Exploration of the Nazarov Cyclization Reaction

by

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Abstract

Allenyl aryl ketones were synthesized and underwent the Nazarov cyclization using Lewis acid catalysts. The aromaticity of the AAKs is destroyed during the electrocyclization and interception of the carbocation intermediates was unsuccessful. The oxyallyl cation likely re-aromatizes more quickly than it can be intercepted by a nucleophile.

The oxyallyl cation derived by the Nazarov reaction of an allenyl vinyl ketone (AVK) is trapped at position **a**. Sterically hindered nucleophiles trap at position **c**, but nothing has trapped at position **b**. Synthesis of a tethered AVK for which intramolecular trapping of the carbocation would be geometrically favorable only at position **b** was not successful.

Divinyl ketones containing internal β-substituents isomerize to undergo the Nazarov reaction. The internal substituent increases the steric interactions in the reactive conformer. An AVK that is disubstituted was synthesized but the efficiency of the cyclization was considerably lowered. However, trapping was successful using allyltrimethylsilane.

List of Abbreviations and Symbols Used

δ	chemical shift or partial charge
A	acid
aq	aqueous
AAK	allenyl aryl ketone
AVK	allenyl vinyl ketone
APCI	atmospheric-pressure chemical ionization
$BF_3.OEt_2$	boron trifluoride diethyl etherate
br	broad
t-Bu	*tert*-butyl
cm^{-1}	wavenumber (s)
COSY	correlation spectroscopy
d	doublet
DCM	dichloromethane
dd	doublet of doublets
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dt	doublet of triplets
ddt	doublet of doublets of triplets
ESI	electrospray ionization
Et	ethyl
FT	Fourier transform
g	gram(s)
h	hour(s)

HMBC	heteronuclear multiple bond coherence
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
hν	light energy
Hz	hertz
IBX	2-iodoxybenzoic acid
IR	infrared
J	coupling constant
LA	Lewis acid
m	multiplet
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
mp	melting point
Ms	methane sulfonyl
n	narrow
NOE	nuclear Overhauser effect
NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
ppm	parts per million

q	quartet
quint	quintet
rt	room temperature
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
td	triplet of doublets
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	2,4,6-trimethoxyphenyl
TMS	tetramethylsilane
TOF	time of flight
Ts	*para*-toluenesulfonyl
UV	ultraviolet

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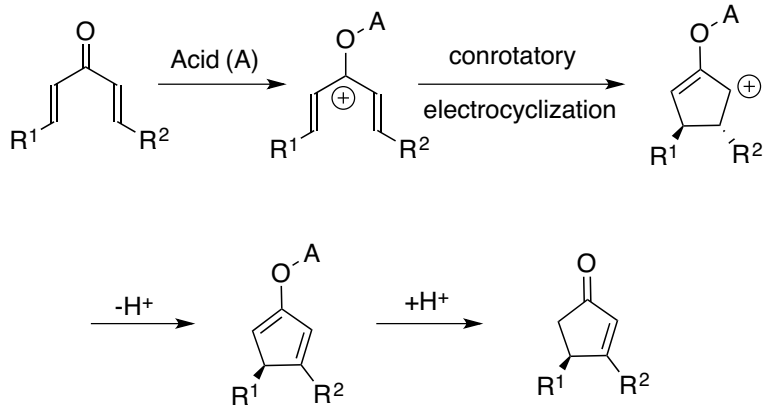
Chapter 1 - Introduction

1.1 The Classical Nazarov Reaction

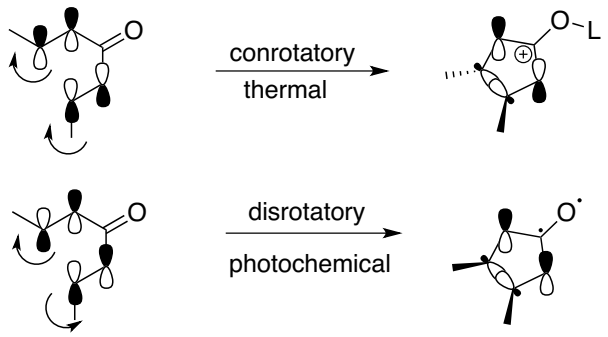
The Nazarov reaction is an important tool for the synthesis of five-membered rings from divinyl ketones. It was first reported by Ivan Nikolaevich Nazarov in 1941.[1] The ketone complexes with an acid to generate a pentadienyl cation intermediate, which undergoes a conrotatory 4π electrocyclization to give an oxyallyl cation (Scheme 1.1). Subsequent elimination of a proton from the oxyallyl cation leads to a cyclopentadiene intermediate, which tautomerizes to give the cyclopentenone product.



Scheme 1.1 Acid-catalyzed Nazarov reaction of a divinyl ketone

Under thermal conditions, the electrocyclization occurs in a conrotatory fashion where the termini of the highest occupied molecular orbital (HOMO) rotate in the same direction. However, when the reaction occurs photochemically the termini rotate in opposite directions to give a disrotatory ring closure since the singly occupied molecular orbital (SOMO) is the reacting orbital. The starting geometry of the double bonds (*cis* or *trans*) and whether the reaction is conrotatory or disrotatory dictates the relative stereochemistry of the final product (Scheme 1.2). Therefore, the outcome of the

Nazarov cyclization can be predicted, and the reaction can be used to synthesize cyclopentenones with varying substitution.



Scheme 1.2 Conrotatory and disrotatory ring closure

1.1.2 Conformational Preference Influenced by α-Substituents

It has been shown that the presence of α-substituents on the divinyl ketone increases the cyclization efficiency.[2,3,4] This phenomenon can be explained partially by the proportion of the reactive *s-trans*/*s-trans* conformer. The figure below shows three conformational minima for an α-substituted divinyl ketone. Alkyl groups (R^1 and R^2) introduce steric interactions with the vinyl hydrogen atoms and increase the proportion of the *s-trans*/*s-trans* conformer. Conversely, hydrogen atoms in the α positions favor to the *s-cis*/*s-cis* conformation and lead to inhibition of the cyclization.

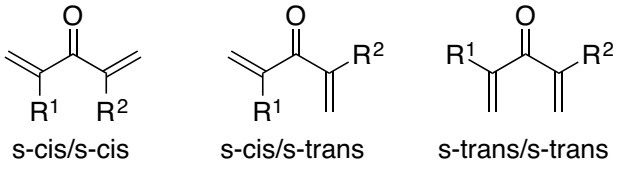
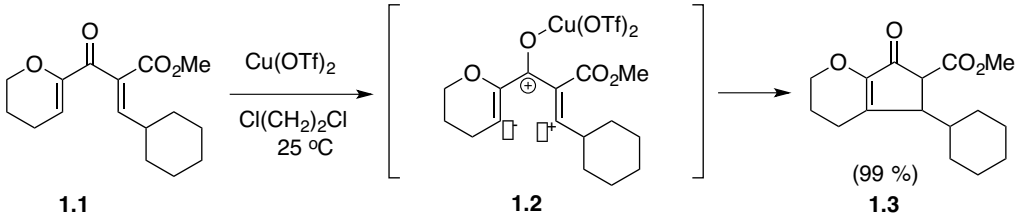


Figure 1.1 Three conformers of α-substituted divinyl ketone

1.1.3 Polarized Nazarov reaction

The electronic effects of α-substituents on the efficiency of the electrocyclization have also been studied.[5,6] Frontier and coworkers explored the polarization of the

pentadienyl cation by adding an electron-donating oxygen and an electron-withdrawing ester group on the two α-positions of **1.1**.[4] This polarized the pentadienyl cation **1.2** and led to a more facile cyclization in the presence of catalytic amounts of $Cu(OTf)_2$ to give **1.3** (Scheme 1.3). The electron-donating and electron-withdrawing groups also increased the regioselectivity of the elimination step as the positive charge was preferably generated on the carbon stabilized by the electron-donating group.

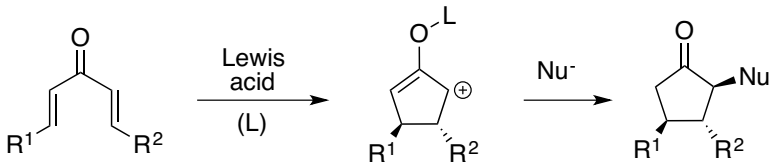


1.1 **1.2** **1.3**

Scheme 1.3 Polarized Nazarov cyclization

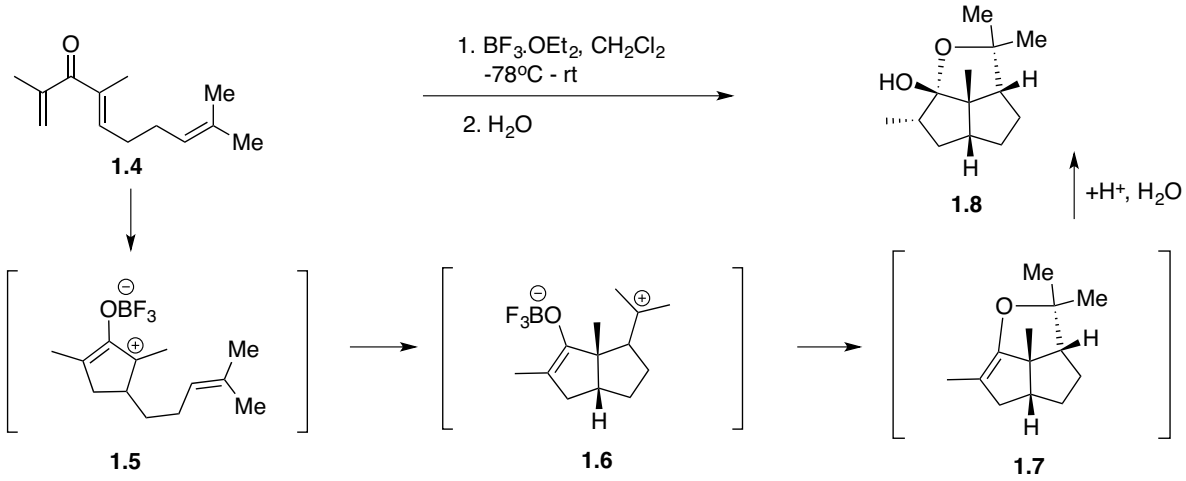
1.2 The Interrupted Nazarov Reaction

In the classical Nazarov reaction, loss of a proton from the oxyallyl cation generates the cyclopentadiene intermediate that tautomerizes to furnish the final cyclopentenone product. The West group introduced the "interrupted" Nazarov reaction, in which a nucleophile or π-system is added to trap the oxyallyl cation intermediate (Scheme 1.4). This synthetically useful development results in the formation of three new stereocentres instead of only one.



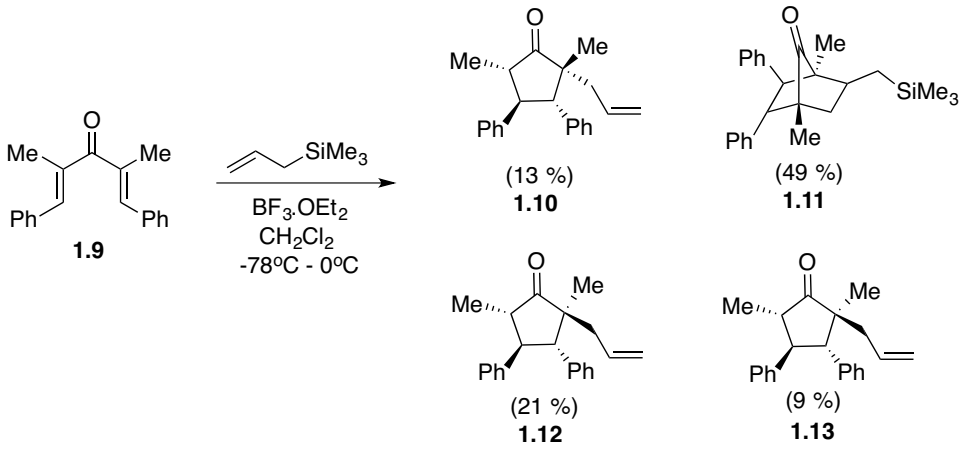
Scheme 1.4 The interrupted Nazarov reaction

The interception of the carbocation intermediate can take place intramolecularly. Trienone substrates underwent an intramolecular interrupted Nazarov cyclization when exposed to Lewis acidic conditions at low temperatures to give the hemiketal product (Scheme 1.5).[7] In the presence of boron trifluoride etherate, the substrate **1.4** cyclized to give the oxyallyl cation **1.5**, which was subsequently trapped by the alkene to give **1.6**. The carbocation was then trapped by the oxygen to give **1.7** and hydration during work-up led to the final product, **1.8**, which contained three newly formed rings and five new stereocentres, showing the synthetic utility of this method.



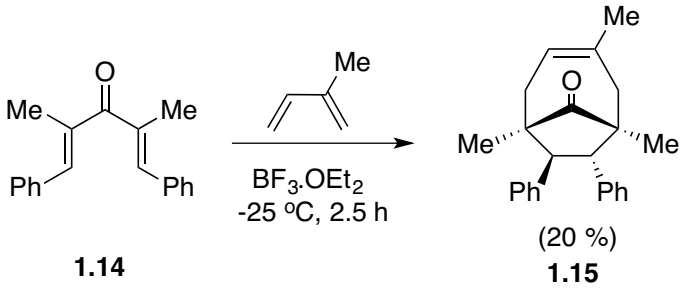
Scheme 1.5 Intramolecular trapping of the oxyallyl cation generated from a trienone substrate

In the course of their development of the interrupted Nazarov reaction, the West group demonstrated the interception of the oxyallyl cation of a divinyl ketone using allyltrimethylsilane by a (3 + 2) cycloaddition.[8] Treatment of the divinyl ketone **1.9** with $BF_3.OEt_2$ at -78 °C gave the (3 + 2) cycloadduct **1.11** as a single diastereomer and also three diastereomers (**1.10**, **1.12**, **1.13**) of the allyl-substituted cyclopentanone (Scheme 1.6).



Scheme 1.6 Oxyallyl cation interception using allyltrimethylsilane

Acyclic dienes and heterocycles, such as furan, have also been shown to trap the oxyallyl cation derived from divinyl ketones to form the cycloadducts of (4 + 3) cycloaddition (Scheme 1.7). Treating divinyl ketone **1.14** with $BF_3.OEt_2$ at a low temperature in the presence of isoprene gave the bridged cycloctene **1.15**.[9] This reaction resulted in the formation of four new stereocentres.



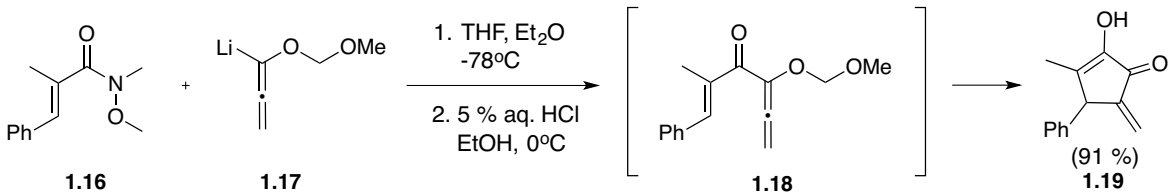
Scheme 1.7 Electrocyclization and tandem (4 + 3) cycloaddition of divinyl ketone

1.2.1 Nazarov Reactions of Allenyl Vinyl Ketones

The substrates used in the original Nazarov reactions were divinyl ketones. Allenyl vinyl ketones (AVKs) have been shown to undergo the Nazarov reactions under milder conditions and are therefore excellent substrates for the Nazarov reactions. AVKs differ

from divinyl ketones in that they have an allene group in the place of one of the vinyl groups.

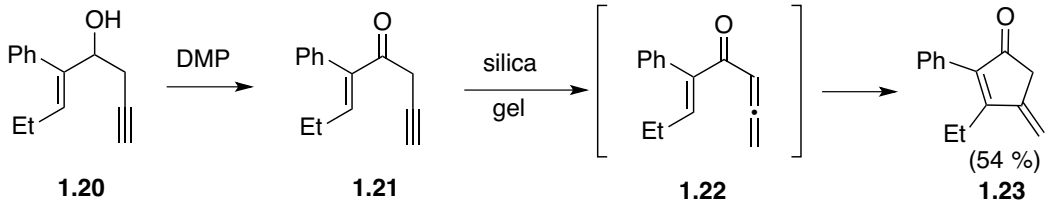
Tius and coworkers reported the first Nazarov reaction of allenyl vinyl ketone substrates. In 1994, they published the synthesis of cross-conjugated cyclopentenones using a Nazarov cyclization.[10] The AVK intermediate **1.18**, which was not observed, was prepared from the Weinreb enamide **1.16** and lithioallene **1.17**. The initially formed product cyclized under acidic work up to give the conjugated cyclopentenone **1.19** (Scheme 1.8). The presence of the ether group polarized the pentadienyl cation, and the final product was obtained from the elimination of a methoxymethyl carbocation and the tautomerization of the initial ketone.



1.16 **1.17** **1.18** **1.19**

Scheme 1.8 Synthesis of a cross-conjugated cyclopentenone from the Nazarov reaction of allene ether

The Hashmi group also observed the Nazarov cyclization of AVKs.[11] Propargyl alcohol **1.20** was prepared and oxidized to the ketone **1.21** using Dess-Martin periodinane (DMP). When the ketone was purified on silica gel, the expected allenyl vinyl ketone **1.22** was not isolated. Instead, they obtained Nazarov product **1.23**, which implies that the alkyne isomerized to an allene and the high reactivity of the allene led to cyclization even under mild acidic condition of silica gel (Scheme 1.9).



Scheme 1.9 Nazarov cyclization of an AVK on silica gel

Allenes have less steric repulsion in the *s-trans/s-trans* conformation, which helps to increase the proportion of the reactive conformer.

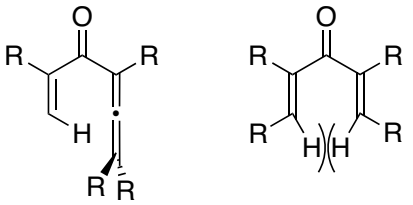
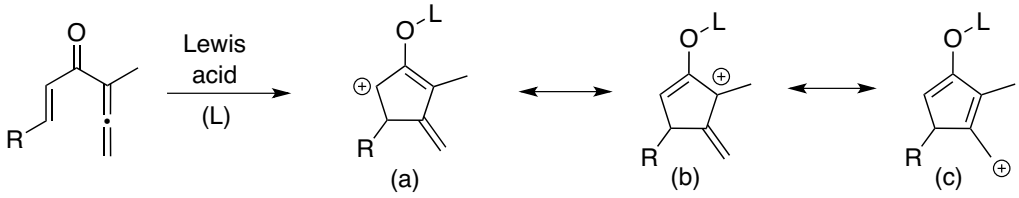


Figure 1.2 The *s-trans/s-trans* conformation of an AVK and a divinyl ketone

1.2.2 Interrupted Nazarov Reactions of Allenyl Vinyl Ketones

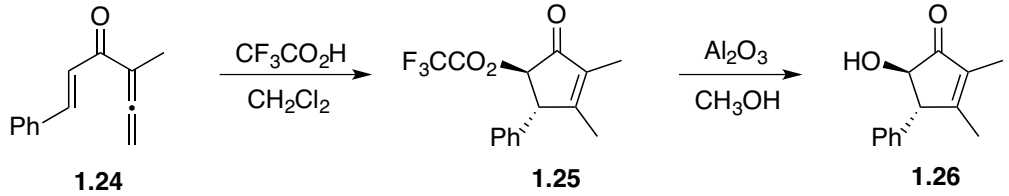
Allenyl vinyl ketones have been shown to be excellent substrates for the interrupted Nazarov reaction.[12-17] The oxyallyl cation generated from an AVKs has three resonance structures and therefore this carbocation should be a longer-lived, more stable carbocation than that generated from a divinyl ketone. In addition, proton elimination from the carbocation intermediate would lead to the formation of a fulvene, which is a disfavored, higher energy product. This increases the likelihood of the cation intermediate of AVKs being intercepted by a nucleophile.



Scheme 1.10 Resonance contributors of the oxyallyl cation formed from an allenyl vinyl ketone

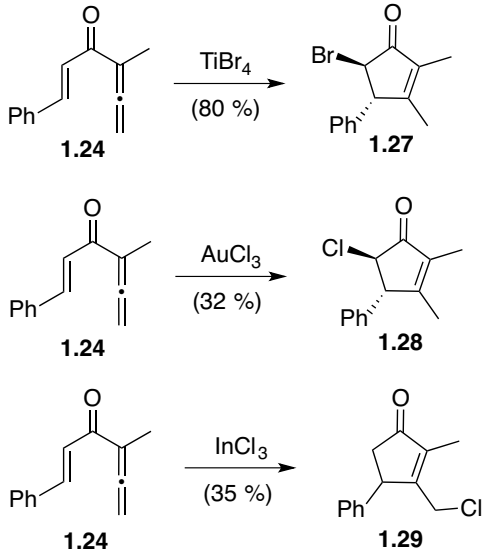
As shown in Scheme 1.10, there are also three possible positions for a nucleophile to trap the oxyallyl cation of an AVK. Computational work conducted on the oxyallyl cation showed that position **a** is the most electrophilic and is therefore the electronically preferred position for trapping.[12]

The conjugate base of the acid used to catalyze the Nazarov cyclization can be the nucleophile that traps the oxyallyl cation. For instance, the synthesis of 5-hydroxycyclopent-2-enones was achieved through the interrupted Nazarov reaction of allenyl vinyl ketones using trifluoroacetic acid.[13] Protonation of the ketone **1.24** was followed by the Nazarov cyclization and subsequent trapping of the oxyallyl intermediate at position **a** with the conjugate base, trifluoroacetate. Purification of the product **1.25** by column chromatography on basic alumina resulted in the solvolysis of the ester and afforded the 5-hydroxycyclopent-2-enone final product **1.26**. The predominant product had a *trans* relationship presumably resulting from a steric interaction of trifluoroacetate with the phenyl group at the C-4 position of the intermediate oxy-allyl cation.



Scheme 1.11 Synthesis of a 5-hydroxycyclopent-2-enone by an interrupted Nazarov reaction

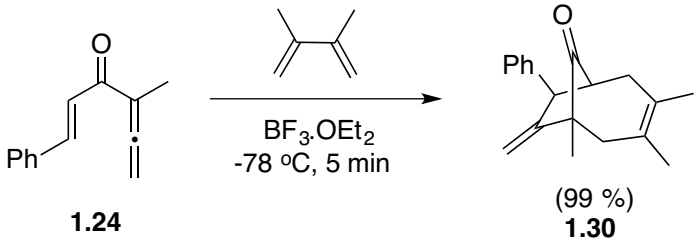
Halogenated cyclopentenones could also be synthesized by trapping the carbocation using a Lewis acid as the halide source.[14] Depending on the Lewis acid used, trapping was observed at either position **a** or **c**. When $TiBr_4$ and $AuCl_3$ were used with AVK **1.24**, the trapped products (**1.27**, **1.28**) were observed with the bromide or chloride at the **a** position (Scheme 1.12). Using $InCl_3$, on the other hand, predominantly gave cyclopentenone **1.29** with the chloride at position **c**.



Scheme 1.12 Halogenated cyclopentenones synthesized by interrupted Nazarov reactions

Acyclic dienes and electron-rich alkenes have been shown to be excellent substrates for the trapping of the oxyallyl cations of AVKs to give products of (4 + 3) and (3 + 2)

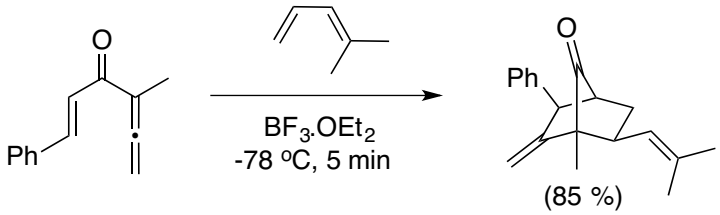
cycloaddition reactions. In work carried out by Marx and Burnell,[15] treatment of AVK **1.24** with $BF_3.OEt_2$ in the presence 2,3-dimethylbutadiene gave the product of (4 + 3) cyclization **1.30** in quantitative yield.



1.24 **1.30**

Scheme 1.13 Nazarov cyclization and tandem (4 + 3) cycloaddition

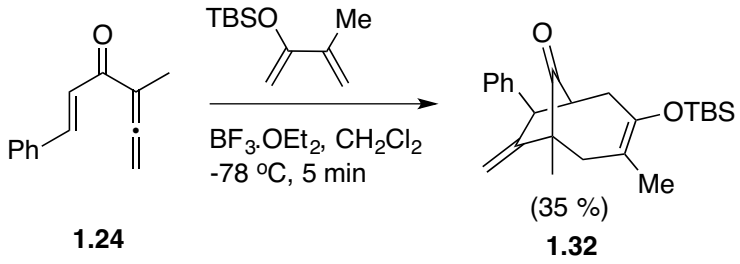
The (4 + 3) cycloaddition occurred by a concerted mechanism, which could only take place when the acyclic diene is in an *s-cis* conformation. Substitution on the dienes can therefore affect their ability to access the *s-cis* conformation and can highly influence the course of the reaction. Treatment of AVK **1.24** with $BF_3.OEt_2$ and 4-methylpenta-1,3-diene exclusively gave the (3 + 2) cyclization product **1.31** in high yield (Scheme 1.14). The presence of the two methyl groups on the double bond of the diene inhibited its ability to access the *s-cis* conformation and would result in steric hindrance in the (4 + 3) transition state. Therefore, the reaction led to the exclusive formation of the (3 + 2) cycloadduct. These reactions are synthetically useful in the formation of new carbon-carbon bonds and the construction of bicyclic ring systems.



1.24 **1.31**

Scheme 1.14 Nazarov cyclization and tandem (3 + 2) cycloaddition

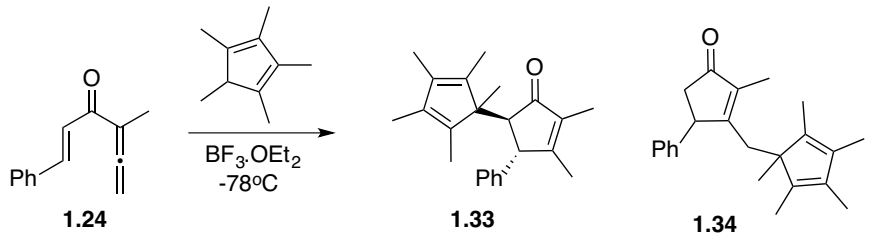
Oxygen-substituted dienes have been shown to give predominantly the (4 + 3) cycloadduct except in the case where steric hindrance inhibited the (4 + 3) cycloaddition.[16] The reaction appeared to take place with high regioselectivity, where the electron-rich end of the alkene reacted with the most electrophilic site of the oxyallyl cation to give **1.32**.



1.24 **1.32**

Scheme 1.15 Nazarov cyclization and tandem (4 + 3) cycloaddition using an oxygen-substituted diene

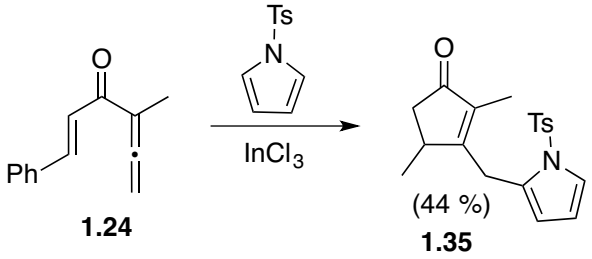
As seen in the previous examples, the (4 + 3) and (3 + 2) cycloadducts are formed by trapping at positions **a** and **b** of the oxyallyl cation. However, trapping at position **c** can be promoted by the use of bulky nucleophiles. The Nazarov reaction of AVK **1.24** in the presence of 1,2,3,4,5-pentamethylcyclopentadiene gave the minor product of trapping at position **a**, **1.33**, and the major project of trapping at the less sterically hindered position **c**, **1.34**.



1.24 **1.33** **1.34**

Scheme 1.16 Trapping at positions a and c using a bulky carbon nucleophile

Nitrogen-containing heterocycles can also be used to trap the oxyallyl cation at both positions **a** and **c**. In work published by *Marx et al*., AVK **1.24** was treated with $BF_3.OEt_2$ in the presence of variously substituted pyrrole rings.[17] *N*-Alkyl-, *N*-aryl-, and *N*-silyl-pyrroles trapped predominantly as position **a** in yields ranging from 31 – 67 %. *N*-Mesyl- and *N*-tosyl-pyrrole trapped at position **c** with improved yields using $InCl_3$ as the Lewis acid. Indole substrates have also been shown to be good trapping agents. Increasing the hindrance of C-3 of the indole, such as with 2-methylindole, influenced the regioselectivity of the reaction by increasing the proportion of the product trapped at position **c**.



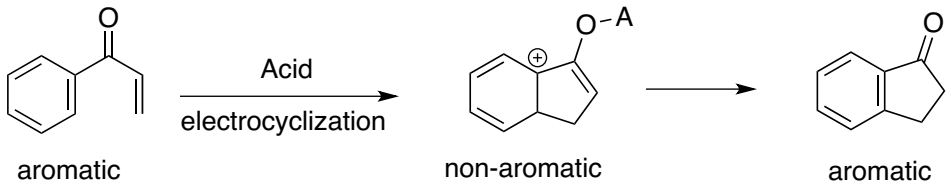
1.24 **1.35**

Scheme 1.17 Trapping of an oxyallyl cation using tosyl-substituted pyrrole

1.3 Nazarov Reaction of Aromatic Substrates

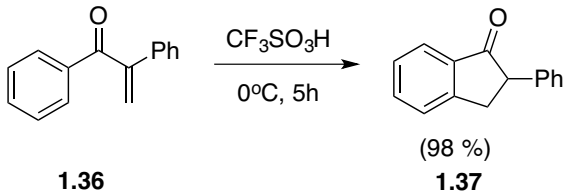
The Nazarov cyclization was first accomplished using divinyl ketone substrates under acidic conditions. Further research showed that allenyl vinyl ketones are more reactive substrates for the reaction due to the inherent reactivity of the allene group and the increase in the proportion of the reactive *s-trans*/*s-trans* conformer. Aryl vinyl ketones have also been used as substrates for Nazarov reactions. However, in order for the electrocyclization to take place, the aromaticity of the molecule must be broken, and

aromaticity is only restored following the proton elimination step. This requires harsher conditions in order to temporarily destroy the molecule's aromaticity.



Scheme 1.18 Nazarov reaction of aryl vinyl ketone

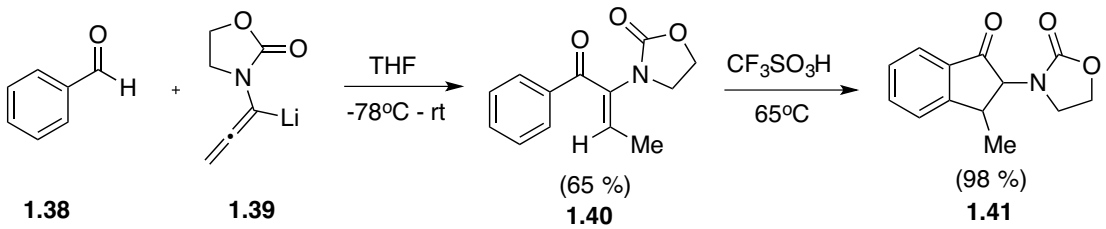
Ohwada and coworkers[18] reported the synthesis of indanones, such as **1.37**, from aryl vinyl ketones (**1.36**) with acids such as trifluoromethanesulfonic acid and trifluoroacetic acid.



Scheme 1.19 Nazarov reaction of aryl vinyl ketone to give an indanone

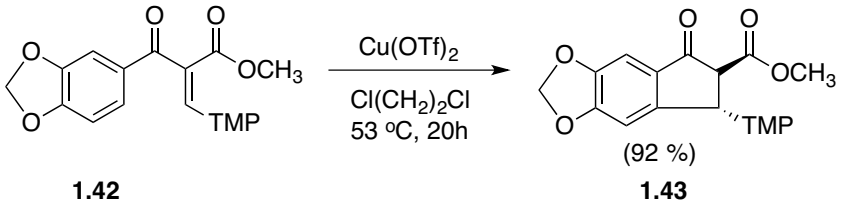
In work reported by West and coworkers, oxazolidinone-substituted aryl vinyl ketones were synthesized from the reaction of aryl aldehydes, such as **1.38**, and lithiated allenamide **1.39** (Scheme 1.20).[19] They suspected that the presence of the electron-withdrawing α-amido group would polarize the pentadienyl cation and increase the efficiency of the cyclization. Treatment of the aryl vinyl ketones with various Lewis acids such as $FeCl_3$ and $Eu(OTf)_3$ only gave starting material back. Indium (III) triflate was the only effective Lewis acid for promoting the electrocyclization, which was only observed with a naphthalene derivative. However, when they used triflic acid as the acid catalyst the cyclized Nazarov products were obtained in yields as high as 98 %, such as

1.41.



Scheme 1.20 Nazarov reaction of oxazolidinone-substituted aryl vinyl ketone

Polarization of the pentadienyl cation of aromatic vinyl ketones can also be achieved by adding electron-donating groups on the aromatic ring and an electron-withdrawing group on the α-position of the vinyl group. Frontier and coworkers used a piperonal-type aromatic vinyl ketone **1.42**, which generated the cyclized product **1.43** in high yield in the presence of a catalytic amount of $Cu(OTf)_2$.[4]



Scheme 1.21 Polarized Nazarov reaction of aromatic vinyl ketone

1.4 Thesis Chapters

The following three chapters of this thesis will highlight the research projects that I have worked on in my Master's studies. The first project focuses on the synthesis of allenyl aryl ketones (AAKs), studying their reactivity in the Nazarov reaction, and attempts to trap the oxyallyl cation intermediate. Allenyl aryl ketones have been shown to undergo the Nazarov cyclization. While AAKs also contain an aromatic group that

can hinder the cyclization, pairing it with the reactive allene moiety could lead to a more facile Nazarov reaction of aromatic systems.

The second project describes the attempt to synthesize substrates that promote intramolecular trapping at position **b**. Position **a** is the preferred electrophilic site for trapping, whereas position **c** is the sterically preferred site. However, trapping at position **b** has rarely been observed.

Finally, the third project explores the Nazarov reaction of an allenyl vinyl ketone substrate that carries two substituents on the β-carbon of the vinyl group.

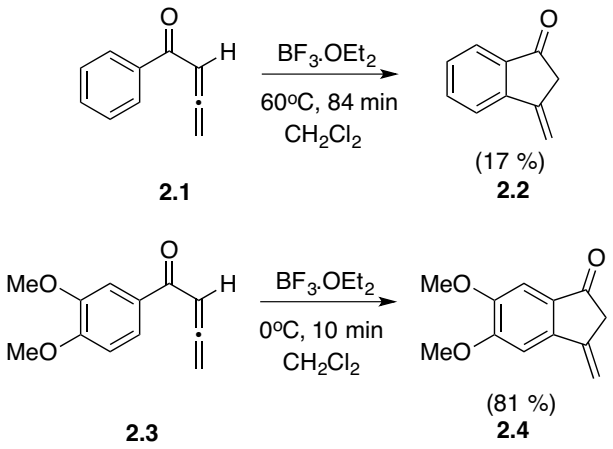
Chapter 2 - Synthesis and Nazarov Cyclization of Allenyl Aryl Ketones

2.1 Introduction

Aromatic substrates should require harsher reaction conditions in order for an electrocyclization to take place. This is because the aromaticity of the molecule is lost in the course of the reaction. However, aromaticity can then be restored in the proton-elimination step. An allenyl aryl ketone (AAK) combines the features of an aromatic substrate with the allene moiety that might increase reactivity of the substrate. However, trapping the oxyallyl cation derived from AAK would be challenging due to the considerable stabilization that would result from elimination of a proton to restore aromaticity. In order to trap the carbocation intermediate, the nucleophile would need to react with the cationic intermediate at a faster rate than the elimination of the proton.

Nagao and coworkers reported the intramolecular cyclization of AAKs through what they believed was a 5-*endo*-mode of Friedel-Crafts cyclization.[20] The reaction was carried out with $BF_3.Et_2O$ and produced some differently substituted cyclopentenones. As shown in Scheme 2.1, the allenyl aryl ketone with an unsubstituted phenyl ring required a high temperature and a long reaction time, compared to the reactions of allenyl vinyl ketones,[11-17] in order to furnish the cyclized product in low yield. However, the presence of electron-donating methoxy groups at the 3- and 4- positions of the aromatic ring resulted in the formation of the cyclized product in 10 minutes at 0 ^{o}C in high yield. Electron-donating groups on the phenyl ring would be expected to increase the efficiency of electrophilic aromatic substitution reactions, but it had been shown that electron-donating groups would also facilitate a Nazarov cyclization.[20] Thus, we were motivated to explore the cyclizations of AAKs both from the synthetic and mechanistic

points of view.



Scheme 2.1 5-*endo*-dig Cyclizations of allenyl aryl ketone reported by Nagao

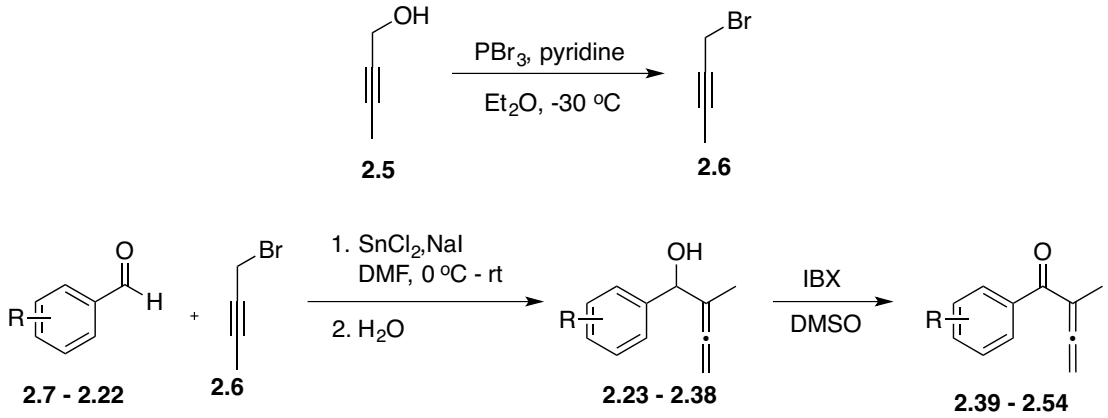
2.2 Results and Discussion

2.2.1 Synthesis

AAKs bearing a methyl group α to the ketone were targeted in the present work because the corresponding allenyl vinyl ketones were found to be more stable.[12] Initially, a Grignard reaction was used with 3-methoxybenzaldehyde to give a mixture of the allenyl alcohol and the alkynyl alcohol.[21] This method was then replaced with a Barbier-type coupling reaction of aryl aldehydes and propargyl bromide,[22] which was prepared from propargyl alcohol and PBr_3. This reaction exclusively gave the allenyl alcohol with no trace of the alkynyl alcohol, but some yields were low due to considerable difficulties in removing residual aldehyde by chromatography.

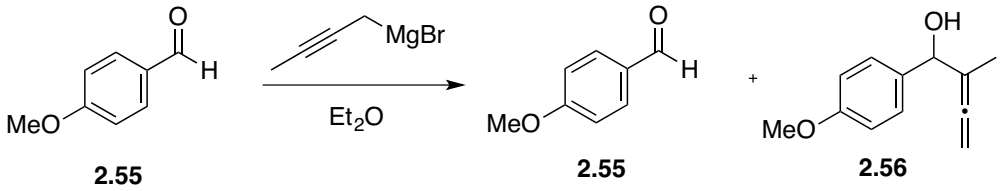
At first, oxidation of the allenyl alcohols was accomplished using MnO_2. However, this reaction took about 24 hours to reach completion and required a large excess of MnO_2. Oxidation was attempted using 2-iodoxybenzoic acid (IBX).[23] Complete reactions giving AAKs were observed in only one hour. These AAKs were used in

subsequent reactions without further purification.



Scheme 2.2 Preparation of allenyl aryl ketones

The stannous chloride coupling reaction, however, did not work for all aldehydes. For instance, 4-methoxybenzaldehyde was recovered unchanged under the reaction conditions. 4-Methoxybenzaldehyde did react with an organomagnesium reagent in a Grignard reaction to give a 1:1 mixture of the allenyl alchol and the starting aldehyde, but this mixture could not be separated by chromatography (Scheme 2.3).



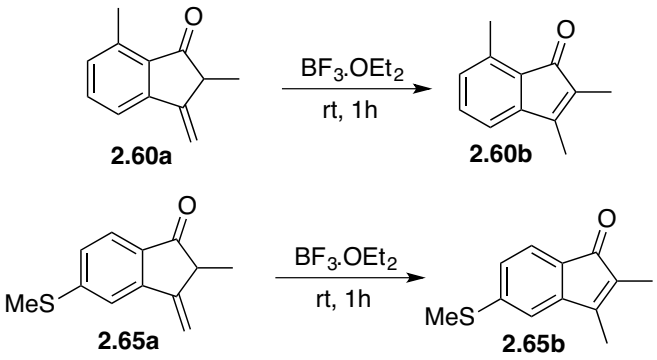
Scheme 2.3 Grignard reaction with 4-methoxybenzaldehyde

2.2.2 Nazarov Reactions

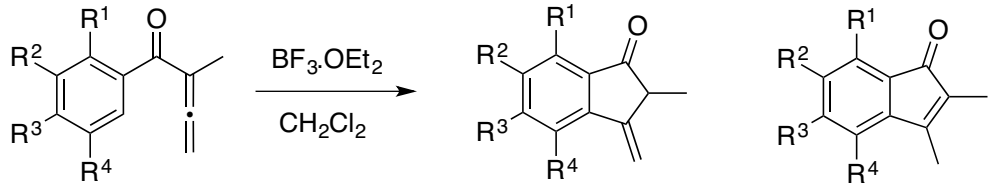
Allenyl vinyl ketones had cyclized rapidly at -78 °C in the presence of $BF_3 \cdot Et_2O$, but, as expected, the AAKs were much less reactive. At first, the Nazarov reaction of an AAK was attempted at -78 °C, but this required a much longer reaction time. Therefore, higher temperatures were necessary, which also led to considerable decomposition of the

AAKs. The reactions were followed by TLC and even though the R_f values for the starting material and product were similar, they turned different colors in vanillin. Low yields were also due to loss of material during chromatography. Table 1 summarizes the results of the Nazarov reactions of variously substituted AAKs.

The immediate product of each cyclization had an exocyclic double bond. This was evident from the downfield methylene signals in the ^{1}H NMR spectrum. In most cases, this product was accompanied by varying proportions of the product of double bond isomerization, as determined from the two methyl signals observed at chemical shifts corresponding to protons near an sp^2 carbon center. These two cyclized products were inseparable by chromatography. In order to confirm the occurrence of this partial isomerization into conjugation during the reaction process, a few products with exocyclic double bonds were re-subjected to the reaction conditions, and this exclusively gave the isomerized products with the endocyclic double bonds (Scheme 2.4).



Scheme 2.4 Isomerization of Nazarov products



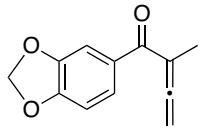
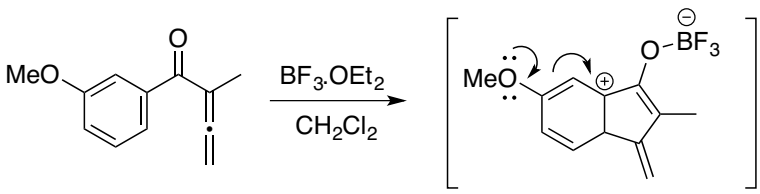
Entry	R^1	R^2	R^3	R^4	T (°C), time	Product	Yield
1	H	H	H	H	rt, 45 min	**2.57**	57
2	H	CF_3	H	H	0 °C, 1 h	**2.58**	0
3	H	H	CF_3	H	0 °C, 1 h	**2.59**	0
4	Me	H	H	H	0 °C, 1 h	**2.60**	14
5	H	Me	H	H	0 °C, 1 h	**2.61**	25
6	H	H	Me	H	0 °C, 2 h	**2.62**	33
7	H	OMe	H	H	-78 °C, 20 min	**2.63**	32
8	H	OMe	OMe	OMe	0 °C, 1.5 h	**2.64**	15
9	H	H	SMe	H	rt, 2.5 h	**2.65**	13
10	H	^{t}Bu	H	^{t}Bu	0 °C, 1.5 h	**2.66**	31
11					0 °C, 45 min	**2.67**	90

Table 1. Nazarov Reactions of allenyl aryl ketones

In many instances, the simplest benzaldehyde-derived substrate gave the cyclized product in better yield than the AAKs with a substituted phenyl ring (Entry 1). No

products were observed for the AAKs having an electron-withdrawing trifluoromethyl group in the *meta* or *para* positions, which could be due to a general withdrawal of π-electron density and/or the destabilization of the carbocation generated (Entries 2 and 3).

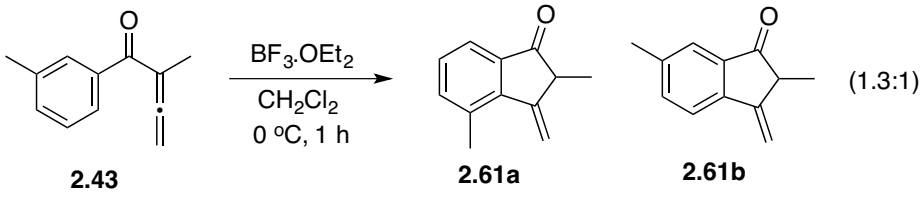
The AAKs with the more electron-rich methyl substituents reacted at 0 °C, but the yields were lower than the benzaldehyde substrate (Entries 4, 5 and 6). Entry 4 shows that the methyl group in the *ortho* position lowered the yield, which could be due the steric effect of forcing the methyl to be coplanar with the carbonyl oxygen. The presence of a *tert*-butyl group in the R^4 position did not appear to significantly impact the reaction, which indicated that steric hindrance near the bottom of the allene did not influence the reaction (Entry 9).



Scheme 2.5 Stabilizing effect of electron-donating group on oxyallyl cation of AAK

Treatment of the AAK with a methoxy group in the *meta* position with $BF_3.OEt_2$ at -78 °C gave the cyclized product in 32 %, which could be due to stabilization of the oxyallyl cation by the electron-donating group (Scheme 2.5). Increasing the number of electron-donating groups to two methoxy groups appeared to significantly increase the efficiency of the reaction to give the cyclized product in 90 % yield. (Entry 11). However, increasing the number of electron-donating groups to three methoxy groups drastically lowered the yield to 15 % (Entry 10). Perhaps increasing the number of oxygen atoms in the molecule alters how the molecule complexes with the BF_3, which could be decreasing the efficiency of the cyclization.

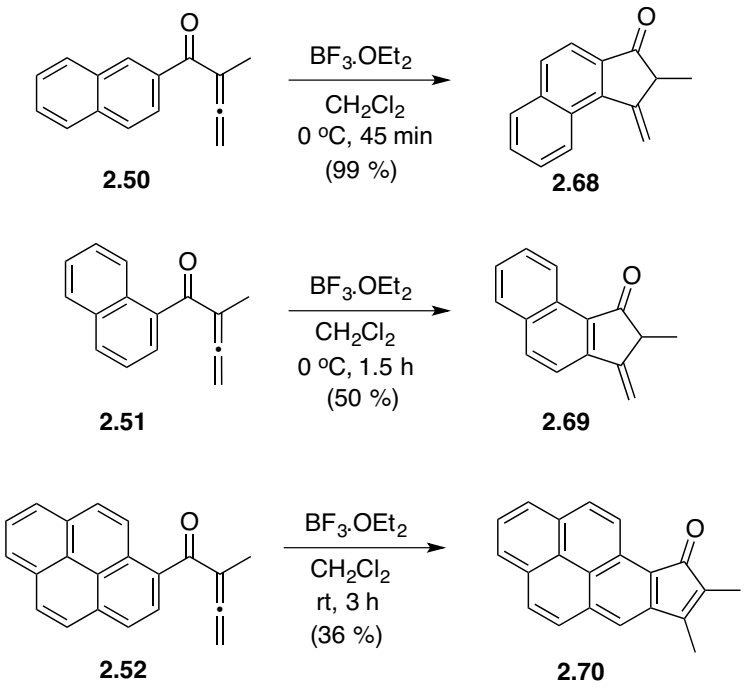
In contrast to the *meta*-methoxy substrate, the AAK with the *meta*-methyl group gave both regioisomers in a 1.3:1 ratio (Scheme 2.6).



2.43 **2.61a** **2.61b**

Scheme 2.6 Two regioisomers obtained from the Nazarov reaction of AAK 2.43

Naphthalene derivatives of AAKs were also synthesized and treated with $BF_3 \cdot Et_2O$. It was predicted that naphthalene derivatives would result in a more facile Nazarov reaction since the aromaticity of the molecule is not completely lost in the electrocyclization.



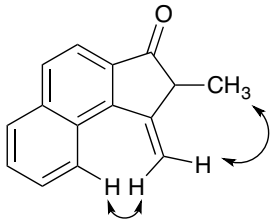
2.50 **2.68**

2.51 **2.69**

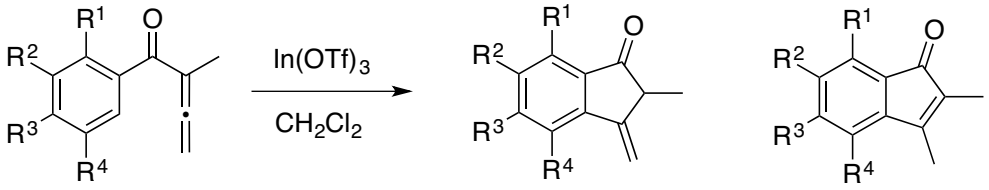
2.52 **2.70**

Scheme 2.7 Nazarov reaction of naphthalene derivatives of AAKs

The substrate synthesized from 2-naphthaldehyde gave the cyclized product in quantitative yield in only 45 minutes at 0 °C and with high regioselectivity (Scheme 2.7). The structure of the product was confirmed using an NOE experiment (Scheme 2.8). In contrast, the substrate synthesized from 1-naphthaldehyde gave the cyclized product in only 50 %. This could be explained by higher reactivity at the α position of naphthalene in electrophilic aromatic substitution.[24] Finally, AAK was also synthesized from mesitaldehyde; however, no cyclized product was obtained from this AAK.



Scheme 2.8 Significant close-contacts revealed from the NOE experiment



Entry	R^1	R^2	R^3	R^4	T (°C), time	Product	Yield
1	H	OMe	H	H	0 °C, 1.5 h	**2.63**	95
2	H	OMe	OMe	OMe	rt, 1 h	**2.64**	85
3	H	Me	H	H	rt, 4.5 h	**2.61**	72
4	H	OMe	OMe	H	rt, 3 h	**2.71**	50
5	H	H	Me	H	rt, 5 h	**2.62**	0
6	H	H	SMe	H	rt, overnight	**2.65**	0

Table 2. Nazarov reactions of AAKs mediated by $In(OTf)_3$

Various Lewis acids were tested to determine how well they can mediate the Nazarov reaction of AAKs, relative to $BF_3.OEt_2$. The 3-methoxy AAK substrate was treated with $TiCl_4$, $SnCl_4$ and $FeCl_3$, but no cyclized product was obtained. However, indium (III) triflate gave the significantly better results with some substrates (Table 2). It is important to note that the $In(OTf)_3$ worked best with the substrates containing methoxy groups. For example, the *meta*-methoxy substrate gave the product of the electrocyclization in 95% yield, and the substrate containing the three methoxy groups gave the product in 85% yield.

