Selectivity in the Interrupted Nazarov Reaction

by

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Abstract

Three allenyl vinyl ketones (AVKs) underwent Lewis acid-mediated Nazarov cyclization in the presence of a variety of dienes. Products arising from the (4+3)- and (3+2)-cycloaddition to the oxyallyl cation intermediate of the Nazarov reaction were obtained. In general, (4+3) products were preferred but heavy substitution of a terminus of the diene led to (3+2) products. Some of the (3+2) products rearranged upon exposure to BF_3•OEt_2, but decomposition was a major competing process. The Gibbs energies of the Nazarov and rearranged products were compared computationally.

AVKs with terminally substituted allenes were synthesized. The AVKs underwent Nazarov cyclization promoted by BF_3•OEt_2 and the oxyallyl cation was trapped by a (4+3)-cycloaddition. The products arose preferentially from cyclization where the terminal allenic substituent had rotated away from the vinyl group. The experimental results suggested that this selectivity was due to steric interactions between allenic and vinyl substituents. If any substituent on the AVK was larger than a methyl group, the torquoselectivity of the process was high. The torquoselectivity was not significantly affected by trapping via (4+3)- or (3+2)-cycloaddition. The products were stable to the reaction conditions. Calculations confirmed the kinetic preference for the observed products and supported the steric rationale for the torquoselectivity. The degree of deformation of the allene in the transition state was identified as a second factor in determining torquoselectivity.

A synthetic method to access AVKs bearing tethered 1,3-dienes, with variable substitution and length, was developed. The dienes were installed using a Julia-Kocienski coupling reaction with an α,β-unsaturated aldehyde to give predominately the *E*-alkenes. Organometallic coupling was carried out using a Grignard reaction to form homopropargyl alcohols. The alcohols were oxidized using Dess-Martin periodinane or 2-iodoxybenzoic acid, and isomerized to AVKs with K_2CO_3. When exposed to BF_3•OEt_2 these molecules underwent a tandem Nazarov/(4+3) or (3+2)-cycloaddition. With a three-carbon tether the cycloaddition was (4+3), while with a four-carbon tether the cycloaddition was (3+2). Diene substitution had a significant effect on the stereoselectivity. In some cases very high diastereoselectivity was observed.

List of Abbreviations and Symbols Used

Å	angstrom
δ	chemical shift or partial charge
Δ	heat
μL	microlitre
Ac	acetate
A	acid
aq	aqueous
AVK	allenyl vinyl ketone
BF_3•OEt_2	boron trifluoride diethyl etherate
Bn	benzyl
br	broad
BOC	tert-butoxycarbonyl
n-Bu	normal-butyl
t-Bu	*tert*-butyl
cm^{-1}	wavenumber(s)
COSY	correlation spectroscopy

*m*CPBA	*meta*-chloroperoxybenzoic acid
DCE	1,2-dichloroethane
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dq	doublet of quartets
dr	diastereomeric ratio
dt	doublet of triplets
EDG	electron donating group
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EWG	electron withdrawing group

FGI	functional group interconversion
FT	Fourier transform
g	gram(s)
h	hour(s)
HFIP	hexafluoroisopropanol
HMBC	heteronuclear multiple bond coherence
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	hertz
IR	infrared
IPr	1,3-bis(2,6-diisopropylphenyl)imidazole
J	coupling constant
kcal/mol	kilocalorie(s) per mol
KHMDS	potassium hexamethyldisilazide
LA	Lewis acid
LDA	lithium diisopropyl amide

LUMO	lowest unoccupied molecular orbital
m	multiplet
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
mp	melting point
Ms	methanesulfonyl
NOE	nuclear Overhauser effect
NMR	nuclear magnetic resonance
Nu	nucleophile
PG	protecting group
Ph	phenyl
ppm	parts per million
i-Pr	isopropyl

q	quartet
rt	room temperature
s	singlet
t	triplet
TBS	*tert*-butyldimethylsilyl
TBAF	tetrabutylammonium fluoride
td	triplet of doublets
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFE	trifluoroethanol
TFP	2,2,3,3-tetrafluoropropoxide
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMP	2,4,6-trimethoxyphenyl
TMS	trimethylsilyl or tetramethylsilane

TOF	time-of-flight
tq	triplet of quartets
Ts	*para*-toluenesulfonyl
p-TSA	*para*-toluenesulfonic acid
UV	ultraviolet

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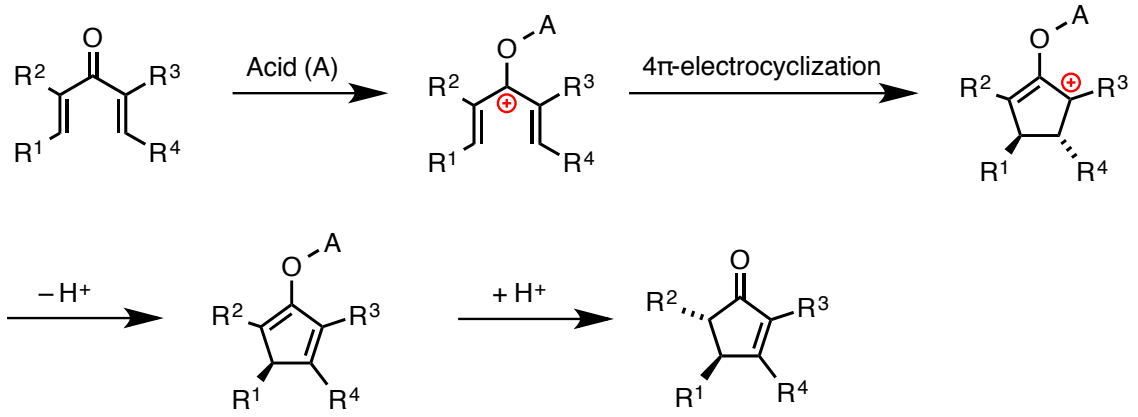
Chapter 1 Introduction

1.1 The Classical Nazarov Reaction

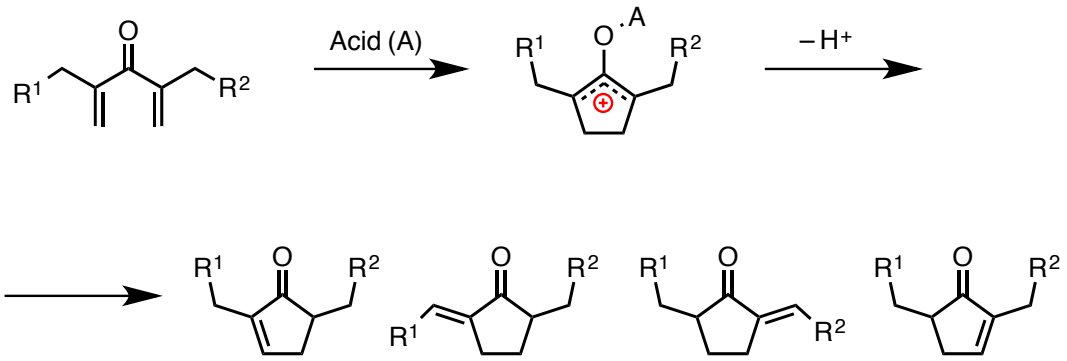
The classical Nazarov reaction is the electrocyclization of a divinyl ketone to form a cyclopentenone.[1-5] The thermal reaction proceeds under acidic conditions and follows the pathway detailed in Scheme 1.1. Complexation of the acid with the ketone generates a pentadienyl cation, which then undergoes conrotatory 4π-electrocyclization to form a cyclic oxyallyl cation. Loss of a proton from the oxyallyl cation leads to a cyclopentadiene intermediate that tautomerizes to furnish the cyclopentenone product.



Scheme 1.1 Acid mediated 4π-electrocyclization of a divinyl ketone.

