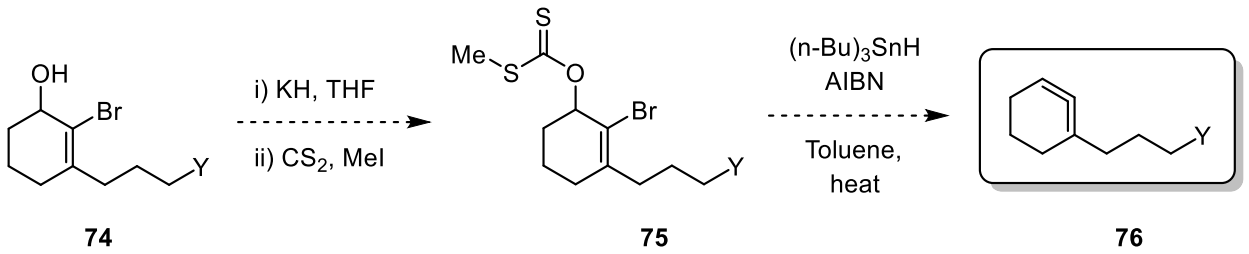
One reaction that interested us as a potential novel allene generation method is the Barton-McCombie radical deoxygenation.[19] This well-known named reaction has a variety of conditions that can be employed to replace an alcohol with hydrogen. In one of the most common sets of conditions alcohols such as **71** are initially converted into xanthates and upon subsequent addition of a radical initiator and tributyltin hydride the xanthate will undergo radical decomposition to give a carbon centered radical that can then gain a hydrogen to give **73** (Scheme 4.15).



Scheme 4.15 - Barton-McCombie Radical Deoxygenation

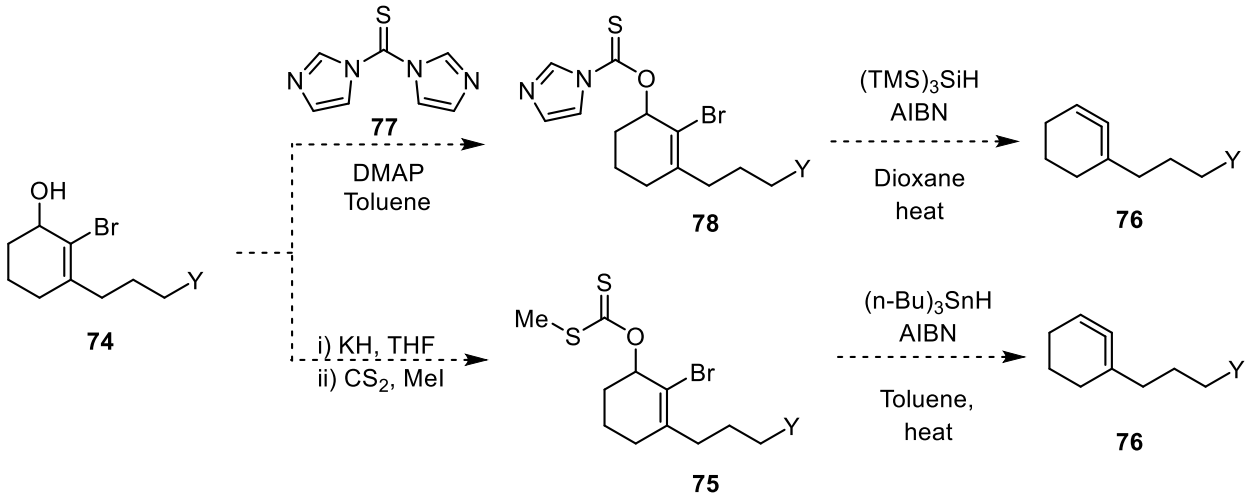
4.4.2 Proposed Allene Generation via Barton-McCombie Radical Deoxygenation

We wondered if we could utilize this pathway as an alternative means of generating a 1,2-cyclohexadiene intermediate. Using substrate **74**, with either a furan or styrene moiety for [4+2] or [2+2] cycloadditions respectively, we envisioned easy accesses to xanthate **75** as the alcohol starting material can be produced through a reduction of the corresponding ketone (Scheme 4.16). With tributyl tin hydride and AIBN we then hoped to follow a Barton-McCombie radical deoxygenation pathway to generate 1,2-cyclohexadiene **76**.



Scheme 4.16 - Proposed Allene Generation via Barton-McCombie Radical Deoxygenation

We envisioned two routes to generate the desired 1,2-cyclohexadiene intermediate **76** (Scheme 4.17). As shown in Scheme 4.16 and 4.17 generating xanthate **75** and then subsequent allene **76** should be possible using standard Barton-McCombie methodology. Alternatively, another pathway involves using thiocarbodimidazole **77** in place of CS_2 to produce xanthate **78**. Using $(TMS)_3SiH$ and AIBN it has been reported that these xanthates can undergo both elimination of the xanthate group and debromination. [20] If both processes were to happen allene **76** could be generated. If either of these generation methods can be successfully employed a series of [4+2] and [2+2] trapping reactions could be developed.



Scheme 4.17 - Two Proposed Pathways to Enable 1,2-Cyclohexadiene Synthesis via Barton-McCombie Radical Deoxygenation

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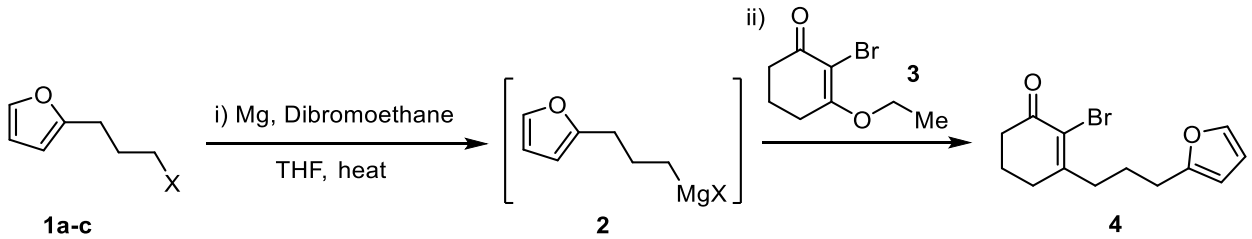
Appendix A.1 Supporting Information for Chapter 2

A.1.1 Stork-Danheiser Transposition Optimization

The Stork-Danheiser transposition was the key step to unite the enone and furan fragments en route to the desired starting materials. The initial synthesis by Lofstrand of tethered enone **4** relied upon formation of Grignard reagent **2** from alkyl chloride **1a**. Upon replication of this procedure no desired product was obtained; instead alkyl chloride **1a** was recovered (Table **A.1.1**, Entry 1). The recovery of the chloride indicated that formation of the Grignard reagent was not taking place; in an attempt to rectify this the amount of initiator was increased (Entry 2), the amount of halide **1** and temperature was increased (Entry 3), and the rate of addition and concentration was decreased (Entry 4). Unfortunately, these changes did not have the desired effect as only trace amounts of **4** were observed with the major isolated compounds being either starting halide **1** or the Wurtz coupling dimer. These results were surprising considering Lofstrand was able to perform this reaction and called into question the quality of reagents being used. To address this concern different magnesium turnings and shavings were used and they were always heated in an oven before use. In order to increase the reactivity of the system brominated starting material **1b** was also tested. With conditions previously used no amount of **4** was observed; instead again the halide was isolated (Entries 5-6). To ensure formation of the Grignard reagent, a full equivalent of dibromoethane as the activator was used in entries 7-12. Furthermore, the dibromoethane was added via syringe pump at the same rate as alkyl halide **1b** to ensure constant activation of the magnesium. It was only when the rate of addition and concentration of halide were decreased that small amounts of **4** were isolated form an otherwise complex reaction mixture (Entry 9-10). Crushing of the magnesium overnight in a flask to expose fresh surface had a small positive effect on the amount of product that could be isolated (Entry 11) and refluxing overnight after halide addition also helped (Entry 12). While small amounts of **4** were isolated in entries 9-12, the reactions themselves were complicated by a variety of uncharacterizable side products. Due to the low yields with the chloroalkyl and bromoalkyl substrates, iodide **1c** was then examined in place of the bromide (Entries 13-16). In conditions with a relatively high concentration of iodide **1c** the Wurtz coupling product was the only product isolated from the reaction mixture (Entries 13-14). With a lower addition rate and concentration, a complex mixture was again obtained where no

products could be deduced from the reaction mixture (Entry 16). From this data it can be gathered that Grignard reagent formation was in many cases not proceeding and when it did form, the desired nucleophilic attack on the carbonyl of **3** was being outcompeted by Wurtz coupling or unknown side reactions leading to complex mixtures. In any case a new approach described in Chapter **2** would enable access to the desired products.

Table A.1.1 - Some of the Attempted Optimization of the Stork-Danheiser Alkylation via a Grignard Reagent



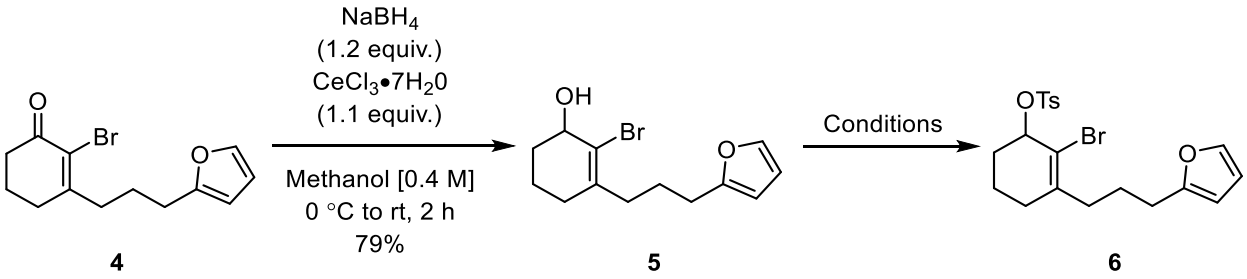
Entry	Halide (X)	Mg (equiv.)	Dibromoethane (equiv.)	Halide (equiv.)	Enone (equiv.)	Grignard Formation (°C)	Rate of Addition (mL/h)	Concentration Alkyl Halide (M)	Yield **4** (%)	Notes
1	Cl-**1a**	4	0.10	1	1	45-50	1	0.60	0	S.M. Recovered
2	Cl-**1a**	4	0.25	1	1	45-50	1	0.60	0	S.M. Recovered
3	Cl-**1a**	6	0.25	1.5	1	reflux	1	0.60	trace	Wurtz Product
4	Cl-**1a**	6	0.25	1.5	1	reflux	0.5	0.15	trace	Wurtz Product
5	Br-**1b**	4	0.25	1.5	1	45-50	1	0.60	0	S.M. Recovered
6	Br-**1b**	4	0.25	1.5	1	reflux	1	0.60	0	S.M. Recovered
7	Br-**1b**	6	1	1.5	1	45-50	1	0.60	Trace	DBE added at same rate as alkyl halide. Complex Mixture.
8	Br-**1b**	6	1	1.5	1	reflux	1	0.60	Trace	DBE added at same rate as alkyl halide. Complex Mixture.
9	Br-**1b**	6	1	1.5	1	45-50	0.5	0.15	5	DBE added at same rate as alkyl halide. Complex Mixture.
10	Br-**1b**	6	1	1.5	1	reflux	0.5	0.15	5	DBE added at same rate as alkyl halide. Complex Mixture.

11	Br-**1b**	6	1	1.5	1	45-50	0.5	0.15	10	DBE added at same rate as alkyl halide. Mg crushed overnight. Complex Mixture.
12	Br-**1b**	6	1	1.5	1	reflux	0.5	0.15	20	DBE added at same rate as alkyl halide. Mg crushed overnight. Reflux overnight.
13	I-**1c**	4	0.10	1	1	reflux	1	0.60	0	Wurtz Product
14	I-**1c**	4	0.25	1	1	reflux	1	0.60	0	Wurtz Product
15	I-**1c**	6	0.25	1.5	1	reflux	1	0.60	0	Wurtz Product
16	I-**1c**	6	0.25	1.5	1	reflux	0.5	0.15	trace	Complex Mixture

A.1.2 Attempted Tosylation of Allylic Alcohol Intermediate

Adapting the route of Lofstrand, Stork-Danheiser product **4** was reduced under Luche reduction conditions to accesses allylic alcohol **5** in 79% yield. The first set of conditions to transform alcohol **5** to tosylate **6** were those reported by Lofstrand (Table **A.1.2**, Entry 1). No reaction of the starting material was observed. Accordingly amounts of base and temperature were increased (Entries 2/3) and trace amounts of product were observed. A switch to pyridine as solvent (Entries 4/5) and the addition of a catalytic amount of DMAP (Entries 6/7) did not result in an increase in observable yield. In most reaction conditions the starting alcohol **5** was re-isolated, indicating a failure of the nucleophilic attack of the alcohol on the tosyl chloride. As described in Chapter **2** a different procedure to synthesize a non-oxygenated 1,2-cyclohexadiene from **5** was eventually discovered and utilized.

Table A.1.2 - Attempted Tosylation of Allylic Alcohol 5



4 **5** **6**

Entry	TsCl (equiv.)	NEt_3 (equiv.)	DMAP	NMe_3·HCl (equiv.)	Solvent	Temp (° C)	Yield of **6** (%)
1	1.5	3	N.A.	1.0	Toluene	0	0
2	1.5	6	N.A.	2.0	Toluene	rt	0
3	1.5	6	N.A	2.0	Toluene	0	trace
4	1.5	N.A.	N.A.	N.A.	Pyridine	0	0
5	1.5	N.A.	N.A.	N.A	Pyridine	rt	trace
6	1.5	N.A.	~10mg	N.A	Pyridine	0	trace
7	1.5	N.A.	~10mg	N.A	Pyridine	rt	trace

A.1.3 X-Ray Crystallography of Compound 48f

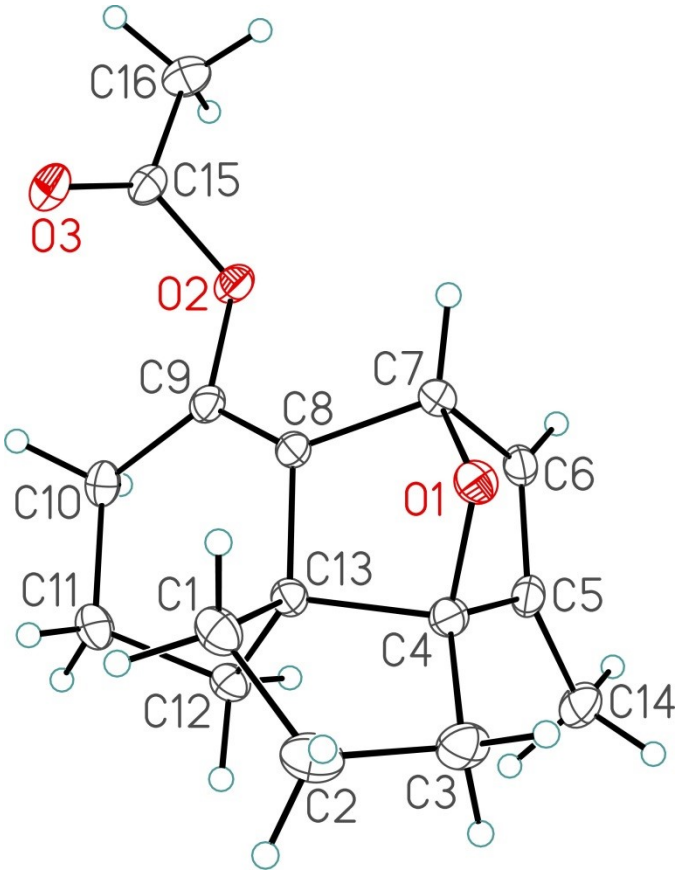
STRUCTURE REPORT

XCL Code: FGW1705 **Date:** 18 May 2017

Compound: 4-Methyl-2,3,6,8,9,10-hexahydro-1*H*-3a,6-epoxycyclopenta[*d*]naphthalen-7-yl acetate

Formula: $C_{16}H_{20}O_3$

Supervisor: F. G. West **Crystallographer:** R. McDonald



Crystallographic Experimental Details

A. Crystal Data

formula	$C_{16}H_{20}O_3$
formula weight	260.32
crystal dimensions (mm)	0.39 × 0.21 × 0.14
crystal system	monoclinic
space group	$P2_1/c$ (No. 14)
unit cell parameters[a]	
a (Å)	14.5618 (4)
b (Å)	14.2703 (4)
c (Å)	13.6887 (4)
β (deg)	107.2198 (12)
V (Å^3)	2717.03 (13)
Z	8
ρ_{calcd} (g cm^{-3})	1.273
μ (mm^{-1})	0.696

B. Data Collection and Refinement Conditions

diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	Cu Kα (1.54178) (microfocus source)
temperature (°C)	–100
scan type	ω and ϕ scans (1.0°) (5 s exposures)
data collection 2θ limit (deg)	147.88
total data collected	19145 (-18 ≤ h ≤ 18, -17 ≤ k ≤ 17, -16<=l<=14)
independent reflections	5304 (R_{int} = 0.0243)
number of observed reflections (*NO*)	4887 [$F_o^2 \geq 2\sigma(F_o^2)$]

structure solution method	direct methods/dual space (*SHELXD*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–2014*[d])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9763–0.7575
data/restraints/parameters	5304 / 0 / 347
goodness-of-fit (*S*)[e] [all data]	1.036
final *R* indices[f]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0385
wR_2 [all data]	0.1044
largest difference peak and hole	0.235 and –0.245 e Å^{-3}

[a]Obtained from least-squares refinement of 9912 reflections with $6.36° < 2\theta < 146.76°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Schneider, T. R.; Sheldrick, G. M. *Acta Crystallogr.* **2002**, *D58*, 1772-1779.

[d]Sheldrick, G. M. *Acta Crystallogr.* **2015**, *C71*, 3–8.

[e]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0540P)^2 + 0.8471P]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$).

[f]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Appendix A.2 Supporting Information for Chapter 3

A.2.1 X-Ray Crystallography of Compound 55d

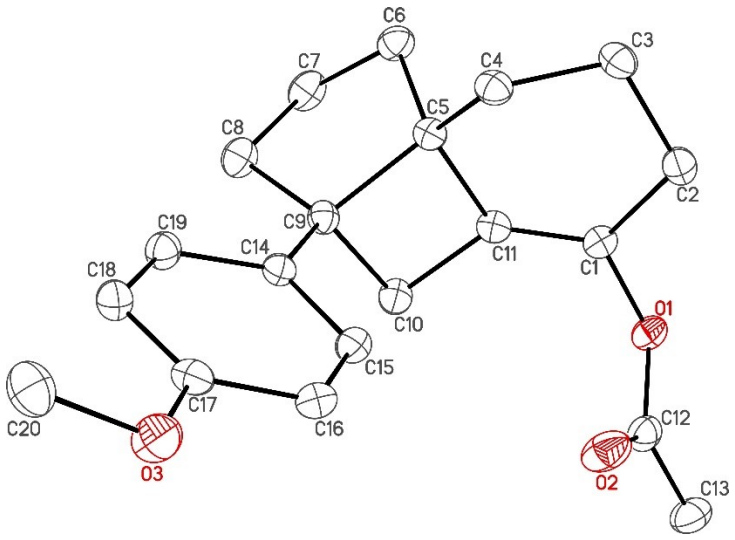
STRUCTURE REPORT

XCL Code: FGW1810 **Date:** 27 September 2018

Compound: 3a-(4-methoxyphenyl)-1,2,3,3a,4,5,6,7,8-octahydrocyclopenta[1,4]cyclobuta[1,2]benzen-5-yl acetate

Formula: $C_{20}H_{24}O_3$

Supervisor: F. G. West **Crystallographer:** Y. Q. Zhou



Crystallographic Experimental Details

A. Crystal Data

formula	$C_{20}H_{24}O_3$
formula weight	312.39
crystal dimensions (mm)	1.33 × 0.08 × 0.03
crystal system	orthorhombic
space group	$P2_12_12_1$ (No. 19)
unit cell parameters[a]	
a (Å)	5.906(4)
b (Å)	9.319(6)
c (Å)	29.596(18)
V (Å^3)	1628.8(17)
Z	4
ρ_{calcd} (g cm^{-3})	1.274
μ (mm^{-1})	0.084

B. Data Collection and Refinement Conditions

diffractometer	PLATFORM/APEX II CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ω scans (0.3°) (30 s exposures)
data collection 2θ limit (deg)	52.84
total data collected	12628 ($-7 \le h \le 7$, $-11 \le k \le 11$, $-37 \le l \le 37$)
independent reflections	3359 (R_{int} = 0.0501)
number of observed reflections (*NO*)	2848 [$F_o^2 \ge 2\sigma(F_o^2)$]

structure solution method	intrinsic phasing (*SHELXT-2014*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–2016*[d])
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.8620–0.8045
data/restraints/parameters	3359 / 0 / 210
Flack absolute structure parameter[e]	1.0(8)
goodness-of-fit (S)[f] [all data]	1.060
final R indices[g]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0420
wR_2 [all data]	0.1047
largest difference peak and hole	0.143 and –0.182 e Å^{-3}

[a]Obtained from least-squares refinement of 3561 reflections with $4.58° < 2\theta < 44.72°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Sheldrick, G. M. *Acta Crystallogr.* **2015**, *A71*, 3–8. (*SHELXT-2014*)

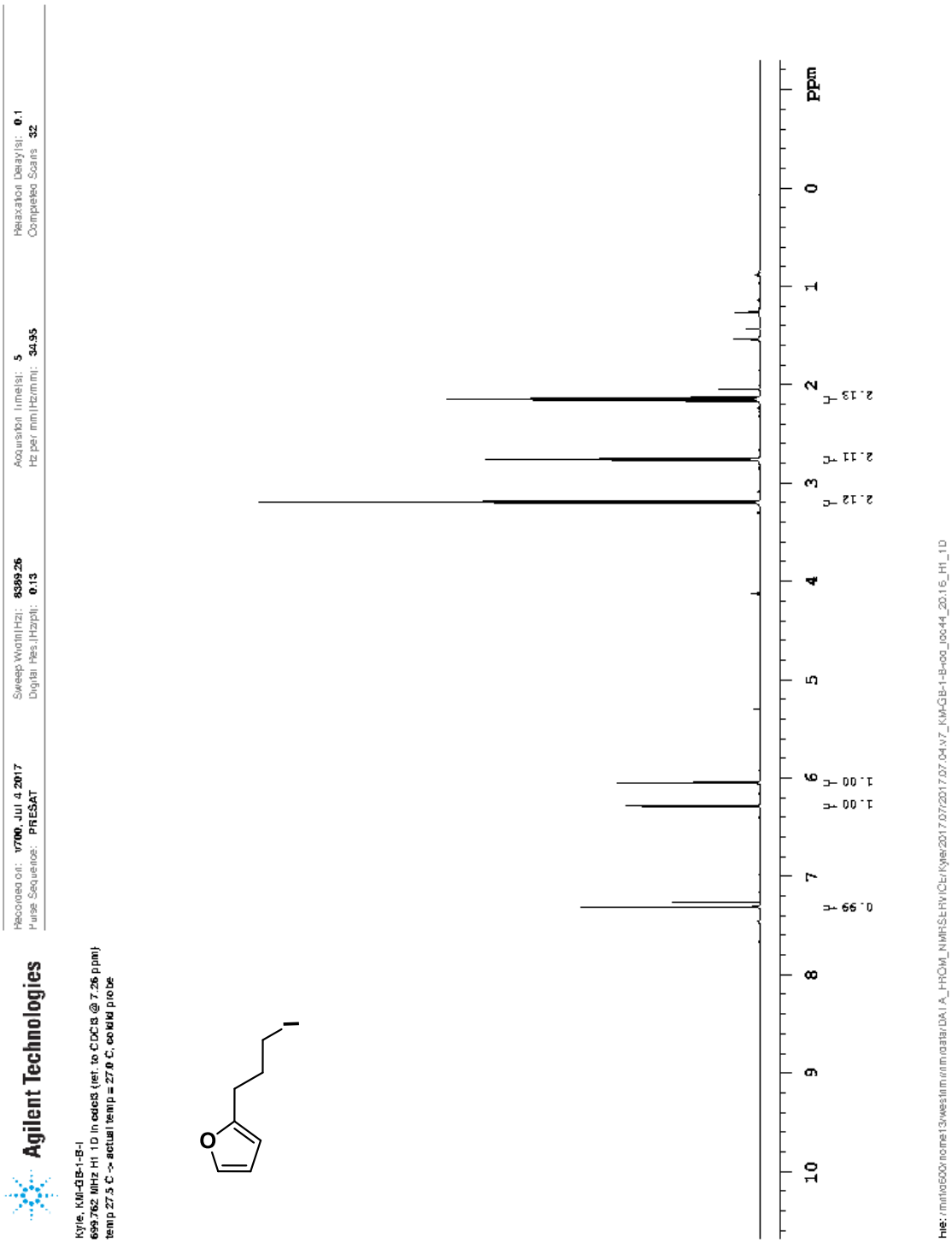
[d]Sheldrick, G. M. *Acta Crystallogr.* **2015**, *C71*, 3–8. (*SHELXL-2016*)

[e]Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr.* **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst.* **2000**, *33*, 1143–1148. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration. The low anomalous scattering power of the atoms in this structure (none heavier than oxygen) implies that the data cannot be used for absolute structure assignment, thus the Flack parameter is provided for informational purposes only.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0485P)^2 + 0.1940P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Appendix A.3 Selected ^{1}H and ^{13}C NMR Spectra.



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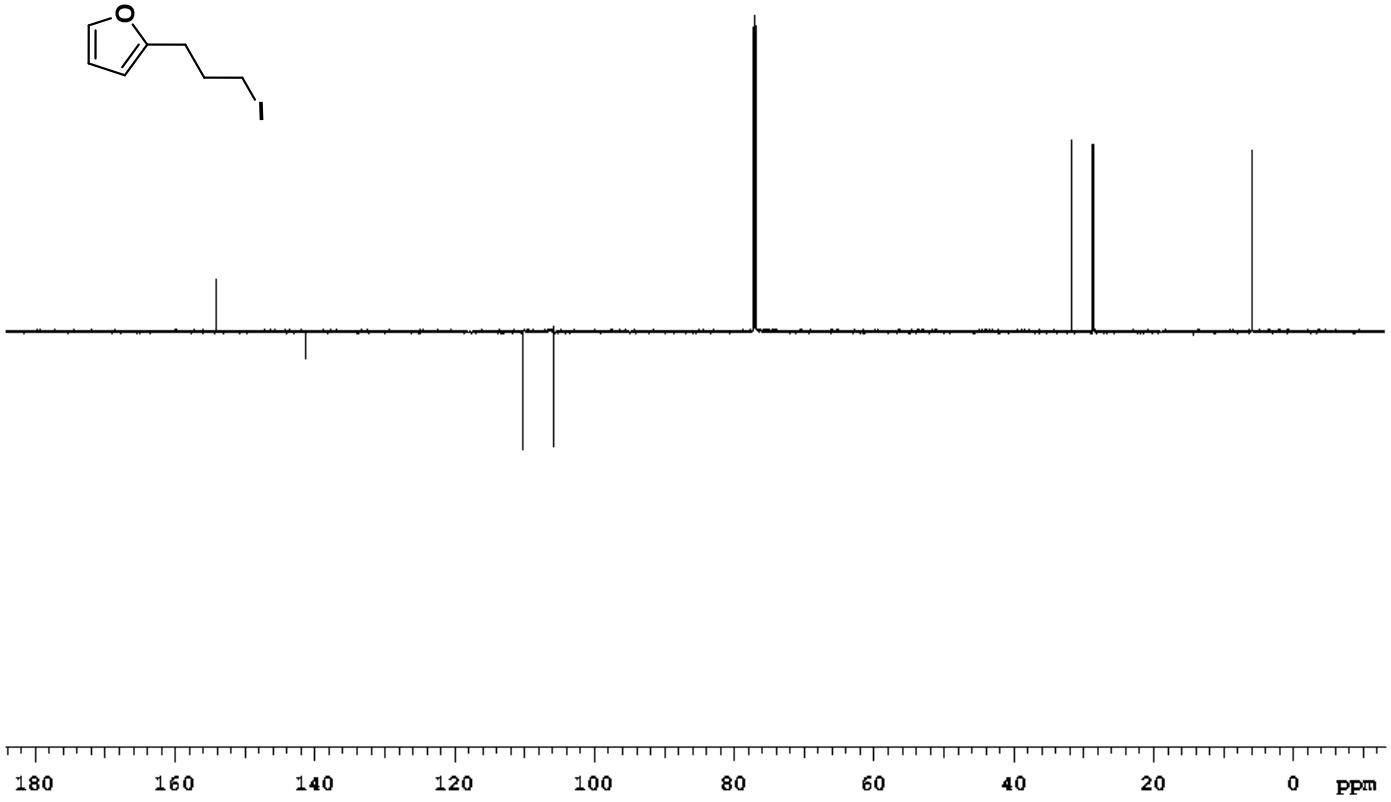
Recorded on:	v700, Jul 4 2017	Sweep Width[Hz]:	34722.2	Acquisition Time[s]:	1	Relaxation Delay[s]:	1
Pulse Sequence:	APT_ad	Digital Res.[Hz/pt]:	0.26	Hz per mm[Hz/mm]:	144.67	Completed Scans	244

Kyle, KM-GB-1-B-iod
175.970 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.5 C -> actual temp = 27.0 C, cold id probe
C & CH2 same, CH & CH3 opposite side of solvent signal



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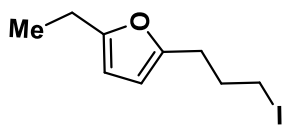
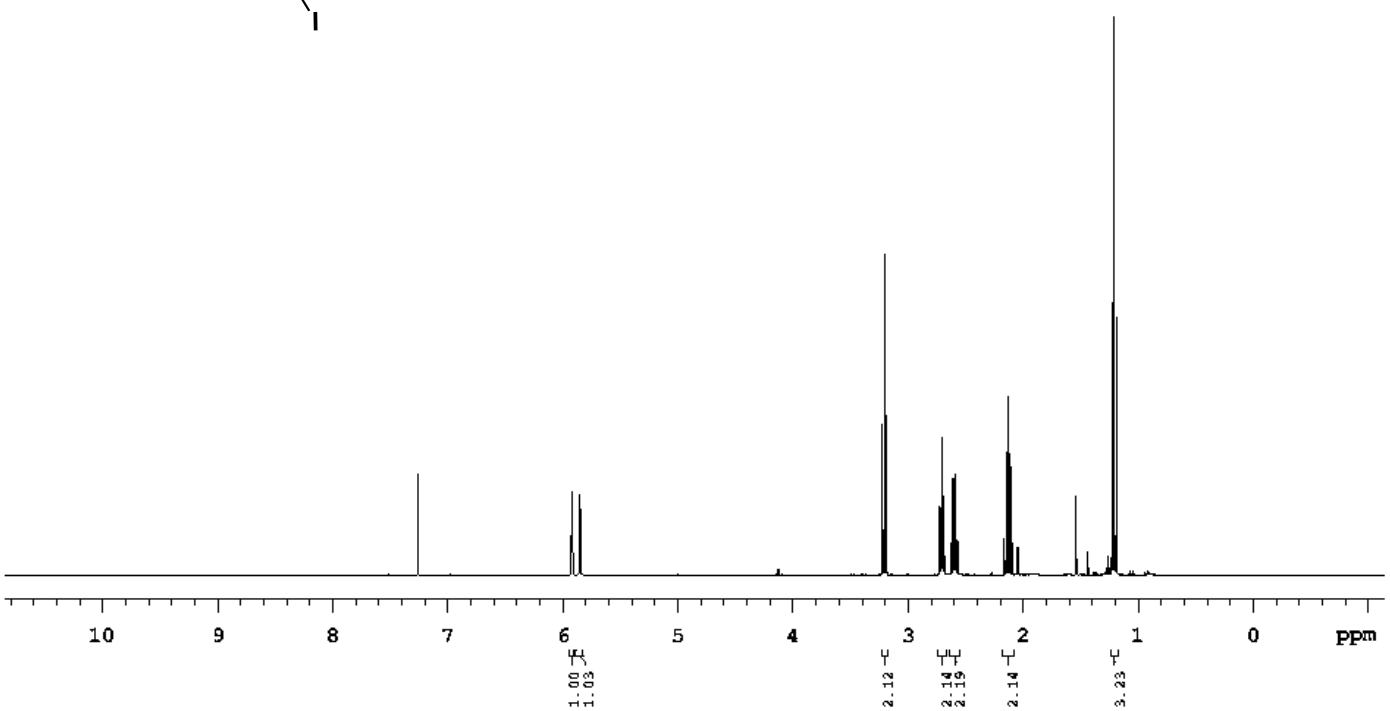
Recorded on:	m400, Feb 6 2017	Sweep Width[Hz]:	4803.07	Acquisition time[s]:	4.997	Relaxation Delay[s]:	0.1
Pulse Sequence:	PRESAT	Digital Res.[Hz/pt]:	0.07	Hz per mm[Hz/mm]:	20.01	Completed Scans	32

Kyle, KM-GB-1-Et-Iod-p
400.389 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.0 C -> actual temp = 27.0 C, m400gz probe





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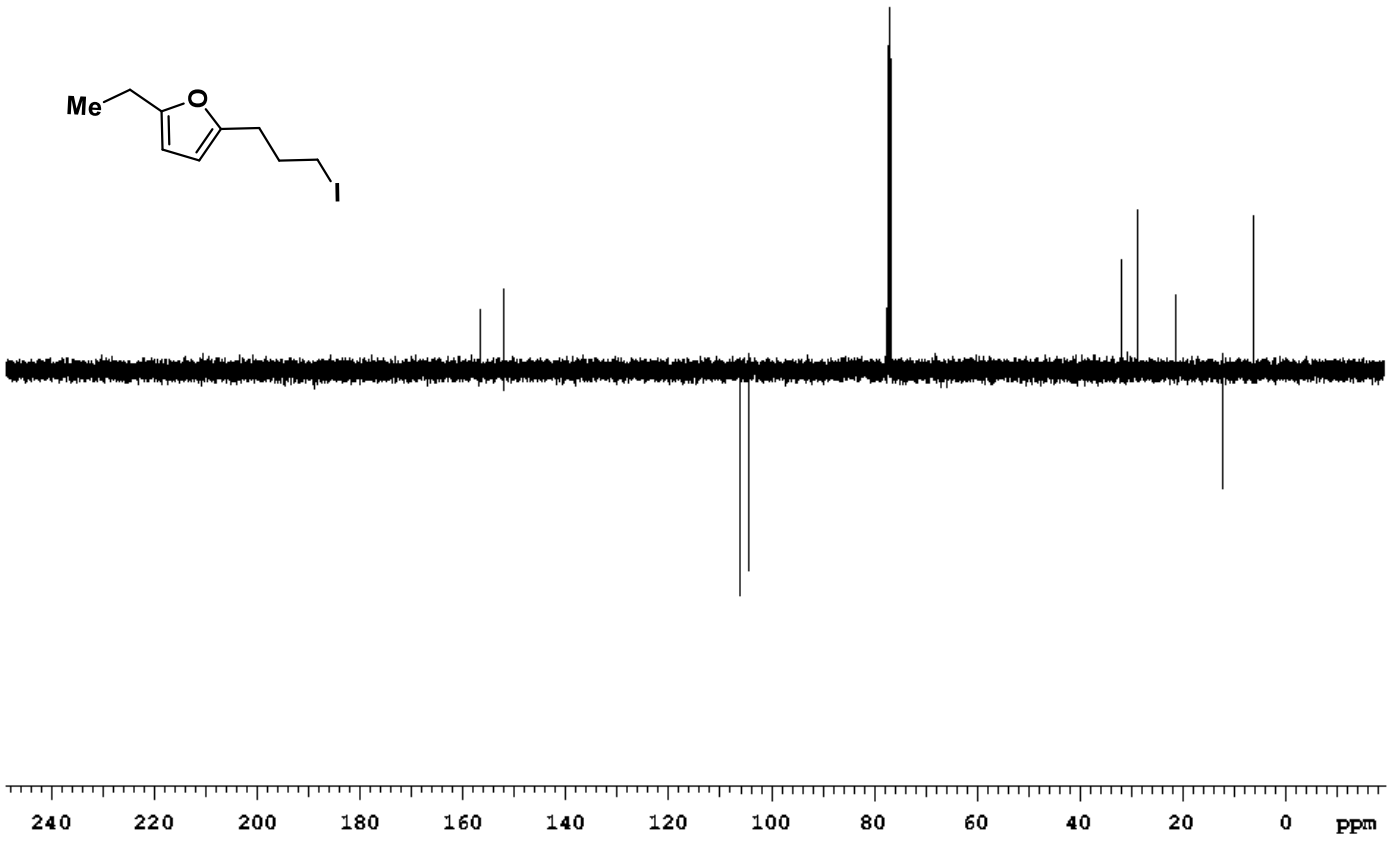
Recorded on: m400, Feb 6 2017	Sweep Width[Hz]: 27027	Acquisition Time[s]: 1	Relaxation Delay[s]: 1
Pulse Sequence: APT_sd	Digital Res.[Hz/pt]: 0.21	Hz per mm[Hz/mm]: 112.61	Completed Scans 844

Kyle, KM-GB-1-Et-Iod-p
100.689 MHz C13 APT_sd in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.0 C -> actual temp = 27.0 C, m400gz probe
C & CH2 same, CH & CH3 opposite side of solvent signal



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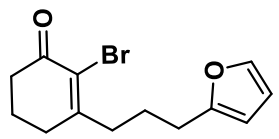
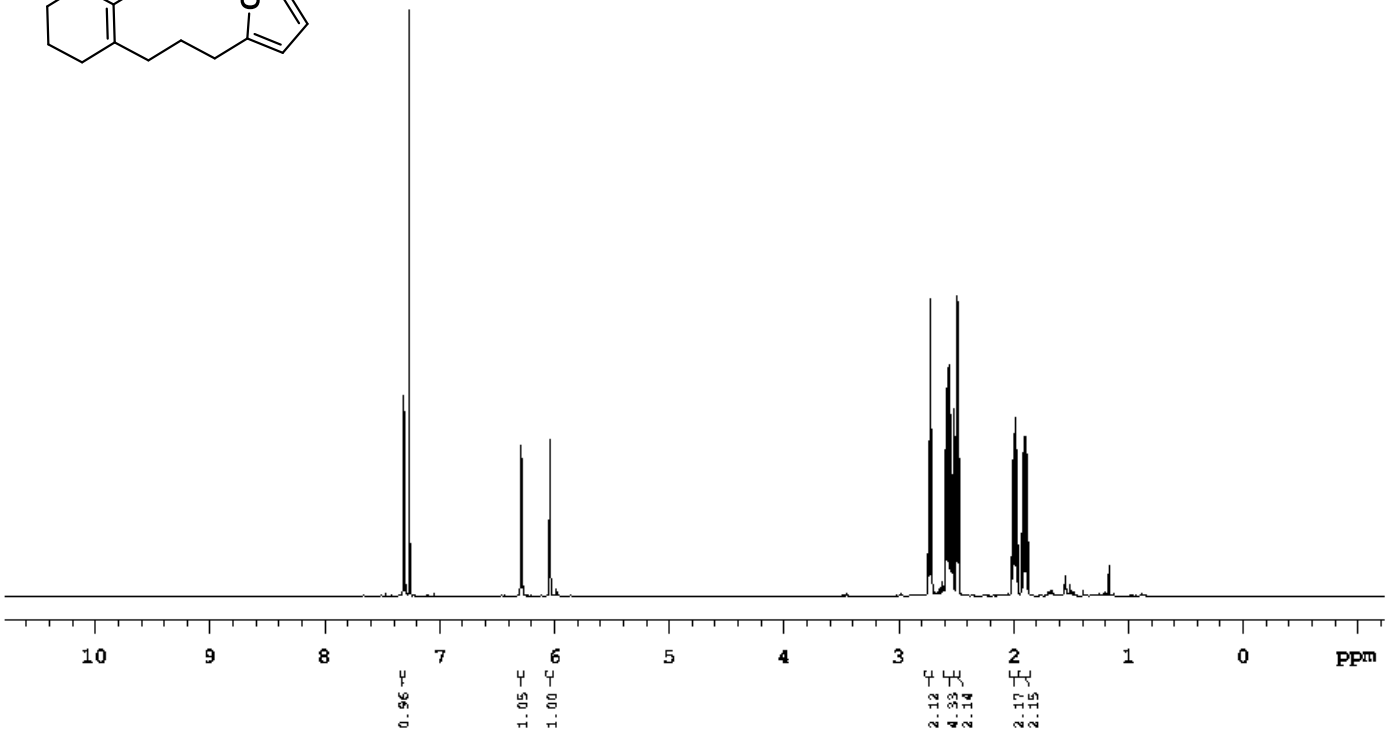
Recorded on:	u500, Oct 25 2018	Sweep Width[Hz]:	6009.62	Acquisition Time[s]:	5	Relaxation Delay[s]:	0.1
Pulse Sequence:	PRESAT	Digital Res.[Hz/pt]:	0.09	Hz per mm[Hz/mm]:	25.04	Completed Scans:	8

Kyle, KM-GB-2-SD-furan-basic
499.797 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.7 C -> actual temp = 27.0 C, cold dual probe





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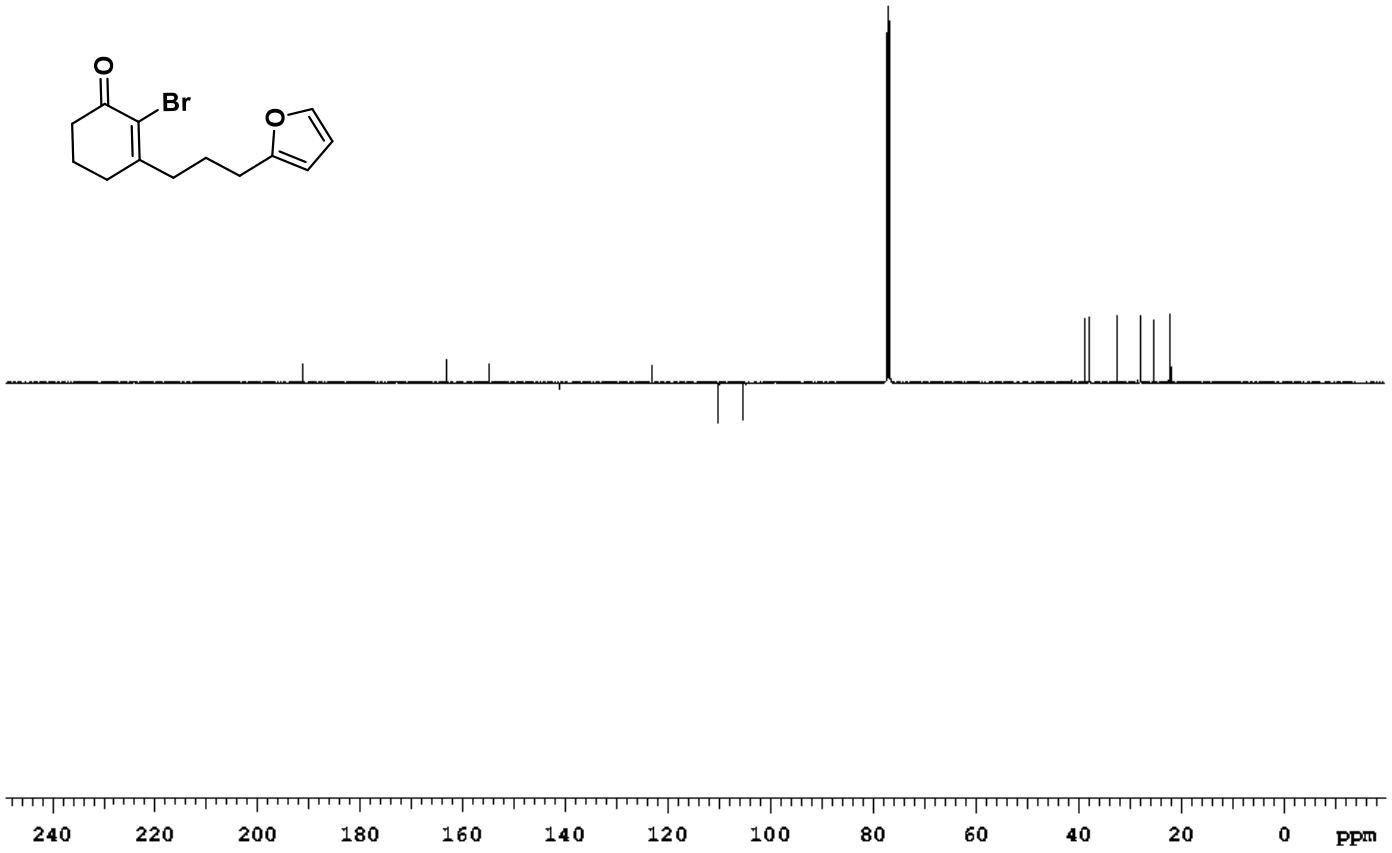
Recorded on: u500, Oct 25 2018	Sweep Width [Hz]: 33783.8	Acquisition Time [s]: 1	Relaxation Delay [s]: 1
Pulse Sequence: APT_sd	Digital Res. [Hz/pt]: 0.26	Hz per mm [Hz/mm]: 140.76	Completed Scans 696

Kyle, KM-GB-2-SD-furan-basic
125.688 MHz C13 APT_sd in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, cerididual probe
C & CH2 same, CH & CH3 opposite side of solvent signal



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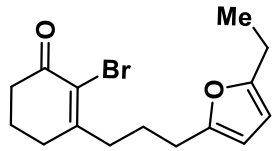
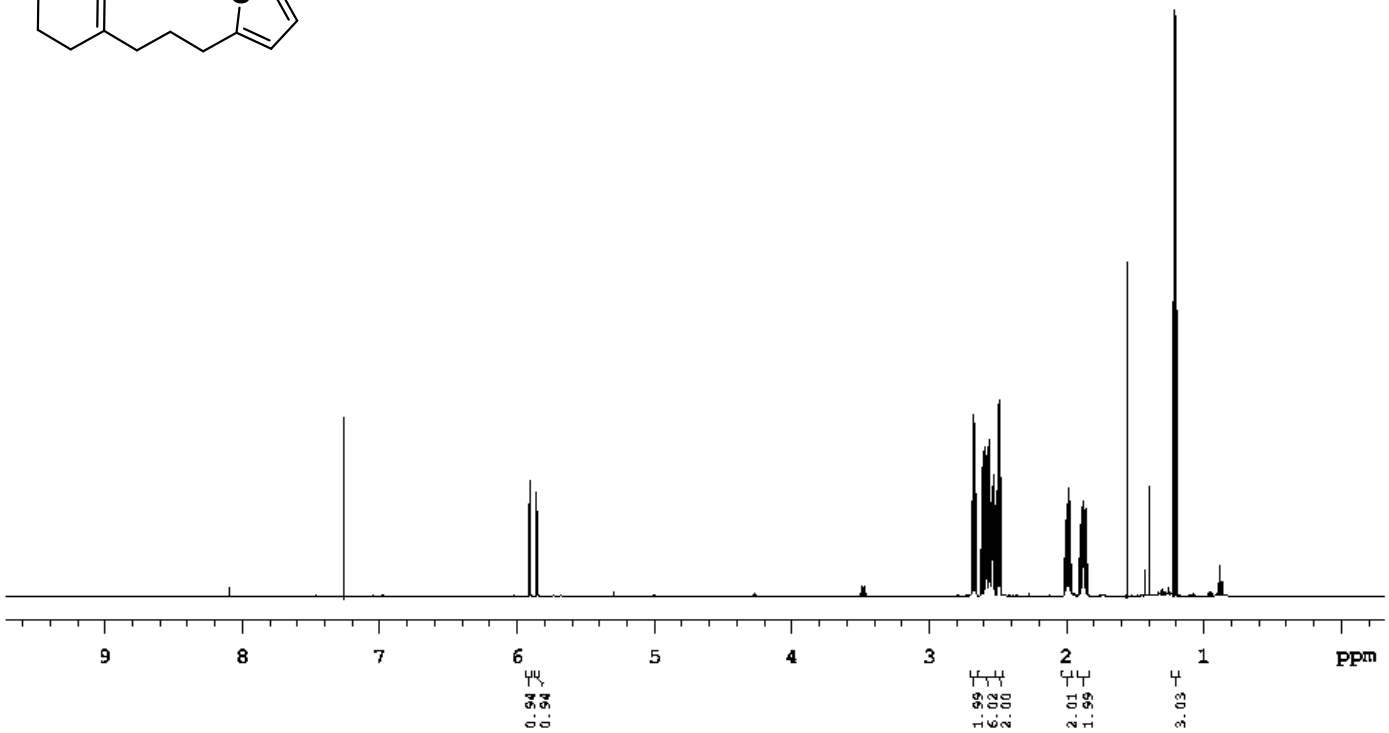
Recorded on:	u500, Feb 9 2017	Sweep Width[Hz]:	6009.62	Acquisition Time[s]:	5	Relaxation Delay[s]:	0.1
Pulse Sequence:	PRESAT	Digital Res.[Hz/pt]:	0.09	Hz per mm[Hz/mm]:	20.91	Completed Scans	32

Kyle, KM-GB-1-Et-SD-Clm
499.797 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.7 C -> actual temp = 27.0 C, cellddual probe





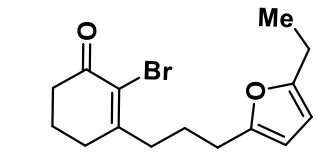
file: /mnt/u500/nmr13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyler/2017/02/2017.02.9.u5_KM-GB-1-Et-SD-Clm-2-p_jcc10_12.36_H1_1D

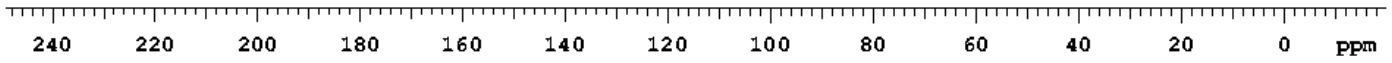
Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on:	u500, Feb 9 2017	Sweep Width [Hz]:	33783.8	Acquisition Time [s]:	1	Relaxation Delay [s]:	1
Pulse Sequence:	APT_sd	Digital Res. [Hz/pt]:	0.26	Hz per mm [Hz/mm]:	140.76	Completed Scans	128

Kyle, KM-GB-1-Et-SD-Clm-2-p
125.688 MHz C13 APT_sd in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, celdidual probe
C & CH2 same, CH & CH3 opposite side of solvent signal





