γ-Functionalization and its Application Towards Total Synthesis

By

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This thesis is dedicated to Shehni.

Contribution of Authors

Chapter 1 is an introduction to γ-alkylation. The challenges of γ-alkylation for natural product synthesis and the advantages of my method are discussed. Chapter 2 represents a manuscript for nickel-catalyzed γ-alkylation which will be submitted for review. I investigated the scope of the reaction that was first developed by Dr. Xiaohong Chen. I also worked on the synthesis of *9-oxoagerophorone*. Chapter 3 represents an unpublished formal synthesis of mesembrine. The route was developed by Dr. Justin Mohr and myself. Chapter 4 represents a series of unpublished experiments and an approach to the synthesis of crotontomentosin A. Sruthi Mohan and I investigated the scope of the aryl- and alkyl-magensium bromides. Chapter 5 represents an approach to the synthesis of propolisbenzofuran b. Chapter 6 represents a series of unpublished work on the γ-hydroxylamination. Dr. Xiaohong Chen was the first to discover this reaction and optimized the reaction conditions. While I tested the reaction scope and discovered synthetic applications.

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List Of Abbreviations

Ac	acetyl
alk	alkyl
aq	aqueous
Ar	aryl
Bipy	2,2'-Bipyridine
Bn	benzyl
Bz	benzoyl
n-Bu	butyl
t-Bu	tert-butyl, tertiary butyl
Calcd	calculated
cat.	catalytic amount
Cbz	Carboxybenzyl
Cy	cyclohexyl
δ	chemical shifts in parts per million downfield from tetramethylsilane (NMR)
2D	two-dimensional (NMR)
d	doublet
DCM	dichloromethane
DCE	1,2-dichloroethane
Dcype	1,2-Bis(dicyclohexylphosphino)ethane
Dppf	1,1′-Ferrocenediyl-bis(diphenylphosphine)
dppe	1,2-Bis(diphenylphosphino)ethane
DMA	dimethylacetamide

LIST OF ABBREVIATIONS (CONTINUED)

DMF	dimethylformamide
DMSO	dimethylsulfoxide
equiv	equivalent
EWG	electron-withdrawing group
EDG	electron-donating group
FMO	Frontier Molecular Orbital
GC	gas chromatography
h	hrs, hour(s)
n-hex	hexyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HR	high resolution (mass spectrometry)
Hz	Hertz
J	spin-spin coupling constant (NMR)
L	ligand
LDA	lithium diisopropylamide
m	multiplet (NMR)
mp	melting point
μ	micro
M	molar
MS	mass spectrometry
Me	methyl

LIST OF ABBREVIATIONS (CONTINUED)

mg	milligram
min	minute
mL	milliliter
mmol	millimole
MNDO	semiempirical molecular orbital calulations
MHz	megahertz
m/z	mass to charge ratio
NBS	*N*-Bromosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
PG	protecting group
Ph	phenyl
PMB	*p*-methoxybenzyl
PMDTA	pentamethyldiethylenetriamine
ppm	parts per million
i-Pr	isopropyl
o-tol	o-tolyl
PMB	*p*-Methoxybenzyl
PNZ	p-nitrobenzyl
Py	pyridine
q	quartet (NMR)
s	singlet (NMR)

LIST OF ABBREVIATIONS (CONTINUED)

sept	septet (NMR)
t	triplet (NMR)
TBS	tert-butyldimethylsilyl
Tc	thiophene-2-carboxylate
Tf	trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TES	triethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	p-toluenesulfonyl

SUMMARY

Synthetic efforts geared towards natural product synthesis highlight a clear deficiency in the synthetic technology directed at γ-functionalization. The γ-alkyl motif exists in numerous natural products and pharmaceutical targets. In order to address these limitations, new synthetic transformations are developed and applied towards the total synthesis of natural products.

To address the challenge of accessing γ-alkyl groups, a nickel-catalyzed γ-alkylation reaction between α-halocarbonyls and silyl dienol ethers is discovered. Endocyclic silyl dienol ethers were previously inaccessible, so a new palladium catalyzed coupling of β-tosyl silyl dienol ethers was developed. To demonstrate the value of γ-functionalization, the γ-alkylation was applied to the total synthesis of (±) mesembrine and crotontomentosin A.

γ-amination also remains a significant synthetic challenge and a motif that exists in numerous pharmaceutical targets. The copper-catalyzed aerobic oxidation of hydroxylamines afforded the nitroso, which reacts with cyclic or acyclic silyl dienol ethers to generate α,β unsaturated γ-hydroxylamines.

CHAPTER 1

γ-ALKYLATION TOWARDS NATURAL PRODUCT SYNTHESIS

1.1 Intro to γ-Alkylation in Natural Product Synthesis

Alkylation are the cornerstone of natural product synthesis and the development of efficient methods for selective functionalization remains a key synthetic challenge. Enones are one of the vital functional groups that synthetic chemists focus their attention on both due to their inherent reactivity and due to their presence in numerous natural products and pharmaceutical targets.

The carbonyl moiety of an enone is often acted upon by nucleophiles such as Grignard reagents or Wittig reagents giving access to new carbon–carbon bonds. The acidity of the α-proton lends itself to the formation of α-enolates which can react with alkyl halides, aldehydes or other soft electrophiles to form new α carbon–carbon bonds. [1] The electrophilic nature of the β-carbon on the enone enables nucleophiles such as organocuprates, malonates or even enolizable carbonyl groups to form new β carbon–carbon bonds.[2]

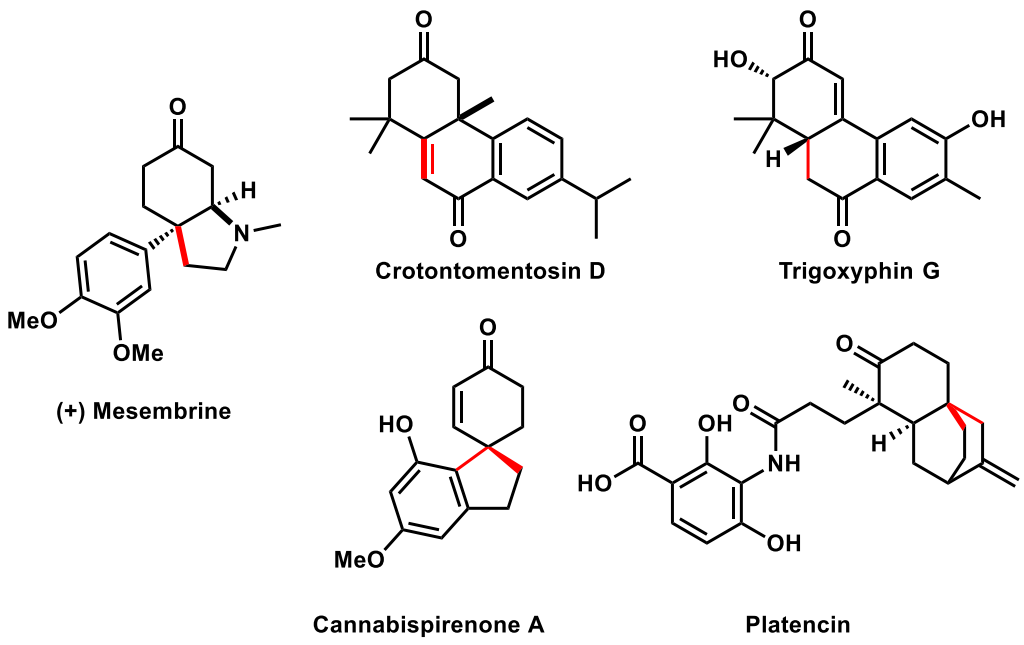


Figure 1.1 Natural Products and Pharmaceutical Targets Containing γ-Alkyl Groups

Efficient and versatile methods for γ-alkylation are vital for the synthesis of numerous natural products and pharmaceutical targets.[3] (Figure 1.1). However, direct methods for alkylation of the remote γ-sites are under-developed or limited by substrate scope.

Recent developments in γ-functionalization have provided new avenues for synthetic chemists to synthesize new bonds on a previously elusive carbon atom. Ideally, the simplest method for γ-alkylation would be the synthesis of a γ-dienolate which would be expected to selectively form a new γ carbon–carbon bond.[4]

1.2 Synthesis and reactivity of γ-dienolate

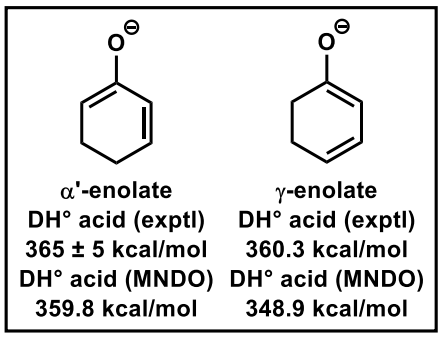
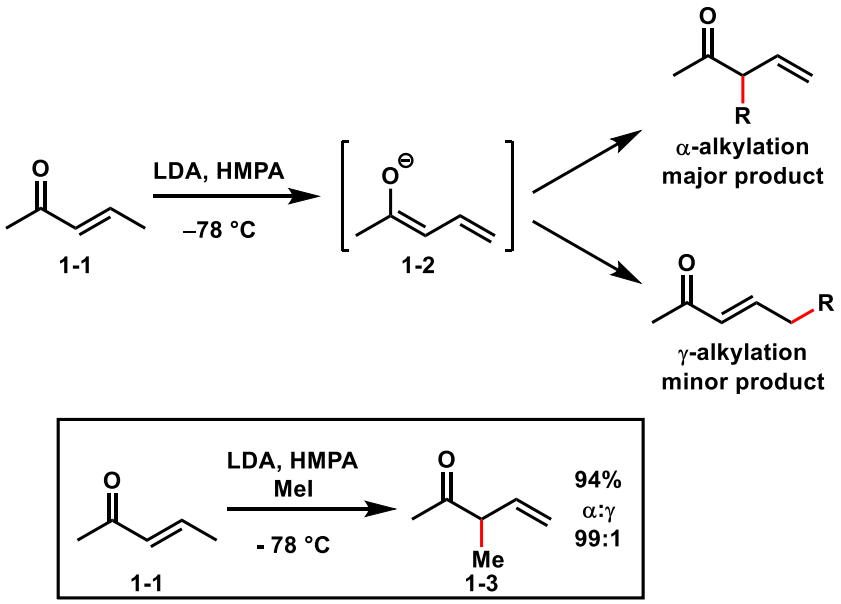


Figure 1.2 Experimental Enthalpy Calculations for Dienolates of Cyclohexenone

Deprotonation of cyclic enones leads to two possible dienolates, the vinylogous γ-dienolate or the cross-conjugated α'-dienolate. The kinetic and thermodynamic acidities of enones were examined, by Kipling and coworkers, in the gas phase to minimize the effects of solvent and counterions.[4] The γ-dienolate of cyclohexenone was determined to be 6.5 ± 0.4 kcal/mol lower in energy than the cross-conjugated α' dienolate.[5] (Figure 1.2). Stereoelectronically, the α-proton is kinetically more acidic as the deprotonation does not require the deconjugation of the alkene. However, the extended conjugation of the γ-dienolate delocalizes the charge more effectively, resulting in a lower energy product.

The γ-dienolate **1-2** was synthesized by Schlessinger and coworkers in 1978, when pent-3-en-2-one was treated LDA and HMPA additive (Scheme 1.1).[6] The authors observed that upon treatment of the γ-dienolate **1-2** with alkyl halides, the α-alkylated product **1-3** was discovered to be the major product. Through simple MO calculations, it was determined that most of the negative charge would reside on the α-carbon, therefore making it more nucleophilic than the γ-carbon.[7]



Scheme 1.1 Regioselectivity of Dienolate Alkylation

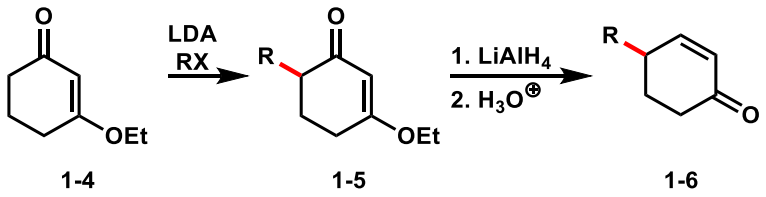
1.3 Dienolates towards γ-functionalization

Numerous methods have been developed and utilized to synthesize the γ-alkyl moiety towards the synthesis of natural products. Herein, we will discuss some of the methods and their applications.

1.3.1 Stork and Danheiser synthesis of β-vetivone

In 1973, Stork and Danheiser developed an indirect protocol for γ-alkylation through vinylogous esters (Scheme 1.2).[8] After converting 1,3-diketones **1-4** to vinylogous esters **1-5**, they

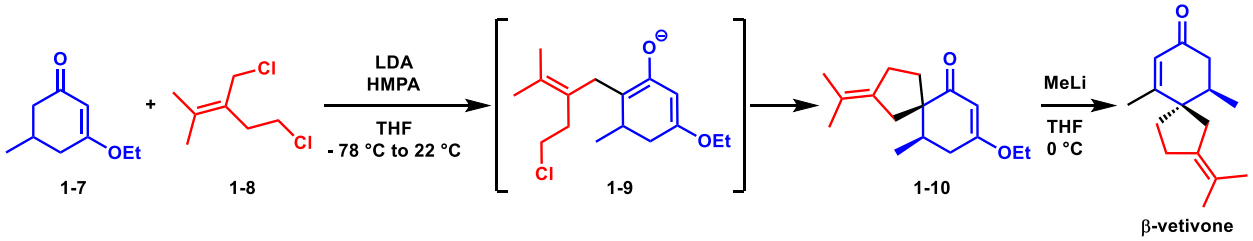
were able to utilize the α'-enolate to form the carbon–carbon bond which would be followed by nucleophilic attack on the carbonyl group and acidic workup to form the γ-alkylated enone **1-6**.



Scheme 1.2 Stork–Danheiser Transposition

The Stork–Danheiser transposition is limited to readily accessible 1,3-diketones which can be difficult to synthesize or to alkyl halides that are not susceptible to nucleophiles or hydrides. Alternatively, protecting group strategies can be utilized for the alky halides.

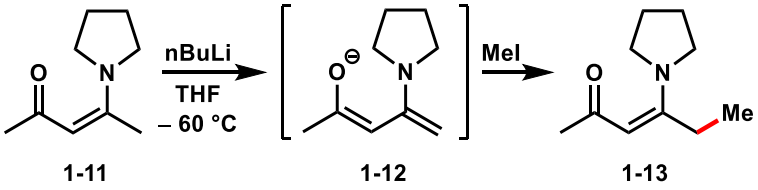
The Stork–Danheiser transposition was applied towards the total synthesis of β-vetivone (Scheme 1.3).[9] The vinylogous ester **1-7** was treated with lithium diisopropylamide to form the α'-enolate. The first alkylation would occur selectively with the allylic chloride **1-7**. Upon treatment with another equivalent of LDA, the enone would form the α'enolate **1-9**. This α'-enolate was alkylated by the homoallylic chloride to form the exocyclic cyclopentenone **1-10**. A single diastereomer would form as the second alkylation would occur selectively from the face opposite of the pseudoaxial methyl group. Grignard addition to the carbonyl, followed by acidic workup would provide the γ-dialkylated natural product, β-vetivone.



Scheme 1.3 Stork Synthesis of β-vetivone

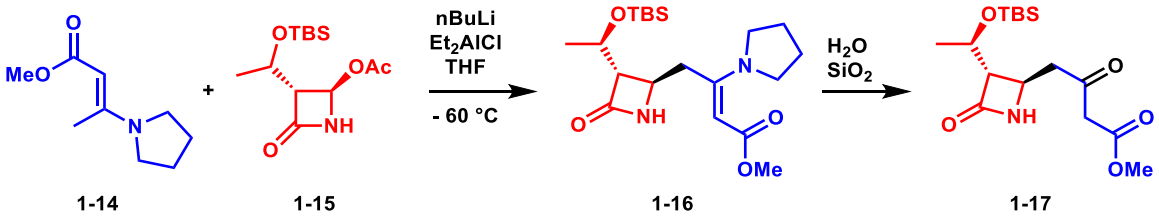
1.3.2 Synthesis of RS-533

Vinylogous amides **1-11** formed the desired γ-dienolate **1-12** as demonstrated by Hiraoka in 1973, for direct γ-alkylation (Scheme 1.4).[10] The electrons on this γ-dienolate are delocalized on the γ-carbon due to the stabilizing of the β-amino group. Alkylation occurs with alkyl bromides or iodides, as well as on α,β unsaturated esters or phenyl ketones. Under this protocol, no O-alkylation or α-alkylation occurs. Aldehydes and ketones are also applicable for γ-alkylation under this protocol to form secondary or tertiary alcohols, respectively.



Scheme 1.4 γ-Alkylation through Vinylogous Amide

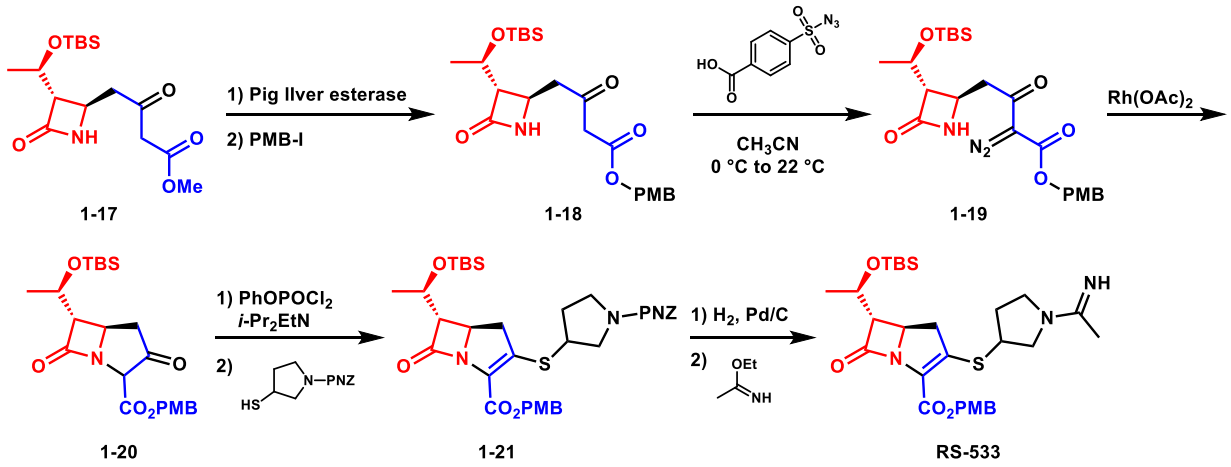
These enaminoketones **1-11** are synthesized through dehydration of 1,3-diketones, so this method is also limited by substrate scope. The use of strong bases for the deprotonation also requires the alkyl halide to not be susceptible to strong bases and for careful control of the temperature.



Scheme 1.5 Synthesis of Carbapenem, RS 533.

Sugawara and coworkers utilized the β-amino dienolate method to synthesis the carbapenem RS-533 (Scheme 1.5).[11] The enamino ester **1-14** was deprotonated by *n*-BuLi in the presence of diethyl aluminum chloride to form the β-amino dienolate. The β-lactam **1-15**

eliminated the acetate group to form an iminium which upon treatment with the β-amino dienolate formed a new γ carbon–carbon bond. The configuration of the new γ carbon–carbon bond was set by the sterically bulky α-alkyl group on the β-lactam.



Scheme 1.6 Final Steps Towards the Synthesis of RS-533

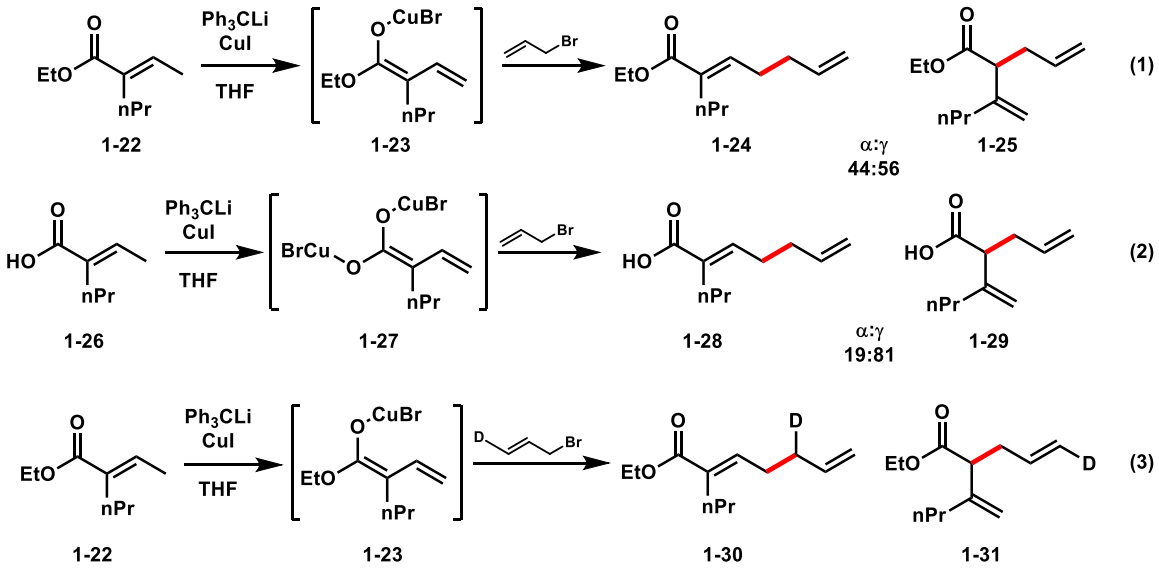
Treatment of the enamino ester **1-16** with silica gel and a drop of water, provided the β-ketoester **1-17** which was subjected to pig liver esterase to form the β-keto carboxylic acid (Scheme 1.6). Alkylation of the carboxylic acid formed the ester **1-18.** Formation of diazo compound **1-19** enabled the Rhodium-catalyzed cyclization to form the carbapenem core **1-20**.[12]

Chlorination of the ketone **1-20** with diphenylphosphoryl chloride provided the vinyl chloride which was then converted to the vinyl thiol **1-21** upon treatment with (S)-1 p-nitrobenzyloxycarbonyl -3-mercaptopyrrolidine. The protecting group on nitrogen was cleaved through hydrogenolysis and then the nitrogen was alkylated to form RS 533.

1.3.3 Synthesis of Lanceol through Copper-Dienolates

The nucleophilic nature of the α-carbon of the γ-dienolate can be modified by counter ions. Copper dienolates **1-23** were compared to lithium dienolates for γ-allylation by Katzenellenbogen and co-workers (Scheme 1.7).[3a] The copper dienolates **1-23** were found to improve the γ-allylation

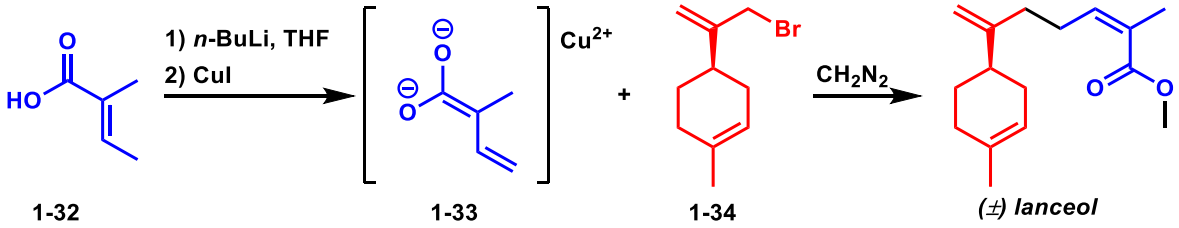
ratio to 56:44 from 95:5 for lithium dienolates (Scheme 1.7, eqn 1). The α,β-unsaturated carboxylic acids **1-26** showed better γ-selectivity as the dianionic acid species **1-27** has more negative charge on the γ-carbon than the monoanionic ester species (Scheme 1.7, eqn 2). Through deuterium labeling experiments, it was determined that the γ-allylation occurred through SN_2' mechanism, whereas the α-allylation occurred through an SN_2 mechanism (Scheme 1.7, eqn 3).



Scheme 1.7 Copper-Dienolate Alkylation

The lack of selectivity in the mode of attack, SN_2 or SN_2', requires the use of symmetrical allyl halides to prevent formation of multiple inseparable isomers. Also, the method is limited to α,β unsaturated esters or carboxylic acids, with the carboxylic acids providing higher selectivity for γ-alkylation. (Scheme 1.7, eqn 3).

The synthesis of (±)-Lanceol began with the formation of the copper dienolate **1-33** from tiglic acid **1-32** (Scheme 1.8).[13] As previously stated, the carboxylic acid-derived copper dienolate showed greater selectivity for γ-alkylation and only γ-alkylation occurred for the tiglic acid derived copper dienolate alkylation with the allyl bromide **1-34**.



Scheme 1.8 Synthesis of (±)-Lanceol

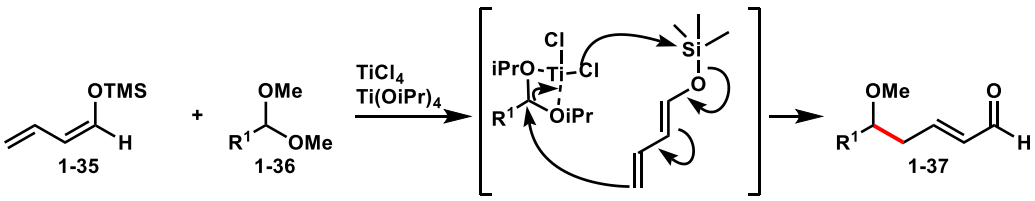
The symmetry of the allyl bromide with respect to allylic transposition prevented the mode of attack SN_2 or SN_2' from altering the product formed. Finally, the methylation of the carboxylic acid formed (±)-Lanceol.

1.4 γ-Functionalization through Lewis-Acid Catalysis

Metallo-dienolates offered selectivity towards γ-alkylation.[14] Alternatively, silyl protected dienolates, due to their stability and reduced nucleophilicity on the α-carbon were found to be a better alternative.[15] The reduced nucleophilicity of the silyl dienolates require activation of the electrophiles which could occur through Lewis acid catalysis.

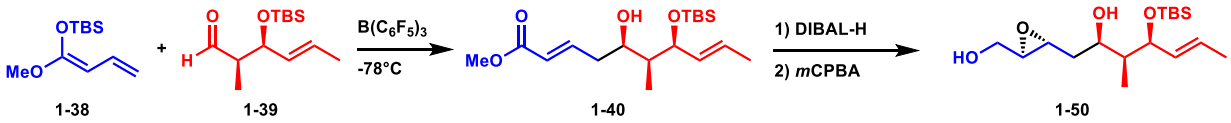
1.4.1 Synthesis of (+)-Ratjadone through Vinylogous Aldol

Titanium tetrachloride was found, by Mukaiyama in 1975, to act as a Lewis acid to catalyze the aldol addition of acetals to silyl ketene acetals (Scheme 1.9).[16] The reaction scope extended to both α,β-unsaturated acetals and saturated acetals. For saturated acetals, both titanium tetrakis(triisopropoxide) and titanium (IV) chloride were necessary to minimize the undesired formation of polymeric side-products. The substrate scope was limited to silyl ketenes acetals which led only to the formation of γ-alkylated aldehydes or esters.



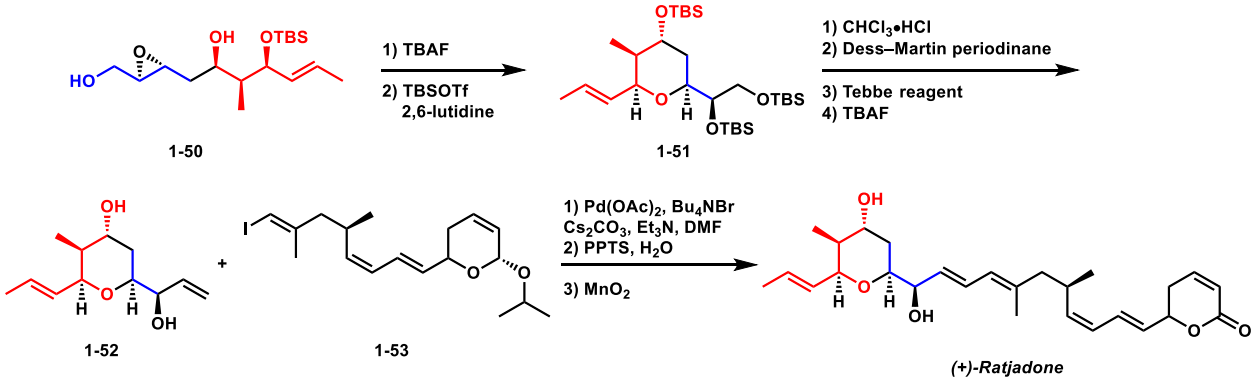
Scheme 1.9 Mechanism for Vinylogous Aldol[17]

Kalesse and coworkers applied the vinylogous aldol reaction towards the synthesis of (+)-ratjadone (Scheme 1.10).[18] The vinylogous aldol of silyl ketene acetal **1-38** and aldehyde **1-39** promoted by tris(pentafluorophenyl)borane to form the δ-alcohol **1-40**. The stereochemistry of the alcohol was set by the methyl group as the silyl ketene acetal will attack from the face opposite to the methyl group.



Scheme 1.10 Synthesis of (+)-Ratjadone through Vinylogous Aldol

Epoxidation of the electron-deficient alkene, and cleavage of the silyl protecting group provided the 6-*exo* ring closure to form the tetrahydropyran moiety **1-51** (Scheme 1.11).



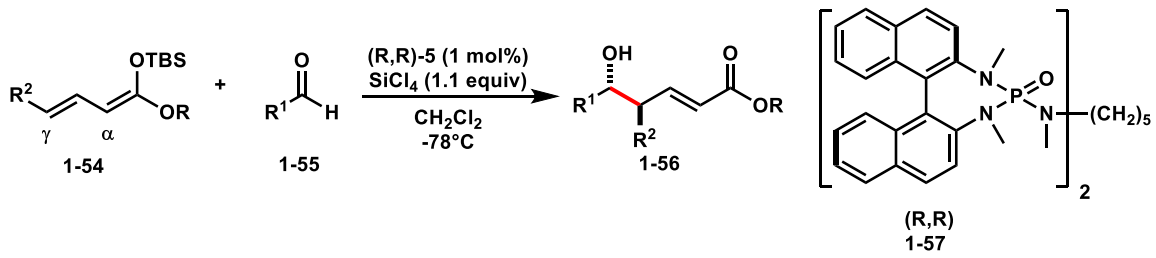
Scheme 1.11 Final Steps for the Synthesis of (+)-Ratjadone

The ester was reduced to the aldehyde which was then converted to the alkene **1-52**. This alkene underwent Heck reaction with Jeffrey's modification with the vinyl iodide **1-53**, followed by deprotection of the lactol and oxidation to the lactone to furnish the (+)-ratjadone.

1.4.2 Synthesis of Macrolactin A through Enantioselective Vinylogous Aldol

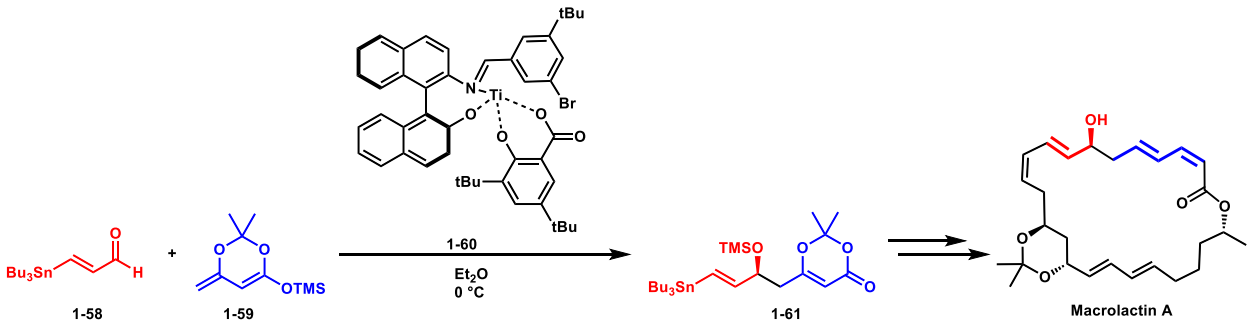
In 2003, Denmark and coworkers, reported an enantioselective variant of the vinylogous aldol using BINAM-derived phosphoramides **1-57** (Scheme 1.12).[3g] This strategy overcame the inherent α-selectivity of the metallo-dienolates through steric preference for the less-substituted γ-

carbon using bulky modifiers. They also proposed that the γ-addition pathway would predominate as the reactions of silyl dienol ethers **1-54** should fall under FMO control as opposed to the electrostatic control of lithium-dienolates. (Scheme 1.12).[19]



Scheme 1.12 Lewis-Acid Catalyzed Vinylogous Aldol Reactions

Another contributing factor is the sensitivity of the bis(phosphoramide) catalyst to the steric demands of the substrates which would then prefer reaction from the less sterically hindered γ-carbon. Despite the high enantio- and diastereoselectivity of this regioselective, chiral Lewis acid catalyzed aldol reaction, this method was limited by its substrate scope of ester-derived dienol ethers and was not found to be applicable to aldehyde or ketone-derived dienol ethers.

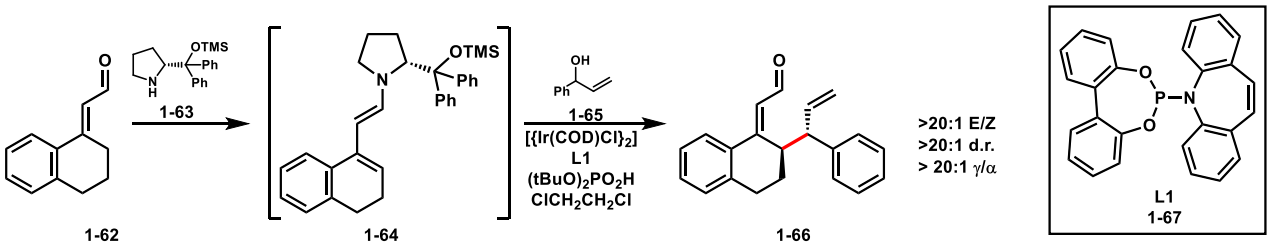


Scheme 1.13 Synthesis of Macrolactin A

In 1998, Carreira and coworkers showed the application of this method towards the total synthesis of macrolactin A (Scheme 1.13).[20] The Meldrum's acid derived silyl ketene acetal **1-59** underwent the titanium catalyzed vinylogous aldol with vinyl tin **1-58** to form the silyl ether **1-61**. The (*S*)-titanium catalyst **1-60** provided the (*S*)-enantiomer of the silyl ether.[21] Further functionalization of the vinyl stannane **1-61** provided macrolactin A.

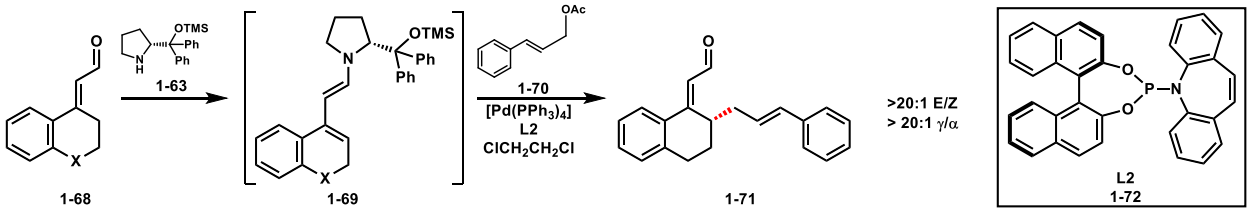
1.4.3 Synthesis α-Tocopherol through Proline-Derived Dienamines

Proline-derived dienamines **1-64** from α,β-unsaturated aldehydes **1-62** were shown to undergo transition metal-catalyzed allylation through iridium-catalyzed γ-allylation by Jorgenson (Scheme 1.14).[22]



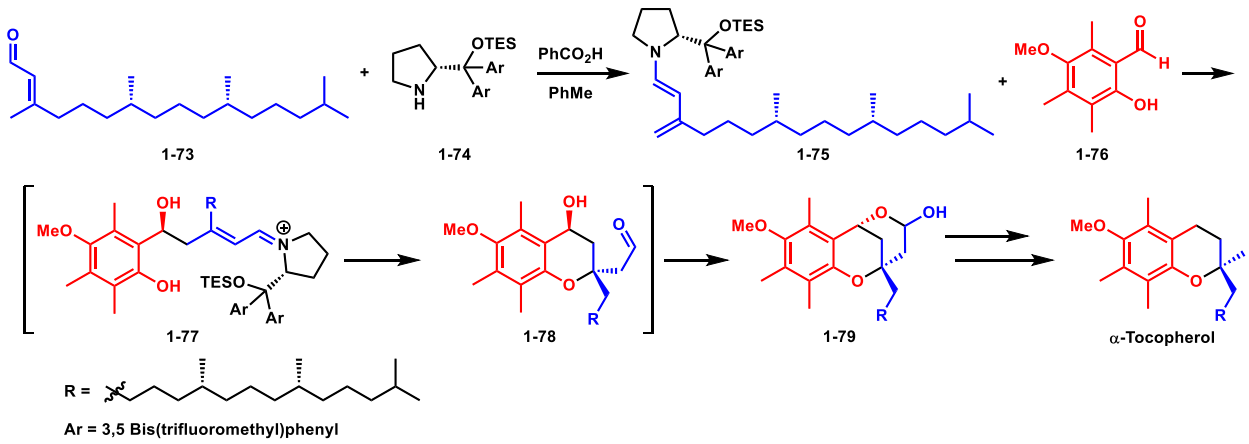
Scheme 1.14 γ-alkylation of Proline-Derived Dienamines through Ir-catalyzed Allylation

The dienamines **1-69** can also act as nucleophiles on allyl-palladium intermediates to form linear allyl products (Scheme 1.15). The phosphine catalyst **1-72** enabled excellent diastereoselectivity in the reaction. The dienamines **1-69** were derived from α,β unsaturated aldehydes **1-68** and limited this method to γ-alkylation of aldehydes.



Scheme 1.15 γ-alkylation of Proline-Derived Dienamines through Pd-Catalyzed Allylation

The proline-derived dienamines have been reported by Woggon and coworkers to successfully undergo alkylation with an aldehyde for the synthesis of α-tocopherol (Scheme 1.16).[23] The proline-derived dienamine **1-75** of aldehyde **1-73** underwent γ-alkylation with benzaldehyde **1-76**. Electron-deficient aryls on the proline were found to better facilitate the γ-alkylation and offered better diastereoselectivity.

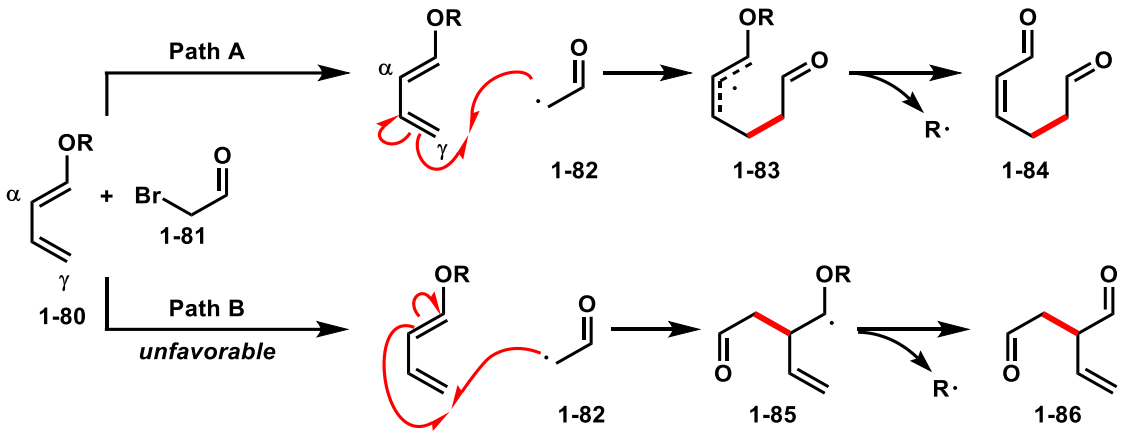


Scheme 1.16 Synthesis of α-Tocopherol

The imine **1-77** that forms after the alkylation is attacked by the phenol to form the pyran **1-78**. The secondary alcohol attacked the nearby aldehyde to form the lactol **1-79**. The resulting Lactol **1-79** was oxidized to the lactone and then hydrolyzed to the carboxylic acid. The rhodium-catalyzed decarbonylation of the aldehyde resulting from the reduction of the carboxylic acid completed the synthesis of α-tocopherol.

1.5 γ-Functionalization through Radical Pathways

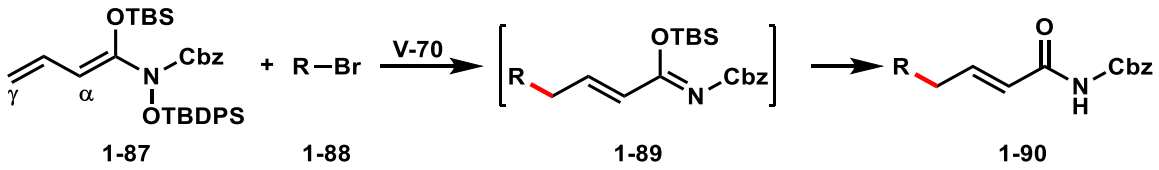
An alternative pathway to γ-alkylation is through alkyl radical addition (Scheme 1.17). Generation of alkyl radicals **1-82** from α-halocarbonyls **1-81** has been well-established.[24] The site selectivity for this reaction was proposed to be controlled by the formation of an alkoxy-allyl radical **1-83** which was only accessible through the γ-addition pathway. The α-addition pathway produces the less stable alkoxy radical **1-85** and no α-alkylated product is formed. Dialkylation whereby the alkyl radical adds to the β-carbon of the enone also fails to occur.[25]



Scheme 1.17 Proposed Radical Addition Pathway

1.5.1 Radical-mediated γ-alkylation through Azo initiators

Kim and coworkers has shown that alkyl radicals formed in situ by treatment of alkyl halides with the radical initiator, V-70, 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile), selectively adds to the γ-carbon of hydroxamic acid-derived silyl dienol ethers **1-87** (Scheme 1.18). [3h] (Scheme 1.18). Upon addition of the carbon centered radical to the γ-carbon, a stable allylic radical would then form. Cleavage of the N–O bond forms intermediate **1-89**, which then isomerizes to the amide. This method is limited to the dienol ethers of hydroxamic acids or esters, and to electrophilic alkyl radicals.[3i]

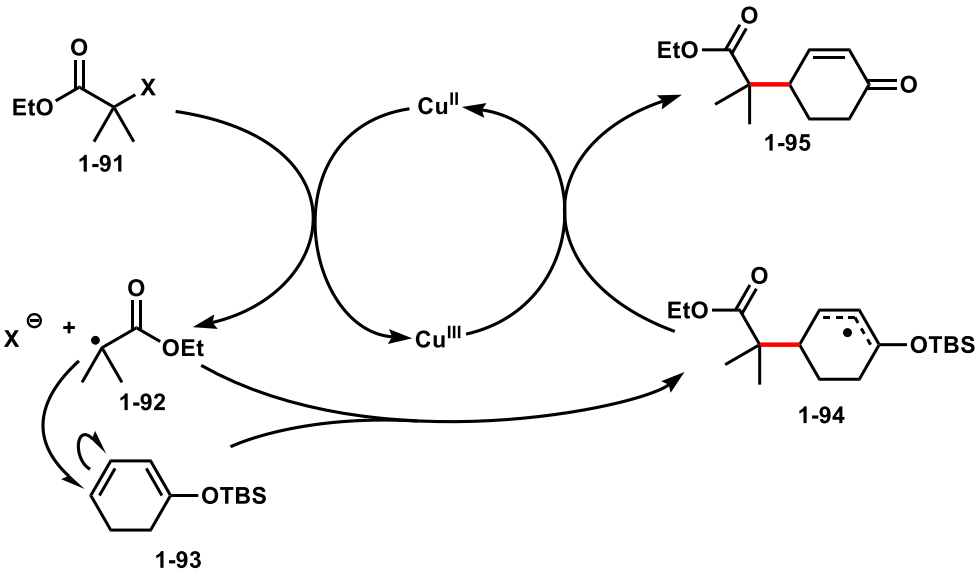


Scheme 1.18 Radical-Mediated γ-Alkylation

1.5.2 Copper-catalyzed radical-mediated γ-alkylation

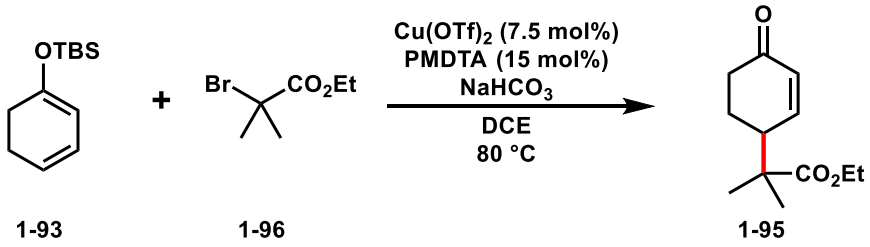
Copper catalysts have been shown to activate α-haloesters towards addition to π-systems.[26] A carbon-centered radical is also proposed to form which would add selectively to the γ-carbon.[27]

Previously, our lab has shown that radical additions to the silyl dienol ethers occur selectively to the γ-carbon.[29]



Scheme 1.19 Proposed Radical Mechanism for Copper-Catalyzed γ-Alkylation

In a recent report by our lab, an α-bromoester **1-96** in the presence of $Cu(OTf)_2$, pentamethyldiethylenetriamine (PMDTA) was shown to γ-alkylate on a readily available silyl dienol ether **1-93** in 1,2-dichloroethane (DCE) (Scheme 1.20).[28] These carbon-centered radicals were only able to form on tertiary or secondary alkyl halides however chemoselectivity for the halogen abstracted offered methods to selectively access dihalogenated γ-esters (Table 1.3).

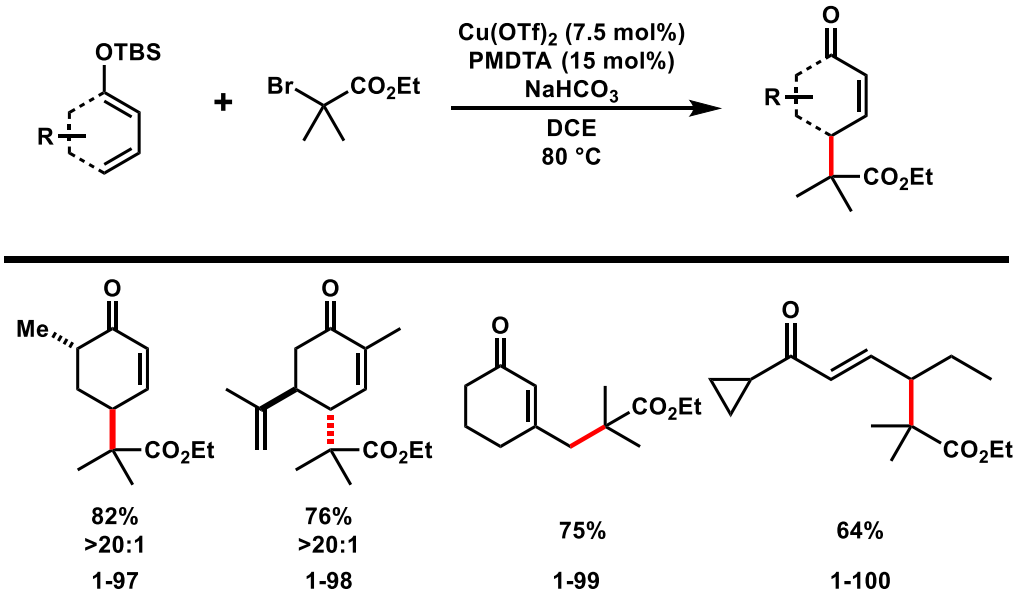


Scheme 1.20 Copper-Catalyzed γ-Alkylation

To examine the reaction scope, we found several silyl dienol ethers to be viable substrates (Table 1.1)[29]. Cyclohexenone-derived silyl dienol ethers with α-substituent were shown to have

excellent stereoselectivity forming a single diastereomer of the 1,6 dicarbonyl product **1-97** after γ-alkylation. Even with β-substituted enones, only the *anti*-diastereomer **1-98** was delivered in high yields.

Table 1.1 Reaction Scope of Silyl Dienol Ethers



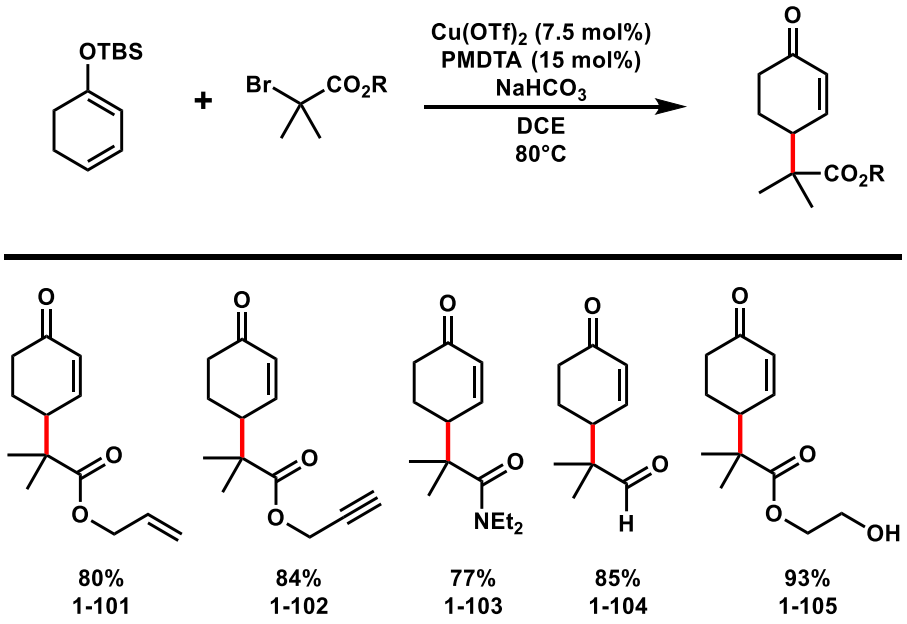
Exocyclic silyl dienol ethers were also found to afford the γ-alkylated enone **1-99** in high yields. Acyclic silyl dienol ethers were also found to undergo γ-alkylation selectively to form the acyclic γ-alkylated enone **1-100**.

The functional group tolerance of this coupling was examined through the modification of the α-halocarbonyl compounds. Alkenes **1-101**, alkynes **1-102**, amides **1-103**, aldehydes **1-104,** and unprotected alcohols **1-105** were shown to be tolerated with this reaction (Table 1.2).

Steric and electronic flexibility of the α-halocarbonyl was evident through the reaction of α-benzylic bromide with an isophorone-derived silyl dienol ether (Table 1.3). Cyclic α-halocarbonyls such as α-bromobutyrolactone, and α-bromocyclohexanone were also found to react readily to form **1-108** and **1-109**, respectively. The brominated derivative of the anti-inflammatory

agent, phenylbutazone was also able to be coupled in good yield to form **1-110** when the reaction was run at 22 °C.

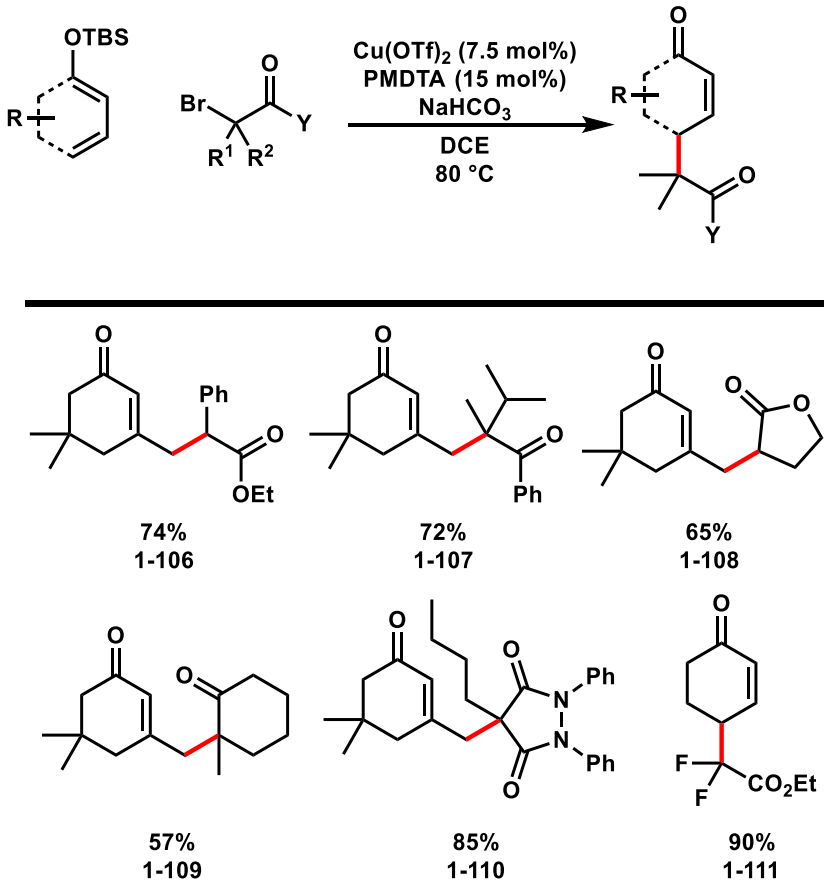
Table 1.2 Scope of α-Bromocarbonyls



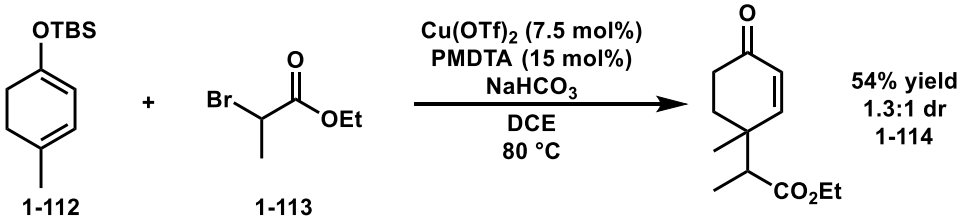
In further examination of the α-halocarbonyl, we observed that the coupling of ethyl bromodifluoroacetate proceeded through selective formation of the carbon radical by cleavage of the C–Br bond to furnish only difluoroacetate derivatives **1-111**.

Synthesis of a γ-quaternary center would be a challenging sterically-congested motif that could arise from coupling of γ-alkylated dienol ethers. Although the coupling failed with tertiary α-haloesters; by coupling with ethyl 2-bromopropionate **1-113**, we found that we formed a quaternary center on the γ-carbon of an enone **1-114** (Scheme 1.21).

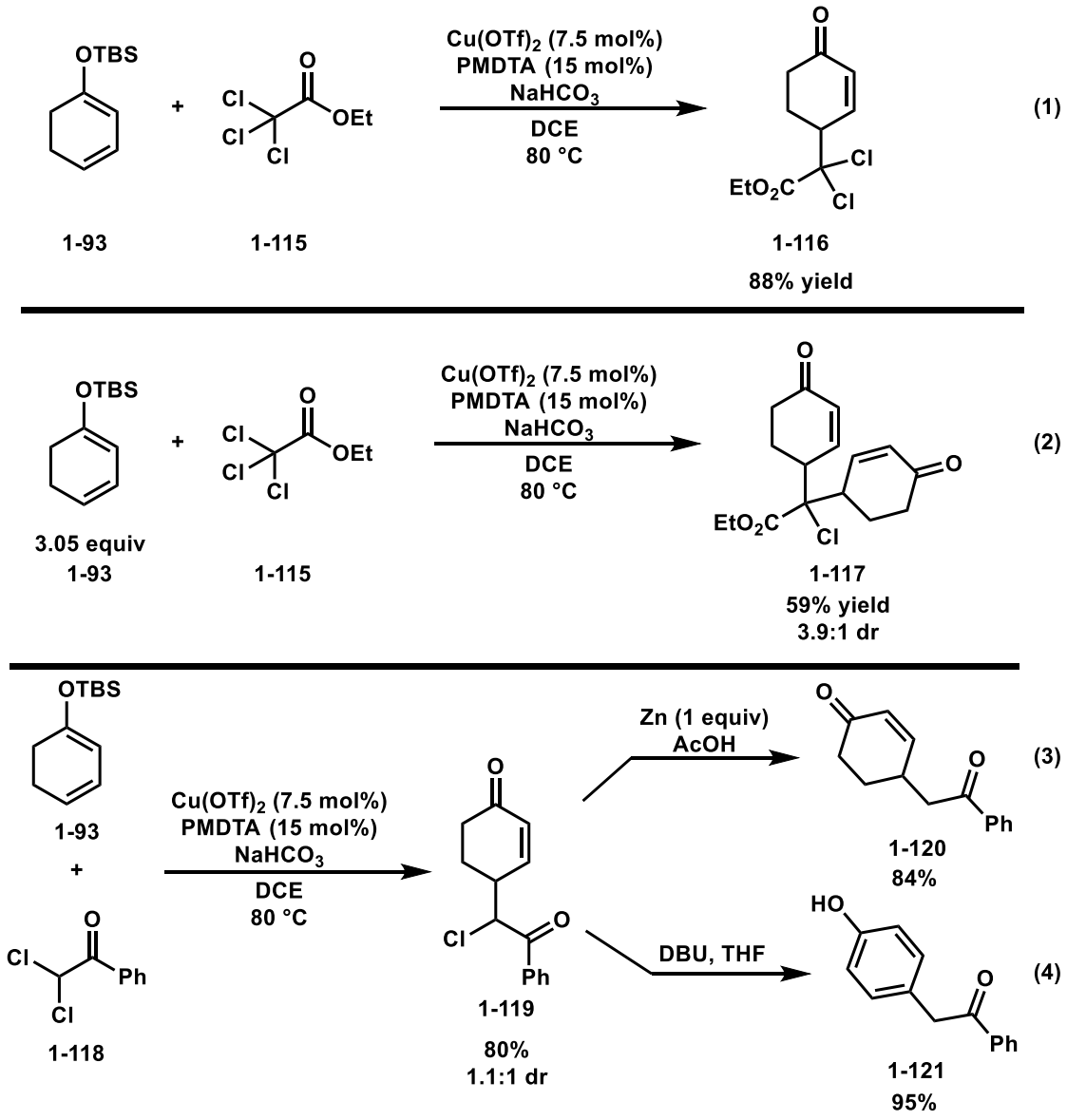
Table 1.3 Scope of Secondary and Tertiary α-Bromocarbonyls



To further test the scope of the α-halocarbonyls, we examined the reaction of α-trihalocarbonyls to determine selectivity of the α-halo and the limitations of the reactions (Scheme 1.22). Upon treatment with ethyl trichloroacetate **1-115**, the reaction proceeded and that under forcing conditions, we could further couple the chloride product **1-116** to undergo γ-dialkylation to form **1-117** (Scheme 1.22, eqn 1-2).

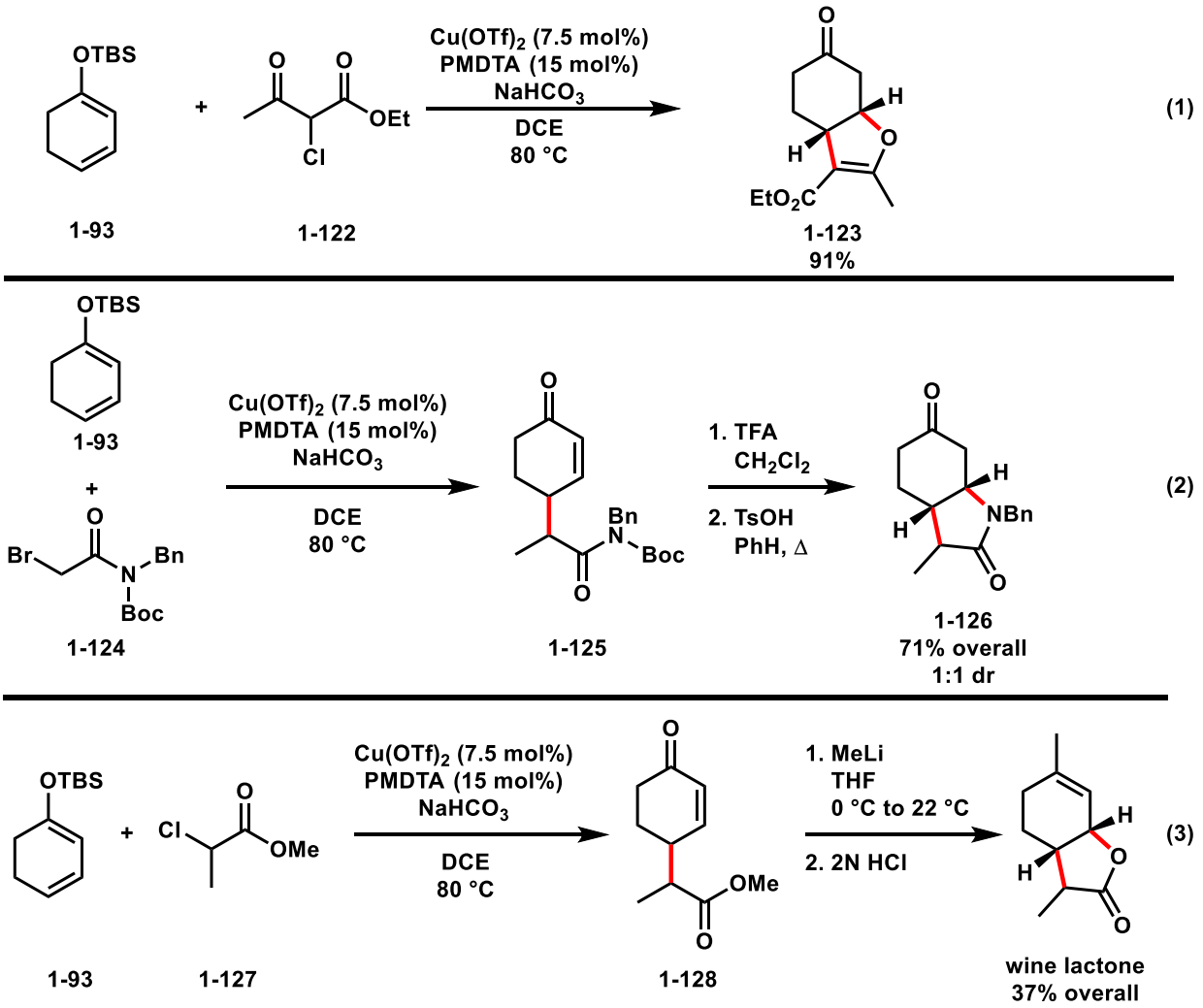


Scheme 1.21 Synthesis of γ-Quaternary Center



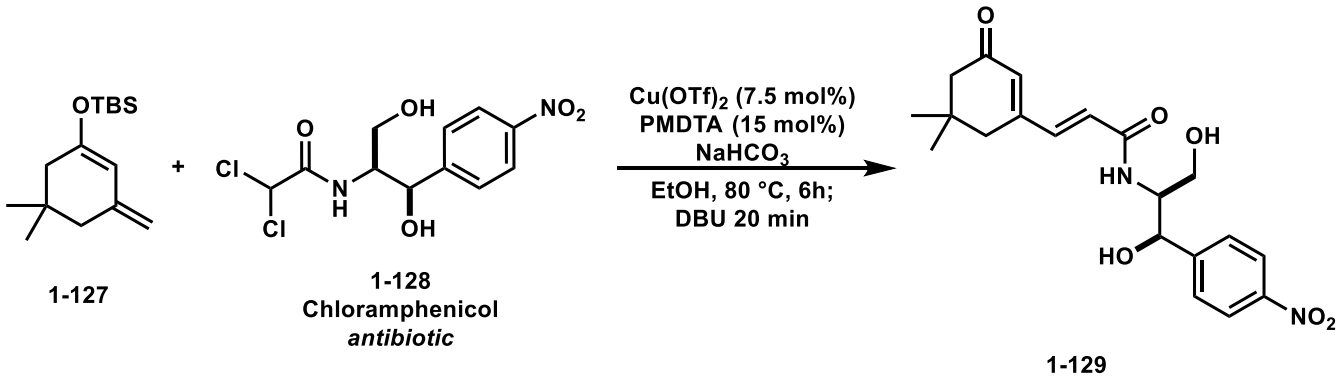
Scheme 1.22 γ-Alkylation of α-Chlorocarbonyls

Along with trihalocarbonyl compounds, dihalocarbonyls **1-118** were also found to be able to undergo the coupling reaction. (Scheme 1.22, eqn 3-4). The coupling of α,α-dichloroacetophenone **1-118** and cyclohexanone-derived silyl dienol ether **1-93** formed a mono-chloro product **1-119** which could be reduced further by treatment with Zn^0 in acetic acid. The mono-chloroproduct **1-119** was also able to undergo elimination under basic conditions to deliver the formally α-arylated product **1-121** (Scheme 1.22).



Scheme 1.23 Synthesis of Heterocycles

To examine the possibility of heterocycle synthesis, α-chloroethyl acetoacetate **1-122** was coupled with silyl dienol ether **1-93** to form the hexahydrobenzofuran **1-123**, which would the [3+2] cycloaddition product. (Scheme 1.23, eqn 1). Towards the formation of *N*-heterocycles, α-bromopropionamide **1-124** was coupled, the Boc group was cleaved and through acid-catalyzed conjugate addition, the lactam **1-125** was formed in two steps with 71% yield. (Scheme 1.23, eqn 2). Another valuable heterocyclic target, wine lactone, was isolated in 37% overall yield by coupling α-chloropropionate **1-127** with silyl dienol ether **1-93**, followed by chemoselective addition of MeLi followed by acidic workup. (Scheme 1.23, eqn 3)

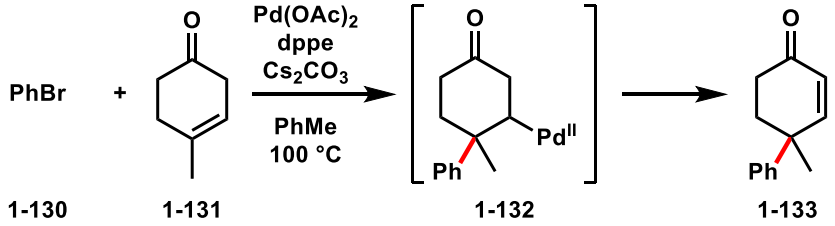


Scheme 1.24 Coupling of Chloramphenicol

Another valuable application was the coupling with unprotected broad-spectrum antibiotic chloramphenicol **1-128** followed by elimination to form the acrylamide **1-129** in 82% overall yield (Scheme 1.24).

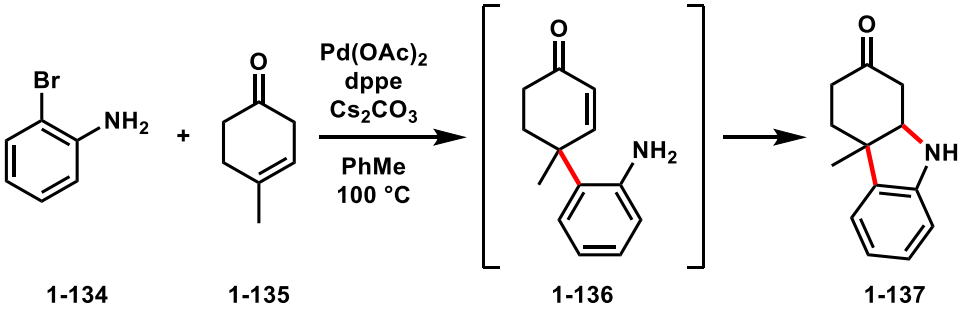
1.6 Palladium-Catalyzed Coupling Reactions

1.6.1 γ-arylation of Silyl Ketene Acetals and the synthesis of (+)-Lysergic Acid



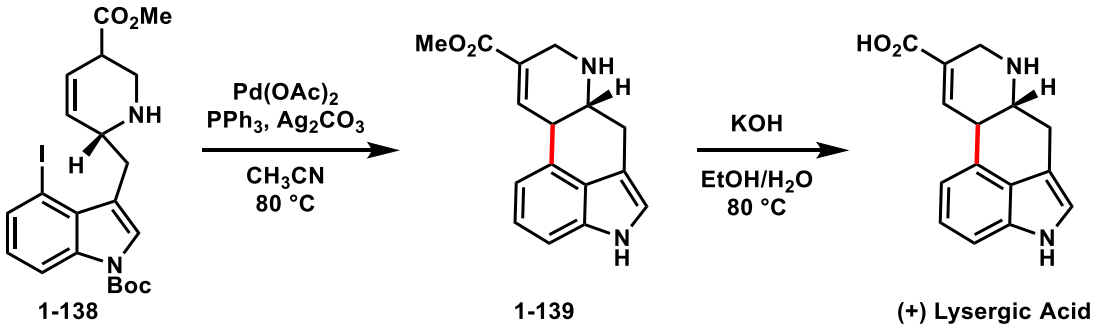
Scheme 1.25 γ-Arylation of β,γ Unsaturated Enones

In 2008, Buchwald developed a palladium-catalyzed γ-arylation method for γ-alkyl β,γ-unsaturated enones **1-133** (Scheme 1.25).[3j] The arylation was site-selective for the γ-carbon as the palladium–carbon bond would prefer to form on the less sterically hindered carbon. The alkyl-palladium species would then undergo β-hydride elimination to form the more stable α,β-unsaturated enone.



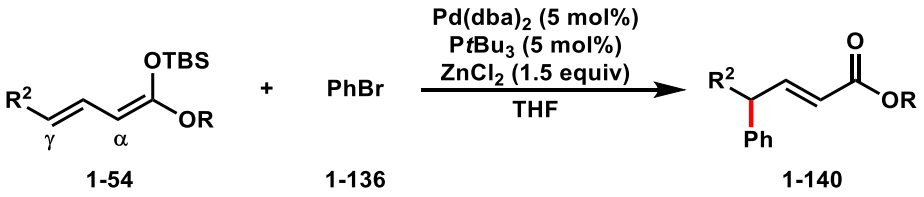
Scheme 1.26 γ-Arylation of β,γ-Unsaturated Enones with 2-Bromoaniline

This method was limited to γ-alkylated enones **1-131** which severely limited the method as did the difficulty in synthesizing β,γ-unsaturated enones. Also, synthesis of these β,γ-enones is often challenging and isomerization to the more thermodynamically favored α,β-enone occurs rapidly. By utilizing 2-bromoanilines **1-135**, the resulting enone **1-136** undergoes conjugate addition to form tricyclic indolines **1-137**. (Scheme 1.26).[3j]



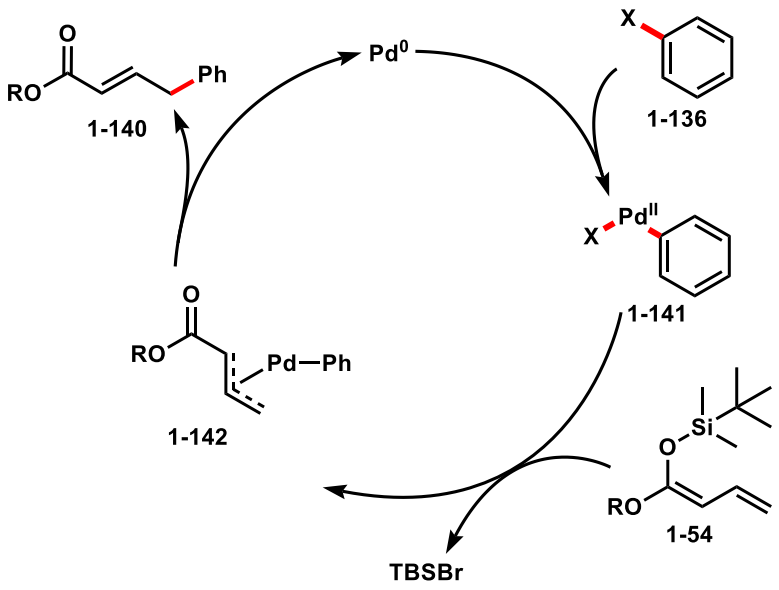
Scheme 1.27 Synthesis of (+)-Lysergic Acid

(+)-Lysergic acid, an ergoline alkaloid, was synthesized by Jia and coworkers in 2013, through an intramolecular γ-arylation of the β,γ-enone **1-138** with the 5-iodoindole moiety (Scheme 1.27).[30] The β-hydride elimination forms the thermodynamically favored α,β-unsaturated ester **1-139**. Hydrolysis of the ester formed the (+)-Lysergic acid.



Scheme 1.28 Palladium Catalyzed γ-Arylation

In 2010, Hartwig and coworkers reported the palladium-catalyzed γ-arylation and γ-vinylation of silyl ketene acetals to form a new γ-C–C bond on α,β-unsaturated esters (Scheme 1.28).[3m] This reaction selectively mono-arylated the γ-position over the α- or β-positions. This reaction proceeds in the absence of a fluoride source, which is often necessary for α-arylation methods.[31]



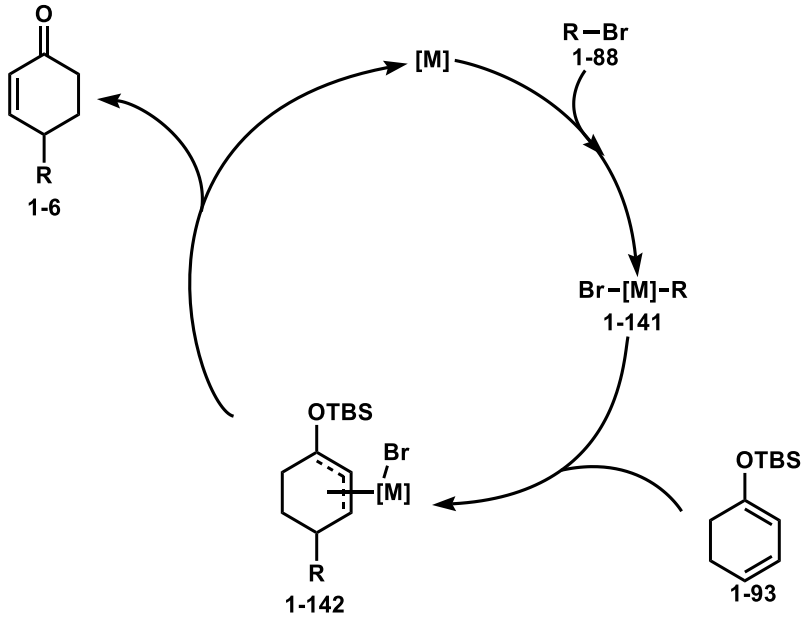
Scheme 1.29 Proposed Mechanism for γ-Arylation of Silyl Ketene Acetals

As with α-arylation of silyl enols, the reaction proceeds by forming a palladium enolate complex facilitated by zinc chloride. The zinc chloride acts as a Lewis acid to labilize the halide on palladium to form the palladium enolate, however Lewis bases were also found to promote the reaction albeit through a different mechanism. The resulting η^3-palladium dienolate **1-142** would undergo selective reductive elimination to form the thermodynamically favored γ-arylated α,β-

unsaturated enone **1-140**. (Scheme 1.29). This method was limited to silyl ketene acetals **1-54** as with Denmark's; also, alkyl halides were unable to perform this coupling reaction.

1.7 Our Method: Cross-Coupling γ-alkylation

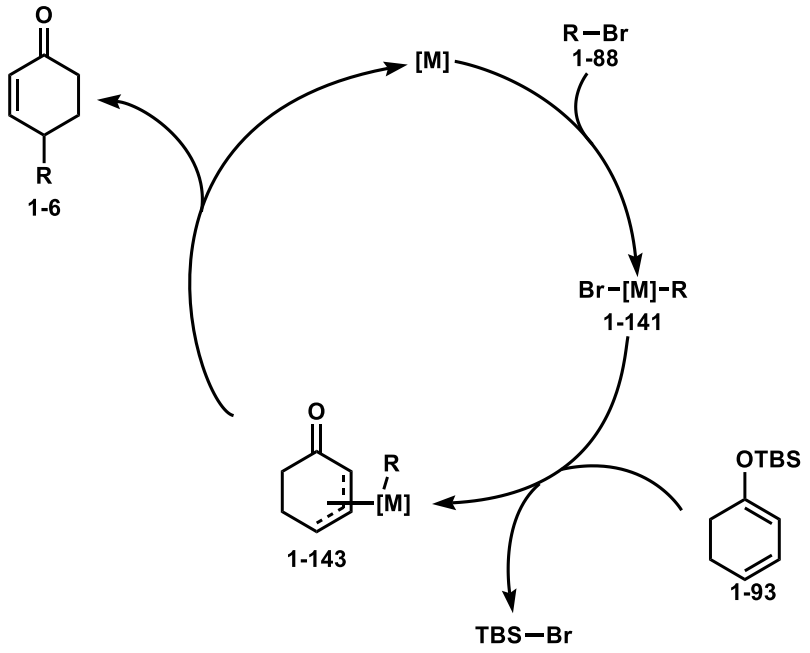
Although the copper-catalyzed method overcame the challenges of γ-alkylation of ketones, the radical intermediate limited the reaction to tertiary and secondary α-halocarbonyls. Therefore, the challenge of γ-alkylation remained. We envisioned that a two-electron process might provide a solution. In the case of metal complex prone to a traditional oxidative insertion mechanism, it may be possible to overcome in radical formation. This putative organometallic intermediate would then need to react with the silyl dienol ethers in a pathway similar to the Hartwig/Buchwald examples.



Scheme 1.30 Proposed Mechanism for γ-Alkylation

We envisioned that oxidative addition of the metal would occur in the alkyl halide bond, followed by alkene coordination to the β,γ-alkene selectively (Scheme 1.30). In this pathway, FMO control which was previously established to control the selectivity should direct coordination to

the β,γ alkene which will then undergo migratory insertion.[19] Then migratory insertion of the metal–alkyl group **1-141** on the γ-carbon of the silyl dienol ether **1-93** will form an η^3 allyl metal species **1-142**. Reductive elimination could occur through a concerted mechanism by which the Si-O bond is cleaved as a new Si-Br bond forms and the electrons leave on the metal and form the enone **1-5**. (Scheme 1.30).



Scheme 1.31 Hartwig/Buchwald Proposed Mechanism for Allylmetal Intermediate

Alternatively, Lewis acid activation of the metal halide species could cleave the Si–O bond and form the η^3-allyl species **1-143** similar to that proposed by Hartwig (Scheme 1.31).[3m] The allyl metal would undergo reductive elimination forming the γ-alkyl bond selectively as this would form the thermodynamically preferred α,β-unsaturated enone.

1.8 Notes and References

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CHAPTER 2

NICKEL CATALYZED γ-ALKYLATION

2.1 Background

Palladium cross-coupling reactions involving a sp^3-C–halogen are often difficult due to the high activation energy for oxidative addition to the more electron-rich sp^3-C than the sp^2-C of an arene.[1] Another challenge of alkyl cross-coupling was the undesired β-hydride elimination that was often facile compared to transmetalation and reductive elimination.

Nickel, as an electropositive late transition metal, is often more facile for oxidative addition which requires loss of electron density around the metal center.[2] The activation energy for oxidative addition into sp^3-C–chlorine bond is +20.1 kcal/mol for nickel and +25.3 kcal/mol for palladium.[3] Also, the migratory insertion is energetically more favorable under nickel catalysis with the activation barrier being +7.7 kcal/mol vs +12.8 kcal/mol for palladium. While palladium catalysts have achieved sp^3C- sp^3C coupling, their methods are limited to primary alkyl halides.[4]

In 2003, secondary alkyl halides with β-hydrogens were first reported to undergo cross-coupling by Fu with organozinc reagents with nickel catalysis.[5a] following this report, nickel was shown to enable this cross-coupling under mild Suzuki, Hiyama, and Stille coupling, whereas palladium was unable to catalyze these types of coupling except under specific conditions. [5b–f]

As described in the preceding chapter, γ–alkylation remains a key challenge for synthetic chemists. Negishi and Suzuki cross-couplings with Nickel catalysis have previously achieved γ–alkylations with γ–chloroenones.[6] However the synthesis of the γ–chloroenones required multiple steps and only acyclic γ–chloroenones were shown. Our copper-catalyzed γ–alkylation coupled acyclic and cyclic enones while also tolerating numerous functional groups in excellent regio- and stereoselectivity. However, the method was limited to tertiary and secondary alkyl halides. Coupled with the ability to synthesize numerous silyl dienol ethers and α–halocarbonyls, we believed that nickel catalysis would enable coupling of primary alkyl halides.

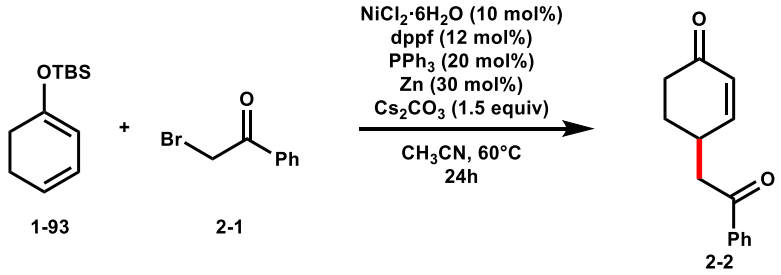
Nickel catalysts have been reported to undergo oxidative addition into an alkyl halide bond via a Ni(0)/Ni(II) catalytic cycle.[7] If the nickel catalyst proceeds through a 2-electron oxidative addition pathway then the subsequent migratory insertion could follow the pathway proposed by Hartwig and provide the γ-alkylated product selectively.[8] Allyl nickel species have been proposed by Weix and others, therefore the Hartwig mechanism is a possible route to achieve γ-alkylation.[9]

Alternatively, nickel has been reported to undergo a Ni(0)/Ni(II)/Ni(I) catalytic cycle to form a radical which adds to an alkene.[10] Under those conditions, we would expect that the mechanism would be more reminiscent of our copper-catalyzed γ-alkylation mechanism that we showed in the previous chapter.[11] This radical pathway would also be viable as we had previously shown that radicals added selectively to the dienol ether on the γ-carbon.[11,12] With the possible modes of action for nickel, we sought to develop a nickel catalyzed γ–alkylation.

2.2 Screening and optimization

2.2.1 Optimization of Conditions

Table 2.1 Initial Catalyst Screening



1-93 2-1 2-2

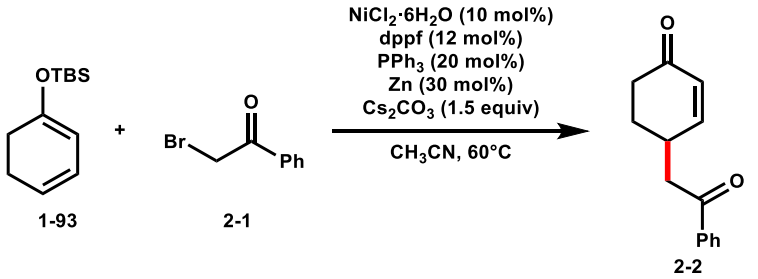
Entry	Ni Catalyst	Ligand	Solvent	% yield[a]
1[b]	None	None	CH_3CN	0%
2	None	dppf	CH_3CN	0%
3[c]	$Ni(COD)_2$	dppf	CH_3CN	37%
4	$NiCl_2$	dppf	CH_3CN	trace
5	$Ni(NO_3)_2·6H_2O$	dppf	CH_3CN	trace
6	$NiSO_4·6H_2O$	dppf	CH_3CN	trace
7	$Ni(PPh_3)_2Cl_2$	dppf	CH_3CN	14%
8	$NiCl_2·6H_2O$	dppf	CH_3CN	65%

[a] Isolated yield

Our initial goal was to utilize nickel catalyst's ability to undergo oxidative addition on alkyl halides. Then the alkyl nickel species would add the alkyl group selectively to the γ-carbon to form either an allyl-metal species or through an allyl-radical species. We chose the silyl dienol ether **1-93** as a test substrate as we had previously shown that they can undergo radical-mediated γ-addition pathways.[12a,b] In accordance with our previous report on nickel-catalyzed γ-arylation, we initially screened our catalyst system in acetonitrile.[13]

Initially, we verified that the reaction could not proceed only in the presence of Cs_2CO_3 through a dienolate alkylation and that a nickel catalyst was necessary for the reaction to proceed.[14] (Table 2.1, entry 1–2). Given our previous success with nickel catalysts and dppf ligand, we screened the reaction with dppf ligand and $Ni(COD)_2$ as a catalyst, yielding the desired γ-alkylated product **2-2** in modest yield. (Table 1, entry 3). However, the Ni(0) catalyst can be generated in situ from Ni(II) precatalysts upon treatment with a substoichiometric quantity of Zn dust with respect to the alkyl halide.[15,16a] (Table 1, entry 4–8). We were pleased to find that $NiCl_2•6H_2O$ proceeded efficiently with 65% yield of the γ-alkylated enone **2-2**.

Table 2.2 Solvent Screening

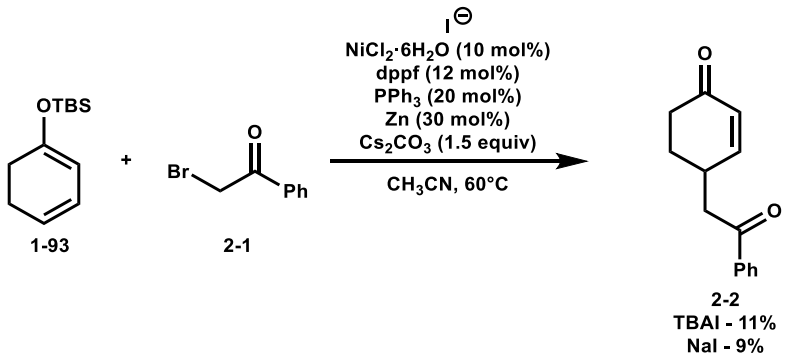


1-93 2-1 2-2

Entry	Ni Catalyst	Ligand	Solvent	% yield[a]
1	$NiCl_2·6H_2O$	dppf	CH_3CN	65%
2	$NiCl_2·6H_2O$	dppf	PhMe	0%
3	$NiCl_2·6H_2O$	dppf	Dioxane	4%
4	$NiCl_2·6H_2O$	dppf	DCE	5%

a. Isolated yield

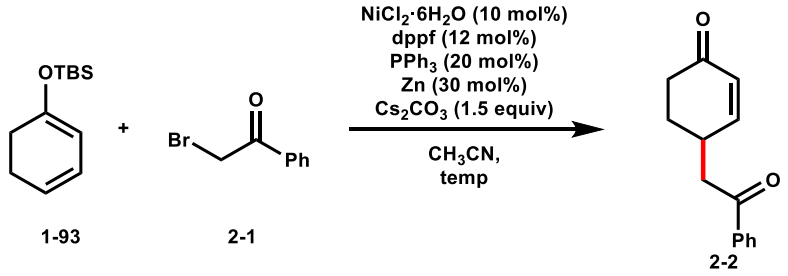
A variety of solvents were tested, and acetonitrile was discovered to be the best solvent (Table 2.2). In situ generation of an alkyl iodide through the Finkelstein reaction using tetrabutylammonium iodide or sodium iodide inhibits the formation of the desired γ-alkylated product. (Scheme 2.1).[17]



Scheme 2.1 In-situ Finkelstein Reaction

Lowering the temperature to 55 °C from 60 °C, yielded 70% of the γ-alkylated enone **2-2**. Increasing the equivalence of α-bromoketone improved the yield to 81% yield (Table 2.3). Also, the reaction did not proceed in the absence of zinc dust.

Table 2.3 Temperature and α-Haloketone Screening

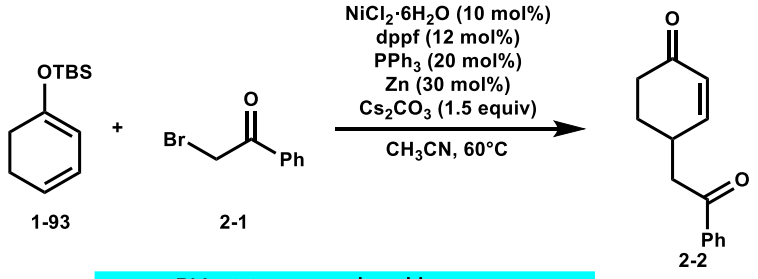


Entry	Equiv of α-haloketone	Temp	Yield[a]
1	1.5 equiv	45 °C	57%
2	1.5 equiv	50 °C	60%
3	1.5 equiv	55 °C	70%
4	1.5 equiv	60 °C	65%
5	1.05 equiv	55 °C	5%
6	1.25 equiv	55 °C	33%
7	1.5 equiv	55 °C	70%
8	1.75 equiv	55 °C	81%
9	2.0 equiv	55 °C	60%
10	2.5 equiv	55 °C	45%

a. Isolated yield

The dual phosphine catalyst system enabled the γ-alkylation to occur more rapidly and so, we tested other phosphine ligands (Table 2.4). The bidentate phosphines, dppe and dcype yielded the γ-alkylated enone **2-2** in 55% and 15%, respectively. The monophosphine ligands, $P(Cy)_3$, $P(o\text{-}tol)_3$ and $P(n\text{-}Bu)_3$ delivered the γ-alkylated enone **2-2** in 78%, 60%, and 77% yield, respectively.

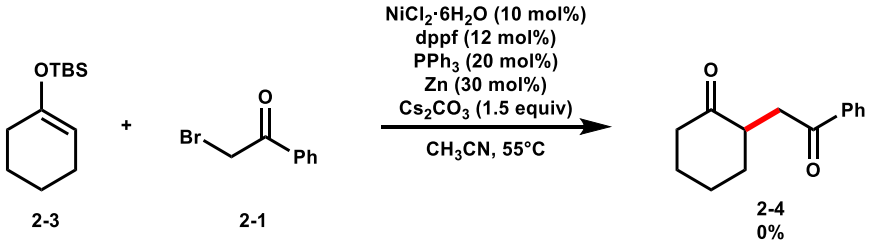
Table 2.4 Ligand Screening



Entry	Bidentate Ligand	monophosphine Ligand	Yield
1	dppf	PPh_3	81%
2	-	PPh_3	12%
3	dppf	-	32%
4	dppe	PPh_3	55%
5	dcype	PPh_3	15%
6	dppf	$P(Cy)_3$	78%
7	dppf	$P(o\text{-}tol)_3$	60%
8	dppf	$P(n\text{-}Bu)_3$	77%

2.3 Substrate Scope

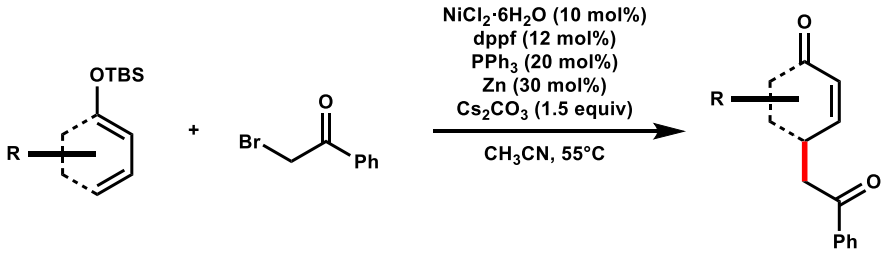
We independently synthesized the silyl enol ether **2-3** and found that it was unable to undergo any conversion to the α-alkylated product (Scheme 2.2). This indicates that the conjugated π-system enabled special reactivity that was not accessible with simple enol ethers.

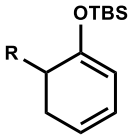
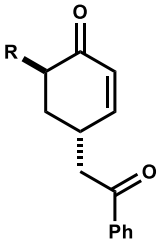
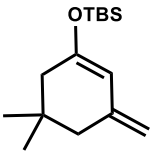
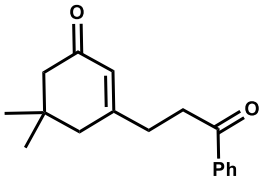


Scheme 2.2 Attempted Coupling of Silyl Enol Ether

A variety of dienol ethers were found to be viable substrates for the γ-alkylation reaction (Table 2.5). The silyl dienol ethers were prepared by straightforward enolization/silylation under basic conditions or through soft enolization techniques.[12]

Table 2.5 Scope of Siloxydiene Coupling Partner



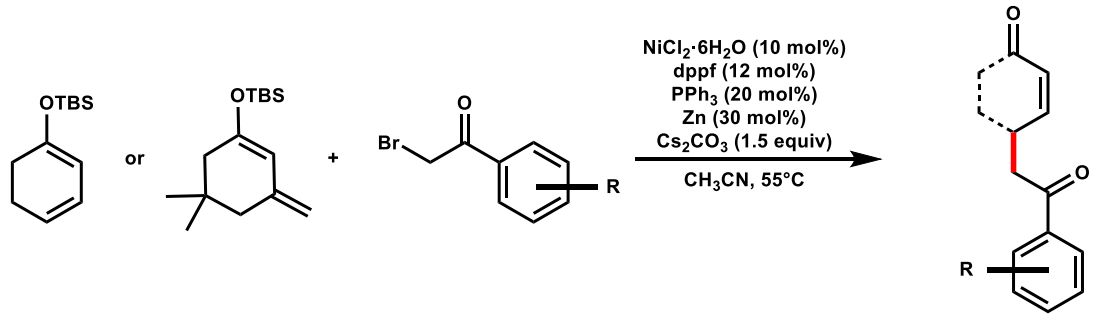
Entry	Siloxydiene		Product			% yield
1		1-93 R= H		2-2		84%
2		2-6 R=Me		2-11	3.7:1 dr	61%
3		2-7 R=Bn		2-12	5.4:1 dr	62%
4		2-8 R= allyl		2-13	6.4:1 dr	72%
5		2-9 R = CH_2CO_2Et		2-14	7.9:1 dr	70%
6		2-10		2-15		83%[b]

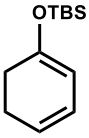
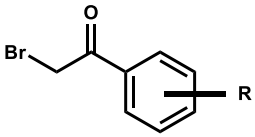
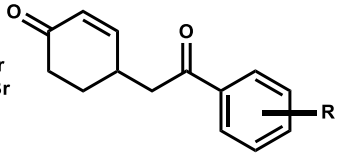
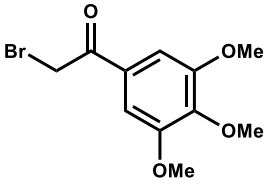
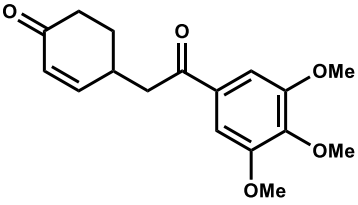
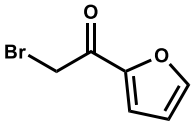
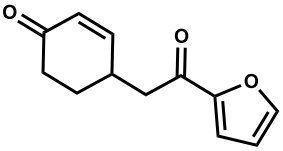
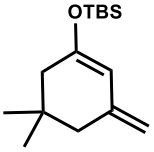
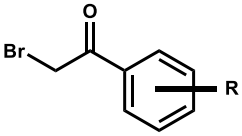
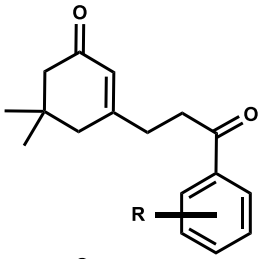
[a] Isolated yield from reaction of dienol ether (0.25 mmol), a-haloketone (1.75 equiv), PPh_3 (20 mol%), Zn powder (30 mol%), and Cs_2CO_3 (1.5 equiv), Ni catalyst (10 mol%), and ligand (12 mol%) in 1.25 mL of solvent at 55 °C for 24 h. [b] 79% yield over two steps

The γ-alkylated products were delivered with stereoselectivity for the *anti*-diastereomer when the enone precursor contained an α-substituent (Table 2.5, entries 2−5).[18] The successful preparation of **2-13** demonstrated chemoselectivity for the conjugated π-system over an isolated alkene (Table 2.5, entry 4). A dienol ether **2-10** containing an exocyclic reactive site also proved to be a very good substrate for the coupling reaction. (Table 2.5, entry 6).

Gratifyingly, modification of the aryl ketone showed excellent functional group tolerance. Even in the presence of 2-bromo, 4-bromo or 4-iodophenyl substituents, the reaction was selective for the alkyl bromide (Table 2.6, entries 1–2, 5–7).

Table 2.6 Scope of α-Haloketones Partner



Entry	Siloxydiene	α-haloketone	Product		
% yield					
1			2-16 X=4-Br 2-17 X= 2-Br		2-27 2-28	83% 81%
2	1-93					
3			2-18		2-29	80%[b]
4			2-19		2-30	61%[b]
5			2-16 X=4-Br 2-17 X= 2-Br 2-20 X=4- I 2-21 X = 4-NH2 2-22 X = 4-Me 2-23 X = 4-OMe 2-24 X = 3-OMe 2-25 X = CN		2-31 2-32 2-33 2-34 2-35 2-36 2-37 2-38	82% 63% 77% 71%[b] 79%[b] 57%[b] 68%[b] 86%
6						
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8						
9						
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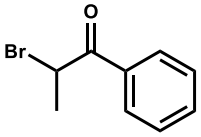
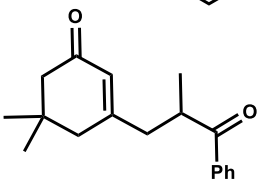
12	2-10					
13			2-26		2-39	72%

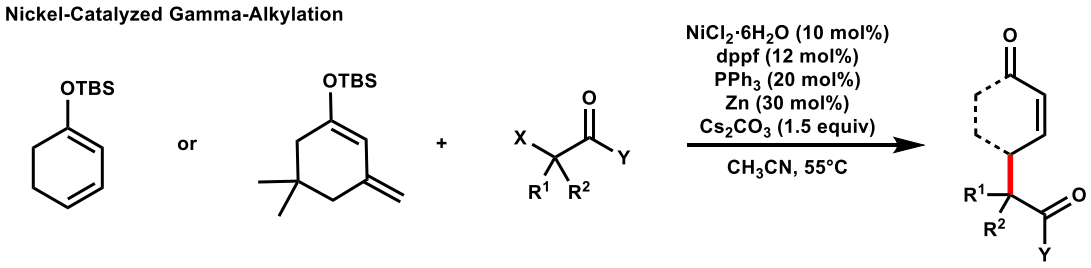
[a] Isolated yield from reaction of dienol ether (0.25 mmol), α–haloketone (1.75 equiv), PPh_3 (20 mol%), Zn powder (30 mol%), and Cs_2CO_3 (1.5 equiv), Ni catalyst (10 mol%), and ligand (12 mol%) in 1.25 mL of solvent at 55 °C for 24 h. b. 48 h.