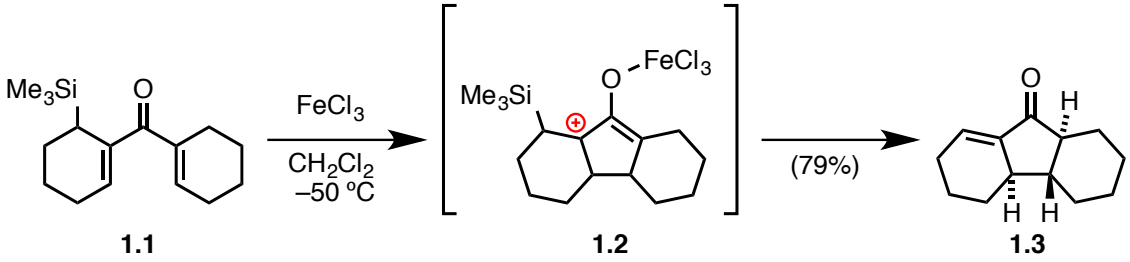
1.1.1 Controlling the Regioselectivity of the Nazarov Reaction

One of the issues regarding the classical Nazarov reaction is the regioselectivity of the proton elimination. The oxyallyl cation generated from the 4π-electrocyclization can lead to several different products, as shown in Scheme 1.2. However, an appropriate choice of the substituents on the divinyl ketone can lead to highly regioselective reactions.



Scheme 1.2 Possible regioisomeric products from the same oxyallyl cation.

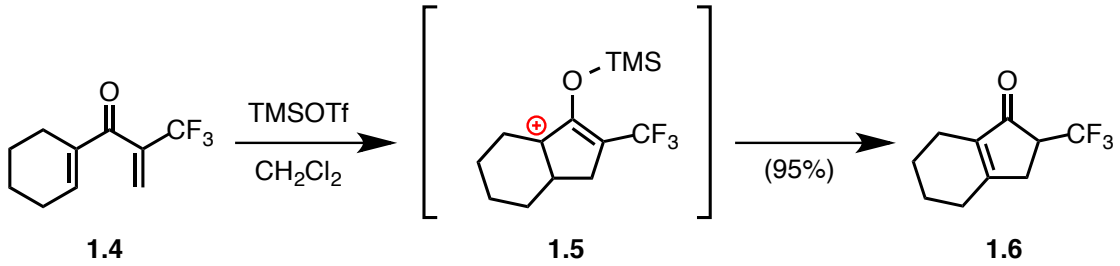
Denmark demonstrated an early example of directing the regioselectivity in the Nazarov reaction using silicon substitution on the divinyl ketone.[6-9] The divinyl ketone **1.1** underwent facile Nazarov cyclization in the presence of a Lewis acid (Scheme 1.3). The oxyallyl cation generated from the electrocyclization, **1.2**, was stabilized by the β-silicon[10] and led to regioisomer **1.3** as essentially the only product.[8]



1.1 **1.2** **1.3**

Scheme 1.3 Silicon-directed Nazarov reaction.

In an orthogonal study, Ichikawa *et al.* showed that substitution on the divinyl ketone by fluorine could also direct the elimination step.[11,12] Treatment of divinyl ketone **1.4** with TMSOTf led to the formation of oxyallyl cation **1.5**. The trifluoromethyl group destabilized the α-carbocation and led to **1.6** as the only regioisomer (Scheme 1.4).[12]



Scheme 1.4 Fluorine-directed Nazarov reaction.

1.1.2 α-Substituent Effects in the Nazarov Reaction

The α-substituents shown in Scheme 1.3 and Scheme 1.4 control the regioselectivity of the proton elimination process but they also have a secondary effect. It has been shown that α-substituents on divinyl ketones can facilitate the Nazarov cyclization.[1-5] It has been suggested that the genesis of this effect lies in the proportion of the reactive conformation of the divinyl ketone.[2] In order to undergo Nazarov cyclization the divinyl ketone must be in an *s-trans/s-trans* conformation (Figure 1.1). If R^1 and R^2 are both alkyl groups, the proportion of the *s-trans/s-trans* increases relative to the *s-trans/s-cis* conformation due to the decrease in steric interactions between R^2 and the vinyl hydrogens.

s-trans/s-cis
R^1 = alkyl, R^2 = H

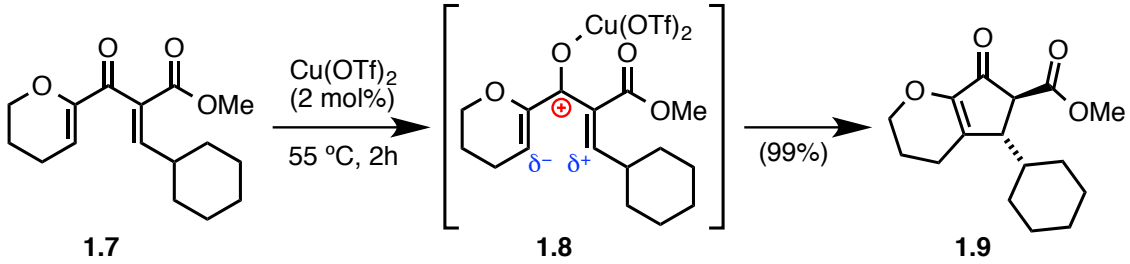
s-trans/s-trans
$R^1 = R^2$ = alkyl

Figure 1.1 Conformational requirement for the Nazarov reaction.

1.1.3 The Polarized Nazarov Reaction

The electronic nature of the substituents on the divinyl ketone has also been shown to affect the Nazarov reaction.[2,13,14] Frontier and co-workers explored the

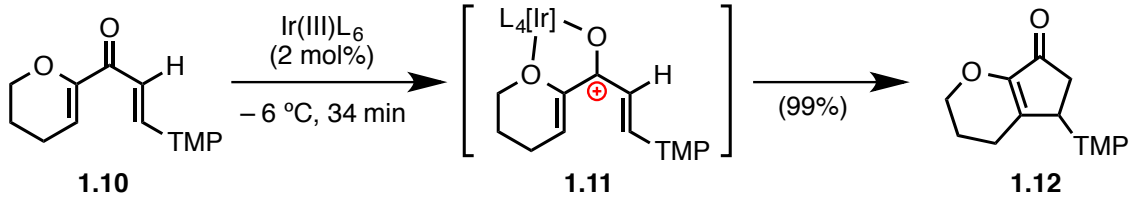
Nazarov reaction of divinyl ketones bearing both electron-donating and electron-withdrawing groups. While the Nazarov reaction typically requires a stoichiometric amount of a strong Lewis or Brønsted acid, Frontier's polarized systems underwent electrocyclization with catalytic amounts of $Cu(OTf)_2$ (Scheme 1.5). The use of both electron-donating and electron-withdrawing groups activated the divinyl ketone **1.7** by localizing the electron density in the pentadienyl cation **1.8**. The regioselectivity of the polarized Nazarov reaction was also very high, and cyclopentenone **1.9** was isolated in quantitative yield.[13,14]



1.7 **1.8** **1.9**

Scheme 1.5 The polarized Nazarov reaction undergoes electrocyclization under catalytic Lewis acid conditions.

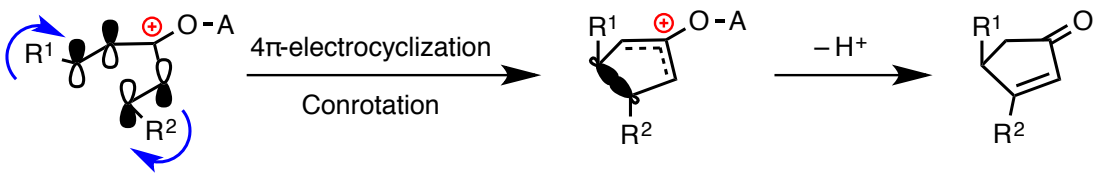
The Frontier group also demonstrated the use of bidentate Lewis acids for the catalysis of the Nazarov reaction. A bidentate Ir(III) catalyst was shown to coordinate to the ketone and the α-ether of divinyl ketone, as shown in **1.11**, which purportedly increased the proportion of *s-trans/s-trans* conformation thus increasing the rate of the reaction.[15] Treatment of **1.10** with 2 mol% of an Ir(III) catalyst led to the formation of **1.12** at – 6 ºC in quantitative yield (Scheme 1.6).



Scheme 1.6 A bidentate Lewis acid promoting the Nazarov reaction.

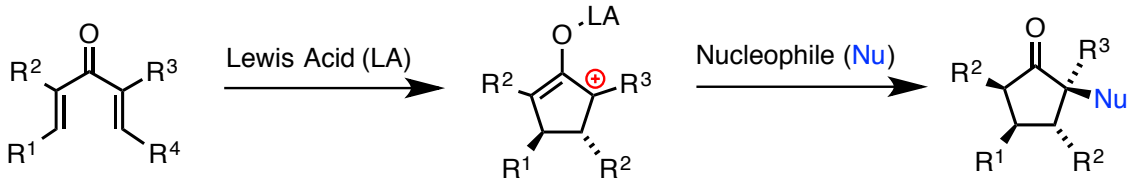
1.2 The Interrupted Nazarov Reaction

The Nazarov reaction is a 4π-electrocyclization and is therefore governed by the Woodward-Hoffman rules. In order to preserve orbital symmetry, the pentadienyl cation must undergo conrotatory cyclization (Scheme 1.7). This process, shown in Scheme 1.7, leads to an oxyallyl cation where R^1 and R^2 have a *trans* relationship. However, when the oxyallyl cation undergoes loss of a proton one of the stereocenters is lost.