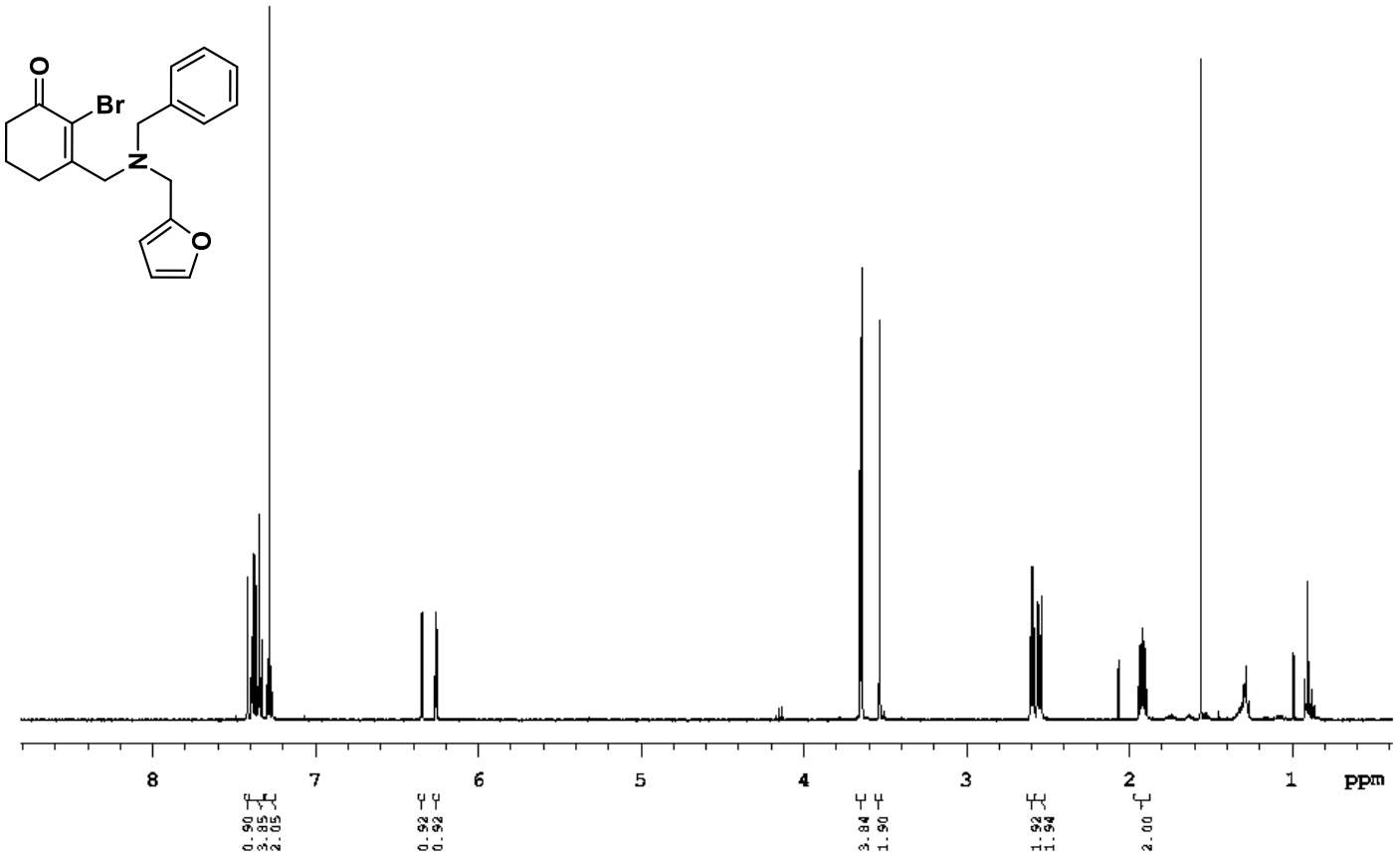
file: /mnt/a500/nmr13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyler/2017/02/2017.02.9.u5_KM-GB-1-Et-SD-Clm-2-p_ccc10_12.39_C13_APT_sd

Agilent Technologies

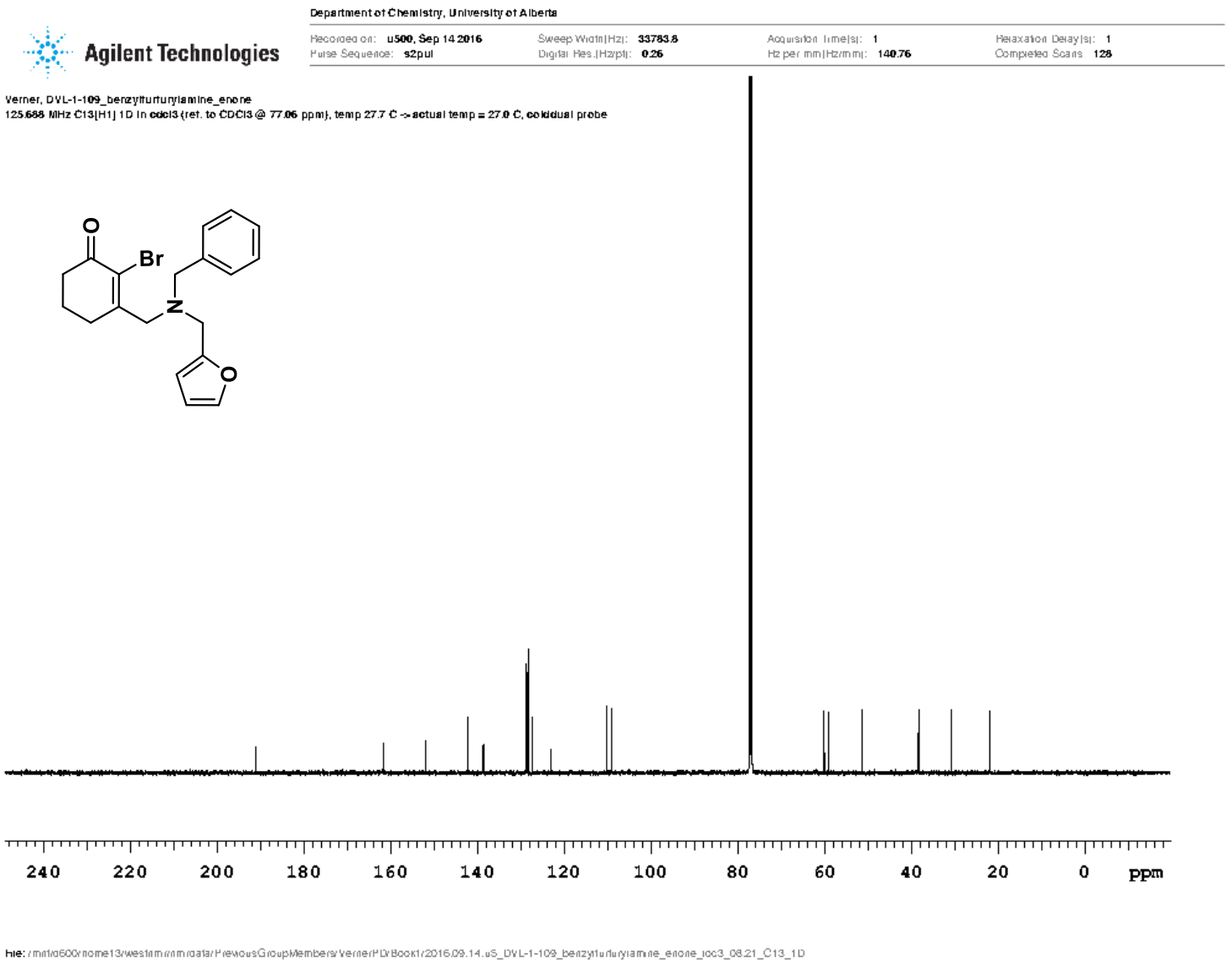
Department of Chemistry, University of Alberta

Recorded on:	lbd5, Oct 17 2016	Sweep Width [Hz]:	6000.6	Acquisition Time [s]:	5	Relaxation Delay [s]:	0.1
Pulse Sequence:	s2pul	Digital Res. [Hz/pt]:	0.09	Hz per mm [Hz/mm]:	17.5	Completed Scans	16

DVL-1-145 benzylfurfurylamine with chloroenone
499.118 MHz H1 1D in cdcl3 {ref. to CDCl3 @ 7.26 ppm}, temp 26.4 C -> actual temp = 27.0 C, autoxdb probe



file: /mnt/d600/nmr13/westfm/nmrdata/PreviousGroupMembers/VernerPDFBook1/2016.10.17.lS_DVL-1-145_benzylfurfurylamine_with_chloroenone_H1_1D

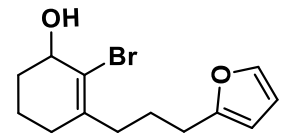

Department of Chemistry, University of Alberta
Agilent Technologies
Recorded on: u500, Sep 14 2016
Sweep Width [Hz]: 33783.8
Acquisition Time [s]: 1
Relaxation Delay [s]: 1
Pulse Sequence: s2pul
Digital Res. [Hz/pt]: 0.26
Hz per mm [Hz/mm]: 140.76
Completed Scans 128
Verner, DVL-1-109_benzylfurfurylamine_enone
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
O
Br
N
O
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm
file: /mnt/u500/nmr13/westfm/nmrdata/PreviousGroupMembers/VernerPDFBook1/2016.09.14.u5_DVL-1-109_benzylfurfurylamine_enone_ioc3_08.21_C13_1D

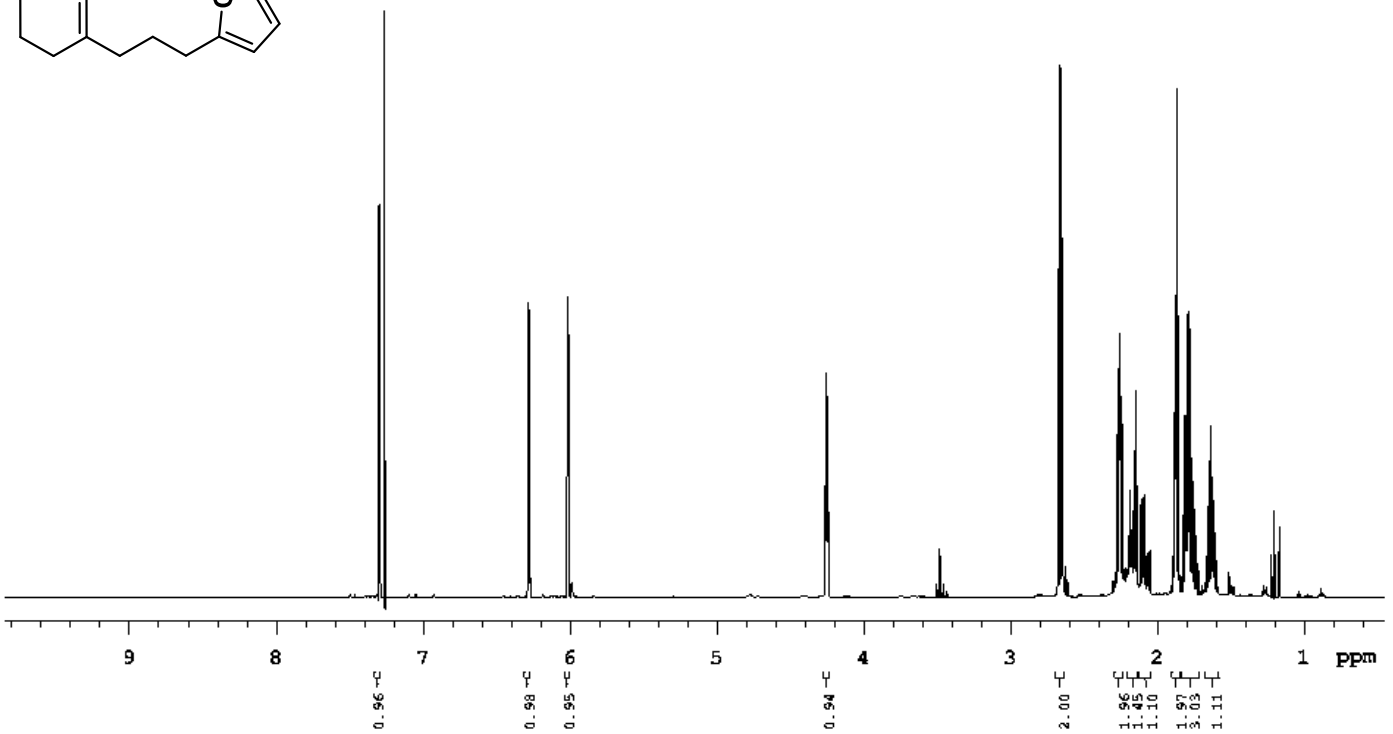
Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: u500, Nov 1 2018	Sweep Width[Hz]: 6009.62	Acquisition time[s]: 5	Relaxation Delay[s]: 0.1
Pulse Sequence: PRESAT	Digital Res.[Hz/pt]: 0.09	Hz per mm[Hz/mm]: 19.57	Completed Scans: 8

Kyle, KM-GB-2-fur-b-LR-prod
499.797 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.7 C -> actual temp = 27.0 C, cold dual probe





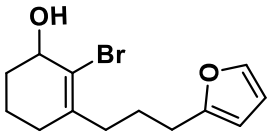
file: /mnt/u500/nmr13/westmr/mnr/data/DATA_FROM_NMRSERVICE/Kyler/2018.11/2018.11.01.u5_KM-GB-2-fur-b-LR-prod_jcc7_16.37_H1_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on:	u500, Nov 1 2018	Sweep Width [Hz]:	33783.8	Acquisition Time [s]:	1	Relaxation Delay [s]:	1
Pulse Sequence:	APT_ad	Digital Res. [Hz/pt]:	0.26	Hz per mm [Hz/mm]:	140.76	Completed Scans	544

Kyle, KM-GB-2-fur-b-LR-prod
125.688 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, celdidual probe
C & CH2 same, CH & CH3 opposite side of solvent signal



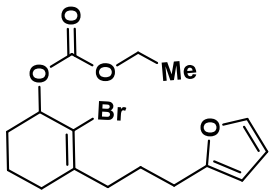
file: /mnt/u500/nmr13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyler2018.11/2018.11.01.uS_KM-GB-2-fur-b-LR-prod_ccc7_16.38_C13_APT_ad

Agilent Technologies

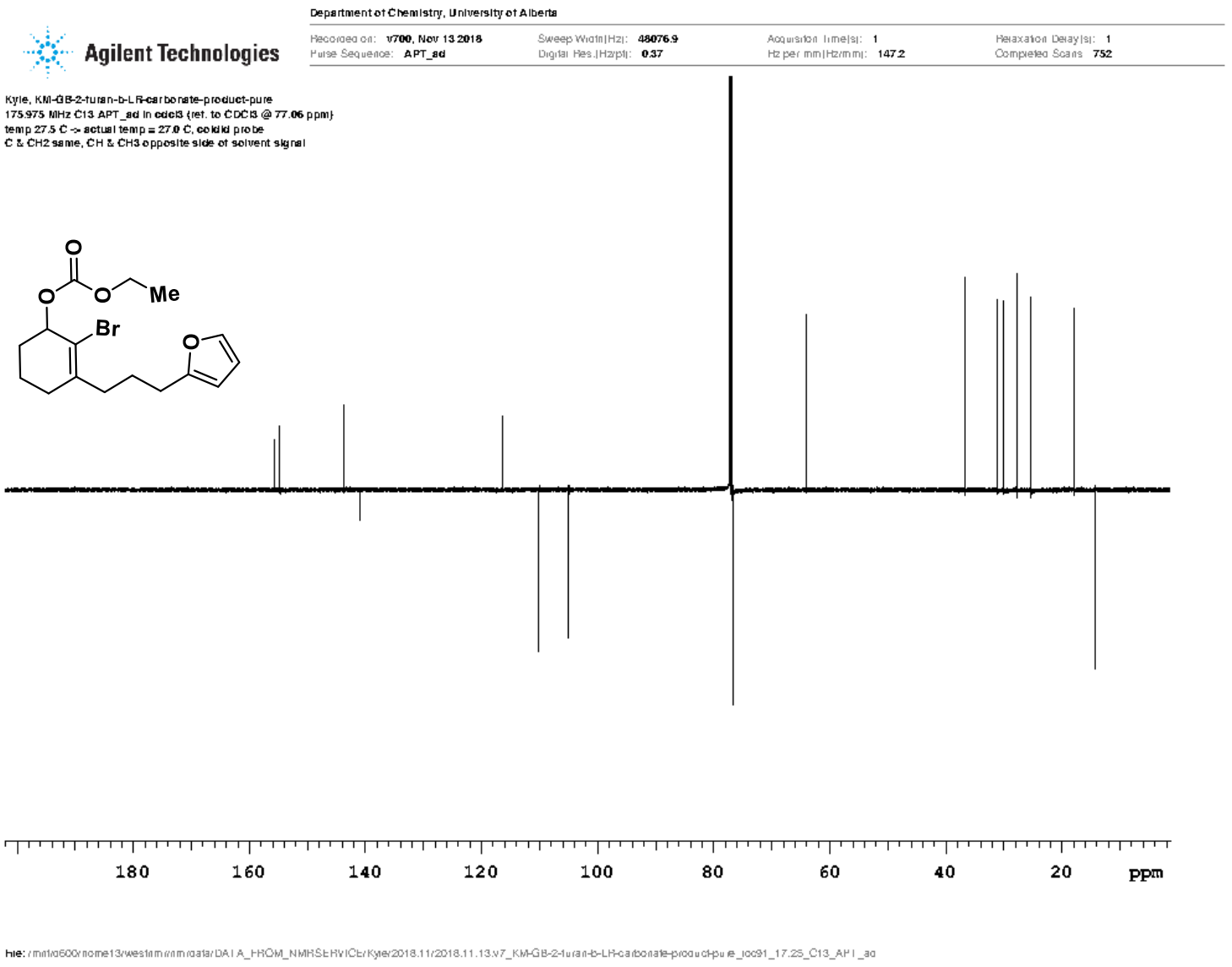
Department of Chemistry, University of Alberta

Recorded on:	lbd5, Nov 13 2018	Sweep Width [Hz]:	6000.6	Acquisition Time [s]:	5	Relaxation Delay [s]:	0.1
Pulse Sequence:	s2pul	Digital Res. [Hz/pt]:	0.09	Hz per mm [Hz/mm]:	25	Completed Scans	16

498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe



file: /mnt/ds500/nmr13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyler/2018.11/2018.11.13/S_KM-GB-2-furan-b-LH-carbonate-product-pure_H1_1D

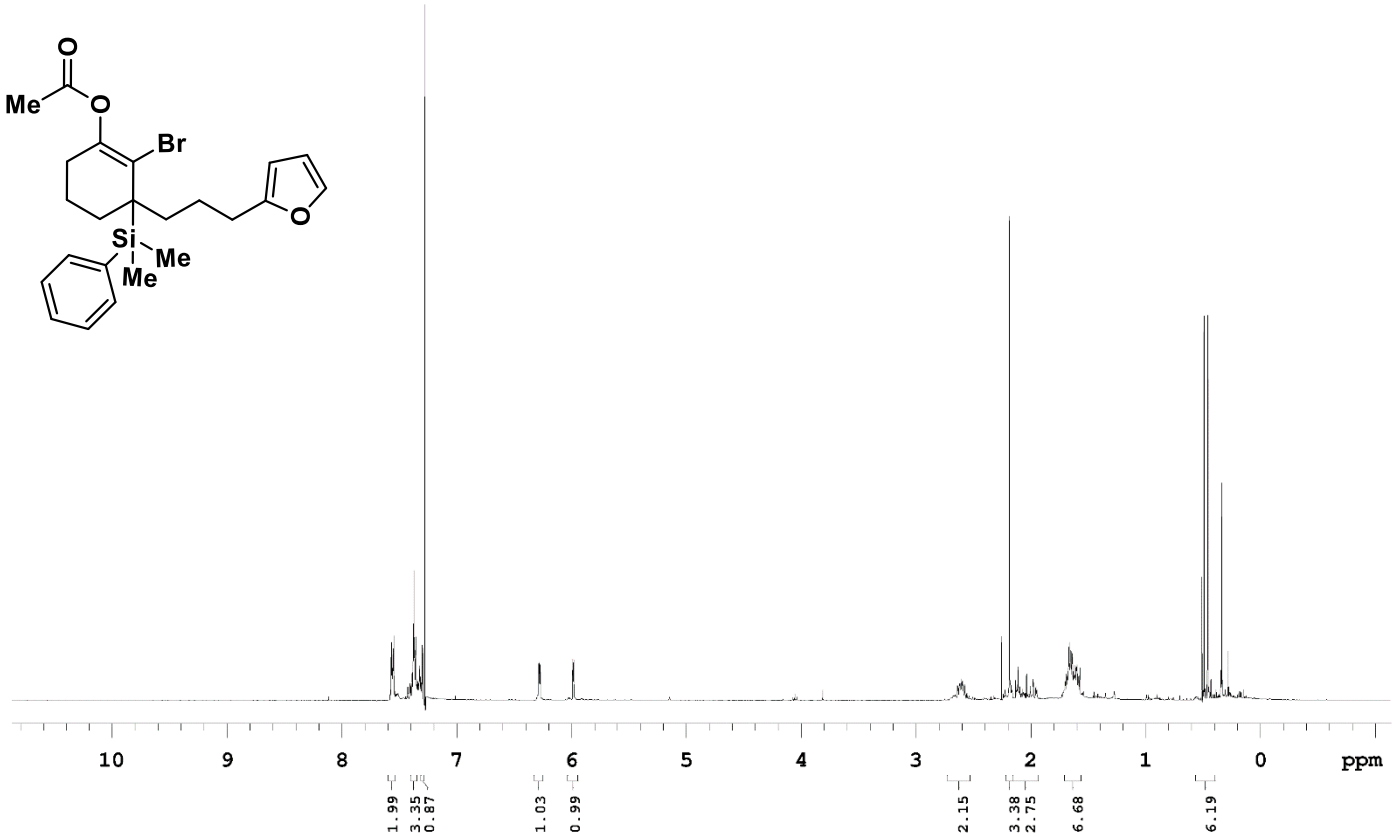

Department of Chemistry, University of Alberta
Agilent Technologies
Recorded on: v700, Nov 13 2018
Sweep Width [Hz]: 48076.9
Acquisition Time [s]: 1
Relaxation Delay [s]: 1
Pulse Sequence: APT_sd
Digital Res. [Hz/pt]: 0.37
Hz per mm [Hz/mm]: 147.2
Completed Scans 752
Kyle, KM-GB-2-furan-b-LR-carbonate-product-pure
175.975 MHz C13 APT_sd in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.5 C -> actual temp = 27.0 C, cold id probe
C & CH2 same, CH & CH3 opposite side of solvent signal
O
O
O
Me
Br
O
180
160
140
120
100
80
60
40
20
ppm
file: /mnt/d600/nmr13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyler/2018.11/2018.11.13.v7_KM-GB-2-furan-b-LR-carbonate-product-pure_jcc91_17.2S_C13_APT_sd

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: **Mar 12 2013**	Sweep Width(Hz): **4801.92**	Acquisiton Time(s): **4.998**	Relaxation Delay(s): **0.1**
Pulse Sequence: **s2pul**	Digital Res.(Hz/pt): **0.07**	Hz per mm(Hz/mm): **20.01**	Completed Scans **16**

399.794 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, autoxdb probe



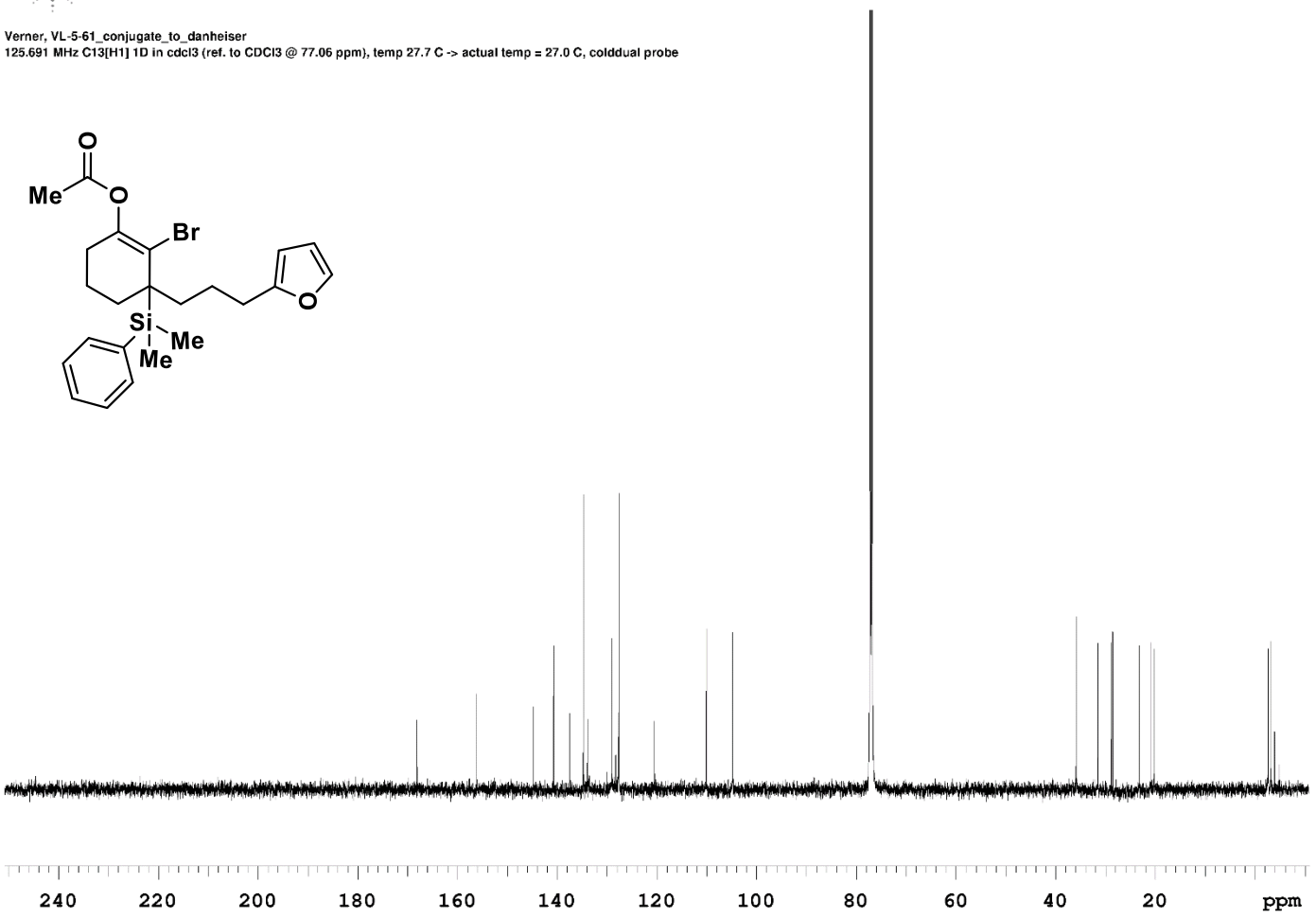
File: /mnt/d600/home13/westnmr/nmrdata/PreviousGroupMembers/Verner/Book5/2013.03.12.i4_VL-5-61_conjugate_to_danheiser_H1_1D

Department of Chemistry, University of Alberta

Agilent Technologies

Recorded on: u500, Mar 12 2013	Sweep Width(Hz): 32894.7	Acquisiton Time(s): 2.5	Relaxation Delay(s): 0.1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.25	Hz per mm(Hz/mm): 137.06	Completed Scans 296

Verner, VL-5-61_conjugate_to_danheiser
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe



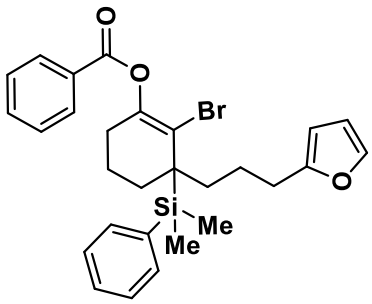
File: /mnt/d600/home13/westnmr/nmrdata/PreviousGroupMembers/Verner/Book5/2013.03.12.u5_VL-5-61_conjugate_to_danheiser_12.22_C13_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: **u500, May 5 2017**	Sweep Width(Hz): **6009.62**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **PRESAT**	Digital Res.(Hz/pt): **0.09**	Hz per mm(Hz/mm): **20.89**	Completed Scans **16**

Kyle, KM-GB-1-Bz-Si
499.797 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



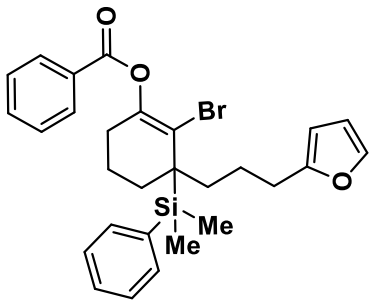
File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2017.05/2017.05.5.u5_KM-GB-1-Bz-Si_loc8_12.27_H1_1D

Department of Chemistry, University of Alberta

Agilent Technologies

Recorded on: u500, May 5 2017	Sweep Width(Hz): 33783.8	Acquisiton Time(s): 1	Relaxation Delay(s): 1
Pulse Sequence: APT_ad	Digital Res.(Hz/pt): 0.26	Hz per mm(Hz/mm): 140.76	Completed Scans 752

Kyle, KM-GB-1-Bz-Si
125.688 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal



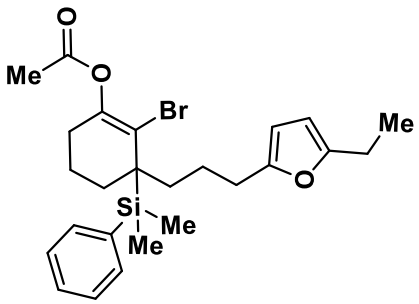
File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2017.05/2017.05.5.u5_KM-GB-1-Bz-Si_loc8_12.28_C13_APT_ad

Agilent Technologies

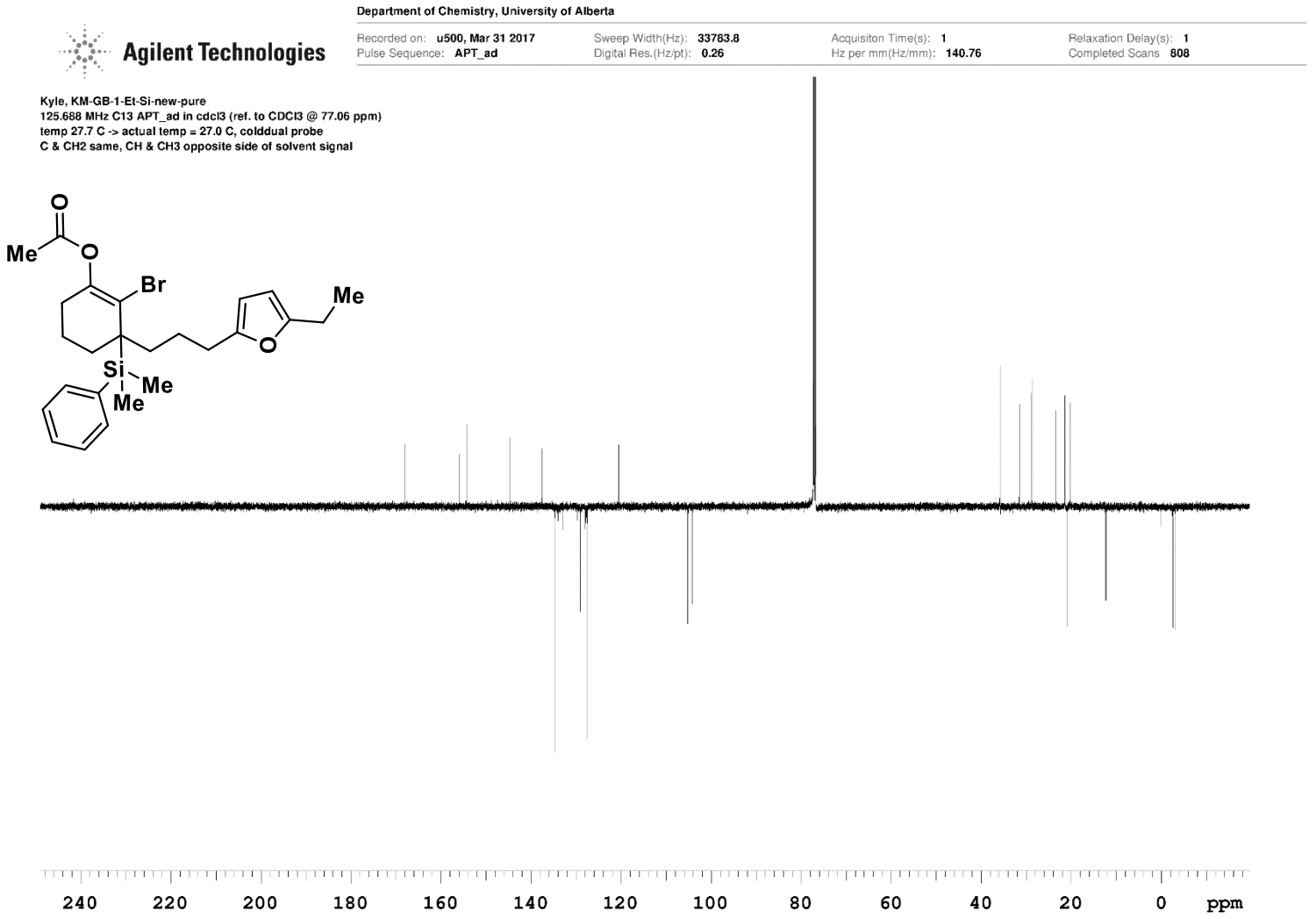
Department of Chemistry, University of Alberta

Recorded on: **ibd5, Mar 31 2017**	Sweep Width(Hz): **6000.6**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **s2pul**	Digital Res.(Hz/pt): **0.09**	Hz per mm(Hz/mm): **25**	Completed Scans **16**

498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe



File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2017.03/2017.03.31.i5_KM-GB-1-Et-Si-new-pure_H1_1D



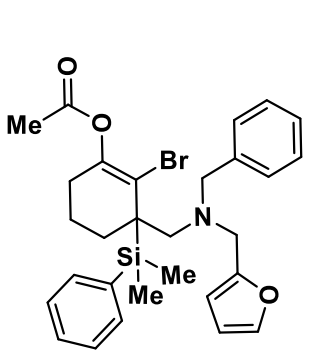
File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2017.03/2017.03.31.u5_KM-GB-1-Et-Si-new-pure_loc6_15.50_C13_APT_ad

Agilent Technologies

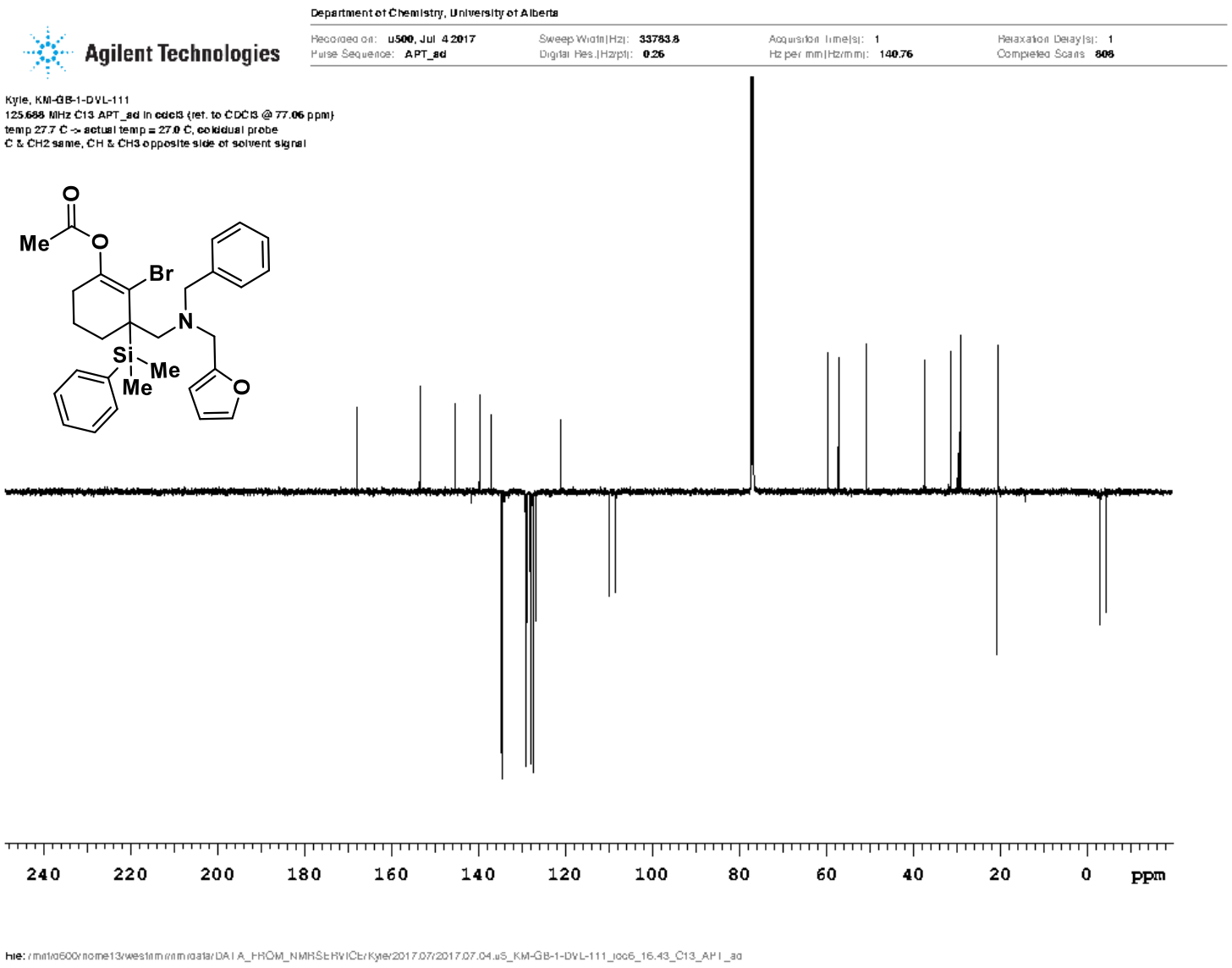
Department of Chemistry, University of Alberta

Recorded on:	mr400, Sep 21 2016	Sweep Width [Hz]:	4807.69	Acquisition Time [s]:	5	Relaxation Delay [s]:	0.1
Pulse Sequence:	s2pul	Digital Res. [Hz/pt]:	0.07	Hz per mm [Hz/mm]:	20.03	Completed Scans	88

DVL-1-111 silylation of furfurylbenzylamine enone
399.978 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe



file: /mnt/d600/nmr13/westfm/mnrdata/PreviousGroupMembers/VernerPDrBook1/2016.09.21.mr4_DVL-1-111_silylation_of_furfurylbenzylamine_enone_with_hexanes_H1_1D

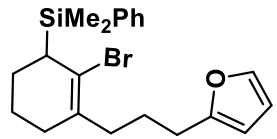

Department of Chemistry, University of Alberta
Agilent Technologies
Recorded on: u500, Jul 4 2017
Sweep Width [Hz]: 33783.8
Acquisition Time [s]: 1
Relaxation Delay [s]: 1
Pulse Sequence: APT_ad
Digital Res. [Hz/pt]: 0.26
Hz per mm [Hz/mm]: 140.76
Completed Scans 808
Kyle, KM-GB-1-DVL-111
125.688 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, cold dual probe
C & CH2 same, CH & CH3 opposite side of solvent signal
Me
O
O
Br
N
Si
Me
Me
O
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm
file: /mnt/u500/nome13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyler/2017/07/2017.07.04.u5_KM-GB-1-DVL-111_jcc5_16.43_C13_APT_ad

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: **v700, Nov 27 2018**	Sweep Width(Hz): **8389.26**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **PRESAT**	Digital Res.(Hz/pt): **0.13**	Hz per mm(Hz/mm): **32.38**	Completed Scans **8**

Kyle, KM-GB-2-f-b-LR-silane-prod
699.762 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.5 C -> actual temp = 27.0 C, coldid probe



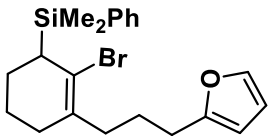
File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2018.11/2018.11.27.v7_KM-GB-2-f-b-LR-silane-prod_loc85_20.02_H1_1D

Department of Chemistry, University of Alberta

Agilent Technologies

Recorded on: **v700, Nov 27 2018**	Sweep Width(Hz): **48076.9**	Acquisiton Time(s): **1**	Relaxation Delay(s): **1**
Pulse Sequence: **APT_ad**	Digital Res.(Hz/pt): **0.37**	Hz per mm(Hz/mm): **161.17**	Completed Scans **724**

Kyle, KM-GB-2-f-b-LR-silane-prod
175.975 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.5 C -> actual temp = 27.0 C, coldid probe
C & CH2 same, CH & CH3 opposite side of solvent signal



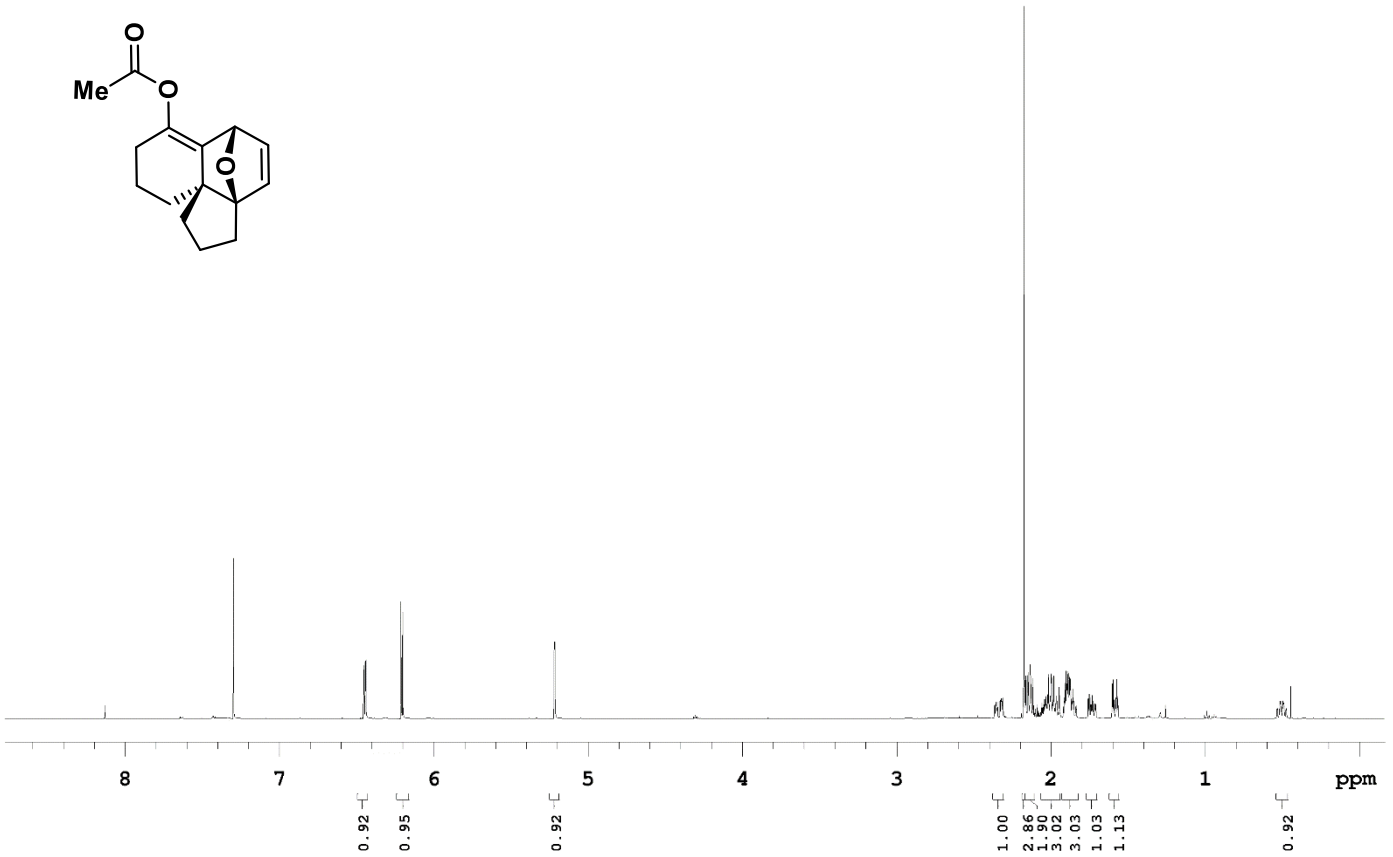
File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2018.11/2018.11.27.v7_KM-GB-2-f-b-LR-silane-prod_loc85_20.03_C13_APT_ad

Department of Chemistry, University of Alberta

Agilent Technologies

Recorded on: **u500, Mar 14 2013**	Sweep Width(Hz): **6009.62**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **PRESAT**	Digital Res.(Hz/pt): **0.18**	Hz per mm(Hz/mm): **18.62**	Completed Scans **16**

499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe



File: /mnt/d600/home13/westnmr/nmrdata/PreviousGroupMembers/Verner/Book5/2013.03.14.u5_VL-5-72b_danheiser_intra_11.30_H1_1D

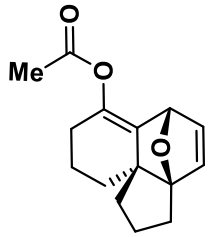
Department of Chemistry, University of Alberta

Agilent Technologies

Recorded on: **u500, Mar 14 2013**	Sweep Width(Hz): **32894.7**	Acquisiton Time(s): **2.5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **s2pul**	Digital Res.(Hz/pt): **0.25**	Hz per mm(Hz/mm): **120.16**	Completed Scans **128**

Verner, VL-5-72b_danheiser_intra

125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe



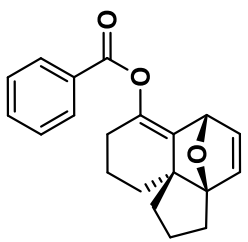
File: /mnt/d600/home13/westnmr/nmrdata/PreviousGroupMembers/Verner/Book5/2013.03.14.u5_VL-5-72b_danheiser_intra_11.32_C13_1D

Agilent Technologies

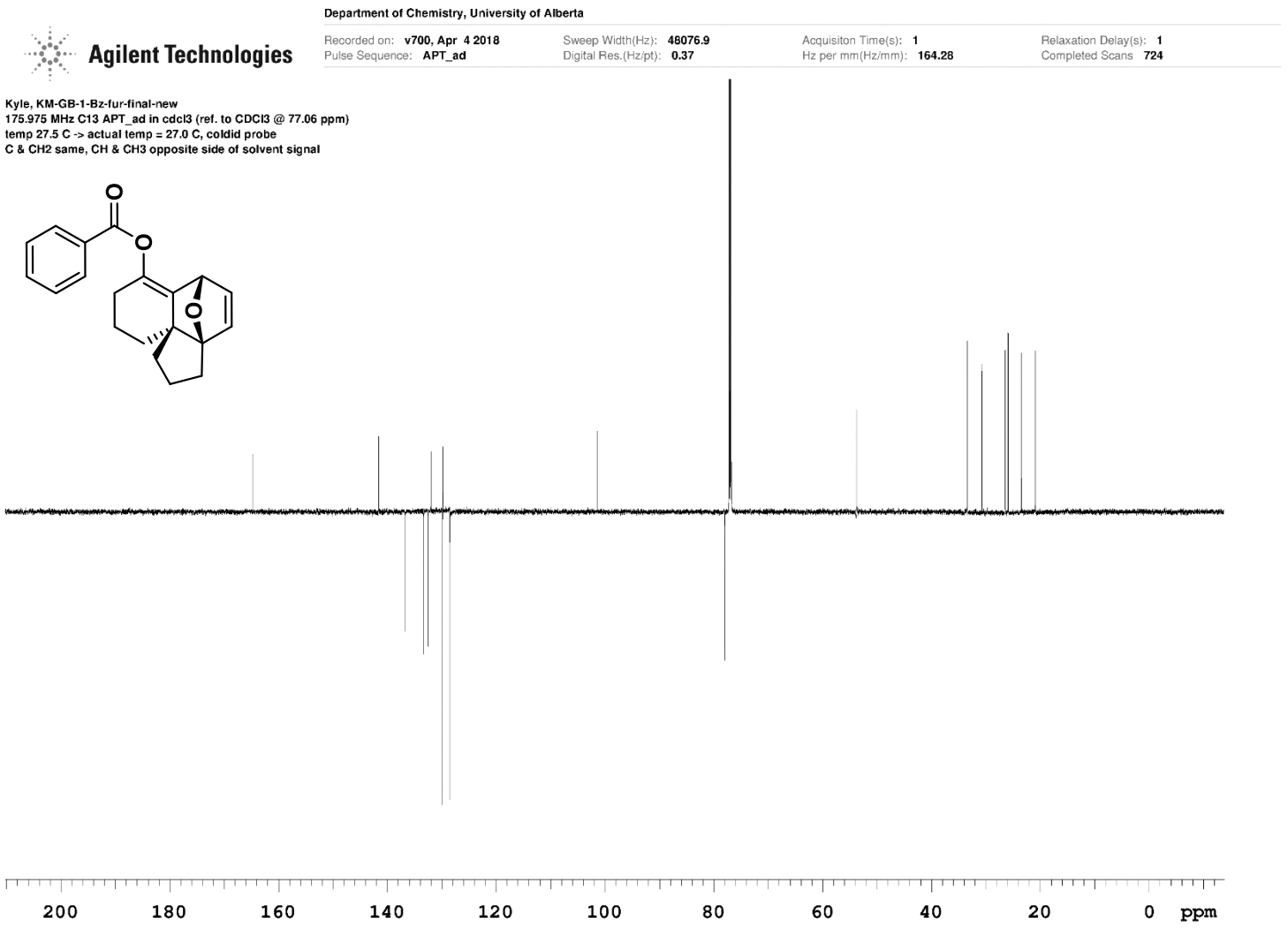
Department of Chemistry, University of Alberta