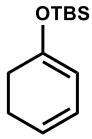
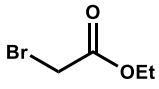
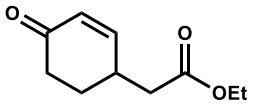
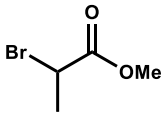
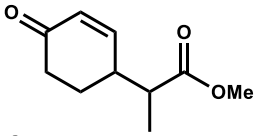
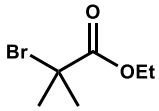
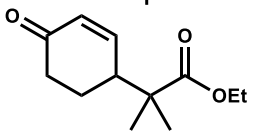
Electron-rich arenes such as 2,3,4-trimethoxyphenyl **2-18**, furan **2-19,** 4-methylphenyl **2-35**, 4-methoxyphenyl **2-36**, and 3-methoxyphenyl **2-37** all furnished the desired γ-alkylated product in good yields albeit with longer reaction times (Table 2.6, entries 3–4, 8–11). An

unprotected aniline **2-21** was also well tolerated with our protocol (Table 2.6, entry 8). Increasing the steric bulk around the sp^3-C–Br by changing the α-bromoketone to 2-bromopropiophenone **2-26** showed a slight decrease in yield (Table 2.6, entry 13).

We also hoped to expand this protocol beyond aryl ketones and we were pleased to discover that α-bromoesters performed well under our protocol (Table 2.7). Altering the steric bulk around the sp^3-C–Br bond from primary **2-40** to secondary **2-41** to tertiary **1-96** showed a clear correlation that increasing the steric hindrance decreased the yield of the reaction (Table 2.7, entries 1–3). The secondary α-bromoester **1-128** formed both diastereomers in a 1:1 ratio (Table 2.7, entry 2). The α-chloroketone **2-43** served as suitable α-haloketones providing the 1,6 diketones **2-48** and **2-49** in moderately good yields albeit with much longer reaction times (Table 2.8, entries 1–2).

Table 2.7 Scope of α-Bromoesters

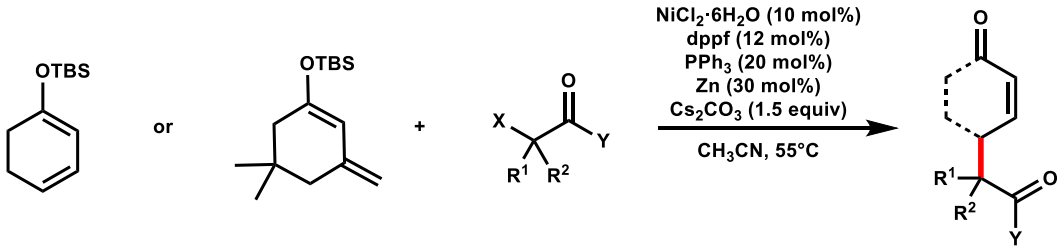


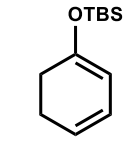
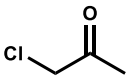
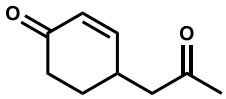
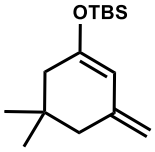
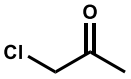
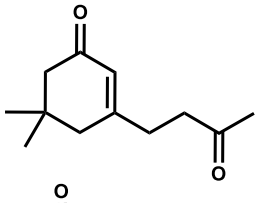
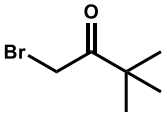
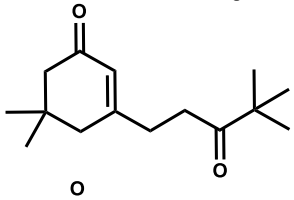
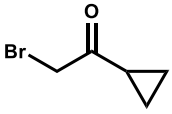
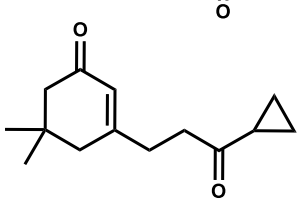
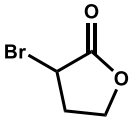
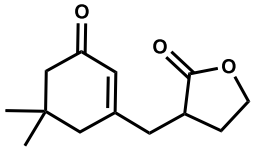
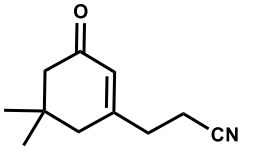
Entry	Siloxydiene	α-halocarbonyl	Product		% yield
1	 1-93	 2-40	 2-42		62%
2		 2-41	 1-128	1:1 dr	55%
3		 1-96	 1-95		41%

[a] Isolated yield from reaction of dienol ether (0.25 mmol), α-haloketone (1.75 equiv), PPh_3 (20 mol%), Zn powder (30 mol%), and Cs_2CO_3 (1.5 equiv), Ni catalyst (10 mol%), and ligand (12 mol%) in 1.25 mL of solvent at 55 °C for 24 h.

A lactone, a *t*-butyl ketone, a cyclopropyl ketone were also found to be well tolerated by this protocol (Table 2.8, entry 3-4). Nitriles were found to be good electron-withdrawing groups for our protocol (Table 2.8, entry 6).

Table 2.8 Scope of α-Haloketone Partners

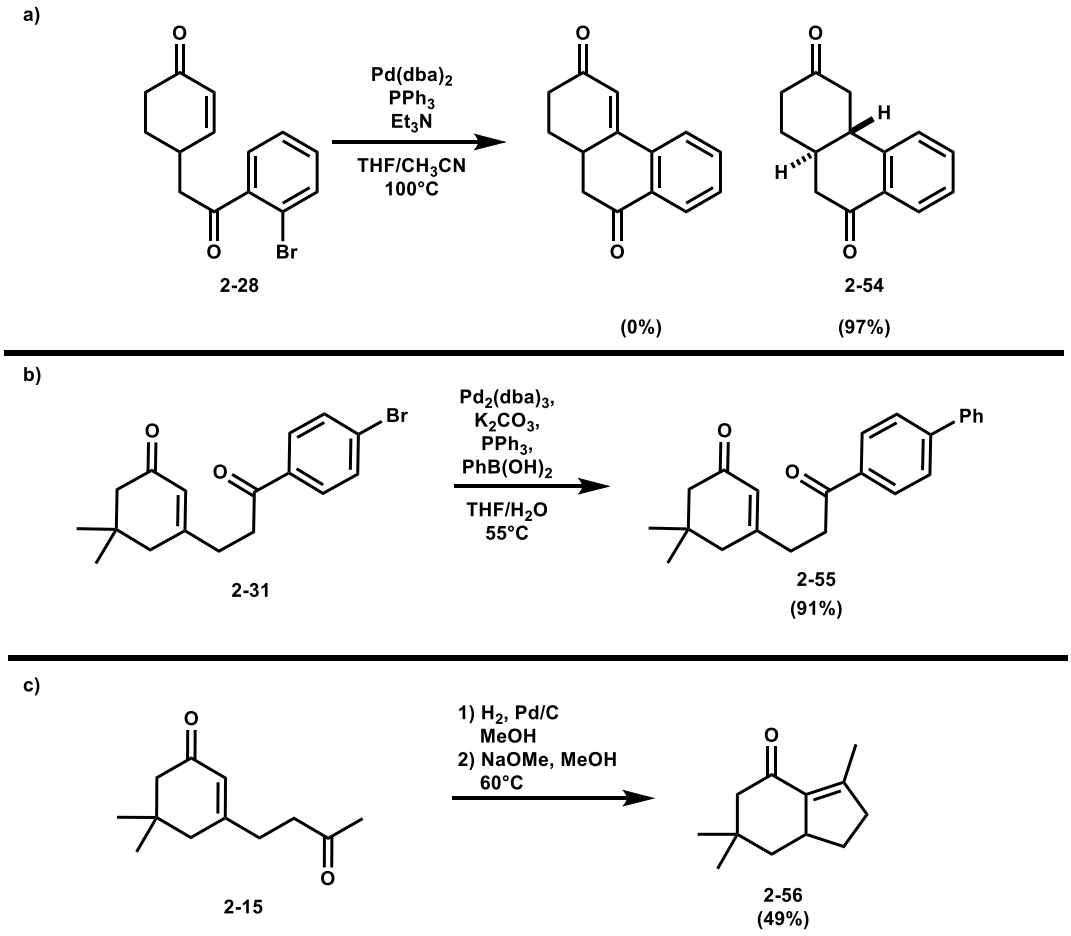


Entry	Siloxydiene		α-halocarbonyl		Product		% yield
1		1-93		2-43		2-48	54% [c]
2		2-10		2-43		2-49	56% [c]
3				2-44		2-50	51%
4				2-45		2-51	40%
5				2-46		2-52	59%
6			$BrCH_2CN$	2-47		2-53	64%

[a] Isolated yield from reaction of dienol ether (0.25 mmol), α-haloketone (1.75 equiv), PPh_3 (20 mol%), Zn powder (30 mol%), and Cs_2CO_3 (1.5 equiv), Ni catalyst (10 mol%), and ligand (12 mol%) in 1.25 mL of solvent at 55 °C for 24 h. [b] 79% yield over two steps [c] 36 hours

2.4 Synthetic Applications

To explore the possibility of intramolecular Heck cyclization, we employed 2-bromobenzene **2-30** and obtained the *trans* decalin **2-54** in 97% yield as the only product.[19,20] Towards the synthesis of a biphenyl moiety, the 4-bromoarene **2-31** underwent a Suzuki–Miyaura coupling with phenylboronic acid to yield the biphenyl **2-55** in 91% yield.[21] To synthesize 5,6-bicyclic ring systems, the enone **2-15** was reduced to the ketone via hydrogenation and then underwent intramolecular aldol condensation to form **2-56** in 49% yield.[22]



Scheme 2.3 Synthetic Applications

2.5 Progress towards the synthesis of 9-oxoageraphorone

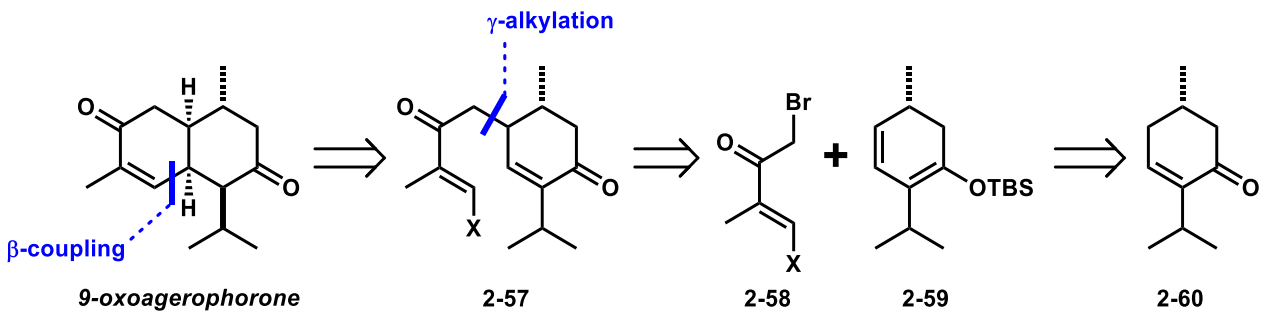
2.5.1 Background

Cadinenes are a family of bicyclic sesquiterpenes that have been isolated from *Eupatorium adenophorum*, a composite plant from the forests of southwestern China.[23] These sesquiterpenes have shown insecticidal, antibacterial properties and potential anti-inflammatory characteristics.[24] Some members of this family have attracted the attention of the synthetic community due to their challenging structures and their valuable biological activity.[25]

The greatest challenge to the synthesis of this family is the γ-alkyl group. However, in this chapter, we presented a new method to access γ-alkylation products from enones and herein, we present our approach to the synthesis of one member of this family, 9-oxoagerophorone.

2.5.2 Retrosynthetic Analysis of 9-oxoageraphorone

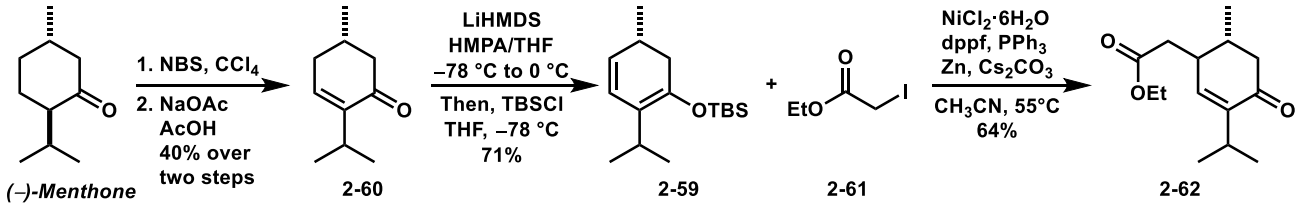
We envisioned that the β-carbon– bond could be formed through the intramolecular β,β coupling of **2-57**. The cyclization would occur from the face opposite of the β'-methyl group to form the *cis* decalin ring system which would be conformationally easier to access. Through the titanium-catalyzed β,β coupling of alkenes, the cyclization is followed by formation of titanium enolates which can be trapped by silyl groups to form the silyl enol ethers.[26] Careful deprotection of the silyl enol ethers can occur through selective protonation from the convex face, leading to the α- isopropyl group being *anti* to the β'-methyl group.



Scheme 2.4 Retrosynthesis of (±)-9-oxoageraphorone

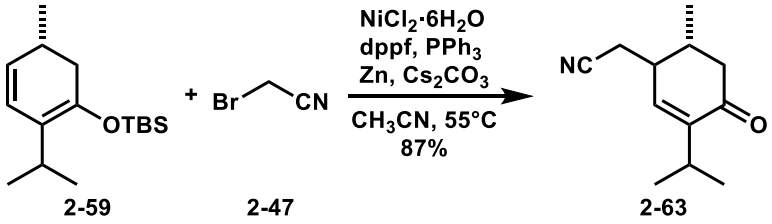
Our plan consisted of γ-alkylation of an α-bromoketone **2-58** on the silyl dienol ether **2-59**, wherein the *anti*-diastereomer would be preferred. The configuration of the β'-methyl group coincides with the stereochemistry of (–)-menthone, so the enone would be derived from readily available (–)-menthone (Scheme 2.4).

2.5.3 Progress Towards the Synthesis of 9-oxoageraphorone



Scheme 2.5 Progress towards 9-oxoageraphorone

Our synthesis commenced with the bromination/elimination of (–)-menthone to form menthenone **2-60**.[27] Subsequent basic enolization/silylation proceeded in 71% yield. The synthesis of α'-bromoenone **2-58** was unsuccessful as bromination occurred preferentially on the alkene or polymerization of the enone occurred rapidly.[28] So, we turned our attention to other electron-withdrawing groups as an alternative.



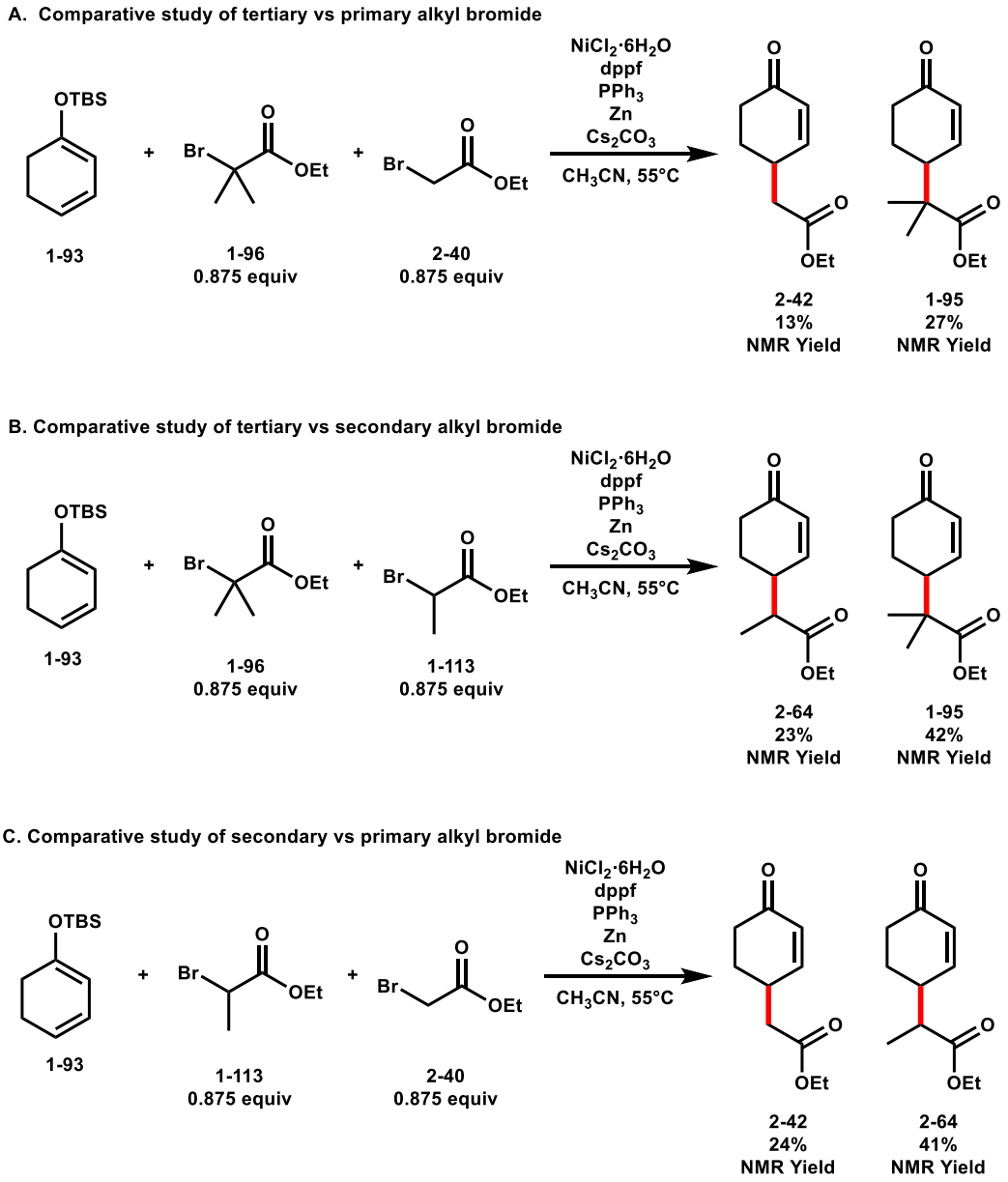
Scheme 2.6 Nickel Alkylation of Bromoacetonitrile

The γ-alkylation of the silyl dienol ether **2-59** proceeded efficiently with methyl iodoacetate **2-61** in 64% yield and with bromoacetonitrile **2-47** in 87% yield.[29] Gilman additions[30] and β,β-coupling[31] all failed to provide the β-addition on either the δ-ester **2-62** or δ-nitrile **2-63**. Grignard

additions to the nitrile[32] or reduction of the nitrile[33] to the aldehyde all performed 1,2-addition to the enone. Attempts are still underway to facilitate the β-addition.

2.6 Mechanistic Insights

2.6.1 Effect of Sterics



Scheme 2.7 Competition Experiments to Probe the Effects of Sterics

We began our investigation into the mechanism by performing a competition reaction between the primary **2-40** and tertiary alkyl halide **1-96** to probe the stereoselectivity of the reaction. Surprisingly, we discovered that the tertiary alkyl halide **1-96** yielded 27% compared to the 12% yield from the primary alkyl halide **2-40** (Scheme 2.7). In the case of the tertiary versus secondary, the tertiary alkyl halide **1-96** yielded 42% of γ-alkylated product **1-95** in comparison to the 23% of γ-alkylated product **2-64** yielded from the of secondary alkyl halide **1-113**.

Lastly, in primary vs secondary alkyl, we discovered the same trend with the primary ester **2-40** yielding 24% and the secondary ester **1-113** yielding 41%. Potentially, this could indicate a nickel-mediated radical formation, in which case the tertiary alkyl halide would form the radical more rapidly. On the other hand, while the nickel oxidative addition into a primary alkyl halide may be more rapid, the migratory insertion of the tertiary nickel(II) species may be more rapid to alleviate the steric strain of the tertiary sp^3-C–nickel bond.

2.6.2 Chemoselectivity

To examine the chemoselectivity of the reaction, we exposed chloroacetonitrile **2-65** and bromoacetonitrile **2-47** to our coupling conditions (Figure 2.1). After 4 h, we found full consumption of the bromoacetonitrile **2-47** and partial consumption of the chloroacetonitrile **2-65**. After 36 h, all of the silyl dienol ether **2-10** was fully consumed, however only 43% of the γ-alkylated product **2-53** formed, with the remainder of the material being isophorone **2-66**.

To investigate the reaction mechanism, we analyzed the effect of altering the electronics of the arene ring on the rate constant. The reactivity of the substrates can depend on whether electron density is built up or reduced at the reaction center. So, to study the mechanism, the rate of reaction for various electron-rich and electron-deficient arenes was measured and we plotted $\log(k/k_H)$ against the Hammett σ_p constants (Figure 2.2).[34] The Hammett plot clearly shows a linear

relationship with the slope of 0.72. The positive slope indicates that the reaction operates through a rate determining step where partial charge or electron density is built up, where electron-withdrawing groups can facilitate the reaction.

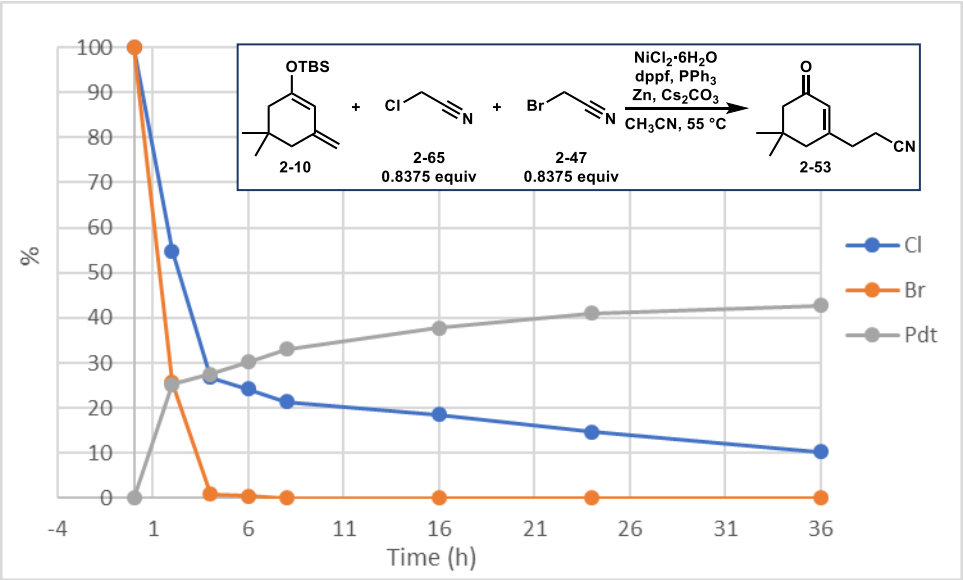


Figure 2.1 Competition Experiment between Chloro- and Bromoacetonitrile

Alternatively, we plotted the $\log(k/k_H)$ against the Hammett σ^*_{jj} constants, which are a set of σ constants used for radical mechanisms (Figure 2.3).[35] From this plot, the slope is 1.13. However, the R^2 value which indicates the goodness-of-fit of a linear fit for the radical Hammett plot was 0.63, and 0.957 for the polar mechanism. This indicates that the polar Hammett plot more accurately represents our mechanism.

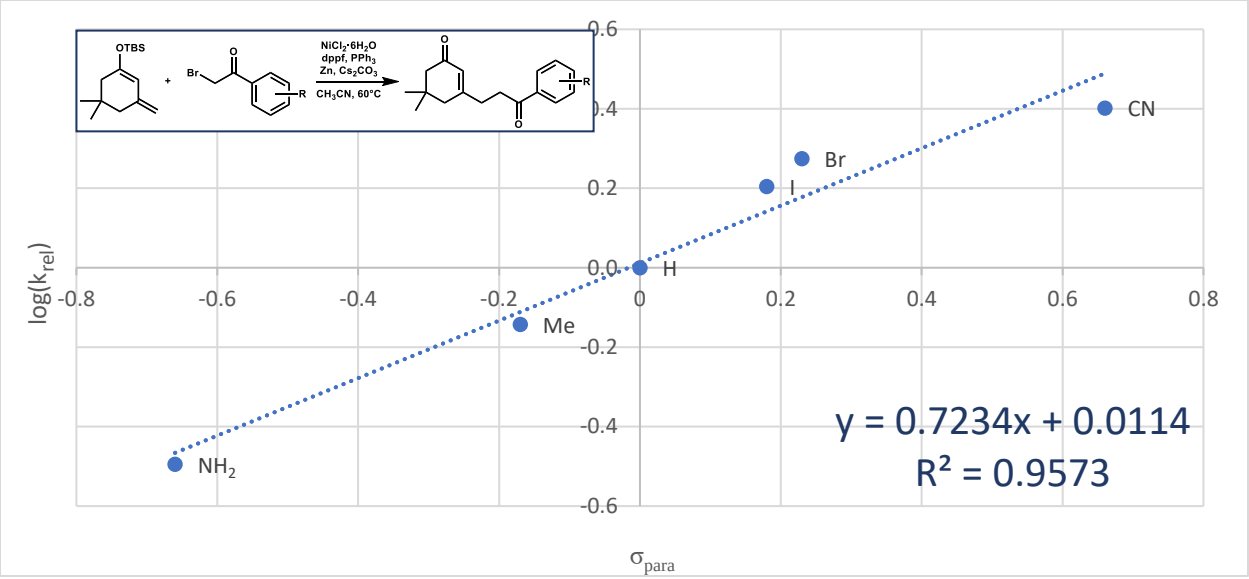


Figure 2.2 Plot of the Rate Constant vs σ_p Values

The Hammett plot suggests that the rate-limiting step is the oxidative addition of the Ni(0) into the alkyl halide. This suggests a pathway where electron density increases ($\rho > 0$) as it would through oxidative addition as opposed to where electron density decreases ($\rho < 0$) as in the case of reductive elimination.[36]

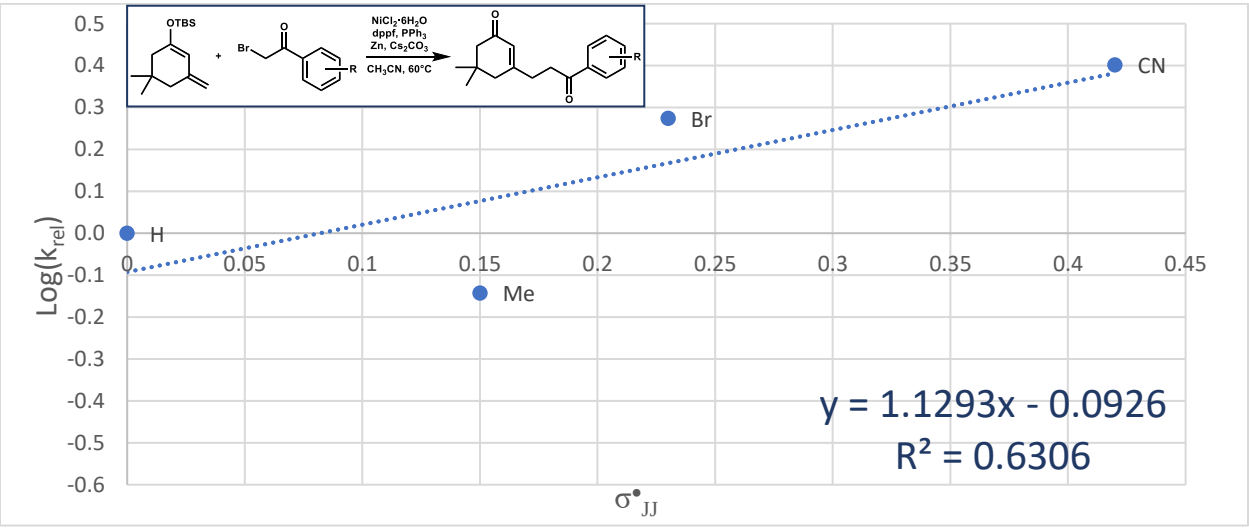


Figure 2.3 Plot of the rate constant vs $\sigma^{\bullet}_{jj}$ values

2.6.3 Ligand Effects

One peculiar aspect to our catalyst is the use of two different phosphine ligands, PPh_3 and dppf, to facilitate the reaction. To verify the need for two separate phosphine ligands, we monitored the reaction as it proceeded and found that the two-ligand system outperformed the dppf ligand system or the PPh_3 ligand systems (Figure 2.4). This graph also clearly indicated that the reaction has an induction period. This would be expected as the Ni(II) catalyst must react with the Zn to form the active Ni(0) species.

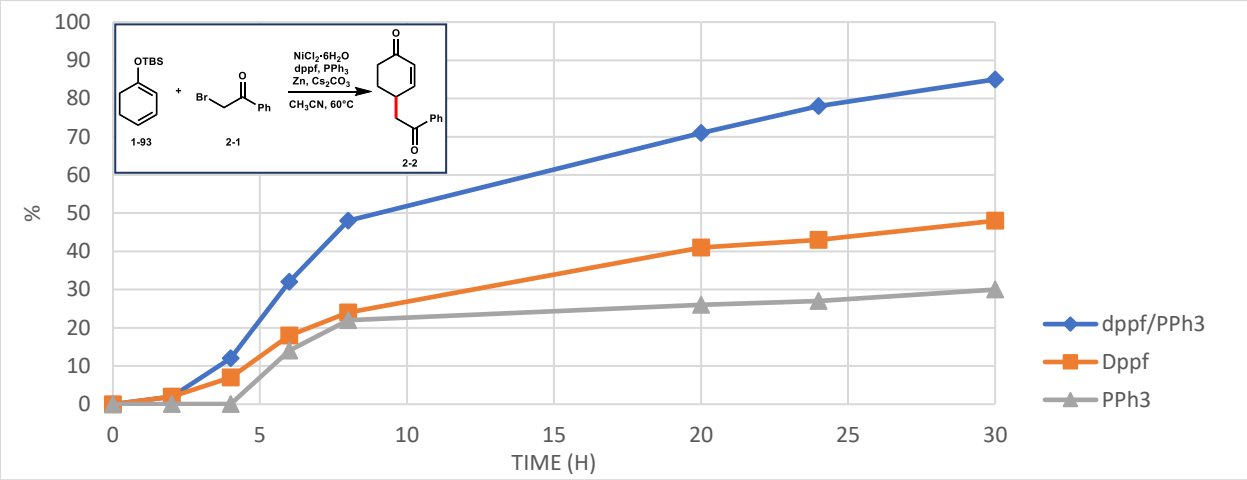


Figure 2.4 Plot of the Effects of Ligands

To verify that the induction period was caused by the formation of the active Ni(0) species, we subjected the Ni(II) precatalyst, Zn dust and the ligands to one another at 55 °C for 5 hours to form the Ni(0) catalyst and then subjected them to the silyl dienol ether and the α-bromoacetophenone (Figure 2.5). In this reaction, we saw rapid consumption of the silyl dienol ether (less than 3 h), compared to previously requiring almost 20 hours. However, the yield of the typical conditions is 84%, whereas the pre-incubated catalyst only provided 63% of the desired γ–alkylated product. The PPh_3-bound Ni(0) catalyst was found to be unstable as the reaction underwent no product formation.

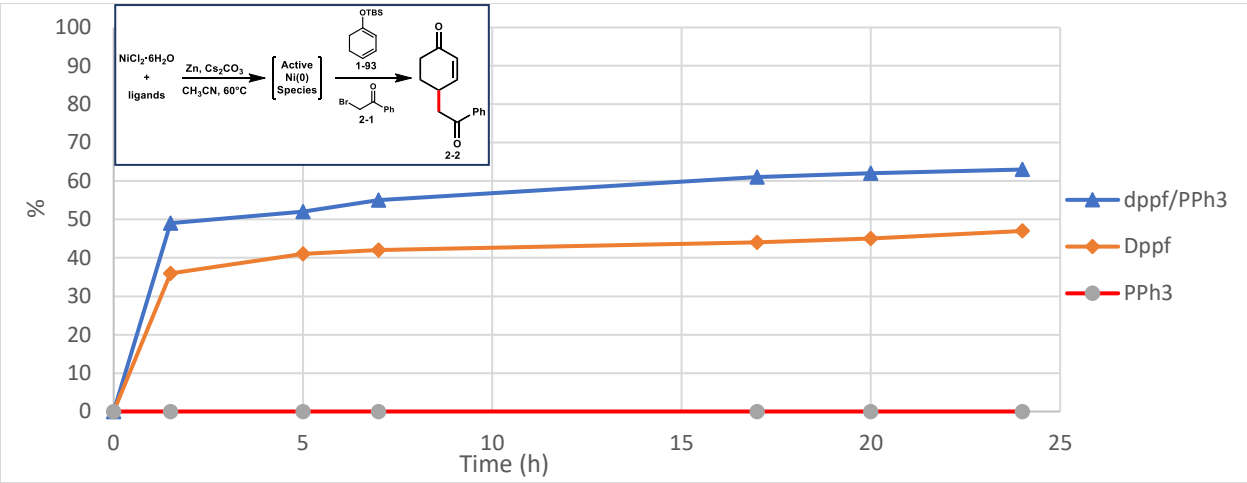


Figure 2.5 Plot of the Effects of Ligands with Pre-Incubation

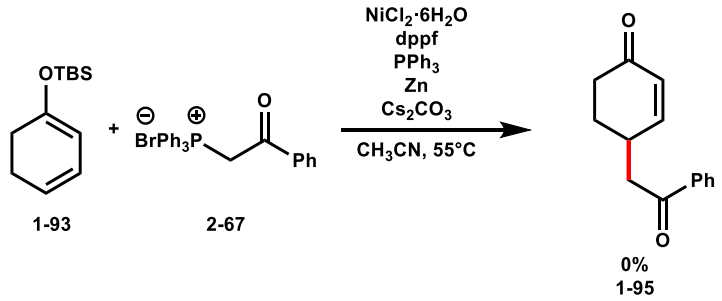
One possibility for the two ligands, dppf and PPh_3, is that ligand exchange occurs during the reaction to enable different stereoelectronic effects on the coupling mechanism. The bite angle of dppf is 98.74°,[37] whereas the cone angle of PPh_3 cone angle is 145°.[38] A larger bite angle is known theoretically and experimentally to increase the rate of migratory insertion.[39] The migratory insertion rate while not rate-limiting can be vital to turnover of the reaction.

Nickel, as with many palladium couplings, is expected to lose a phosphine ligand to open a coordination site, prior to oxidative addition and for alkene coordination.[36b] This dissociation is reported to occur readily in Pd(dppf) systems as the P–Pd–P angle is quite large.[40] In the case of the radical mechanism, the nickel(0) species only requires one open coordination site which opens the possibility of the formation of a Ni(0) species with three phosphine ligands which would be electron-rich and facilitate the formation of the alkyl radical.

2.6.4 Proposed Mechanisms

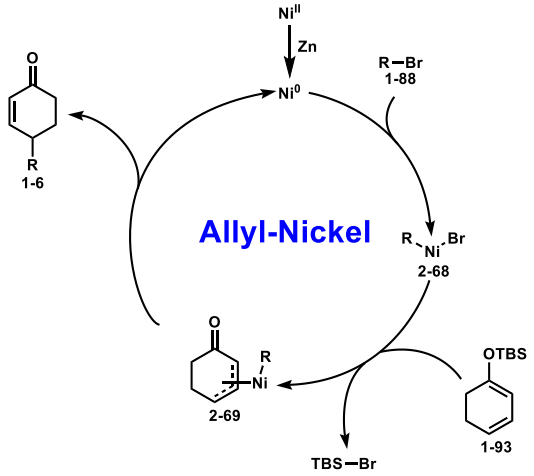
Through our mechanistic investigations, two prevailing mechanisms, allyl-nickel and radical appear to be the most viable. From the reaction rate graphs, it appears that the formation of a Ni(0) catalyst would be the expected first step of the reaction. The rate-determining step as

evidenced by our Hammett plot and the competition experiment between the chloro- and bromo-acetonitrile, is the oxidative addition into the alkyl halide, which operates through a two-electron pathway.[36a,c] Insertion of the nickel(0) does not occur on a phosphonium salt as evidenced by our attempts to couple a phosphonium salt through our conditions (Scheme 2.8).[41]



Scheme 2.8 Coupling with Phosphonium Salt

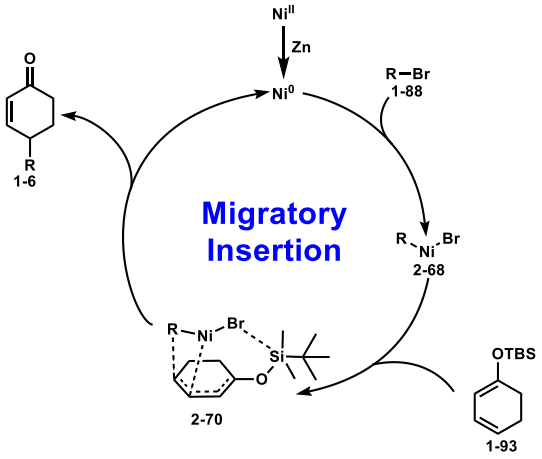
The oxidative addition pathway is still under investigation, as it can occur through the concerted three-centered σ-complex or an SN_2 pathway. However, the next step in the mechanism has three alternative pathways, the γ-migratory insertion and formation of the allyl nickel species, the one-step migratory insertion/reductive elimination, or the homolytic bond cleavage for the radical mechanism.



Scheme 2.9 Proposed Mechanism for Allyl Nickel Intermediate

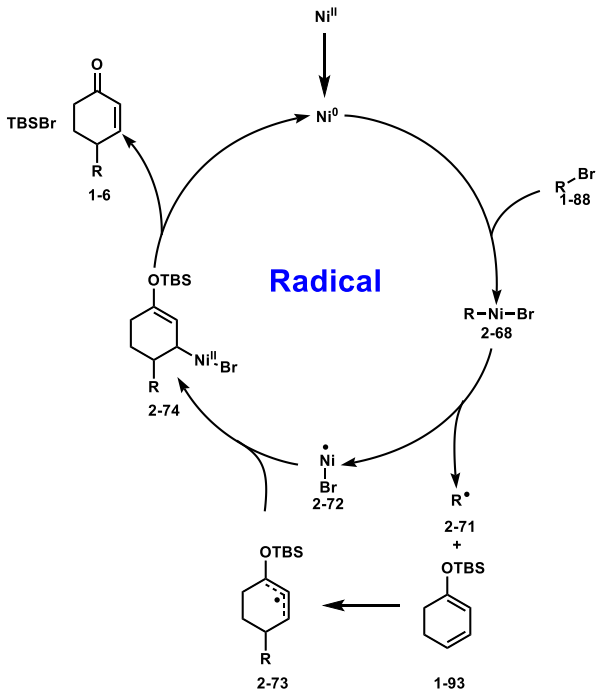
The mechanism can occur through a two-electron pathway. In this mechanism, the migratory insertion would occur selectively on the γ-carbon which would occur through the energetically favored allyl nickel species, similar to that proposed by Hartwig.[8] In Hartwig's mechanism, oxidative addition of the palladium into the aryl halide, is followed by transmetallation between the silicon and palladium. The zinc chloride acts as a Lewis acid to cleave the metal-halogen group and initiate formation of the allylpalladium species.[42] In our conditions, we can form zinc chloride in situ from the $NiCl_2$ precatalyst and Zn(0), however in the case of $Ni(COD)_2$, the reaction still occurs in the absence of the Lewis acid, $ZnCl_2$.[43] Alternatively, Hartwig showed that the reaction could also occur through a Lewis base, such as tetraalkylammonium halides, however the mechanism was not the same as for the Lewis Acid mechanism.

We propose that the silyl group engages in halogen atom abstraction to facilitate the formation of the allylnickel species **2-69** (Scheme 2.9).[44] This allylnickel **2-69** then undergoes migratory insertion of the alkyl group to the sterically less hindered γ-carbon and reductive elimination to form the Ni(0) catalyst. Also, if the alkene is coordinated to the Ni(II) species, then delocalization of the nickel d electrons to the π*-antibonding orbitals of the alkene would result in rapid reductive elimination.



Scheme 2.10 One-Step Migratory Insertion/Reductive Elimination Pathway

Alternatively, the entire process can go through a one-step migratory insertion/reductive elimination (Scheme 2.10). The close proximity of the halogen to the silyl group during the migratory insertion could indicate the probability of this intermediate. In this γ-alkyation method with the same catalyst system, a γ-aryl silyl dienol ether does not undergo α-alkylation despite the increased steric demands of γ-alkylation.[45] Previous examples of migratory insertion of Heck reactions show that insertion of the alkyl groups occurs preferentially on the more electron-deficient carbon.[47] So, electronically, α-alkylation would be preferred as the α–carbon would be more electron-deficient, due to the nearby carbonyl group, than the γ–carbon. In the case of a γ-aryl silyl dienol ether, the β,γ enone would be conjugation with the aryl group, which should be the thermodynamic product, we still do not see α-arylation occur.[46]



Scheme 2.11 Proposed Radical Mechanism

Therefore, the allylnickel intermediate most likely does not persist long enough for the alkylnickel species to add to the α-carbon, which suggests that the one-step migratory insertion/reductive elimination pathway may be preferred over the allylnickel intermediate mechanism. However, the polar one-step migratory insertion/reductive elimination shows the wrong selectivity in the insertion step. Migratory insertion should add the alkyl group to the more electron-deficient carbons, the silyl ether carbon or the β–carbon.[47]

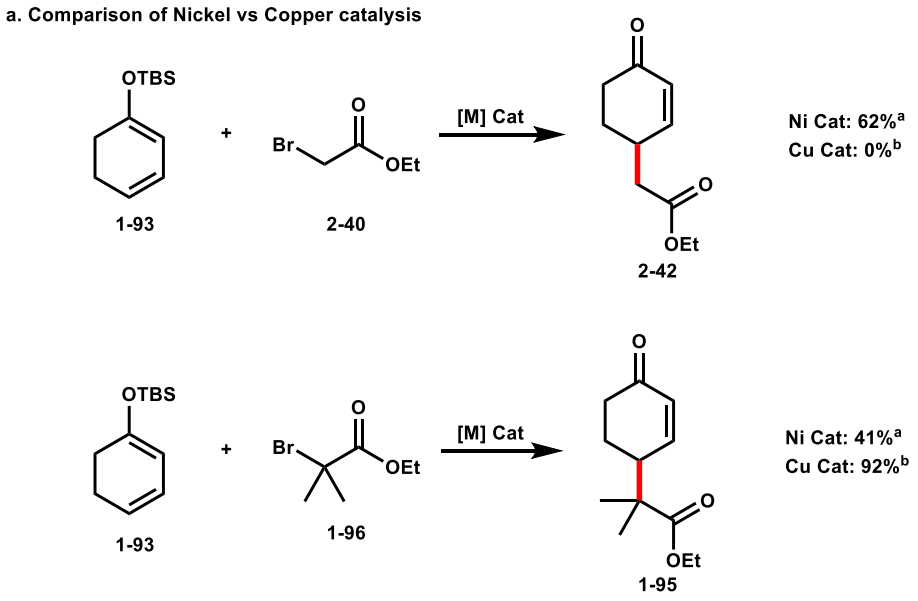
An alternative to the traditional 2-electron Heck reaction mechanism is a radical mechanism (Scheme 2.11). After oxidative addition of the Ni(0) to the alkyl halide, bond homolysis would form the alkyl radical **2-71** which has been previously proposed to occur through the Ni(0) catalyst.[10] The electron-deficient alkyl radical **2-71** is expected to add selectively to the γ-carbon as it is the more electron-rich carbon.[48] This would also allow the formation of the allyl radical **2-73** which is lower in energy than any other intermediate.[46] This allyl radical could then recombine with the nickel radical to form a Ni(II) species **2-4**, which can then undergo reductive elimination to form the enone **1-6** and Ni(0).

The primary radical would likely be unstable and may not persist for long enough to engage in an intermolecular reaction, so it is possible that coordination of the Ni(0) would occur prior to the homolytic bond cleavage, thereby enabling the unstable radical to react rapidly with the nearby alkene.[49] The coordination of the alkene to the nickel to facilitate oxidative addition was reported by Yamamoto and coworker, as the alkenes can act as ligands to facilitate alkyl cross-coupling reactions.[50]

2.7 Comparison to Copper catalysis system

Seeking to test the limitations and advantages of our nickel protocol over our copper protocol, we tested both systems with a primary and tertiary α-bromoester (Scheme 3).[11] In the

case of the primary alkyl halide **2-40**, we found that the copper system failed to catalyze the reaction which is expected for the proposed radical pathway as the formation of the primary radical would be difficult and the resulting radical would be too unstable for an intermolecular reaction, whereas the Ni protocol yielded 62% of the desired γ-alkylated product **2-42**. The tertiary alkyl halide showed a preference for the copper system yielding a 92% of the γ-alkylated product **1-95** compared to the 41% γ-alkylated product **1-95** from the Ni system. (Scheme 2.11).



[a] Isolated yield from reaction of dienol ether (0.25 mmol), a-haloketone (1.75 equiv), PPh_3 (20 mol%), Zn powder (30 mol%), and Cs_2CO_3 (1.5 equiv), Ni catalyst (10 mol%), and ligand (12 mol%) in 1.25 mL of solvent at 55 °C for 24 h. [b] Isolated yield from reaction of dienol ether (0.25 mmol), a-haloketone (1.5 equiv), $Cu(OTf)_2$ (7.5 mol %), PMDTA (15 mol %), $NaHCO_3$ (1.0 equiv) in 1 mL of DCE at 80 °C for 24 h.

Scheme 2.11 Copper vs Nickel Catalysis

2.8 Summary

In order to address a significant deficiency in γ-alkylation methods, we sought to develop a strategy to cross-couple primary alkyl halides with silyl dienol ethers. This work provides direct access to valuable γ-alkylated enones from readily available silyl dienol ethers. The reactivity and chemoselectivity has proven to be quite general with respect to substrate steric bulk, and diverse

functional groups. We have demonstrated the value of these γ-alkylated enones by their conversion to a number of different structural motifs and their application to an approach to the synthesis of 9-oxoagerophorone. Further studies into its application towards total synthesis are ongoing.[51]

2.9 Experimental Details

Unless otherwise stated, reactions were performed in oven-dried glassware under a N_2 atmosphere using dry, deoxygenated solvents. Anhydrous acetonitrile, dichloromethane, pentane, toluene, and THF (BHT-free) were purchased from Aldrich, degassed with argon, and dried by passage through activated drying columns[52] on a Pure Process Technology system. Cesium carbonate (Cs_2CO_3) was purchased from Fischer Chemical and used as received. Deuterated chloroform ($CDCl_3$, 99.9%, extra dry) was purchased from Cambridge Isotope Laboratories, Inc. and was used without further purification. Reaction temperatures were controlled by an IKAmag immersion temperature modulator. Thin-layer chromatography (TLC) was performed using Silicycle silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or staining with *p*-anisaldehyde or $KMnO_4$ solutions. Flash chromatography[53] was performed using Silicycle SiliaFlash® P60 silica gel (40–63 μm particle size). Melting points were determined using a Mel-Temp electrothermal capillary melting point apparatus and the values reported are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 (at 500 and 126 MHz, respectively) or DPX-400 instrument (at 400 and 101 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, br s = broad singlet. Data for ^{13}C NMR spectra

are reported in terms of chemical shift relative to Me_4Si (δ 0.0). Infrared (IR) spectra were recorded on a Nicolet iS5 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). GC/MS analyses were performed on a Hewlett Packard Model 6890 gas chromatograph interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS).

Enone starting materials, including 2-cyclohexen-1-one and isophorone, were purchased from Aldrich, Alfa Aesar, or Oakwood Chemical and used as received. 2-Bromo-4'methoxyacetophenone,[54] 2-bromo-3'methoxyacetophenone,54 2-bromo-4'methylacetophenone,54 2-bromo-3',4',5'methoxyacetophenone,54 2-bromofuranone,[55] 1-bromo-3,3-dimethylbutan-2-one,[55] 2-bromo-4'aminoacetophenone,[56] and 2-bromo-1-cyclopropylethan-1-one[57] were prepared according to literature procedures. TBS-dienol ethers were synthesized by enolization with LiHMDS or by soft enolization according to our previous publication.[12] (-) Menthenone was synthesized according to reported publication.[27]

Procedure for Optimization Reactions:

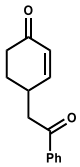
The Ni catalyst, ligand, triphenylphosphine, Zn powder, base, and 2-bromoacetophenone (74.6 mg, 1.5 equiv, 0.375 mmol) were added to an oven-dried 20 mL vial equipped with a magnetic stirring bar. Then the vial was sealed with a septum cap and then evacuated and backfilled with dry N_2 (three cycles). Anhydrous acetonitrile (1.25 mL) was added and then the mixture was stirred for 20 min. Neat *tert*-butyl(cyclohexa-1,3-dien- 1-yloxy)dimethylsilane **1-93** (52.6 mg, 0.25 mmol, 1.0 equiv) was then injected into the vial via syringe. The mixture was warmed to 60 °C and stirred. After 24 h, the reaction was cooled to room temperature and the solvent was

removed *in vacuo*. The crude compound was purified by flash column chromatography on silica gel.

General Procedure for Ni-Catalyzed γ-Alkylation:

Solid $NiCl_2 \cdot 6H_2O$ (5.9 mg, 0.025 mmol, 10 mol %), 1,1'-bis(diphenylphosphino)ferrocene (dppf, 16.6 mg, 0.030 mmol, 12 mol %), triphenylphosphine (13.1 mg, 0.050 mmol, 20 mol %), Zn powder (5.1 mg, 0.075 mmol, 30 mol %), cesium carbonate (122.1 mg, mmol, 1.5 equiv), and α-haloketone (0.44 mmol, 1.75 equiv) were added to an oven-dried 20 mL vial equipped with a magnetic stirring bar. The vial was sealed with a septum cap and then evacuated and backfilled with dry N_2 (three cycles of 15 min each). Anhydrous CH_3CN (1.25 mL) was added and the mixture was stirred for 30 min. Neat TBS dienol ether (0.25 mmol, 1.0 equiv) were added sequentially via syringe. The mixture was heated to 55 °C and stirred for 24 h. The mixture was cooled to room temperature and the solvent was removed by rotary evaporation under vacuum. The crude material was purified by flash column chromatography on silica gel.

2.9.1 Experimental Data for γ-Alkylation Products



2-2

4-(2-oxo-2-phenylethyl)cyclohex-2-en-1-one:

The title compound was prepared according to the General Procedure using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.5 mg, 0.25 mmol) and 2-bromoacetophenone **2-1** (87.1

mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 6:1 hexanes/EtOAc), the title compound was isolated as a white solid.

1st run: 45.3 mg (85% yield)

2nd run: 44.5 mg (83% yield)

MP 82–84 °C

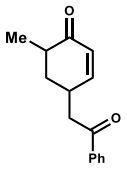
TLC (SiO_2) R_f = 0.43 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.4 Hz, 2H), 7.58 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 6.89 (d, *J* = 10.9 Hz, 1H), 6.00 (dd, *J* = 10.3, 2.5 Hz, 1H), 3.20 (m, 1H), 3.13 (m, 2H), 2.47 (m, 2H), 2.21 (m, 1H), 1.78 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.3, 197.7, 154.0, 136.6, 133.5, 129.5, 128.8, 128.0, 42.5, 36.9, 31.9

IR (neat) 3061, 3041, 2953, 2929, 2903, 2880, 1686, 1668, 1595, 1508, 1389, 1220 cm^{-1}

GC/MS (*m/z*) 214.1 (2%), 185 (1%), 179.6 (1%), 171.0 (2%), 156.9 (2%), 142.2 (1%), 129.0 (1%), 120.0 (50%), 115.0 (1%), 105.0 (100%), 95.0 (15%), 77.1 (50%), 65.0 (2%), 51.0 (10%)



2-11

6-methyl-4-(2-oxo-2-phenylethyl)cyclohex-2-en-1-one:

The title compound was prepared according to the General Procedure using *tert*-butyldimethyl((6-methylcyclohexa-1,3-dien-1-yl)oxy)silane **2-6** (56.1 mg, 0.25 mmol) and 2-bromoacetophenone **2-1** (87.1 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1

hexanes/EtOAc), the title compound **2-11** was isolated as a yellow oil, comprising a 3.7:1 mixture of diastereomers (based on ^{1}H NMR of purified material).

1st run: 34.1 mg (60% yield)

2nd run: 35.1 mg (62% yield)

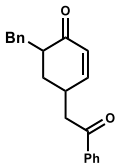
TLC (SiO_2) R_f = 0.47 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) for major diastereomer: δ 7.97 (dd, *J* = 8.5 Hz, 2H), 7.59 (t, *J* = 8.5 Hz, 1H), 7.48 (t, *J* = 7.0 Hz, 2H), 6.90 (dd, *J* = 10.3, 4.0 Hz, 1H), 5.96 (d, *J* = 10.3 Hz, 1H), 3.26 (m, 1H), 3.18 (d, *J* = 7.8 Hz, 2H), 2.55 (m, 1H), 2.01 (m, 1H), 1.93 (m, 1H), 1.18 (d, *J* = 7.2 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.1, 197.9, 152.6, 136.7, 133.5, 128.8, 128.0, 41.8, 38.5, 35.5, 29.5, 15.3

IR (neat) 3060, 3029, 2964, 2928, 2871, 1673, 1620, 1597, 1550, 1408, 1322, 1148 cm^{-1}

GC/MS (*m/z*) 228.0 (2%), 171.0 (1%), 157.9 (1%), 142.1 (1%), 120.0 (30%), 105.0 (100%), 91.0 (2%), 77.0 (38%), 65.0 (3%), 51.0 (5%)



2-12

6-benzyl-4-(2-oxo-2-phenylethyl)cyclohex-2-en-1-one:

The title compound was prepared according to the General Procedure using *tert*-butyldimethyl((6-benzylcyclohexa-1,3-dien-1-yl)oxy)silane **2-7** (75.0 mg, 0.25 mmol) and 2-bromoacetophenone **2-1** (87.1 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc),

the title compound **2-12** was isolated as a white solid, comprising a 5.4:1 mixture of diastereomers (based on ^{1}H NMR of purified material).

1st run: 47.7 mg (63% yield)

2nd run: 45.7 mg (60% yield)

MP 85–88 °C

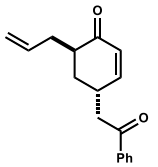
TLC (SiO_2) R_f = 0.56 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) for major diastereomer δ 7.92 (d, *J* = 9.5 Hz, 2H), 7.59 (t, *J* = 10.0 Hz, 1H), 7.47 (dd, *J* = 10.0, 10.0 Hz, 2H), 7.28 (dd, *J* =10.0 Hz, 2H), 7.21 (m, 3H), 6.94 (dd, *J* = 12.3, 4.0 Hz, 1H), 6.02 (dd, *J* = 12.3, 2.1 Hz, 1H), 3.31 (m, 1H), 3.10 (m, 3H), 2.70 (m, 2H), 1.94 (m, 1H), 1.79 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.4, 197.9, 152.6, 139.2, 136.6, 133.5, 129.1, 128.7, 128.5, 128.0, 126.4, 46.1, 42.2, 35.6, 31.9, 29.3

IR (neat) 3061, 3028, 2923, 2862, 1671, 1616, 1597, 1448, 1302, 1029 cm^{-1}

GC/MS (*m/z*) 304.0 (1%), 267.1 (1%), 213.1 (3%), 184.1 (100%), 167.0 (2%), 121.0 (5%), 105.0 (53%), 91.1 (41%), 77.0 (40%), 65.1 (9%), 51.1 (9%)



2-13

6-allyl-4-(2-oxo-2-phenylethyl)cyclohex-2-en-1-one:

The title compound was prepared according to the General Procedure using *tert*-butyldimethyl((6-allylcyclohexa-1,3-dien-1-yl)oxy)silane **2-8** (62.5 mg, 0.25 mmol) and 2-bromoacetophenone **2-1**

(87.1 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-13** was isolated as a yellow oil, comprising a 6.4:1 mixture of diastereomers (based on ^{1}H NMR of purified material).

1st run: 45.8 mg (72% yield)

2nd run: 44.5 mg (70% yield)

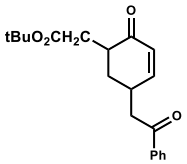
TLC (SiO_2) R_f = 0.61 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) for major diastereomer δ 7.97 (d, *J* = 9.5 Hz, 2H), 7.60 (t, *J* = 9.5, 1H), 7.49 (t, *J* = 9.5 Hz, 2H), 6.92 (dd, *J* = 12.5, 4.5 Hz, 1H), 5.98 (dd, *J* = 12.5, 2.5 Hz, 1H), 5.76 (m, 1H), 5.06 (m, 2H), 3.27 (m, 1H), 3.15 (d, *J* = 8.6 Hz, 2H), 2.5 (m, 2H), 2.24 (m, 1H), 2.07 (m, 1H), 1.91 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.8, 197.9, 152.6, 136.7, 135.6, 133.5, 128.8, 128.0, 117.2, 43.7, 42.1, 34.0, 32.3, 29.4

IR (neat) 3063, 3029, 2918, 1672, 1640,1597, 1448, 1159 cm^{-1}

GC/MS (*m/z*) 254.1 (1%), 226.1 (1%), 149.1 (4%), 134.0 (56%), 120.0 (21%), 77.0 (51%), 65.1 (1%), 51.1 (10%)



2-14

***tert*-butyl 2-oxo-5-(2-oxo-2-phenylethyl)cyclohex-3-en-1-yl)acetate:**

The title compound was prepared according to the General Procedure using *tert*-butyl 2-(2-((*tert*-butyldimethylsilyl)oxy)cyclohexa-2,4-dien-1-yl)acetate **2-9** (81.1 mg, 0.25 mmol) and 2-

bromoacetophenone **2-1** (87.1 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-14** was isolated as a yellow solid, comprising a 7.9:1 mixture of diastereomers (based on ^1H NMR of purified material).

1st run: 57.9 mg (71% yield)

2nd run: 56.6 mg (69% yield)

MP 84–87 °C

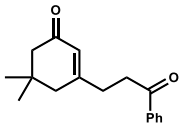
TLC (SiO_2) R_f = 0.49 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.1, 2H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 7.1, 7.1 Hz, 2H), 6.96 (dd, *J* = 10.1, 2.5 Hz, 1H), 5.95 (d, *J* = 10.4 Hz, 1H), 3.24 (m, 2H), 2.94 (m, 1H), 2.71 (dd, *J* = 16.8, 5.2 Hz, 1H), 2.19 (dd, *J* = 16.4, 7.8 Hz, 1H), 2.08 (dt, *J* = 11.6, 2.8 Hz, 1H), 1.95 (m, 1H), 1.40 (s, 9H)

13C NMR (126 MHz, $CDCl_3$) δ 199.3, 197.4, 171.3, 152.2, 136.4, 133.5, 128.5, 128.1, 80.5, 40.9, 39.8, 35.7, 32.8, 30.1, 28.1

IR (neat) 3060, 2978, 2929, 1723, 1678, 1619, 1597, 1581, 1366, 1148 cm^{-1}

GC/MS (*m/z*) 328.1 (12%), 326.9 (38%), 264.9 (8%), 250.8 (10%), 221.0 (12%), 147.0 (65%), 73.0 (100%), 59.0 (10%)



2-15

5,5-dimethyl-3-(3-oxo-3-phenylpropyl)cyclohex-2-en-1-one:

The title compound was prepared according to the General Procedure with *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0 mg, 0.25 mmol) and 2-bromoacetophenone **2-1** (87.1 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-15** was isolated as a white solid.

1st run: 53.3 mg (85% yield)

2nd run: 51.8 mg (81% yield)

MP 62–63 °C

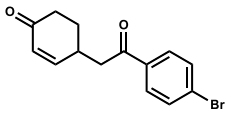
TLC (SiO_2) R_f = 0.48 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.7 Hz, 2H), 7.57 (t, *J* = 6.5 Hz, 1H), 7.47 (dd, *J* = 7.3, 7.3 Hz, 2H), 5.88 (s, 1H), 3.20 (t, *J* = 7.5 Hz, 2H), 2.64 (t, *J* = 7.5 Hz, 2H), 2.25(s, 2 H), 2.22 (s, 2H), 1.04 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.0, 197.9, 162.8, 136.5, 133.4, 128.7, 127.9, 124.3, 50.9, 44.4, 35.4, 31.6, 28.2

IR (neat) 3065, 2950,2927, 2899, 2864, 1683, 1654, 1625, 1597, 1581, 1361, 1206 cm^{-1}

GC/MS (*m/z*) 256.1 (2%), 241.2 (3%), 223.1 (5%), 180.9 (1%), 172.0 (1%), 151.1 (90%), 136.1 (5%), 129.0 (1%), 121.1 (35%), 115.0 (1%), 105% (100%), 95.0 (15%), 83.0 (1%), 77.0 (50%), 67.0 (5%), 51.0 (7%)



2-27

4-(2-(4-bromophenyl)-2-oxoethyl)cyclohex-2-en-1-one

The title compound was prepared according to the General Procedure using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane 1-93 (52.5 mg, 0.25 mmol) and 2-bromo-4'-bromoacetophenone **2-16** (121.6 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 6:1 hexanes/EtOAc), the title compound **2-27** was isolated as a white solid.

1st run: 59.3 mg (81% yield)

2nd run: 61.4 mg (84% yield)

MP 101–104 °C

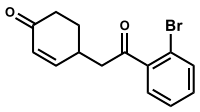
TLC (SiO_2) R_f = 0.42 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 10.2 Hz, 1H), 6.02 (dd, *J* = 10.2, 2.4 Hz, 1H), 3.20 (m, 1H), 3.10 (m, 2H), 2.49 (m, 2H), 2.21 (m, 1H), 1.79, (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.3, 196.6, 153.2, 135.6, 132.3, 129.6, 128.7, 42.8, 36.7, 32.0, 29.1

IR (neat) 2951, 2932, 2890, 2873, 1669, 1633, 1582, 1568, 1393, 1317 cm^{-1}

GC/MS (*m/z*) 293.1 (2%), 291.9 (2%), 199.2 (69%), 197.9 (69%), 184.9 (100%), 182.4 (100%), 154.9 (38%), 152.9 (38%), 109.0 (50%), 95.0 (25%), 76.0 (32%), 53.1 (10%)



2-28

4-(2-(2-bromophenyl)-2-oxoethyl)cyclohex-2-en-1-one:

The title compound was prepared according to the General Procedure using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.5 mg, 0.25 mmol) and 2-bromo-2'-bromoacetophenone

2-17 (121.6 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 6:1 hexanes/EtOAc), the title compound **2-28** was isolated as a white solid.

1st run: 58.5 mg (80% yield)

2nd run: 57.9 mg (79% yield)

MP 58–60 °C

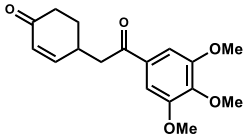
TLC (SiO_2) R_f = 0.25 in 4:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 4.5 Hz, 2H), 7.30 (m, 1H), 6.88 (d, *J* = 10.5 Hz, 1H), 6.00 (d, *J* = 10.5 Hz, 1H), 3.17 (m, 1H), 3.09 (m, 2H), 2.47 (m, 2H), 2.22 (m, 1H), 1.79 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.8, 199.1, 153.4, 14.4, 133.8, 131.9, 129.7, 128.3, 127.6, 118.9, 46.9, 36.7, 32.1, 28.8

IR (neat) 3028, 2949, 2889, 2838, 1698, 1651, 1583, 1466, 1455, 1385, 1050 cm^{-1}

GC/MS (*m/z*) 335.9 (4%), 318.9 (5%), 302.9 (4%)



2-29

4-(2-oxo-2-(3,4,5-trimethoxyphenyl)ethyl)cyclohex-2-en-1-one:

The title compound was prepared according to the General Procedure using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.5 mg, 0.25 mmol) and 2-bromo-3',4',5'-trimethoxyacetophenone **2-18** (126.6 mg, 0.438 mmol). After purification by flash

chromatography (SiO_2, 6:1 hexanes/EtOAc), the title compound **2-29** was isolated as a yellow solid.

1st run: 59.0 mg (78% yield)

2nd run: 62.1 mg (82% yield)

MP 91–93 °C

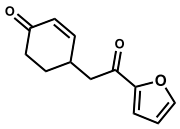
TLC (SiO_2) R_f = 0.16 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (s, 2H), 6.87 (d, *J* = 9.7 Hz, 1H), 5.99 (d, *J* = 9.7 Hz, 1H), 3.90 (s, 9H), 3.18 (m, 1H), 3.08 (m, 2H), 2.47 (m, 2H), 2.19 (m, 1H), 1.77 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.1, 196.4, 153.8, 153.2, 142.8, 132.0, 129.4, 105.4, 61.0, 56.4, 42.4, 36.7, 32.1, 29.0

IR (neat) 3002, 2940, 2839, 1674, 1584, 1505, 1412, 1246 cm^{-1}

GC/MS (*m/z*) 304.1 (29%), 252.9 (1%), 210.1 (61%), 195.1 (100%), 168.1 (29%), 153.0 (25%), 137.0 (20%), 77.0 (24%), 65.9 (20%), 53.0 (22%)



2-30

4-(2-(furan-2-yl)-2-oxoethyl)cyclohex-2-en-1-one

The title compound was prepared according to the General Procedure using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.5 mg, 0.25 mmol) and 2-bromo-furanone **2-19** (82.8 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 6:1 hexanes/EtOAc), the title compound **2-30** was isolated as a yellow solid.

1st run: 30.1 mg (59% yield)

2nd run: 31.9 mg (63% yield)

MP 52–55 °C

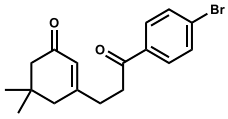
TLC (SiO_2) R_f = 0.25 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 1.1 Hz, 1H), 7.22 (d, *J* = 4.4 Hz, 1H), 6.86 (d, *J* = 10.5 Hz, 1H), 6.56 (d, *J* = 3.1 Hz, 1H), 5.98 (d, *J* = 10.5 Hz, 1H), 3.15 (m, 1H), 2.98 (d, *J* = 7.2 Hz, 2H), 2.44 (m, 2H), 2.18 (m, 1H), 1.77 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.1, 187.1, 153.6, 152.4, 146.8, 129.7, 117.3, 112.3, 42.3, 36.5, 31.7, 29.2,

IR (neat) 3131, 2928, 2869, 1761, 1668, 1568, 1466, 1328, 1159 cm^{-1}

GC/MS (*m/z*) 204.0 (3%), 186.0 (1%), 147.0 (1%), 110.0 (100%), 95.0 (68%), 81.0 (19%), 67.0 (5%), 53.0 (16%)



2-31

3-(3-(4-bromophenyl)-3-oxopropyl)-5,5-dimethylcyclohex-2-en-1-one

The title compound was prepared according to the General Procedure with *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0. mg, 0.25 mmol) and 2-bromo-4'-bromooacetophenone **2-16** (121.6 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-31** was isolated as a yellow solid.

1st run: 68.5 mg (82% yield)

2nd run: 70.2 mg (83% yield)

MP 102–105 °C

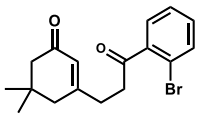
TLC (SiO_2) R_f = 0.43 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 5.86 (s, 1H), 3.15 (m, 2H), 2.62 (m, 2H), 2.24 (s, 2H), 2.21 (s, 2H), 1.03 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.7, 197.0, 162.1, 135.1, 132.0, 129.3, 128.4, 124.3, 51.0, 44.6, 35.2, 33.8, 31.5, 28.1

IR (neat) 3054, 2957, 2923, 2867, 1688, 1652, 1624, 1581, 1484, 1410, 1397, 1204 cm^{-1}

GC/MS (*m/z*) 335.9 (3%), 318.9 (8%), 302.9 (11%), 182.9 (43%), 182.9 (43%), 151.1 (100%), 121.1 (38%), 95.1 (11%), 76.0 (8%), 55.0 (2%)



2-32

3-(3-(2-bromophenyl)-3-oxopropyl)-5,5-dimethylcyclohex-2-en-1-one

The title compound was prepared according to the General Procedure with *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0 mg, 0.25 mmol) and 2-bromo-2'-bromoacetophenone **2-17** (121.6 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-32** was isolated as a yellow oil.

1st run: 52.5 mg (63% yield)

2nd run: 52.1 mg (62% yield)

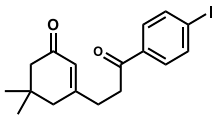
TLC (SiO_2) R_f = 0.36 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.5 Hz, 1H), 7.37 (m, 2H), 7.31 (m, 1H), 5.88 (s, 1H), 3.15 (t, *J* = 8.4 Hz, 2H), 2.62 (t, *J* = 6.9 Hz, 2H), 2.22 (s, 2H), 2.21 (s, 2H), 1.04 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.0, 199.5, 161.7, 140.9, 131.9, 128.6, 127.5, 124.7, 118.7, 51.0, 44.2, 39.6, 33.6, 31.7, 28.2

IR (neat) 3056, 2958, 2892, 2869, 1699, 1661, 1629, 1563, 1409, 1299 cm^{-1}

GC/MS (*m/z*) 335.5 (3%), 319.1 (2%), 300.9 (1%), 221.0 (55), 183.1 (70%), 182.9 (70%), 151.1 (100%), 136.0 (5%), 121.0 (50%), 105.0 (3%), 95.0 (5%), 77.0 (8%), 67.0 (5%), 55.1 (3%)



2-33

3-(3-(4-iodophenyl)-3-oxopropyl)-5,5-dimethylcyclohex-2-en-1-one

The title compound was prepared according to the General Procedure with *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0 mg, 0.25 mmol) and 2-bromo-4'-iodoacetophenone **2-20** (142.1 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-33** was isolated as a yellow oil.

1st run: 67.8 mg (71% yield)

2nd run: 67.2 mg (72% yield)

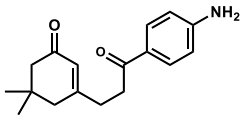
TLC (SiO_2) R_f = 0.22 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 5.86 (s, 1H), 3.14 (t, *J* = 7.1 Hz, 2H), 2.61 (dd, *J* = 7.1, 6.7 Hz, 2H), 2.23 (s, 2H), 2.21 (s, 2H), 1.03 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.7, 197.4, 162.2, 138.0, 135.7, 129.4, 124.4, 101.5, 50.8, 44.6, 35.0, 33.8, 31.7, 28.4

IR (neat) 3080, 3052, 2956, 2924, 2912, 2865, 1688, 1652, 1625, 1577, 1563, 1481, 1357, 1003 cm^{-1}

GC/MS (*m/z*) 382.0 (3%), 367.0 (4%), 355.0 (3%), 348.0 (2%), 326.8 (2%), 267.0 (2%), 253.0 (2%), 230.9 (54%), 190.8 (2%), 151.1 (100%), 133.0 (6%), 121.0 (36%), 103.9 (8%), 76.0 (20%), 65.1 (2%), 55.1 (2%)



2-34

3-(3-(4-aminophenyl)-3-oxopropyl)-5,5-dimethylcyclohex-2-en-1-one

The title compound was prepared according to the General Procedure with *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0 mg, 0.25 mmol) and 2-bromo-4'-aminoacetophenone **2-21** (93.7 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-34** was isolated as a red solid.

1st run: 52.7 mg (78% yield)

2nd run: 50.6 mg (75% yield)

MP 127–131 °C

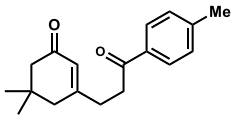
TLC (SiO_2) R_f = 0.12 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.5 Hz, 2H), 6.61 (d, *J* = 7.5 Hz, 2H), 5.85 (s, 1H), 4.32 (br s, 2H), 3.05 (t, *J* = 8.1 Hz, 2H), 2.57 (t, *J* = 8.1 Hz, 2H), 2.21 (s, 2H), 2.18 (s, 2H), 1.00 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.0, 195.2, 163.0, 148.6, 133.5, 129.1, 127.8, 124.2, 114.3, 108.2, 51.0, 44.4, 34.6, 33.6, 31.8, 28.3

IR (neat) 3422, 3348, 3239, 2958, 2926, 2905, 2867, 1650, 1626, 1588, 1561, 1465, 1358 cm^{-1}

GC/MS (*m/z*) 269.5 (5%), 266.9 (14%), 252.9 (16%), 221.0 (35%), 207.0 (100%), 190.8 (16%), 147.0 (48%), 133.0 (18%), 96.0 (14%), 73.0 (84%), 58.9 (5%)



2-35

3-(3-(4-methylphenyl)-3-oxopropyl)-5,5-dimethylcyclohex-2-en-1-one

The title compound was prepared according to the General Procedure with *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0 mg, 0.25 mmol) and 2-bromo-4'-methylacetophenone **2-22** (93.3 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-35** was isolated as a white solid.

1st run: 52.8 mg (78% yield)

2nd run: 54.1 mg (80% yield)

MP 75–77 °C

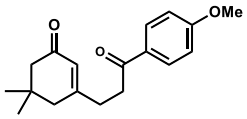
TLC (SiO_2) R_f = 0.45 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.7 Hz, 2H), 7.26 (d, J= 7.7 1H), 5.86 (s, 1H), 3.16 (t, *J* = 7.2 Hz, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 2.25 (s, 2H), 2.21 (s, 2H), 1.04 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.8, 197.8, 162.5, 144.3, 134.0, 129.4, 128.1, 124.4, 51.0, 44.4, 35.2, 33.6, 28.3, 21.6

IR (neat) 3065, 3034, 2965, 2945, 2923, 2891, 2864, 1677, 1658, 1625, 1608, 1575, 1412, 1202 cm^{-1}

GC/MS (*m/z*) 270.1 (5%), 255.1 (2%), 237.1 (5%), 186.1 (1%), 163.0 (1%), 151.1 (96%), 135.0 (2%), 119.0 (100%), 91.0 (40%), 77.0 (2%), 65.0 (10%), 55.0 (1%)



2-36

3-(3-(4-methoxyphenyl)-3-oxopropyl)-5,5-dimethylcyclohex-2-en-1-one

The title compound was prepared according to the General Procedure with *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0 mg, 0.25 mmol) and 2-bromo-4'-methoxyacetophenone **2-23** (100.3 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-36** was isolated as a white solid.

1st run: 41.9 mg (59% yield)

2nd run: 38.9 mg (54% yield)

MP 58–61 °C

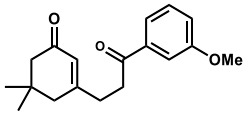
TLC (SiO_2) R_f = 0.27 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 9.8 Hz, 2H), 6.93 (d, *J* = 9.8 Hz, 2H) 5.88 (s, 1H), 3.87 (s, 3H), 3.14 (t, *J* = 8.5 Hz, 2H), 2.62 (t, *J* = 8.5 Hz, 2H), 2.23 (s, 2H), 2.20 (s, 2H), 1.04 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.0, 196.5, 163.9, 162.7, 130.3, 129.5, 124.2, 114.0, 55.4, 51.1, 44.4, 35.1, 33.5, 31.7, 28.3

IR (neat) 3084, 3058, 3000, 2957, 2930, 2899, 2868, 2837, 1657, 1620, 1598, 1512, 1441, cm^{-1}

GC/MS (*m/z*) 286.1 (1%), 253.0 (1%), 163.0 (2%), 151.1 (40%), 135.0 (105%), 107.0 (3%), 92.0 (3%), 77.0 (5%), 64.1 (1%), 55.0 (1%)



2-37

3-(3-(3-methoxyphenyl)-3-oxopropyl)-5,5-dimethylcyclohex-2-en-1-one

The title compound was prepared according to the General Procedure with *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0 mg, 0.25 mmol) and 2-bromo-3'-methoxyacetophenone **2-24** (100.3 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-37** was isolated as a white solid.

1st run: 47.8 mg (67% yield)

2nd run: 49.3 mg (69% yield)

MP 63–66 °C

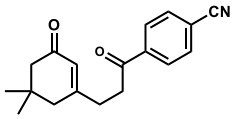
TLC (SiO_2) R_f = 0.43 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.7 Hz, 2H), 7.45 (s, 1H), 7.35 (dd, *J* = 7.1, 7.1 Hz, 1H), 7.09 (d, *J* = 7.1 Hz, 1H), 5.86 (s, 1H), 3.83 (s, 3H), 3.17 (t, *J* = 7.2 Hz, 2H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.24 (s, 2H), 2.21 (s, 2H), 1.01 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.0, 197.9, 162.6, 159.9, 137.7, 129.6, 124.3, 120.7, 119.7, 112.2, 55.5, 50.9, 44.4, 35.5, 33.6, 31.5, 28.3

IR (neat) 3078, 3032, 2962, 2935, 2902, 2835, 1686, 1657, 1633, 1593, 1387, 1290 cm^{-1}

GC/MS (*m/z*) 286.1 (5%), 253.1 (11%), 196.9 (1%), 187.0 (1%), 163.1 (2%), 151.1 (100%), 135.0 (80%), 121.0 (36%), 107.0 (24%), 92.0 (20%), 77.0 (28%), 64.0 (5%), 55.0 (5%)



2-38

3-(3-(3-methoxyphenyl)-3-oxopropyl)-5,5-dimethylcyclohex-2-en-1-one

The title compound was prepared according to the General Procedure with *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0 mg, 0.25 mmol) and 2-bromo-4'-cyanoacetophenone **2-25** (98.0 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-38** was isolated as a yellow solid.

1st run: 61.2 mg (87% yield)

2nd run: 59.8 mg (85% yield)

MP 118–121 °C

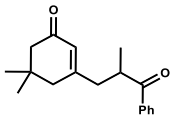
TLC (SiO_2) R_f = 0.17 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.6 Hz, 2H), 7.76 (d, *J* = 8.6 Hz, 2H), 5.83 (s, 1H), 3.20 (t, *J* = 7.2 Hz, 2H), 2.62 (t, *J* = 7.2 Hz, 2H) 2.23 (s, 2H), 2.20 (s, 2H), 1.01 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.5, 196.6, 161.5, 139.3, 132.6, 128.3, 124.3, 117.7, 116.6, 51.0, 44.1, 36.0, 31.1, 28.4,

IR (neat) 2960, 2937, 2911, 2229, 1689, 1656, 1626, 1606, 1405, 1302, 1203, 1020 cm^{-1}

GC/MS (*m/z*) 281.3 (12%), 266.1 (15%), 248.0 (8%), 196.0 (5%), 180.9 (2%), 151.1 (100%), 136.0 (11%), 130.0 (77%0, 121.0 (80%), 102.0 (50%), 91.0 (15%), 79.0 (13%), 67.0 (14%), 53.0 (5%)



2-39

5,5-dimethyl-3-(2-methyl-3-oxo-3-phenylpropyl)cyclohex-2-en-1-one

The title compound was prepared according to the General Procedure with *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0 mg, 0.25 mmol) and 2-bromopropiophenone **2-26** (67 µL, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-39** was isolated as a yellow oil.

1st run: 49.4 mg (73% yield)

2nd run: 47.8 mg (71% yield)

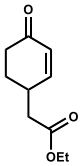
TLC (SiO_2) R_f = 0.50 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.57 (t, *J* = 8.2 Hz, 1H), 7.47 (dd, *J* = 8.2, 8.2 Hz, 2H), 5.85 (s, 1H), 3.20 (sextet, *J* = 6.7 Hz, 1H), 2.73 (dd, *J* = 7.1 Hz, 1H), 2.31 (d, *J* = 7.0, 8.3 Hz, 1H), 2.16 (m, 4H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.99 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.4, 199.7, 161.3, 135.7, 133.0, 128.8, 128.3, 125.8, 50.9, 44.5, 40.9, 38.4, 33.6, 28.4, 28.1, 18.0

IR (neat) 3065, 2957, 2933, 2869, 1663, 1627, 1596, 1579, 1424, 1299, 1197 cm^{-1}

GC/MS (*m/z*) 270.1 (2%), 255.1 (3%), 237.1 (4%), 185.1 (1%), 165.1 (69%), 149.1 (2%), 136.0 (2%), 121.1 (15%), 105.0 (100%), 91.0 (2%), 77.0 (39%), 67.0 (2%), 51.0 (3%)



2-42

Ethyl 2-(4-oxocyclohex-2-en-1-yl)acetate

The title compound was prepared according to the General Procedure using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.5 mg, 0.25 mmol) and ethyl bromoacetate **2-40** (49.0 µL, 0.438 mmol). After purification by flash chromatography (SiO_2, 6:1 hexanes/EtOAc), the title compound **2-42** was isolated as a white solid.

1st run: 28.5 mg (63% yield)

2nd run: 27.4 mg (60% yield)

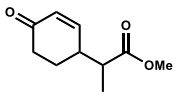
TLC (SiO_2) R_f = 0.18 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (d, *J* = 10.9 Hz, 1H), 5.97 (dd, *J* = 10.9, 2.6 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.92 (m, 1H), 2.43 (m, 4H), 2.14 (m, 1H), 1.73 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.9, 171.1, 152.8, 129.3, 60.7, 39.0, 36.9, 33.0, 28.6, 14.2

IR (neat) 2980,2935, 2871, 1728, 1678, 1616, 1389, 1269 cm^{-1}

GC/MS (*m/z*) 182.0 (5%), 137.0 (54%), 126.0 (15%), 109.0 (91%), 95.0 (75%), 88.0 (100%), 81.0 (98%), 68.0 (50%), 60.0 (22%), 53.0 (51%)



1-128

Methyl 2-(4-oxocyclohex-2-en-1-yl)propanoate

The title compound was prepared according to the General Procedure using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.6 mg, 0.25 mmol, 1.0 equiv) and methyl 2-bromopropanoate **2-41** (49.0 µL, 0.438 mmol, 1.75 equiv) at 55 °C for 24 h. Crude ^{1}H NMR prior to purification indicated a 1:1 mixture of diastereomers. After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **1-128** was isolated as a colorless oil, comprising a 1:1 mixture of diastereomers (based on ^{1}H NMR of purified material) with spectral characteristics consistent with those reported previously.[11]

1st run: 24.4 mg (54% yield, dr = 1:1)

2nd run: 25.1 mg (55% yield, dr = 1:1)

TLC (SiO_2) R_f = 0.25 in 4:1 hexanes/EtOAc, *p*-anisaldehyde stain

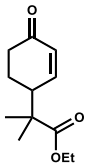
^{1}H NMR (500 MHz, $CDCl_3$) for both diastereomers δ 6.83 (d, *J* = 10.3 Hz, 1H), 6.72 (d, *J* = 10.3 Hz, 1H), 5.92 (m, 2H), 3.61 (s, 3H), 3.60 (s, 3H), 2.71 (m, 2H), 2.54 (m, 2H), 2.41 (m, 2H), 2.28 (m, 2H), 1.96 (m, 2H), 1.71 (m, 2H), 1.13 (d, *J* = 4.2 Hz, 3H), 1.12 (d, *J* = 4.2 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.9, 175.0, 174.9, 152.0, 151.5, 130.0, 129.9, 51.8, 51.7, 42.9,

42.6, 38.9, 36.9, 26.7, 25.6

IR (neat) 2979, 1726, 1678, 1452, 1418, 1344, 1257, 1173, 1145, 1022, 951, 845, 784, 741 cm^{-1}

GC/MS (*m/z*) 182.1 (2%), 151.0 (16%), 123.1 (83%), 111.0 (22%), 95.0 (88%), 88.0 (100%), 79.0 (25%), 67.1 (44%), 55.0 (22%), 51.0 (5%)



1-95

Ethyl 2-methyl-2-(4-oxocyclohex-2-en-1-yl)propanoate

The title compound was prepared according to the General Procedure using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.6 mg, 0.25 mmol, 1.0 equiv) and ethyl 2-bromo-2-methylpropanoate **1-96** (64.3 µL, 0.438 mmol, 1.75 equiv) at 55 °C for 22 h. After purification, by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **1-95** was isolated as a colorless oil with spectral characteristics consistent with those reported previously.[11]

1st run: 21.5 mg (41% yield)

2nd run: 22.1 mg (42% yield)

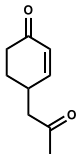
TLC (SiO_2) R_f = 0.45 in 4:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, *J* = 10.4 Hz, 1H), 5.95 (dd, *J* = 10.4, 2.3 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 2.74 (m, 1H), 2.45 (m, 1H), 2.30 (m, 1H), 1.94 (m, 1H), 1.69 (m, 1H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.15 (s, 3H), 1.13 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.1, 176.5, 151.2, 130.1, 60.7, 44.8, 43.7, 37.5, 24.3, 22.4, 22.0, 14.1

IR (neat) 2977, 1722, 1683, 1468, 1386, 1368, 1304, 1257, 1141, 1068, 1022, 961, 857, 831, 774, 736, 657 cm–1

GC/MS (m/z): 210.1 (2%), 137.1 (100%), 116.1(85%), 107.1 (25%), 95.1 (66%), 81.1 (18%), 67.1 (27%), 59.1 (19%)



2-48

4-(2-oxopropyl)cyclohex-2-en-1-one

The title compound was prepared according to the General Procedure with *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.5 mg, 0.25 mmol) and chloroacetone **2-43** (34.8 µL, 0.438 mmol). After purification by flash chromatography (SiO_2, 6:1 hexanes/EtOAc), the title compound **2-48** was isolated as a yellow oil.

1st run: 20.1 mg (53% yield)

2nd run: 20.4 mg (54% yield)

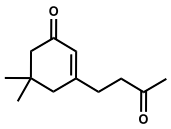
TLC (SiO_2) R_f = 0.38 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (d, *J* = 10.0 Hz, 1H), 5.98 (dd, *J* = 10.0, 2.7 Hz, 1H), 2.99 (m, 1H), 2.61 (t, *J* = 7.1 Hz, 2H), 2.44 (m, 2H), 2.19 (s, 3H), 2.13 (m, 1H), 1.69 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 206.2, 199.1, 153.6, 129.3, 109.6, 47.7, 36.7, 31.5, 30.4, 28.8

IR (neat) 2952, 2923, 2870, 1712, 1673, 1615, 1452, 1388, 1210 cm^{-1}

GC/MS (*m/z*) 152.0 (1%), 109.0 (100%), 94.0 (64%), 81.0 (83%), 66.1 (18%), 58.1 (9%), 53.1 (29%)



2-49

3-(3-cyclopropyl-3-oxopropyl)-5,5-dimethylcyclohex-2-en-1-one

The title compound was prepared according to the General Procedure with *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0 mg, 0.25 mmol) and chloroacetone **2-43** (34.8 µL, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-49** was isolated as a yellow oil.

1st run: 28.1 mg (58%)

2nd run: 26.8 mg (55%)

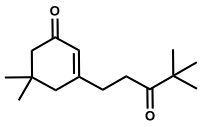
TLC (SiO_2) R_f = 0.44 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (s, 1H), 2.63 (t, *J* = 7.5 Hz, 2H), 2.43 (t, *J* = 7.5 Hz, 2H), 2.17 (m, 7H), 1.00 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 206.6, 199.7, 162.1, 124.5, 50.9, 44.2, 40.2, 33.5, 31.1, 29.9, 28.2

IR (neat) 2957, 2869, 1715, 1660, 1628, 1411, 1366, 1299 cm^{-1}

GC/MS (*m/z*) 194.1 (27%), 179.1 (30%), 161.1 (57%), 151.1 (83%), 136.1 (14%), 121.0 (88%), 109.1 (23%), 95.0 (100%), 77.0 (14%), 67.0 (27%), 53.0 (13%)



2-50

3-(4,4-dimethyl-3-oxopentyl)-5,5-dimethylcyclohex-2-en-1-one

The title compound was prepared according to the General Procedure with *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0 mg, 0.25 mmol) and 1-bromo-3,3-dimethylbutan-2-one **2-44** (78.3 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-50** was isolated as a yellow oil.

1st run: 29.1 mg (49% yield)

2nd run: 31.3 mg (53% yield)

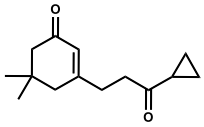
TLC (SiO_2) R_f = 0.63 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (s, 1H), 2.68 (t, *J* = 7.5 Hz, 2H), 2.39 (t, *J* = 7.5 Hz, 2H), 2.16 (s, 4H), 1.12 (s, 9H), 0.99 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 214.0, 199.5, 163.0, 124.3, 51.0, 44.6, 33.5, 31.3, 28.1, 26.5

IR (neat) 2957, 2906, 2870, 1704, 1662, 1629, 1477, 1467, 1386, 1187 cm^{-1}

GC/MS (*m/z*) 236.1 (15%), 203.1 (18%), 151.1(100%), 1381. (28%), 123.0 (25%), 109.1 (22%), 95.1 (29%), 83.1 (20%), 67.1 (20%), 57.1 (98%), 51.0 (1%)



2-51

3-(3-cyclopropyl-3-oxopropyl)-5,5-dimethylcyclohex-2-en-1-one

The title compound was prepared according to the General Procedure with *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0 mg, 0.25 mmol) and 2-bromo-1-cyclopropylethan-1-one **2-45** (71.3 mg, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-51** was isolated as a yellow oil.

1st run: 22.4 mg (41% yield)

2nd run: 21.1 mg (38% yield)

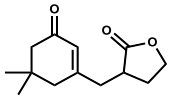
TLC (SiO_2) R_f = 0.40 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (s, 1H), 2.77 (t, *J* = 6.4 Hz, 2H), 2.47 (t, *J* = 7.5 Hz, 2H), 2.20 (s, 2H), 2.18 (s, 2H), 1.92 (m, 1H), 1.02 (s, 9H), 0.90 (m, 2H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.1, 200.0, 162.3, 124.3, 51.0, 44.2, 40.2, 33.5, 31.4, 28.3, 20.6, 11.0

IR (neat) 3008, 2960, 2894, 2869, 1697, 1661, 1628, 1446, 1385, 1299 cm^{-1}

GC/MS (*m/z*) 220.0 (14%), 205.0 (16%), 187.1 (10%), 151.1 (100%), 121.1 (43%), 95.1 (11%), 69.0 (62%), 55.0 (8%)



2-52

3-((5,5-dimethyl-3-oxocyclohex-1-en-1-yl)methyl)dihydrofuran-2(3H)-one

The title compound was prepared according to the General Procedure with *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0 mg, 0.25 mmol) and 3-bromodihydrofuran-2(3H)-one **2-46** (40.4 μL, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-52** was isolated as a white solid with spectral characteristics consistent with those reported previously.[11]

1st run: 31.7 mg (57% yield)

2nd run: 33.8 mg (61% yield)

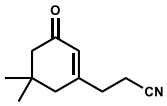
TLC (SiO_2) R_f = 0.35 in 1:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (s, 1H), 4.38 (m, 1H), 4.22 (m, 1H), 2.80 (m, 1H), 2.40 (m, 1H), 2.27 (m, 5H), 2.20 (s, 2H), 1.93 (m, 1H), 1.06 (s, 3H), 1.03 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.5, 178.1, 159.5, 126.0, 66.5, 51.0, 43.7, 38.7, 37.2, 33.7, 28.6, 28.5, 28.0

IR (neat) 2957, 2925, 1759, 1712, 1663, 1557, 1371, 1018, 931 cm^{-1}

GC/MS (m/z): 222.1 (22%), 207.1 (56%), 189.0 (80%), 161.1 (100%), 138.0 (42%), 121.0 (82%), 107.0 (20%), 91.0 (34%), 82.0 (94%), 67.0 (26%), 55.1 (44%)



2-53

3-(5,5-dimethyl-3-oxocyclohex-1-en-1-yl)propanenitrile

The title compound was prepared according to the General Procedure with *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0 mg, 0.25 mmol) and bromoacetonitrile **2-47** (30.5 µL, 0.438 mmol). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the title compound **2-53** was isolated as a yellow solid.

1st run: 28.9 mg (65% yield)

2nd run: 27.3 mg (62% yield)

MP 48–50 °C

TLC (SiO_2) R_f = 0.17 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

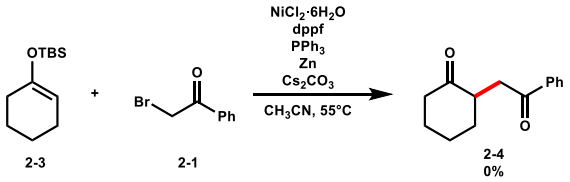
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (s, 1H), 2.52 (m, 4H), 2.20 (s, 2H), 2.17 (s, 2H), 1.01 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.1, 158.0, 125.6, 118.5, 50.8, 43.3, 33.6, 32.7, 28.2, 14.9

IR (neat) 2963, 2937, 2868, 2245, 1709, 1655, 1628, 1463, 1371, 1265 cm^{-1}

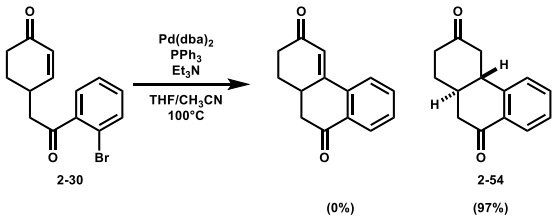
GC/MS (*m/z*) 177.1 (15%), 162.1 (16%), 121.0 (100%), 93.1 (17%), 81.0 (11%), 66.1 (10%), 53.1 (11%)

Attempted Coupling of a Simple Silyl Enol Ether



The reaction was performed according to the General Procedure using *tert*-butyl(cyclohex-1-en-1-yloxy)dimethylsilane **2-3** (53.1 mg, 0.25 mmol) and bromoacetophenone **2-1** (87.1 mg, 0.438 mmol). No alkylated product was detected in the crude product by ^{1}H NMR using CH_2Br_2 as an internal standard.

2.9.2 Procedures and Experimental Data for Synthetic Applications



Intramolecular Heck Reaction[20]

4-(2-(2-Bromophenyl)-2-oxoethyl)cyclohex-2-en-1-one **2-30** (73.3 mg, 0.25 mmol, 1.0 equiv), $Pd(dba)_2$ (7.2 mg, 0.0125 mmol, 5 mol %), and PPh_3 (6.6 mg, 0.025 mmol, 10 mol %) were weighed into a flame-dried 25 mL flask equipped with a magnetic stir bar. The flask was sealed

with a rubber septum and then it was evacuated and backfilled with dry nitrogen (three cycles). The flask was then charged with THF (1 mL), CH_3CN (1 mL), and Et_3N (70 μL, 0.50 mmol, 2 equiv). The mixture was heated to 100 °C for 24 h. After purification by flash chromatography (SiO_2, 2:1 hexanes:diethyl ether), the title compound **2-54** was isolated as a single diastereomer as a white solid (51.7 mg, 97%)

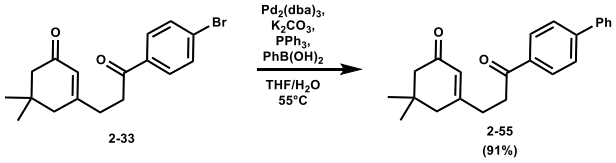
TLC (SiO_2) R_f = 0.30 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.2 Hz, 1H), 7.54 (dt, *J* = 8.2, 1.4 Hz, 1H), 7.36 (m, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 3.44 (ddd, *J* = 15.8, 10.7, 4.8 Hz, 1H), 2.98 (m, 1H), 2.73 (m, 3H), 2.60 (m, 1H), 2.44 (m, 2H), 2.08 (m, 1H), 2.01 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.3, 197.0, 145.1, 134.3, 128.1, 127.6, 127.5, 44.9, 41.4, 39.0, 36.9, 32.9, 29.5

IR (neat) 3021, 2925, 2866, 1710, 1679, 1598, 1451, 1434, 1265, 1127 cm^{-1}

GC/MS (*m/z*) 214.0 (100%), 185.0 (2%), 171.0 (96%), 157.0 (36%), 144.0 (29%), 131.0 (64%), 115.0 (50%), 103.0 (36%), 77.0 (36%), 55.1 (21%)



Suzuki–Miyaura Coupling[21]

Aryl bromide **2-33** (83.8 mg, 0.25 mmol, 1.0 equiv), PPh_3 (6.6 mg, 0.025 mmol, 10 mol %), $PhB(OH)_2$ (67 mg, 0.50 mmol, 2.0 equiv), and sodium acetate (20.5 mg, 0.25 mmol, 1.0 equiv) were weighed into a flame-dried 25 mL flask equipped with a magnetic stir bar. The flask was sealed with a rubber septum and then it was evacuated and backfilled with dry nitrogen (three

cycles). The flask was then charged with THF (1 mL) and H_2O (0.1 mL), followed by a 0.005 M solution of $Pd_2(dba)_3$ (0.5 mL, 0.0025 mmol, 1 mol %). The mixture was heated to reflux for 24 h. After cooling, deionized water (2.0 mL) was added and the mixture was poured into a separatory funnel. The aqueous phase was extracted with EtOAc (3 x 10.0 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. After purification by flash chromatography (SiO_2, 2:1 hexanes/diethyl ether), the biaryl compound **2-55** was isolated as a yellow solid (75.6 mg, 91%).

MP 84–86 °C

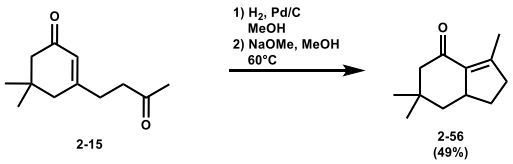
TLC (SiO_2) R_f = 0.52 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 7.0 Hz, 2H), 7.62 (m, 2H), 7.47 (dd, *J* = 8.5, 8.5 Hz, 2H), 7.40 (m, 1H), 5.89 (m, 1H), 3.19 (m, 2H), 2.64 (m, 2H), 2.25 (m, 4H), 1.05 (s, 3H), 1.03 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.9, 197.8, 162.5, 146.1, 139.7, 135.2, 132.0, 129.5, 129.0, 128.6, 128.3, 127.3, 127.3, 124.4, 51.0, 44.4, 35.4, 33.6, 31.6, 28.3

IR (neat) 3054, 3032, 2952, 2922, 2890, 2862, 1686, 1655, 1625, 1600, 1582, 1514, 1468, 1121 cm^{-1}

GC/MS (*m/z*) 332.2 (15%), 317.2 (5%), 181.0 (96%), 151.1 (100%), 135.0 (8%), 121.0 (29%), 91.0 (3%), 73.0 (5%), 55.1 (2%)



Hydrogenation/Aldol Cyclization[22]

Enone **2-15** (38.1 mg, 0.20 mmol, 1.0 equiv) and 5% Pd/C (25 mg, 0.020 mmol, 10 mol %) were weighed into a flame-dried 25 mL flask equipped with a magnetic stir bar. The flask was sealed with a rubber septum and then it was evacuated and backfilled with H_2 gas from a balloon. The flask was charged with MeOH (2 mL) and the mixture was stirred for 1 h at room temperature, at which time TLC showed total consumption of the starting material. The mixture was filtered through Celite and then the filtrate was concentrated. The crude diketone, sodium methoxide (32 mg, 0.60 mmol, 3.0 equiv), and MeOH (2 mL) were added to a 25 mL flask. The mixture was heated to reflux for 24 h, at which time TLC showed total consumption of the starting material. After cooling, saturated aq NH_4Cl solution (3.0 mL) was added and the mixture was poured into a separatory funnel. The aqueous phase was extracted with CH_2Cl_2 (3 x 10.0 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. After purification by flash chromatography (SiO_2, 40:1 hexanes:diethyl ether), the title compound **2-56** was isolated as a yellow oil (75.6 mg, 49% over two steps).