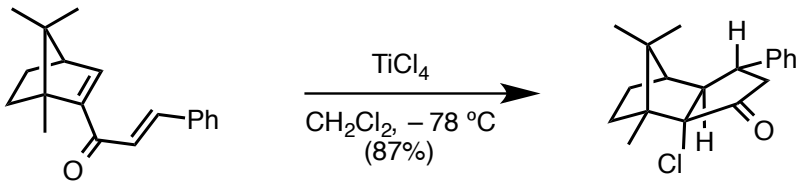
Scheme 1.7 Conrotation in the thermal Nazarov reaction.

One of the most significant contributions to Nazarov chemistry was the development of the "interrupted" Nazarov reaction by the West group. In the presence of a suitable nucleophile the oxyallyl cation generated from the Nazarov reaction could be intercepted.[16] The trapping reaction forms a new bond and preserves the stereochemistry generated from the electrocyclization (Scheme 1.8).



Scheme 1.8 Trapping the oxyallyl cation from the Nazarov reaction with a nucleophile.

In some cases the nucleophile was generated from the Lewis acid that was used to promote the reaction.[17] For instance, treatment of **1.13** with $TiCl_4$ led to the formation of cyclopentanone **1.14** (Scheme 1.9). The chloride that was liberated from the $TiCl_4$ intercepted the oxyallyl cation in a highly stereo- and regioselective manner. The Nazarov reaction has since been intercepted with many different nucleophiles including alkenes, arenes, and hydride.[17-27]

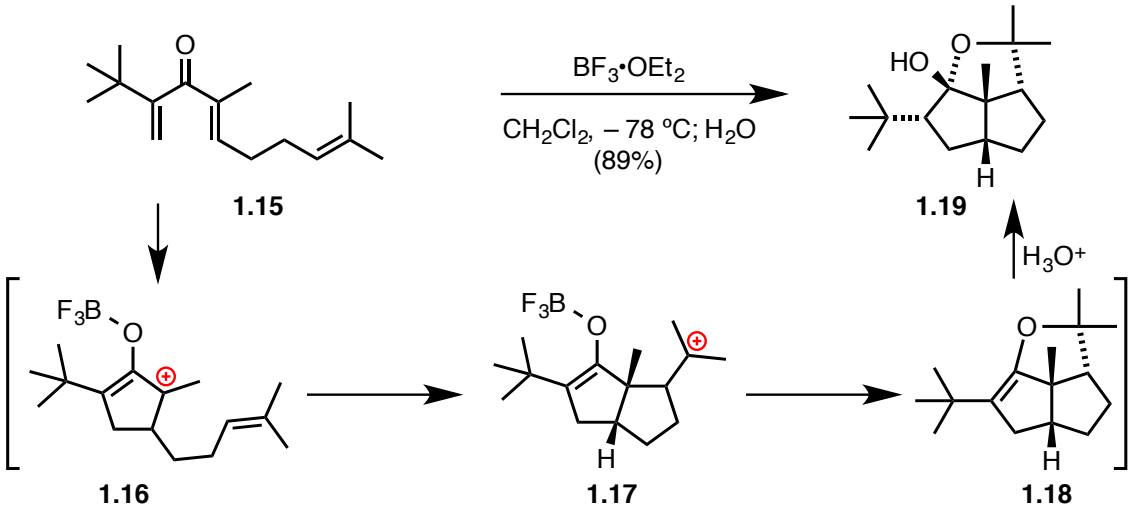


1.13 **1.14**

Scheme 1.9 Trapping the Nazarov reaction intermediate with a halide.

The Nazarov intermediate could also be trapped intramolecularly.[28] Trienone **1.15** cyclized efficiently under Lewis acid conditions to form tricyclic hemiketal **1.19** (Scheme 1.10). The oxyallyl cation, **1.16**, formed from the electrocyclization was intercepted intramolecularly by the pendent alkene to form **1.17**. The oxygen of the boron enolate then trapped the tertiary carbocation, and hydration of the resulting enol ether **1.18** during the aqueous work-up led to the final product. The overall result of this

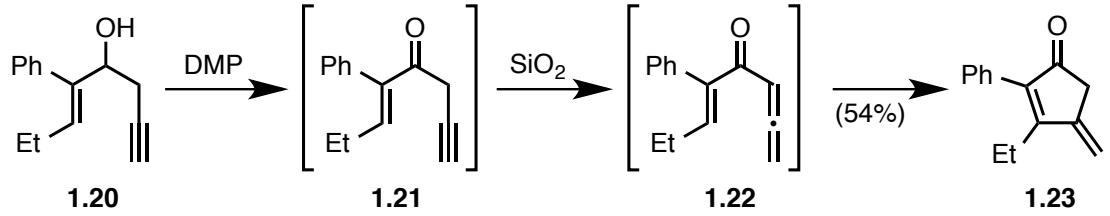
reaction was the formation of three new rings and five new stereocenters in a single operation.



Scheme 1.10 Intramolecular trapping of the Nazarov reaction with a tethered alkene.

1.3 The Nazarov Reaction of Allenyl Vinyl Ketones

Allenyl vinyl ketones (AVKs) differ from divinyl ketones in that one alkene is replaced with an allene. AVKs have been shown to be excellent substrates for the Nazarov reaction. An early example of the Nazarov reaction of AVKs came from the Hashmi group.[29] They reported on their attempts to synthesize allenyl vinyl ketones from homopropargyl alcohols. Oxidation of the alcohol **1.20** with Dess-Martin periodinane led to homopropargyl ketone **1.21**. However, attempts to purify **1.21** by silica gel chromatography led only to cyclopentenone **1.23**. Hashmi suggested that this unexpected product was the result of the homopropargyl ketone isomerizing to the allenyl vinyl ketone **1.22**, which underwent concomitant spontaneous Nazarov cyclization.



Scheme 1.11 Isomerization and Nazarov reaction of a homopropargyl ketone on exposure to silica gel.

AVKs have features that further increase their reactivity. The release of allenic strain is considered a factor that increases the rate of an AVKs reaction. Another factor may be the effect of substitution on conformation. There is less steric repulsion in the *s-trans/s-trans* conformation of an allenyl vinyl ketone compared to divinyl ketones (Figure 1.2).[1,2] This means that a higher proportion of AVKs may be set up to undergo Nazarov cyclization.

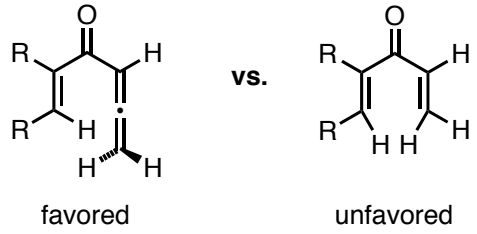
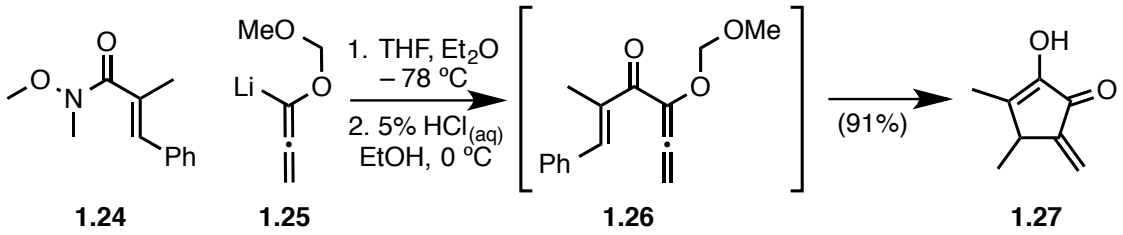


Figure 1.2 Reactive conformations of allenyl vinyl ketones compared to divinyl ketones.