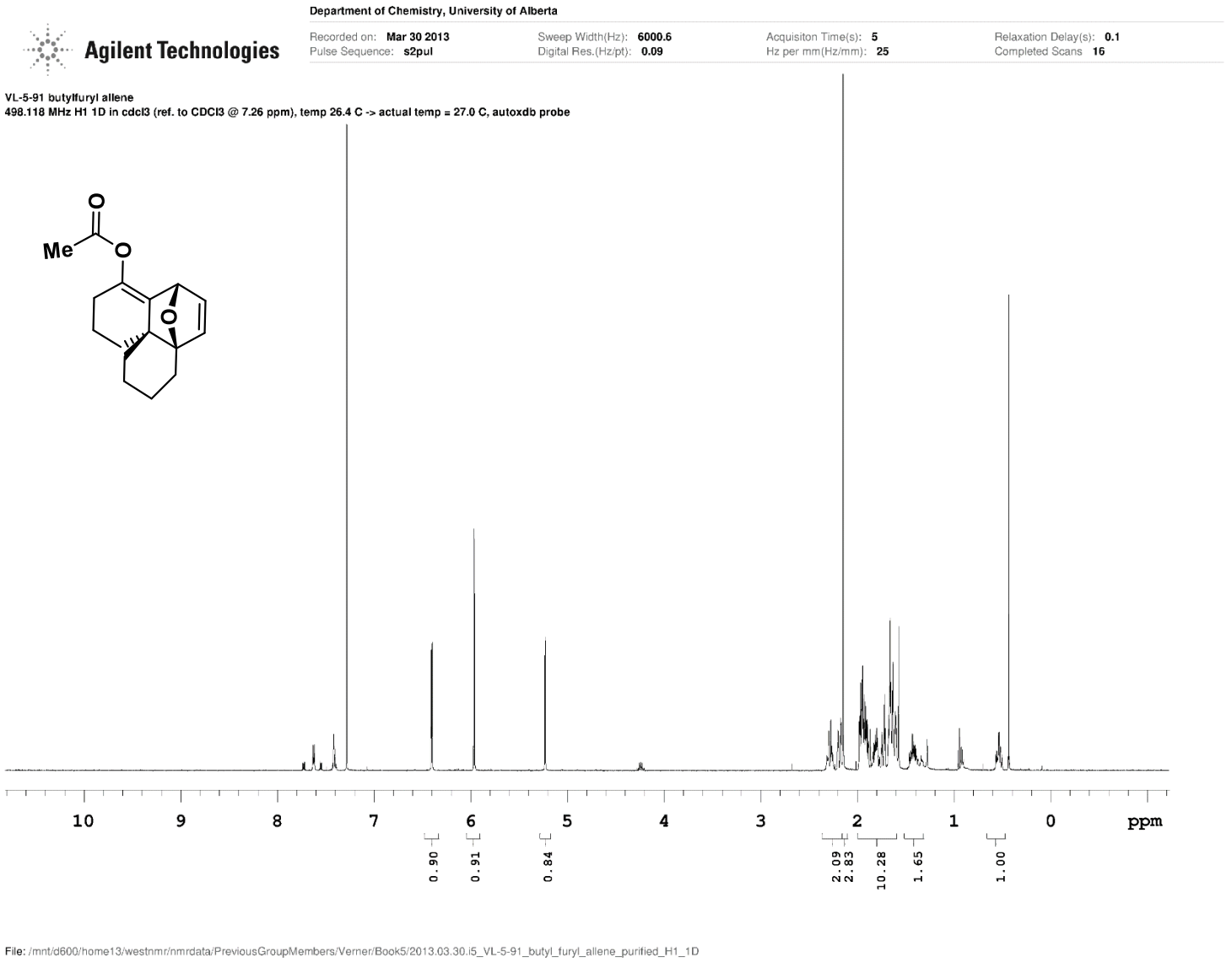
Recorded on: **v700, Apr 4 2018**	Sweep Width(Hz): **8389.26**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **PRESAT**	Digital Res.(Hz/pt): **0.13**	Hz per mm(Hz/mm): **34.95**	Completed Scans **16**

Kyle, KM-GB-1-Bz-fur-final-new
699.762 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.5 C -> actual temp = 27.0 C, coldid probe



File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2018.04/2018.04.04.v7_KM-GB-1-Bz-fur-final-new_loc85_15.23_H1_1D


Agilent Technologies
Department of Chemistry, University of Alberta
Recorded on: v700, Apr 4 2018
Pulse Sequence: APT_ad
Sweep Width(Hz): 48076.9
Digital Res.(Hz/pt): 0.37
Acquisiton Time(s): 1
Hz per mm(Hz/mm): 164.28
Relaxation Delay(s): 1
Completed Scans 724
Kyle, KM-GB-1-Bz-fur-final-new
175.975 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.5 C -> actual temp = 27.0 C, coldid probe
C & CH2 same, CH & CH3 opposite side of solvent signal
200
180
160
140
120
100
80
60
40
20
0
ppm
File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2018.04/2018.04.04.v7_KM-GB-1-Bz-fur-final-new_loc85_15.25_C13_APT_ad



File: /mnt/d600/home13/westnmr/nmrdata/PreviousGroupMembers/Verner/Book5/2013.03.30.i5_VL-5-91_butyl_furyl_allene_purified_H1_1D

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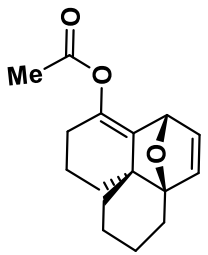
Agilent Technologies

Recorded on: u500, Mar 28 2013	Sweep Width(Hz): 32894.7	Acquisiton Time(s): 2.5	Relaxation Delay(s): 0.1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.25	Hz per mm(Hz/mm): 107.17	Completed Scans 252

Verner, VL-5-91_butylfurylallene

125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe



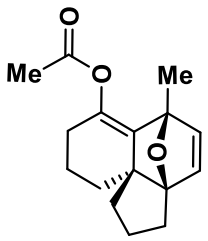
File: /mnt/d600/home13/westnmr/nmrdata/PreviousGroupMembers/Verner/Book5/2013.03.28.u5_VL-5-91_butylfurylallene_20.05_C13_1D

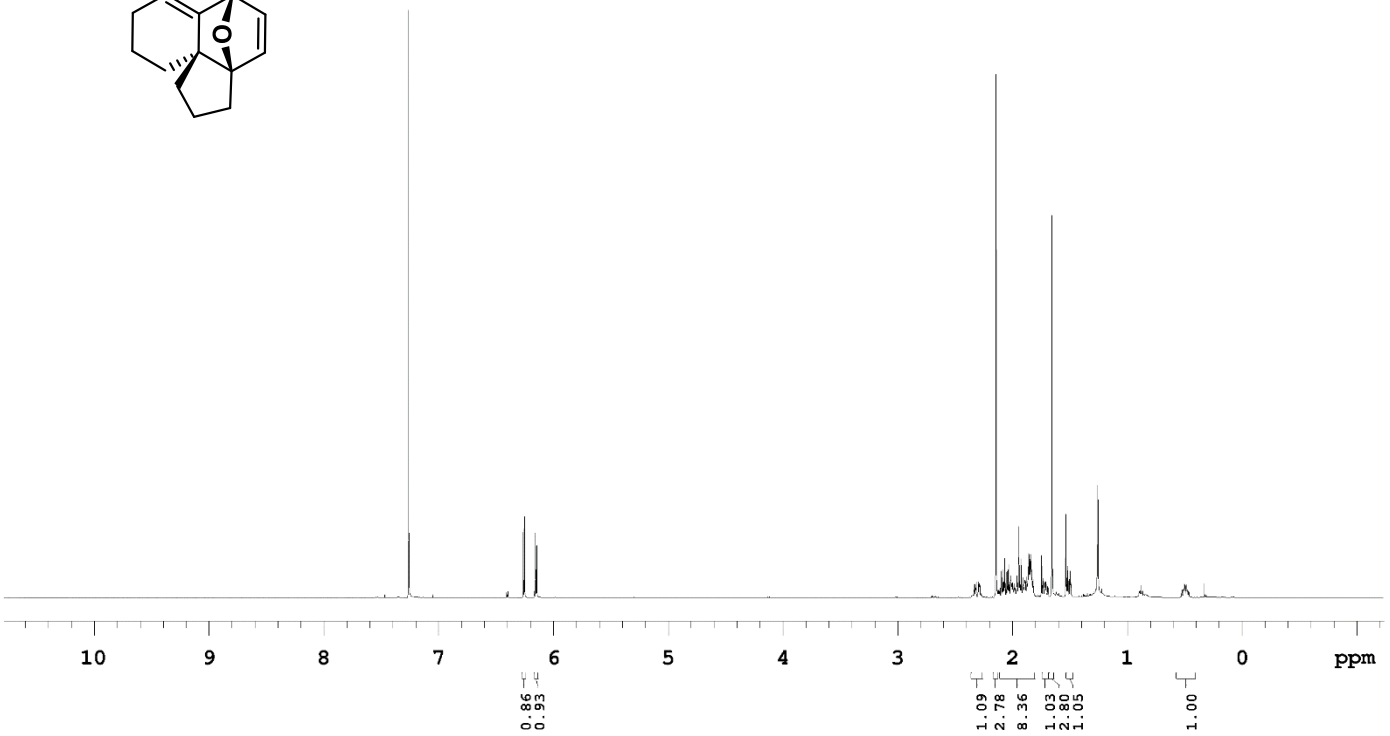
Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: **u500, Feb 9 2018**	Sweep Width(Hz): **6009.62**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **PRESAT**	Digital Res.(Hz/pt): **0.09**	Hz per mm(Hz/mm): **25.04**	Completed Scans **16**

Kyle, KM-GB-2-M5-new-prod-pure
499.797 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe





File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2018.02/2018.02.09.u5_KM-GB-2-M5-new-prod-pure_loc6_12.44_H1_1D

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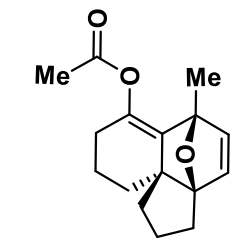
Recorded on: **u500, Feb 9 2018**	Sweep Width(Hz): **33783.8**	Acquisiton Time(s): **1**	Relaxation Delay(s): **1**
Pulse Sequence: **APT_ad**	Digital Res.(Hz/pt): **0.26**	Hz per mm(Hz/mm): **140.76**	Completed Scans **724**

Kyle, KM-GB-2-M5-new-prod-pure
125.688 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal



File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2018.02/2018.02.09.u5_KM-GB-2-M5-new-prod-pure_loc6_12.46_C13_APT_ad

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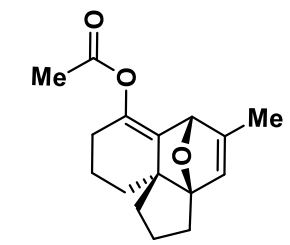
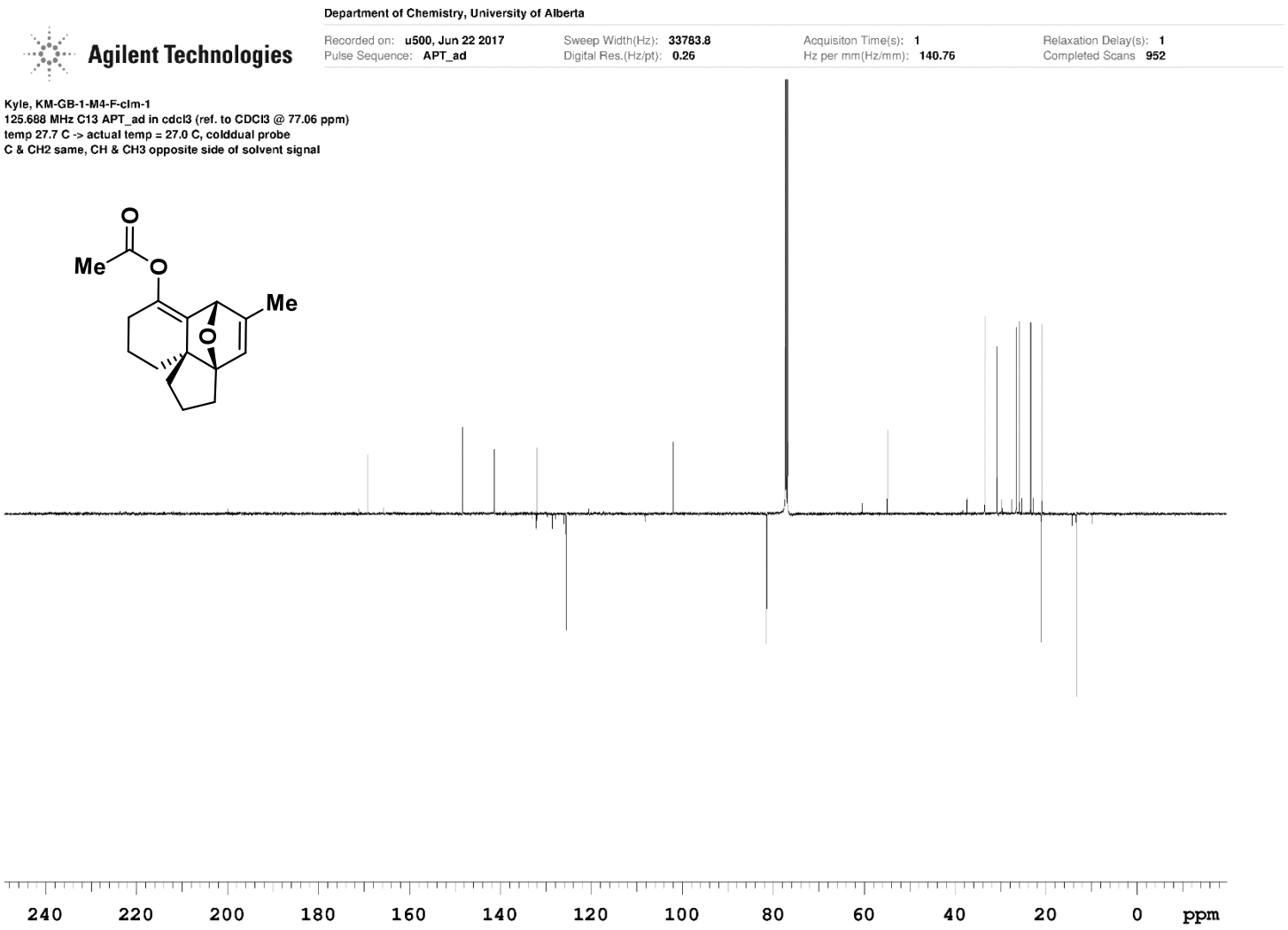
Agilent Technologies

Recorded on: **u500, Jun 22 2017**	Sweep Width(Hz): **6009.62**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **PRESAT**	Digital Res.(Hz/pt): **0.09**	Hz per mm(Hz/mm): **25.04**	Completed Scans **64**

Kyle, KM-GB-1-M4-F-clm-1
499.797 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2017.06/2017.06.22.u5_KM-GB-1-M4-F-clm-1_loc4_20.03_H1_1D



File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2017.06/2017.06.22.u5_KM-GB-1-M4-F-clm-1_loc4_20.08_C13_APT_ad

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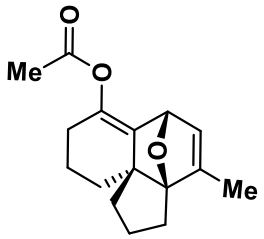
Recorded on: **ibd5, Apr 10 2017**	Sweep Width(Hz): **6000.6**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **s2pul**	Digital Res.(Hz/pt): **0.09**	Hz per mm(Hz/mm): **19.55**	Completed Scans **50**

498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe



File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2017.04/2017.04.10.i5_KM-GB-1-M3-F_H1_1D

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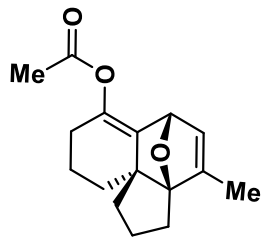
Recorded on: **u500, Apr 10 2017**	Sweep Width(Hz): **33783.8**	Acquisiton Time(s): **1**	Relaxation Delay(s): **1**
Pulse Sequence: **APT_ad**	Digital Res.(Hz/pt): **0.26**	Hz per mm(Hz/mm): **140.76**	Completed Scans **808**

Kyle, KM-GB-1-M3-F
125.688 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal



File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2017.04/2017.04.10.u5_KM-GB-1-M3-F_loc1_12.09_C13_APT_ad

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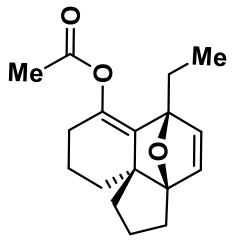
Agilent Technologies

Recorded on: u500, Apr 4 2017	Sweep Width(Hz): 6009.62	Acquisiton Time(s): 5	Relaxation Delay(s): 0.1
Pulse Sequence: PRESAT	Digital Res.(Hz/pt): 0.09	Hz per mm(Hz/mm): 25.04	Completed Scans 32

Kyle, KM-GB-1-Et-F
499.797 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2017.04/2017.04.4.u5_KM-GB-1-Et-F-last-spt4_loc9_23.00_H1_1D

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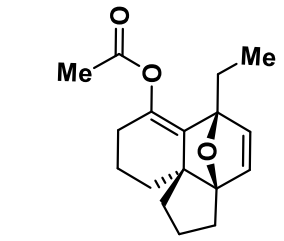
Recorded on: u500, Apr 4 2017	Sweep Width(Hz): 33783.8	Acquisiton Time(s): 1	Relaxation Delay(s): 1
Pulse Sequence: APT_ad	Digital Res.(Hz/pt): 0.26	Hz per mm(Hz/mm): 140.76	Completed Scans 1024

Kyle, KM-GB-1-Et-F-last-spt4
125.688 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal



File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2017.04/2017.04.4.u5_KM-GB-1-Et-F-last-spt4_loc9_23.03_C13_APT_ad

Agilent Technologies

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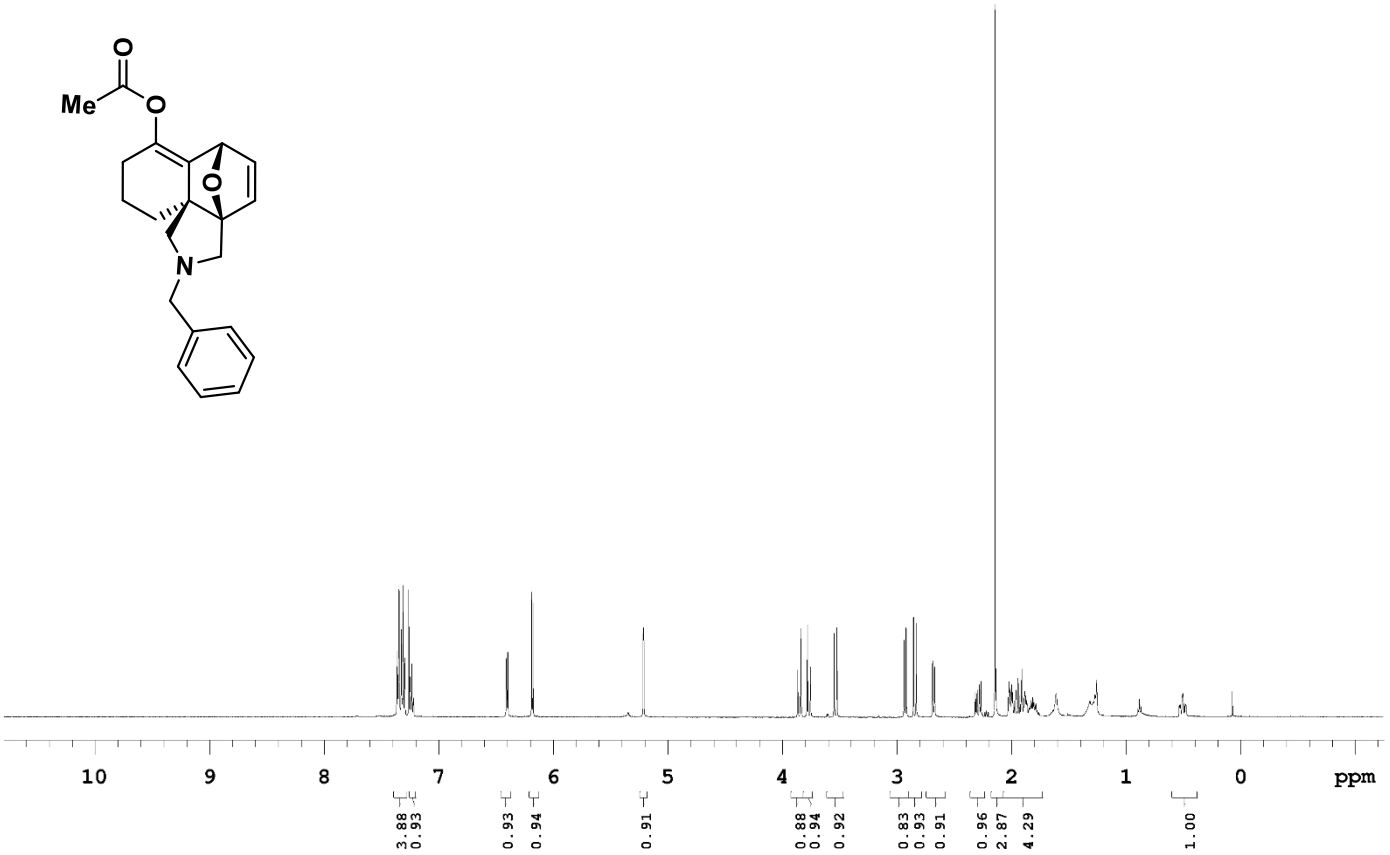
Recorded on: **ibd5, Oct 4 2016**	Sweep Width(Hz): **6000.6**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **s2pul**	Digital Res.(Hz/pt): **0.09**	Hz per mm(Hz/mm): **25**	Completed Scans **16**

DVL-1-135 intramolecular DA benzylfurfurylamine acetoxyallene
498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe



File: /mnt/d600/home13/westnmr/nmrdata/PreviousGroupMembers/VernerPD/Book1/2016.10.04.i5_DVL-1-135_intramolecular_DA_benzylfurfurylamine_acetoxyallene_H1_1D

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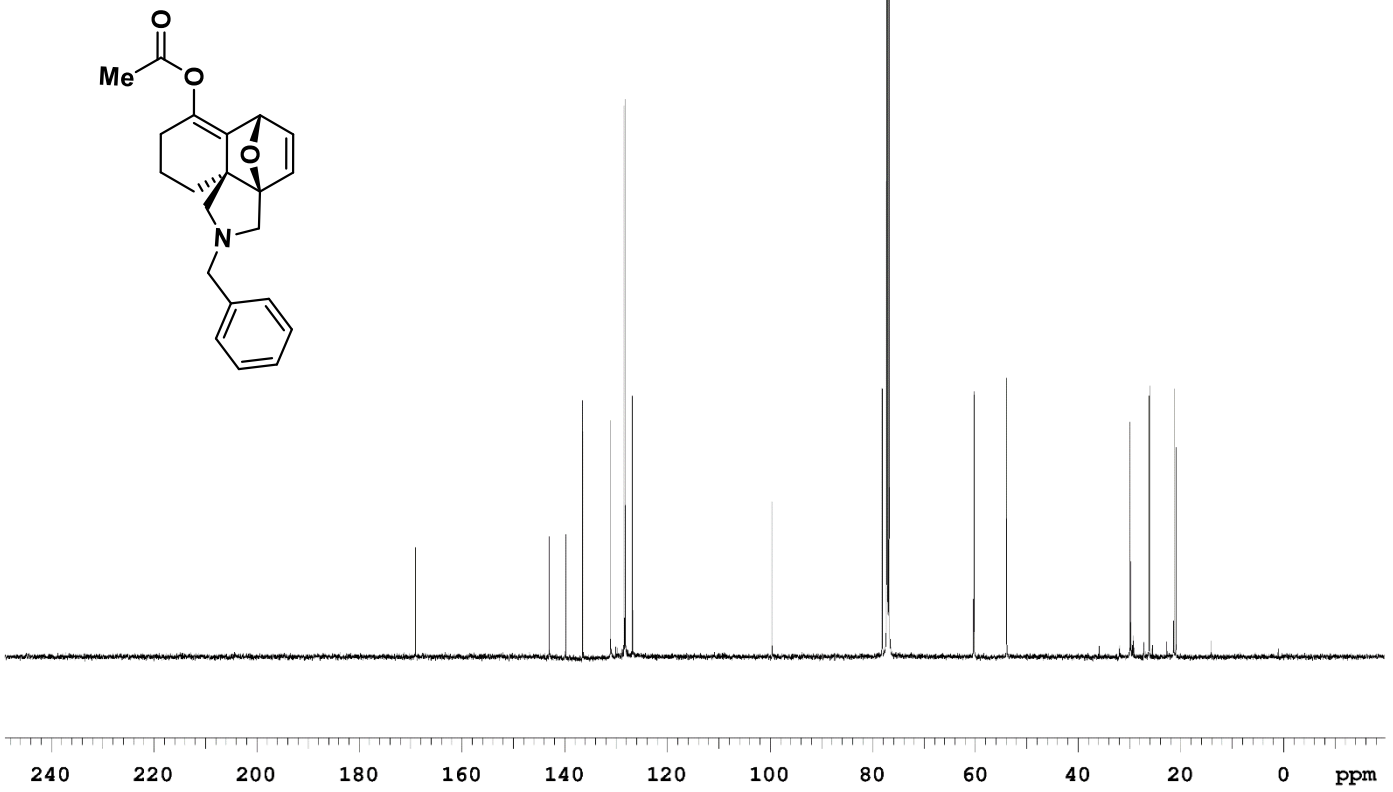
Agilent Technologies

Recorded on: u500, Oct 4 2016	Sweep Width(Hz): 33783.8	Acquisiton Time(s): 1	Relaxation Delay(s): 1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.26	Hz per mm(Hz/mm): 140.76	Completed Scans 616

Verner, DVL-1-135_intramolecularDA_benzylfurfurylamine_acetoxyallene
125.688 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe



File: /mnt/d600/home13/westnmr/nmrdata/PreviousGroupMembers/VernerPD/Book1/2016.10.4.u5_DVL-1-135_intramolecularDA_benzylfurfurylamine_acetoxyallene_loc7_14.56_C13_1D

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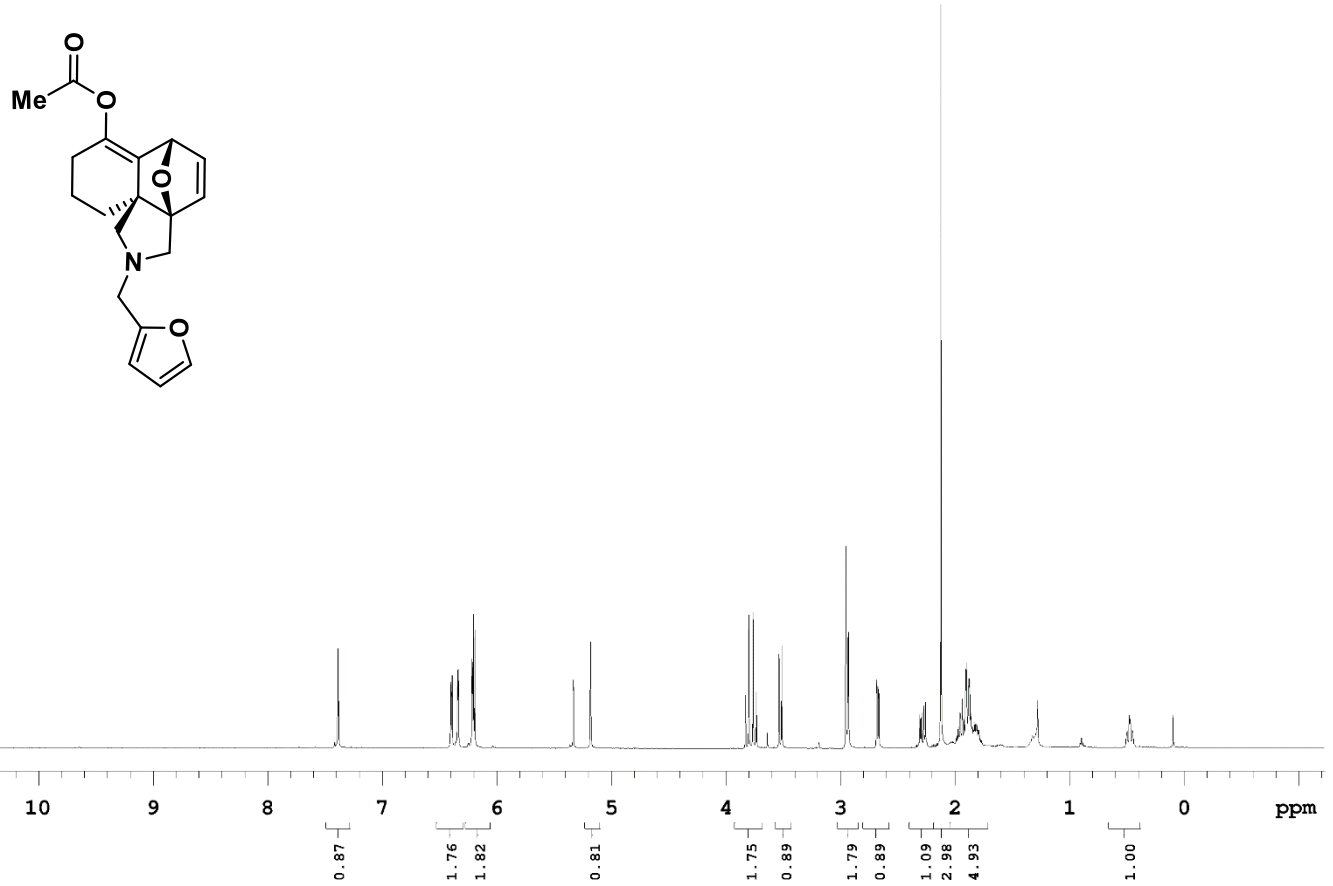
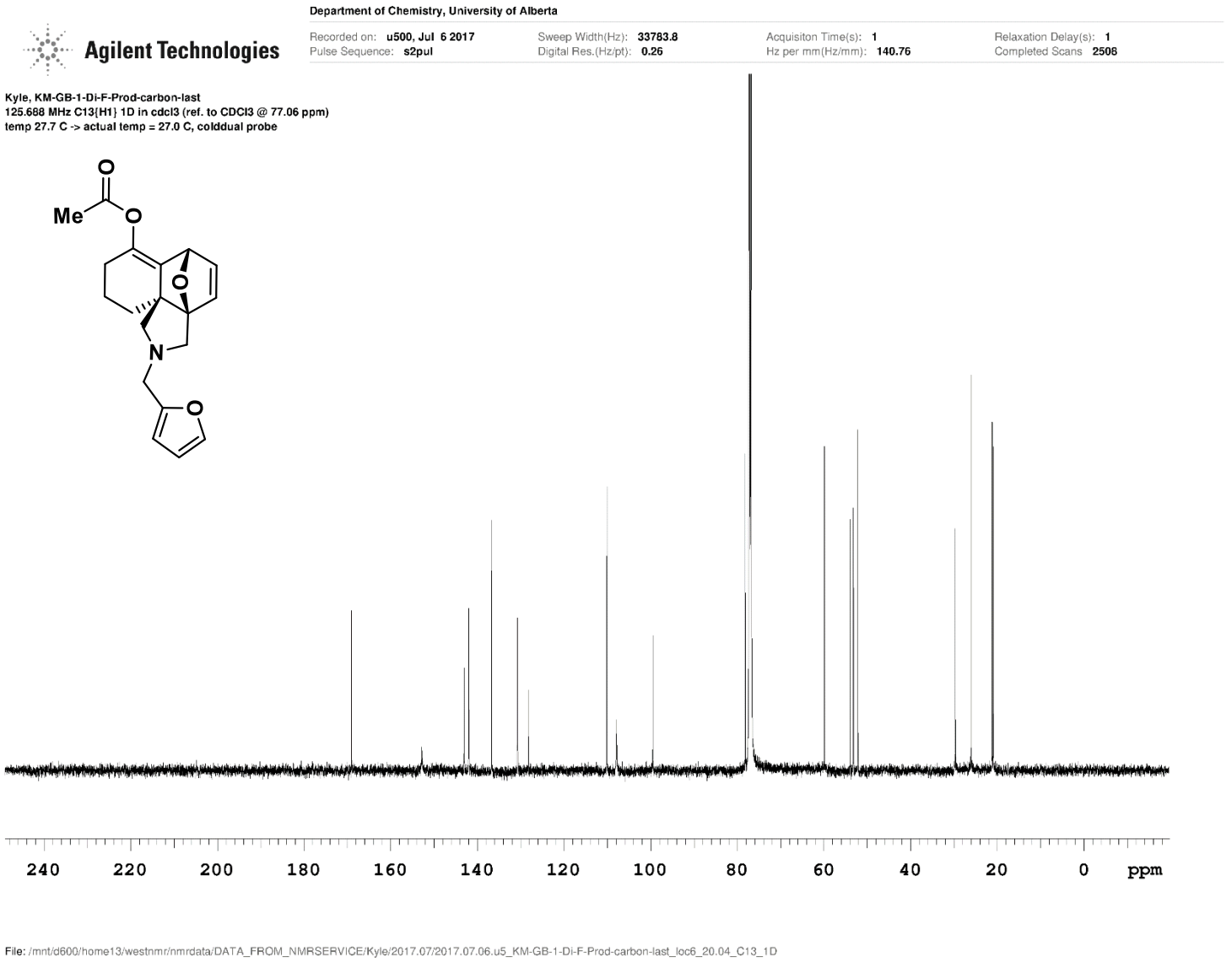
Recorded on: **ibd5, Sep 30 2016**	Sweep Width(Hz): **6000.6**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **s2pul**	Digital Res.(Hz/pt): **0.09**	Hz per mm(Hz/mm): **25**	Completed Scans **16**

DVL-1-129 intramolecular DA difurfurylamine acetoxycyclic allene roomtemp
498.119 MHz H1 1D in cd2cl2 (ref. to CD2Cl2 @ 5.32 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe



File: /mnt/d600/home13/westnmr/nmrdata/PreviousGroupMembers/VernerPD/Book1/2016.09.30.i5_DVL-1-129_intramolecular_DA_difurfurylamine_acetoxycyclic_allene_roomtemp_H1_1D


Department of Chemistry, University of Alberta
Agilent Technologies
Recorded on: u500, Jul 6 2017
Pulse Sequence: s2pul
Sweep Width(Hz): 33783.8
Digital Res.(Hz/pt): 0.26
Acquisiton Time(s): 1
Hz per mm(Hz/mm): 140.76
Relaxation Delay(s): 1
Completed Scans 2508
Kyle, KM-GB-1-Di-F-Prod-carbon-last
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
Me
O
O
O
N
O
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm
File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2017.07/2017.07.06.u5_KM-GB-1-Di-F-Prod-carbon-last_loc6_20.04_C13_1D

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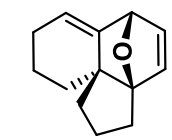
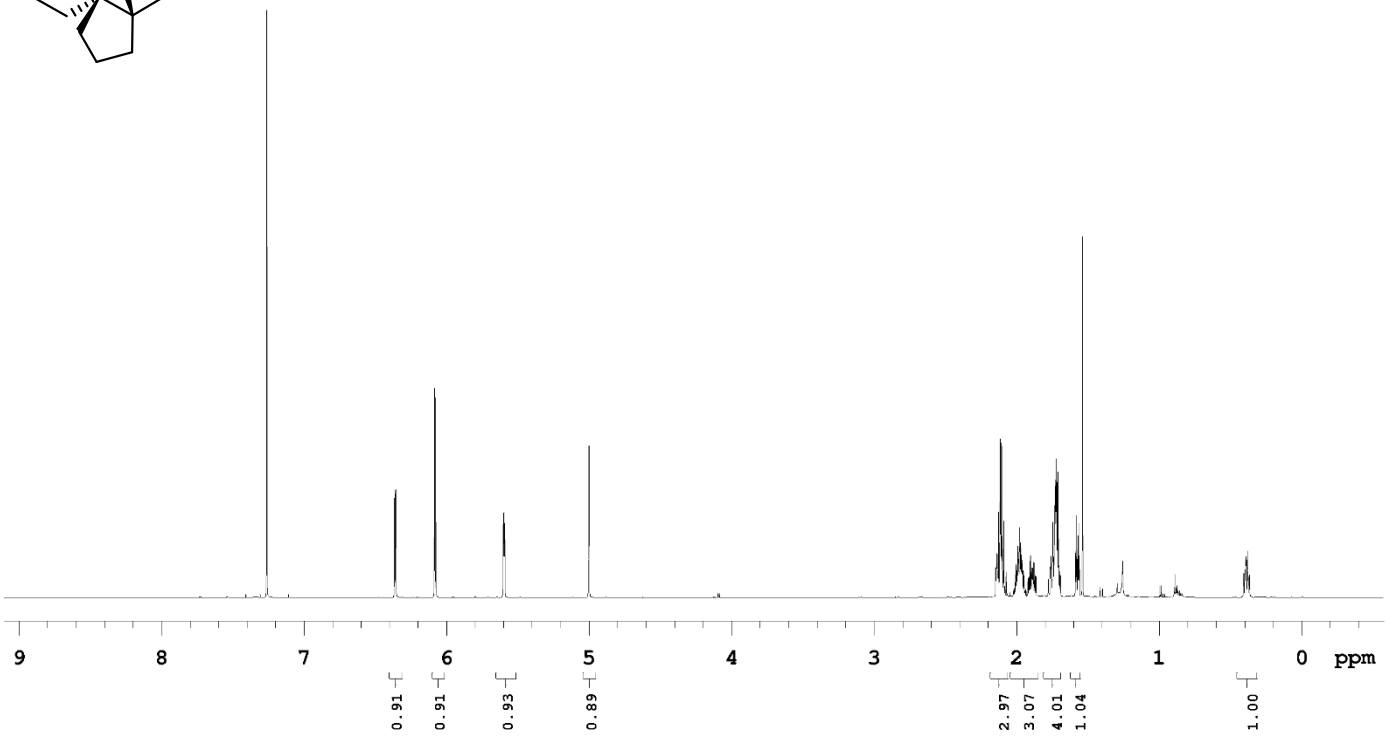
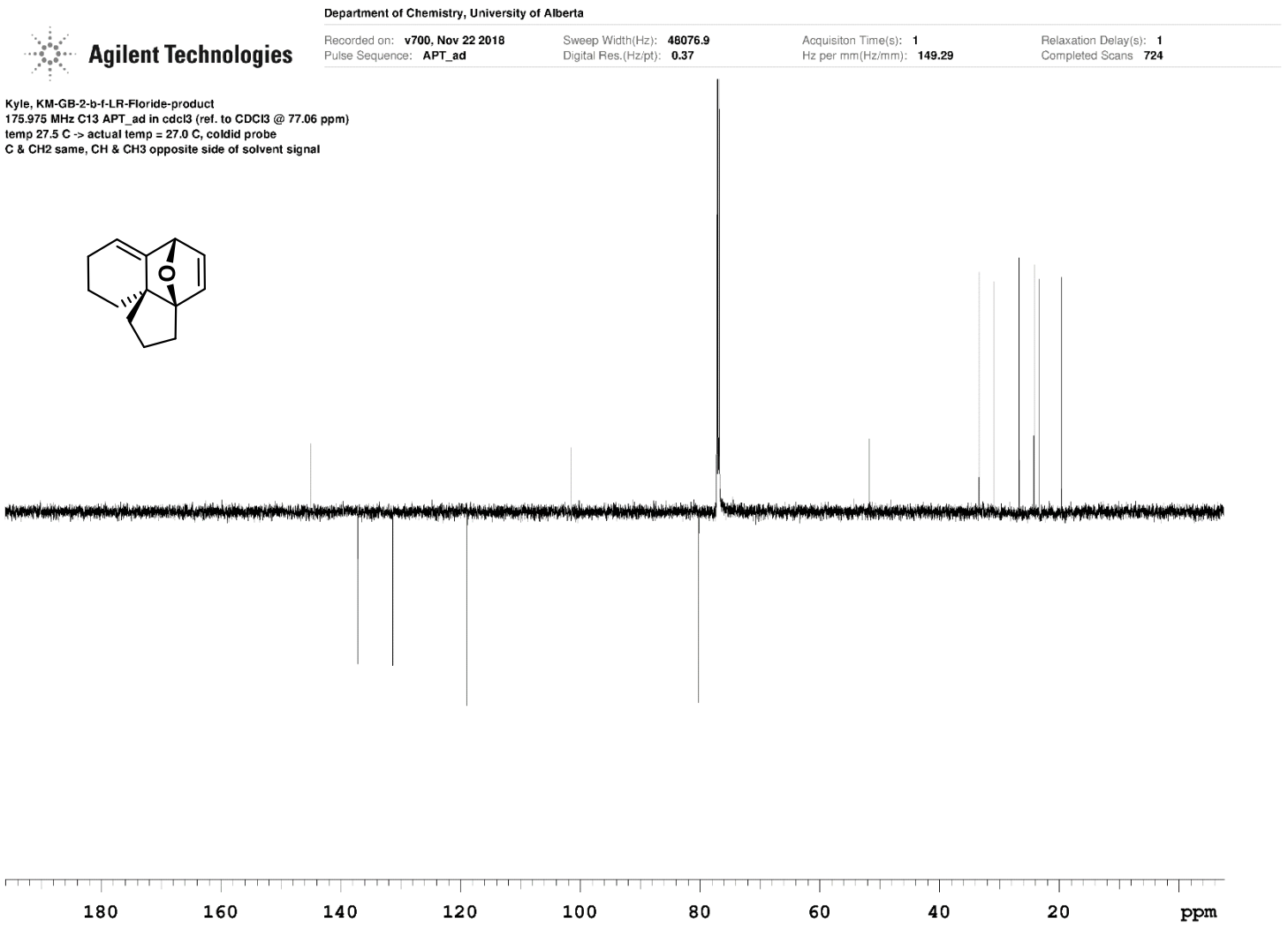
Recorded on: **v700, Nov 22 2018**	Sweep Width(Hz): **8389.26**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **PRESAT**	Digital Res.(Hz/pt): **0.13**	Hz per mm(Hz/mm): **28.23**	Completed Scans **8**

Kyle, KM-GB-2-b-f-LR-Floride-product
699.762 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.5 C -> actual temp = 27.0 C, coldid probe





File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2018.11/2018.11.22.v7_KM-GB-2-b-f-LR-Floride-product_loc61_17.36_H1_1D



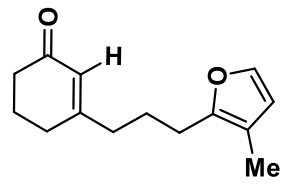
File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2018.11/2018.11.22.v7_KM-GB-2-b-f-LR-Floride-product_loc61_17.37_C13_APT_ad

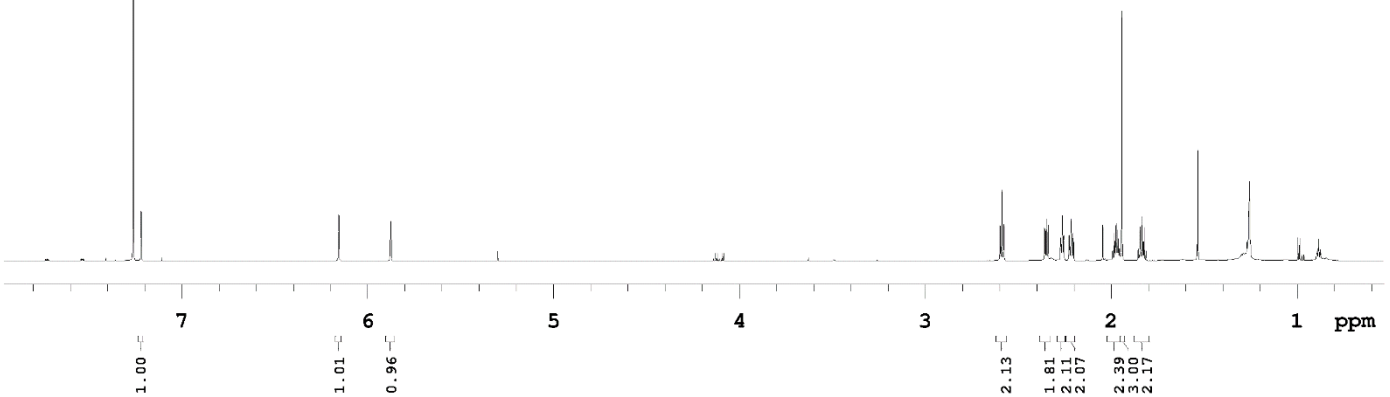
Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on:	v700, Feb 26 2019	Sweep Width(Hz):	8389.26	Acquisiton Time(s):	5	Relaxation Delay(s):	0.1
Pulse Sequence:	PRESAT	Digital Res.(Hz/pt):	0.13	Hz per mm(Hz/mm):	21.65	Completed Scans	32

Kyle, KM-GB-2-M3-deprotection-retroDA-prod
699.762 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.5 C -> actual temp = 27.0 C, coldid probe





File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2019.02/2019.02.26.v7_KM-GB-2-M3-deprotection-retroDA-prod_loc79_21.49_H1_1D

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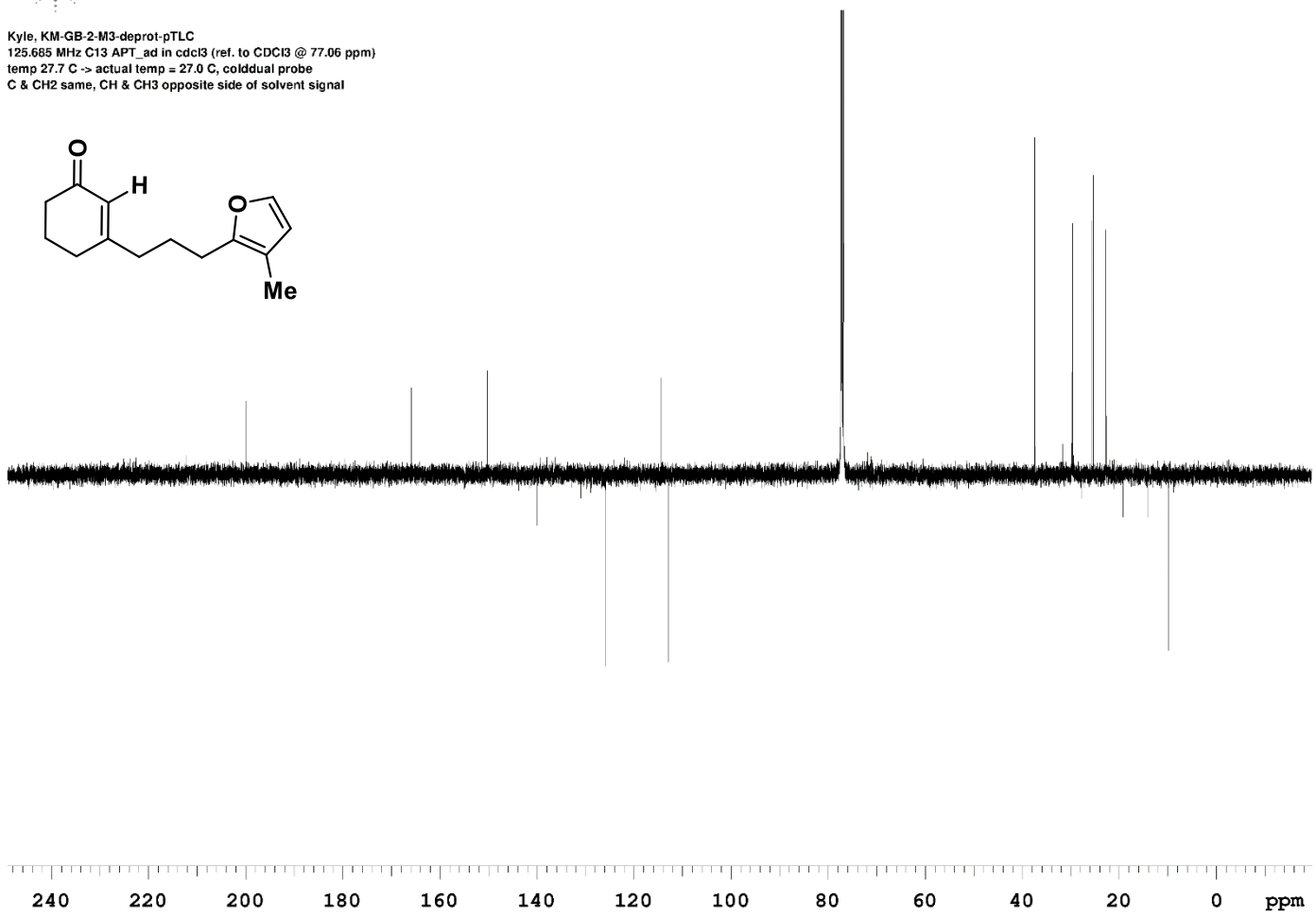
Agilent Technologies

Recorded on: **u500, Feb 28 2019**	Sweep Width(Hz): **33783.8**	Acquisiton Time(s): **1**	Relaxation Delay(s): **1**
Pulse Sequence: **APT_ad**	Digital Res.(Hz/pt): **0.26**	Hz per mm(Hz/mm): **140.76**	Completed Scans **2488**

Kyle, KM-GB-2-M3-deprot-pTLC
125.685 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal



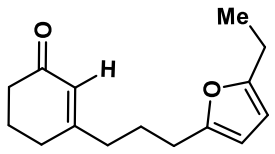
File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2019.02/2019.02.28.u5_KM-GB-2-M3-deprot-pTLC_loc6_20.03_C13_APT_ad

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: **v700, Feb 15 2019**	Sweep Width(Hz): **8389.26**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **PRESAT**	Digital Res.(Hz/pt): **0.13**	Hz per mm(Hz/mm): **28.37**	Completed Scans **8**

Kyle, KM-GB-2-Et-oxo-d20
699.762 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.5 C -> actual temp = 27.0 C, coldid probe



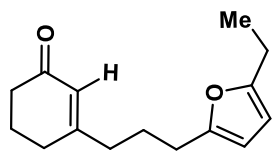
File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2019.02/2019.02.15.v7_KM-GB-2-Et-oxo-d20_loc79_20.03_H1_1D

Department of Chemistry, University of Alberta

Agilent Technologies

Recorded on: u500, Jun 6 2017	Sweep Width(Hz): 33783.8	Acquisiton Time(s): 1	Relaxation Delay(s): 1
Pulse Sequence: APT_ad	Digital Res.(Hz/pt): 0.26	Hz per mm(Hz/mm): 140.76	Completed Scans 668

Kyle, KM-GB-1-Et-oxo_1-f
125.688 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal



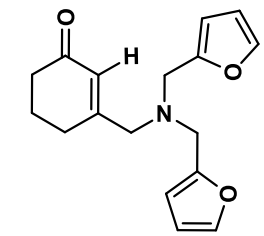
File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2017.06/2017.06.06.u5_KM-GB-1-Et-oxo_1-f_loc5_12.31_C13_APT_ad

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on:	v700, Feb 27 2019	Sweep Width(Hz):	8389.26	Acquisiton Time(s):	5	Relaxation Delay(s):	0.1
Pulse Sequence:	PRESAT	Digital Res.(Hz/pt):	0.13	Hz per mm(Hz/mm):	34.95	Completed Scans	32

Kyle, KM-GB-2-Difurylamine-deprotection-MeLi-crude
699.762 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.5 C -> actual temp = 27.0 C, coldid probe