TLC (SiO_2) R_f = 0.41 in 20:1 hexanes/EtOAc, *p*-anisaldehyde stain

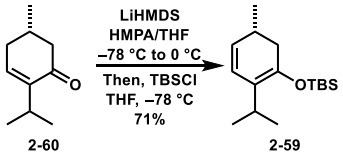
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.02 (m, 1H), 2.46 (m, 1H), 2.28 (m, 1H), 2.16 (m, 3H), 2.04 (s, 3H), 1.78 (m, 1H), 1.45 (septet, *J* = 11.2 Hz, 1H), 1.25 (t, *J* = 12.8 Hz, 1H), 1.01 (s, 3H), 0.97 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.7, 152.3, 134.8, 55.2, 45.5, 43.3, 38.8, 34.5, 32.1, 31.6, 26.2, 16.2

IR (neat) 2952, 2927, 2865, 1676, 1622, 1454, 1410, 1163 cm^{-1}

GC/MS (*m/z*) 178.1 (50%), 163.1 (21%), 135.1 (14%), 122.0 (51%), 107.0 (29%), 94.1 (100%), 79.1 (79%), 65.1 (8%), 53.0 (5%)

Progress towards the synthesis of 9-Oxoageraphorone



The silyl dienol ethers were synthesized according to the previously reported method[12]:

An oven-dried 100 mL round bottom flask equipped with a magnetic stirring bar, was sealed with a rubber septum and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with a solution of enone **2-60** (304.5 mg, 2 mmol, 1.0 equiv) in anhydrous THF (8 mL) and HMPA (0.87 mL, 5.0 mmol, 2.5 equiv) and then cooled to –78 °C. After stirring the mixture for 5 min, a solution of LiHMDS (1.0 M solution in THF, 2.2 mL, 2.2 mmol, 1.1 equiv) was added dropwise over 3 min. Stirring was continued for 1 h at –78 °C, and then the mixture was warmed to 0 °C and stirred for 1 h. The reaction mixture was cooled to –78 °C and a solution of TBSCl (452 mg, 3 mmol, 1.5 equiv) in THF (4 mL) was added dropwise over 5 min. Stirring was continued for 30 min, at which time TLC indicated complete consumption of the enone. The reaction was quenched by addition of saturated $NaHCO_3$ solution (20 mL) and then hexanes (30 mL) was added. The phases were separated, and the aqueous phase was extracted with hexanes (2 x 20 mL). The combined organic phases were washed with brine (1 x 20 mL), dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated in vacuo. After purification by flash chromatography (SiO2, hexanes), the title compound **2-59** was isolated as a yellow oil. (945.9 mg, 3.55 mmol, 71%)

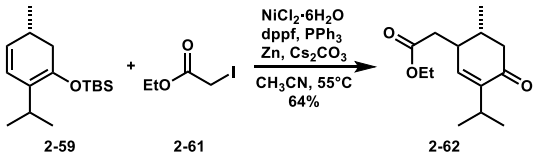
TLC (SiO_2) R_f = 0.60 20:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (d, J = 9.8 Hz, 1H), 5.38 (d, J = 9.8, 3.7 Hz, 1H), 3.03 septet, J = 6.3 Hz, 1H), 2.48 (m, 1H), 2.23 (dd, J = 16.5, 9.8 Hz, 1H), 2.00 (dd, J = 12.3, 16.5 Hz, 1H), 1.02 (d, J = 6.3 Hz, 3H), 0.96 (s, 9H), 0.15 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.8, 126.2, 123.2, 119.5, 37.5, 30.2, 25.8, 24.4, 21.2, 21.1, 20.2, 18.2

IR (neat) 303, 2965, 2935, 2887, 2868, 1645, 1575, 1417 cm^{-1}

GC/MS (*m/z*): 266.4 (5%), 252.2 (20%), 209.1 (40%), 150.1 (80%), 131.1 (40%), 91.0 (100%) 75.1 (38%), 55.1 (23%)



$NiCl_2 \cdot 6H_2O$ (5.9 mg, 0.025 mmol, 10 mol%), K_2CO_3 (51.8 mg, 0.375 mmol, 1.5 equiv), Zn (8.2 mg, 0.125 mmol, 0.5 equiv), PPh_3 (13.1 mg, 0.05 mmol, 20 mol%) and dppf (16.6 mg, 0.03 mmol, 12 mol%) were added to an oven-dried 20 mL vial equipped with a magnetic stirring bar. The vial was sealed with a septum cap and then evacuated and backfilled with dry N2 (three cycles). Anhydrous degassed[58] acetonitrile (1.25 mL) was injected into the vial via syringe and the mixture was stirred at 22 °C for 30 min. Then ethyl iodoacetate **2-61** (51.8 μL, 0.4375 mmol, 1.75 equiv), TBS dienol ether **2-59** (66.5 mg, 0.25 mmol, 1.0 equiv) were injected to the vial sequentially via syringe. The mixture was warmed to 60 °C and stirred for 48 h. After the reaction was complete (monitored by TLC), the mixture was cooled to room temperature, and the solvent was removed in vacuo. After purification by flash chromatography (SiO_2, hexanes/EtOAc = 5:1), the title compound **2-62** was isolated as a mixture of diastereomers as a colorless oil. (38.1 mg, 0.16 mmol, 64% yield, 4.7:1 dr, based on ^{1}H NMR of purified material).

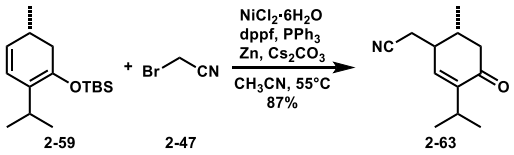
TLC (SiO_2) R_f = 0.25 5:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (m, 1H), 4.15 (q, J = 6.9 Hz, 1H), 2.82 (septet, J = 6.4 Hz, 1H), 2.61 (dd, J = 14.6, 5.1 Hz, 1H), 2.56 (m, 1H), 2.47 (dd, J = 14.6, 3.6 Hz, 1H), 2.34 (m, 1H), 2.16 (dd, J = 15.6, 11.5 Hz, 1H), 1.89 (m, 1H), 1.25 (t, J = 6.3 Hz, 3H), 1.04 (d, J = 6.4 Hz, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.88 (s, 3H)

^{12}C NMR (126 MHz, $CDCl_3$) δ 198.6, 198.1, 172.0, 145.0, 144.8, 144.2, 60.6, 45.9, 44.6, 40.2, 37.5, 36.8, 35.4, 34.6, 32.2, 26.2, 25.6, 21.8, 21.7, 21.7, 19.3, 15.0, 14.2

IR (neat) 2960, 2934, 2874, 1732, 1674, 1463, 1417 cm^{-1}

GC/MS (*m/z*): 238.1 (25%), 193.0 (15%), 165.1 (17%), 150.1 (80%), 135.1 (100%), 121.1 (50%), 109.1 (55%), 95.1 (25%), 79.1 (20%), 69.0 (15%), 55.1 (15%)



$NiCl_2 \cdot 6H_2O$ (5.9 mg, 0.025 mmol, 10 mol%), K_2CO_3 (51.8 mg, 0.375 mmol, 1.5 equiv), Zn (8.2 mg, 0.125 mmol, 0.5 equiv), PPh_3 (13.1 mg, 0.05 mmol, 20 mol%) and dppf (16.6 mg, 0.03 mmol, 12 mol%) were added to an oven-dried 20 mL vial equipped with a magnetic stirring bar. The vial was sealed with a septum cap and then evacuated and backfilled with dry N2 (three cycles). Anhydrous degassed[58] acetonitrile (1.25 mL) was injected into the vial via syringe and the mixture was stirred at 22 °C for 30 min. Then bromoacetonitrile **2-47** (30.5 μL, 0.4375 mmol, 1.75 equiv) TBS dienol ether **2-59** (66.5 mg, 0.25 mmol, 1.0 equiv) were injected to the vial sequentially via syringe. The mixture was warmed to 60 °C and stirred for 36 h. After the reaction was complete (monitored by TLC), the mixture was cooled to room temperature, and the solvent was removed

in vacuo. After purification by flash chromatography (SiO_2, hexanes/EtOAc = 5:1), the title compound **2-63** was isolated as a mixture of diastereomers as a colorless oil. (41.6 mg, 0.22 mmol, 87% yield, 4:1 dr, determined by 1H NMR of purified material).

TLC (SiO_2) R_f = 0.25 4:1 hexanes/EtOAc, *p*-anisaldehyde stain

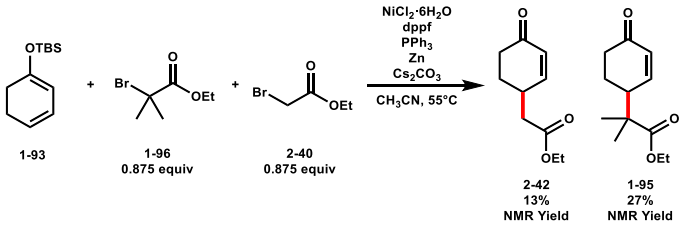
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (m, 1H), 4.15 (q, J = 6.9 Hz, 1H), 2.82 (septet, J = 6.4 Hz, 1H), 2.61 (dd, J = 14.6, 5.1 Hz, 1H), 2.56 (m, 1H), 2.47 (dd, J = 14.6, 3.6 Hz, 1H), 2.34 (m, 1H), 2.16 (dd, J = 15.6, 11.5 Hz, 1H), 1.89 (m, 1H), 1.25 (t, J = 6.3 Hz, 3H), 1.04 (d, J = 6.4 Hz, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.88 (s, 3H)

^{12}C NMR (126 MHz, $CDCl_3$) δ 198.6, 198.1, 172.0, 145.0, 144.8, 144.2, 60.6, 45.9, 44.6, 40.2, 37.5, 36.8, 35.4, 34.6, 32.2, 26.2, 25.6, 21.8, 21.7, 21.7, 19.3, 15.0, 14.2

IR (neat) 2963, 2934, 2875, 2248, 1673, 1463, 1422, 1386 cm^{-1}

GC/MS (*m/z*): 191.2 (20%), 151.1 (100%), 135.1 (40%), 123.1 (15%), 109.1 (40%), 91.1 (25%), 79.1 (40%), 67.1 (15%), 53.1 (10%)

Competition Experiments



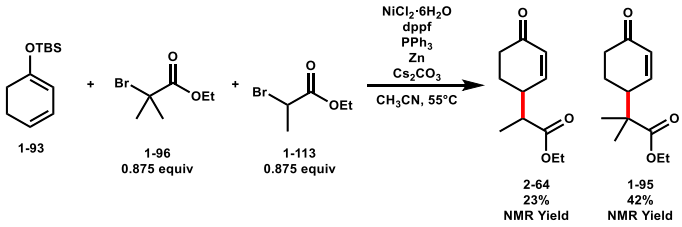
1-93 | 1-96, 0.875 equiv | 2-40, 0.875 equiv

2-42, 13% NMR Yield | 1-95, 27% NMR Yield

Competitive Coupling Between Primary and Tertiary α-Haloesters

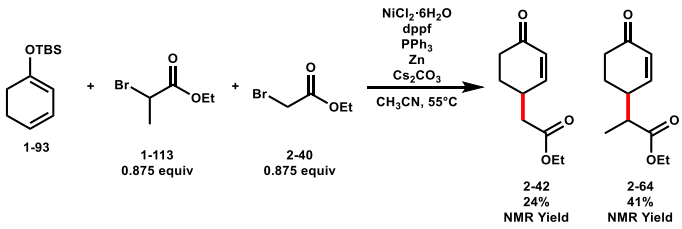
The reaction was performed according to the General Procedure using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.5 mg, 0.25 mmol) and both ethyl bromoacetate **2-40** (24.3

μL, 0.219 mmol, 0.875 equiv) and ethyl 2-bromo-2-methylpropanoate **1-96** (32.1 μL, 0.219 mmol, 0.875 equiv). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the two esters were isolated as yellow oils. (**2-42**, 5.9 mg, 0.0325 mmol, 13% and **1-95**, 14.2 mg, 0.0675 mmol, 27%).



Competitive Coupling Between Secondary and Tertiary α-Haloesters

The reaction was performed according to the General Procedure using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.5 mg, 0.25 mmol) and both ethyl 2-bromopropionate **1-113** (27 μL, 0.219 mmol, 0.875 equiv) and ethyl 2-bromo-2-methylpropanoate **1-96** (32.1 μL, 0.219 mmol, 0.875 equiv). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the two esters were isolated as yellow oils. (**2-64**, 11.3 mg, 0.0575 mmol, 23% and **1-95**, 22.1 mg, 0.105 mmol, 42%).



Competitive Coupling Between Primary and Secondary α-Haloesters

The reaction was performed according to the General Procedure using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.5 mg, 0.25 mmol) and both ethyl bromoacetate **2-40** (24.3

µL, 0.219 mmol, 0.875 equiv) and ethyl 2-bromopropanoate **1-113** (27 µL, 0.219 mmol, 0.875 equiv). After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the two esters were isolated as yellow oils. (**2-42**, 10.9 mg, 0.06 mmol, 24% and **2-64**, 20.1 mg, 0.103 mmol, 41%).

Competitive Coupling Between chloro- and bromoacetonitrile:

The reaction was performed according to the General Procedure using *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0 mg, 0.25 mmol) and both chloroacetonitrile **2-65** (13.9 µL, 0.219 mmol, 0.875 equiv) and bromoacetonitrile **2-47** (15.3 µL, 0.219 mmol, 0.875 equiv) and 1.25 mL CD_3CN and CH_2Br_2 (17.5 µL, 0.25 mmol) as an internal standard.[59] After various time periods, 50 µL of the crude reaction mixture was filtered through silica gel and dissolved in CD_3CN. The ratios of chloro- **2-65**, bromoacetonitrile **2-47** and product **2-53** were detected by ^1H NMR using CH_2Br_2 as an internal standard.

Table 2.9 The Chemoselectivity of Cl vs Br

h	% of $ClCH_2CN$ **2-65**	% of $BrCH_2CN$ **2-47**	% of **Pdt 2-53**
0	100	100	0
2	55	26	25
4	27	1	28
6	24	0	30
8	21	0	33
16	19	0	38
24	15	0	41
36	10	0	43

Hammett plot

The reaction was performed according to the General Procedure using *tert*-butyl((5,5-dimethyl-3-methylenecyclohex-1-en-1-yl)oxy)dimethylsilane **2-10** (63.0 mg, 0.25 mmol) and the appropriate bromoacetophenone (0.438 mmol). After 48 h, the reaction was cooled to room temperature and the solvent was removed by rotary evaporation under vacuum. The crude material was purified by flash column chromatography on silica gel. The γ-alkylated product was detected by ^{1}H NMR using CH_2Br_2 as an internal standard. Each reaction was performed twice, and the percent yields were calculated as an average of the two runs.

Table 2.10 Hammett Plot Values

Functional Group	σ_p[34]	σ^*_{jj}[35]	Yield Trial 1	Yield Trial 2	Average yield	Log(k/k_H)
para-NH_2	-0.66	0.15	10	8	9	-0.34679
para-CH_3	-0.17	0	22	18	20	-0.20412
H	0		36	25	31	0.00000
para-Iodo	0.18	0.23	51	40	46	0.07004
para-Bromo	0.23	0.42	57	47	52	0.19728
Para-CN	0.66		82	63	73	0.25828

Comparative reactions between ligands:

The reaction was performed according to the General Procedure using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.5 mg, 0.25 mmol) and 2-bromoacetophenone **2-1** (87.1 mg, 0.438 mmol) in 1.25 ml CD_3CN and CH_2Br_2 (, 0.25 mmol) as an internal standard.[59] After various

time periods, 50 μL of the crude reaction mixture was filtered through silica and dissolved in CD_3CN. The γ-alkylated product **2-2** was detected by ^1H NMR using CH_2Br_2 as an internal standard.

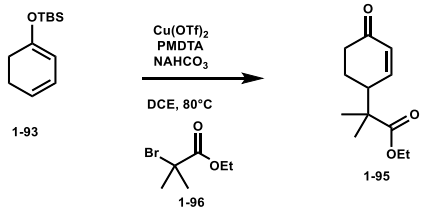
Table 2.11 The Effects of Ligands

h	% of **2-2** ($dppf/PPh_3$)	% of **2-2** (dppf)	% of **2-2** (PPh_3)
0	0	0	0
2	2	2	0
4	12	7	1
6	32	18	14
8	48	24	22
20	71	41	26
24	78	43	27
30	85	48	30

Table 2.12 The Effects of Ligands with pre-incubation

H	% of **2-2** ($dppf/PPh_3$)	% of **2-2** (dppf)	% of **2-2** (PPh_3)
0	0	0	0
1.5	49	36	0
5	52	41	0
7	55	42	0
17	61	44	0
20	62	45	0
24	63	47	0

Procedure for Cu-Catalyzed Couplings



Cu-Catalyzed Alkylation[11]

Anhydrous $Cu(OTf)_2$ (6.8 mg, 0.01875 mmol, 7.5 mol %) and $NaHCO_3$ (21 mg, 0.25 mmol, 1.0 equiv) were added to an oven-dried 20 mL vial equipped with a magnetic stirring bar. Then the vial was sealed with a septum cap and then evacuated and backfilled with dry N_2 (three cycles). Anhydrous 1,2-dichloroethane (1 mL) and *N,N,N',N'',N''*-pentamethyldiethylenetriamine (7.8 µL, 0.0375 mmol, 15 mol%) were injected into the vial via syringe and the mixture was stirred at 22 °C for 10 min. Then, bromoester (0.375 mmol, 1.5 equiv) and TBS dienol ether **1-93** (52.5 mg, 0.25 mmol, 1.0 equiv) were injected to the vial sequentially via syringe. The mixture was warmed to 80 °C and stirred. After the reaction was complete (monitored by TLC, typically after 22 h), the mixture was cooled to room temperature, and the solvent was removed in vacuo. After purification by flash chromatography (SiO_2, 4:1 hexanes/EtOAc), the enone **1-95** was isolated as a colorless oil (48.2 mg, 92%).

Using ethyl 2-bromo-2-methylpropanoate **1-96** (55.4 µL, 0.375 mmol, 1.5 equiv):

Isolated **1-95** 48.2 mg (92% yield)

Using ethyl bromoacetate **2-40** (41.6 µL, 0.375 mmol, 1.5 equiv):

γ-alkylated product **2-42** was not visible in crude ^{1}H NMR

2.10 Notes and References

[1] For mechanistic explanation of palladium alkyl cross-couplings: Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed*. **2003**, *42*, 5749–5752. For an account addressing regioselectivity in Heck reactions with Pd, see: (a) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7.

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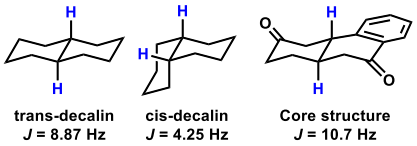
[18] ^{1}D NOE experiment showed a NOE effect between the γ–proton and the methyl protons.

[19] J-couplings of the γ-proton were used to verify the trans/cis ring junction:



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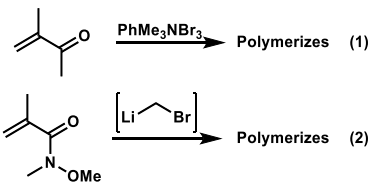
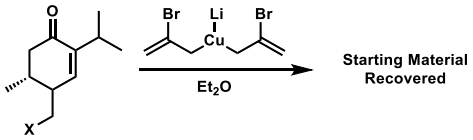
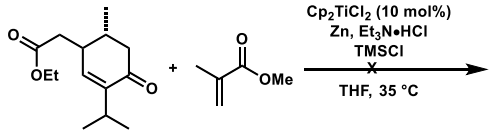
[28] 

[29] Note: Ethyl bromoacetate only provided the γ-alkylated product in 35% yield.

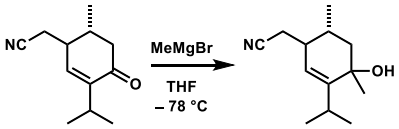
[30] For the Gilman addition shown below, we only recover starting material.



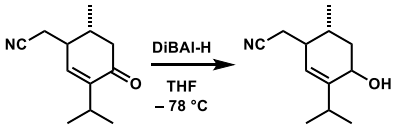
[31] For the β,β-coupling below, no reaction occurs.



[32]



[33]



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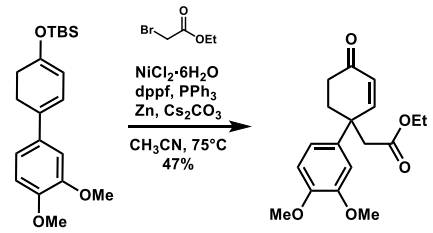
[45] In the following chapter, I will show the following example for γ-alkylation:



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[51] For further synthetic applications, see Chapters 3 and 4.

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[59] After 72 h, no reaction is detected between the silyl dienol ether and dibromomethane.

CHAPTER 3

FORMAL SYNTHESIS OF (±)-MESEMBRINE

3.1 Background

(–)-Mesembrine, a bicyclic alkaloid, was first isolated in 1957 by Bodendorf and coworkers from a South African plant, *Sceletium Tortuosum* (Figure 1).[1] *Sceletium Tortuosum*, known colloquially as *kanna*, was of pharmaceutical interest due mesembrine's anti-anxiety and potential anti-addiction effects.[2] Mesembrine has been shown to inhibit the serotonin transporter, 5-HT transporter (K_i = 1.4 nM), and acts as an inhibitor of the enzyme phosphodiesterase 4, PDE4, (K_i = 7,800 nM).[2] The challenging γ-quaternary center has sparked the interest of countless scientists who have already reported over 40 synthetic pathways.[3]

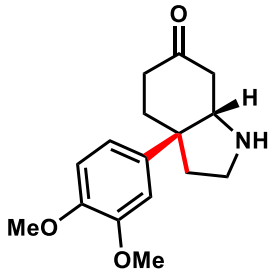


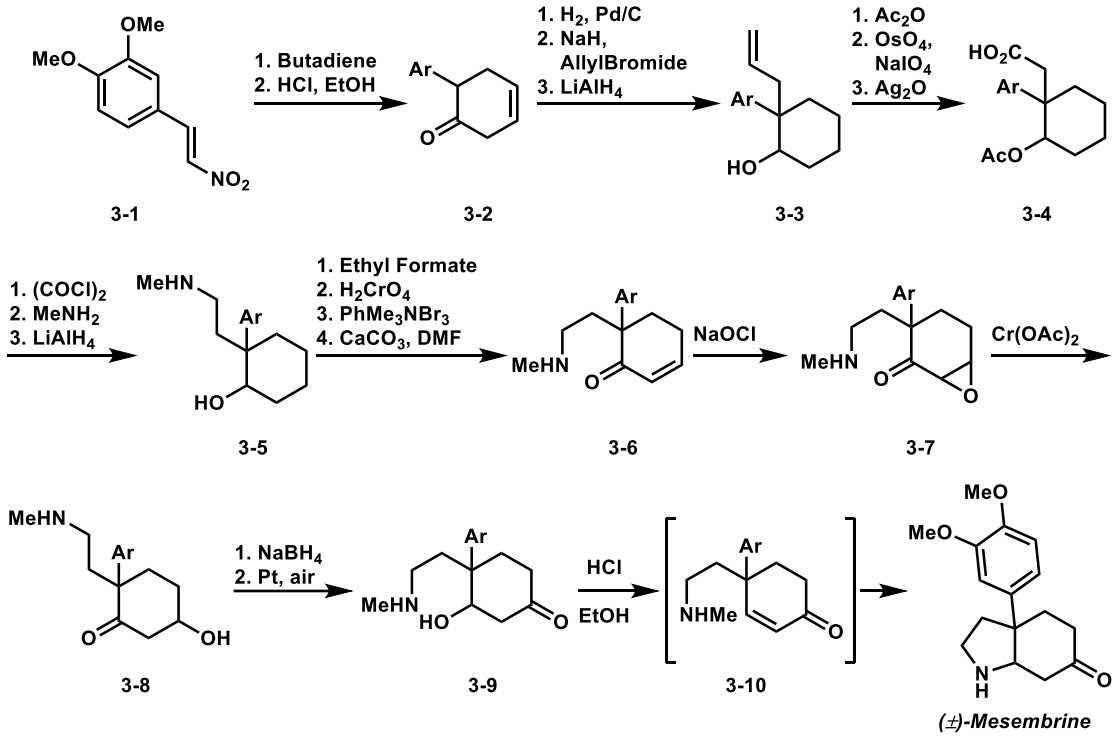
Figure 3.1 (–)-Mesembrine

3.2 Previous Syntheses of Mesembrine

3.2.1 Shamma Synthesis of Mesembrine

In 1965, Shamma achieved the first total synthesis of (±)-mesembrine (Scheme 3.1). [3a] Starting from the nitrostyrene **3-1**, treatment with butadiene followed by ethanolic hydrochloric acid generated the β,γ-cyclohexanone **3-2**. Reduction of the alkene by hydrogenation with palladium on carbon was followed by α-alkylation on the more sterically-hindered α-carbon by enolization with sodium hydride and treatment with allyl bromide. The ketone was then reduced by lithium aluminum hydride to generate the alcohol **3-3**. Protection of the alcohol by acetic anhydride, followed by Lemieux–Johnson oxidation with osmium tetroxide and sodium periodate formed the aldehyde, which was oxidized by silver oxide to form the carboxylic acid **3-4**. The

amine **3-5** was generated by treatment of the carboxylic acid **3-4** with oxalyl chloride, followed by treatment with methyl amine to form the amide which was reduced by lithium aluminum hydride.

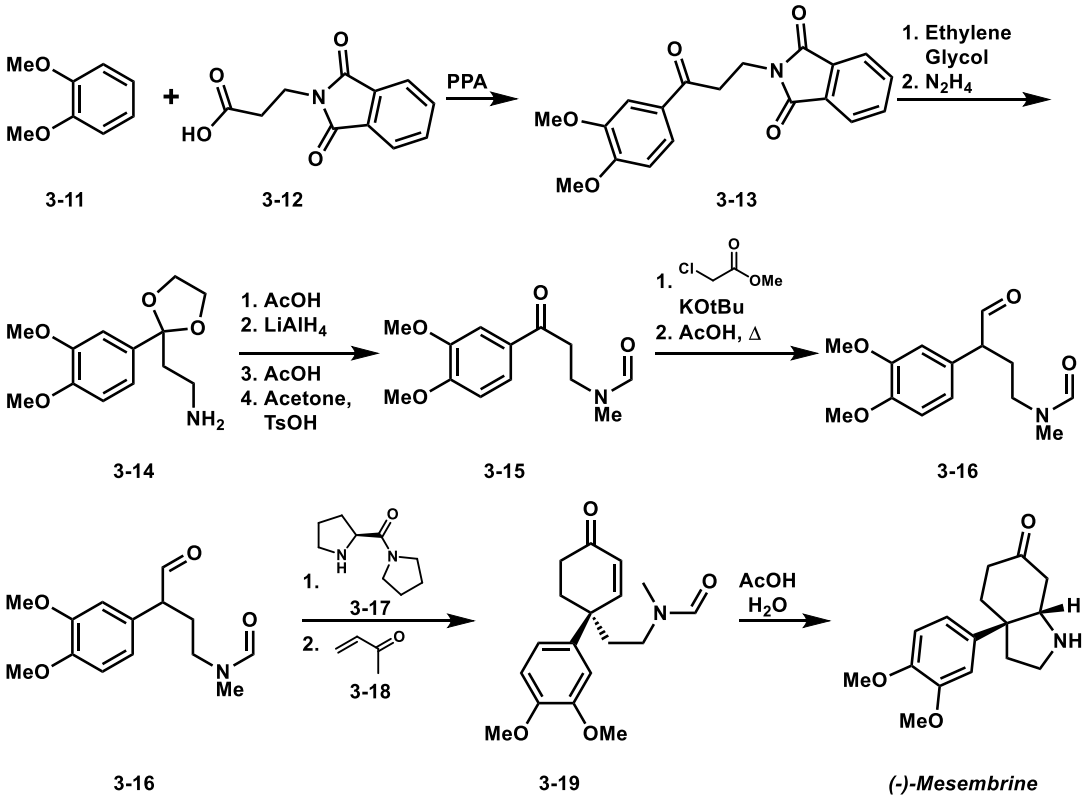


Scheme 3.1 Shamma synthesis of (±)-Mesembrine

The amine **3-5** was protected by ethyl formate to generate an amide, and the alcohol was oxidized to the ketone by Jones oxidation. The enone **3-6** was synthesized by α-bromination of the ketone by phenyltrimethyl ammonium tribromide followed by dehydrohalogenation. Epoxidation by Clorox® was followed by reduction with chromium acetate to form the β-hydroxyketone **3-8**.[4] Reduction of the ketone **3-8** was achieved with sodium borohydride and the less sterically-hindered alcohol was oxidized to the ketone by Pt/air to form **3-9**. The β-hydroxy ketone **3-9** was dehydrated and the resulting enone **3-10** underwent conjugate addition by the deprotected amine to form (±)-mesembrine in 21 steps with 2.6% overall yield.

3.2.2 Yamada Asymmetric Synthesis of (–)-Mesembrine

The first asymmetric synthesis of (–)-mesembrine was achieved by Yamada in 1971 through a proline-derived enamine conjugate addition/annulation (Scheme 3.2).[3a] Dimethoxybenzene **3-11** was condensed with carboxylic acid **3-12** to furnish the β-aminoketone **3-13**. The amine **3-14** was deprotected by treatment with hydrazine following protection of the ketone.



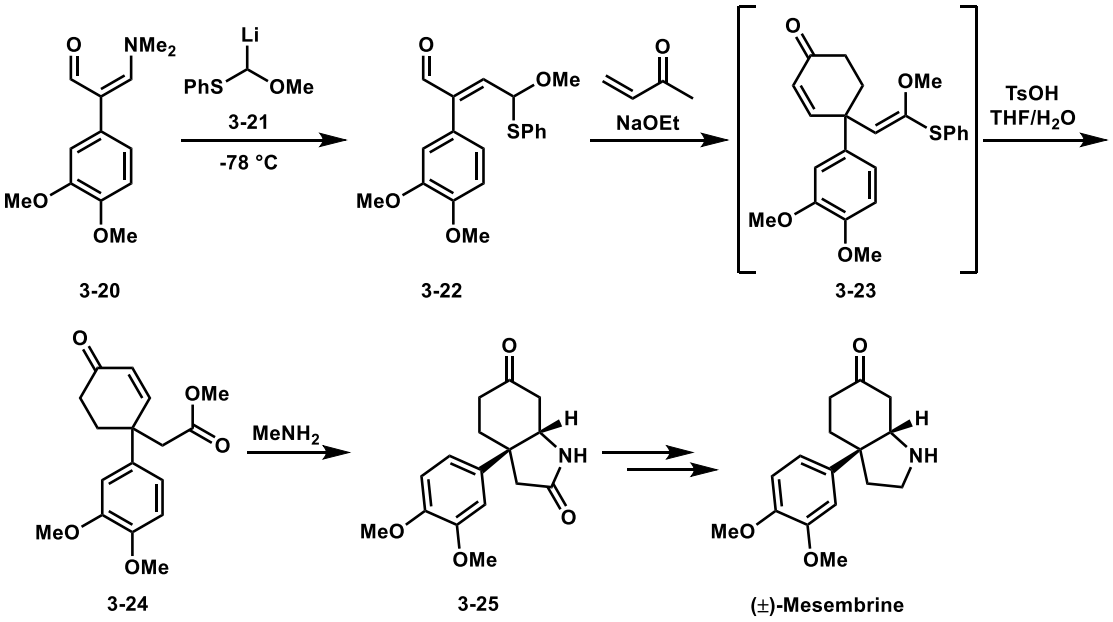
Scheme 3.2 Yamada synthesis of (–)-Mesembrine

The β-methylamino ketone **3-15** was synthesized by acylation of the amine **3-14** which was reduced, followed acylation of the amine and deprotection of the ketone. A modification of Darzen's method generated the aldehyde **3-16**.[5] Dehydration of the aldehyde **3-16** and proline-derived amine **3-17** generated the dienamine. Methyl vinyl ketone **3-18** was added to the dienamine to form the optically active cyclohexanone **3-19**.[3b] The synthesis of (–)-mesembrine was completed

by deprotection of the amine **3-19** and acid-catalyzed conjugate addition in 14 steps with 8.9% overall yield.

3.2.3 Livinghouse Formal Synthesis of (±)-Mesembrine

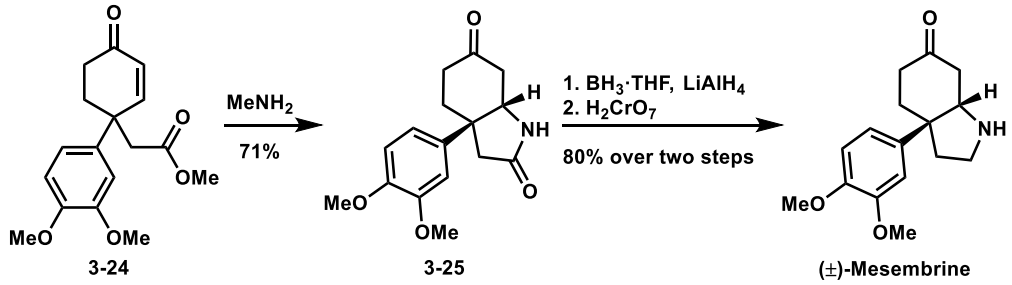
In 1986, Livinghouse approached the γ-alkylation through the α-alkylation of a β-(methoxy(phenylthiol)methylidene enolate.[3f] (Methoxy(phenylthiol)methyllithium) **3-21** was added to the β-aminoaldehyde **3-20** followed by hydrolysis to form the γ-thiomethoxy enone **3-22**. The cyclohexenone 3-23 was formed from the Robinson annulation of the γ-thiomethoxy enone 3-22 and methyl vinyl ketone.[6] Acid-catalyzed hydrolysis of the thiol **3-23** provided the corresponding methyl ester **3-24**. The methyl ester was condensed with methyl amine to afford the methyl amide **3-25**.



Scheme 3.3 Livinghouse Formal Synthesis of (±)-Mesembrine

The synthesis of (±)-mesembrine was previously completed from the amide **3-25** through reduction of the lactam by diborane and lithium aluminum hydride to the aminoalcohol and then the alcohol oxidized by Jones oxidation to furnish (±)-mesembrine.[3g] Alternatively, the ketone can

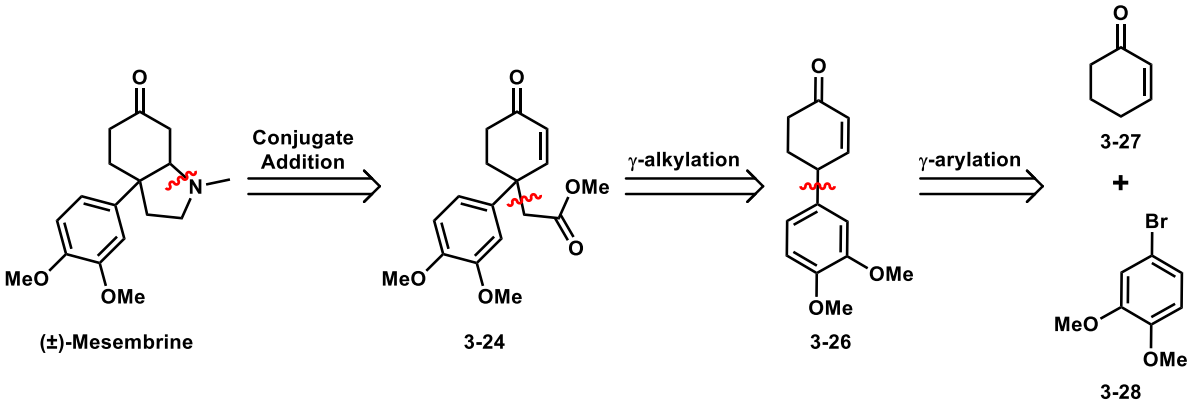
be protected by ethylene glycol and the lactam reduced by lithium aluminum hydride, followed by deprotection of the acetal to furnish (±)-mesembrine.[3h]



Scheme 3.4 Completion of the Synthesis of (±)-Mesembrine from the γ-Ester 3-24.

3.3 Retrosynthesis of (±)-Mesembrine

We envisioned that we could synthesize the challenging γ-quaternary center through a nickel–catalyzed γ–alkylation. Our plan consisted of coupling of the γ-arylketone **3-26** with α-bromoester. Given our previous synthesis of the γ-arylketone **3-26** from the cyclohexanone-derived silyl dienol ether, the remaining challenge was synthesizing the silyl dienol ether of that γ-arylketone.



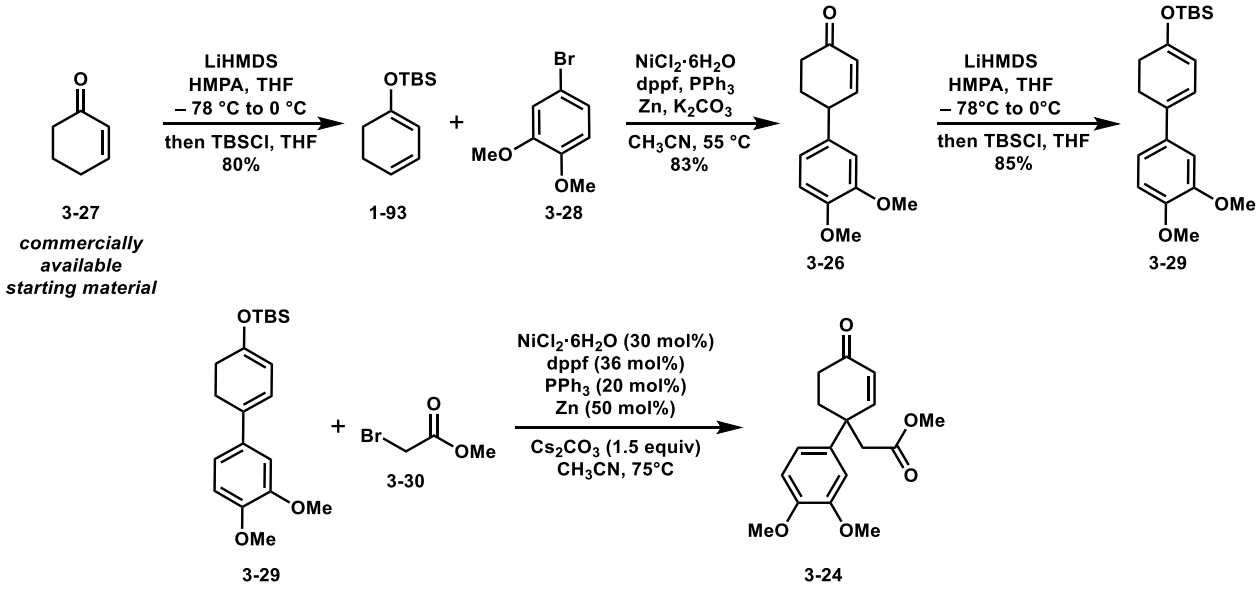
Scheme 3.5 Synthetic Strategy for (±)-Mesembrine

3.4 Our Formal Synthesis of (±)-Mesembrine

Our synthesis commenced with the basic enolization/silylation of commercially available cyclohexanone **3-27** which proceeds in gram-scale in 80% yield.[7] The γ-arylation of the silyl dienol

ether **1-93** proceeds with commercially available bromoveratrole **3-28** in 85% yield.[8] The basic enolization/silylation of the γ-arylated enone **3-26** proceeded in 85% yield on a gram–scale. We attempted to perform the basic enolization in the absence of HMPA due to its toxic effects as the aryl moiety would decrease the pK_a of the γ-proton, however we found that the reaction failed to proceed, and we only obtained the α'-silyl dienol ether. Soft enolization conditions formed the γ-silyl dienol ether **3-29** and the α'-silyl dienol ether in a 1:1 inseparable mixture.

The γ-alkylation proved challenging as competing oxidation to the phenol occurred. We overcame the oxidative side reaction by increasing the Zn loading to 50%. The γ-alkylation with methyl bromoacetate **3-30** proved slow and only partial consumption of the silyl dienol ether occurred.[9] Increasing the temperature to 75 °C and increasing the equivalence of α-bromoester to 10 equiv proved to improve the rate of the reaction. After 2 days, these modified conditions furnished the γ-alkylated enone **3-24** in 47% yield with the remainder of the material being the enone **3-26**.



Scheme 3.6 Formal Synthesis of (±)-Mesembrine

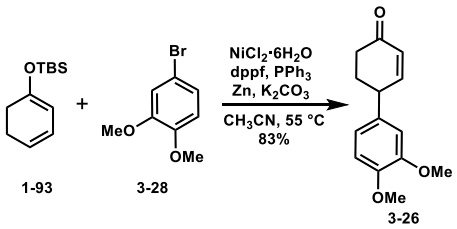
3.5 Summary

In summary, we report the brief formal synthesis of (±)-mesembrine. Our route includes 4 linear steps from commercially available cyclohexanone **3-27**. Employing our recently developed γ-arylation method, we accessed the γ-arylketone in good yield from commercially available bromoveratrole. Basic enolization and silylation of the γ-arylketone proceeded efficiently and the γ-alkylation proceeded in modest yields.

3.6 Experimental Details

Unless otherwise stated, reactions were performed in oven–dried glassware under a N_2 atmosphere using dry, deoxygenated solvents. Anhydrous acetonitrile, toluene and THF (BHT-free) were purchased from Aldrich, degassed with argon, and dried by passage through activated drying columns[10] on a Pure Process Technology system. Potassium carbonate, lithium carbonate, cesium carbonate and tribasic potassium phosphate were purchase from Chem Impex International and used as received. Starting materials, including 2-cyclohexen-1-one, were purchased from Aldrich, Alfa Aesar, or Oakwood Chemical and used as received. Nickel(II) chloride hexahydrate was purchased from Sigma–Aldrich. Triphenylphosphine, and 1,1'-ferrocenediyl-bis(diphenylphosphine) were purchased from Oakwood Chemical. Zinc powder was purchased from Flinn Scientific Inc. Deuterated chloroform ($CDCl_3$, 99.9%, extra dry) was purchased from Cambridge Isotope Laboratories, Inc. and was used without further purification. Reaction temperatures were controlled by an IKAmag immersion temperature modulator. Thin-layer chromatography (TLC) was performed using Silicycle silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or staining with *p*–anisaldehyde or $KMnO_4$ solutions. Flash chromatography[11] was performed using Silicycle

SiliaFlash® P60 silica gel (40–63 μm particle size). Melting points were determined using a Mel-Temp electrothermal capillary melting point apparatus and the values reported are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 (at 500 and 126 MHz, respectively) or DPX-400 instrument (at 400 and 101 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, br s = broad singlet. Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). Infrared (IR) spectra were recorded on a Nicolet iS5 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). GC/MS analyses were performed on a Hewlett Packard Model 6890 gas chromatograph interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). TBS-dienol ether was synthesized by enolization with LiHMDS or by soft enolization according to our previous publication.[7]



3',4'-Dimethoxy-2,3-dihydro-[1,1'-biphenyl]-4(*1H*)-one :

This compound was synthesized according to reported procedure[13]:

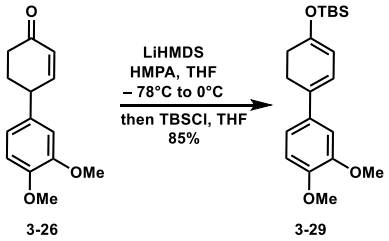
$NiCl_2·6H_2O$ (5.9 mg, 0.025 mmol, 10 mol%), K_2CO_3 (51.8 mg, 0.375 mmol, 1.5 equiv), Zn (8.2 mg, 0.125 mmol, 0.5 equiv), PPh_3 (13.1 mg, 0.05 mmol, 20 mol%) and dppf (16.6 mg, 0.03 mmol, 12 mol%) were added to an oven–dried 20 mL vial equipped with a magnetic stirring bar.

The vial was sealed with a septum cap and then evacuated and backfilled with dry N_2 (three cycles). Anhydrous degassed[12] acetonitrile (1.25 mL) was injected into the vial via syringe and the mixture was stirred at 22 °C for 30 min. Then bromoveratrole **3-28** (53.9 μL, 0.375 mmol, 1.5 equiv) TBS dienol ether **1-93** (52.6 mg, 0.25 mmol, 1.0 equiv) were injected to the vial sequentially via syringe. The mixture was warmed to 60 °C and stirred for 36 h. After the reaction was complete (monitored by TLC), the mixture was cooled to room temperature, and the solvent was removed in vacuo. After purification by flash chromatography (SiO_2, CH_2Cl_2/EtOAc = 50:1 then CH_2Cl_2/EtOAc = 20:1), the title compound **3-26** was isolated as a colorless oil with spectral characteristics consistent with those reported previously.[13] (48.1 mg, 0.21 mmol, 83% yield).

TLC (SiO_2) R_f = 0.20 in 4:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 6.91 (ddd, *J* = 10.1, 2.5, 1.3 Hz, 1H), 6.25 (dd, *J* = 10.2, 2.5 Hz, 1H), 4.21 (m, 1H), 2.57 (m, 2H), 2.48 (m, 1H), 2.05 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.4, 150.1, 146.4, 133.4, 131.2, 127.9, 127.8, 117.5, 112.2, 40.7, 36.8, 31.7



tert-butyl((3',4'-dimethoxy-2,3-dihydro-[1,1'-biphenyl]-4-yl)oxy)dimethylsilane:

The silyl dienol ether was synthesized according to reported procedure[7]:

An oven-dried 100 mL round bottom flask equipped with a magnetic stirring bar, was sealed with a rubber septum and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with a solution of enone **3-26** (1.16g, 5 mmol, 1.0 equiv) in anhydrous THF (20 mL) and HMPA (2.17 mL, 12.5 mmol, 2.5 equiv) and then cooled to –78 °C. After stirring the mixture for 5 min, a solution of LiHMDS (1.0 M soln in THF, 5.5 mL, 5.5 mmol, 1.1 equiv) was added dropwise over 3 min. Stirring was continued for 1 h at –78 °C, and then the mixture was warmed to 0 °C and stirred for 1 h. The reaction mixture was cooled to –78 °C and a solution of TBSCl (1.13 g, 7.5 mmol, 1.5 equiv) in THF (10 mL) was added dropwise over 5 min. Stirring was continued for 30 min, at which time TLC indicated complete consumption of the enone. The reaction was quenched by addition of saturated $NaHCO_3$ solution (20 mL) and then hexanes (30 mL) was added. The phases were separated, and the aqueous phase was extracted with hexanes (2 x 20 mL). The combined organic phases were washed with brine (1 x 20 mL), dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated in vacuo. After purification by flash chromatography (SiO_2, hexanes/EtOAc = 20:1), the title compound **3-29** was isolated as a white solid. (1.47 g, 4.26 mmol, 85%)

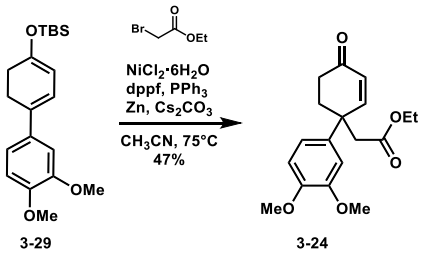
TLC (SiO_2) R_f = 0.21 in 20:1 Hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (m, 2H), 6.81 (d, *J* = 9.0 Hz, 1H), 6.17 (d, *J* = 6.5 Hz, 1H), 5.27 (d, *J* = 6.5 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.70 (t, *J* = 10.1 Hz, 2H), 2.38 (t, *J* = 10.5 Hz, 2H), 0.96 (s, 9H), 0.20 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8, 148.8, 147.5, 134.0, 128.1, 120.2, 116.8, 111.0, 108.1, 103.0, 56.1, 29.3, 27.1, 25.6, 4.4 ppm

IR (neat) 3011, 2955, 2935, 1642, 1599, 1564, 1514, 1464, 1379 cm^{-1}

GC/MS (*m/z*): 346.2 (100%), 331.2 (9%), 287.1 (38%), 272.1 (14%), 257.1 (5%), 229.1 (9%), 151.1 (24%), 73.1 (57%), 59.0 (9%)



ethyl 2-(3',4'-dimethoxy-4-oxo-3,4-dihydro-[1,1'-biphenyl]-1(2H)-yl)acetate:

$NiCl_2 \cdot 6H_2O$ (14.3mg, 30 mol %), 1,1'-Bis(diphenylphosphino)ferrocene, dppf, (39.9 mg, 36%), triphenylphosphine (10.5 mg, 20%), zinc powder (6.5 mg, 50%), and cesium carbonate (97.7 mg, 1.5 equiv) was added to an oven-dried 20 mL vial equipped with a magnetic stirring bar. The vial was sealed with a septum cap then evacuated and backfilled with nitrogen (three cycles of 15 min each). Then anhydrous CH_3CN (0.75 mL) was added, followed by methyl bromoacetate (0.22 mL, 2.0 mmol, 10 equiv) and then, TBS dienol ether **3-29** (69.3mg, 0.20 mmol, 1.0 equiv), dissolved in 0.25 mL CH_3CN were added into the vial sequentially. The mixture was heated to 75 °C and stirred for 72 h. After the reaction was complete (monitored by TLC), the mixture was cooled to room temperature, and the solvent was removed under vacuum. After purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1), the title compound **3-24** was isolated as a yellow oil with spectral characteristics consistent with those reported previously.[3f] (29.7 mg, 0.093 mmol, 47%).

TLC (SiO_2) R*f* = 0.21 in 20:1 Hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (m, 2H), 6.81 (d, *J* = 9.0 Hz, 1H), 6.17 (d, *J* = 6.5 Hz, 1H), 5.27 (d, *J* = 6.5 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.70 (t, *J* = 10.1 Hz, 2H), 2.38 (t, *J* = 10.5 Hz, 2H), 0.96 (s, 9H), 0.20 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8, 148.8, 147.5, 134.0, 128.1, 120.2, 116.8, 111.0, 108.1, 103.0, 56.1, 29.3, 27.1, 25.6, 4.4

3.7 Notes and References

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[6] (a) Rapson, W. S.; Robinson, R. *J. Chem Soc*. **1935**, 1285-1288 (b) DuFeu, E. C.; McQuillin, F. J.; Robinson, R. *J. Chem. Soc*. **1937**, 53-60.

[7] Liu, X.; Chen, X.; Mohr, J. T. *Org. Lett.* **2015**, *17*, 3572− 3575.

[8] The reaction proceeds in 65% yield on a gram scale with 75% zinc dust and in a sealed pressure-tube.

[9] γ-alkylation with the unprotected amide or Boc-protected amide results mostly in protonation of the silyl dienol ether to form the enone. γ-alkylation with bromoacetonitrile yielded 38% of the desired γ–alkylated enone but reduction of or functionalization of the nitrile proved difficult.

[10] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518–1520.

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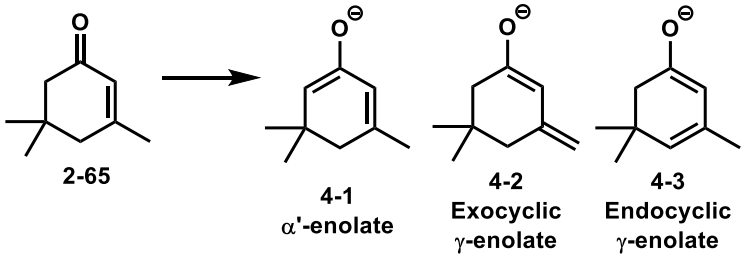
CHAPTER 4

γ-FUNCTIONALIZATION OF 3-ALKYLCYCLOHEXENONES

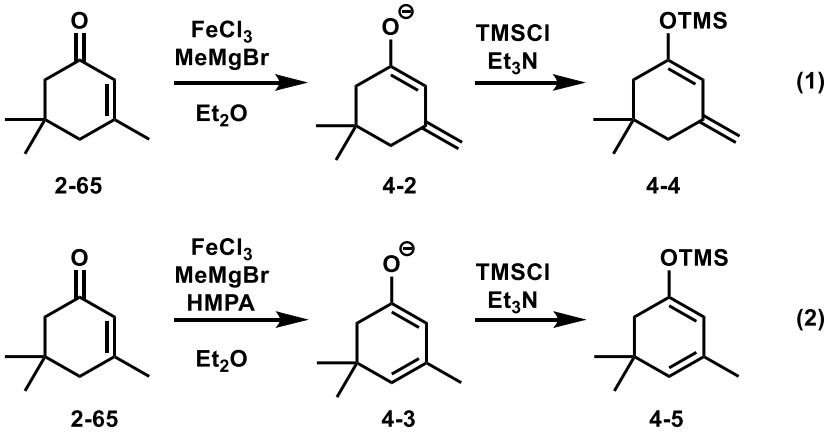
4.1 Background

In the preceding chapter, we reported the γ-alkylation of isophorone **2-66**, 3,5,5-trimethylcyclohexenone through the exocyclic silyl dienol ether **2-10**. However, the endocyclic silyl dienol ether was never engaged in γ-functionalization as the endocyclic silyl dienol ether was inaccessible through silylation/enolization through basic conditions or soft enolization conditions.[1] Three possible enolates can form from isophorone **2-66** (Scheme 4.1). The α'-enolate **4-1**, the kinetically preferred enolate,[2] is easily accessible through LDA conditions, while the γ-enolate **4-2**, due to the extended conjugation is the thermodynamic enolate and accessible through soft enolization conditions. (Scheme 4.1). The endocyclic γ-dienolate **4-3** of isophorone is higher in energy than the exocyclic dienolate **4-2** due to the $A^{1,2}$ interactions with the 5,5-dimethyl group.



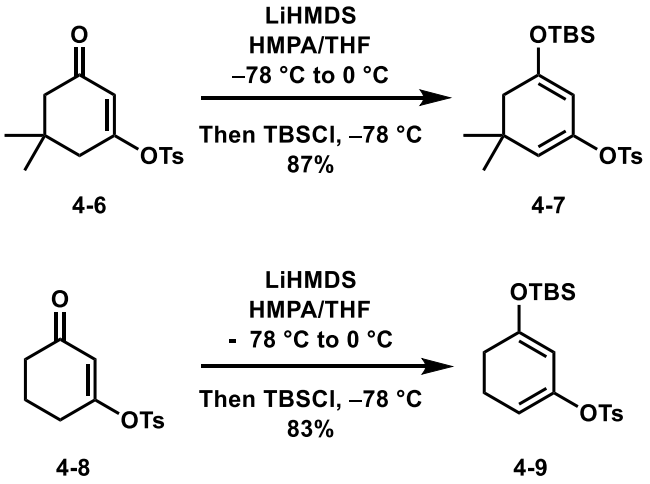
Scheme 4.1 Enolates of Isophorone

Kharasch reported, in 1945, the synthesis of the silyl-protected exocyclic enolates along with the other two isomers derived from isophorone **2-66**.[3] Difficulties with isolation of a single isomer from the undesired γ-endocyclic and α'-enolates limited this method, as well as difficulty in reproducing the original results. After thorough analysis by Meinwald in 1970, it was determined that the presence of excess magnesium reagent in the Grignard enabled a reductive dimerization side-reaction.[4] In the absence of excess magnesium, the desired deconjugation of isophorone to β-isophorone proceeded in 73% yield.



Scheme 4.2 Synthesis of Silyl Dienol Ethers of Isophorone through Kharasch Reagent

Krafft and coworkers further studied the Kharasch reagent to synthesize the exocyclic silyl dienol ether **4-4** of isophorone **2-66** through quenching with trimethylsilyl chloride and triethylamine (Scheme 4.2, eqn 1).[5] This method was expanded to the endocyclic silyl dienol ether **4-5** by addition of HMPA, however, these results required rigorous exclusion of oxygen and still provided a mixture of isomers (Scheme 4.2, eqn 2).



Scheme 4.3 Synthesis of β-Tosyl Silyl Dienol Ether

To overcome the challenges with the Kharasch reagents, we designed a strategy to synthesize a silyl dienol ethers wherein the β-carbon was a coupling partner that could undergo

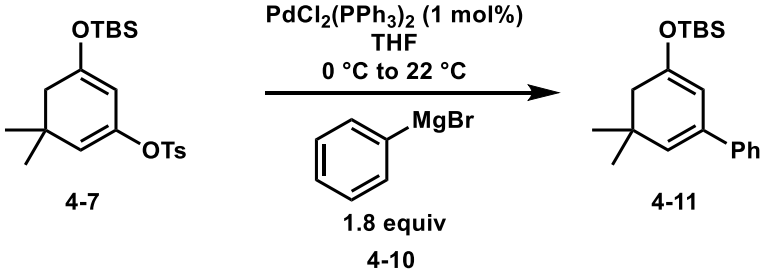
direct coupling to form the endocyclic silyl dienol ether or undergo γ-functionalization to form a enone with a β-coupling partner.

The approach for the β-functionality began with the vinylogous iodide, however the vinylogous iodide was often difficult to purify and the product was unstable.[6] The vinyl tosylates[7] **4-6, 4-8** were selected as the β-functionalized enone due its better stability than the vinyl iodide or vinyl bromide. Basic enolization/silylation of the vinylogous tosylate **4-6** and **4-8** proceeded in 87% yield, and 83%, respectively.[8] (Scheme 4.3).

4.2 Optimization of β-Coupling

Based on reports by Tanabe in 2008, we knew that *E*-isomer of vinylogous tosylates underwent Negishi coupling reactions with $PdCl_2(PPh_3)_2$ and alkyl zinc chlorides.[9] Initially, we verified that the reaction did not proceed through a substitution with the vinyl tosylate by running the reaction in the absence of palladium catalyst.

Table 4.1 Optimization of Catalyst



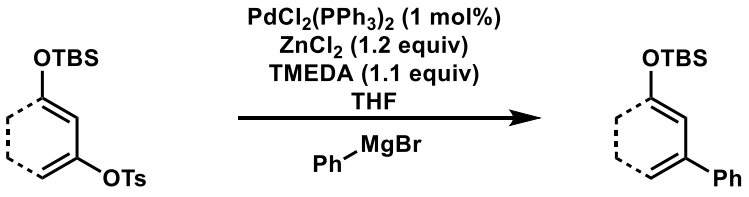
Entry	Catalyst	R-MgBr equiv	$ZnCl_2$ equiv	Ligand	Yield
1	no Pd	1.8	0	-	0
2	$PdCl_2(PPh_3)_2$	1.8	1.8	-	20
3	$PdCl_2(PPh_3)_2$	1.8	0	-	50
4	$PdCl_2(PPh_3)_2$	1.8	1.2	-	68
5	$PdCl_2(PPh_3)_2$	1.8	1.2	TMEDA	99
6	$PdCl_2(PPh_3)_2$	1.8	1.0	TMEDA	82
7	$PdCl_2(PPh_3)_2$	1.8	0.75	TMEDA	77
8	$PdCl_2(PPh_3)_2$	1.8	0.5	TMEDA	32
9	$PdCl_2(PPh_3)_2$	1.8	6 (LiCl)	TMEDA	51

The aryl zinc reagent was generated in-situ by treatment of an aryl Grignard reagent with zinc chloride. Gratifyingly, we saw that the reaction proceeded in 20% yield. (Table 4.1, entry 2). However, in the absence of zinc chloride, we saw the reaction proceed with 50% yield. (Table 4.1, entry 3).

TMEDA has been proven to act as a chelating agent for the aryl Grignard reagents and reduced the degree of aggregation, so the addition of TMEDA in our reaction provided the β-coupled product in 99% yield (87% isolated yield).[10] (Table 4.1, entry 5–9). After careful analysis of zinc chloride equivalence, we found that 1.2 equiv of zinc chloride improved the yield to 99%.[11] (Table 4.1, entry 5–8). Replacement of the zinc chloride with LiCl failed to improve the yield. (Table 4.1, entry 9).

4.3 Scope of β-Coupling

Table 4.2 Scope of β-Coupling for β-Aryl Silyl Dienol Ethers



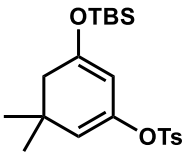
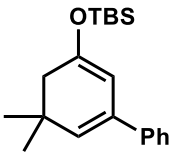
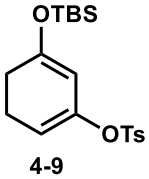
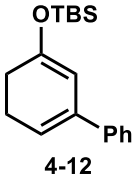
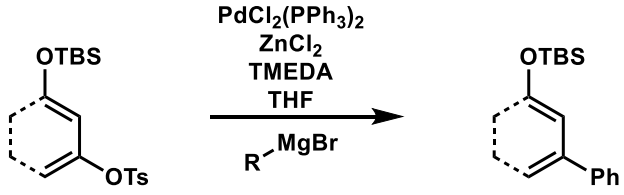
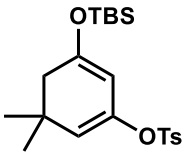
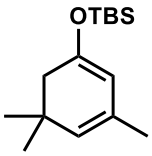
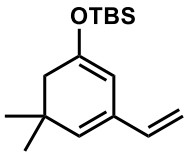
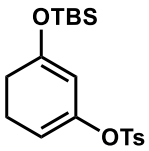
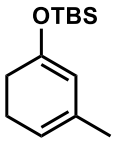
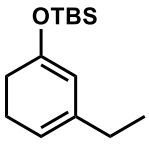
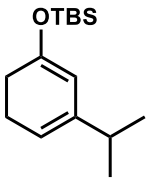
Entry	Siloxydiene	Product	% yield
1	 4-7	 4-11	87%
2	 4-9	 4-12	78%

Table 4.3 Scope of Alkyl and Vinyl Magnesium Bromides



Entry	Siloxydiene	Product	% yield
1	 4-7	 4-13	66%
2		 4-14	48%
3	 4-9	 4-15	64%
4		 4-16	83%
5		 4-17	77%

The β-coupling products of β-tosyl silyl dienol ether **4-7** and β-tosyl silyl dienol ether **4-9** with phenylmagnesium bromide **4-10** were isolated in 87% and 78% yield, respectively. (Table 4.2) Alkyl β-coupling were also found to be successful under our conditions. The β-coupling with

methyl magnesium bromide proceeded in 72% NMR yield (66% isolated yield) to provide the endocyclic silyl dienol ether **4-5** of isophorone. (Table 4.3, entry 1).

With the success of both aryl or alkyl magnesium bromides, we turned our attention to other β-alkyl silyl dienol ethers. Methyl, ethyl and isopropyl magnesium bromides were all successful in the coupling to form **4-15**, **4-16**, **4-17** in 64%, 83%, and 77%, respectively. (Table 4.3, entry 4-5). These endocyclic β-alkyl silyl dienol ethers are otherwise inaccessible through direct enolization.

Through direct enolization, the β-vinyl cyclohexanones fail to form the endocylic silyl dienol ethers as the deconjugation of the 1,3-diene failed to occur and only the α'-silyl dienol ether was isolated.[12] Through our method, the β-vinyl silyl dienol ether **4-15** was synthesized in 48% yield. (Table 4.3, entry 2).

4.4 Applications of β-Coupling to Total Synthesis of Natural Products

4.4.1 Total Synthesis of (±)-Crotontomentosin A

Crotontomentosins A–E and were isolated from the leaves of *croton caudatus Geisel. var. tomentosus Hook*, a shrub found in Yunnan, China in 2015.[13] Crotontomentosin A, an abietane terpenoid showed moderate to weak inhibitory activity against HeLa human cervical carcinoma (IC_{50} 24.0 ± 2.6), human liver carcinoma Hep G2 (IC_{50} 87.9 ± 4.5), MDA-MB-231 human metastatic breast adenocarcinoma (IC_{50} 54.1 ± 2.1), and A-549 human lung adenocarcinoma (IC_{50} 40.6 ± 3.9).

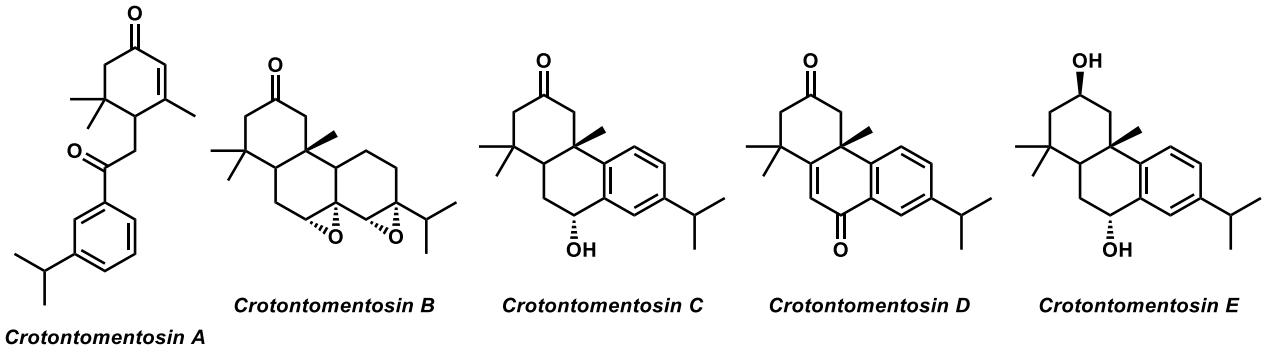
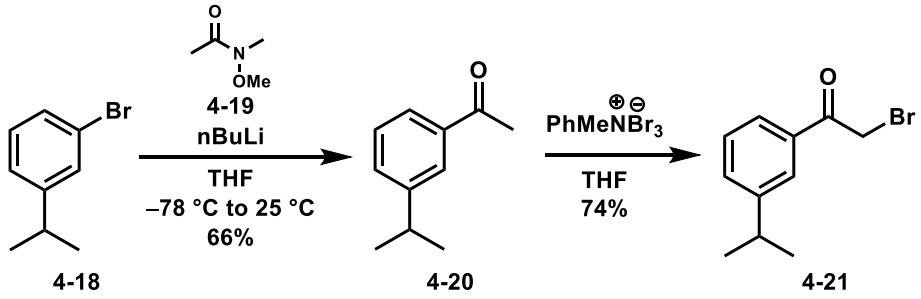


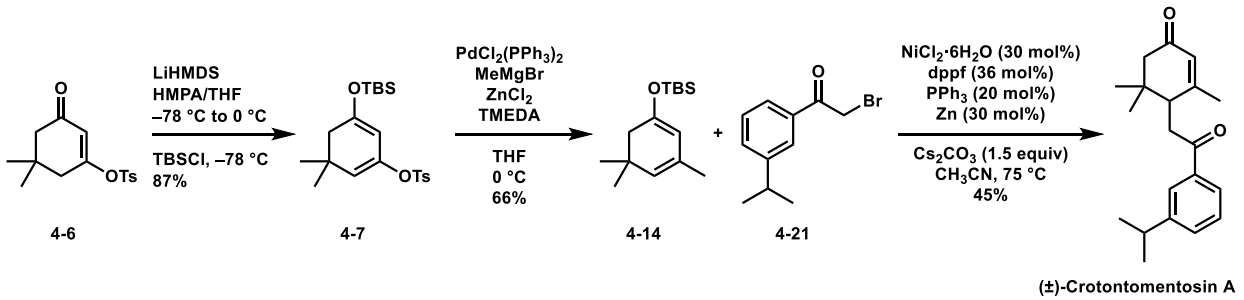
Figure 4.1 Structures of *Crotontomentosin* Family

The β-coupling of a β-tosyl silyl dienol ether **4-7** would provide the endocylic silyl dienol ether **4-14** necessary for the γ-alkylation. The synthesis began with the generation of the α-bromoketone **4-21**. Following a procedure reported by Danhesier, 1-bromo-3-isopropylbenzene **4-18** formed an aryllithium species by addition of *n*-BuLi, which added to the Weinreb amide **4-19**.[14] The α-bromination of the ketone **4-20** proceeded in 74% with phenyltrimethylammonium tribromide.



Scheme 4.4 Synthesis of α-Bromoketone

Previously in this chapter, we showed that the β-coupling of the silyl tosyl dienol diether **4-7** provided the endocyclic silyl dienol ether **4-3** in 66% yield. The neopentyl γ-carbon proved challenging for the γ-alkylation. Increasing the temperature to 75 °C and the catalyst loading to 30% provided the natural product in 45% yield.



Scheme 4.5 Final Steps of Synthesis of (±)-Crotontomentosin A

4.5 Summary

Herein, we have reported a new method to access endocyclic silyl dienol ethers through a β-coupling of β-tosyl silyl dienol ethers. This method expanded the previous scope for our γ-functionalization methods. We then applied this new coupling to the synthesis of (±)-crotontomentosin A, which was completed in 4 steps with 14.5% overall yield, starting from commercially available starting materials.

4.6 Experimental Details

General Information

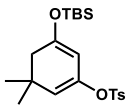
Unless otherwise stated, reactions were performed in oven-dried glassware under a N_2 atmosphere using dry, deoxygenated solvents. Anhydrous acetonitrile, dichloromethane, pentane, toluene and THF (BHT-free) were purchased from Aldrich, degassed with argon, and dried by passage through activated drying columns[15] on a Pure Process Technology system. Cesium carbonate (Cs_2CO_3) was purchase from Fischer Chemical and used as received. Starting materials, including 2-cyclohexen-1-one, were purchased from Aldrich, Alfa Aesar, or Oakwood Chemical and used as received. Deuterated chloroform ($CDCl_3$, 99.9%, extra dry) was purchased from Cambridge Isotope Laboratories, Inc. and was used without further purification. Reaction temperatures were controlled by an IKAmag immersion temperature modulator. Thin-layer chromatography (TLC)

was performed using Silicycle silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or staining with p-anisaldehyde or $KMnO_4$ solutions. Flash chromatography[16] was performed using Silicycle SiliaFlash® P60 silica gel (40–63 μm particle size). Melting points were determined using a Mel-Temp electrothermal capillary melting point apparatus and the values reported are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 (at 500 and 126 MHz, respectively) or DPX-400 instrument (at 400 and 101 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, br s = broad singlet. Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me4Si (δ 0.0). Infrared (IR) spectra were recorded on a Nicolet iS5 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). GC/MS analyses were performed on a Hewlett Packard Model 6890 gas chromatograph interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). The vinyl tosylate were synthesized according to previous publication.[7] The TBS dienol ether were synthesized by enolization with LiHMDS according to our previous publication.[1]

Synthesis of Silyl Dienol Ethers[8]:

An oven-dried 100 mL round bottom flask equipped with a magnetic stirring bar, was sealed with a rubber septum and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with a solution of vinylogous tosylate (5 mmol, 1.0 equiv) in anhydrous THF (20 mL) and HMPA (2.17 mL, 12.5 mmol, 2.5 equiv) and then cooled to –78 °C. After stirring the mixture for

5 min, a solution of LiHMDS (1.0 M soln in THF, 5.5 mL, 5.5 mmol, 1.1 equiv) was added dropwise over 3 min. Stirring was continued for 1 h at –78 °C, and then the mixture was warmed to 0 °C and stirred for 1 h. The reaction mixture was cooled to –78 °C and a solution of TBSCl (1.13 g, 7.5 mmol, 1.5 equiv) in THF (10 mL) was added dropwise over 5 min. Stirring was continued for 30 min, at which time TLC indicated complete consumption of the enone. The reaction was quenched by addition of saturated $NaHCO_3$ solution (20 mL) and then hexanes (30 mL) was added. The phases were separated, and the aqueous phase was extracted with hexanes (2 x 20 mL). The combined organic phases were washed with brine (1 x 20 mL), dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the desired product.



4-7

5-((tert-butyldimethylsilyl)oxy)-3,3-dimethylcyclohexa-1,5-dien-1-yl 4-methylbenzenesulfonate:

The title compound was prepared according to the general procedure, using vinyl tosylate **4-6** (1.47 g, 5.0 mmol). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 20:1), the title compound was isolated as a yellow oil. (1.78 g, 4.35 mmol, 87%)

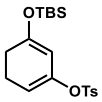
TLC (SiO_2) R_f = 0.52 in 20:1 CH_2Cl_2/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 4.79 (s, 1H), 4.76 (s, 1H), 2.43 (s, 3H), 2.16 (s, 2H), 2.00 (s, 2H), 0.94 (s, 6H), 0.88 (s, 9H), 0.08 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7, 144.9, 144.6, 132.9, 129.5, 128.6, 117.5, 99.3, 43.4, 32.8, 30.9, 28.1, 25.5, 21.6, 17.9

IR (neat) 2955, 2929, 2895, 2885, 1678, 1652, 1602, 1471, 1371, 1098 cm^{-1}

GC/MS (m/z): 408.2 (14%), 393.2 (100%), 335.1 (2%), 253.1 (7%), 229.0 (15%), 206.9 (10%), 181.0 (33%), 155.0 (25%), 91.0 (50%), 73.0 (60%), 57.1 (4%)



4-9

5-((tert-butyldimethylsilyl)oxy)cyclohexa-1,5-dien-1-yl 4-methylbenzenesulfonate: The title compound was prepared according to General Procedure, using vinyl tosylate **4-8** (1.33 g, 5.0 mmol). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 20:1), the title compound was isolated as a yellow oil. (1.57 g, 4.35 mmol, 83%)

TLC (SiO_2) R_f = 0.49 in 20:1 CH_2Cl_2/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.9 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 4.99 (m, 1H), 4.76 (s, 1H), 2.21 (m, 2H), 2.12 (m, 2H), 0.87 (s, 9H), 0.07 (s, 6H)

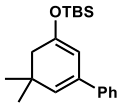
^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7, 146.1, 144.9, 133.0, 129.5, 128.5, 106.0, 100.2, 28.2, 25.5, 21.7, 17.9

IR (neat) 2975, 2938, 2887, 2883, 1648, 1623, 1598, 1485, 1371, 1098 cm^{-1}

GC/MS (m/z): 380.2 (6%), 365.1 (100%), 265.1 (50%), 229.0 (25%), 206.9 (10%), 181.0 (33%), 155.0 (20%), 91.0 (45%), 73.0 (55%), 57.1 (15%)

General Procedure for Kumada coupling

Anhydrous $ZnCl_2$ (85.2 mg, 0.625 mmol, 1.25 equiv) was added to an oven-dried 20 mL vial equipped with a magnetic stirring bar. The vial was sealed with a septum cap and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with TMEDA (82 µL, 0.55 mmol, 1.1 equiv) and 0.5 mL THF. The reaction mixture was cooled to 0 °C and then R-MgBr or R–MgCl (0.9 mmol, 1.8 equiv) in THF was added. After stirring the mixture for 30 min, a solution of tosylate (0.5 mmol, 1.0 equiv), $PdCl_2(PPh_3)_2$ (3.5 mg, 1 mol%) in 1.0 mL THF was added. The reaction was warmed to room temperature naturally and stirred for 2 h until TLC indicated complete consumption of the enone. (If starting material remains after 2 h, then another equivalent of R–MgBr was added). The reaction was quenched by addition of saturated $NaHCO_3$ solution (4 mL) and then hexanes (20 mL) was added. The phases were separated, and the aqueous phase was extracted with hexanes (2 x 10 mL). The combined organic phases were washed with brine (1 x 5 mL), dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the desired product.



4-12

tert-butyl((5,5-dimethyl-4,5-dihydro-[1,1'-biphenyl]-3-yl)oxy)dimethylsilane: The title compound was prepared according to the General Kumada Procedure using β-tosyl silyl dienol ether **4-7** (204.7 mg, 0.5 mmol, 1 equiv) and 3M PhMgBr in Et2O (0.3 ml, 0.9 mmol, 1.8 equiv). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 20:1), the title compound **4-12** was isolated as a colorless oil.

1st run: 136.9 mg (87% yield)

2nd run: 135.8 mg (86% yield)

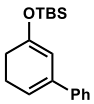
TLC (SiO_2) R*f* = 0.50 in hexanes, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, CDCl3) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.50 (dd, *J* = 8.4, 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 1H), 5.58 (s, 1H), 5.53 (s, 1H), 2.25 (s, 2H), 1.19 (s, 6H), 1.04 (s, 9 H), 0.30 (s, 6H)

^{13}C NMR (126 MHz, CDCl3) δ 154.2, 141.2, 134.3, 128.8, 128.4, 127.2, 125.7, 102.7, 43.8, 34.0, 31.5, 28.2, 25.5, 14.2

IR (neat) 3032, 2985, 2955, 1633, 1588, 1562, 1417, 1371 cm^{-1}

GC/MS (*m/z*): 314.2 (20%), 299.1 (100%), 241.1 (10%), 225.1 (7%), 165.0 (5%), 152.1 (3%), 115.0 (5%), 73.1 (25%), 59.0 (2%)



4-13

tert-butyl((4,5-dihydro-[1,1'-biphenyl]-3-yl)oxy)dimethylsilane: The title compound was prepared according to the General Kumada Procedure using β-tosyl silyl dienol ether **4-9** (190.1mg, 0.5 mmol, 1 equiv) and 3M PhMgBr in Et2O (0.3 ml, 0.9 mmol, 1.8 equiv). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 20:1), the title compound **4-13** was isolated as a colorless oil.

1st run: 100.3 mg (70% yield)

2nd run: 95.3 mg (67% yield)

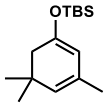
TLC (SiO_2) R_f = 0.46 in hexanes, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 6.9 Hz, 2H), 7.38 (dd, *J* = 6.9, 6.9 Hz, 2H), 7.29 (t, *J* = 6.9 Hz, 1H), 5.79 (t, *J* = 4.6 Hz, 1H), 5.62 (s, 1H), 2.51 (dt, *J* = 9.7, 4.6 Hz, 2H), 2.34 (t, *J* = 9.7 Hz, 2H), 1.05 (s, 9H), 0.30 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 141.1, 136.9, 128.3, 126.8, 125.5, 115.4, 104.1, 28.8, 25.7, 24.4, 18.2

IR (neat) 3023, 2955, 2913, 1640, 1580, 1565, 1495 cm^{-1}

GC/MS (*m/z*): 286.1 (1%), 284.1 (5%), 227.1 (100%), 211.0 (46%), 152.0 (18%), 113.5 (7%), 75.0 (11%), 57.0 (4%)



4-14

tert-butyldimethyl((3,5,5-trimethylcyclohexa-1,3-dien-1-yl)oxy)silane: The title compound was prepared according to the General Kumada Procedure using β-tosyl silyl dienol ether **4-7** (204.7 mg, 0.5 mmol, 1 equiv) and 3M MeMgBr in Et_2O (0.3 ml, 0.9 mmol, 1.8 equiv). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 20:1), the title compound **4-14** was isolated as a colorless oil.

1st run: 83.8 mg (66% yield)

2nd run: 85.3 mg (68% yield)

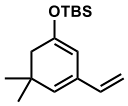
TLC (SiO_2) R_f = 0.50 in hexanes, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.97 (m, 1H), 4.88 (m, 1H), 2.03 (s, 2H), 1.69 (s, 3H), 0.99 (s, 6H), 0.94 (s, 9H), 0.16 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 129.3, 125.0, 104.6, 43.5, 33.3, 28.6, 25.8, 21.7, 18.0

IR (neat) 3013, 2933, 2923, 2868, 1654, 1545, 1371 cm^{-1}

GC/MS (*m/z*): 252.2 (15%), 237.2 (100%), 179.1 (30%), 163.1 (2%), 123.1 (5%), 105.1 (5%), 91.0 (4%), 73.1 (30%), 59.1 (5%)



4-14

tert-butyl((5,5-dimethyl-3-vinylcyclohexa-1,3-dien-1-yl)oxy)dimethylsilane: The title compound was prepared according to the General Kumada Procedure using β-tosyl silyl dienol ether **4-7** (204.7 mg, 0.5 mmol, 1 equiv) and 1M PhMgBr in THF (0.9 ml, 0.9 mmol, 1.8 equiv). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 20:1), the title compound **4-14** was isolated as a colorless oil.

1st run: 62.3 mg (48% yield)

2nd run: 62.9 mg (48% yield)

TLC (SiO_2) R_f = 0.50 in hexanes, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (dd, *J* = 21.1, 13.2 Hz, 1H), 5.43 (s, 1H), 5.20 (s, 1H), 5.16 (d, *J* = 21.1 Hz, 1H), 4.96 (d, *J* = 13.2 Hz, 1H), 2.12 (s, 2H), 1.06 (s, 6H), 0.96 (s, 9H), 0.21 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0 137.3, 132.1, 131.5, 110.4, 98.5, 43.9, 33.6, 28.0, 25.7, 18.0

IR (neat) 3024, 2935, 2887, 1644, 1617, 1597, 1583 cm^{-1}

GC/MS (*m/z*): 264.1 (25%), 249.2 (100%), 205.0 (1%), 191.0 (13%), 177.0 (5%), 163.0 (2%), 135.1 (10%), 115.0 (8%), 105.0 (5%), 91.1 (15%), 73.1 (50%), 59.0 (10%)

4-15

tert-butyldimethyl((3-methylcyclohexa-1,3-dien-1-yl)oxy)silane: The title compound was prepared according to the General Kumada Procedure using β-tosyl silyl dienol ether **4-9** (190.1 mg, 0.5 mmol, 1 equiv) and 3M MeMgBr in Et_2O (0.3 ml, 0.9 mmol, 1.8 equiv). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 20:1), the title compound **4-15** was isolated as a colorless oil.

1st run: 70.6 mg (63% yield)

2nd run: 72.9 mg (65% yield)

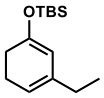
TLC (SiO_2) R_f = 0.59 in hexanes, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.12 (m, 1H), 5.01 (s, 1H), 2.21 (m, 2H), 2.15 (t, *J* = 8.4 Hz, 2H), 1.70 (s, 3H), 0.94 (s, 9H), 0.18 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 141.1, 136.9, 128.3, 126.8, 125.5, 115.4, 104.1, 28.8, 25.7, 24.4, 18.2

IR (neat) 3042, 2929, 2858, 1644, 1583 cm^{-1}

GC/MS (*m/z*): 224.1 (58%), 165.0 (100%), 151.1 (12%), 135.0 (10%), 91.0 (29%), 75.0 (71%), 59.0 (17%)



4-16

tert-butyl((3-ethylcyclohexa-1,3-dien-1-yl)oxy)dimethylsilane: The title compound was prepared according to the General Kumada Procedure using β-tosyl silyl dienol ether **4-9** (190.1mg, 0.5 mmol, 1 equiv) and 3M EtMgBr in Et_2O (0.3 ml, 0.9 mmol, 1.8 equiv). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 20:1), the title compound **4-16** was isolated as a colorless oil.

1st run: 101.9 mg (85% yield)

2nd run: 97.1 mg (81% yield)

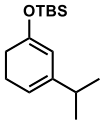
TLC (SiO_2) R_f = 0.50 in hexanes, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.13 (m, 1H), 5.10 (s, 1H), 2.23 (m, 2H), 2.17(d, *J* = 9.4Hz, 2H), 2.00 (d, *J* = 7.4 Hz, 2H), 1.00 (t, *J* = 7.4 Hz), 3H), 0.94 (s, 9H), 0.18 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 138.4, 110.8, 105.2, 28.9, 28.7, 25.6, 23.9, 18.1, 12.9

IR (neat) 3033, 2988, 2924, 2818, 1616, 1611, 1583 cm^{-1}

GC/MS (*m/z*): 238.1 (95%), 223.1 (5%), 209.1 (11%), 179.1 (100%), 163.0 (7%), 151.0 (25%), 137.0 (5%), 124.1 (3%), 107.1 (4%), 91.0 (10%), 75.0 (75%). 59.0 (30%)



4-17

tert-butyl((3-isopropylcyclohexa-1,3-dien-1-yl)oxy)dimethylsilane: The title compound was prepared according to the General Kumada Procedure using β-tosyl silyl dienol ether **4-9** (190.1mg, 0.5 mmol, 1 equiv) and 3M *i*-PrMgBr in Et2O (0.3 ml, 0.9 mmol, 1.8 equiv). After

purification by flash chromatography (SiO_2, hexanes/EtOAc = 20:1), the title compound **4-17** was isolated as a colorless oil.

1st run: 98.0 mg (78% yield)

2nd run: 94.1 mg (75% yield)

TLC (SiO_2) R_f = 0.51 in hexanes, *p*-anisaldehyde stain

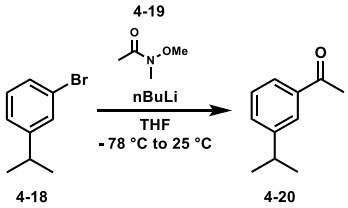
^{1}H NMR (500 MHz, $CDCl_3$) Mixture of Isomers: δ 5.12 (t, *J* = 4.1 Hz, 1H), 5.10 (s, 1H), 2.22 (m, 2H), 2.16 (m, 2H), 1.95 (m, 1H), 1.40 (septet, *J* = 7.4 Hz, 1H), 1.00 (d, *J* = 7.4 Hz, 6H), 0.94 (s, 9H), 0.18 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 142.7, 136.6, 112.5, 109.8, 105.3, 104.1, 33.4, 28.9, 25.7, 23.7, 21.7, 18.1, 13.7

IR (neat) 3024, 2956, 2913, 2858, 1656, 1589, 1456 cm^{-1}

GC/MS (*m/z*): 252.2 (100%), 237.1 (20%), 209.1 (15%), 193.1 (16%), 181.1 (10%), 151.0 (85%), 137.0 (5%), 121.1 (4%), 105.1 (5%), 91.0 (8%), 73.1 (85%), 59.0 (20%)

5.6.3 Total synthesis of (±)-Crotontomentosin A

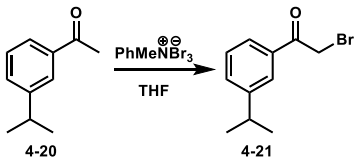


1-(3´-Isopropylphenyl)ethanone[14]. An oven-dried 100 mL round bottom flask equipped with a magnetic stirring bar, was sealed with a rubber septum and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with 3-bromocumene **4-18** (0.52 mL, 3.33 mmol, 1.0 equiv), and 33 mL THF, and then cooled to –78 °C. After stirring for 5 min, 2.5M nBuLi in

Hexanes (3.33 mL, 8.33 mmol, 2.5 equiv) was added dropwise. The reaction was stirred for 30 min, then N-methoxy-N-methylacetamide **4-19** (515.6 mg, 5 mmol, 1.5 equiv) in 1 mL THF was added dropwise. The resulting solution was naturally warmed to room temperature. The reaction was then quenched by the addition of 5 mL of water. The resulting solution was diluted with 20 mL of EtOAc, washed with 2x10 mL of brine, dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated in vacuo. After purification by flash chromatography (SiO2, hexanes/EtOAc = 20:1), the title compound **4-20** was isolated as a yellow oil with spectral characteristics consistent with those reported previously.[14] (351.1 mg, 2.16 mmol, 65%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1 H), 7.78 (app dt, *J* = 7.6, 1.5 Hz, 1 H), 7.45 (app dt, *J* = 7.7, 1.4 Hz, 1 H), 7.39 (app t, *J* = 7.6 Hz, 1 H), 2.98 (sept, *J* = 7.0 Hz, 1 H), 2.62 (s, 3 H), 1.29 (d, *J* = 7.0 Hz, 6 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7, 149.6, 137.4, 131.6, 128.7, 126.4, 126.3, 34.3, 26.9, 24.1.



2-bromo-1-(3-isopropylphenyl)ethan-1-one. A 25 mL flask was charged with 1-(3´-Isopropylphenyl)ethenone **4-20** (766.7 mg, 4.72 mmol, 1 equiv) and THF. Then $PhMe_3NBr_3$ (1.96 g, 5.22 mmol, 1.10 equiv) was added. The reaction slowly changed colors from red to yellow and a white precipitate formed. After 12 hours, the reaction was filtered through celite with 20 mL Et2O and then concentrated in vacuo. After purification by flash chromatography (SiO_2, hexanes/EtOAc = 20:1), the title compound **4-21** was isolated as a colorless oil. (796.4 mg, 3.30 mmol, 70%)

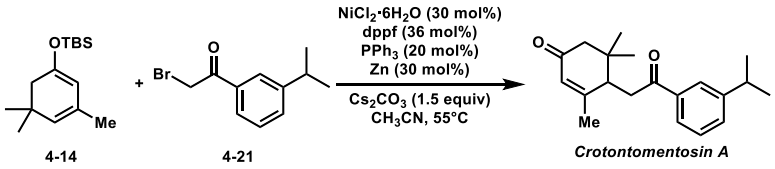
TLC (SiO_2) R_f = 0.45 in 20:1 CH_2Cl_2/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.41 (dd, *J* = 7.6, 7.6 Hz, 1H), 4.46 (s, 2H), 2.99 (sept, *J* = 6.8 Hz, 1H), 1.28 (d, *J* = 6.8 Hz, 6H)

^{12}C NMR (126 MHz, $CDCl_3$) δ 191.5, 150.1, 134.0, 132.3, 128.8, 126.9, 126.6, 34.1, 31.1, 23.8

IR (neat) 3061, 3051, 2960, 2927, 2868, 1697, 1679, 1623, 1620, 1494, 1287, 1197 cm^{-1}

GC/MS (*m/z*): 240.1 (5%), 162.1 (10%), 1471. (100%), 133.1 (8%), 117.1 (20%), 103.0 (5%), 91.0 (8%), 77.0 (5%), 51.0 (2%)



(±)-Crotontomentosin A. $NiCl_2 \cdot 6H_2O$ (14.3 mg, 30 mol %), 1,1'-Bis(diphenylphosphino)ferrocene, dppf, (39.8 mg, 36%), Triphenylphosphine (10.5 mg, 20%), Zinc powder (6.5 mg, 50%), and Cesium carbonate (97.7 mg, 1.5 equiv) was added to an oven-dried 20 mL vial equipped with a magnetic stirring bar. The vial was sealed with a septum cap then evacuated and backfilled with nitrogen (three cycles of 15 min each). Then added 0.75 mL of freeze-dried anhydrous CH_3CN, followed by bromoacetophenone **4-21** (84.4 mg, 0.35 mmol, 1.75 equiv) TBS dienol ether **4-14** (50.5 mg, 0.2 mmol, 1.0 equiv), dissolved in 0.25 mL CH_3CN were added into the vial sequentially. The mixture was heated to 80°C and stirred for 72 h. After the reaction was complete (monitored by TLC), the mixture was cooled to room temperature, and the solvent was removed under vacuum. After purification by flash chromatography (SiO2, hexanes/EtOAc = 10:1), the natural product was isolated as a yellow oil with spectral characteristics consistent with those reported previously.[13] (26.8 mg, 0.09 mmol, 45%).

TLC (SiO_2) R_f = 0.44 in 5:1 Hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.41 (dd, *J* = 7.6, 7.6 Hz, 1H), 5.89 (s, 1H), 3.37 (dd, *J* = 18.0, 6.5 Hz, 1H), 3.11 (t, *J* = 5.3 Hz, 1H), 2.99 (quintet, *J* = 6.8 Hz, 1H), 2.81 (dd, *J* = 18.0, 4.3 Hz, 1H), 2.37 (d, *J* = 17.0 Hz, 1H), 2.14 (d, *J* = 17.0 Hz, 1H), 1.92 (s, 3H), 1.26 (d, *J* = 6.9 Hz, 6H), 1.10 (s, 3H), 0.91 (s, 3H)

^{12}C NMR (126 MHz, $CDCl_3$) δ 199.2, 198.2, 164.4, 149.8, 136.8, 131.9, 128.9, 126.2, 126.0, 125.8, 47.6, 45.1, 38.1, 36.2, 34.3, 28.1, 26.6, 24.1, 24.0, 23.8

IR (neat) 3433, 2965, 2875, 1667, 1633, 1394 cm^{-1}

GC/MS (*m/z*): 298.1 (8%), 283.1 (17%), 265.1 (4%), 206.9 (6%), 151.1 (100%), 134.9 (15%), 119.1 (20%), 104.0 (10%), 91.0 (37%), 77.1 (8%), 65.0 (4%), 53.1 (2%)

4.7 Notes and References

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[6] The decomposition of the vinylogous iodide would occur immediately to form a pinkish color.

[7] Carotti, A.; Casini, G.; Ferappi, M.; Cingolani, G. M. *Journal of Heterocyclic Chemistry*, **1980**, *17*, 1577–1584.

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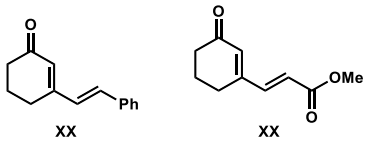
[10] Hatakeyama, T.; Yoshimoto, Y.; Ghorai, S. K.; Nakamura, M. *Org. Lett*. **2010**, *12*, 1516–1519.

[11] The purpose of $ZnCl_2$ is not yet known.

[12] β–styrene XX and β–enones XX were also attempted as the alkene would also be in conjugation with the phenyl or the carbonyl group, respectively, perhaps lowering the energy required to break the conjugation of the 1,3 dione. However, these only formed the α'–silyl dienol ether.



[13] Song, J.–T.; Han, Y.; Wang, X.–L.; Shen, T.; Lou, H.–X.; Wang, X.–N. *Fitoterapia*. **2015,** *107*, 54–59.

[14] Dalton, A. M.; Zhang, Y.; Davie, C. P.; Danheiser, R. L. *Org. Lett.* **2002**, *4*, 2465–2468.

[15] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518–1520.

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CHAPTER 5

PROGRESS TOWARDS THE SYNTHESIS OF

(±)-PROPOLISBENZOFURAN B

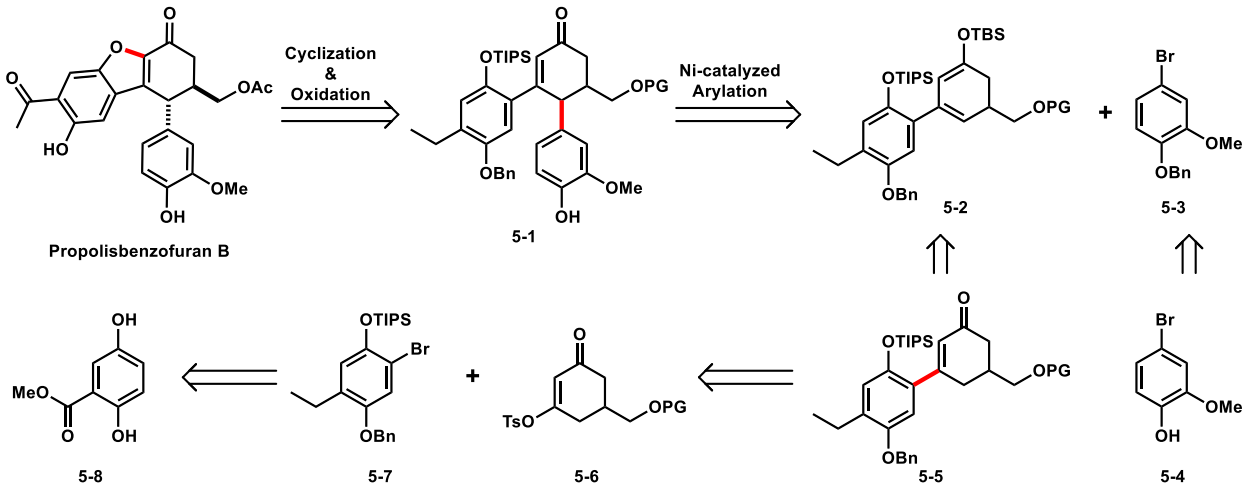
5.1 Background

Propolisbenzofuran B has shown cytotoxic effects toward murine colon 26-L5 carcinoma (13.7 mg/mL), and human HT-1080 fibrosarcoma cells (43.7 mg/mL). This benzofuran was isolated by Banskota and coworkers in 2000 from *Brazilian propolis*, a resin that has often been used for folk medicine as an antibiotic, antiviral and antifungal.[1]

Herein, we report our progress towards the synthesis of (±)-propolisbenzofuran B. The principal challenge to the synthesis would be the formation of the key γ-aryl group on the sterically hindered γ-carbon. Previous syntheses of propolisbenzofuran B utilized convergent oxidative coupling,[2] or a [1,3] O-to-C rearrangement.[3]

5.2 Retrosynthetic Analysis of (±)-Propolisbenzofuran B

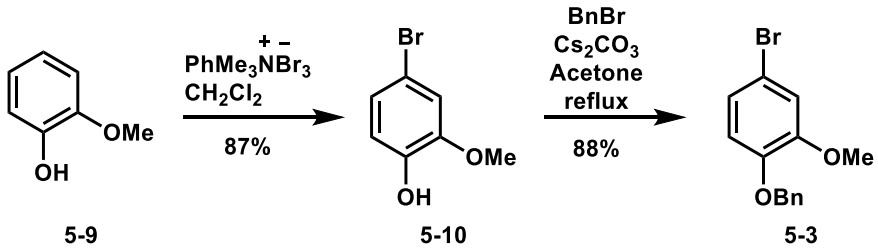
We envisioned a different strategy for the installation of the γ-aryl group through the γ-arylation method that had been developed in our laboratories.[4] Our plan consisted of coupling the silyl dienol ether **5-2** with the aryl halide **5-3** to form the new γ-aryl enone. The precursor of **5-2** would come from the conjugate addition of aryl halide **5-7** to the vinylogous ester **5-6**.



Scheme 5.1 Retrosynthesis of Propolisbenzofuran B

5.3 Progress towards the Synthesis of (±)-Propolisbenzofuran B

5.3.1 Synthesis of γ-Aryl Coupling Partner

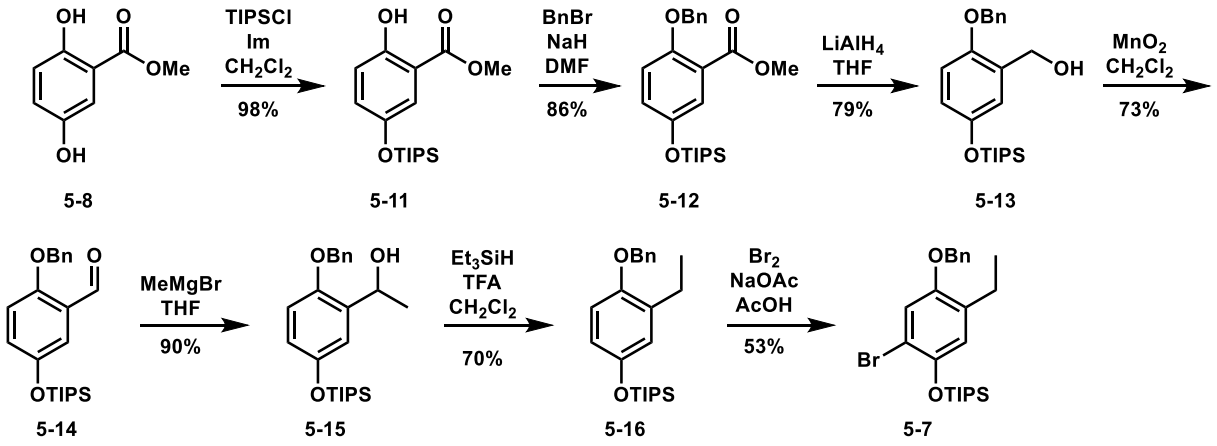


Scheme 5.2 Synthesis of Aryl Halide 5-3

Based on work by Hartung, we synthesized the bromophenol **5-10** with an ammonium tribromide salt (Scheme 5.2).[5] Knowing that the deprotection of the 5-hydroxy of the benzofuran moiety and the 4-hydroxy of the bromophenol would occur as the last step of the synthesis, we sought to engage the same deprotection methods for both phenols. So, we protected the bromophenol with a benzyl group to form the benzyl ether **5-3**.