1.3.1 Nazarov Reactions of Allene Ethers

The Tius group expanded the use of allenyl vinyl ketones for the Nazarov reaction.[1,30,31] They reported that ether-substituted AVKs underwent very facile electrocyclization. In fact, the AVK could not be isolated.[1,32] Addition of lithioallene **1.25** to Weinreb amide **1.24** gave the cyclopentenone **1.27** directly (Scheme 1.12). Unlike in a classical Nazarov reaction, Tius' allenyl ethers did not undergo proton loss.

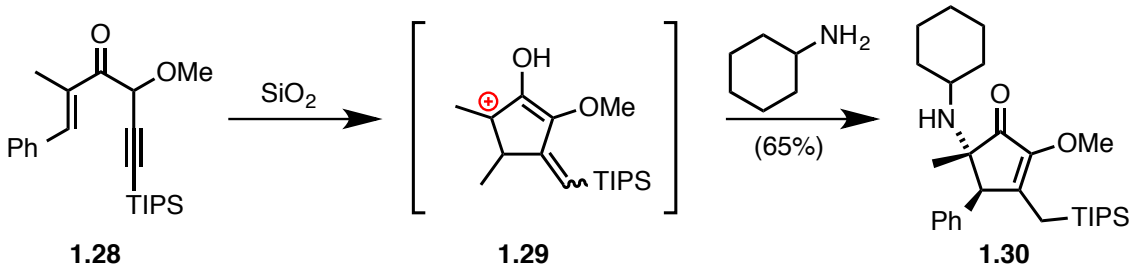
Instead, loss of the methoxymethyl group occurred to generate a hydroxycyclopentenone, a completely enolized α-diketone This sort of elimination process would obviously be restricted to AVKs in which the allene ether has a substituent that can be lost as a stable carbocation.[1]



1.24 **1.25** **1.26** **1.27**

Scheme 1.12 Allene ether containing AVKs undergo spontaneous Nazarov cyclization.

Allene ethers can also be used for more straightforward interrupted Nazarov reactions. Tius has shown that in the presence of primary and secondary amines[33] or indoles,[34] the Nazarov reaction results in nitrogen-trapped products. For instance, exposure of homopropargyl ketone **1.28** to silica gel led to isomerization and Nazarov cyclization, and the resulting oxyallyl cation, **1.29,** was then trapped with cyclohexylamine to form **1.30** (Scheme 1.13). In this case the ether substituent was preserved and the exocyclic olefin migrated into the ring to become conjugated with the ketone.

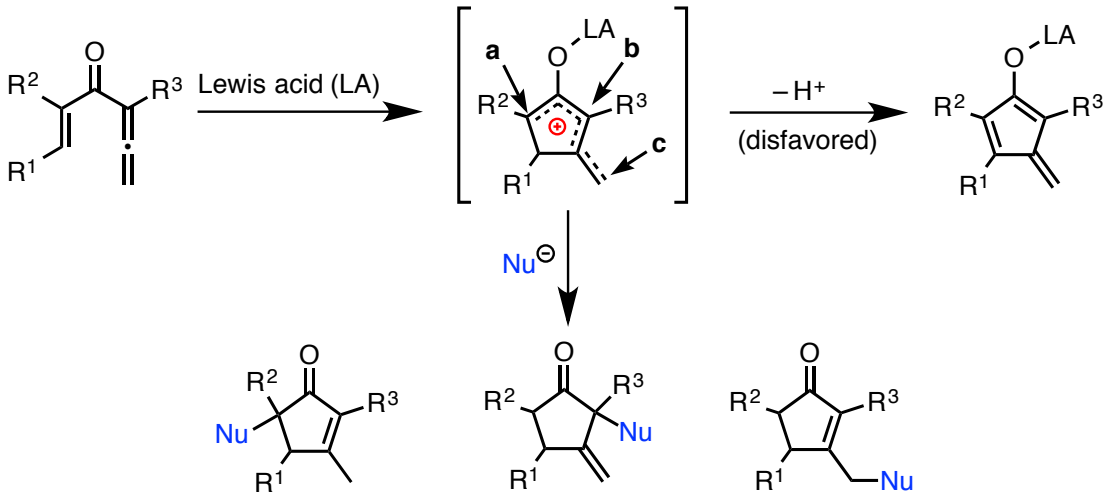


1.28 **1.29** **1.30**

Scheme 1.13 Trapping the oxyallyl cation from the Nazarov reaction of an ether-bearing AVK with an amine.

1.3.2 Development of the Interrupted Nazarov Reaction of Carbon Substituted AVKs

Allenyl vinyl ketones of the general type shown in Scheme 1.14 should be particularly well suited to participate in the interrupted Nazarov reaction.[35] The oxyallyl cation of an AVK has three resonance forms that should render it more stable than the analogous oxyallyl cation of a divinyl ketone. It is also worth noting that the immediate elimination product would be a fullvene that would be relatively high in energy and therefore disfavored (Scheme 1.14). However, trapping such an AVK can also be more complicated. There are three possible sites, **a**, **b** and **c,** on the oxyallyl cation, as shown in Scheme 1.14, at which a nucleophile might attack, but this offers the potential to make a diverse set of products from a single AVK starting material.



Scheme 1.14 Possible trapping sites on the oxyallyl cation derived from an allenyl vinyl ketone.

A series of substituted AVKs was synthesized by the Burnell group to test their abilities to undergo the Nazarov reaction. The AVKs were divided into three groups based on their substitution pattern. Type I AVKs have an alkyl substituent α to the ketone on the allene, Type II AVKs have an alkyl substituent α to the ketone on the alkene, and AVKs of Type III have hydrogens in both α positions (Figure 1.3).[36]

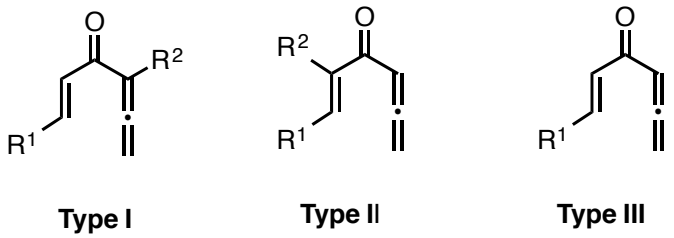
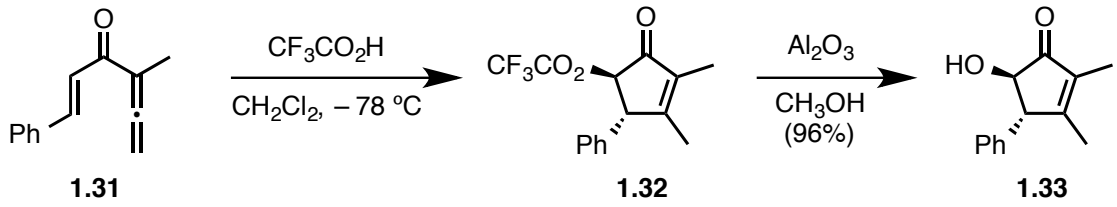


Figure 1.3 Types of allenyl vinyl ketones.

All three types of AVK were shown to undergo the Nazarov reaction. However, the relative rates of reaction and stability of the molecules were quite different. Type III AVKs could be purified by flash chromatography on silica gel but were the least reactive. Relatively long reaction times were necessary, and the intermediate oxyallyl

cation could not be trapped due to competing Michael reactions or Diels-Alder reactions involving the allene. AVKs of Type II underwent rapid Nazarov cyclization and the reaction could be interrupted with a diene. Unfortunately, purification of this type of AVK was very difficult as they decomposed on exposure to silica. They must be used immediately after preparation due to very significant degradation in solution. Finally, Type I AVKs underwent the Nazarov reaction rapidly, but if the oxyallyl cation were not intercepted by a nucleophile or alkene then the product was intractable material. Nevertheless, Type I AVKs were very good substrates for a variety of interrupted Nazarov reactions. Furthermore, they can be purified by flash chromatography and are stable for several months at –20 ºC. It was determined from a computational study that the electronically preferred point of trapping in an AVK is position **a** (Scheme 1.14), α to the ketone on the alkene, even when that position is substituted as in a Type II AVK.[36]

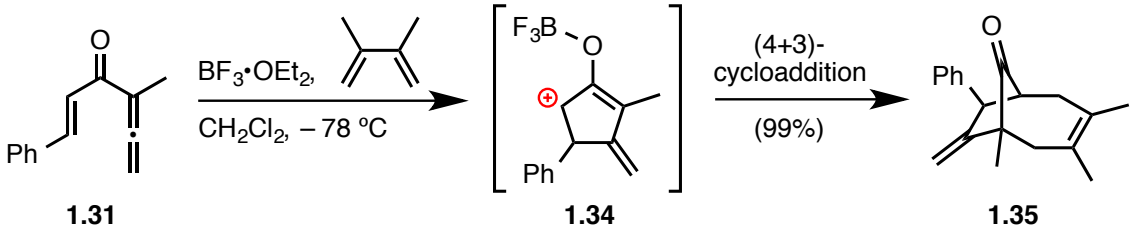
Nazarov reactions of allenyl vinyl ketones were initiated by protic and Lewis acids.[35] The reaction of AVK **1.31** with trifluoroacetic acid promoted the electrocyclization, and the conjugate base intercepted the oxyallyl cation to yield trifluoroacetate **1.32**. Purification on basic alumina furnished the hydroxycyclopentenone **1.33** in excellent yield. (Scheme 1.15).[35]



Scheme 1.15 Trapping of trifluoroacetate in the interrupted Nazarov reaction.