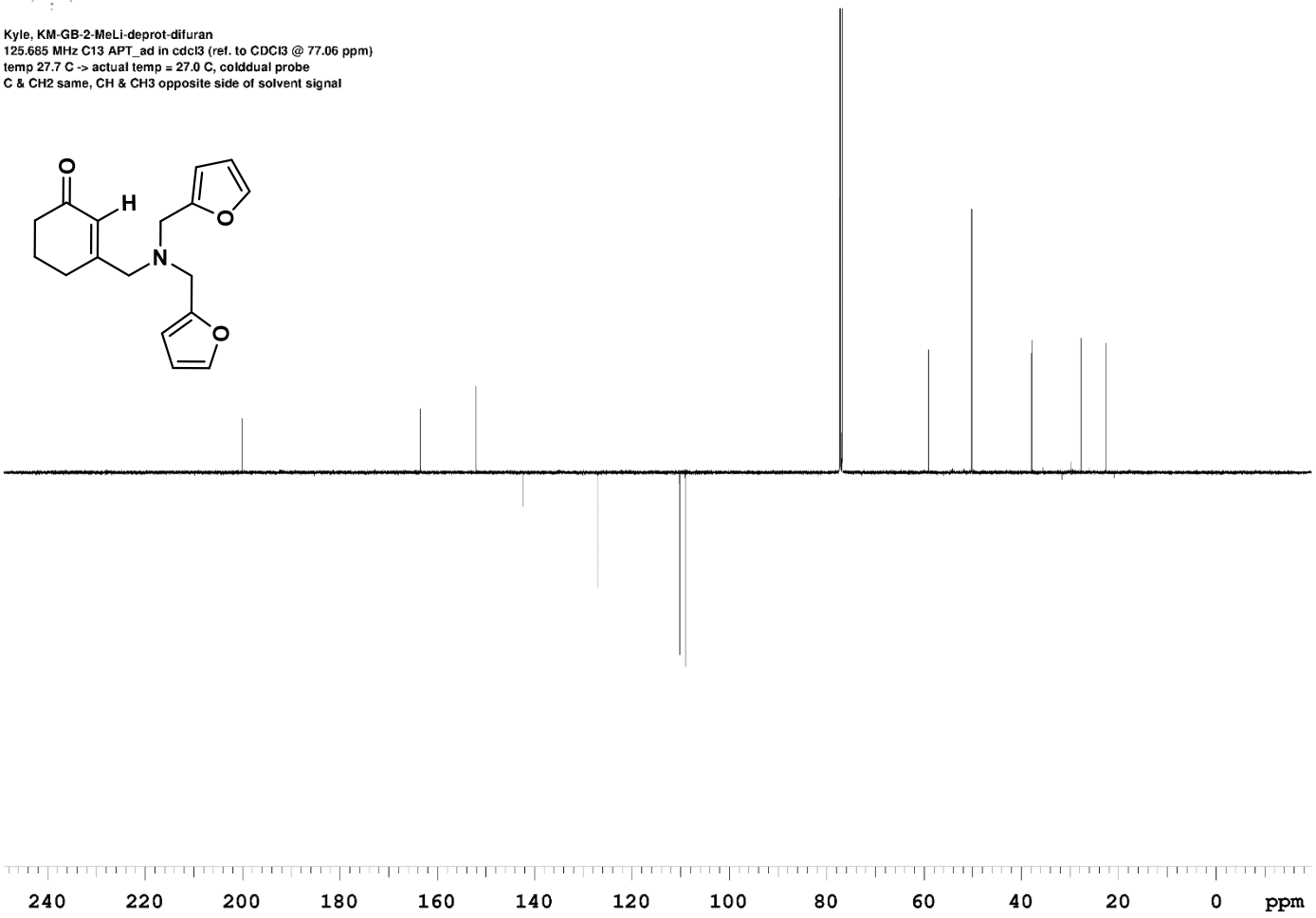
File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2019.02/2019.02.27.v7_KM-GB-2-Difurylamine-deprotection-MeLi-crude_loc80_00.14_H1_1D

Department of Chemistry, University of Alberta

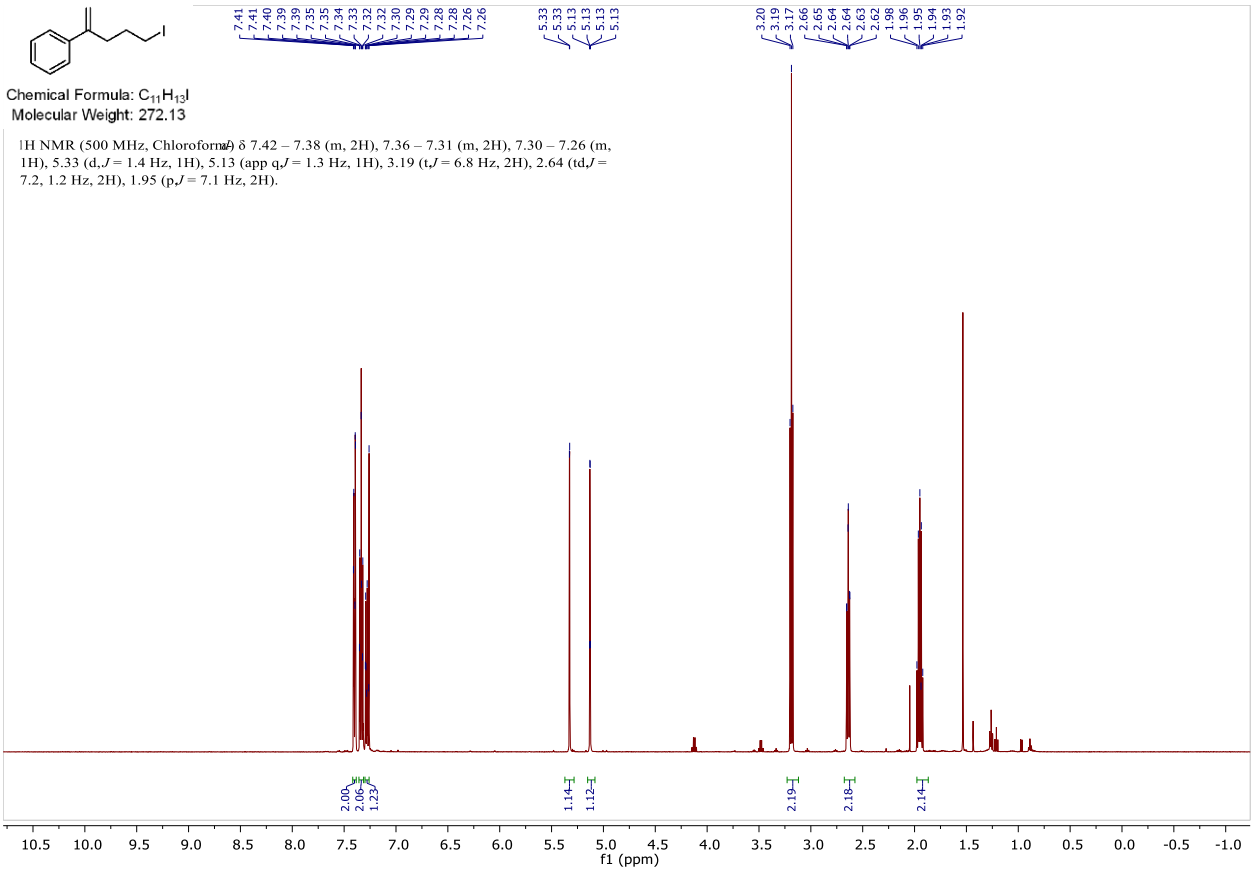
Agilent Technologies

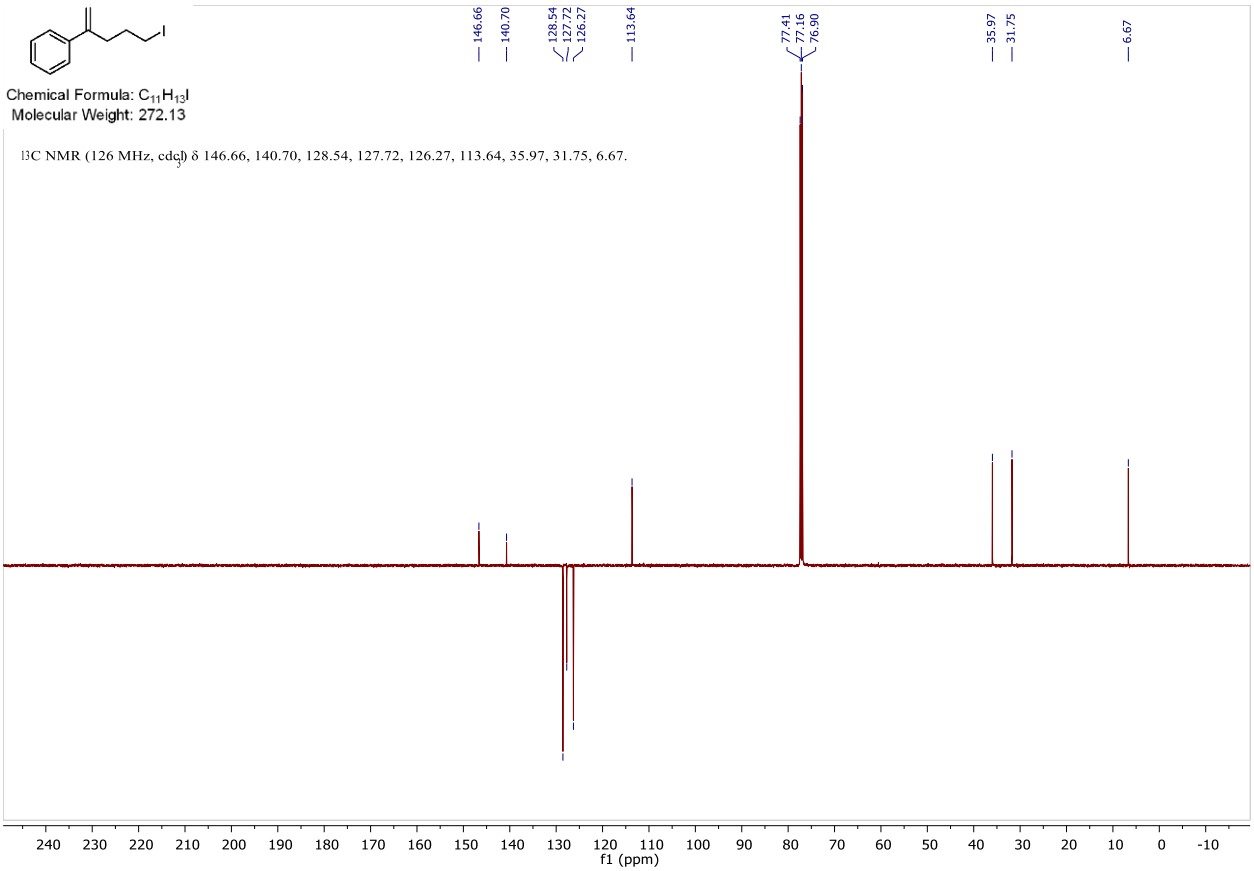
Recorded on: **u500, Feb 28 2019**	Sweep Width(Hz): **33783.8**	Acquisiton Time(s): **1**	Relaxation Delay(s): **1**
Pulse Sequence: **APT_ad**	Digital Res.(Hz/pt): **0.26**	Hz per mm(Hz/mm): **140.76**	Completed Scans **412**

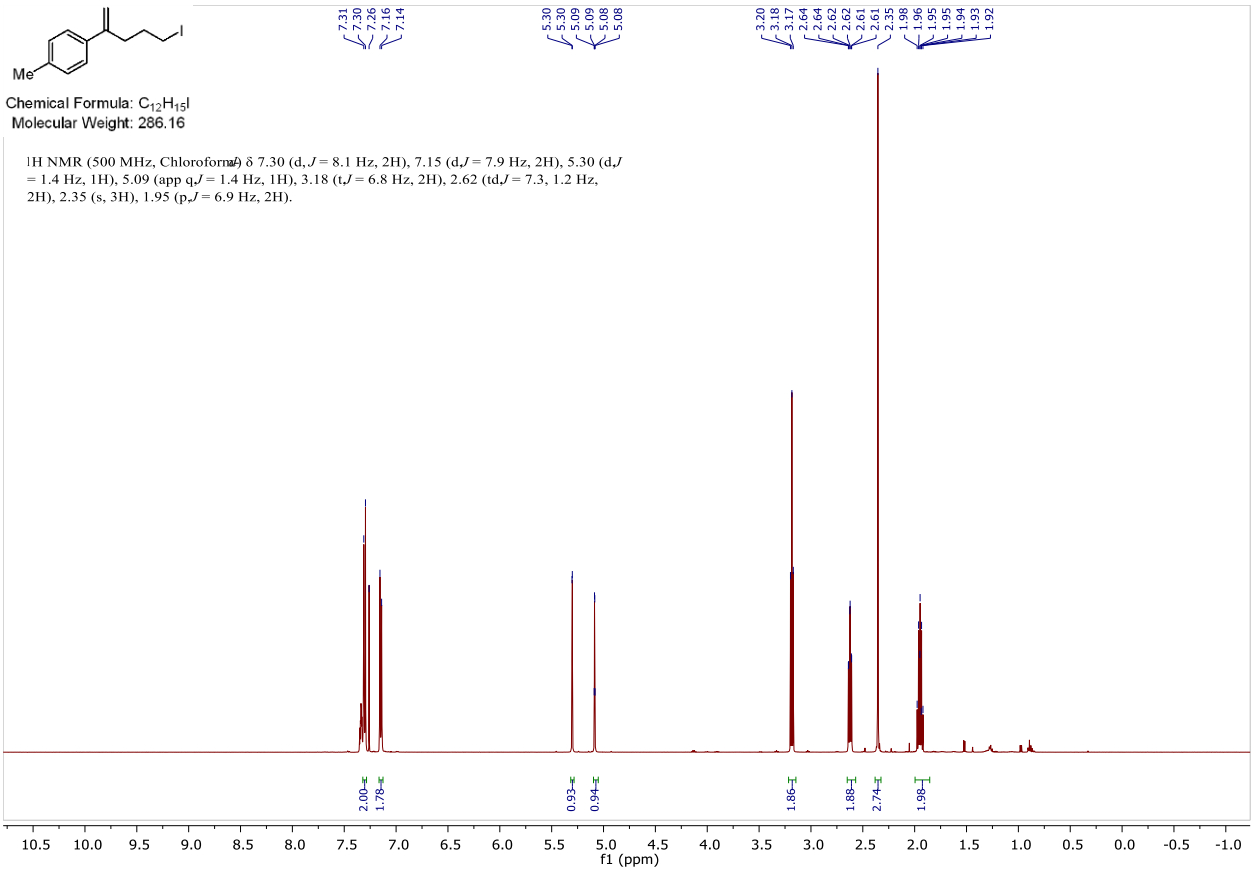
Kyle, KM-GB-2-MeLi-deprot-difuran
125.685 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal

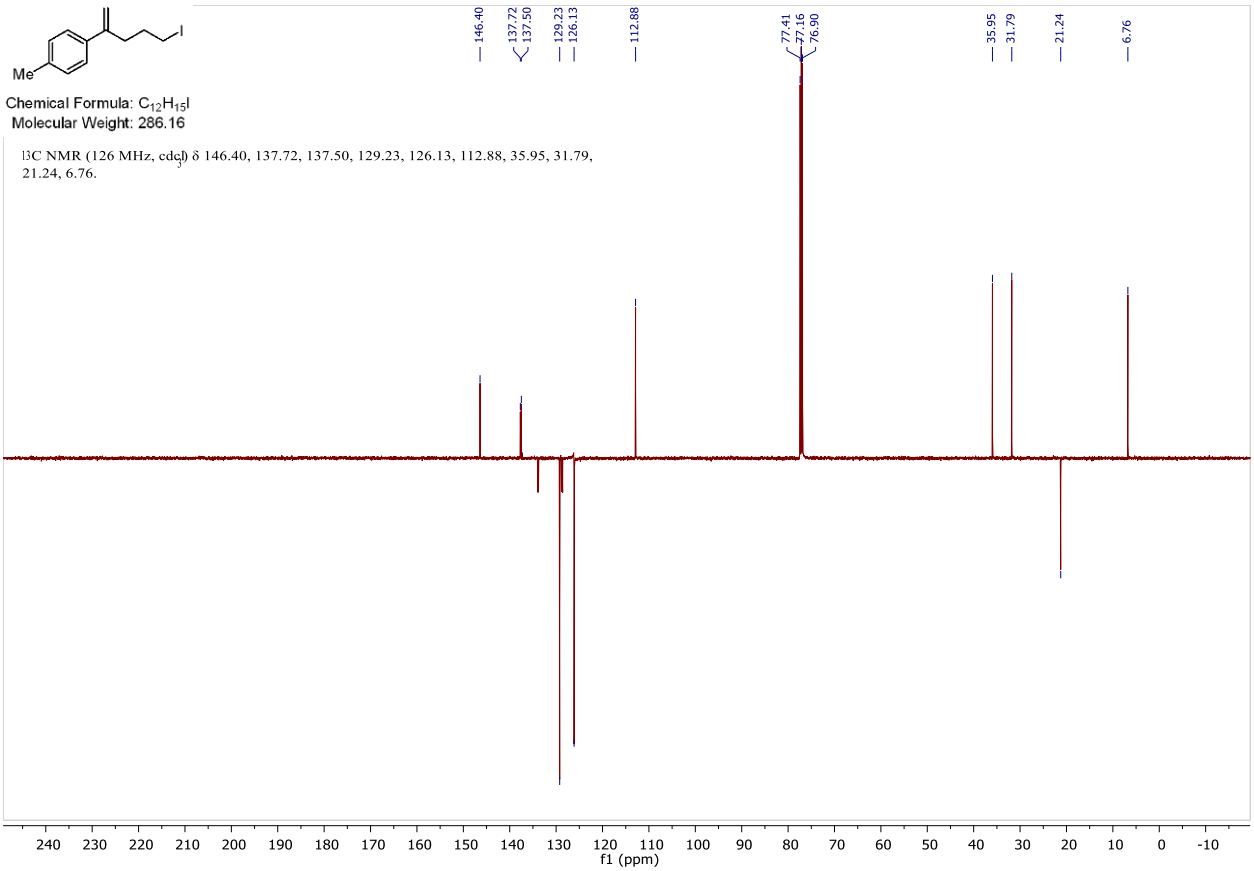


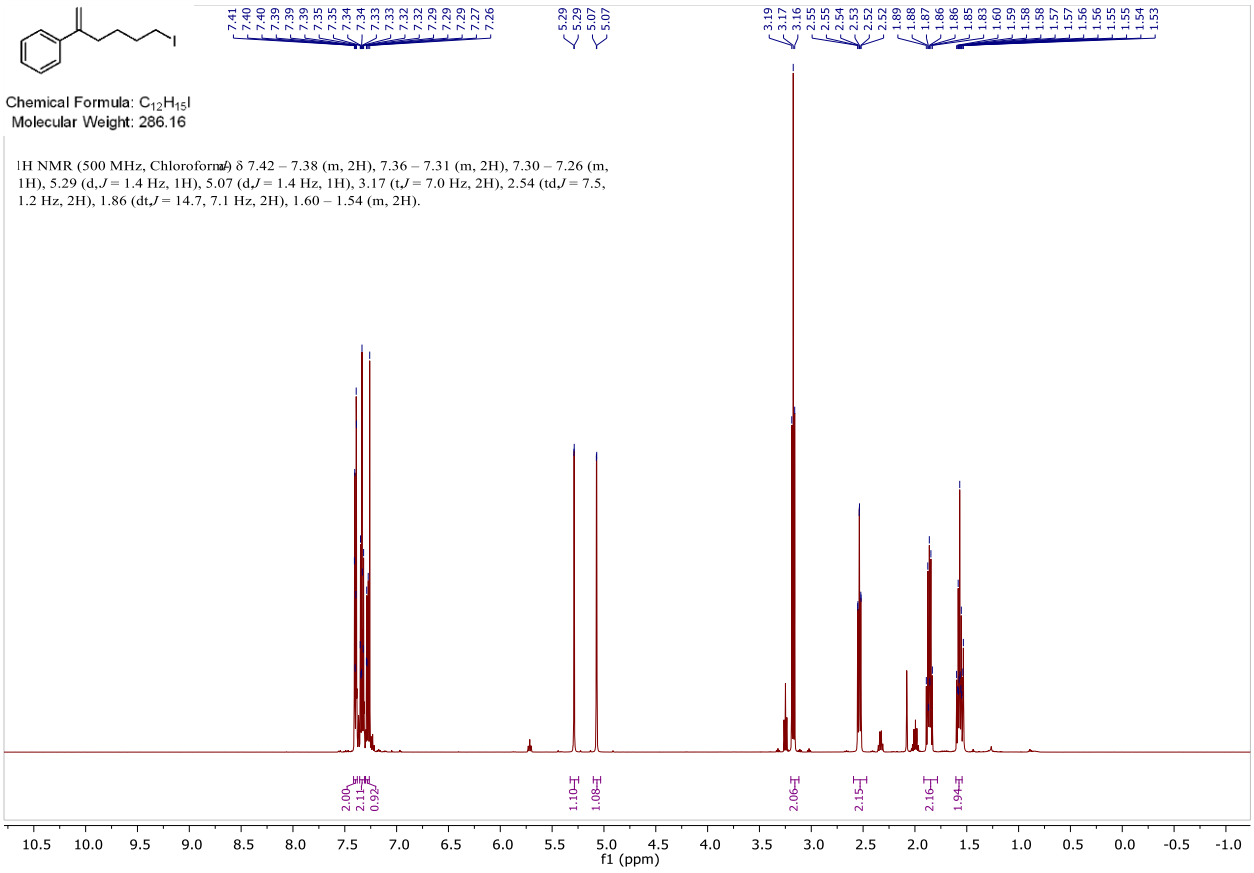
File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Kyle/2019.02/2019.02.28.u5_KM-GB-2-MeLi-deprot-difuran_loc7_21.30_C13_APT_ad

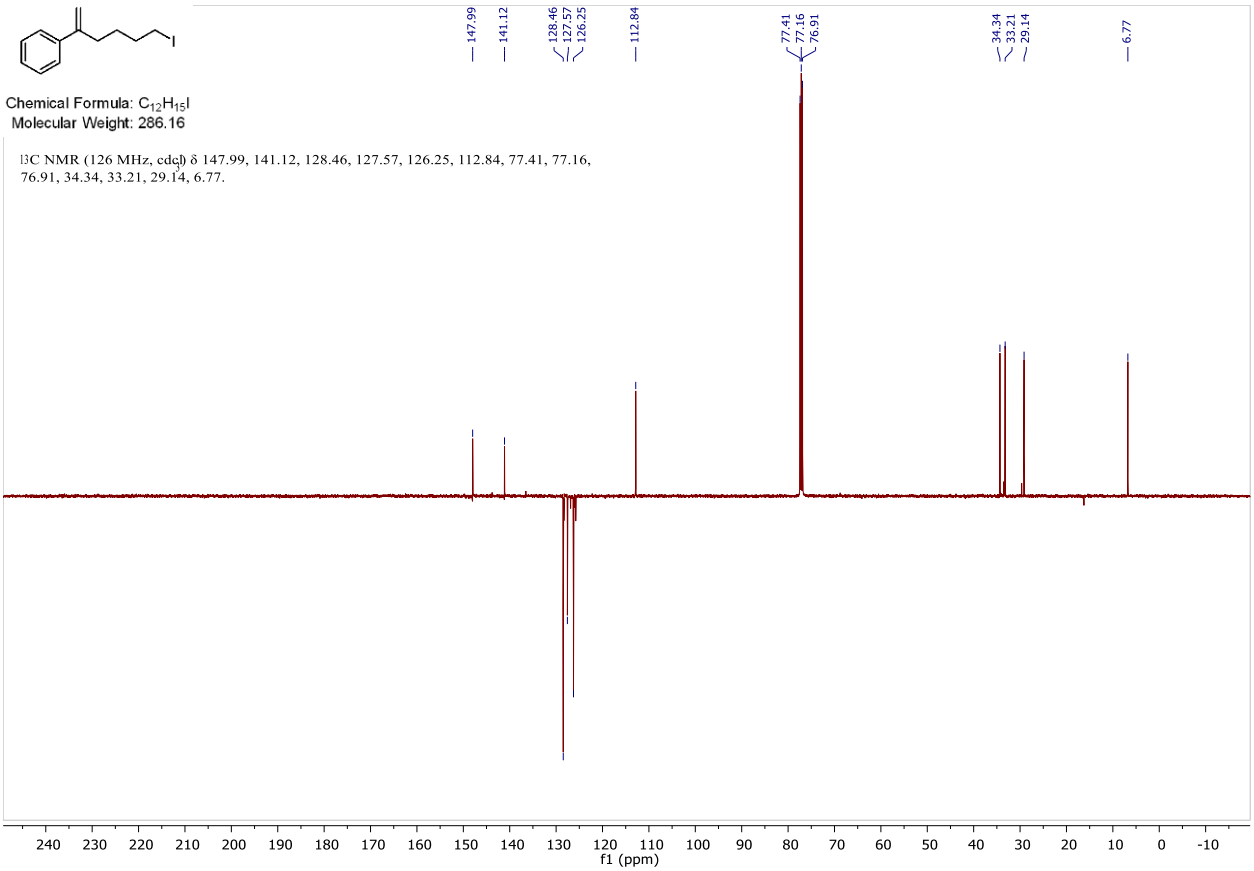

Chemical Formula: C11H13I
Molecular Weight: 272.13
1H NMR (500 MHz, Chloroform-d) δ 7.42 – 7.38 (m, 2H), 7.36 – 7.31 (m, 2H), 7.30 – 7.26 (m, 1H), 5.33 (d, J = 1.4 Hz, 1H), 5.13 (app q, J = 1.3 Hz, 1H), 3.19 (t, J = 6.8 Hz, 2H), 2.64 (td, J = 7.2, 1.2 Hz, 2H), 1.95 (p, J = 7.1 Hz, 2H).
f1 (ppm)

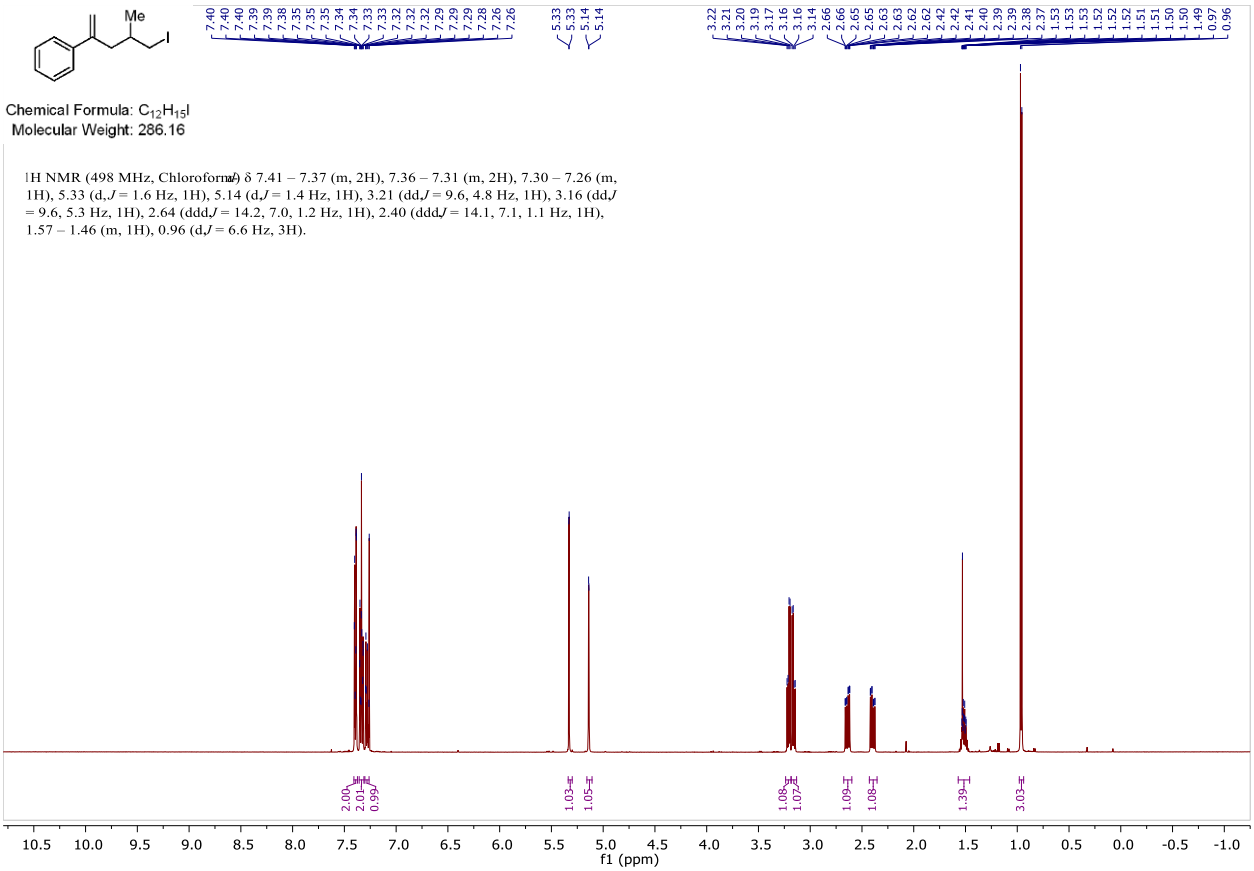

Chemical Formula: C11H13I
Molecular Weight: 272.13
13C NMR (126 MHz, cdcl3) δ 146.66, 140.70, 128.54, 127.72, 126.27, 113.64, 35.97, 31.75, 6.67.
146.66
140.70
128.54
127.72
126.27
113.64
77.41
77.16
76.90
35.97
31.75
6.67
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

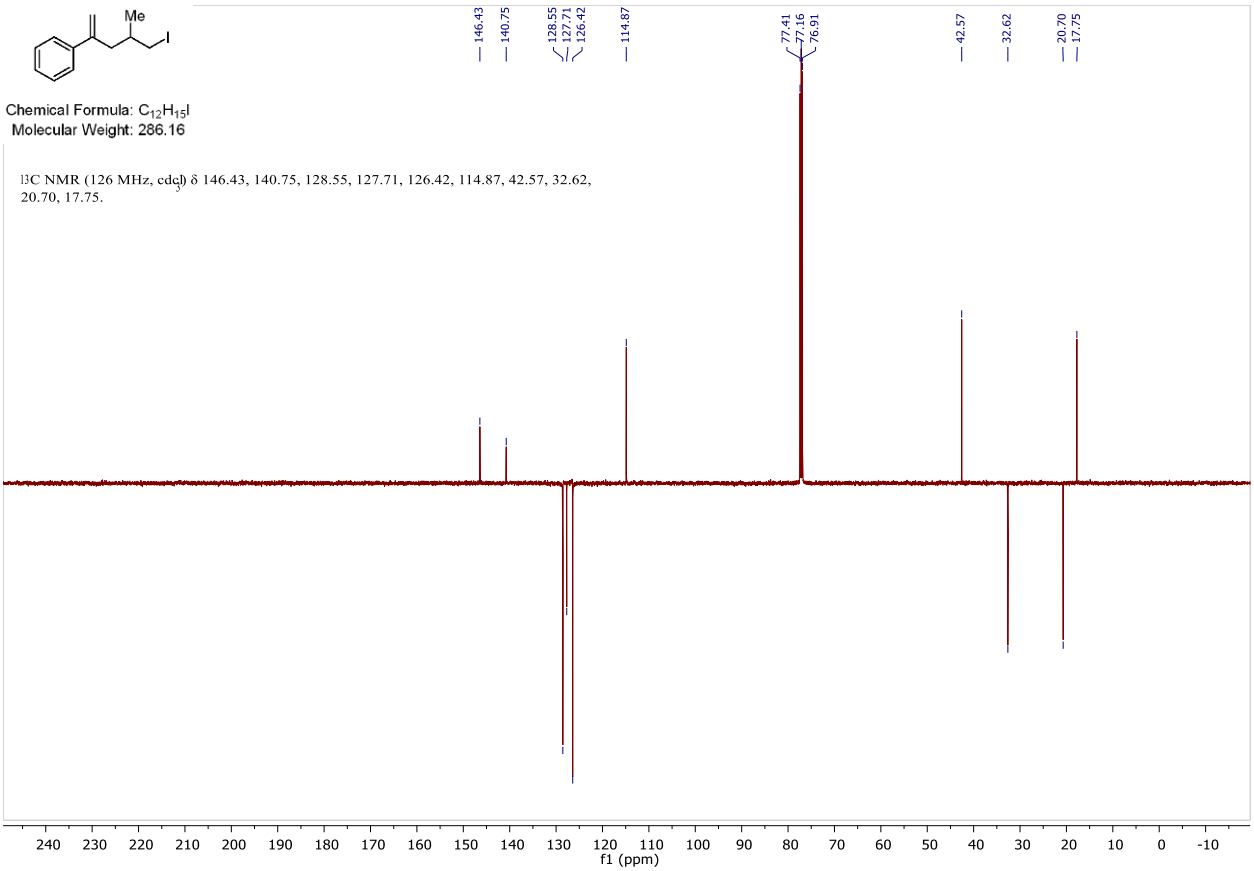

Me
I
Chemical Formula: C12H15I
Molecular Weight: 286.16
1H NMR (500 MHz, Chloroform-d) δ 7.30 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 5.30 (d, J = 1.4 Hz, 1H), 5.09 (app q, J = 1.4 Hz, 1H), 3.18 (t, J = 6.8 Hz, 2H), 2.62 (td, J = 7.3, 1.2 Hz, 2H), 2.35 (s, 3H), 1.95 (p, J = 6.9 Hz, 2H).
7.31
7.30
7.26
7.16
7.14
5.30
5.30
5.09
5.09
5.08
5.08
3.20
3.18
3.17
2.64
2.64
2.62
2.62
2.61
2.61
2.35
1.98
1.96
1.95
1.95
1.94
1.93
1.92
2.00
1.78
0.93
0.94
1.86
1.88
2.74
1.98
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

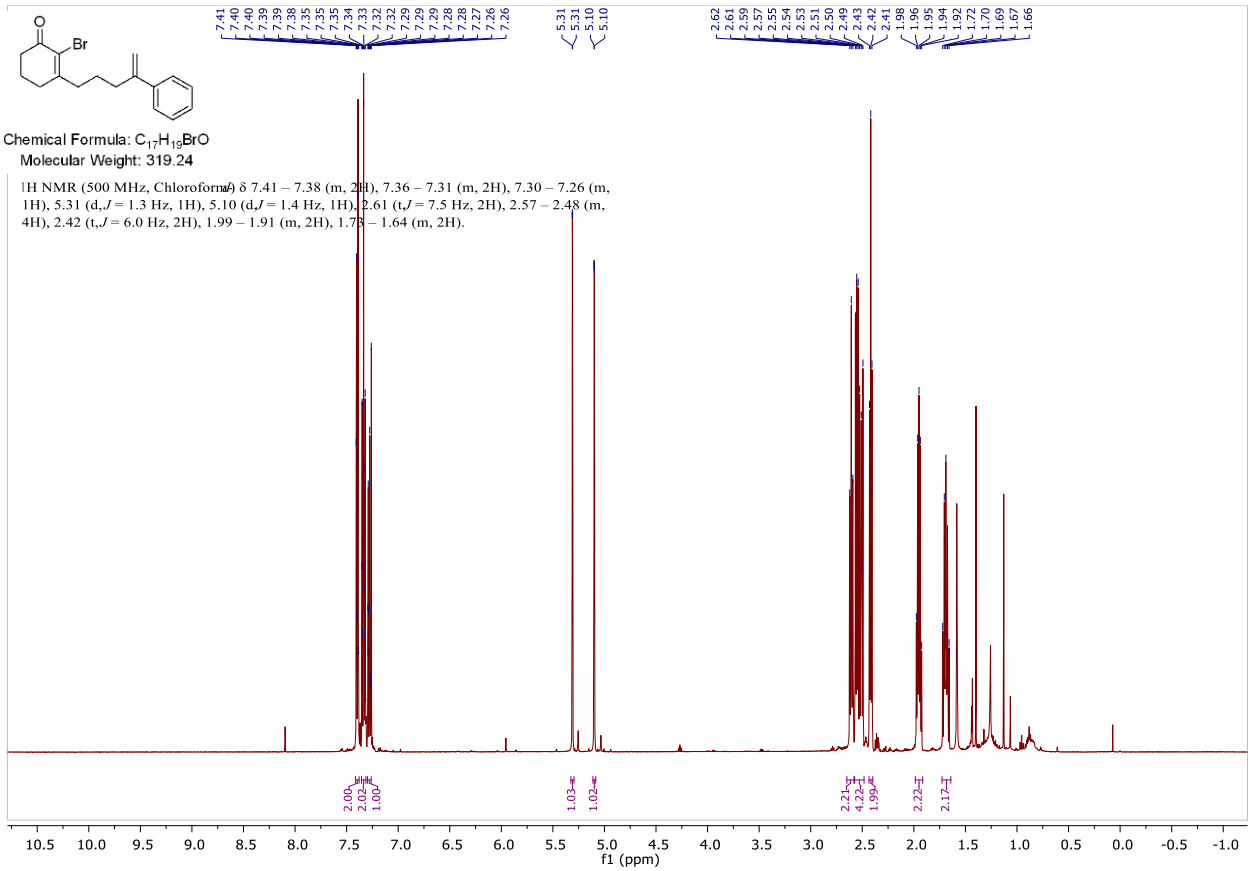

Me
I
Chemical Formula: C12H15I
Molecular Weight: 286.16
13C NMR (126 MHz, cdcl3) δ 146.40, 137.72, 137.50, 129.23, 126.13, 112.88, 35.95, 31.79, 21.24, 6.76.
146.40
137.72
137.50
129.23
126.13
112.88
77.41
77.16
76.90
35.95
31.79
21.24
6.76
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

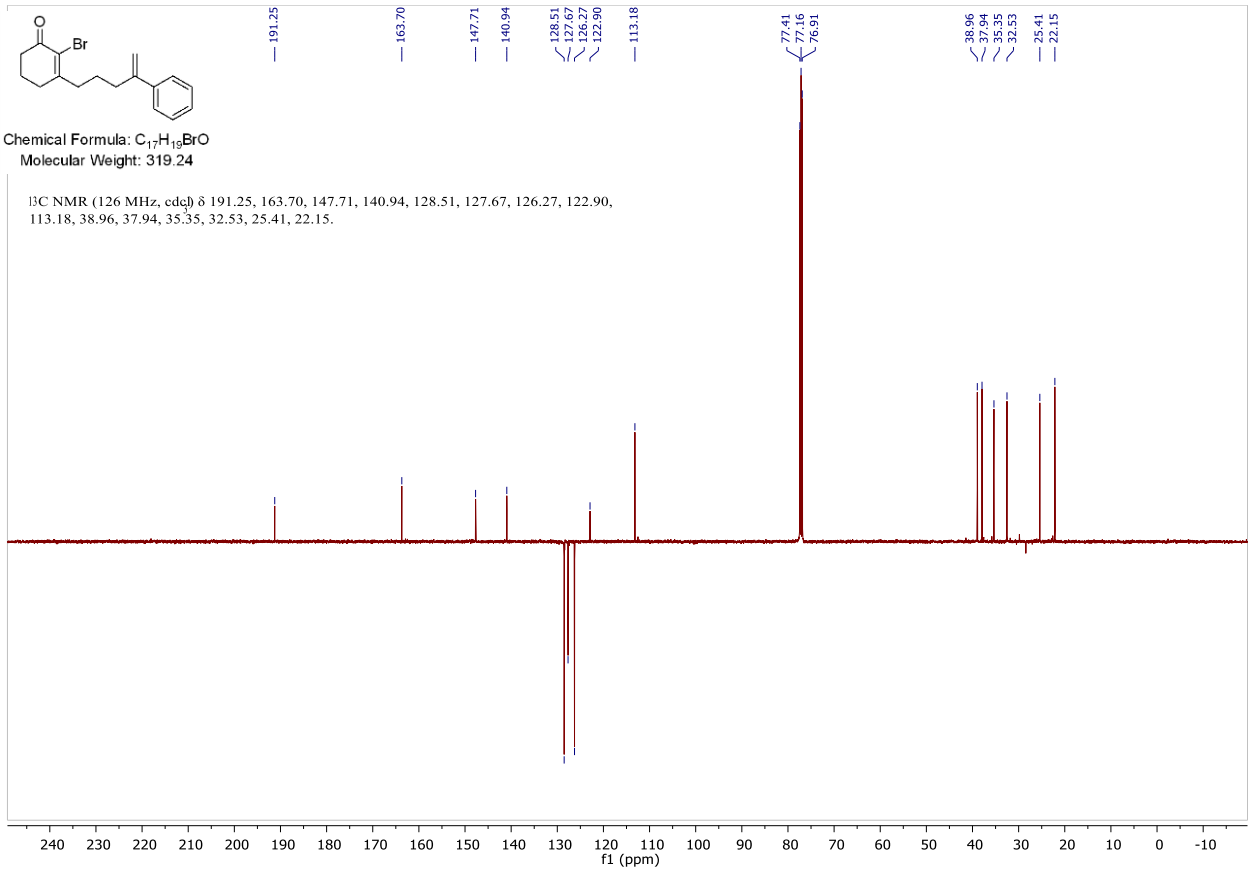

Chemical Formula: C12H15I
Molecular Weight: 286.16
1H NMR (500 MHz, Chloroform-d) δ 7.42 – 7.38 (m, 2H), 7.36 – 7.31 (m, 2H), 7.30 – 7.26 (m, 1H), 5.29 (d, J = 1.4 Hz, 1H), 5.07 (d, J = 1.4 Hz, 1H), 3.17 (t, J = 7.0 Hz, 2H), 2.54 (td, J = 7.5, 1.2 Hz, 2H), 1.86 (dt, J = 14.7, 7.1 Hz, 2H), 1.60 – 1.54 (m, 2H).
f1 (ppm)

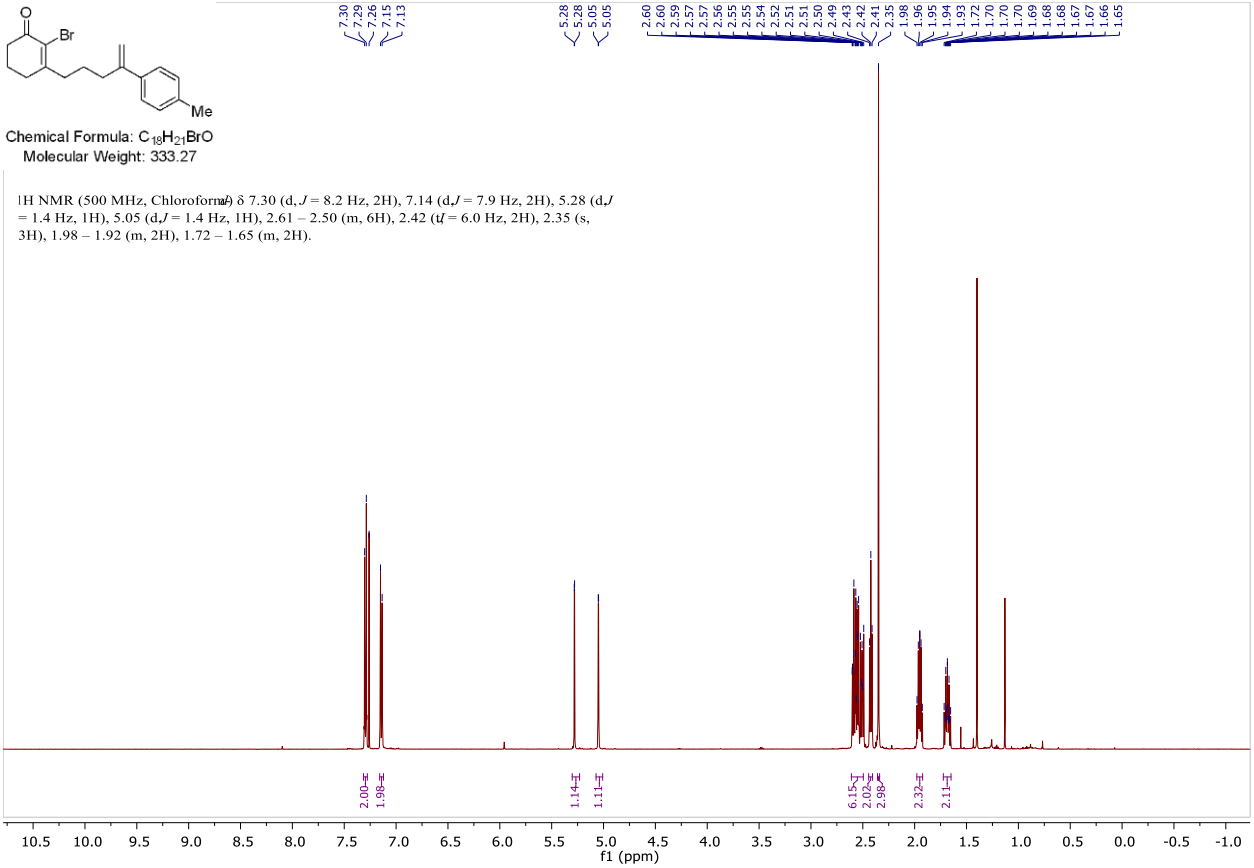

Chemical Formula: C12H15I
Molecular Weight: 286.16
13C NMR (126 MHz, cdcl3) δ 147.99, 141.12, 128.46, 127.57, 126.25, 112.84, 77.41, 77.16, 76.91, 34.34, 33.21, 29.14, 6.77.
147.99
141.12
128.46
127.57
126.25
112.84
77.41
77.16
76.91
34.34
33.21
29.14
6.77
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
I
Chemical Formula: C12H15I
Molecular Weight: 286.16
1H NMR (498 MHz, Chloroform-d) δ 7.41 – 7.37 (m, 2H), 7.36 – 7.31 (m, 2H), 7.30 – 7.26 (m, 1H), 5.33 (d, J = 1.6 Hz, 1H), 5.14 (d, J = 1.4 Hz, 1H), 3.21 (dd, J = 9.6, 4.8 Hz, 1H), 3.16 (dd, J = 9.6, 5.3 Hz, 1H), 2.64 (ddd, J = 14.2, 7.0, 1.2 Hz, 1H), 2.40 (ddd, J = 14.1, 7.1, 1.1 Hz, 1H), 1.57 – 1.46 (m, 1H), 0.96 (d, J = 6.6 Hz, 3H).
f1 (ppm)


Me
I
Chemical Formula: C12H15I
Molecular Weight: 286.16
13C NMR (126 MHz, cdcl3) δ 146.43, 140.75, 128.55, 127.71, 126.42, 114.87, 42.57, 32.62, 20.70, 17.75.
146.43
140.75
128.55
127.71
126.42
114.87
77.41
77.16
76.91
42.57
32.62
20.70
17.75
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

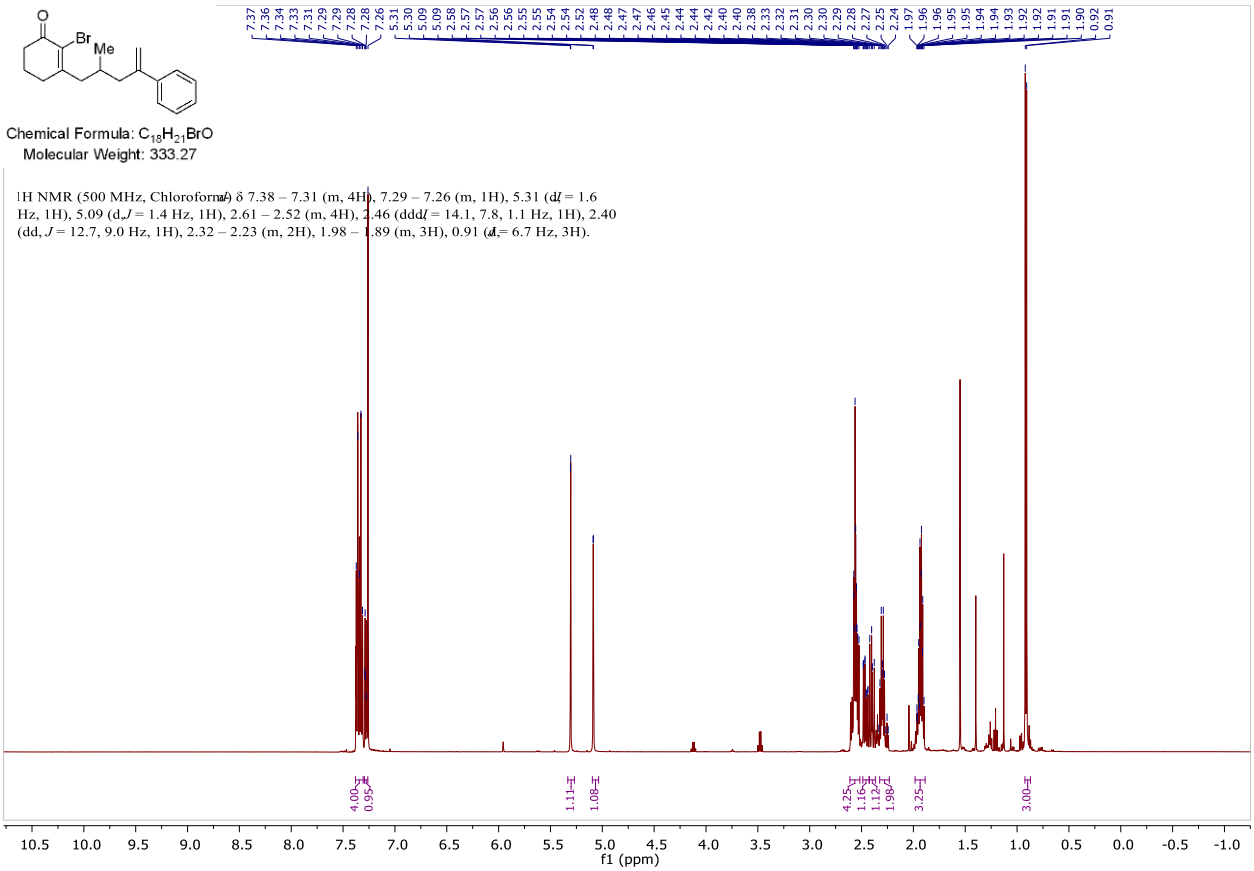

Chemical Formula: C17H19BrO
Molecular Weight: 319.24
1H NMR (500 MHz, Chloroform-d) δ 7.41 – 7.38 (m, 2H), 7.36 – 7.31 (m, 2H), 7.30 – 7.26 (m, 1H), 5.31 (d, J = 1.3 Hz, 1H), 5.10 (d, J = 1.4 Hz, 1H), 2.61 (t, J = 7.5 Hz, 2H), 2.57 – 2.48 (m, 4H), 2.42 (t, J = 6.0 Hz, 2H), 1.99 – 1.91 (m, 2H), 1.73 – 1.64 (m, 2H).
f1 (ppm)