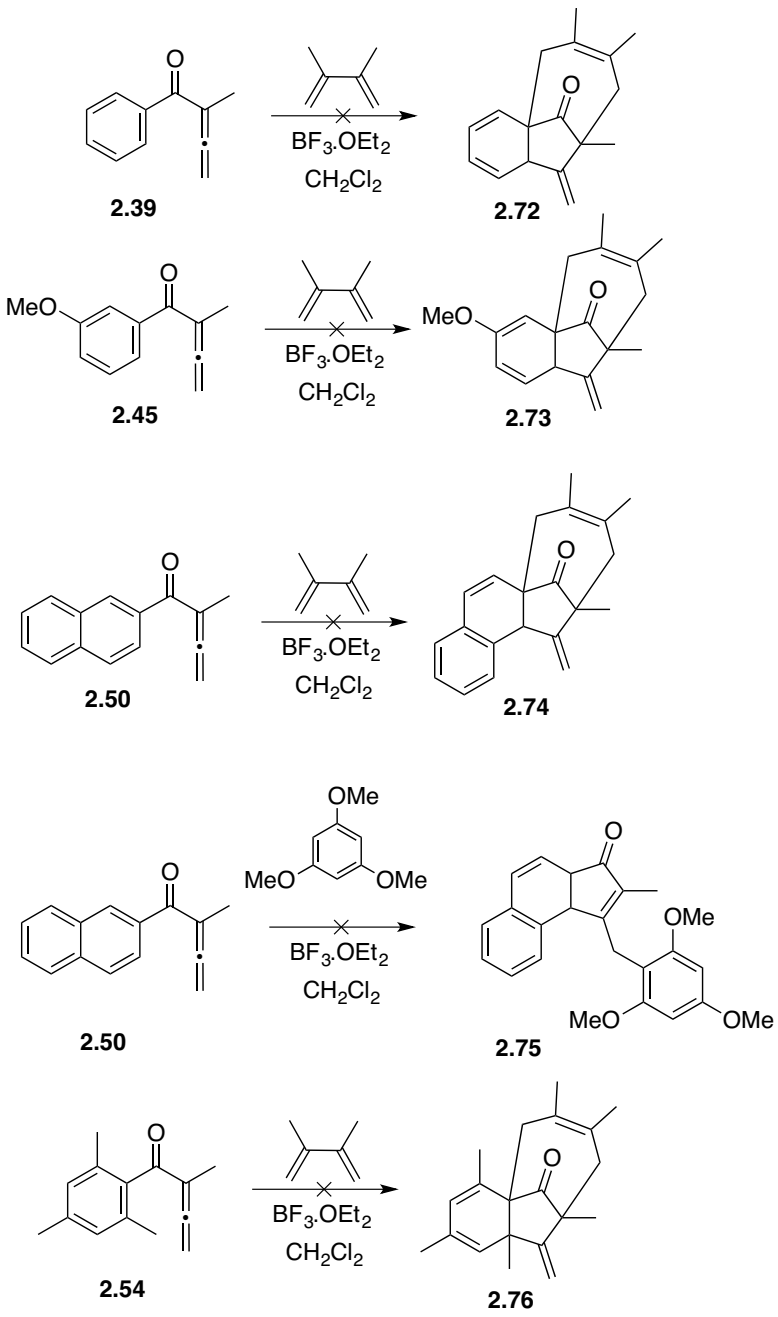
The AAK containing the methyl group in the *meta* position (Entry 3) gave four

isomers of the cyclized product, with endocyclic and exocyclic double bonds and with both regiochemistries. The *para*-methyl and *para*-methylthio substrates gave no cyclized products after extended reaction times at room temperature (Entries 5 and 6). The AAK synthesized from 3,4-dimethoxybenzalehyde gave the cyclized product with the exocyclic double bond in a yield of 50%. When this was re-subjected to the reaction conditions it gave the isomerized product.

With some exceptions, the yields of the cyclized products were disappointing, so the cyclizations of AAKs are synthetically useful for only a narrow range of substrates. However, there is a mechanistic aspect to the results that is interesting. Nagao and coworkers had stated that the cyclizations of AAKs have an ionic mechanism, i.e., that the mechanism is an electrophilic aromatic substitution. The large effect on rate of substitution by strong π-donors is well known for electrophilic aromatic substitution. The reaction times shown in Table 1 and Scheme 2.7 are consistent with some differences in rate, but not differences of orders of magnitude. It can be suggested that the alternative mechanistic possibility, an electrocyclization, appears much more likely.

2.2.3 Interrupted Nazarov reaction

Trapping the oxyallyl cation derived from an aromatic substrate has never been reported. An AAK substrate is aromatic and the Nazarov cyclization would initially destroy the aromaticity. Elimination of a proton allows the molecule to re-aromatize. This must be a highly favorable process, and trapping of the oxyallyl cation would prevent the re-aromatization of the oxyallyl cation intermediate. Therefore, it was recognized that interception of the oxyallyl cation would likely be very challenging.



Scheme 2.9 Attempted trapping of the oxyallyl cations of AAKs

2,3-Dimethylbutadiene is the best trapping agent discovered so far for allenyl vinyl ketones. The AAKs from benzaldehyde, 3-methoxybenzaldehyde, and 4-(trifluoromethyl)benzaldehyde were treated with $BF_3.OEt_2$ in the presence of 2,3-dimethylbutadiene in the hope of obtaining the products of (4 + 3) cycloaddition. Only

the elimination products were observed. Subsequently, trapping of oxyallyl cation of the 2-naphthaldehyde derivative was attempted using 2,3-dimethylbutadiene and using 1,3,5-trimethoxybenzene. It was predicted that since the substrate contains a naphthalene group, some aromaticity would still be retained in the oxyallyl cation, and this might increase the chances of trapping. However, trapping was not accomplished.

2.2.4 Computational Work

In the publication by Nagao, the mechanism reported for the cyclization of AAKs was a 5-*endo*-dig ionic process, i.e., a type of electrophilic aromatic substitution. The differences in the times taken for the cyclizations reported above did not seem to be consistent with the large differences in rate that would be expected for an ionic cyclization mechanism. This prompted a computational examination of the cyclization of AAKs by Dr. Zhe Li of this Department. The hope was that computationally it might be determined whether the acid-mediated cyclization of AAKs proceeds through an ionic mechanism or an electrocyclization. A brief synopsis of some of Dr. Li's findings are summarized here.

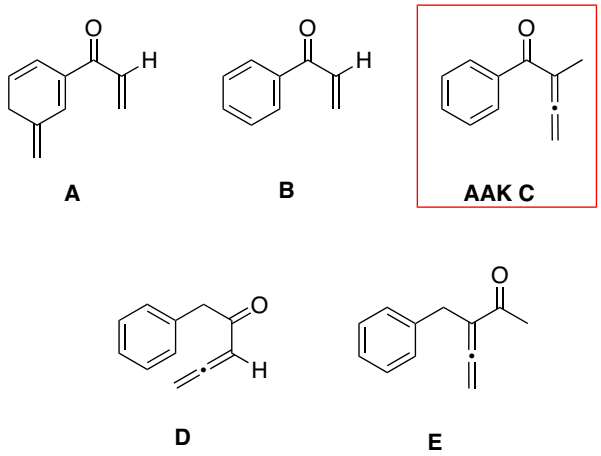


Figure 2.1 Five substrates from the computational study

The transition state geometries of BF_3-mediated cyclizations of five substrates (Figure 2.1) were determined. The first substrate **A** was a divinyl ketone that had the same number of π-electrons as the aryl vinyl ketone **B**. The substrates **A** and **B** would be expected to cyclize by an electrocyclic (Nazarov) mechanism because an ionic cyclization would be via a disfavoured 5-*endo*-trig closure. Substrates **D** and **E** cannot cyclize by an electrocyclic mechanism, and so such cyclization would necessarily be by an ionic process. Substrate **C** is the simplest AAK, and it might cyclize by either an electrocyclic or an ionic mechanism.

The transition state for each cyclization was located computationally using the ωB97X-D density functional with the 6-31G basis set.[25,26] In the transition state geometries of **A** and **B**, C-3 was not perpendicular to the aromatic ring. The dihedral angle 1,2,3,4 was close to 138°. At the transition states for substrates **D** and **E**, the middle carbon of the allene was almost perpendicular to the aromatic ring, as expected for electrophilic aromatic substitution, i.e., the dihedral angle is closer to 90°. In addition, the incipient bond lengths for **D** and **E** were shorter than the incipient bond lengths in **A** and **B**. The allenyl aryl ketone **C** had a dihedral angle of 138.4°, and the incipient bond length was very close to that of **B**. By comparing the transition state geometries, it was evident that the transition state of **C** was similar to the geometries of the transition states for **A** and **B**, which cyclized through an electrocyclic mechanism. Therefore, it was concluded that allenyl aryl ketones cyclize through a Nazarov reaction. The effects of substitution on the barrier to the cyclization were also consistent with an electrocyclic mechanism.

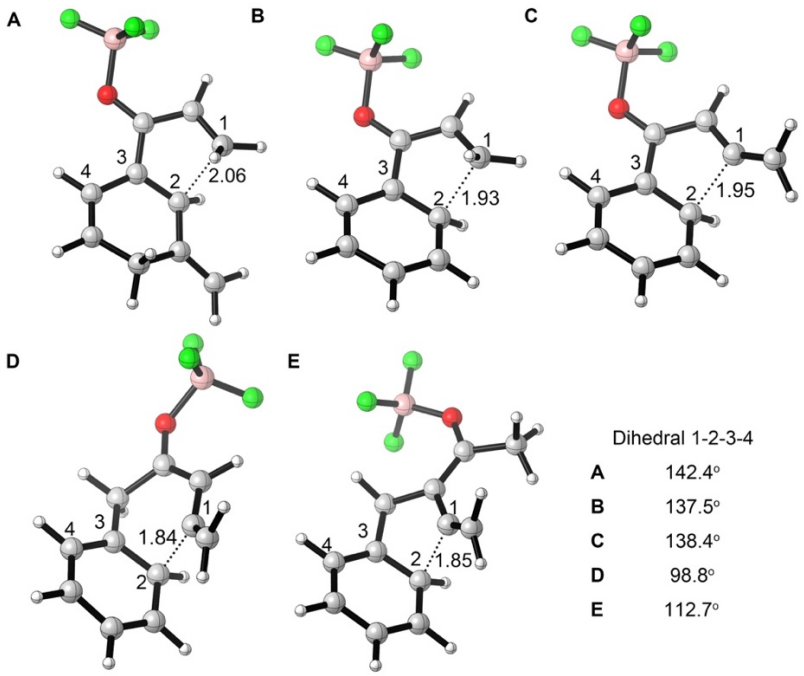


Figure 2.2 Computed (ωB97X-D/6-31G) transition state geometries for the BF_3-mediated cyclizations of A, B, C, D, and E

2.3 Conclusions and Future Work

The purpose of this project was to explore the synthesis and cyclizations of allenyl aryl ketones. Allenyl aryl ketones were synthesized and underwent Nazarov cyclization at higher temperatures and over longer reaction times than had allenyl vinyl ketones because the aromaticity is temporarily lost during the course of the reaction. It was found that electron-withdrawing groups on the aromatic ring inhibited the cyclization, whereas more electron-rich substituents enhanced the efficiency of the reaction. Indium (III) triflate was found to catalyze the reaction better than $BF_3.OEt_2$ in some cases. Trapping of the oxyallyl cation derived from AAKs was not successful, most likely due to the proton elimination occurring at a rate that does not allow the nucleophile to intercept the

carbocation intermediate. Finally, computational work was conducted on BF_3-mediated cyclizations, which confirmed that allenyl aryl ketones do indeed cyclize by a electrocyclic process.

Future work for this project would be to extend the scope of this reaction by synthesizing AAKs with different substituents on the phenyl ring to determine how substitution influences the reaction. In addition, more Lewis acids could be tested to determine if they would be better catalysts for the Nazarov cyclization of allenyl aryl ketones.

2.4 Experimental Section

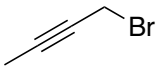
2.4.1 General Information

All the reactions were carried out in a fume-hood under an atmosphere of dry nitrogen. Reagents were purchased from Sigma-Aldrich or Alfa Aesar and were used without further purification. Dichloromethane was distilled over calcium hydride. The progress of reactions was followed by thin-layer chromatography (TLC). Compounds were visualized on the TLC plates with UV light and vanillin dip. The TLC analysis was carried out using SiliCycle precoated plates with aluminum backing (silica gel 60 F254). Products were purified using flash chromatography with an appropriate mixture of diethyl ether and pentane. Flash chromatography was carried out using SiliCycle SiliaFlash silica gel (40-63 μm particle size, 230-240 mesh). IR spectra were recorded on an FT instrument on NaCl plates and only significant absorption bands (in cm^{-1}) are reported. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 500 and 300 spectrometers. Tetramethylsilane (TMS) was used as the internal standard in the solvent,

$CDCl_3$. Structures were determined using ^1H and ^{13}C NMR spectra, including two-dimensional NMR experiments (COSY, HSQC and HMBC). HRMS data were obtained on a TOF mass spectrometer by positive-ion ESI.

2.4.2 Synthesis and Characterization

1-bromo-2-butyne (2.6)

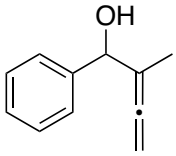


PBr_3 (4.8 mL, 50 mmol, 4.1 equiv) and 2-butyn-1-ol (10.0 g, 140 mmol, 11.6 mmol) were added to pyridine (1 mL, 10 mmol, 1 equiv) in 100 mL of Et_2O at -30 ºC over 30 min. The reaction mixture was stirred for 1 h at rt and then heated at reflux for 1 h. The mixture was slowly poured over an aqueous solution of NaCl at 0 ºC in a separatory funnel and the phases were separated. The aqueous layer was extracted with ether (60 mL), and the organic layer was dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to give 9.37 g (50 %) of 1-bromo-2-butyne. ^1H NMR (300 MHz, $CDCl_3$): δ 3.92 (q, J = 2.5 Hz, 2H), 1.90 (t, J = 2.5 Hz, 3H). The ^1H NMR data are in agreement with the literature.[27]

General procedure for allenyl alcohols: [22] 1-Bromo-2-butyne was added to a mixture of $SnCl_2$ and NaI in DMF and the solution was stirred at rt for 1 h and then it was cooled to 0 ºC. A solution of aldehyde in DMF was then added and the solution was stirred overnight. The reaction was quenched by the addition of water and the aqueous layer was extracted with ether (×3). The combined organic layers were washed with water (×3) and a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered and

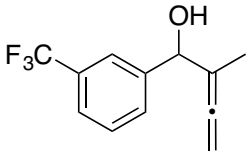
concentrated by rotary evaporation. The crude product was purified by flash chromatography, 5-20% Et_2O/pentane.

2-Methyl-1-phenylbuta-2,3-dien-1-ol (2.23)



$SnCl_2$ (0.66 g, 3.5 mmol), NaI (0.53 g, 3.5 mmol), 1-bromo-2-butyne (0.34 mL, 3.0 mmol) and benzaldehyde (0.26 g, 2.5 mmol) in DMF (10 mL) gave, after chromatography (15% Et_2O/pentane) compound **2.23** (0.20 g, 51 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 4H), 7.29 (t, *J* = 7.0 Hz, 1H), 5.11 (n m, 1H), 4.91 (br quint, 2H), 2.16 (br s, 1H), 1.58 (br t, *J* = 3.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 141.8, 128.3, 127.8, 126.6, 102.7, 77.8, 74.7, 14.6. ESI HRMS calculated for $C_{11}H_{12}O\ Na^+$ 183.0780, found 183.0782. The ^{1}H NMR data are in agreement with the literature.[28]

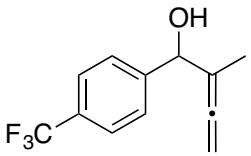
2-Methyl-1-(3-(trifluoromethyl)phenyl)buta-2,3-dien-1-ol (2.24)



$SnCl_2$ (1.21 g, 6.4 mmol), NaI (0.95 g, 6.4 mmol), 1-bromo-2-butyne (0.48 mL, 5.5 mmol) and 3-(trifluoromethyl)benzaldehyde (0.80 g, 4.6 mmol) in DMF (15 mL) gave, after chromatograph (10 % Et_2O/pentane) compound **2.24** (305 mg, 29 %) as an oil. IR 3374, 1960, 1448, 1373 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.60 (t, *J* = 8.0 Hz,

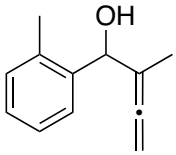
2H), 7.51 (t, J = 7.7 Hz, 1H), 5.24 – 5.22 (m, 1H), 4.96 (quint, J = 2.5 Hz, 2H), 2.26 (d, J = 4.0 Hz, 1H), 1.62 (t, J = 3.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.0, 142.8, 130.7 (q, J = 32 Hz), 129.90, 128.7, 124.1 (q, J = 272 Hz), 124.5 (q, J = 4 Hz), 123.3 (q, J = 4 Hz), 102.1, 78.1, 74.3, 14.3. ESI HRMS calculated for $C_{12}H_{11}F_3ONa^+$ 251.0654, found 251.0649.

2-Methyl-1-(4-(trifluoromethyl)phenyl)buta-2,3-dien-1-ol (2.25)



$SnCl_2$ (2.61 g, 13.8 mmol), NaI (2.00 g, 13.8 mmol), 1-bromo-2-butyne (0.98 mL, 11.1 mmol) and 4-(trifluoromethyl)benzaldehyde (1.58 g, 9.07 mmol) in DMF (30 mL) gave compound **2.25** (1.05 g, 51 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 5.24 (n m, 1H), 4.95 (m, 2H), 2.28 (br s, 1H), 1.62 (t, J = 3.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.0, 145.8, 129.9 (q, J = 32 Hz), 126.8, 125.2 (q, J = 4 Hz), 102.1, 78.0, 74.3, 14.2 (CF_3 signal is not visible).

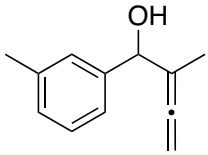
2-Methyl-1-*o*-tolylbuta-2,3-dien-1-ol (2.26)



$SnCl_2$ (1.32 g, 7.0 mmol), NaI (1.05 g, 7.0 mmol), 1-bromo-2-butyne (0.53 mL, 7.0 mmol) and o-tolualdehyde (0.59 mL, 5.0 mmol) in DMF (15 mL) gave, after chromatography (15 % Et_2O/pentane) compound **2.26** (403 mg, 49 %) as an oil. IR 3555,

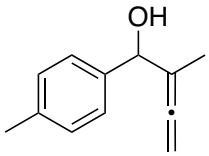
1959, 1604, 1488, 1460 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.0 Hz, 1H), 7.22 – 7.14 (m, 3H), 5.34 (n m, 1H), 4.86 – 4.84 (m, 2H), 2.34 (s, 3H), 2.03 (d, *J* = 3.5 Hz, 1H), 1.58 (t, *J* = 3.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 139.4, 135.8, 130.5, 127.5, 126.3, 125.9, 101.6, 77.2, 71.8, 19.1, 14.5. ESI HRMS calculated for $C_{12}H_{14}O\ Na^+$ 197.0937, found 197.0930.

2-Methyl-1-*m*-tolylbuta-2,3-dien-1-ol (2.27)



$SnCl_2$ (1.32 g, 7.0 mmol), NaI (1.05 g, 7.0 mmol), 1-bromo-2-butyne (0.53 mL, 6.0 mmol) and m-tolualdehyde (0.59 mL, 5.0 mmol) in DMF (15 mL) gave, after chromatography (15% Et_2O/pentane) compound **2.27** (526 mg, 60 %) as an oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.5 Hz, 1H), 7.19 – 7.16 (m, 2H), 7.10 (d, *J* = 7.5 Hz, 1H), 5.08 – 5.06 (m, 1H), 4.92 (quint, *J* = 3.0 Hz, 2H), 2.36 (s, 3H), 2.14 (d, *J* = 4.0 Hz, 1H), 1.58 (t, *J* = 3.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.6, 141.7, 138.0, 128.5, 128.3, 127.2, 123.7, 102.7, 77.8, 74.6, 21.4, 14.6. ESI HRMS calculated for $C_{12}H_{14}O\ Na^+$ 197.0937, found 197.0937.

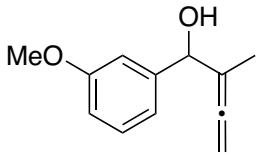
2-Methyl-1-*p*-tolylbuta-2,3-dien-1-ol (2.28)



$SnCl_2$ (2.62 g, 13.8 mmol), NaI (1.97 g, 13.8 mmol), 1-bromo-2-butyne (1.04 mL, 11.8 mmol) and p-tolualdehyde (1.23 g, 10.3 mmol) in DMF (30 mL) gave, after

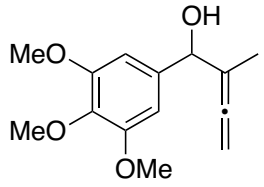
chromatography (20% Et_2O/pentane) compound **2.28** (1.50 g, 84 %) as an oil. IR 3373, 1959, 1609, 1511, 1435 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 5.06 (t, *J* = 2.4 Hz, 1H), 4.89 (quint, *J* = 3.0 Hz, 2H), 2.34 (s, 3H), 1.56 (t, *J* = 3.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.6, 138.8, 137.4, 129.0, 126.5, 102.7, 77.8, 74.4, 21.1, 14.6; ESI HRMS calculated for $C_{12}H_{14}O\ Na^+$ 197.0937, found 197.0940. The ^1H NMR data are in agreement with the literature[28]

1-(3-methoxyphenyl)-2-methylbuta-2,3-dien-1-ol (2.29)



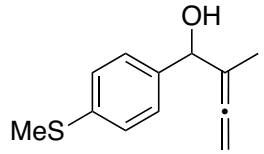
$SnCl_2$ (1.55 g, 8.20 mmol), NaI (1.23 g, 8.20 mmol), 1-bromo-2-butyne (0.61 mL, 7.0 mmol) and 3-methoxybenzaldehyde (0.80 g, 5.8 mmol) in DMF (15 mL) gave, after chromatography (30 % Et_2O/pentane) compound **2.29** (609 mg, 54 %) as an oil. IR 3423, 1959, 1610, 1586, 1487 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.9 Hz, 2H), 7.01 – 6.98 (m, 2H), 6.87 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 5.13 (n m, 1H), 4.95 (quint, *J* = 2.9 Hz, 2H), 3.86 (s, 3H), 2.21 (br s, 1H), 1.62 (t, *J* = 3.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 159.7, 143.5, 129.3, 118.9, 113.2, 112.1, 102.5, 77.8, 74.6, 55.2, 14.5. ESI HRMS calculated for $C_{12}H_{14}O_2\ Na^+$ 213.0886, found 213.0894.

2-Methyl-1-(3,4,5-trimethoxyphenyl)buta-2,3-dien-1-ol (2.30)



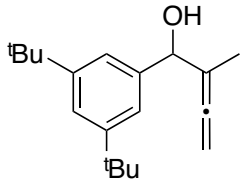
$SnCl_2$ (1.32 g, 7.0 mmol), NaI (1.05 g, 7.0 mmol), 1-bromo-2-butyne (0.77 mL, 6.0 mmol) and 3,4,5-trimethoxybenzaldehyde (0.98 g, 5.0 mmol, 1.4 equiv) in DMF (15 mL) gave, after chromatography (15% Et_2O/pentane) compound **2.30** (720 mg, 57 %) as an oil. ^1H NMR (500 MHz, $CDCl_3$) δ 6.61 (s, 2H), 5.05 (n m, 1H), 4.93 (n m, 2H), 3.87 (s, 6H), 3.84 (s, 3H), 2.17 (br s, 1H), 1.60 (br t, J = 3.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 153.2, 137.6, 137.4, 103.6, 77.8, 74.8, 60.8, 56.1, 41.0, 14.6. ESI HRMS calculated for $C_{14}H_{18}O_4$ Na^+ 273.1097, found 273.1100.

2-Methyl-1-(4-(methylthio)phenyl)buta-2,3-dien-1-ol (2.31)



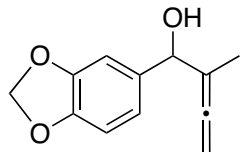
$SnCl_2$ (0.53 g, 2.8 mmol), NaI (0.42 g, 2.8 mmol), 1-bromo-2-butyne (0.27 mL, 2.4 mmol) and 4-(methylthio)benzaldehyde (0.30 g, 2.4 mmol) and DMF (10 mL) gave, after chromatography (5% Et_2O/pentane) compound **2.31** (227 mg, 55 %) as an oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 5.07 (n m, 1H), 4.91 (br q, J = 2.5 Hz, 2H), 2.48 (s, 3H), 2.15 (br s, 1H), 1.56 (t, J = 2.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.6, 138.7, 137.9, 127.1, 126.6, 102.5, 77.9, 74.2, 15.9, 14.5. ESI HRMS calculated for $C_{12}H_{14}OS$ Na^+ 229.0658, found 229.0662.

1-(3,5-di-*tert*-butylphenyl)-2-methylbuta-2,3-dien-1-ol (2.32)



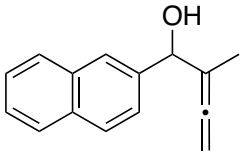
$SnCl_2$ (1.32 g, 7.0 mmol), NaI (1.05 g, 7.0 mmol), 1-bromo-2-butyne (0.52 mL, 6.0 mmol) and 3,5-ditertbutylbenzaldehyde (0.5 g, 5.0 mmol) in DMF (15 mL) gave, after chromatography (20 % Et_2O/pentane) compound **2.32** (170 mg, 13 %) as an oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, *J* = 1.6 Hz, 1H), 7.20 (d, *J* = 1.6 Hz, 2H), 5.09 – 5.07 (m, 1H), 4.90 (quint, *J* = 2.9 Hz, 2H), 2.12 (d, *J* = 4.4 Hz, 1H), 1.61 (t, *J* = 3.1 Hz, 3H), 1.32 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.9, 150.7, 140.9, 121.8, 120.8, 102.8, 77.6, 75.3, 34.9, 31.5, 14.9. ESI HRMS calculated for $C_{19}H_{28}ONa^+$ 295.2023, found 295.2023.

1-(Benzo[*d*][1,3]dioxol-5-yl)-2-methylbuta-2,3-dien-1-ol (2.33)



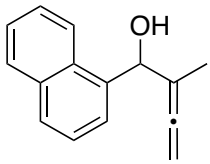
$SnCl_2$ (2.50 g, 13.2 mmol), NaI (1.99 g, 13.2 mmol), 1-bromo-2-butyne (1.06 mL, 12.0 mmol) and piperonaldehyde (1.48 g, 9.86 mmol) in DMF (15 mL) gave, after chromatography (5% Et_2O/pentane) compound **2.33** (1.89 g, 94 %) as an oil. IR 3404, 2894, 1959, 1609, 1503, 1487 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.92 (s, 2H), 4.98 (n m, 1H), 4.89 (quint, *J* = 3.0 Hz, 2H), 2.39 (br s, 1H), 1.55 (t, *J* = 3.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 147.7, 147.2, 135.8, 120.2, 107.9, 107.0, 102.8, 101.0, 78.1, 74.3, 14.7. ESI HRMS calculated for $C_{12}H_{12}O_3\ Na^+$ 227.0679, found 227.0672.

2-Methyl-1-(naphthalen-2-yl)buta-2,3-dien-1-ol (2.34)



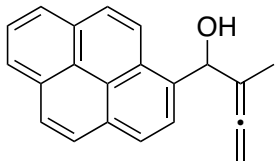
$SnCl_2$ (2.47 g, 13.0 mmol,), NaI (1.95 g, 13.0 mmol), 1-bromo-2-butyne (1.04 mL, 11.8 mmol) and 2-naphthaldehyde (1.48 g, 9.48 mmol) in DMF (30 mL) gave compound **2.34** (1.34 g, 67 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 – 7.81 (m, 4H), 7.48 – 7.44 (m, 3H), 5.27 (n m, 1H), 4.94 (quint, *J* = 3.0 Hz, 2H), 2.29 (d, *J* = 3.5 Hz, 1H), 1.59 (t, *J* = 3.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 139.1, 133.2, 133.1, 128.2, 128.0, 127.6, 126.1, 125.9, 125.4, 124.5, 102.5, 77.9, 74.8, 14.5. ESI HRMS calculated for $C_{15}H_{14}ONa^+$ 233.0937, found 233.0927.

2-Methyl-1-(naphthalen-1-yl)buta-2,3-dien-1-ol (2.35)



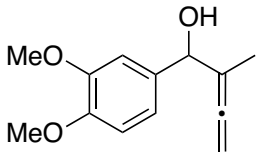
$SnCl_2$ (2.55 g, 13.4 mmol), NaI (1.99 g, 13.4 mmol), 1-bromo-2-butyne (1.08 mL, 12.1 mmol) and 1-naphthaldehyde (1.25 g, 8.0 mmol) in DMF (30 mL) gave compound **2.35** (1.43 g, 85 %) as an oil. IR 3363, 1959, 1597, 1510, 1436 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 7.0 Hz, 1H), 7.52 – 7.45 (m, 3H), 5.88 (n m, 1H), 4.89 (q, *J* = 2.7 Hz, 2H), 2.27 (br s, 1H), 1.60 (t, *J* = 3.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 136.9, 133.9, 131.0, 128.7, 128.4, 125.9, 125.5, 125.1, 124.3, 123.8, 102.1, 77.4, 65.8, 14.6. ESI HRMS calculated for $C_{15}H_{14}ONa^+$ 233.0937, found 233.0938.

2-Methyl-1-(pyren-1-yl)buta-2,3-dien-1-ol (2.36)



$SnCl_2$ (2.61 g, 13.7 mmol), NaI (1.93 g, 13.0 mmol), 1-bromo-2-butyne (1.03 mL, 11.7 mmol) and 1-pyrenecarboxaldehyde (1.11 g, 4.81 mmol) in DMF (30 mL) gave compound **2.36** (0.91 g, 67 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 9.3 Hz, 1H), 8.19 (s, 3H), 8.18 (s, 1H), 8.12 (d, J = 9.3 Hz, 1H), 8.06 (s, 2H), 8.01 (t, J = 7.6 Hz, 1H), 6.19 (n m, 1H), 4.95 (br quint, J = 2.4 Hz, 2H), 2.45 (br s, 1H), 1.63 (t, J = 3.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 134.8, 131.3, 131.0, 130.7, 128.5, 127.62, 127.48, 127.43, 126.0, 125.30, 125.16, 124.99, 124.85, 124.79, 124.5, 123.1, 102.9, 77.9, 72.2, 14.9. ESI HRMS calculated for $C_{21}H_{16}ONa^+$ 307.1093, found 307.1107.

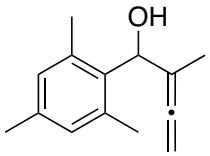
1-(3,4-dimethoxyphenyl)-2-methylbuta-2,3-dien-1-ol (2.37)



$SnCl_2$ (0.79 g, 4.2 mmol), NaI (0.63 g, 4.2 mmol), 1-bromo-2-butyne (0.3 mL, 3.6 mmol) and 3,4-dimethoxybenzaldehyde (0.45 g, 2.7 mmol) in DMF (30 mL) gave, after chromatography (5 % Et_2O/pentane) compound **2.37** (298 mg, 45 %) as an oil. IR 3463, 2924, 1960, 1633, 1511, 1459 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96 – 6.94 (m, 2H), 6.87 (d, J = 7.9 Hz, 1H), 5.08 (n m, 1H), 4.96 (q, J = 3.0 Hz, 2H), 3.92 (d, J = 7.3 Hz, 6H), 1.62 (t, J = 3.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ^{13}C NMR (125 MHz,

$CDCl_3$): δ 204.6, 148.7, 134.4, 119.1, 110.9, 110.0, 109.7, 102.8, 77.9, 74.4, 55.94, 55.90, 14.8. ESI HRMS calculated for $C_{13}H_{16}O_3Na^+$ 243.0992, found 243.0987.

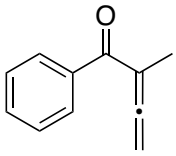
1-Mesityl-2-methylbuta-2,3-dien-1-ol (2.38)



$SnCl_2$ (2.54 g, 13.4 mmol), NaI (1.93 g, 13.4 mmol), 1-bromo-2-butyne (0.94 mL, 11 mmol), and mesitaldehyde (1.36 g, 9.24 mmol) in DMF (30 mL) gave compound **2.38** (1.251 g, 68 %) as an oil. IR 3440, 1960, 1616, 1448 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.81 (s, 2H), 5.56 (t, J = 4.4 Hz, 1H), 4.90 (n m, 2H), 2.37 (s, 6H), 2.25 (s, 3H), 1.55 (br t, J = 2.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.8, 137.3, 137.0, 133.4, 130.0, 102.5, 78.8, 69.5, 20.8, 20.4, 15.7. ESI HRMS calculated for $C_{14}H_{18}O\ Na^+$ 225.1250, found 225.1249.

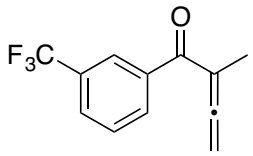
General procedure for oxidation: [23] IBX was dissolved in DMSO and the alcohol dissolved in DMSO was added. The mixture was stirred for 1 h at rt. Water was added to precipitate IBX byproducts, which were removed by filtration through a sintered glass funnel. The aqueous layer was extracted with EtOAc (×3), and the combined organic layers were washed with water (×3) and a saturated aqueous solution of NaCl. The solution was dried over Na_2SO_4 and concentrated by rotary evaporation to yield the product.

2-Methyl-1-phenylbuta-2,3-dien-1-one (2.39)



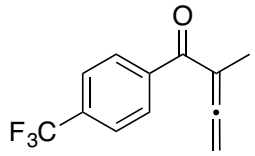
IBX (0.24 g, 0.9 mmol), alcohol (100 mg, 0.6 mmol) in DMSO (2.0 mL) gave compound **2.39** (35 mg, 35%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 – 7.74 (m, 2H), 7.50 – 7.47 (m, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 5.01 (q, *J* = 3.0 Hz, 2H), 2.01 (t, *J* = 3.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.4, 194.9, 138.2, 131.8, 128.9, 127.7, 102.1, 78.3, 14.7. ESI HRMS calculated for $C_{11}H_{10}O\ Na^+$ 181.0624, found 181.0625. The ^{1}H NMR and ^{13}C NMR data are in agreement with the literature.[29]

2-Methyl-1-(3-(trifluoromethyl)phenyl)buta-2,3-dien-1-one (2.40)



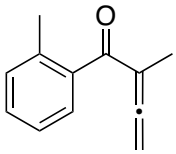
IBX (0.34 g, 1.2 mmol), alcohol (200 mg, 0.8 mmol) in DMSO (3.0 mL) gave compound **2.40** (106 mg, 54 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 5.10 (q, *J* = 2.9 Hz, 2H), 2.06 (t, *J* = 2.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 218.0, 193.6, 138.6, 132.0, 130.3 (q, *J* = 33 Hz), 128.5, 128.2 (q, *J* = 4 Hz), 126.0 (q, *J* = 4 Hz), 102.2, 78.9, 14.4 (CF_3 signal is not visible). ESI HRMS calculated for $C_{12}H_9F_3ONa^+$ 249.0498, found 249.0487.

2-Methyl-1-(4-(trifluoromethyl)phenyl)buta-2,3-dien-1-one (2.41)



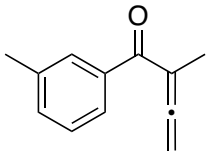
IBX (0.92 g, 3.3 mmol), alcohol (0.575 g, 2.52 mmol) in DMSO (15 mL) gave compound **2.41** (433 mg, 76 %)as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 5.10 (br q, *J* = 3.0 Hz, 2H), 2.05 (br t, *J* = 3.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 218.0, 194.0, 141.2, 133.2 (q, *J* = 32 Hz), 129.1, 124.8 (q, *J* = 4 Hz), 102.4, 79.0, 30.9, 14.4 (CF_3 signal is not visible). ESI HRMS calculated for $C_{12}H_{10}F_3O^+$ 227.0678, found 227.0673.

2-Methyl-1-*o*-tolylbuta-2,3-dien-1-one (2.42)



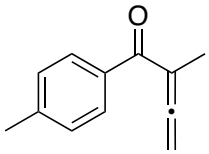
IBX (0.47 g, 1.7 mmol), alcohol (210 mg, 1.2 mmol) in DMSO (2.5 mL) gave compound **2.42** (76 mg, 36 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.27 (m, 2H), 7.19 – 7.13 (m, 2H), 4.87 (q, *J* = 3.0 Hz, 2H), 2.32 (s, 3H), 1.98 (t, *J* = 3.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.4, 198.4, 139.4, 135.6, 130.5, 129.6, 127.7, 124.6, 104.3, 78.0, 19.5, 13.5. ESI HRMS calculated for $C_{12}H_{12}ONa^+$ 195.0780, found 195.0786.

2-Methyl-1-*m*-tolylbuta-2,3-dien-1-one (2.43)



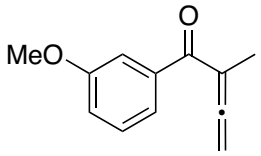
IBX (1.17 g, 4.17 mmol), alcohol (520 mg, 2.98 mmol) in DMSO (5.0 mL) gave compound **2.43** (308 mg, 60 %) as an oil. IR ($CDCl_3$) 1935, 1651 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.54 (m, 2H), 7.31 – 7.25 (m, 2H), 5.00 (q, *J* = 3.0 Hz, 2H), 2.38 (s, 3H), 2.00 (t, *J* = 3.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.5, 195.2, 138.1, 137.6, 132.6, 129.5, 127.5, 126.2, 102.0, 78.2, 21.3, 14.7. ESI HRMS calculated for $C_{12}H_{12}ONa^+$ 195.0780, found 195.0784.

2-Methyl-1-*p*-tolylbuta-2,3-dien-1-one (2.44)



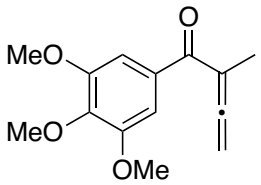
IBX (1.11 g, 3.96 mmol), alcohol (511 mg, 2.93 mmol) in DMSO (15 mL) gave compound **2.44** (229 mg, 44 %) as an oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.01 (q, *J* = 3.0 Hz, 2H), 2.39 (s, 3H), 2.00 (t, *J* = 3.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.1, 194.6, 142.6, 135.4, 129.2, 128.5, 101.9, 78.1, 21.5, 14.8. ESI HRMS calculated for $C_{12}H_{12}ONa^+$ 195.0780, found 195.0780.

1-(3-methoxyphenyl)-2-methylbuta-2,3-dien-1-one (2.45)



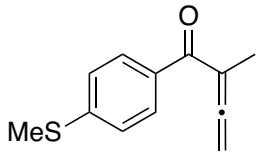
IBX (0.35 g, 1.2 mmol), alcohol (170 mg, 0.9 mmol) in DMSO (4.0 mL) gave compound **2.45** (64 mg, 38 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.6 Hz, 1H), 7.33 – 7.30 (m, 2H), 7.07 (dd, *J* = 8.1, 2.5 Hz, 1H), 5.05 (br q, *J* = 2.7 Hz, 2H), 3.85 (s, 3H), 2.03 (t, *J* = 2.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.4, 194.7, 159.1, 139.4, 128.7, 121.6, 118.2, 113.6, 102.0, 78.3, 55.3, 14.8. ESI HRMS calculated for $C_{12}H_{12}O\ Na^+$ 211.0730, found 211.0728.

2-Methyl-1-(3,4,5-trimethoxyphenyl)buta-2,3-dien-1-one (2.46)



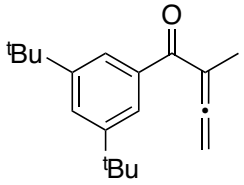
IBX (1.09 g, 4.0 mmol), alcohol (700 mg, 2.7 mmol) in DMSO (5.0 mL) gave compound **2.46** (489 mg, 71 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (s, 2H), 5.05 (q, *J* = 3.0 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 6H), 2.02 (t, *J* = 3.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.6, 193.4, 152.5, 141.7, 132.9, 106.9, 101.7, 78.0, 60.9, 56.2, 15.7. ESI HRMS calculated for $C_{14}H_{16}O_4\ Na^+$ 271.0941, found 271.0942.

2-Methyl-1-(4-(methylthio)phenyl)buta-2,3-dien-1-one (2.47)



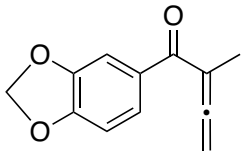
IBX (0.41 g, 1.4 mmol), alcohol (220 mg, 1.0 mmol) in DMSO (5.0 mL) gave compound **2.47** (159 mg, 73%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.02 – 5.01 (m, 2H), 2.50 (s, 3H), 1.99 (t, *J* = 2.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.9, 193.8, 144.3, 134.3, 129.6, 124.5, 101.8, 78.2, 14.9. ESI HRMS calculated for $C_{12}H_{12}OS\ Na^+$ 227.0501, found 227.0492.

1-(3,5-di-*tert*-butylphenyl)-2-methylbuta-2,3-dien-1-one (2.48)



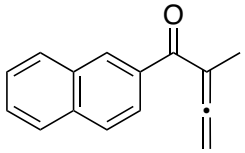
IBX (0.24 g, 0.8 mmol), alcohol (170 mg, 0.6 mmol) in DMSO (2.0 mL) gave compound **2.48** (53 mg, 32 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 2.0 Hz, 2H), 7.55 (t, *J* = 1.5 Hz, 1H), 4.99 (q, *J* = 3.0 Hz, 2H), 2.00 (t, *J* = 3.0 Hz, 3H), 1.32 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.3, 195.6, 150.2, 137.4, 126.0, 123.6, 101.9, 77.7, 34.9, 31.3, 15.0. ESI HRMS calculated for $C_{19}H_{26}O\ Na^+$ 293.1876, found 293.1872.

1-(Benzo[*d*][1,3]dioxol-5-yl)-2-methylbuta-2,3-dien-1-one (2.49)



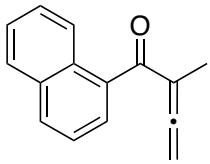
IBX (3.62 g, 12.9 mmol), alcohol (1.89 g, 9.25 mmol) in DMSO (15 mL) gave compound **2.49** (1.702 g, 91 %) as an oil. IR 1687, 1638, 1602, 1037 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.29 (d, *J* = 1.5 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.01 (s, 2H), 5.02 (q, *J* = 3.0 Hz, 2H), 1.99 (t, *J* = 3.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.3, 192.9, 151.0, 147.4, 132.3, 125.1, 109.2, 107.3, 101.6, 78.0, 76.8, 15.1. ESI HRMS calculated for $C_{12}H_{10}O_3Na^+$ 225.0522, found 225.0524.

2-Methyl-1-(naphthalen-2-yl)buta-2,3-dien-1-one (2.50)



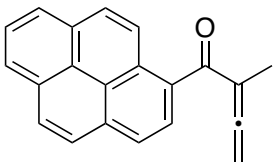
IBX (3.39 g, 12.1 mmol), alcohol (1.34 g, 6.37 mmol) in DMSO (10 mL) gave compound **2.50** (1.05 g, 79 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.58 – 7.51 (m, 3H), 5.03 (q, *J* = 1.8 Hz, 2H), 2.07 (t, *J* = 1.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.4, 194.9, 135.4, 135.0, 132.1, 130.3, 129.2, 127.9, 127.7, 127.6, 126.5, 125.3, 102.2, 78.3, 14.8. ESI HRMS calculated for $C_{15}H_{12}ONa^+$ 231.0780, found 231.0784.

2-Methyl-1-(naphthalen-1-yl)buta-2,3-dien-1-one (2.51)



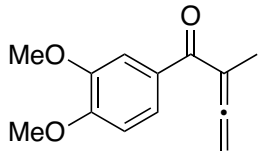
IBX (2.65 g, 9.46 mmol), alcohol (0.82 g, 3.9 mmol) in DMSO (15 mL) gave compound **2.51** (706 mg, 87 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 4.5 Hz, 1H), 7.91 – 7.84 (m, 2H), 7.57 – 7.41 (m, 4H), 4.79 (q, *J* = 1.5 Hz, 2H), 2.08 (t, *J* = 1.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.6, 197.5, 136.9, 133.5, 130.6, 130.5, 128.2, 126.9, 126.5, 126.1, 125.3, 123.9, 104.9, 78.2, 13.8. ESI HRMS calculated for $C_{15}H_{12}ONa^+$ 231.0780, found 231.0784.

2-Methyl-1-(pyren-1-yl)buta-2,3-dien-1-one (2.52)



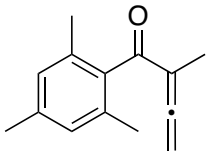
IBX (0.35 g, 1.2 mmol) and alcohol (260 mg, 0.9 mmol) in DMSO (2.5 mL) gave compound **2.52** (172 mg, 67 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 9.2 Hz, 1H), 8.26 (d, *J* = 7.6 Hz, 2H), 8.18 – 8.15 (m, 3H), 8.12 – 8.10 (m, 2H), 8.07 (t, *J* = 7.6 Hz, 1H), 4.79 (q, *J* = 2.9 Hz, 2H), 2.21 (t, *J* = 2.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.9, 198.0, 134.2, 132.6, 131.2, 130.7, 129.0, 128.72, 128.54, 127.2, 126.2, 126.01, 125.82, 125.67, 124.7, 124.65, 124.54, 123.4, 105.4, 78.4, 14.0. ESI HRMS calculated for $C_{21}H_{14}ONa^+$ 305.0937, found 305.0939.

1-(3,4-dimethoxyphenyl)-2-methylbuta-2,3-dien-1-one (2.53)



IBX (0.53 g, 1.9 mmol), alcohol (298 mg, 1.4 mmol) in DMSO (4.0 mL) gave compound **2.53** (165 mg, 56 %) as an oil. IR 2931, 1934, 1681, 1642, 1513, 1459 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 5.05 (q, *J* = 3.0 Hz, 2H), 3.96 (s, 3H), 3.95 (s, 3H), 2.04 (t, *J* = 3.0 Hz, 3H). ^{13}C NMR (126 MHz; $CDCl_3$): δ 216.3, 193.2, 148.5, 130.2, 123.8, 111.8, 109.6, 109.0, 101.6, 77.9, 55.99, 55.95, 15.2. ESI HRMS calculated for $C_{13}H_{16}O_3Na^+$ 241.0835, found 241.0833.

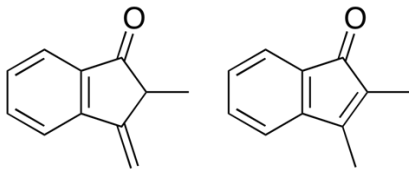
1-Mesityl-2-methylbuta-2,3-dien-1-one (2.54)



IBX (1.21 g, 4.32 mmol, 1.4 equiv) and alcohol (620 mg, 3.06 mmol, 1.0 equiv) in DMSO (15 mL) gave **2.54** (457 mg, 74 %) as an oil. IR 1741, 1662 cm^{-1}. ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.76 (s, 2H), 4.81 (m, 2H), 2.25 (s, 3H), 2.13 (s, 6H), 1.95 (t, 3H, *J* = 2.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 218.0, 201.4, 137.9, 133.6, 127.8, 110.0, 105.1, 77.5, 21.1, 19.0, 12.8. ESI HRMS calculated for $C_{14}H_{16}ONa^+$ 223.1093, found 223.1093.

General procedure for Nazarov reaction catalyzed by $BF_3.OEt_2$: The AAK was dissolved in DCM (dry) and cooled to 0 °C. $BF_3.Et_2O$ was added to the reaction mixture and stirred for 1h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$, and the aqueous layer extracted with DCM (×3). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and the residue was purified using flash chromatography 5-20% Et_2O/pentane.

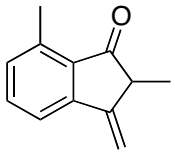
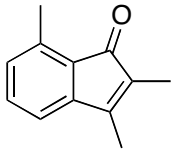
2-Methyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.57a) and 2,3-dimethyl-1*H*-inden-1-one (2.57b)



6.6:1

Ketone (60 mg, 0.4 mmol), $BF_3.Et_2O$ (0.07 mL, 0.5 mmol) in DCM (5.0 mL) for 45 min at rt gave compounds **2.57a** and **2.57b** (34 mg, 57 %) as oils. **2.57a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 5.83 (s, 1H), 5.30 (s, 1H), 3.13 (q, *J* = 7.5 Hz, 1H), 1.38 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1, 148.8, 146.3, 135.7, 135.0, 129.4, 123.7, 121.3, 107.0, 46.0, 14.6. **2.57b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.1 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 7.0 Hz, 1H), 2.11 (s, 3H), 1.82 (s, 3H). ESI HRMS calculated for $C_{11}H_{10}ONa^+$ 181.0624, found 181.0618. The ^{1}H NMR data for the minor product are in agreement with the literature.[30]

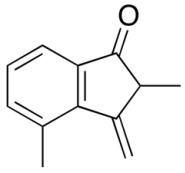
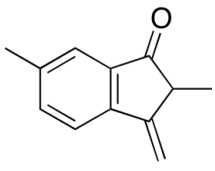
2,7-Dimethyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.60a) and 2,3,7-trimethyl-1*H*-inden-1-one (2.60b)

5.6:1

Ketone (50 mg, 0.3 mmol), $BF_3.Et_2O$ (0.04 mL, 0.3 mmol) in DCM (5.0 mL) for 1 h at 0°C gave **2.60a** and **2.60b** (7 mg, 14 %) as oils. **2.60a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.0 Hz, 1H), 5.80 (d, *J* = 2.0 Hz, 1H), 5.25 (d, *J* = 1.5 Hz, 1H), 3.09 (qt, *J* = 7.5, 1.8 Hz, 1H), 2.66 (s, 3H), 1.37 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7, 149.3, 146.3, 138.8, 134.0, 131.1, 118.5, 106.2, 46.2, 18.4, 14.6. **2.60b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.84 (d, *J* = 7.1 Hz, 1H), 2.50 (s, 3H), 2.08 (s, 3H), 1.79 (s, 3H). ESI HRMS calculated for $C_{12}H_{12}ONa$ + 195.0780, found 195.0786.

2,4-Dimethyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.61a) and 2,6-dimethyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.61b)

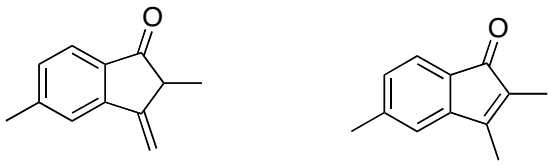
1.3:1

Ketone (80 mg, 0.4 mmol), $BF_3.Et_2O$ (0.08 mL, 0.7 mmol) in DCM (5.0 mL) for 1 h at 0°C gave **2.61a** and **2.61b** (20 mg, major: 14%, minor: 11%) as oils. IR 1738, 1639, 1602, 1486, 1439 cm^{-1}. **2.61a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (br d, *J* = 7.5 Hz, 1H), 7.46

(br d, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 5.86 (d, *J* = 2.0 Hz, 1H), 5.46 (d, *J* = 1.5 Hz, 1H), 3.20 – 3.12 (m, 1H), 2.64 (s, 3H), 1.42 (d, *J* = 7.5 Hz, 3H),

2.61b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (br s, 1H), 7.49 (br d, *J* = 8.1 Hz, 1H), 5.79 (d, *J* = 2.0 Hz, 1H), 5.27 (d, *J* = 1.5 Hz, 1H), 3.20 – 3.12 (m, 1H), 2.46 (s, 3H), 1.40 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0, 147.6, 146.4, 146.3, 145.8, 139.6, 137.2, 137.0, 136.1, 136.0, 135.8, 128.8, 123.4, 121.4, 121.0, 111.0, 105.8, 47.0, 46.3, 22.3, 14.8. ESI HRMS calculated for $C_{12}H_{12}ONa$ + 195.0780, found 195.0786.

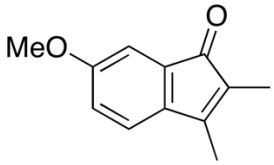
2,5-Dimethyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.62a) and 2,3,5-trimethyl-1*H*-inden-1-one (2.62b)



6.5:1

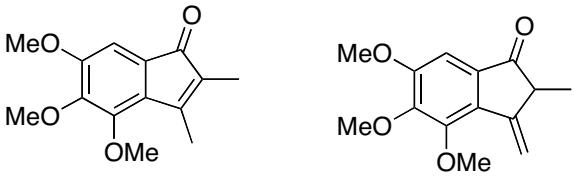
Ketone (123 mg, 0.71 mmol), $BF_3.Et_2O$ (0.3 mL, 2 mmol) in DCM (5.0 mL) for 2 h at 0°C gave compounds **2.62a** and **2.62b** (40 mg, 32 %) as oils. **2.62a**: Yield (28 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 5.81 (d, *J* = 2.0 Hz, 1H), 5.27 (d, *J* = 1.5 Hz, 1H), 3.14 – 3.09 (m, 1H), 2.48 (s, 3H), 1.38 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 149.0, 146.4, 146.0, 133.6, 130.7, 123.4, 121.3, 106.5, 46.2, 22.0, 14.7. **2.62b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, *J* = 7.1 Hz, 1H), 6.93 (d, *J* = 7.1 Hz, 1H), 6.81 (s, 1H), 2.34 (s, 3H), 2.08 (s, 3H), 1.80 (s, 3H). ESI HRMS calculated for $C_{12}H_{12}ONa$ + 195.0780, found 195.0774.