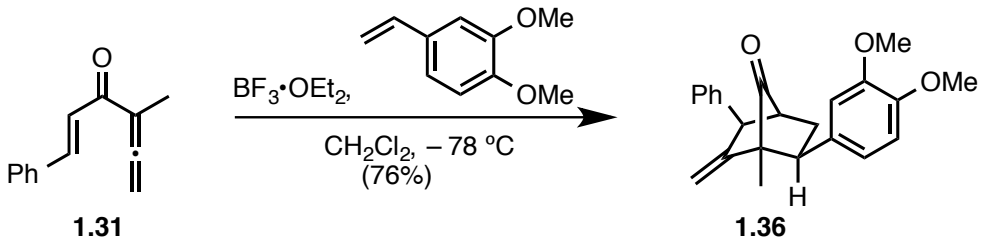
When BF_3•OEt_2 was employed as the acid, the Lewis acid did not generate a nucleophilic counterion, and it was possible to add a nucleophilic species to trap the oxyallyl cation. The oxyallyl cations generated from the Nazarov reaction of AVKs have been trapped with a variety of nucleophiles including halides,[37] phosphines,[38] nitrogen heterocycles,[39] and nucleophilic carbon species.[36,40-42] The most synthetically useful of all of these modes of trapping are those that lead to the creation of new carbon-carbon bonds.

Electron-rich alkenes and 1,3-butadienes have been shown to be effective trapping reagents in interrupted Nazarov reactions.[18,20,22] These reagents were also useful for interrupted Nazarov reactions of allenyl vinyl ketones.[40] Treatment of AVK **1.31** with BF_3•OEt_2 in the presence of 2,3-dimethylbutadiene at –78 ºC led to the quantitative formation of bicyclic compound **1.35** by a (4+3)-cycloaddition onto the oxyallyl cation **1.34** (Scheme 1.16**)**. The tandem Nazarov reaction/(4+3)-cycloaddition is a particularly attractive synthetic process with an AVK since overall three new carbon-carbon bonds are formed and in many instances the process is highly regio- and stereoselective.



Scheme 1.16 Nazarov reaction followed by (4+3)-cycloaddition.

Electron-rich alkenes intercepted the oxyallyl cations resulting from the Nazarov reactions of AVKs by (3+2)-cycloadditions. Nazarov reaction of AVK **1.31** in the presence of 3,4-dimethoxystyrene led to the formation of the (3+2) adduct **1.36** in good yield (Scheme 1.17) and with very high regio- and stereoselectivity. The addition of the diene and styrene occurred exclusively to the face of the oxyallyl cation opposite the phenyl substituent. The more electron-rich end of the alkene of styrene added to the electrophilic position, **a**, of the oxyallyl cation.



Scheme 1.17 Nazarov reaction of 1.31 followed by (3+2)-cycloaddition of 2,3-dimethoxystyrene.

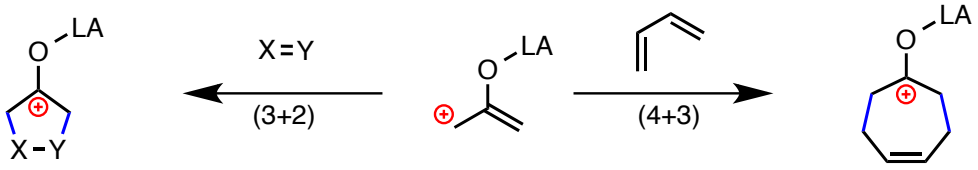
This thesis highlights some current developments in the use of allenyl vinyl ketones as substrates for the interrupted Nazarov reaction. The experimental results presented here focus on the various selectivities that arise in the course of the Nazarov reaction. Chapter 2 describes the factors that affect the (3+2) or (4+3)-cycloaddition of substituted dienes to the oxyallyl cation generated from the Nazarov reaction of AVKs.

In Chapter 3 the torquoselectivity of AVKs bearing terminally substituted allenes is explored. Finally, Chapter 4 details the development of a synthetic methodology for the synthesis of allenyl vinyl ketones bearing tethered 1,3-dienes.

Chapter 2
(3+2)- Versus (4+3)-Cycloadditions of Substituted Dienes onto Oxyallyl Cations Derived from the Nazarov Reaction of Allenyl Vinyl Ketones

2.1 Introduction

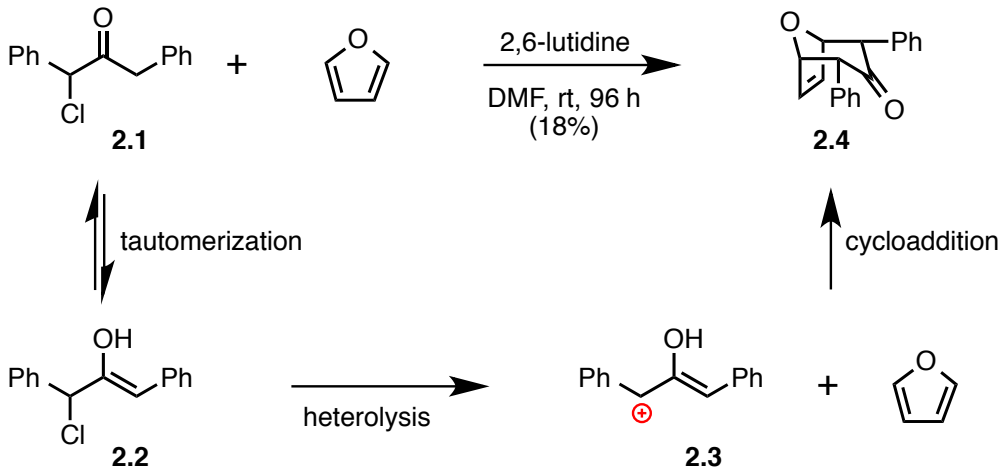
The chemistry of allyl cations has been widely studied in recent decades.[43,44] Of particular synthetic interest in the context of the Nazarov reaction are cycloaddition reactions of oxyallyl cations.[44-49] In the presence of an appropriate 2π donor, oxyallyl cations can be intercepted by a (3+2)-cycloaddition.[49] Due to the orbital requirements, the (3+2) addition must occur by a stepwise mechanism. Many different 2π systems are capable of undergoing (3+2)-cycloadditions to oxyallyl cations including alkenes, alkynes, carbonyls, and even diethyl azodicarboxylate.[49] This generality allows for the formation of many cyclic and heterocyclic systems. The reaction of a 1,3-diene with an oxyallyl cation provides a convenient method for the synthesis of seven-membered rings from simple starting materials via a (4+3)-cycloaddition, although (4+3) additions onto oxyallyl cations typically require electron-rich dienes. The oxygen function on an oxyallyl cation helps to stabilize the allyl cation through electron donation, and it provides a convenient handle for further synthetic manipulation.



Scheme 2.1 Illustration of (3+2)- and (4+3)-cycloadditions of oxyallyl cations.