Chemical Formula: C17H19BrO
Molecular Weight: 319.24
13C NMR (126 MHz, cdcl) δ 191.25, 163.70, 147.71, 140.94, 128.51, 127.67, 126.27, 122.90, 113.18, 38.96, 37.94, 35.35, 32.53, 25.41, 22.15.
191.25
163.70
147.71
140.94
128.51
127.67
126.27
122.90
113.18
77.41
77.16
76.91
38.96
37.94
35.35
32.53
25.41
22.15
f1 (ppm)

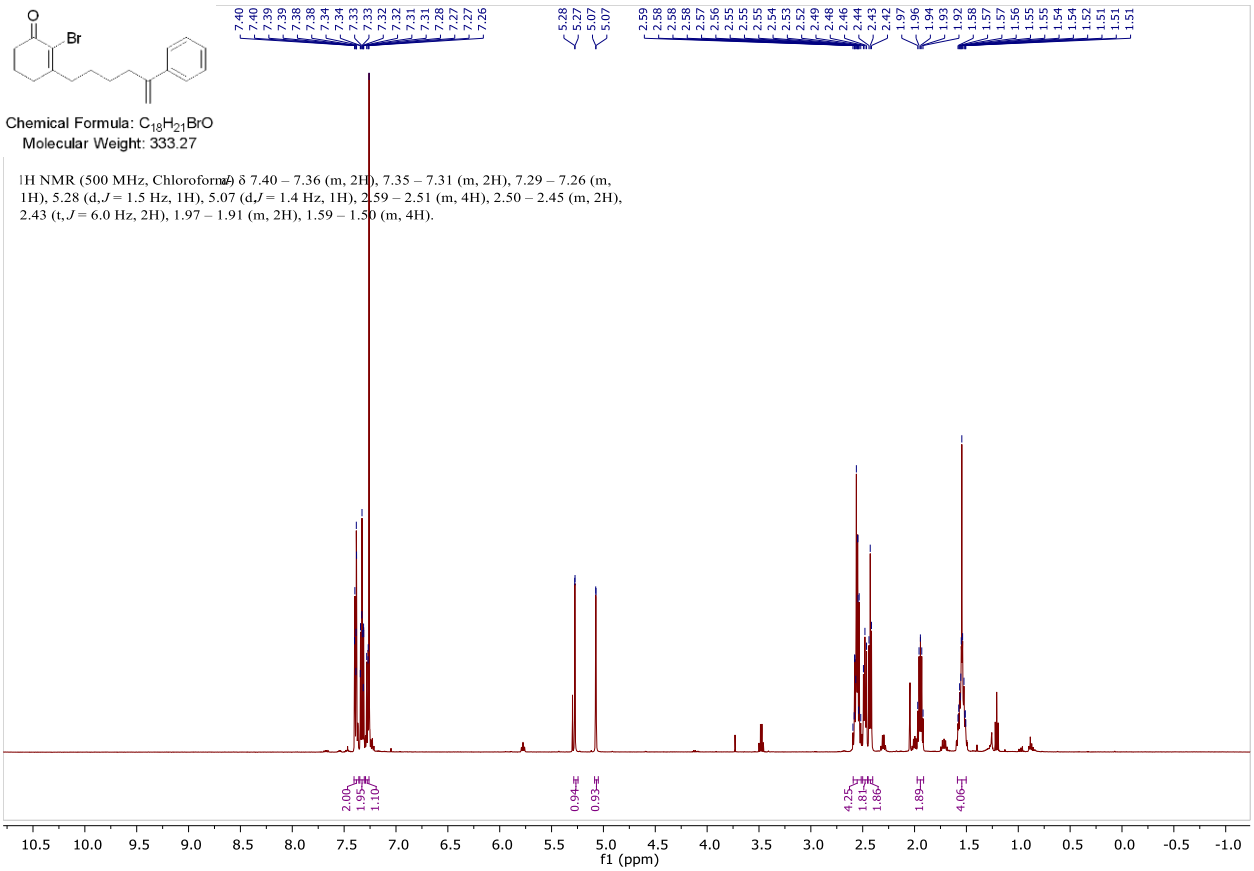

Br
Me
Chemical Formula: C18H21BrO
Molecular Weight: 333.27
1H NMR (500 MHz, Chloroform-d) δ 7.30 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 5.28 (d, J = 1.4 Hz, 1H), 5.05 (d, J = 1.4 Hz, 1H), 2.61 – 2.50 (m, 6H), 2.42 (t, J = 6.0 Hz, 2H), 2.35 (s, 3H), 1.98 – 1.92 (m, 2H), 1.72 – 1.65 (m, 2H).
f1 (ppm)

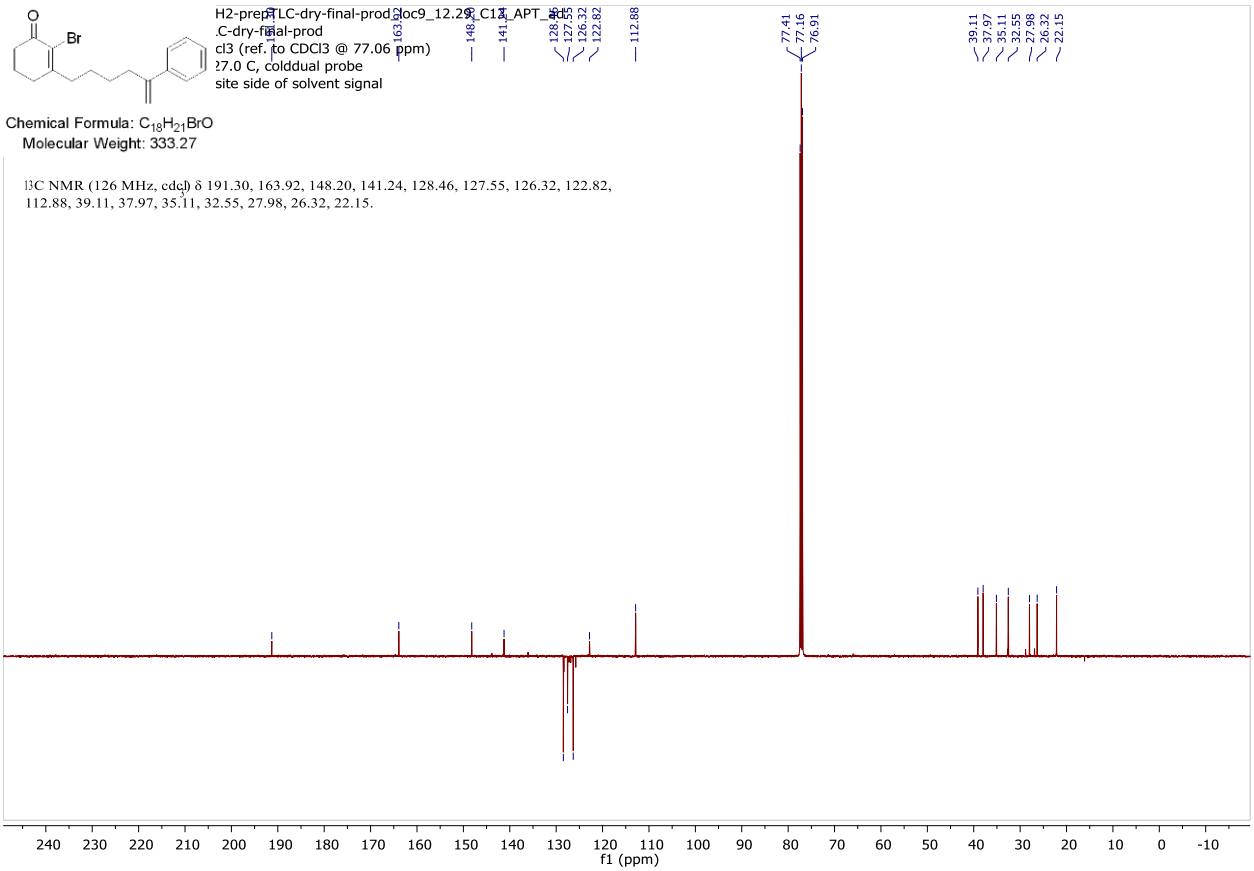
Chemical Formula: $C_{18}H_{21}BrO$
Molecular Weight: 333.27

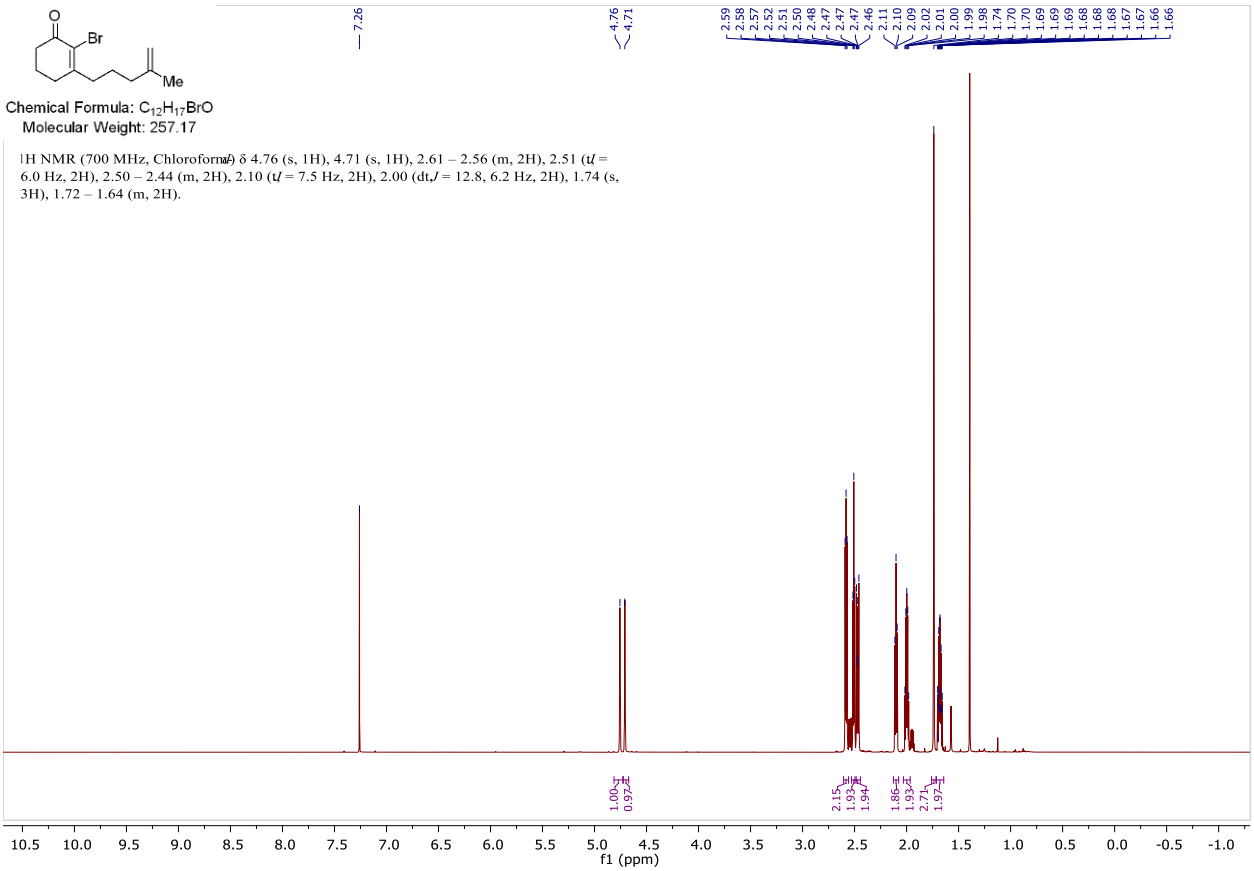
^{13}C NMR (126 MHz, $CDCl_3$) δ 191.24, 163.76, 147.50, 137.99, 137.44, 129.21, 126.13, 122.89, 112.40, 39.00, 37.95, 35.37, 32.54, 25.49, 22.16, 21.24.


Br
Me
Chemical Formula: C18H21BrO
Molecular Weight: 333.27
1H NMR (500 MHz, Chloroform-d) δ 7.38 – 7.31 (m, 4H), 7.29 – 7.26 (m, 1H), 5.31 (dt, J = 1.6 Hz, 1H), 5.09 (d, J = 1.4 Hz, 1H), 2.61 – 2.52 (m, 4H), 2.46 (ddd, J = 14.1, 7.8, 1.1 Hz, 1H), 2.40 (dd, J = 12.7, 9.0 Hz, 1H), 2.32 – 2.23 (m, 2H), 1.98 – 1.89 (m, 3H), 0.91 (d, J = 6.7 Hz, 3H).
f1 (ppm)

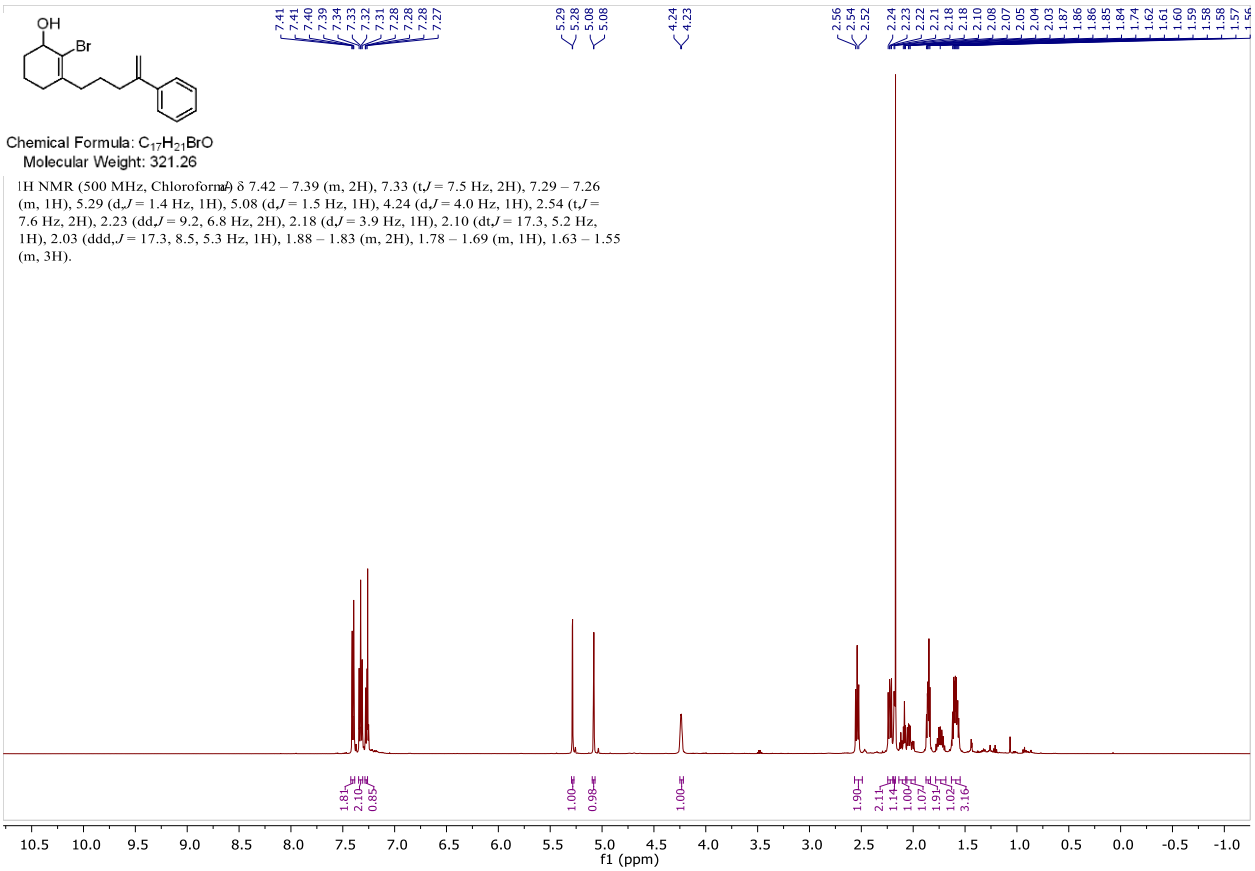

Chemical Formula: C18H21BrO
Molecular Weight: 333.27
13C NMR (126 MHz, cdcl3) δ 191.47, 163.42, 147.20, 141.22, 128.79, 127.93, 126.67, 124.35, 114.95, 46.34, 43.82, 38.38, 33.22, 30.87, 22.42, 19.96.
191.47
163.42
147.20
141.22
128.79
127.93
126.67
124.35
114.95
77.67
77.41
77.16
46.34
43.82
38.38
33.22
30.87
22.42
19.96
f1 (ppm)

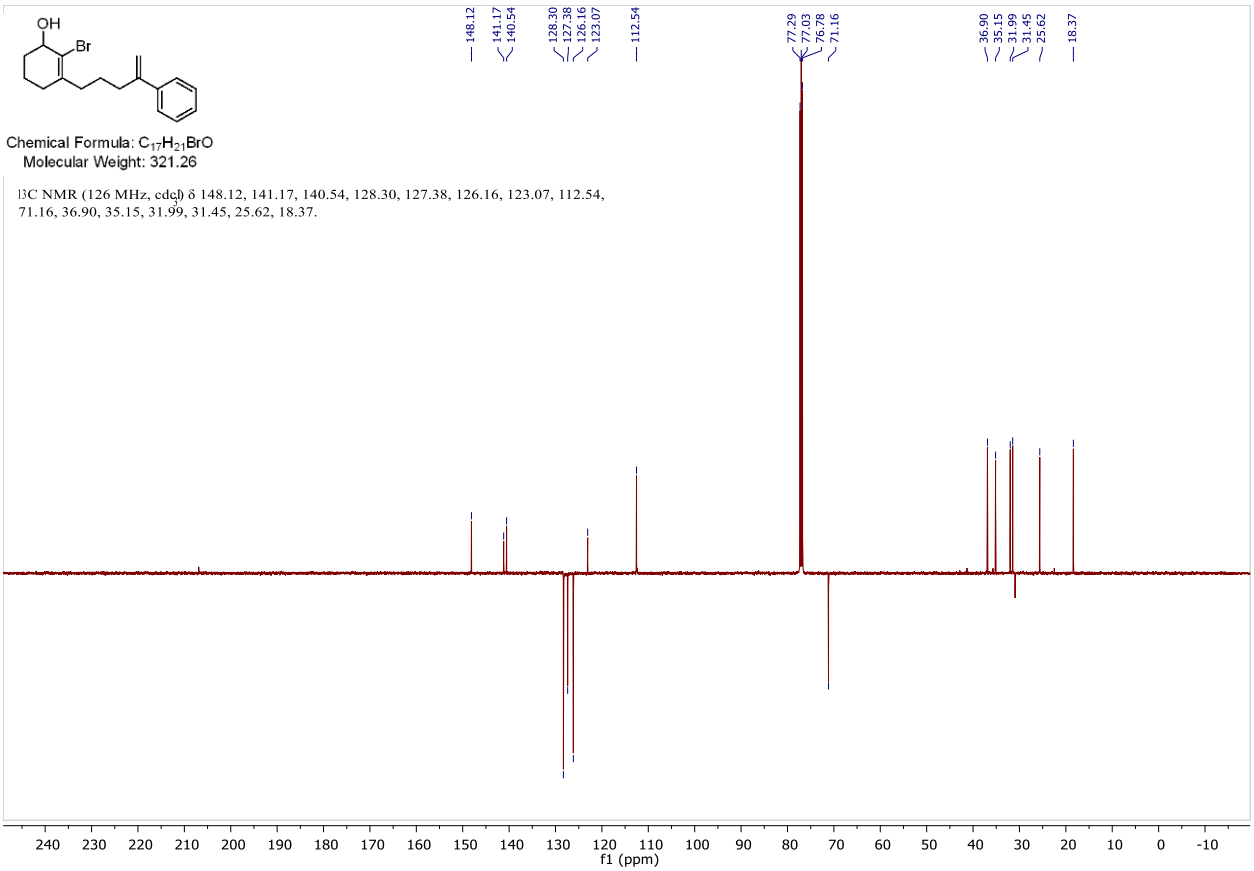

Br
O
Chemical Formula: C18H21BrO
Molecular Weight: 333.27
1H NMR (500 MHz, Chloroform-d) δ 7.40 – 7.36 (m, 2H), 7.35 – 7.31 (m, 2H), 7.29 – 7.26 (m, 1H), 5.28 (d, J = 1.5 Hz, 1H), 5.07 (d, J = 1.4 Hz, 1H), 2.59 – 2.51 (m, 4H), 2.50 – 2.45 (m, 2H), 2.43 (t, J = 6.0 Hz, 2H), 1.97 – 1.91 (m, 2H), 1.59 – 1.50 (m, 4H).
f1 (ppm)

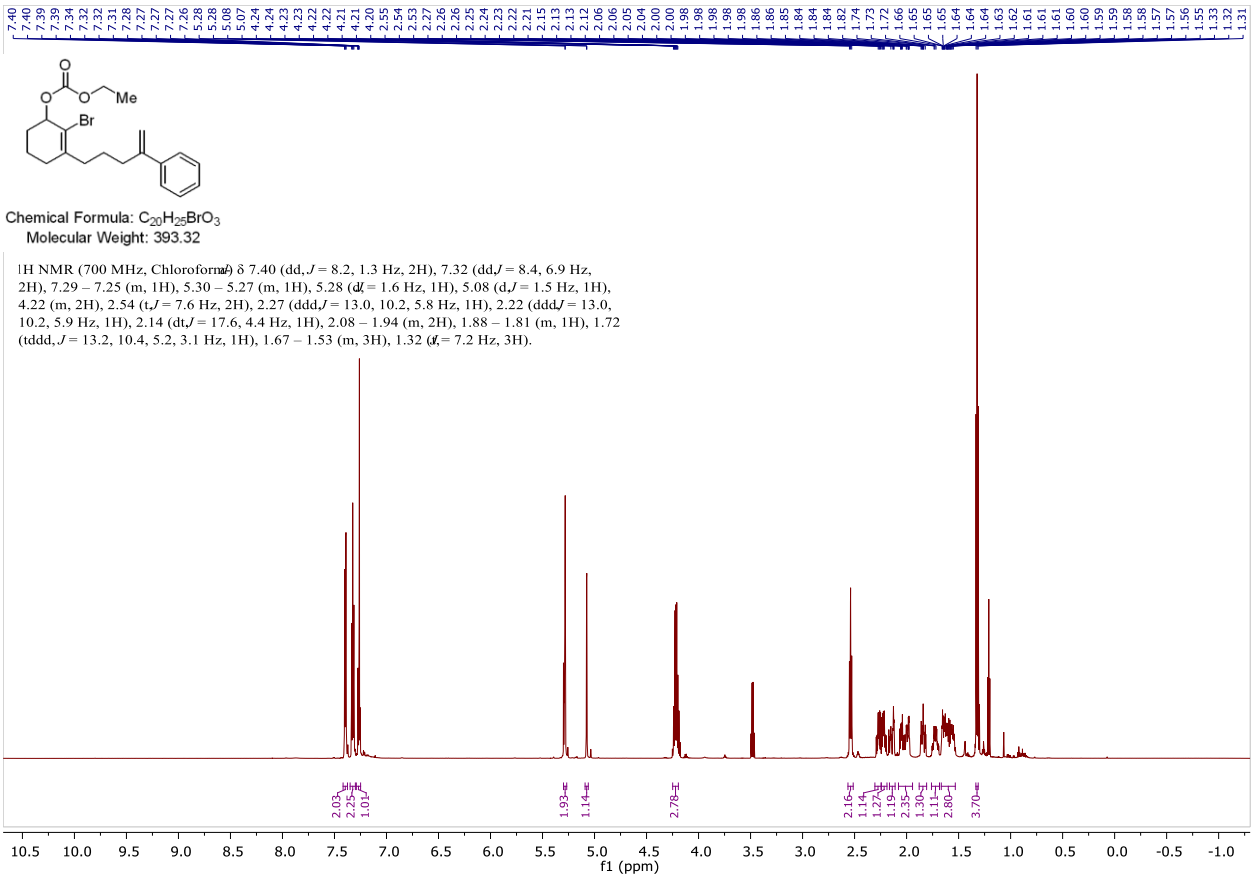

Br
Chemical Formula: C18H21BrO
Molecular Weight: 333.27
13C NMR (126 MHz, cdcl) δ 191.30, 163.92, 148.20, 141.24, 128.46, 127.55, 126.32, 122.82, 112.88, 39.11, 37.97, 35.11, 32.55, 27.98, 26.32, 22.15.
H2-prep-TLC-dry-final-prod.2.doc9_12.29_C13_APT_ed
.C-dry-final-prod
cl3 (ref. to CDCl3 @ 77.06 ppm)
27.0 C, colddual probe
site side of solvent signal
163.92
148.20
141.24
128.46
127.55
126.32
122.82
112.88
77.41
77.16
76.91
39.11
37.97
35.11
32.55
27.98
26.32
22.15
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Br
Me
Chemical Formula: C12H17BrO
Molecular Weight: 257.17
1H NMR (700 MHz, Chloroform-d) δ 4.76 (s, 1H), 4.71 (s, 1H), 2.61 – 2.56 (m, 2H), 2.51 (t, J = 6.0 Hz, 2H), 2.50 – 2.44 (m, 2H), 2.10 (t, J = 7.5 Hz, 2H), 2.00 (dt, J = 12.8, 6.2 Hz, 2H), 1.74 (s, 3H), 1.72 – 1.64 (m, 2H).
7.26
4.76
4.71
2.59
2.58
2.57
2.52
2.51
2.50
2.48
2.47
2.47
2.47
2.46
2.11
2.10
2.09
2.02
2.01
2.00
1.99
1.98
1.74
1.70
1.70
1.69
1.69
1.69
1.68
1.68
1.68
1.67
1.66
1.66
1.00
0.97
2.15
1.93
1.94
1.86
1.93
2.71
1.97
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


O
Br
Me
Chemical Formula: C12H17BrO
Molecular Weight: 257.17
13C NMR (176 MHz, cdcl3) δ 191.28, 163.90, 144.89, 122.83, 110.82, 39.03, 37.97, 37.76, 32.67, 24.76, 22.42, 22.20.
191.28
163.90
144.89
122.83
110.82
77.34
77.16
76.98
39.03
37.97
37.76
32.67
24.76
22.42
22.20
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

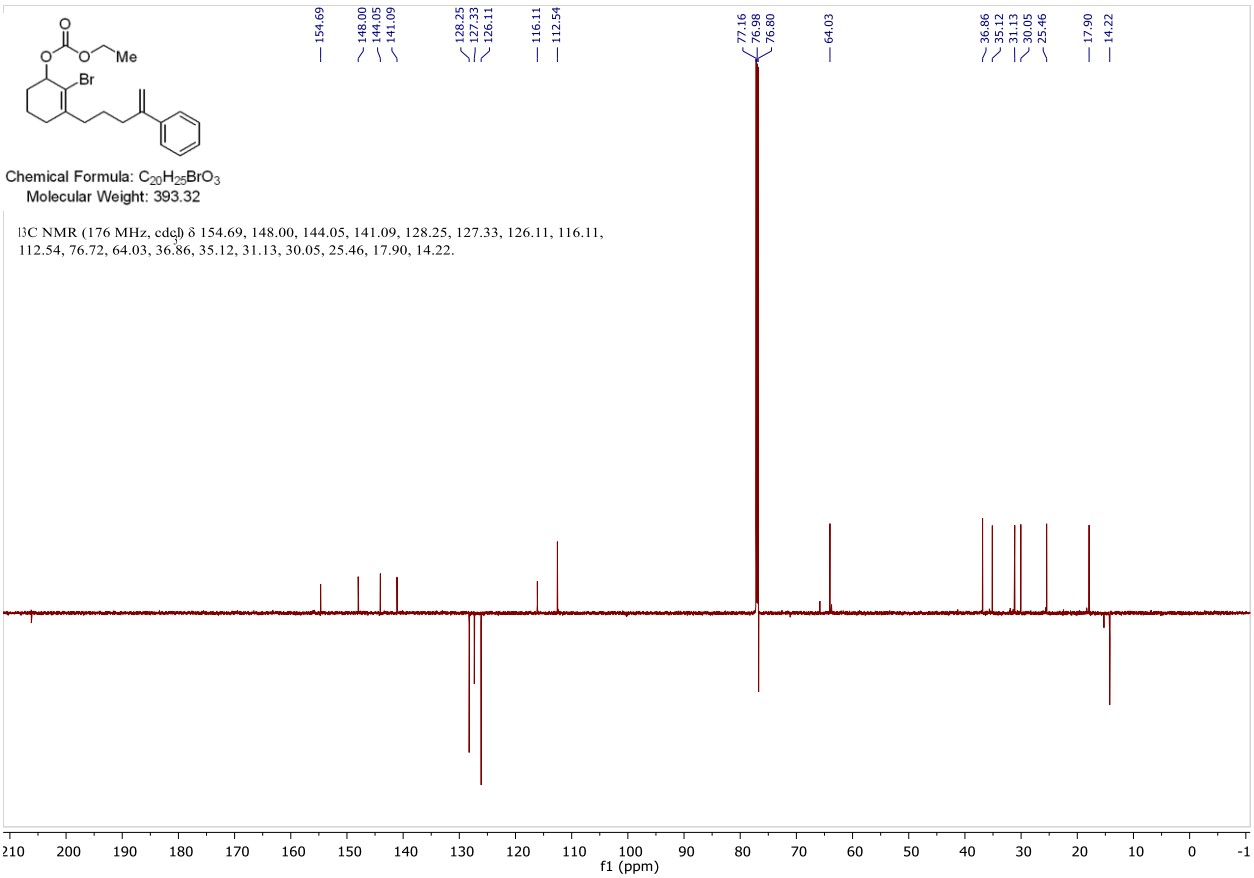

OH
Br
Chemical Formula: C17H21BrO
Molecular Weight: 321.26
1H NMR (500 MHz, Chloroform-d) δ 7.42 – 7.39 (m, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.29 – 7.26 (m, 1H), 5.29 (d, J = 1.4 Hz, 1H), 5.08 (d, J = 1.5 Hz, 1H), 4.24 (d, J = 4.0 Hz, 1H), 2.54 (t, J = 7.6 Hz, 2H), 2.23 (dd, J = 9.2, 6.8 Hz, 2H), 2.18 (d, J = 3.9 Hz, 1H), 2.10 (dt, J = 17.3, 5.2 Hz, 1H), 2.03 (ddd, J = 17.3, 8.5, 5.3 Hz, 1H), 1.88 – 1.83 (m, 2H), 1.78 – 1.69 (m, 1H), 1.63 – 1.55 (m, 3H).
f1 (ppm)


OH
Br
Chemical Formula: C17H21BrO
Molecular Weight: 321.26
13C NMR (126 MHz, cdcl) δ 148.12, 141.17, 140.54, 128.30, 127.38, 126.16, 123.07, 112.54, 71.16, 36.90, 35.15, 31.99, 31.45, 25.62, 18.37.
148.12
141.17
140.54
128.30
127.38
126.16
123.07
112.54
77.29
77.03
76.78
71.16
36.90
35.15
31.99
31.45
25.62
18.37
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



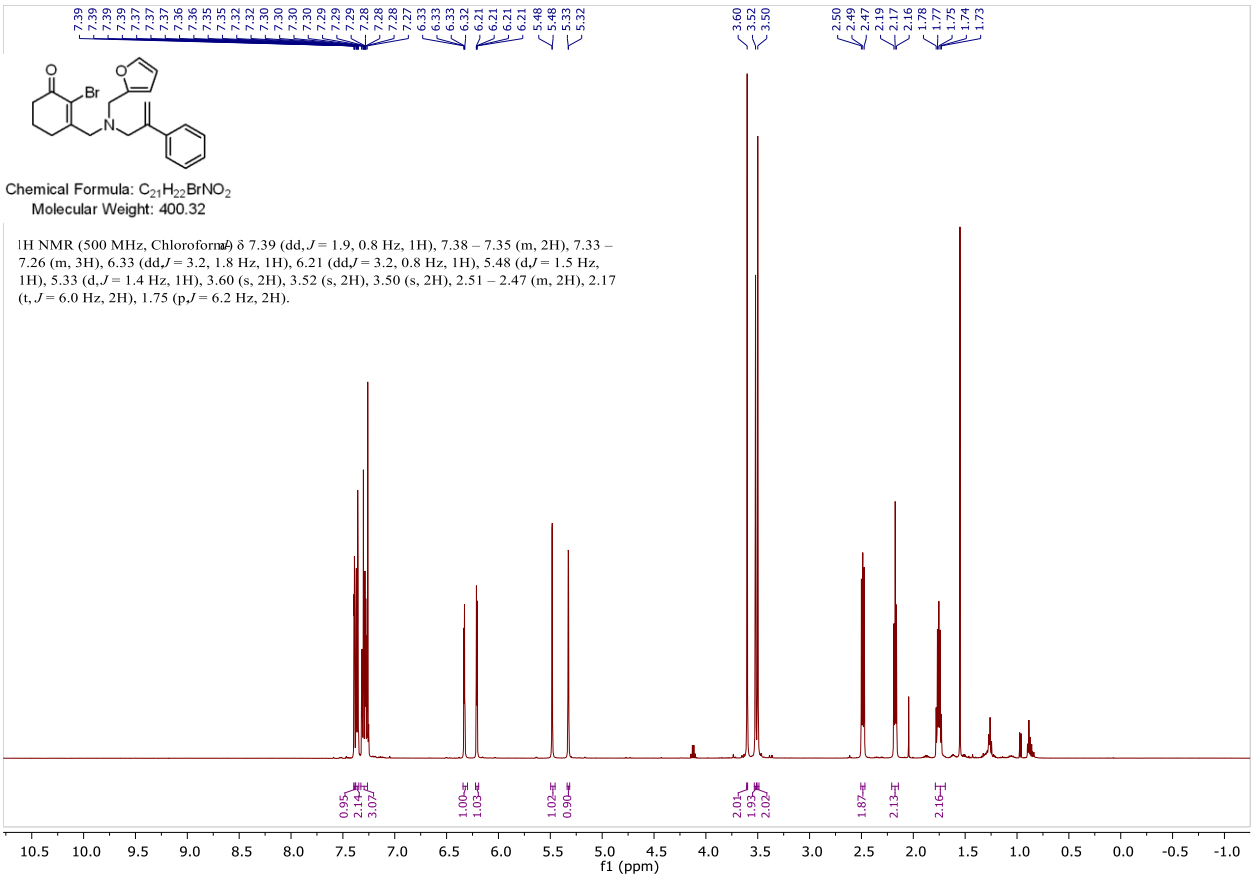
Chemical Formula: $C_{20}H_{25}BrO_3$
Molecular Weight: 393.32

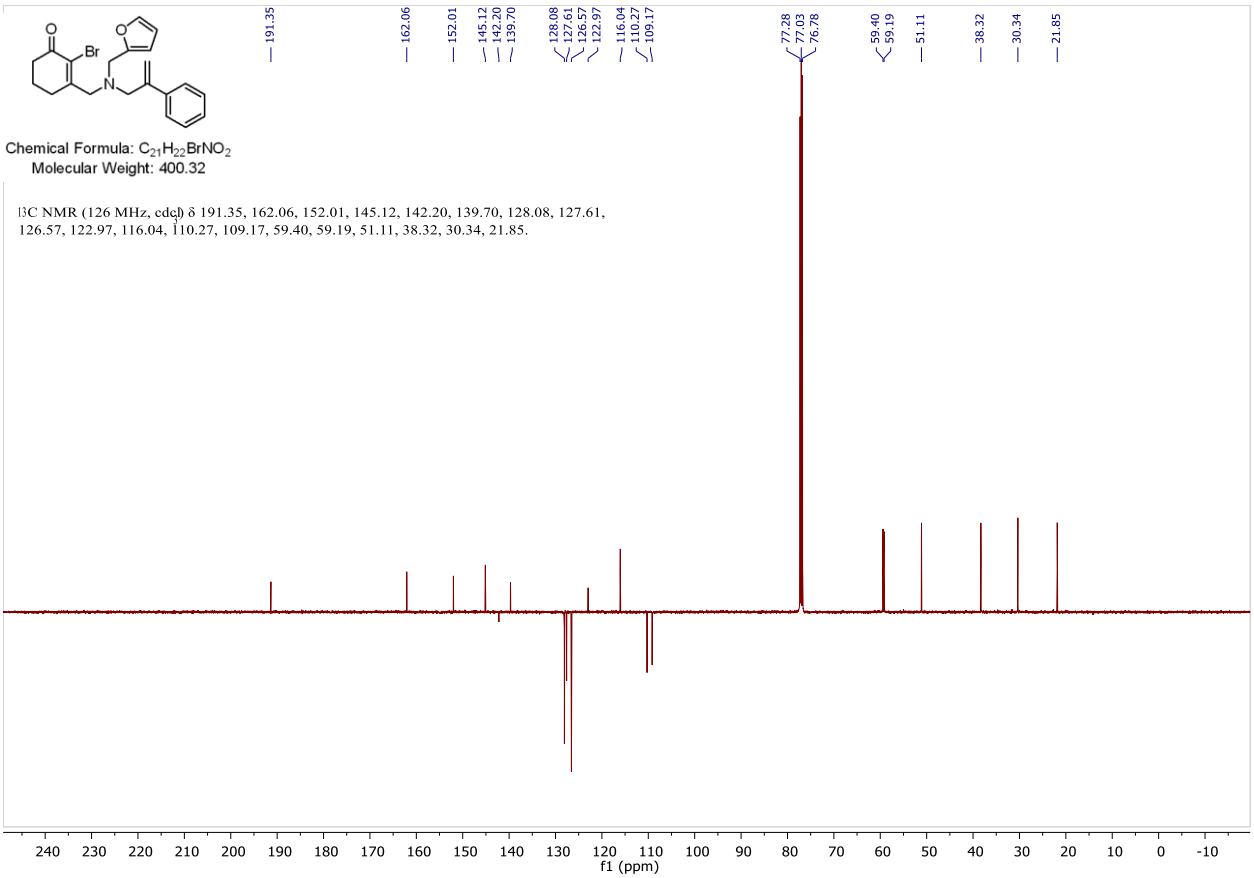
^{1}H NMR (700 MHz, Chloroform-d) δ 7.40 (dd, J = 8.2, 1.3 Hz, 2H), 7.32 (dd, J = 8.4, 6.9 Hz, 2H), 7.29 – 7.25 (m, 1H), 5.30 – 5.27 (m, 1H), 5.28 (d, J = 1.6 Hz, 1H), 5.08 (d, J = 1.5 Hz, 1H), 4.22 (m, 2H), 2.54 (t, J = 7.6 Hz, 2H), 2.27 (ddd, J = 13.0, 10.2, 5.8 Hz, 1H), 2.22 (ddd, J = 13.0, 10.2, 5.9 Hz, 1H), 2.14 (dt, J = 17.6, 4.4 Hz, 1H), 2.08 – 1.94 (m, 2H), 1.88 – 1.81 (m, 1H), 1.72 (tddd, J = 13.2, 10.4, 5.2, 3.1 Hz, 1H), 1.67 – 1.53 (m, 3H), 1.32 (J = 7.2 Hz, 3H).

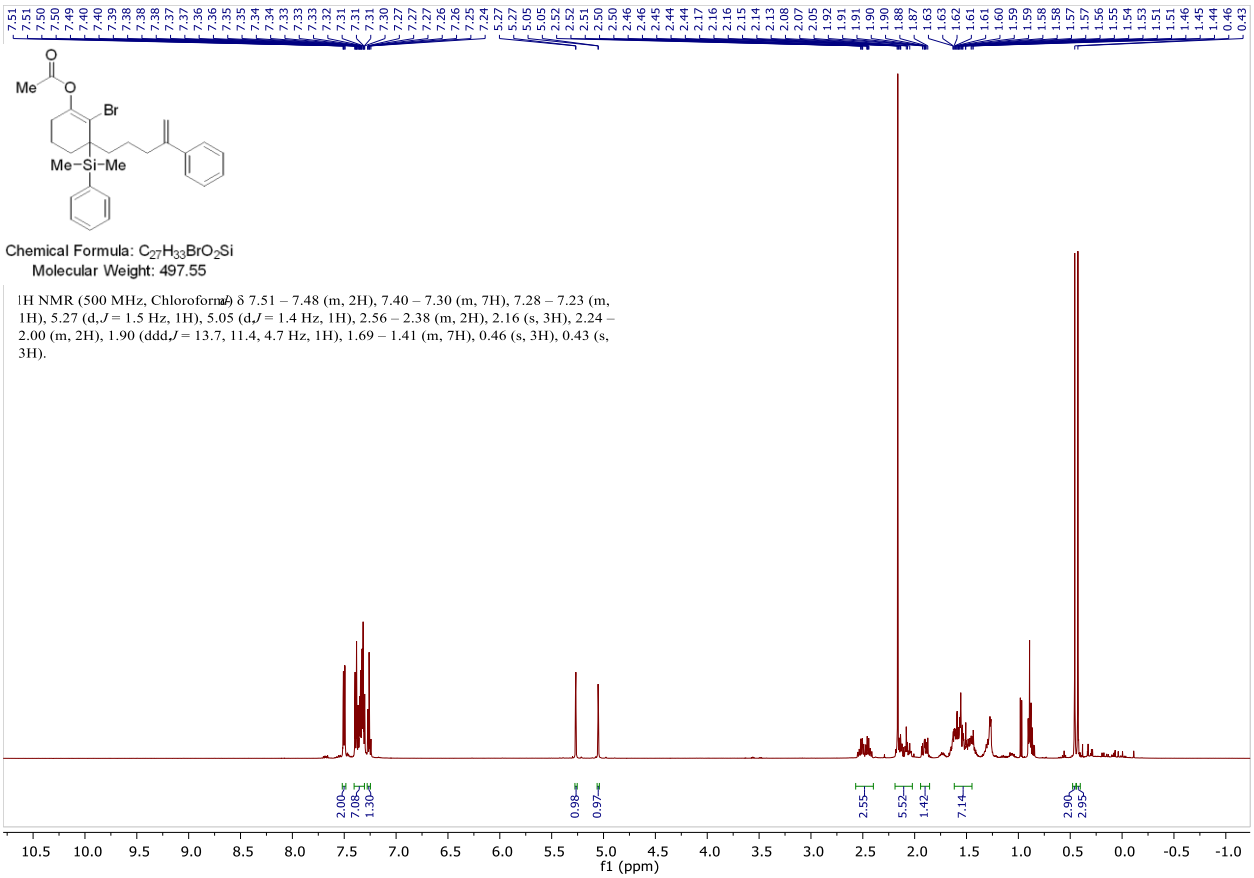


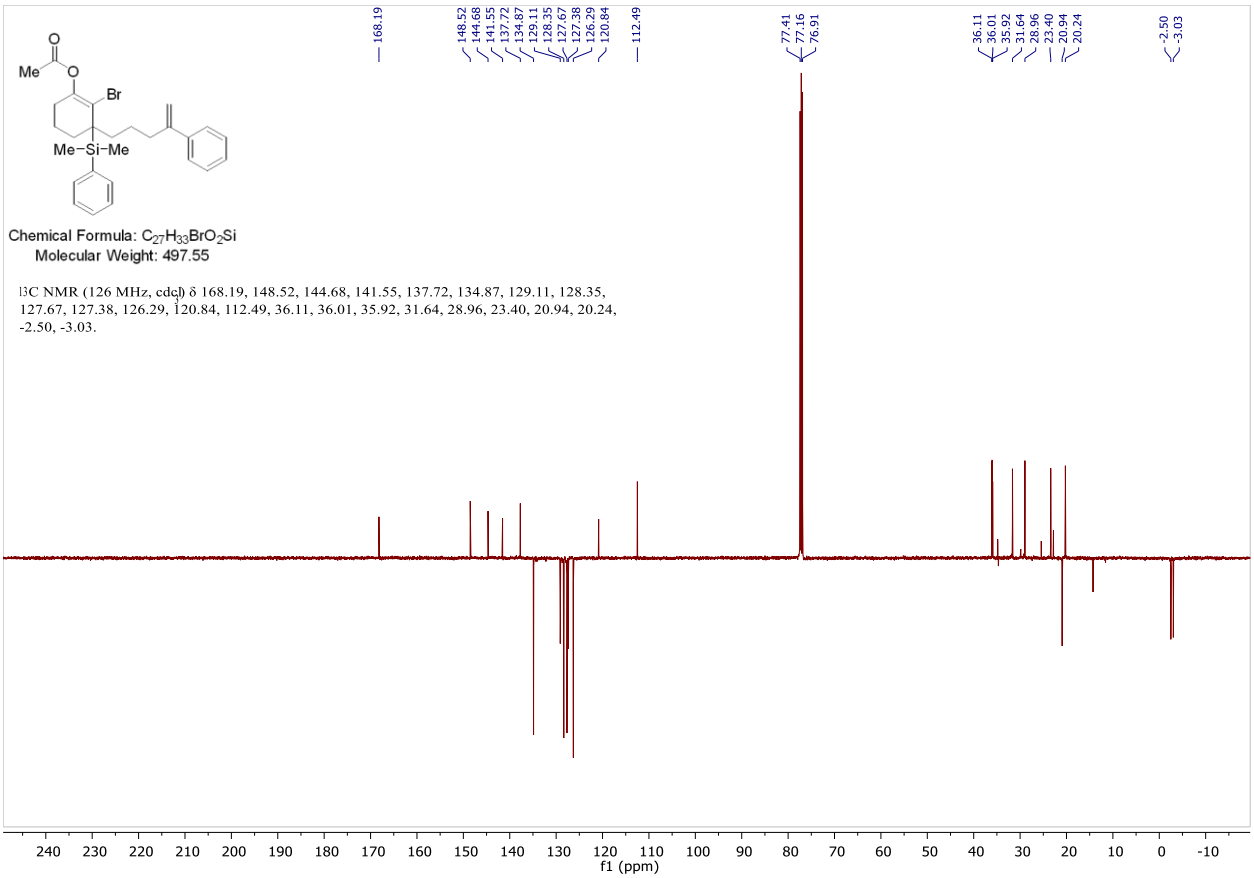
Chemical Formula: $C_{20}H_{25}BrO_3$
Molecular Weight: 393.32

^{13}C NMR (176 MHz, cdcl) δ 154.69, 148.00, 144.05, 141.09, 128.25, 127.33, 126.11, 116.11, 112.54, 76.72, 64.03, 36.86, 35.12, 31.13, 30.05, 25.46, 17.90, 14.22.