6-Methoxy-2,3-dimethyl-1*H*-inden-1-one (2.63)



Ketone (36 mg, 0.34 mmol), $BF_3.Et_2O$ (0.04 mL, 0.5 mmol) in DCM (5.0 mL) for 1 h at 0°C gave compound **2.63** (11 mg, 17 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.03 (d, *J* = 2.1 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.77 (dd, *J* = 7.9, 2.1 Hz, 1H), 3.84 (s, 3H), 2.11 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.9, 160.4, 154.8, 138.3, 133.1, 129.6, 119.1, 115.6, 109.9, 55.7, 11.6, 7.6. APCI calculated for $C_{12}H_{13}O_2Na^+$ 189.910, found 189.0913.

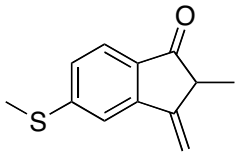
4,5,6-Trimethoxy-2,3-dimethyl-1*H*-inden-1-one (2.64a) and 4,5,6-trimethoxy-2-methyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.64b)



Ketone (60 mg, 0.2 mmol), $BF_3.Et_2O$ (0.09 mL, 0.7 mmol) in DCM (4.0 mL) for 1 h at 0°C gave, after chromatography (15 % Et_2O/pentane) compounds **2.64a** (16 mg, 27 %) and **2.64b** (5 mg, 8 %) as oils. The products were sensitive to chromatography; however, the isomers were separated and characterized. **2.64a**: IR ($CDCl_3$) 1708, 1608, 1471, 1091 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 2.24 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 154.5, 153.4, 148.2, 146.7, 129.3, 127.2, 104.1, 61.4, 60.9, 56.5, 14.2, 7.3 **2.64b**: IR ($CDCl_3$) 1708 cm^{-1}. ^{1}H

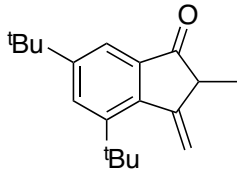
NMR (500 MHz, $CDCl_3$): δ 7.07 (s, 1H), 6.14 (s, 1H), 5.32 (s, 1H), 3.99 (s, 1H), 3.97 (s, 1H), 3.92 (s, 3H), 3.08 (q, *J* = 7.5 Hz, 1H), 1.36 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.1, 155.3, 150.5, 148.6, 144.2, 135.1, 132.1, 109.7, 100.6, 61.1, 60.1, 56.3, 46.6, 14.8. ESI HRMS calculated for $C_{14}H_{16}O_4\ Na^+$ 271.0941, found 271.0939.

2-Methyl-3-methylene-5-(methylthio)-2,3-dihydro-1*H*-inden-1-one (2.65)



Ketone (40 mg, 0.20 mmol), $BF_3.Et_2O$ (0.09 mL, 0.8 mmol) in DCM (4.0 mL) for 2 h at 0°C gave, after chromatography (20% Et_2O/pentane) compound **2.65** (10 mg, 25 %) as an oil. IR 1708, 1589 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.71 (dd, *J* = 8.2, 0.6 Hz, 1H), 7.56 (br d, *J* = 1.3 Hz, 1H), 7.31 (dd, *J* = 8.2, 1.6 Hz, 1H), 5.85 (d, *J* = 2.1 Hz, 1H), 5.34 (d, *J* = 1.7 Hz, 1H), 3.16 (qt, *J* = 7.5, 1.9 Hz, 1H), 2.61 (s, 3H), 1.41 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.6, 149.1, 148.5, 146.1, 132.6, 126.7, 123.7, 116.6, 107.2, 46.2, 14.98, 14.81. ESI HRMS calculated for $C_{12}H_{12}OSNa^+$ 227.0501, found 227.0496.

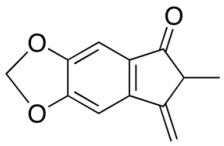
4,6-Di-*tert*-butyl-2-methyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.66)



Ketone (80 mg, 0.3 mmol), $BF_3.Et_2O$ (0.05 mL, 0.4 mmol) in DCM (5.0 mL) for 1.5 h at 0°C gave compound **2.66** (25 mg, 31 %) as an oil. IR 1717, 1605, 1480 cm^{-1}. ^1H NMR

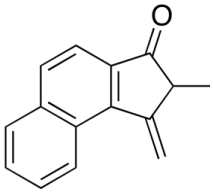
(500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 2.0 Hz, 1H), 7.73 (d, *J* = 2.0 Hz, 1H), 5.95 (d, *J* = 1.5 Hz, 1H), 5.58 (d, *J* = 1.5 Hz, 1H), 3.17 (q, *J* = 7.5 Hz, 1H), 1.56 (s, 9H), 1.39 (d, *J* = 7.0 Hz, 3H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.2, 152.6, 148.5, 146.7, 142.8, 139.0, 130.6, 118.0, 114.6, 48.4, 35.5, 35.1, 31.1, 30.1, 15.5. ESI HRMS calculated for $C_{19}H_{26}ONa$ + 293.1876, found 293.1875.

6-Methyl-7-methylene-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxol-5-one (2.67)



Ketone (100 mg, 0.5 mmol), $BF_3.Et_2O$ (0.3 mL, 2 mmol) in DCM (5.0 mL) for 45 min at 0°C gave compound **2.67** (90 mg, 90 %) as an oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.0 Hz, 2H), 6.08 (s, 2H), 5.62 (s, 1H), 5.19 (s, 1H), 3.11 (q, *J* = 7.5 Hz, 1H), 1.34 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 154.7, 150.0, 146.7, 146.0, 131.1, 105.5, 102.4, 101.9, 100.2, 46.3, 14.8. ESI HRMS calculated for $C_{12}H_{10}O_3Na^+$ 225.0522, found 225.0529.

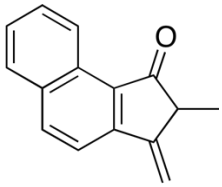
2-Methyl-1-methylene-1*H*-cyclopenta[*a*]naphthalen-3(2*H*)-one (2.68)



Ketone (103 mg, 0.48 mmol), $BF_3.Et_2O$ (0.3 mL, 2 mmol) in DCM (5.0 mL) for 1 h at 0°C gave compound **2.68** (102 mg, 99 %) as an oil. ^1H NMR (500 MHz, $CDCl_3$): δ 8.59 – 8.57 (m, 1H), 7.92 – 7.90 (m, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.65 - 7.63

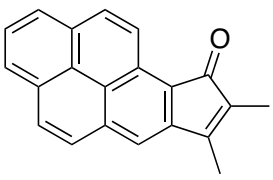
(m, 2H), 6.22 (s, 1H), 5.54 (s, 1H), 3.28 (q, J = 7.4 Hz, 1H), 1.45 (d, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 147.3, 146.8, 137.5, 135.3, 130.9, 129.6, 129.2, 128.7, 128.0, 125.8, 119.1, 111.4, 47.7, 14.6. ESI HRMS calculated for $C_{15}H_{11}ONa^+$ 231.0780, found 231.0785.

2-Methyl-3-methylene-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one (2.69)



Ketone (100 mg, 0.5 mmol), $BF_3.Et_2O$ (0.5 mL, 4 mmol) in DCM (5.0 mL) for 1 h at 0°C gave compound **2.69** (50 mg, 50 %) as an oil. IR 1687, 1637, 1602 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (d, J = 5.1 Hz, 1H), 8.04 (d, J = 5.1 Hz, 1H), 7.87 – 7.74 (m, 2H), 7.66 (t, J = 4.2 Hz, 1H), 7.55 (t, J = 4.5 Hz, 1H), 5.88 (s, 1H), 5.36 (s, 1H), 3.24 (q, J = 4.5 Hz, 1H), 1.43 (d, J = 4.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.3, 150.4, 146.7, 135.9, 133.7, 129.8, 129.2, 129.1, 128.1, 127.2, 125.1, 118.3, 107.4, 46.3, 14.8. ESI HRMS calculated for $C_{15}H_{11}ONa^+$ 231.0780, found 231.0781.

7,8-Dimethyl-9*H*-cyclopenta[*a*]pyren-9-one (2.70)

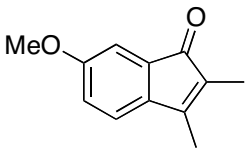


Ketone (28 mg, 0.1 mmol), $BF_3.Et_2O$ (0.02 mL, 0.2 mmol) in DCM (1.2 mL) for 3 h at rt gave compounds **2.70**. (10 mg, 36 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, J =

9.2 Hz, 1H), 8.19 (d, *J* = 7.7 Hz, 1H), 8.12 (dd, *J* = 8.0, 3.0 Hz, 2H), 8.05 (d, *J* = 9.2 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.95 (t, *J* = 7.6 Hz, 1H), 7.65 (s, 1H), 2.27 (d, *J* = 0.9 Hz, 3H), 1.94 (d, *J* = 0.6 Hz, 3H). ESI HRMS calculated for $C_{21}H_{14}ONa^+$ 305.0937, found 305.0943.

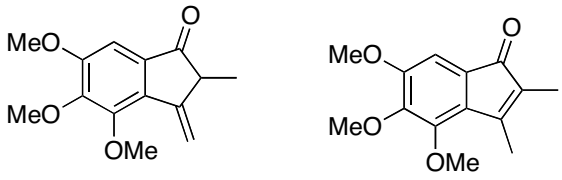
General procedure for Nazarov reaction catalyzed by In(OTf)$_3$: The AAK was dissolved in DCM (dry). $(CF_3SO_3)_3In$ was added to the reaction mixture and allowed to stir. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$, and the aqueous layer extracted with DCM (×3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure.

6-Methoxy-2,3-dimethyl-1*H*-inden-1-one (2.63)



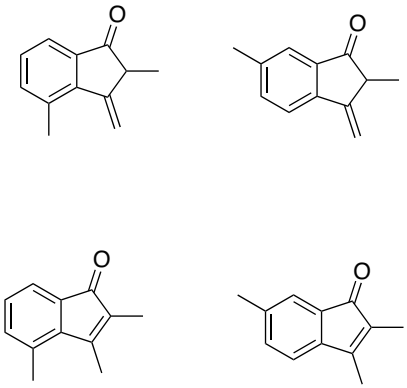
AAK (76 mg, 0.40 mmol), $(CF_3SO_3)_3In$ (0.25 g, 0.44 mmol) in DCM (7 mL) for 1.5 h at 0 °C gave compound **2.66** (72 mg, 95 %).

4,5,6-Trimethoxy-2,3-dimethyl-1*H*-inden-1-one (2.64b) and 4,5,6-trimethoxy-2-methyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.64a)



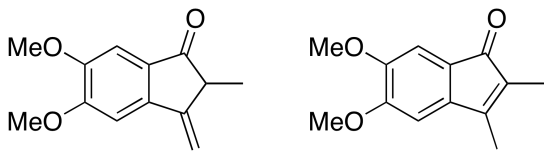
AAK (40 mg, 0.2 mmol), $(CF_3SO_3)_3In$ (9 mg, 0.02 mmol) in DCM (3.0 mL) for 1 h at rt gave compounds **2.64a** and **2.64b** (34 mg, 85 %).

2,4-Dimethyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.61a), 2,6-dimethyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.61b), 2,3,4-trimethyl-1*H*-inden-1-one (2.61c) and 2,3,6-trimethyl-1*H*-inden-1-one (2.61d)



AAK (90 mg, 0.5 mmol), $(CF_3SO_3)_3In$ (290 mg, 0.5 mmol) in DCM (7.0 mL) for 4.5 h at rt gave compounds **2.61a**, **2.61b**, **2.61c** and **2.61d** (65 mg, 72 %).

5,6-Dimethoxy-2-methyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.71a) and 5,6-dimethoxy-2,3-dimethyl-1*H*-inden-1-one (2.71b)



1:1.3

AAK (107 mg, 0.5 mmol), $(CF_3SO_3)_3In$ (270 mg, 0.5 mmol) in DCM (5.0 mL) for 3 h at rt gave compounds **2.71a** and **2.71b** (49 mg, 46 %). **2.71a**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.19 (s, 1H), 7.14 (s, 1H), 5.67 (d, J = 1.9 Hz, 1H), 5.21 (d, J = 1.5 Hz, 1H), 4.01 (s,

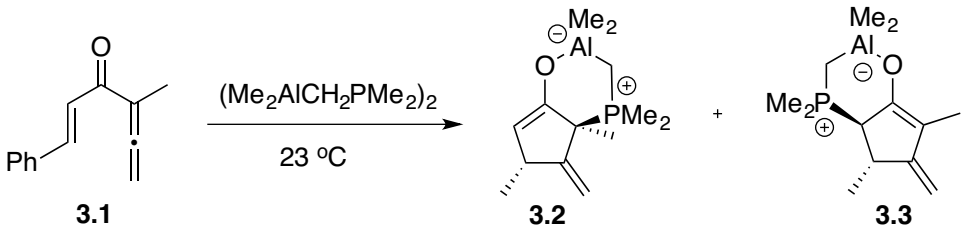
3H), 3.93 (s, 3H), 3.09 (qt, J = 7.5, 1.6 Hz, 1H), 1.36 (d, J = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 204.5, 155.7, 151.3, 148.2, 146.4, 143.9, 129.3, 104.8, 101.8, 45.9, 14.8. **2.71b:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.03 (s, 1H), 6.62 (s, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 2.07 (d, J = 1.3 Hz, 3H), 1.77 (d, J = 1.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.8, 152.6, 151.8, 148.2, 140.8, 129.4, 123.1, 103.7, 107.0, 11.7, 7.6. ESI HRMS calculated for $C_{13}H_{14}O_3Na^+$ 241.0835, found 241.0833. *It was difficult to identify methoxy signals in the carbon spectra.

Chapter 3 - Attempted Synthesis of a Tethered Allenyl Vinyl Ketone

3.1 Introduction

The oxyallyl cation generated from an allenyl vinyl ketone has three resonance contributors, which gives rise to three possible positions that could be trapped by a nucleophile. Position **a** is the electronically preferred trapping site, whereas position **c** is the sterically preferred trapping site. Most nucleophiles have been shown to trap at position **a**, but trapping at position **c** can be promoted using bulky nucleophiles. Dienes and alkenes have also been used to trap at positions **a** and **b** by (3 + 2) and (4 +3) cycloadditions. However, trapping at only position **b** has not been observed, except in one instance.

The ambiphilic molecule $(PMe_2CH_2AlMe_2)_2$ reacted with AVK **3.1** at room temperature in an NMR experiment to give the products trapped at positions **a** and **b** in a 3:7 ratio.[31] However, no product from trapping at only **b** was isolated because conversion to **3.3** was observed, and after 20 h **3.3**, which is a thermodynamic product, was the only species observed. Under kinetic control, however, the predominant product appeared to be **3.2**. Computational work suggested that a very weak hydrogen bond between one of the lone pairs on phosphine and the hydrogen atoms on the methyl group at position **b** might have guided the reaction towards **3.2**.



3.1 **3.2** **3.3**

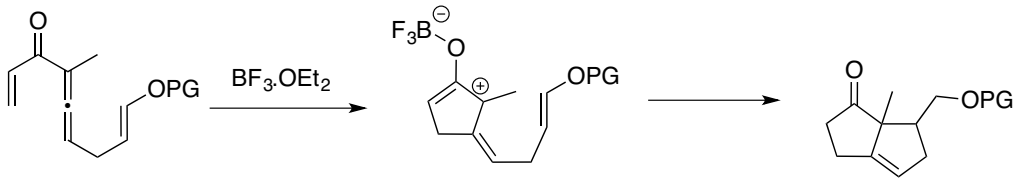
Scheme 3.1 Trapping of oxyallyl cation using an ambiphilic molecule

This project was focused on the synthesis of a tethered AVK for which intramolecular trapping of the oxyallyl cation would be geometrically favored only at position **b**. The idea was that an intramolecular delivery of the nucleophile might generate an isolable product at which a new σ bond had formed only at position **b**.

3.2 Results and Discussion

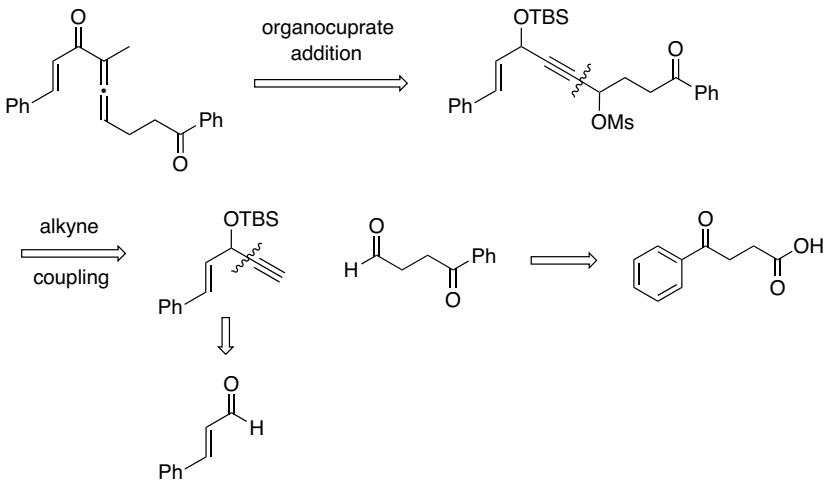
3.2.1 Synthesis

An AVK with a 3-carbon tether was targeted since trapping at position **b** would result in the favorable formation of a five-membered ring (Scheme 3.2).



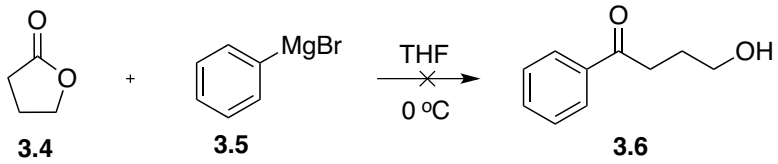
Scheme 3.2 Trapping at of a tethered AVK at position b

The initial retrosynthetic analysis for the synthesis of the tethered AVK is shown in Scheme 3.3. The propargyl alcohol might be obtained from an alkyne coupling step, which can be followed by an organocuprate addition and loss of the oxygen leaving group, and this would result in the formation of the substituted allene.[32]



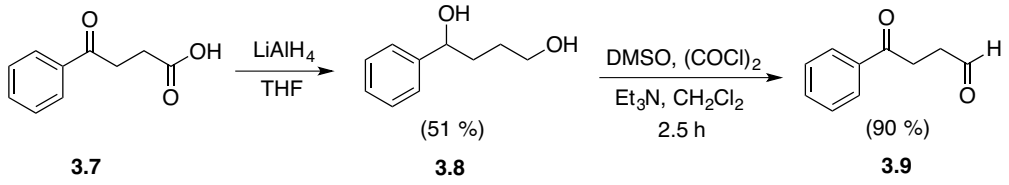
Scheme 3.3 Retrosynthetic analysis for the synthesis of tethered AVK

The first step in this attempt was a Grignard reaction between γ-butyrolactone **3.4** and phenylmagnesium bromide (Scheme 3.4).[33] This reaction gave a mixture of products that was not separable by chromatography.



Scheme 3.4 Grignard reaction with butyrolactone

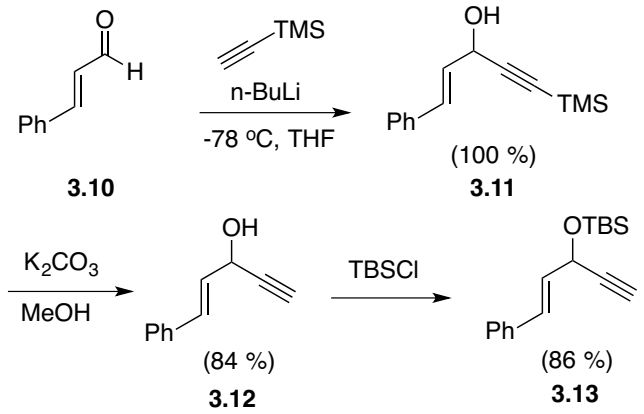
A different approach was used with 3-benzoylpropionic acid as the starting material. The acid **3.7** was first reduced using $LiAlH_4$,[34] and the diol **3.8** was re-oxidized by a Swern oxidation to give the keto-aldehyde **3.9** (Scheme 3.5).



3.7 **3.8** **3.9**

Scheme 3.5 Synthesis of keto-aldehyde 3.9

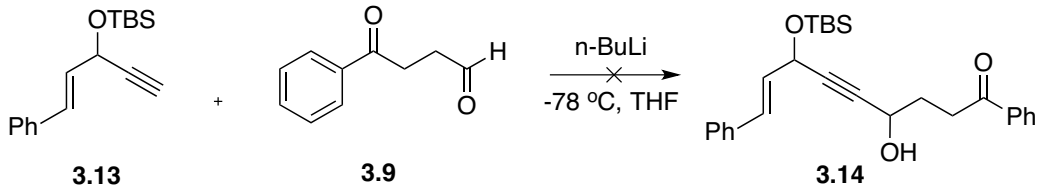
The protected propargyl alcohol **3.13** was synthesized from *trans*-cinnamaldehyde (Scheme 3.6). Reacting *trans*-cinnamaldehyde with *n*-BuLi and ethynyltrimethylsilane in THF gave **3.11** in quantitative yield, and the TMS group was removed by stirring with K_2CO_3 in methanol to give **3.12**. The final step was the protection of the alcohol as a silyl ether using TBSCl and imidazole.



3.10 **3.11** **3.12** **3.13**

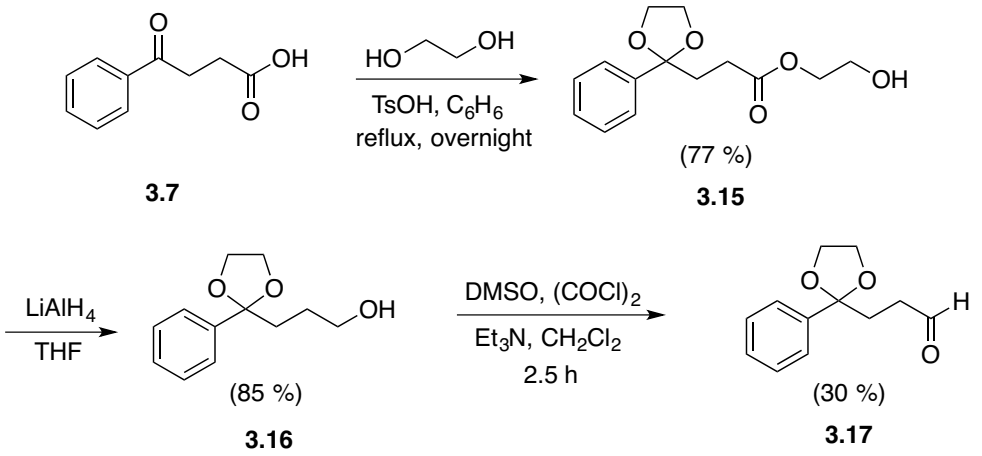
Scheme 3.6 Synthesis of protected propargyl alcohol

With the keto-aldehyde and the protected propargyl alcohol on hand, the alkyne coupling step was attempted using *n*-BuLi to deprotonate the alkyne. The ^{1}H NMR spectrum revealed a complex mixture of products that could have resulted from the acetylide reacting with both the ketone and the aldehyde. There appeared to be many diastereomers.



Scheme 3.7 Attempted alkyne coupling reaction with keto-aldehyde

In order to get around this problem, the ketone was protected using a cyclic acetal in the hope of preventing the anion from attacking the ketone carbonyl.[35] Protection of the ketone was accomplished by reacting the acid **3.7** with ethylene glycol in the presence of *p*-toluenesulfonic acid.

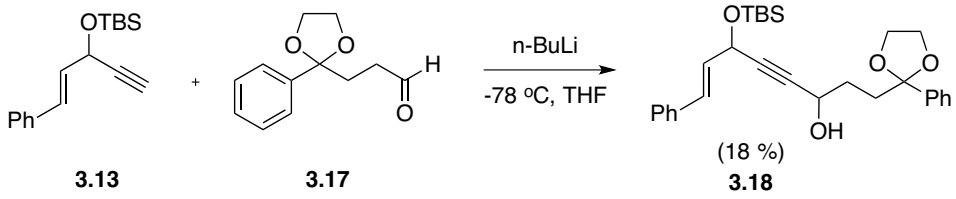


Scheme 3.8 Synthesis of protected keto-aldehyde

The ^{1}H NMR spectrum showed that the cyclic acetal did form but ethylene glycol also formed the ester from the carboxylic acid. However, reduction of **3.15** using $LiAlH_4$ reduced the ester, and re-oxidation gave the desired product **3.17** (Scheme 3.8).

The reaction of **3.17** with the protected propargy alcohol **3.13** gave the coupled product **3.18** but in a low yield of 18 % (Scheme 3.9). Purification by column chromatography seemed to have resulted in significant loss of material, most likely due

to sensitivity of the acetal group. The organocuprate addition reaction was attempted first by converting the alcohol to a mesylate using triethylamine and methanesulfonyl chloride, and the cuprate reagent was added to the crude mesylate reaction mixture without further purification of **3.18**, but the desired substituted allene product was not obtained.

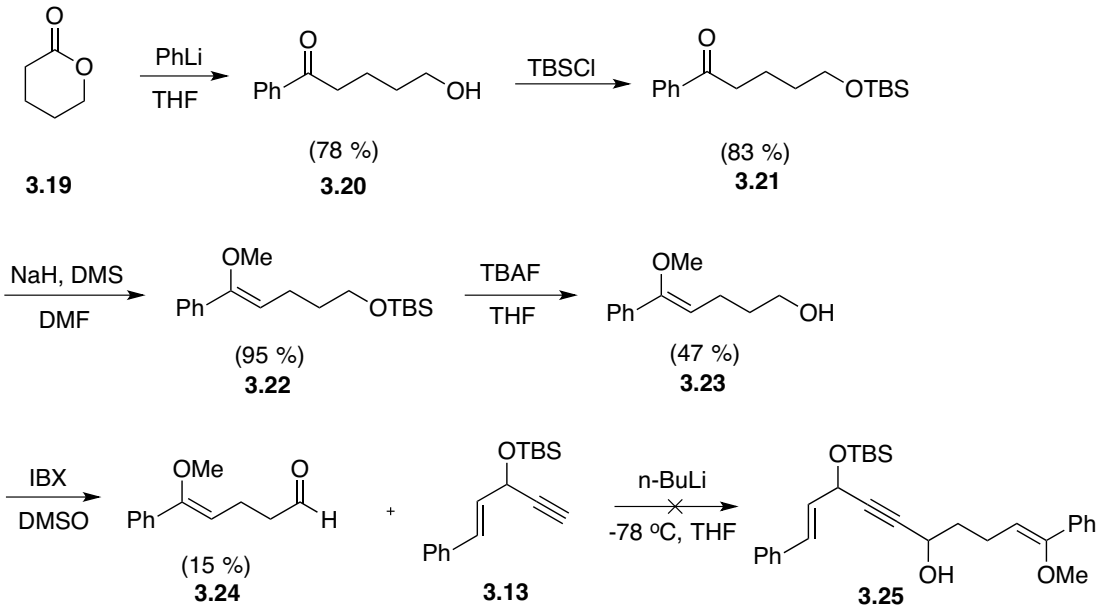


3.13 **3.17** **3.18**

Scheme 3.9 Alkyne coupling reaction with protected keto-aldehyde

A new approach for the synthesis of the tethered AVK was used with δ-valerolactone as the starting material and an enol ether as a more robust protecting group (Scheme 3.10). Phenyllithium reacted with the lactone[36] to give **3.20** and the terminal alcohol was protected as a silyl ether. Sodium hydride was used as a base to deprotonate α to the ketone, and dimethyl sulfate was used as an alkylating agent to produce the enol ether. The TBS protecting group was then removed, and oxidation was attempted using a Swern reaction, but the aldehyde was not obtained. Oxidation with IBX did give the aldehyde in low yield. However, the alkyne coupling reaction still did not give the desired product. Instead, the protected propargyl alcohol was recovered, while the aldehyde was no longer observed in the ^{1}H NMR spectrum indicating that it decomposed. The reaction was attempted again with 2 equiv of aldehyde (rather than 1), which gave the same result. In an attempt to understand why the alkyne coupling reaction did not work, *n*-BuLi was added to the protected propargyl alcohol followed by

quenching with D_2O to determine whether the anion was forming. The ^1H NMR spectrum revealed that the signal for the alkynyl proton had disappeared, and so the anion had formed.



Scheme 3.10 Attempted synthesis of the tethered AVK

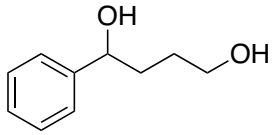
3.3 Conclusions

Protected propargyl alcohol and different keto-aldehydes were successfully synthesized, but attempts to couple them to obtain a tethered AVK were not successful, although the anion of the alkyne had formed by the addition of *n*-BuLi. It is unclear why the coupled product is not formed. Under Lewis acidic conditions, it was predicted that the oxyallyl cation formed from a Nazarov reaction could be trapped intramolecularly at position **b**.

3.4 Experimental Section

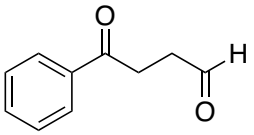
3.4.1 Synthesis and Characterization

1-Phenylbutane-1,4-diol (3.8)



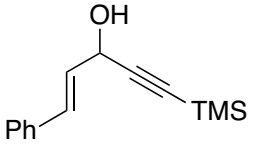
$LiAlH_4$ (2.27 g, 60 mmol) was dissolved in THF (30 mL), and the solution cooled to 0 °C. 4-Oxo-4-phenylbutanoic acid (2.67 g, 15 mmol) in THF (40 mL) was added to the solution dropwise, and the solution was stirred overnight at rt. The solution was cooled to 0 °C, the reaction was quenched with H_2O (15 mL) followed by 15 % NaOH (3 mL) and then H_2O (10 mL). The mixture was stirred for 1 h, dried over $MgSO_4$, concentrated by rotary evaporation and the residue was purified using flash chromatography (50 % EtOAc/hexanes) to yield **3.8** (1.26 g, 51 %) as a solid (mp 64 – 66 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 4H), 7.32 – 7.28 (m, 1H), 4.74 (t, J = 6.3 Hz, 1H), 3.72 – 3.66 (m, 2H), 2.99 (br s, 1H), 2.48 (br s, 1H), 1.88 (apparent q, J = 6.8 Hz, 2H), 1.75 – 1.66 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 128.4, 127.5, 125.8, 74.4, 62.8, 36.3, 29.2. ESI HRMS calculated for $C_{10}H_{14}O_2Na^+$ 189.0886, found 189.0880. The ^{1}H NMR data are in agreement with the literature.[37]

4-Oxo-4-phenylbutanal (3.9)



DMSO (1.61 mL, 22.7 mmol) was added to a solution of oxalyl chloride (1.3 mL, 15 mmol) in CH_2Cl_2 (40 mL) at -78 °C. After 10 min, **3.8** (630 mg, 3.7 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The solution was stirred for 10 min and Et_3N (5.3 mL, 38 mmol) was added. The solution was stirred at rt for 2.5 h. Et_2O (80 mL) was added, and the solution was washed with H_2O (×3) and saturated aqueous NaCl, then dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. The residue was purified by flash chromatography (1:4 EtOAc/hexane to 1:2 EtOAc/hexane) to give **3.9** (553 mg, 90 %) as a clear yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.95 (br t, J = 0.7 Hz, 1H), 8.03-8.01 (m, 2H), 7.64 – 7.60 (m, 1H), 7.53 – 7.50 (m, 2H), 3.37 (t, J = 6.3 Hz, 2H), 2.98 (td, J = 6.3, 0.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 197.8, 136.5, 133.3, 128.7, 128.1, 37.6, 31.0. ESI HRMS calculated for $C_{10}H_{10}O_2Na^+$ 185.0573, found 185.0574. The ^{1}H and ^{13}C NMR data are in agreement with the literature.[38]

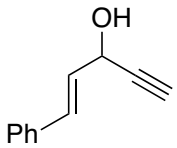
(*E*)-1-Phenyl-5-(trimethylsilyl)pent-1-en-4-yn-3-ol (3.11)



n-BuLi [2.5 M/hexane] (5.7 mL, 14 mmol) was added to a solution of ethylnyltrimethylsilane (2.0 mL, 14 mmol) of THF (20 mL) at -78°C. The solution was

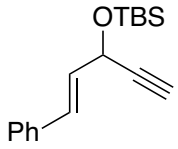
stirred for 15 min and *trans*-cinnamaldehyde (1.6 mL, 13 mmol) was added slowly at -78°C, and the mixture was stirred for 1 h. The reaction was quenched with aqueous NH_4Cl, and the organic layer was extracted with Et_2O (×3). The combined organic layers were washed with aqueous NaCl, dried over $MgSO_4$, and concentrated by rotary evaporation to yield **3.11** (3.23 g, 99 %). ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.46-7.44 (m, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.32-7.31 (m, 1H), 6.81 (dd, *J* = 15.8, 0.8 Hz, 1H), 6.33 (dd, *J* = 15.8, 6.0 Hz, 1H), 5.08 (t, *J* = 5.5 Hz, 1H), 1.99 (d, *J* = 6.1 Hz, 1H), 0.25 (s, 9H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 136.1, 132.1, 128.6, 128.1, 127.9, 126.8, 104.2, 91.4, 63.4, -0.1. ESI HRMS calculated for $C_{14}H_{18}OSiNa^+$ 253.1019, found 253.1013.

(*E*)-1-Phenylpent-1-en-4-yn-3-ol (3.12)



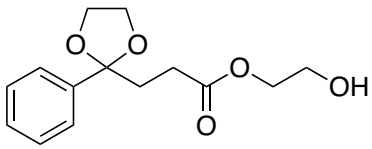
K_2CO_3 (604 mg, 4.3 mmol) was added to a solution of **3.11** (3.0 g, 13 mmol) in MeOH (30 mL), and the mixture was stirred for 1 h. Solvent was removed under reduced pressure, and the residue was partitioned between Et_2O and NH_4Cl (aq). The organic layer was extracted with Et_2O (×3) and washed with H_2O and NaCl (aq). The combined organic layers were dried over $MgSO_4$ and concentrated by rotary evaporation to yield **3.12** (1.73 g, 84 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.3 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 7.2 Hz, 1H), 6.85 (d, *J* = 15.6 Hz, 1H), 6.35 (dd, *J* = 15.8, 5.9 Hz, 1H), 5.11 (m, 1H), 2.68 (d, *J* = 2.2 Hz, 1H), 2.12 (d, *J* = 5.6 Hz, 1H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 136.0, 132.3, 128.6, 128.2, 127.5, 126.8, 82.8, 74.6, 62.8. ESI HRMS calculated for $C_{11}H_{10}ONa^+$ 181.0624, found 181.0618.

(*E*)-*tert*-Butyldimethyl(1-phenylpent-1-en-4-yn-3-yloxy)silane (3.13)



Imidazole (1.48 g, 22 mmol) and TBSCl (2.13 g, 14 mmol) were added to a solution of **3.12** (1.73 g, 11 mmol) in CH_2Cl_2 (30 mL), and the solution was stirred for 1 h. The reaction was quenched with aqueous NH_4Cl, and the mixture was extracted with CH_2Cl_2 (×3). The combined organic layers were dried over $MgSO_4$ and concentrated by rotary evaporation. The residue was purified by flash chromatography (10 % Et_2O/pentane) to give **3.13** (2.57 g, 86 %) as an oil. ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.45-7.43 (m, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.27 (m, 1H), 6.75 (dd, *J* = 15.7, 1.2 Hz, 1H), 6.28 (dd, *J* = 15.7, 5.6 Hz, 1H), 5.11 (dt, *J* = 5.5 Hz, *J* = 1.8 Hz, 1H), 2.59 (d, *J* = 2.2 Hz, 1H), 0.99 (s, 9H), 0.22 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 136.4, 130.5, 128.9, 128.6, 127.8, 126.7, 83.6, 73.5, 63.3, 25.8, 18.4, -4.5, -4.7. ESI HRMS calculated for $C_{17}H_{24}OSiNa^+$ 295.1489, found 295.1480.

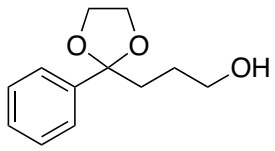
2-(Hydroxyethyl) 3-(2-phenyl-1,3-dioxolan-2-yl)propanoate (3.15)



3-Benzoylpropionic acid (8.14 g, 45 mmol), *p*-toluenesulfonic acid (0.12 g, 0.7 mmol), and ethylene glycol (8.6 mL, 154 mmol) were dissolved in benzene (45 mL). The flask was equipped with a Dean-Stark trap (wrapped in glass wool), and the mixture was heated under reflux overnight. The solution was then cooled to rt, and an aqueous

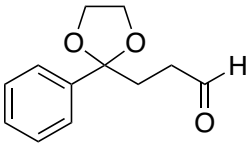
solution of K_2CO_3 (30 mL) was added slowly. The solution was diluted with Et_2O (30 mL) and transferred to a separatory funnel. Et_2O (30 mL) and K_2CO_3 (30 mL) were added, and the aqueous layer was re-extracted with Et_2O (×3). The combined organic layers were washed with H_2O (30 mL), aqueous $NaHCO_3$ (50 mL) and aqueous NaCl (50 mL), dried over Na_2SO_4, and concentrated by rotary evaporation to yield **3.15** (9.41 g, 77 %) as an oil. The product was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 - 7.42 (m, 2H), 7.37 – 7.32 (m, 3H), 4.27 – 4.24 (m, 2H), 4.06 – 4.01 (m, 2H), 3.86 – 3.77 (m, 4H), 2.53 – 2.48 (m, 2H), 2.33 – 2.28 (m, 2H).

3-(2-Phenyl-1,3-dioxolan-2-yl)propan-1-ol (3.16)



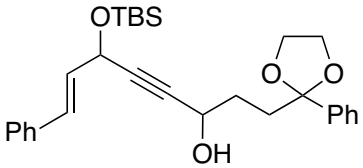
$LiAlH_4$ (2.28 g, 60 mmol) was dissolved in THF (30 mL) and cooled to 0°C. A solution of **3.15** (4.0 g, 15 mmol) in THF (40 mL) was added dropwise, and the solution was stirred for 1 h. The reaction was quenched with H_2O (3.0 mL) followed by 15 % NaOH (3.0 mL) and then H_2O (9 mL). $MgSO_4$ was added and the solution was stirred for 30 min. The solution was concentrated by rotary evaporation to yield **3.16** (2.65 g, 85 %) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 – 7.46 (m, 2H), 7.39 – 7.30 (m, 3H), 4.08 – 4.03 (m, 2H), 3.82 – 3.78 (m, 2H), 3.64 (q, J = 6.0 Hz, 2H), 2.03 (t, J = 7.4 Hz, 2H), 1.92 (t, J = 5.7 Hz, 1H), 1.71 – 1.61 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.3, 128.1, 127.9, 125.7, 110.3, 64.5, 62.9, 37.1, 26.8. The ^{1}H and ^{13}C NMR data are in agreement with the literature.[35]

3-(2-Phenyl-1,3-dioxolan-2-yl)propanal (3.17)



Oxalyl chloride (4.3 mL, 51 mmol) was dissolved in CH_2Cl_2 (130 mL) at -78°C. DMSO (5.4 mL, 83 mmol) was added to the solution, which was stirred for 10 min. A solution of **3.16** (2.65 g, 13 mmol) in CH_2Cl_2 (70 mL) was added dropwise, and the solution was stirred for 10 min. Et_3N (17.7 mL, 127 mmol) was added, and the solution was stirred at rt. Et_2O (80 mL) was added, and the solution was washed with H_2O (×3) and aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation to yield **3.17** (786 mg, 30 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.50 – 7.48 (m, 2H), 7.40 – 7.33 (m, 3H), 4.04 – 4.01 (m, 2H), 3.82 – 3.79 (m, 2H), 2.55 (td, *J* = 7.0, 2.0 Hz, 2H), 2.30 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 142.1, 128.3, 125.6, 109.5, 64.6, 38.4, 33.3. The ^{1}H and ^{13}C NMR data are in agreement with the literature.[35]

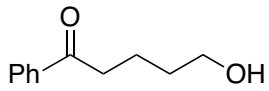
(*E*)-6-(*tert*-butyldimethylsilyloxy)-8-phenyl-1-(2-phenyl-1,3-dioxolan-2-yl)oct-7-en-4-yn-3-ol (3.18)



n-BuLi [2.5 M/hexane] (0.4 mL, 0.96 mmol) was added to a solution of **3.13** (240 mg, 0.88 mmol) in THF (3.0 mL) at -78 °C, and the solution was stirred for 20 min. A solution of **3.17** (200 mg, 0.96 mmol) in THF (2.0 mL) was added, and the solution was stirred to rt. The reaction was quenched with aqueous NaCl, and the aqueous layer was

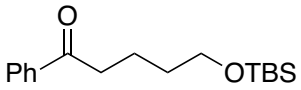
extracted with Et_2O (×3). The combined organic layers were dried over $MgSO_4$ and concentrated by rotary evaporation. The residue was purified by flash chromatography (30 % Et_2O/pentane) to yield **3.18** (76 mg, 18%) as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.42 (m, 2H), 7.38 – 7.26 (m, 8H), 6.66 (dd, *J* = 15.8, 1.2 Hz, 1H), 6.20 (dd, *J* = 15.7, 5.5 Hz, 1H), 5.09 (dt, *J* = 5.5, 1.5 Hz, 1H), 4.46 (t, *J* = 5.6 Hz, 1H), 4.04 – 3.95 (m, 2H), 3.78 – 3.73 (m, 2H), 2.19 – 2.03 (m, 2H), 1.87 – 1.80 (m, 2H), 0.93 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H).

5-Hydroxy-1-phenylpentan-1-one (3.20)



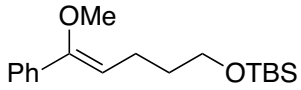
Phenyllithium [1.8 M/dibutyl ether] (11 mL, 20 mmol) was added over 30 min to a solution of δ-valerolactone (2.0 g, 20 mmol) in THF (20 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C before the reaction was quenched using a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted using EtOAc (×3), and the organic layers were combined and washed with a saturated solution of NaCl, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified by flash chromatography (0-70 Et_2O/pentane) to yield **3.20** (2.78 g, 78 %) as an oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.3 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 3.69 (t, *J* = 6.4 Hz, 2H), 3.04 (t, *J* = 7.1 Hz, 2H), 2.16 (br s, 1H), 1.89-1.83 (m, 2H), 1.70-1.65 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 133.0, 128.6, 128.1, 126.0, 62.3, 38.1, 32.2, 20.3. The ^1H and ^{13}C NMR data are in agreement with the literature.[36]

5-((*tert*-Butyldimethylsilyl)oxy)-1-phenylpentan-1-one (3.21)



Compound **3.20** (2.32 g, 13 mmol) was dissolved in CH_2Cl_2 (30 mL). Imidazole (1.77 g, 26 mmol) and TBSCl (2.56 g, 17 mmol) were added, and the solution stirred for 1 h. The reaction was quenched with saturated NH_4Cl, the organic layer re-extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated by rotary evaporation. The residue was purified by flash chromatography (7 % Et_2O/pentane) to yield **3.21** (3.14 g, 83 %) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 – 7.94 (m, 2H), 7.58 – 7.52 (m, 1H), 7.48 – 7.39 (m, 2H), 3.66 (t, *J* = 6.3 Hz, 2H), 3.00 (t, *J* = 7.3 Hz, 2H), 1.86 – 1.76 (m, 2H), 1.66 – 1.59 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H).

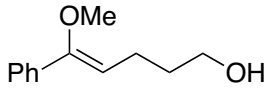
(*Z*)-*tert*-Butyl(5-methoxy-5-phenylpent-4-enyloxy)dimethylsilane (3.22)



Sodium hydride (0.55 g, 23 mmol) was dissolved in DMF (8.0 mL), and the solution was cooled to 0 °C. Compound **3.21** (2.2 g, 7.5 mmol) was added, the mixture was stirred for 1 h and then cooled back down to 0 °C. Dimethyl sulfate (1.1 mL, 11 mmol) was added, and the solution was stirred for 1 h. The reaction was quenched with H_2O, and the aqueous layer was extracted with Et_2O (×3). The combined organic layers were washed with H_2O, dried over $MgSO_4$ and concentrated by rotary evaporation to give **3.22** (2.18 g, 95 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.43 (m, 2H), 7.35 – 7.31 (m, 3H), 7.28 – 7.26 (m, 1H), 5.32 (t, *J* = 7.4 Hz, 1H), 3.68 (t, *J* = 6.5 Hz, 2H), 3.51 (s, 3H), 2.32 (q, *J* = 7.5 Hz, 2H), 1.69 – 1.63 (m, 2H), 0.91 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (125

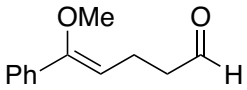
MHz, $CDCl_3$) δ 154.9, 136.0, 128.3, 127.7, 125.9, 114.2, 62.9, 58.6, 40.3, 33.0, 26.0, 22.0, -5.2.

(*Z*)-5-Methoxy-5-phenylpent-4-en-1-ol (3.23)



Compound **3.22** (200 mg, 0.65 mmol) was dissolved in THF (1.0 mL), TBAF (1.3 mL, 1.3 mmol) was added, and the solution stirred for 1.5 h. The reaction was quenched with H_2O. The aqueous layer was extracted with EtOAc (×3), and the organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation. The residue was purified by flash chromatography (7 % Et_2O/pentane) to yield **3.23** (58 mg, 47 %) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 2H), 7.38 – 7.36 (m, 1H), 7.34 – 7.28 (m, 2H), 5.30 (t, *J* = 7.7 Hz, 1H), 3.68 (t, *J* = 6.3 Hz, 2H), 3.55 (s, 3H), 2.39 (q, *J* = 7.4 Hz, 2H), 1.76 – 1.67 (m, 2H), 1.23 (d, *J* = 6.9 Hz, 1H).

(*Z*)-5-Methoxy-5-phenylpent-4-enal (3.24)



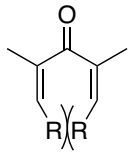
IBX (0.20 g, 0.8 mmol) was dissolved in DMSO (2.0 mL) and **3.23** (118 mg, 0.6 mmol) dissolved in DMSO (1.0 mL) was added. The mixture was stirred for 1 h at rt. Water was added to precipitate IBX byproducts, which were removed by filtration through a sintered glass funnel. The aqueous layer was extracted with EtOAc (×3), and the combined organic layers were washed with water (×3) and a saturated aqueous solution of NaCl. The organic layer was dried over Na_2SO_4 and concentrated by rotary

evaporation. The residue was purified by flash chromatography (4 % Et_2O/pentane) to give **3.24** (17 mg, 15 %) as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 9.84 (d, J = 1.6 Hz, 1H), 7.45 – 7.42 (m, 2H), 7.39 – 7.32 (m, 3H), 5.28 – 5.23 (m, 1H), 3.54 (s, 3H), 2.62 – 2.59 (m, 4H).

Chapter 4 - Trapping of Allenyl Vinyl Ketone by Allyltrimethylsilane

4.1 Introduction

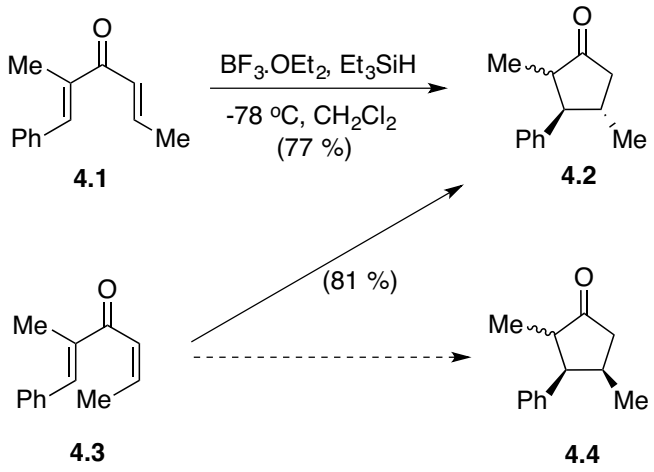
The reactive conformation required for the Nazarov reaction to take place is an *s-trans/s-trans* conformation. In *s-cis* conformations, alkyl α-substituents on divinyl ketones result in steric interactions with the vinyl hydrogen atoms, which increases the population of the reactive conformer. Conversely, β-substituents in the internal position of divinyl ketones introduce steric effects that reduce the population of the reactive conformation (Figure 4.1). Therefore, it is expected that the presence of β-substituents would increase the activation barrier for the electrocyclization.



s-trans/s-trans

Figure 4.1 Steric interactions in the *s-trans/s-trans* conformation of divinyl ketone with β-substituents

West and coworkers reported the Nazarov reaction of both *cis*- and *trans*-disubstituted enones.[39] Conrotatory cyclization of the *trans* isomer **4.1** gave the cyclized cyclopentanone **4.2**. However, the product of conrotatory cyclization of the *cis* isomer **4.3** was not observed (Scheme 4.1). Instead, they obtained the same cyclopentanone **4.2**. This indicated that the *cis* isomer underwent isomerization under the acidic reaction conditions to give the *trans* isomer, and then cyclized to give the final product. The purpose of this project was to synthesize an allenyl vinyl ketone with an internal β-substituent on the vinyl group, to explore its Nazarov reactivity, and, if the Nazarov reaction was successful, whether its oxyallyl cation intermediate could be intercepted.

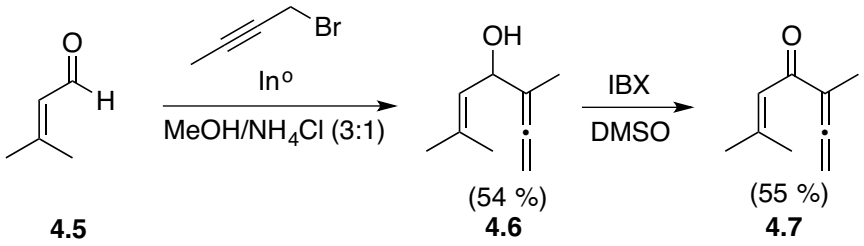


Scheme 4.1 Nazarov cyclization of *cis* and *trans* divinyl ketones

4.2 Results and Discussion

4.2.1 Synthesis

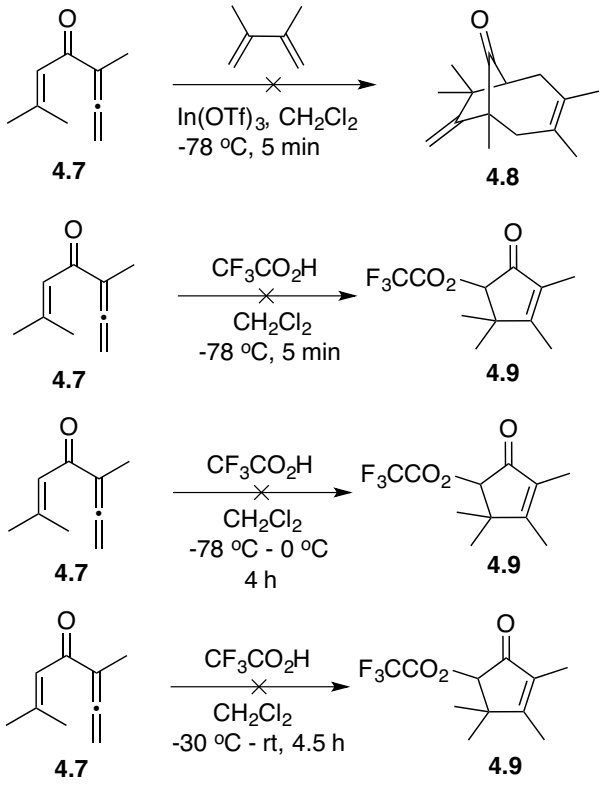
The allenyl alcohol was synthesized from 3-methyl-2-butenal and 1-bromo-2-butyne using a Barbier-type coupling reaction.[17] Oxidation of the alcohol was first attempted using DMP, which did not afford the ketone. IBX was then used to give the allenyl vinyl ketone in modest yield.