5.3.2 Preparation of the Benzofuran Moiety

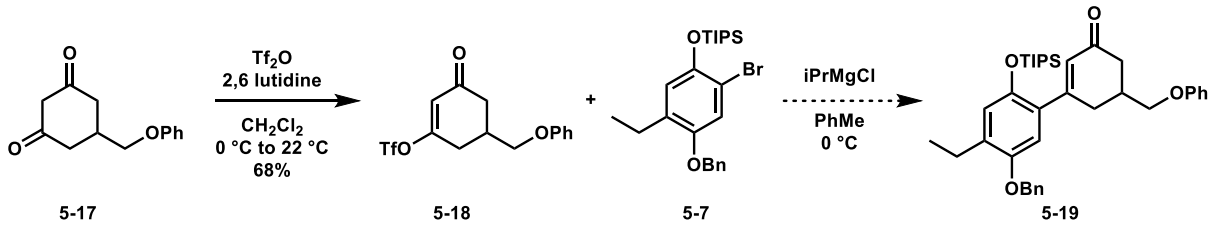
Our synthesis of the benzofuran moiety commenced with the selective protection of the 5-hydroxy of 2,5 dihydroxy methyl benzoate **5-8** with triisopropylsilyl chloride and imidazole (Scheme 5.3). Subsequent protection of the 2-hydroxy moiety provided the benzoate **5-12**. Reduction via lithium aluminum hydride followed by oxidation with manganese dioxide provided the aldehyde **5-14**. To convert the aldehyde **5-14** to the ethyl benzene **5-16**, we carried out a Grignard addition on the aldehyde, then a reduction of the alcohol **5-15** with triethylsilane in the presence of trifluoroacetic acid. The OTIPS and ethyl group would direct the bromintion to occur regioselectively in the para position to the ethyl group to form aryl halide **5-7**.



Scheme 5.3 Synthesis of Hydroquinone Derivative 5-7

5.3.3 Synthesis of Enone Core

Focusing our attention on the enone core structure, we prepared the 1,3-dione **5-17** from bromoacetaldehyde diethyl acetal.[6] Birch reduction of 3,5-dimethoxy methyl benzoate to provide the dione failed to proceed in more than 10% yield and the yield was often irreproducible.[7] The vinylogous tosylate from the 1,3-dione **5-17** decomposed rapidly on upon standing and on silica, so we turned our attention to the vinylogous triflate which was used crude to undergo the Grignard addition followed by Stork-Danheiser transposition to form β-aryl enone **5-19** (Scheme 5.4).[8]



Scheme 5.4 Synthesis of Enone Core

One possible side reaction that would occur is the tandem carbanion addition/carbon–carbon bond cleavage to form an alkynyl ketone.[9] By switching the solvent to non-polar toluene, the fragmentation pathway should be inoperable as the MgOTf ion pair that cleaves during the course of the reaction would not be stabilized by the nonpolar solvent. However,

the Grignard addition failed to occur and the vinylogous triflate also rapidly decomposed to the 1,3 dione **5-17**. Further attempts to functionalize the 1,3-dione are underway.

5.4 Summary

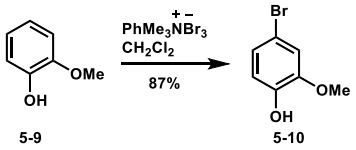
Herein, we report the progress towards the total synthesis of (±)-Propolisbenzofuran b. The aryl halide **5-3** and the hydroquinone derivative **5-7** were successfully synthesized, however the synthesis of enone **5-19** was unsuccessful. Further attempts to synthesize this moiety are underway.

5.5 Experimental Details

General Information

Unless otherwise stated, reactions were performed in oven-dried glassware under a N_2 atmosphere using dry, deoxygenated solvents. Anhydrous acetonitrile, dichloromethane, pentane, toluene and THF (BHT-free) were purchased from Aldrich, degassed with argon, and dried by passage through activated drying columns[10] on a Pure Process Technology system. Cesium bicarbonate (Cs_2CO_3) was purchase from Fischer Chemical and used as received. Starting materials, including 2-cyclohexen-1-one, were purchased from Aldrich, Alfa Aesar, or Oakwood Chemical and used as received. Deuterated chloroform ($CDCl_3$, 99.9%, extra dry) was purchased from Cambridge Isotope Laboratories, Inc. and was used without further purification. Reaction temperatures were controlled by an IKAmag immersion temperature modulator. Thin-layer chromatography (TLC) was performed using Silicycle silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or staining with p-anisaldehyde or KMnO4 solutions. Flash chromatography[11] was performed using Silicycle SiliaFlash® P60 silica gel (40–63 μm particle size). Melting points were determined using a Mel-Temp electrothermal capillary melting point apparatus and the values reported are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a

Bruker Avance DRX-500 (at 500 and 126 MHz, respectively) or DPX-400 instrument (at 400 and 101 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, br s = broad singlet. Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me4Si (δ 0.0). Infrared (IR) spectra were recorded on a Nicolet iS5 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). GC/MS analyses were performed on a Hewlett Packard Model 6890 gas chromatograph interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). 1,3 cyclohexadione was synthesized according to previous reports.[6]



5-9 5-10

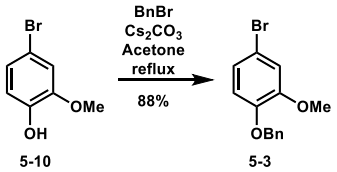
Guaiacol **5-9** (1.11 mL, 10 mmol, 1 equiv) was dissolved in 50 mL CH_2Cl_2 with a magnetic stirring bar in a 20 mL vial. Then $PhMe_3NBr_3$ was added and the reaction was stirred until the red color disappeared. 50 mL Et_2O was added and the reaction mixture was filtered through celite and the filtrate was dried over $MgSO_4$ and concentrated by use of a rotary evaporator to form slightly yellow crystals. The product 5-10 was isolated as a yellow solid (1.77 g, 8.73mmol, 87%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (m, 2H), 6.80 (d, *J* = 8.2 Hz, 1H), 5.57 (br s, 1H), 3.88 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.1, 144.9, 124.1, 115.7, 114.2, 111.5, 56.0

IR (neat) 3249, 3076, 2959, 2932, 1603, 1585, 1497, 1461 cm^{-1}

GC/MS (m/z): 294.0 (5%), 292.0 (5%), 173.0 (1%), 144.9 (1%), 91.1 (100%), 79.0 (7%), 65.0 (14%), 51.1 (5%)



5-10 5-3

The benzyl ether **5-3 (1.76g, 8.67 mmol)** was synthesized according to reported procedure.[12] The product 5-3 was isolated as a white solid (2.24g, 7.6 mmo, 88%).

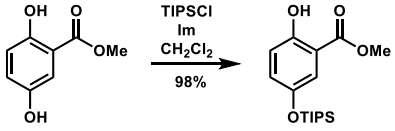
TLC (SiO_2) Rf = 0.30 in 10:1 hexanes/EtOAc, p-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ7.37 (m, 5H), 7.01 (d, 2.7 Hz, 1H), 6.96 (dd, J = 10.5, 2.7 Hz, 1H), 6.74 (d, J = 10.5 Hz, 1H), 5.12 (s, 2H), 3.88 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.7, 134.8, 128.7, 127.9, 127.3, 123.3, 115.4, 71.1, 56.2

IR (neat) 3006, 2940, 1579, 1499, 1464, 1442, 1417 cm^{-1}

GC/MS (m/z): 202.0 (100%), 200.0 (100%), 188.9 (80%), 186.9 (80%), 158.9 (40%), 156.9 (40%), 144.9 (5%), 142.9 (5%), 132.9 (8%), 130.9 (8%), 79.0 (20%), 63.0 (20%), 51.0 (35%)



5-8 5-11

Methyl Benzoate **5-8** (3.36g, 20 mmol, 1 equiv), imidazole (2.04g, 30 mmol, 1.5 equiv), 145 ml CH_2Cl_2 and a magnetic stir bar was charged to a 250 mL round bottom flask. Next, triisopropylsilyl chloride (4.50 mL, 21 mmol, 1.05 equiv) was added dropwise and the mixture was then stirred overnight at rt. The reaction was quenched with 20 mL NH_4Cl. The mixture was added to a

separatory funnel and extracted with CH_2Cl_2 (3 X 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The residue was purified by flash column chromatography on silica gel using 100:1 hexanes: ethyl acetate as eluent to yield the product **5-11** as a clear oil (6.36 g, 19.6 mmol, 98%)

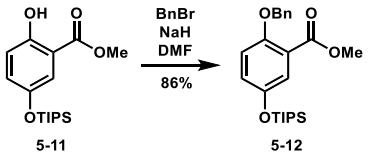
TLC (SiO_2) Rf = 0.51 in 20:1 hexanes/EtOAc, p-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.36 (brs, 1H), 7.30 (d, *J* = 3.1 Hz, 1H), 7.03 (dd, *J* = 8.9, 3.1 Hz, 1H), 6.85 (d, *J* = 8.9 Hz), 3.92 (s, 3H), 1.23 (m, *J* = 7.9 Hz, 3H), 1.09 (d, *J* = 7.9 Hz, 18H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 155.8, 148.0, 128.3, 119.0, 118.1, 111.8, 52.3, 18.2, 12.5

IR (neat) 3217, 2945, 2867, 1682, 1614, 1589, 1484 cm^{-1}

GC/MS (m/z): 324.2 (38%), 281.1 (77%), 253.1 (46%), 239.1 (8%), 225.1 (100%), 211.0 (46%), 193.0 (23%), 179.1 (12%), 163.0 (19%), 149.0 (8%), 135.0 (12%), 112.5 (19%), 89.1 (23%), 75.1 (12%), 59.0 (23%)



5-11 5-12

A 50mL round bottom flask was charged with sodium hydride (660 mg, 16.48 mmol, 1.3 equiv), dimethylformamide (25mL) and a magnetic stir bar under a nitrogen atmosphere. The solution was cooled to 0°C and then TIPS ether **5-11** (4.12g, 12.68 mmol, 1 equiv) in 30 mL DMF was added dropwise. After 10 minutes, then BnBr (2.0 mL, 16.48 mmol, 1.3 equiv) was added dropwise to the flask. The mixture was stirred for 5 h at room temperature at which time TLC showed total consumption of the starting material. The reaction was then quenched with 10 mL NH_4Cl and then extracted with ethyl acetate (20 mL X 3). The combined organic layers were dried over $MgSO_4$

and concentrated by use of a rotary evaporator. The residue was purified by flash column chromatography on silica gel using 10:1 hexanes: ethyl acetate as eluent to yield the product **5-12** as a clear oil (4.54 g, 11.0 mmol, 86%)

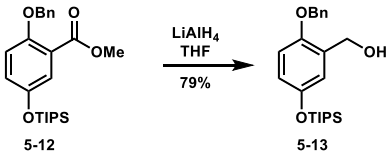
TLC (SiO_2) Rf = 0.37 in 20:1 hexanes/EtOAc, p-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.38 (m, 3H), 7.31 (d, *J* = 3.1 Hz, 1H), 6.96 (dd, *J* = 8.9, 3.1 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 1H), 5.13 (s, 2H), 3.91 (s, 3 H), 1.25 (m, *J* = 7.9 Hz, 3H), 1.11 (d, *J* = 7.9 Hz, 18H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 152.8, 149.7, 137.1, 128.5, 127.7, 127.0, 124.5, 122.3, 121.5, 116.0, 71.9, 52.0, 17.9, 12.6

IR (neat) 2945, 2866, 1731, 1709, 1577, 1494, 1454, 1436 cm^{-1}

GC/MS (m/z): 414.3 (33%), 371.2 (16%), 339.2 (23%), 311.1 (5%), 280.1 (2%), 238.1 (2%), 195.0 (2%), 157.1 (27%), 115.1 (20%), 91.1 (100%), 59.1 (20%)



5-12 5-13

Preparation of alcohol:

A 50mL round bottom flask was charged with $LiAlH_4$ (407 mg, 10.7 mmol, 1.1 equiv), THF (33 mL) and a magnetic stir bar under a nitrogen atmosphere. The solution was cooled to 0°C and then a solution of ester **5-12** (4.05 g, 9.75 mmol, 1.0 equiv) in 15 mL in THF. The mixture was stirred for 2 h at room temperature at which time TLC showed total consumption of the starting material. At 0°C, the reaction was then quenched with 0.4 mL H_2O, then 1.2 mL 15% NaOH solution, followed by another 3 mL H_2O. The mixture was stirred for 30 min, then 50 mL Et_2O was added

and the reaction mixture was filtered through celite and the filtrate was dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The residue was purified by flash column chromatography on silica gel using 10:1 hexanes: ethyl acetate as eluent to yield the product **5-13** as a clear oil (2.96 g, 7.66 mmol, 79%)

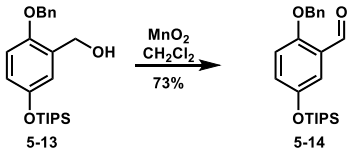
TLC (SiO_2) Rf = 0.17 in 10:1 hexanes/EtOAc, p-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (m, 5H), 6.87 (d, *J* = 3.1 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.76 (dd, *J* = 8.8, 3.1 Hz, 1H), 5.05 (s, 2H), 4.65 (s, 2H), 2.37 (brs, 1H), 1.25 (m, *J* = 7.9 Hz, 3H), 1.13 (d, *J* = 7.9 Hz, 18H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.8, 150.1, 137.0, 130.5, 128.6, 128.0, 127.4, 120.3, 118.9, 112.7, 70.5, 61.9, 17.9, 12.7

IR (neat) 3421, 2942, 2891, 2865, 1588, 1492, 1461, 1424 cm^{-1}

GC/MS (m/z): 384.2 (13%), 292.0 (18%), 206.9 (21%), 157.0 (12%), 115.1 (8%), 91.0 (100%), 58.9 (13%)



5-13 5-14

Preparation of Aldehyde:

A 50mL round bottom flask was charged with alcohol **5-13** (2.96 g, 7.66 mmol, 1 equiv), MnO_2 (3.33 g, 38.3 mmol, 5 equiv), 40 mL CH_2Cl_2 and a magnetic stir bar. The mixture was stirred for 2 weeks at room temperature at which time TLC showed total consumption of the starting material. The mixture was then filtered through celite and the filtrate was concentrated by use of a rotary

evaporator. The residue was purified by flash column chromatography on silica gel using 20:1 hexanes: ethyl acetate as eluent to yield the product **5-14** as a clear oil (2.15 g, 5.59 mmol, 73%)

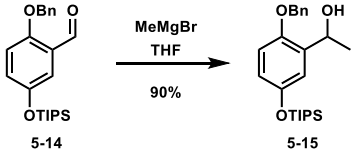
TLC (SiO_2) Rf = 0.50 in 10:1 hexanes/EtOAc, p-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.5 (s, 1H), 7.40 (m, 5H), 7.08 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.95 (d, *J* = 9.0 Hz, 1H), 5.14 (s, 2H), 1.25 (m, *J* = 7.9 Hz, 3H), 1.13 (d, *J* = 7.9 Hz, 18H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 189.4, 155.7, 150.2, 136.4, 128.7, 128.2, 127.5, 127.4, 125.8, 117.8, 114.6, 71.2, 17.9, 12.6

IR (neat) 2944, 2890, 2866, 1683, 1608, 1579, 1462, 1454 cm^{-1}

GC/MS (m/z): 384.2 (11%), 341.2 (2%), 323.2 (1%), 292.1 (1%), 249.1 (1%), 179.0 (2%), 157.1 (5%), 115.1 (4%), 91.1 (100%), 59.1 (10%)



5-14 5-15

Preparation of alcohol:

A 50mL round bottom flask was charged with aldehyde **5-14** (1.90 g, 4.95 mmol, 1 equiv), 5 mL THF and a magnetic stir bar under a nitrogen atmosphere. The solution was cooled to 0°C and then 3M methylmagnesium bromide in Et_2O (2.5 mL, 7.5 mmol, 1.5 equiv) was added dropwise to the reaction. The mixture was stirred for 5 h at room temperature at which time TLC showed total consumption of the starting material. The reaction was then quenched with 5 mL NH_4Cl and then extracted with ethyl acetate (20 mL X 3). The combined organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The residue was purified by flash column

chromatography on silica gel using 10:1 hexanes: ethyl acetate as eluent to yield product **5-15** as a clear oil (1.79 g, 4.47 mmol, 90%)

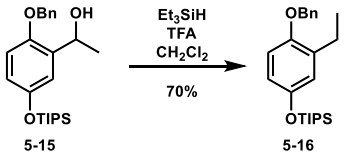
TLC (SiO_2) Rf = 0.26 in 10:1 hexanes/EtOAc, p-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ7.40 (m, 5H), 6.93 (d, *J* = 3.1 Hz, 1H), 6.80 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.73 (d, *J* = 9.0 Hz, 1H), 5.10 (q, *J* = 6 Hz, 1H), 5.05 (s, 2H), 1.49 (d, *J* = 6 Hz, 3 H), 1.25 (m, *J* = 7.9 Hz, 3H), 1.13 (d, *J* = 7.9 Hz, 18H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.2, 149.8, 136.9, 134.9, 128.6, 128.0, 127.4, 118.4, 117.9, 112.8, 70.8, 66.4, 23.0, 17.8, 12.8

IR (neat) 3439, 3033, 2945, 2892, 2866, 1607, 1586, 1490, 1462, 1454 cm^{-1}

GC/MS (m/z): 400.3 (10%), 382.3 (20%), 339.2 (8%), 309.2 (5%), 291.1 (34%), 249.1 (15%), 177.1 (10%), 157.1 (25%), 115.1 (40%), 91.1 (100%), 75.0 (20%), 59.0 (20%)



Preparation of alkane:

Alcohol **5-15** (1.72 g, 4.30 mmol, 1 equiv), 21.5 mL CH_2Cl_2 and a magnetic stir bar under a nitrogen atmosphere. Triethylsilane (3.43 mL, 21.5 mmol, 5 equiv) was added dropwise to the reaction mixture, followed by dropwise addition of trifluoroacetic acid (1.65 mL, 21.5mmol, 5 equiv). The mixture was stirred for 2 h at room temperature at which time TLC showed total consumption of the starting material. The reaction was then quenched with 5 mL saturated $NaHCO_3$ solution and then extracted with dichloromethane (20 mL X 3). The combined organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The residue was

purified by flash column chromatography on silica gel using 10:1 hexanes: ethyl acetate as eluent to yield product **5-16** as a clear oil (1.16 g, 3.01 mmol, 70%)

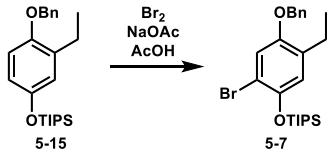
TLC (SiO_2) Rf = 0.27 hexanes, p-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.2 Hz, 2H), 7.39 (t, *J* = 8.2 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.65 (dd, *J* = 9.1, 3.3 Hz, 1H), 5.02 (s, 2H), 2.66 (q, *J* = 9.1 Hz, 2H), 1.23 (m, 6H), 1.11 (d, *J* = 7.2 Hz, 18H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 149.8, 137.8, 134.1, 128.4, 127.6, 127.1, 120.7, 116.9, 112.6, 70.7, 23.3, 17.9, 14.2, 12.6

IR (neat) 3033, 2960, 2942, 2891, 2866, 1607, 1587, 1492, 1462, 1454 cm^{-1}

GC/MS (m/z): 384.2 (12%), 355.1 (5%), 339.1 (8%), 309.1 (6%), 291.1 (31%), 249.2 (12%), 207.0 (9%), 117.0 (7%), 157.0 (25%), 115.1 (27%), 91.1 (100%), 75.0 (25%), 59.0 (30%)



Preparation of aryl bromide:

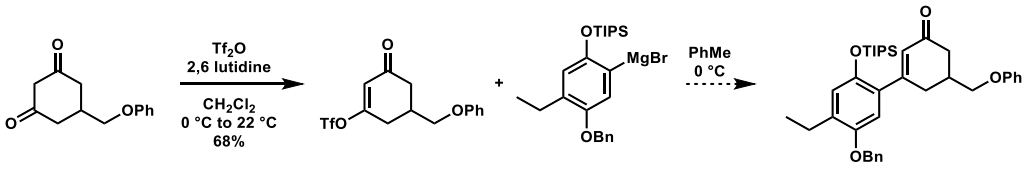
Ethylbenzene **5-15** (1.16g, 3.01 mmol, 1 equiv), sodium acetate (260 mg, 3.16 mmol, 1.05 equiv), 7.9 mL in Acetic Acid and a magnetic stir bar under a nitrogen atmosphere. Bromine (0.16 mL, 3.16 mmol, 1.05 equiv) was added over 10 min. After stirring for an additional 5 minutes, the reaction was quenched with 5 mL $NaHSO_3$, until a constant yellow color persisted. The solution was diluted with 10 mL H_2O and then extracted with CH_2Cl_2 (20 mL X 3). The combined organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator to form slightly yellow crystals **5-7**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (m, 5H), 7.06 (s, 1H), 6.77 (s, 1H), 4.99 (s, 2H), 2.61 (q, *J* = 10.3 Hz, 2H), 1.32 (septet, *J* = 9.4 Hz, 3H), 1.18 (t, *J* = 10.3 Hz, 3H), 1.15 (d, *J* = 9.4 Hz, 18H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.8, 146.9, 137.2, 133.2, 128.5, 127.9, 127.2, 120.0, 116.6, 110.8, 70.7, 23.0, 18.0, 14.0, 13.0

IR (neat) 2958, 2942, 2864, 1503, 1484, 1463, 1454, 1394 cm^{-1}

GC/MS (m/z): 464.2 (5%), 462.3 (5%), 421.2 (18%), 419.2 (18%), 373.1 (5%), 371.1 (5%), 157.1 (32%), 137.0 (11%), 135.0 (11%), 115.1 (21%), 91.1 (100%), 59.1 (18%)



Dione **5-17** (344.7 mg, 1.58 mmol, 1.0 equiv), 2,6-lutidine (0.36 mL, 3.15 mmol, 2 equiv), and 3.2 mL CH_2Cl_2 with a magnetic stirring bar in a 20 mL vial. The reaction was cooled to 0 °C. and then triflic anhydride (0.40 mL, 2.37 mmol, 1.5 equiv) was added dropwise. The reaction was quenched with 5 mL 1 N HCl and extracted with dichloromethane (20 mL X 2). The combined organic layers were washed with 5 mL H_2O and 5 mL Brine. Then the organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator.

The crude triflate **5-18** was dissolved in 1.0 mL of PhMe, and then added to a 0 °C cooled solution of 1M aryl magnesium bromide in PhMe (1.89 ml, 1.89 mmol, 1.2 equiv). The reaction was warmed naturally to room temperature. After TLC indicated full consumption, the reaction was The reaction was quenched with 5 mL 1 N HCl and extracted with EtOAc (20 mL X 2). The

combined organic layers were washed with 5 mL H_2O and 5 mL Brine. Then the organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator.

5.6 Notes and References

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CHAPTER 6

COPPER-CATALYZED γ-HYDROXYLAMINATION

6.1 Cycloaddition Reactions

Pericyclic reactions, such as Diels–Alder reactions are a valuable tool for synthetic chemists to form two new bonds, regio- and stereoselectively.[1] Silyl dienol ethers have been previously used by Corey,[2] Danishefsky,[3] and others as diene partners for this type of cycloaddition. However, the heteronuclear Diels-Alder reaction has become the focus of many research groups to synthesize various carbon–nitrogen or carbon–oxygen bonds.[4] So, we sought to engage this method for the γ-amination of silyl dienol ethers.

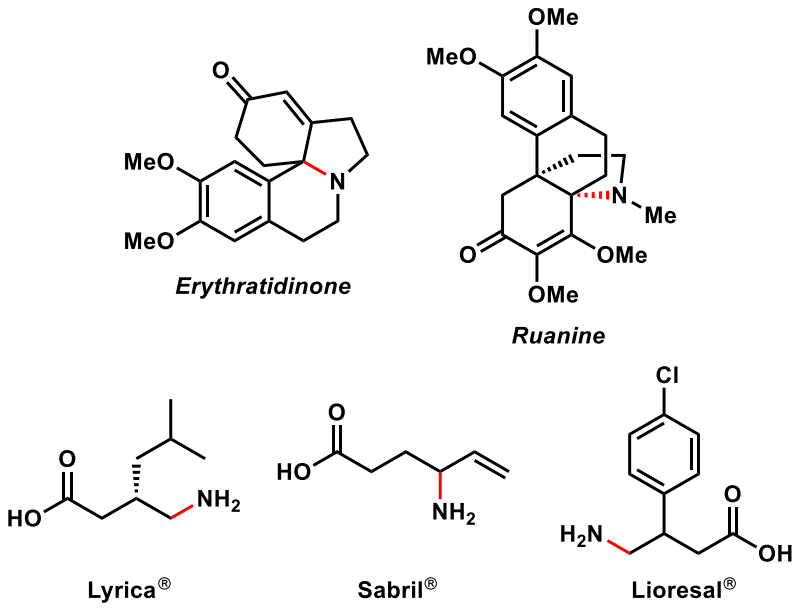
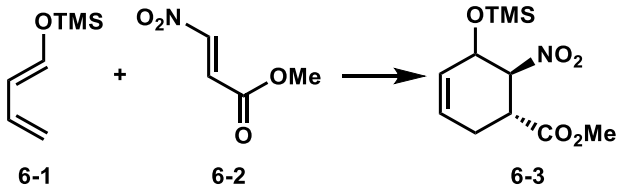


Figure 6.1 Natural Products and Pharmaceutical Targets Containing γ-Amino Group

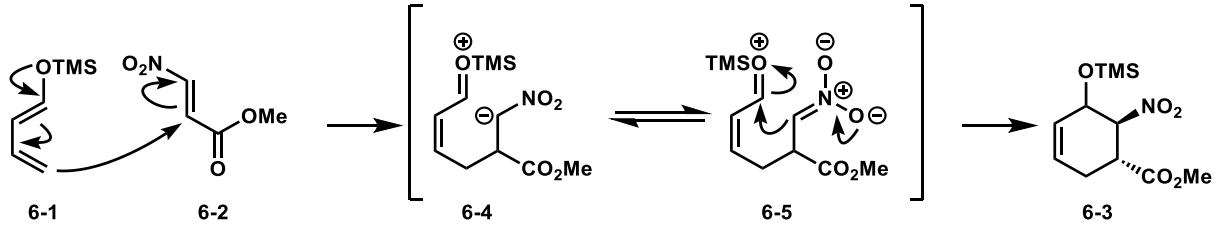
γ-Amino groups are prevalent in natural products and pharmaceutical targets (Figure 6.1). Current methods for γ-amination requires the use of more reactive imines, or azo groups as electrophilic amine sources.[5] While hydrolysis of β-lactams leads to ring-opening to form the β-amino esters, the ring opening of γ-lactam is much slower and ring-opening is not an efficient methods for the synthesis of γ-amino groups.[6]

6.1.2 Silyl Dienol Ethers as Dienes



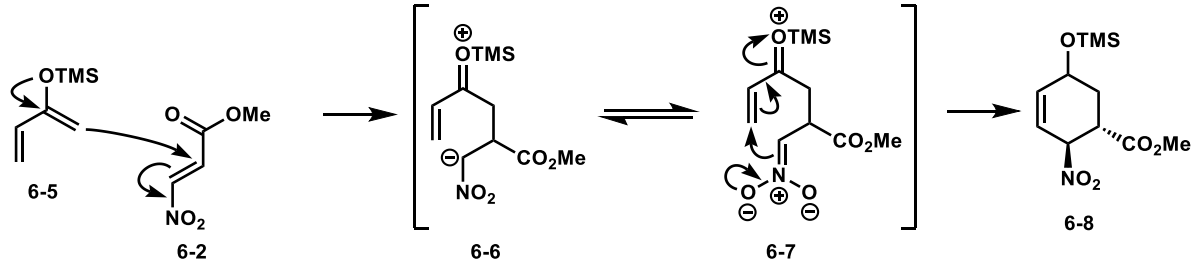
Scheme 6.1 Diels–Alder reaction of Silyl Dienol Ether

In 1978, Corey and coworkers showed the Diels–Alder reaction of the silyl dienol ether **6-1** and β-nitromethyl acrylate **6-2** (Scheme 6.1).[2] This reaction formed a single regioisomer with the nitro-group being ortho to the silyl ether group. This indicates that in a Diels–Alder reaction with silyl dienol ethers, the expected regioisomer **6-3** would bear the more electron-withdrawing group ortho to the silyl ether in the case of 1-siloxydienes **6-1**.



Scheme 6.2 Stepwise Mechanism for Diels–Alder Reaction of γ–Silyl Dienol Ether

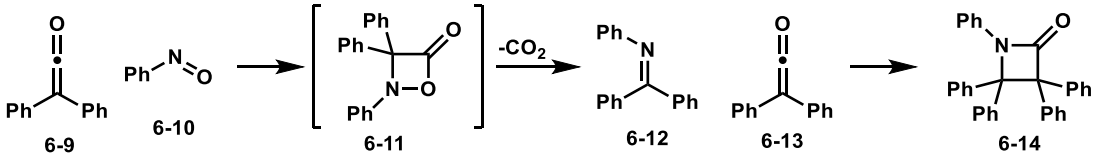
If we envision a step-wise mechanism for the cyclization (Scheme 6.2). FMO theory, as previously discussed, dictates that the γ–carbon of the γ–silyl dienol ether **6-1** would be more nucleophilic and so attack would occur from the γ–carbon. The conjugate addition of the silyl dienol ether **6-1** would occur on the carbon beta to the nitro group as that would be the most electrophilic carbon of the enone. The subsequent addition to the oxocarbenium ion **6-5** would form the cyclized product **6-3** with the anti-stereochemistry.



Scheme 6.3 Stepwise Mechanism for Diels–Alder Reaction of α'–Silyl Dienol Ether

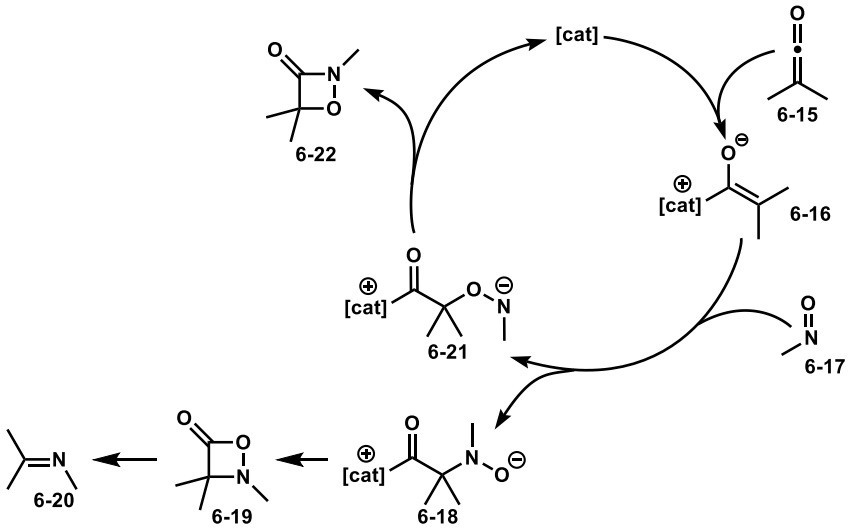
On the α'–silyl dienol ether **6-5**, the nucleophilic α'–carbon would add to the β–carbon to the nitro group (Scheme 6.3). Therefore, the α'–silyl dienol ethers **6-5** would have a para relationship with the electron-withdrawing group after cyclization.

6.1.3 [2+2] Cycloadditions of Nitroso compounds



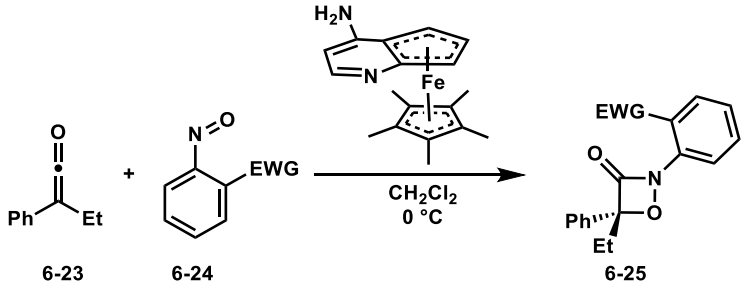
Scheme 6.4 Staudinger Cycloadditions of Ketenes and Nitroso Groups

[2+2] Cycloadditions of nitroso compounds have been thoroughly researched by numerous group to synthesize 1,2-oxazetidin-3-ones **6-22** (Scheme 6.4).[7] Initial results showed that the cycloaddition occurred preferentially with the oxygen binding to the electron-deficient ketene carbon (Scheme 6.5).[7a] According to the proposed mechanism for the nucleophile-catalyzed cycloaddition of nitroso compounds **6-17** and ketenes **6-15** , both zwitterion **6-18** and **6-21** form to produce both regioisomers **6-19** and **6-22**.



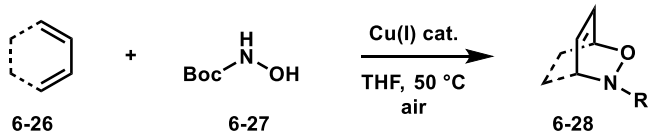
Scheme 6.5 Mechanism of Cycloaddition of Ketene and Nitroso

Fu designed a solution to overcome this selectivity by modifying the steric and electronic characteristics of the aryl group on the nitrogen to prefer formation of zwitterion **6-21** over **6-18**.[7f] By incorporating a strongly electron-withdrawing group, CF_3, in the ortho position of the aromatic ring, the regioselectivity for cycloaddition reversed with the 1,2-oxazetidin-3-one **6-25** being the major product (Scheme 6.6).



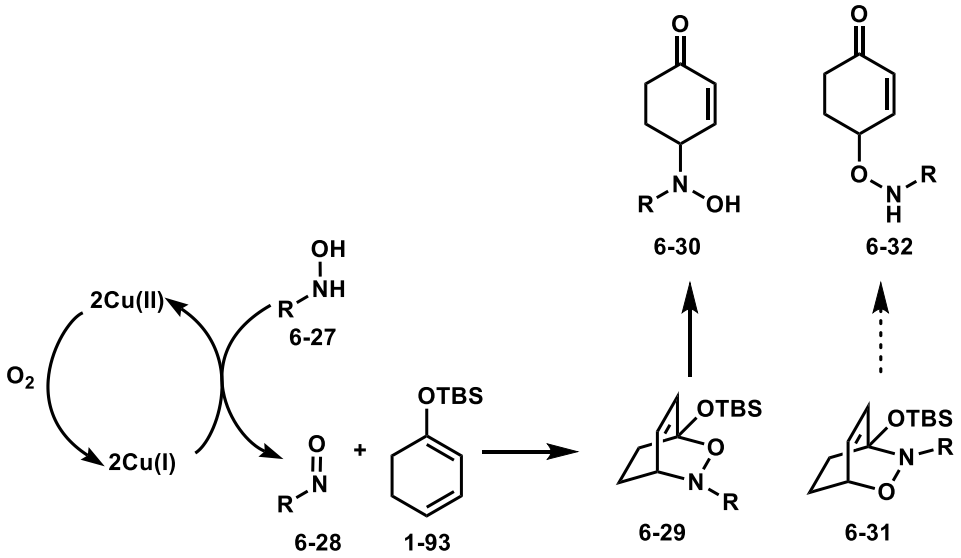
Scheme 6.6 Fu Cycloadditions of Ketenes and Nitroso Compounds

6.1.4 Diels–Alder Cycloadditions of nitroso groups



Scheme 6.7 Diels–Alder Reaction of Dienes and Nitroso Compounds

One limitation of nitroso group cycloadditions is the formation of nitroso groups. Aromatic substitution reactions,[8] alkyl substitution reactions from nitrosyl chloride,[9] acid-catalyzed dimethylnitrosamine addition to alkenes,[10] and oxidation of amines[11] are some of the many methods for synthesis of nitroso groups. However, most of the methods for C-nitroso group synthesis rely on stoichiometric oxidants or require the removal of toxic by-products.[12] Whiting[13] and Read de Alaniz[14] developed an aerobic oxidation of N-hydroxycarbamates **6-27** to nitroso compounds **6-28**.



Scheme 6.8 Proposed Mechanism for γ-Hydroxylamination of Silyl Dienol Ethers.

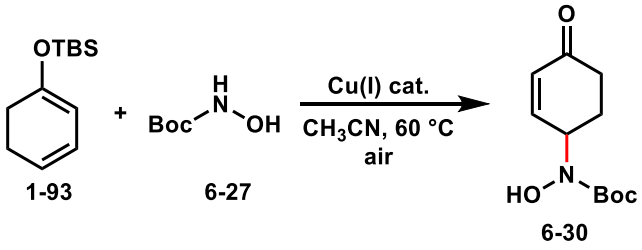
These acyl nitroso compounds **6-28** could be generated in situ to then undergo hetero-Diels–Alder reactions as reported by Read de Alaniz,[15] Whiting,[13] and coworkers (Scheme 6.7). We hoped to utilize the copper-catalyzed aerobic oxidation to generate the acyl nitroso compounds **6-28** in-situ which would undergo Diels–Alder reactions with silyl dienol ethers.

Fu had shown that by appending an electron-withdrawing group to the nitrogen atom of the nitroso, addition of the enolate occurred selectively on the oxygen atom. Also, Corey has shown that the more electron-withdrawing group prefers to be ortho to the silyl ether carbon.[16] If the

Diels–Alder cyclization occurred in the same fashion, then the γ-carbon–oxygen bond would form selectively. However, Diels–Alder reactions can often be dictated by sterics as well. We envisioned that the steric hindrance from the carbamate group nitrogen would overcome the electronic preference. So that the new carbon–nitrogen would form such that the nitrogen adds to the γ–carbon over the sterically bulky silyl ether carbon. We envisioned that the resulting 1,2 oxazine moiety **6-29** would be sterically strained and most likely undergo a ring opening reaction to form the γ-hydroxylamine product **6-30** (Scheme 6.8).

6.2 Screening and optimization

Table 6.1 Optimization of Catalyst and Ligand



1-93 6-27 6-30

Entry	Catalyst	Conditions	% yield
1	CuCl		trace
2	CuI		trace
3	Cu(OAc)		34%
4	$FeCl_2$		24%
5	$FeCl_3$		18%
6	$Cu(CH_3CN)_4 \cdot BF_4$		39%
7	$Cu(CH_3CN) \cdot PF_6$		20%
8	$Cu(CH_3CN)_4 \cdot BF_4$	TMEDA	50%
9	$Cu(CH_3CN)_4 \cdot BF_4$	PMDTA	34%
10	$Cu(CH_3CN)_4 \cdot BF_4$	Bipy	87%
11	$Cu(CH_3CN)_4 \cdot BF_4$	iPr_2NEt	trace
12	$Cu(CH_3CN)_4 \cdot BF_4$	Et_3N	trace
13	$Cu(CH_3CN)_4 \cdot BF_4$	Pyridine	57%
14	$Cu(CH_3CN)_4 \cdot BF_4$	Bipy, 50 °C	90%

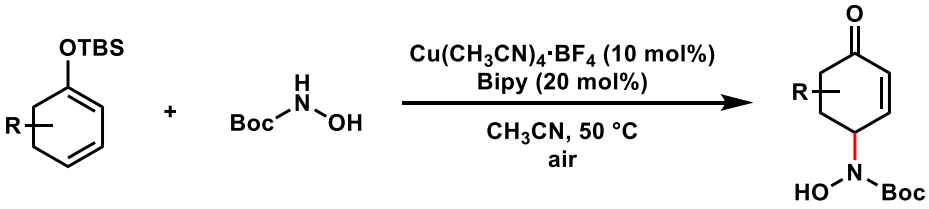
Our initial goal was to show that the silyl dienol ethers were amenable to aerobic oxidation conditions so that they could undergo the hetero-Diels–Alder reactions to form the γ-carbon–nitrogen group. We tested silyl dienol ether **1-93** as our test substrate and the *N*-Boc-hydroxylamine **6-27**. In accordance with Read de Alaniz' report, we initially tested numerous

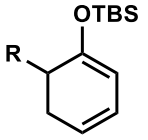
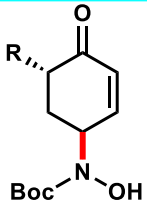
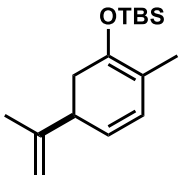
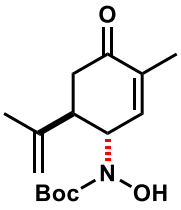
Cu(I) catalysts which failed to provide the desired γ-hydroxylamine **6-30** in good yields, instead hydrolyzing the silyl dienol ether **1-93** to form cyclohexenone. Iron(II) chloride and iron(III) chloride were able to catalyze the aerobic oxidation but the cationic copper catalyst, $Cu(CH_3CN)_4 \bullet BF_4$ provided the γ-hydroxylamine **6-30** in 39% yield.

The use of mono and bidentate amines for copper catalysts has been well-established and we sought to utilize their reactivity to enhance our reaction.[17] Amines, diamines, triamines and aromatic amines all improved the yield, with Bipy providing 87% of the hydroxylamine **6-30**. Lowering the temperature to 50 °C brought the yield to 90%.

6.3 Substrate Scope

Table 6.2 Scope of Silyl Dienol Ether



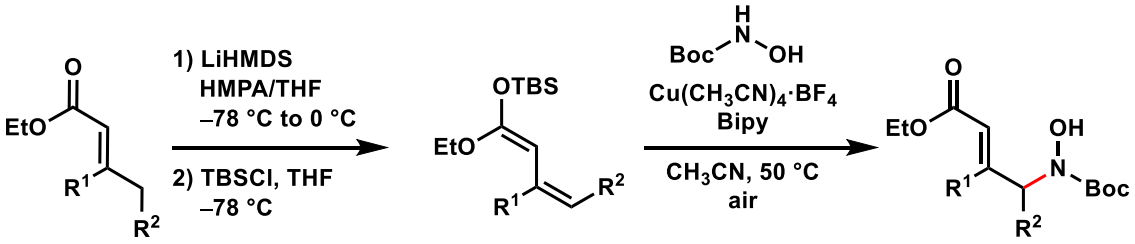
Entry	Siloxydiene		Product		% yield
1		1-93 R = H		6-30	90%
2		2-6 R = Me		6-34	67%
3		2-7 R = Bn		6-35	84%
4		2-8 R = allyl		6-36	57%
5		6-33		6-37	62%

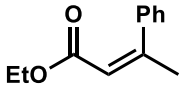
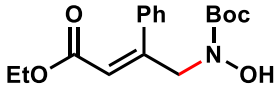
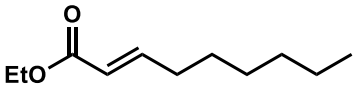
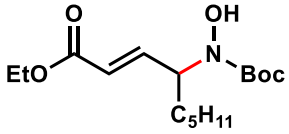
[a] Isolated yield from reaction of dienol ether (0.25 mmol), *N*-hydroxycarbamate (1.5 equiv), $Cu(Ch_3CN)_4 \bullet BF_4$ (10 mol%), Bipy (20 mol%) in 2.5 mL of CH_3CN at 50 °C open to air for 24 h.

The α'-substituted silyl dienol ethers formed only the *anti*-diastereomer as did the β'-substituted silyl dienol ether[18] (Table 5.2, entries 1–5). Isolated alkenes were unaffected by these

reaction conditions (Table 5.2, entries 4–5). Turning our attention to acyclic esters, we performed the γ-hydroxylamination on crude silyl ketene acetals[19] (Table 6.3). The acyclic γ-hydroxylamine products only formed the *E*-alkene.[20]

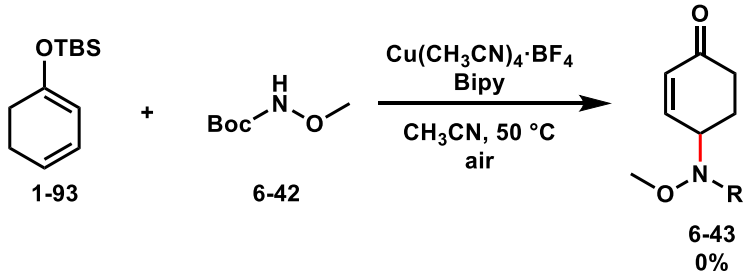
Table 6.3 γ-Hydroxylamination of Acyclic Esters



Entry	Ester		Product		% yield[b]
1		6-38		6-39	29%
2		6-40		6-41	25%

[a] Isolated yield from reaction of dienol ether (0.25 mmol), *N*-hydroxycarbamate (1.5 equiv), $Cu(CH_3CN)_4 \bullet BF_4$ (10 mol%), Bipy (20 mol%) in 2.5 mL of CH_3CN at 50 °C open to air for 24 h. [b] Yield over two steps

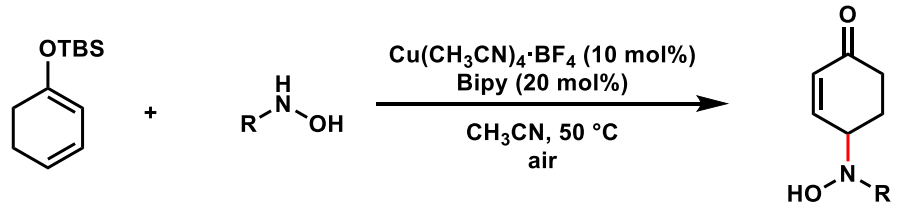
The *O*-methyl *N*-Boc hydroxylamine **6-54** failed to proceed under our reaction conditions (Scheme 6.9). To test the likelihood of a nitroso intermediate, we treated O-methylated hydroxylamine **6-42** with our reaction conditions. We found that the nitroso compound did not form as expected and the γ-hydroxylamine **6-43** did not form.

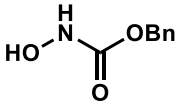
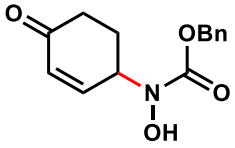
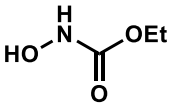
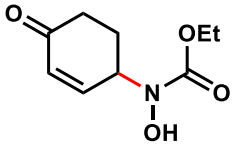
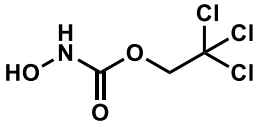
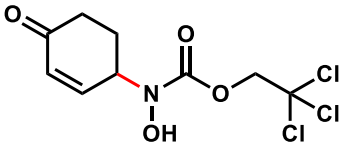
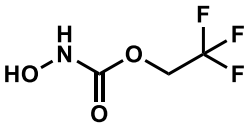
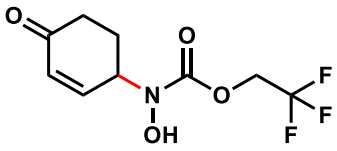
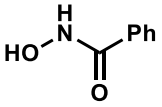
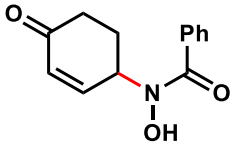


Scheme 6.9 Attempted Coupling of *O*-Methyl Hydroxylamine

Other hydroxycarbamates and hydroxyamides showed that the reaction could tolerate numerous protecting groups on the amine functionality. (Table 6.4). A Gram-scale reaction of the benzyl amide provided the γ-hydroxylamine **6-53** in 77% yield after 72 h.

Table 6.4 Modification of the Protecting Group on the Hydroxylamine

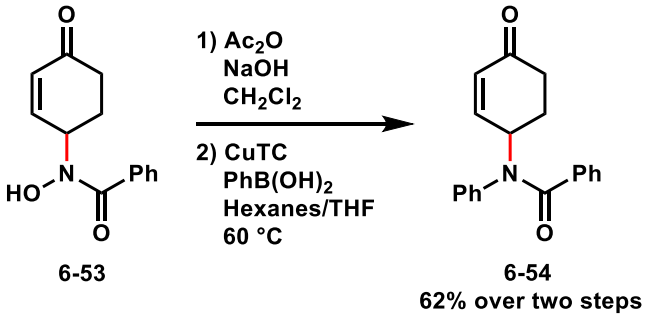


Entry	Hydroxylamine		Product		% yield
1		6-44		6-45	53%
2		6-46		6-47	61%
3		6-48		6-49	45%
4		6-50		6-51	49%
5		6-52		6-53	85% 77%[b]

[a] Isolated yield from reaction of dienol ether (0.25 mmol), *N*-hydroxycarbamate (1.5 equiv), $Cu(Ch_3CN)_4 \bullet BF_4$ (10 mol%), Bipy (20 mol%) in 2.5 mL of CH_3CN at 50 °C open to air for 24 h. [b] Gram-scale

The N–O bond can act as a reactive functional group for transition metal-mediated cross-coupling reactions.[21] To explore the possibility for cross-coupling reactions, the

benzoylhydroxylamine **6-53** was acetylated and then underwent a copper-catalyzed arylation with phenylboronic acid in 62% over two steps (Scheme 6.9).



Scheme 6.10 Cross-Coupling of Hydroxylamine and Boronic Acid

This strategy enables the synthesis of complex γ–aminocarbonyl compounds in a modular fashion. Cleavage of the carbonyl group would lead to a secondary amine which can be further functionalized to a tertiary amine. This strategy would enable the functionalization of the amine with three different functional groups.

6.4 Summary

Herein we report a new method for the γ-hydroxylamination of enones through silyl dienol ethers. This provides access to valuable γ-aminoketones or γ-aminoesters from α,β-unsaturated ketones and esters. Critical to our success was generation of the nitroso through copper-catalyzed aerobic oxidation, which then presumably undergoes the Diels–Alder reaction with the silyl dienol ether. The transformation was uniformly regio- and diastereoselective across a range of substrates with varying steric bulk. We have demonstrated the utility of this method by converting the hydroxylamine to the tertiary amine.

6.5 Experimental Details

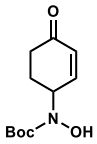
Unless otherwise stated, reactions were performed in oven–dried glassware under a N_2 atmosphere using dry, deoxygenated solvents. Anhydrous acetonitrile was purchased from Aldrich, degassed with argon, and dried by passage through activated drying columns[22] on a Pure Process Technology system. Starting materials, including 2-cyclohexen-1-one, were purchased from Aldrich, Alfa Aesar, or Oakwood Chemical and used as received. Deuterated chloroform ($CDCl_3$, 99.9%, extra dry) was purchased from Cambridge Isotope Laboratories, Inc. and was used without further purification. Reaction temperatures were controlled by an IKAmag immersion temperature modulator. Thin-layer chromatography (TLC) was performed using Silicycle silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or staining with *p*-anisaldehyde or $KMnO_4$ solutions. Flash chromatography[23] was performed using Silicycle SiliaFlash® P60 silica gel (40–63 μm particle size). Melting points were determined using a Mel-Temp electrothermal capillary melting point apparatus and the values reported are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 (at 500 and 126 MHz, respectively) or DPX-400 instrument (at 400 and 101 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, br s = broad singlet. Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). ^{19}F NMR spectra were recorded on a Bruker Avance DRX-400 at 376 MHz and are reported relative to the internal standard α,α,α-trifluorotoluene (δ –63.1 ppm). Infrared (IR) spectra were recorded on a Nicolet iS5 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). GC/MS analyses were performed on a Hewlett Packard Model

6890 gas chromatograph interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, H*P*-5MS). TBS-dienol ethers were synthesized by enolization with LiHMDS or by soft enolization according to our previous publication.[24] The tbutylcarbamate,[25] ethyl carbamate,[26] benzyl carbamate,[27] trifluoroethylcarbamate,[28] trichloroethyl carbamate[28] and benzyl hydroxylamine[29] were synthesized through previously reported methods.

Procedure for Cu-catalyzed hydroxylamination with stable dienol ethers:

Anhydrous $Cu(CH_3CN)_4 \cdot BF_4$ (7.9 mg, 0.025 mmol, 10 mol%) was added to an oven-dried 20 mL vial equipped with a magnetic stirring bar in the glovebox. The vial was sealed with a septum cap and transferred out of the glovebox. Anhydrous CH_3CN (2.5 mL), BocNHOH (50 mg, 1.5 equiv), bipy (7.8 mg, 0.0375mmol, 15 mol%), and TBS dienol ether (0.25 mmol, 1.0 equiv) were added into the vial sequentially. The septum was pierced with a needle so that it was open to air and the mixture was heated to 50 °C and stirred for 24 h. After the reaction was complete (monitored by TLC), the mixture was cooled to room temperature, and the solvent was removed under vacuum. The crude material was purified by flash column chromatography on silica gel.

V. Experimental Data for Hydroxylamines



6-30

***tert*-butyl hydroxy(4-oxocyclohex-2-en-1-yl)carbamate:**

The title compound **6-30** was prepared according to General Procedure, using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.5 mg, 0.25 mmol) and *tert*-butyl *N*-hydroxycarbamate **6-27** (50 mg, 0.375 mmol). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 2:1), the title compound **6-30** was isolated as a white solid.

1st run: 51.9 mg (91% yield)

2nd run: 50.1 mg (88% yield)

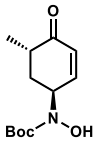
TLC (SiO_2) R_f = 0.21 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 6.89 (d, *J* = 9.5 Hz, 1H), 6.04 (dd, *J* = 9.5 Hz, *J* = 1.5 Hz, 1H), 4.83 (m, 1H), 2.59 (m, 1H), 2.40 (m, 1H), 2.13 (m, 1H), 1.46 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.4, 156.7, 150.1, 131.1, 82.9, 56.0, 36.9, 28.2, 25.6

IR (neat) 3261, 2978, 2938, 2872, 1682, 1626, 1460, 1376, 1187, 1099 cm^{-1}

HRMS (ES) *m/z* calc'd for $C_{11}H_{17}NO_4$ [M+Na] 250.1055, found 250.1046



6-34

tert-butyl hydroxy((1S,5S)-5-methyl-4-oxocyclohex-2-en-1-yl)carbamate:

The title compound **6-34** was prepared according to General Procedure, using *tert*-butyldimethyl((6-methylcyclohexa-1,3-dien-1-yl)oxy)silane **1-93** (56.1 mg, 0.25 mmol) and *tert*-Butyl N-hydroxycarbamate **6-27** (50 mg, 0.375 mmol). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1), the title compound **6-34** was isolated as a single diastereomer after purification as a yellow oil.

1st run: 41.3 mg (68% yield)

2nd run: 39.1 mg (66% yield)

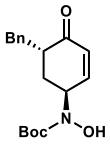
TLC (SiO_2) R_f = 0.34 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (br s, 1H), 6.82 (dd, *J* = 27.8 Hz, *J* = 10.0 Hz, 1H), 6.04 (d, *J* = 10.0 Hz, 1H), 4.89 (m, 1H), 2.82 (m, 1H), 2.44 (m, 1H), 2.18 (m, 1H), 1.95(m, 1H) 1.50 (s, 9H), 1.17 (t, *J* = 7.1 Hz)

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.1, 156.9, 146.8, 130.1, 82.8, 52.9, 39.1, 32.9, 28.4, 15.9

IR (neat) 3317, 3280, 2977, 2933, 1702, 1678, 1605, 1542, 1477, 1391, 1163 cm^{-1}

HRMS (ES) *m/z* calc'd for $C_{12}H_{19}NO_4Na$ [M+Na] 264.1212, found 264.1212



6-35

tert-butyl ((1S,5S)-5-benzyl-4-oxocyclohex-2-en-1-yl)(hydroxy)carbamate:

The title compound **6-35** was prepared according to General Procedure A, using *tert*-butyldimethyl((6-benzylcyclohexa-1,3-dien-1-yl)oxy)silane **1-93** (75.0 mg, 0.25 mmol) and *tert*-Butyl N-hydroxycarbamate **6-27** (50 mg, 0.375 mmol). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1), the title compound **6-35** was isolated as a single diastereomer after purification as a yellow oil.

1st run: 66.3 mg (84% yield)

2nd run: 67.3 mg (85% yield)

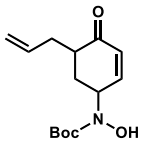
TLC (SiO_2) R_f = 0.37 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 6.84 (d, *J* = 10.0 Hz, 1H), 6.09 (d, *J* = 10.0 Hz, 1H), 4.94 (m, 1H), 3.04 (m, 1H), 2.93 (m, 1H), 2.65 (m, 1H), 2.33 (m, 1H) 1.86 (m, 1H), 1.45 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.1, 156.7, 148.9, 138.4, 130.4, 129.0, 128.5, 126.5, 82.9, 52.9, 46.4, 35.5, 39.1, 32.9, 28.6

IR (neat) 3329, 3003, 2978, 2932, 1710, 1674, 1603, 1478, 1365, 1163, 1090 cm^{-1}

HRMS (ES) *m/z* calc'd for $C_{18}H_{23}NO_4$ [M+Na] 340.1525, found 340.1522



6-36

tert-butyl (5-allyl-4-oxocyclohex-2-en-1-yl)(hydroxy)carbamate:

The title compound **6-36** was prepared according to General Procedure A, using *tert*-butyldimethyl((6-allylcyclohexa-1,3-dien-1-yl)oxy)silane **1-93** (62.5 mg, 0.25 mmol) and *tert*-Butyl N-hydroxycarbamate **6-27** (50 mg, 0.375 mmol). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1), the title compound **6-36** was isolated as a single diastereomer as a yellow oil.

1st run: 36.7 mg (55% yield)

2nd run: 40.3 mg (60% yield)

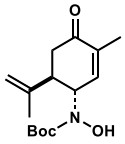
TLC (SiO_2) R_f = 0.42 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (br s, 1H), 6.82 (d, *J* = 9.7 Hz, 1H), 6.04 (d, *J* = 9.7 Hz, 1H), 5.76 (m, 1H), 5.10 (m, 2H), 4.88 (m, 1H), 2.72 (m, 1H), 2.43 (m, 2H), 2.20 (m, 1H), 2.04 (m, 1H) 1.49 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.4, 156.7, 148.0, 135.1, 130.6, 117.7, 82.8, 53.1, 44.1, 34.6, 29.4, 28.3

IR (neat) 3304, 3253, 3242, 3002, 2978, 2931, 1715, 1672, 1603, 1478, 1391, 1322, 1108 cm^{-1}

HRMS (ES) *m/z* calc'd for $C_{14}H_{21}NO_4$ [M+Na] 290.1368, found 290.1369



6-37

tert-butyl hydroxy((1S,6R)-3-methyl-4-oxo-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl)carbamate:

The title compound **6-37** was prepared according to General Procedure, (*S*)-*tert*-butyldimethyl((2-methyl-5-(pro*p*-1-en-2-yl)cyclohexa-1,3-dien-1-yl)oxy)silane **1-93** (66.0 mg, 0.25 mmol) and *tert*-Butyl N-hydroxycarbamate **6-27** (50 mg, 0.375 mmol). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1), the title compound **6-37** was isolated as a single diastereomer as a yellow oil.

1st run: 37.0 mg (61% yield)

2nd run: 37.5 mg (62% yield)

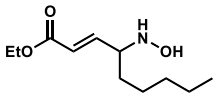
TLC (SiO_2) R_f = 0.18 in 5:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (s, 1H), 4.93 (s, 1H), 4.85 (m, 2H), 3.29 (m, 1H), 2.51 (m, 2H), 1.80 (s, 3H), 1.74 (s, 3H), 1.47 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.3, 156.3, 145.7, 142.6, 137.0, 115.0, 82.8, 58.7, 45.8, 41.6, 28.1, 18.8, 15.7

IR (neat) 3332, 3002, 2978, 2860, 1711, 1677, 1477, 1362, 116, 1101 cm^{-1}

HRMS (ES) *m/z* calc'd for $C_{10}H_{15}NO_2$ [M–Boc+Na] 182.1181, found 182.1183



6-39

ethyl (E)-4-(hydroxyamino)non-2-enoate:

The title compound **6-39** was prepared according to General Procedure, *tert*-butyl((1-ethoxynona-1,3-dien-1-yl)oxy)dimethylsilane **6-38** (74.6 mg, 0.25 mmol) and *tert*-Butyl N-hydroxycarbamate **6-27** (50 mg, 0.375 mmol). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 8:1), the title compound **6-39** was isolated as a yellow oil.

1st run: 19.5 mg (25% yield)

2nd run: 19.1 mg (24% yield)

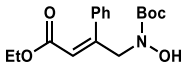
TLC (SiO_2) Rf = 0.32 in 5:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (dd, *J*= 6.2 Hz, *J* = 15.5 Hz, 1H), 6.75 (br s, 1H), 5.94 (d, *J*= 15.5 Hz, 1H), 4.53 (m, 1H), 4.19 (q, *J* = 7.3 Hz, 2 Hz), 1.87 (m, 1H), 1.47 (s, 9H), 1.28 (m, 9H), 0.88 (m, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 156.7, 145.3, 122.2, 82.4, 60.8, 59.5, 31.4, 30.8, 28.3, 25.6, 22.5, 14.2, 14.0

IR (neat) 3359, 3288, 2957, 2930, 2871, 1713, 1654, 1634, 1495, 1304, 1220 cm^{-1}

HRMS (ES) *m/z* calc'd for $C_{11}H_{21}NO_3$ [M–Boc] 214.1443, found 214.1445



6-41

ethyl (E)-4-((tert-butoxycarbonyl)(hydroxy)amino)-3-phenylbut-2-enoate:

The title compound **6-41** was prepared according to General Procedure, *tert*-butyl((1-ethoxy-3-phenylbuta-1,3-dien-1-yl)oxy)dimethylsilane **1-93** (76.0 mg, 0.25 mmol) and *tert*-Butyl N-hydroxycarbamate **6-27** (50 mg, 0.375 mmol). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 8:1), the title compound **6-41** was isolated as a yellow oil.

1st run: 24.5 mg (30% yield)

2nd run: 22.5 mg (28% yield)

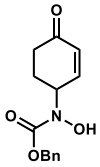
TLC (SiO_2) Rf = 0.24 in 5:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (m, 2H), 7.35 (m, 3H), 7.32 (m, 1H), 6.15 (s, 1H), 5.20 (s, 1H), 4.22 (q, *J*= 7Hz, 2H), 1.41 (s, 9H), 1.31 (t, *J*= 7Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 166.4, 155.9, 154.1, 149.2, 138.8, 137.1, 129.0, 128.5, 127.3, 123.7, 121.2, 82.1, 60.3, 48.8, 28.0, 14.3

IR (neat) 3309, 3061, 3026, 2980, 2933, 2874, 2858, 1749, 1731, 1710, 1661, 1616, 1448, 1219, 1079 cm^{-1}

HRMS (ES) *m/z* calc'd for $C_{12}H_{14}NO_3$ [M–Boc] 220.1013, found 220.0612



6-45

benzyl hydroxy(4-oxocyclohex-2-en-1-yl)carbamate:

The title compound **6-45** was prepared according to General Procedure, using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.5 mg, 0.25 mmol) and benzyl hydroxycarbamate **6-44** (62.7 mg, 0.375 mmol). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 2:1), the title compound **6-45** was isolated as a yellow oil.

1st run: 35.3 mg (54% yield)

2nd run: 33.9 mg (52% yield)

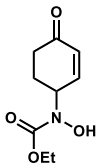
TLC (SiO_2) R_f = 0.23 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.35 (s, 5H), 6.84 (d, *J* = 9.5 Hz, 1H), 6.06 (dd, *J* = 9.5, 2.3 Hz, 1H), 5.20 (s, 2H), 4.94 (m, 1H), 2.58 (m, 1H), 2.40 (m, 2H), 2.12 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.6, 157.4, 149.9, 135.4, 131.4, 128.7, 128.6, 128.2, 68.2, 56.3, 35.9, 26.2

IR (neat) 3269, 2953, 1682, 1661, 1497, 1402, 1284, 1092, 1029 cm^{-1}

HRMS (ES) *m/z* calc'd for $C_{14}H_{15}NO_4$ [M+Na] 284.0899, found 284.0896



6-47

ethyl hydroxy(4-oxocyclohex-2-en-1-yl)carbamate:

The title compound **6-47** was prepared according to General Procedure, using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.5 mg, 0.25 mmol) and ethyl hydroxycarbamate **6-46** (39.4 mg, 0.375 mmol). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 2:1), the title compound **6-47** was isolated as a white solid.

1st run: 31.6 mg (63% yield)

2nd run: 29.4 mg (59% yield)

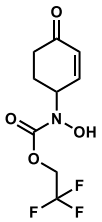
TLC (SiO_2) R_f = 0.125 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (br s, 1H), 6.90 (d, *J* = 9.8 Hz, 1H), 6.08 (dd, *J* = 9.8, 2.1 Hz, 1H), 4.94 (m, 1H), 4.23 (q, *J* = 7.2, 2H), 2.63 (m, 1H), 2.43 (m, 2H), 2.17 (m, 1H), 1.30 (t, *J* = 7.2, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.6, 158.0, 150.2, 130.8, 63.0, 55.8, 36.2, 25.9, 14.4

IR (neat) 3272, 2979, 2934, 1681, 1656, 1512, 1444, 1377, 1212, 1096 cm^{-1}

HRMS (ES) *m/z* calc'd for $C_9H_{14}NO_4$ [M+H] 200.0923, found 200.0924



6-49

2,2,2-trifluoroethyl hydroxy(4-oxocyclohex-2-en-1-yl)carbamate:

The title compound **6-49** was prepared according to General Procedure A, using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.5 mg, 0.25 mmol) and 2,2,2-

trifluoroethyl hydroxycarbamate **6-48** (59.6 mg, 0.375 mmol). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 2:1), the title compound **6-49** was isolated as a white solid.

1st run: 32.9 mg (43% yield)

2nd run: 34.9 mg (46% yield)

TLC (SiO_2) R_f = 0.23 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

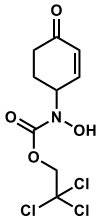
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (br s, 1H), 6.89 (d, J = 10.3 Hz, 1H), 6.13 (dd, J = 10.3, 2.3 Hz, 1H), 5.00 (m, 1H), 4.58 (m, 3H), 2.67 (m, 1H), 2.47 (m, 2H), 2.22 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7, 155.8, 148.9, 131.3, 122.8 (q, J_{C-F} = 283.1 Hz), 62.0 (q, J_{C-F} = 35.9 Hz), 56.0, 35.8, 26.2

^{19}F NMR (376 MHz, $CDCl_3$) δ –74.7 (t, J = 7.6 Hz, 3F)

IR (neat) 3291, 3190, 3003, 2956, 2933, 2926, 1742, 1709, 1686, 1667, 1454, 1408, 1057 cm^{-1}

HRMS (ES) *m/z* calc'd for $C_9H_{11}NO_4F_3$ [M+H] 254.0640, found 254.0634



6-51

2,2,2-trichloroethyl hydroxy(4-oxocyclohex-2-en-1-yl)carbamate:

The title compound **6-51** was prepared according to General Procedure, using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.5 mg, 0.25 mmol) and 2,2,2-trichloroethyl *N*-hydroxycarbamate **6-50** (78.2 mg, 0.375 mmol). After purification by flash

chromatography (SiO_2, hexanes/EtOAc = 2:1), the title compound **6-51** was isolated as a white solid.

1st run: 31.2 mg (51% yield)

2nd run: 29.5 mg (47% yield)

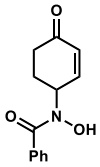
TLC (SiO_2) R_f = 0.25 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (br s, 1H), 6.94 (d, *J*= 10.7 Hz, 1H), 6.14 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.03 (m, 1H), 4.82 (q, *J* = 14.3 Hz, 2H), 2.67 (m, 1H), 2.47 (m, 2H), 2.27 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.2, 155.2, 148.9, 131.3, 94.7, 75.5, 56.3, 36.2, 26.2

IR (neat) 3267, 2958, 2933, 2926, 1743, 1709, 1686, 1666, 1408, 1112 cm^{-1}

HRMS (ES) *m/z* calc'd for $C_9H_{10}NO_4Cl_3$ [M+] 301.9754, found 301.9747



6-53

N-hydroxy-N-(4-oxocyclohex-2-en-1-yl)benzamide

The title compound **6-53** was prepared according to General Procedure, using *tert*-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane **1-93** (52.5 mg, 0.25 mmol) and *N*-hydroxybenzamide **6-52** (78.2 mg, 0.375 mmol). After purification by flash chromatography (SiO_2, hexanes/EtOAc = 2:1), the title compound **6-53** was isolated as a white solid.

1st run: 39.9 mg (69% yield)

2nd run: 38.7 mg (67% yield)

TLC (SiO_2) Rf = 0.09 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

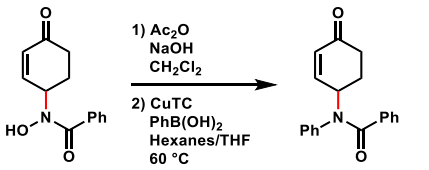
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (br s, 1H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.63 (dd, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.00 (dt, *J* = 10.3, 2.2 Hz, 1H), 6.04 (d, *J* = 10.3, 2.2 Hz, 1H), 5.28 (m, 1H), 2.59 (m, 2H), 2.35 (m, 1H), 2.17 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.3, 148.9, 132.3, 131.7, 131.3, 128.8, 127.8, 126.9, 116.4, 56.6, 36.3, 26.6

IR (neat) 3207, 2956, 2940, 2868, 1704, 1687, 1659, 1640, 1567, 1525, 1386, 1249, 1017 cm^{-1}

HRMS (ES) *m/z* calc'd for $C_{13}H_{14}NO_3$ [M+H] 232.0974, found 232.0966

Synthesis of Tertiary **Amine**



To an oven-dried flask was added the *N*-Benzoyl hydroxylamine **6-53** (115.6 mg, 0.50 mmol) in 1.9 mL CH_2Cl_2. Then 2 M aq NaOH (0.37 mL, 0.75 mmol, 1.25 equiv) was added. After 10 min, acetic anhydride (71 µL, 0.75 mmol, 1.25 equiv) was added. After 8 h, the two phase were separated and the aqueous reaction was extracted with 2 x 10 mL CH_2Cl_2. The combined organic phases were washed with brine (1 x 10 mL), dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated in vacuo. The crude material was used in the next step without purification.

Anhydrous Cu(Tc) (91.5 mg, 0.48 mmol, 1 equiv) and $PhB(OH)_2$ (70 mg, 0.57 mmol, 1.2 equiv) were added to an oven-dried 20 mL vial equipped with a magnetic stirring bar in the glovebox.[21a] The vial was sealed with a septum cap and transferred out of the glovebox. The *O*-acetyl hydroxylamine in 12 mL THF was added to the vial. The mixture was heated to 60 °C and stirred for 24 h. After the reaction was complete (monitored by TLC), the mixture was cooled to room temperature, and the solvent was removed under vacuum. The crude material was purified by flash column chromatography on silica gel and the product **6-54** was isolated (90.5 mg, 0.31 mmol, 62%).

TLC (SiO_2) Rf = 0.15 in 2:1 hexanes/EtOAc, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.2 Hz, 2H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.39 (dd, *J* = 7.2, 7.2 Hz, 2H), 6.86 (m, 2H), 6.01 (dd, *J* = 10.3, 2.5 Hz, 1H), 5.04 (m, 1H), 2.53 (m, 2H), 2.37 (m, 1H), 2.02 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.5, 167.4, 151.0, 135.6, 133.7, 132.9, 132.2, 131.9, 130.3, 128.6, 127.9, 127.4, 127.1, 46.2, 36.3, 29.9

IR (neat) 3056, 1677, 1642, 1602, 1578, 1529, 1488 cm^{-1}

GC/MS (*m/z*): 291.1 (5%), 215.0 (10%), 159.0 (8%), 122.0 (40%), 105.0 (100%), 94.0 (10%), 77.1 (60%), 66.1 (5%), 51.0 (8%)

6.6 Notes and References

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The rate of ring opening for β-lactam is 2.37×10^{-4} $M^{-1}s^{-1}$ compared to 5.59×10^{-6} $M^{-1}s^{-1}$ for γ-lactams.

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[18] This was verified by NOE experiment which showed correlation between the γ-proton and the methyl protons. We expect that the other α'-substituted cyclohexenones would be analogous.

[19] The acyclic silyl ketene acetals were more unstable than the cyclic silyl dienol ethers and the hydroxylamination reaction hydrolyzed the acyclic silyl ketene acetals rapidly.

[20] Notes: (a) The isomer was verified by the *J*-Coupling (*J* = 15.8 Hz). (b) Isophorone-derived silyl dienol ethers and other silyl dienol ethers locked in the s-*trans* conformation could not undergo the reaction.

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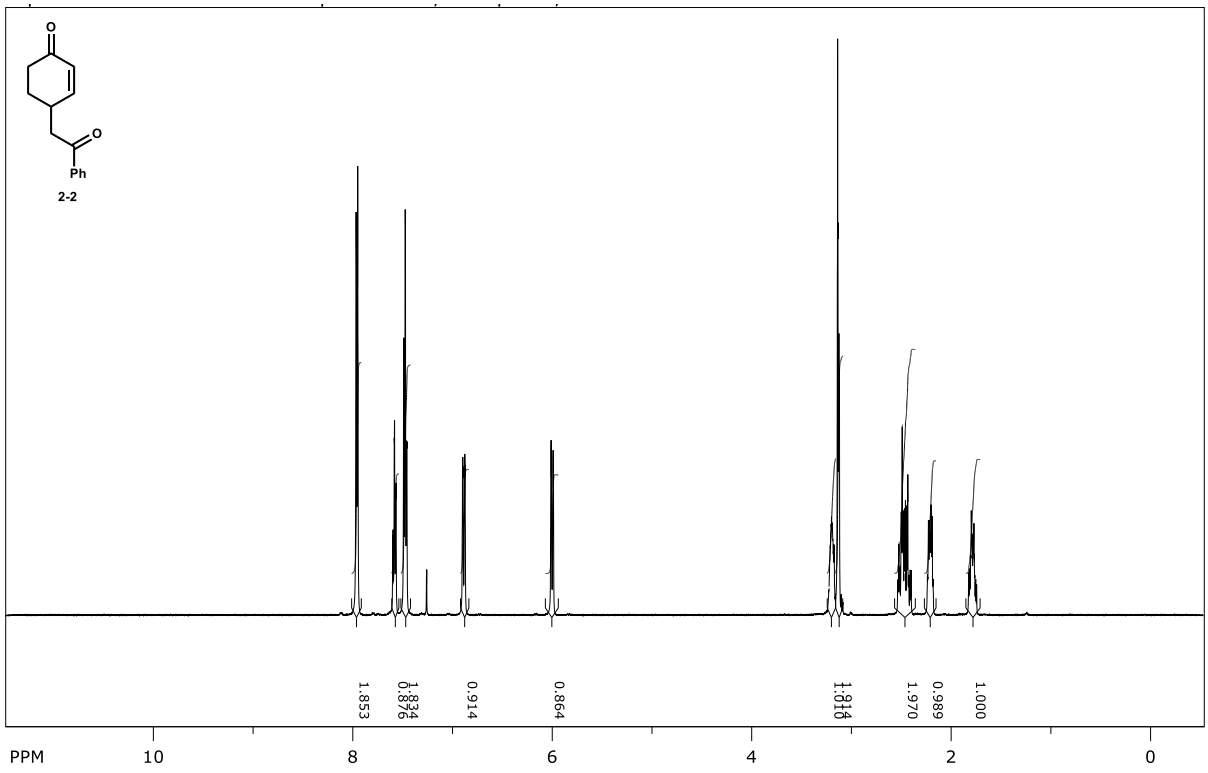
APPENDIX 1: SELECTED NMR SPECTRA



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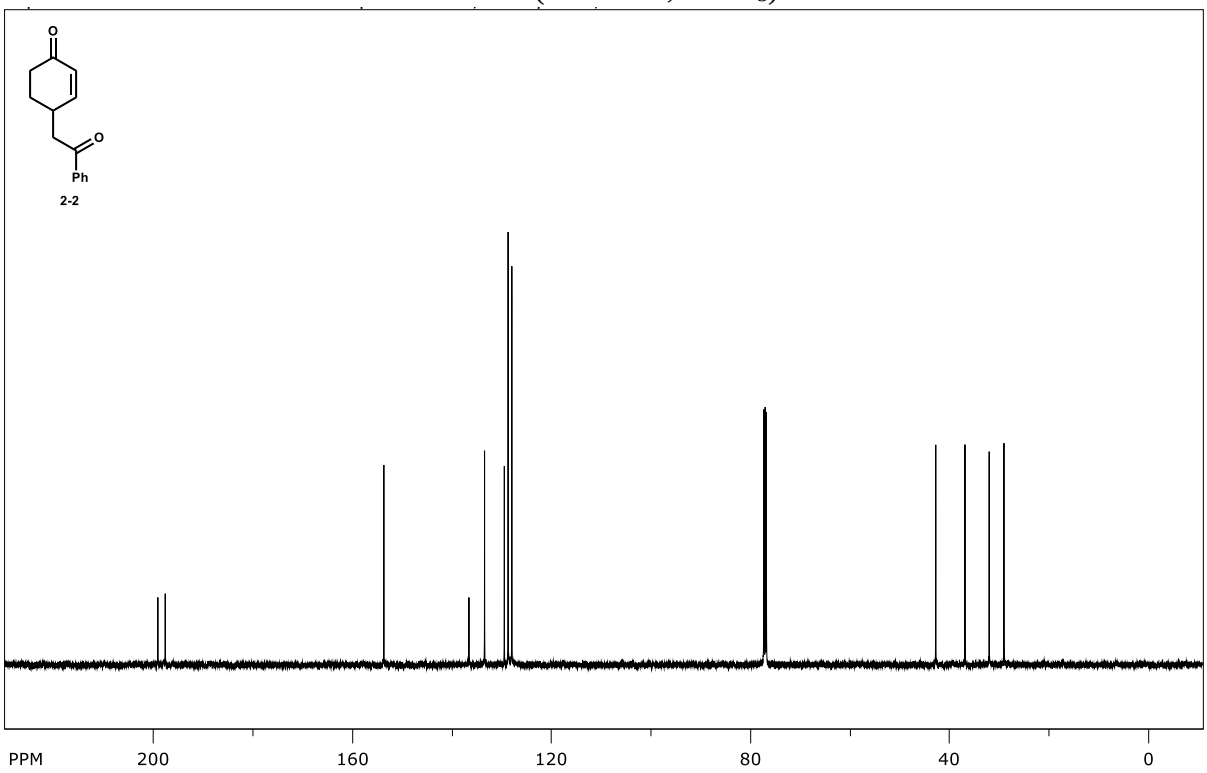

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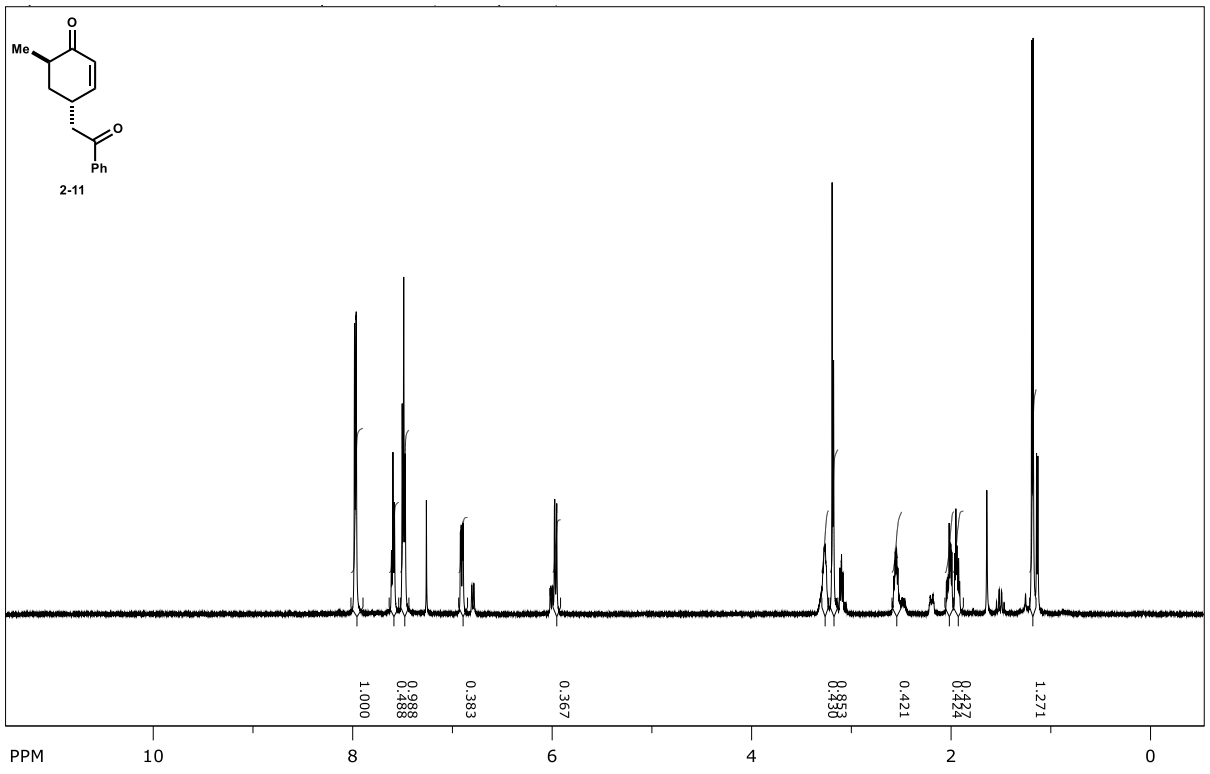

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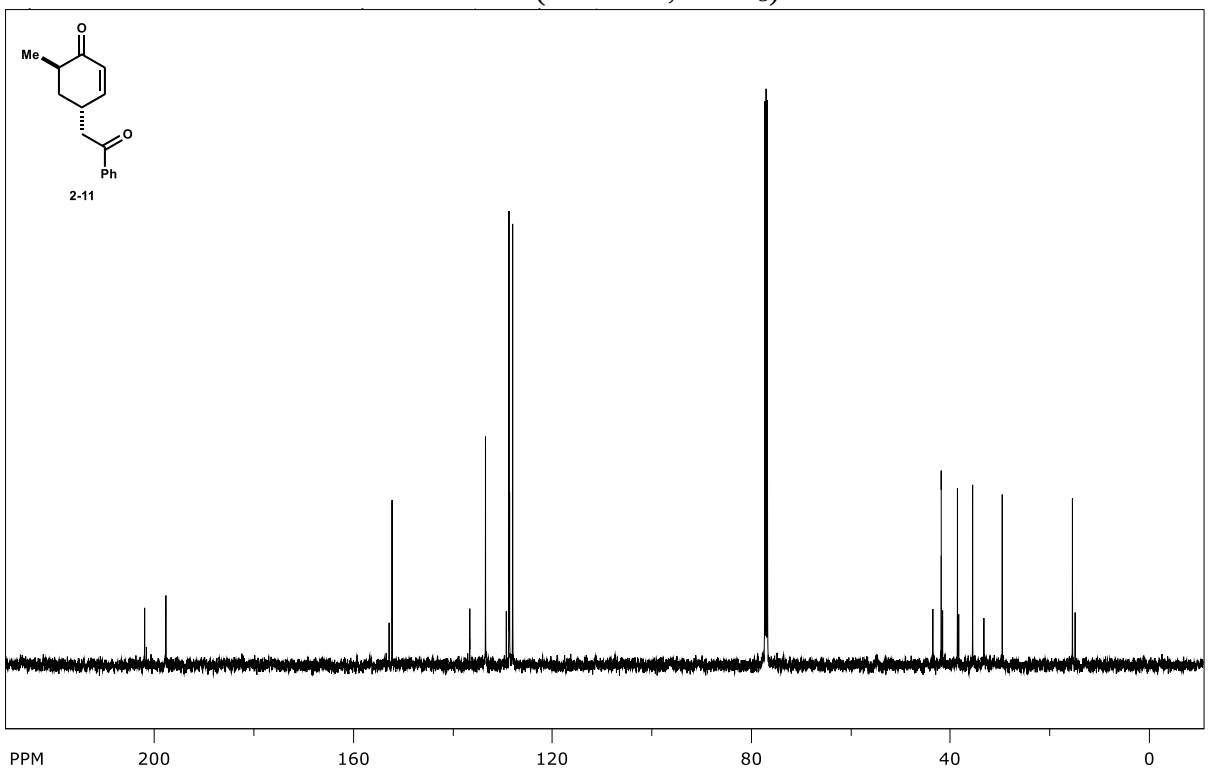

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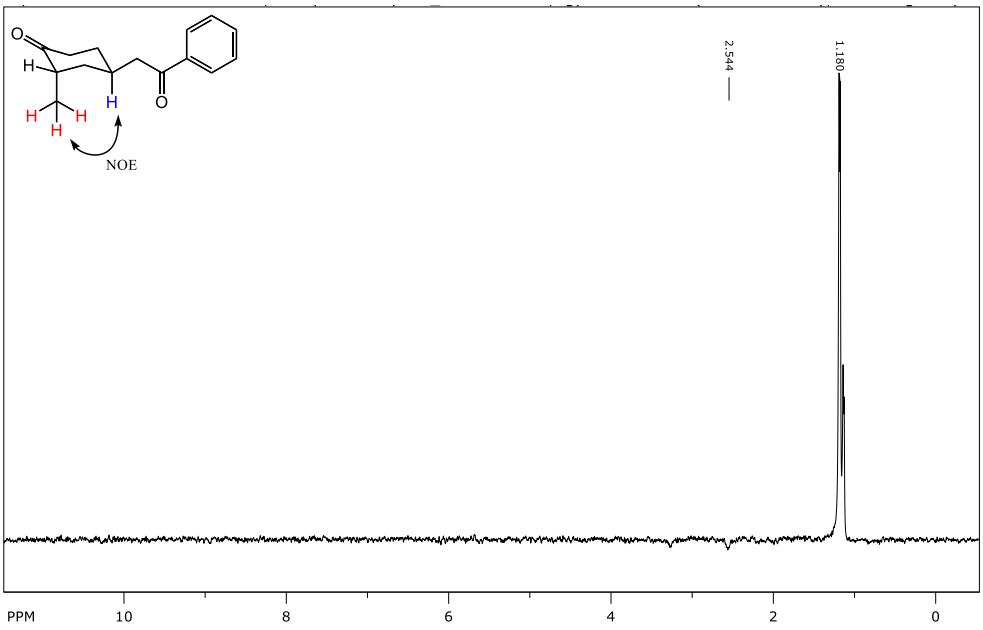
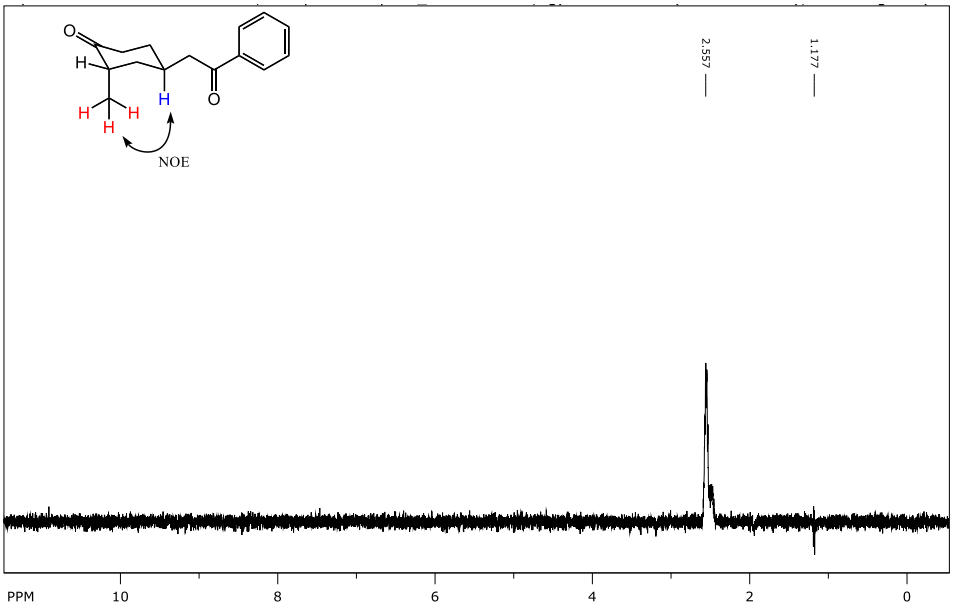
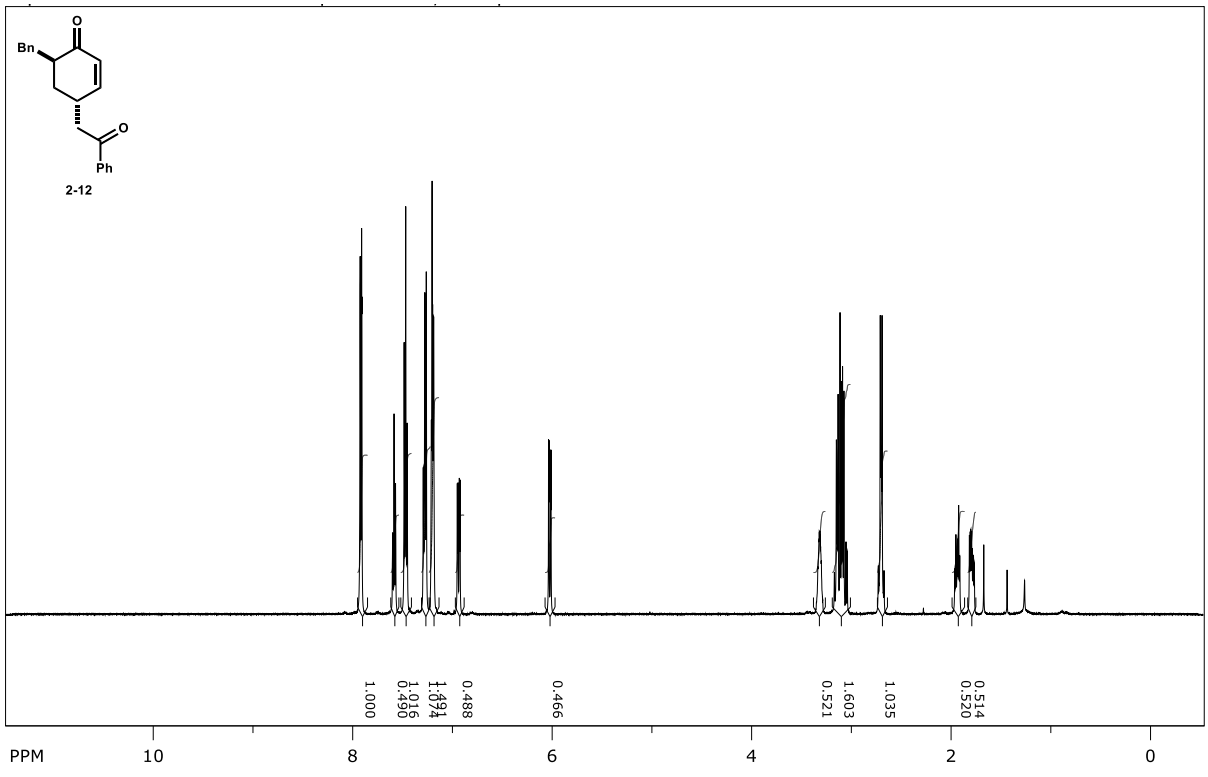


NOE (2.544 pm)



NOE (1.18 ppm)



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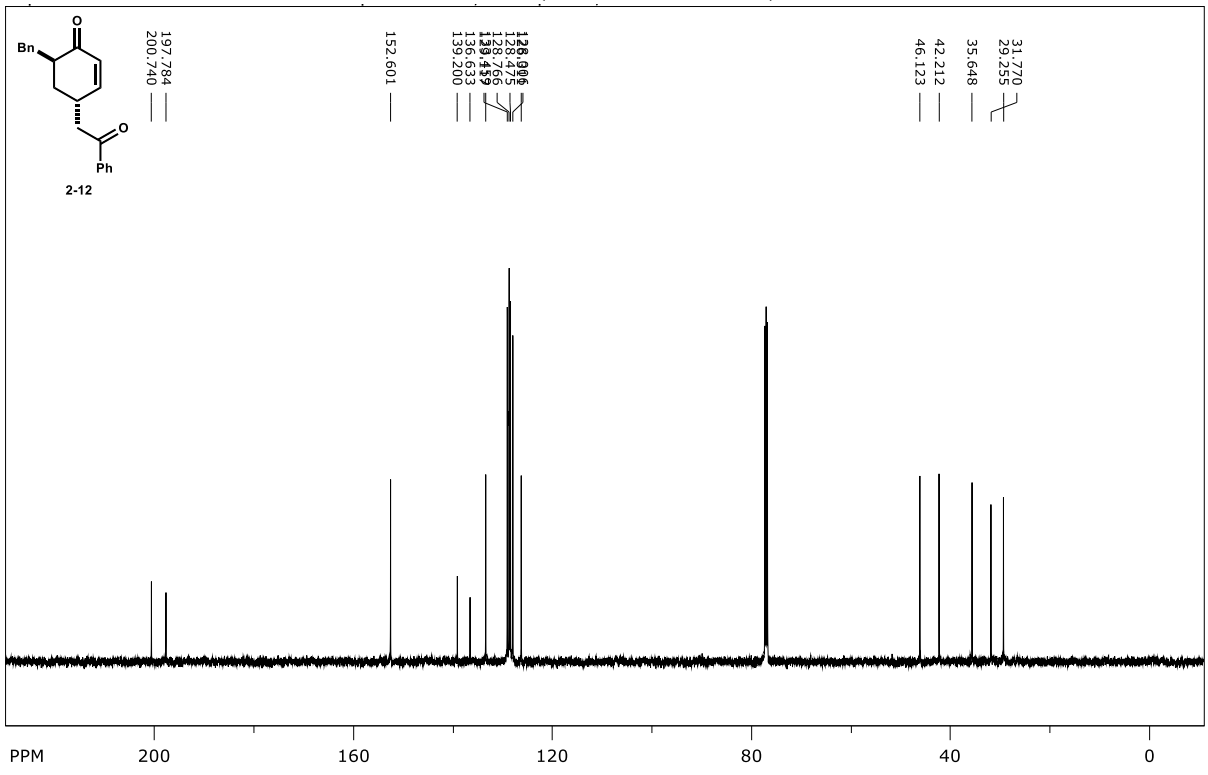

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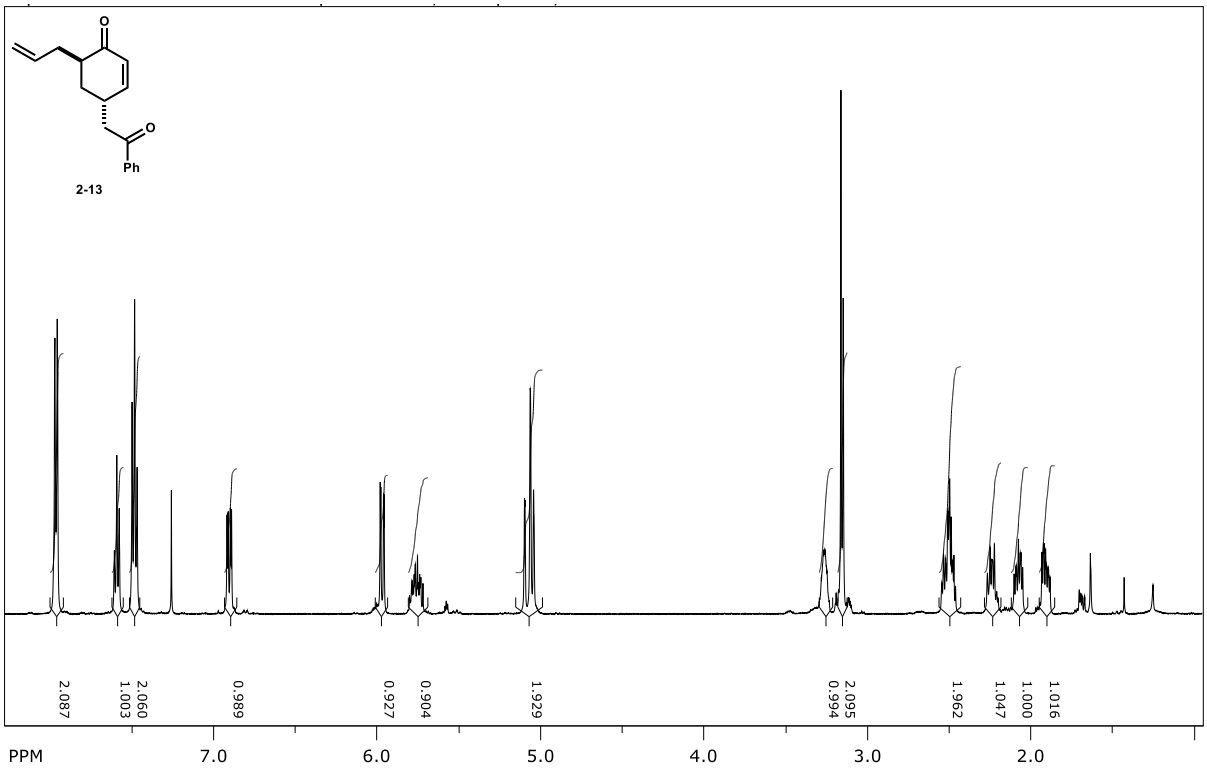

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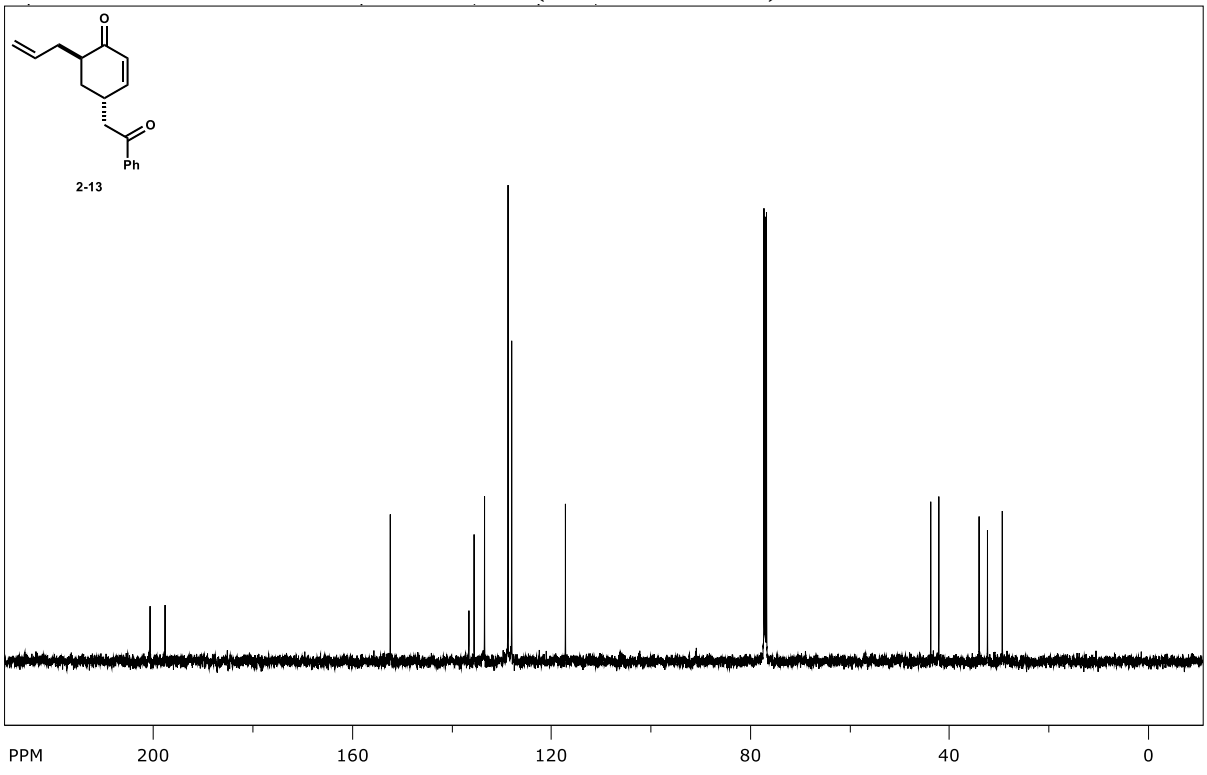