Chemical Formula: $C_{21}H_{22}BrNO_2$
Molecular Weight: 400.32
^{1}H NMR (500 MHz, Chloroform-d) δ 7.39 (dd, J = 1.9, 0.8 Hz, 1H), 7.38 – 7.35 (m, 2H), 7.33 – 7.26 (m, 3H), 6.33 (dd, J = 3.2, 1.8 Hz, 1H), 6.21 (dd, J = 3.2, 0.8 Hz, 1H), 5.48 (d, J = 1.5 Hz, 1H), 5.33 (d, J = 1.4 Hz, 1H), 3.60 (s, 2H), 3.52 (s, 2H), 3.50 (s, 2H), 2.51 – 2.47 (m, 2H), 2.17 (t, J = 6.0 Hz, 2H), 1.75 (p, J = 6.2 Hz, 2H).
f1 (ppm)

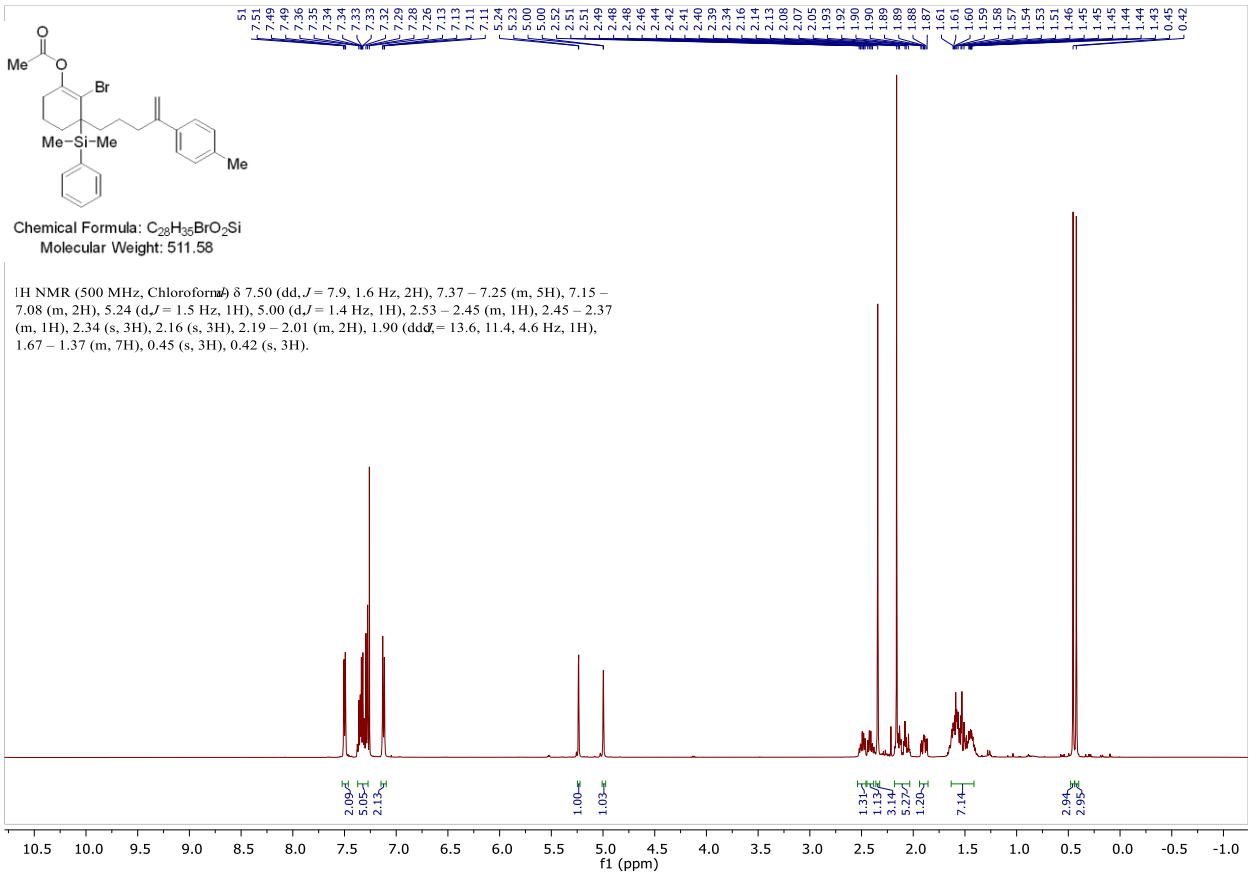

Chemical Formula: $C_{21}H_{22}BrNO_2$
Molecular Weight: 400.32
13C NMR (126 MHz, cdcl3) δ 191.35, 162.06, 152.01, 145.12, 142.20, 139.70, 128.08, 127.61, 126.57, 122.97, 116.04, 110.27, 109.17, 59.40, 59.19, 51.11, 38.32, 30.34, 21.85.
191.35
162.06
152.01
145.12
142.20
139.70
128.08
127.61
126.57
122.97
116.04
110.27
109.17
77.28
77.03
76.78
59.40
59.19
51.11
38.32
30.34
21.85
f1 (ppm)

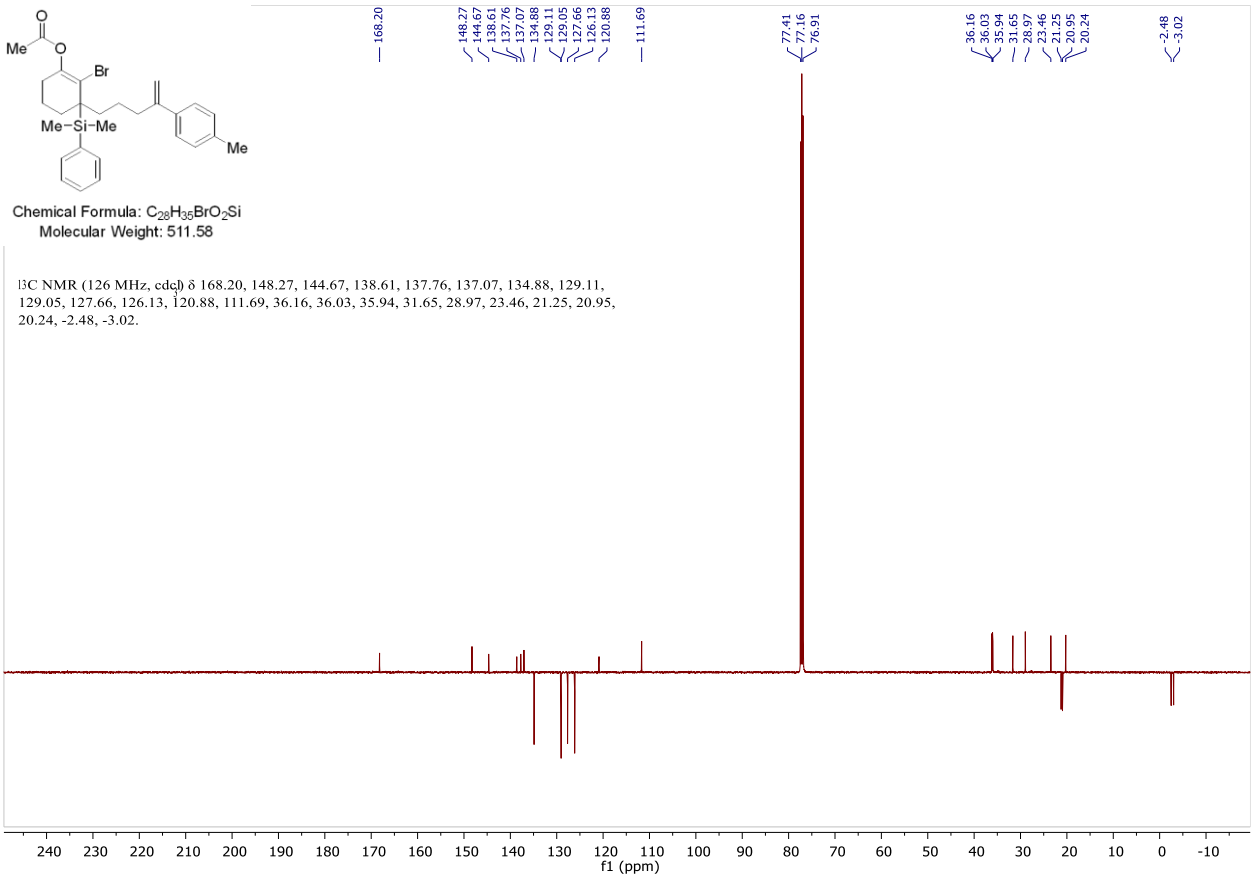

Me
O
O
Br
Me–Si–Me
Chemical Formula: C27H33BrO2Si
Molecular Weight: 497.55
1H NMR (500 MHz, Chloroform-d) δ 7.51 – 7.48 (m, 2H), 7.40 – 7.30 (m, 7H), 7.28 – 7.23 (m, 1H), 5.27 (d, J = 1.5 Hz, 1H), 5.05 (d, J = 1.4 Hz, 1H), 2.56 – 2.38 (m, 2H), 2.16 (s, 3H), 2.24 – 2.00 (m, 2H), 1.90 (ddd, J = 13.7, 11.4, 4.7 Hz, 1H), 1.69 – 1.41 (m, 7H), 0.46 (s, 3H), 0.43 (s, 3H).
2.00
7.08
1.30
0.98
0.97
2.55
5.52
1.42
7.14
2.90
2.95
f1 (ppm)



Chemical Formula: $C_{27}H_{33}BrO_2Si$
Molecular Weight: 497.55

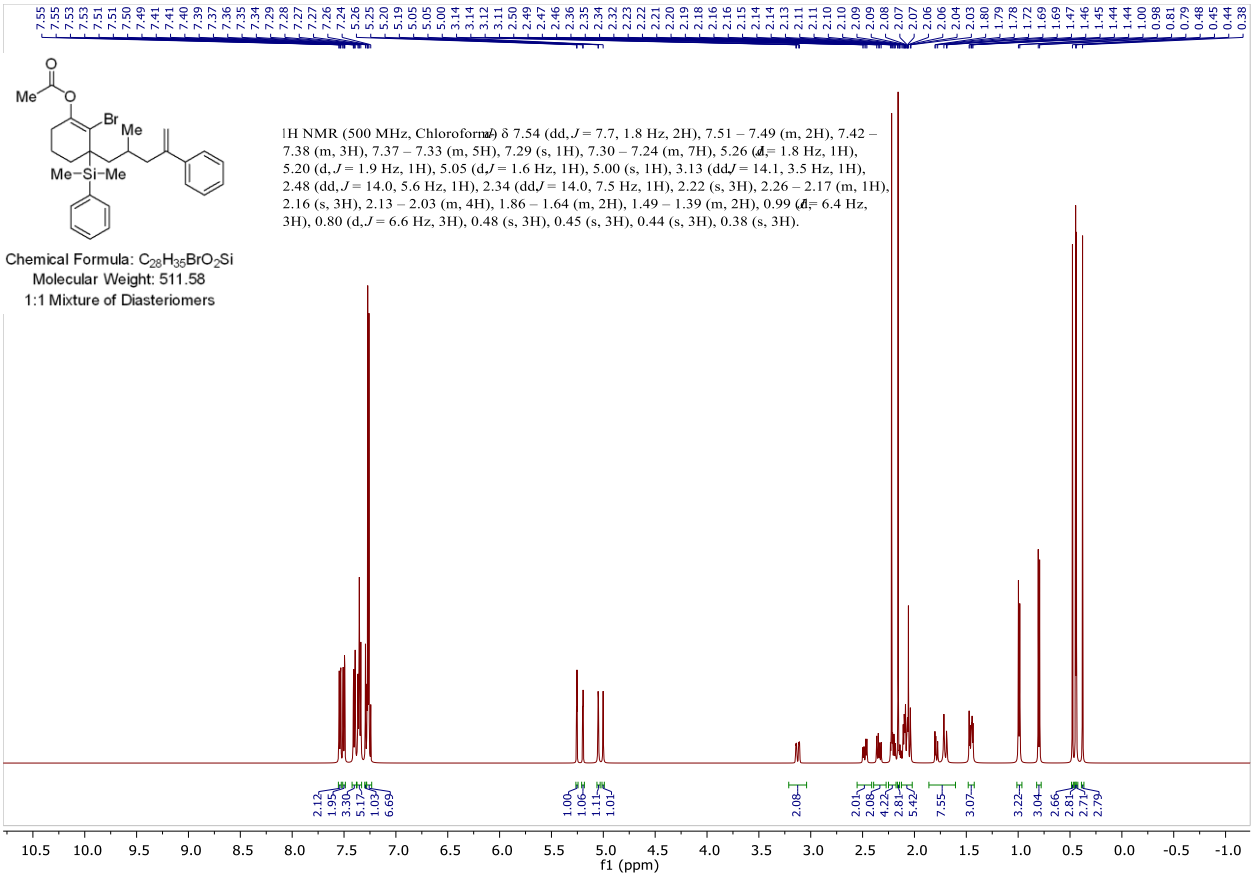
^{13}C NMR (126 MHz, cdcl) δ 168.19, 148.52, 144.68, 141.55, 137.72, 134.87, 129.11, 128.35, 127.67, 127.38, 126.29, 120.84, 112.49, 36.11, 36.01, 35.92, 31.64, 28.96, 23.40, 20.94, 20.24, -2.50, -3.03.

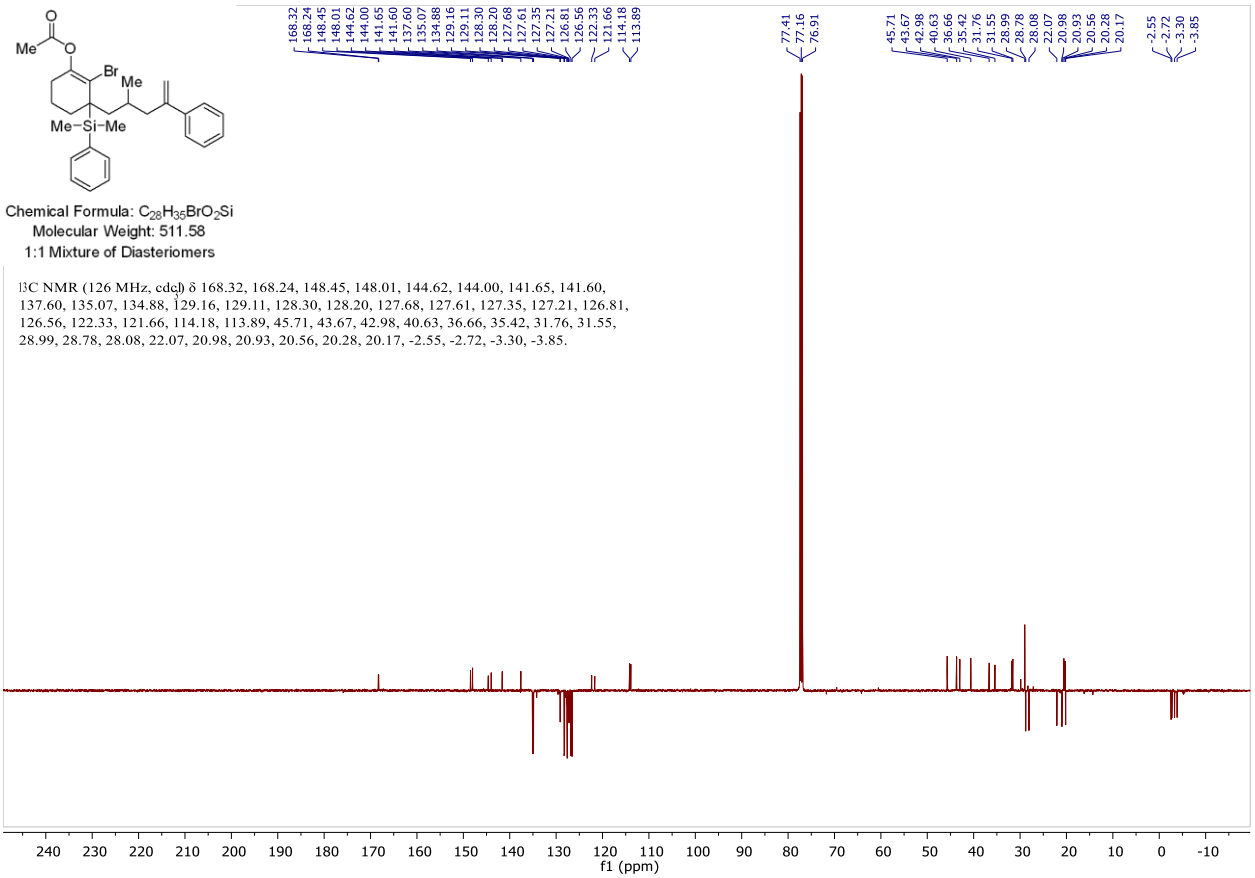

Me
O
O
Br
Me–Si–Me
Me
Chemical Formula: C28H35BrO2Si
Molecular Weight: 511.58
1H NMR (500 MHz, Chloroform-d) δ 7.50 (dd, J = 7.9, 1.6 Hz, 2H), 7.37 – 7.25 (m, 5H), 7.15 – 7.08 (m, 2H), 5.24 (d, J = 1.5 Hz, 1H), 5.00 (d, J = 1.4 Hz, 1H), 2.53 – 2.45 (m, 1H), 2.45 – 2.37 (m, 1H), 2.34 (s, 3H), 2.16 (s, 3H), 2.19 – 2.01 (m, 2H), 1.90 (ddd, J = 13.6, 11.4, 4.6 Hz, 1H), 1.67 – 1.37 (m, 7H), 0.45 (s, 3H), 0.42 (s, 3H).
2.09
5.05
2.13
1.00
1.03
1.31
1.13
3.14
5.27
1.20
7.14
2.94
2.95
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)



Chemical Formula: $C_{28}H_{35}BrO_2Si$
Molecular Weight: 511.58

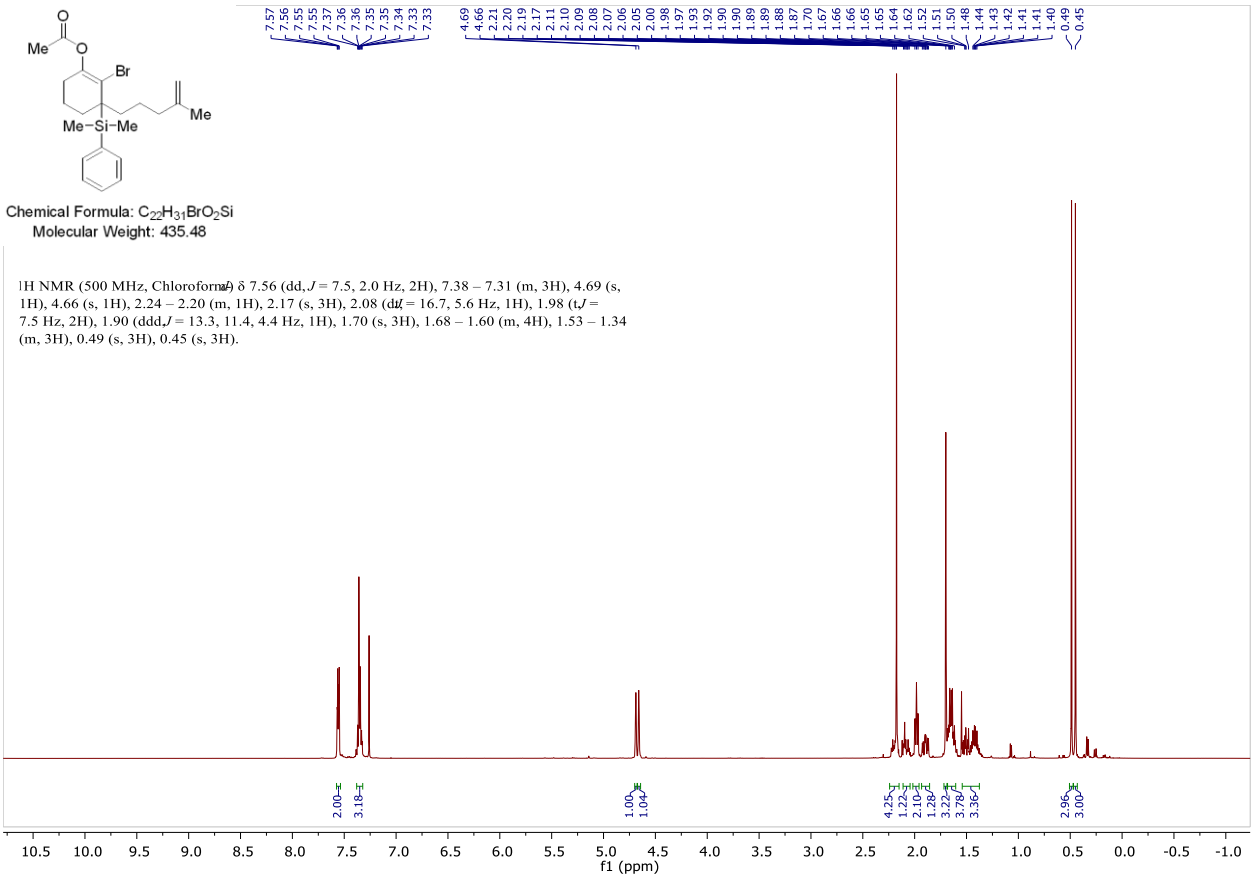
^{13}C NMR (126 MHz, cdcl) δ 168.20, 148.27, 144.67, 138.61, 137.76, 137.07, 134.88, 129.11, 129.05, 127.66, 126.13, 120.88, 111.69, 36.16, 36.03, 35.94, 31.65, 28.97, 23.46, 21.25, 20.95, 20.24, -2.48, -3.02.

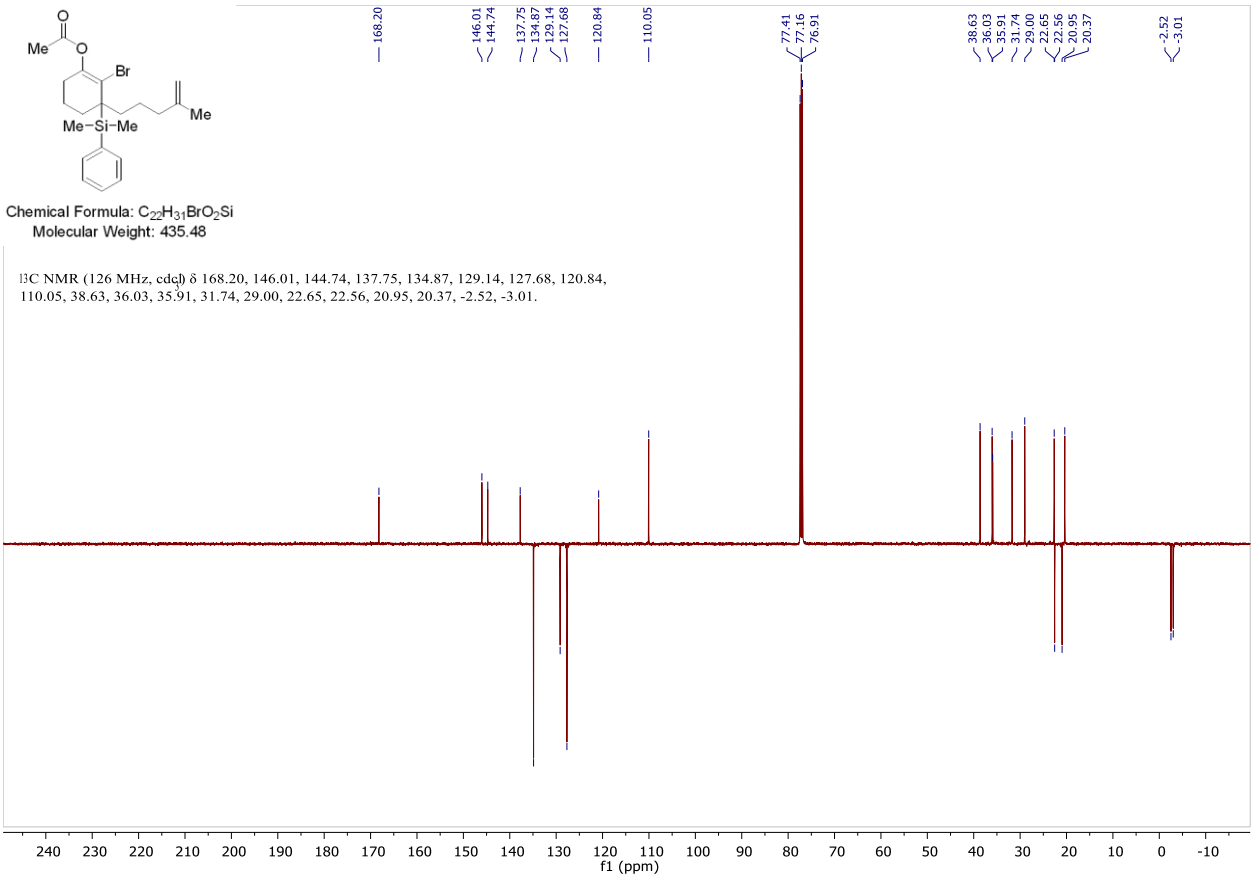

Me
O
O
Br
Me
Me–Si–Me
Chemical Formula: C28H35BrO2Si
Molecular Weight: 511.58
1:1 Mixture of Diasteriomers
1H NMR (500 MHz, Chloroform-d) δ 7.54 (dd, J = 7.7, 1.8 Hz, 2H), 7.51 – 7.49 (m, 2H), 7.42 – 7.38 (m, 3H), 7.37 – 7.33 (m, 5H), 7.29 (s, 1H), 7.30 – 7.24 (m, 7H), 5.26 (d, J = 1.8 Hz, 1H), 5.20 (d, J = 1.9 Hz, 1H), 5.05 (d, J = 1.6 Hz, 1H), 5.00 (s, 1H), 3.13 (dd, J = 14.1, 3.5 Hz, 1H), 2.48 (dd, J = 14.0, 5.6 Hz, 1H), 2.34 (dd, J = 14.0, 7.5 Hz, 1H), 2.22 (s, 3H), 2.26 – 2.17 (m, 1H), 2.16 (s, 3H), 2.13 – 2.03 (m, 4H), 1.86 – 1.64 (m, 2H), 1.49 – 1.39 (m, 2H), 0.99 (d, J = 6.4 Hz, 3H), 0.80 (d, J = 6.6 Hz, 3H), 0.48 (s, 3H), 0.45 (s, 3H), 0.44 (s, 3H), 0.38 (s, 3H).
f1 (ppm)

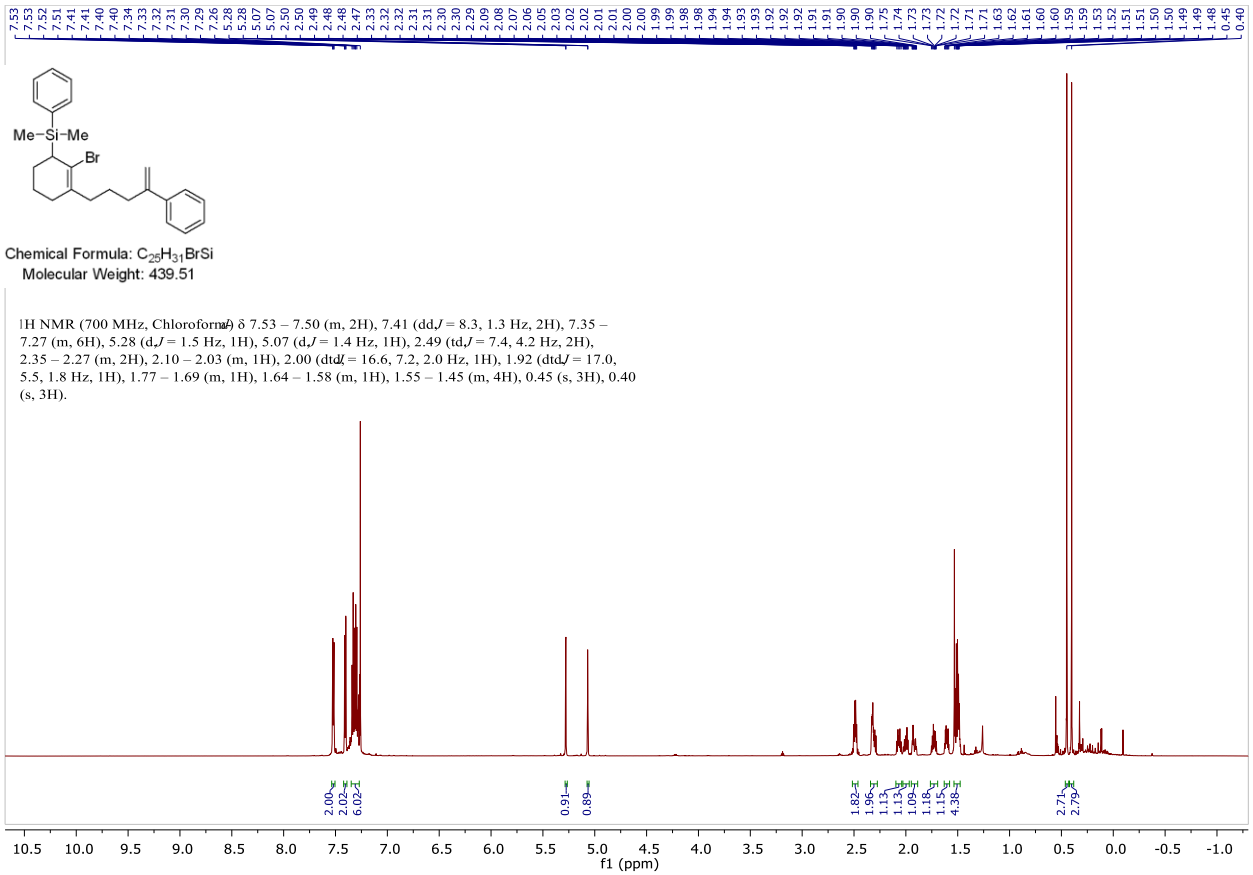


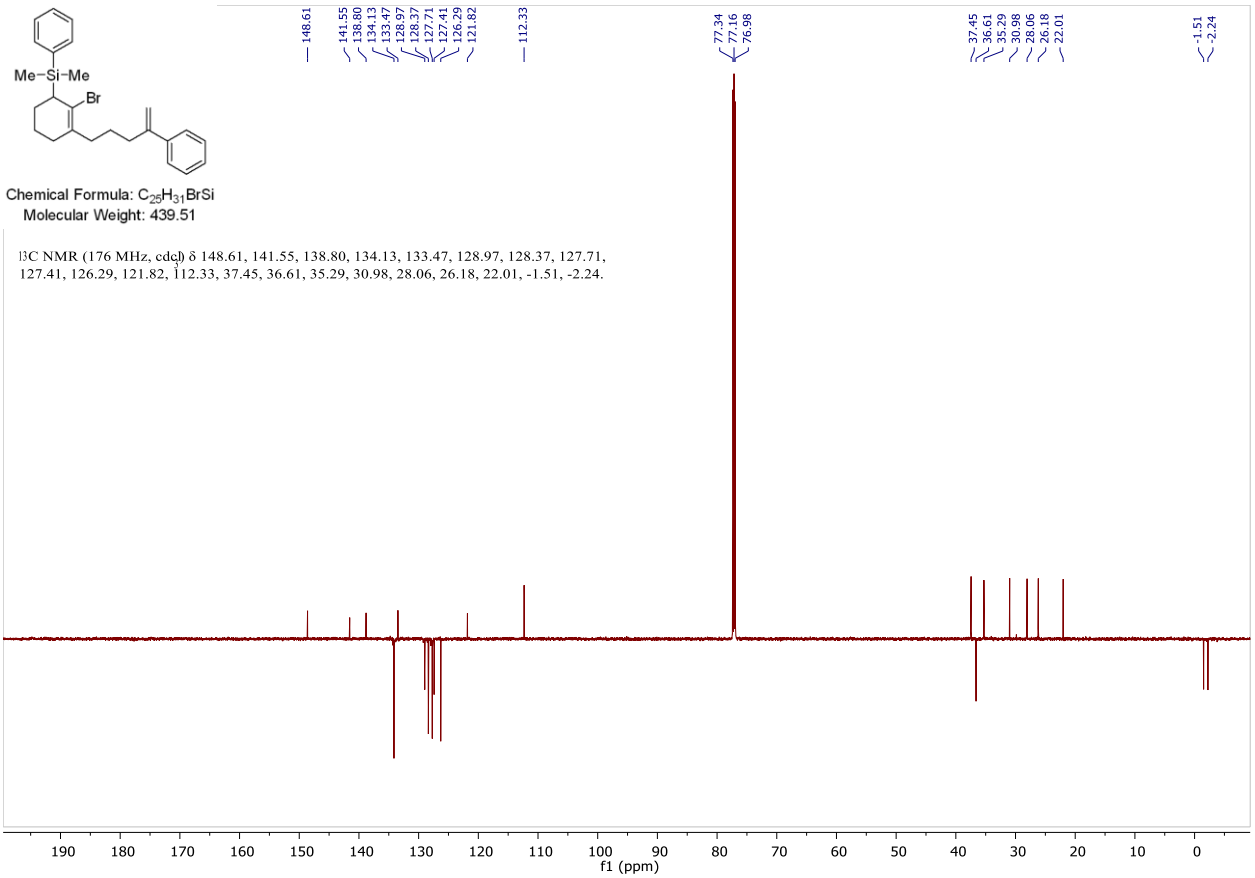
Chemical Formula: $C_{28}H_{35}BrO_2Si$
Molecular Weight: 511.58
1:1 Mixture of Diasteriomers

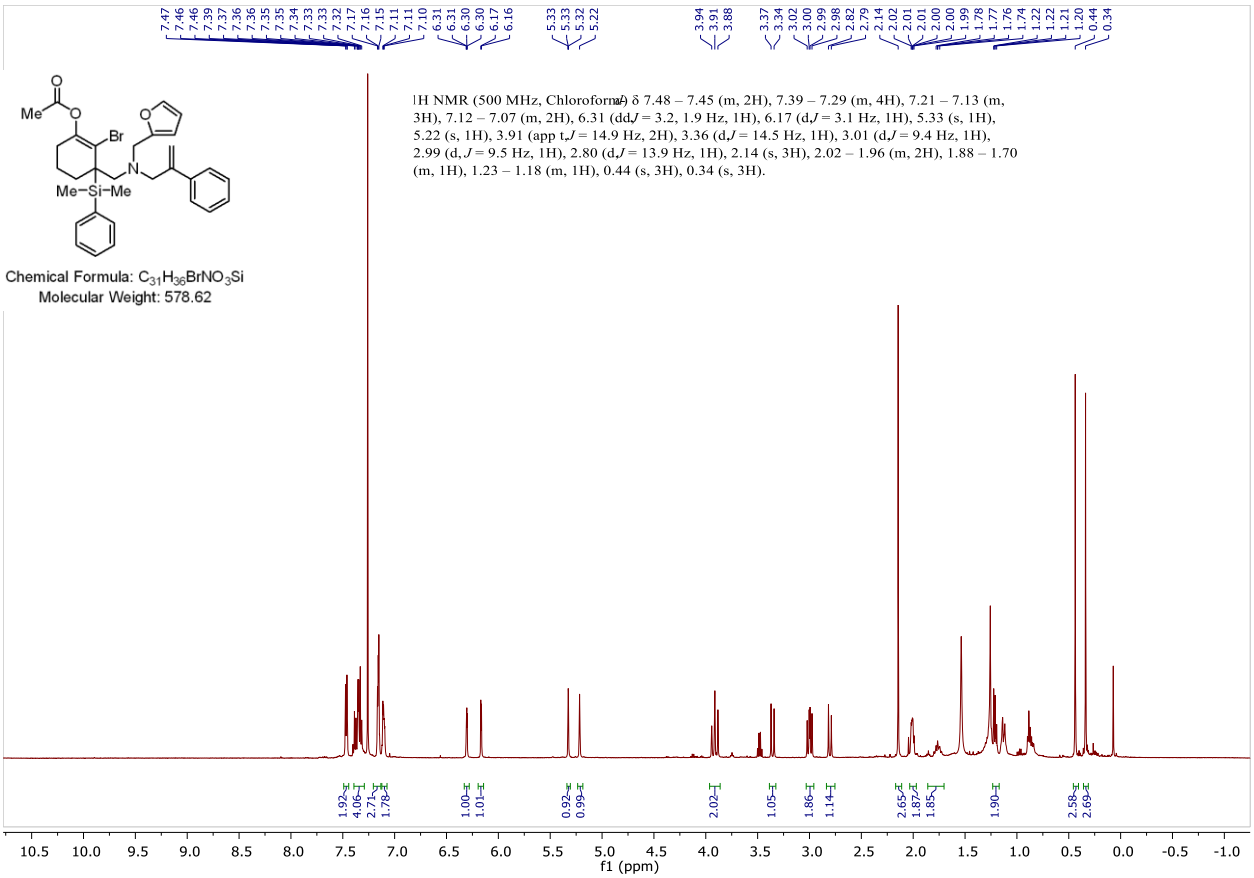
^{13}C NMR (126 MHz, cdcl) δ 168.32, 168.24, 148.45, 148.01, 144.62, 144.00, 141.65, 141.60, 137.60, 135.07, 134.88, 129.16, 129.11, 128.30, 128.20, 127.68, 127.61, 127.35, 127.21, 126.81, 126.56, 122.33, 121.66, 114.18, 113.89, 45.71, 43.67, 42.98, 40.63, 36.66, 35.42, 31.76, 31.55, 28.99, 28.78, 28.08, 22.07, 20.98, 20.93, 20.56, 20.28, 20.17, -2.55, -2.72, -3.30, -3.85.

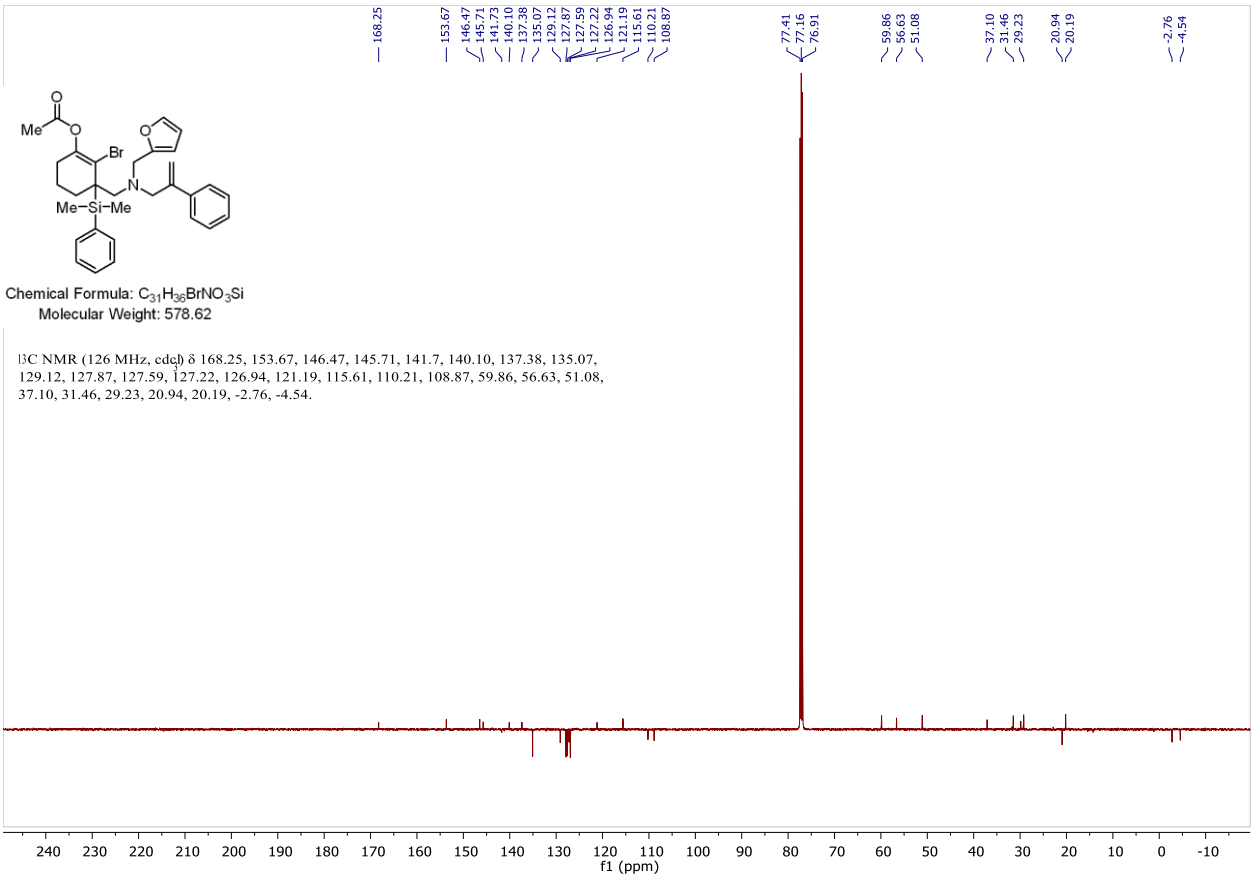

Me
O
O
Br
Me
Me–Si–Me
Chemical Formula: C22H31BrO2Si
Molecular Weight: 435.48
1H NMR (500 MHz, Chloroform-d) δ 7.56 (dd, J = 7.5, 2.0 Hz, 2H), 7.38 – 7.31 (m, 3H), 4.69 (s, 1H), 4.66 (s, 1H), 2.24 – 2.20 (m, 1H), 2.17 (s, 3H), 2.08 (dd, J = 16.7, 5.6 Hz, 1H), 1.98 (t, J = 7.5 Hz, 2H), 1.90 (ddd, J = 13.3, 11.4, 4.4 Hz, 1H), 1.70 (s, 3H), 1.68 – 1.60 (m, 4H), 1.53 – 1.34 (m, 3H), 0.49 (s, 3H), 0.45 (s, 3H).
f1 (ppm)


Me
O
O
Br
Me
Me–Si–Me
Chemical Formula: C22H31BrO2Si
Molecular Weight: 435.48
13C NMR (126 MHz, cdcl3) δ 168.20, 146.01, 144.74, 137.75, 134.87, 129.14, 127.68, 120.84, 110.05, 38.63, 36.03, 35.91, 31.74, 29.00, 22.65, 22.56, 20.95, 20.37, -2.52, -3.01.
168.20
146.01
144.74
137.75
134.87
129.14
127.68
120.84
110.05
77.41
77.16
76.91
38.63
36.03
35.91
31.74
29.00
22.65
22.56
20.95
20.37
-2.52
-3.01
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me–Si–Me
Br
Chemical Formula: C25H31BrSi
Molecular Weight: 439.51
1H NMR (700 MHz, Chloroform-d) δ 7.53 – 7.50 (m, 2H), 7.41 (dd, J = 8.3, 1.3 Hz, 2H), 7.35 – 7.27 (m, 6H), 5.28 (d, J = 1.5 Hz, 1H), 5.07 (d, J = 1.4 Hz, 1H), 2.49 (td, J = 7.4, 4.2 Hz, 2H), 2.35 – 2.27 (m, 2H), 2.10 – 2.03 (m, 1H), 2.00 (dtd, J = 16.6, 7.2, 2.0 Hz, 1H), 1.92 (dtd, J = 17.0, 5.5, 1.8 Hz, 1H), 1.77 – 1.69 (m, 1H), 1.64 – 1.58 (m, 1H), 1.55 – 1.45 (m, 4H), 0.45 (s, 3H), 0.40 (s, 3H).
f1 (ppm)

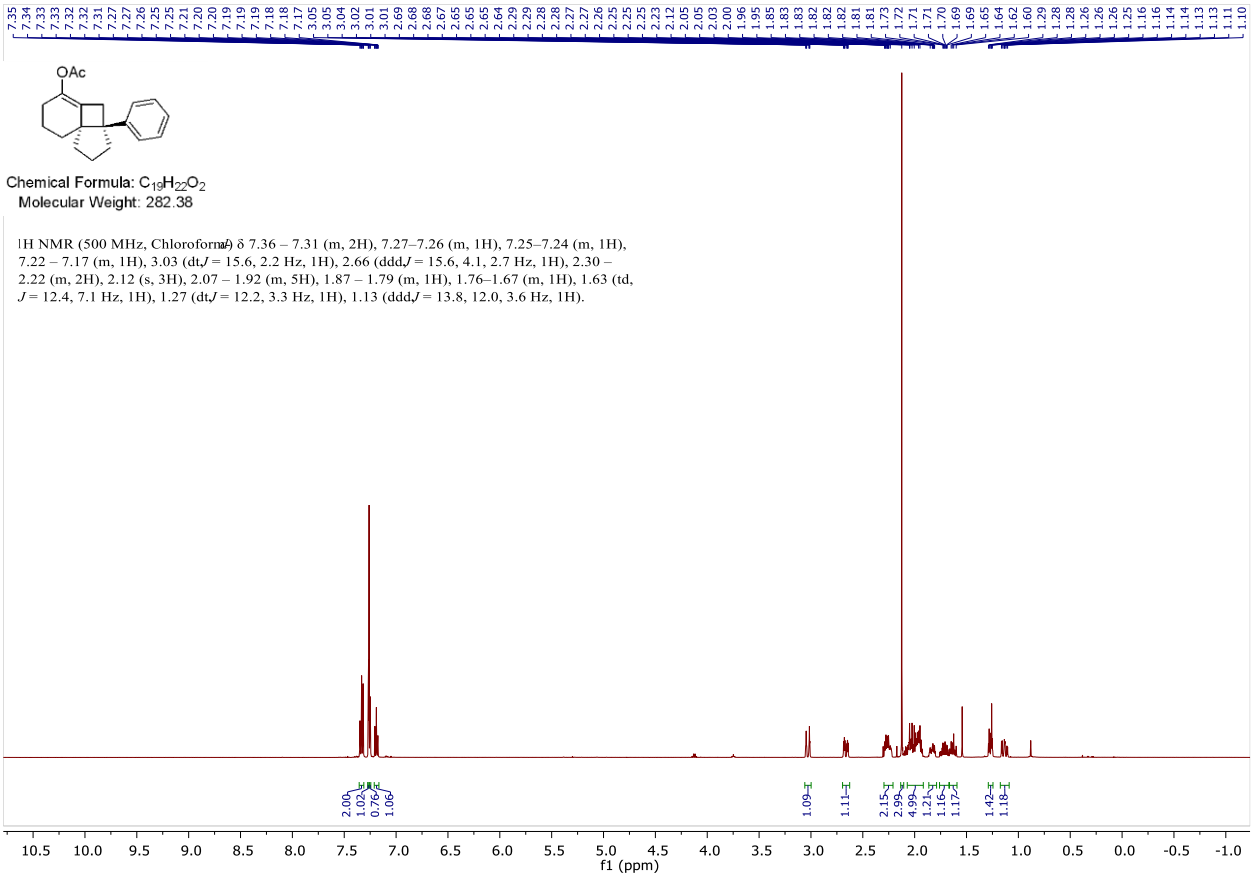

Me–Si–Me
Br
Chemical Formula: C25H31BrSi
Molecular Weight: 439.51
13C NMR (176 MHz, cdcl) δ 148.61, 141.55, 138.80, 134.13, 133.47, 128.97, 128.37, 127.71, 127.41, 126.29, 121.82, 112.33, 37.45, 36.61, 35.29, 30.98, 28.06, 26.18, 22.01, -1.51, -2.24.
148.61
141.55
138.80
134.13
133.47
128.97
128.37
127.71
127.41
126.29
121.82
112.33
77.34
77.16
76.98
37.45
36.61
35.29
30.98
28.06
26.18
22.01
-1.51
-2.24
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

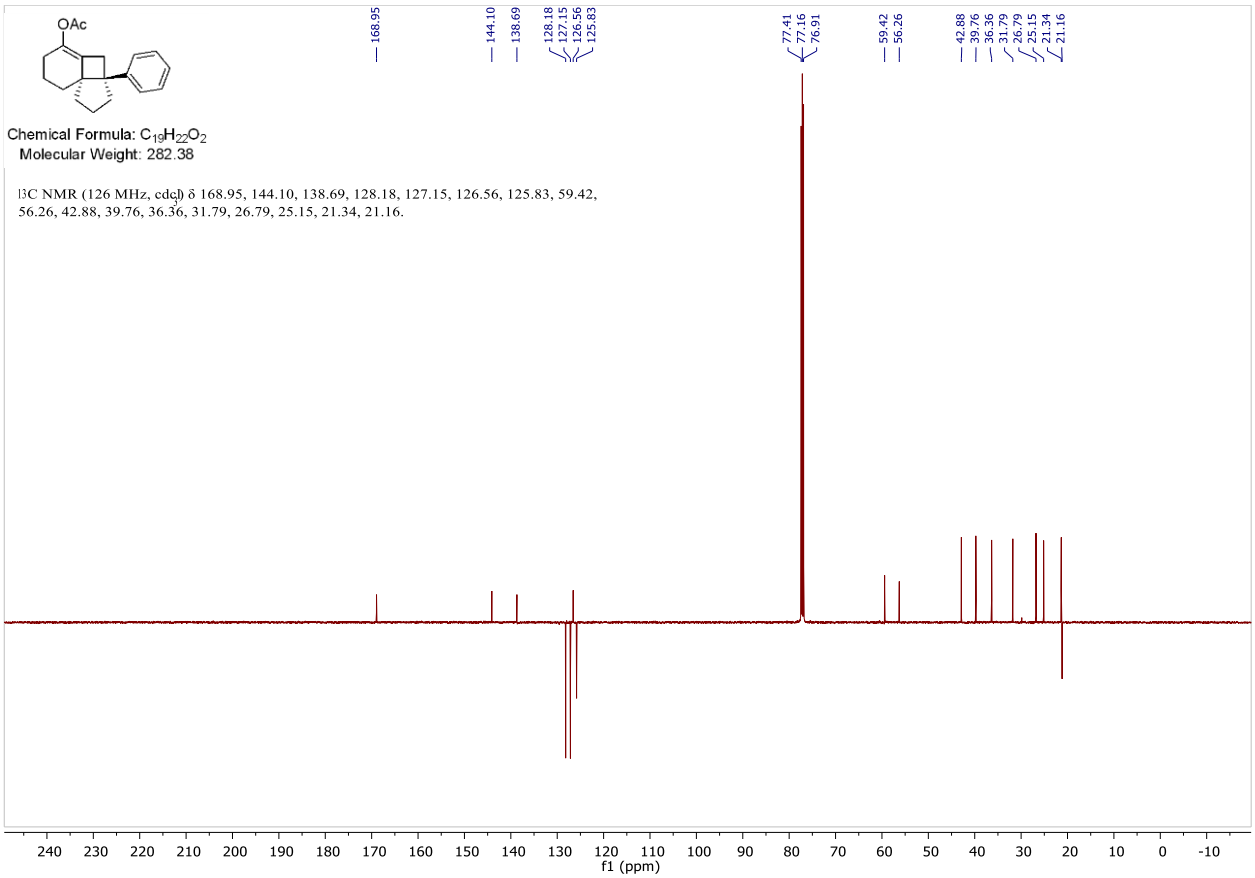

Me
O
O
Br
O
N
Me–Si–Me
Chemical Formula: C31H36BrNO3Si
Molecular Weight: 578.62
1H NMR (500 MHz, Chloroform-d) δ 7.48 – 7.45 (m, 2H), 7.39 – 7.29 (m, 4H), 7.21 – 7.13 (m, 3H), 7.12 – 7.07 (m, 2H), 6.31 (dd, J = 3.2, 1.9 Hz, 1H), 6.17 (d, J = 3.1 Hz, 1H), 5.33 (s, 1H), 5.22 (s, 1H), 3.91 (app t, J = 14.9 Hz, 2H), 3.36 (d, J = 14.5 Hz, 1H), 3.01 (d, J = 9.4 Hz, 1H), 2.99 (d, J = 9.5 Hz, 1H), 2.80 (d, J = 13.9 Hz, 1H), 2.14 (s, 3H), 2.02 – 1.96 (m, 2H), 1.88 – 1.70 (m, 1H), 1.23 – 1.18 (m, 1H), 0.44 (s, 3H), 0.34 (s, 3H).
7.47 7.46 7.46 7.39 7.37 7.36 7.36 7.35 7.35 7.34 7.33 7.33 7.32 7.17 7.16 7.15 7.11 7.11 7.10 6.31 6.31 6.30 6.30 6.17 6.16
5.33 5.33 5.32 5.22
3.94 3.91 3.88
3.37 3.34 3.02 3.00 2.99 2.98 2.82 2.79
2.14 2.02 2.01 2.01 2.00 2.00 1.99 1.78 1.77 1.76 1.74 1.22 1.22 1.21 1.20 0.44 0.34
1.92 4.06 2.77 1.78
1.00 1.01
0.92 0.99
2.02
1.05
1.86 1.14
2.65 1.87 1.85
1.90
2.58 2.69
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

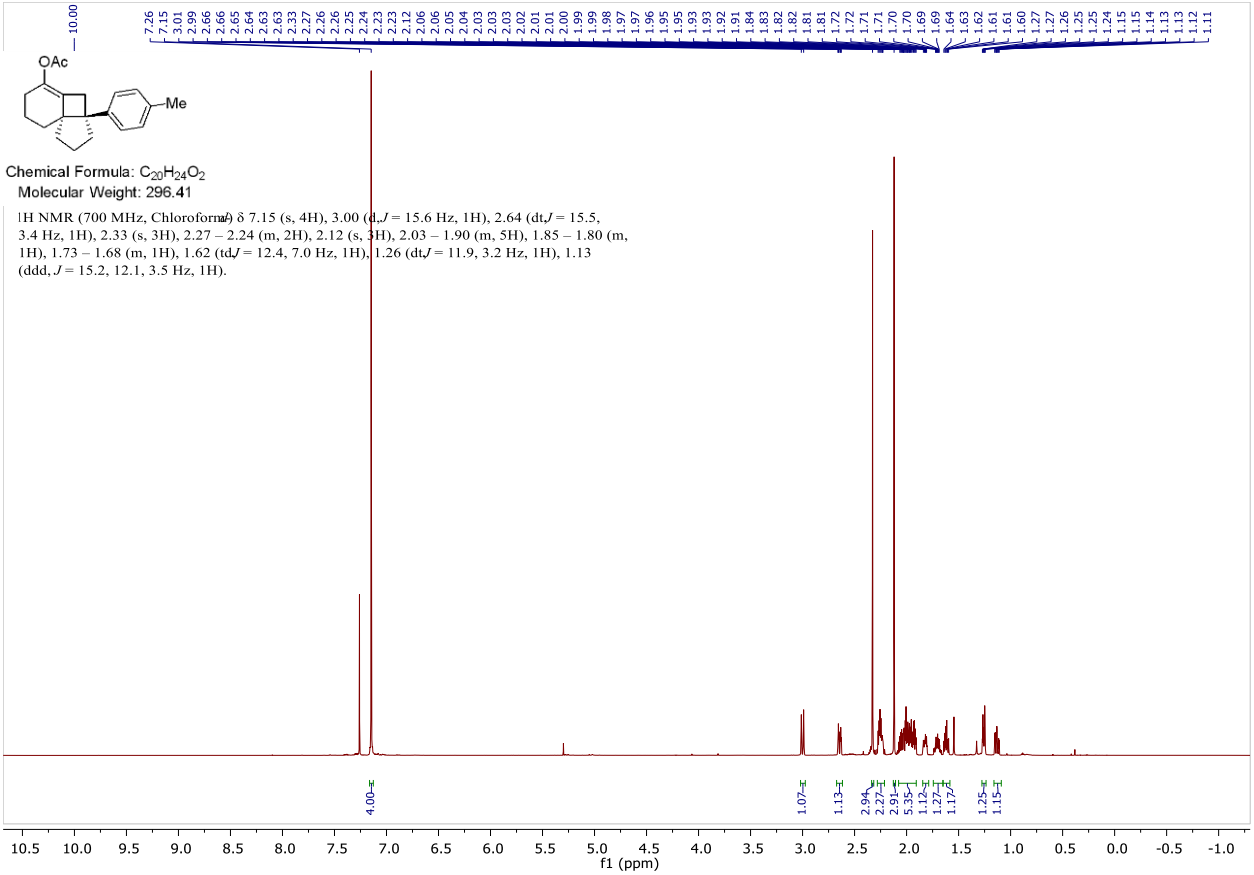


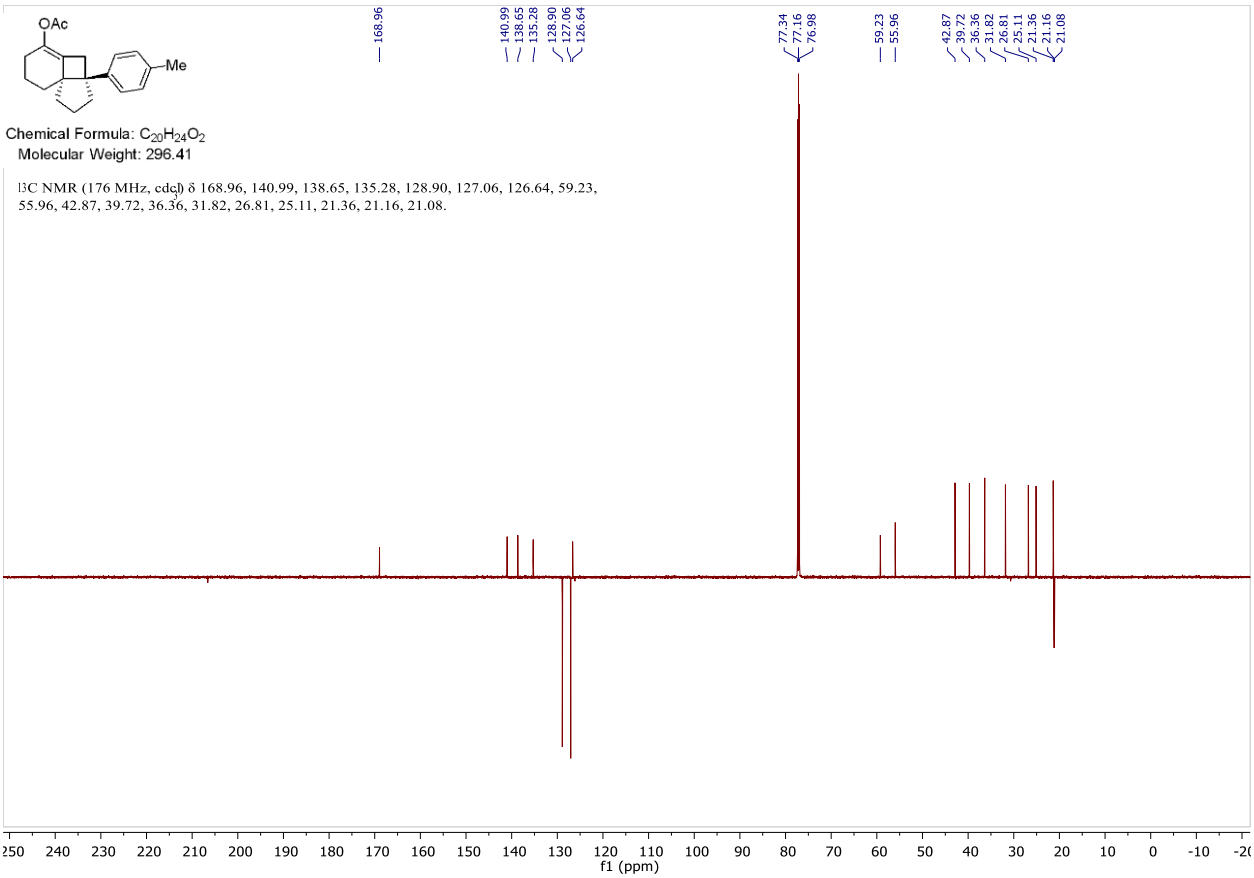
Chemical Formula: $C_{31}H_{36}BrNO_3Si$
Molecular Weight: 578.62

^{13}C NMR (126 MHz, cdcl) δ 168.25, 153.67, 146.47, 145.71, 141.7, 140.10, 137.38, 135.07, 129.12, 127.87, 127.59, 127.22, 126.94, 121.19, 115.61, 110.21, 108.87, 59.86, 56.63, 51.08, 37.10, 31.46, 29.23, 20.94, 20.19, -2.76, -4.54.