Scheme 4.2 Synthesis of AVK with internal substituent

The first reaction attempted involved treating the AVK with $BF_3.OEt_2$ in the presence of 2,3-dimethylbutadiene in the hope of obtaining the product of a (4 + 3) cycloaddition. However, it appeared that the diene polymerized, and the AVK was destroyed. Since indium (III) triflate as the Lewis acid gave better results for some

allenyl aryl ketones, the trapping reaction mediated by $In(OTf)_3$ was attempted, but it did not afford the desired product. Reactions of AVKs using trifluoroacetic acid had resulted in the interception of the oxyallyl cation intermediate by trifluoroacetate, which solvolyzed during chromatography to 5-hydrocyclopent-2-enones in excellent yield.[13] Therefore, The Nazarov reaction was attempted using trifluoroacetic acid at -78 °C for 5 min, but only starting material was obtained. The reaction was repeated at higher temperatures and over longer reaction times, but this resulted in destruction of the starting material.

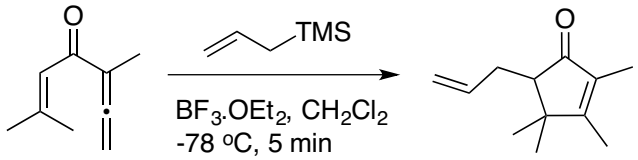


Scheme 4.3 Attempted interrupted Nazarov reactions of an AVK with a *Z* β-substituent

The presence of an internal β-substituent appeared to completely inhibit the cyclization. The reason is likely that the pentadienyl cation suffers from steric hindrance

when it adopts the *s-trans*/*s-trans* conformation required for the cyclization to take place.[4]

Allyltrimethylsilane has been shown to be an efficient trapping agent for both allenyl vinyl ketones and divinyl ketones. It can trap at position **a** to give allyl-substituted cyclopentanones, and it can also undergo a cycloaddition reaction with the oxyallyl cation to give the [3 + 2] cycloadduct.[8,15] Treatment of the AVK with $BF_3.OEt_2$ at -78 °C in the presence of allyltrimethylsilane gave the allyl-substituted cyclopentanone trapped at position **a**, but in a very low yield. No product of (3 + 2) cycloaddition was observed.



4.7 **4.10**

Scheme 4.4 Intercepting the Nazarov reaction of an AVK with a *Z* β-substituent using allyltrimethylsilane

4.3 Conclusions

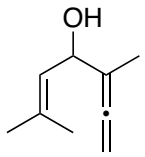
An allenyl vinyl ketone that is disubstituted at the β-position was synthesized from the starting aldehyde over two steps. Various reaction conditions and trapping agents were tested; however, the efficiency of the reaction was very greatly reduced due presumably to increased steric interactions in the *s-trans*/*s-trans* conformation by the β-substituents. The presence of the substituents likely also increased the steric interactions with the incoming nucleophile and decreases the chances of trapping. In addition, since there are two substituents on the vinyl group, there is no isomerization process that could

decrease the steric hindrance present. Finally, allyltrimethylsilane was successfully used to trap the oxyallyl cation generated from the Nazarov reaction of the AVK, but the efficiency of the process was very low.

4.4 Experimental

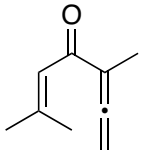
4.4.1 Synthesis and Characterization

3,6-Dimethylhepta-1,2,5-trien-4-ol (4.6)



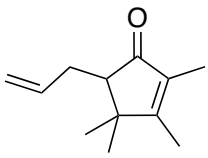
1-Bromo-2-butyne (0.12 mL, 1.3 mmol) and 3-methyl-2-butenal (100 mg, 1.2 mmol) were dissolved in a 3:1 mixture of MeOH/NH_4Cl (4.0 mL). The solution was cooled to 0 °C, and indium powder (0.15 g, 1.3 mmol) was added in portions over 15 min. The mixture was stirred for 1 h at rt before being filtered over Celite, and Et_2O (10 mL) was added. The phases were separated, and the organic layer washed with saturated aqueous NaCl. The aqueous phase was re-extracted with Et_2O (×3). The combined organic layers were dried over $MgSO_4$ and concentrated by rotary evaporation to give compound **4.6** (89 mg, 54 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (ddt, *J* = 8.8, 2.7, 1.4 Hz, 1H), 4.86 (quintet, *J* = 3.0 Hz, 2H), 4.78 (dt, *J* = 8.8, 2.4 Hz, 1H), 1.79 (d, *J* = 1.2 Hz, 3H), 1.76 (d, *J* = 1.3 Hz, 3H), 1.72 (t, *J* = 3.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 125.5, 102.6, 77.5, 69.0, 25.8, 18.3, 14.7. ESI HRMS calculated for $C_9H_{14}ONa^+$ 161.0937, found 161.0944.

3,6-Dimethylhepta-1,2,5-trien-4-one (4.7)



IBX (0.14 g, 0.5 mmol) was dissolved in DMSO (2.0 mL) and **4.6** (50 mg, 0.4 mmol) dissolved in DMSO (1.0 mL) was added. The mixture was stirred for 1 h at rt. Water was added to precipitate IBX byproducts, which were removed by filtration through a sintered glass funnel. The aqueous solution was extracted with EtOAc (×3), and the combined organic layers were washed with water (×3) and a saturated aqueous solution of NaCl. The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation to give **4.7** (27 mg, 55 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 – 6.63 (m, 1H), 5.13 (q, *J* = 3.0 Hz, 2H), 2.18 (s, 3H), 1.91 (s, 3H), 1.85 (t, *J* = 3.0 Hz, 3H). ESI HRMS calculated for $C_9H_{12}ONa^+$ 159.0780, found 159.0773.

5-Allyl-2,3,4,4-tetramethylcyclopent-2-enone (4.10)



AVK **4.7** (42 mg, 0.3 mmol) and allyltrimethylsilane (0.09 mL, 0.6 mmol) were dissolved in CH_2Cl_2 (20 mL), and the solution was cooled to -78 °C. $BF_3.OEt_2$ (0.04 mL, 0.3 mmol) was added, and the solution was stirred for 5 min. The reaction was quenched with aqueous $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation, and the residue was purified by flash chromatography (2-5 % Et_2O/pentane)

to give **4.10** (4 mg, 7 %) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 – 5.95 (m, 1H), 5.18 – 5.14 (m, 1H), 5.09 – 5.07 (m, 1H), 2.72 – 2.67 (m, 1H), 2.18 – 2.13 (m, 2H), 1.97 (s, 3H), 1.71 (s, 3H), 1.22 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.5, 175.3, 138.0, 133.3, 115.8, 56.5, 44.9, 31.0, 26.5, 23.1, 11.7, 8.2. ESI HRMS calculated for $C_{12}H_{18}ONa^{+}$ 201.1250, found 201.1253.

Chapter 5 – Conclusion

The work presented in this thesis aimed to study the reactivity of various substrates in the Nazarov reaction and the interception of the oxyallyl cation intermediates generated over the course of the reaction. In Chapter 2, allenyl aryl ketones were successfully synthesized over a two-step process from starting aldehydes. The substrates underwent the Nazarov reactions, which required higher temperatures and longer reaction times compared to allenyl vinyl ketones because the aromaticity of the AAKs is destroyed during the electrocyclization. It was determined that substituting the aromatic group with electron-donating groups enhanced the efficiency reaction, while no reaction was observed with substrates containing electron-withdrawing groups. $BF_3.OEt_2$ and $In(OTf)_3$ were used to catalyze the Nazarov reactions, and it was found that $In(OTf)_3$ provided better results for some substrates. Interception of the oxyallyl cations derived from the Nazarov reactions of AAKs was unsuccessful. The oxyallyl cation must likely re-aromatize by elimination of a proton much faster than the nucleophile is able to intercept the cation.

Previous research has shown that nucleophiles trap at the electronically favored position **a**, while sterically hindered nucleophiles trap at position **c**. Chapter 3 summarized the attempts to synthesize a tethered AVK that should lead to interception at position **b**. Different keto-aldehydes were synthesized with the objective of coupling them to the protected propargyl alcohol using an alkyne coupling reaction. However, attempts to obtain a tethered AVK were not successful. Future work can aim at developing a different synthetic route to obtain the tethered AVK.

Chapter 4 presented research on the interception of the oxyallyl cation derived from an AVK disubstituted at the β-position. Divinyl ketones containing an internal β-substituent have been shown to isomerize to decrease the steric strain in the reactive conformer before undergoing the electrocyclization. However, because the disubstituted AVK contains two substituents at the β-position, there is no isomerization process that can occur. Many attempts were carried out to trap the oxyallyl cation but the reaction was significantly hindered by the β-substituent. The interception of the carbocation intermediate was finally successful using allyltrimethylsilane. Future work can include the synthesis of various disubstituted AVKs and attempting to intercept them with other nucleophiles.

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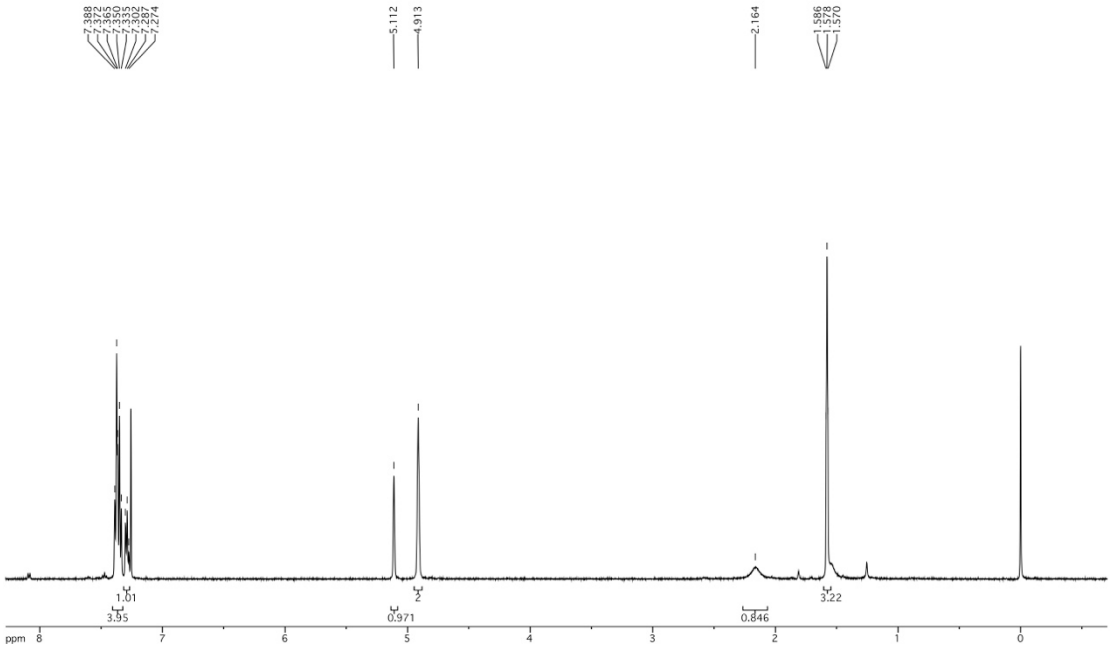
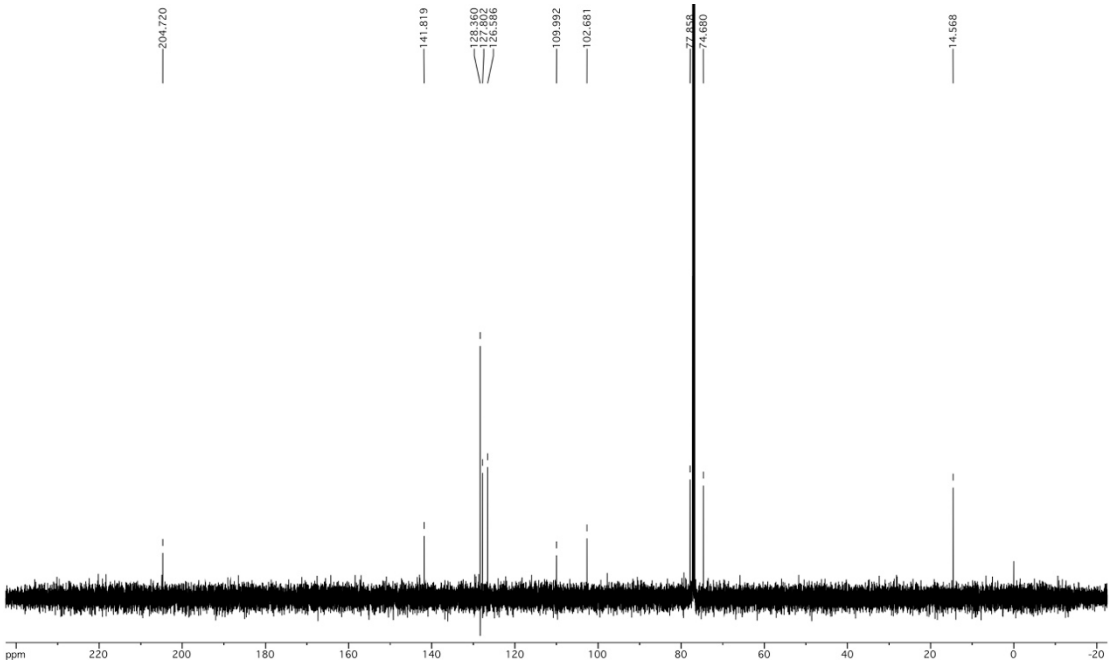
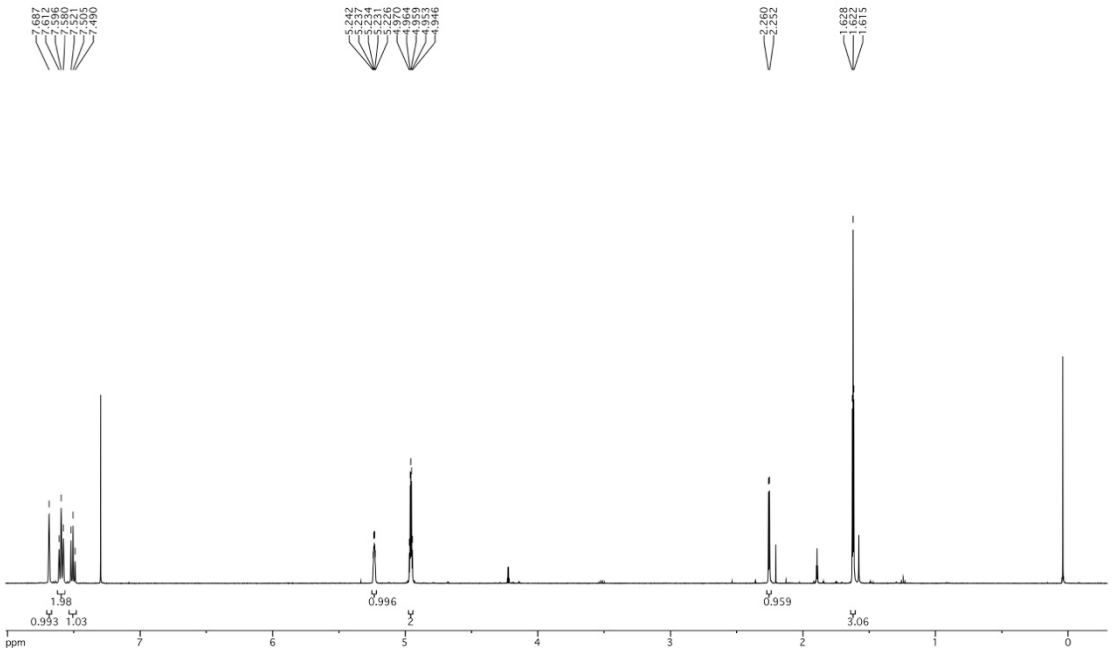
Appendix A – NMR spectra for Chapter 2

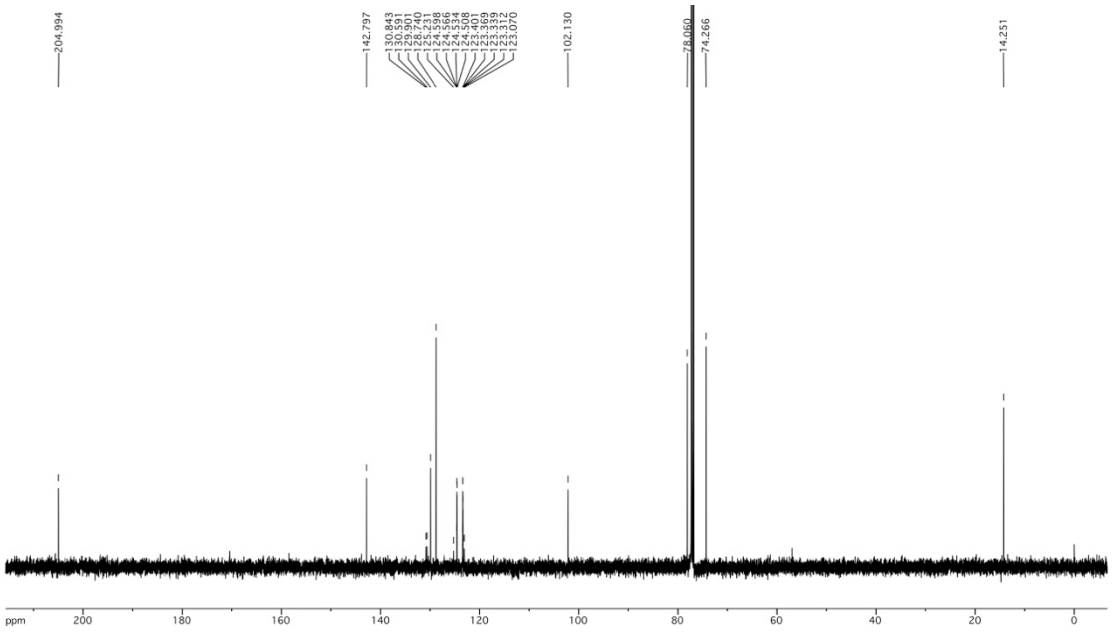
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-phenylbuta-2,3-dien-1-ol (2.23)



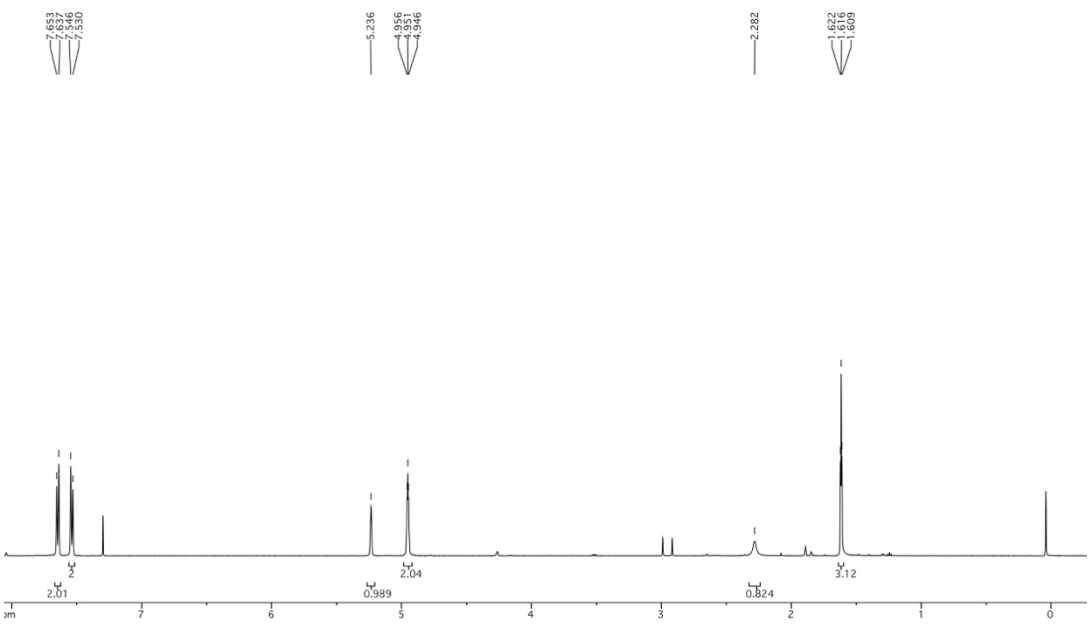


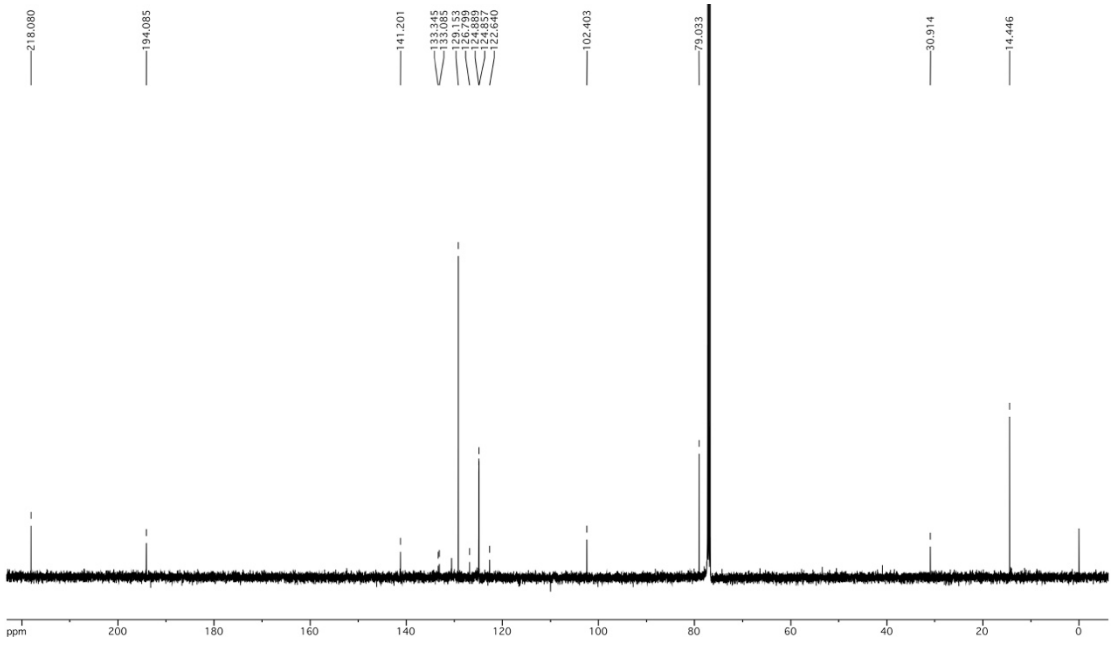
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-(3-(trifluoromethyl)phenyl)buta-2,3-dien-1-ol (2.24)



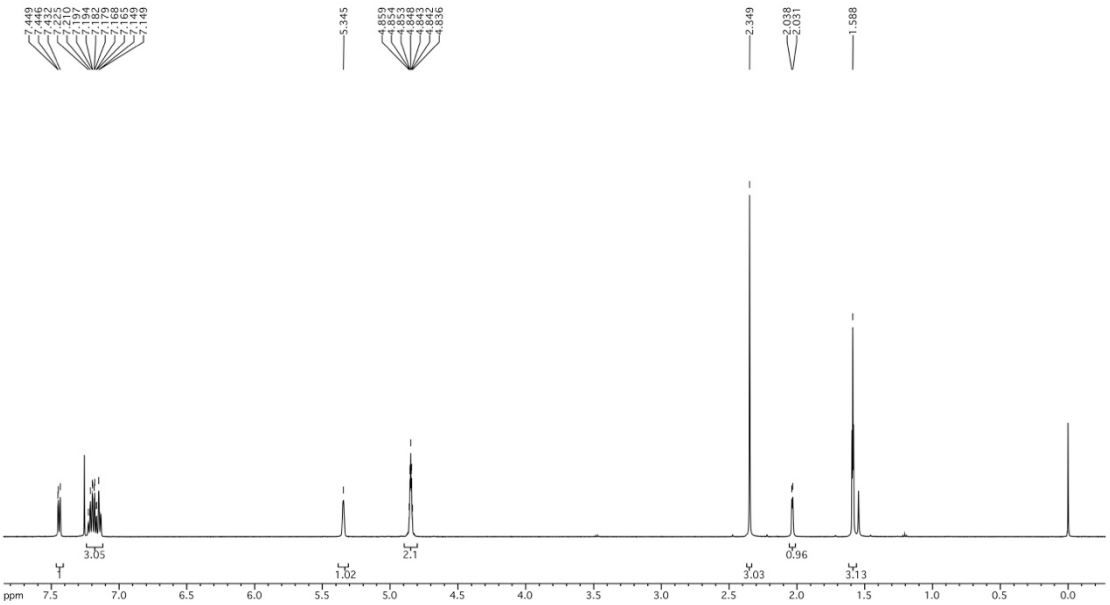


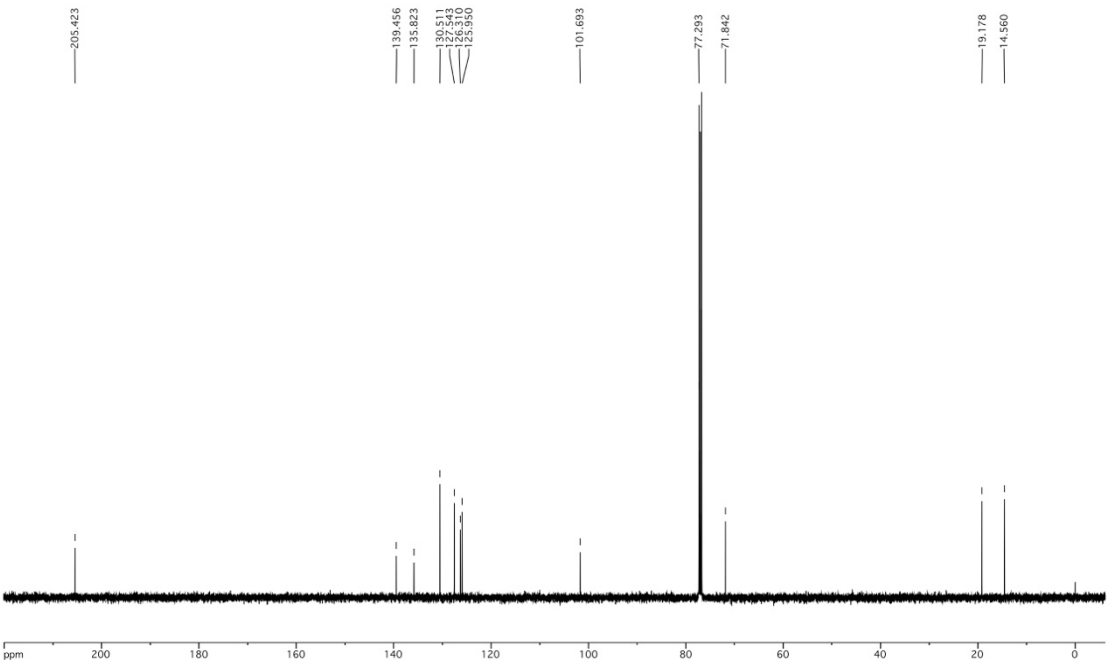
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-(4-(trifluoromethyl)phenyl)buta-2,3-dien-1-ol (2.25)



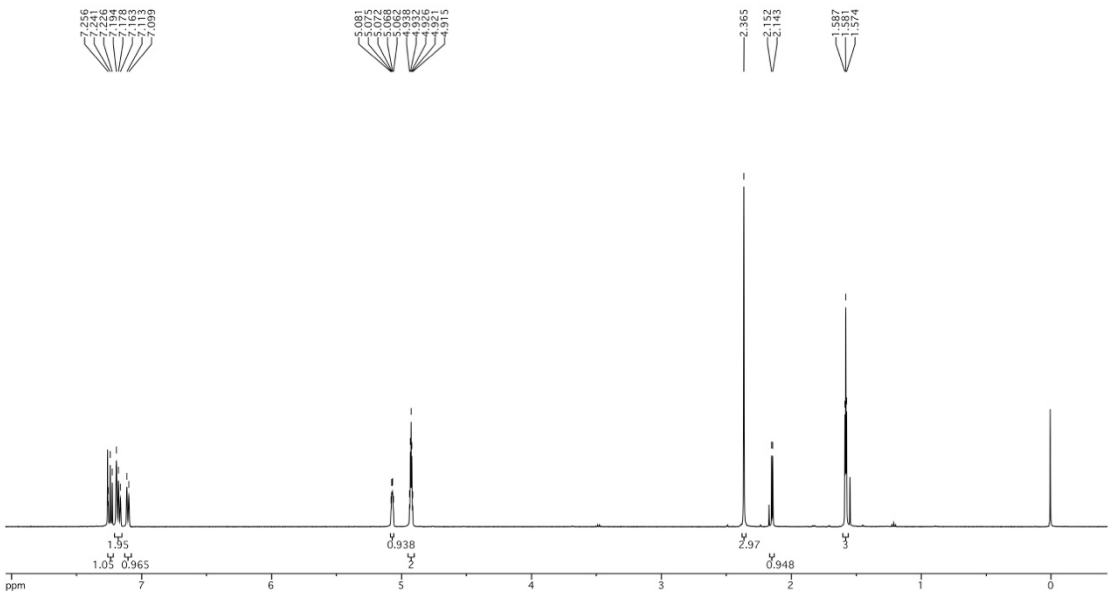


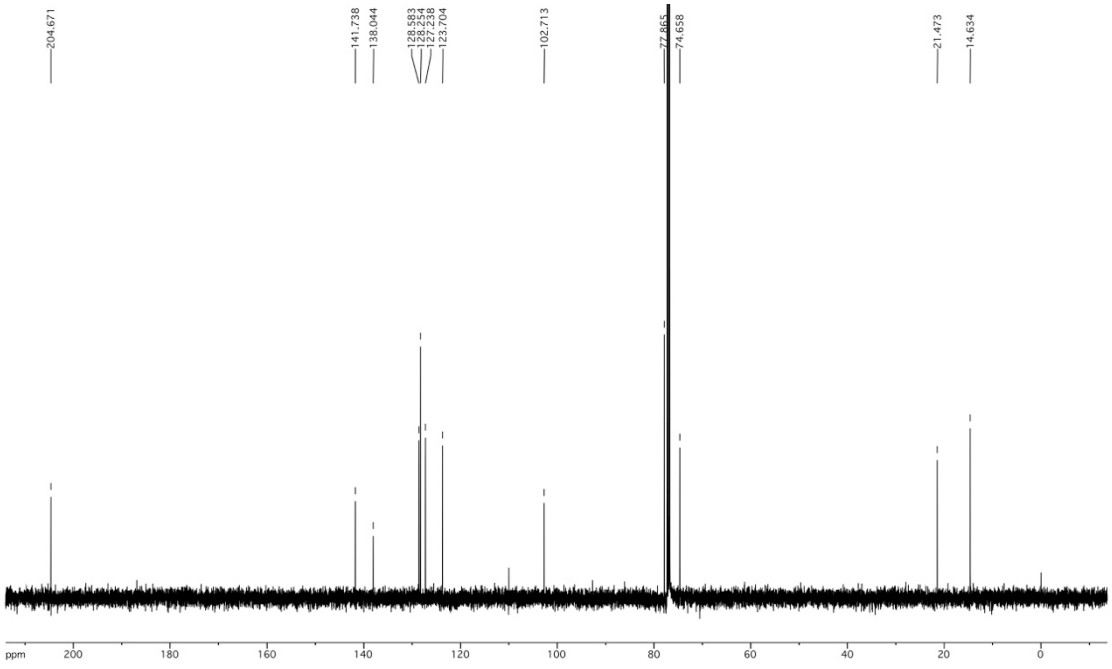
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-*o*-tolylbuta-2,3-dien-1-ol (2.26)



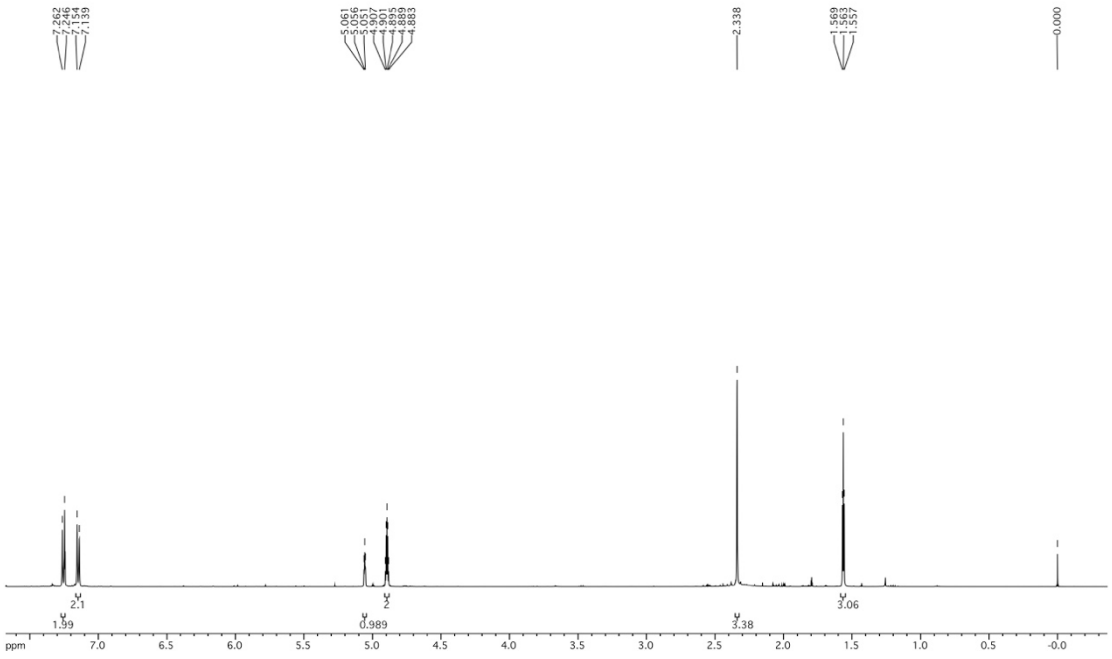


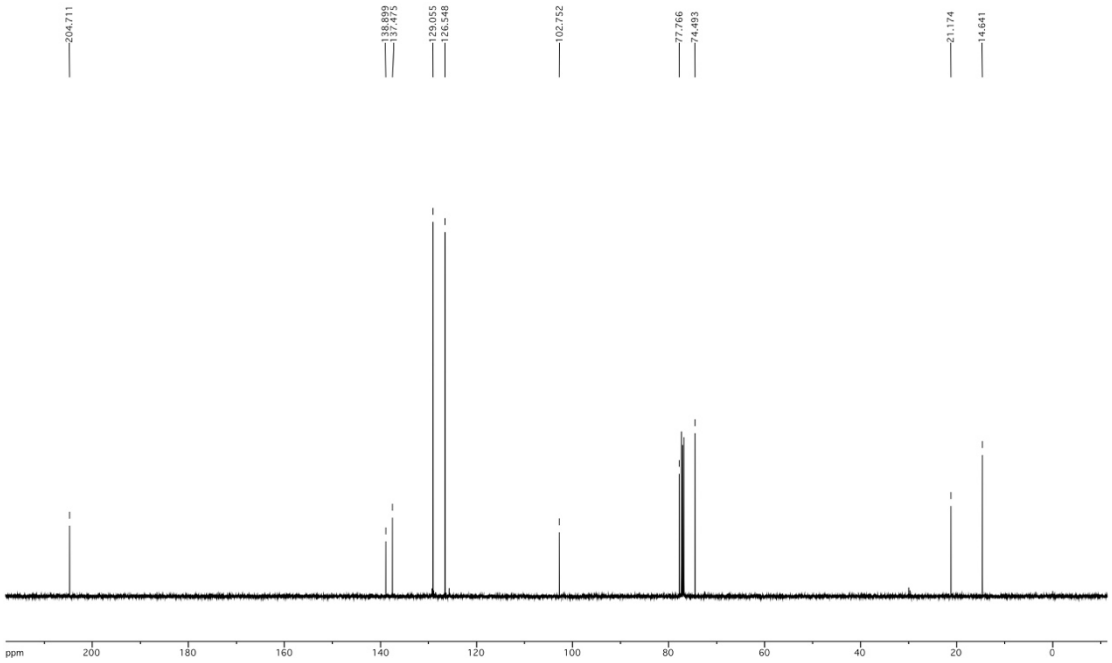
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-*m*-tolylbuta-2,3-dien-1-ol (2.27)



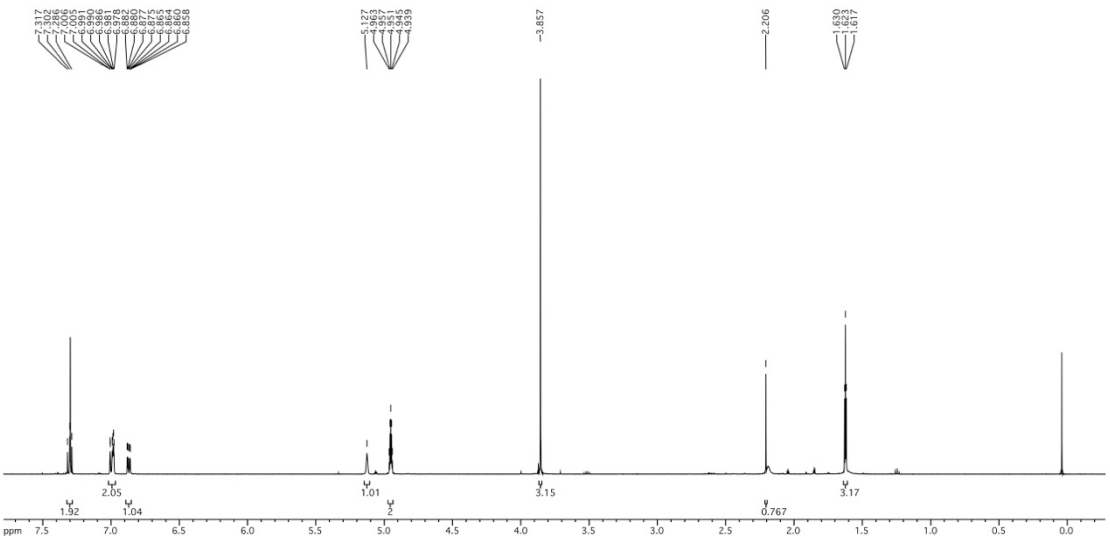


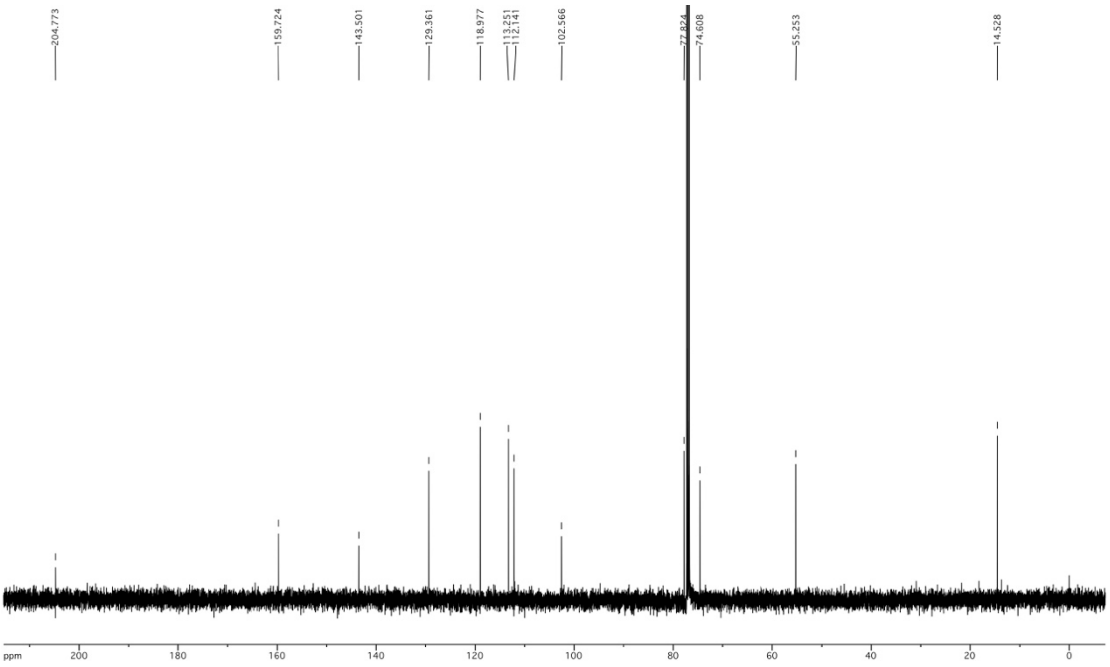
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-*p*-tolylbuta-2,3-dien-1-ol (2.28)



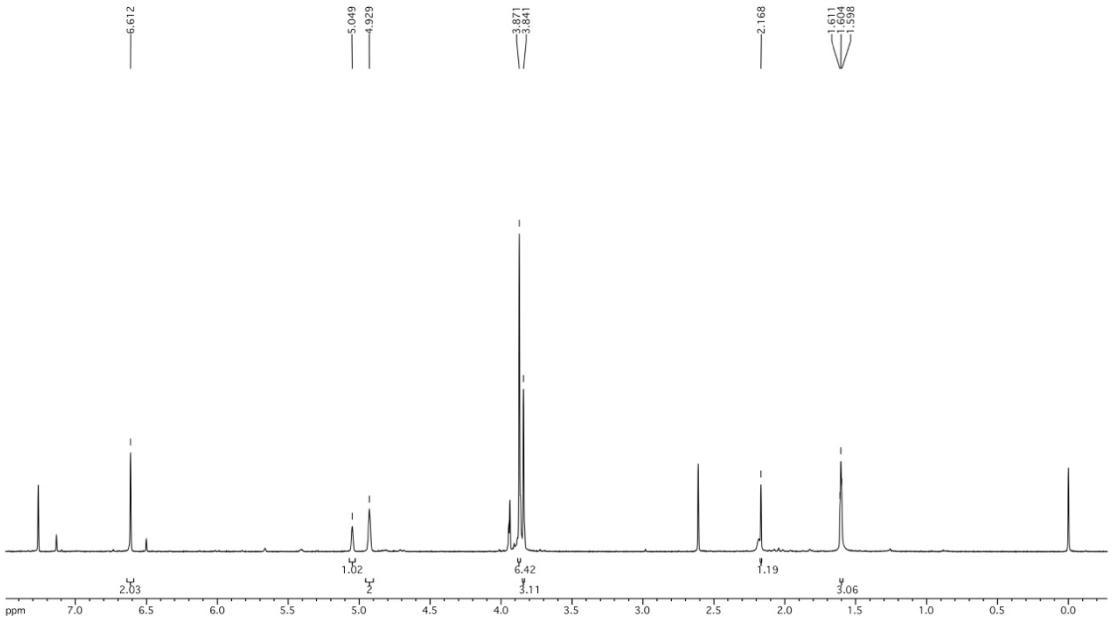


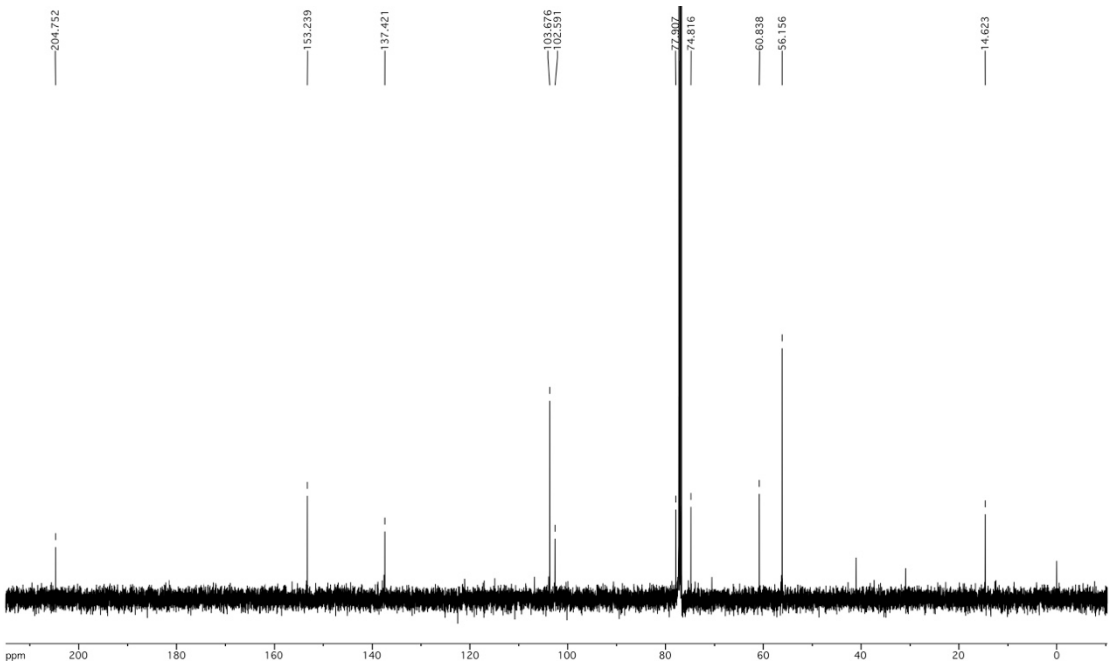
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 1-(3-methoxyphenyl)-2-methylbuta-2,3-dien-1-ol (2.29)



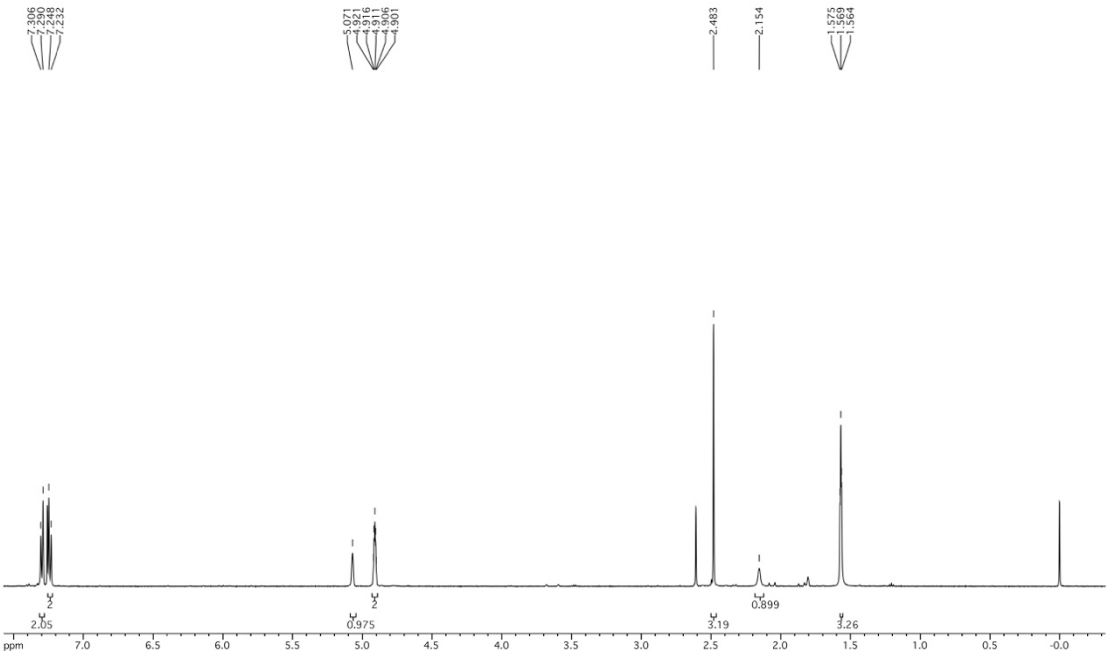


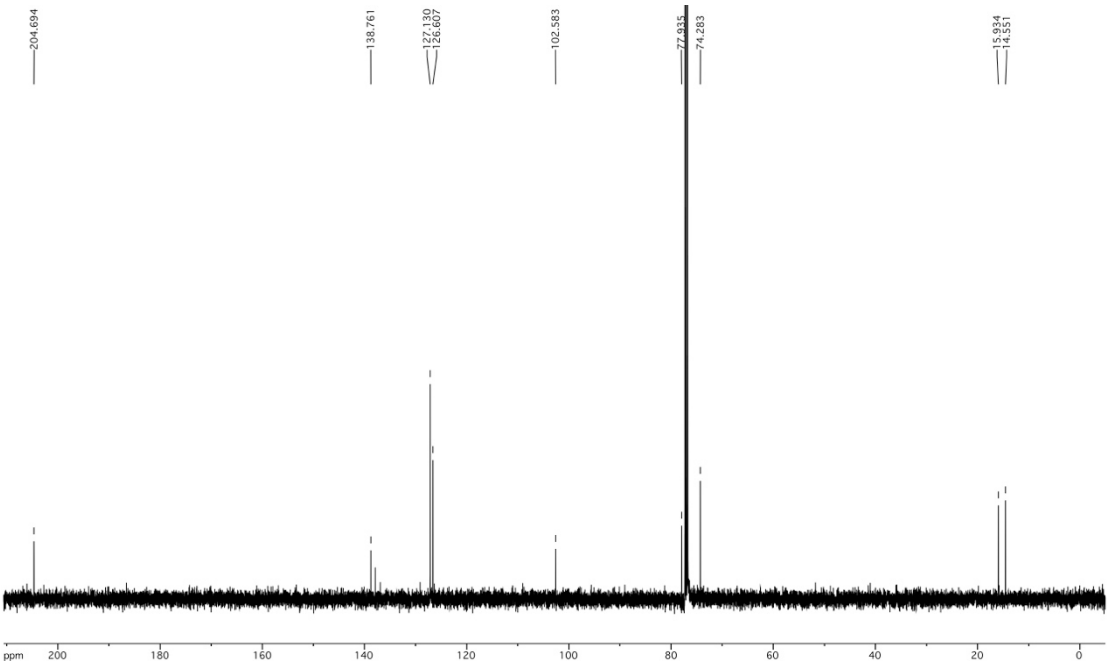
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-(3,4,5-trimethoxyphenyl)buta-2,3-dien-1-ol (2.30)



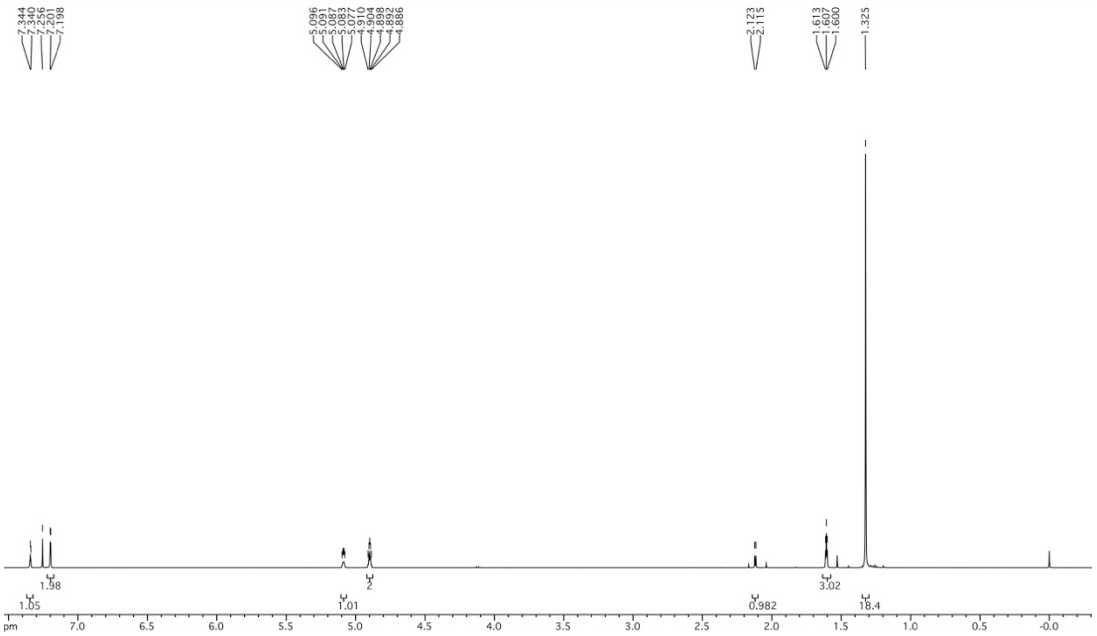


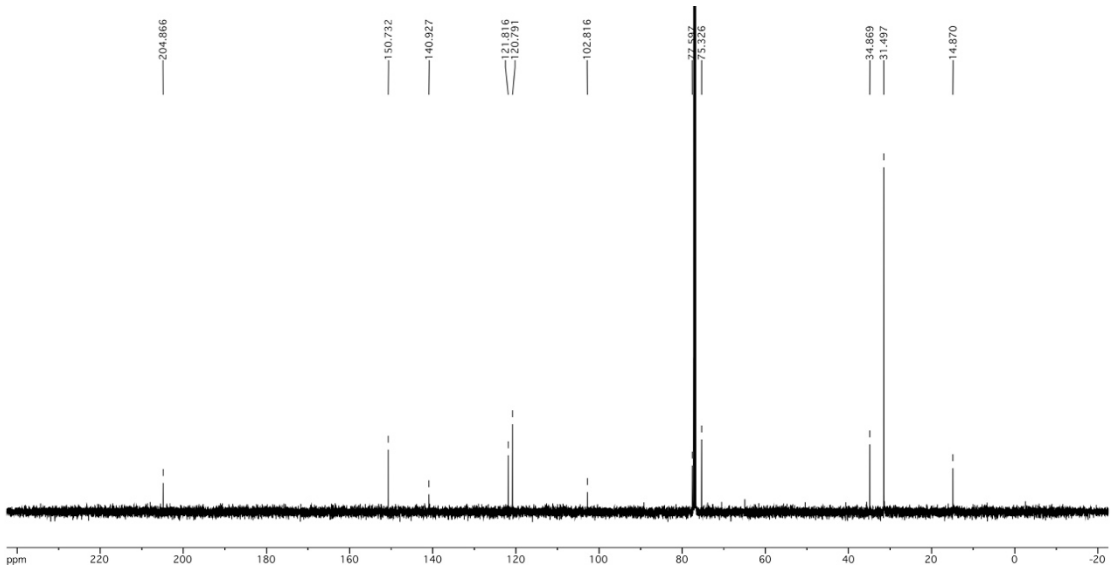
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-(4-(methylthio)phenyl)buta-2,3-dien-1-ol (2.31)