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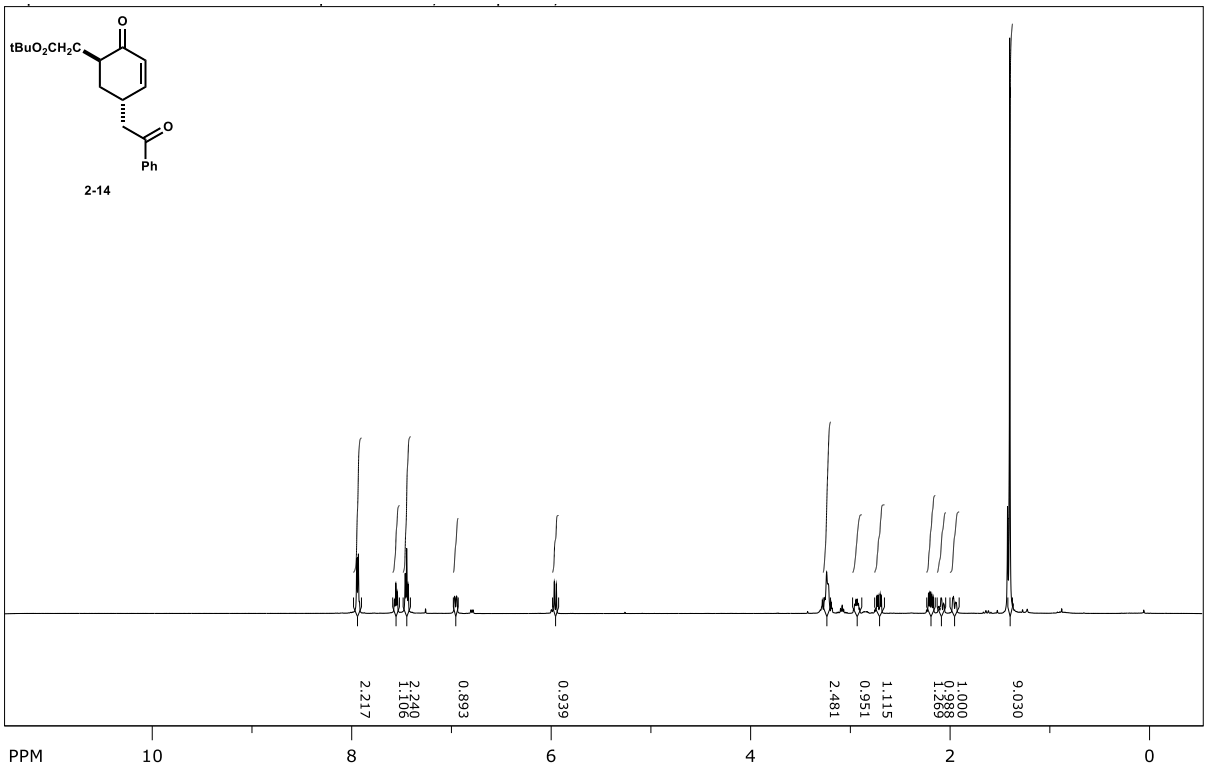

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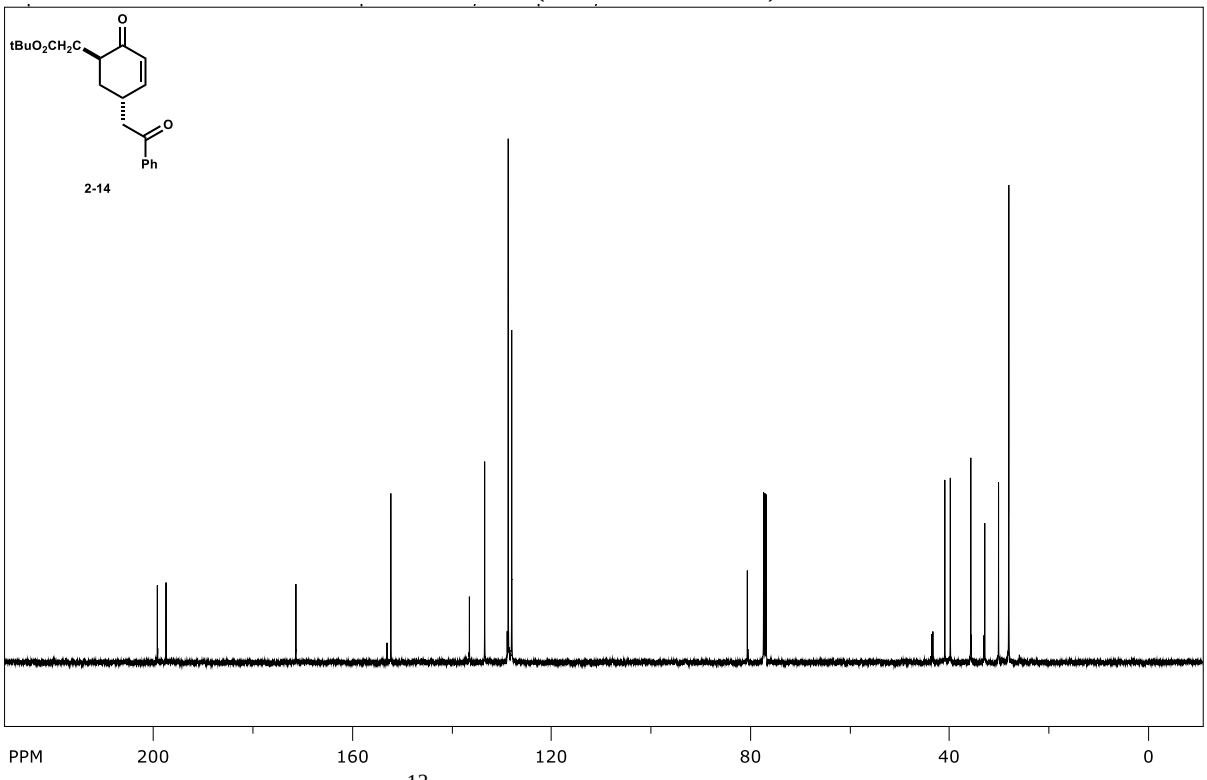

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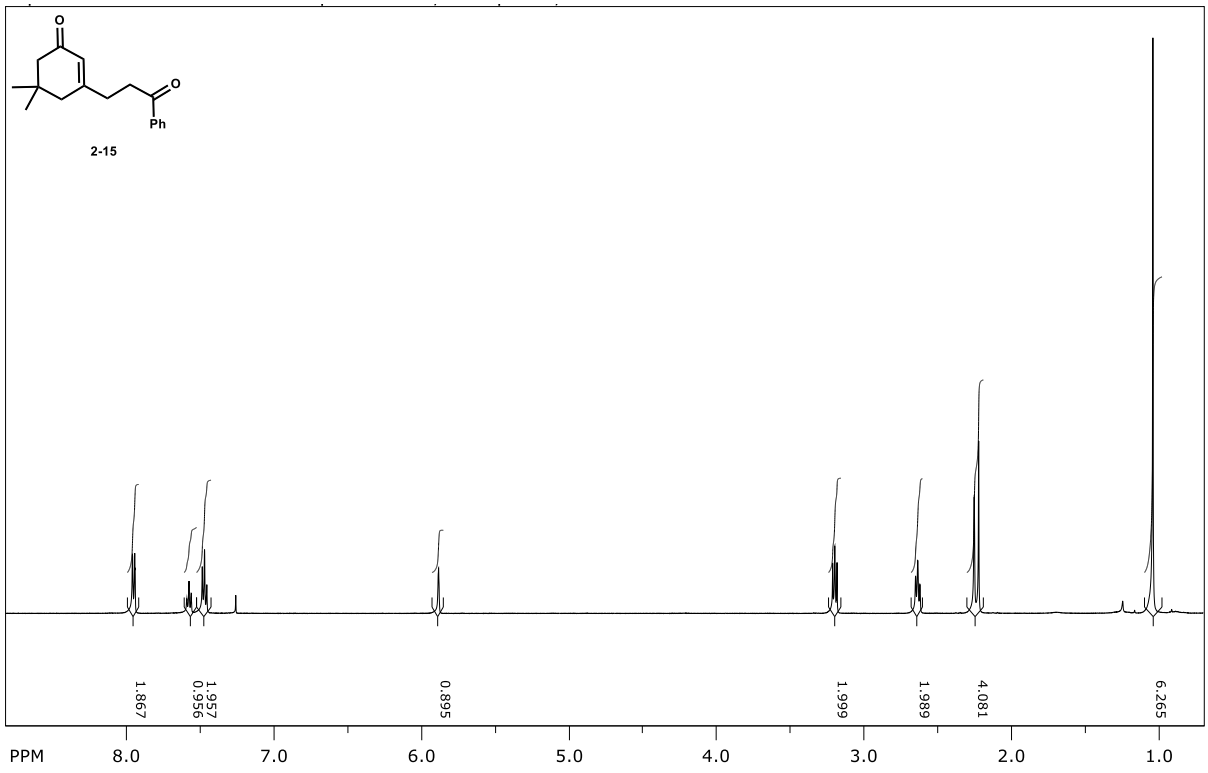

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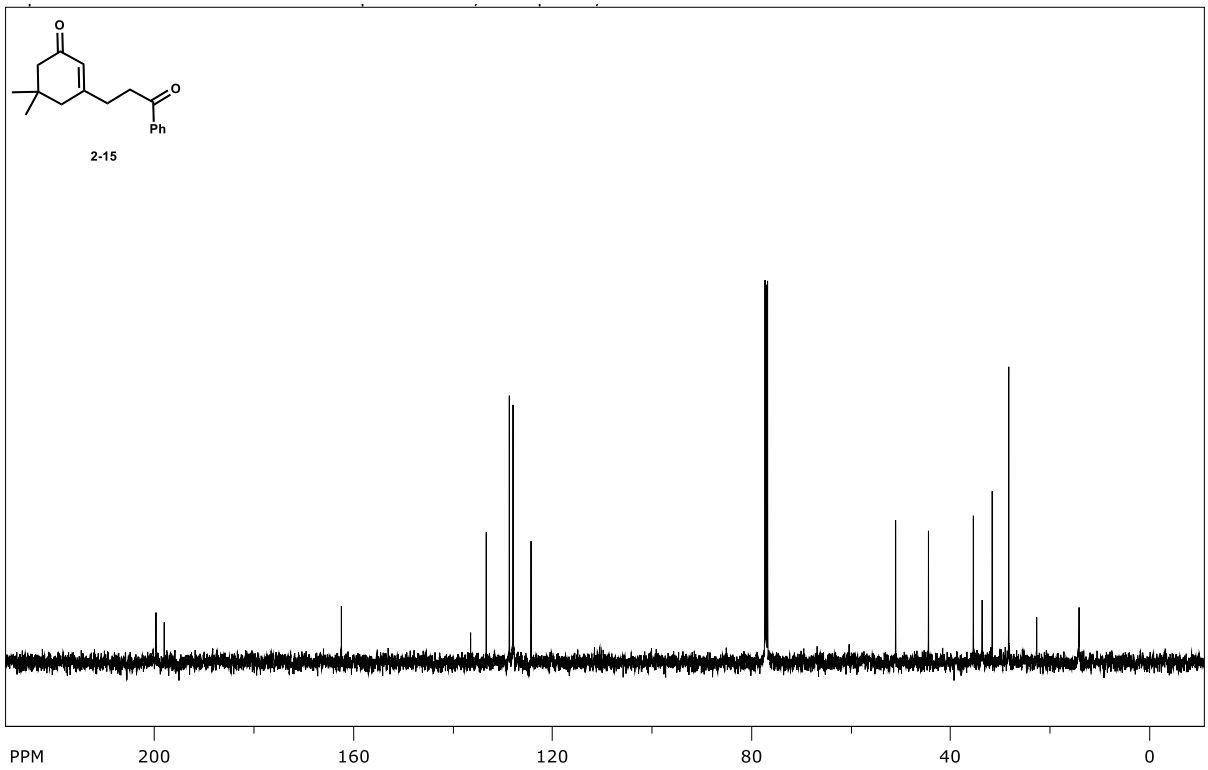

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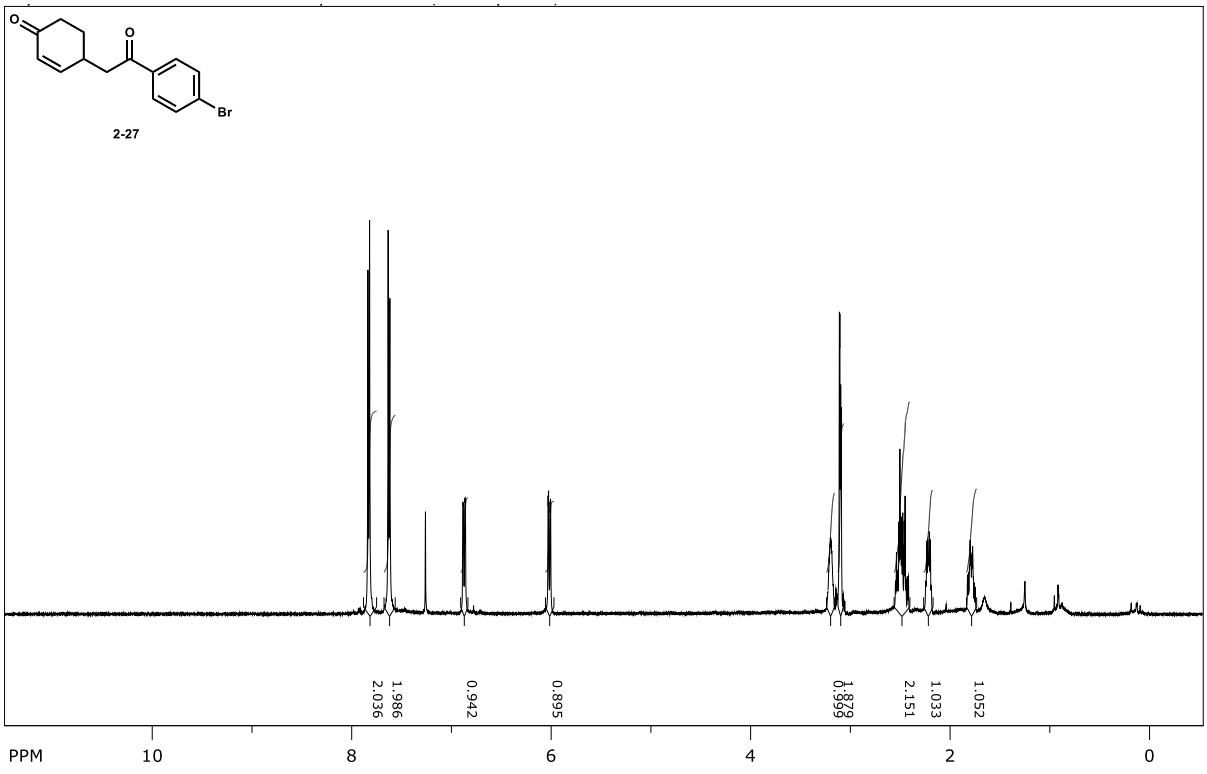

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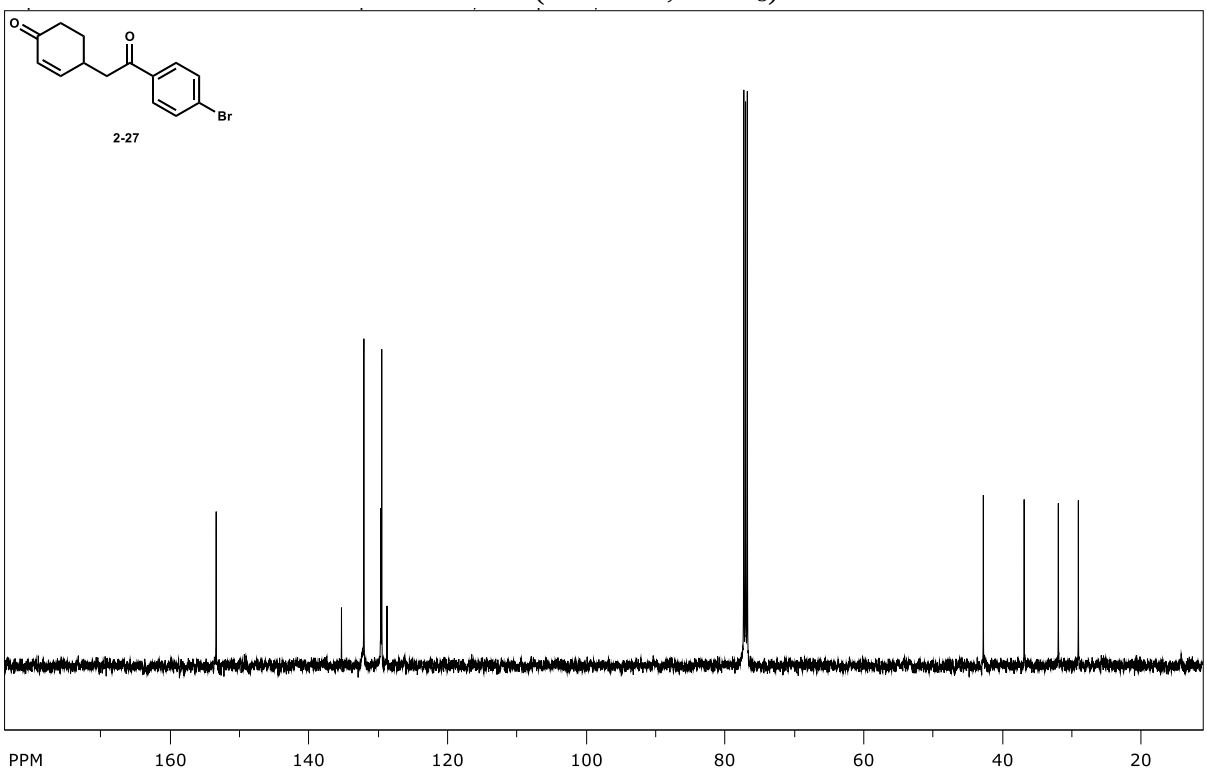

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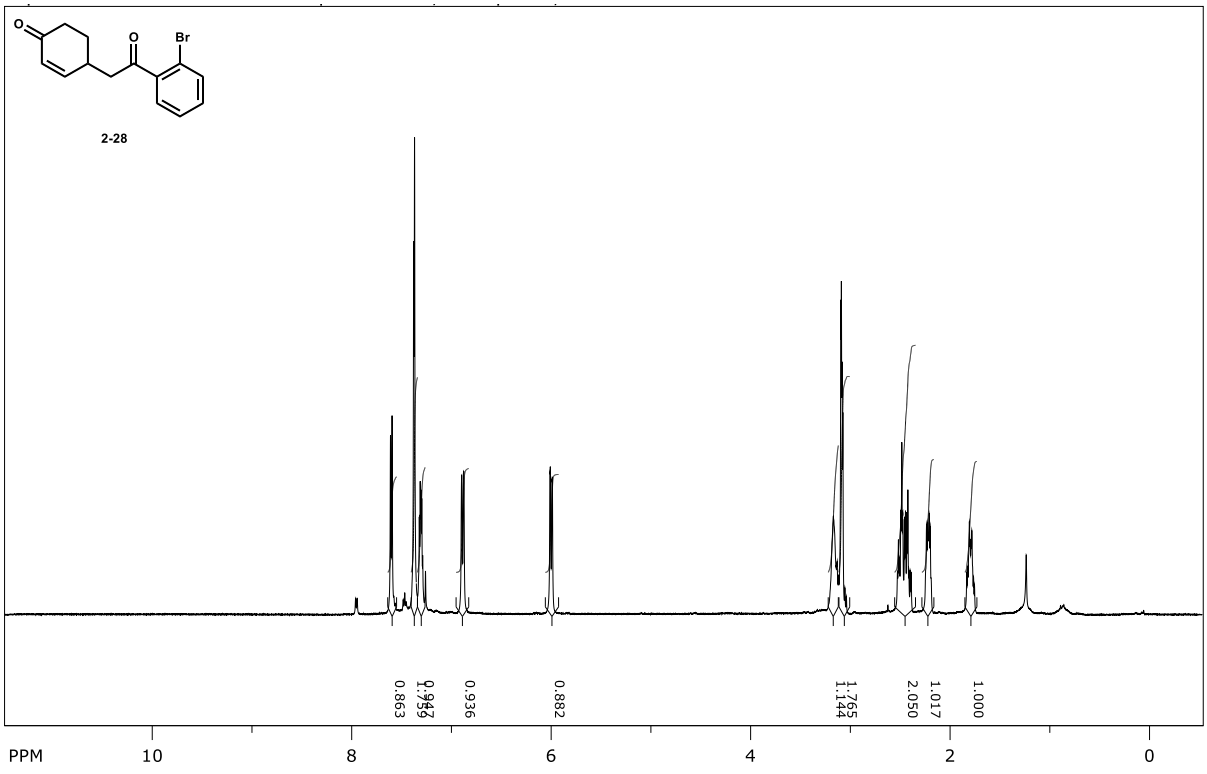

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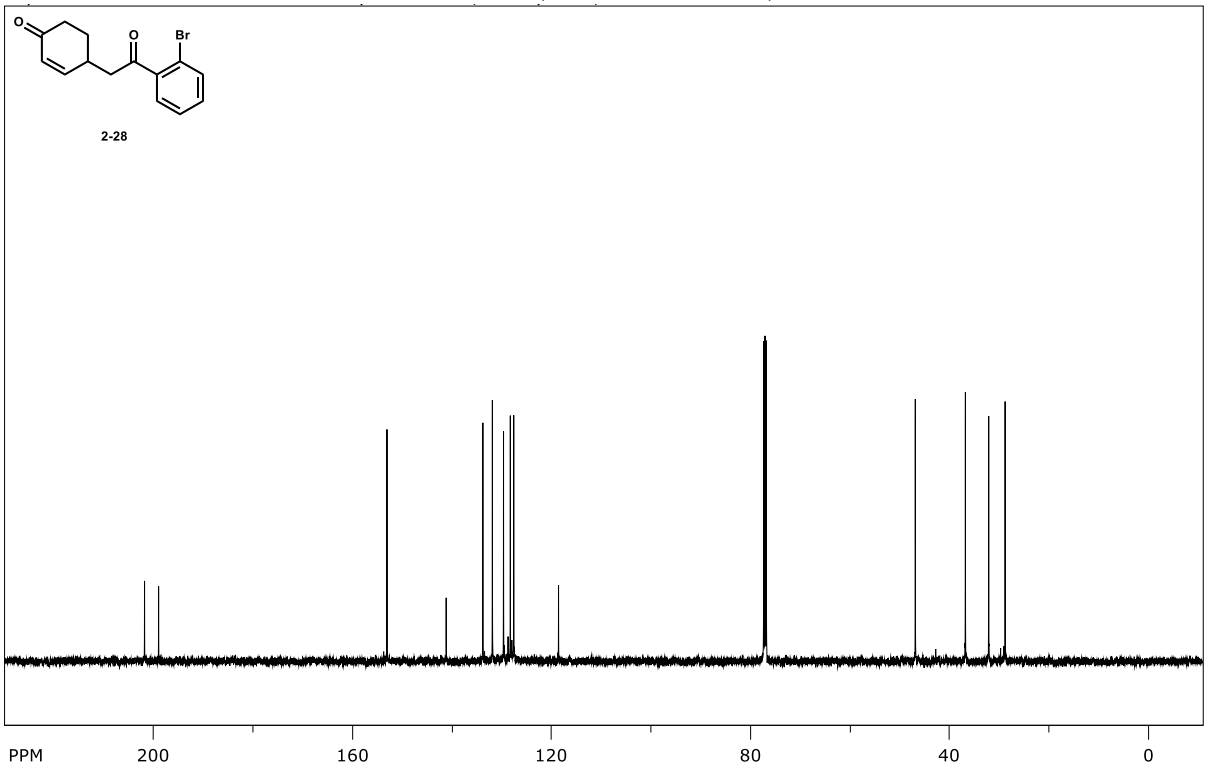

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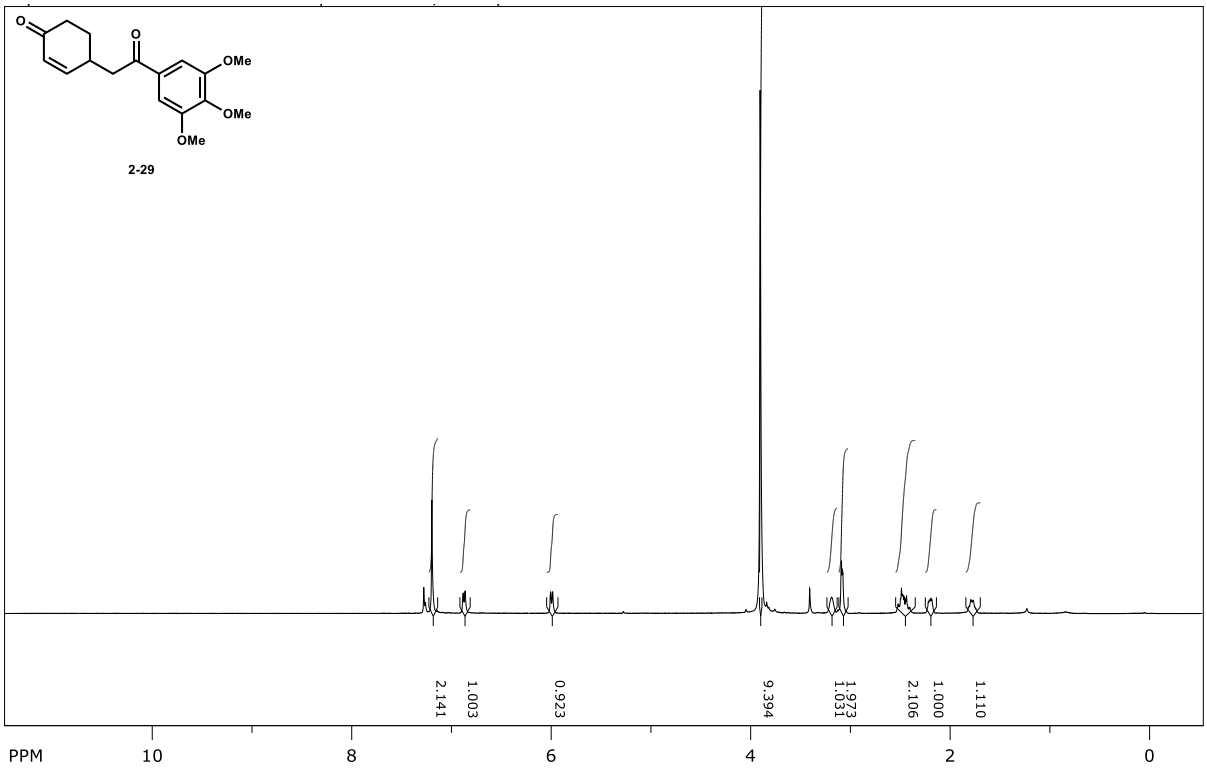

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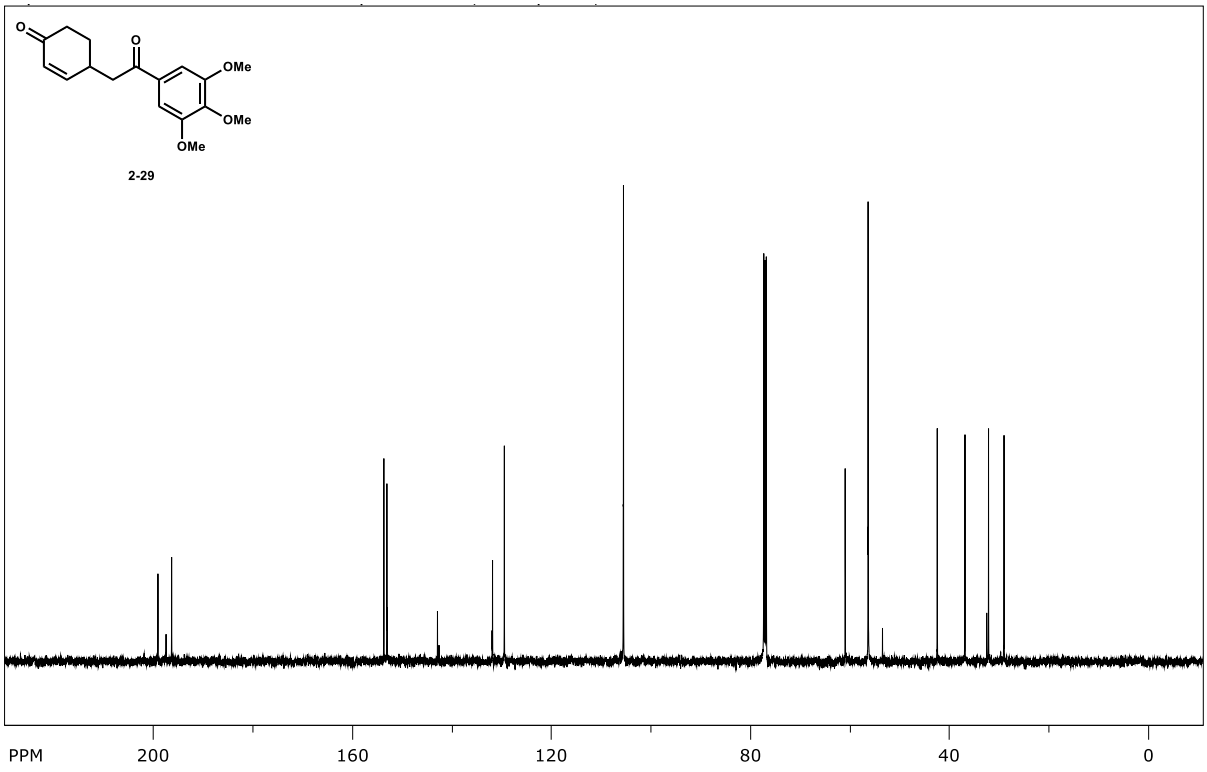

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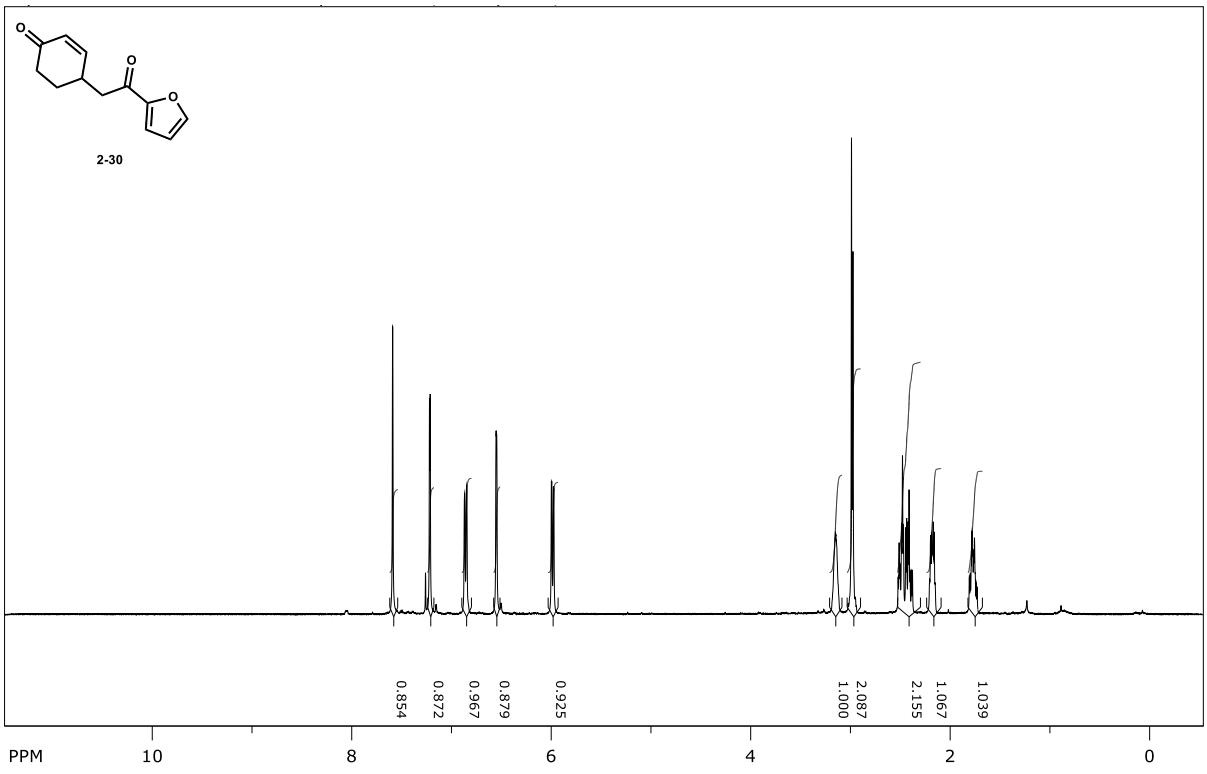

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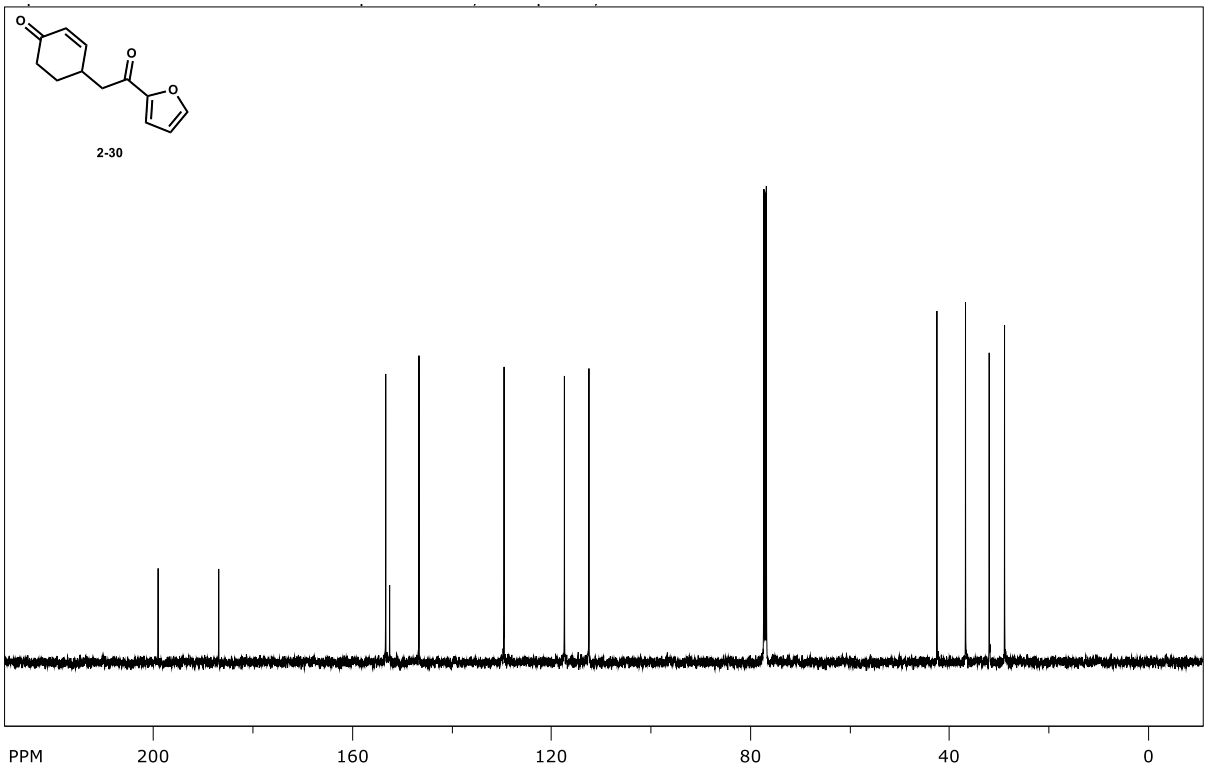

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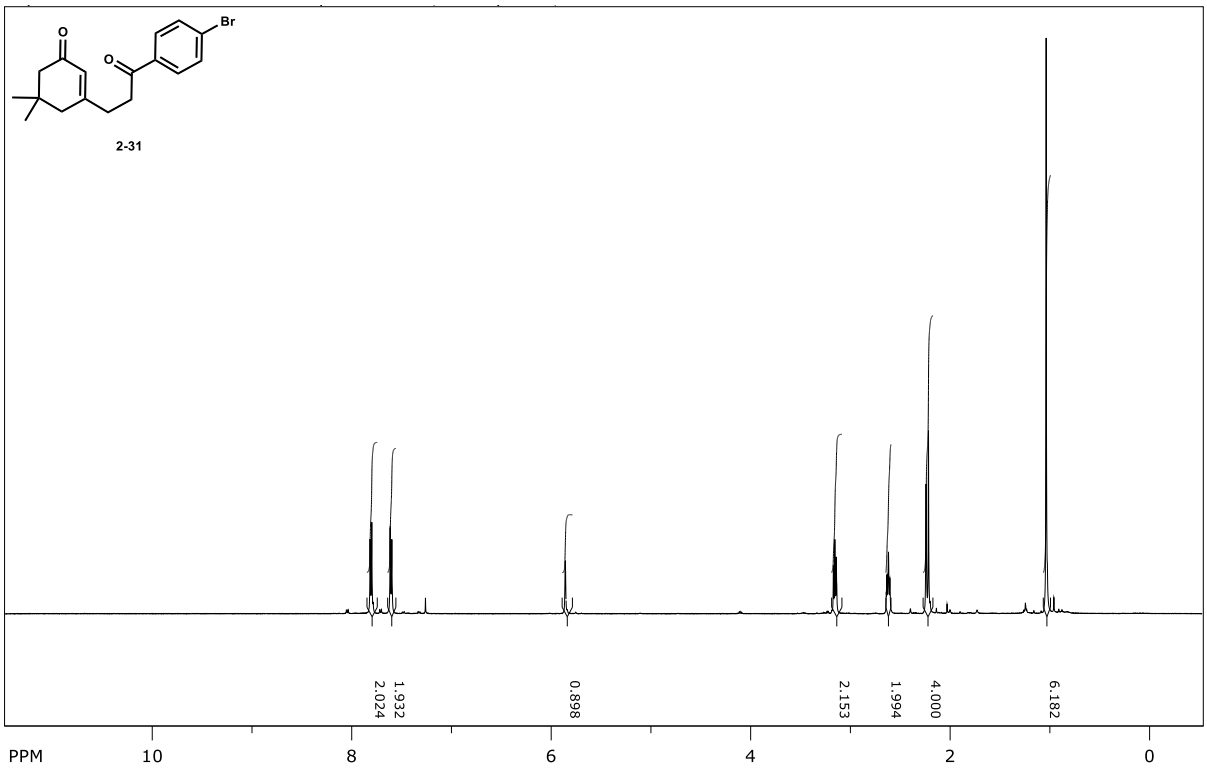

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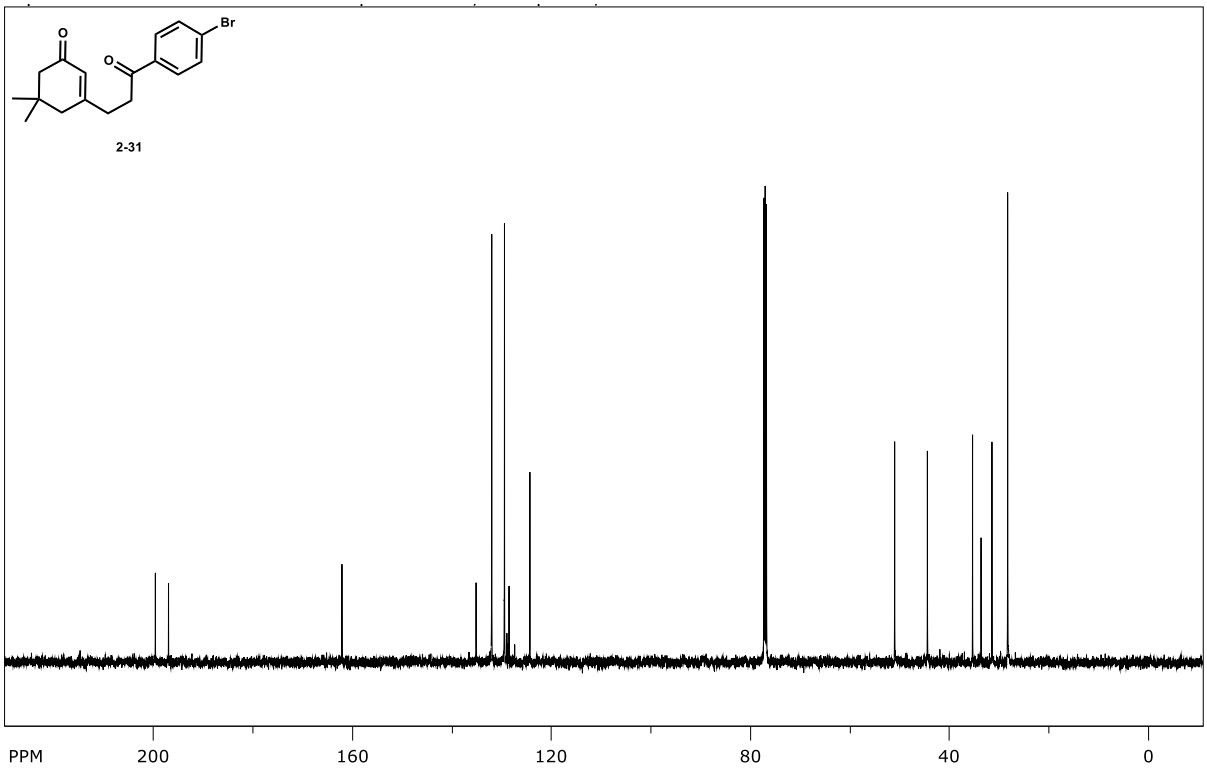

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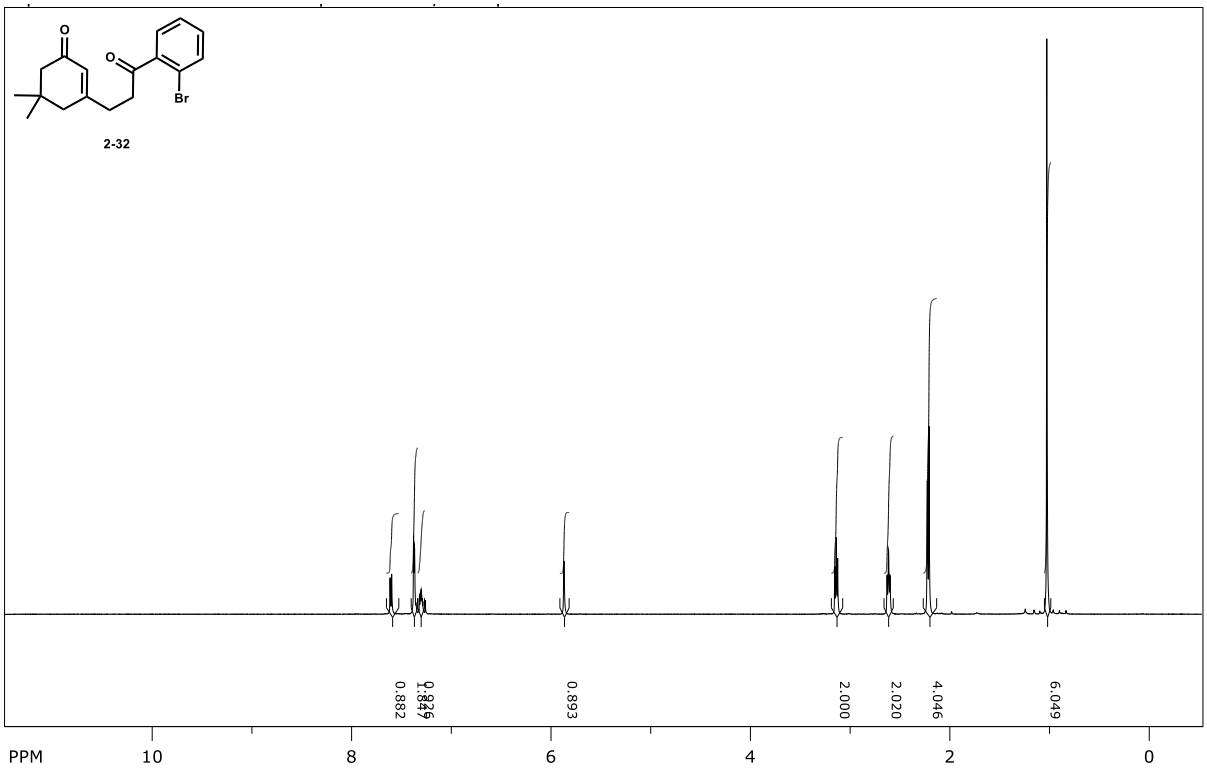

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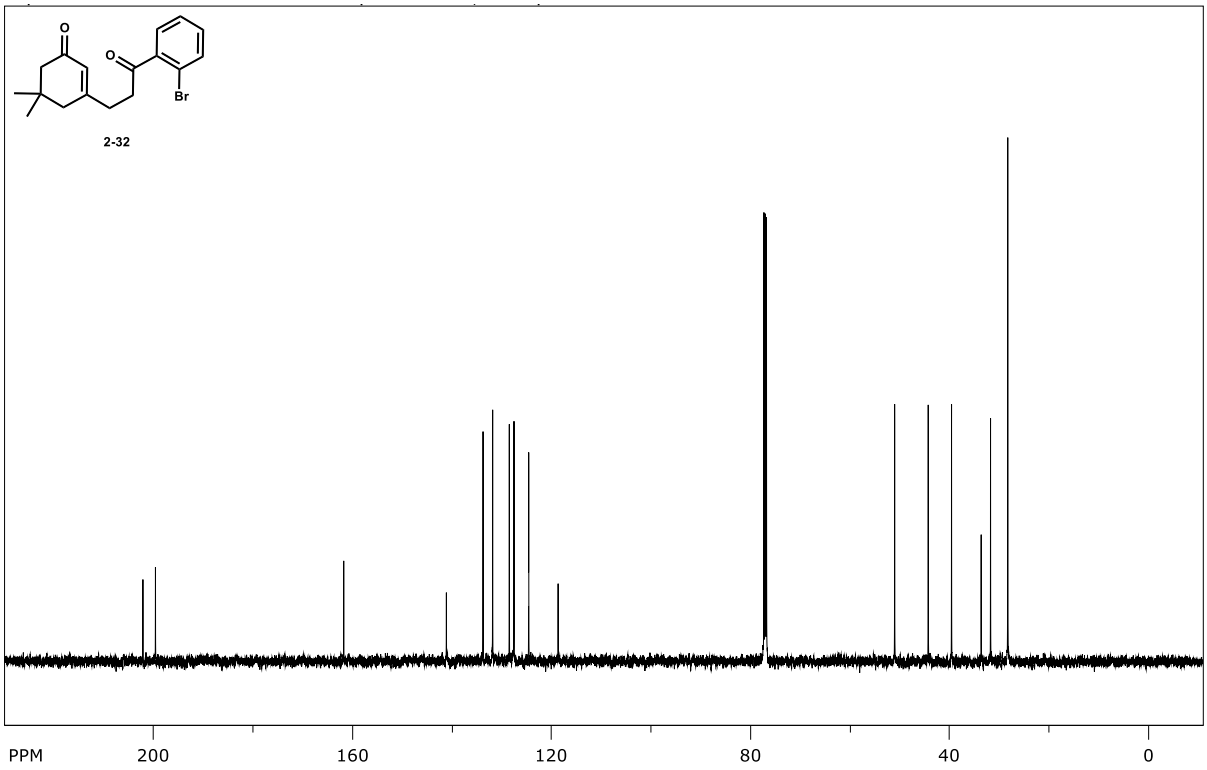

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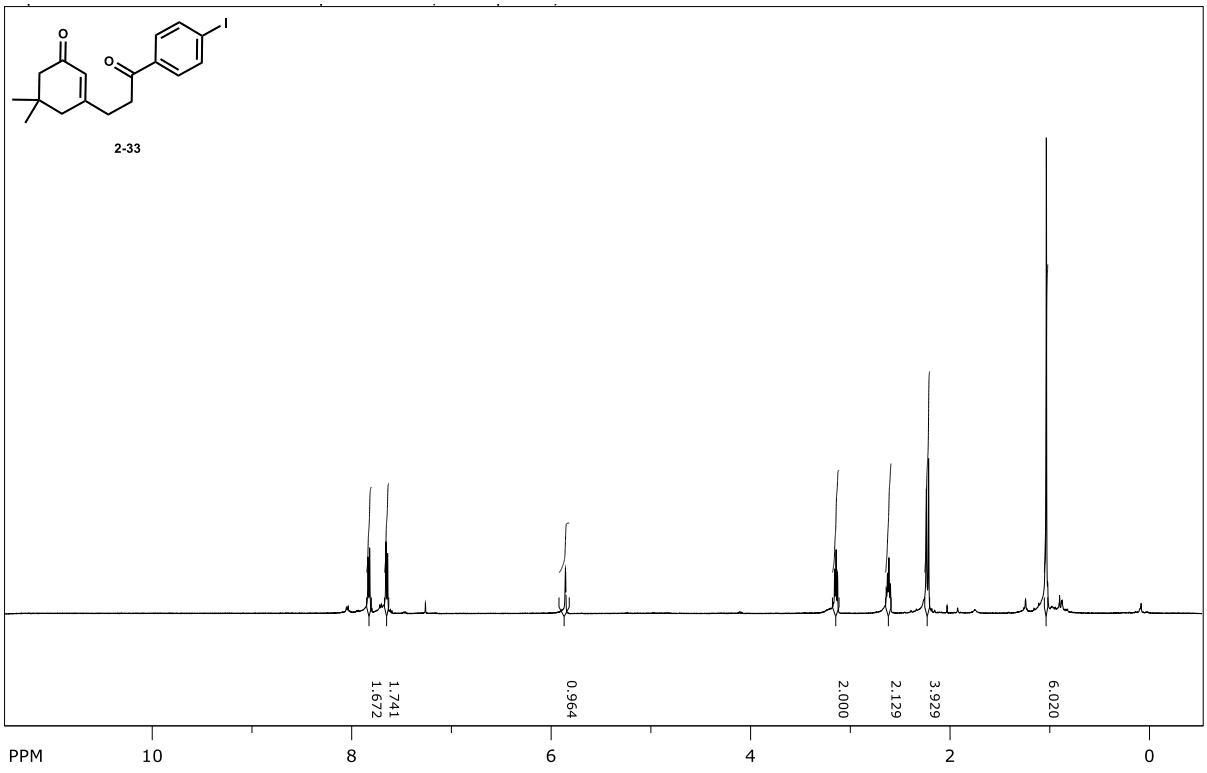

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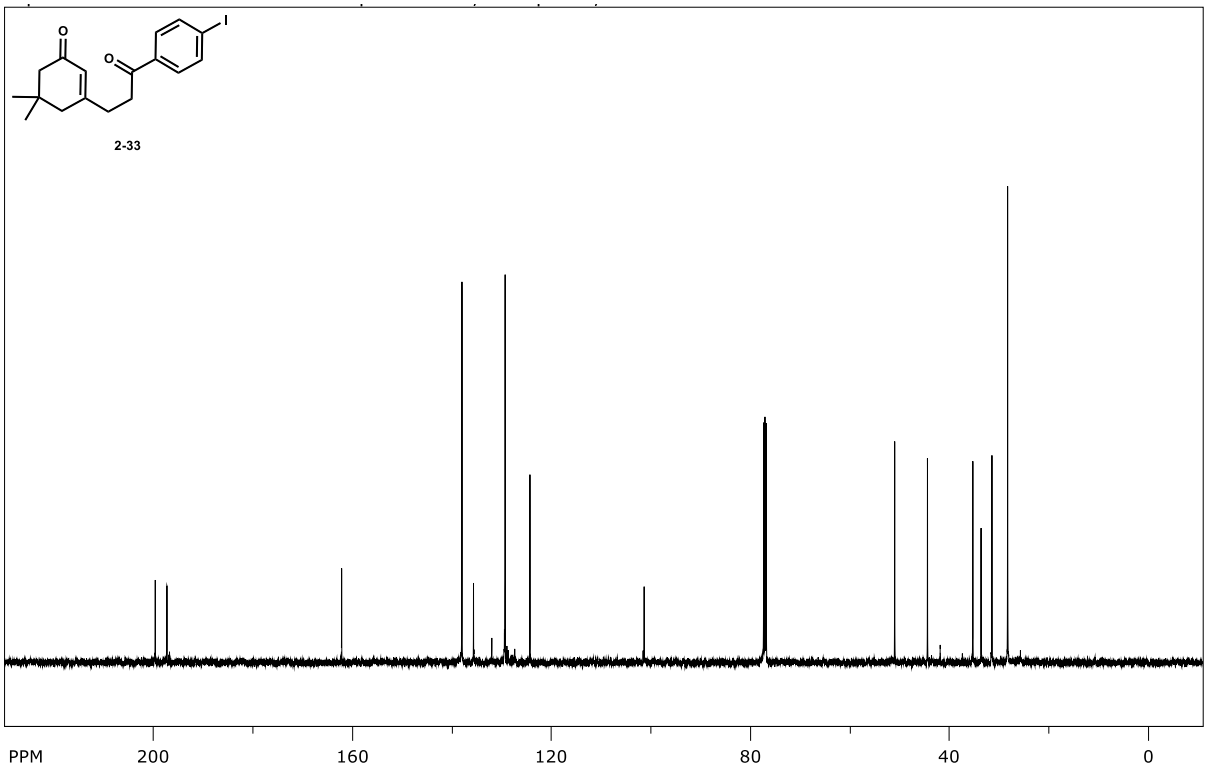

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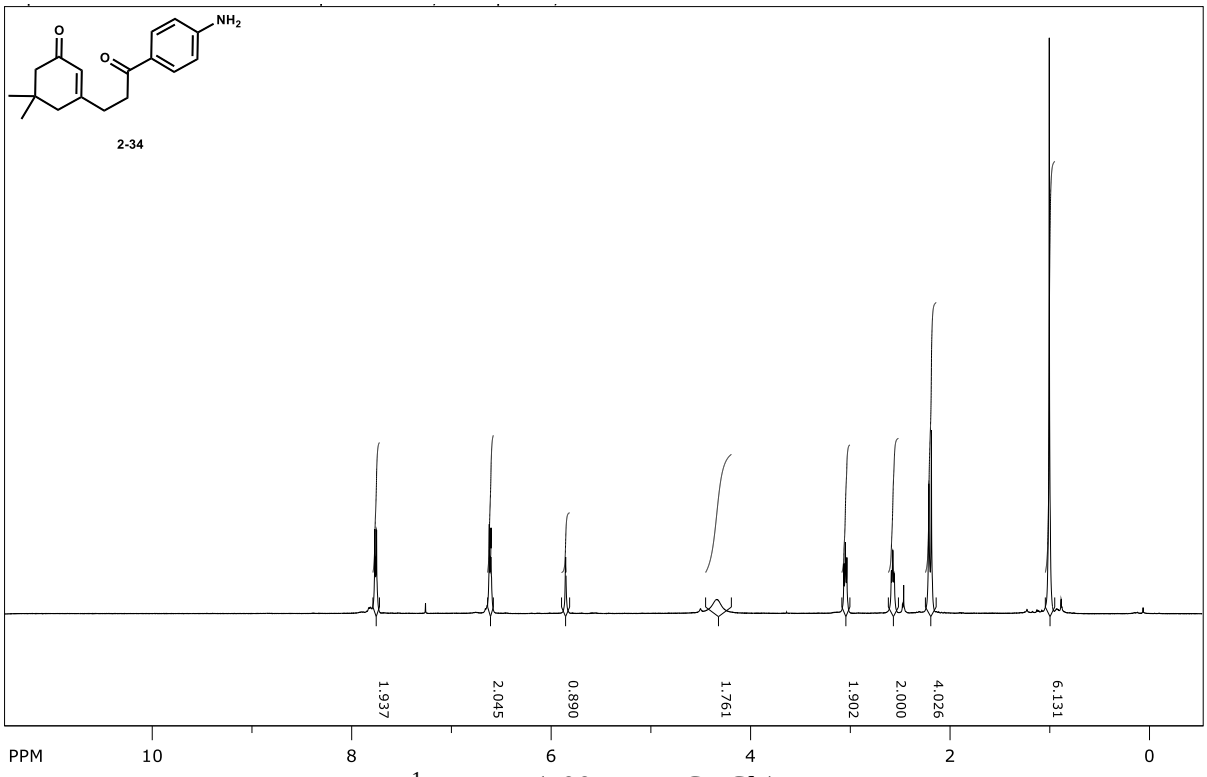

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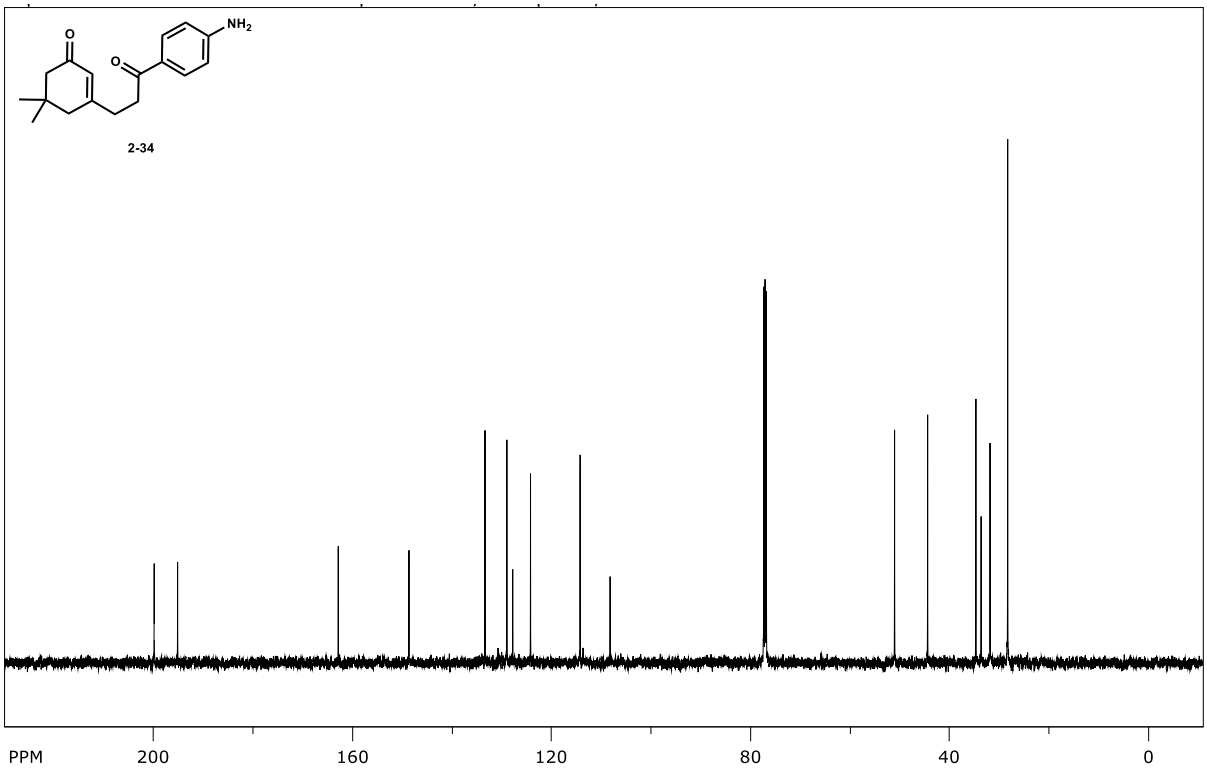
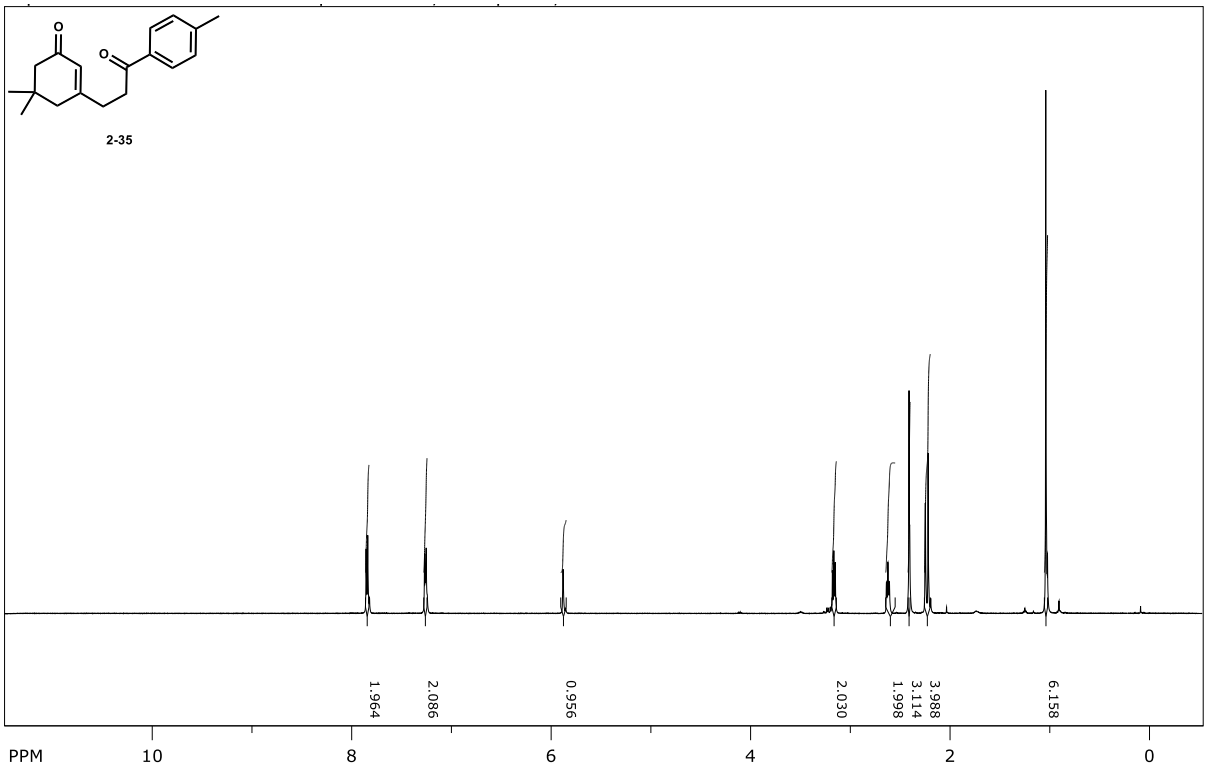
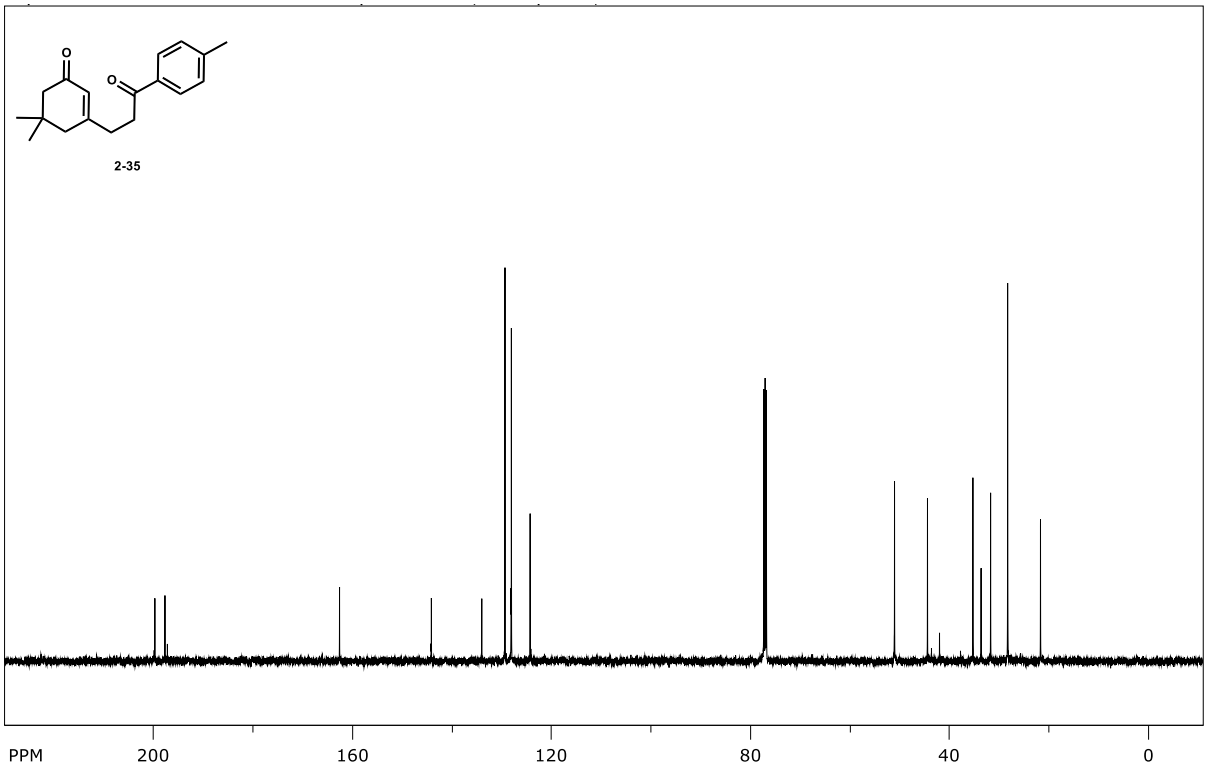


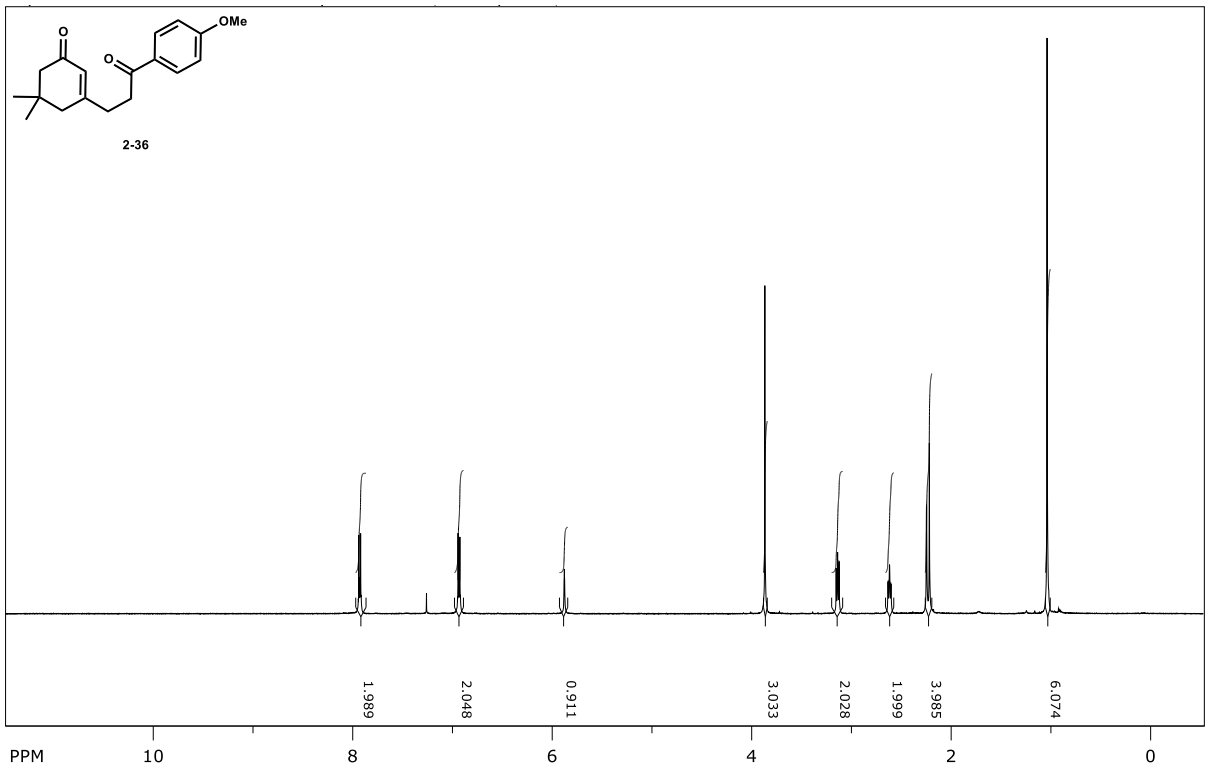
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



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



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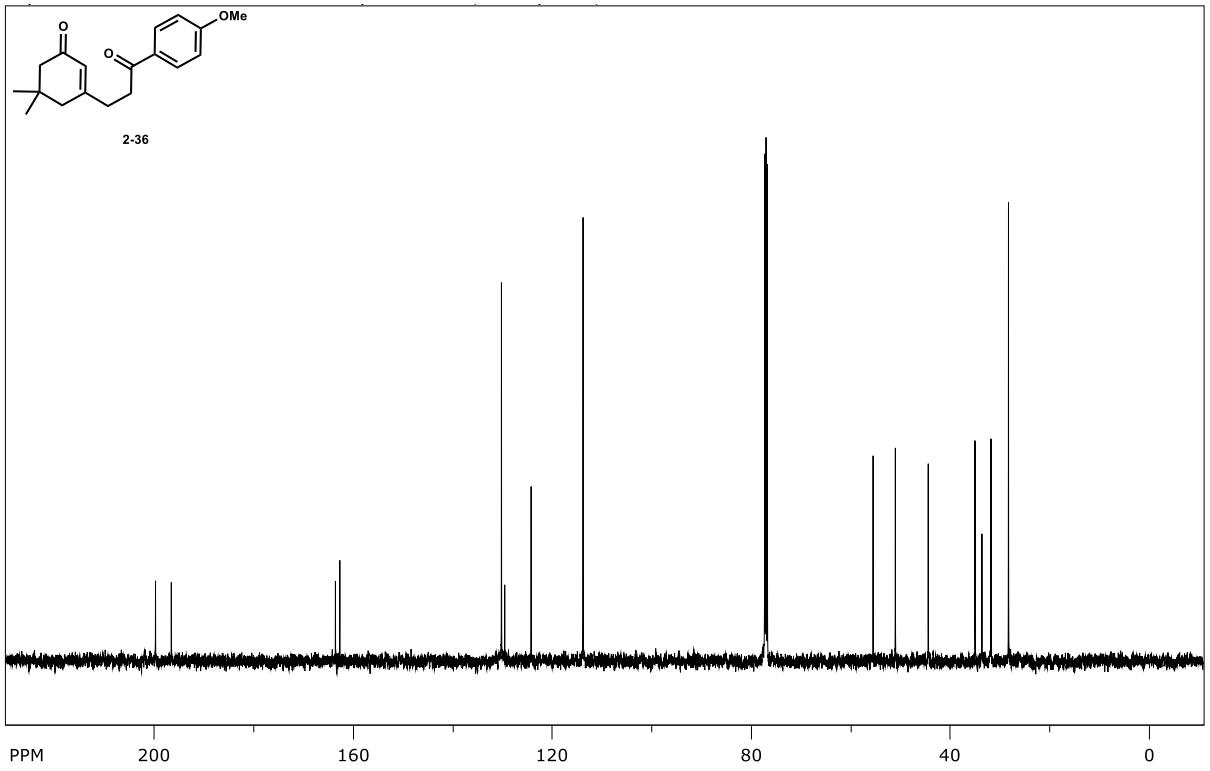

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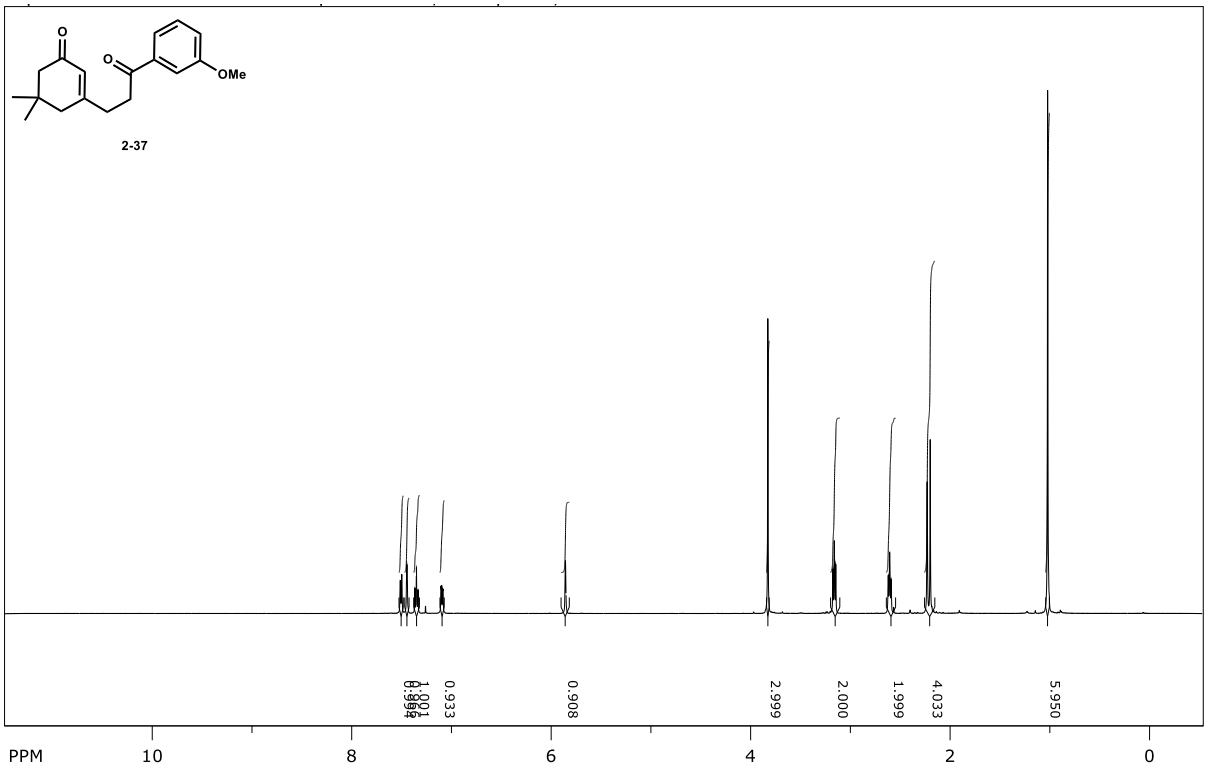

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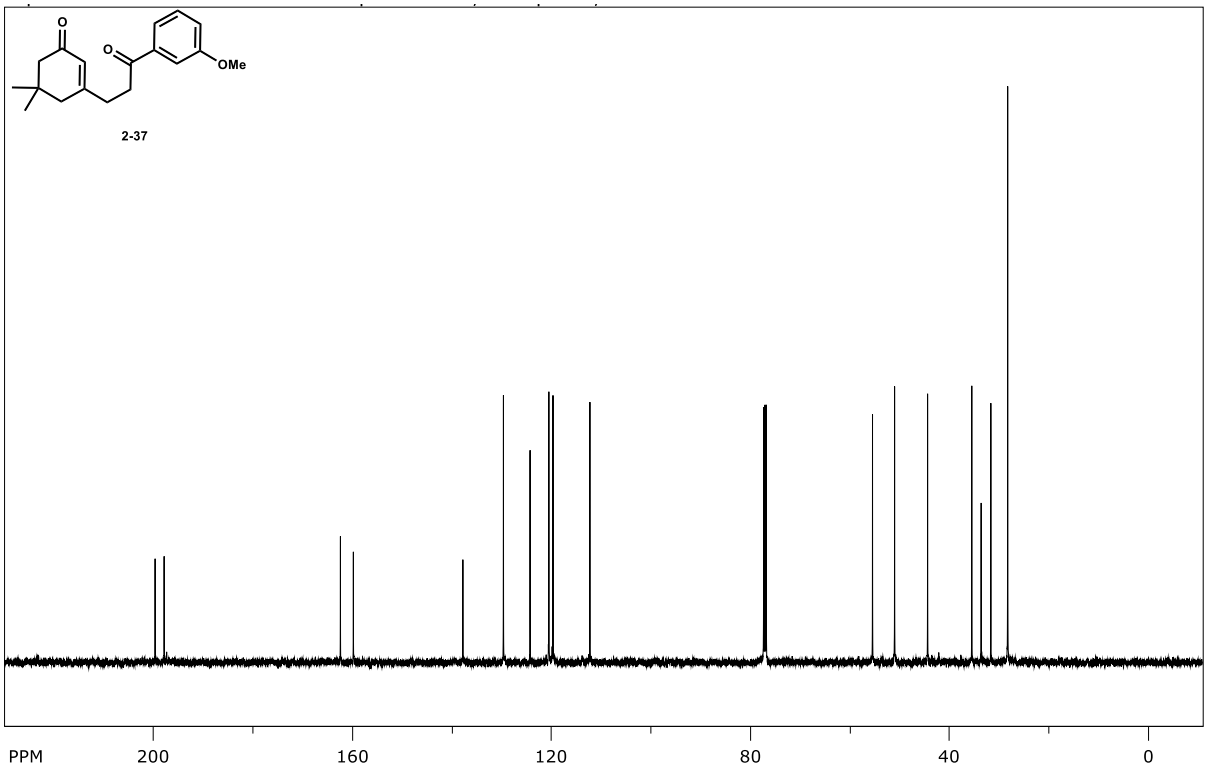

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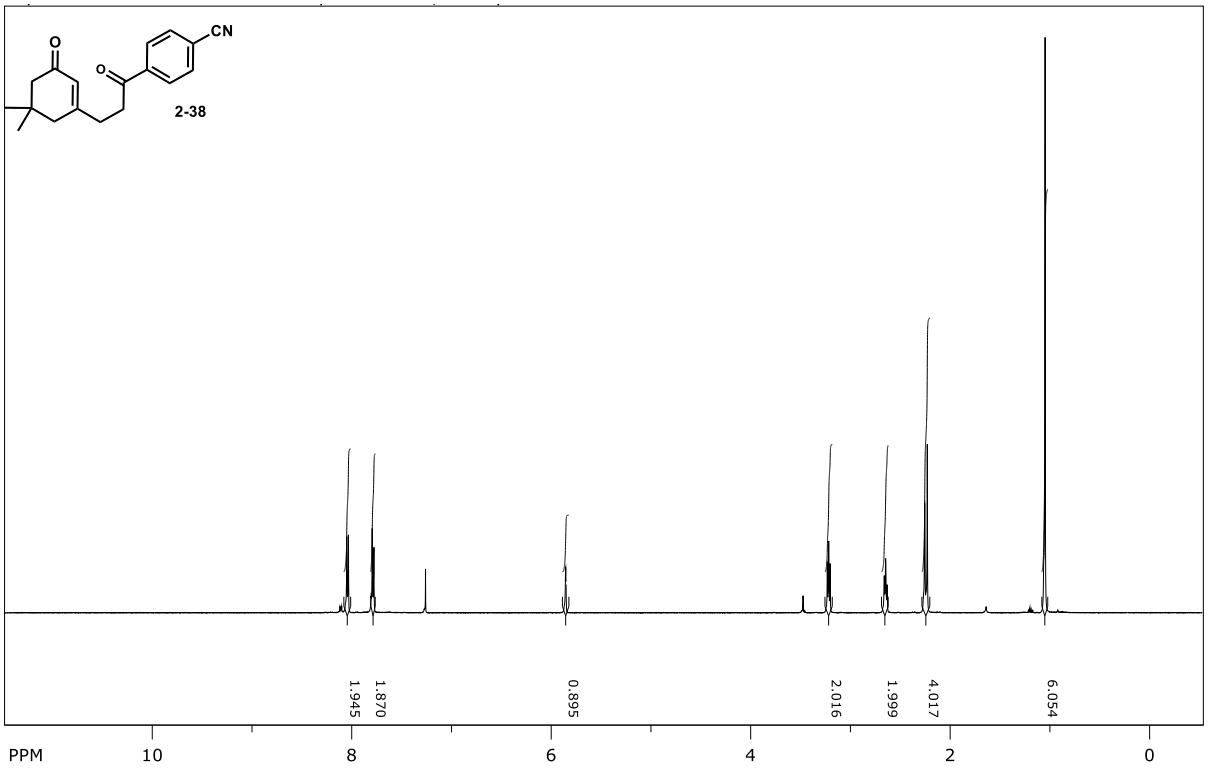

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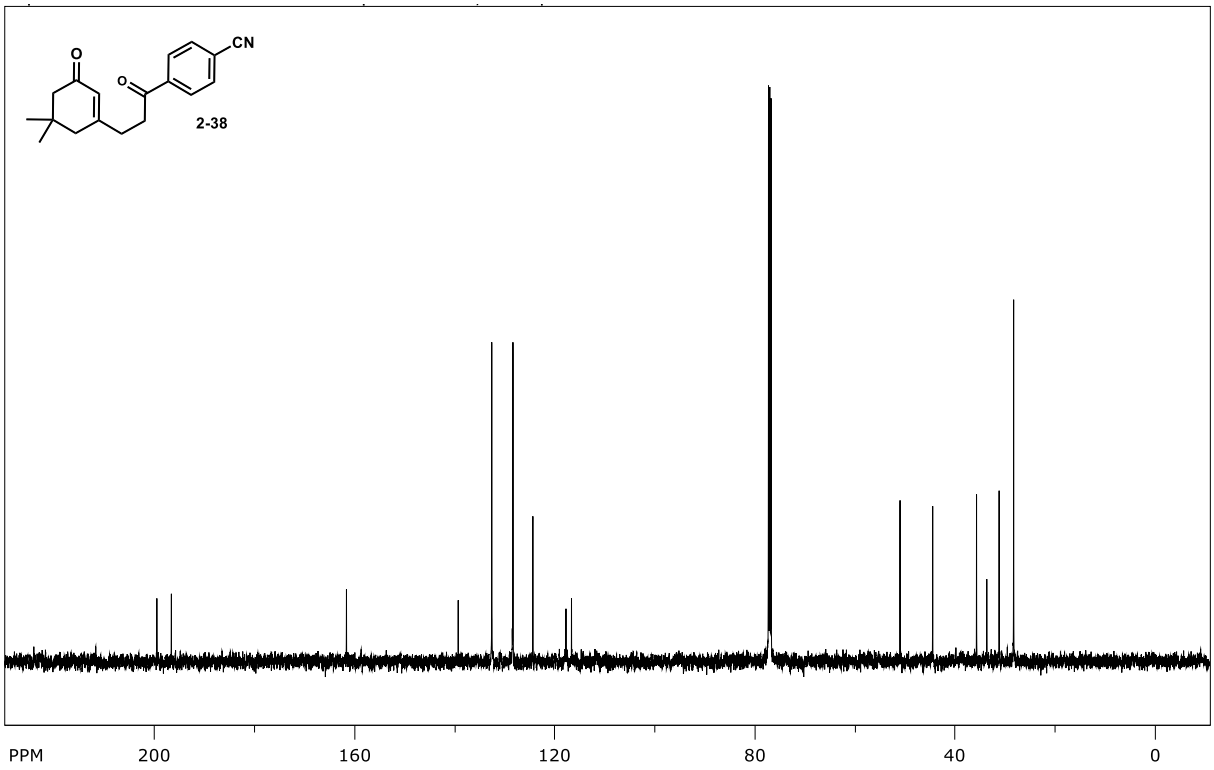

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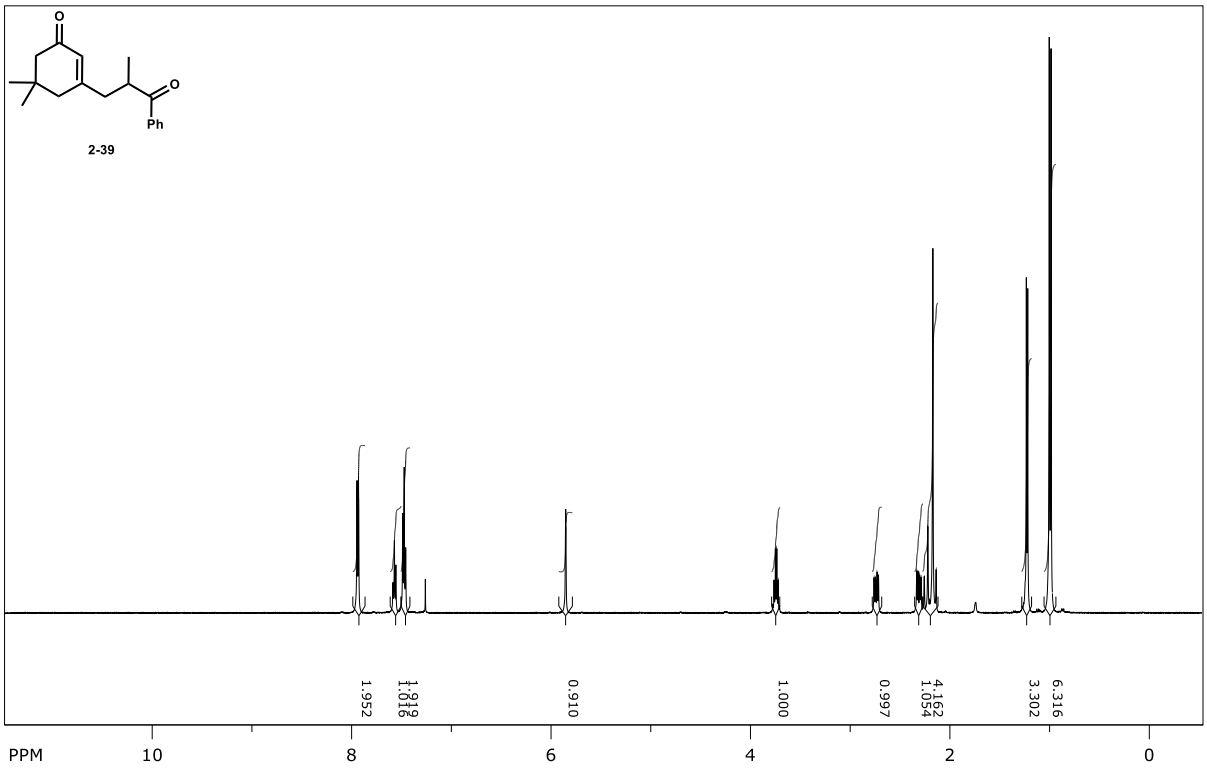

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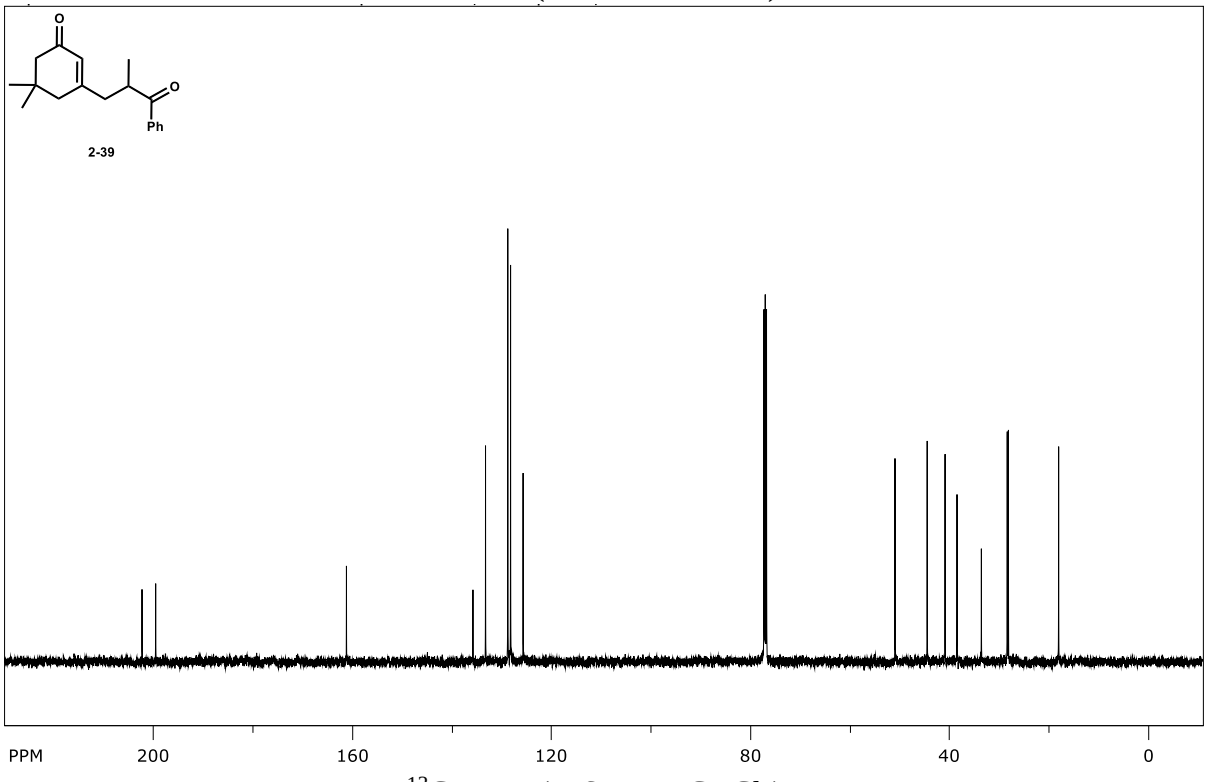

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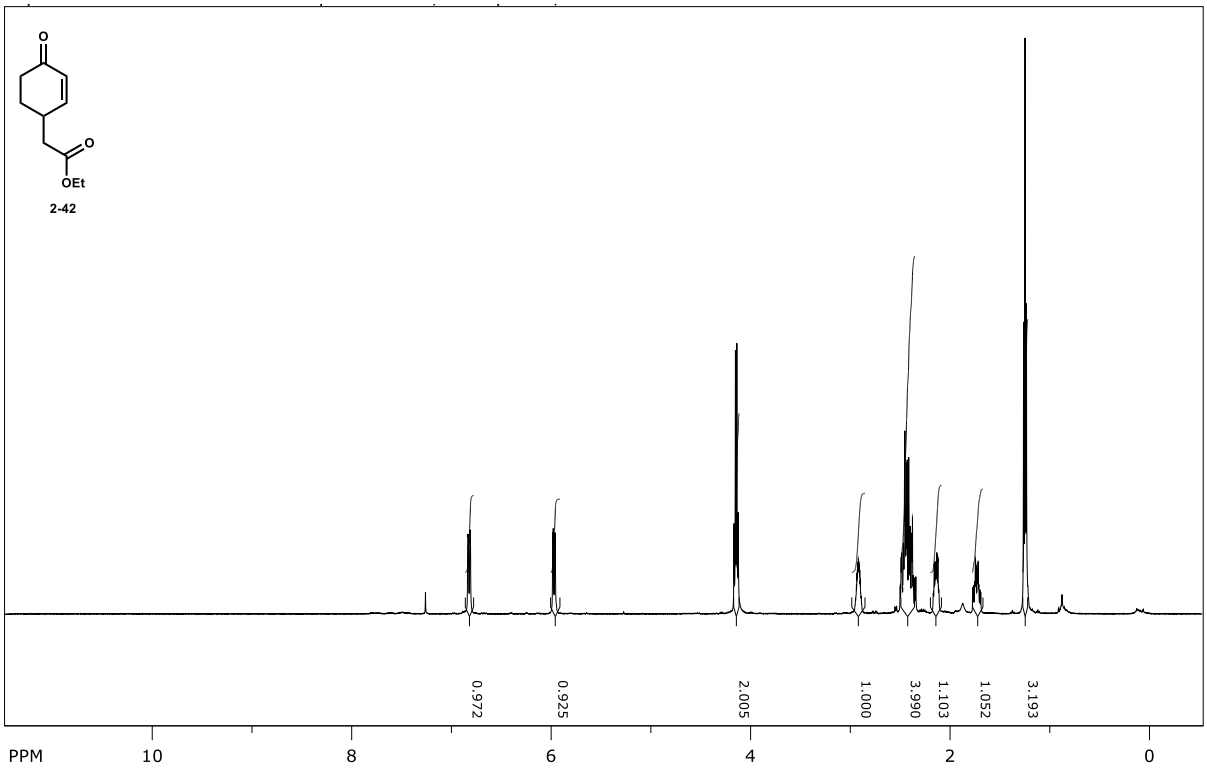

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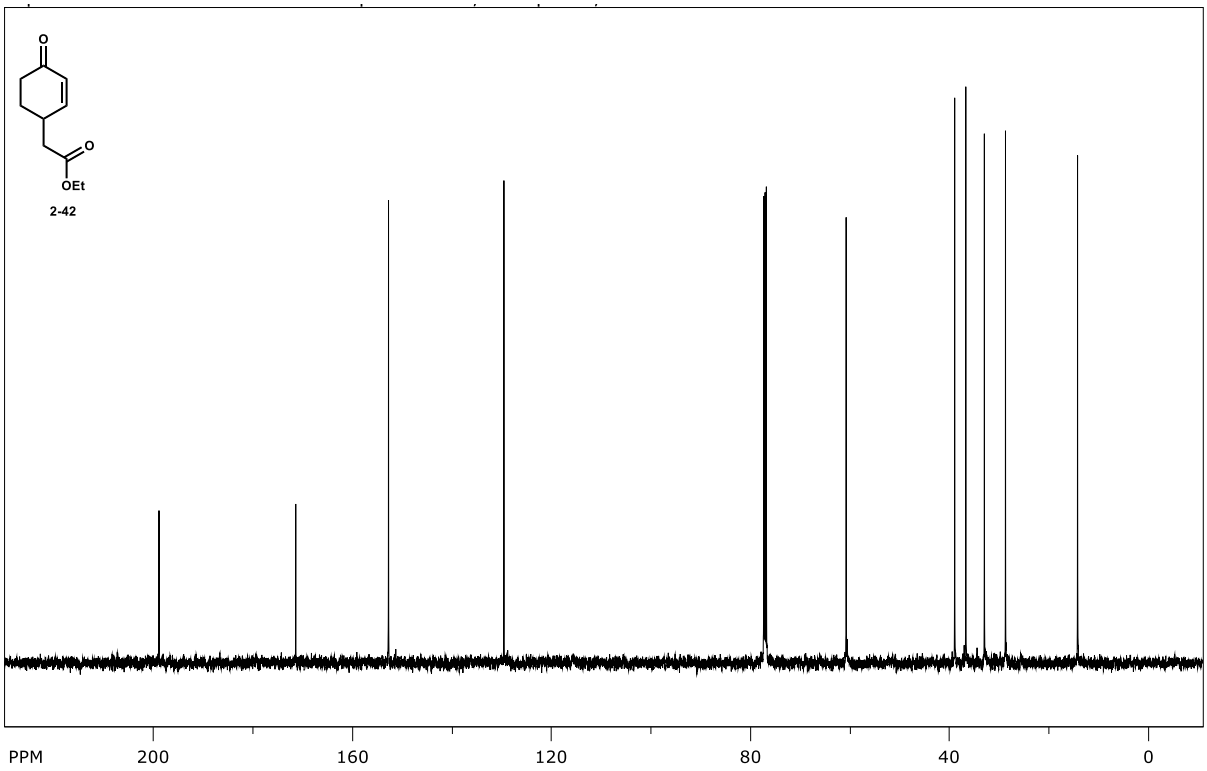

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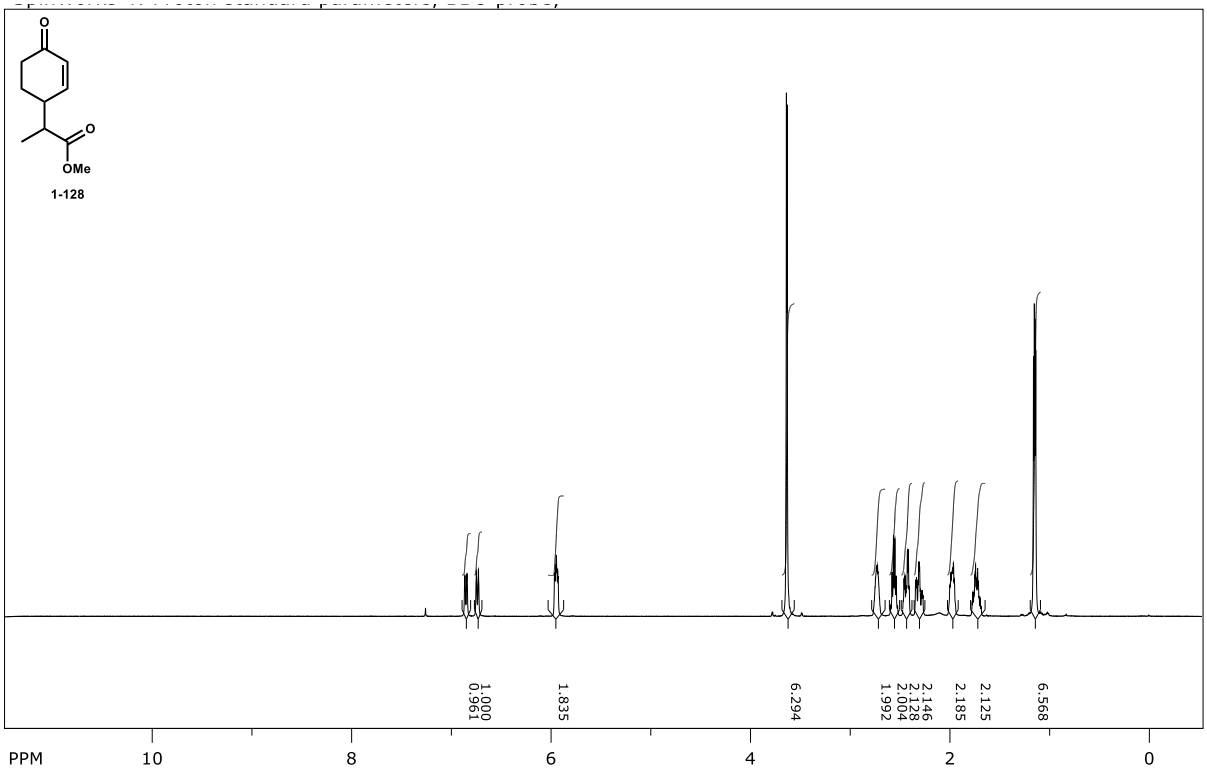