2.1.1 Generation of Oxyallyl Cations and Their Cycloadditions

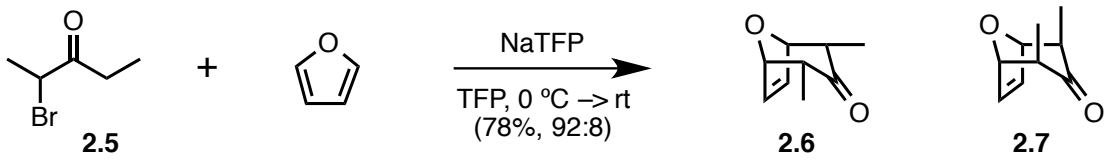
A key process leading to the cycloadditions of oxyallyl cations is the generation of the allyl cation itself. The method of generating the allyl cation has been reported to play a role in its reactivity.[41,43,44,50,51] One of the earliest reports of an oxyallyl cation undergoing a cycloaddition was by Fort in 1962.[52] Treatment of α-chloroketone **2.1** with 2,6-lutidine in the presence of furan led to the isolation of bicyclic compound **2.4**, albeit in low yield. This result was consistent with the formation of enol **2.2** followed by loss of chloride to form oxyallyl cation **2.3**. This intermediate could then undergo cycloaddition with furan to form **2.4**.



Scheme 2.2 Generation of an oxyallyl cation from an α-haloketone.

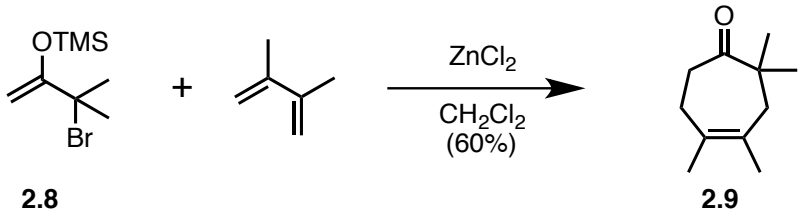
The generation of oxyallyl cations from α-haloketones was further developed by Föhlisch *et al.*[53-56] The use of polar solvents had a beneficial effect on the cycloaddition reaction of oxyallyl cations. The reaction of 2-bromopentan-3-one, **2.5**, with sodium 2,2,3,3-tetrafluoropropoxide (TFP) led to the formation of **2.6** and **2.7** in good yield. If the (4+3)-cycloaddition was concerted the major product, **2.6**, would have arisen from a "compact" transition state. A compact transition state would have the diene moiety of

furan *endo* to the oxyallyl cation. The "extended" transition state that would have led to **2.7** would have placed furan's diene moiety *exo* to the oxyallyl cation.



Scheme 2.3 (4+3)-Cycloaddition of furan and the oxyallyl cation derived from 2-bromopentan-3-one.

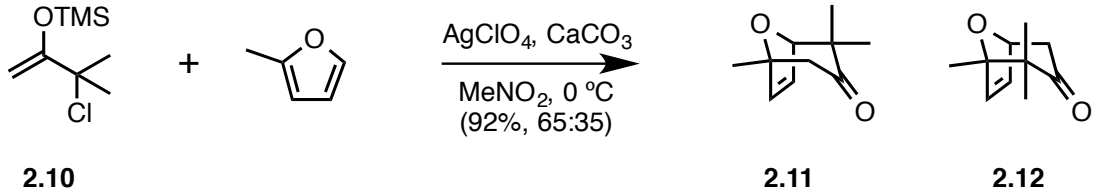
The oxyallyl cations in Scheme 2.2 and Scheme 2.3 both arose from α-haloketones. Other leaving groups can be substituted for halogens, including mesyloxy[54] and tosyloxy[57] groups, in order to form oxyallyl cations by the same base mediated process. An alternative approach for generating oxyallyl cations involves the use of reagents to actively "pull off" the leaving group.[43] The TMS enol ether **2.8** was treated with $ZnCl_2$ in the presence of 2,3-dimethyl-1,3-butadiene to form cycloheptenone **2.9**.[58]



Scheme 2.4 Generation of an oxyallyl cation by "pulling" bromide off TMS enol ether 2.8.

A similar approach was used by Shimizu to generate allyl cations from 2-(trimethylsiloxy)allyl chlorides. The chloride could be abstracted using $AgClO_4$ in the presence of a diene to initiate (4+3)-cycloadditions.[59] The reaction of the TMS enol

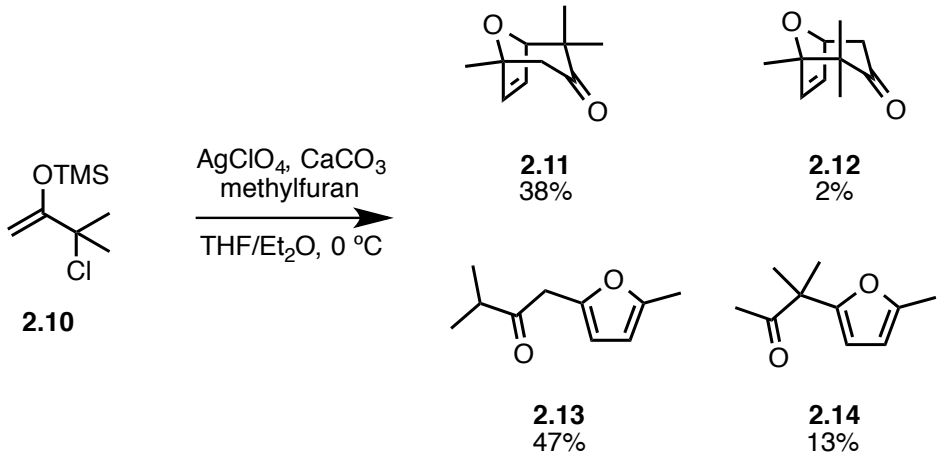
ether **2.10** and methylfuran with $AgClO_4$ led to (4+3) products **2.11** and **2.12** in high yield but with modest regioselectivity (Scheme 2.5).



2.10 **2.11** **2.12**

Scheme 2.5 Chloride extraction with $AgClO_4$ to generate an oxyallyl cation from TMS enol ether 2.10.

Shimizu also noted a profound solvent effect on the reaction of **2.10** with 2-methylfuran. When the reaction was carried out in THF/Et_2O, instead of $MeNO_2$, the same (4+3) products, **2.11** and **2.12**, were obtained. The yield was lower but the selectivity was much higher. However, the major product from the reaction was furan **2.13**. The change in product distribution was rationalized as arising from a change in mechanism. In the polar solvent, $MeNO_2$, the reaction appeared to occur via a concerted mechanism. The change to less polar THF/Et_2O led to a stepwise mechanism.



Scheme 2.6 Reaction of 2.10 with methylfuran in THF/Et_2O solvent.

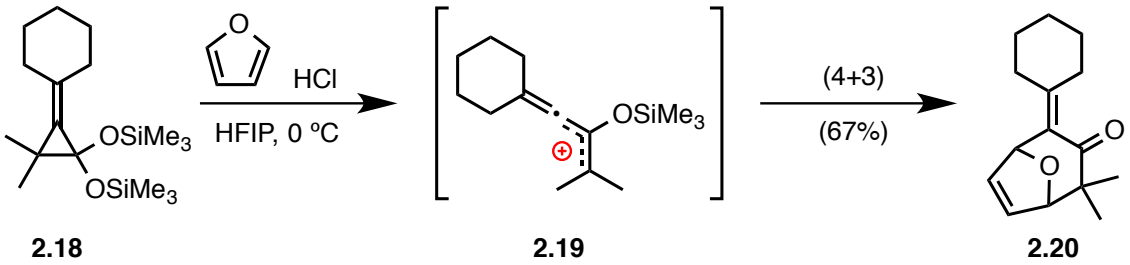
The reduction of α,α'-dihaloketones is a well studied method for the generation of oxyallyl cations.[43,45,60,61] It has been demonstrated that the reactions of oxyallyl cations change as a result of the reductant. For example, using NaI/Cu to initiate the reaction of 2,3-dibromo-3-pentanone with furan led to the formation of products **2.15**, **2.16**, and **2.17** in a ratio of 91:3:6. However, when Zn/Cu was used as the reducing agent the same products were formed in a 75:10:15 ratio.[50] The use of $Fe_2(CO)_9$ led to the formation of only **2.15** and **2.17** in a ratio of 44:56 (Table 2.1).[62] Harmata suggested that the (4+3) products **2.15** and **2.16** arose from a concerted reaction with furan.[43] The product with substituents up and down, **2.17**, was thought to form by a stepwise addition of furan to the oxyallyl cation.[43]

Table 2.1 Product Ratios from the Cycloaddition of Furan to an Oxyallyl Cation under Different Initiation Conditions.