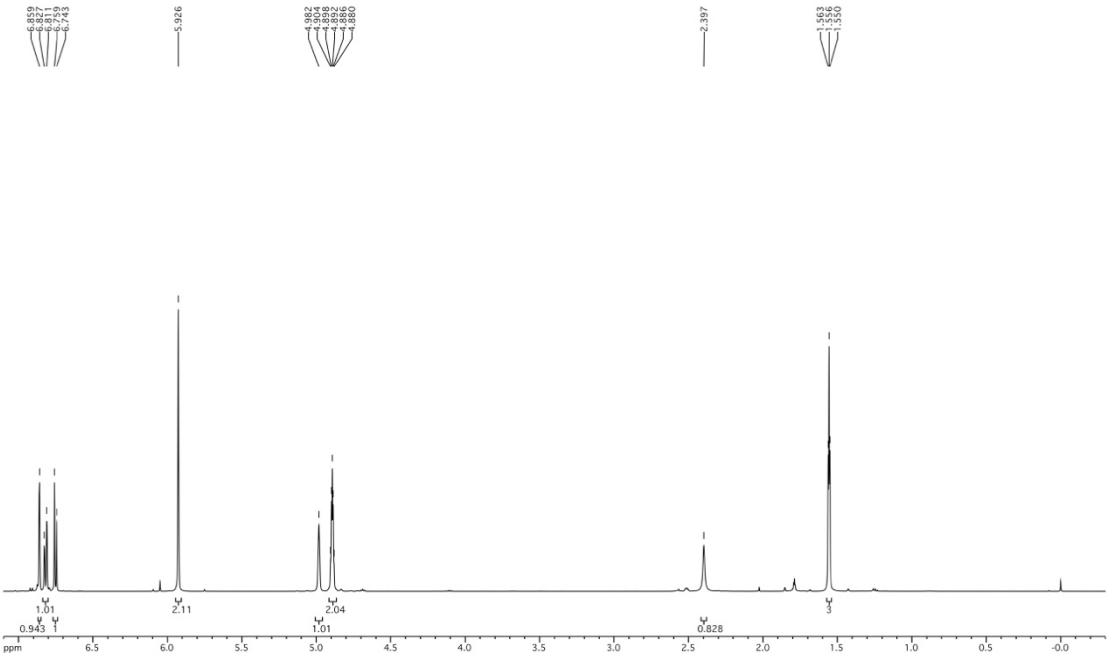


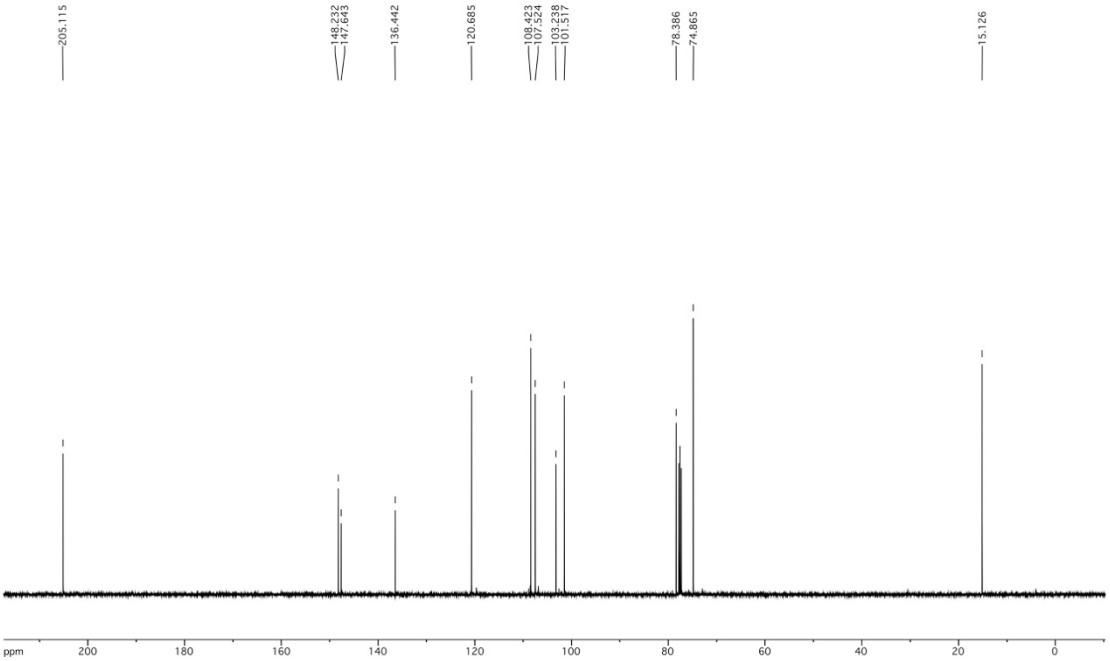
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 1-(3,5-di-*tert*-butylphenyl)-2-methylbuta-2,3-dien-1-ol (2.32)



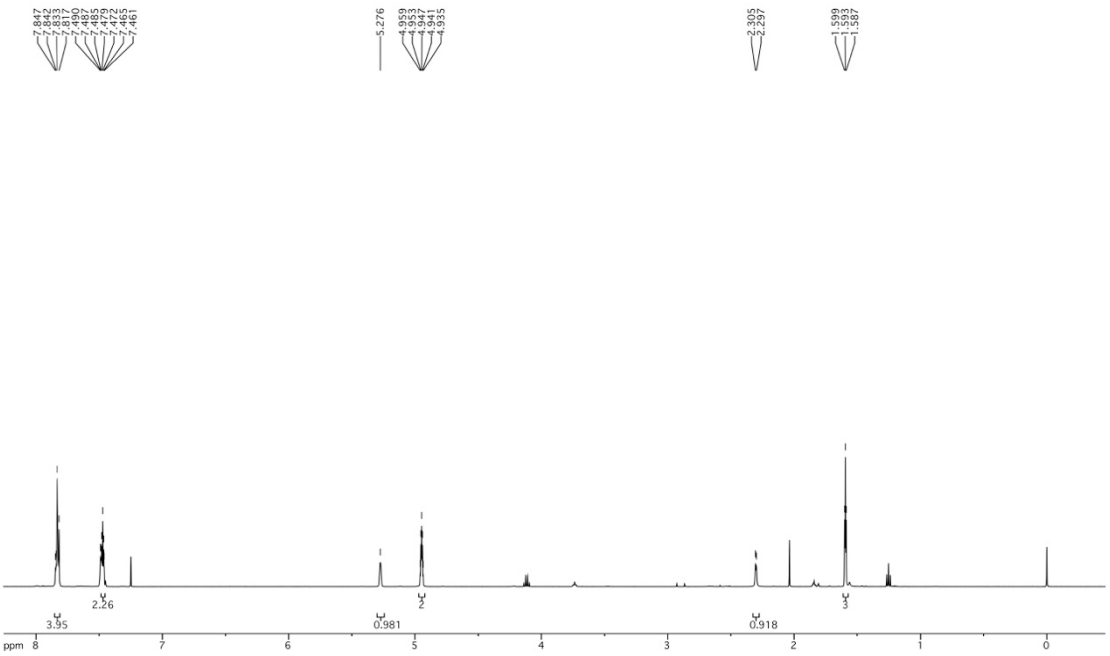


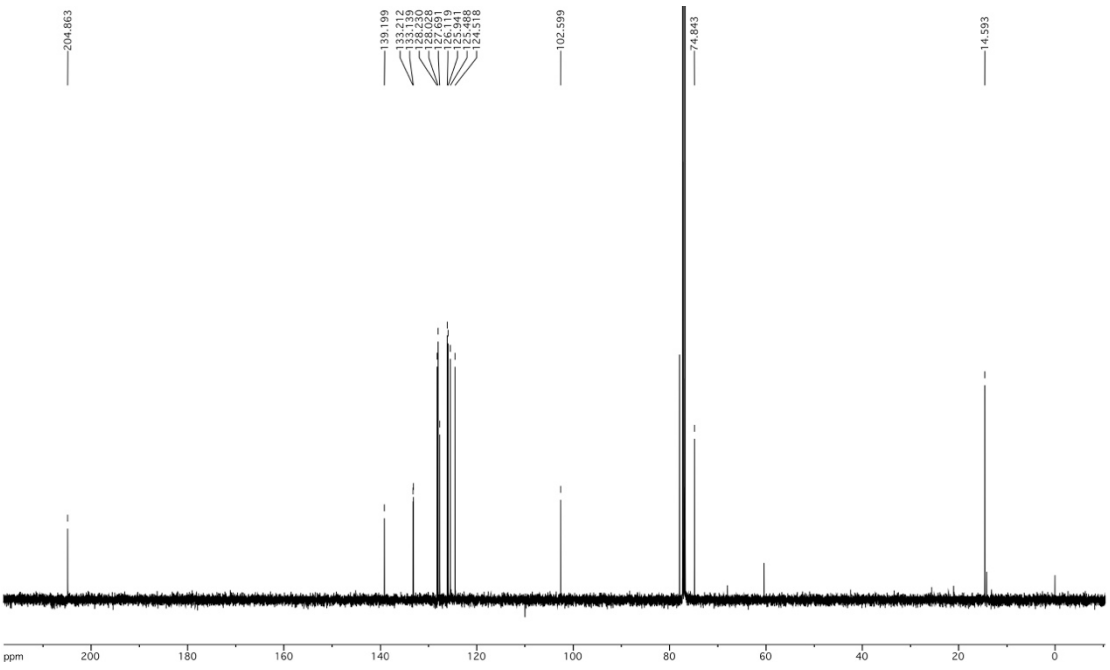
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 1-(benzo[*d*][1,3]dioxol-5-yl)-2-methylbuta-2,3-dien-1-ol (2.33)



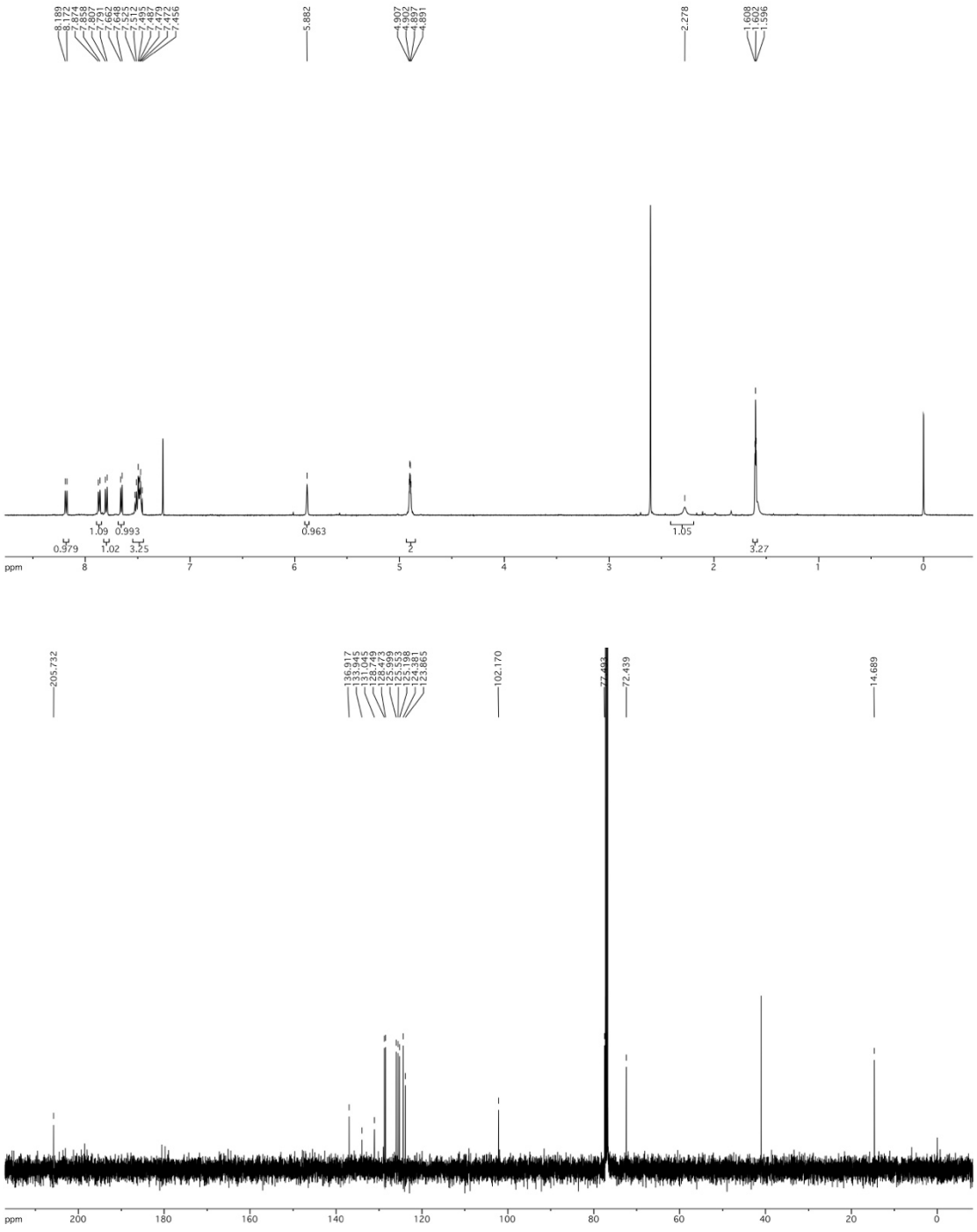


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-(naphthalen-2-yl)buta-2,3-dien-1-ol (2.34)

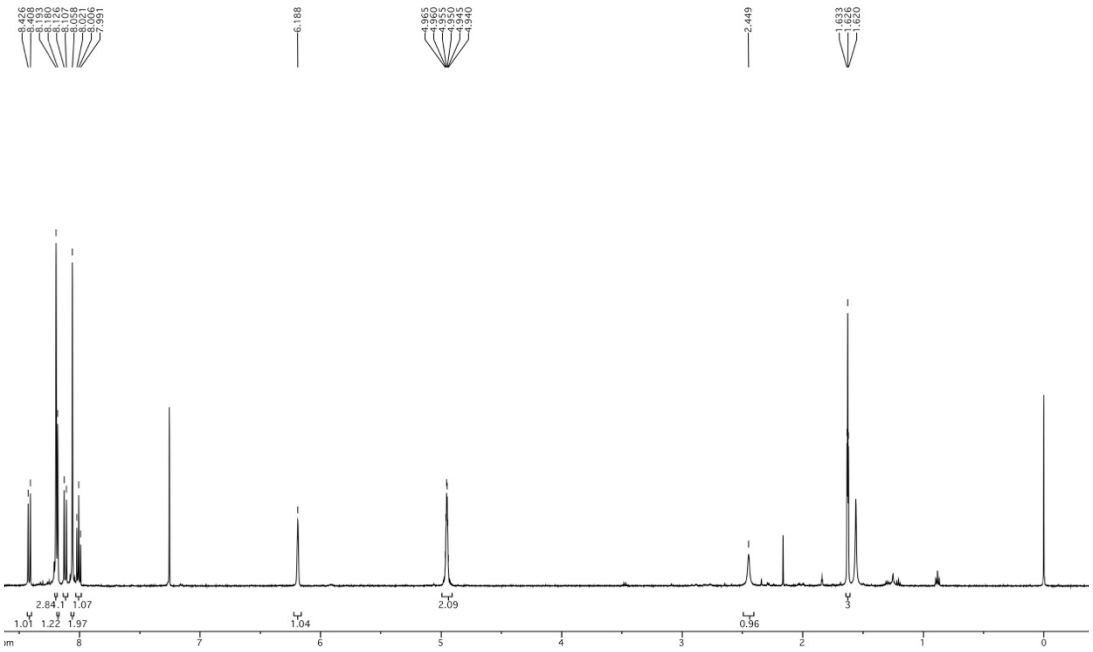


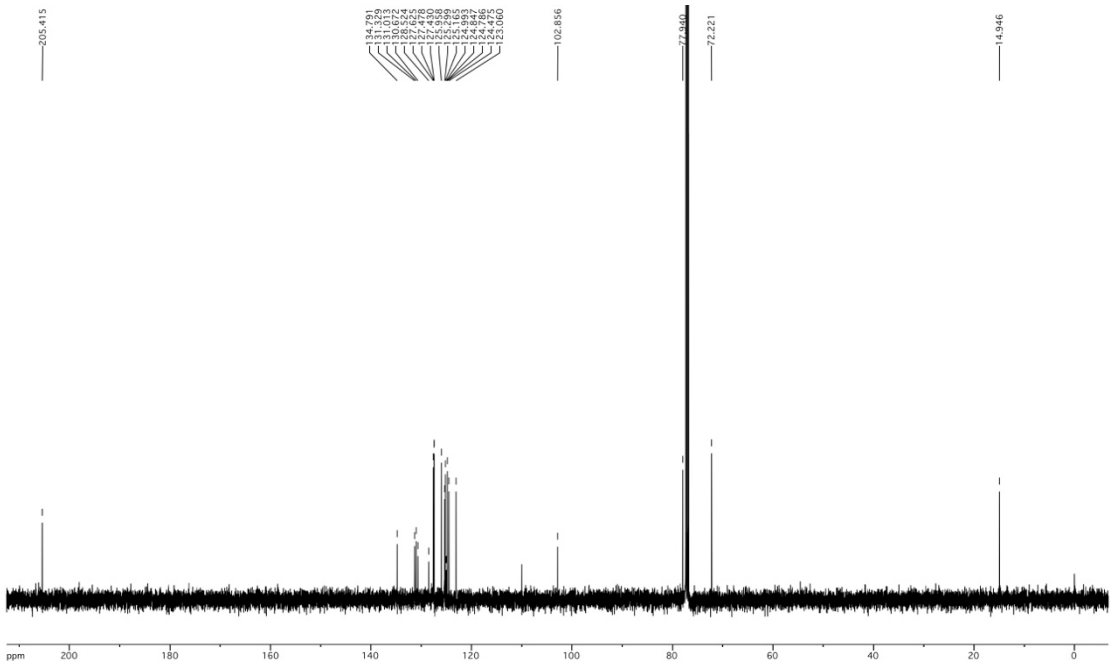


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-(naphthalen-1-yl)buta-2,3-dien-1-ol (2.35)

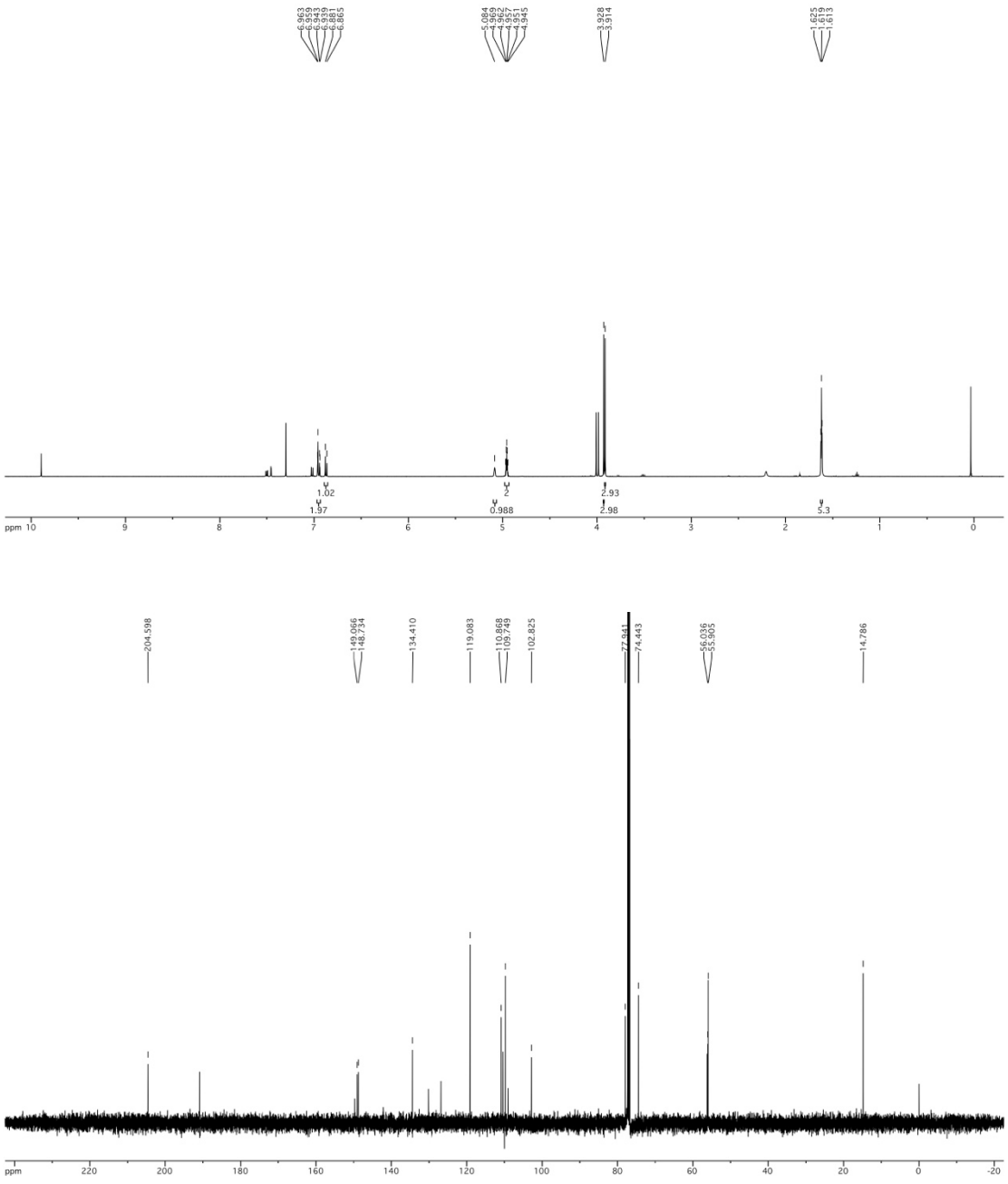


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-Methyl-1-(pyren-1-yl)buta-2,3-dien-1-ol (2.36)



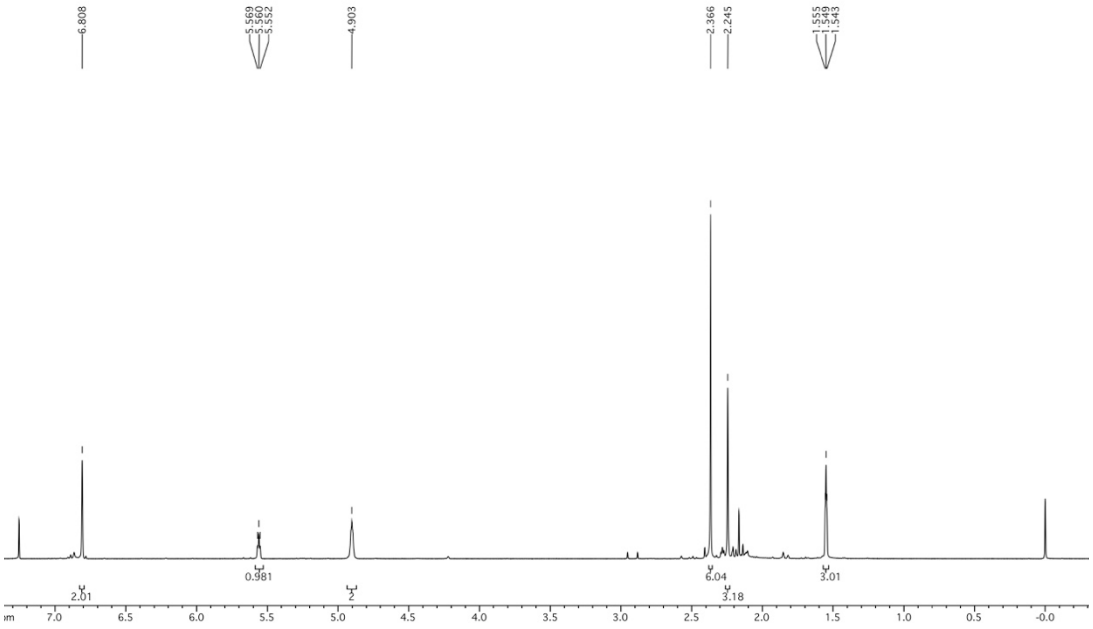


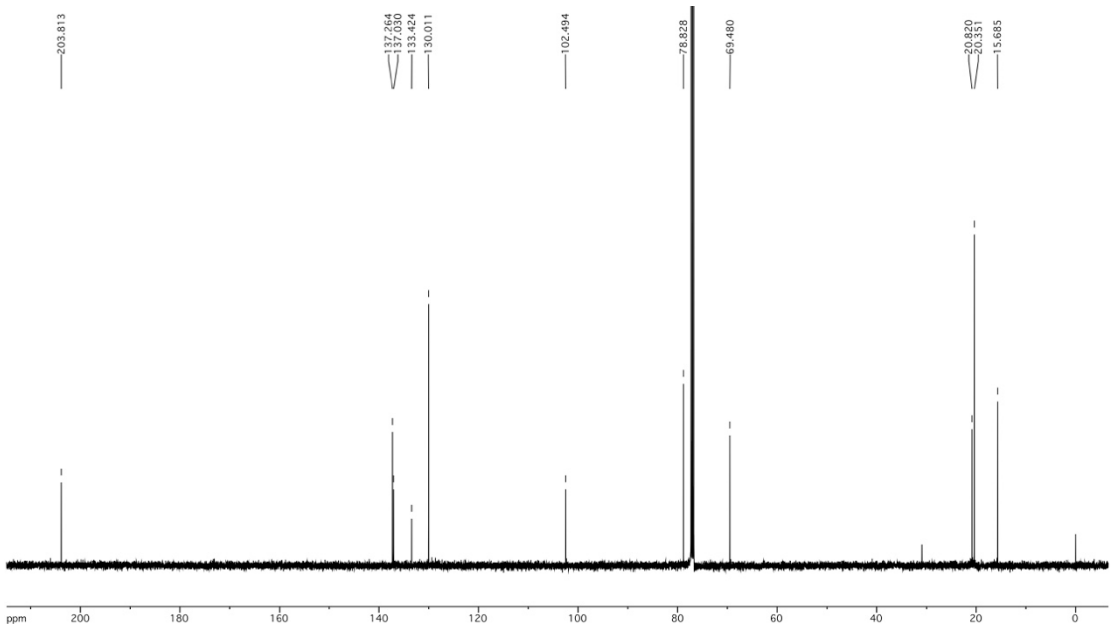
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 1-(3,4-dimethoxyphenyl)-2-methylbuta-2,3-dien-1-ol (2.37)*



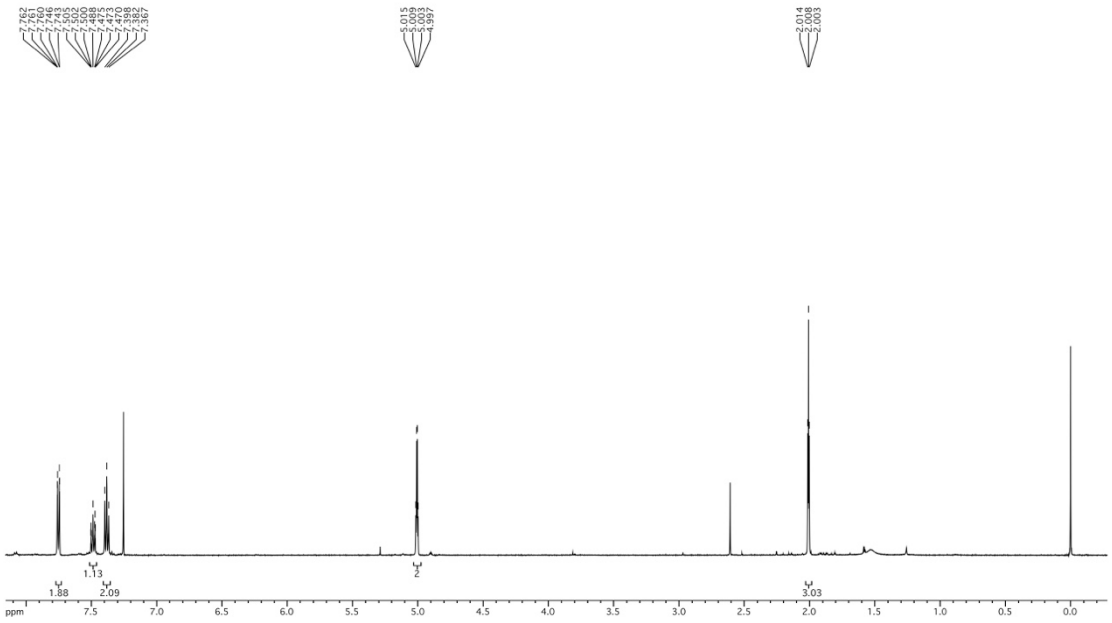
*Mixture of 2.35 and starting aldehyde

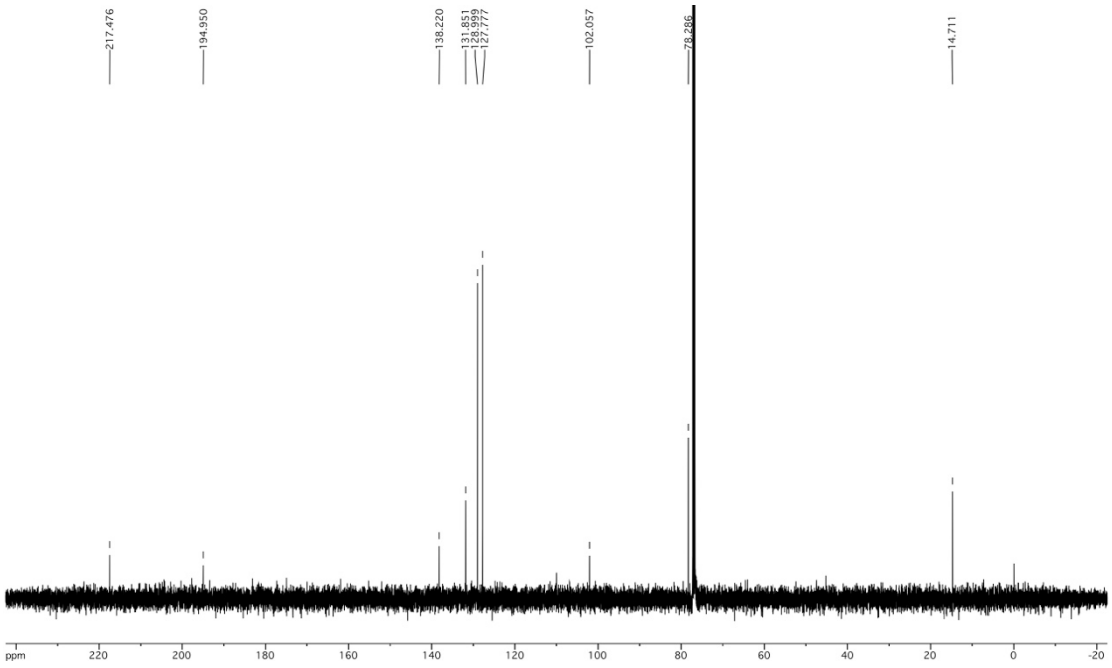
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 1-mesityl-2-methylbuta-2,3-dien-1-ol (2.38)



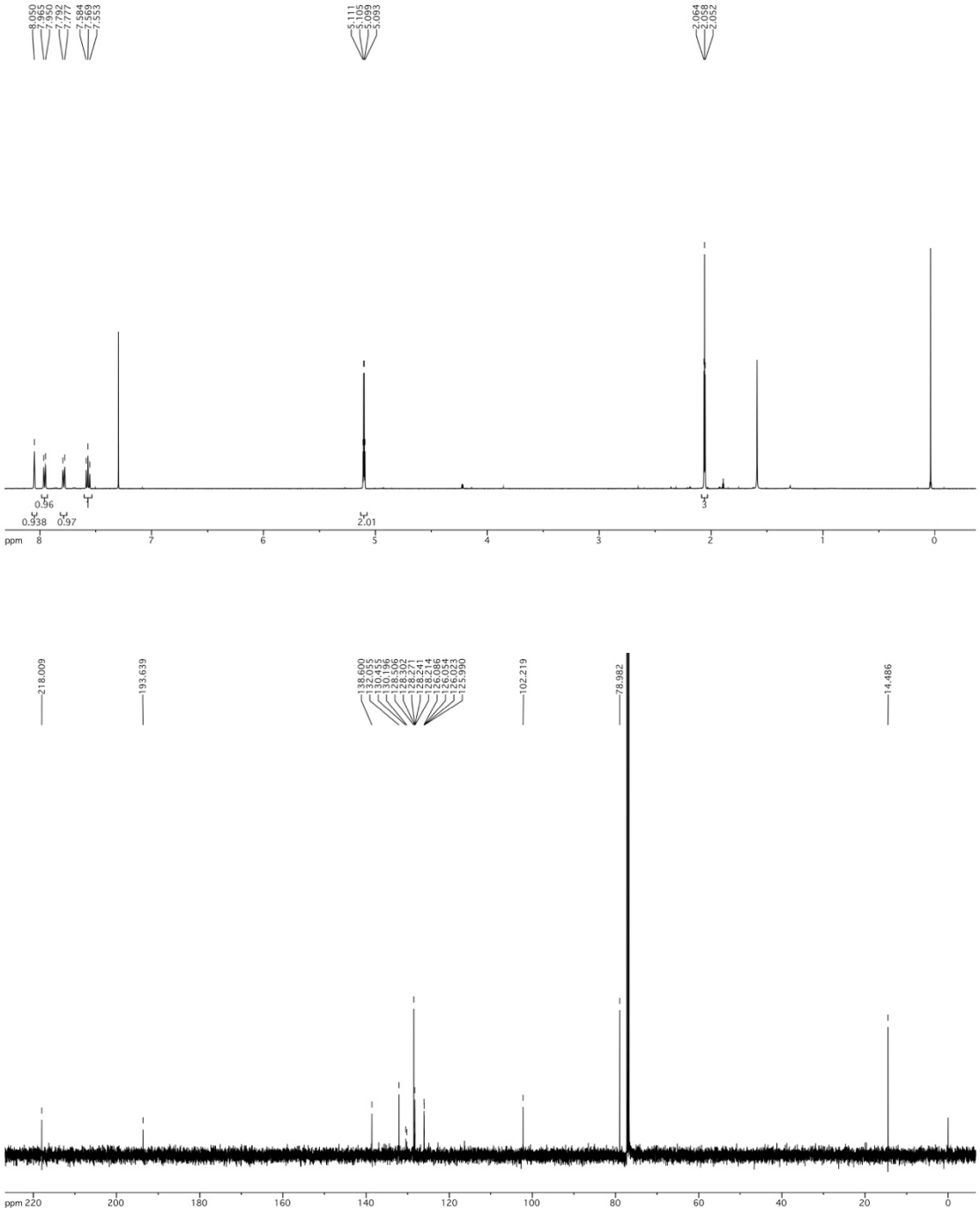


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-phenylbuta-2,3-dien-1-one (2.39)

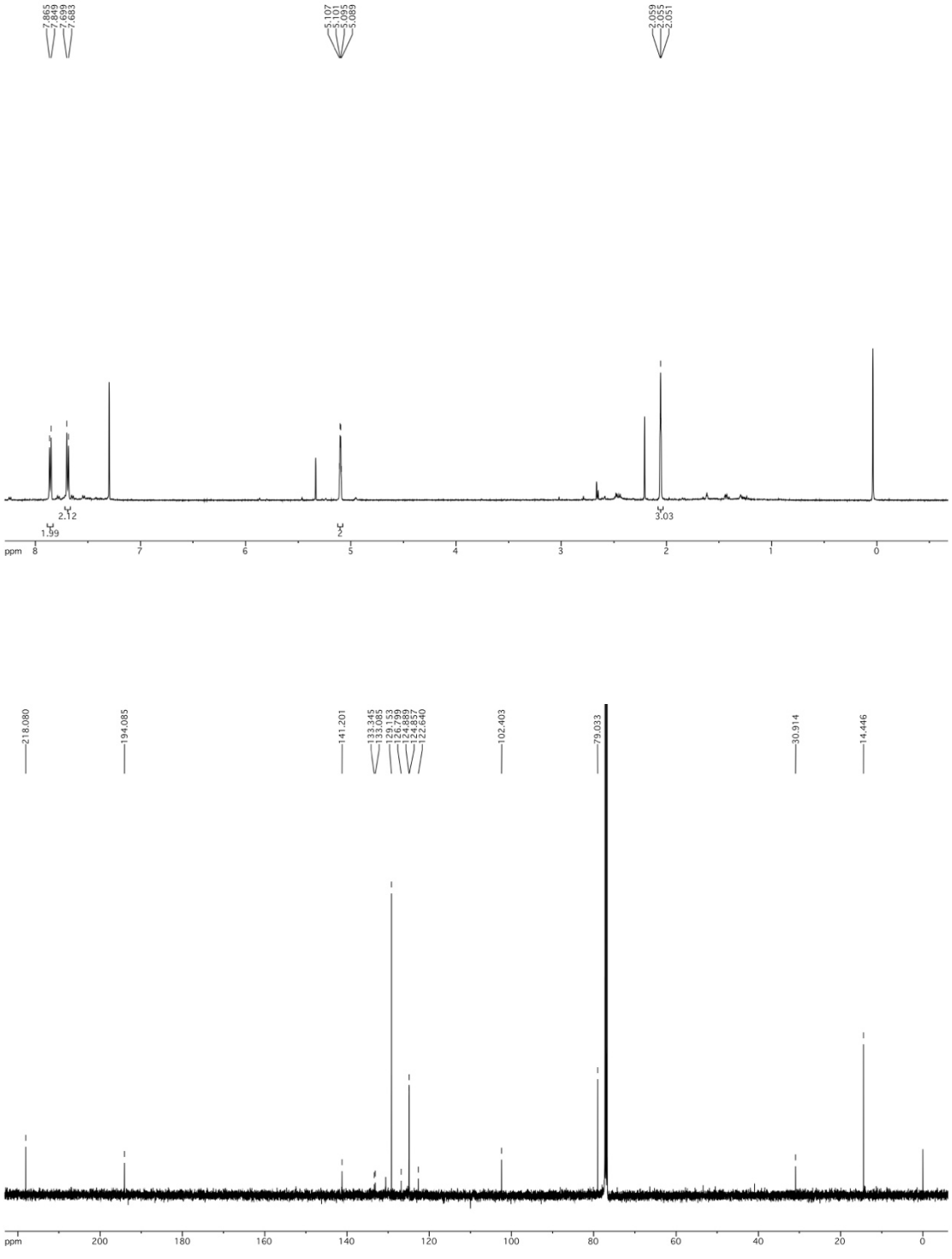




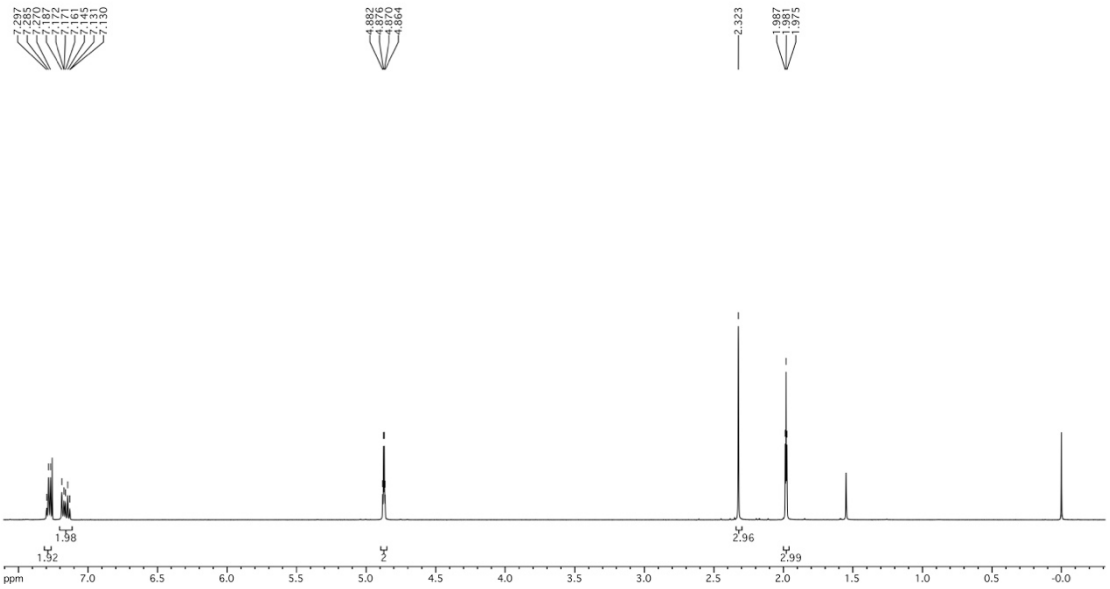
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-(3-(trifluoromethyl)phenyl)buta-2,3-dien-1-one (2.40)

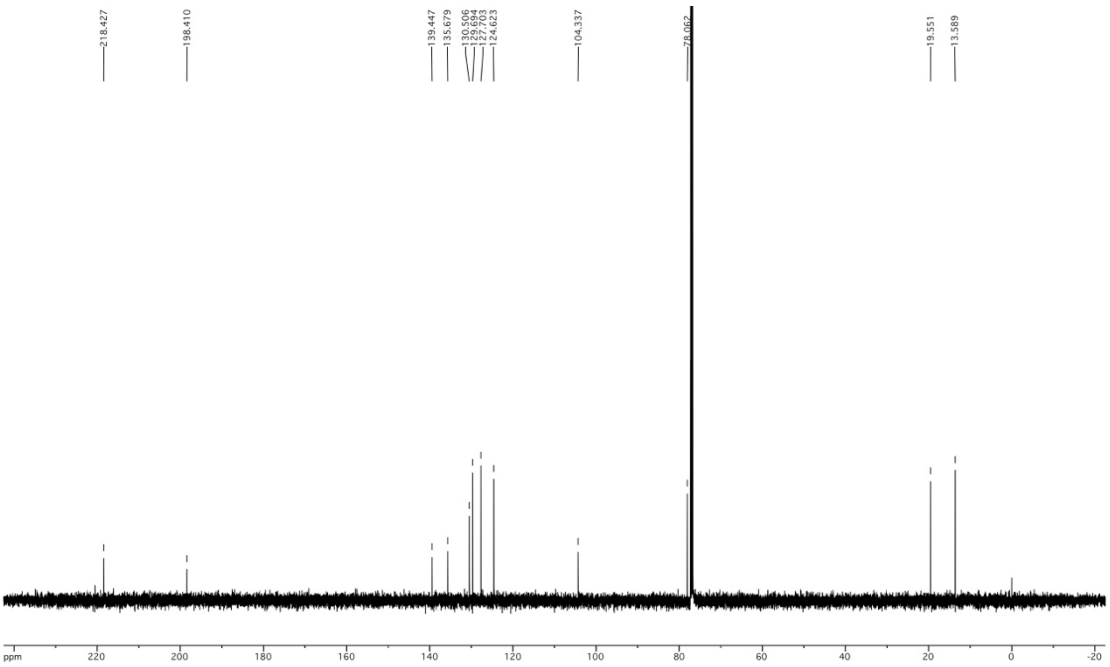


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-(4-(trifluoromethyl)phenyl)buta-2,3-dien-1-one (2.41)

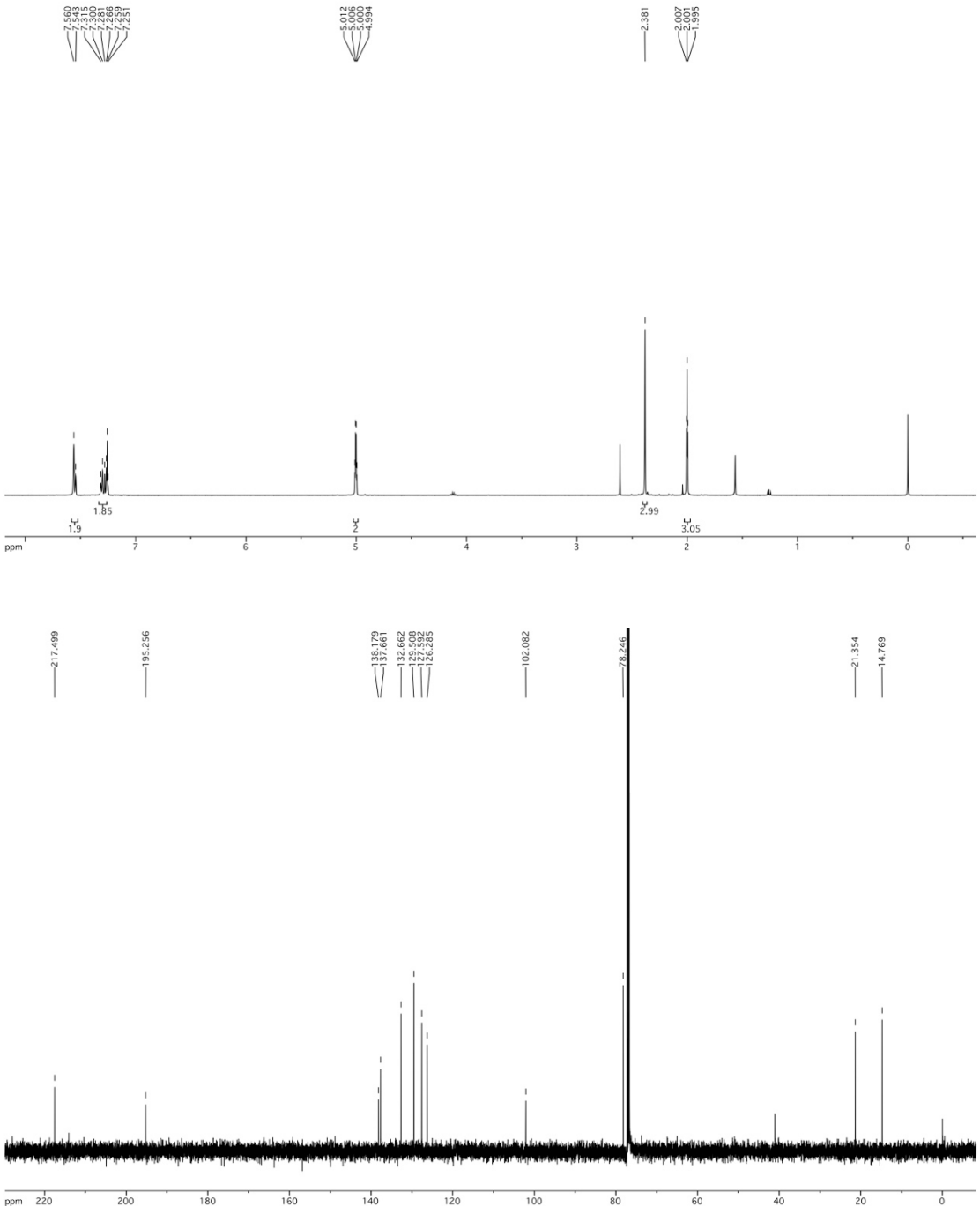


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-*o*-tolylbuta-2,3-dien-1-one (2.42)

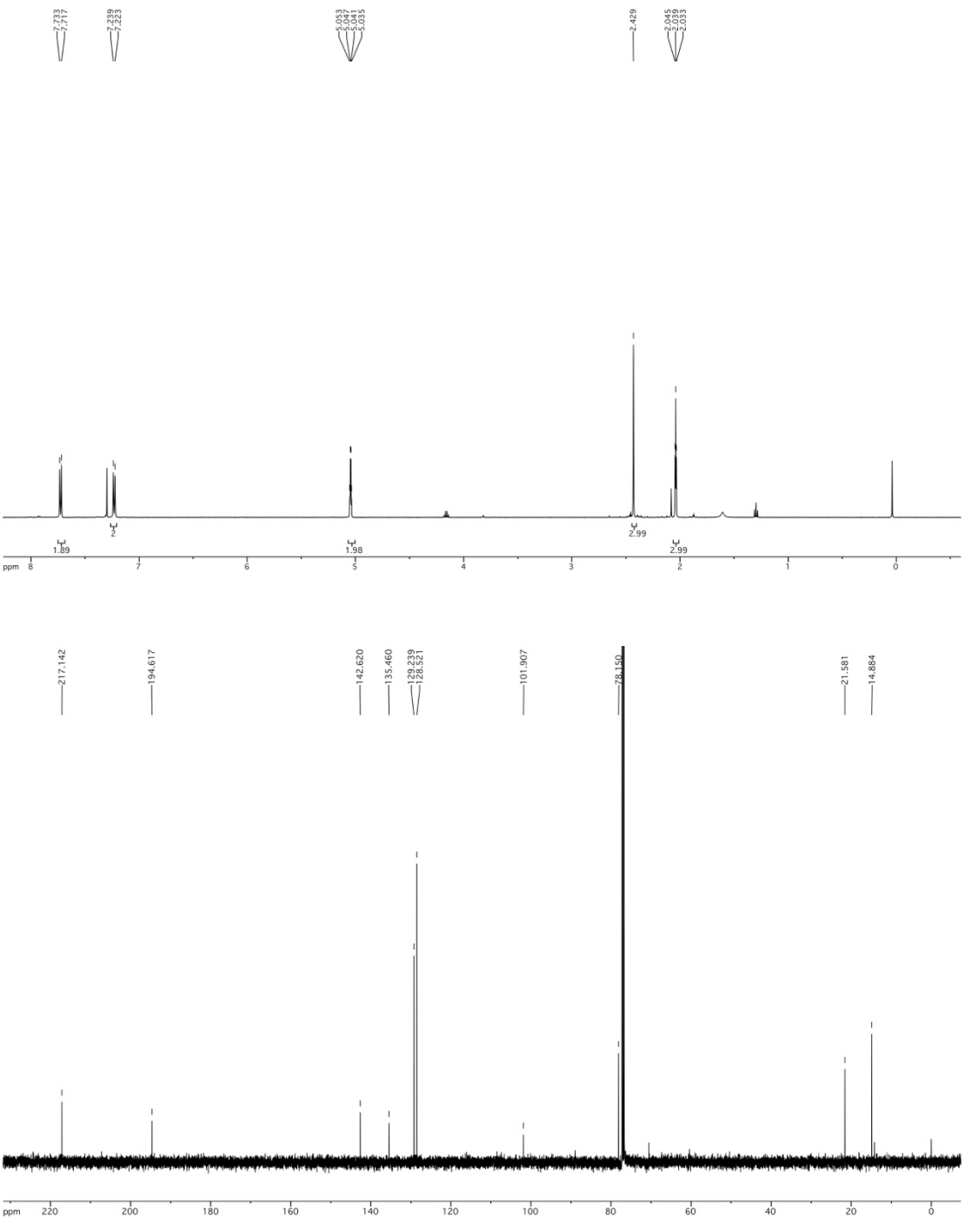




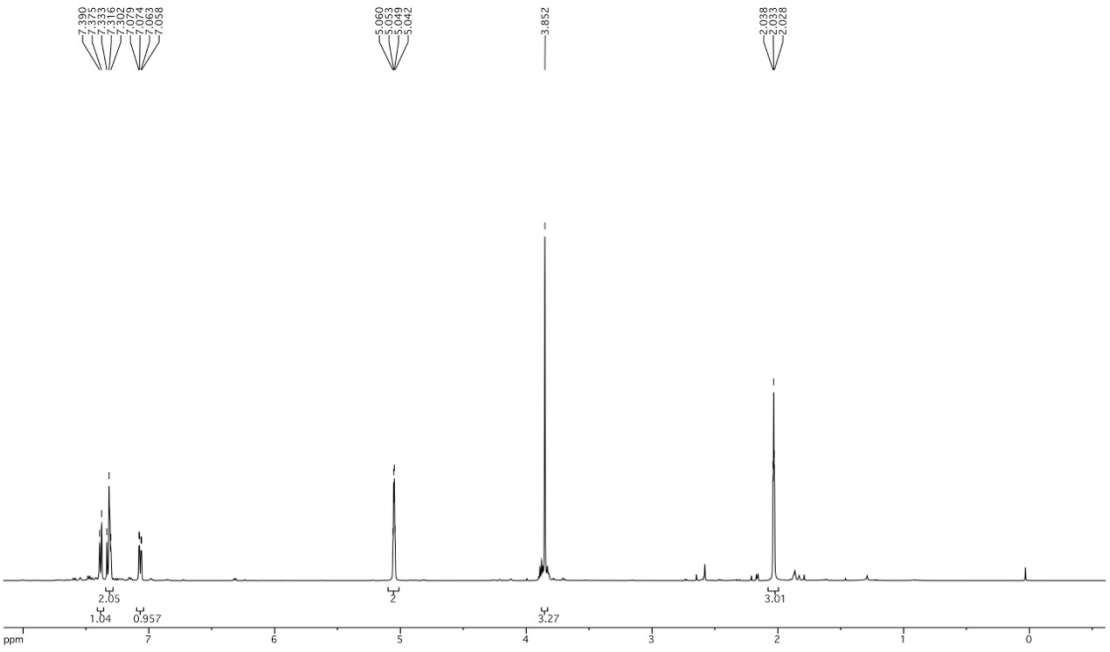
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-*m*-tolylbuta-2,3-dien-1-one (2.43)