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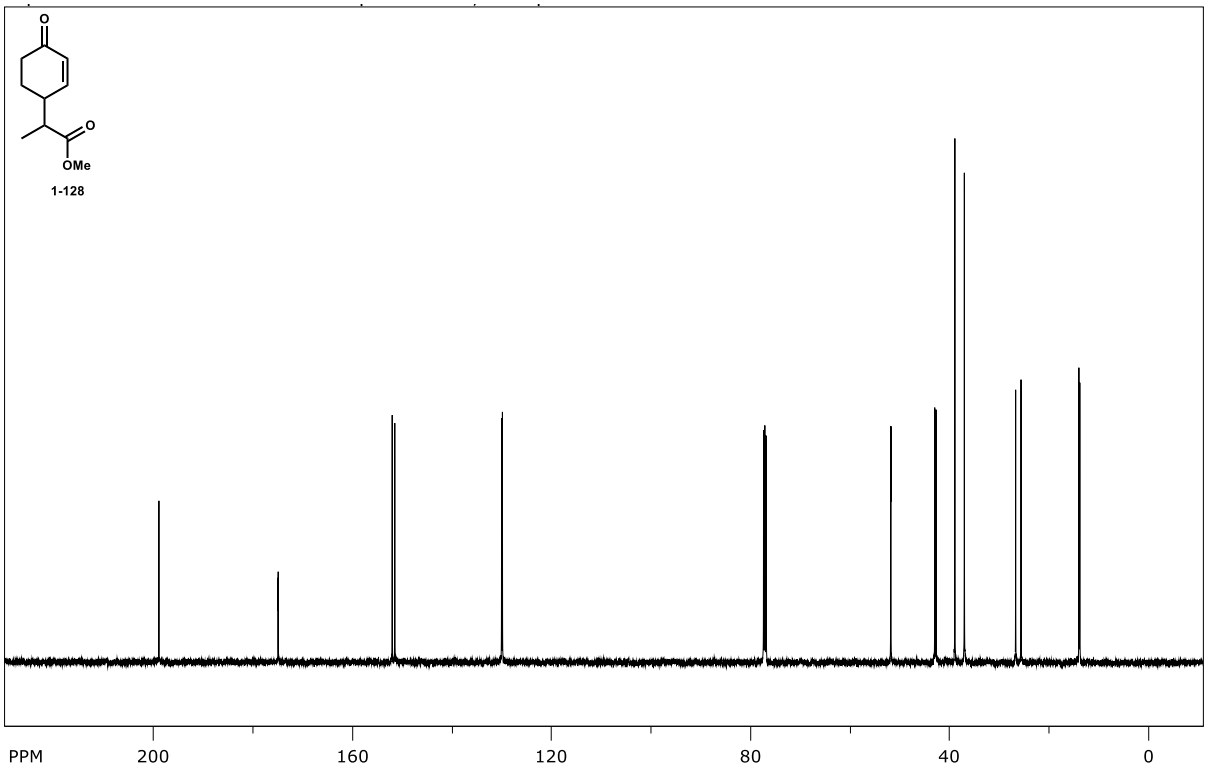

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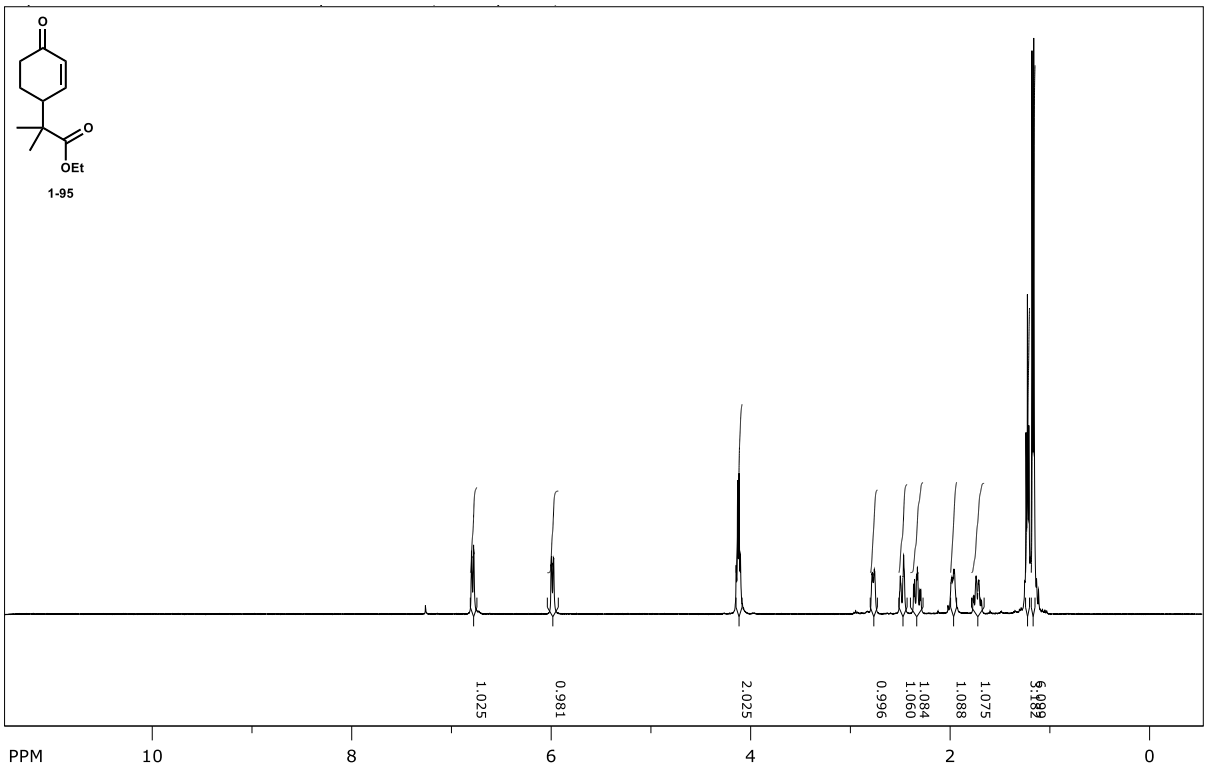

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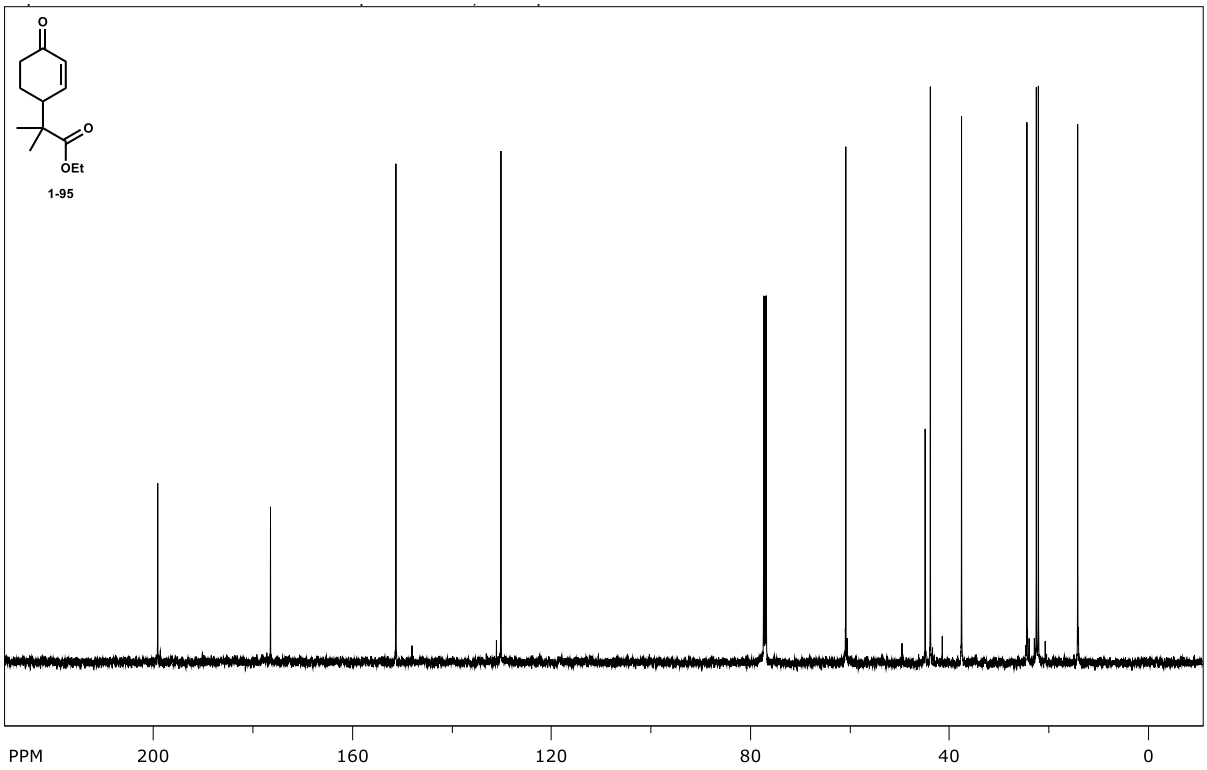

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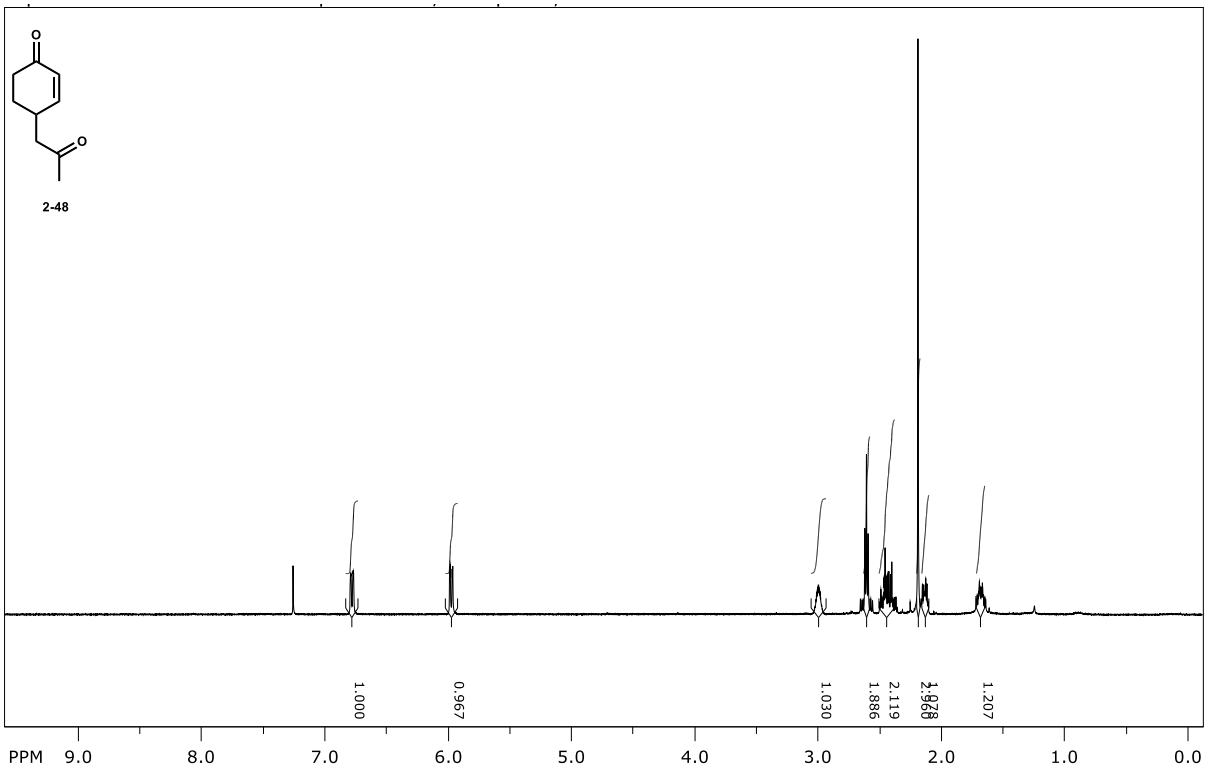

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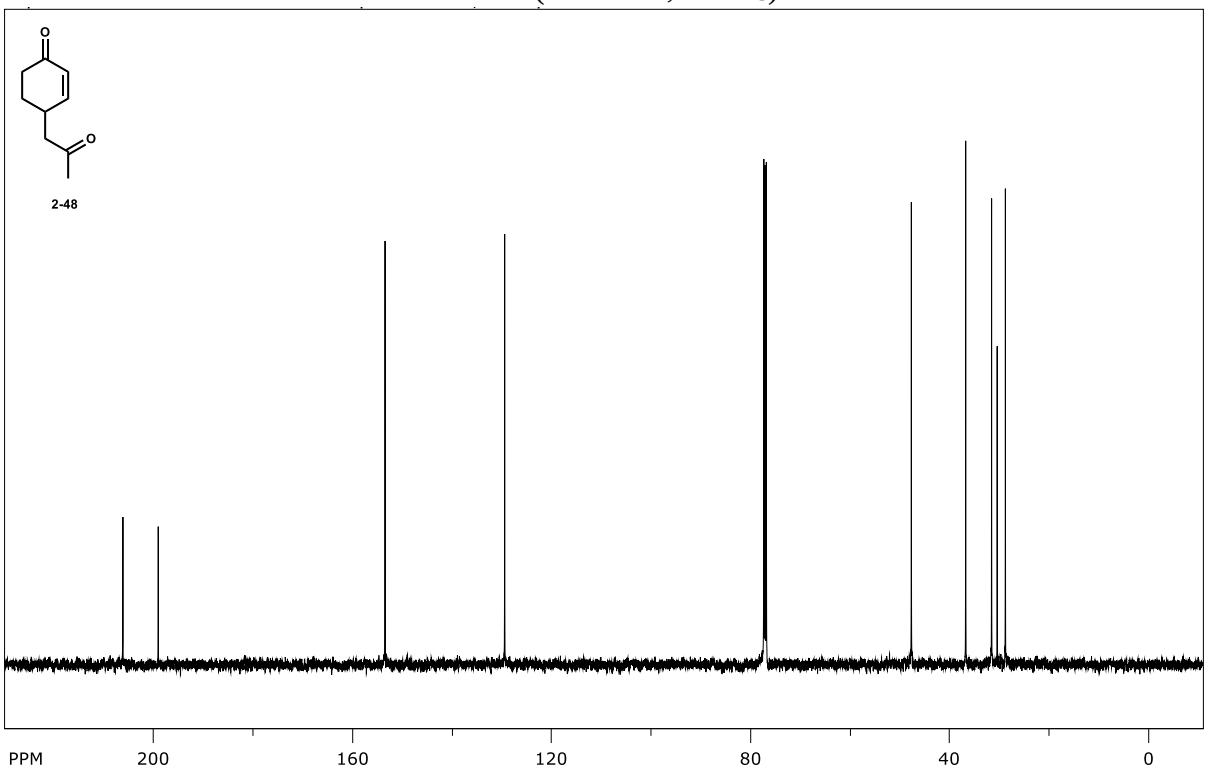

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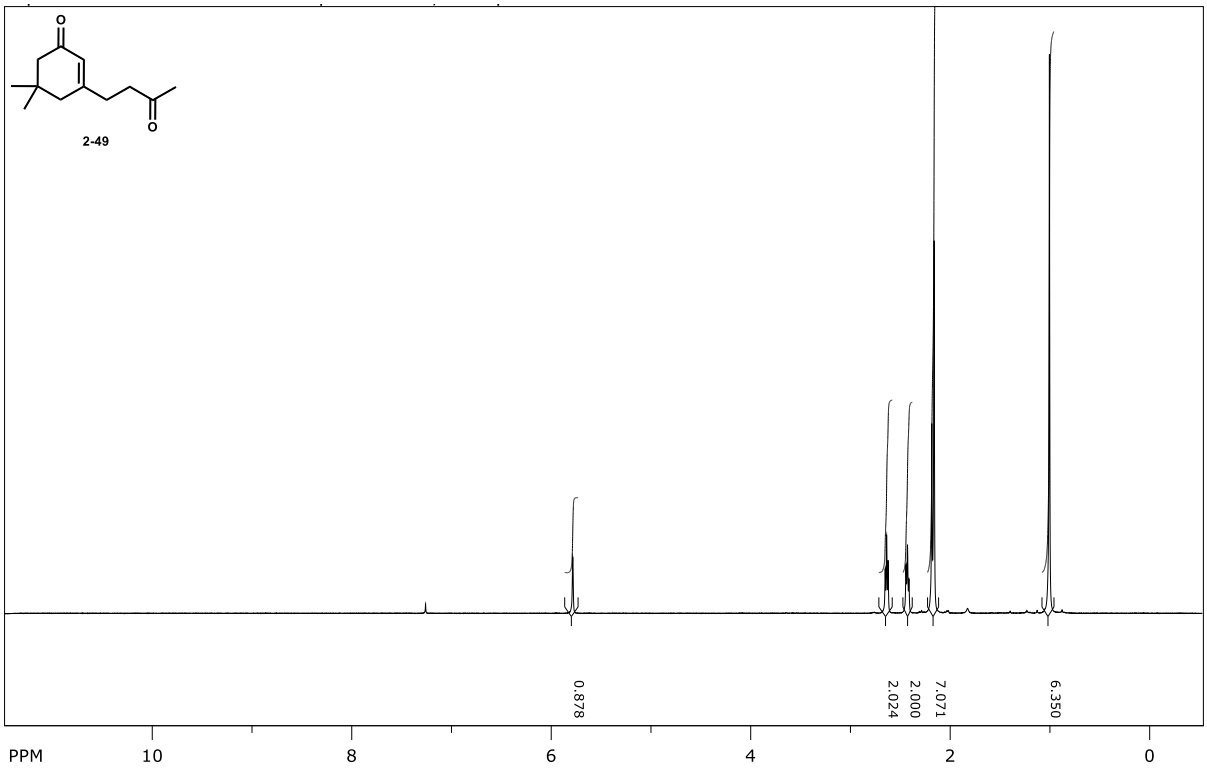

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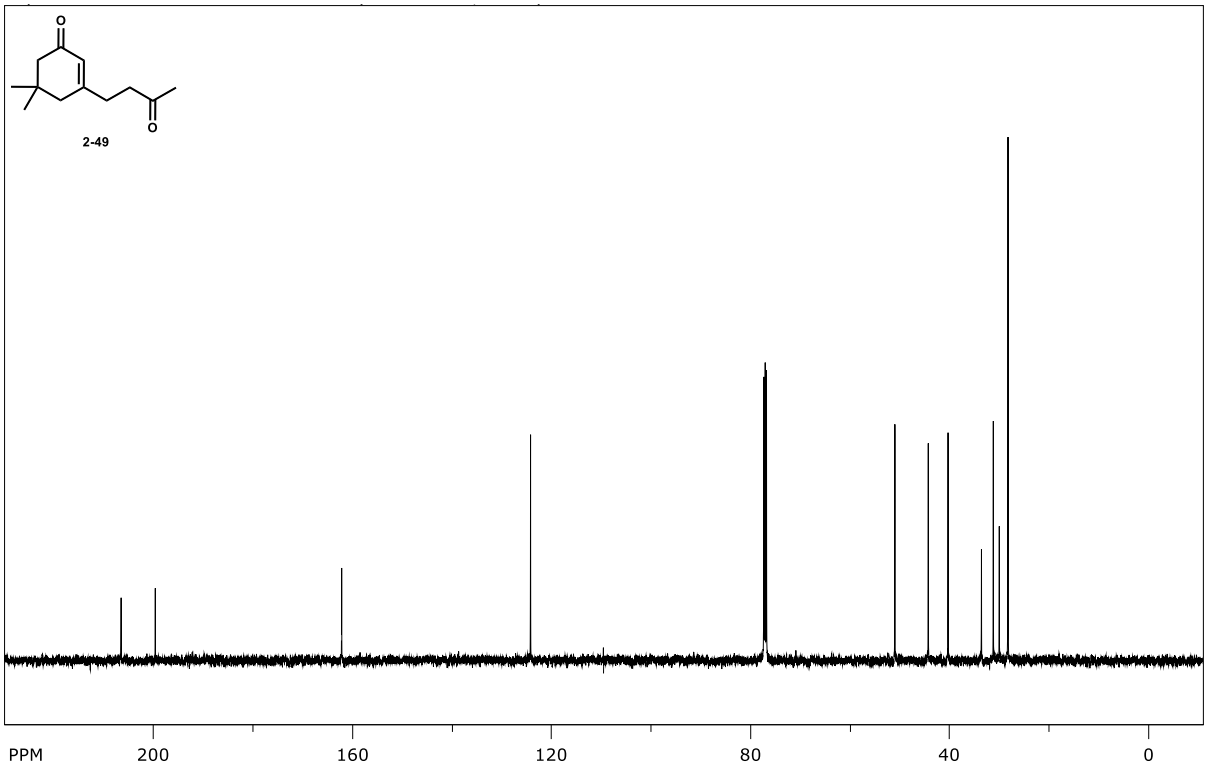

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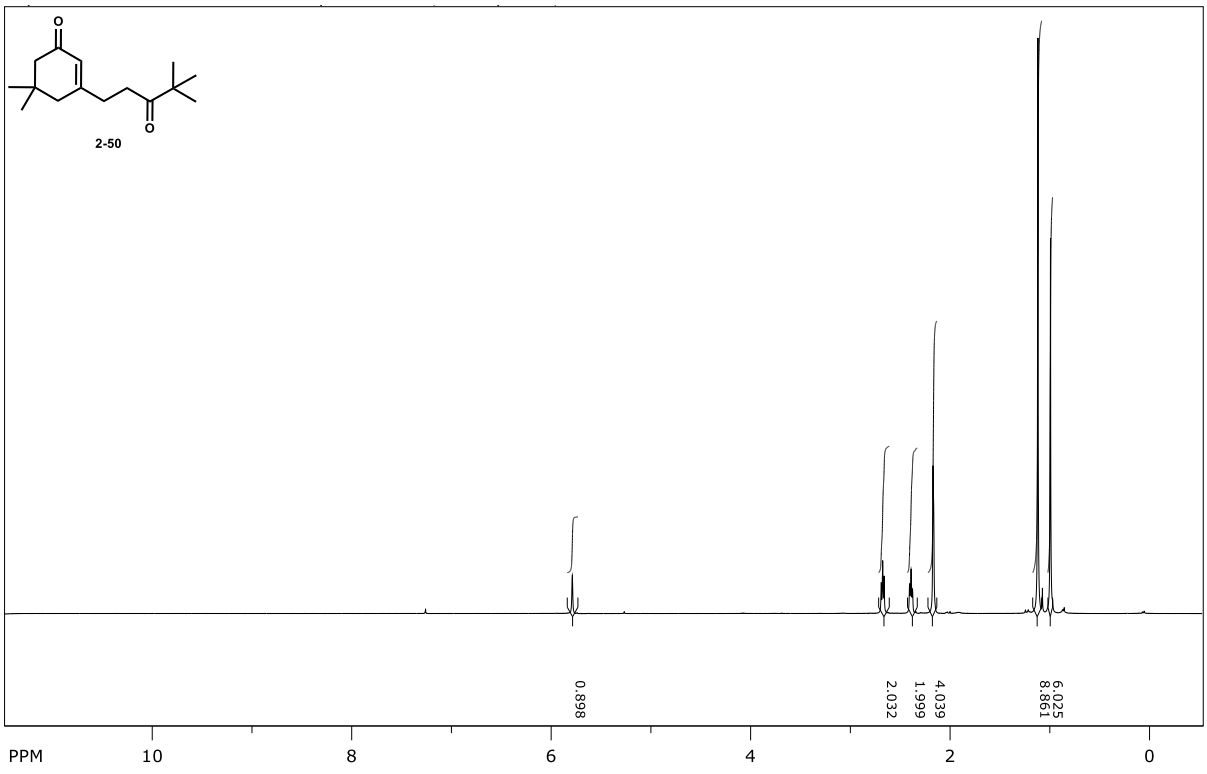

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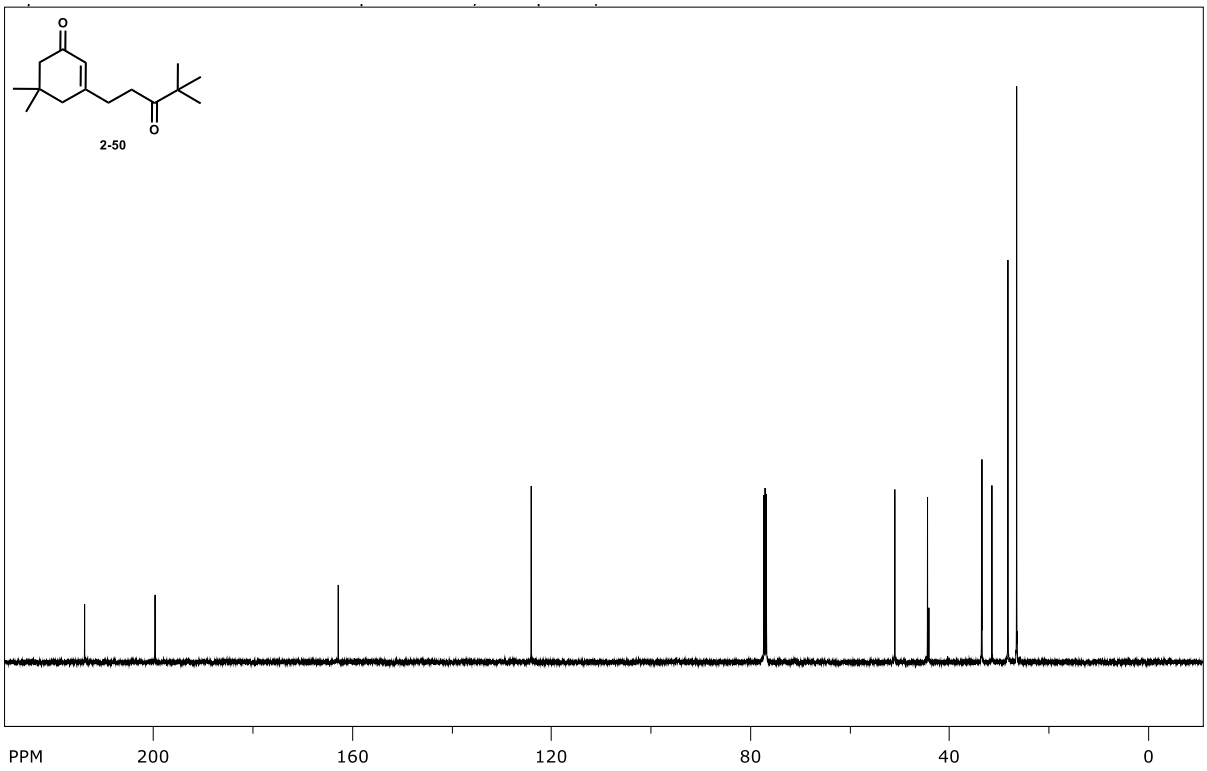

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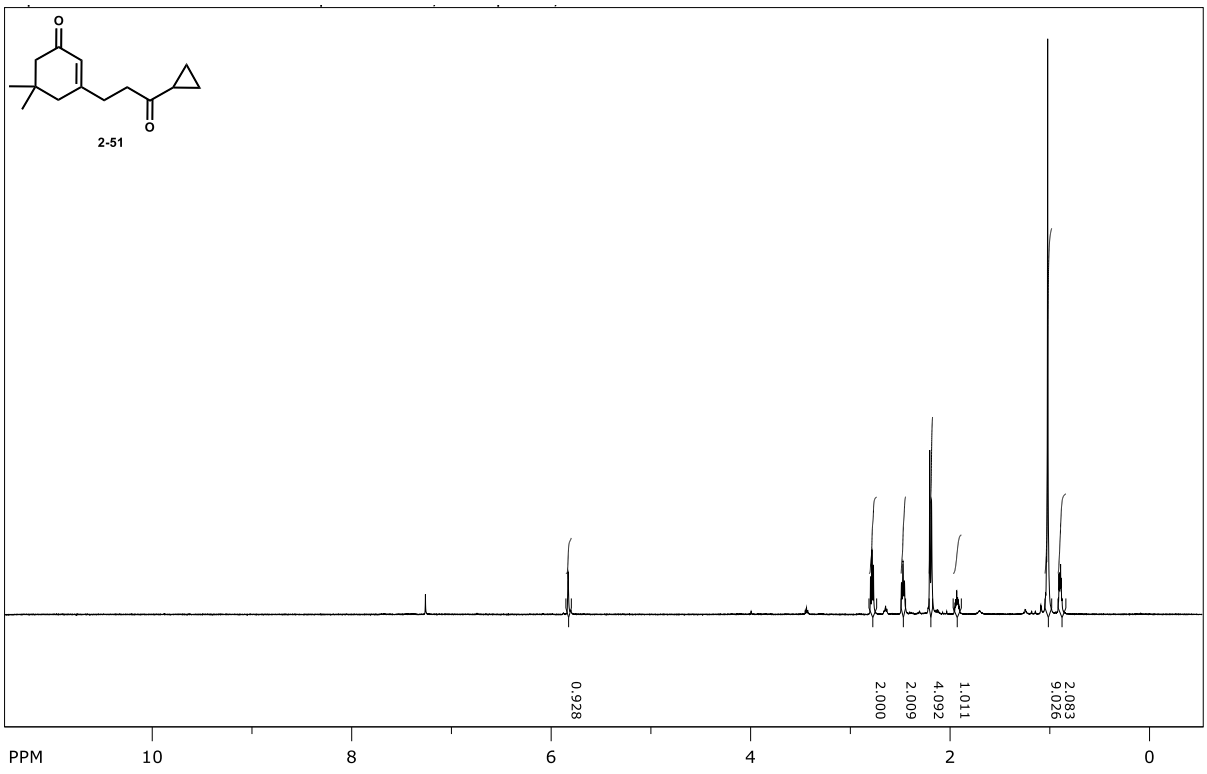

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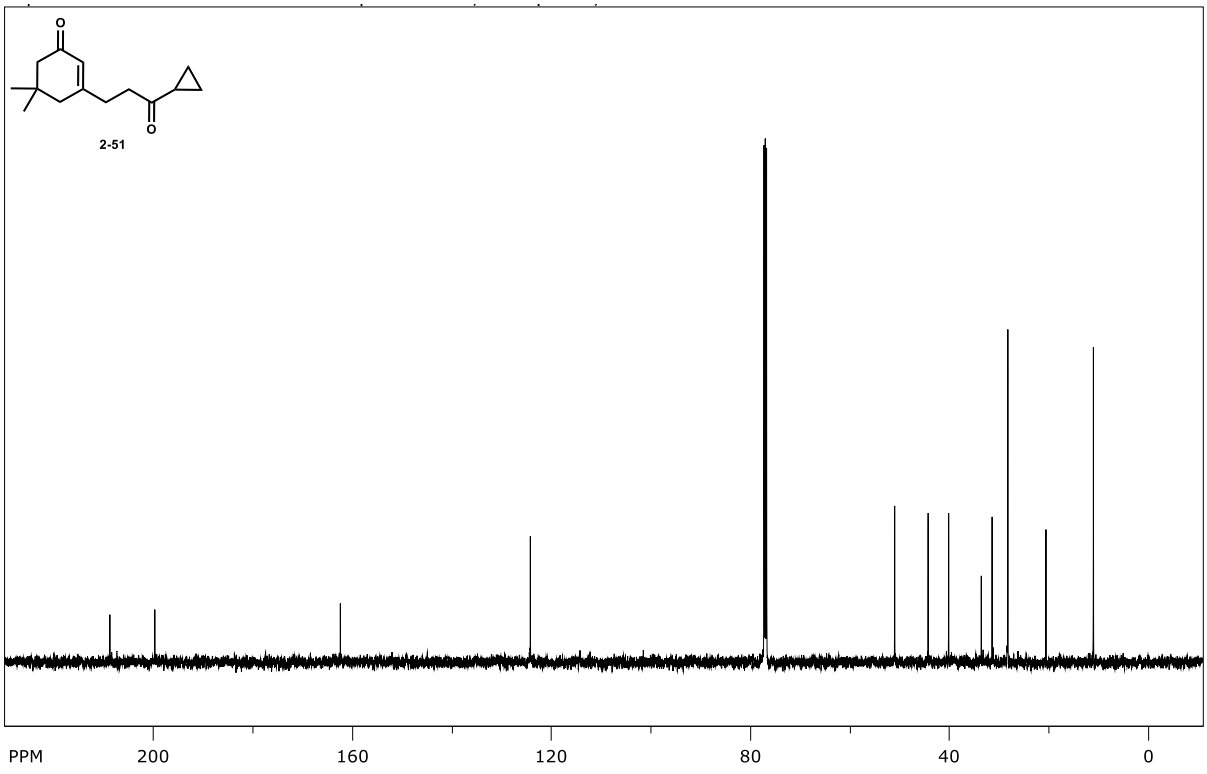

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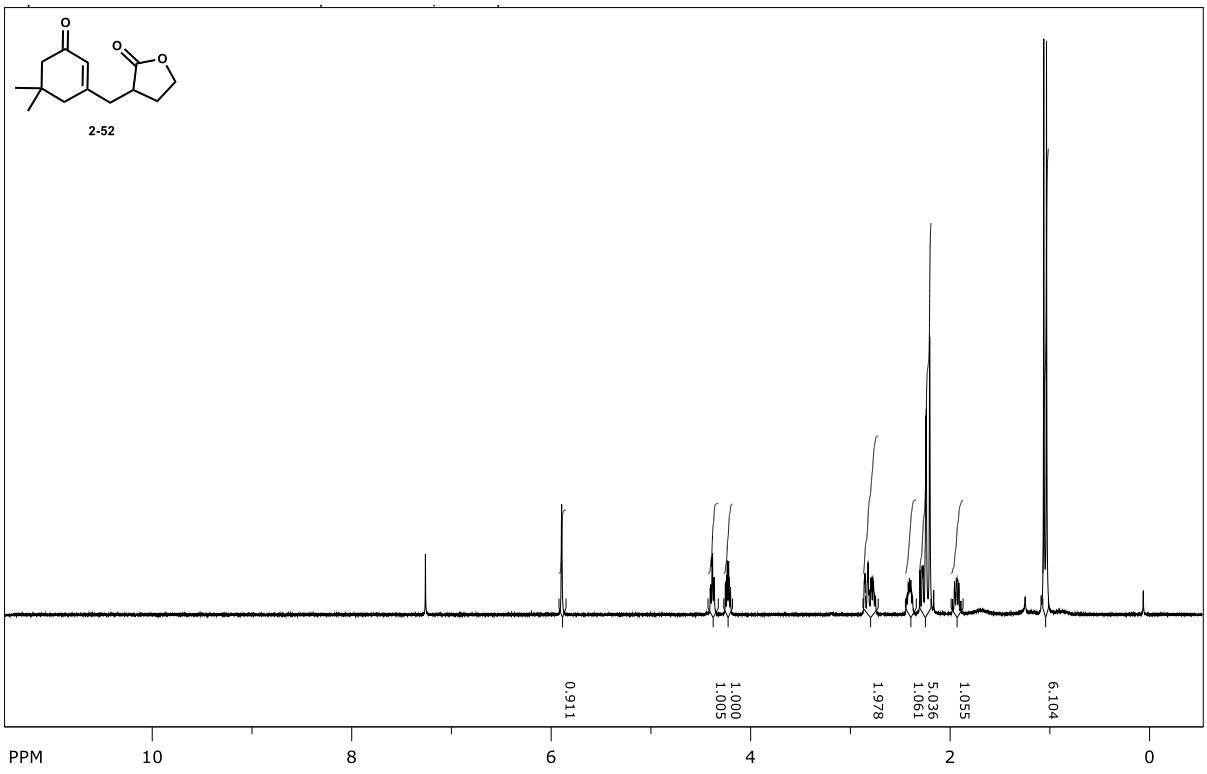

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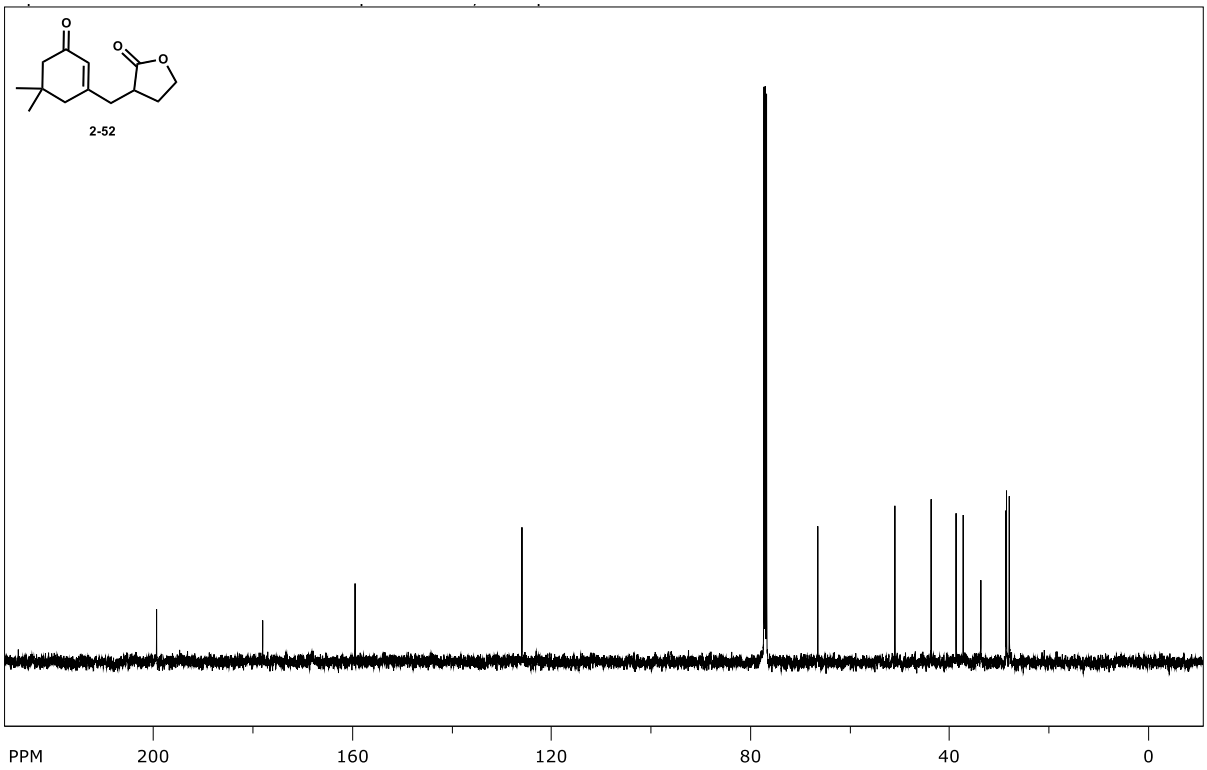

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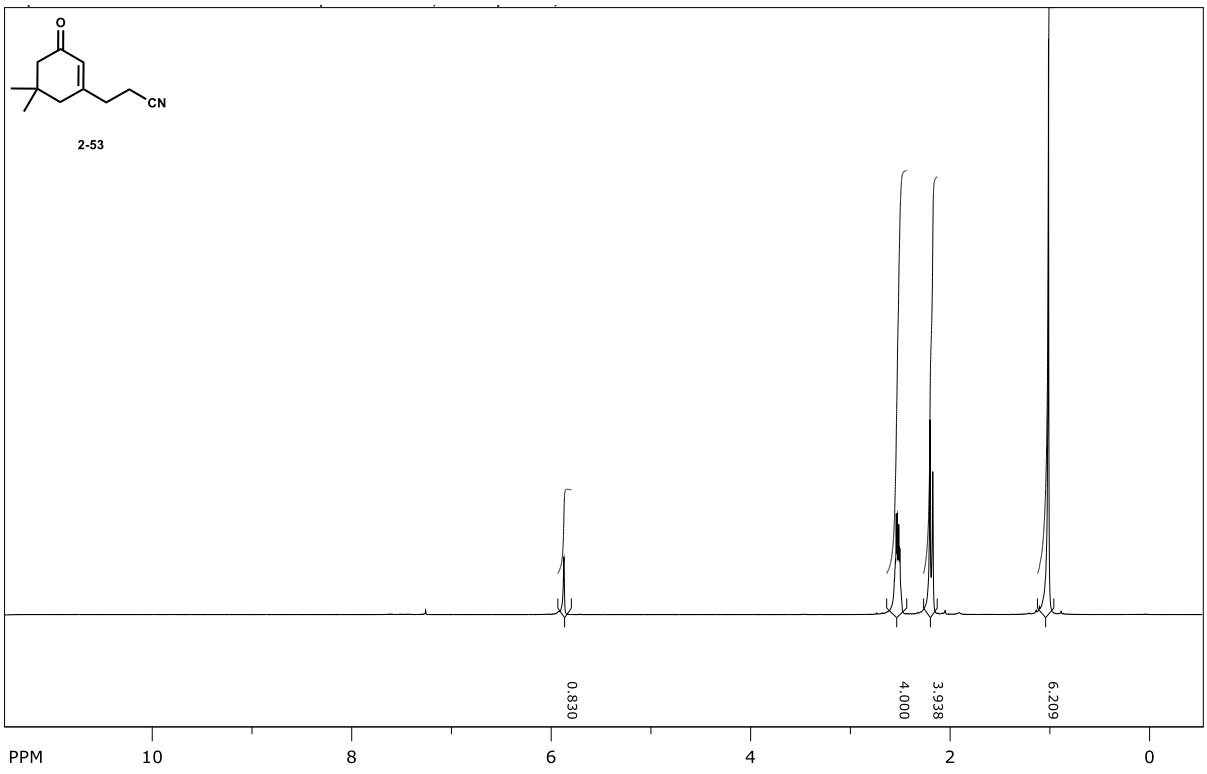

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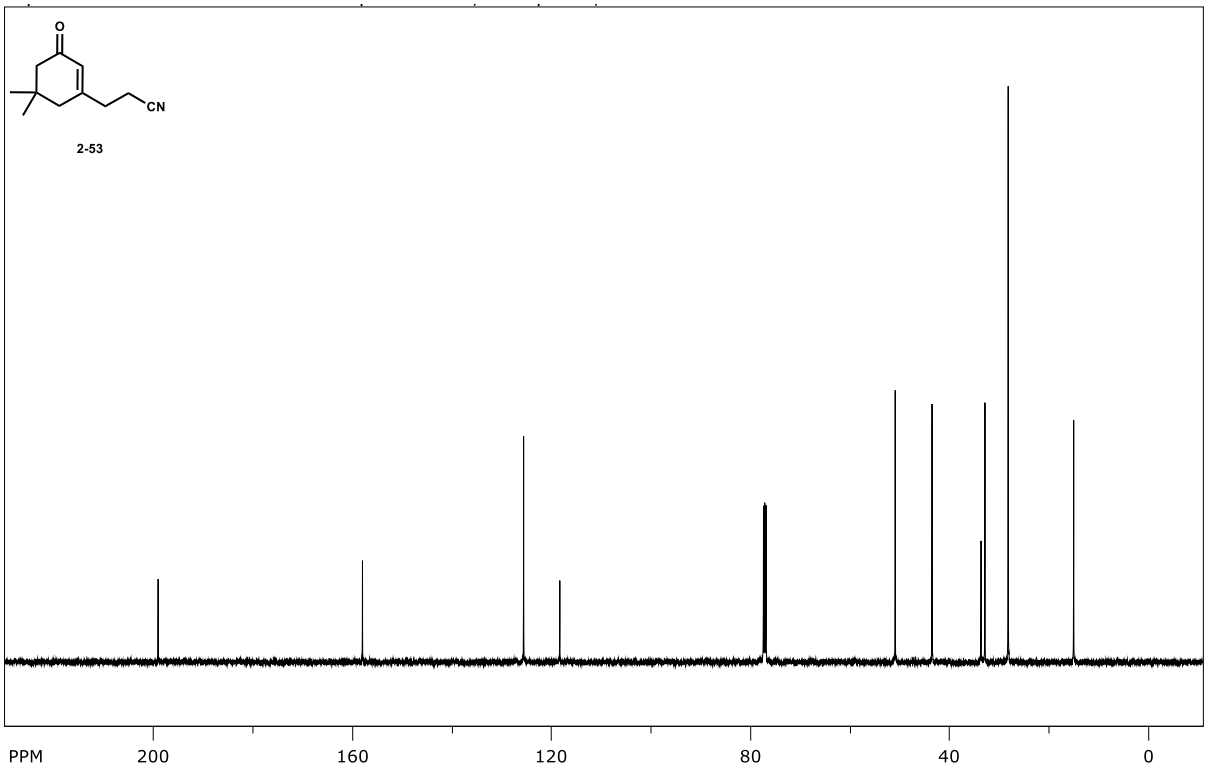

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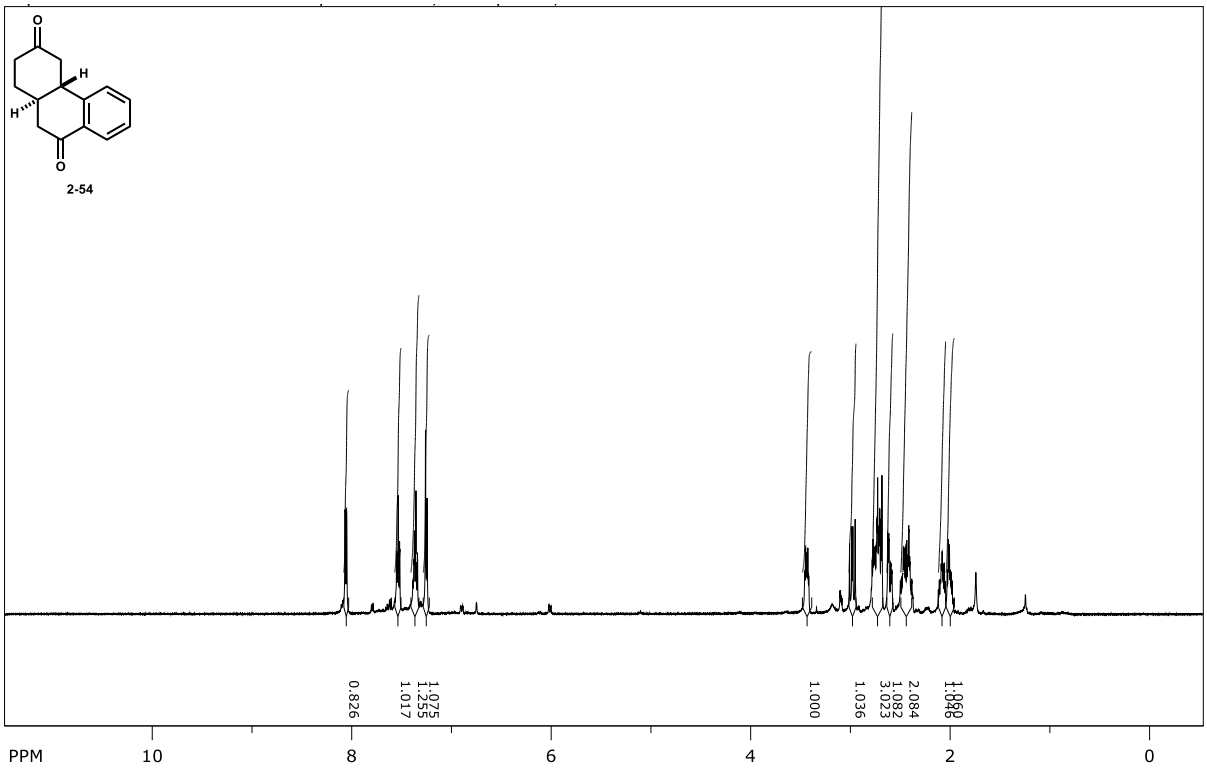

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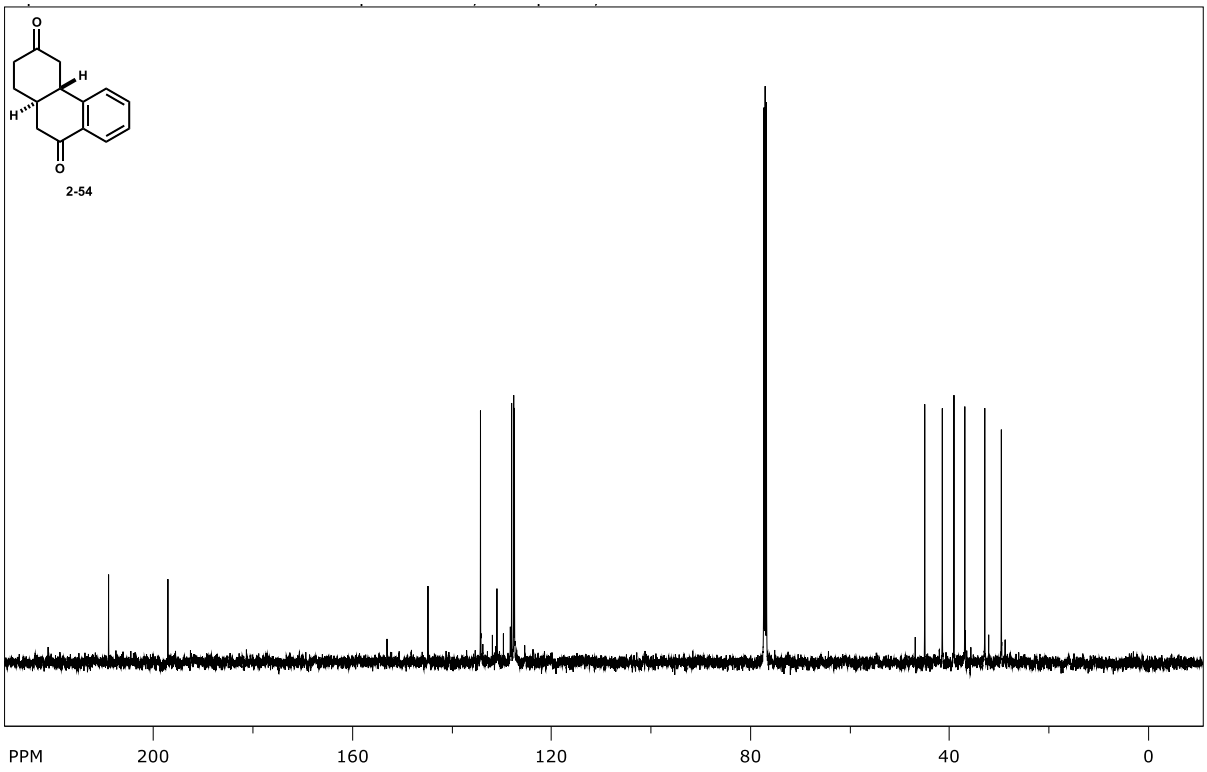

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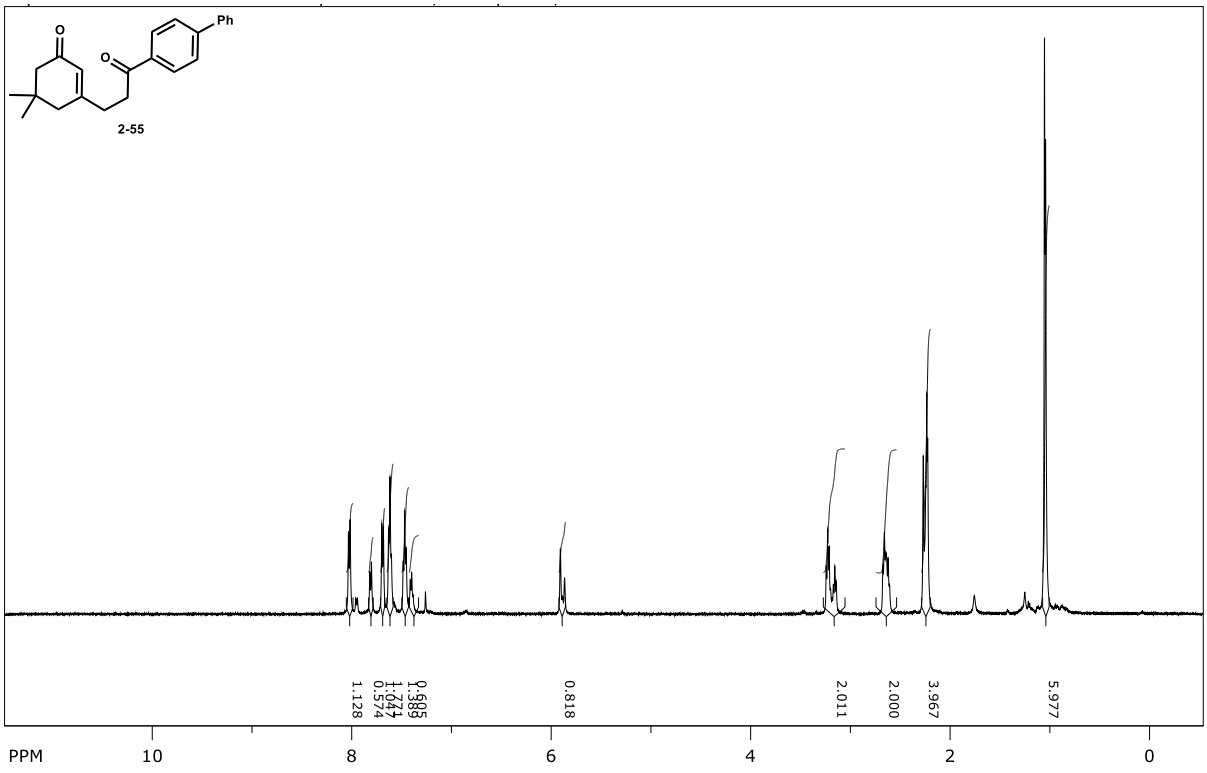

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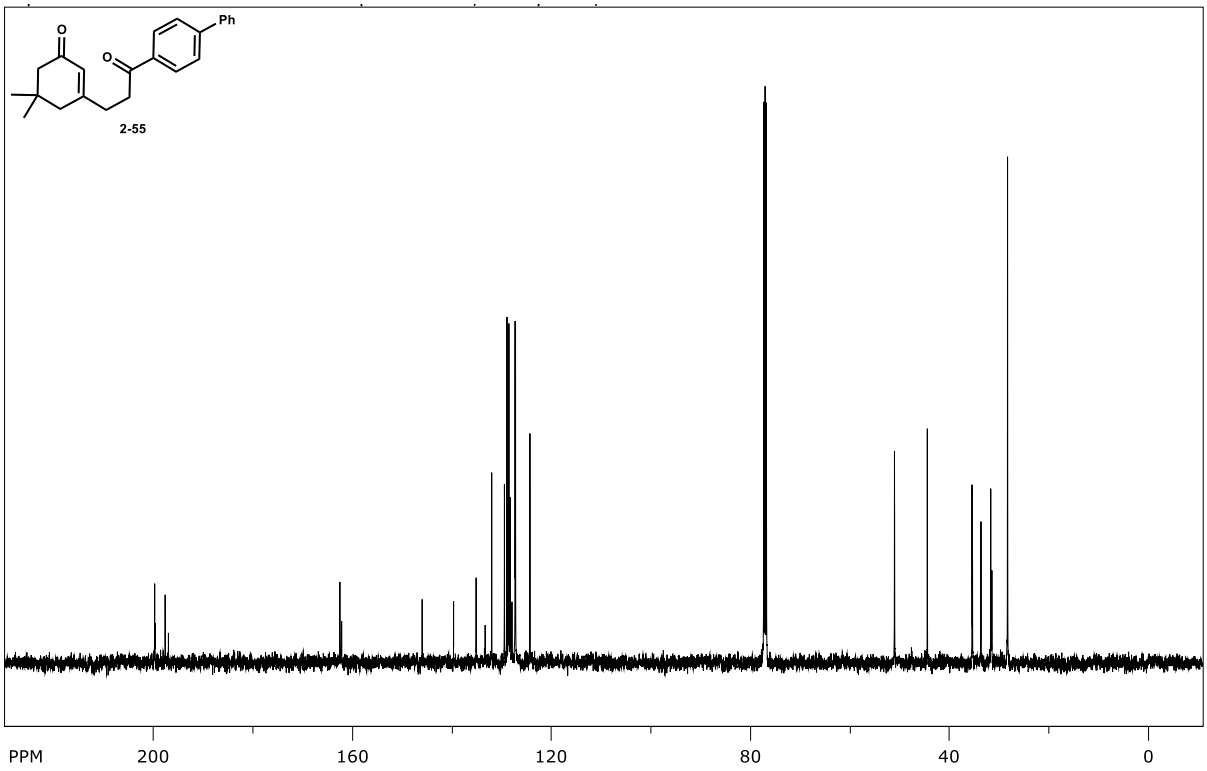

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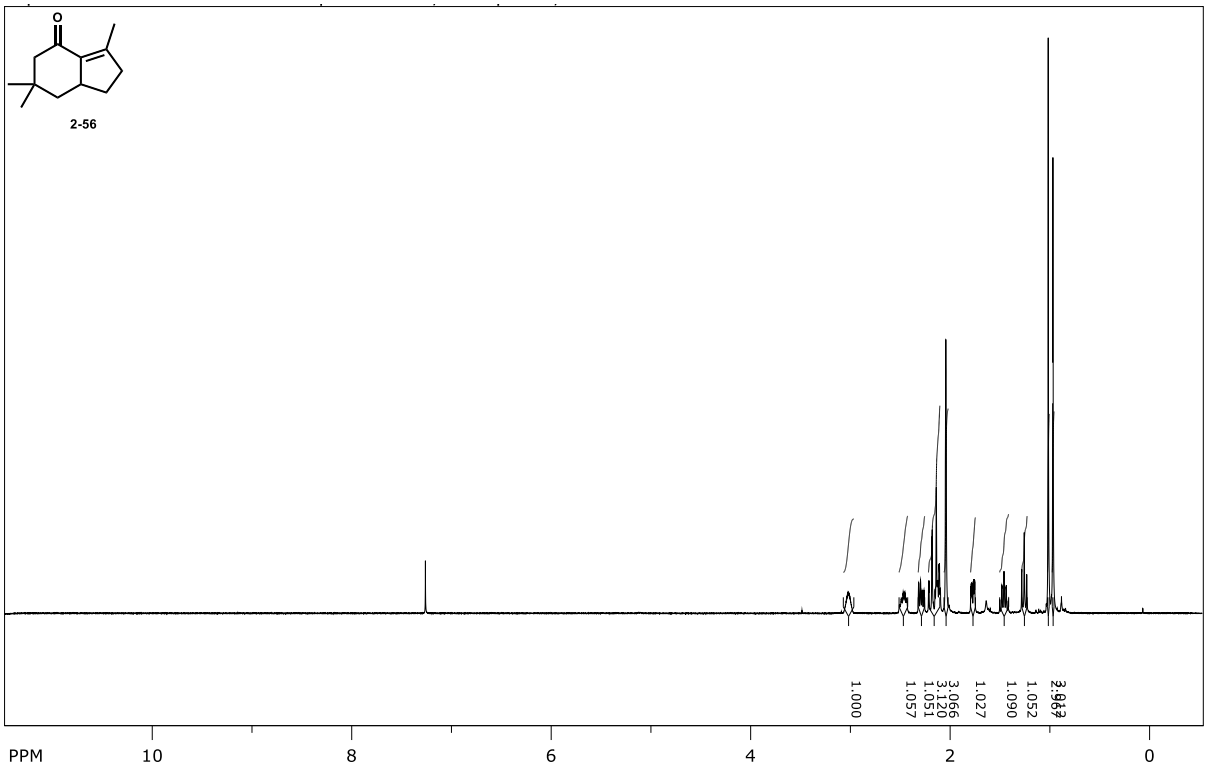

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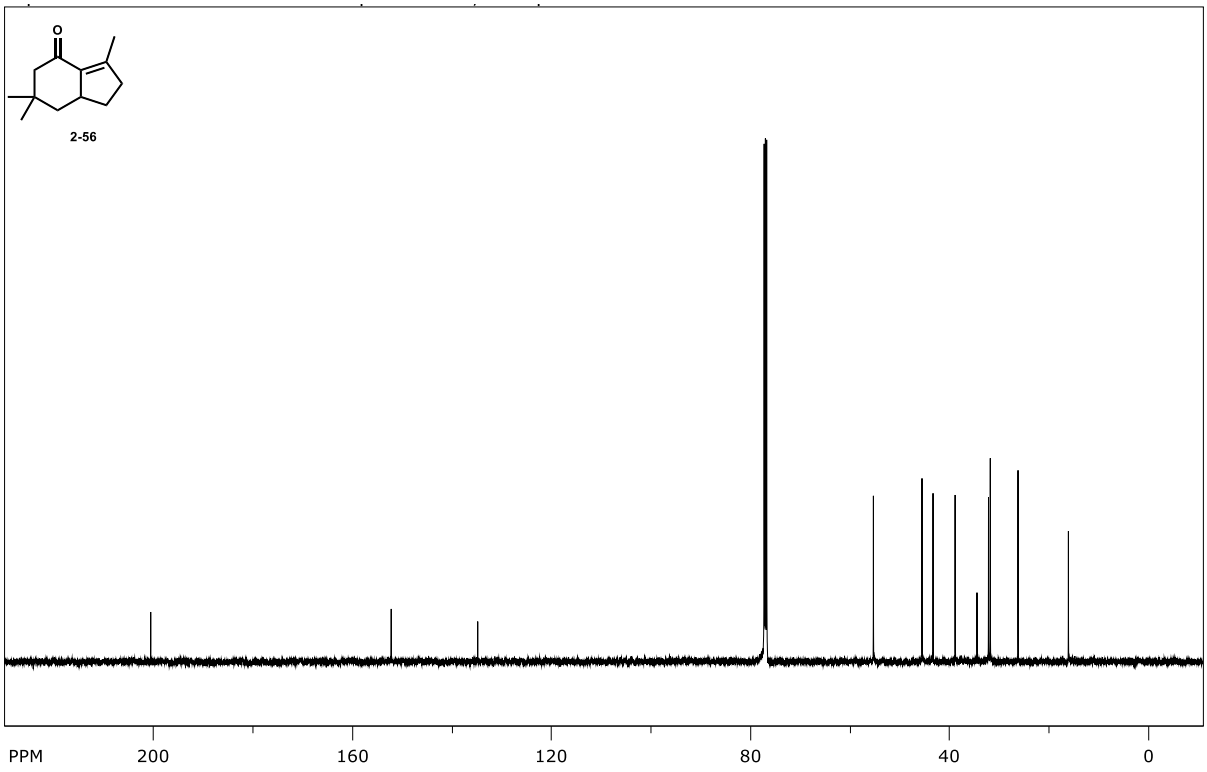

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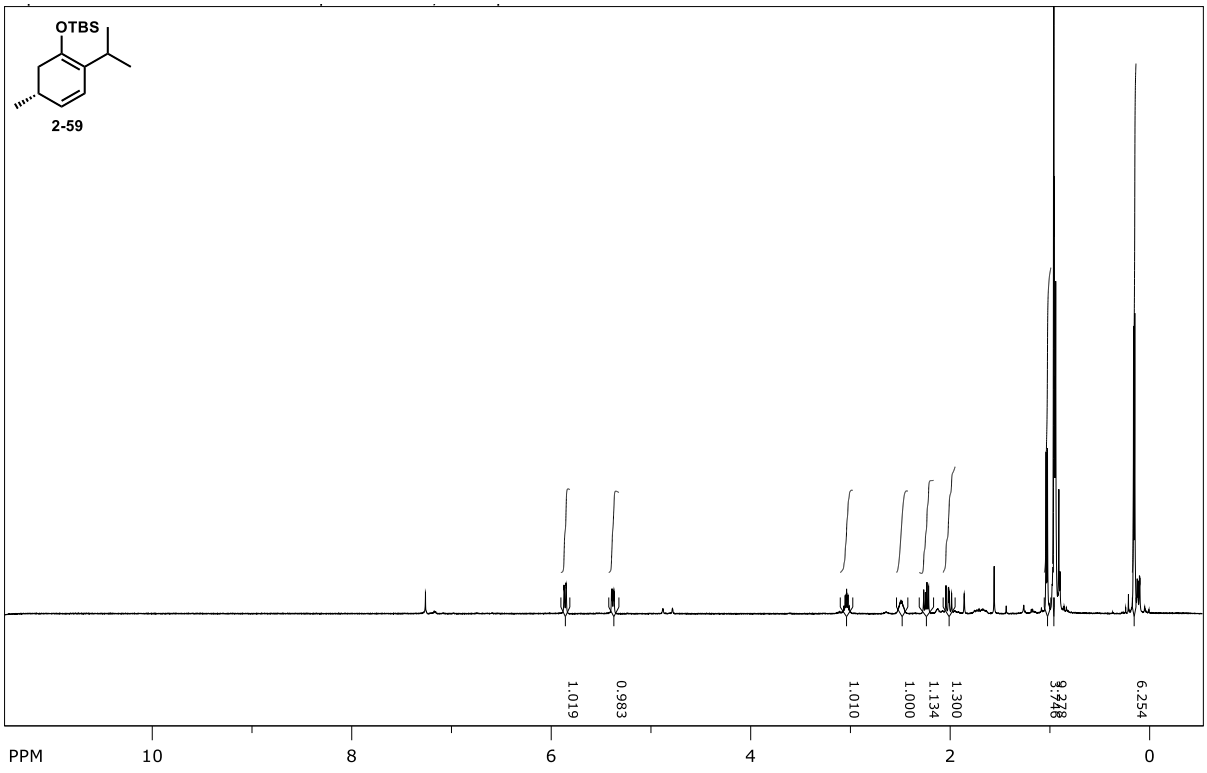

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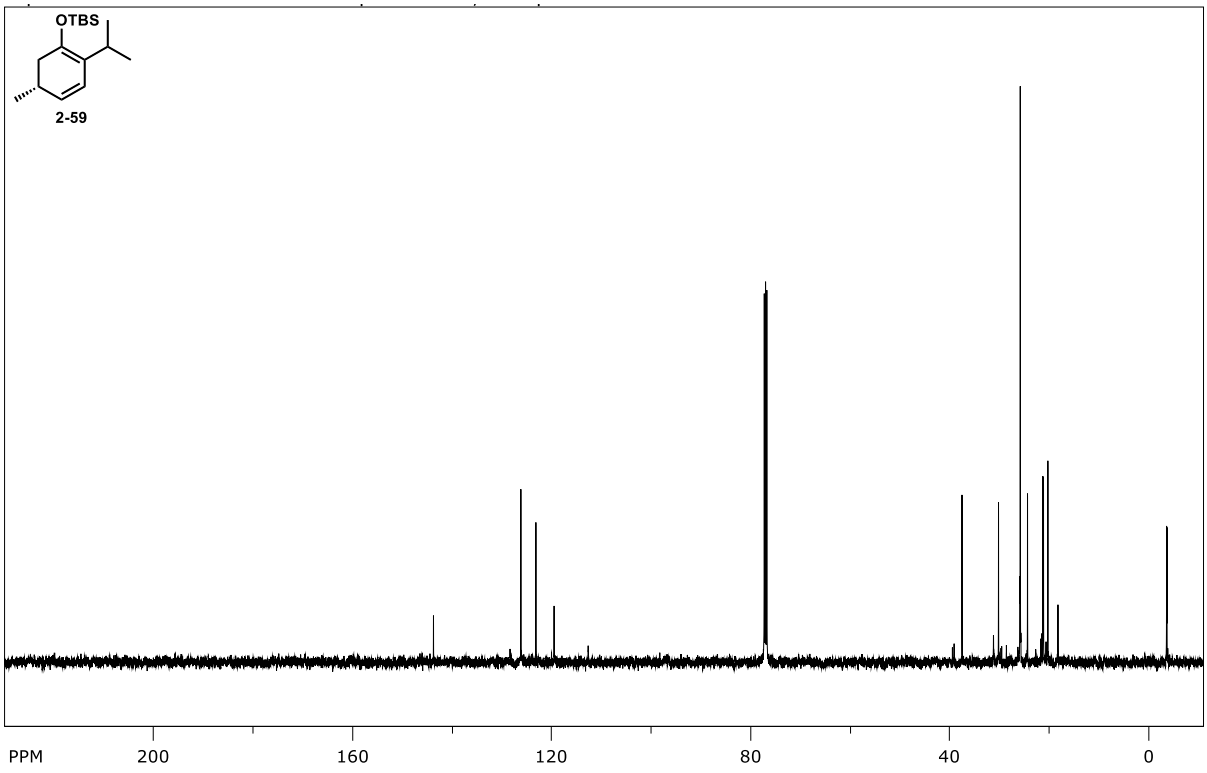

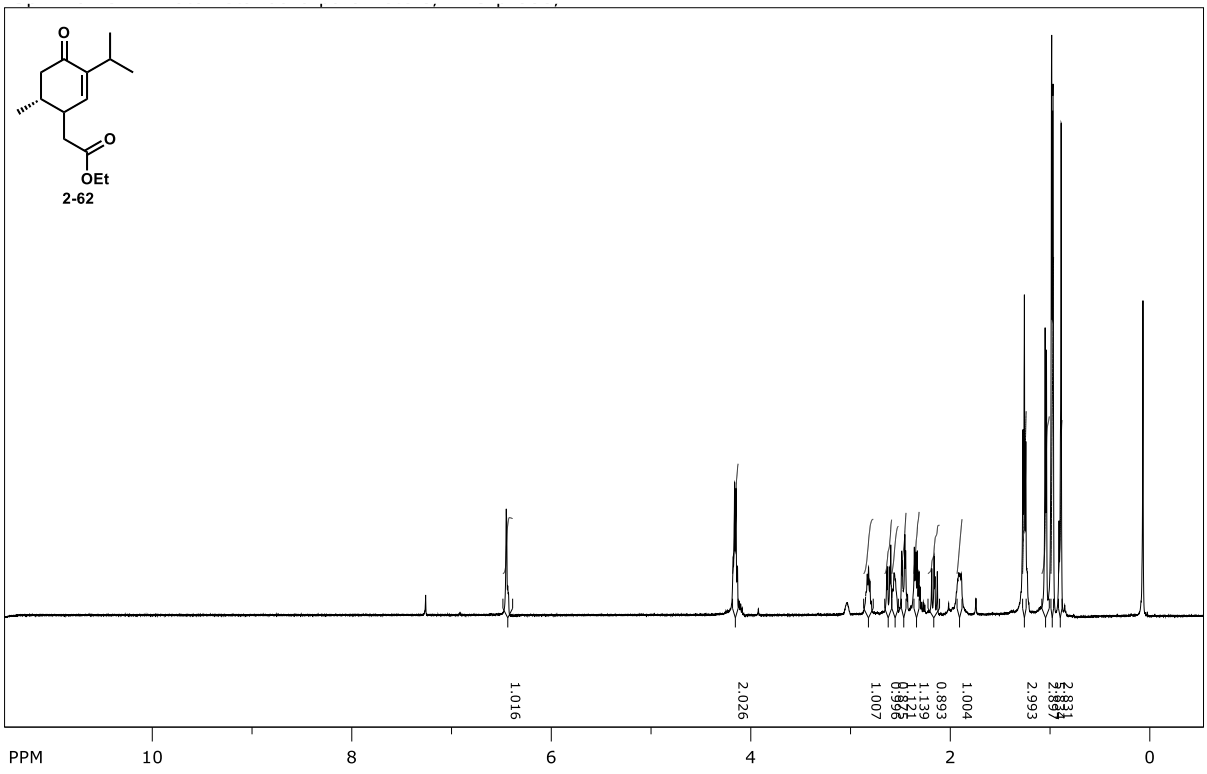

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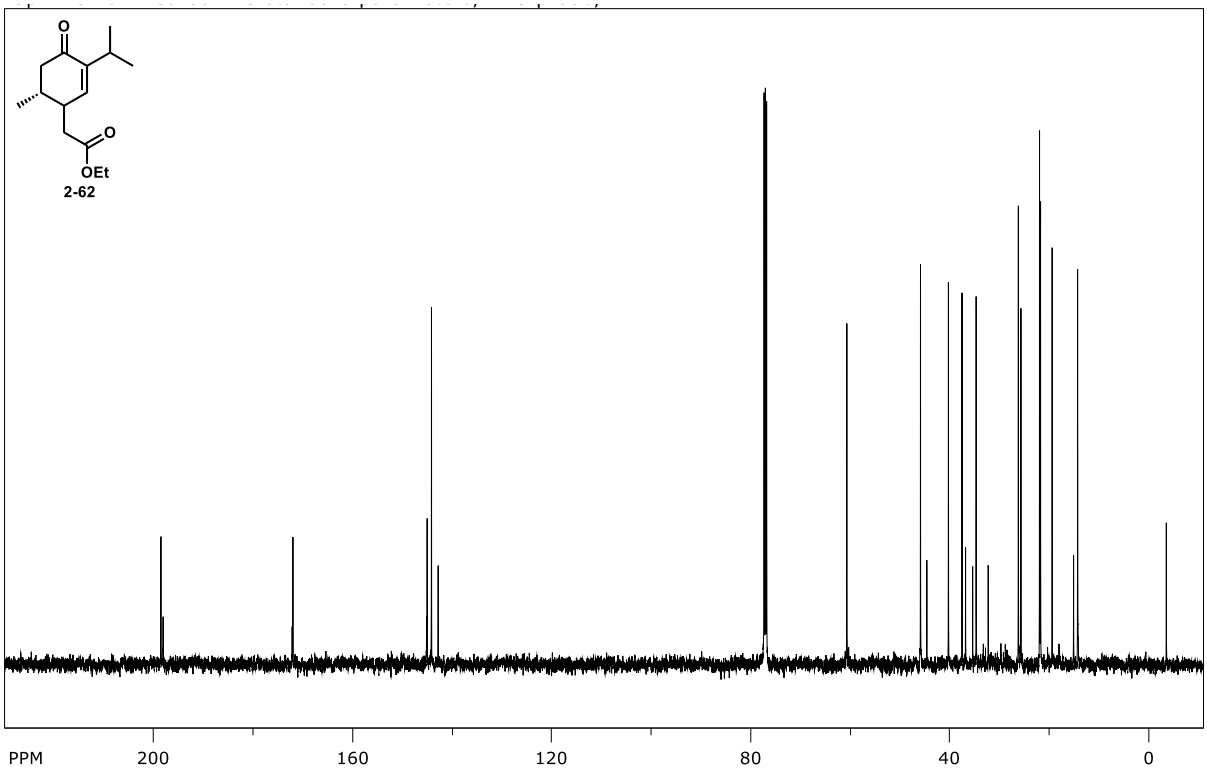
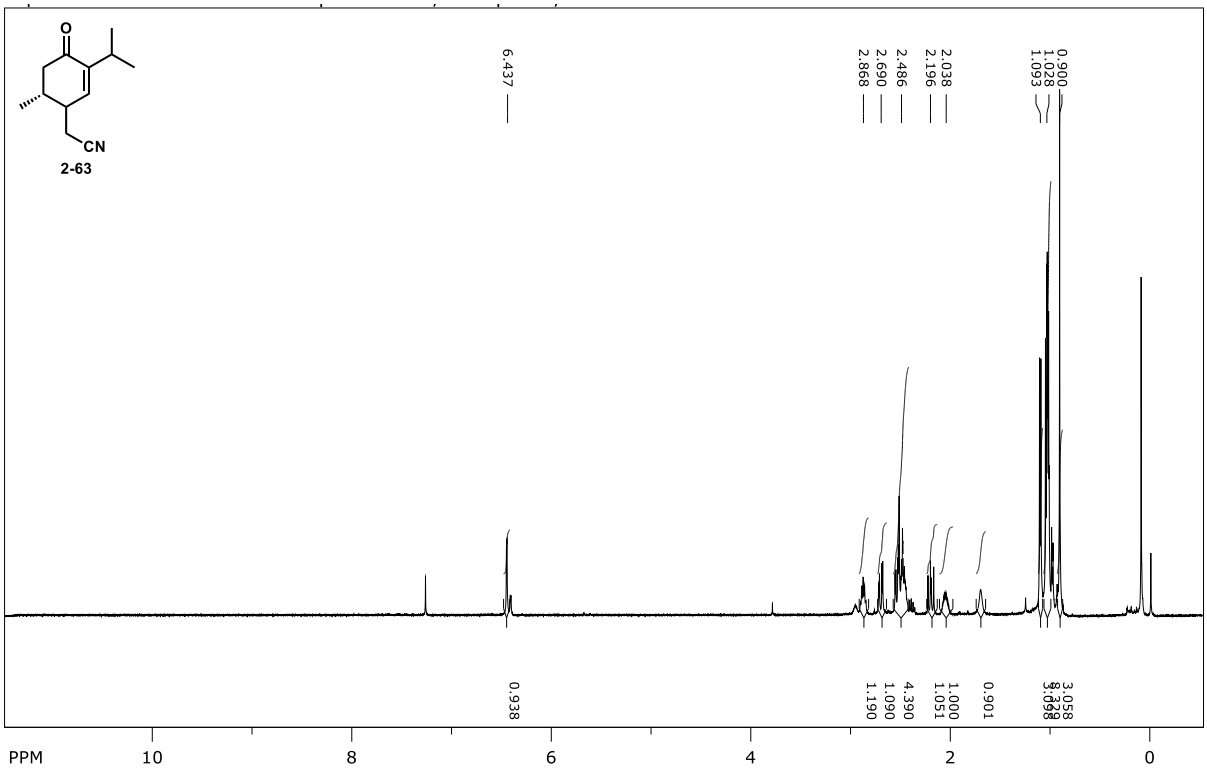


^{13}C NMR (126 MHz, $CDCl_3$)



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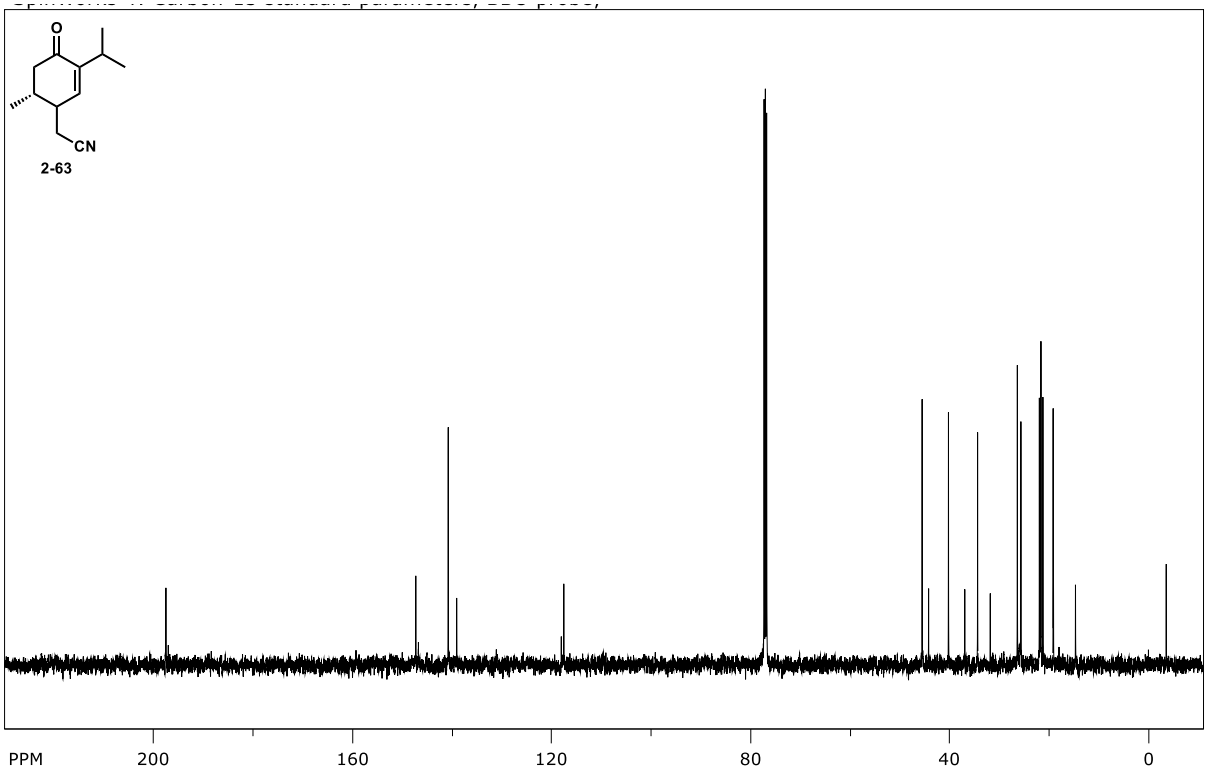

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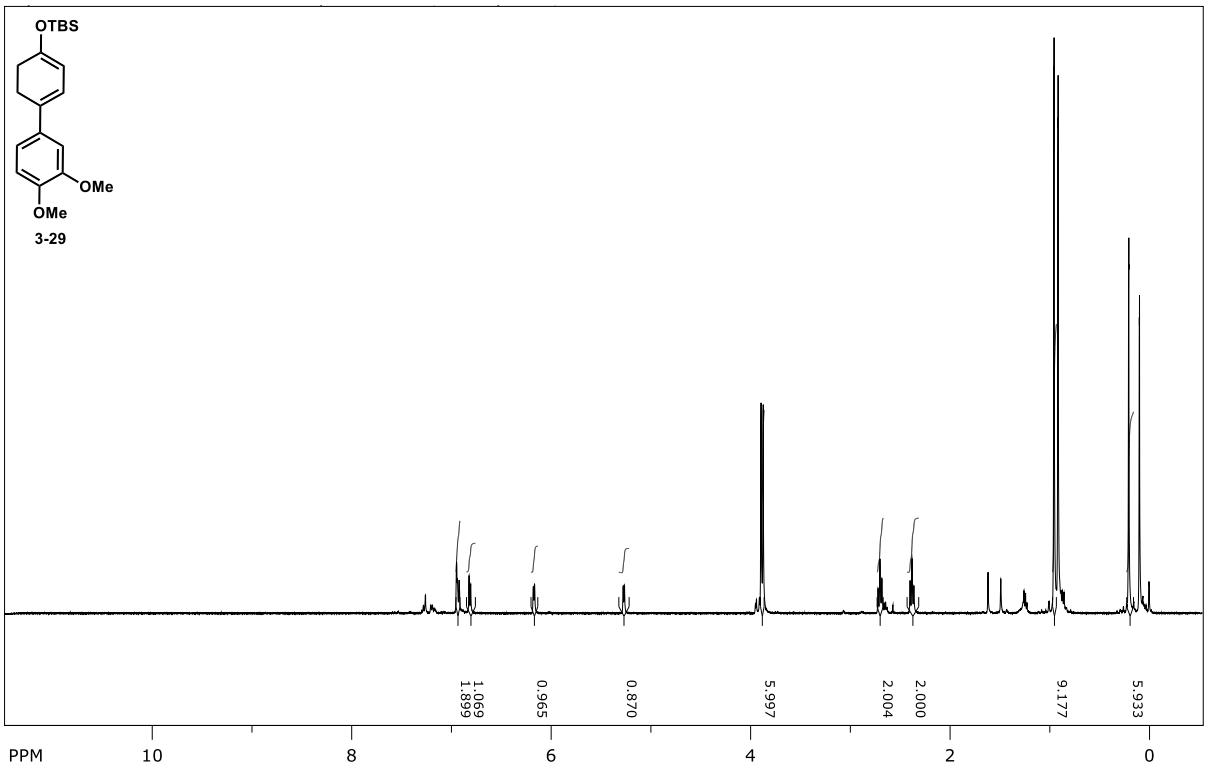

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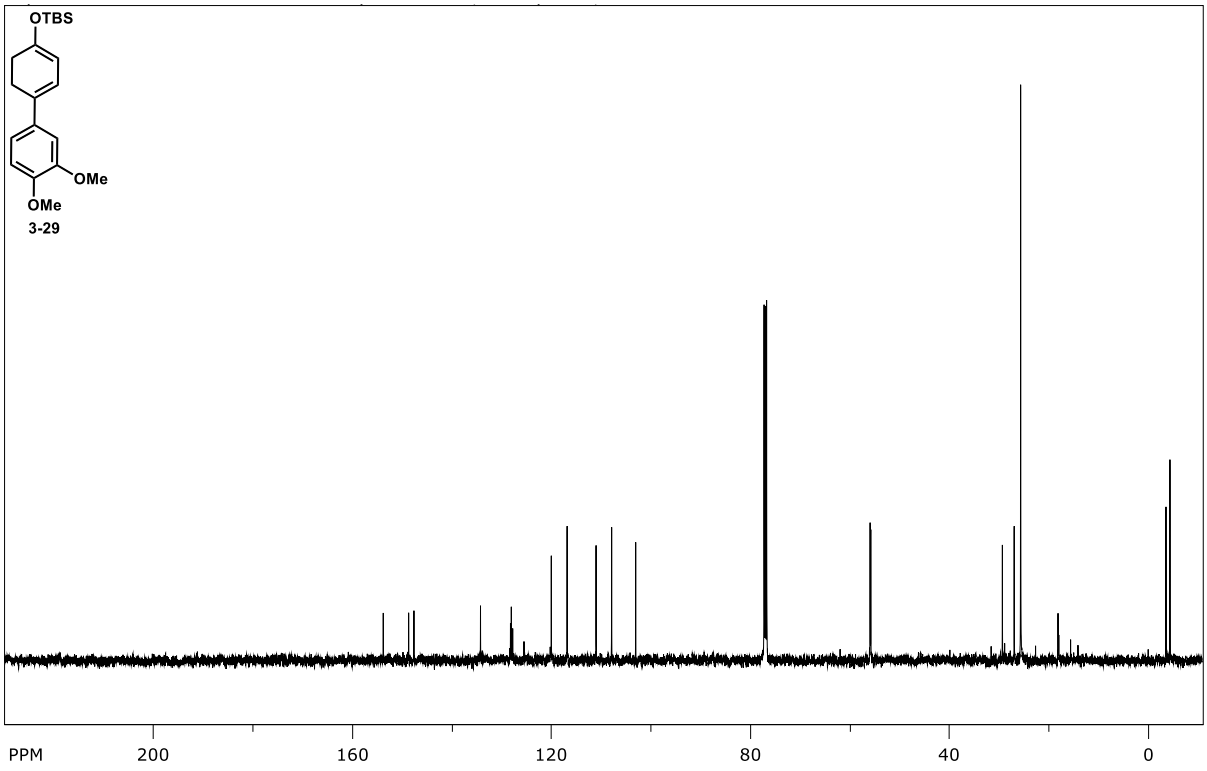

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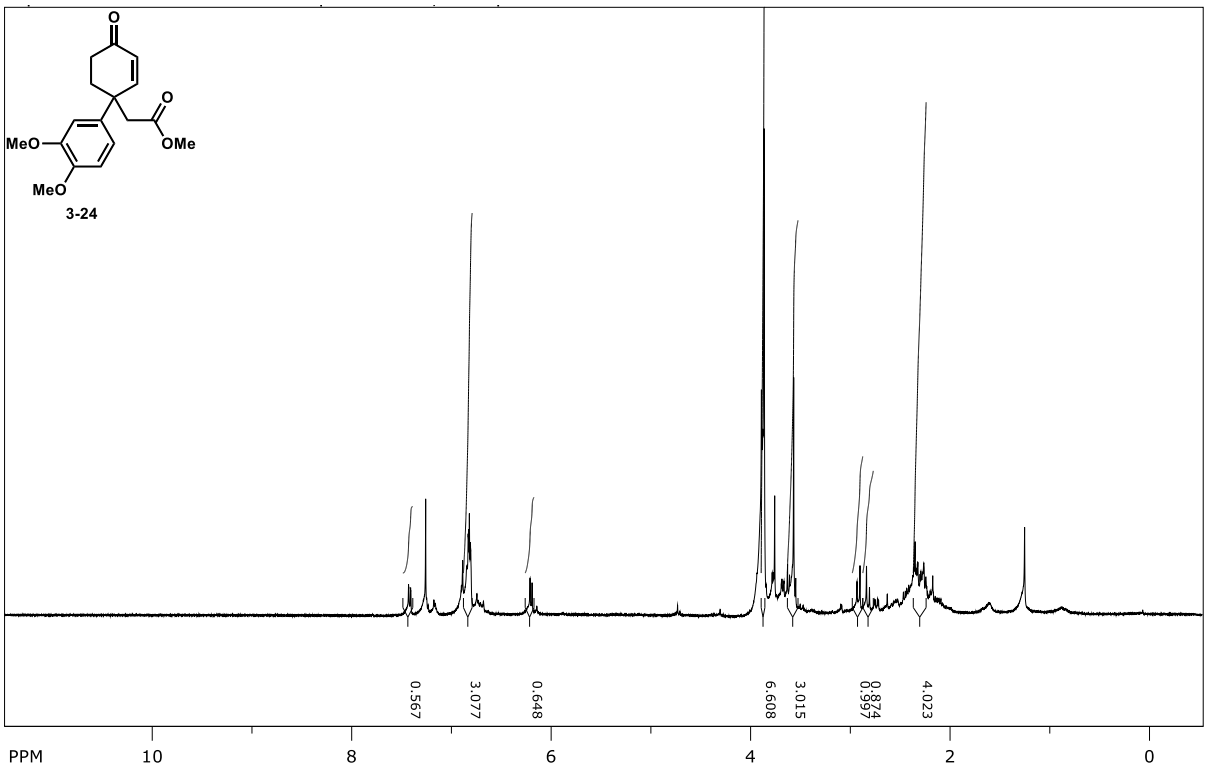

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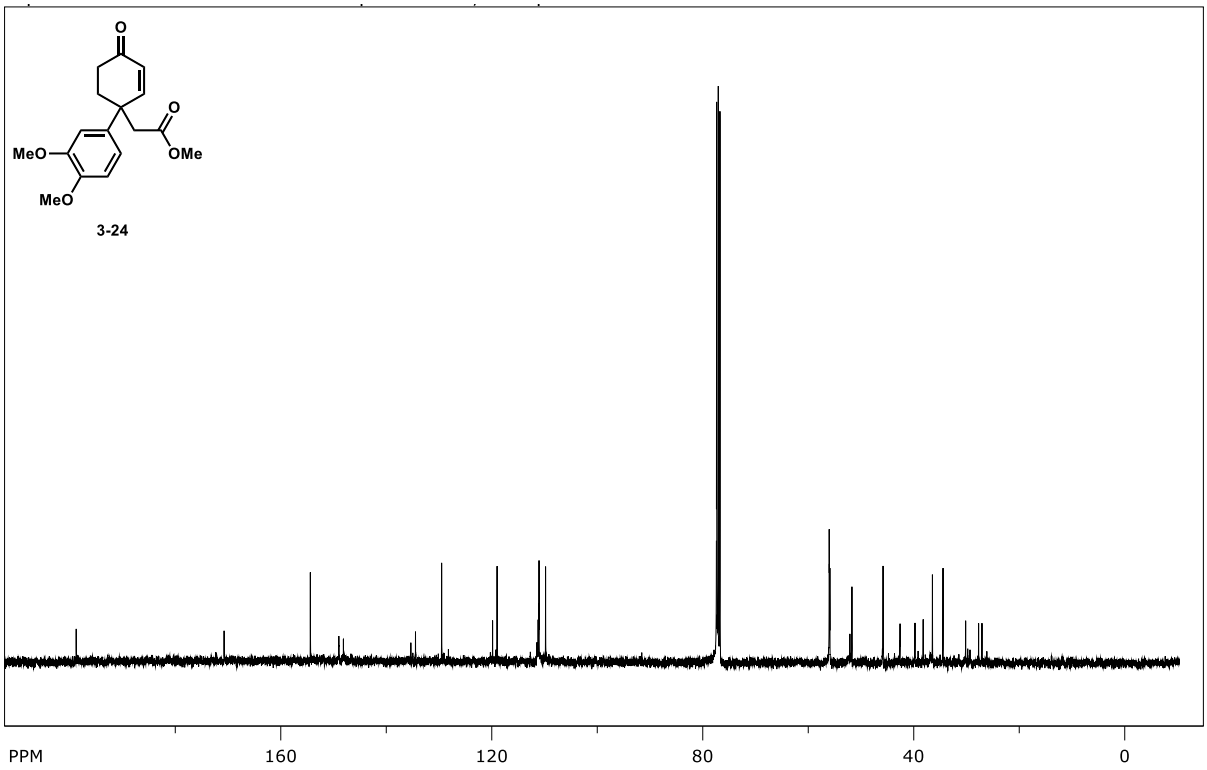

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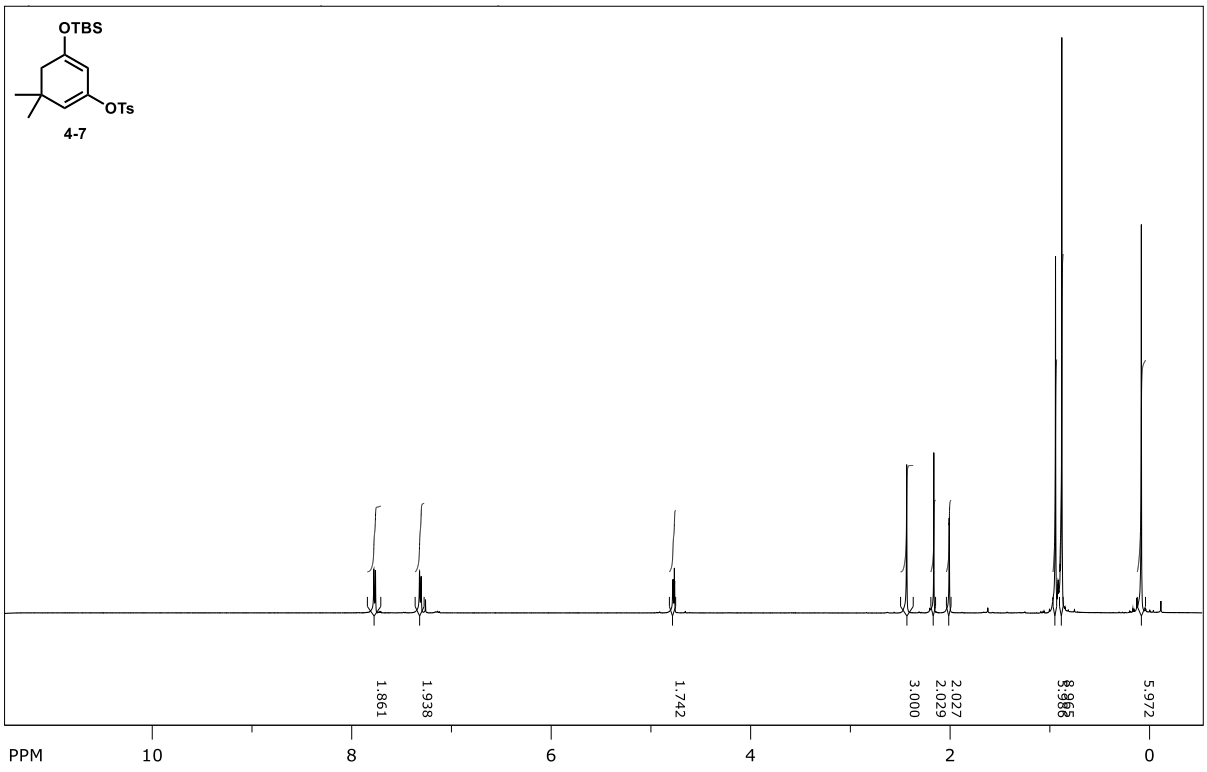

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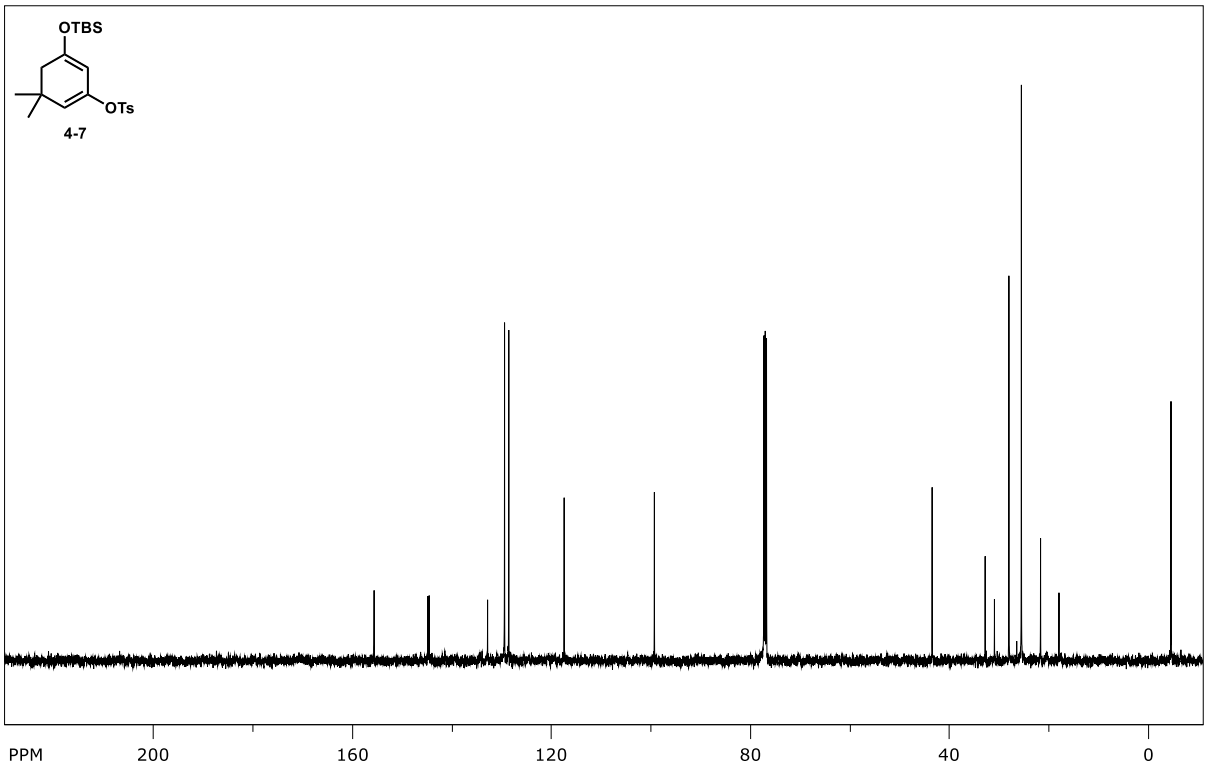
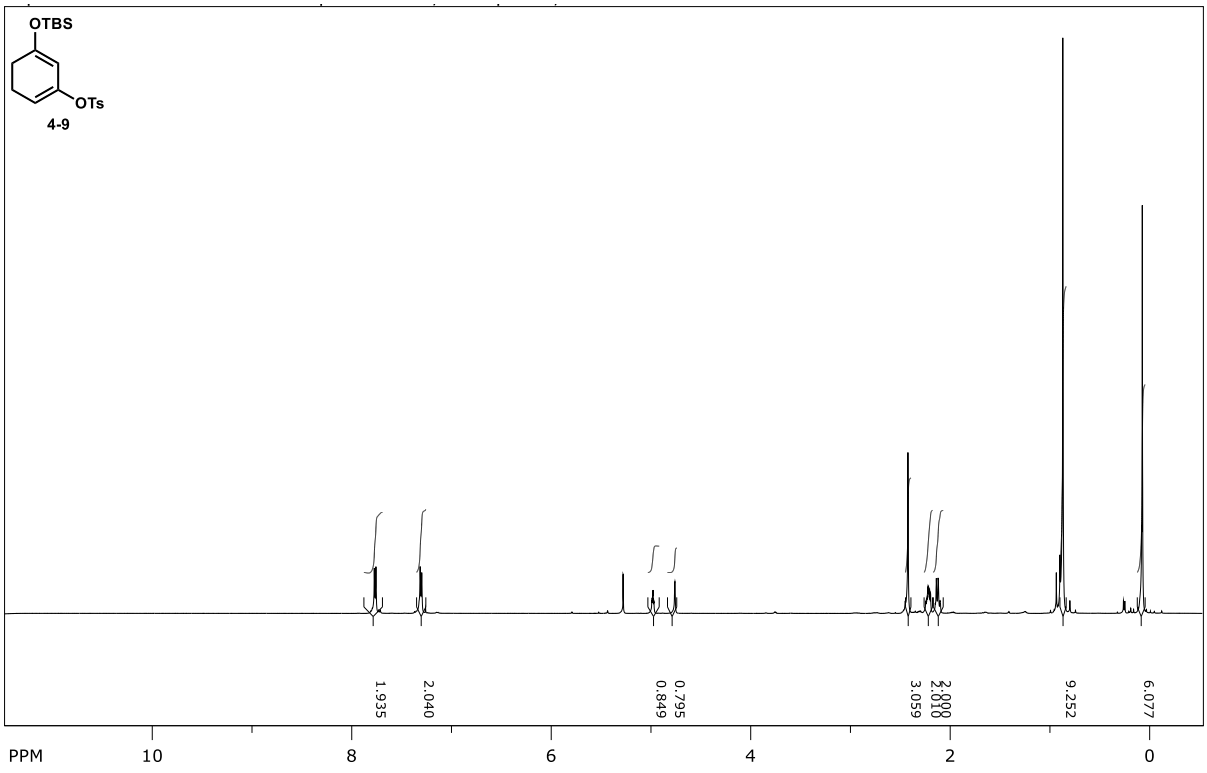