Reagents	2.15	2.16	2.17
NaI/Cu	91	3	6
Zn/Cu	75	10	15
$Fe_2(CO)_9$	44	0	56

2.1.2 Reaction of Oxyallyl Cations from Alkylidenecyclopropanone Acetals

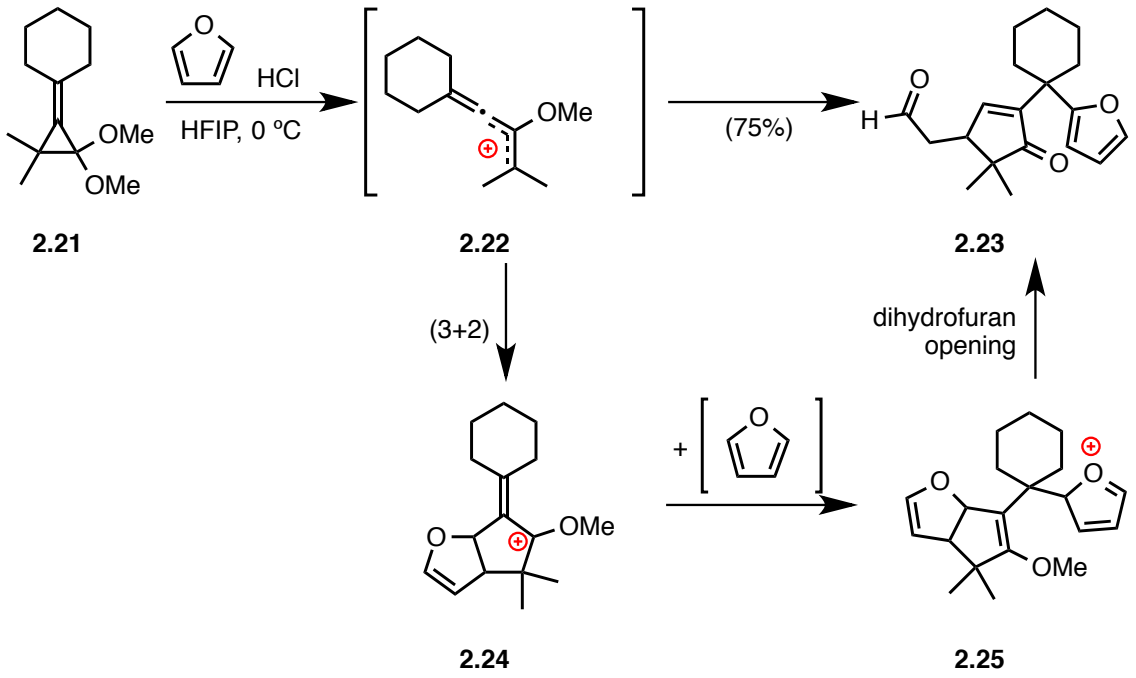
Fujita and co-workers reported reactions of alkylideneoxyallyl cations formed from the acid-mediated ring opening of alkylidenecyclopropanone acetals.[63-65] They reported both (4+3)- and (3+2)-cycloaddition reactions.[51] The reaction of bis(trimethylsilyl)acetal **2.18** with HCl in the presence of furan produced **2.20** as the sole product (Scheme 2.7). The formation of **2.20** was consistent with a (4+3)-cycloaddition of furan onto oxyallyl cation **2.19**.



2.18 **2.19** **2.20**

Scheme 2.7 (4+3)-Cycloaddition of furan with silyloxyallyl cation 2.19.

When the reaction was carried out with the dimethyl acetal **2.21**, the tricyclic compound **2.23** was formed as the only product in good yield. Though not immediately obvious, the formation of **2.23** probably proceeded via initial (3+2)-cycloaddition of furan to oxyallyl cation **2.22** to form intermediate **2.24**, as shown in Scheme 2.8. Addition of a second equivalent of furan to the allyl cation **2.24** would form **2.25**, which upon acid-mediated ring-opening of the bicyclic furan and loss of a methyl group would furnish **2.23**.

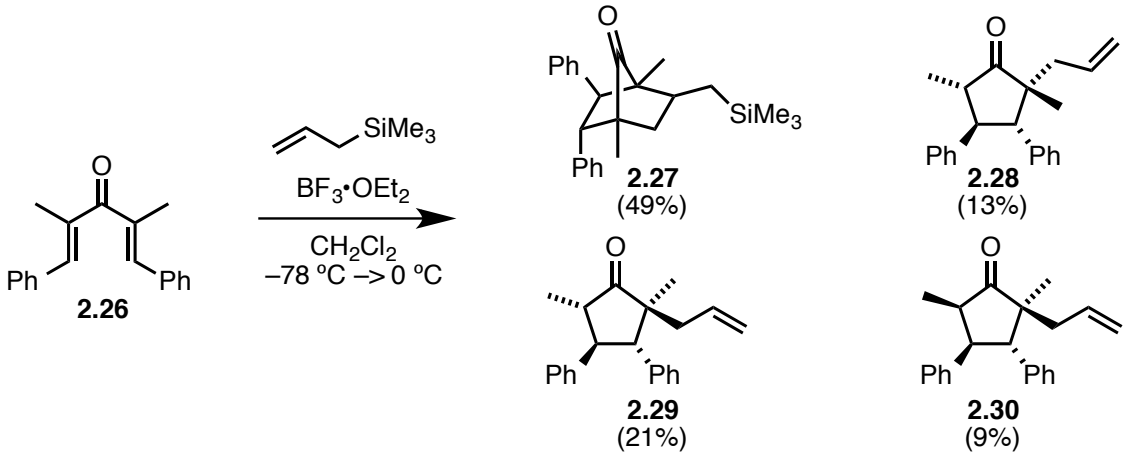


Scheme 2.8 Formation of 2.23 through the double addition of furan to methoxyallyl cation 2.22.

2.1.3 Intercepting the Oxyallyl Cation from the Nazarov Reaction of Divinyl Ketones

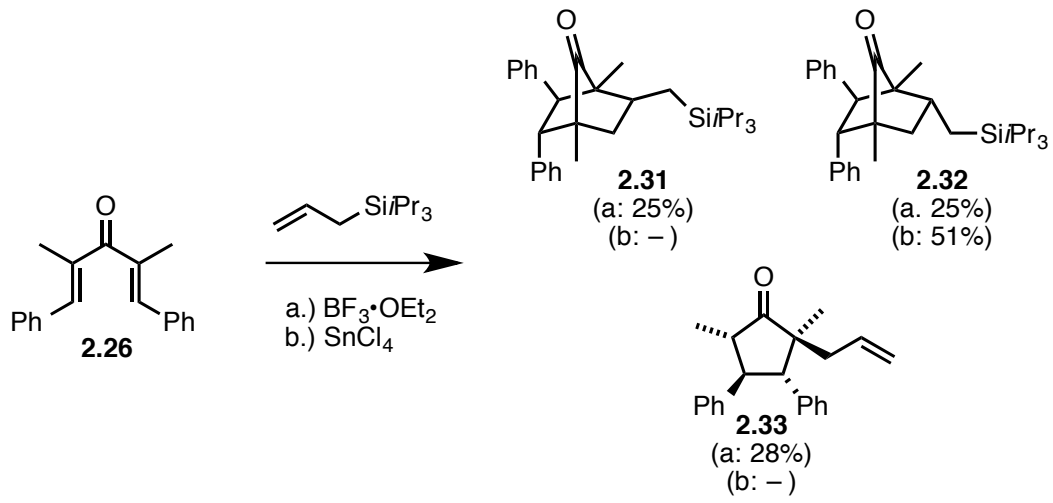
The West group has devoted considerable effort in the development of the interrupted Nazarov reaction (0 - 1.2). In 2000 they showed that the oxyallyl cation derived from a Nazarov reaction could be intercepted using an allyl silane by (3+2)-

cycloaddition.[18] Treatment of dienone **2.26** with BF_3•OEt_2 at –78 ºC in the presence of allyltrimethylsilane led to the isolation of the (3+2) adduct **2.27** as a single diastereomer (Scheme 2.9). The reaction also gave three diastereomeric allylated cyclopentenones **2.28-2.30** in a combined yield of 43%.



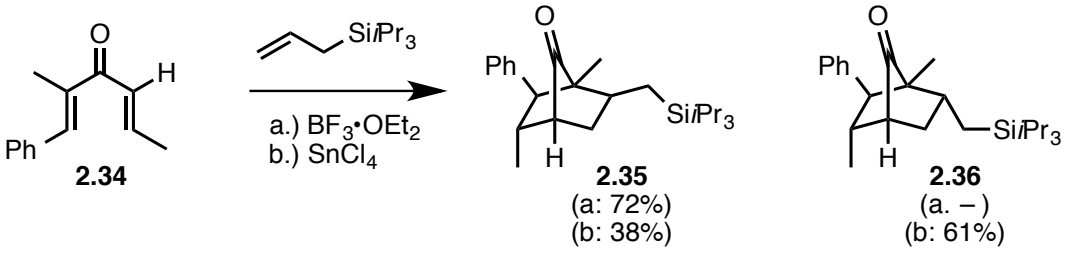
Scheme 2.9 An interrupted Nazarov reaction with allyltrimethylsilane.