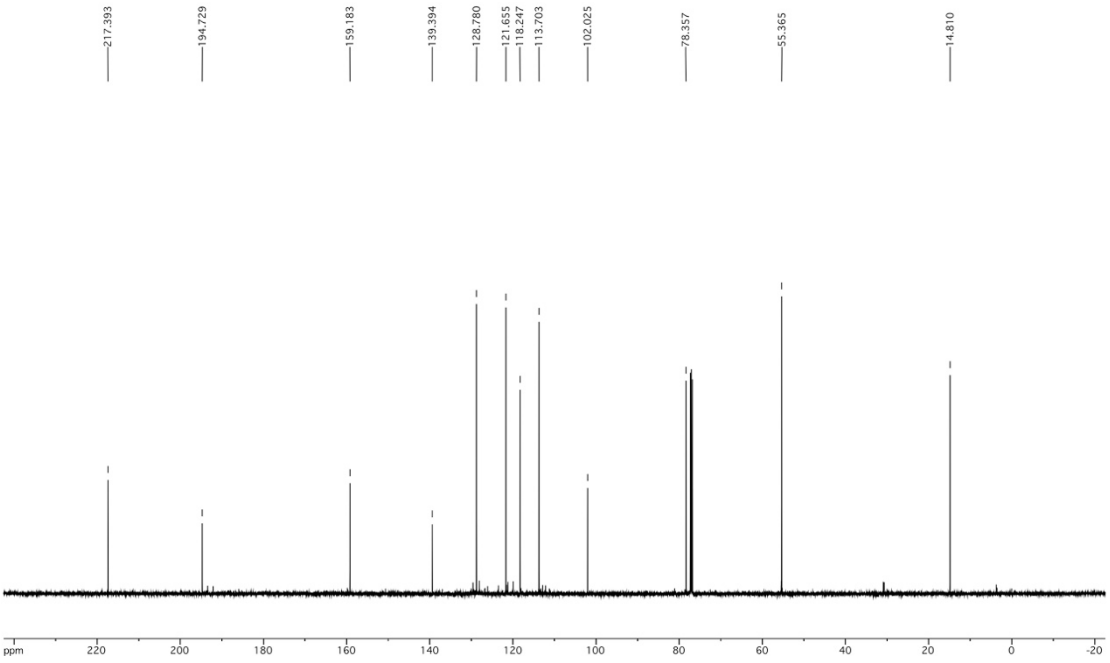


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-*p*-tolylbuta-2,3-dien-1-one (2.44)

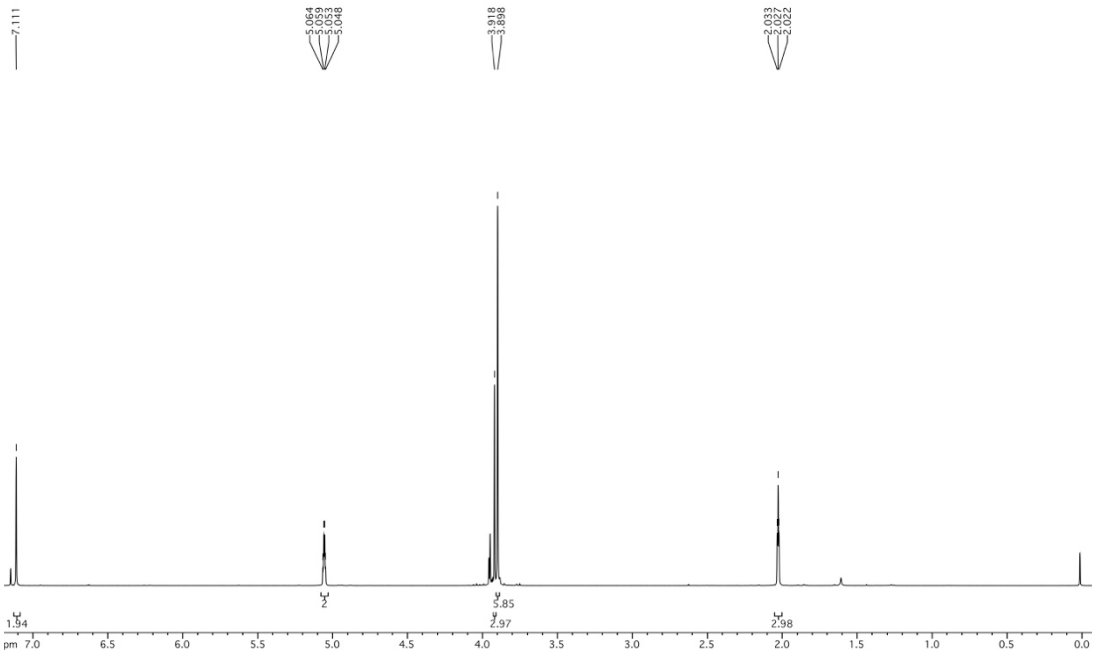


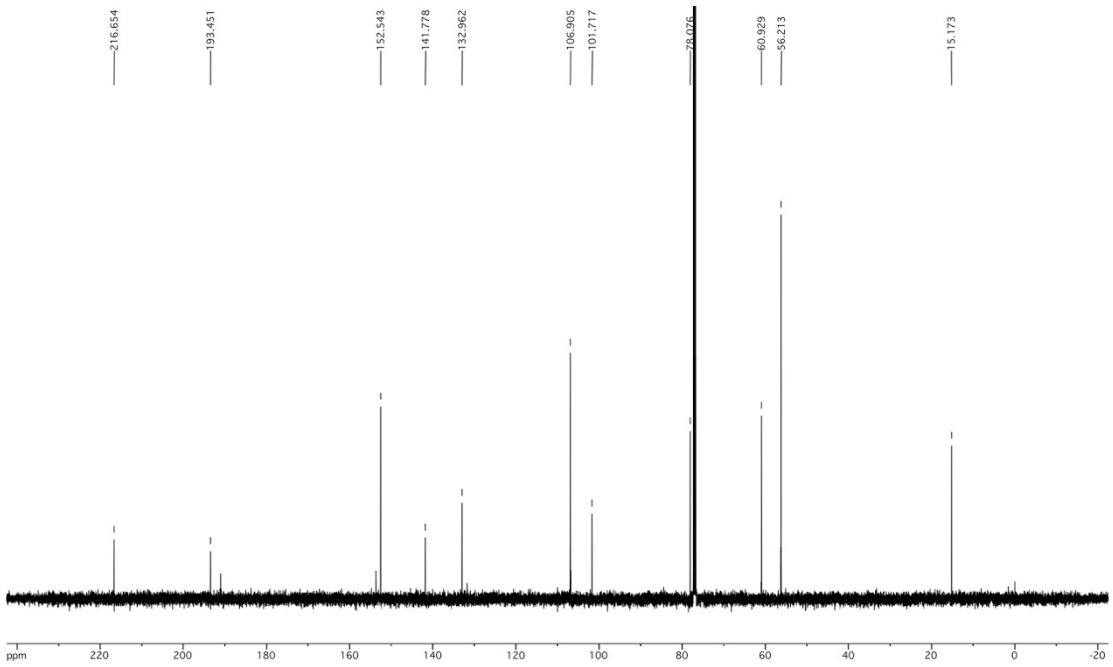
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 1-(3-methoxyphenyl)-2-methylbuta-2,3-dien-1-one (2.45)



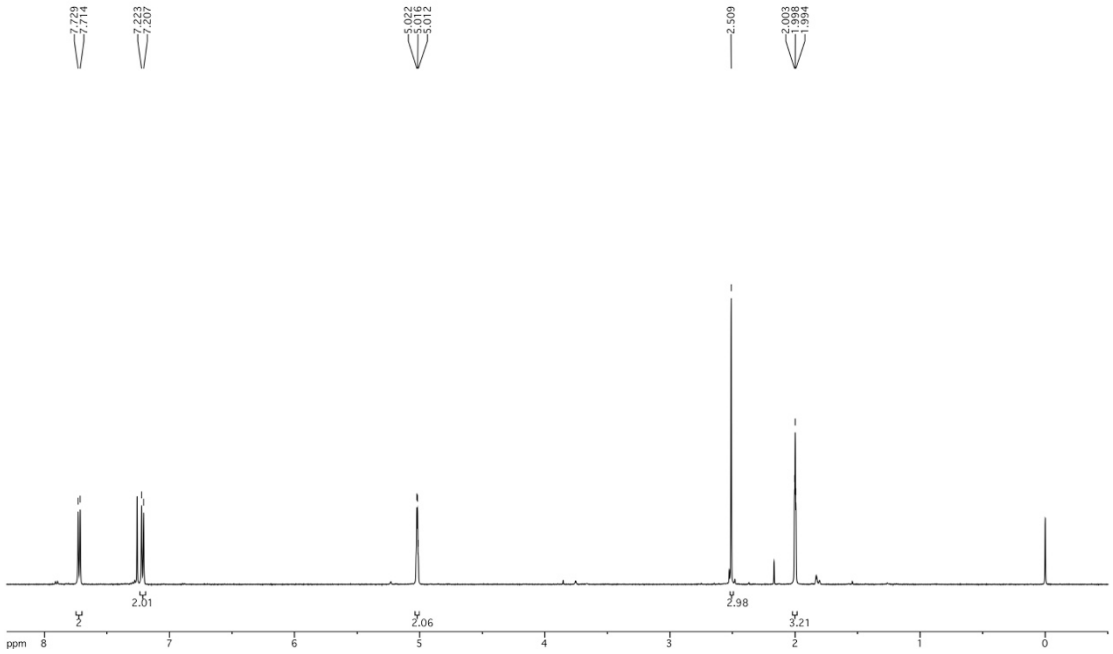


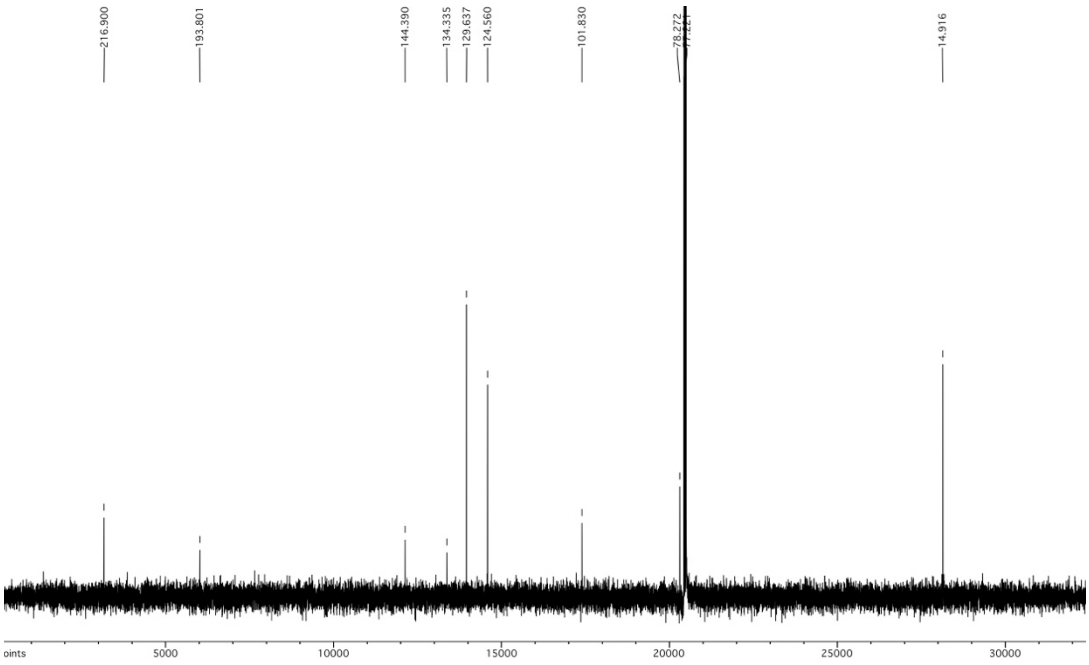
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-(3,4,5-trimethoxyphenyl)buta-2,3-dien-1-one (2.46)



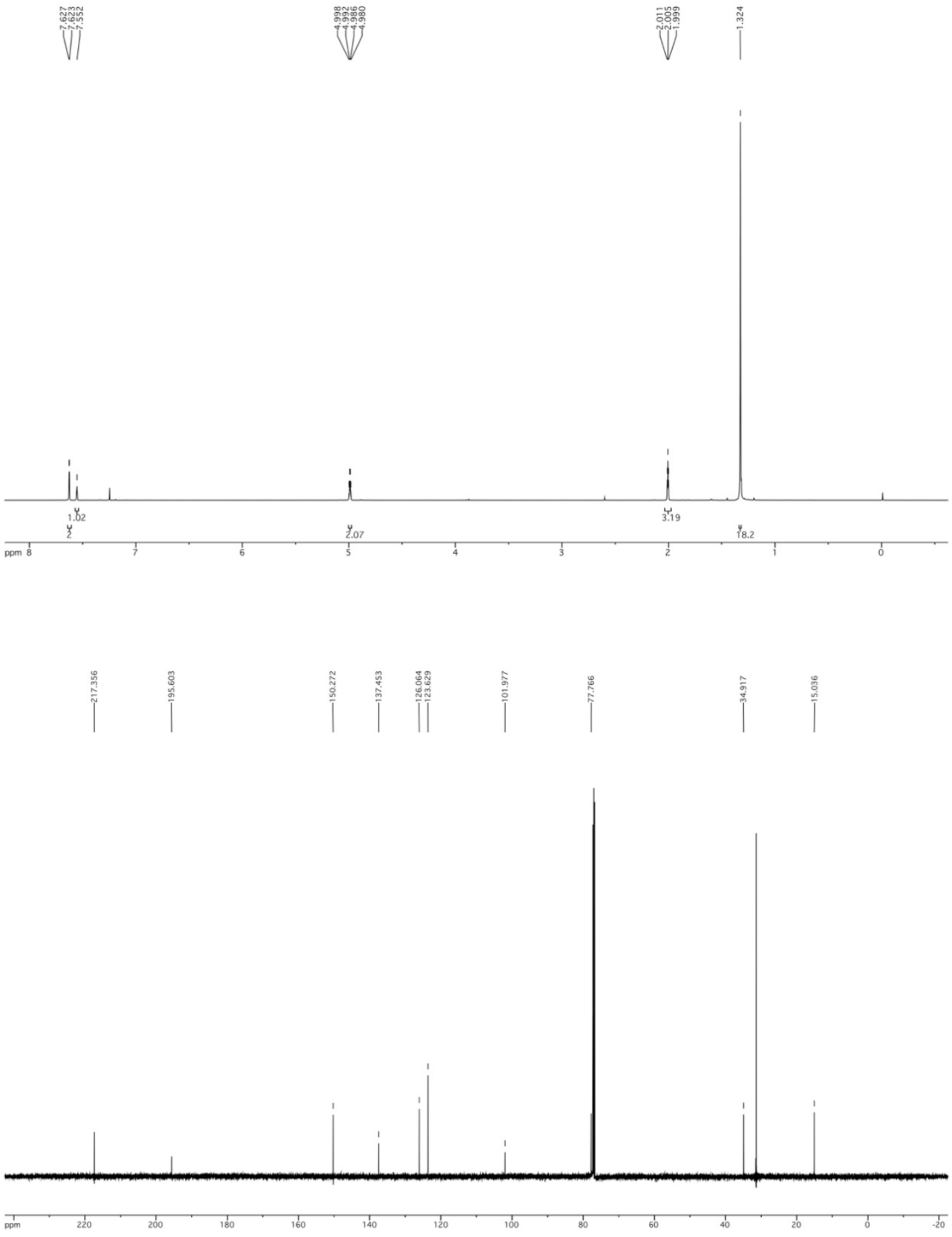


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-(4-(methylthio)phenyl)buta-2,3-dien-1-one (2.47)

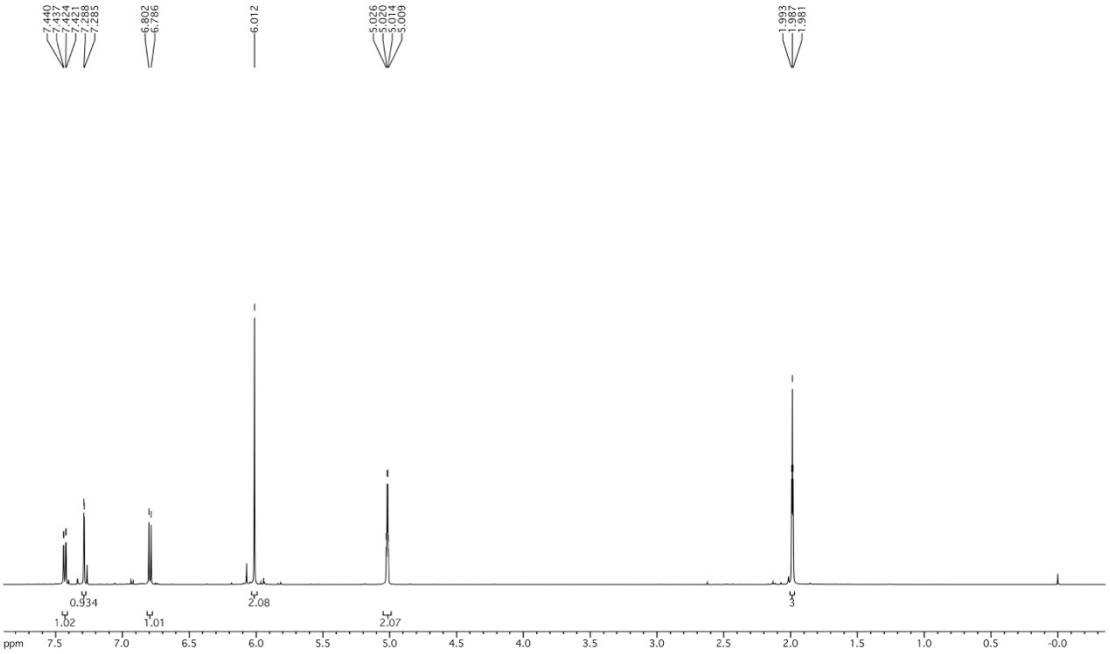


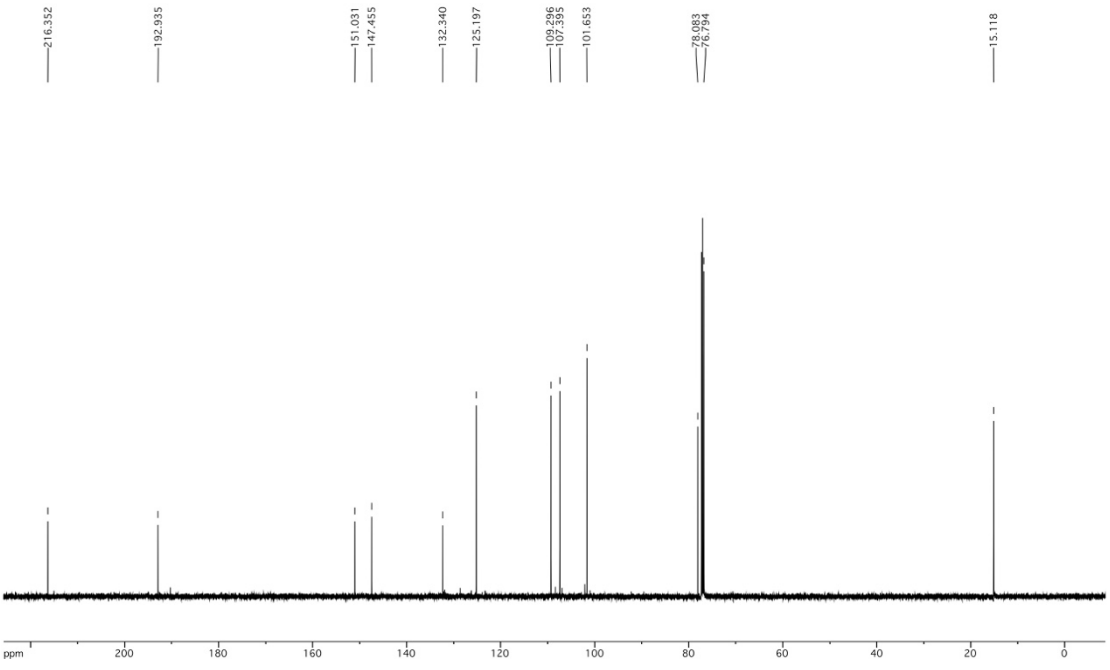


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 1-(3,5-di-*tert*-butylphenyl)-2-methylbuta-2,3-dien-1-one (2.48)

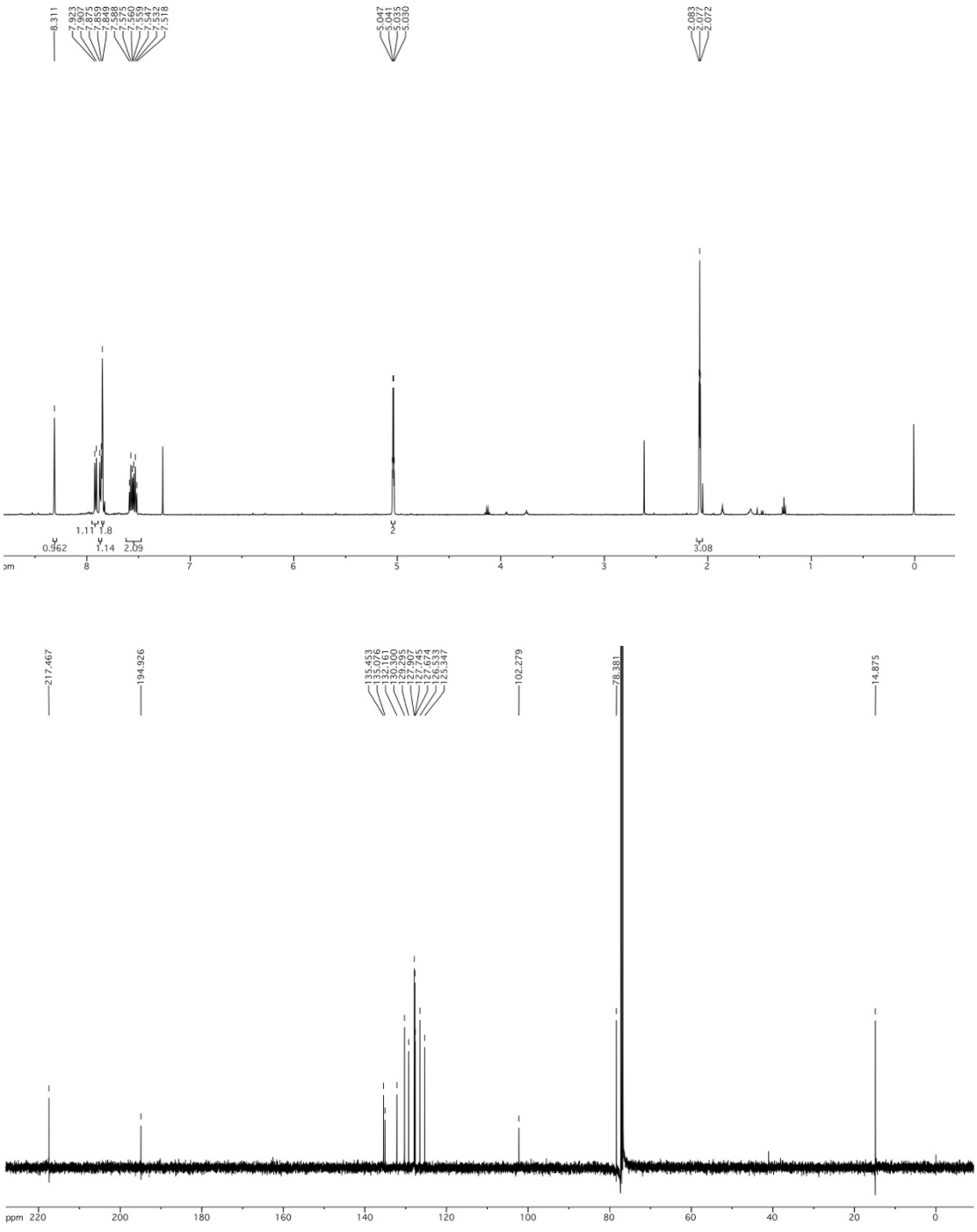


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 1-(benzo[*d*][1,3]dioxol-5-yl)-2-methylbuta-2,3-dien-1-one (2.49)

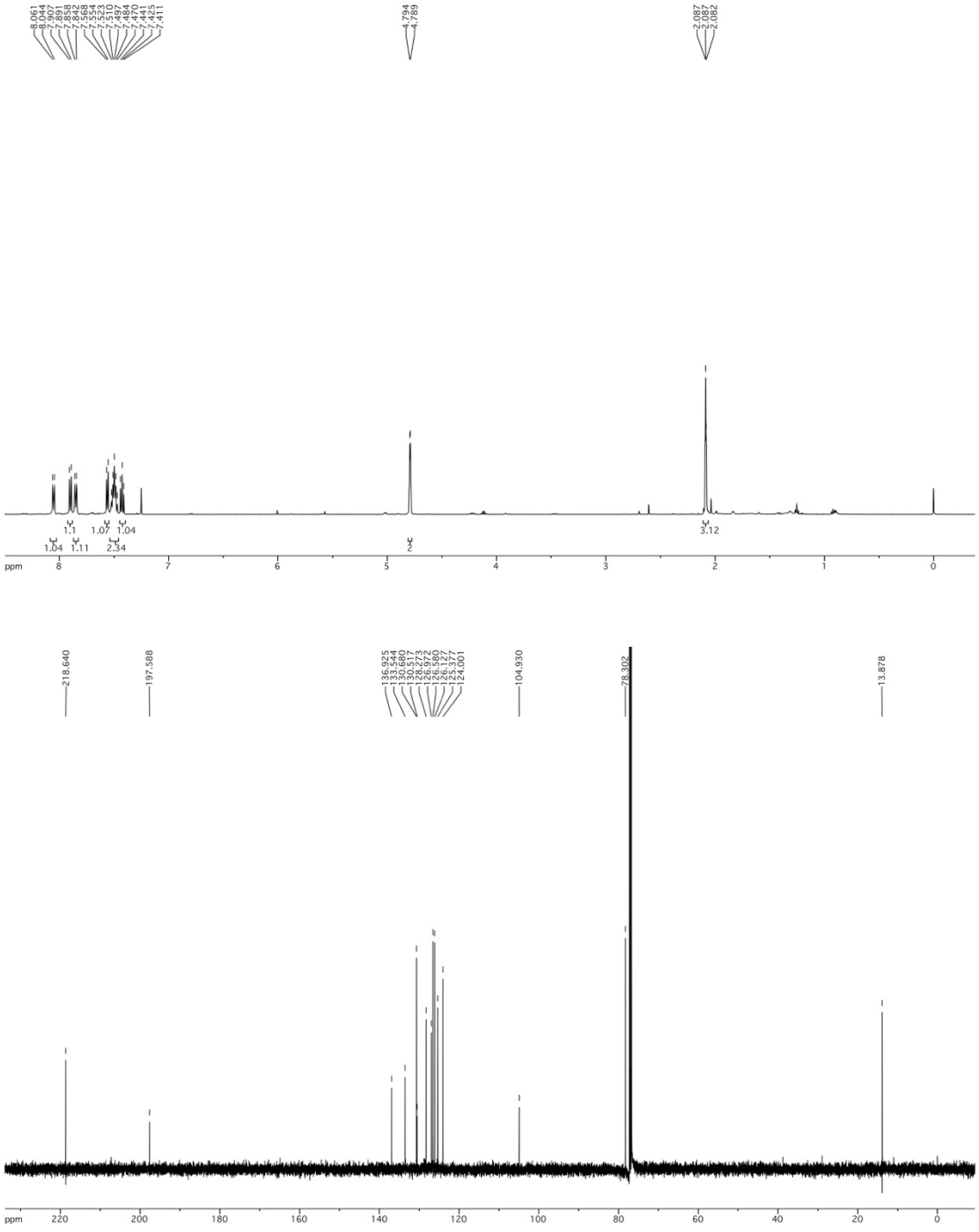




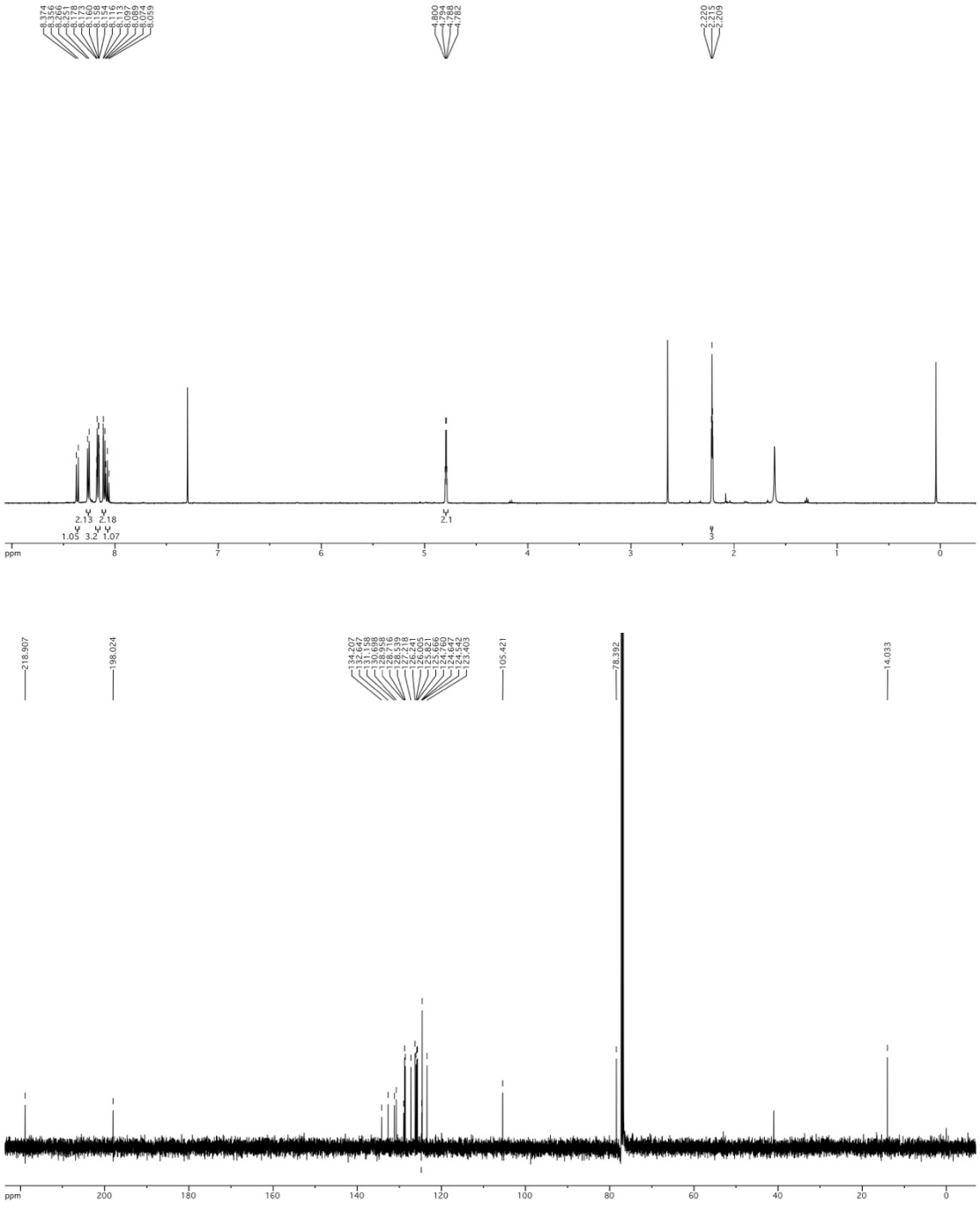
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-(naphthalen-2-yl)buta-2,3-dien-1-one (2.50)



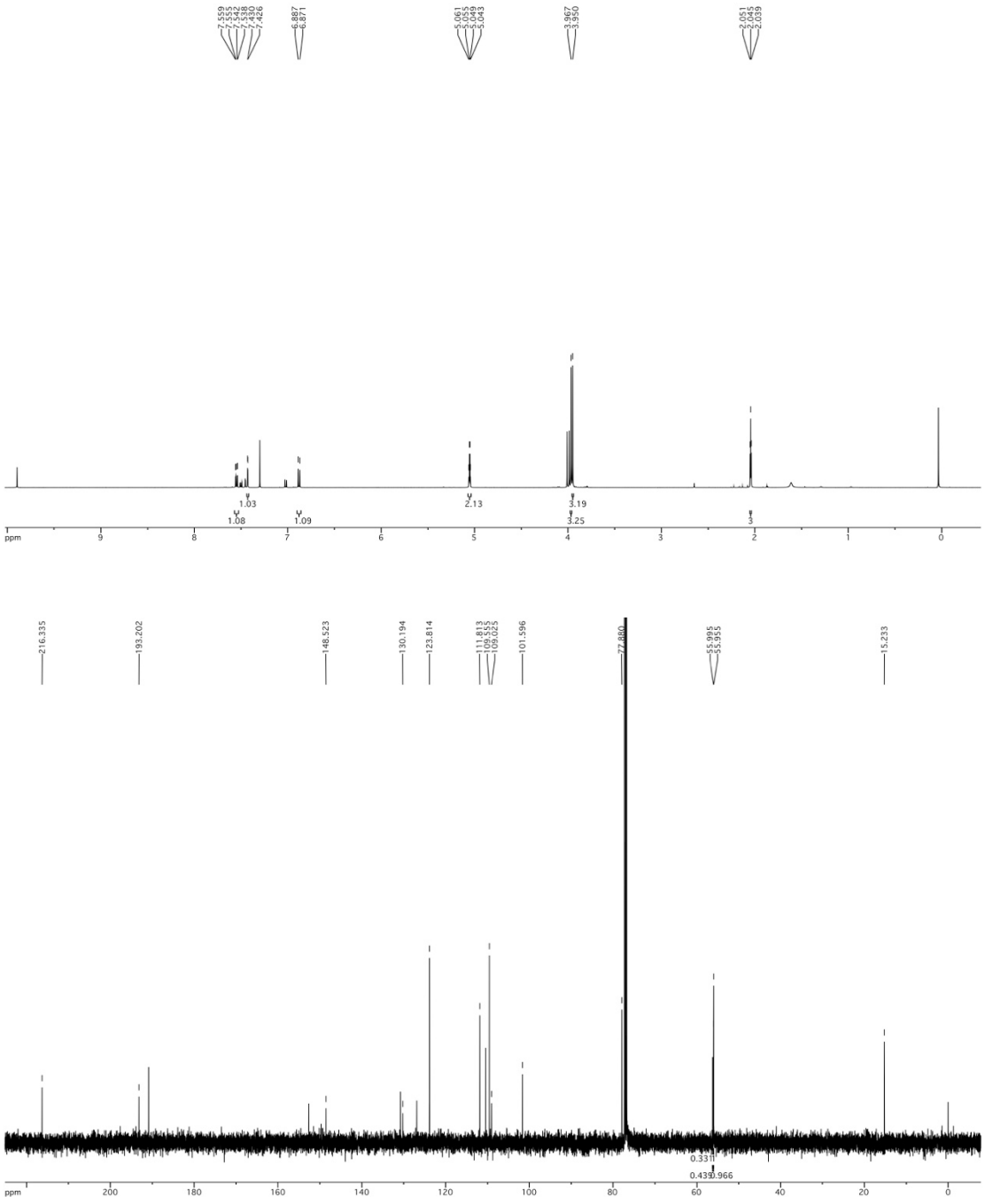
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-1-(naphthalen-1-yl)buta-2,3-dien-1-one (2.51)



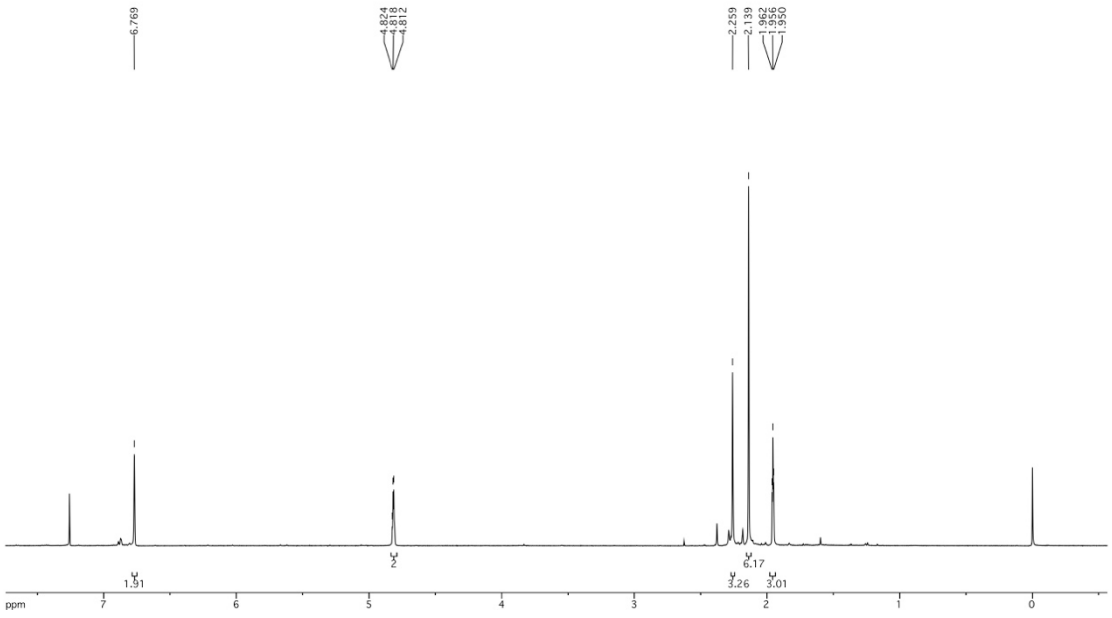
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-Methyl-1-(pyren-1-yl)buta-2,3-dien-1-one (2.52)

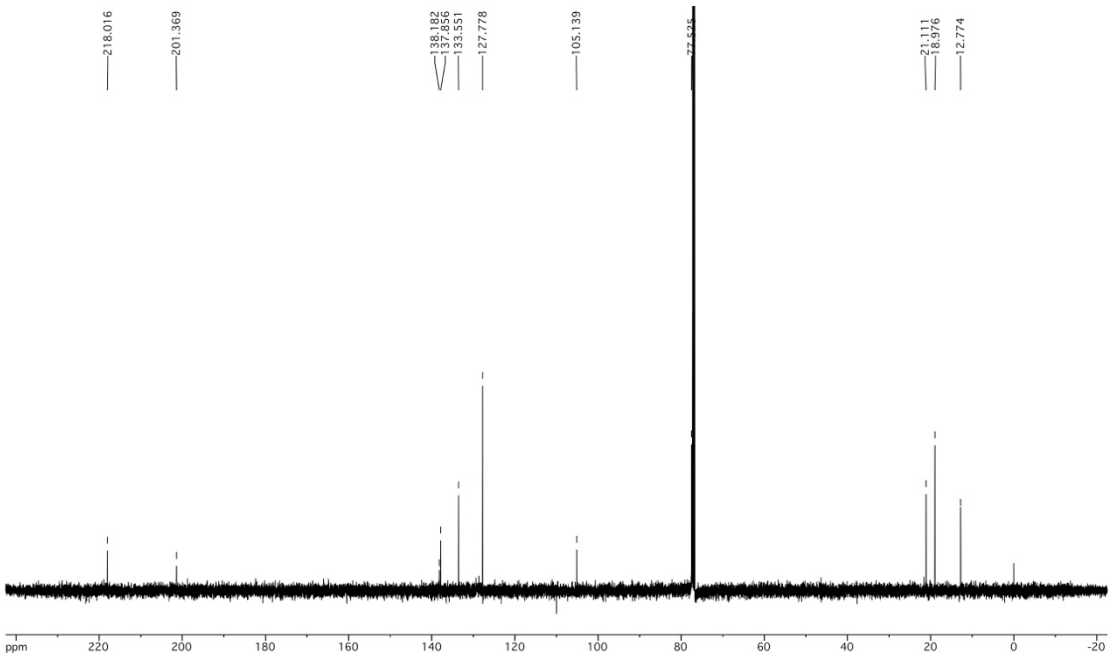


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 1-(3,4-dimethoxyphenyl)-2-methylbuta-2,3-dien-1-one (2.53)

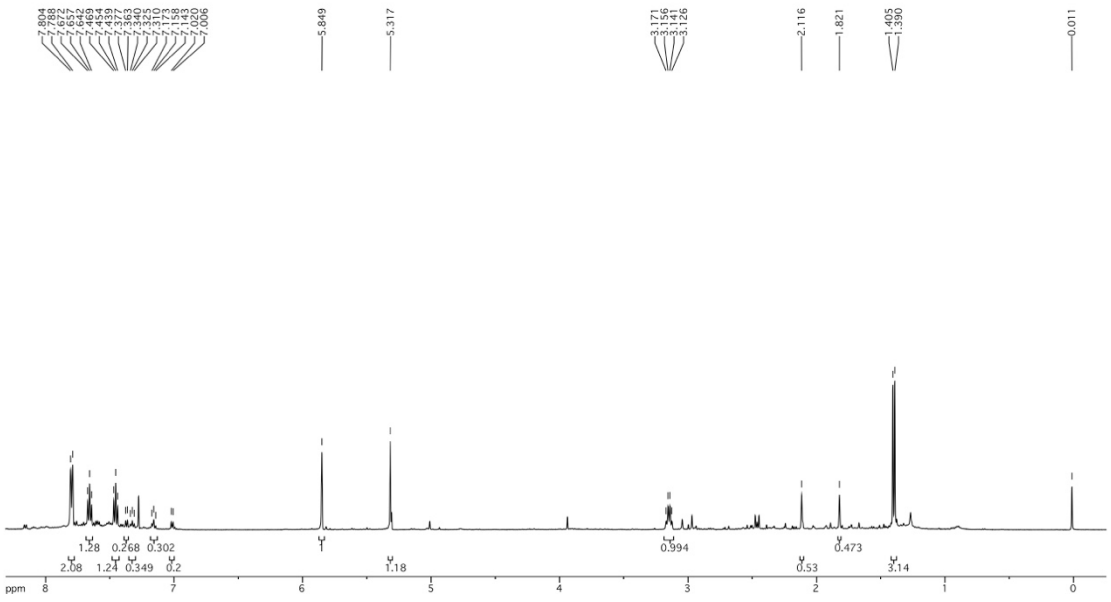


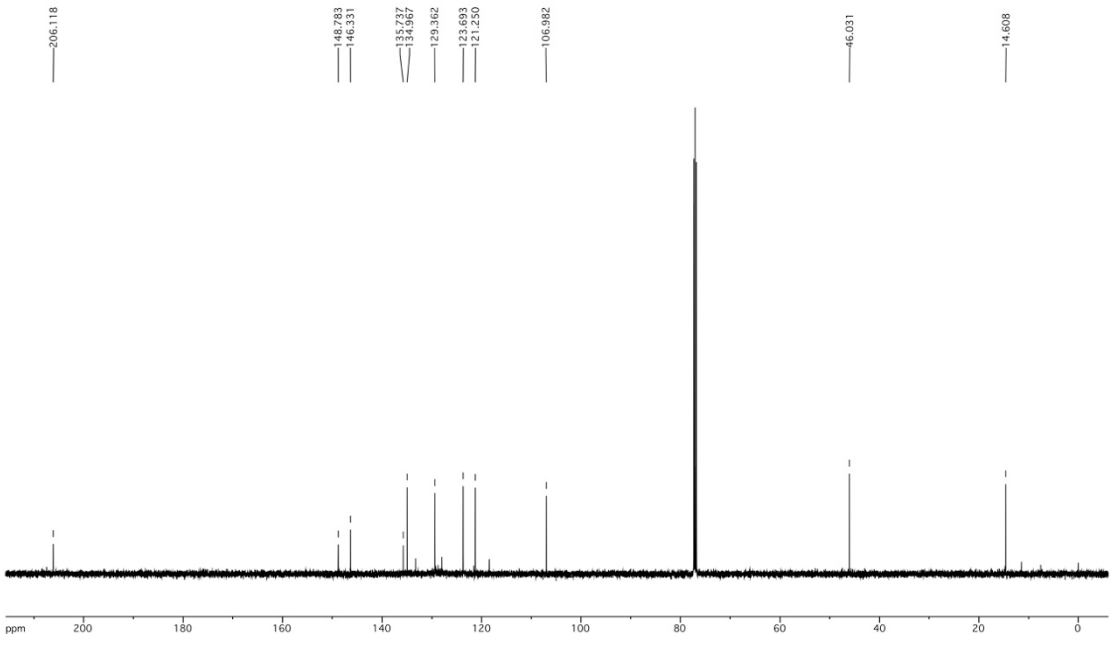
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 1-mesityl-2-methylbuta-2,3-dien-1-one (2.54)



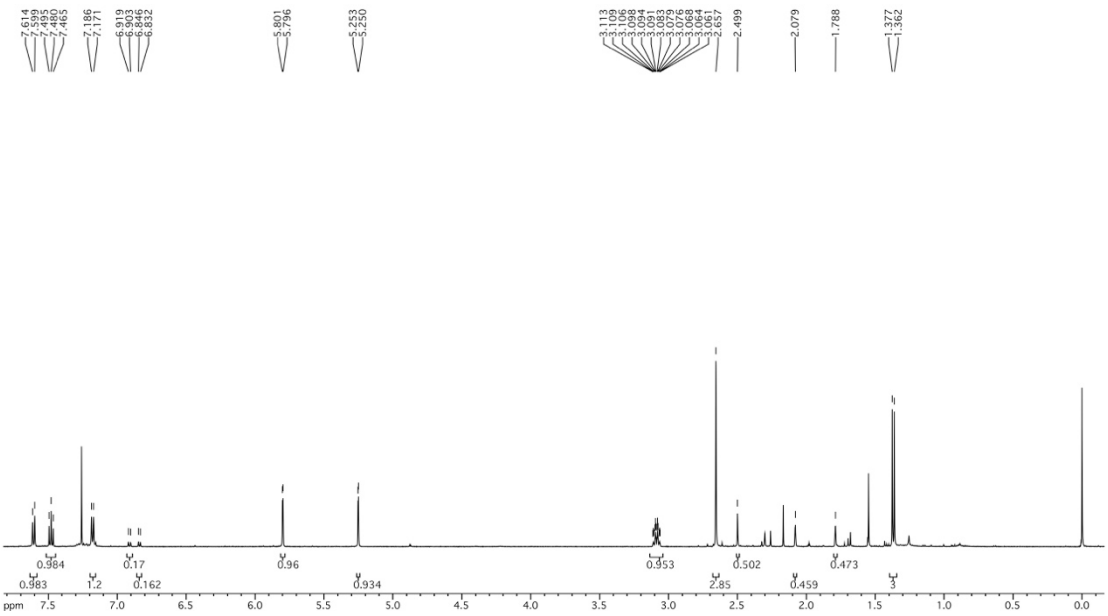


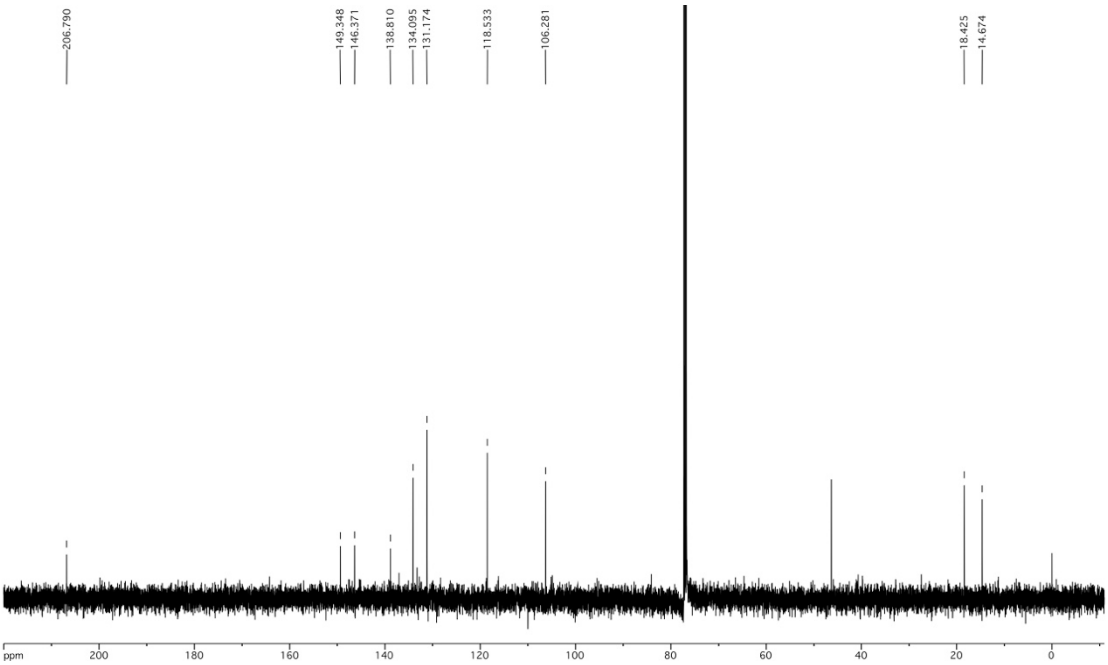
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-methyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.57a) and 2,3-dimethyl-1*H*-inden-1-one (2.57b)