^{13}C NMR (126 MHz, $CDCl_3$)



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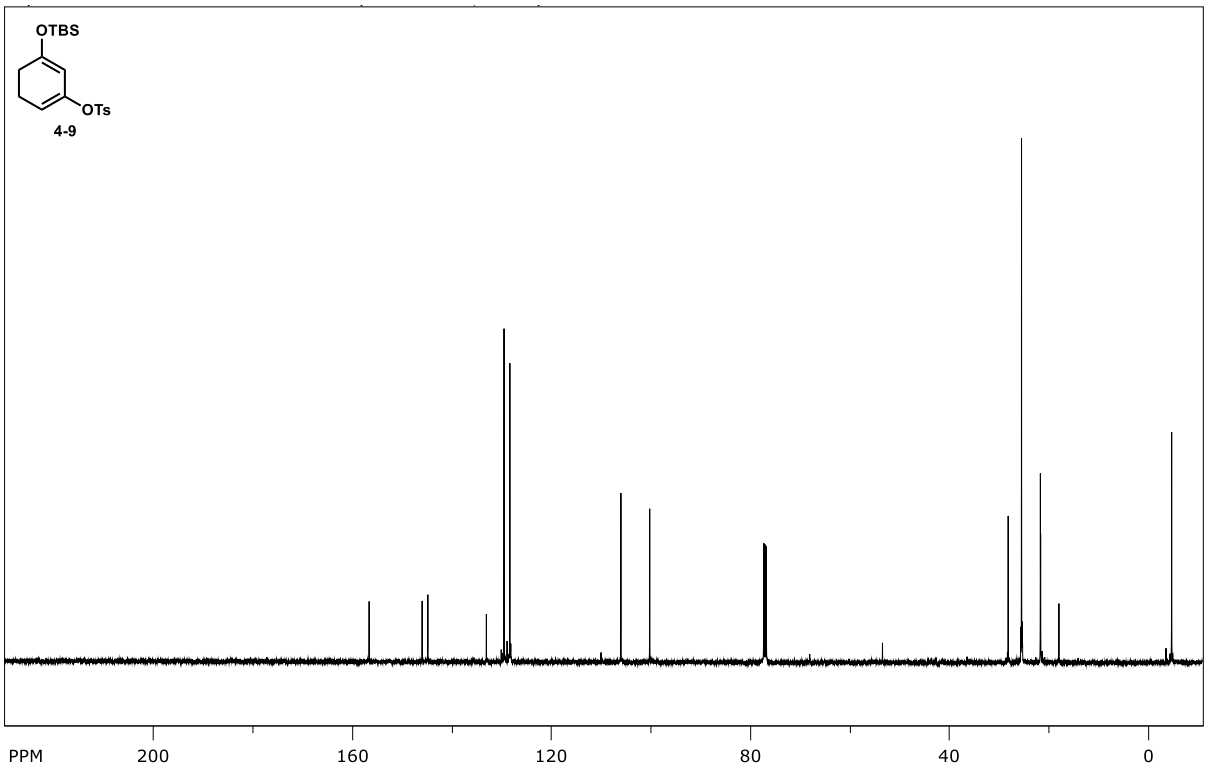

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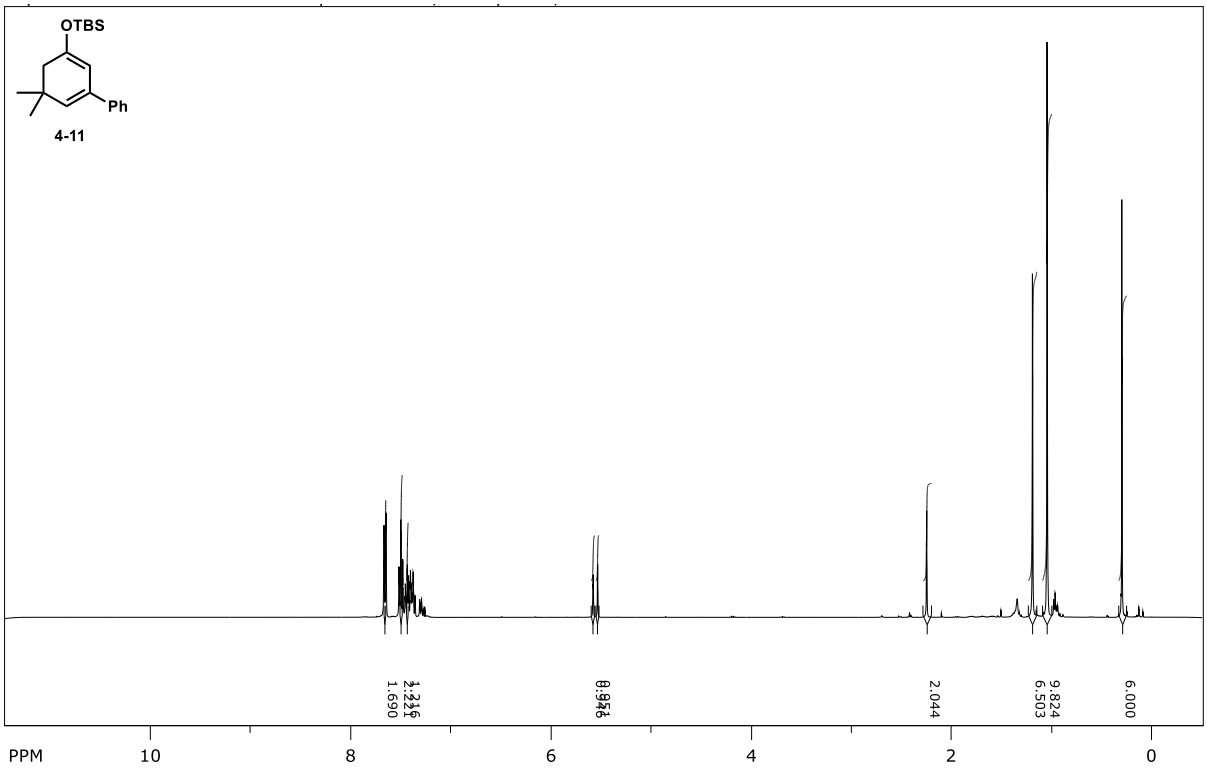

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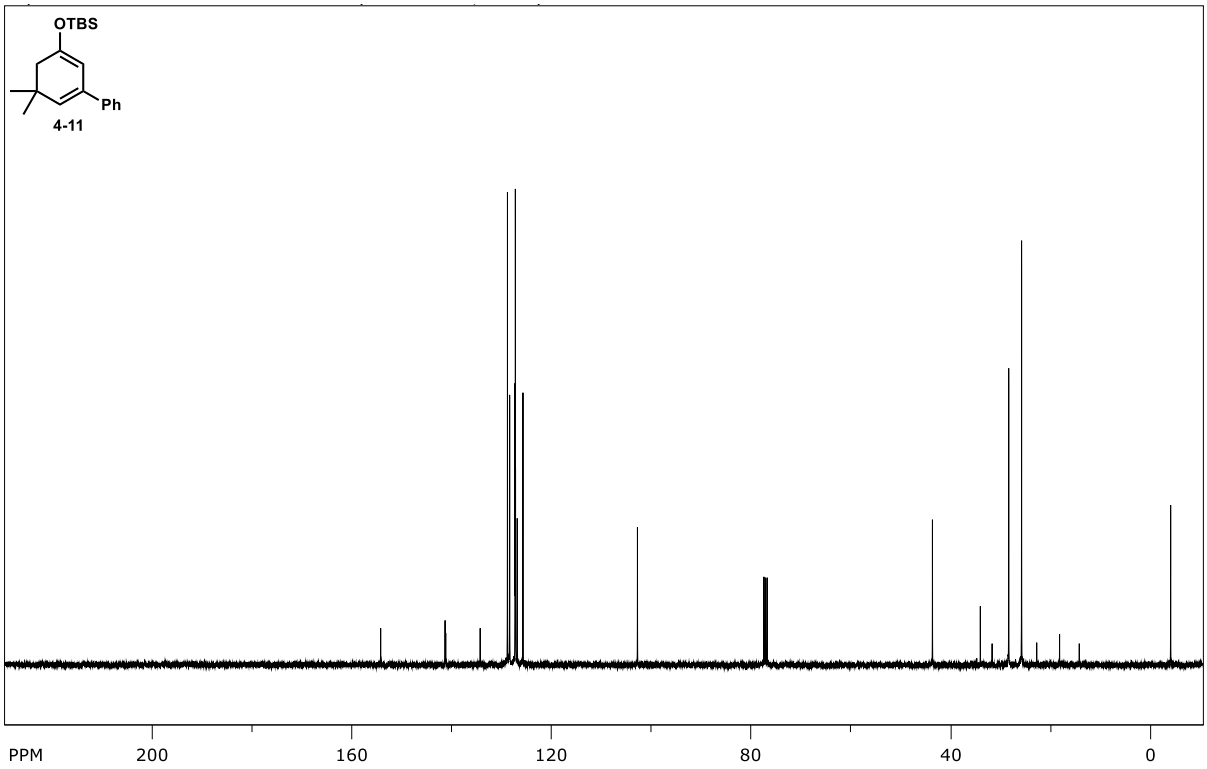
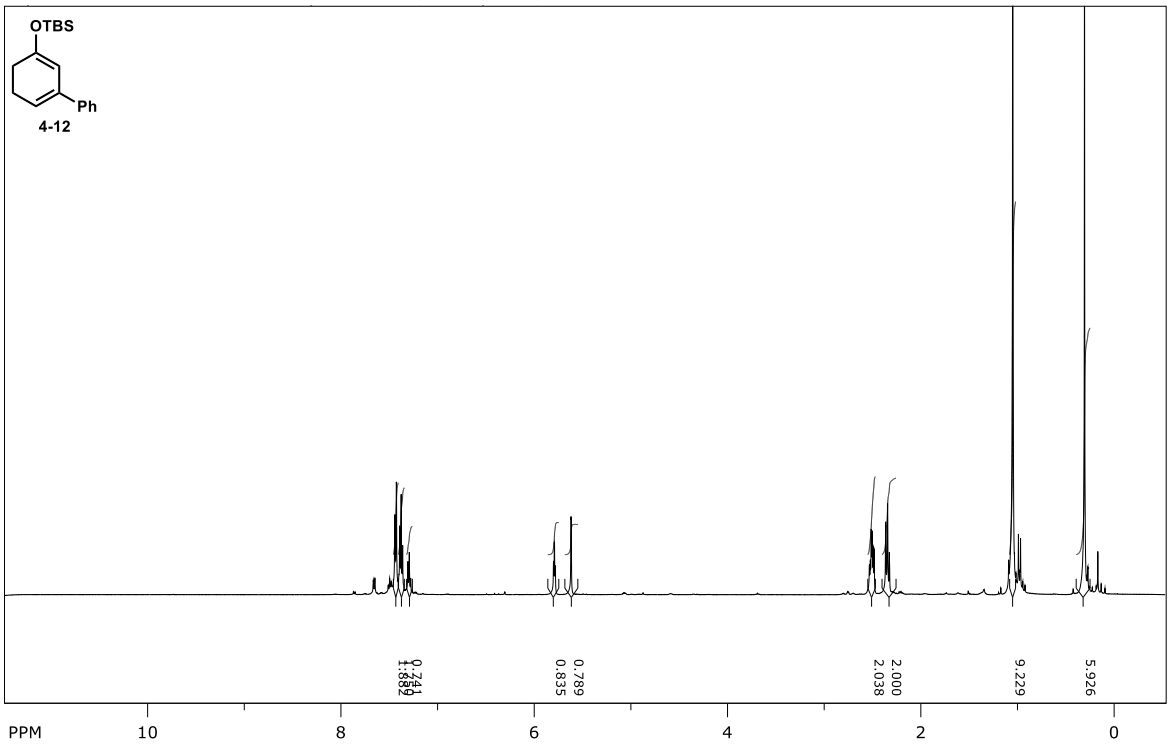
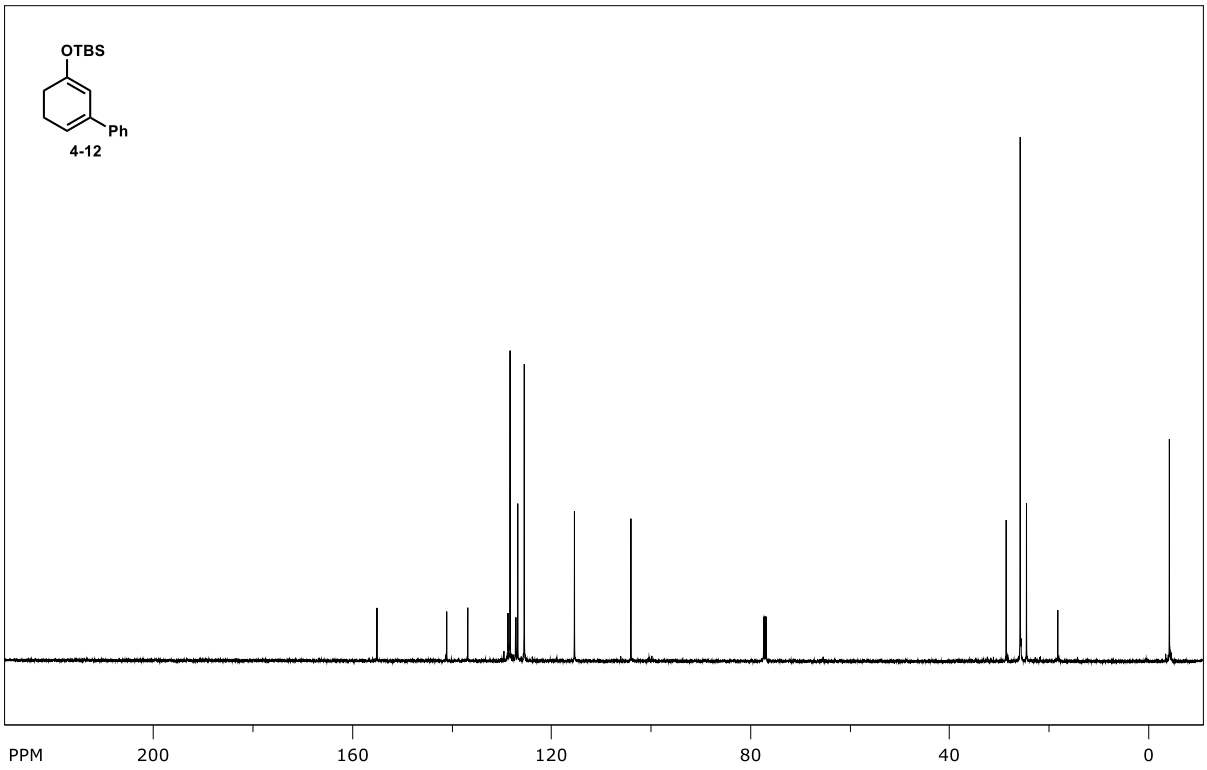


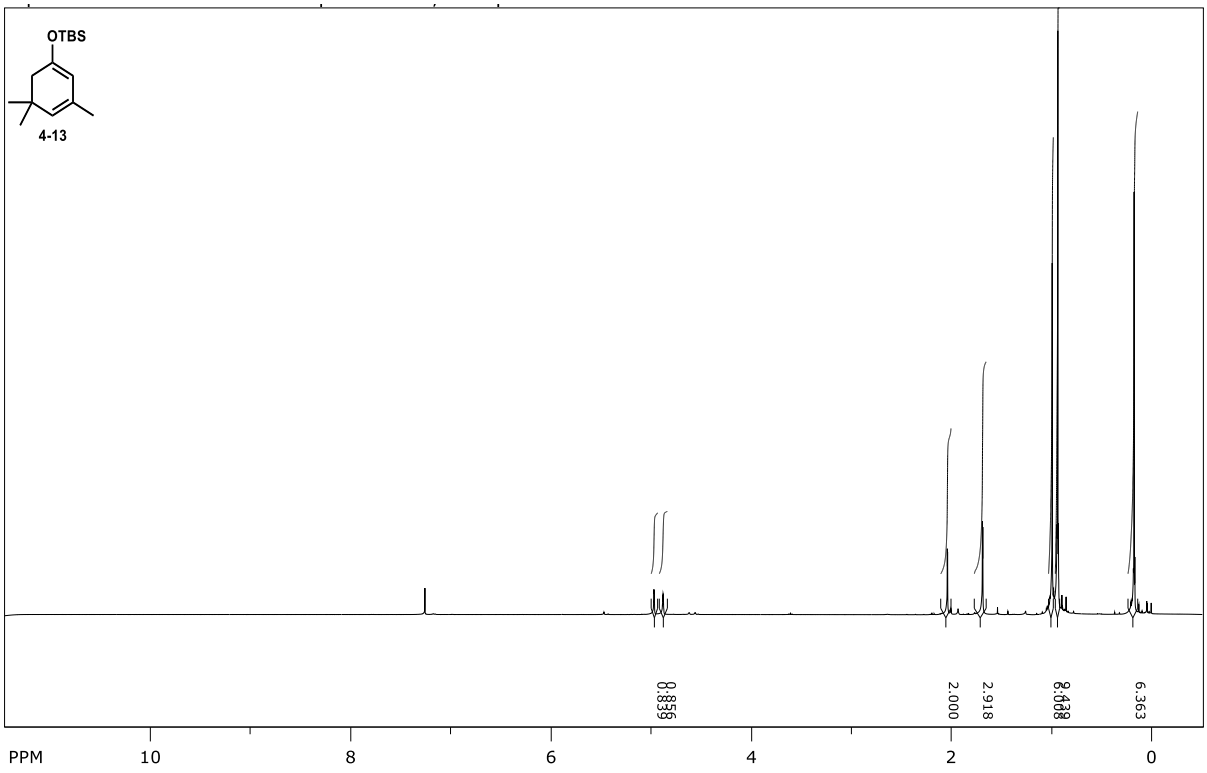
^{13}C NMR (126 MHz, $CDCl_3$)



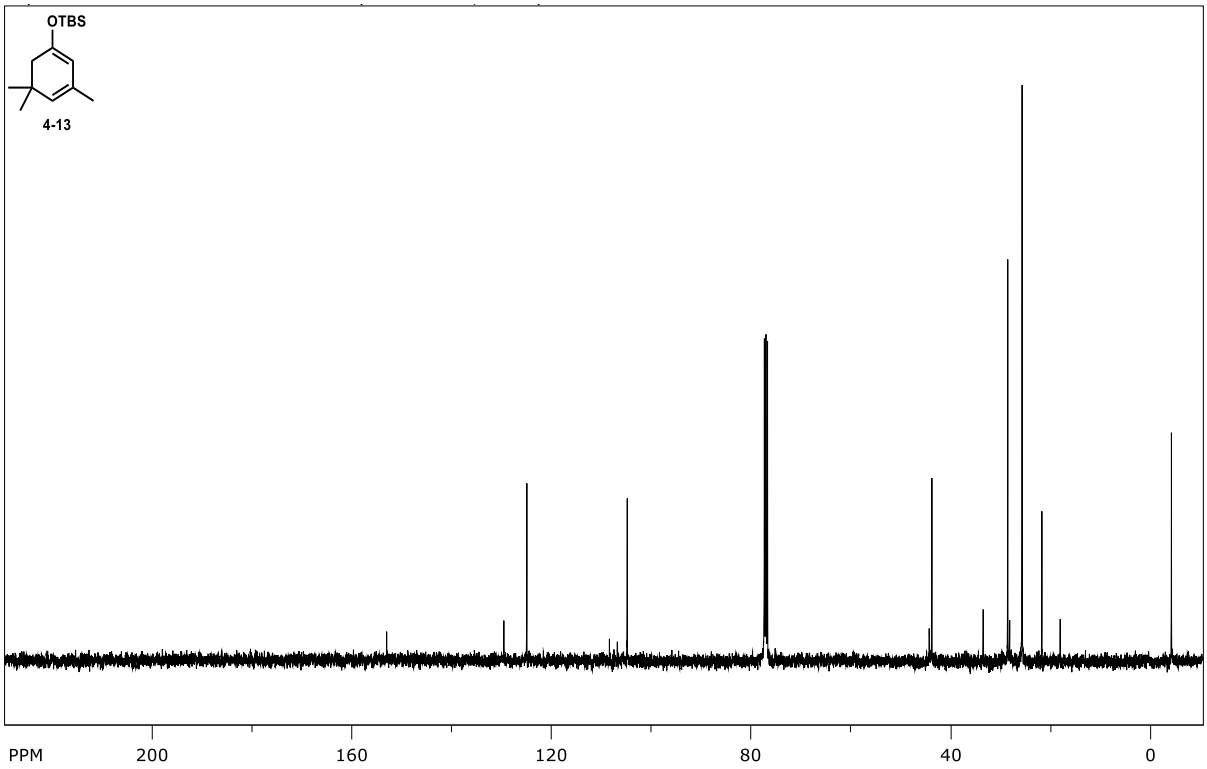
^{1}H NMR (500 MHz, $CDCl_3$)



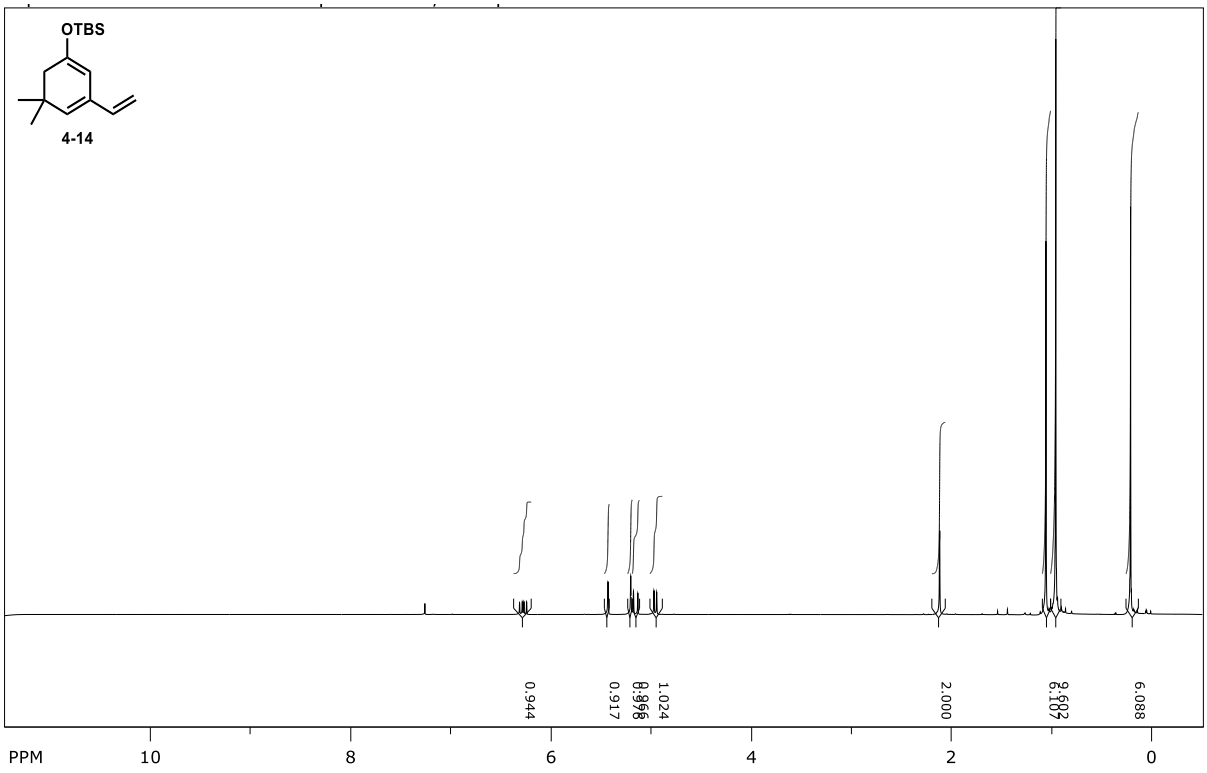
^{13}C NMR (126 MHz, $CDCl_3$)



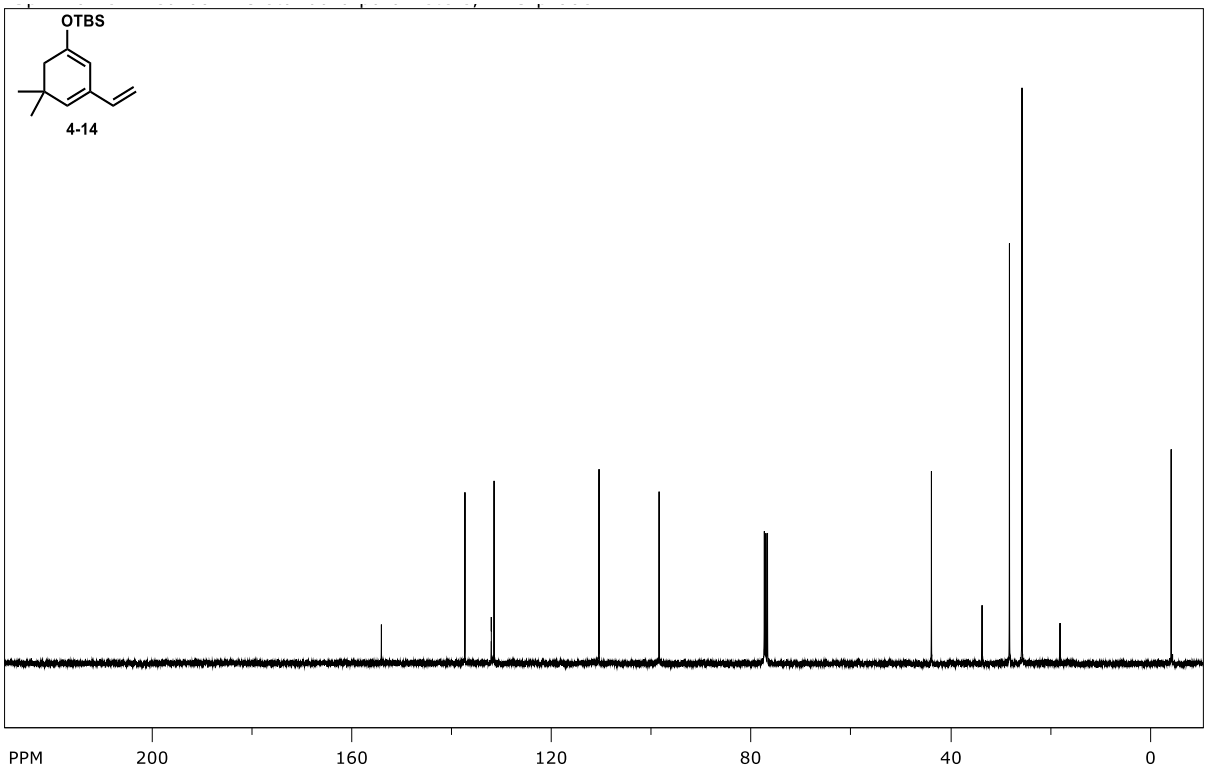
^{1}H NMR (500 MHz, $CDCl_3$)



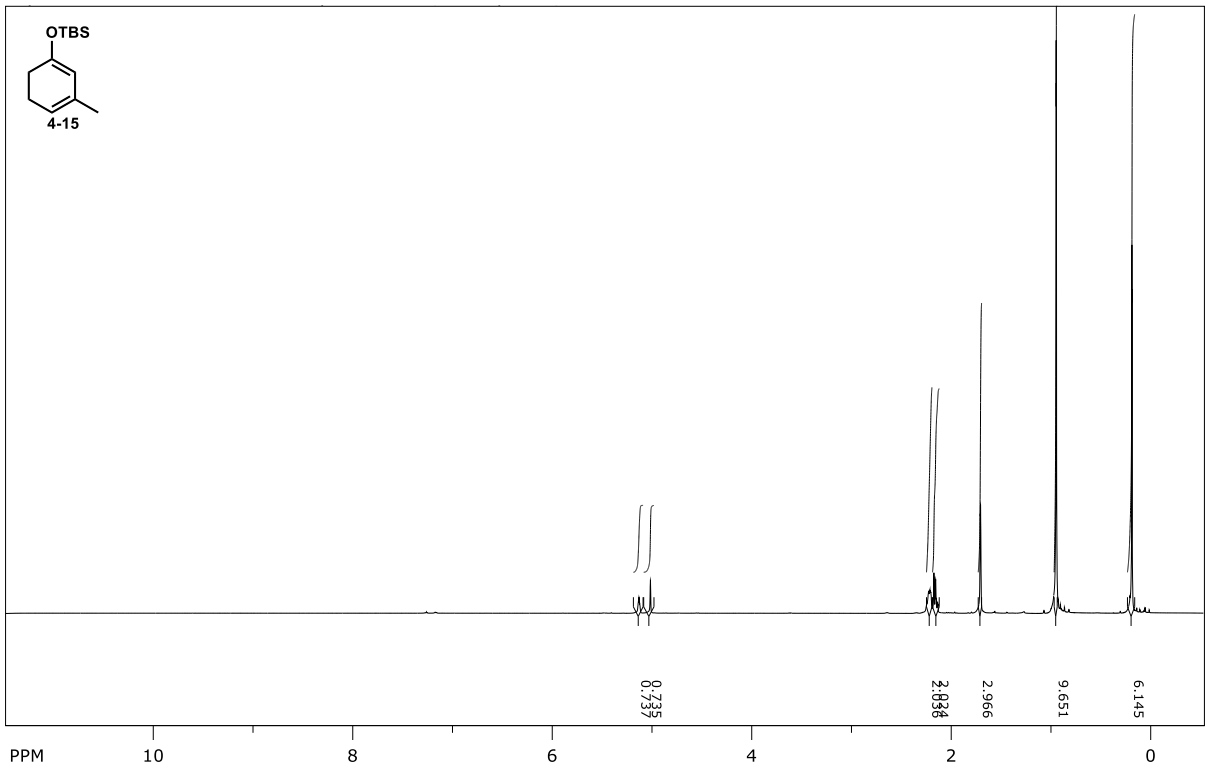
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



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



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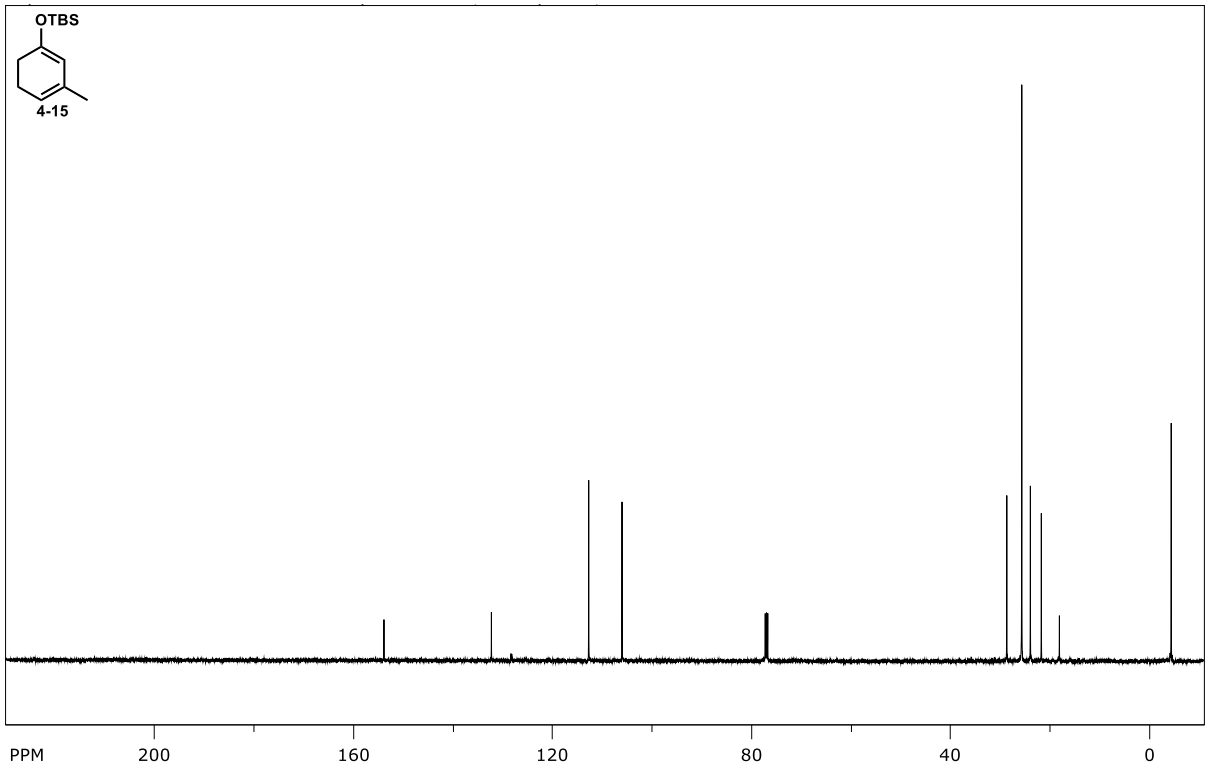
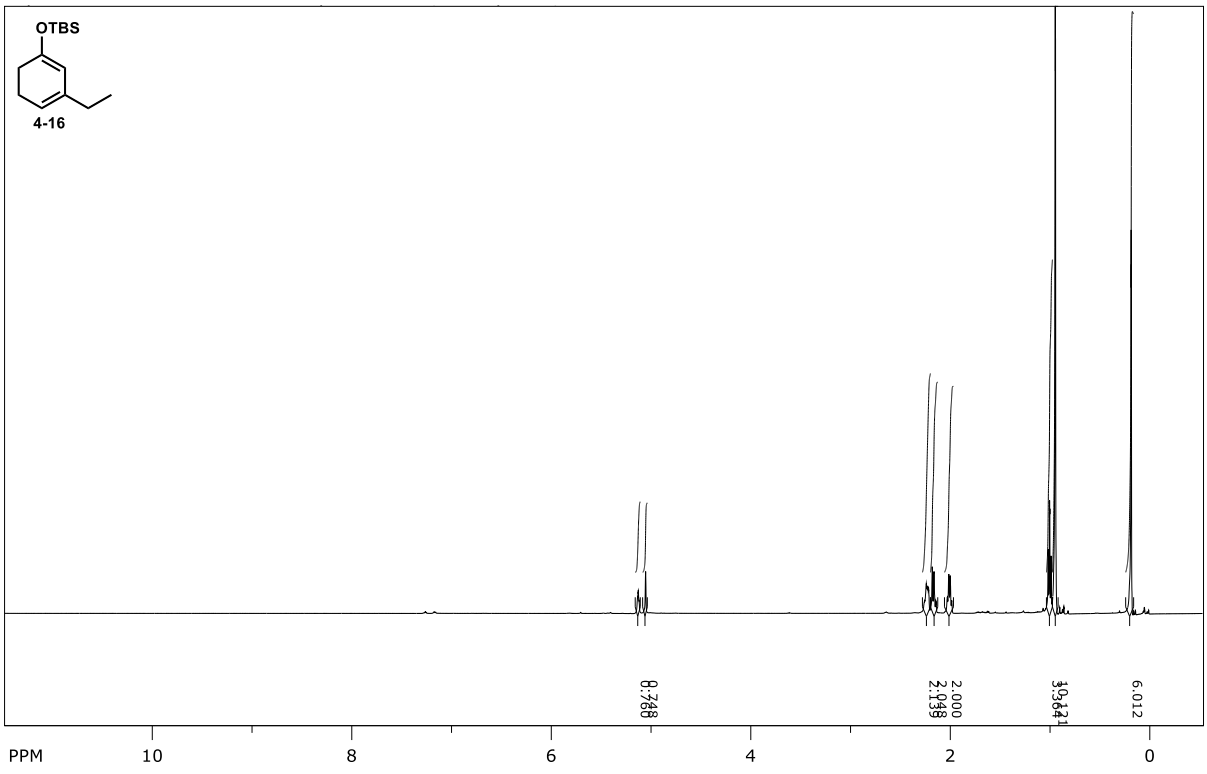


^{13}C NMR (126 MHz, $CDCl_3$)



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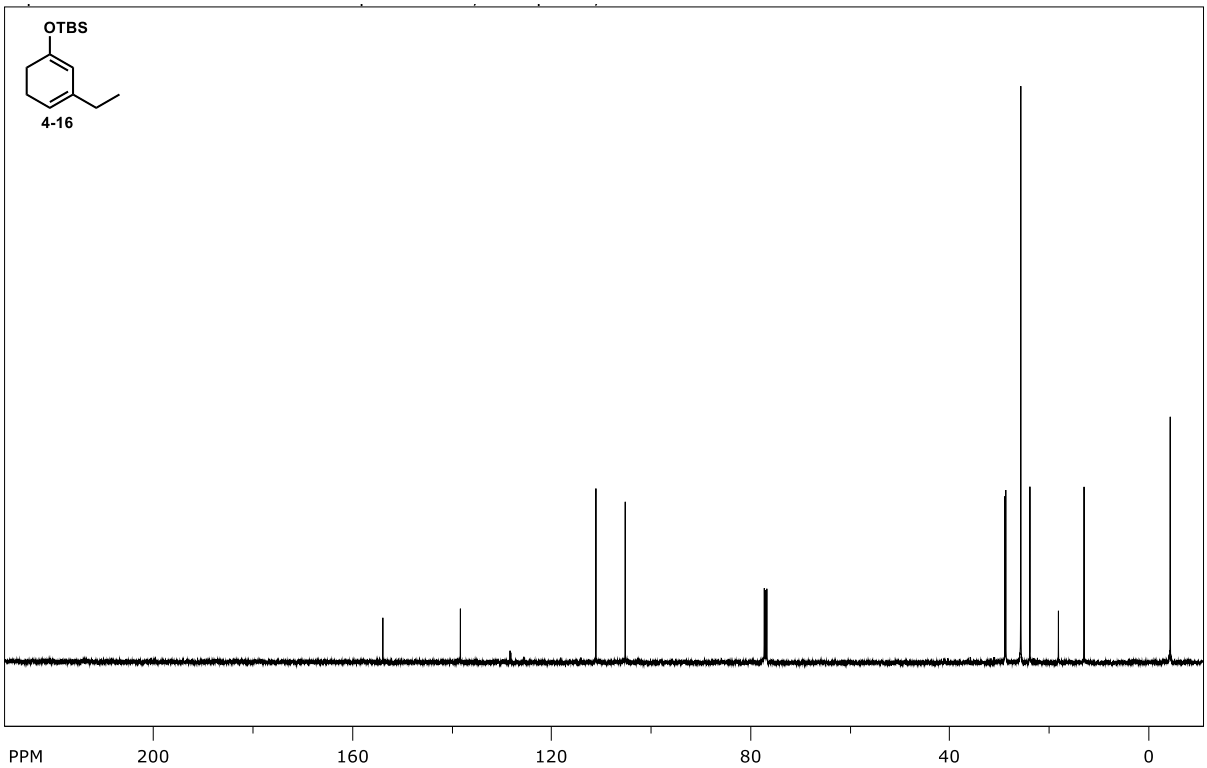
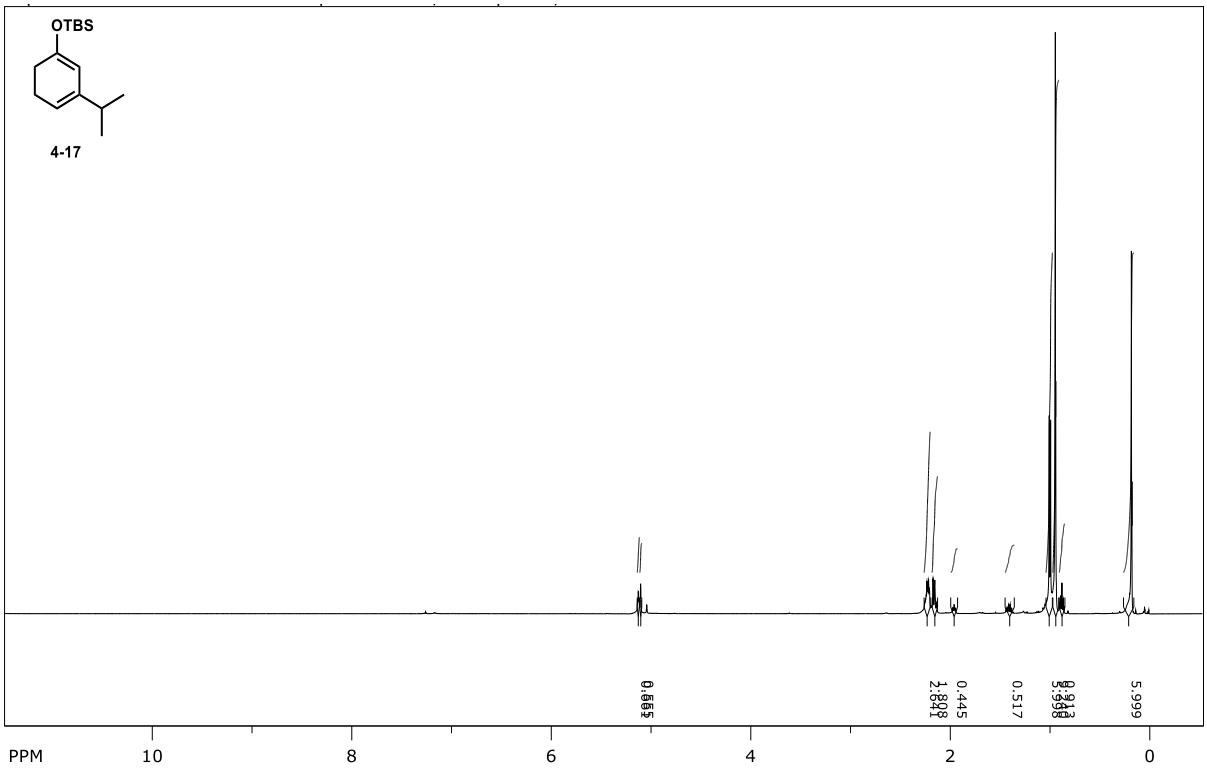
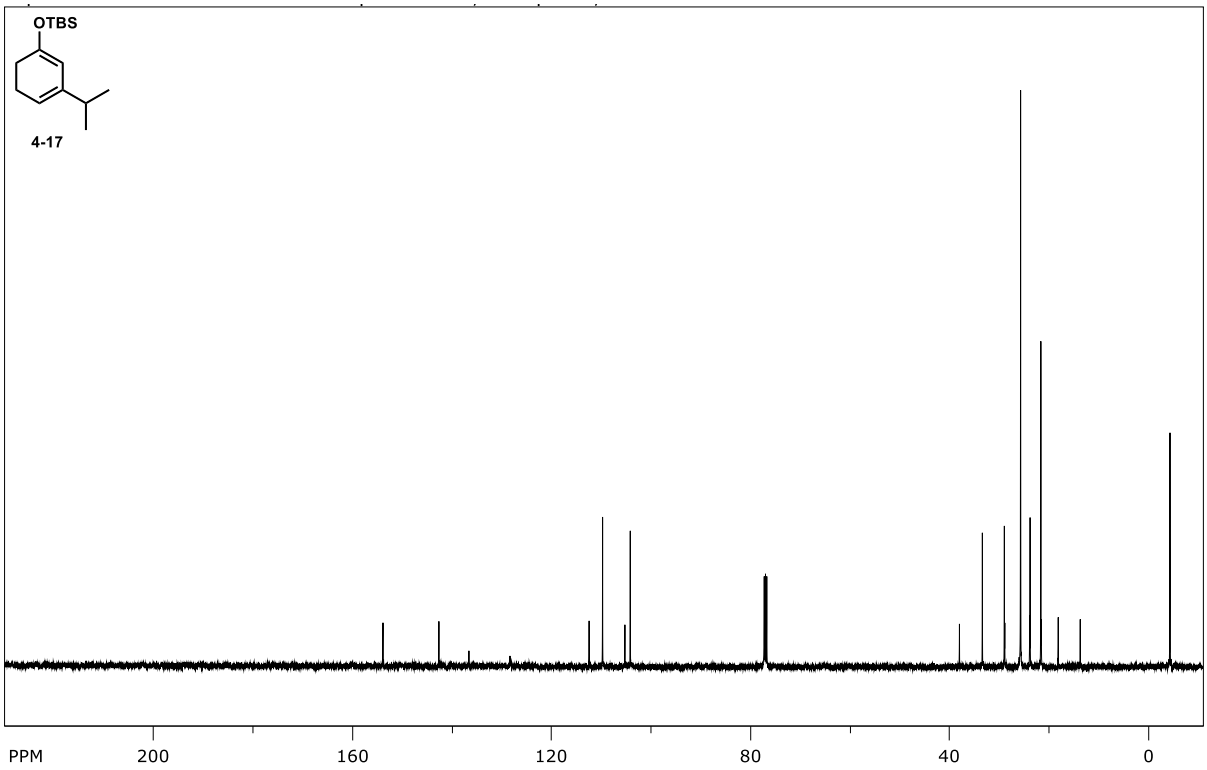


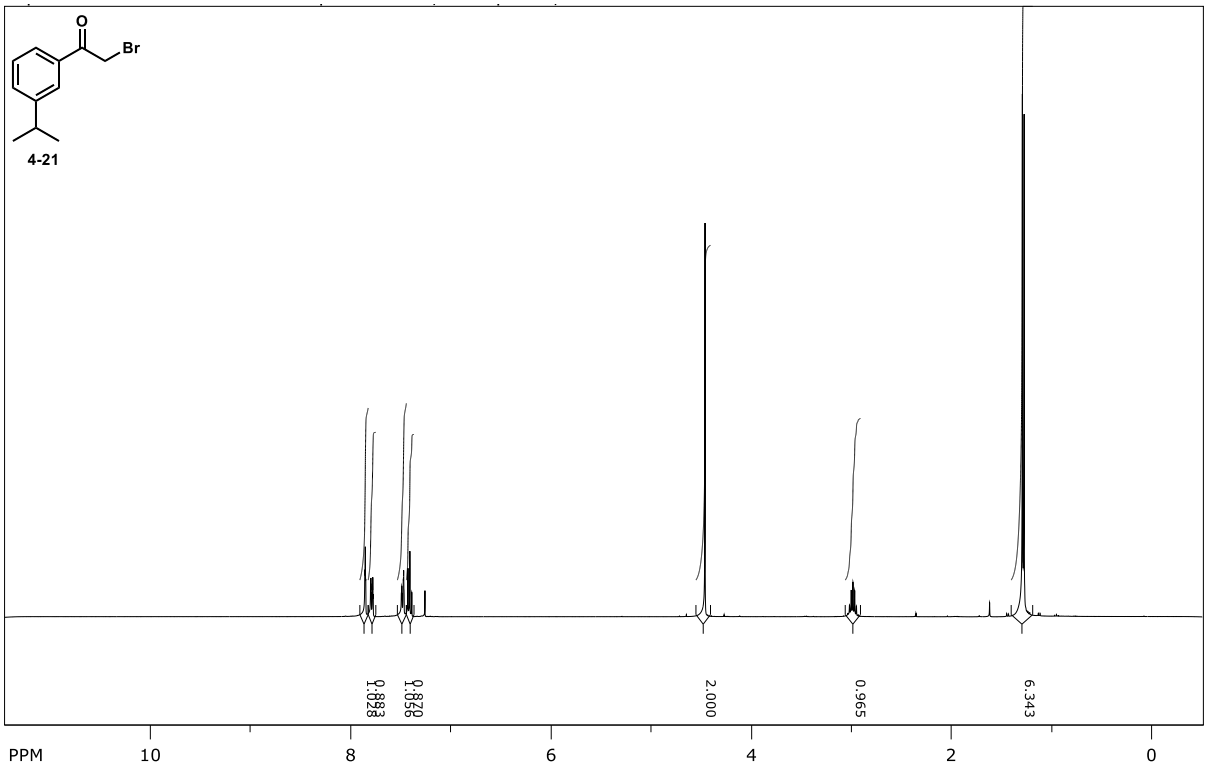
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



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



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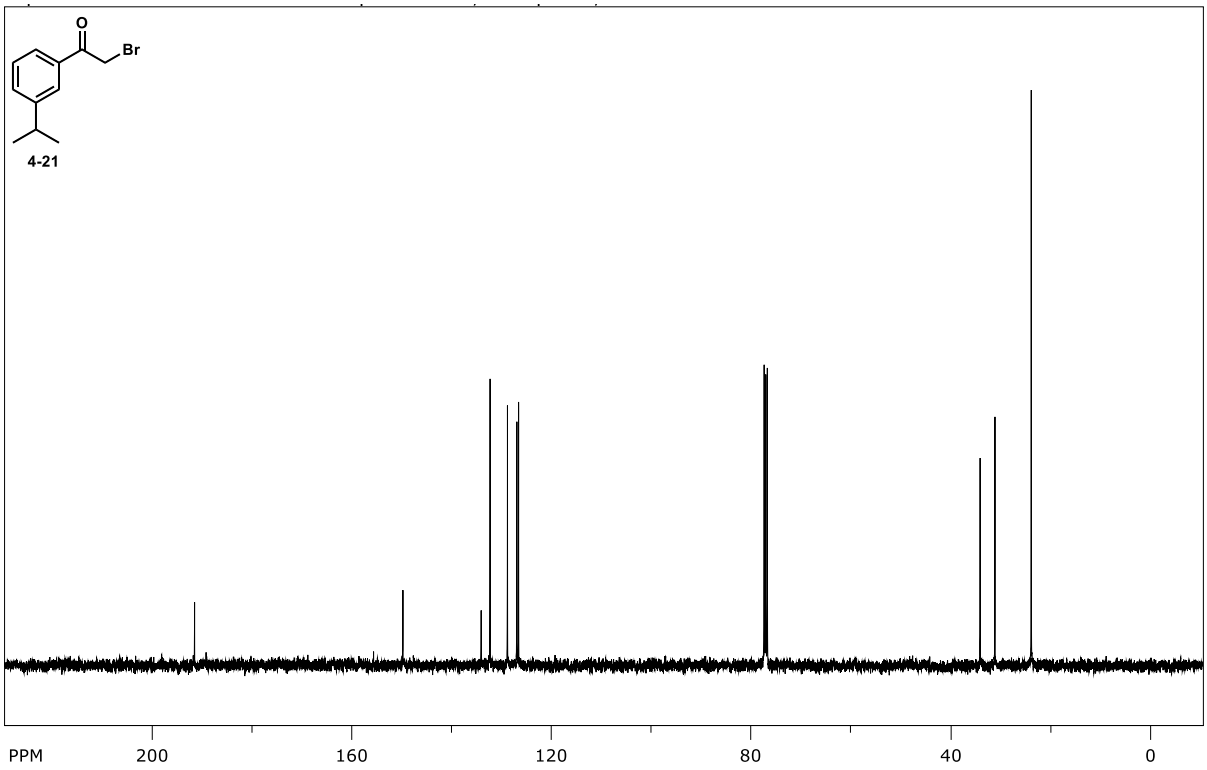
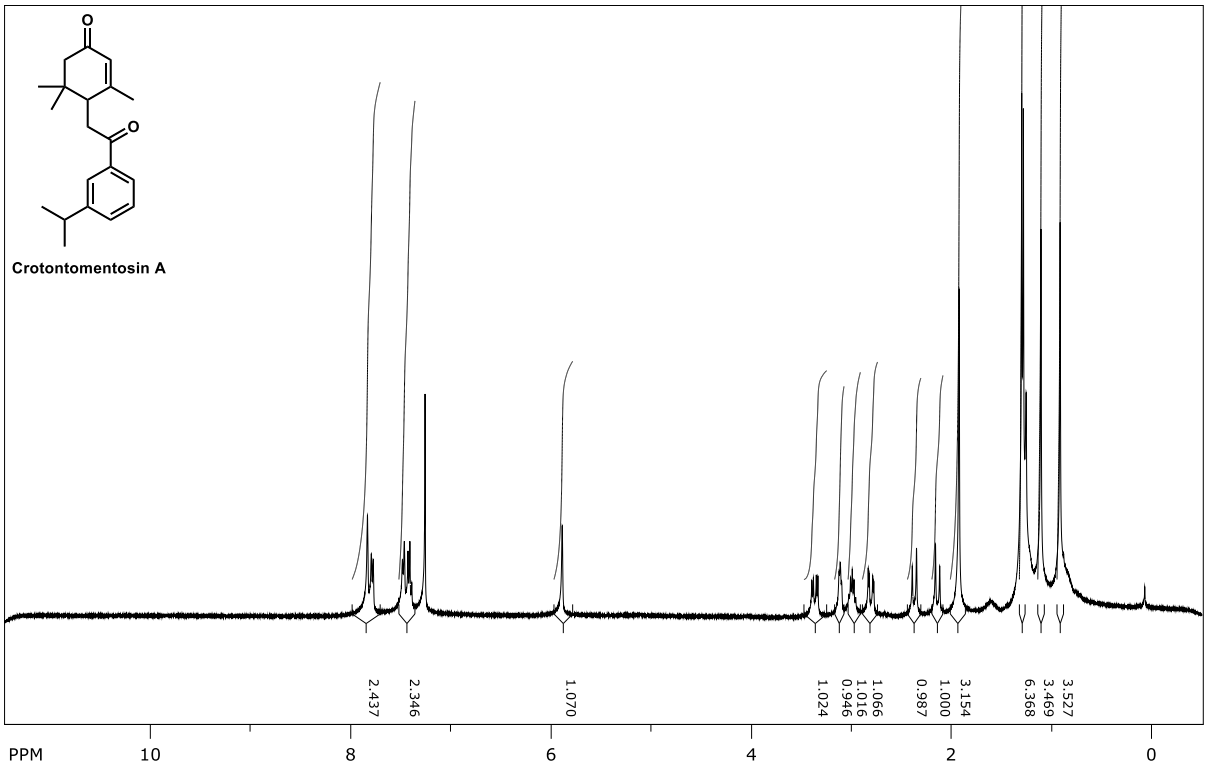
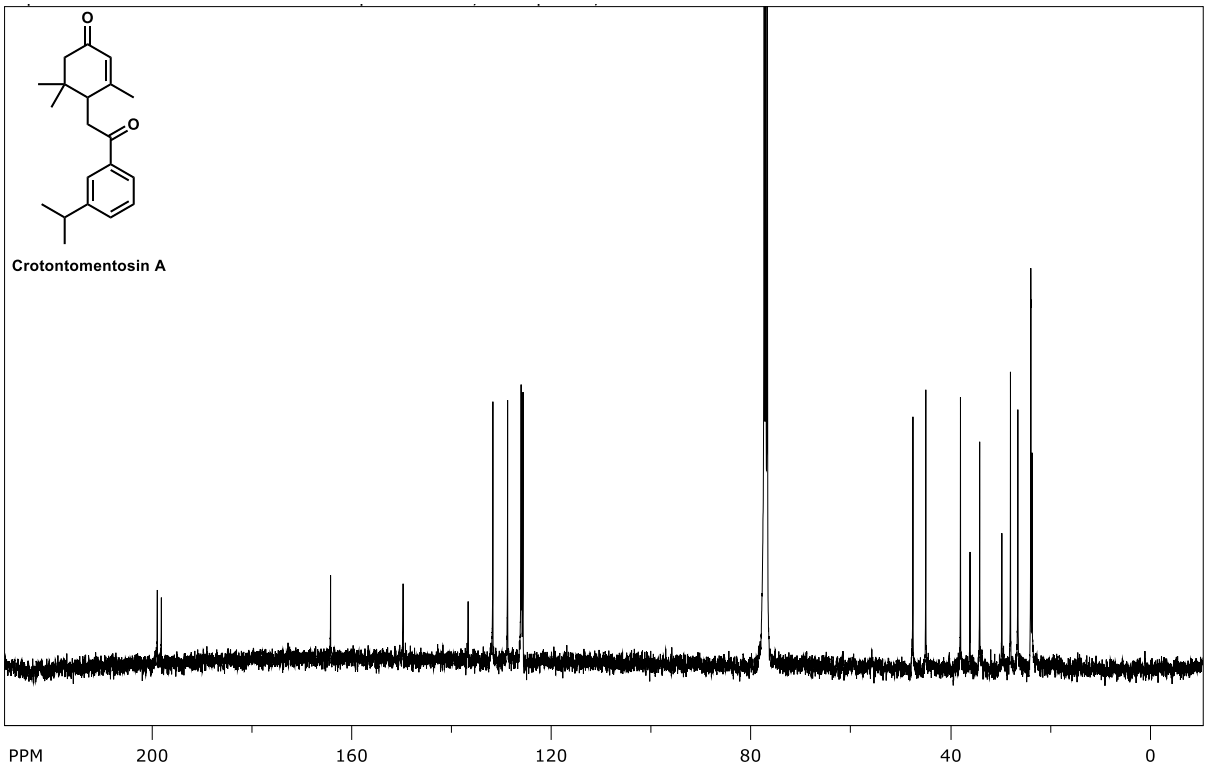


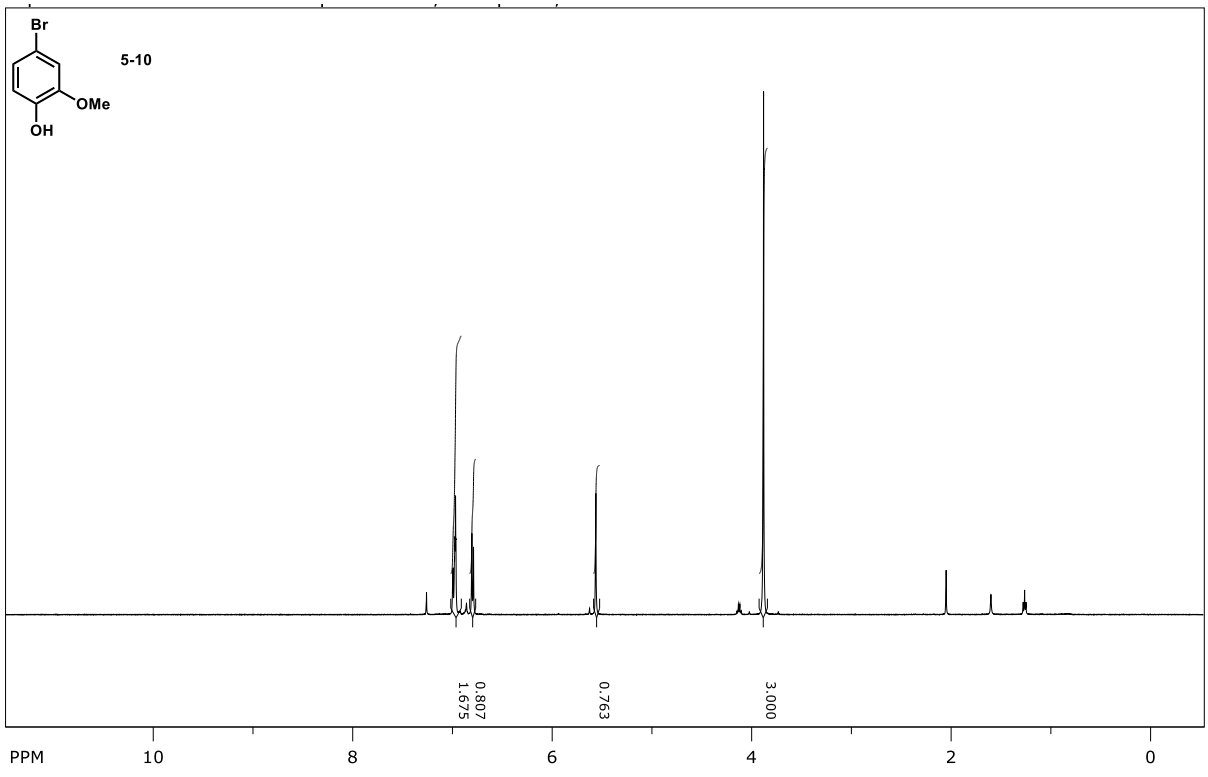
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



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



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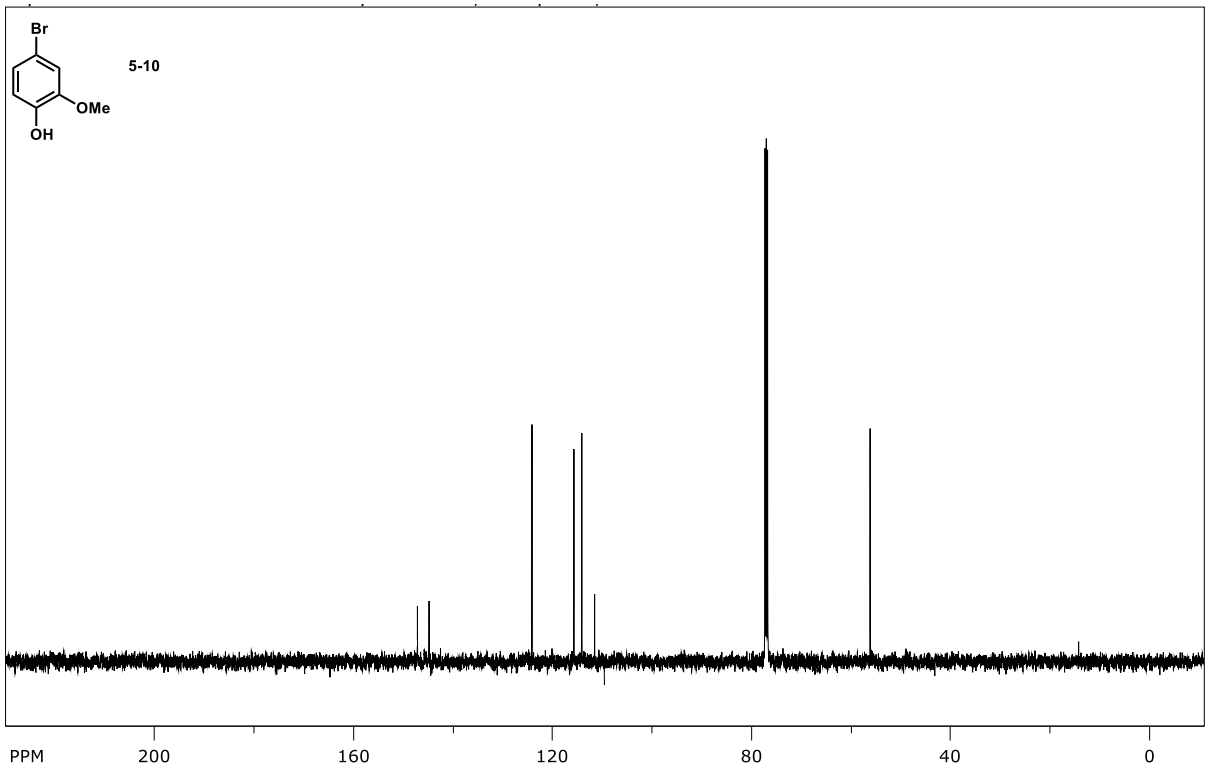

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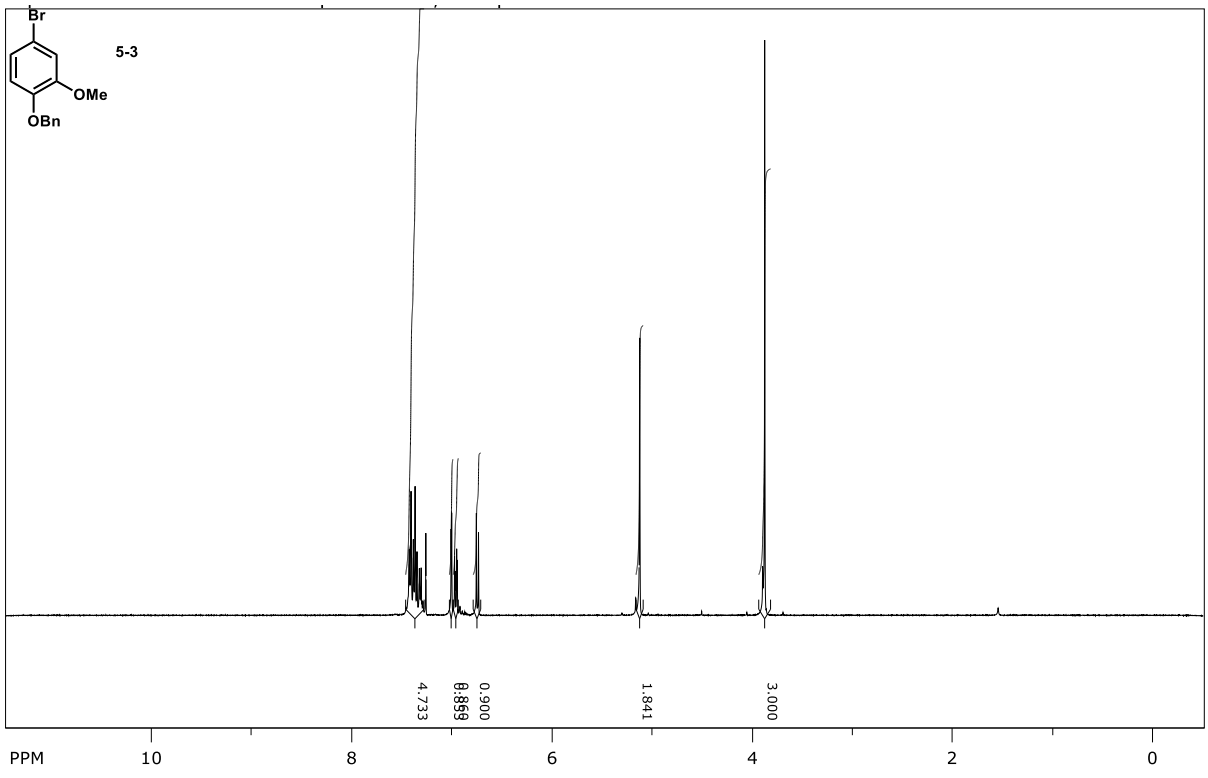

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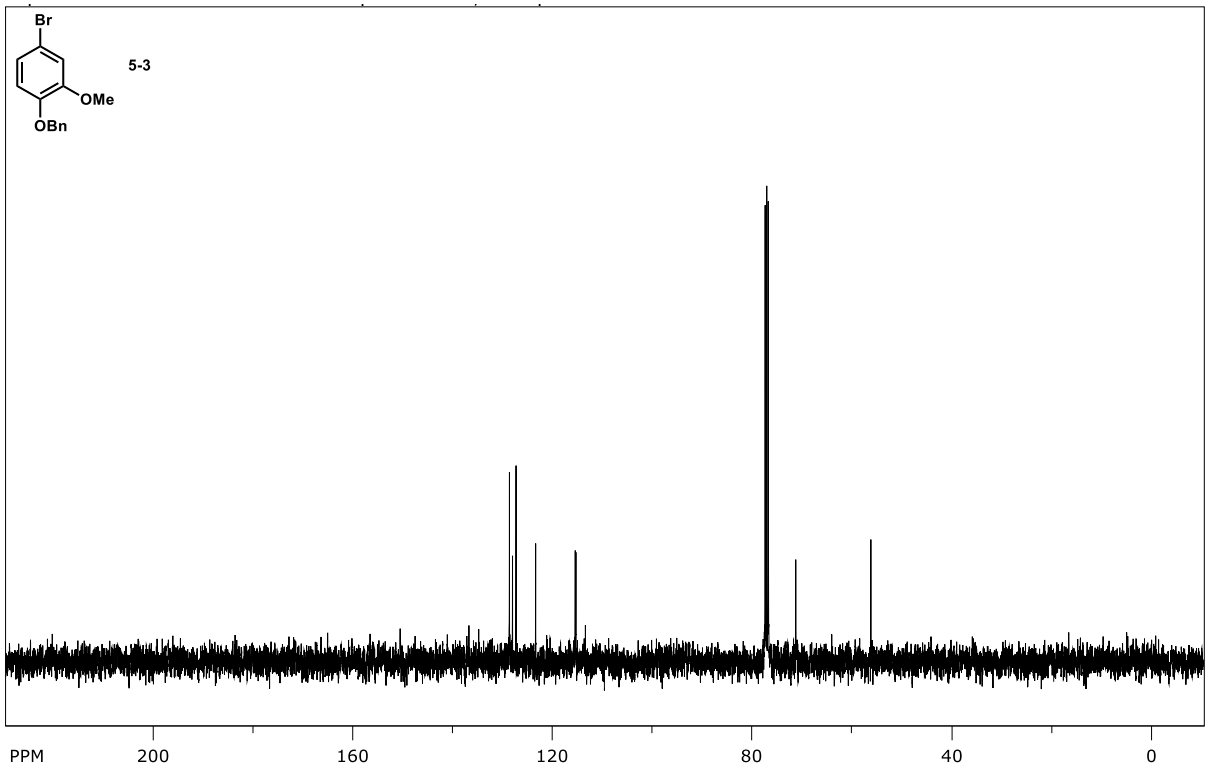

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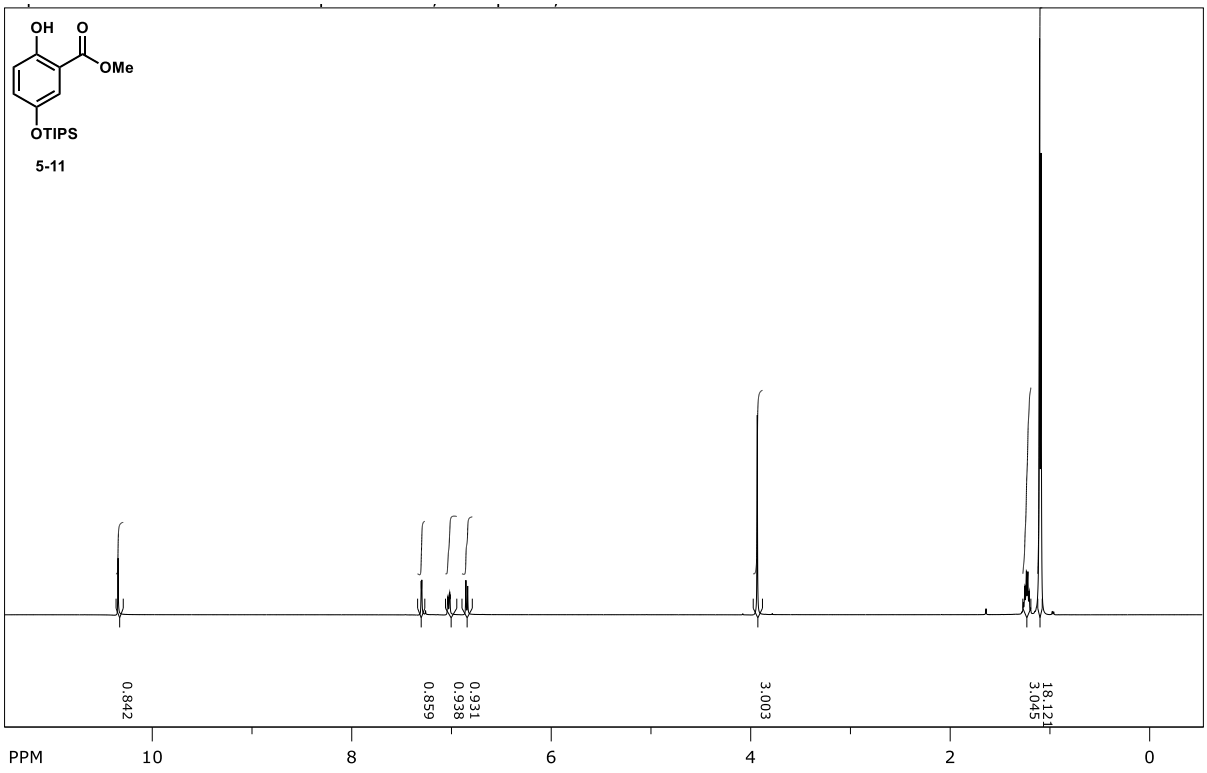
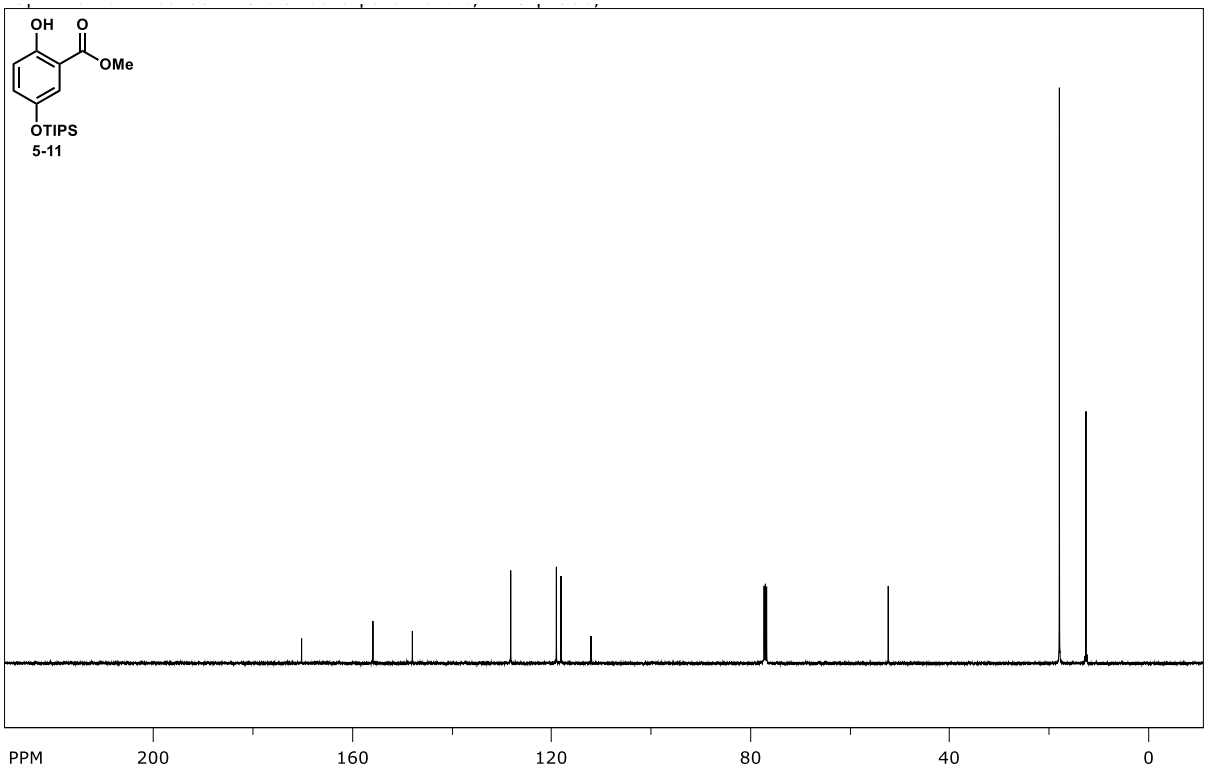
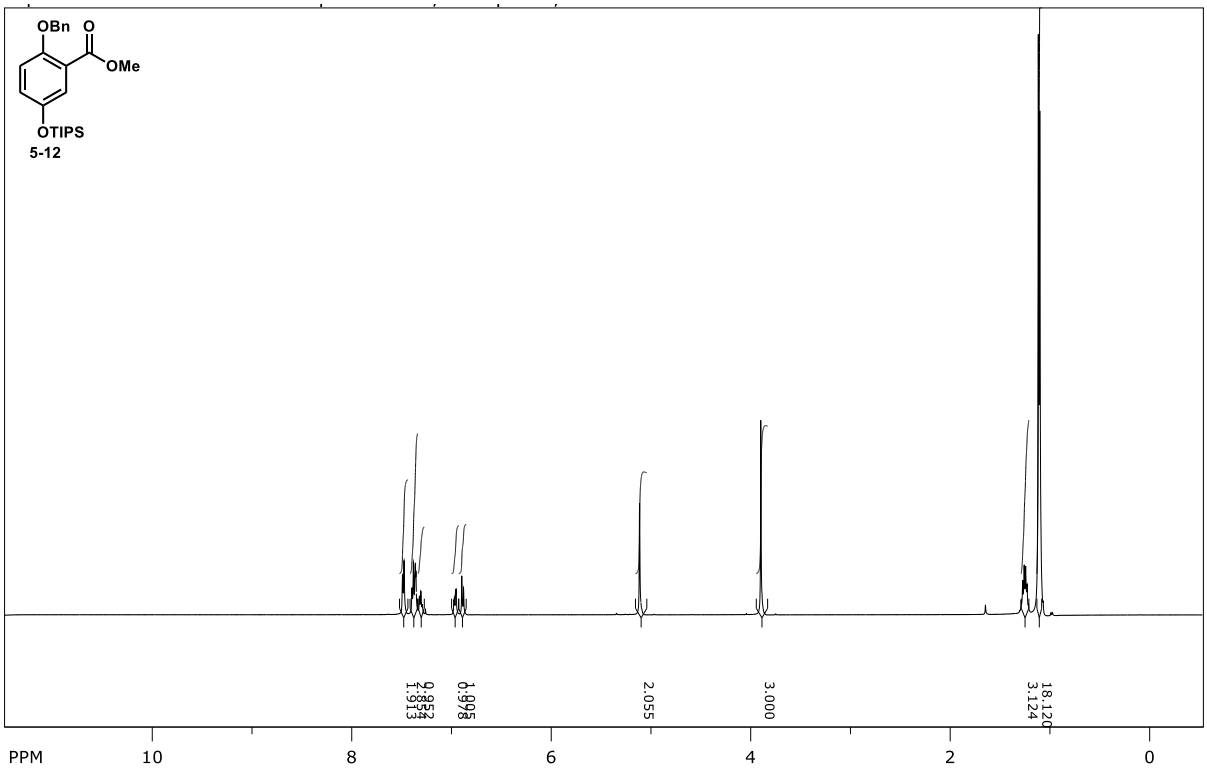


^{1}H NMR (500 MHz, $CDCl_3$)



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



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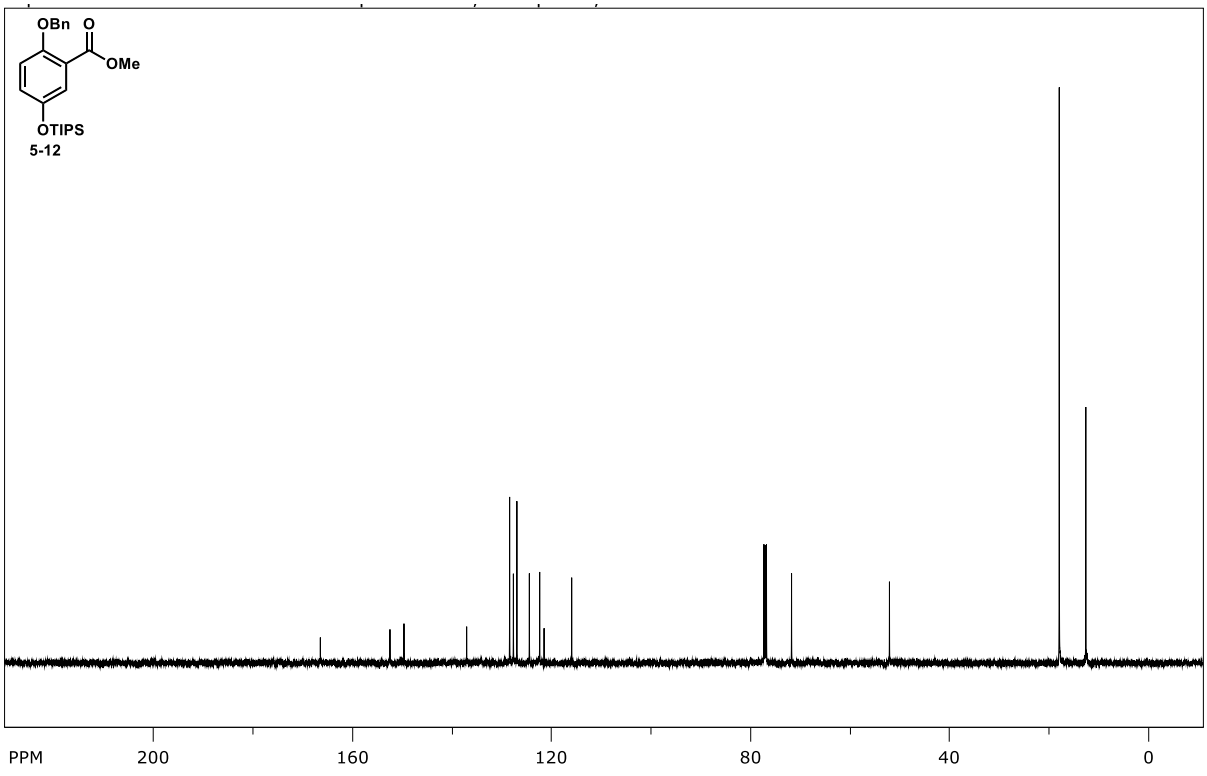

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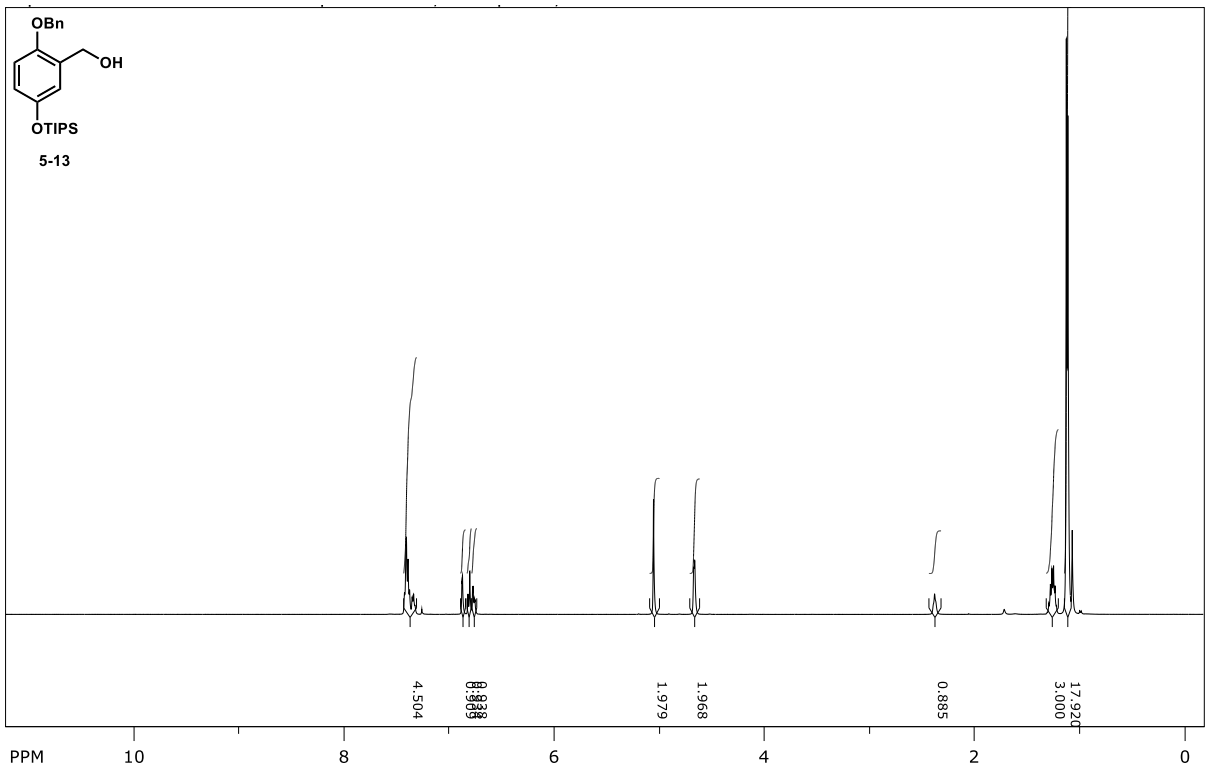

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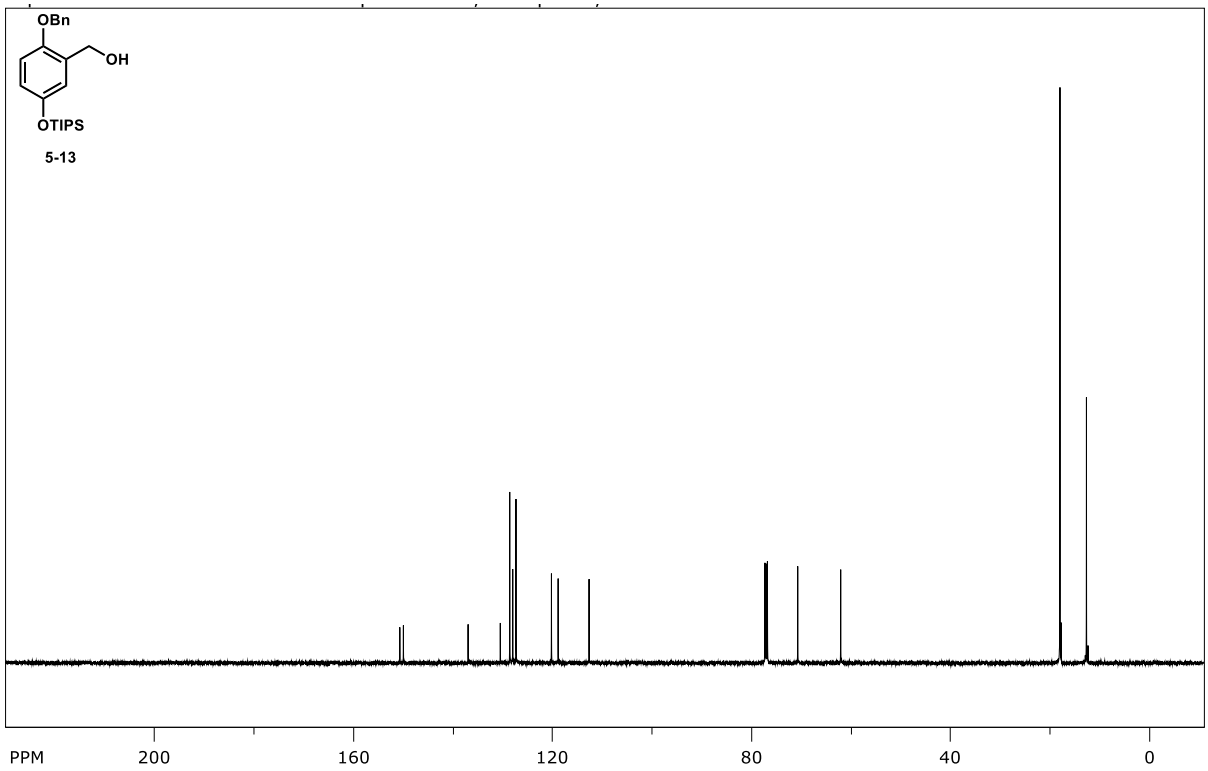

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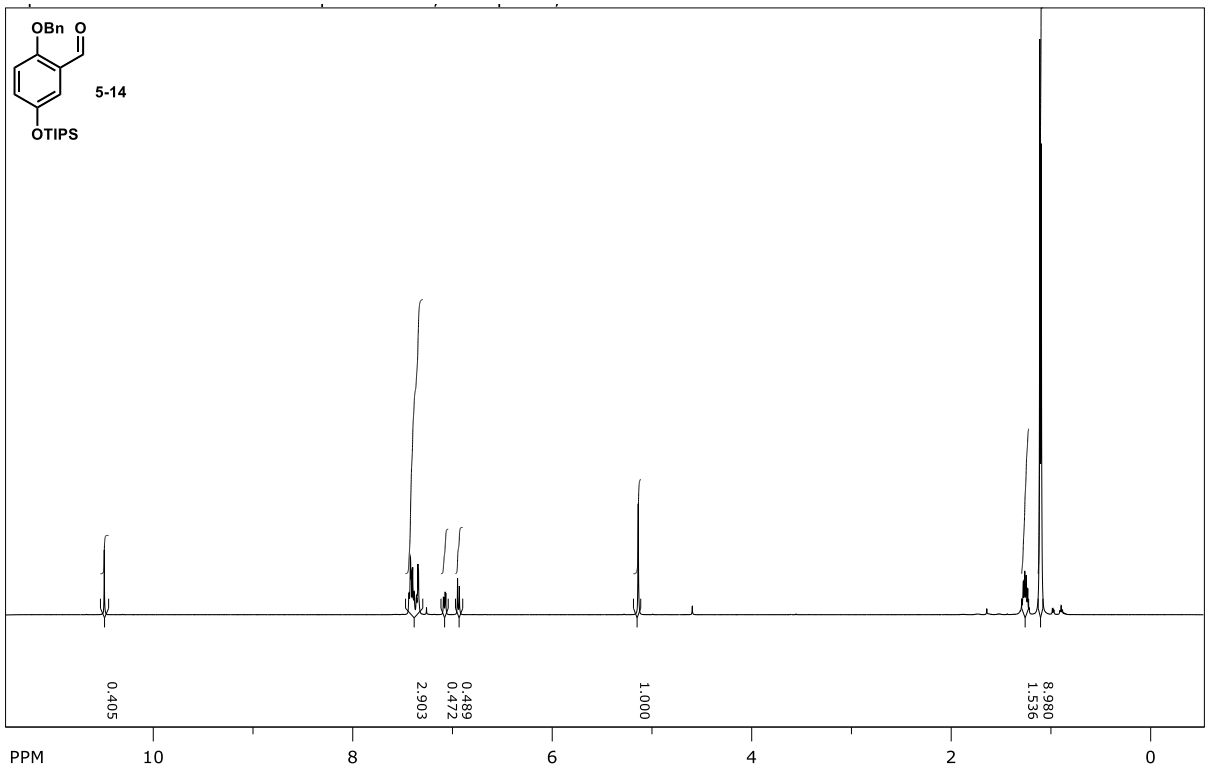

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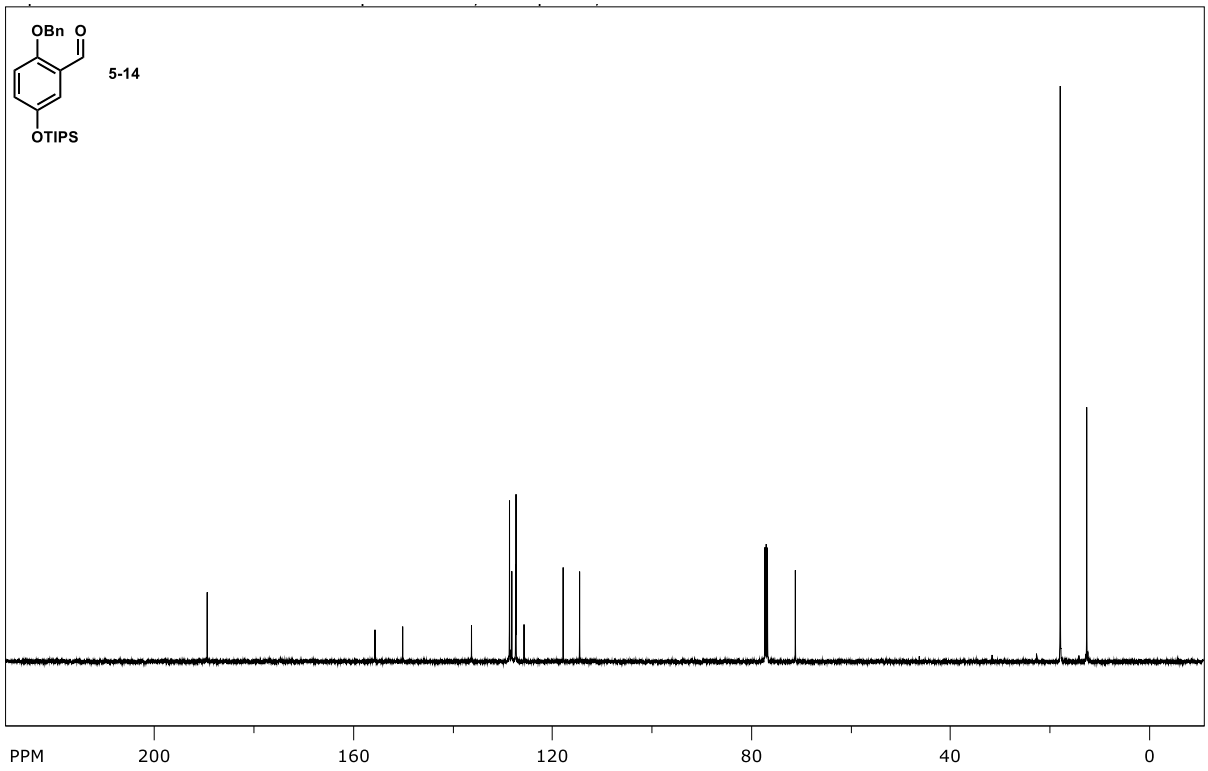

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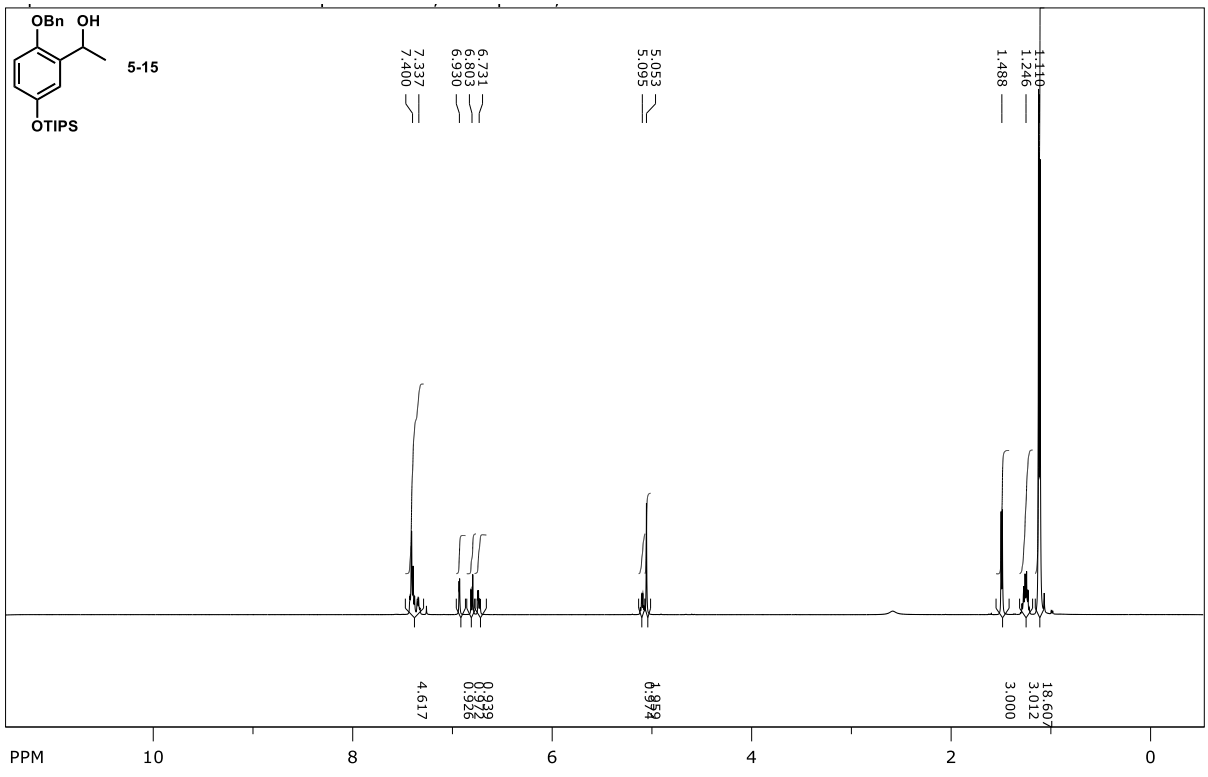

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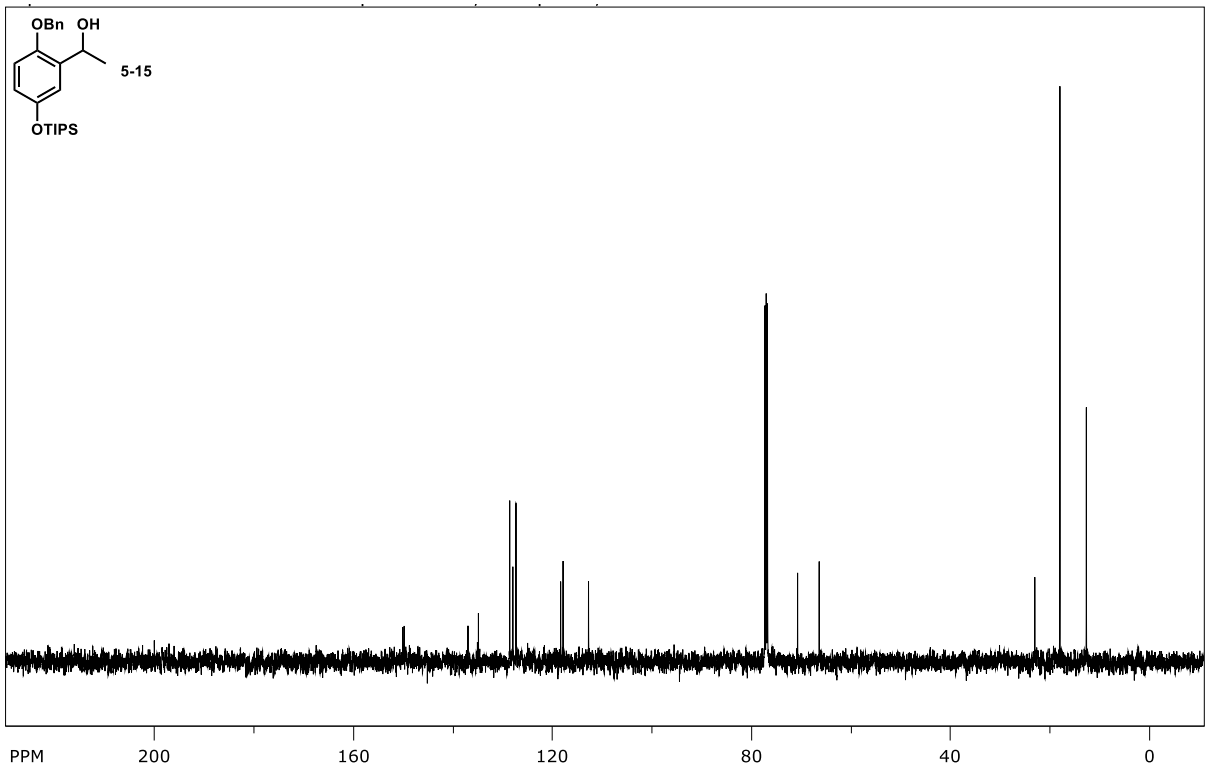
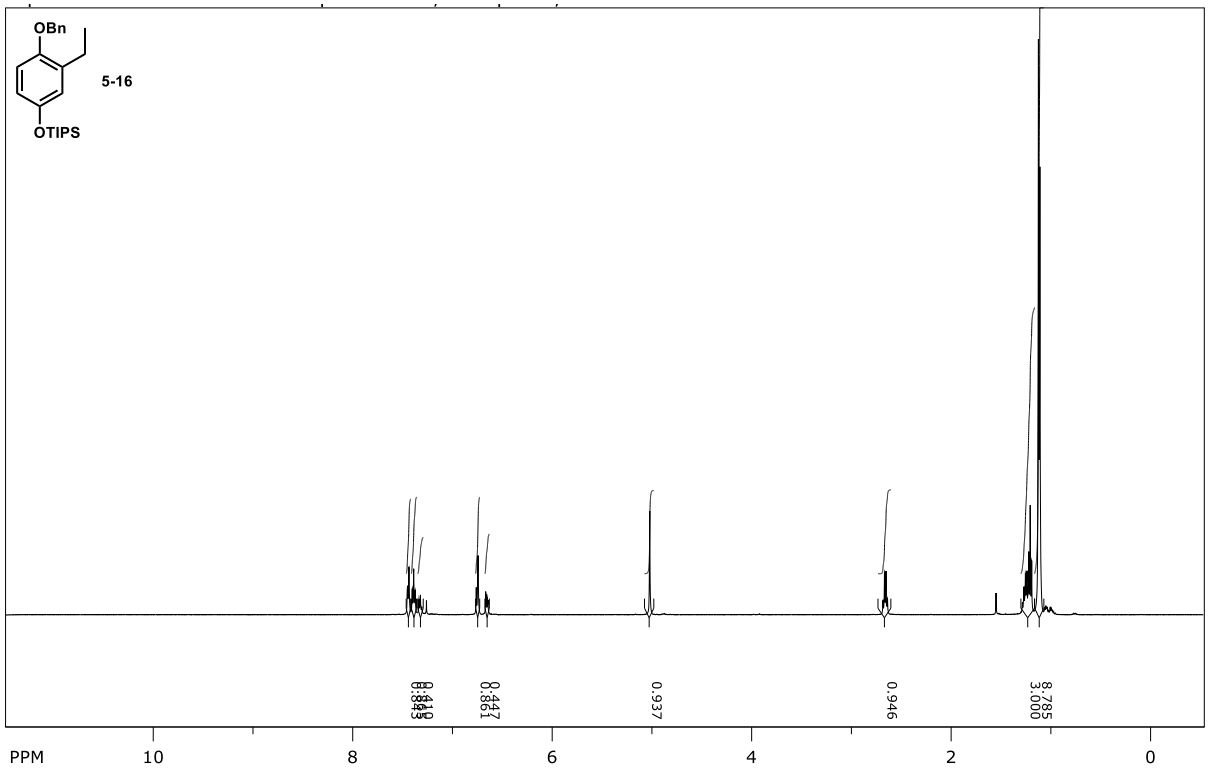