OAc
Chemical Formula: C19H22O2
Molecular Weight: 282.38
1H NMR (500 MHz, Chloroform-d) δ 7.36 – 7.31 (m, 2H), 7.27–7.26 (m, 1H), 7.25–7.24 (m, 1H), 7.22 – 7.17 (m, 1H), 3.03 (dt, J = 15.6, 2.2 Hz, 1H), 2.66 (ddd, J = 15.6, 4.1, 2.7 Hz, 1H), 2.30 – 2.22 (m, 2H), 2.12 (s, 3H), 2.07 – 1.92 (m, 5H), 1.87 – 1.79 (m, 1H), 1.76–1.67 (m, 1H), 1.63 (td, J = 12.4, 7.1 Hz, 1H), 1.27 (dt, J = 12.2, 3.3 Hz, 1H), 1.13 (ddd, J = 13.8, 12.0, 3.6 Hz, 1H).
f1 (ppm)

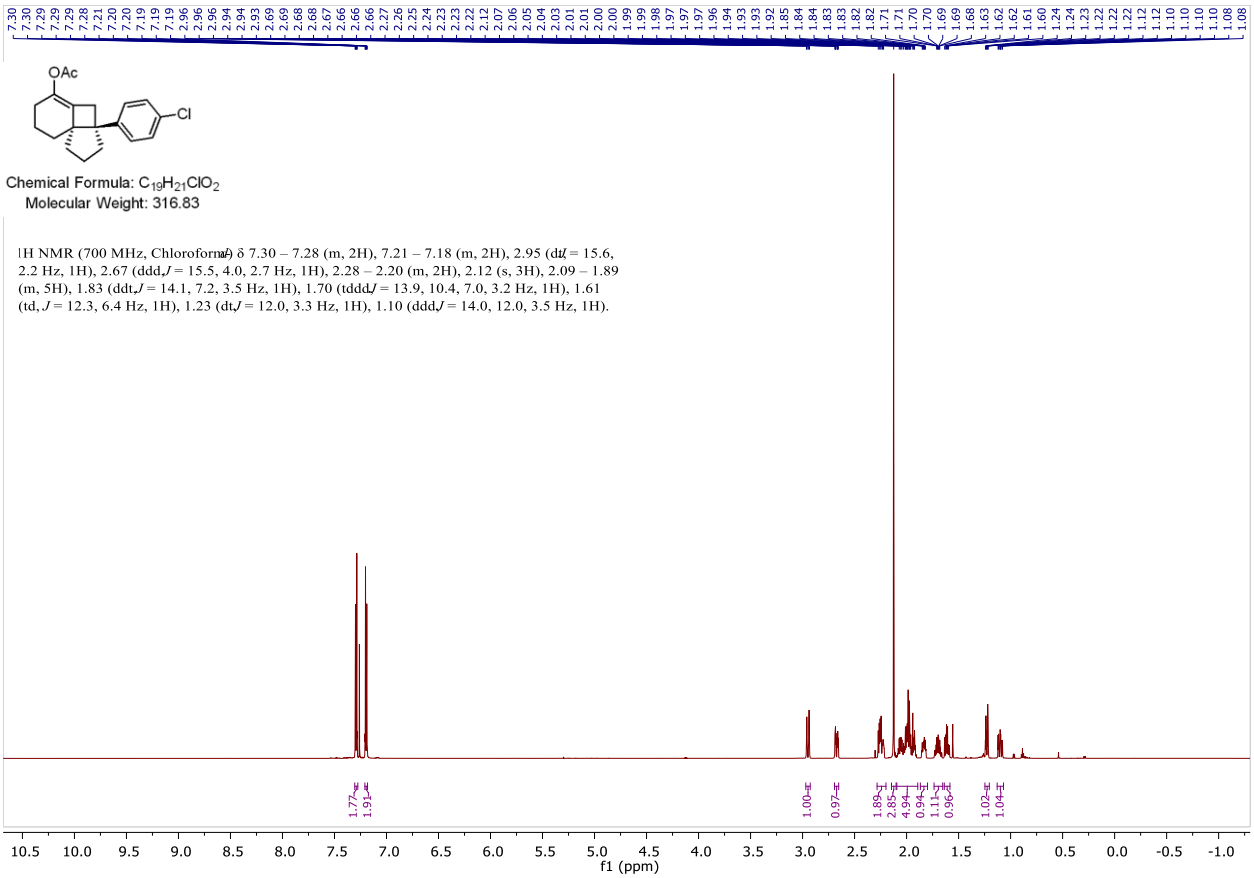

OAc
Chemical Formula: C19H22O2
Molecular Weight: 282.38
13C NMR (126 MHz, cdcl) δ 168.95, 144.10, 138.69, 128.18, 127.15, 126.56, 125.83, 59.42, 56.26, 42.88, 39.76, 36.36, 31.79, 26.79, 25.15, 21.34, 21.16.
168.95
144.10
138.69
128.18
127.15
126.56
125.83
77.41
77.16
76.91
59.42
56.26
42.88
39.76
36.36
31.79
26.79
25.15
21.34
21.16
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

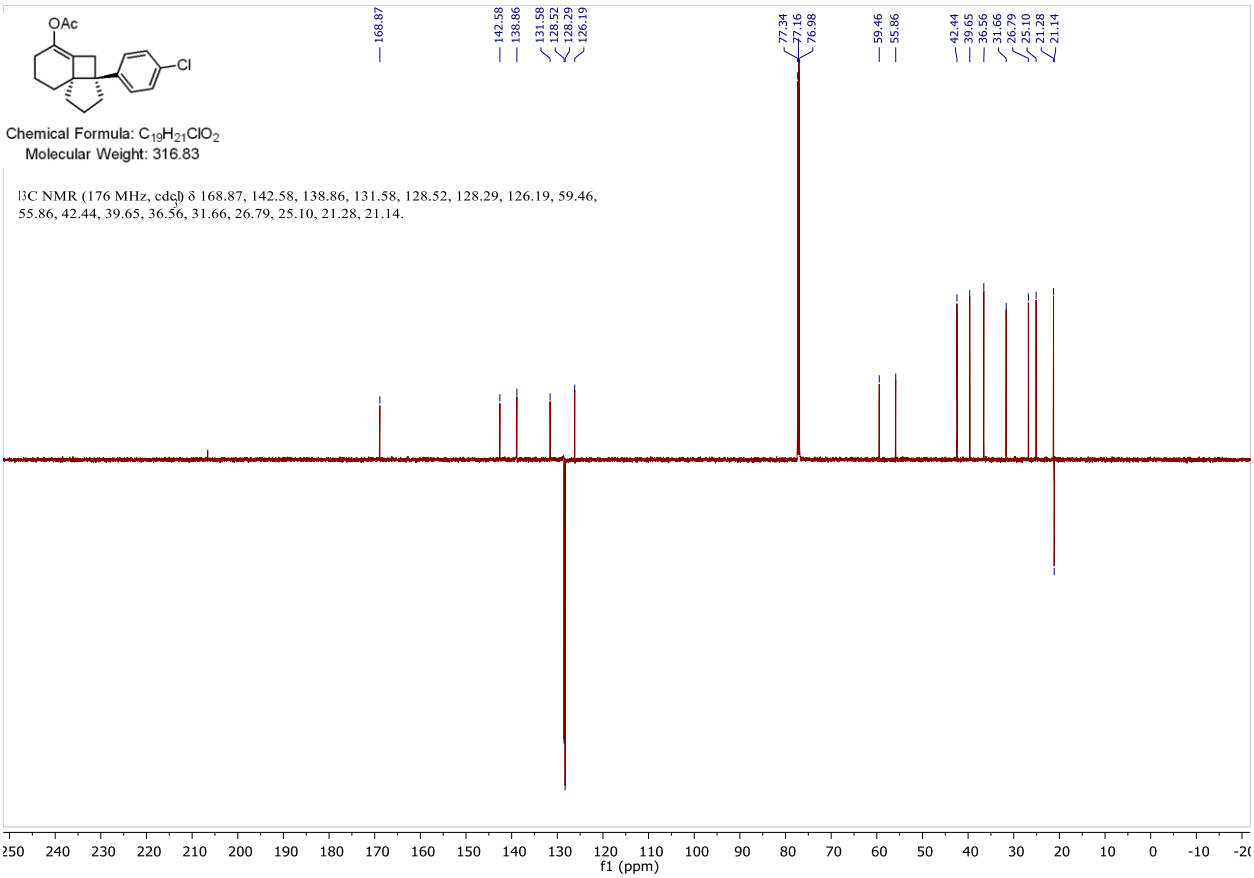

OAc
Me
Chemical Formula: C20H24O2
Molecular Weight: 296.41
1H NMR (700 MHz, Chloroform-d) δ 7.15 (s, 4H), 3.00 (d, J = 15.6 Hz, 1H), 2.64 (dt, J = 15.5, 3.4 Hz, 1H), 2.33 (s, 3H), 2.27 – 2.24 (m, 2H), 2.12 (s, 3H), 2.03 – 1.90 (m, 5H), 1.85 – 1.80 (m, 1H), 1.73 – 1.68 (m, 1H), 1.62 (td, J = 12.4, 7.0 Hz, 1H), 1.26 (dt, J = 11.9, 3.2 Hz, 1H), 1.13 (ddd, J = 15.2, 12.1, 3.5 Hz, 1H).
f1 (ppm)

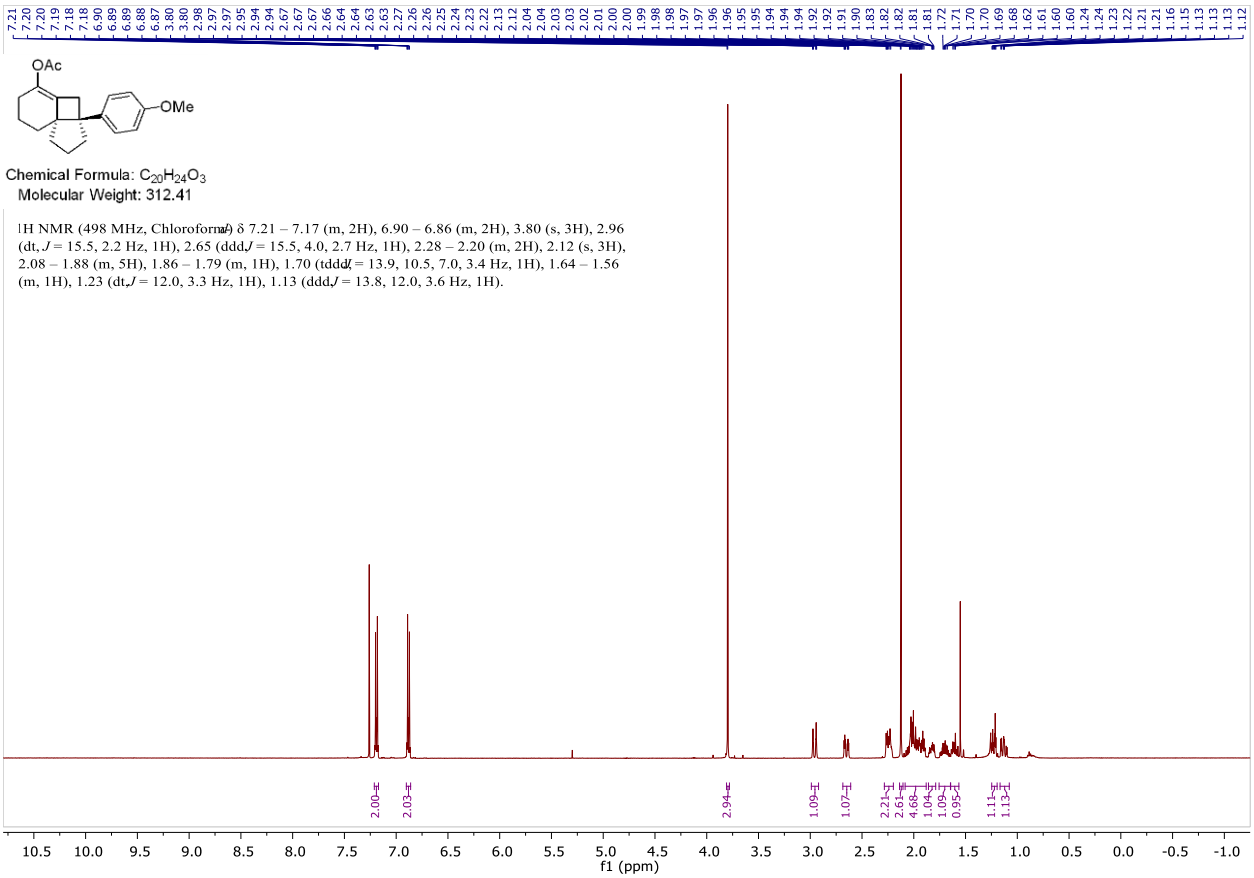


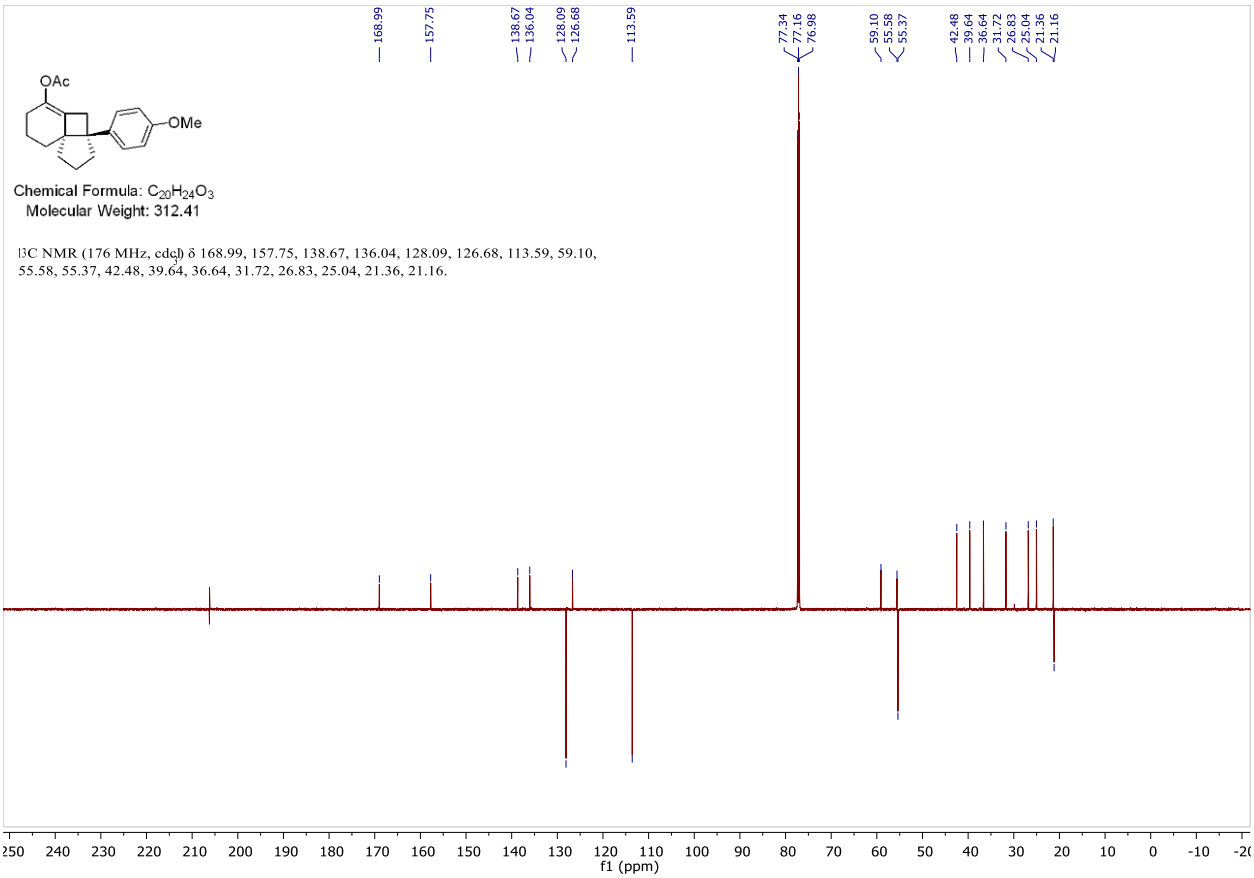
Chemical Formula: $C_{20}H_{24}O_2$
Molecular Weight: 296.41

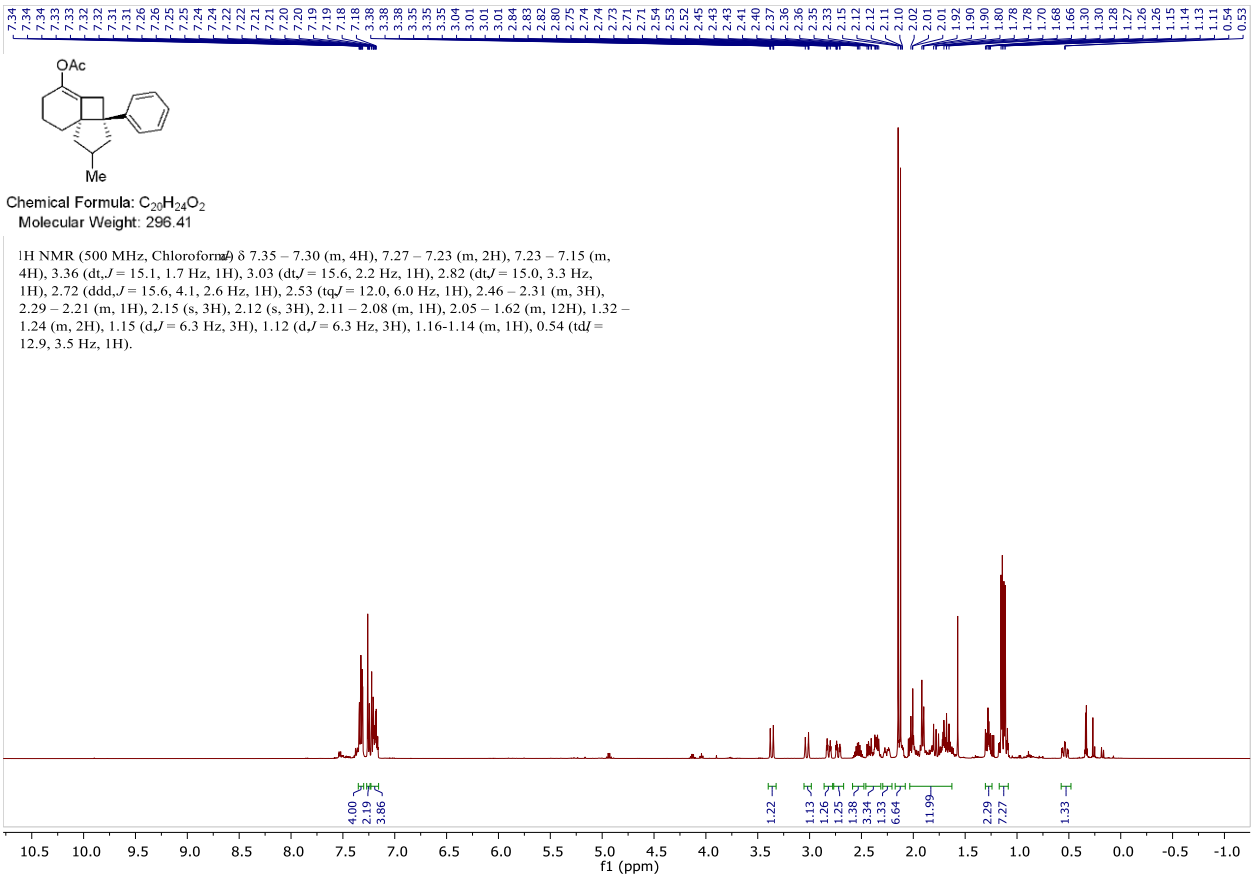
^{13}C NMR (176 MHz, cdcl) δ 168.96, 140.99, 138.65, 135.28, 128.90, 127.06, 126.64, 59.23, 55.96, 42.87, 39.72, 36.36, 31.82, 26.81, 25.11, 21.36, 21.16, 21.08.


OAc
Cl
Chemical Formula: C19H21ClO2
Molecular Weight: 316.83
1H NMR (700 MHz, Chloroform-d) δ 7.30 – 7.28 (m, 2H), 7.21 – 7.18 (m, 2H), 2.95 (dt, J = 15.6, 2.2 Hz, 1H), 2.67 (ddd, J = 15.5, 4.0, 2.7 Hz, 1H), 2.28 – 2.20 (m, 2H), 2.12 (s, 3H), 2.09 – 1.89 (m, 5H), 1.83 (ddt, J = 14.1, 7.2, 3.5 Hz, 1H), 1.70 (tddd, J = 13.9, 10.4, 7.0, 3.2 Hz, 1H), 1.61 (td, J = 12.3, 6.4 Hz, 1H), 1.23 (dt, J = 12.0, 3.3 Hz, 1H), 1.10 (ddd, J = 14.0, 12.0, 3.5 Hz, 1H).
1.77
1.91
1.00
0.97
1.89
2.85
4.94
0.94
1.11
0.96
1.02
1.04
f1 (ppm)

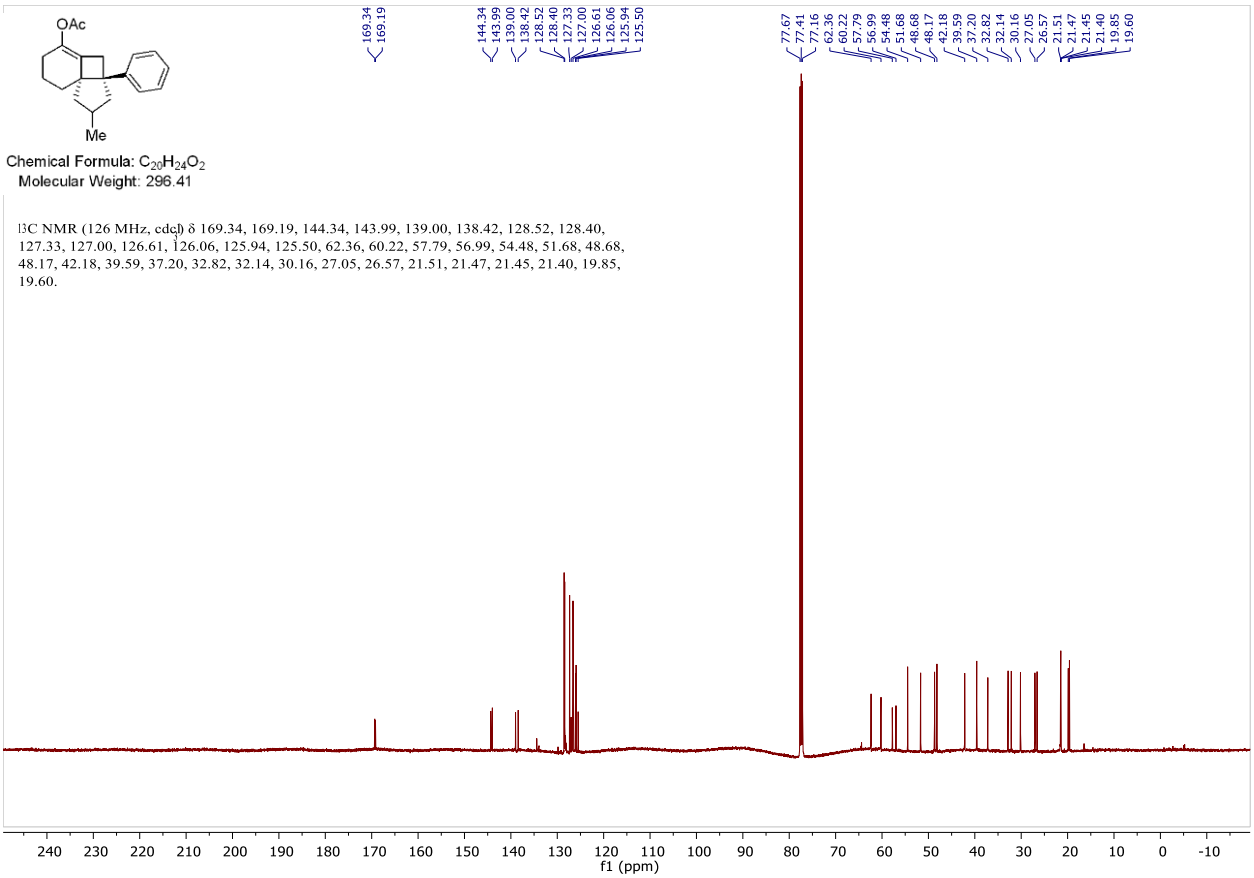

OAc
Cl
Chemical Formula: C19H21ClO2
Molecular Weight: 316.83
13C NMR (176 MHz, cdcl) δ 168.87, 142.58, 138.86, 131.58, 128.52, 128.29, 126.19, 59.46, 55.86, 42.44, 39.65, 36.56, 31.66, 26.79, 25.10, 21.28, 21.14.
168.87
142.58
138.86
131.58
128.52
128.29
126.19
77.34
77.16
76.98
59.46
55.86
42.44
39.65
36.56
31.66
26.79
25.10
21.28
21.14
f1 (ppm)

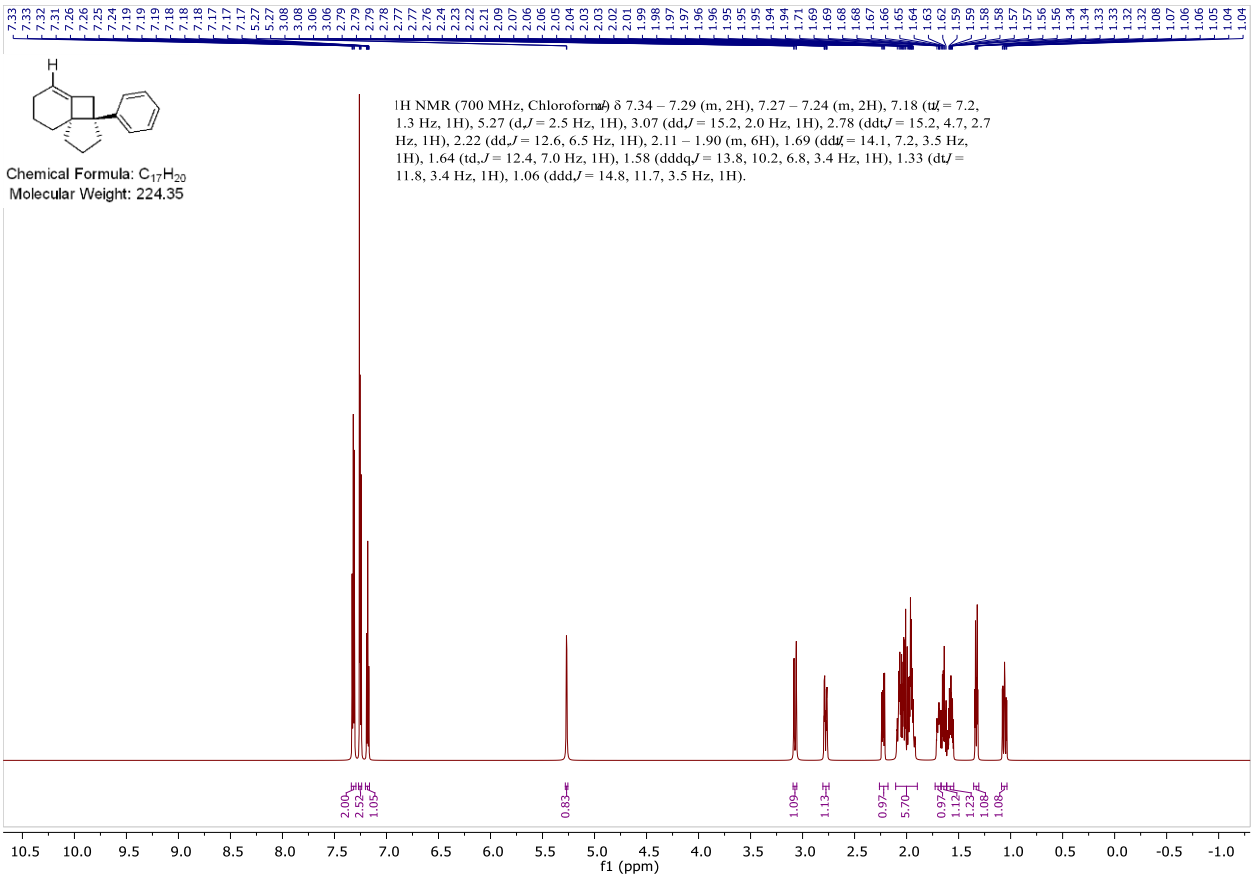

OAc
OMe
Chemical Formula: C20H24O3
Molecular Weight: 312.41
1H NMR (498 MHz, Chloroform-d) δ 7.21 – 7.17 (m, 2H), 6.90 – 6.86 (m, 2H), 3.80 (s, 3H), 2.96 (dt, J = 15.5, 2.2 Hz, 1H), 2.65 (ddd, J = 15.5, 4.0, 2.7 Hz, 1H), 2.28 – 2.20 (m, 2H), 2.12 (s, 3H), 2.08 – 1.88 (m, 5H), 1.86 – 1.79 (m, 1H), 1.70 (tddd, J = 13.9, 10.5, 7.0, 3.4 Hz, 1H), 1.64 – 1.56 (m, 1H), 1.23 (dt, J = 12.0, 3.3 Hz, 1H), 1.13 (ddd, J = 13.8, 12.0, 3.6 Hz, 1H).
f1 (ppm)

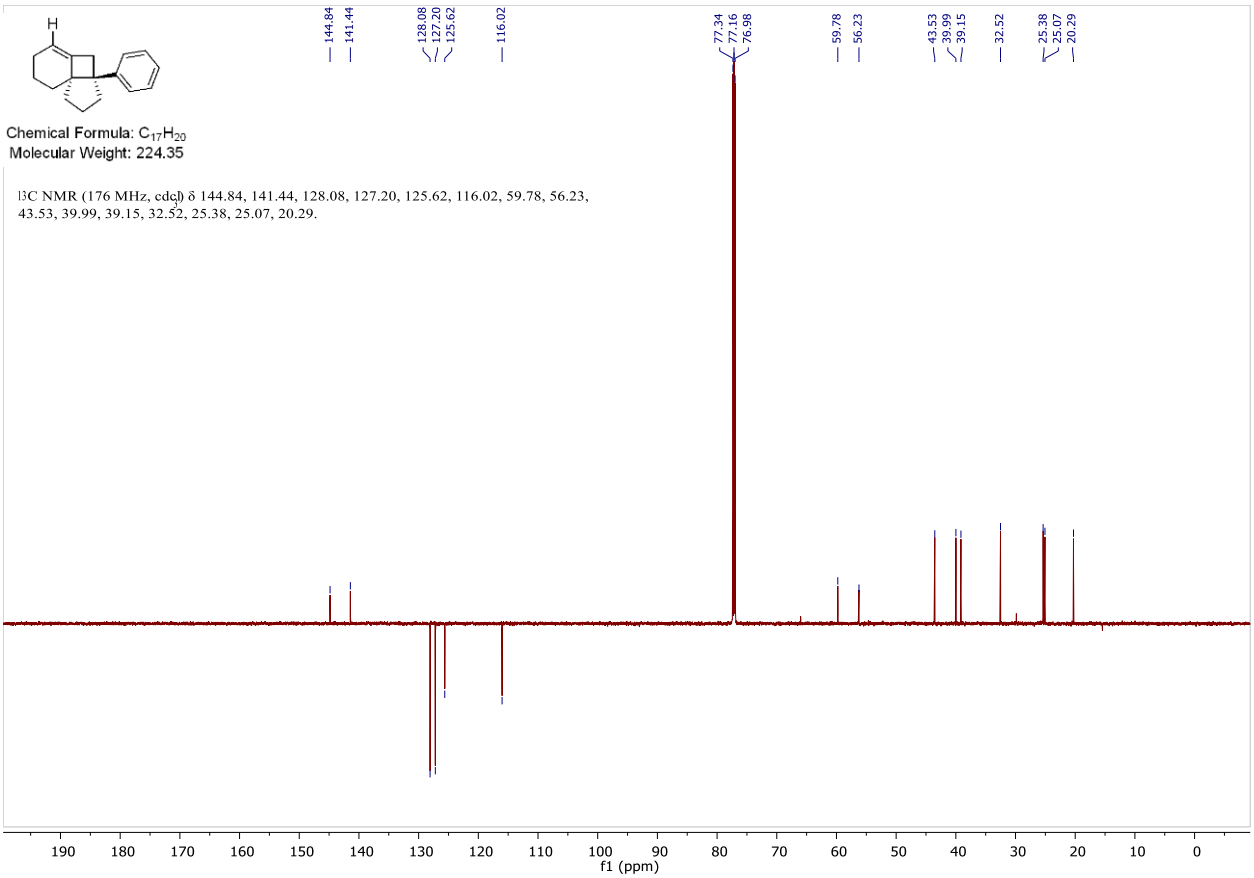

168.99
157.75
138.67
136.04
128.09
126.68
113.59
77.34
77.16
76.98
59.10
55.58
55.37
42.48
39.64
36.64
31.72
26.83
25.04
21.36
21.16
OAc
OMe
Chemical Formula: C20H24O3
Molecular Weight: 312.41
13C NMR (176 MHz, cdcl3) δ 168.99, 157.75, 138.67, 136.04, 128.09, 126.68, 113.59, 59.10, 55.58, 55.37, 42.48, 39.64, 36.64, 31.72, 26.83, 25.04, 21.36, 21.16.
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

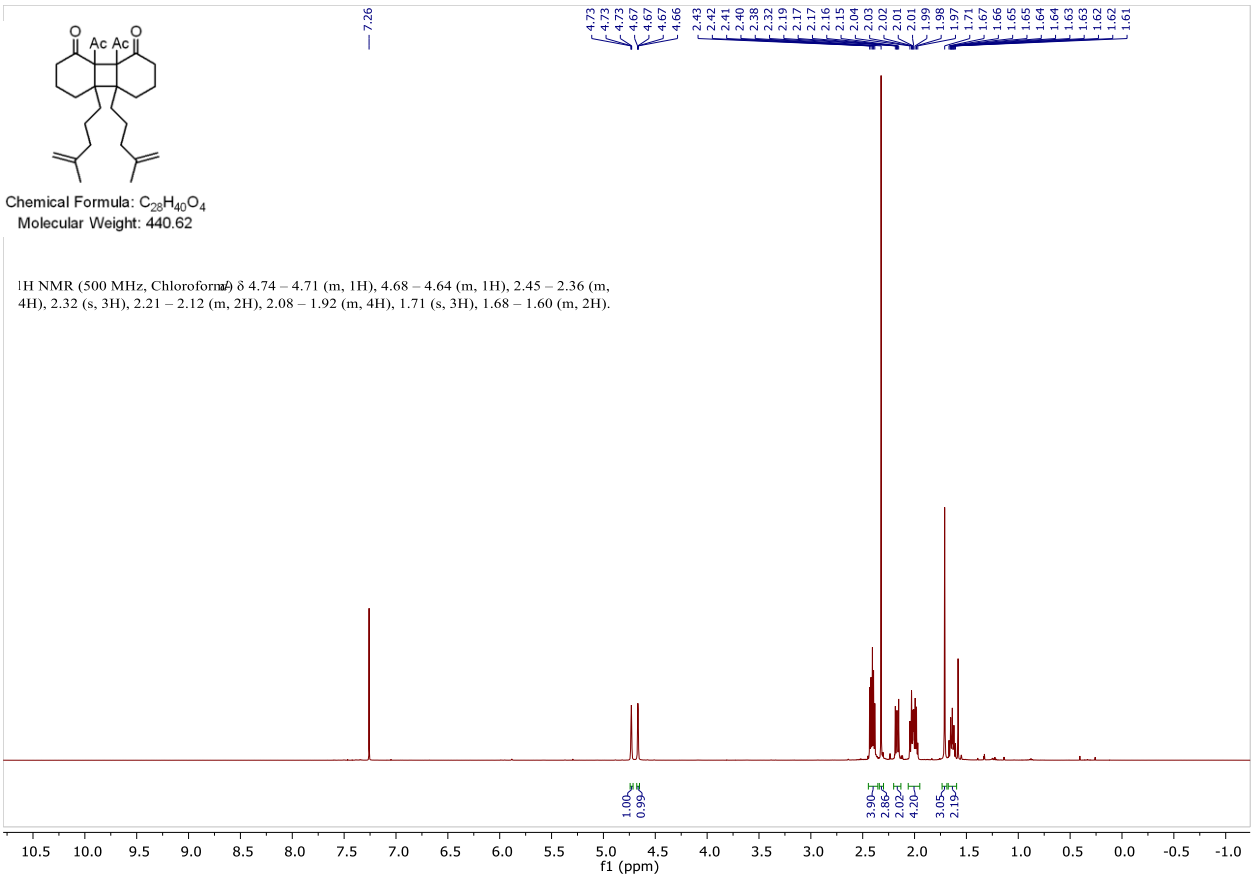


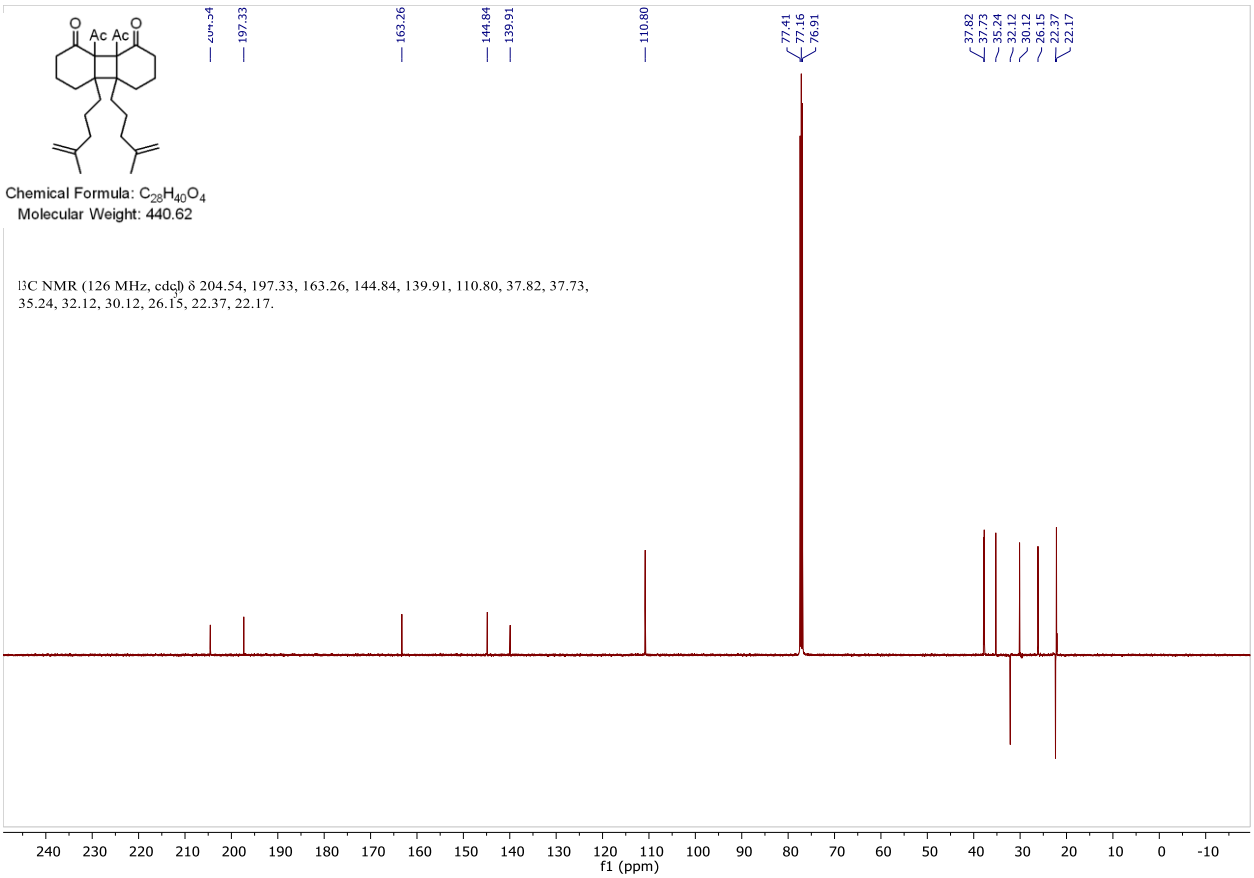
^{1}H NMR (500 MHz, Chloroform-d) δ 7.35 – 7.30 (m, 4H), 7.27 – 7.23 (m, 2H), 7.23 – 7.15 (m, 4H), 3.36 (dt, J = 15.1, 1.7 Hz, 1H), 3.03 (dt, J = 15.6, 2.2 Hz, 1H), 2.82 (dt, J = 15.0, 3.3 Hz, 1H), 2.72 (ddd, J = 15.6, 4.1, 2.6 Hz, 1H), 2.53 (tq, J = 12.0, 6.0 Hz, 1H), 2.46 – 2.31 (m, 3H), 2.29 – 2.21 (m, 1H), 2.15 (s, 3H), 2.12 (s, 3H), 2.11 – 2.08 (m, 1H), 2.05 – 1.62 (m, 12H), 1.32 – 1.24 (m, 2H), 1.15 (d, J = 6.3 Hz, 3H), 1.12 (d, J = 6.3 Hz, 3H), 1.16-1.14 (m, 1H), 0.54 (td, J = 12.9, 3.5 Hz, 1H).