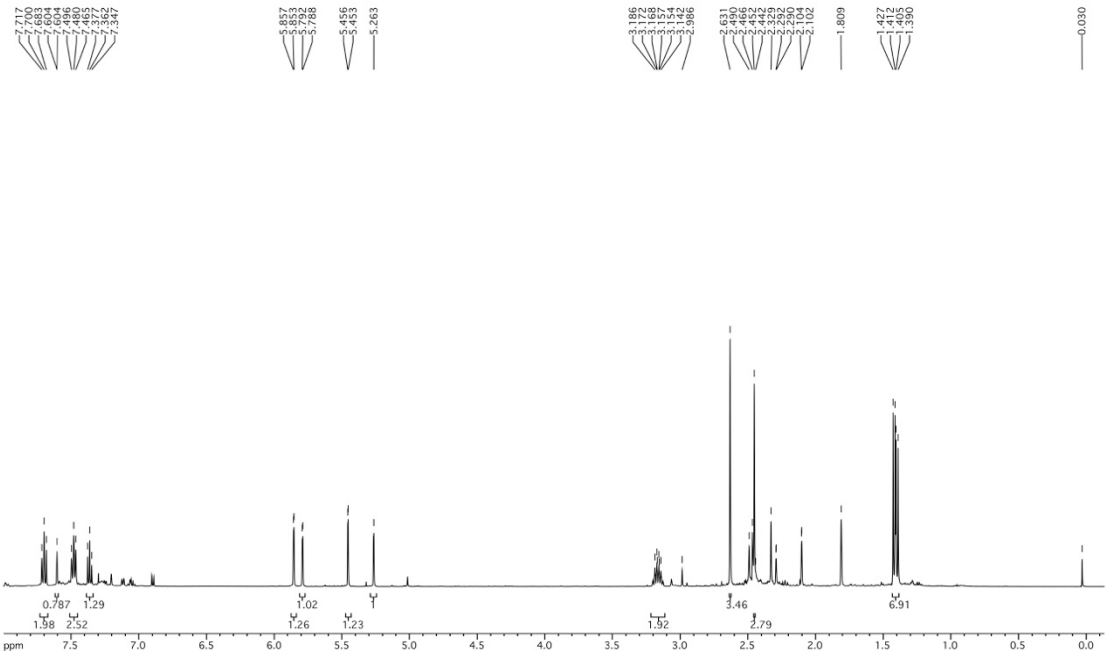


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2,7-dimethyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.60a) and 2,3,7-trimethyl-1*H*-inden-1-one (2.60b)

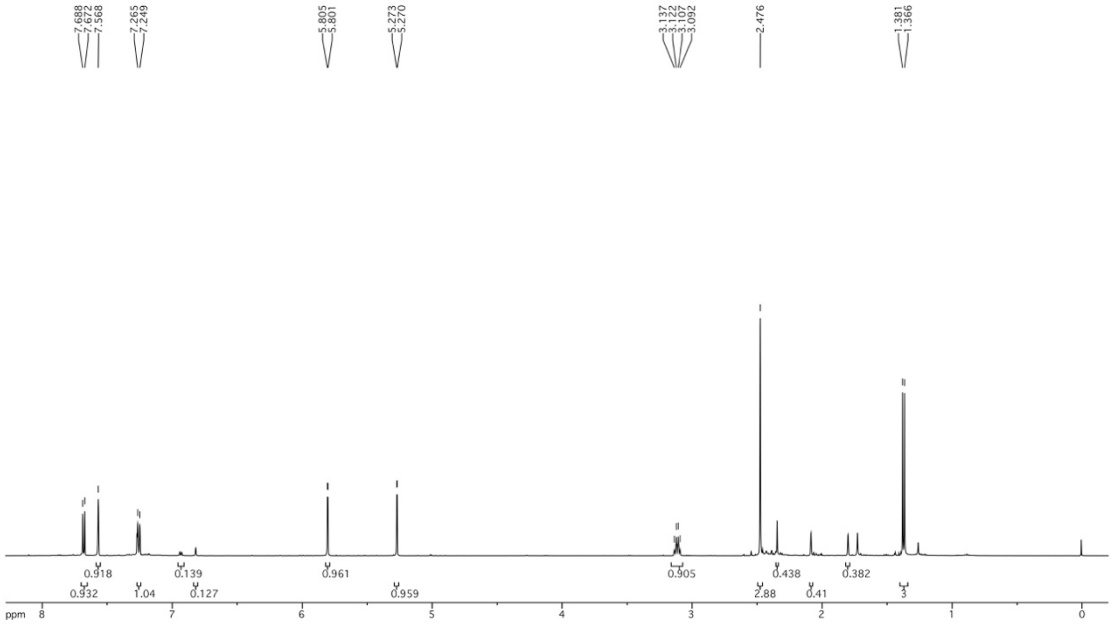


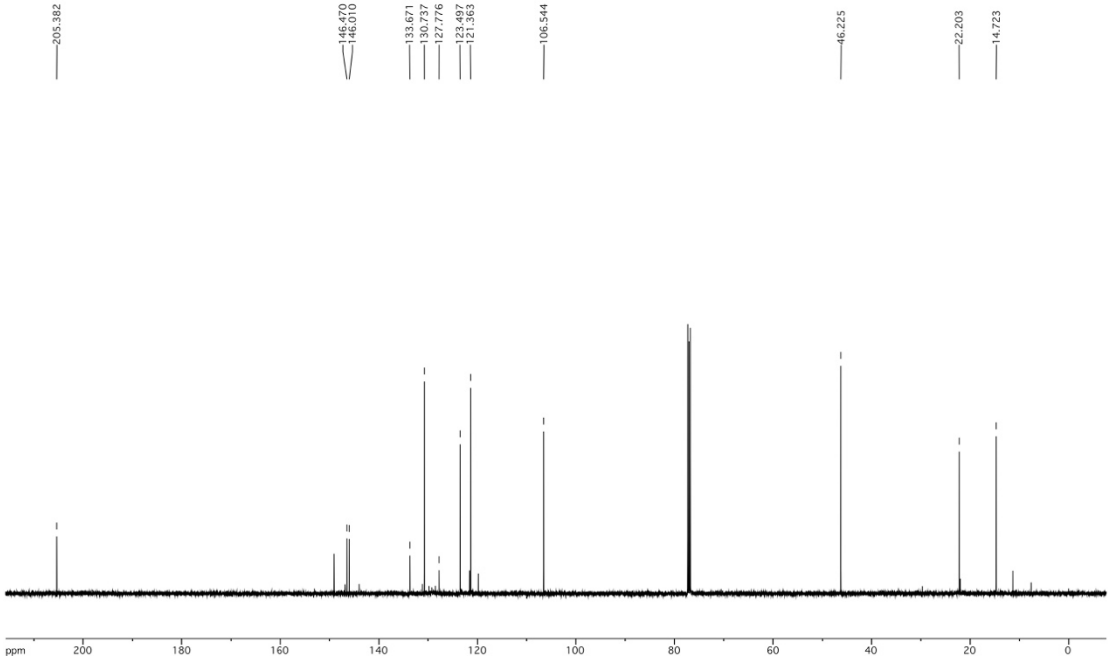


^{1}H NMR (500 MHz, $CDCl_3$) for 2,7-dimethyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.61a) and 2,3,7-trimethyl-1*H*-inden-1-one (2.61b)

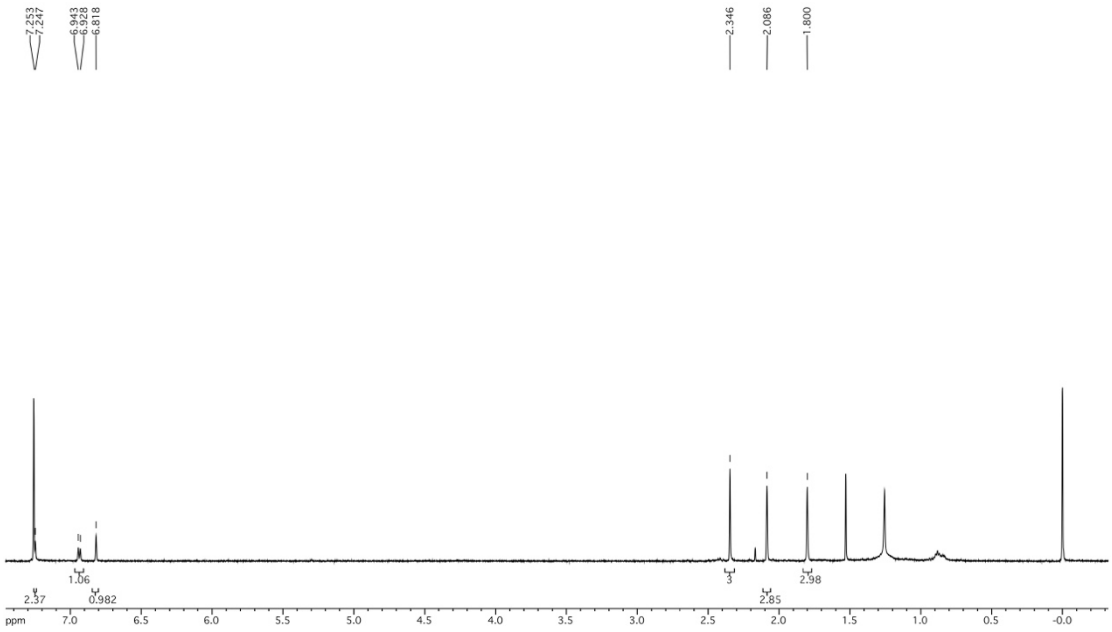


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2,5-dimethyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.62a) and 2,3,5-trimethyl-1*H*-inden-1-one (2.62b)

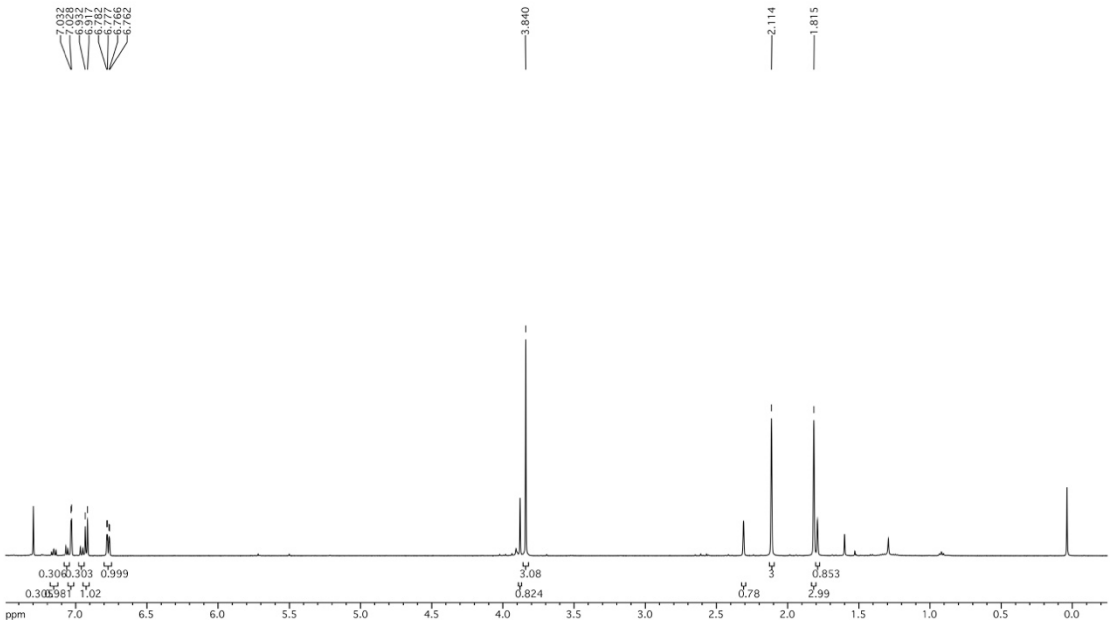


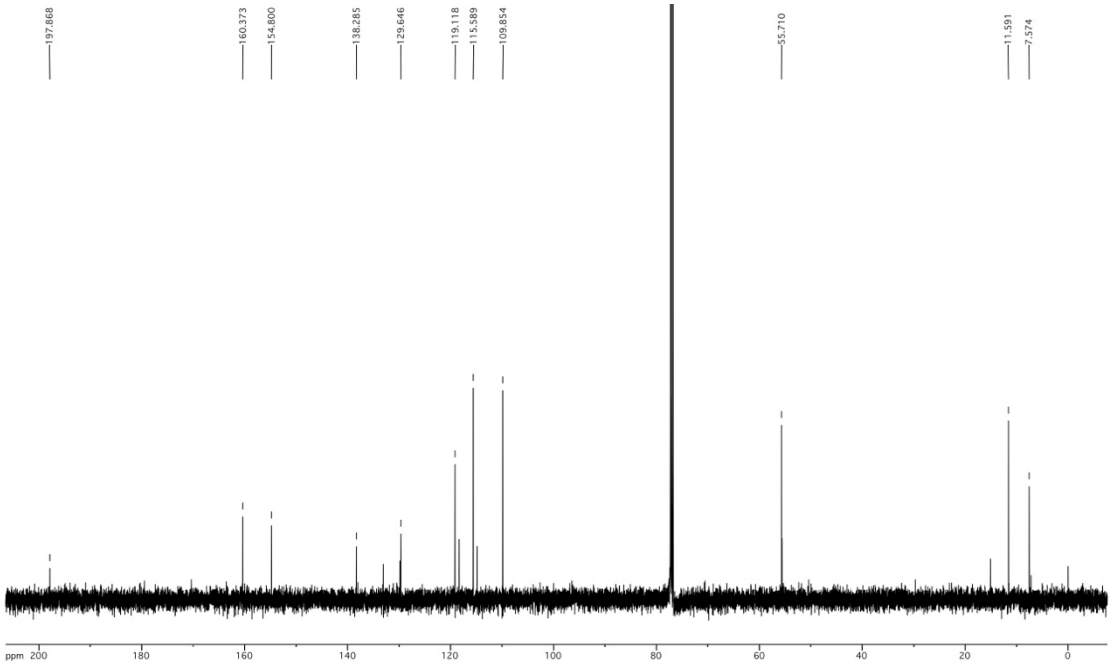


^{1}H NMR (500 MHz, $CDCl_3$) for 2,3,5-trimethyl-1*H*-inden-1-one (2.62b)

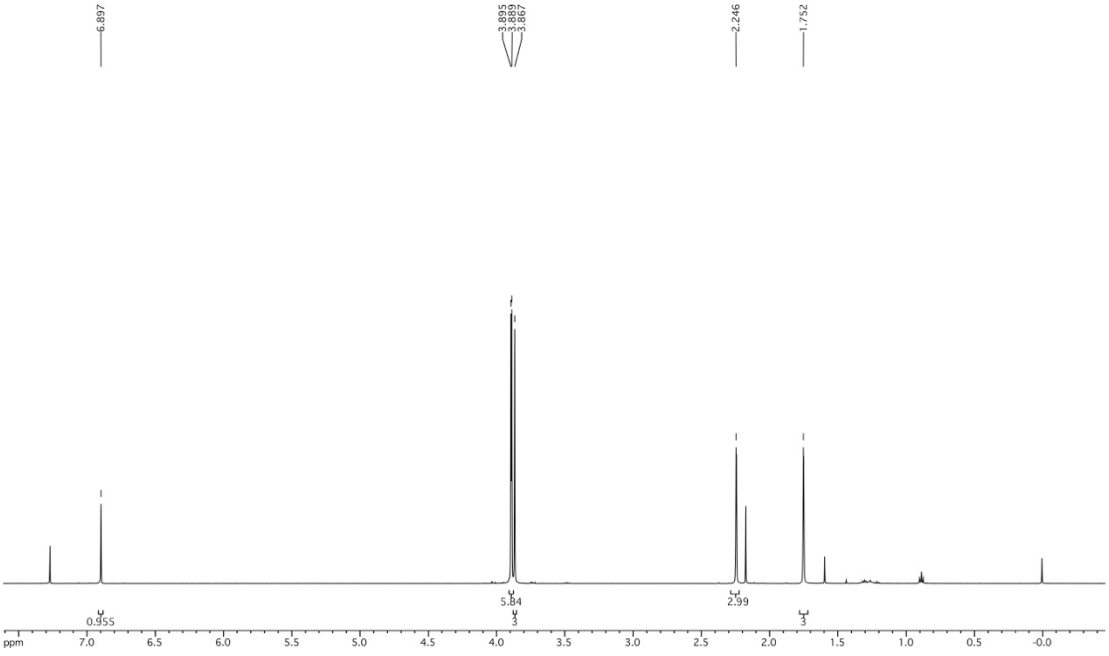


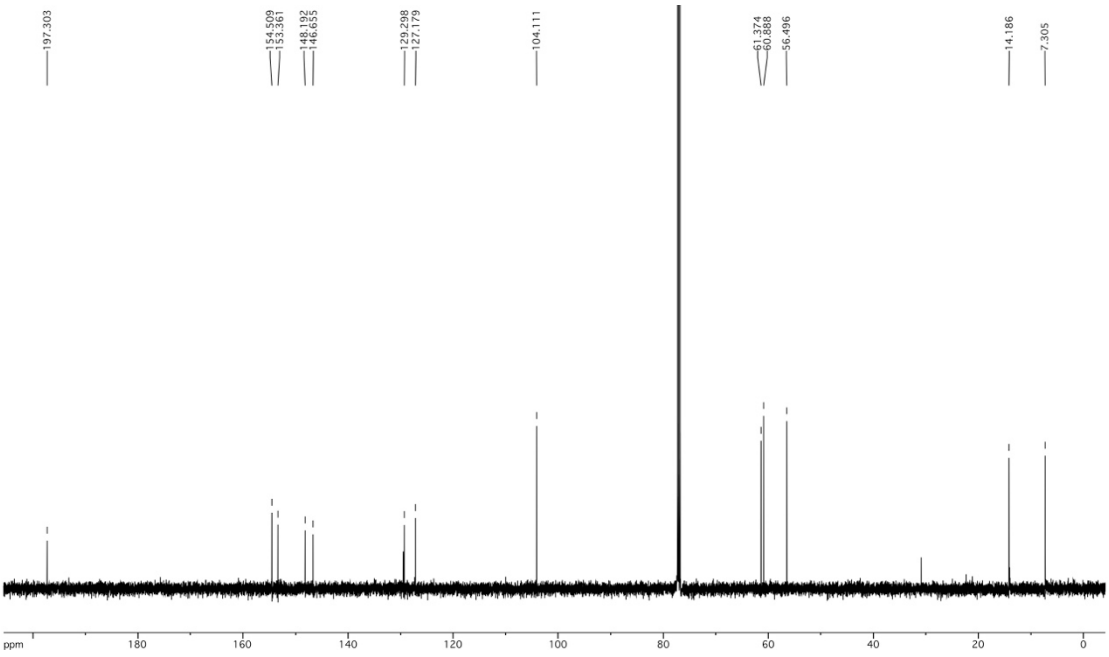
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 6-Methoxy-2,3-dimethyl-1*H*-inden-1-one (2.63)



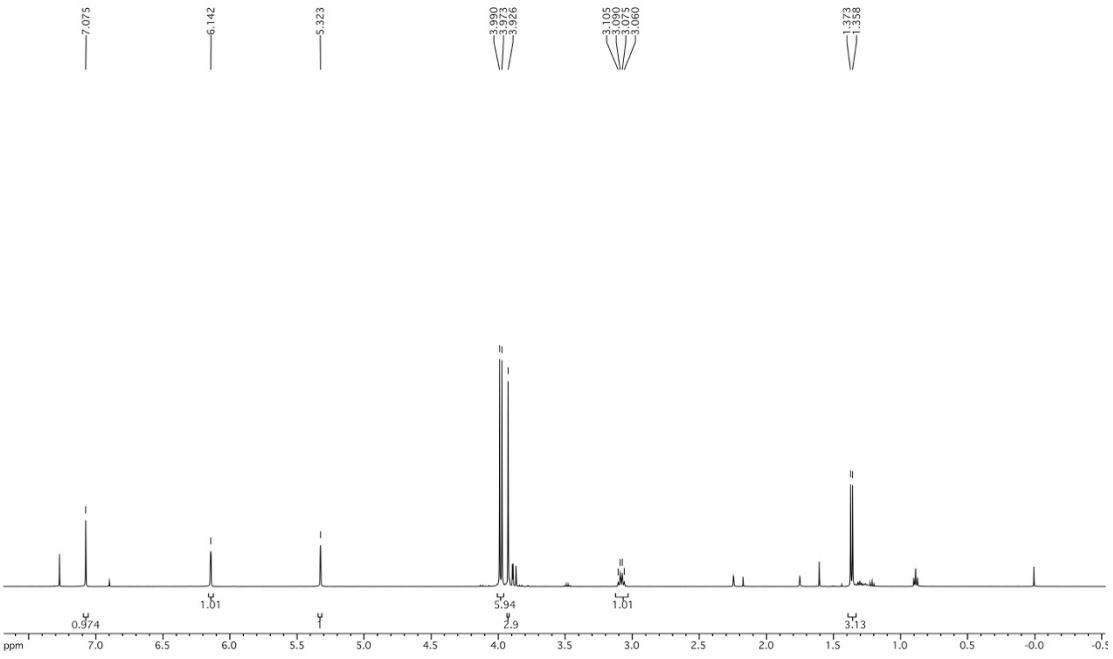


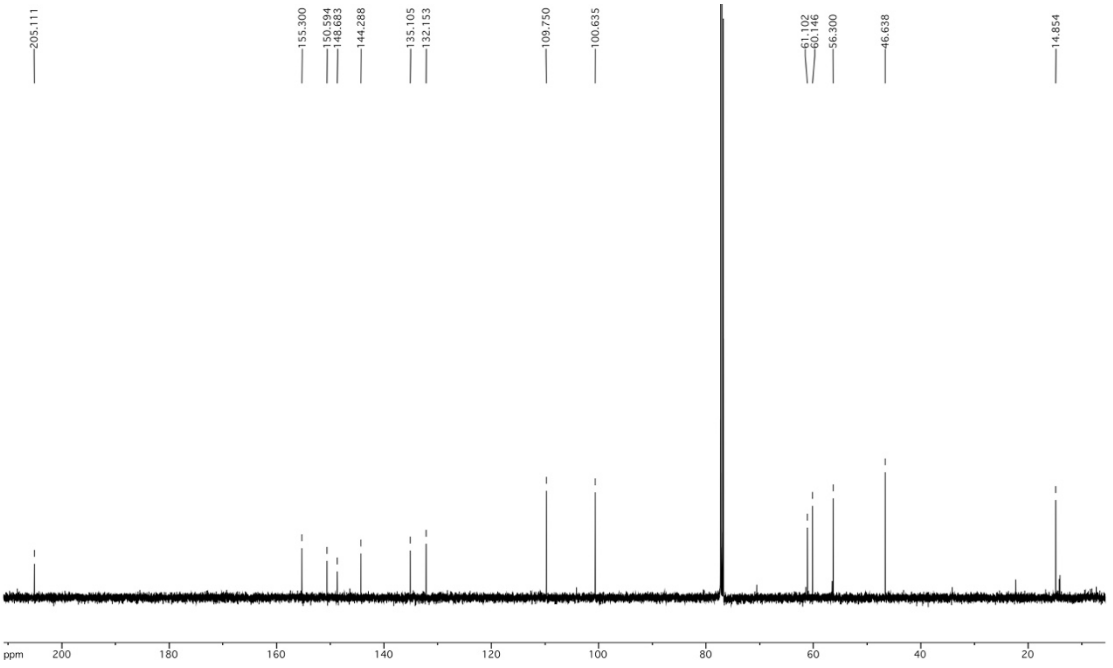
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 4,5,6-Trimethoxy-2,3-dimethyl-1*H*-inden-1-one (2.64a)



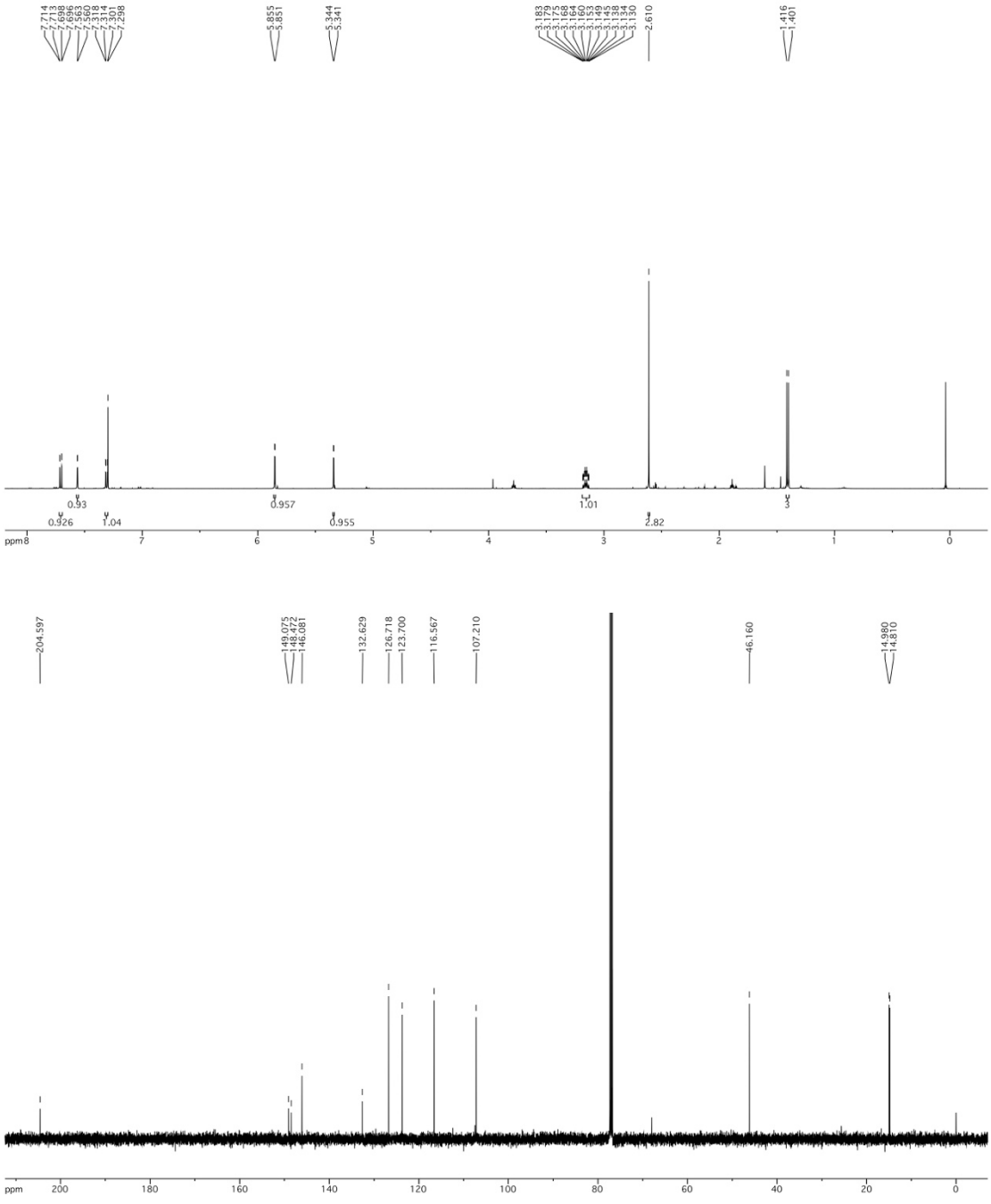


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 4,5,6-trimethoxy-2-methyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.64b)

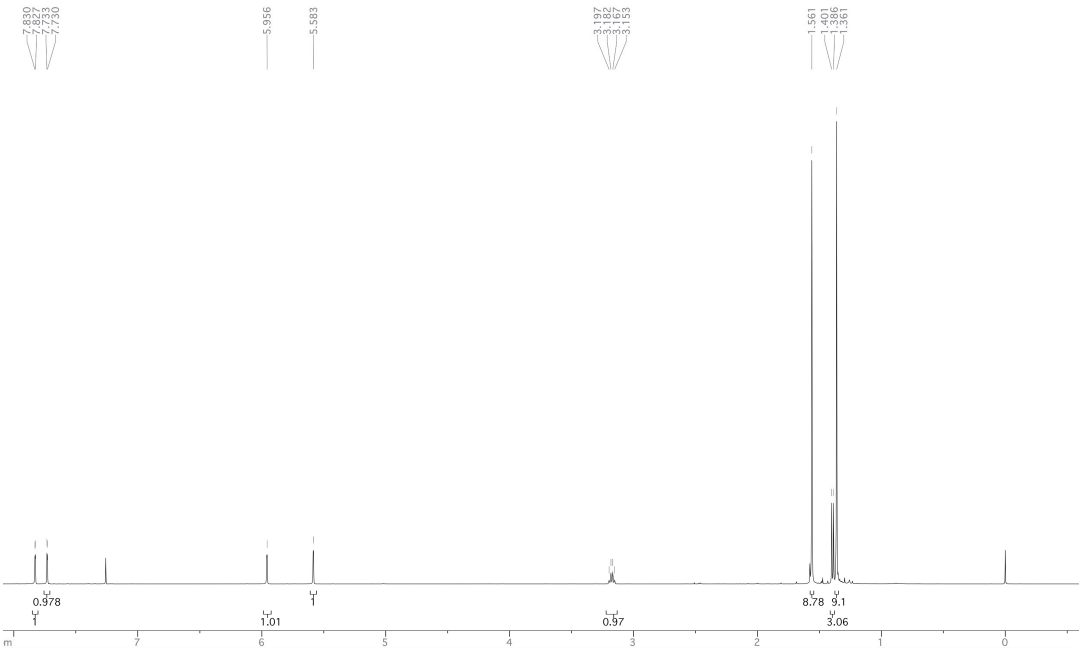


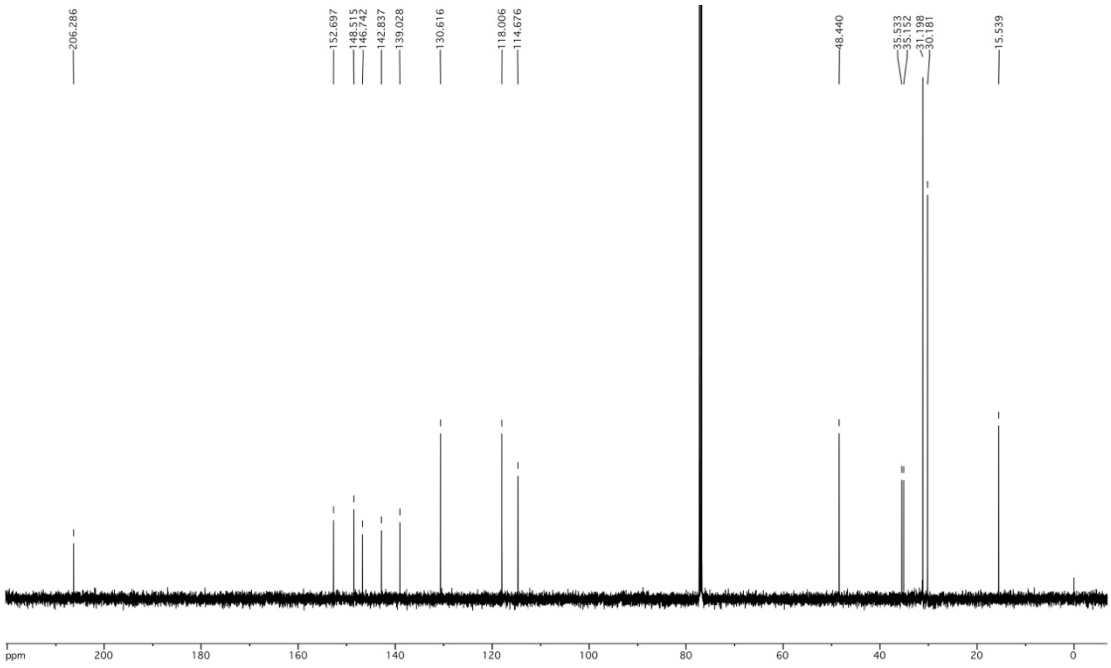


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-Methyl-3-methylene-5-(methylthio)-2,3-dihydro-1*H*-inden-1-one (2.65)

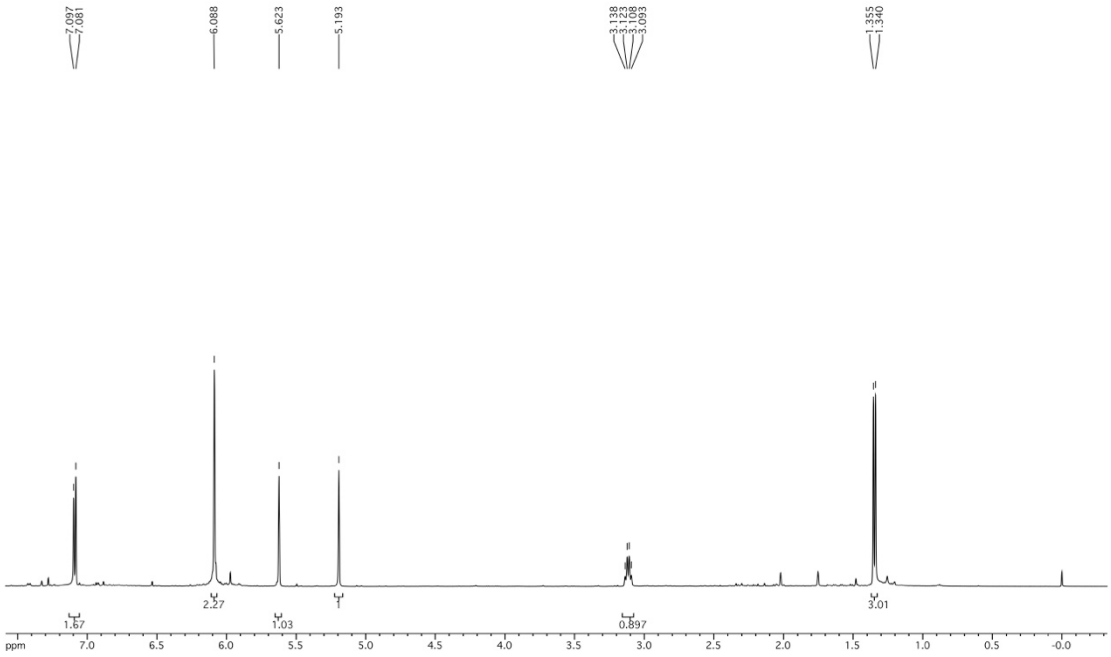


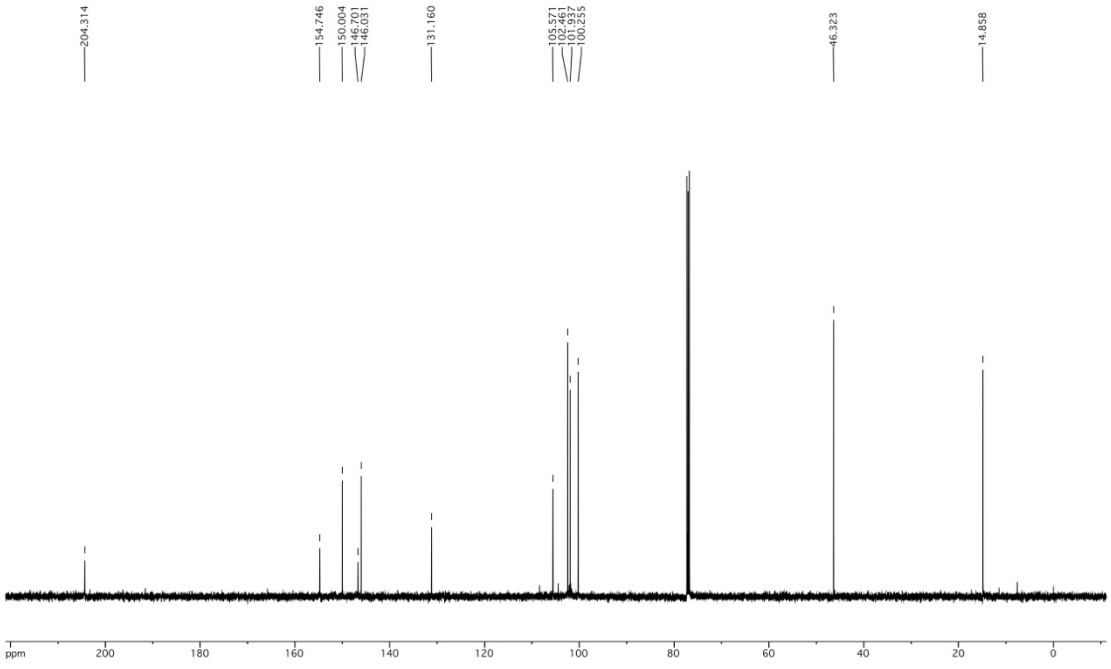
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 4,6-Di-*tert*-butyl-2-methyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.66)



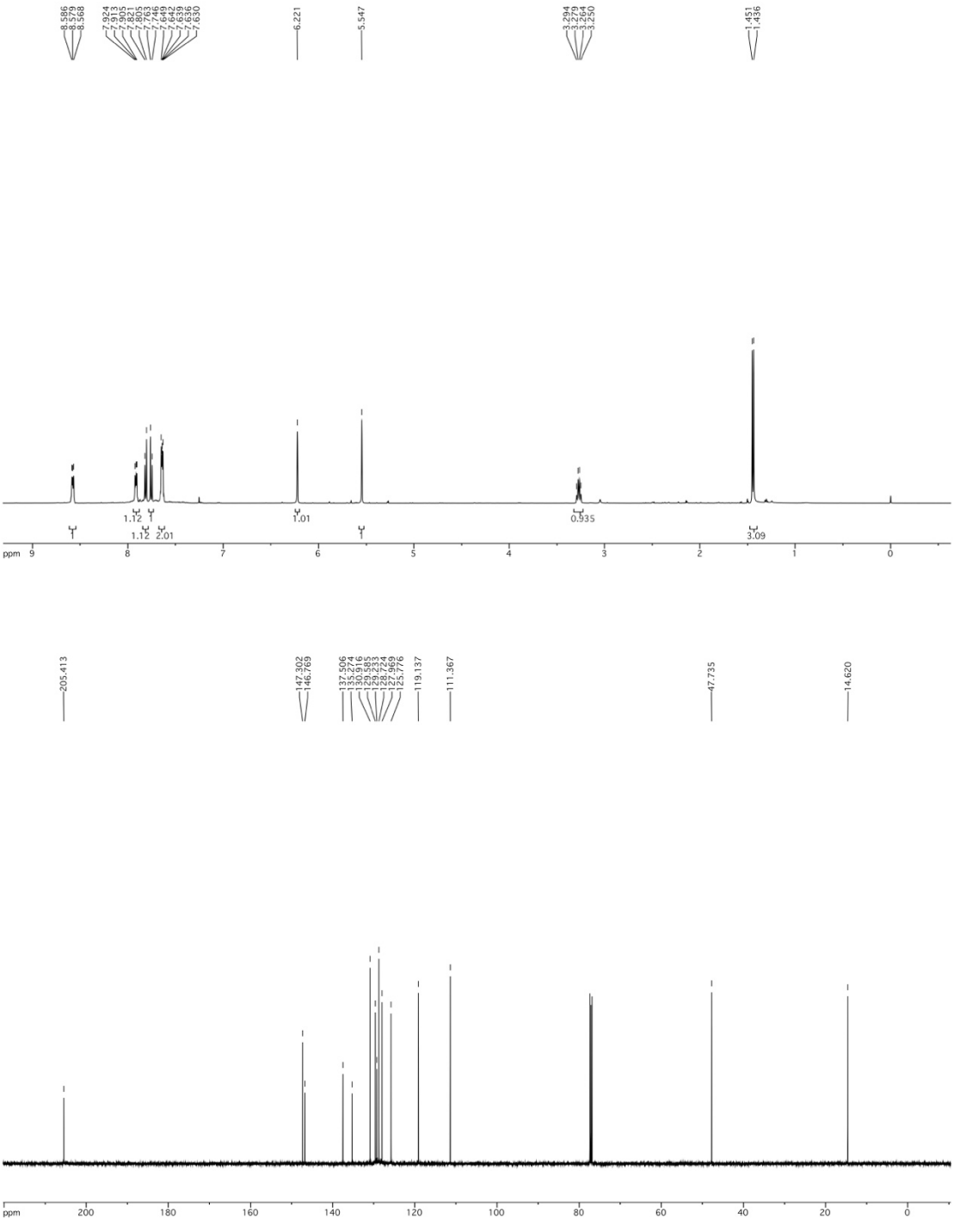


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 6-Methyl-7-methylene-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxol-5-one (2.67)

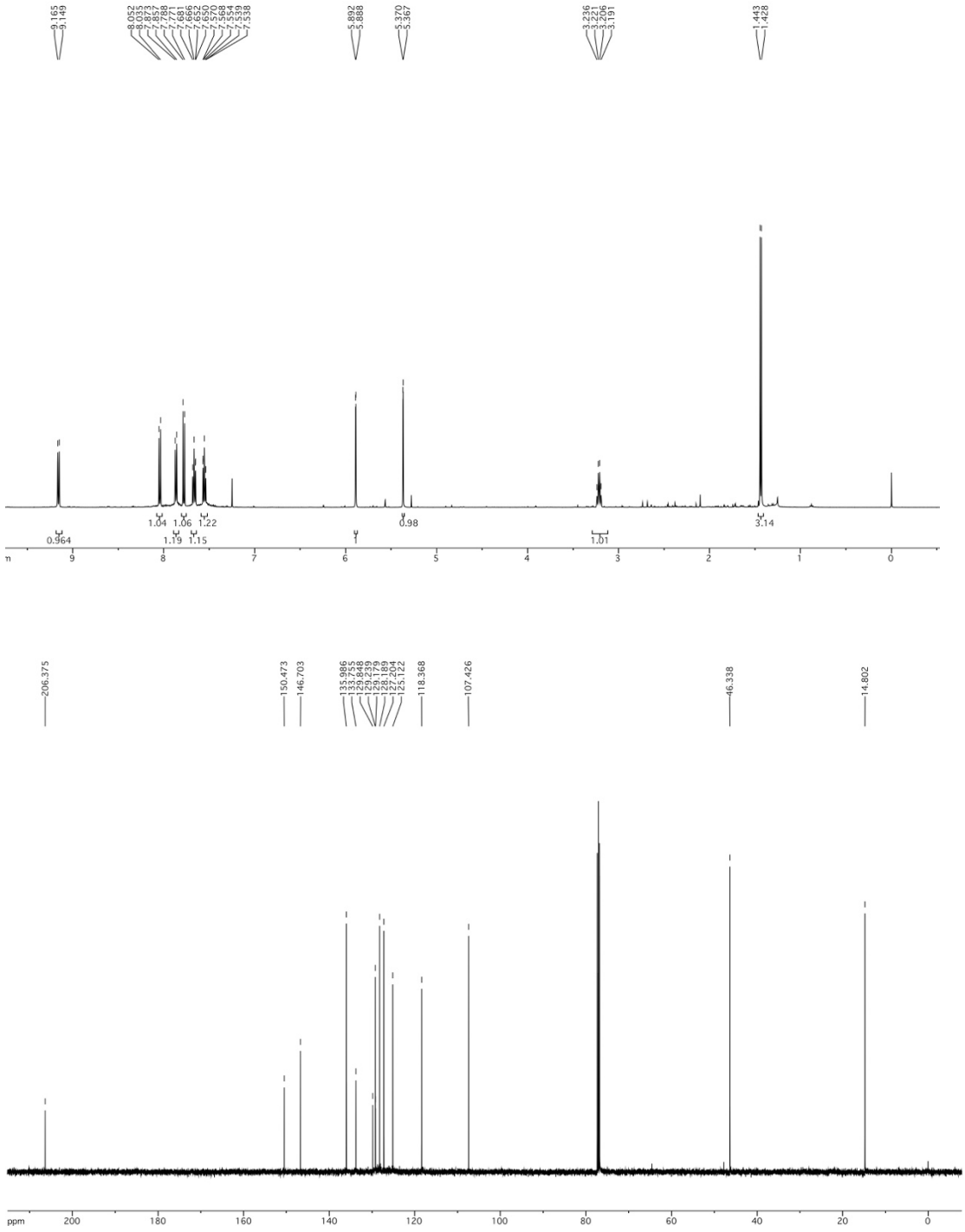




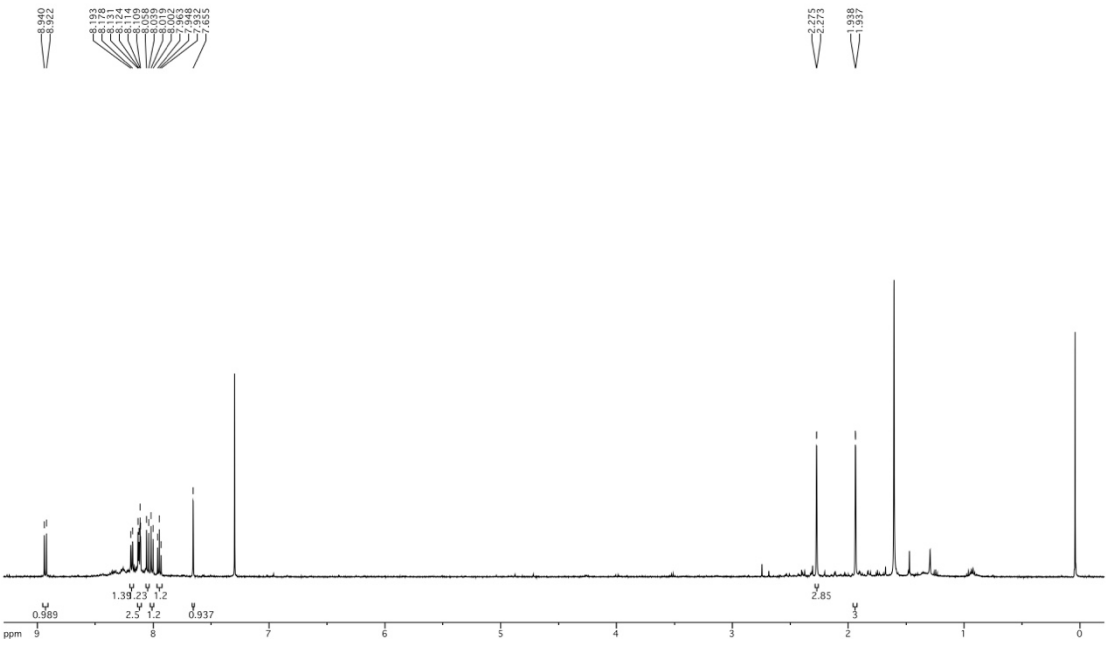
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-Methyl-1-methylene-1*H*-cyclopenta[*a*]naphthalen-3(2*H*)-one (2.68)



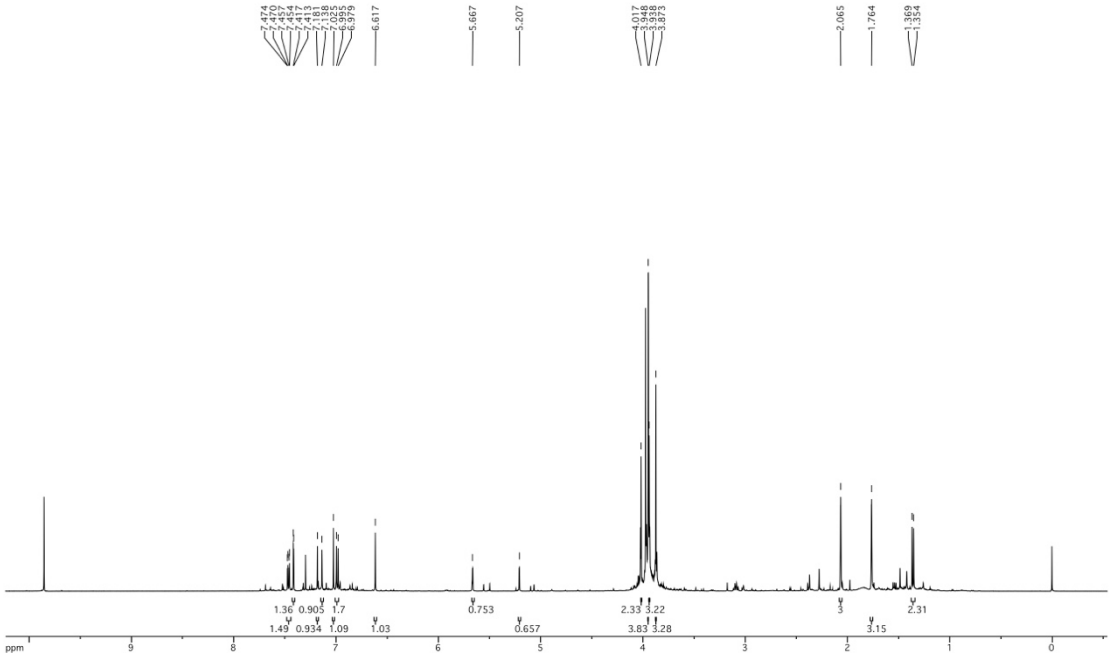
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-Methyl-3-methylene-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one (2.69)



^{1}H NMR (500 MHz, $CDCl_3$) for 7,8-Dimethyl-9*H*-cyclopenta[*a*]pyren-9-one (2.70)

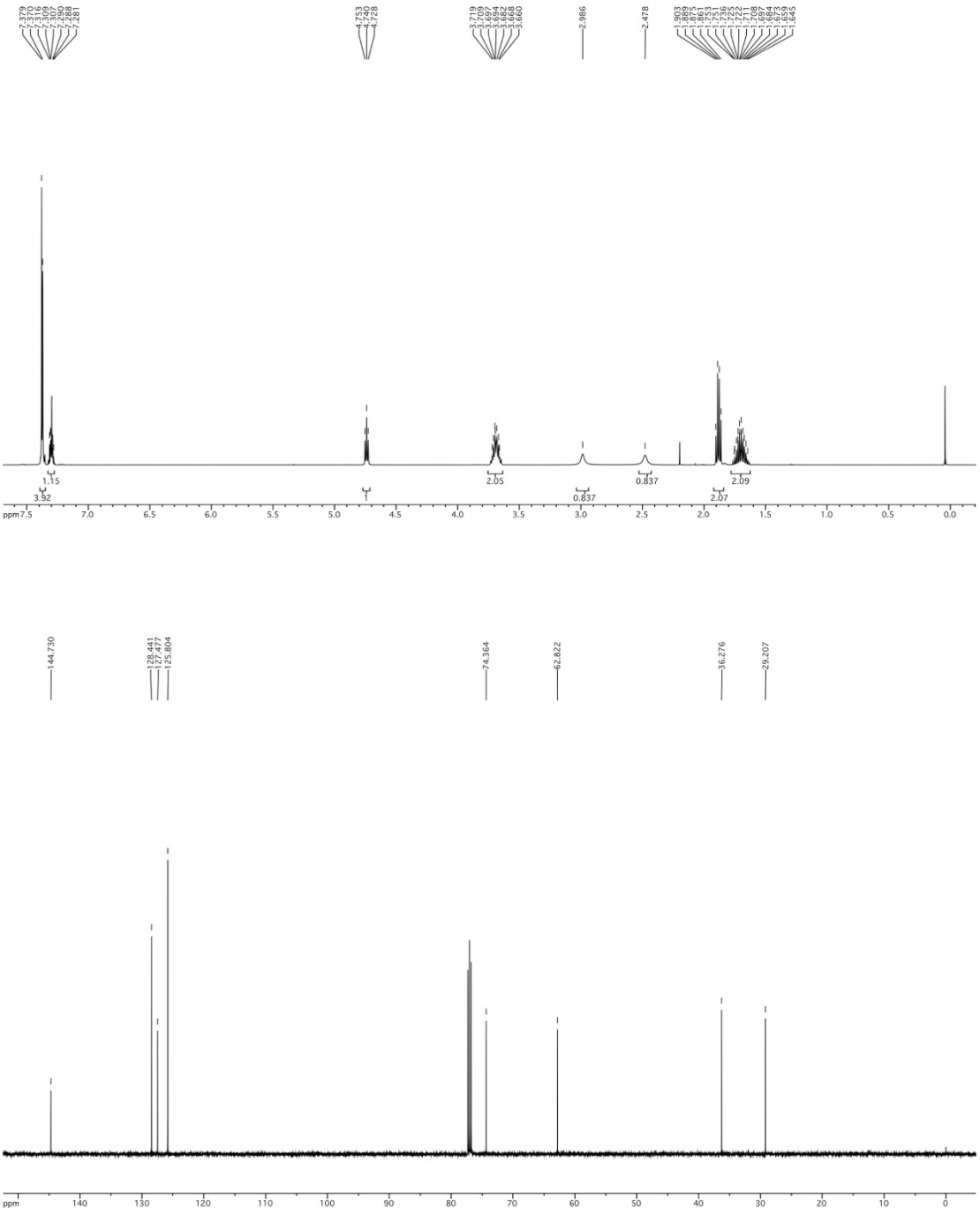


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 5,6-Dimethoxy-2-methyl-3-methylene-2,3-dihydro-1*H*-inden-1-one (2.71a) and 5,6-dimethoxy-2,3-dimethyl-1*H*-inden-1-one (2.71b)