^{13}C NMR (126 MHz, $CDCl_3$)



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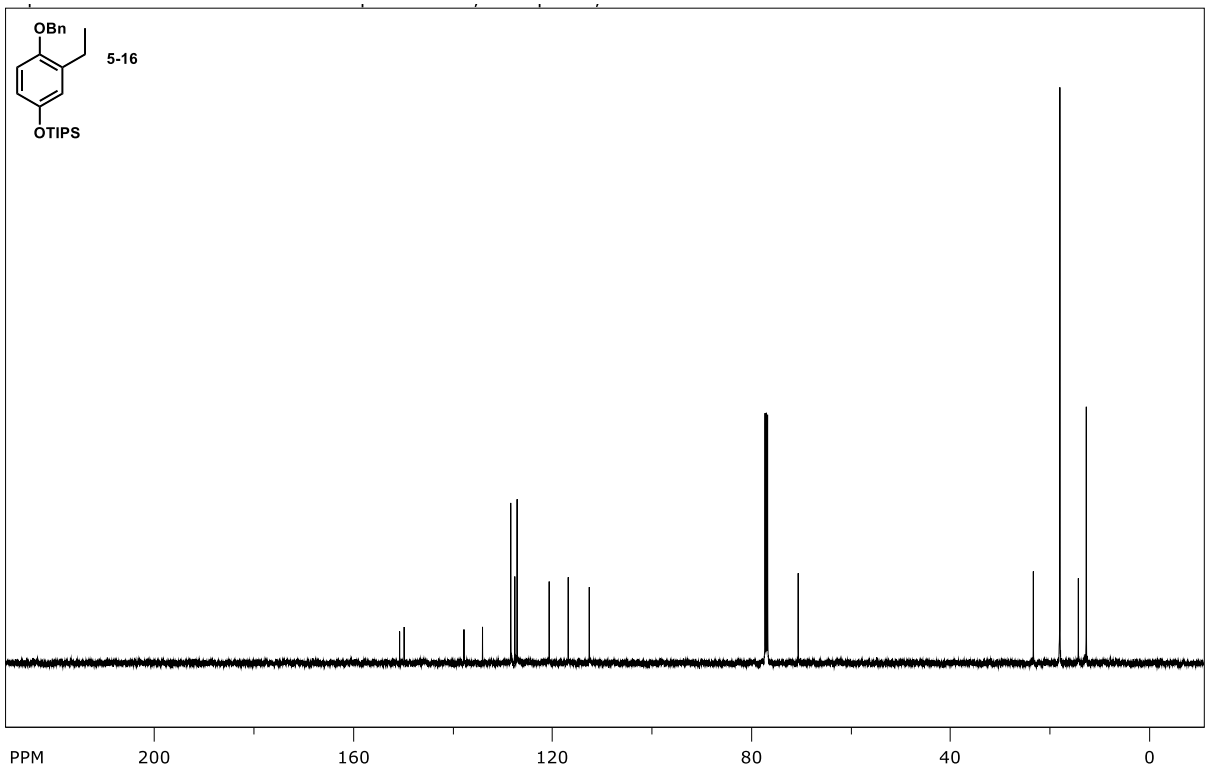
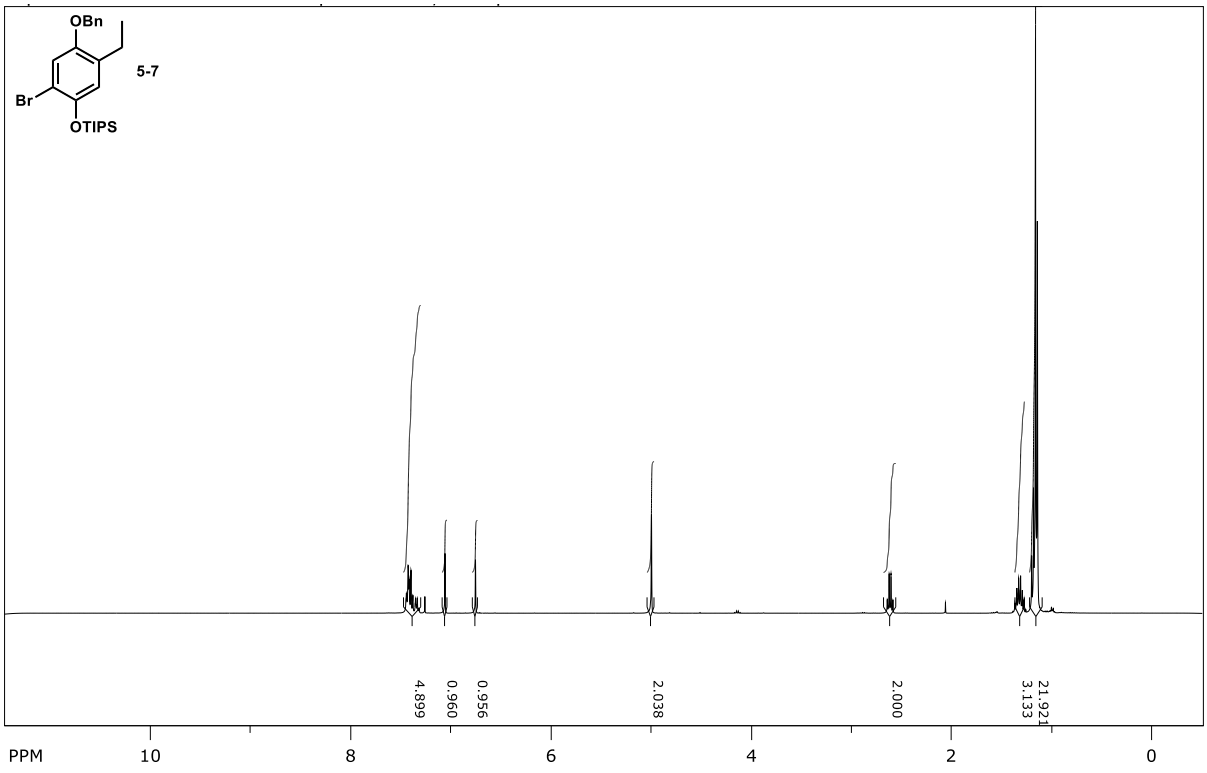


^{13}C NMR (126 MHz, $CDCl_3$)



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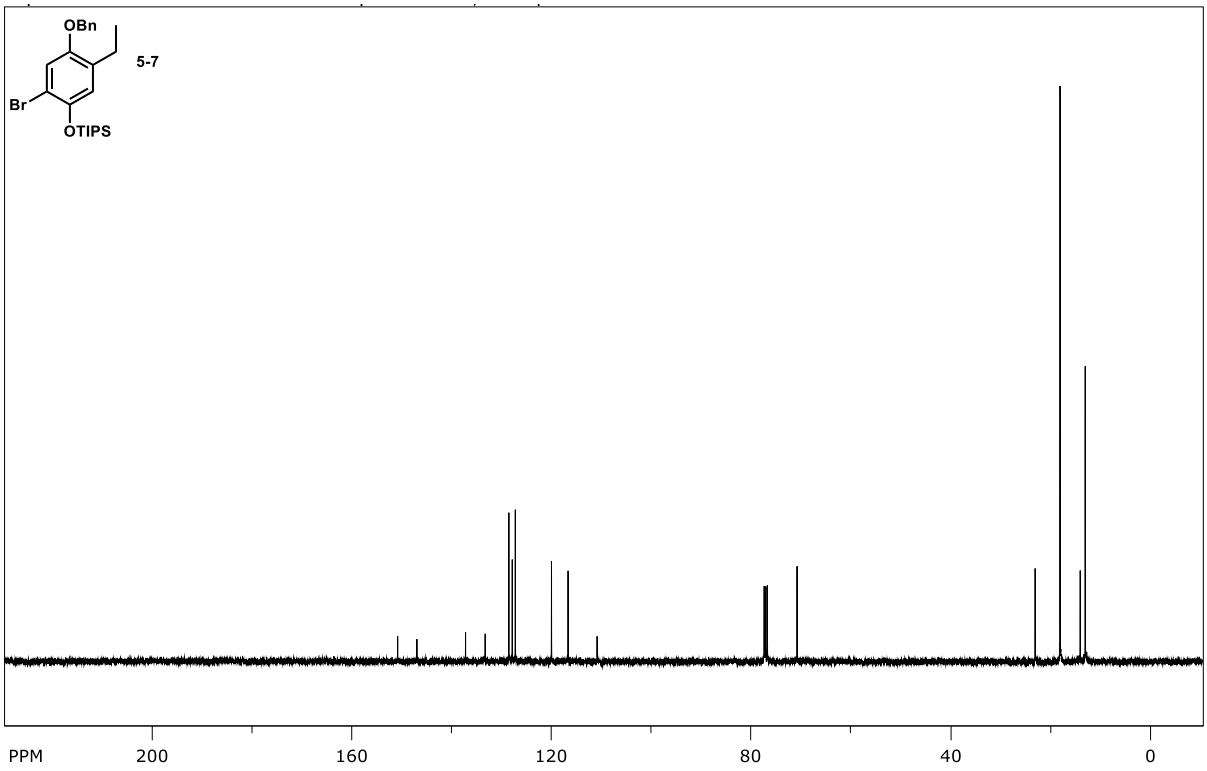
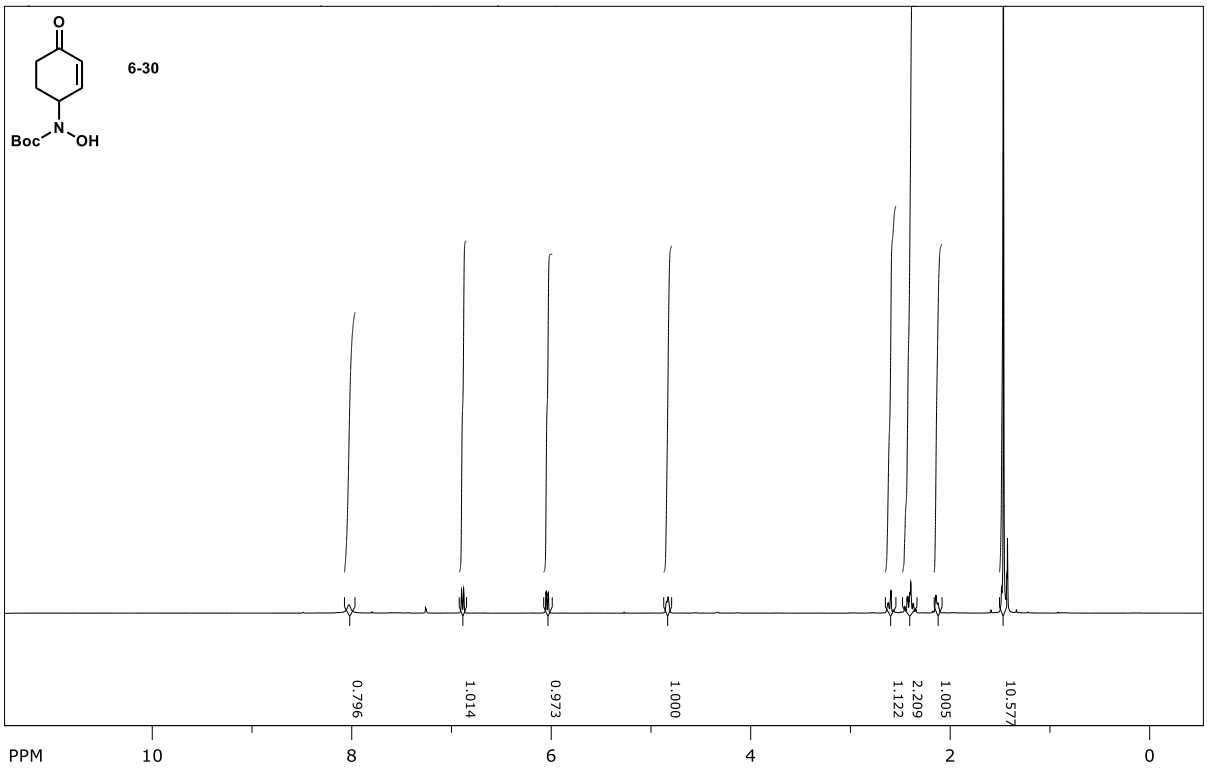
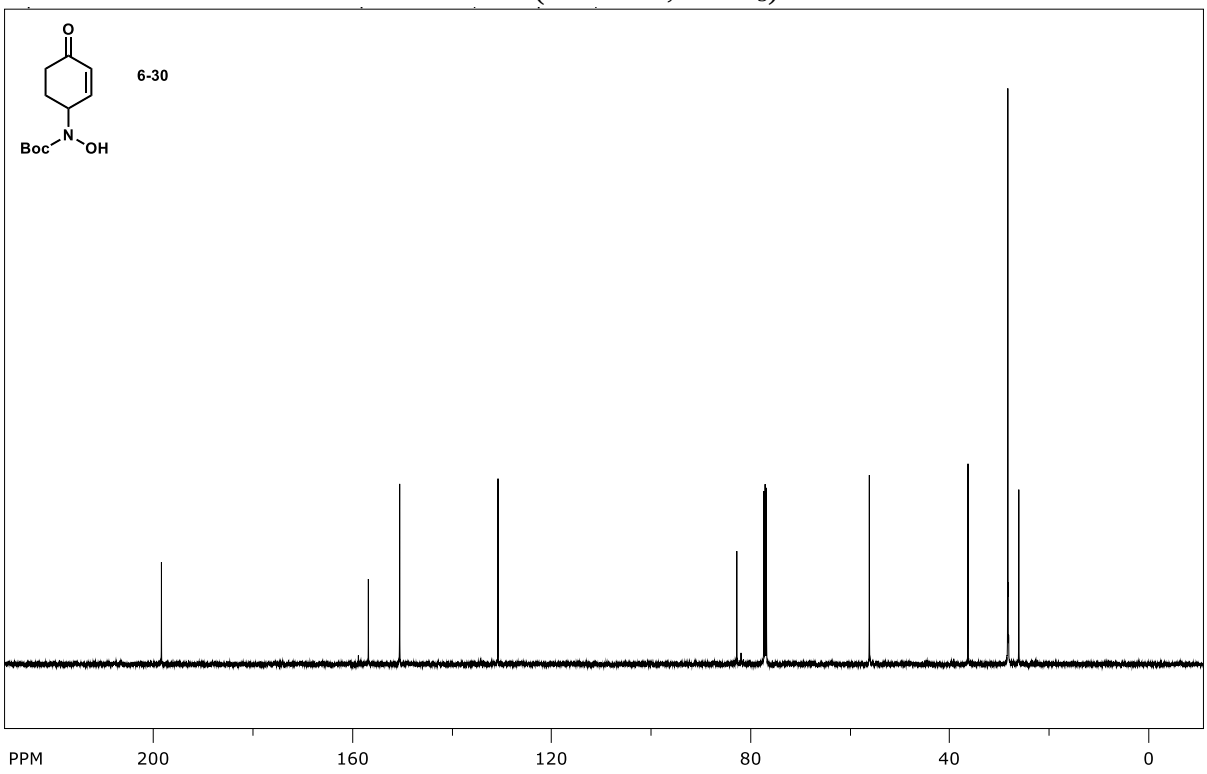


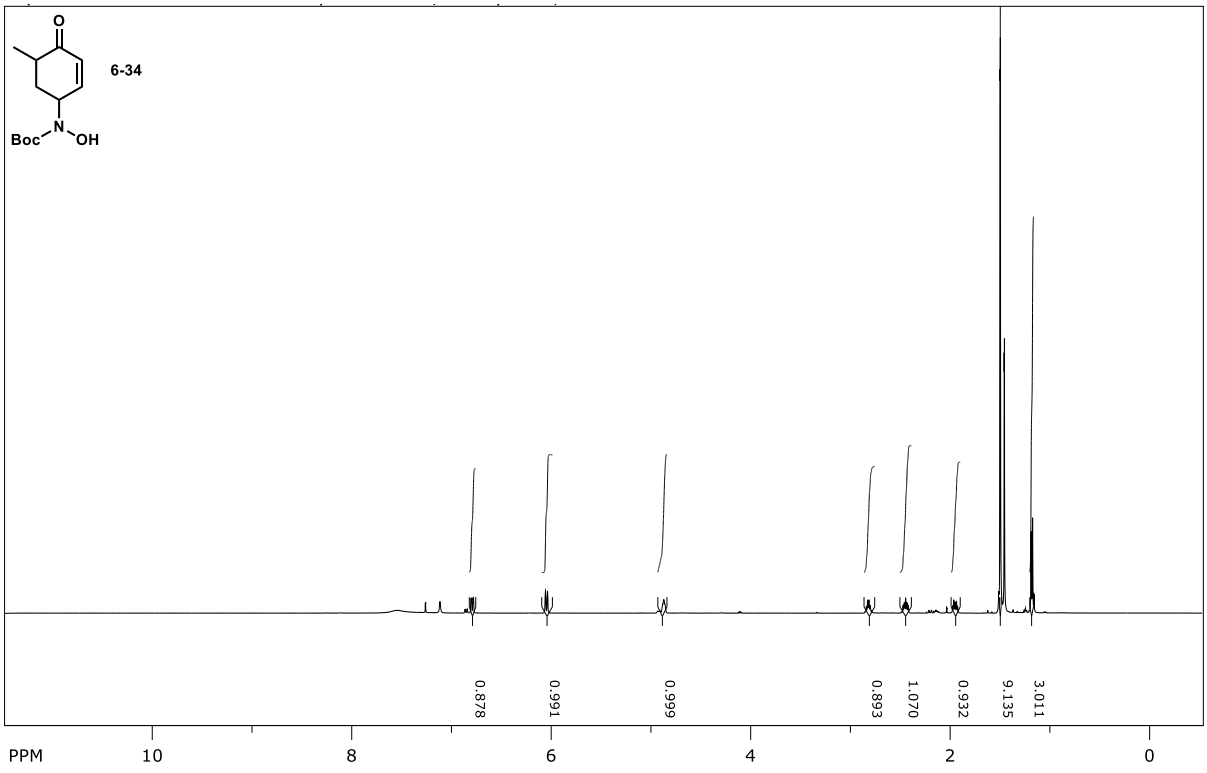
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



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



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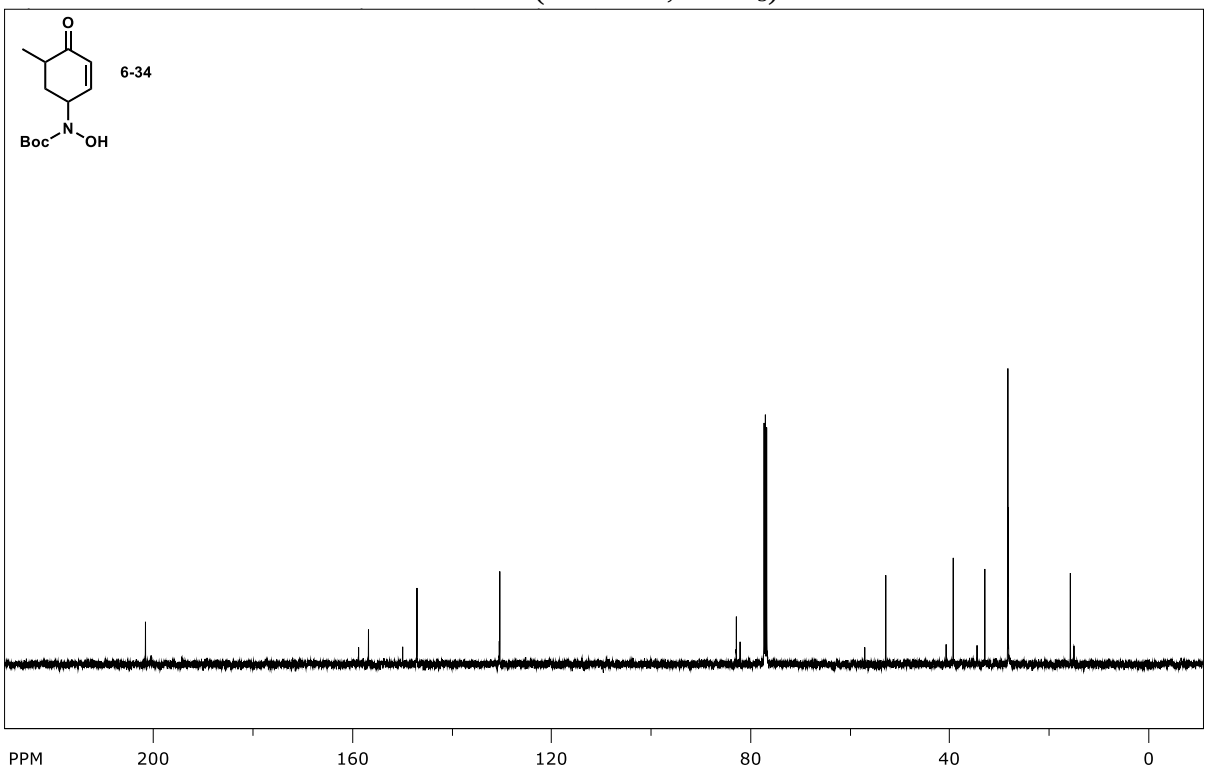
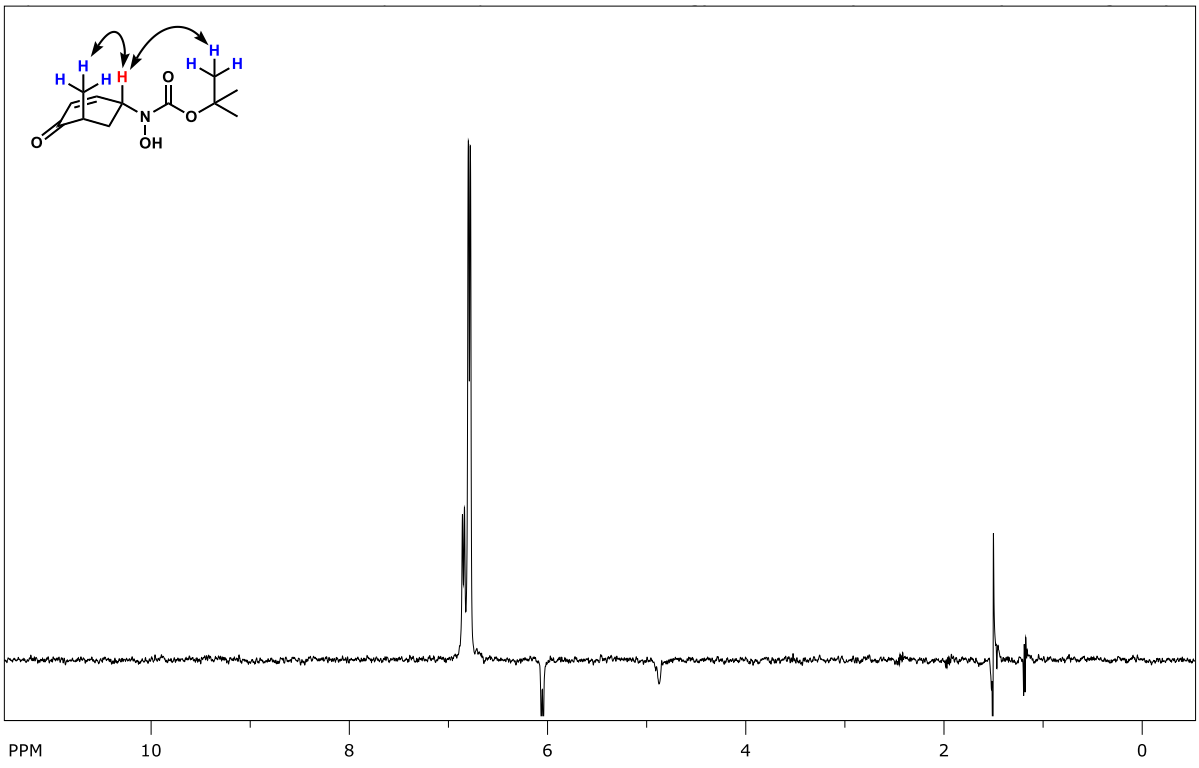
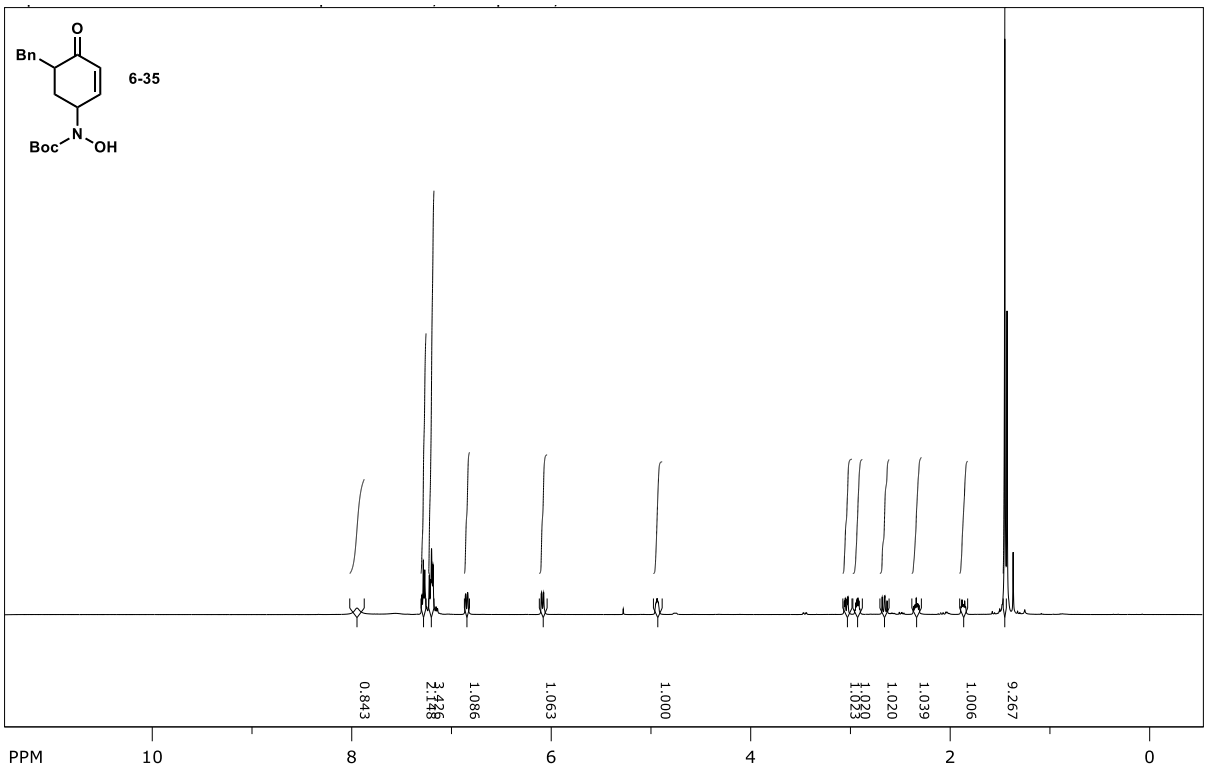


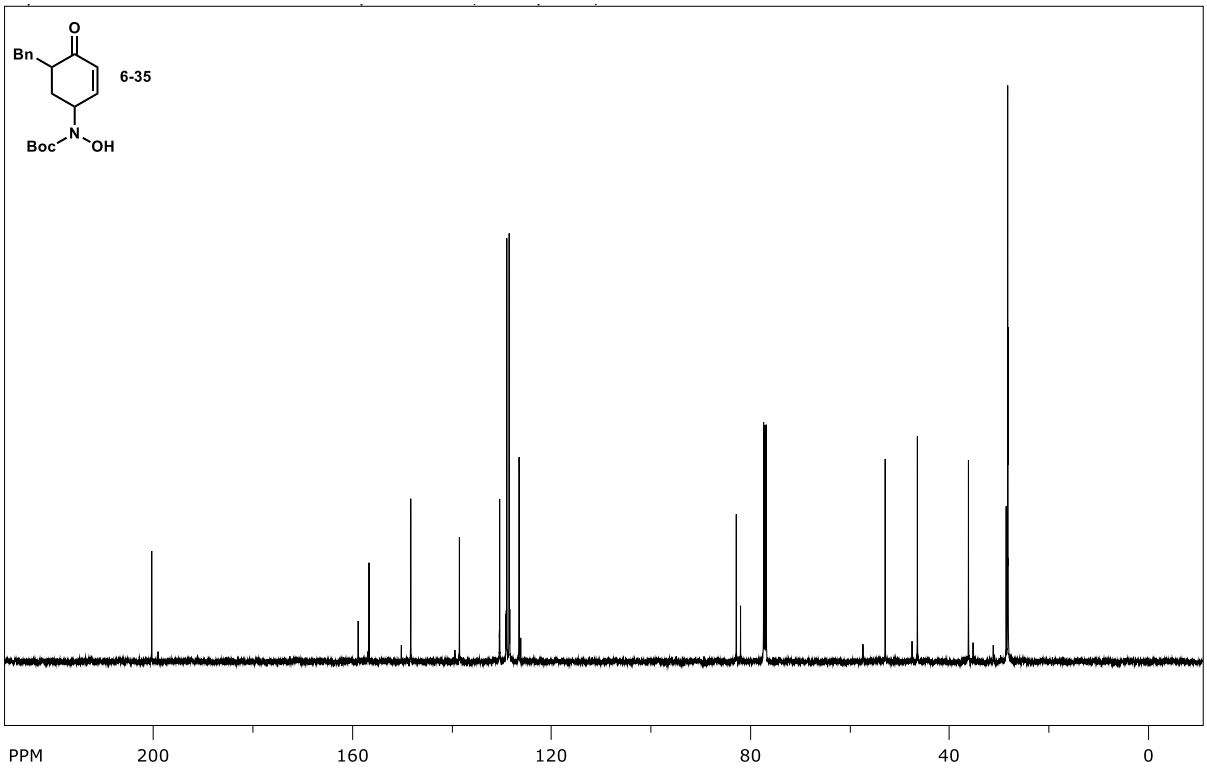
^{13}C NMR (126 MHz, $CDCl_3$)



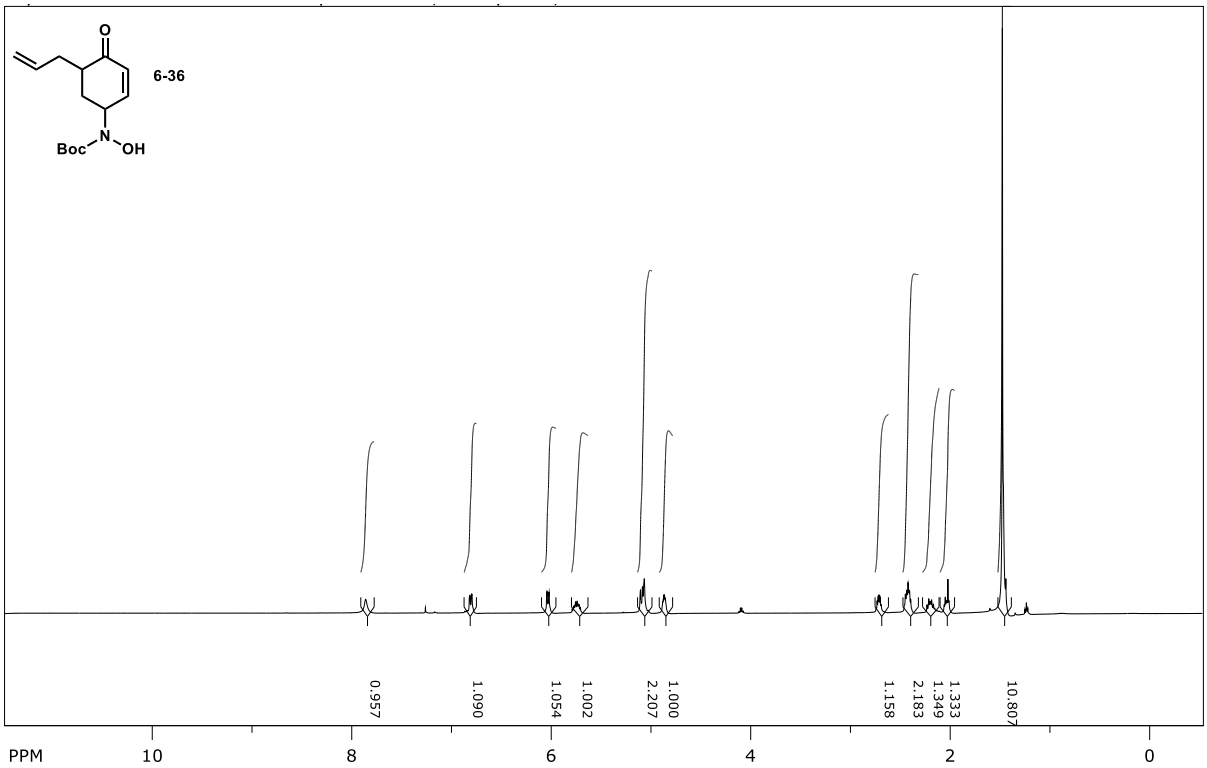
NOE at 4.8 ppm



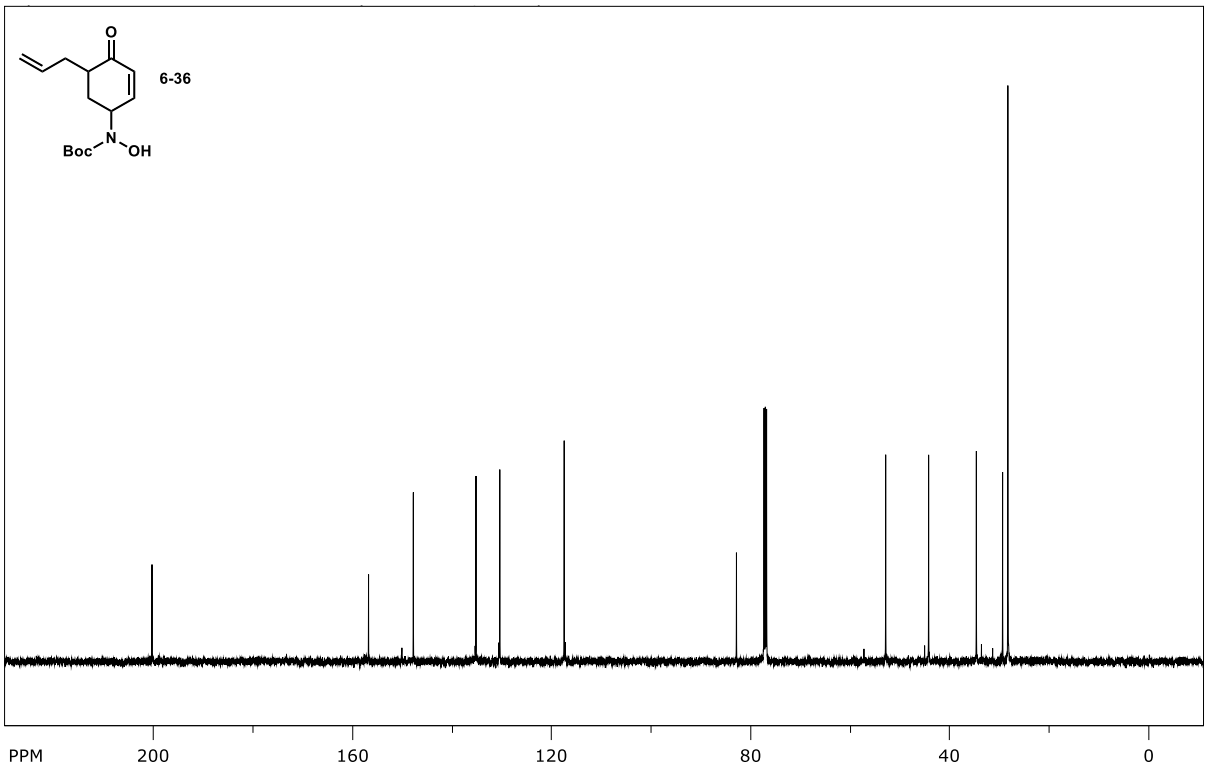
^{1}H NMR (500 MHz, $CDCl_3$)



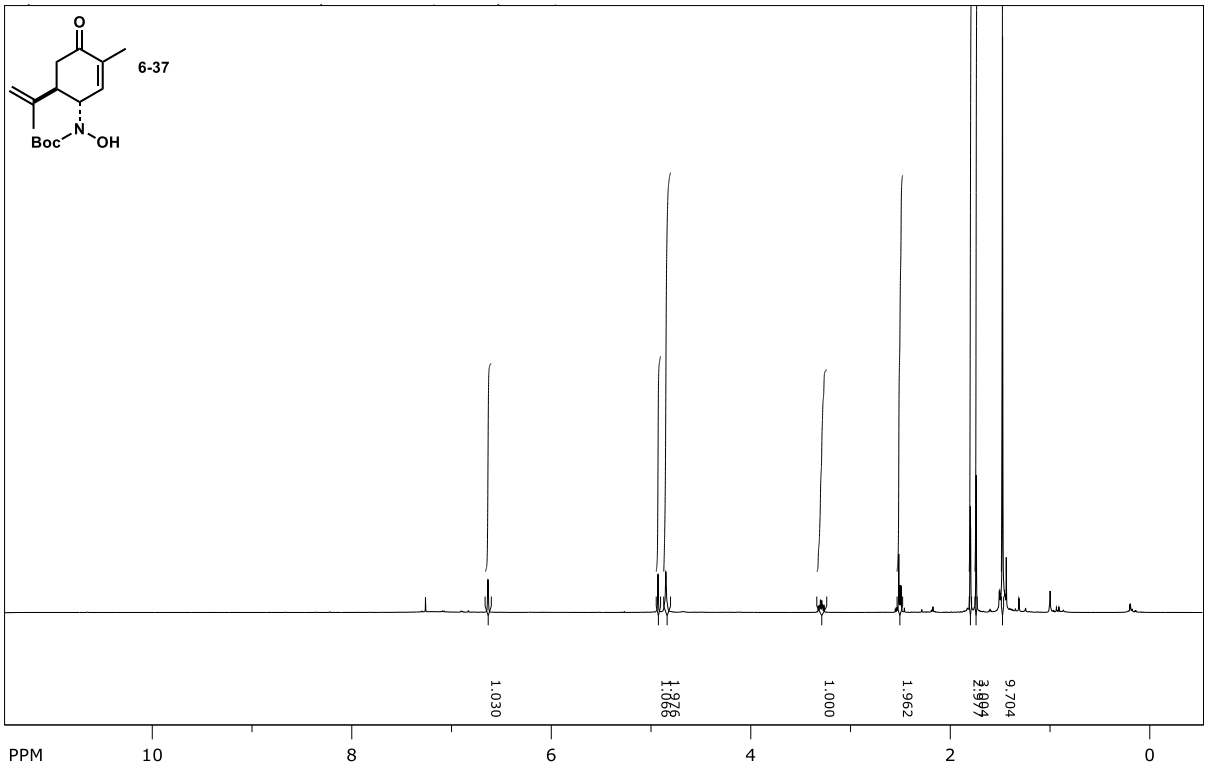
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



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



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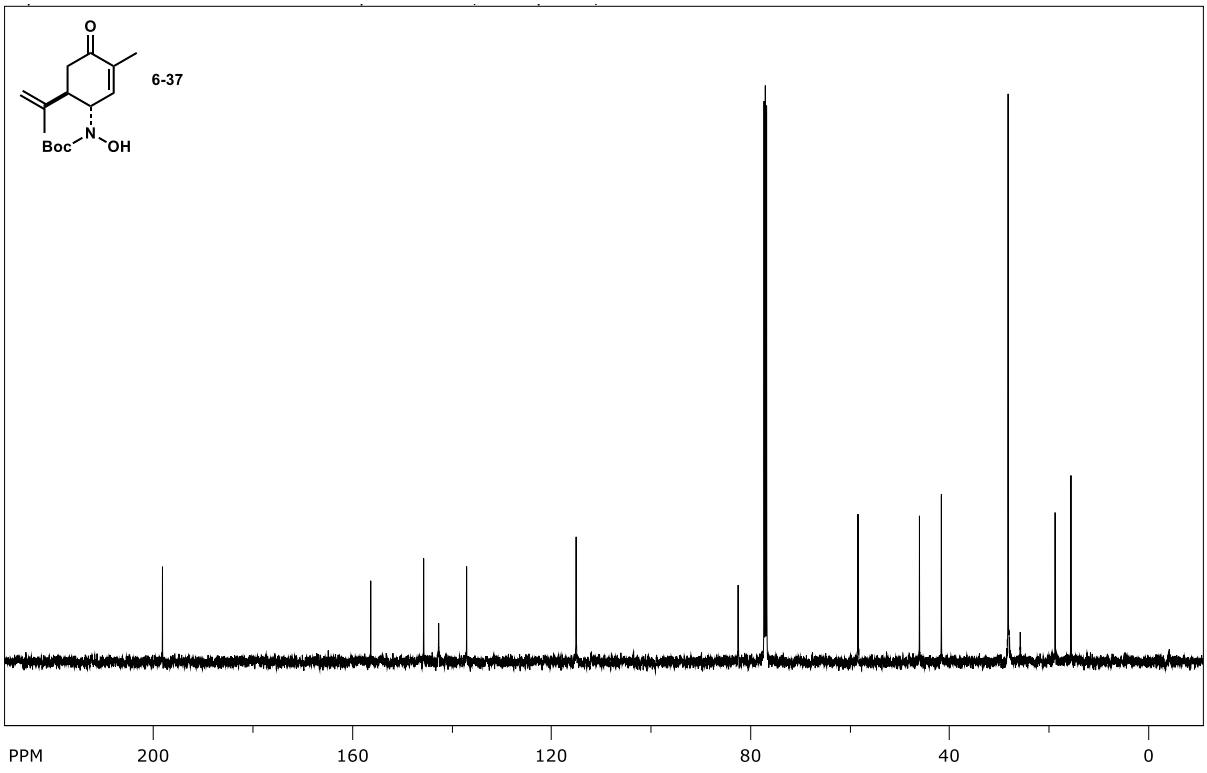
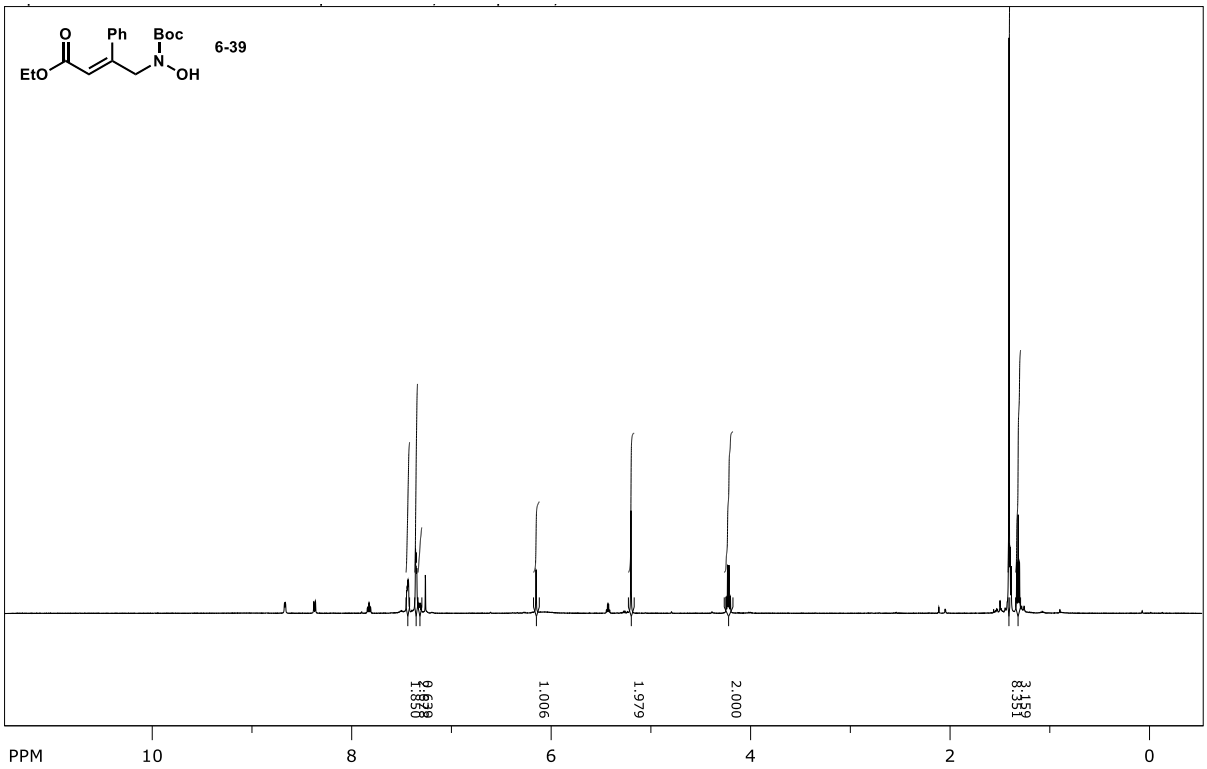
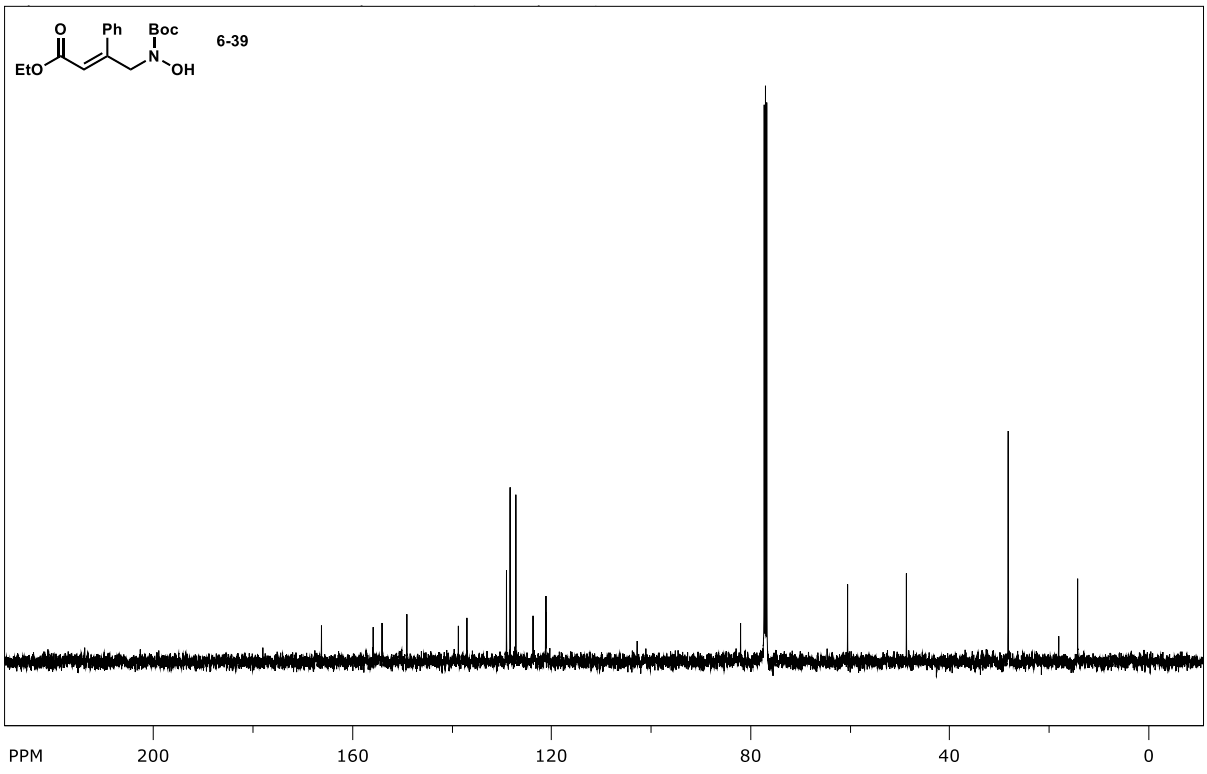


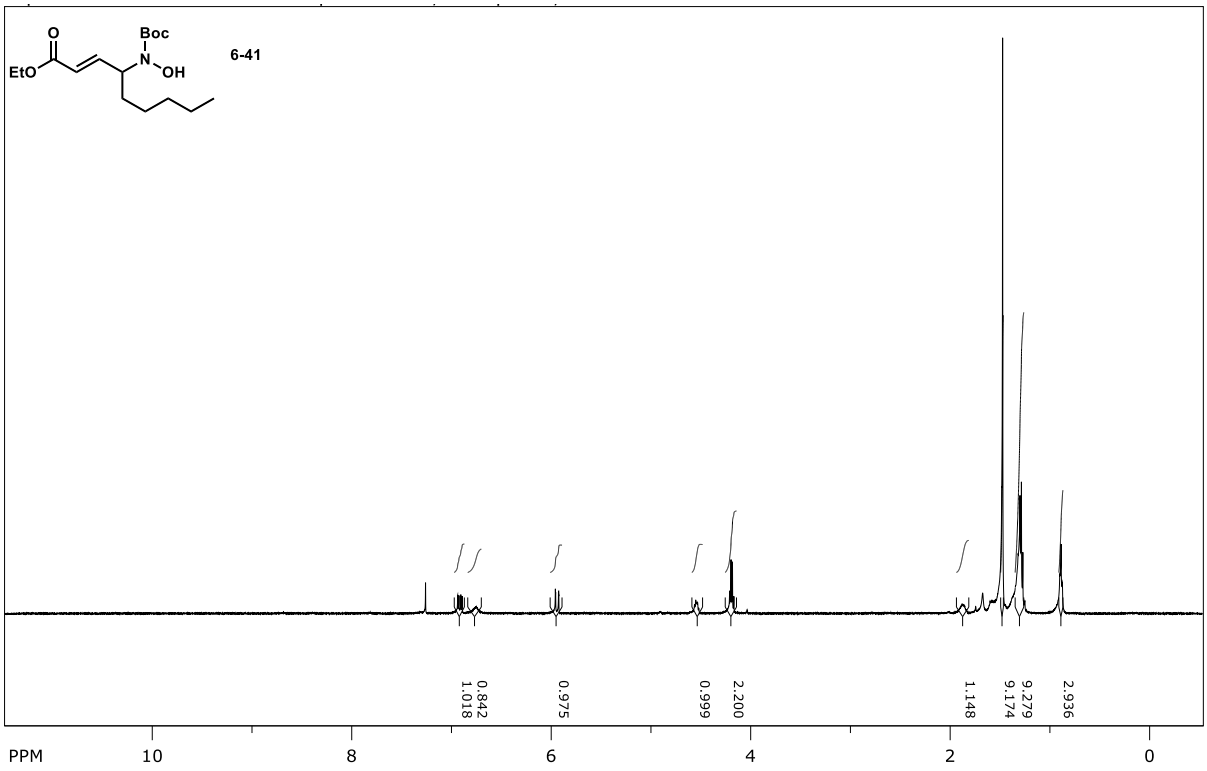
^{13}C NMR (126 MHz, $CDCl_3$)



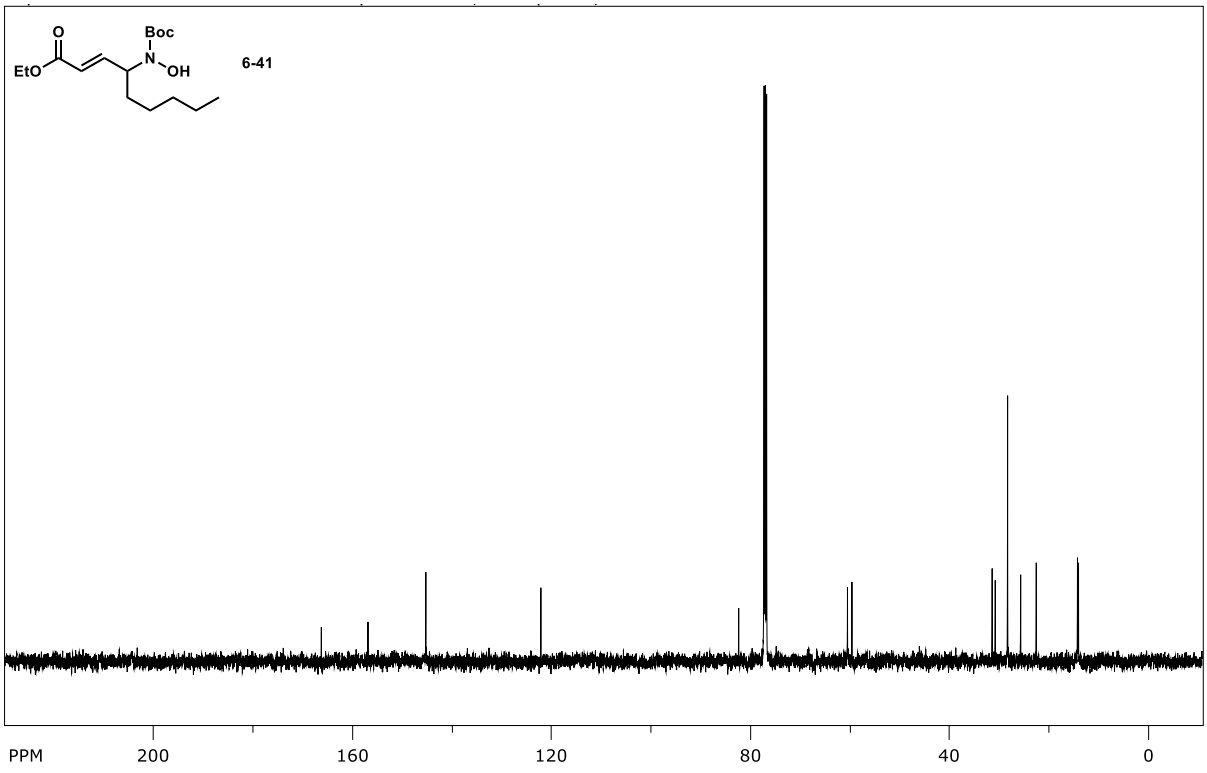
^{1}H NMR (500 MHz, $CDCl_3$)



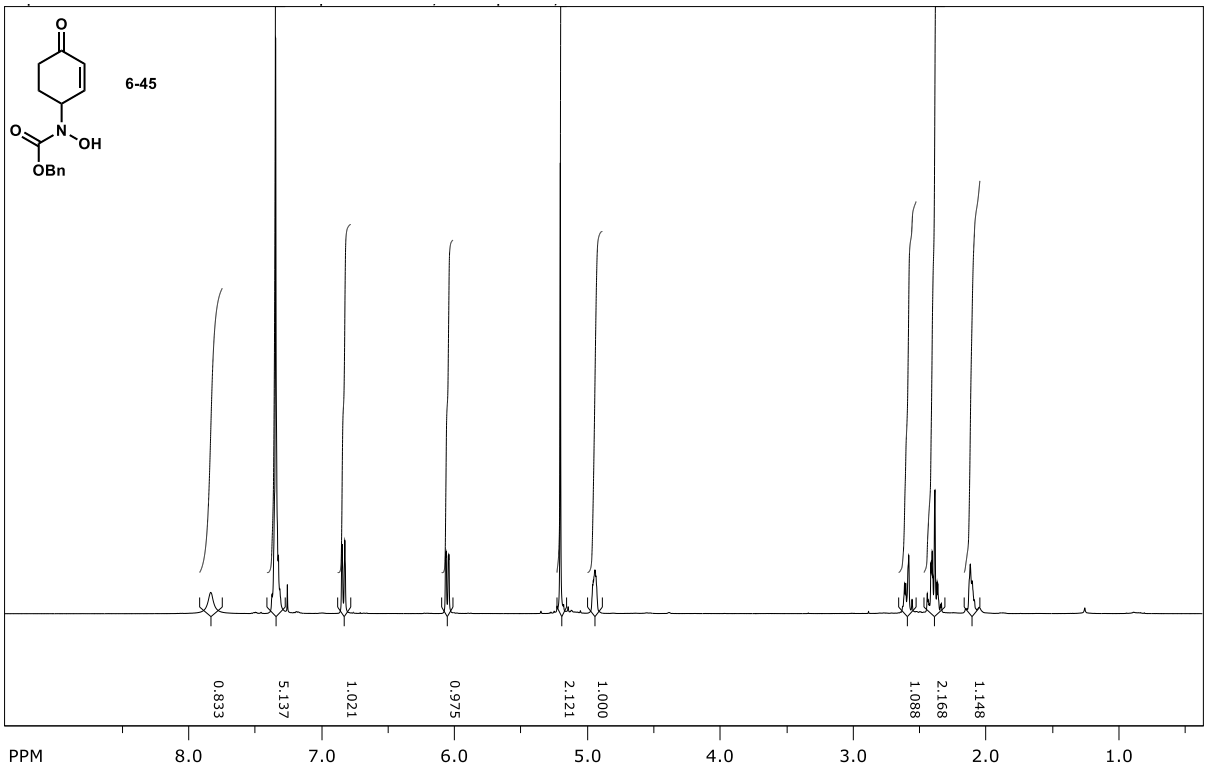
^{13}C NMR (126 MHz, $CDCl_3$)



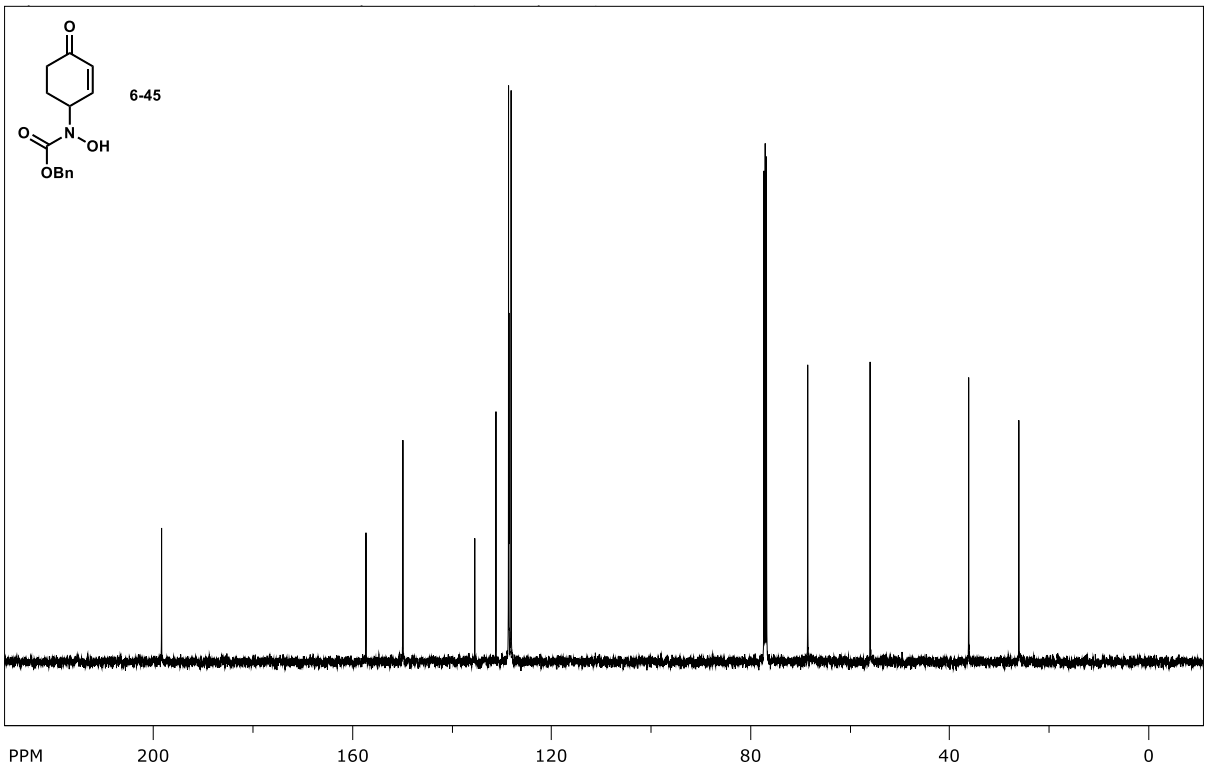
^{1}H NMR (500 MHz, $CDCl_3$)



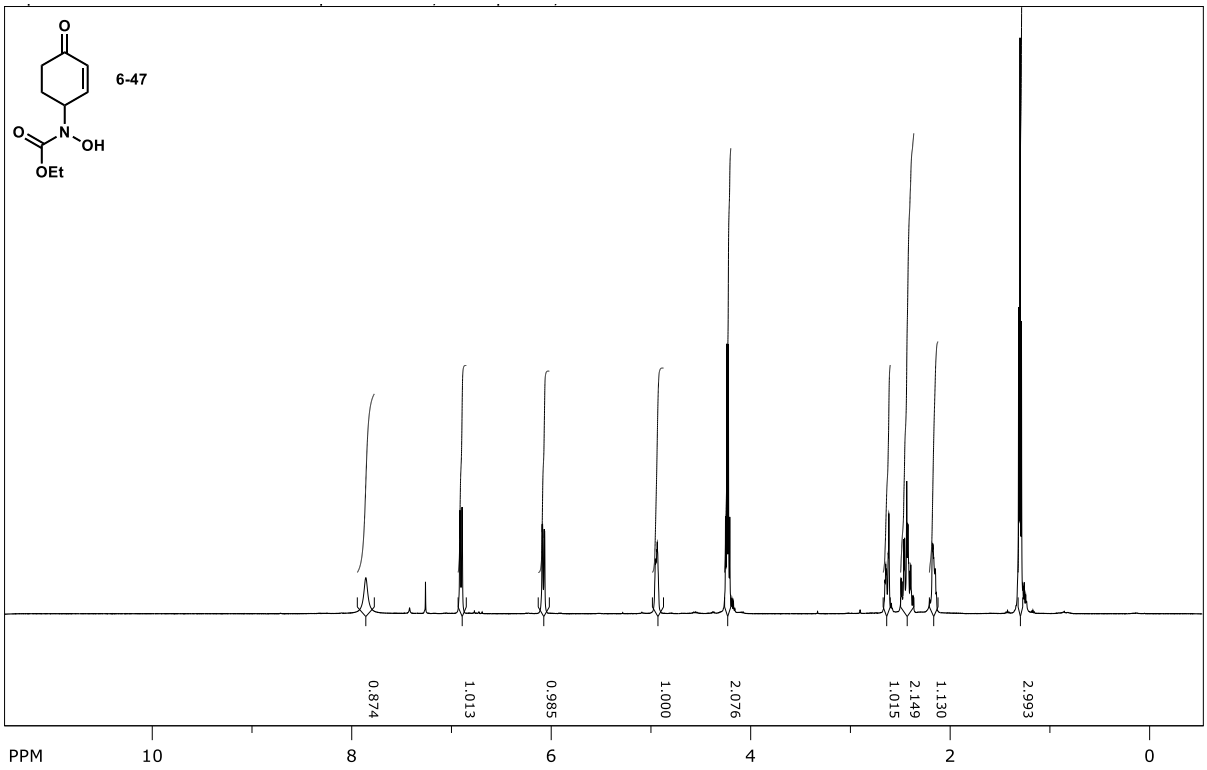
^{13}C NMR (126 MHz, $CDCl_3$)



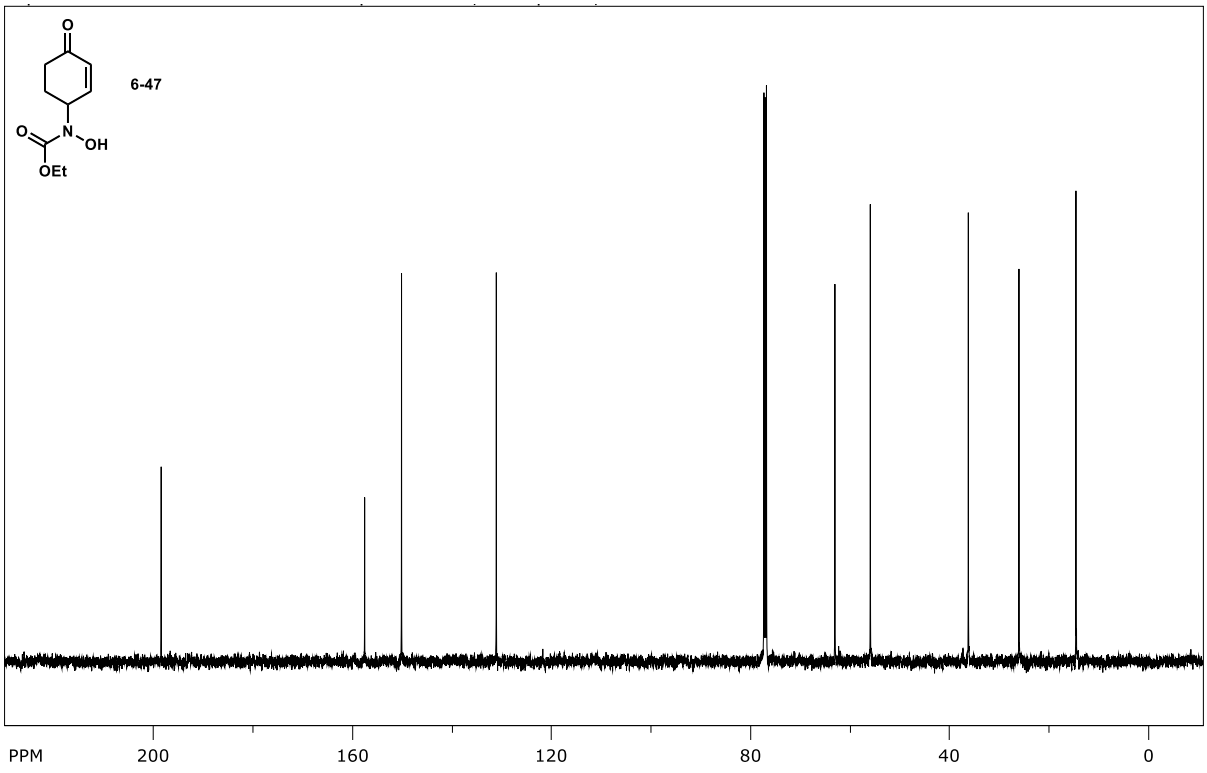
^{1}H NMR (500 MHz, $CDCl_3$)



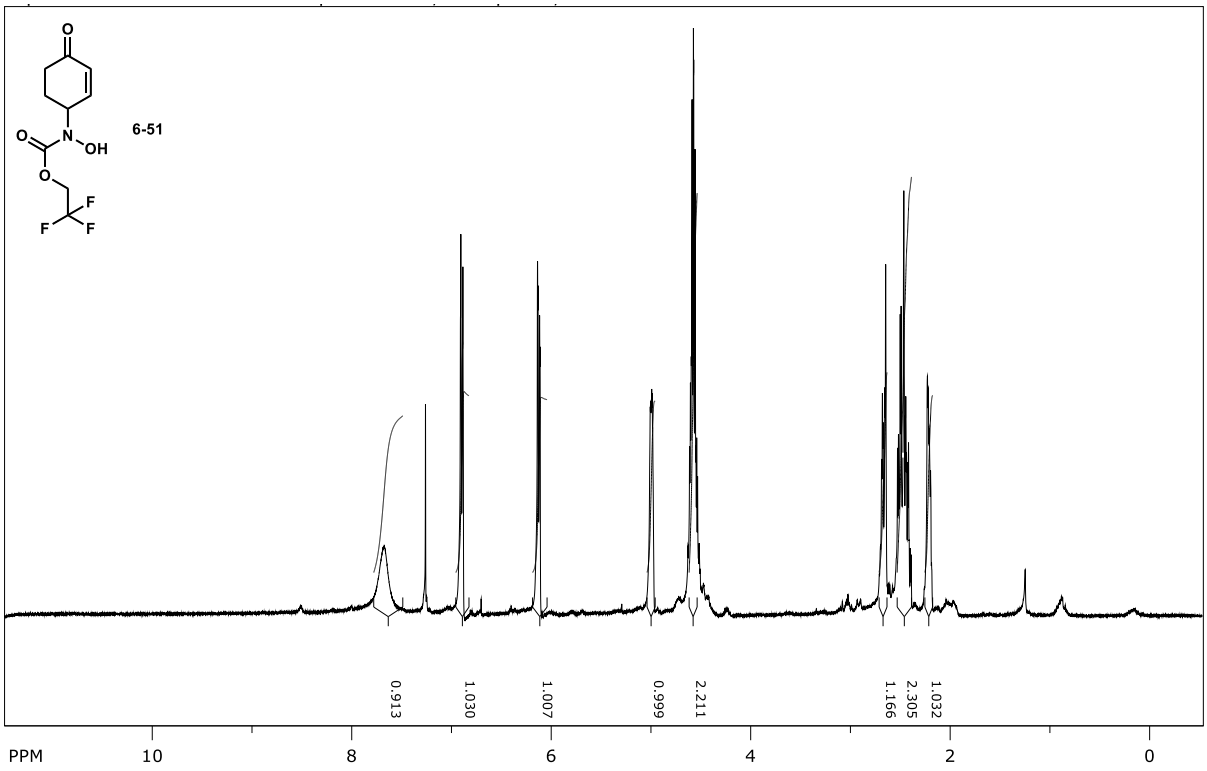
^{13}C NMR (126 MHz, $CDCl_3$)



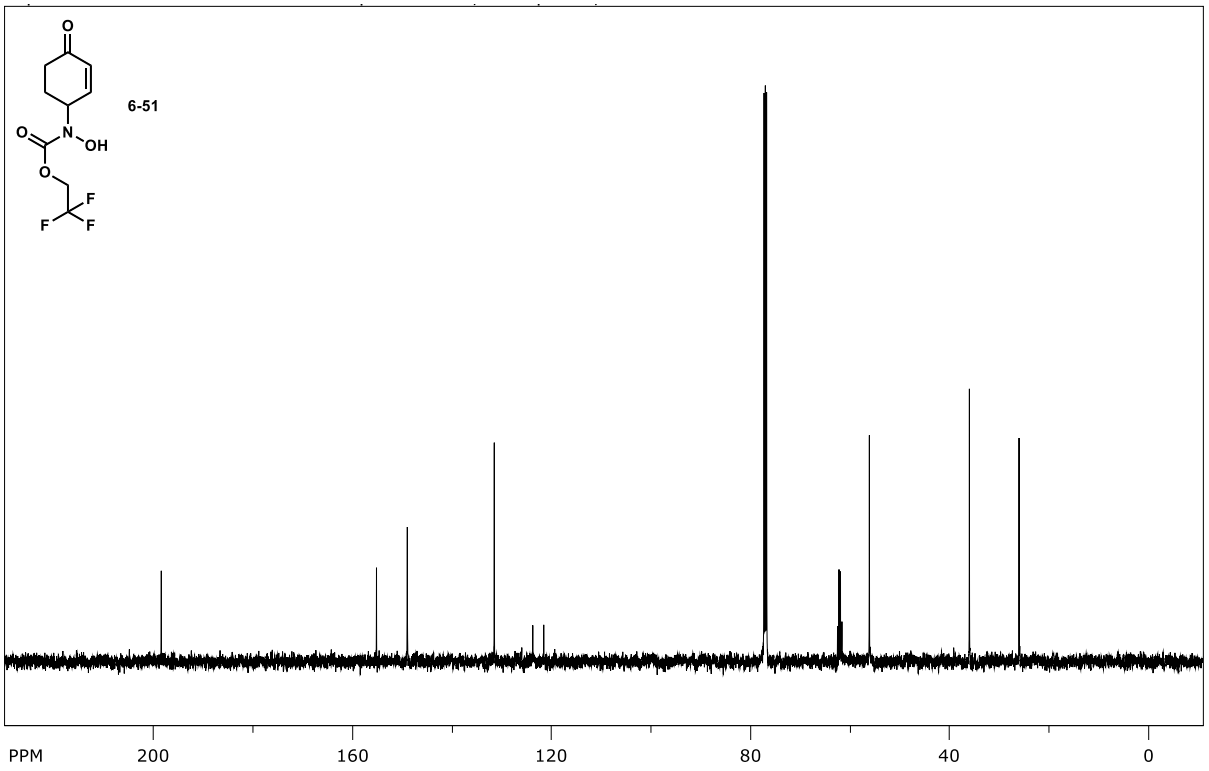
^{1}H NMR (500 MHz, $CDCl_3$)



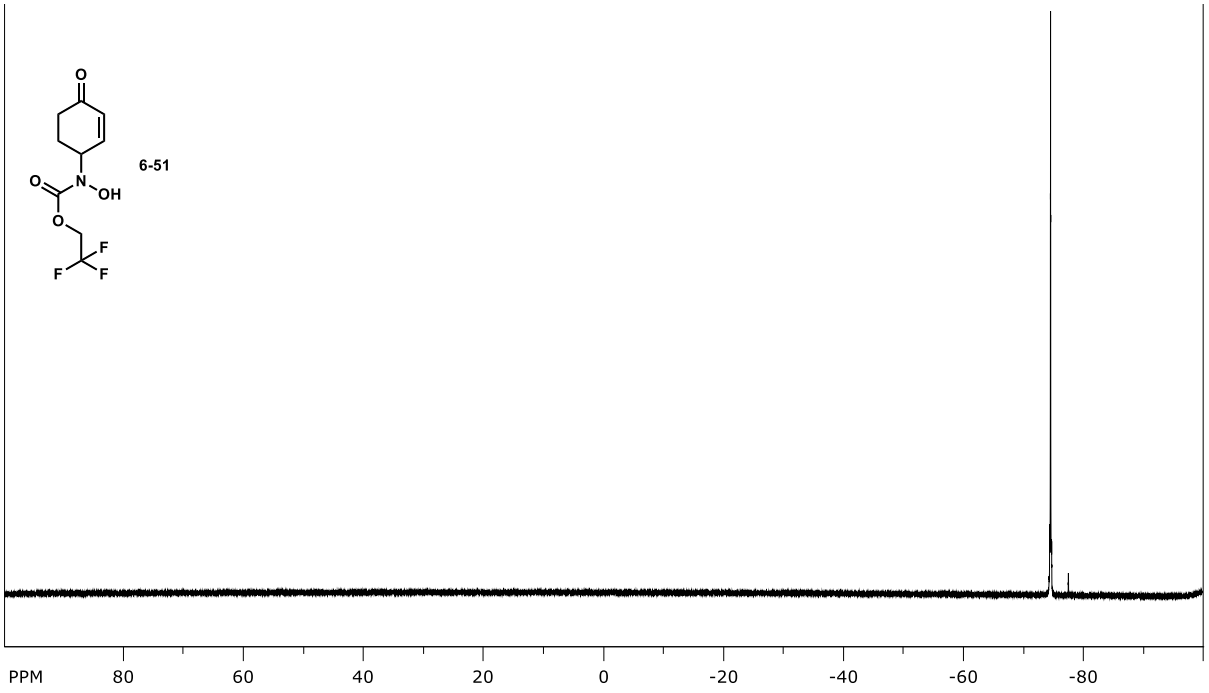
^{13}C NMR (126 MHz, $CDCl_3$)



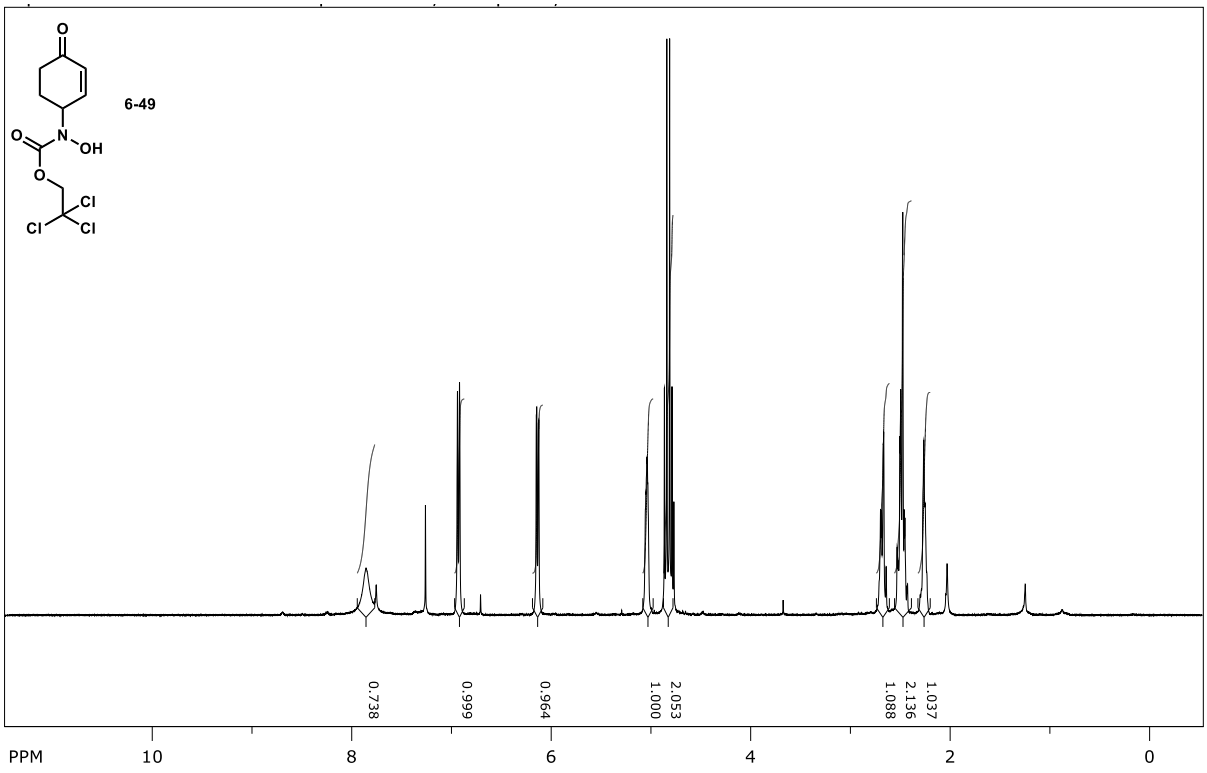
^{1}H NMR (500 MHz, $CDCl_3$)



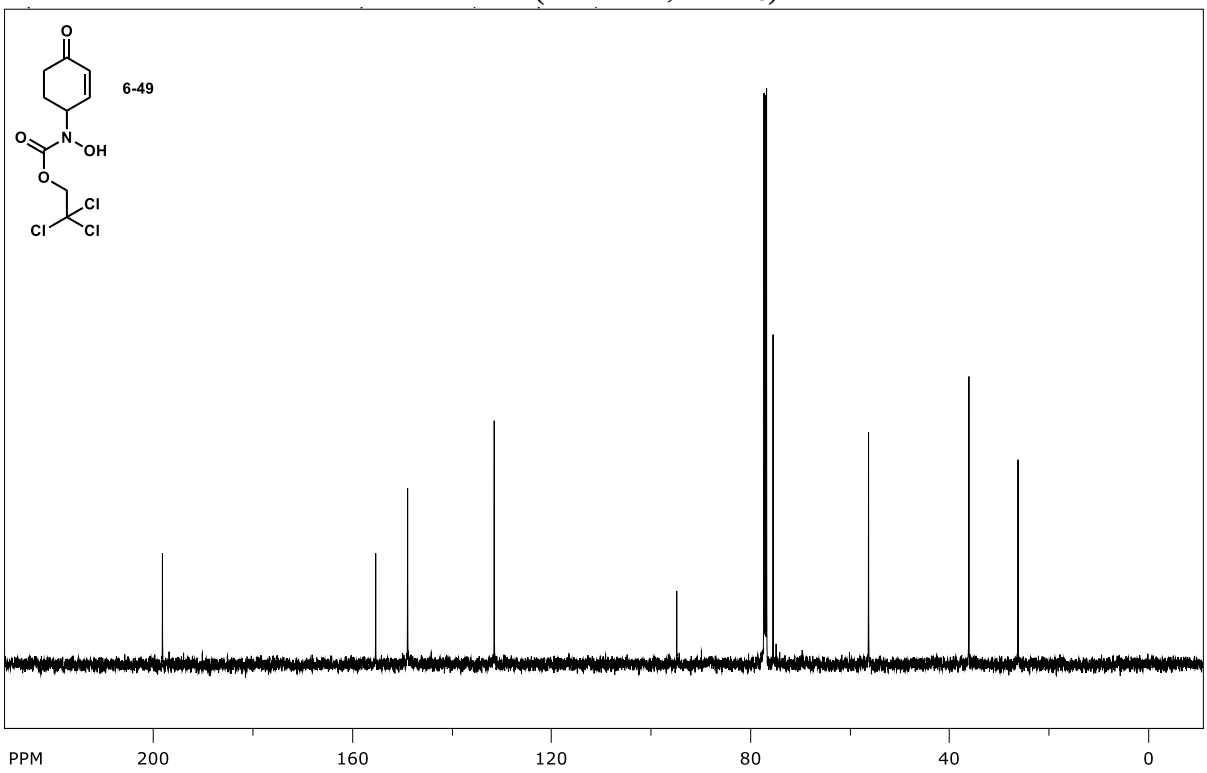
^{13}C NMR (126 MHz, $CDCl_3$)



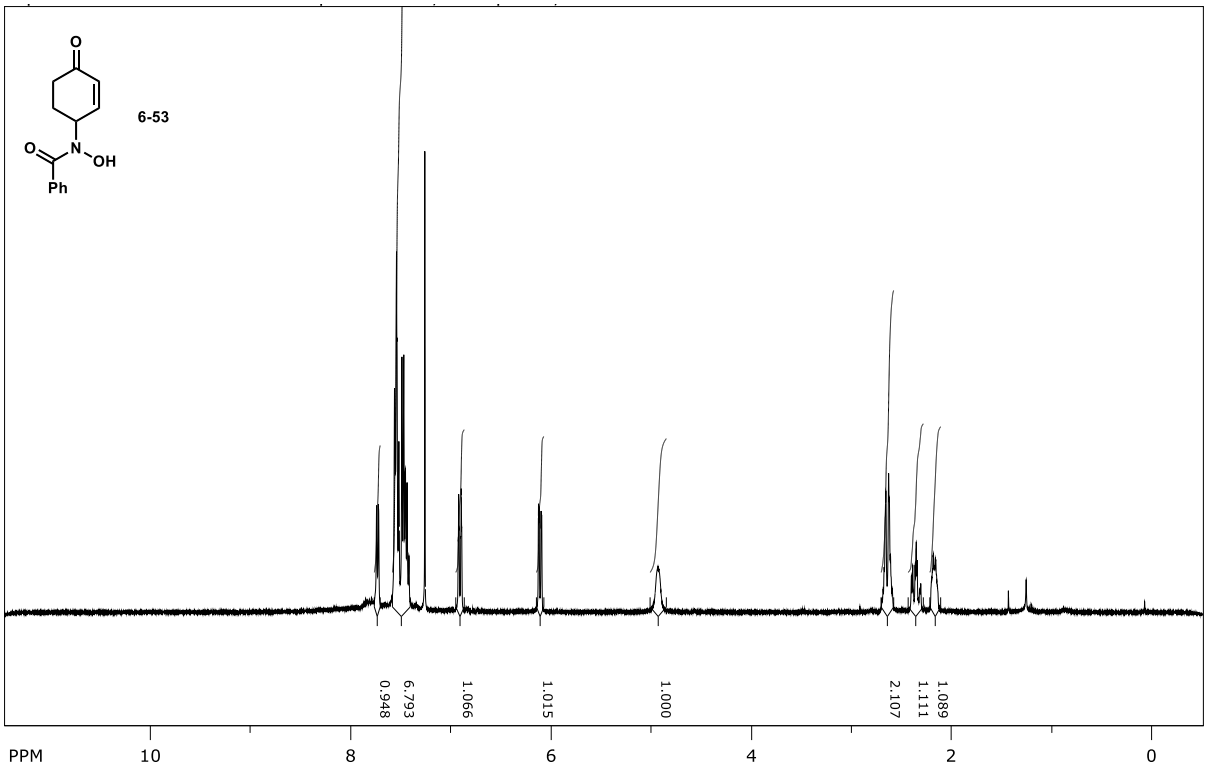
^{19}F NMR (376 MHz, $CDCl_3$)



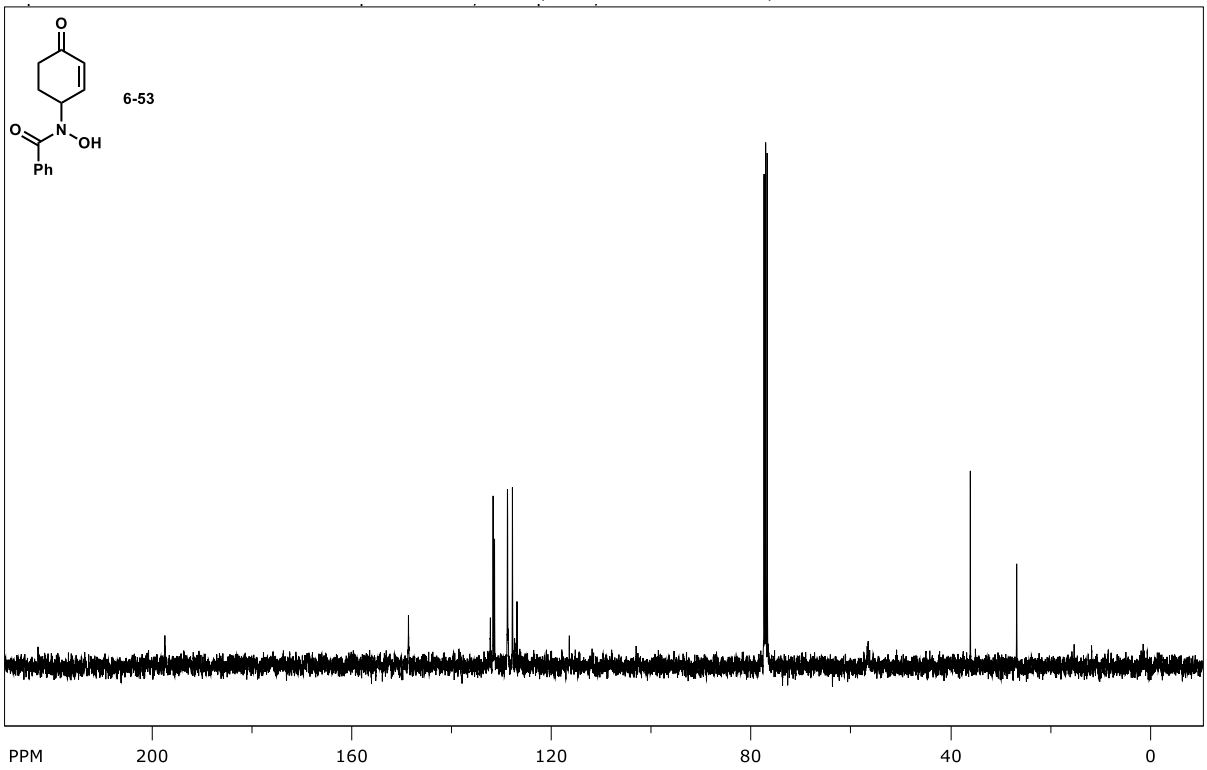
^{1}H NMR (500 MHz, $CDCl_3$)



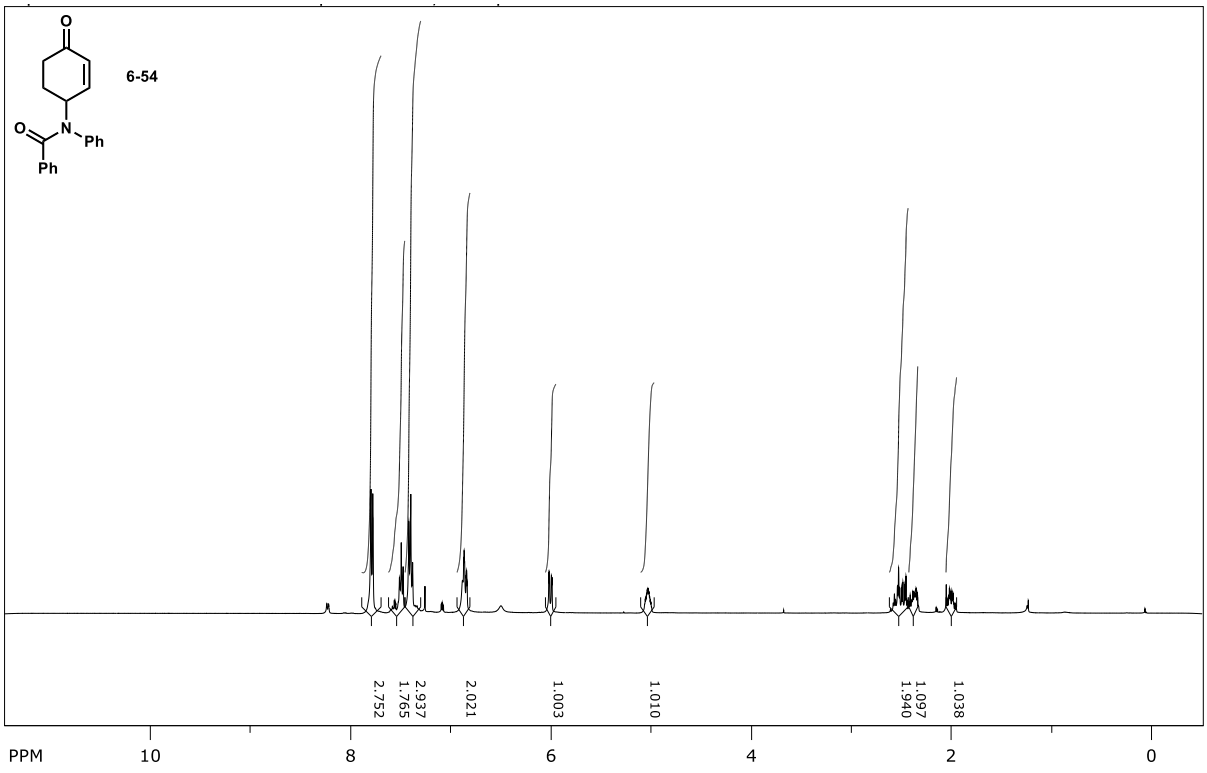
^{13}C NMR (126 MHz, $CDCl_3$)



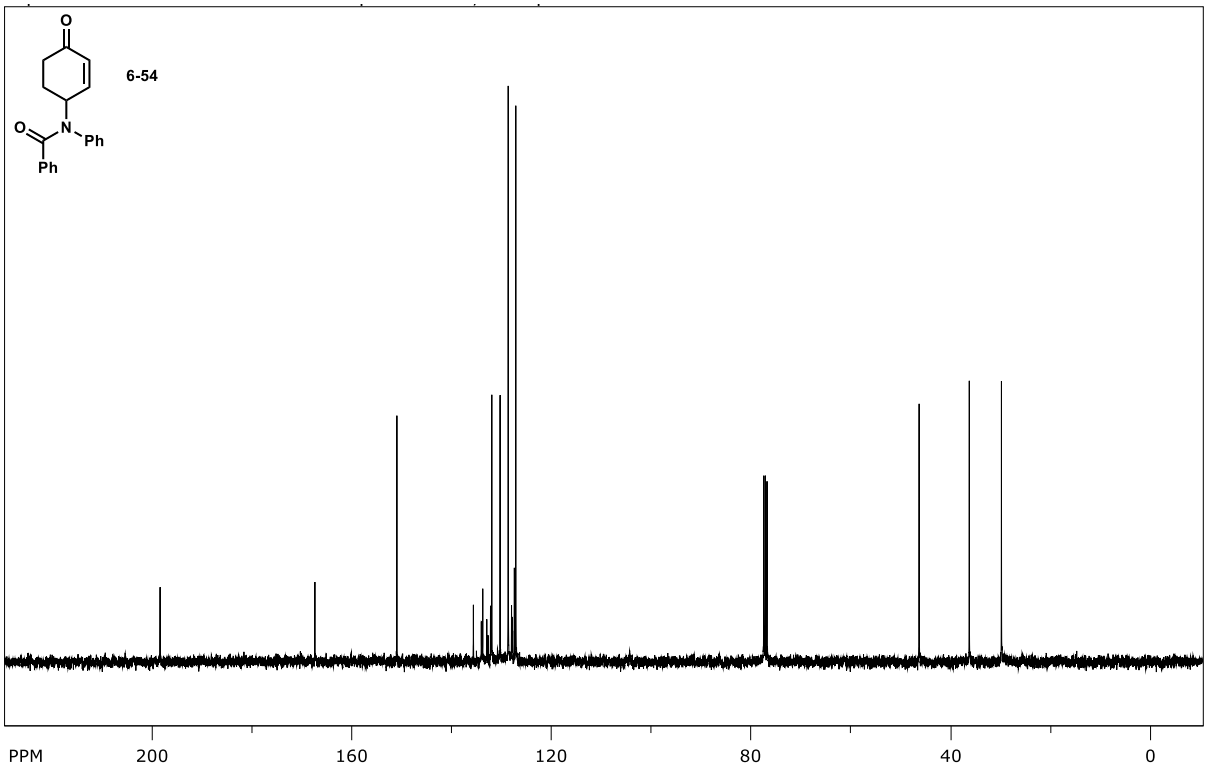
^{1}H NMR (500 MHz, $CDCl_3$)



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



^{1}H NMR (500 MHz, $CDCl_3$)



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

NABEELAH KAUSER

735 S Claremont Ave, Chicago, IL 60612 | (630) 962-0048 | nikauser04@gmail.com

EDUCATION

University of Illinois at Chicago, Chicago, IL

PhD in Organic Chemistry **2012-Present**

"γ-functionalization of enones and the total synthesis of *crotontomentosin A, and mesembrine*."

Benedictine University, Lisle, IL

B.S. in Chemistry **2012**

"Enantioselective Hydrogenation of Racemic 3,3,5 Trimethylcyclohexenone"

AWARDS

FloHet Poster Winner **2018**

DFI Fellow **2015 – 2018**

ACS Undergraduate Award in Analytical Chemistry **2010 – 2011**

MEMBERSHIPS

Iota Sigma Pi Aurum Iodide **2010 – 2017**

PUBLICATIONS AND PAPERS

Deng, Y.; Kauser, N.; Mohr, J. T. "Ag(II)-Mediated Synthesis of β-Fluoroketones via Oxidative Cyclopropanol Opening" *European Journal of Organic Chemistry. Eur. J. Org. Chem.* **2017**, *39*, 5872-5879.

PRESENTATIONS:

Kauser, N.; Chen, X. " *γ-functionalization of enones via silyl dienol ethers."* Poster Presentation, *18th Florida Heterocyclic and Synthetic Chemistry (FloHet) Conference,* Gainesville, Fl, **2018**.

Kauser, N.; Chen, X. " *γ-functionalization of enones via silyl dienol ethers."* Poster Presentation, *National Organic Symposium*, Davis, Ca, **2017**.

RESEARCH EXPERIENCE

University of Illinois at Chicago, Chicago, IL

Justin T Mohr, Advisor **2012 – Present**

Total Synthesis of Natural Products

- The total synthesis of Crotontomentosin A through the Nickel-catalyzed γ-alkylation of enones and β-alkylation through Suzuki coupling
- The total synthesis of Propolisbenzofuran B through the Nickel-catalyzed γ-arylation of enones from silyl dienol ethers and bromoarenes

β- or γ-Functionalization of enone

- Developed a new method for the nickel-catalyzed γ-alkylation of enones from silyl dienol ethers and α-halocarbonyls.
- Developed a new method for the copper-catalyzed γ-hydroxylamination of enones.
- Development of a method for β-fluoroketones through a silver-catalyzed cyclopropanol ring opening.

Synthesis of [3.2.1] Oxabicycles

- Developed a method for regioselective bond fission with cyclopropylcarbinyl radicals as a ring expansion method for [3.2.1] oxabicycles.

TEACHING EXPERIENCE

University of Illinois at Chicago, Chicago, IL
Teaching Assistant – Organic Chemistry I & II **2012 - 2017**
Collaborated on curriculum, met with students upon request, and graded all quizzes and exams.

University of Illinois at Chicago, Chicago, IL
Teaching Assistant – Organic Chemistry Lab **2012 - 2017**
Demonstrated proper use of laboratory equipment, supervised students as they performed laboratory experiments, met with students upon request, and graded all written work, including laboratory reports.

WORK EXPERIENCE

Laboratory Technician
Suburban Labs - Hillside, IL **2012**

- Prepared drinking water, ground water and soil samples for ICP or ICP/MS testing
- Prepared water and soil samples for and tested for Mercury using CVAA
- Performed turbidity tests on drinking water samples.

Office Assistant
Moser College –Naperville, IL **2010-2012**

- Created and organized Excel spreadsheets
- Created folders for Student and Faculty orientations;
- Created check requisitions and updated budgets

Office Assistant
New York University –New York, NY **2010-2012**

- Created and sent out press releases to media outlets

CONFERENCES

2017 National Organic Symposium, Davis, CA
2018 Florida Heterocyclic and Synthetic Chemistry (FloHet) Conference