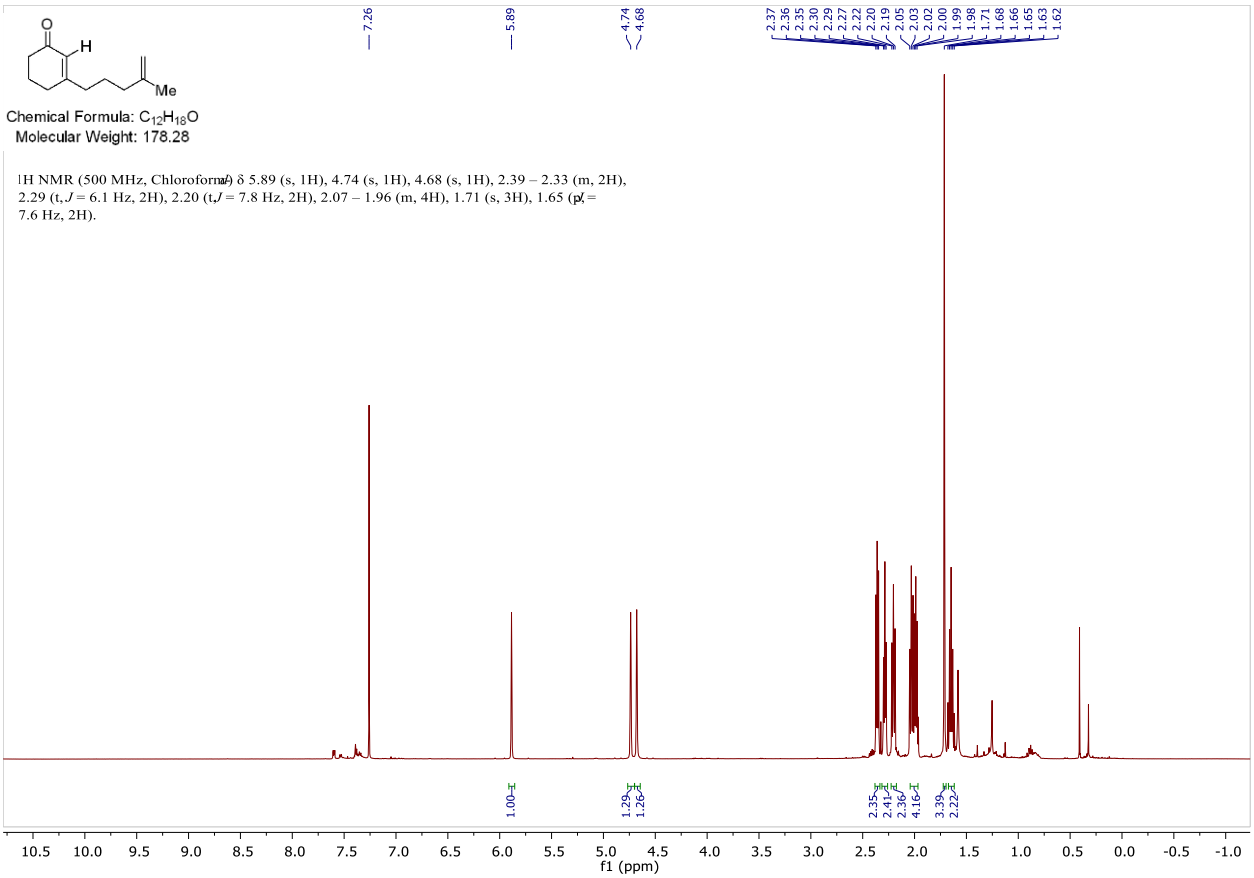

OAc
Me
Chemical Formula: C20H24O2
Molecular Weight: 296.41
13C NMR (126 MHz, cdcl) δ 169.34, 169.19, 144.34, 143.99, 139.00, 138.42, 128.52, 128.40, 127.33, 127.00, 126.61, 126.06, 125.94, 125.50, 62.36, 60.22, 57.79, 56.99, 54.48, 51.68, 48.68, 48.17, 42.18, 39.59, 37.20, 32.82, 32.14, 30.16, 27.05, 26.57, 21.51, 21.47, 21.45, 21.40, 19.85, 19.60.
169.34
169.19
144.34
143.99
139.00
138.42
128.52
128.40
127.33
127.00
126.61
126.06
125.94
125.50
77.67
77.41
77.16
62.36
60.22
57.79
56.99
54.48
51.68
48.68
48.17
42.18
39.59
37.20
32.82
32.14
30.16
27.05
26.57
21.51
21.47
21.45
21.40
19.85
19.60
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

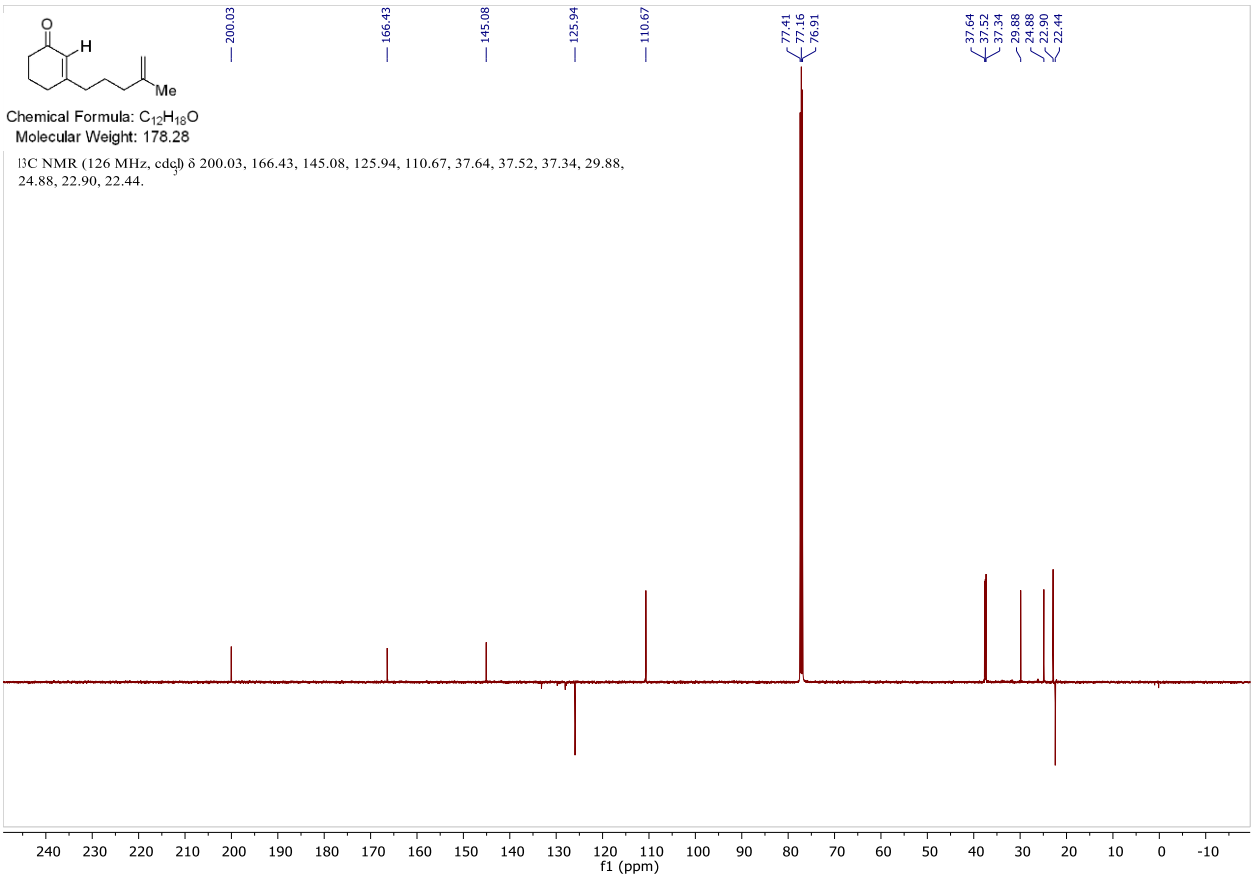

Chemical Formula: C17H20
Molecular Weight: 224.35
1H NMR (700 MHz, Chloroform-d) δ 7.34 – 7.29 (m, 2H), 7.27 – 7.24 (m, 2H), 7.18 (td, J = 7.2, 1.3 Hz, 1H), 5.27 (d, J = 2.5 Hz, 1H), 3.07 (dd, J = 15.2, 2.0 Hz, 1H), 2.78 (ddt, J = 15.2, 4.7, 2.7 Hz, 1H), 2.22 (dd, J = 12.6, 6.5 Hz, 1H), 2.11 – 1.90 (m, 6H), 1.69 (ddd, J = 14.1, 7.2, 3.5 Hz, 1H), 1.64 (td, J = 12.4, 7.0 Hz, 1H), 1.58 (dddq, J = 13.8, 10.2, 6.8, 3.4 Hz, 1H), 1.33 (dt, J = 11.8, 3.4 Hz, 1H), 1.06 (ddd, J = 14.8, 11.7, 3.5 Hz, 1H).
2.00
2.52
1.05
0.83
1.09
1.13
0.97
5.70
0.97
1.12
1.23
1.08
1.08
f1 (ppm)

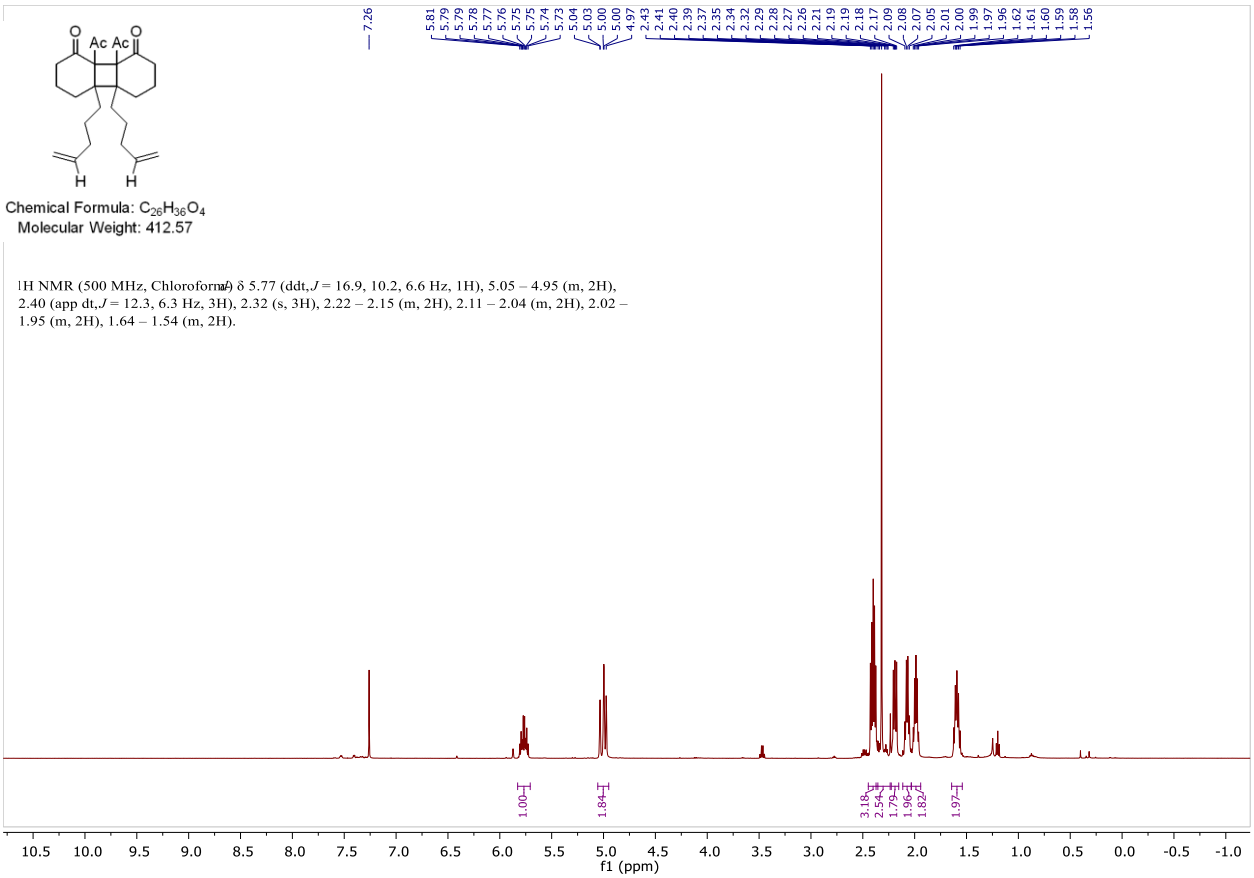

Chemical Formula: C17H20
Molecular Weight: 224.35
13C NMR (176 MHz, cdcl3) δ 144.84, 141.44, 128.08, 127.20, 125.62, 116.02, 59.78, 56.23, 43.53, 39.99, 39.15, 32.52, 25.38, 25.07, 20.29.
144.84
141.44
128.08
127.20
125.62
116.02
77.34
77.16
76.98
59.78
56.23
43.53
39.99
39.15
32.52
25.38
25.07
20.29
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

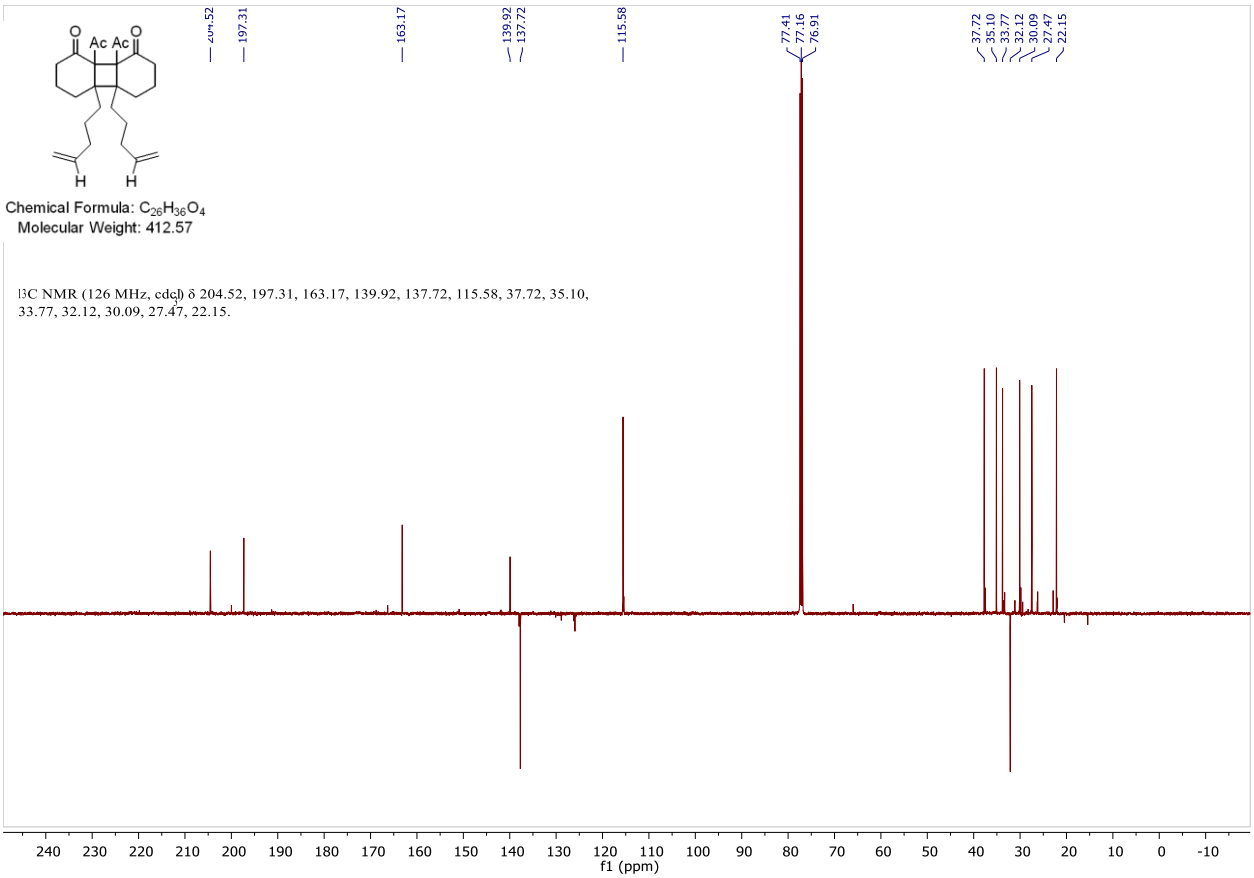

Ac Ac
Chemical Formula: C28H40O4
Molecular Weight: 440.62
1H NMR (500 MHz, Chloroform-d) δ 4.74 – 4.71 (m, 1H), 4.68 – 4.64 (m, 1H), 2.45 – 2.36 (m, 4H), 2.32 (s, 3H), 2.21 – 2.12 (m, 2H), 2.08 – 1.92 (m, 4H), 1.71 (s, 3H), 1.68 – 1.60 (m, 2H).
7.26
4.73 4.73 4.73 4.67 4.67 4.67 4.66
2.43 2.42 2.41 2.40 2.38 2.32 2.19 2.17 2.17 2.16 2.15 2.04 2.03 2.02 2.01 2.01 1.99 1.98 1.97 1.71 1.67 1.66 1.65 1.65 1.64 1.64 1.63 1.63 1.62 1.62 1.61
1.00
0.99
3.90
2.86
2.02
4.20
3.05
2.19
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

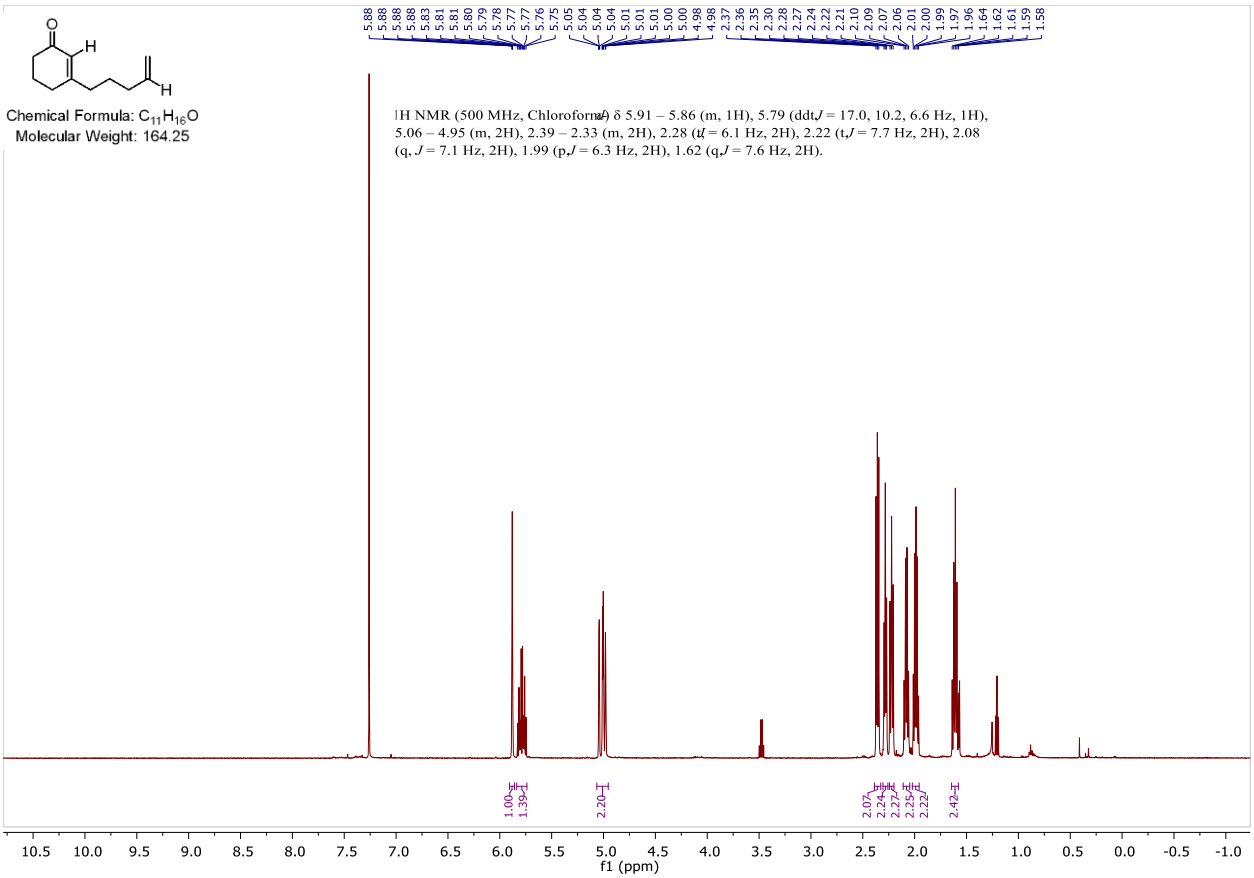

Ac Ac
Chemical Formula: C28H40O4
Molecular Weight: 440.62
13C NMR (126 MHz, cdcl) δ 204.54, 197.33, 163.26, 144.84, 139.91, 110.80, 37.82, 37.73, 35.24, 32.12, 30.12, 26.15, 22.37, 22.17.
197.33
163.26
144.84
139.91
110.80
77.41
77.16
76.91
37.82
37.73
35.24
32.12
30.12
26.15
22.37
22.17
f1 (ppm)

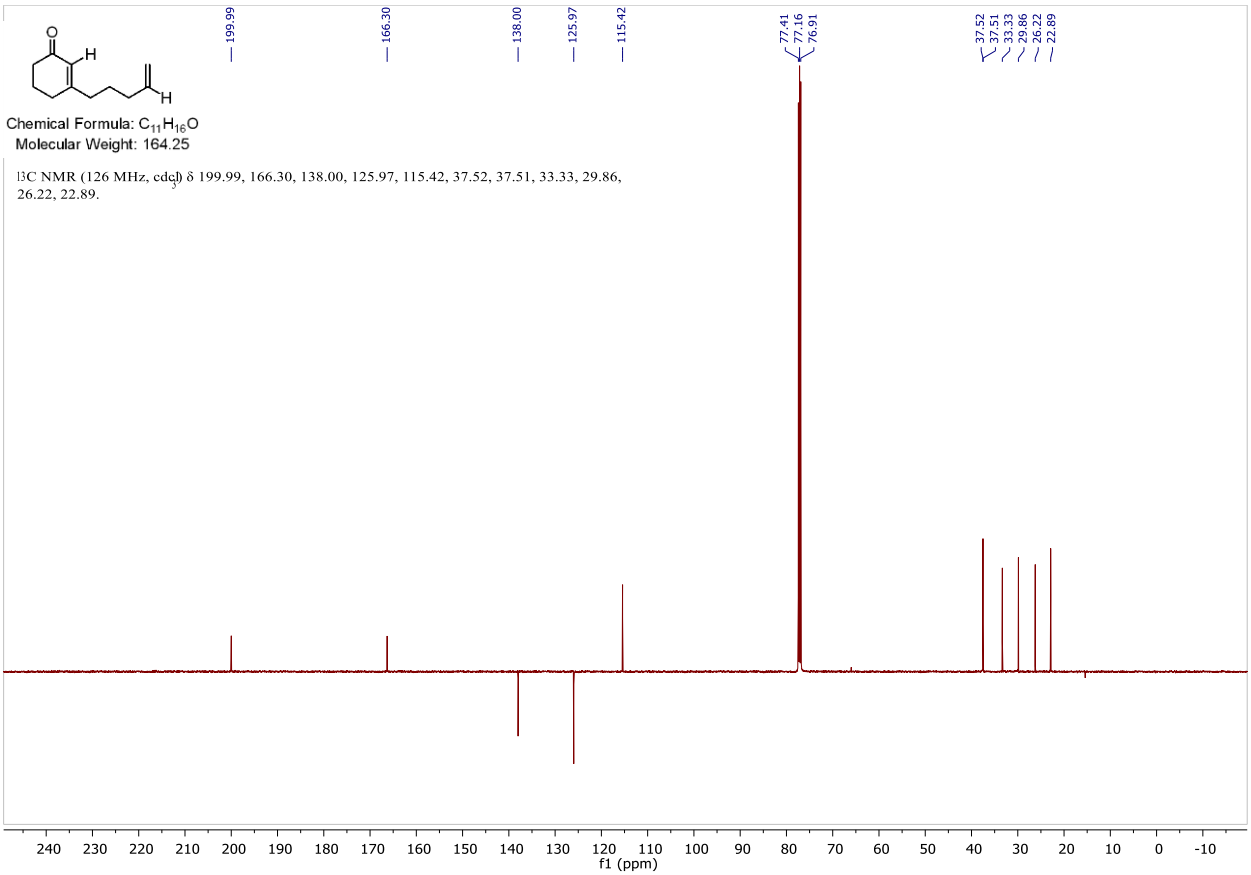

O
H
Me
Chemical Formula: C12H18O
Molecular Weight: 178.28
1H NMR (500 MHz, Chloroform-d) δ 5.89 (s, 1H), 4.74 (s, 1H), 4.68 (s, 1H), 2.39 – 2.33 (m, 2H), 2.29 (t, J = 6.1 Hz, 2H), 2.20 (t, J = 7.8 Hz, 2H), 2.07 – 1.96 (m, 4H), 1.71 (s, 3H), 1.65 (p, J = 7.6 Hz, 2H).
7.26
5.89
4.74
4.68
2.37
2.36
2.35
2.30
2.29
2.27
2.22
2.20
2.19
2.05
2.03
2.02
2.00
1.99
1.98
1.71
1.68
1.66
1.65
1.63
1.62
1.00
1.29
1.26
2.35
2.41
2.36
4.16
3.39
2.22
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

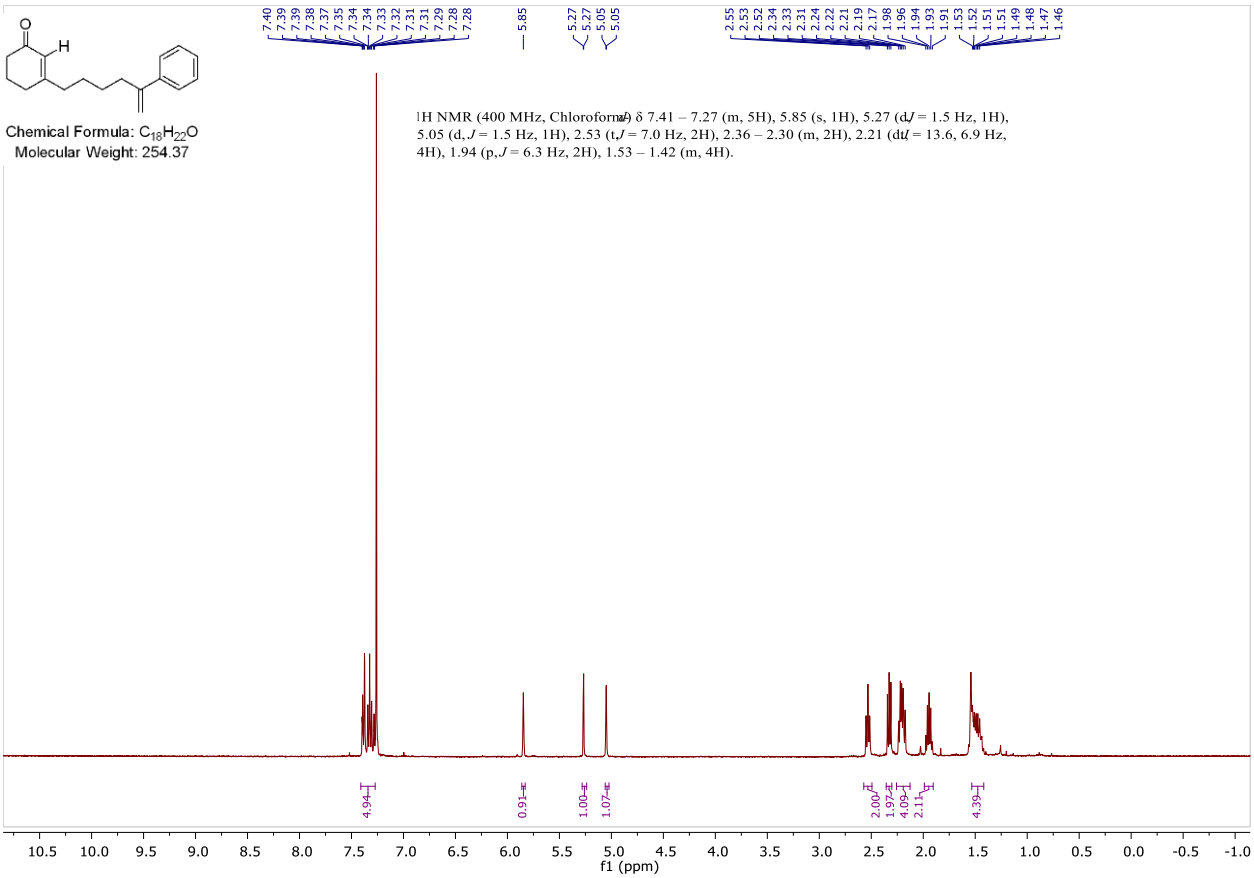

O
H
Me
Chemical Formula: C12H18O
Molecular Weight: 178.28
13C NMR (126 MHz, cdcl3) δ 200.03, 166.43, 145.08, 125.94, 110.67, 37.64, 37.52, 37.34, 29.88, 24.88, 22.90, 22.44.
200.03
166.43
145.08
125.94
110.67
77.41
77.16
76.91
37.64
37.52
37.34
29.88
24.88
22.90
22.44
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

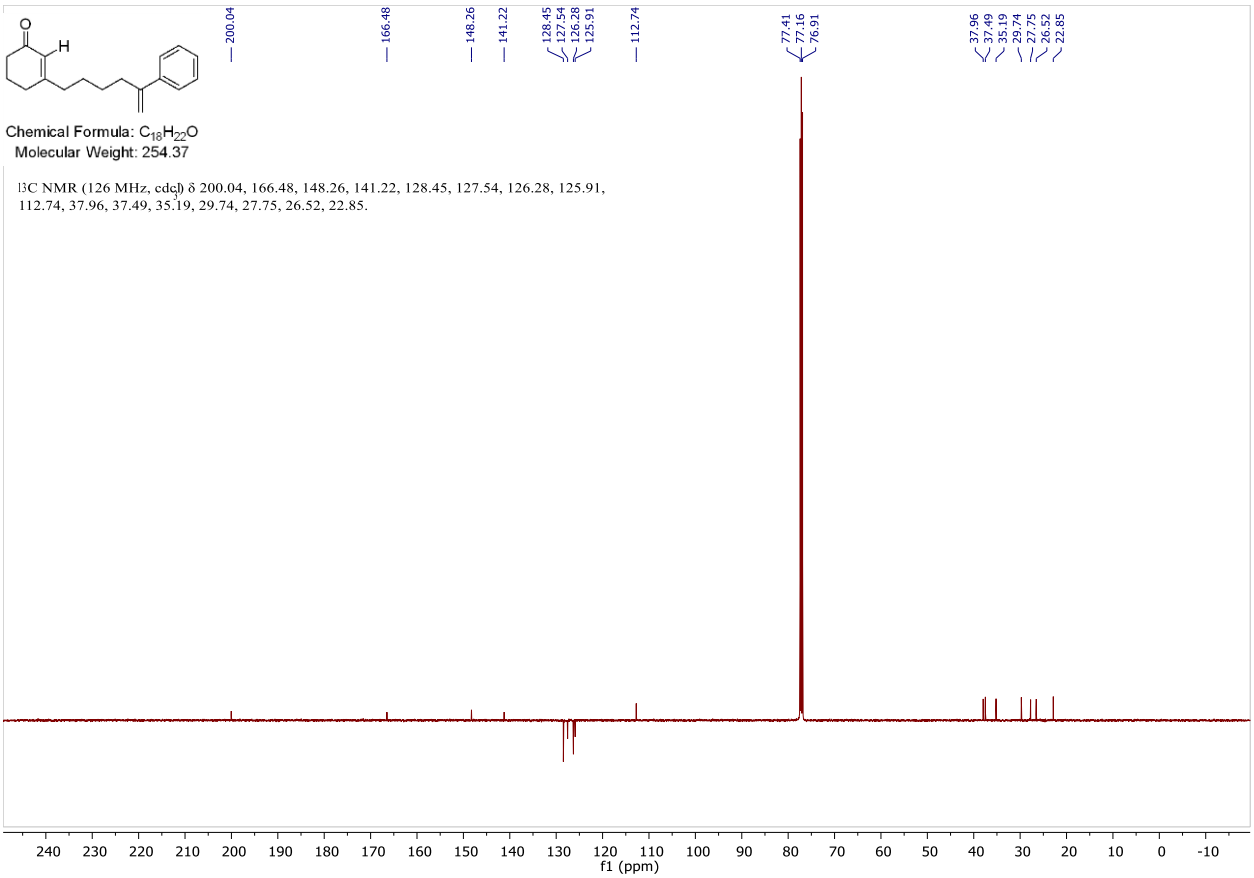

Ac Ac
H H
Chemical Formula: C26H36O4
Molecular Weight: 412.57
1H NMR (500 MHz, Chloroform-d) δ 5.77 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.05 – 4.95 (m, 2H), 2.40 (app dt, J = 12.3, 6.3 Hz, 3H), 2.32 (s, 3H), 2.22 – 2.15 (m, 2H), 2.11 – 2.04 (m, 2H), 2.02 – 1.95 (m, 2H), 1.64 – 1.54 (m, 2H).
7.26
5.81 5.79 5.79 5.78 5.77 5.76 5.75 5.75 5.74 5.73 5.04 5.03 5.00 5.00 4.97 2.43 2.41 2.40 2.39 2.37 2.35 2.34 2.32 2.29 2.28 2.27 2.26 2.21 2.19 2.19 2.18 2.17 2.09 2.08 2.07 2.05 2.01 2.00 1.99 1.97 1.96 1.62 1.61 1.60 1.59 1.58 1.56
1.00 1.84 3.18 2.54 1.79 1.96 1.82 1.97
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

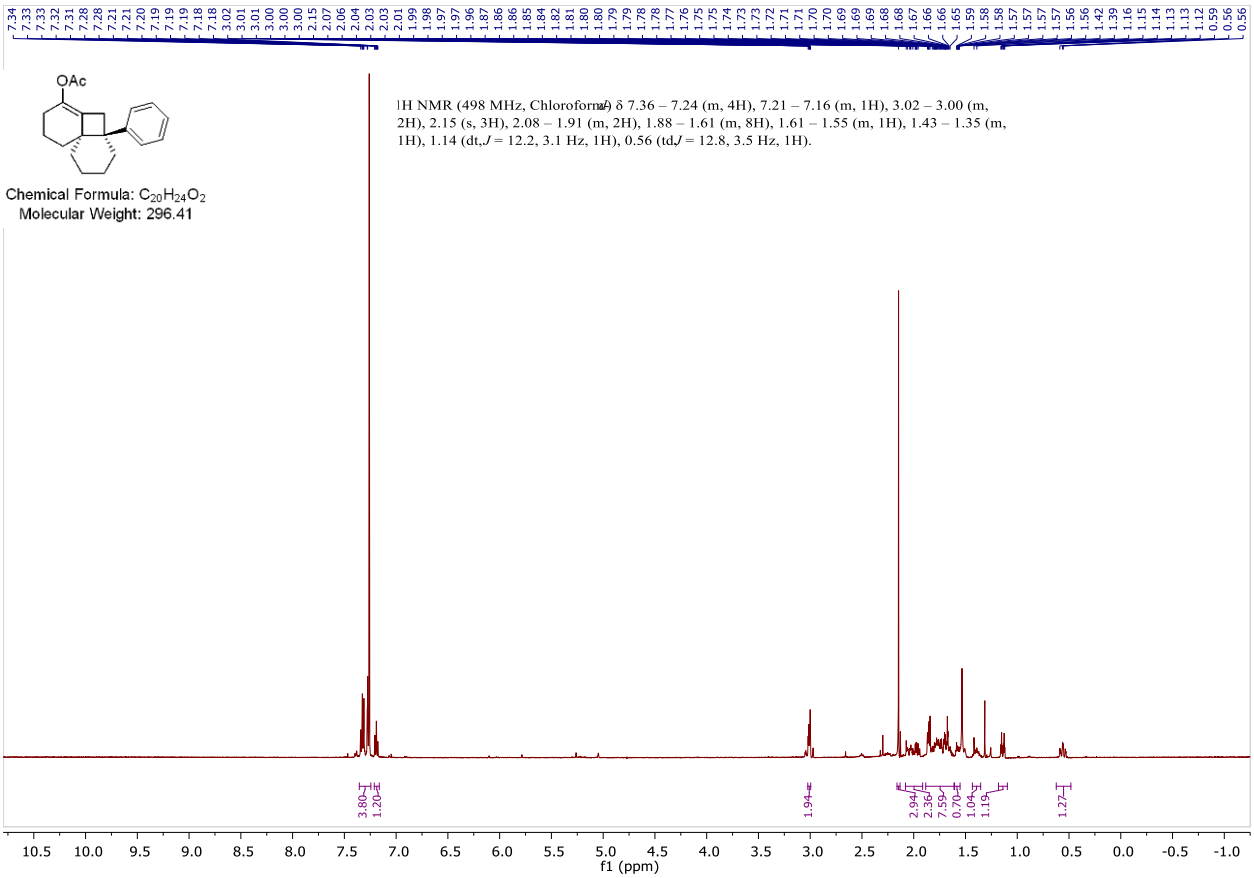

Ac Ac
H H
Chemical Formula: C26H36O4
Molecular Weight: 412.57
13C NMR (126 MHz, cdcl) δ 204.52, 197.31, 163.17, 139.92, 137.72, 115.58, 37.72, 35.10, 33.77, 32.12, 30.09, 27.47, 22.15.
204.52
197.31
163.17
139.92
137.72
115.58
77.41
77.16
76.91
37.72
35.10
33.77
32.12
30.09
27.47
22.15
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

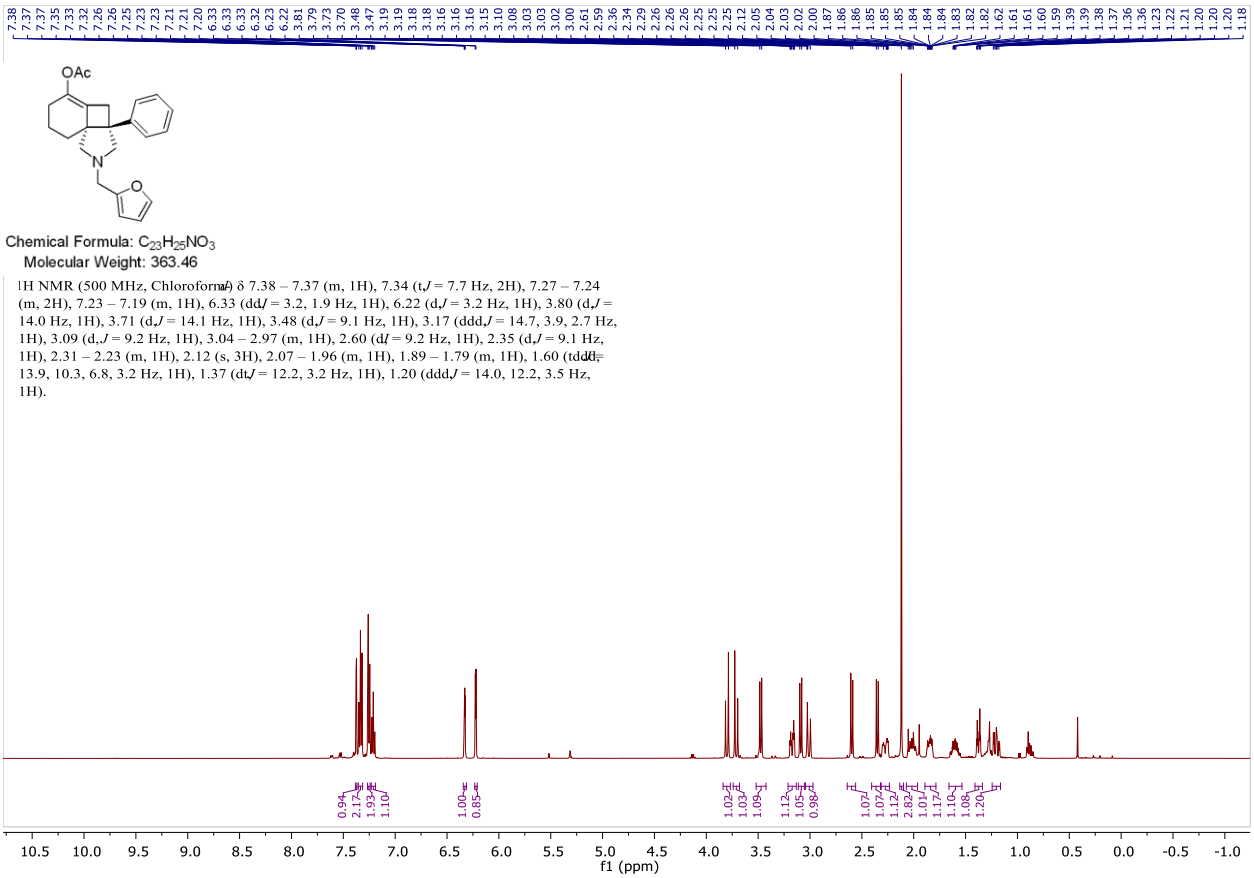

Chemical Formula: C11H16O
Molecular Weight: 164.25
1H NMR (500 MHz, Chloroform-d) δ 5.91 – 5.86 (m, 1H), 5.79 (ddt, J = 17.0, 10.2, 6.6 Hz, 1H), 5.06 – 4.95 (m, 2H), 2.39 – 2.33 (m, 2H), 2.28 (t, J = 6.1 Hz, 2H), 2.22 (t, J = 7.7 Hz, 2H), 2.08 (q, J = 7.1 Hz, 2H), 1.99 (p, J = 6.3 Hz, 2H), 1.62 (q, J = 7.6 Hz, 2H).
f1 (ppm)


199.99
166.30
138.00
125.97
115.42
77.41
77.16
76.91
37.52
37.51
33.33
29.86
26.22
22.89
Chemical Formula: C11H16O
Molecular Weight: 164.25
13C NMR (126 MHz, cdcl3) δ 199.99, 166.30, 138.00, 125.97, 115.42, 37.52, 37.51, 33.33, 29.86, 26.22, 22.89.
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Chemical Formula: C18H22O
Molecular Weight: 254.37
1H NMR (400 MHz, Chloroform-d) δ 7.41 – 7.27 (m, 5H), 5.85 (s, 1H), 5.27 (d, J = 1.5 Hz, 1H), 5.05 (d, J = 1.5 Hz, 1H), 2.53 (t, J = 7.0 Hz, 2H), 2.36 – 2.30 (m, 2H), 2.21 (dt, J = 13.6, 6.9 Hz, 4H), 1.94 (p, J = 6.3 Hz, 2H), 1.53 – 1.42 (m, 4H).
f1 (ppm)

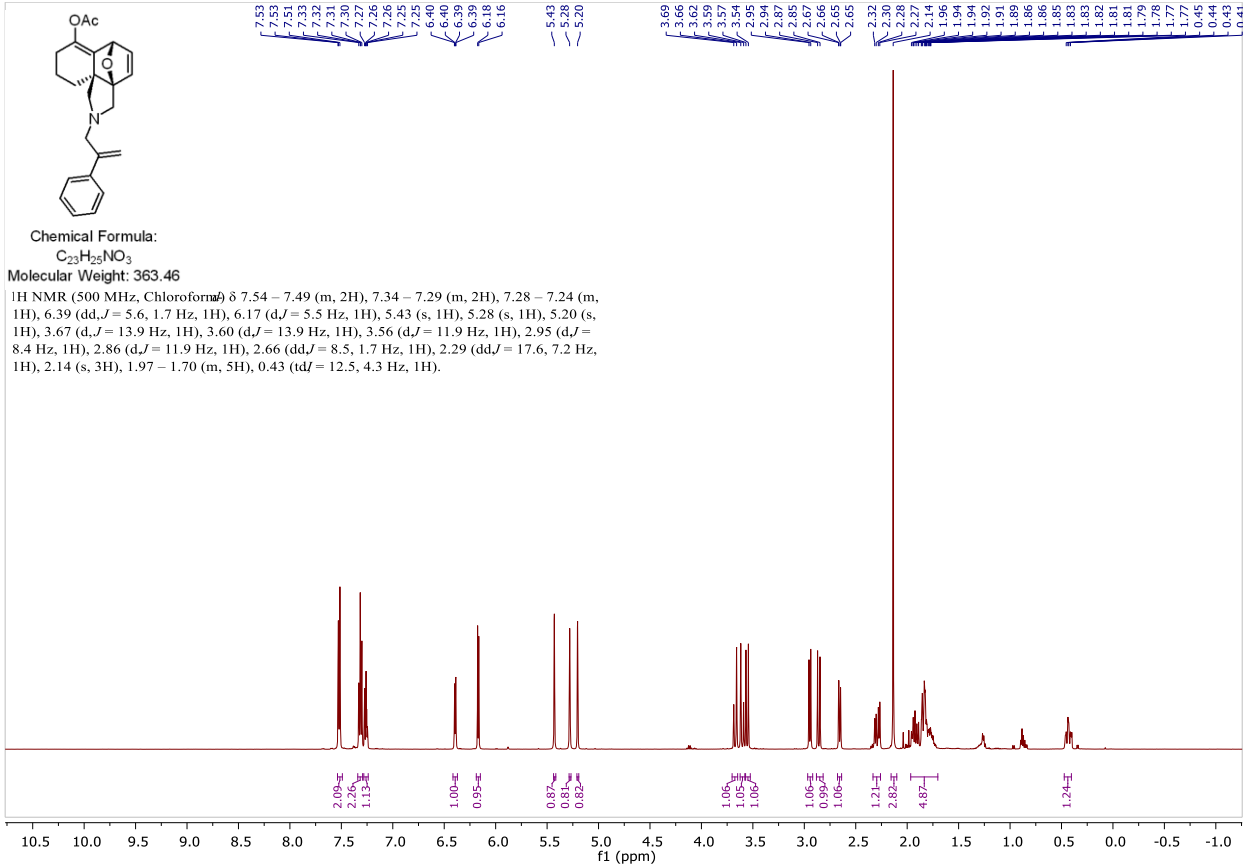

Chemical Formula: C18H22O
Molecular Weight: 254.37
13C NMR (126 MHz, cdcl) δ 200.04, 166.48, 148.26, 141.22, 128.45, 127.54, 126.28, 125.91, 112.74, 37.96, 37.49, 35.19, 29.74, 27.75, 26.52, 22.85.
200.04
166.48
148.26
141.22
128.45
127.54
126.28
125.91
112.74
77.41
77.16
76.91
37.96
37.49
35.19
29.74
27.75
26.52
22.85
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

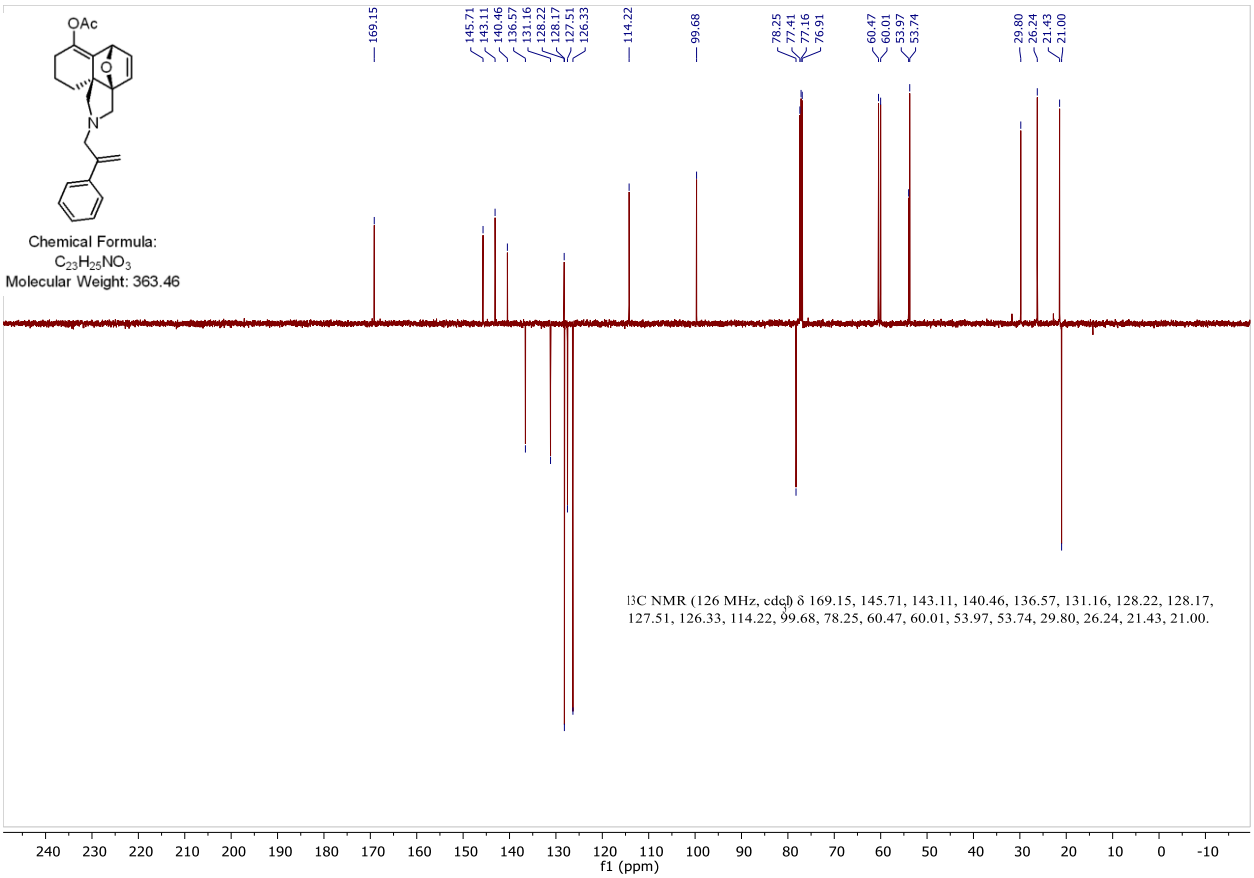

OAc
Chemical Formula: C20H24O2
Molecular Weight: 296.41
1H NMR (498 MHz, Chloroform-d) δ 7.36 – 7.24 (m, 4H), 7.21 – 7.16 (m, 1H), 3.02 – 3.00 (m, 2H), 2.15 (s, 3H), 2.08 – 1.91 (m, 2H), 1.88 – 1.61 (m, 8H), 1.61 – 1.55 (m, 1H), 1.43 – 1.35 (m, 1H), 1.14 (dt, J = 12.2, 3.1 Hz, 1H), 0.56 (td, J = 12.8, 3.5 Hz, 1H).
3.80
1.20
1.94
2.94
2.36
7.59
0.70
1.04
1.19
1.27
f1 (ppm)


OAc
N
O
Chemical Formula: C23H25NO3
Molecular Weight: 363.46
1H NMR (500 MHz, Chloroform-d) δ 7.38 – 7.37 (m, 1H), 7.34 (t, J = 7.7 Hz, 2H), 7.27 – 7.24 (m, 2H), 7.23 – 7.19 (m, 1H), 6.33 (dd, J = 3.2, 1.9 Hz, 1H), 6.22 (d, J = 3.2 Hz, 1H), 3.80 (d, J = 14.0 Hz, 1H), 3.71 (d, J = 14.1 Hz, 1H), 3.48 (d, J = 9.1 Hz, 1H), 3.17 (ddd, J = 14.7, 3.9, 2.7 Hz, 1H), 3.09 (d, J = 9.2 Hz, 1H), 3.04 – 2.97 (m, 1H), 2.60 (d, J = 9.2 Hz, 1H), 2.35 (d, J = 9.1 Hz, 1H), 2.31 – 2.23 (m, 1H), 2.12 (s, 3H), 2.07 – 1.96 (m, 1H), 1.89 – 1.79 (m, 1H), 1.60 (tdd, J = 13.9, 10.3, 6.8, 3.2 Hz, 1H), 1.37 (dt, J = 12.2, 3.2 Hz, 1H), 1.20 (ddd, J = 14.0, 12.2, 3.5 Hz, 1H).
f1 (ppm)

Chemical Formula: $C_{23}H_{25}NO_3$
Molecular Weight: 363.46

^{13}C NMR (126 MHz, cdcl) δ 168.88, 152.85, 141.87, 141.07, 138.55, 128.25, 127.46, 126.31, 126.10, 110.21, 108.03, 67.59, 65.97, 58.86, 55.44, 51.58, 37.53, 29.53, 26.82, 21.50, 21.10.


OAc
O
N
Chemical Formula:
$C_{23}H_{25}NO_3$
Molecular Weight: 363.46
^{1}H NMR (500 MHz, Chloroform-d) δ 7.54 – 7.49 (m, 2H), 7.34 – 7.29 (m, 2H), 7.28 – 7.24 (m, 1H), 6.39 (dd, J = 5.6, 1.7 Hz, 1H), 6.17 (d, J = 5.5 Hz, 1H), 5.43 (s, 1H), 5.28 (s, 1H), 5.20 (s, 1H), 3.67 (d, J = 13.9 Hz, 1H), 3.60 (d, J = 13.9 Hz, 1H), 3.56 (d, J = 11.9 Hz, 1H), 2.95 (d, J = 8.4 Hz, 1H), 2.86 (d, J = 11.9 Hz, 1H), 2.66 (dd, J = 8.5, 1.7 Hz, 1H), 2.29 (dd, J = 17.6, 7.2 Hz, 1H), 2.14 (s, 3H), 1.97 – 1.70 (m, 5H), 0.43 (td, J = 12.5, 4.3 Hz, 1H).
f1 (ppm)


OAc
O
N
Chemical Formula:
$C_{23}H_{25}NO_3$
Molecular Weight: 363.46
169.15
145.71
143.11
140.46
136.57
131.16
128.22
128.17
127.51
126.33
114.22
99.68
78.25
77.41
77.16
76.91
60.47
60.01
53.97
53.74
29.80
26.24
21.43
21.00
13C NMR (126 MHz, cdcl) δ 169.15, 145.71, 143.11, 140.46, 136.57, 131.16, 128.22, 128.17, 127.51, 126.33, 114.22, 99.68, 78.25, 60.47, 60.01, 53.97, 53.74, 29.80, 26.24, 21.43, 21.00.
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)