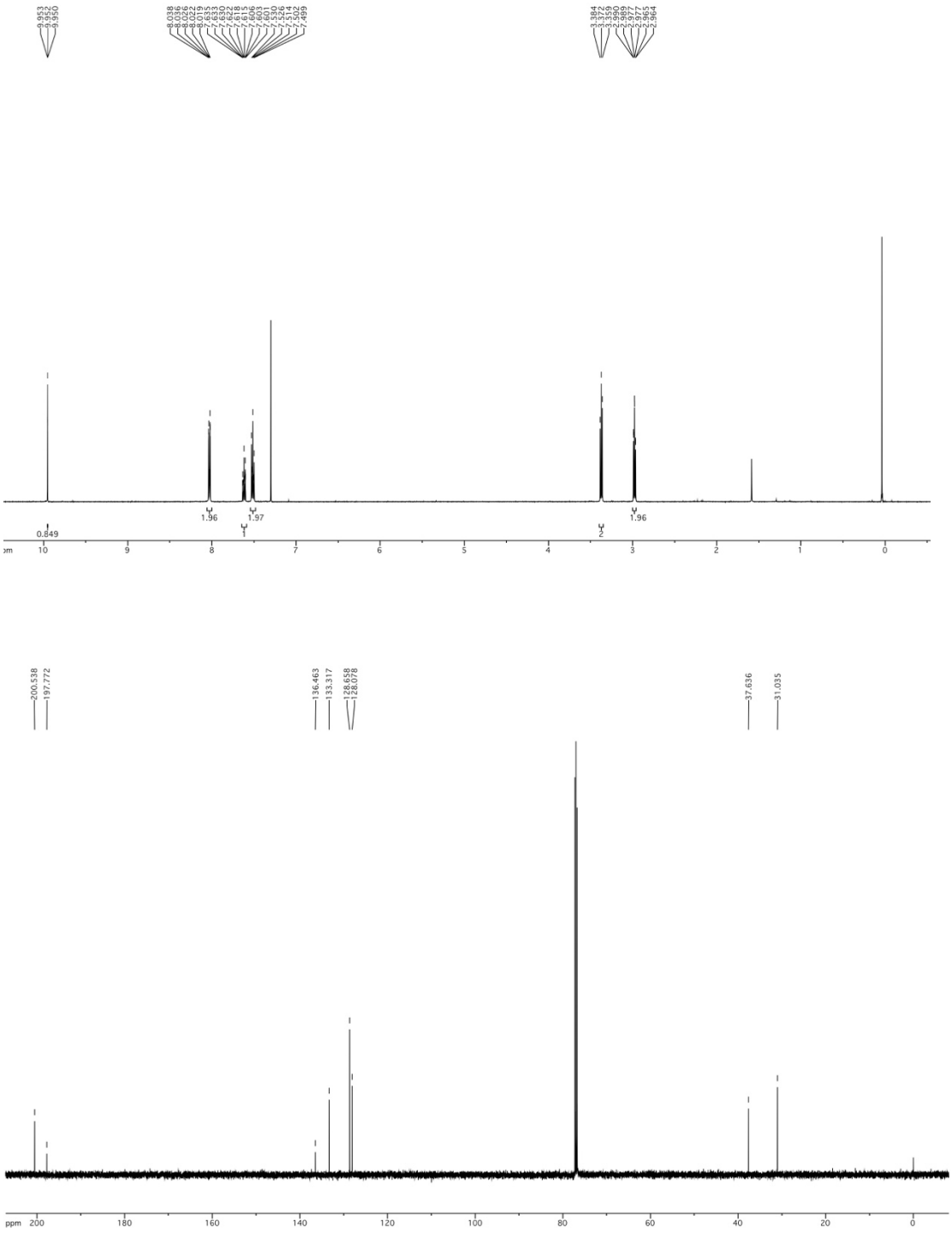


Appendix B – NMR spectra for Chapter 3

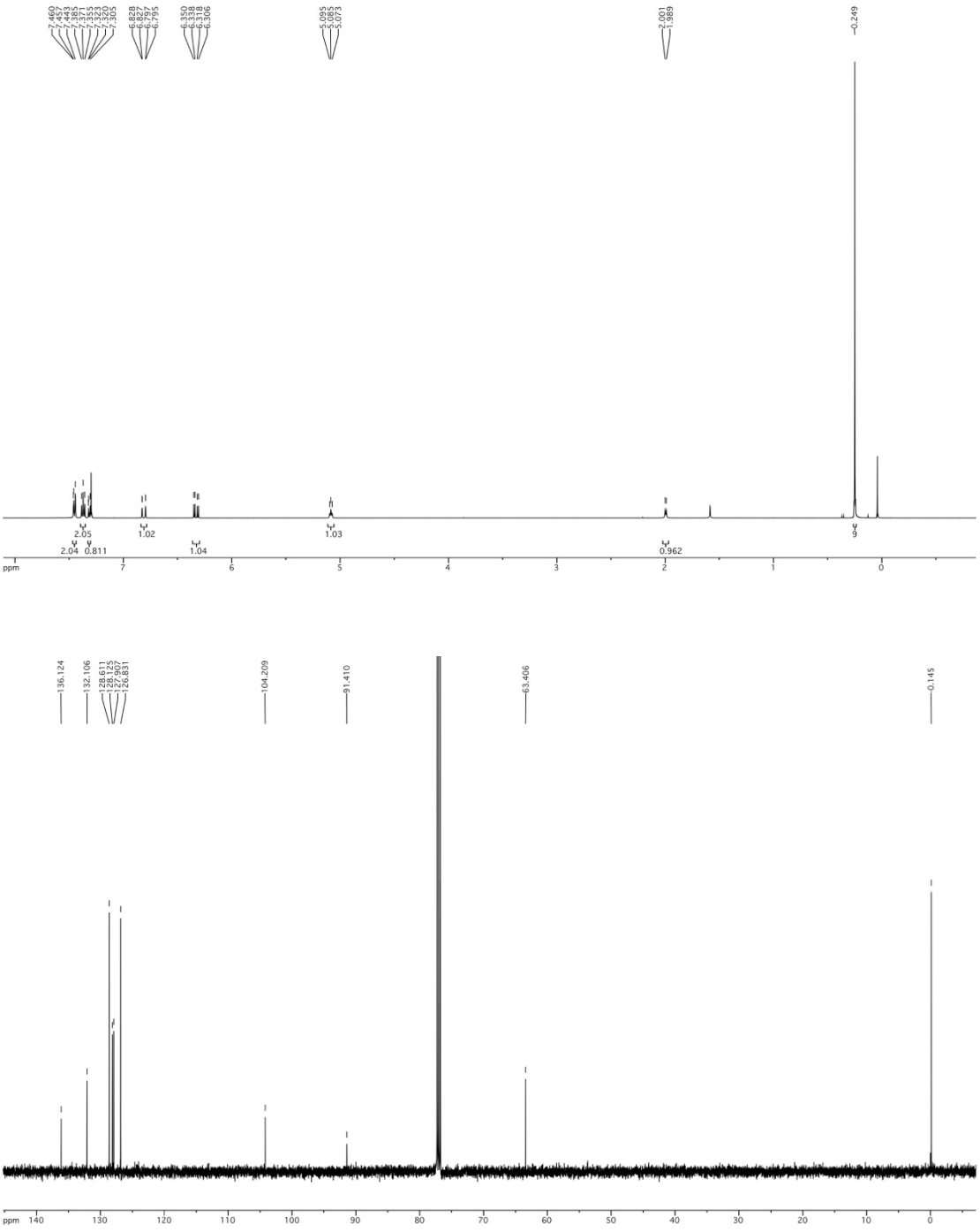
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 1-Phenylbutane-1,4-diol (3.8)



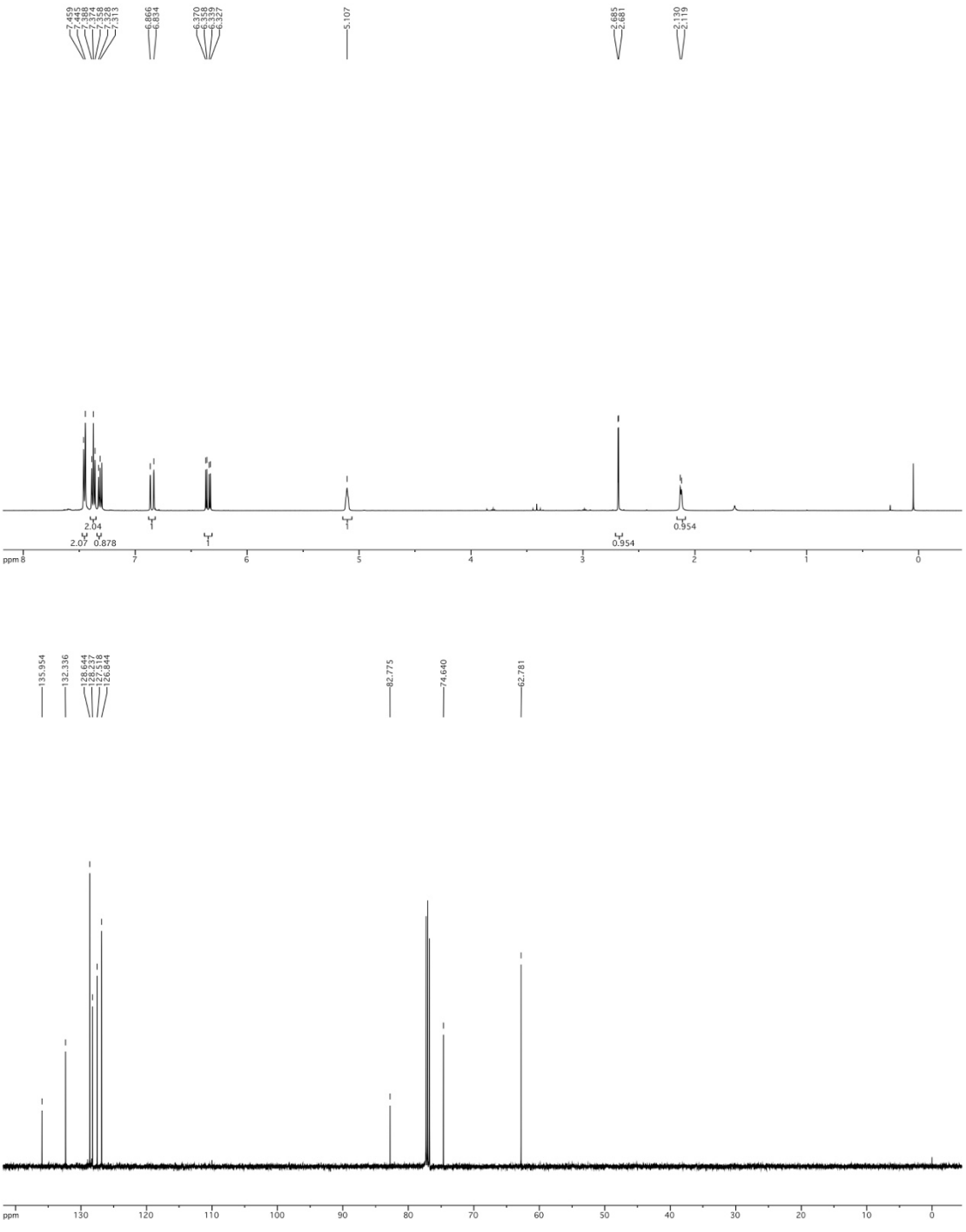
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 4-Oxo-4-phenylbutanal (3.9)



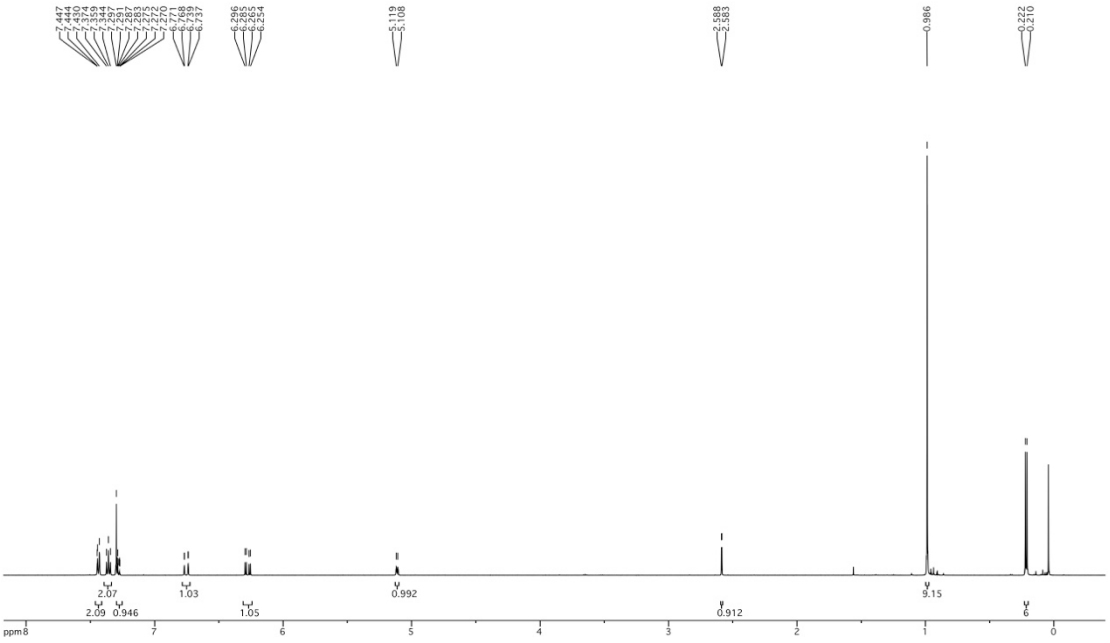
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for (*E*)-1-Phenyl-5-(trimethylsilyl)pent-1-en-4-yn-3-ol (3.11)

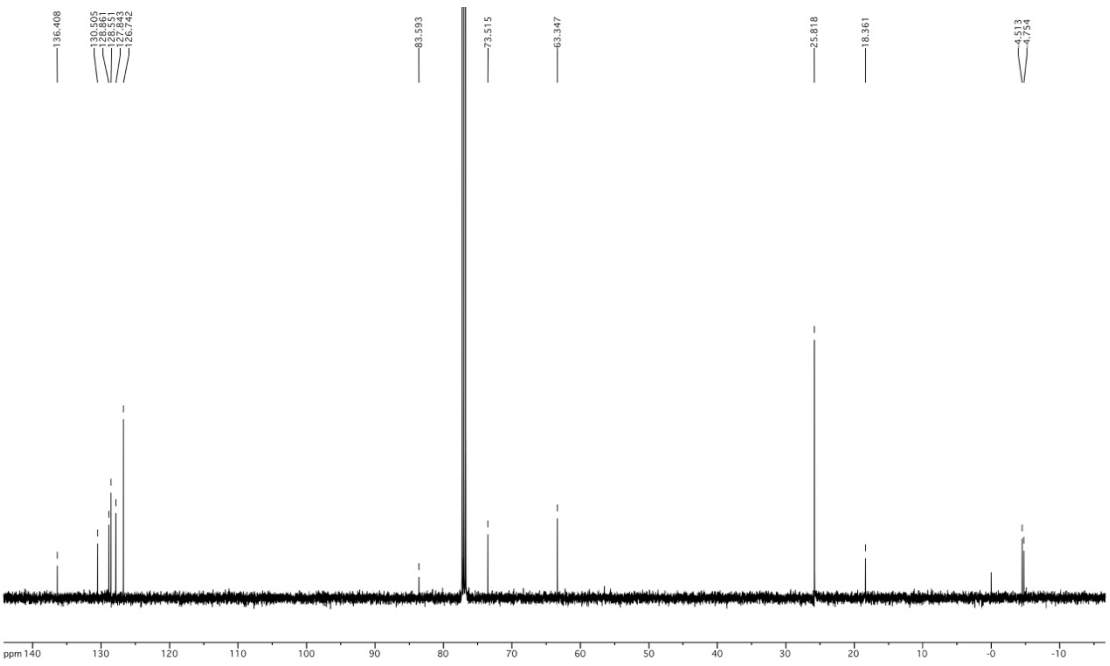


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for (*E*)-1-phenylpent-1-en-4-yn-3-ol (3.12)

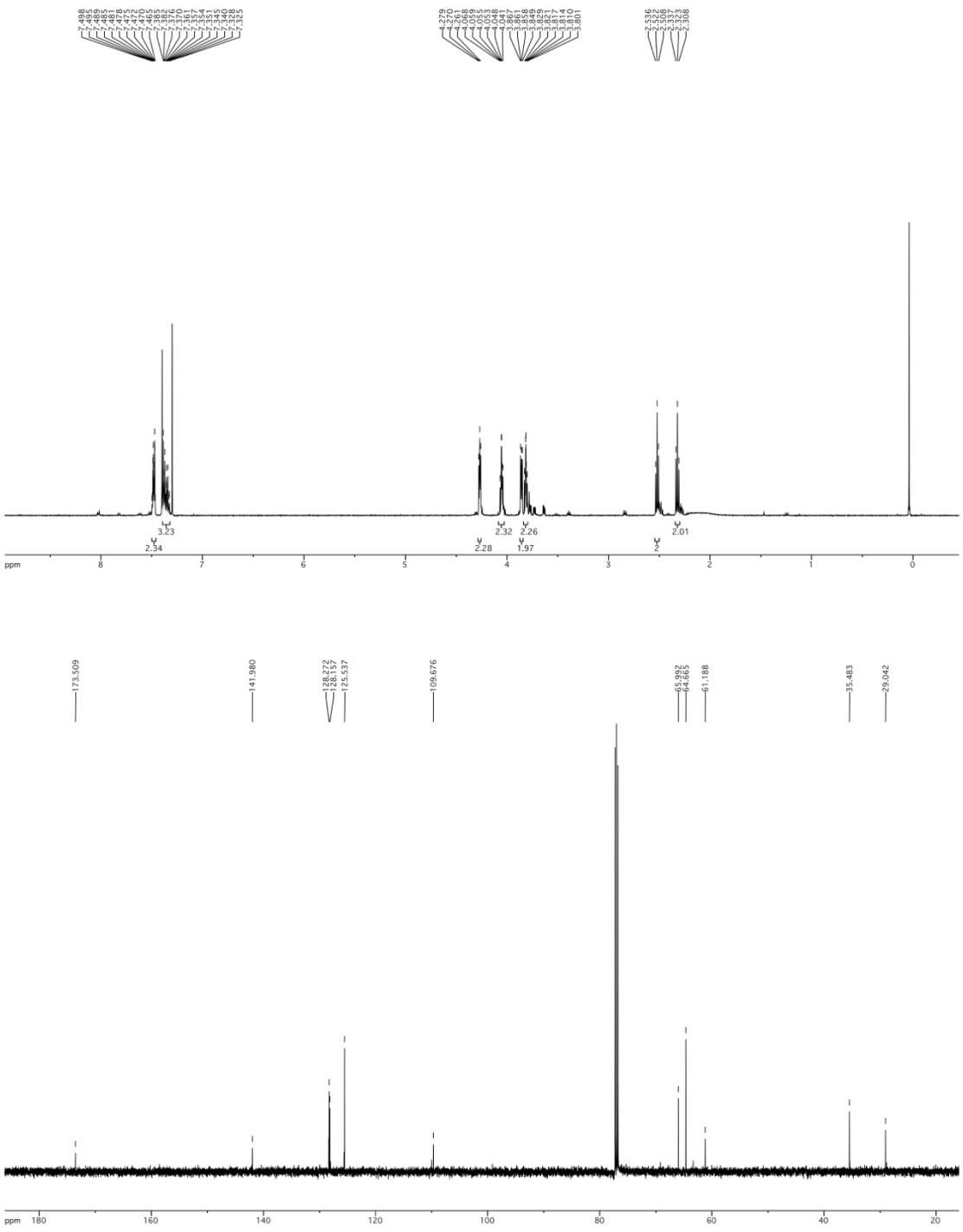


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for (*E*)-*tert*-butyldimethyl(1-phenylpent-1-en-4-yn-3-yloxy)silane (3.13)

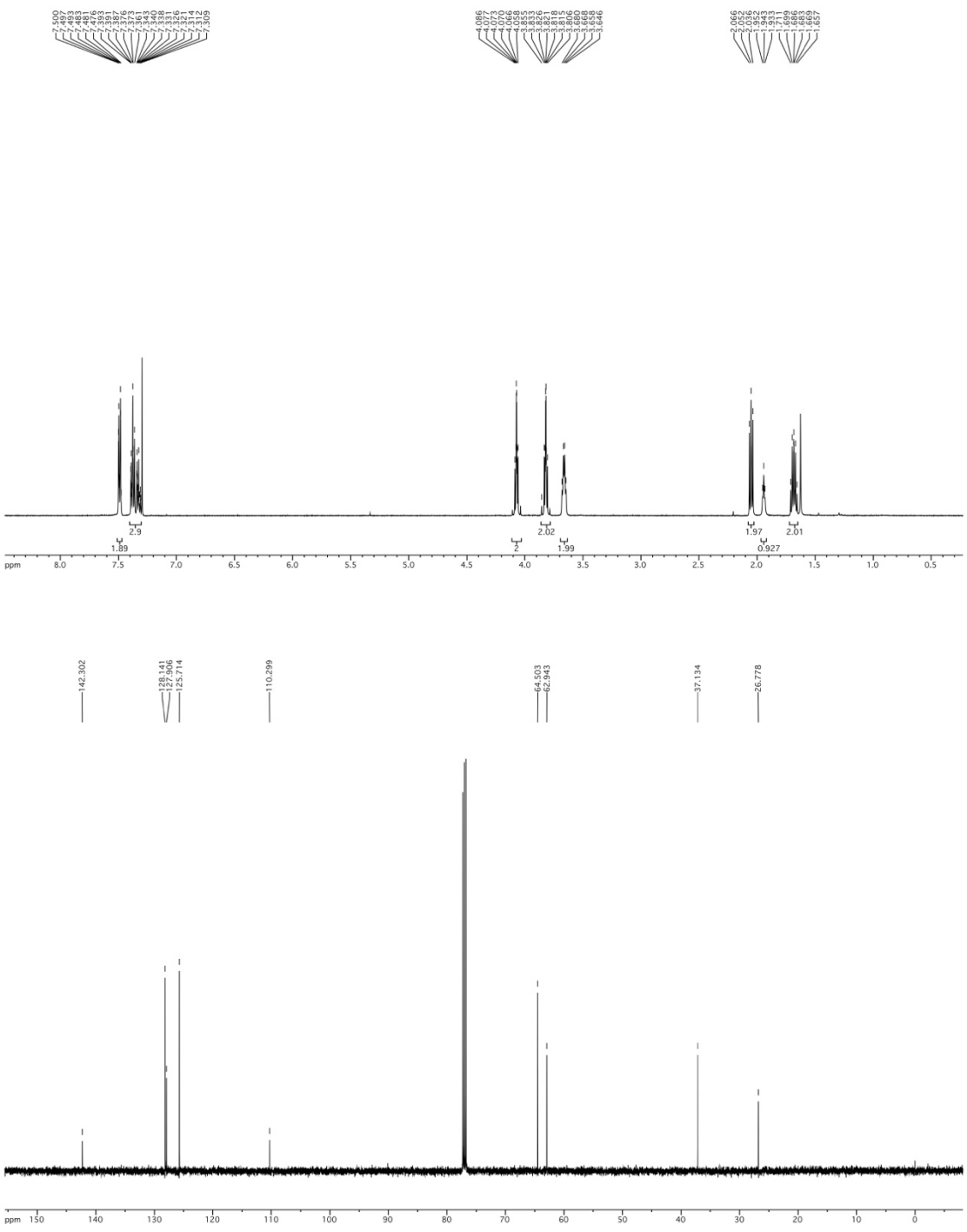




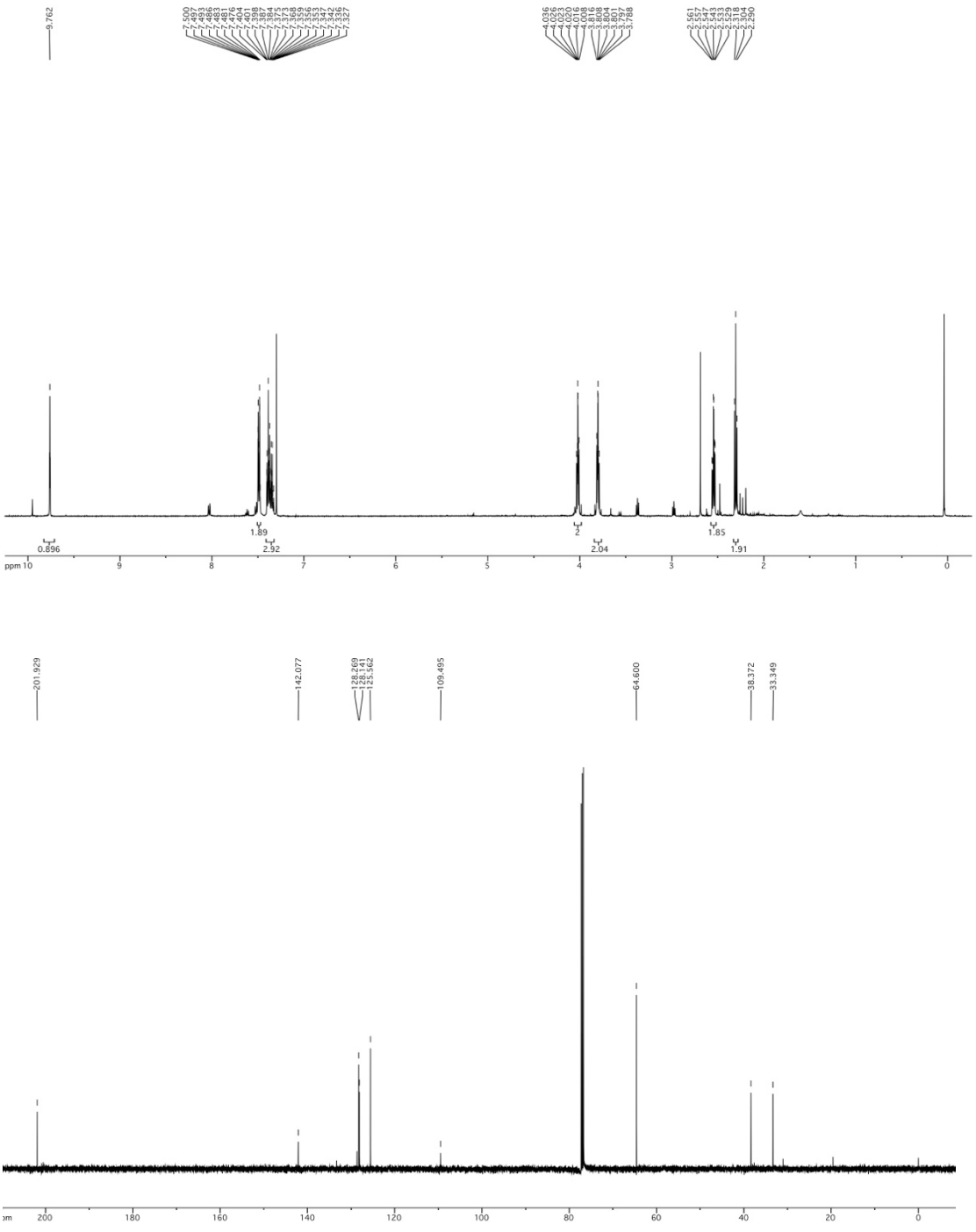
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 2-Hydroxyethyl 3-(2-phenyl-1,3-dioxolan-2-yl)propanoate (3.15)



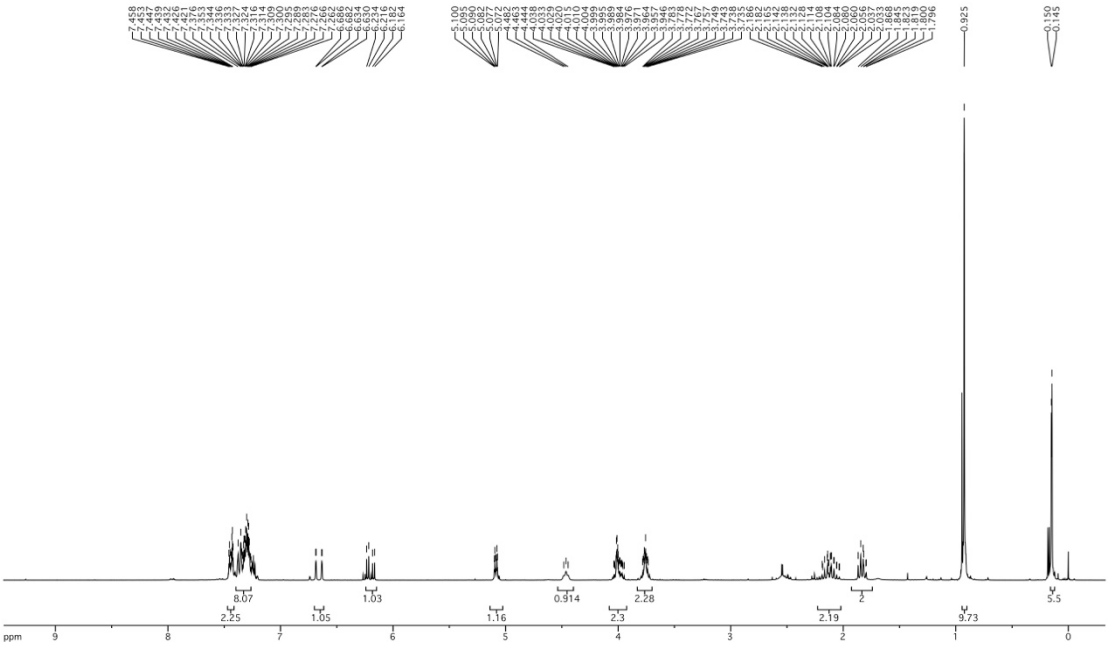
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 3-(2-phenyl-1,3-dioxolan-2-yl)propan-1-ol (3.16)



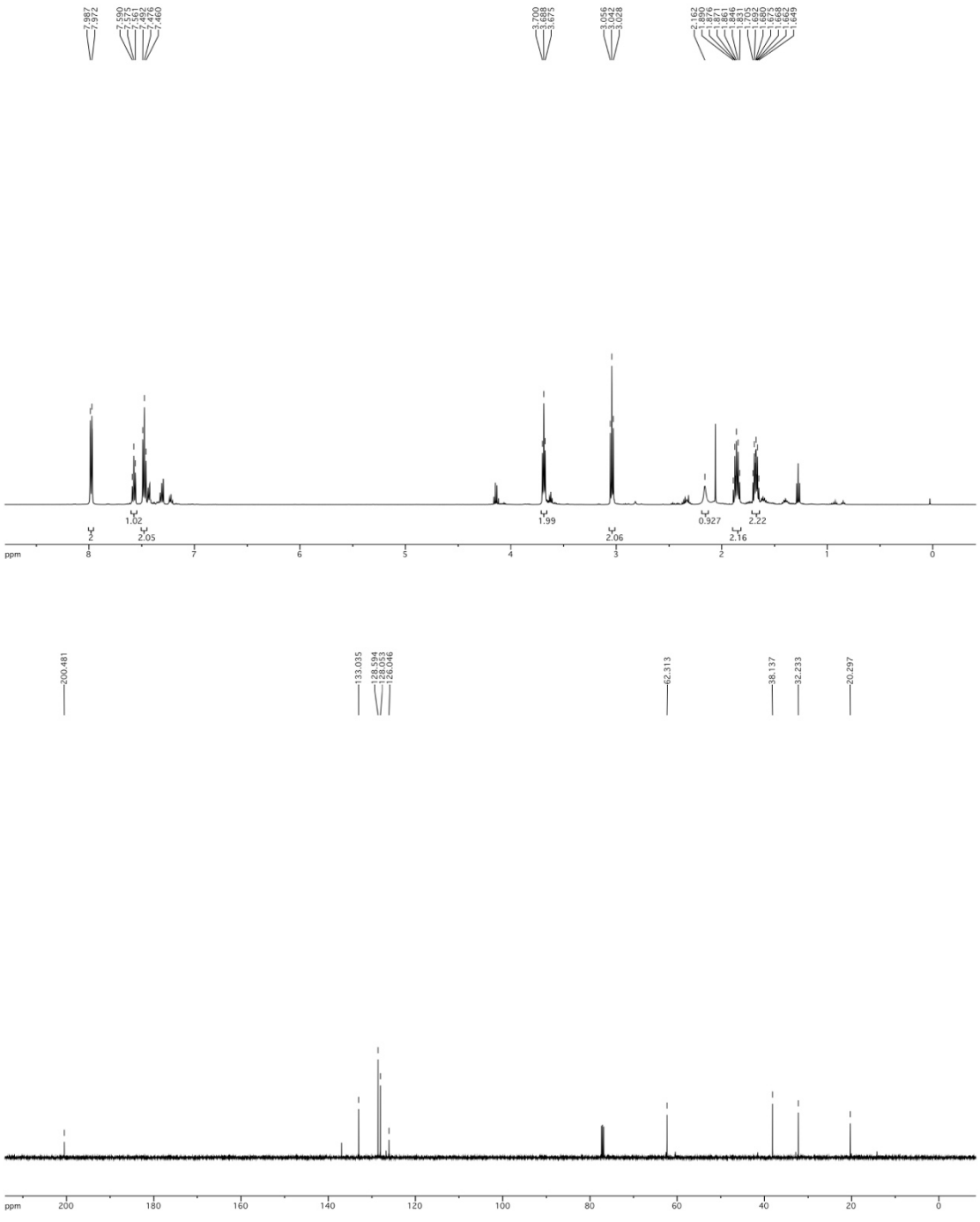
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 3-(2-phenyl-1,3-dioxolan-2-yl)propanal (3.17)



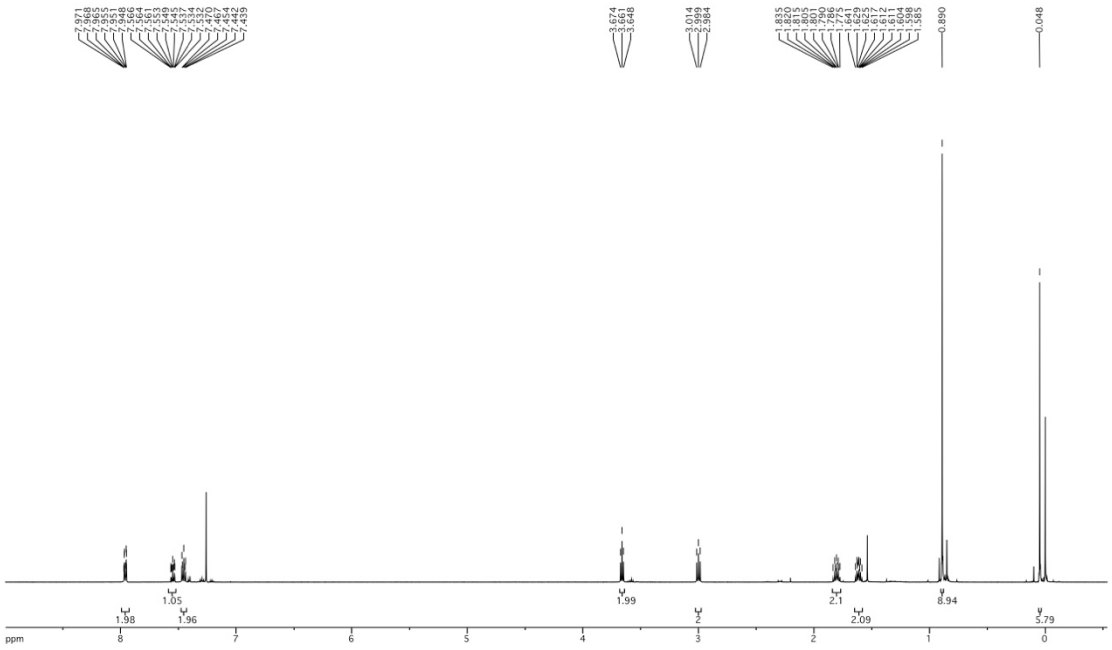
^{1}H NMR (500 MHz, $CDCl_3$) for (*E*)-6-(*tert*-butyldimethylsilyloxy)-8-phenyl-1-(2-phenyl-1,3-dioxolan-2-yl)oct-7-en-4-yn-3-ol (3.18)



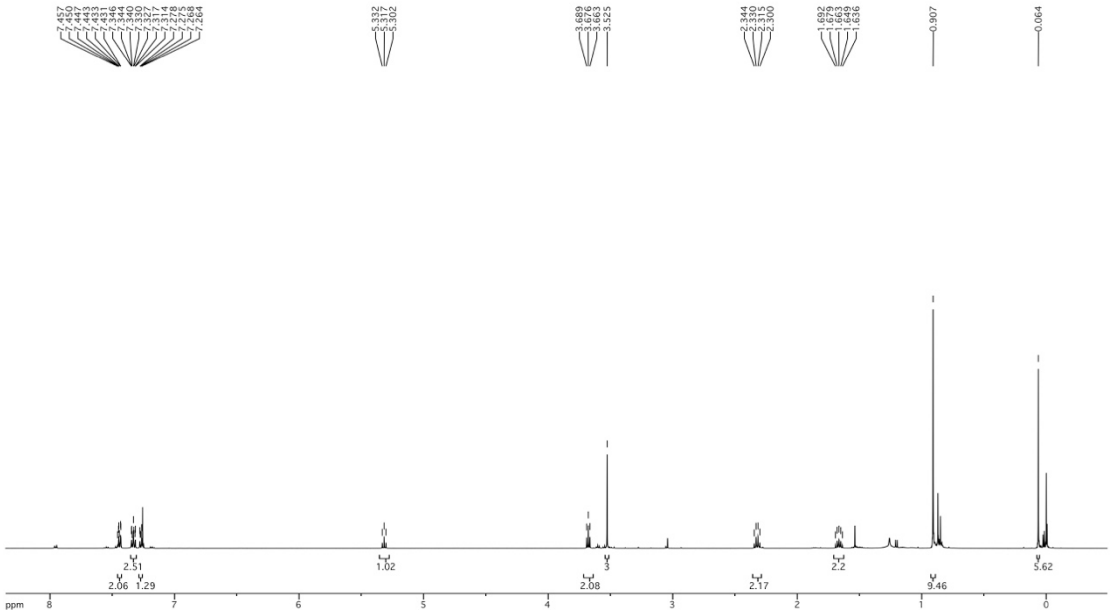
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 5-Hydroxy-1-phenylpentan-1-one (3.20)

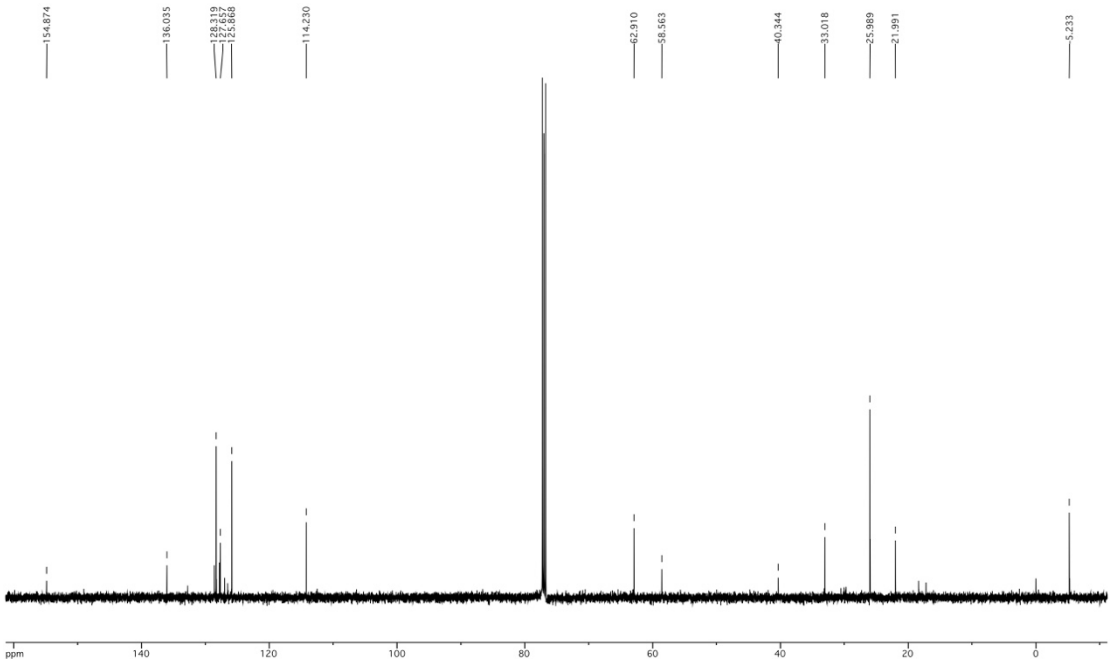


^{1}H NMR (500 MHz, $CDCl_3$) for 5-(*Tert*-butyldimethylsilyloxy)-1-phenylpentan-1-one (3.21)

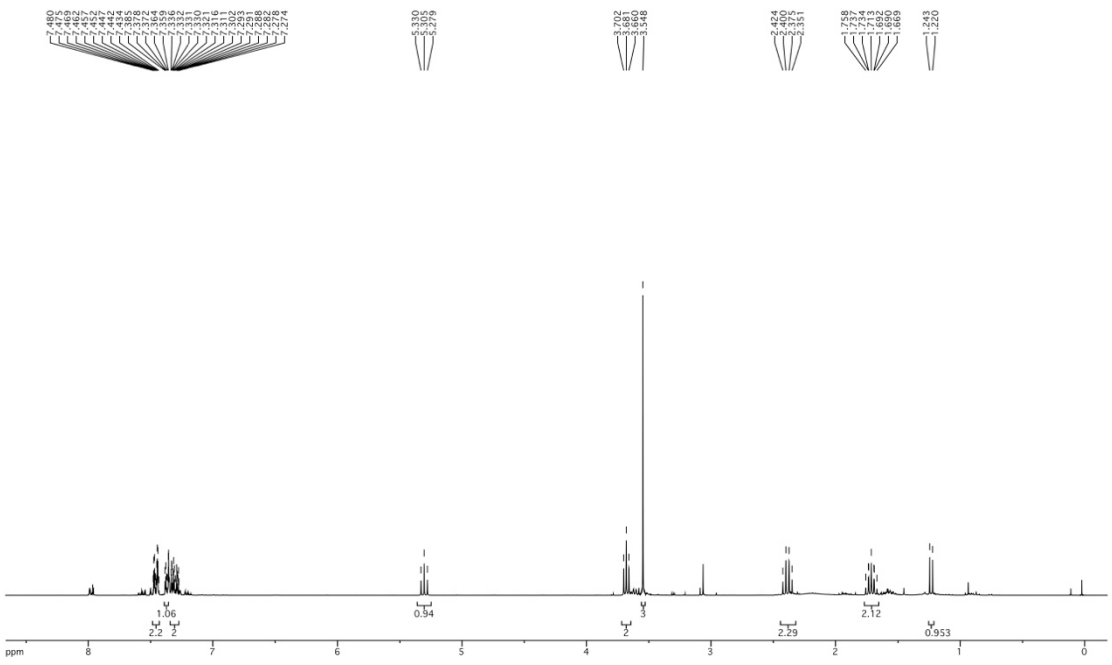


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for (*Z*)-*tert*-butyl(5-methoxy-5-phenylpent-4-enyloxy)dimethylsilane (3.22)

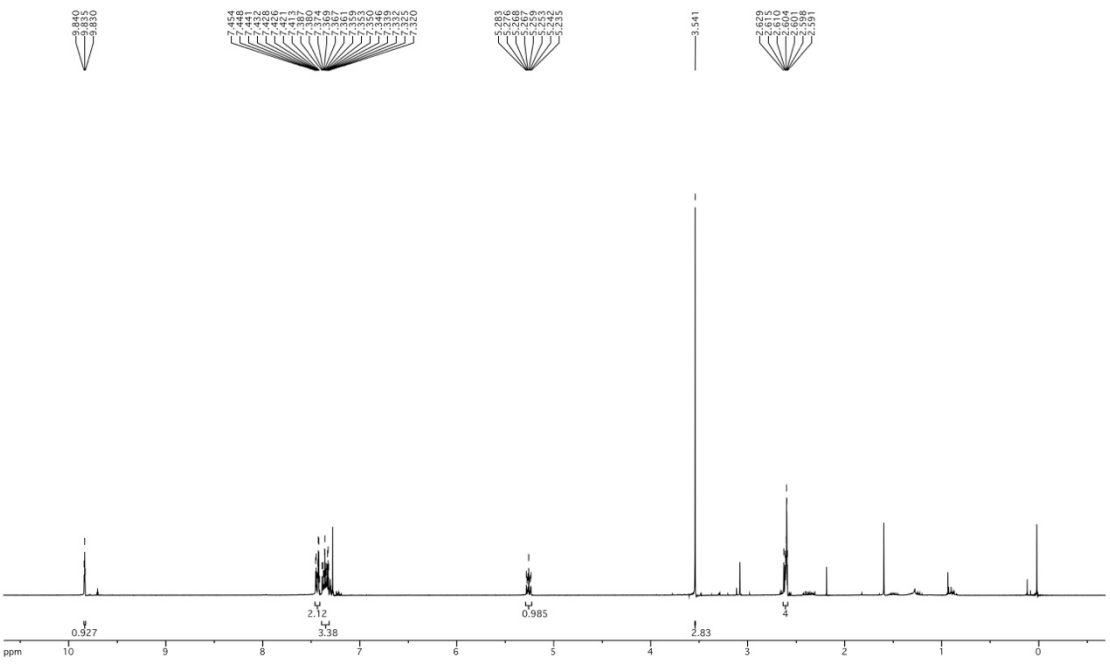




^{1}H NMR (500 MHz, $CDCl_3$) for (*Z*)-5-methoxy-5-phenylpent-4-en-1-ol (3.23)

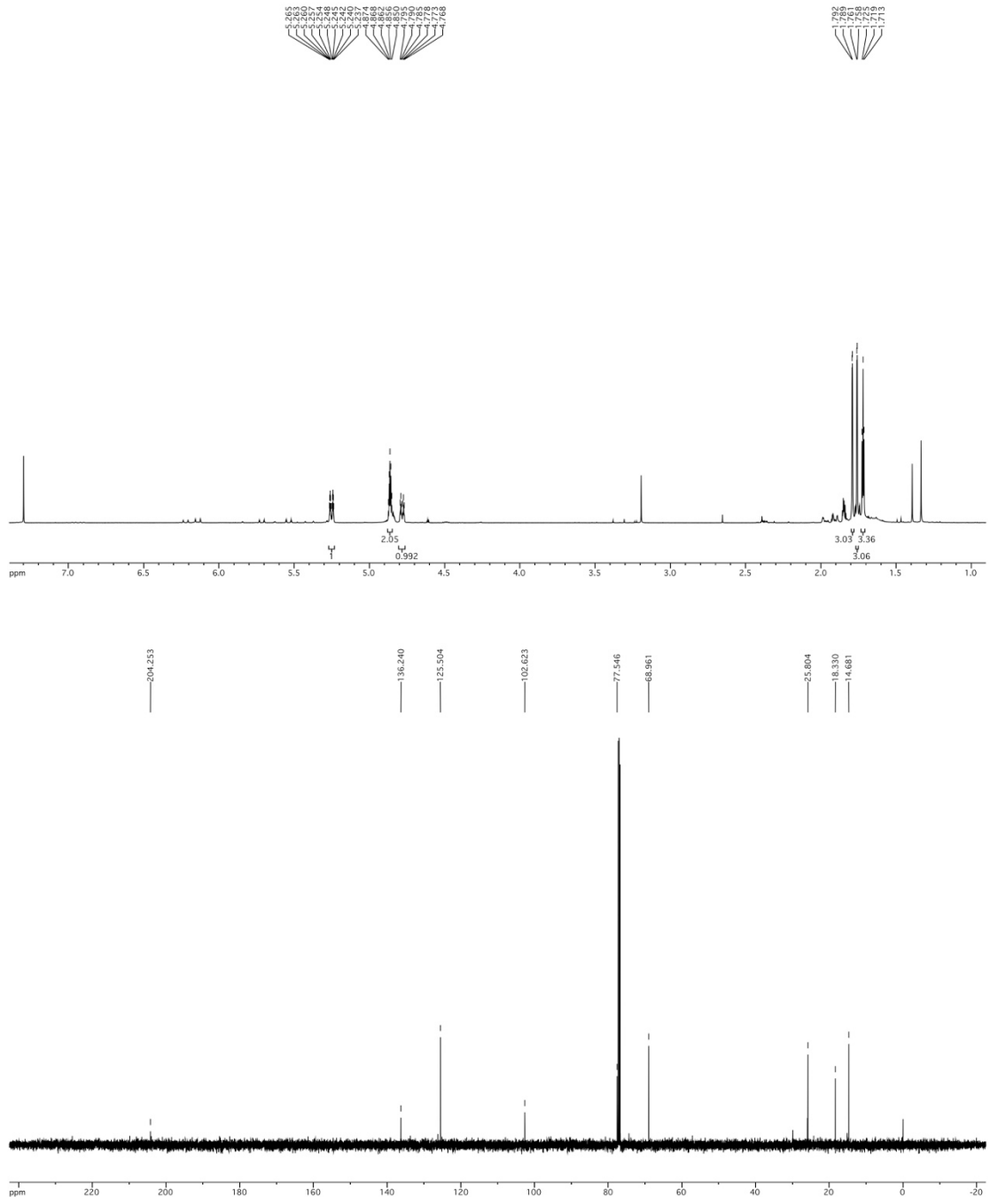


^{1}H NMR (500 MHz, $CDCl_3$) for (*Z*)-5-methoxy-5-phenylpent-4-enal (3.24)

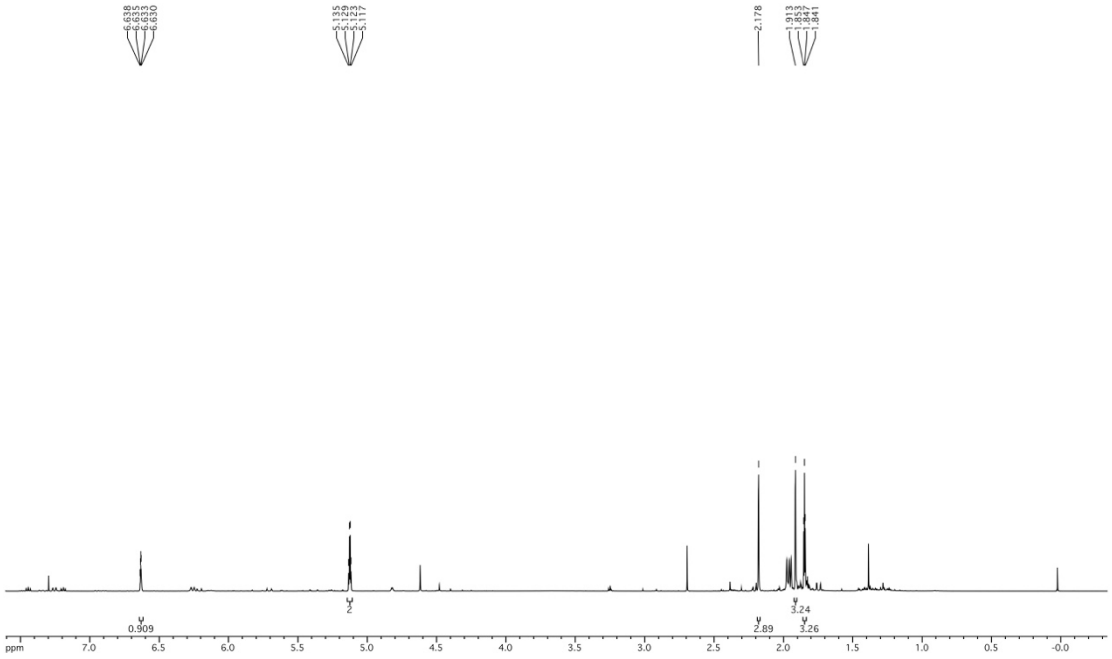


Appendix C – NMR spectra for Chapter 4

^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 3,6-Dimethylhepta-1,2,5-trien-4-ol (4.6)



^{1}H NMR (500 MHz, $CDCl_3$) for 3,6-Dimethylhepta-1,2,5-trien-4-one (4.7)



^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) for 5-Allyl-2,3,4,4-tetramethylcyclopent-2-enone (4.10)