In an effort to increase the proportion of the (3+2) product, allyltriisopropylsilane was employed as the trapping reagent. The bulkier triisopropylsilane was expected to retard the desilylation process and thus favor the (3+2)-cycloaddition. Exposure of a mixture of **2.26** and allyltriisopropylsilane to BF_3•OEt_2 led to less of the allylated products, but the yield of (3+2) product was still modest and the diastereoselectivity was poor. As shown in Scheme 2.10, products **2.31** and **2.32** were formed in nearly equal amounts. However, it was discovered that the Lewis acid played an important role in the diastereoselectivity of the reaction. When $SnCl_4$ was used instead of BF_3•OEt_2 only product **2.32** was isolated (Scheme 2.10).



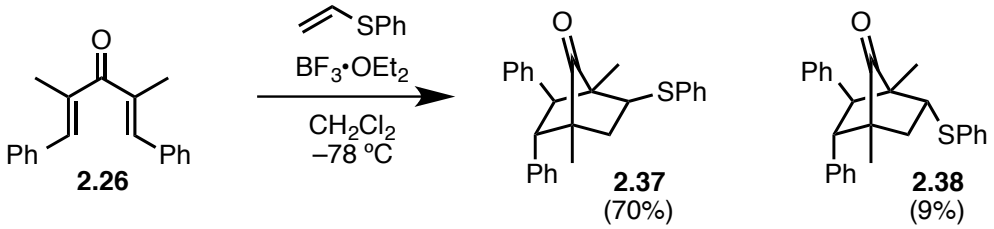
Scheme 2.10 Nazarov reaction promoted by BF_3•OEt_2 or $SnCl_4$ followed by trapping of the oxyallyl cation with allyltriisopropylsilane.

The regioselectivity of the (3+2)-cycloaddition was very high. When the unsymmetrical dienone **2.34** was trapped with triisopropylallylsilane using BF_3•OEt_2 a single diastereomer, **2.35**, was obtained in good yield (Scheme 2.11). When $SnCl_4$ was used to promote the Nazarov reaction a slight preference for the other epimer, **2.36**, was observed, but once again the regioselectivity was very high. The regioselectivity in these systems was consistent with a rationale proposed by Noyori that initial bond formation results in the more stable enolate.[66]



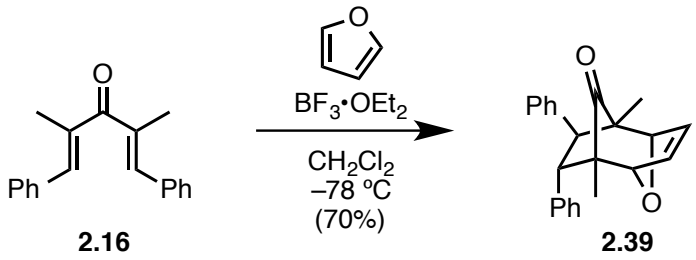
Scheme 2.11 Regioselectivity in the tandem Nazarov/(3+2) reaction with an unsymmetrical dienone and an allylsilane.

In a follow-up study, the West group extended the tandem Nazarov/(3+2)-cycloaddition to vinyl sulfides.[22] The sulfide functional group was chosen because it offers greater versatility for further chemical manipulation than a silyl group. Reaction of **2.26** with BF_3•OEt_2 and phenyl vinyl sulfide efficiently yielded bicyclic products **2.37** and **2.38** (Scheme 2.12). The diastereomer with the sulfide group "up" was the preferred product as it had been in the reactions with the allylsilanes. Substitution at the β position of the vinyl sulfides was tolerated but the yields decreased substantially.



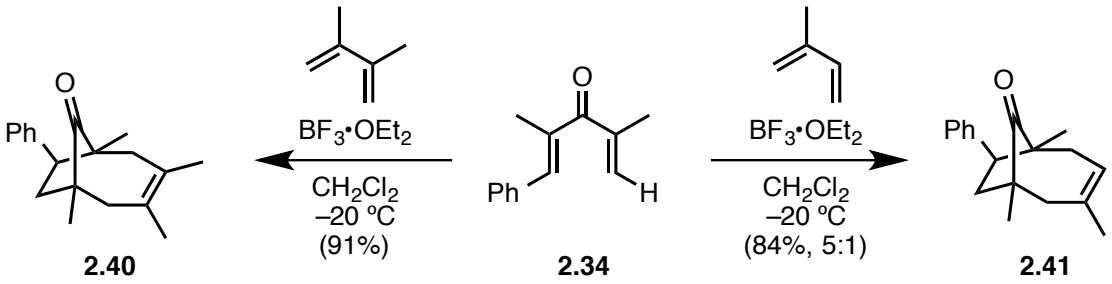
Scheme 2.12 Trapping the oxyallyl cation intermediate with phenyl vinyl sulfide.

The success of the tandem Nazarov/(3+2)-cycloaddition reaction prompted the West group to examine the related reaction with 1,3-dienes.[20] The study began with dienone **2.26** and furan (Scheme 2.13). Furan has often been used for (4+3)-cycloaddition reactions. It is electron rich, and the diene moiety is frozen in the *s-cis* geometry that would be required for a concerted cycloaddition. The result was the single product **2.39**, which would have arisen by (4+3)-cycloaddition via a compact transition state.



Scheme 2.13 Tandem Nazarov/(4+3)-cycloaddition of a divinyl ketone and furan.

When unsymmetrical dienone **2.34** was cyclized in the presence of 2,3-dimethyl-1,3-butadiene and isoprene the cycloadducts **2.40** and **2.41**, respectively, were isolated in very good yields. The reaction with isoprene also exhibited reasonably high regioselectivity forming predominantly the isomer shown in Scheme 2.14.



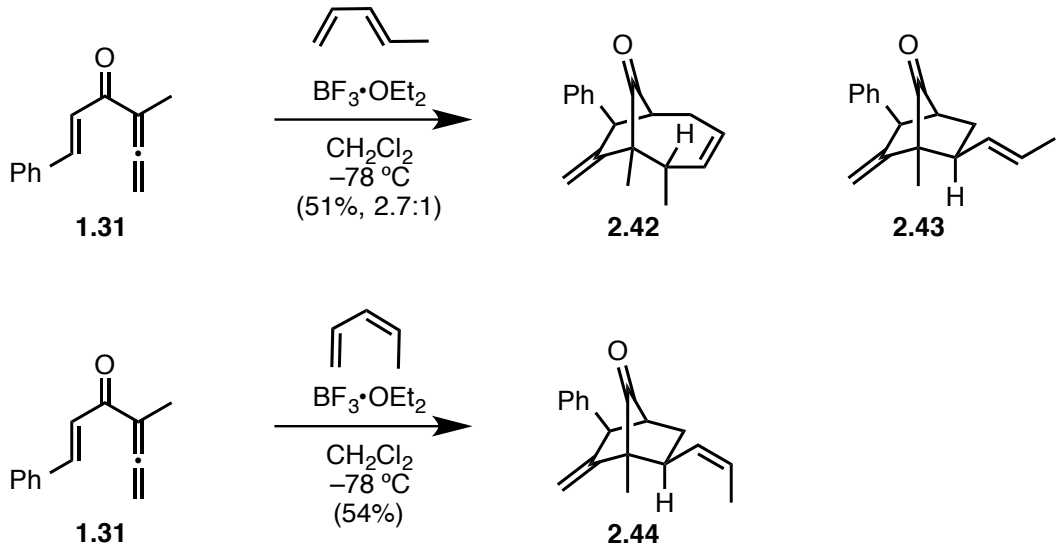
Scheme 2.14 Trapping an unsymmetrical oxyallyl cation with acylic dienes.

The oxyallyl cation derived from the Nazarov reaction of divinyl ketones is a remarkably good partner for cycloaddition reactions. The variety of alkenes and dienes that undergo (3+2) and (4+3) reactions to intercept Nazarov reactions highlights the synthetic potential of this process.

2.1.4 (3+2) versus (4+3)-Cycloadditions of Allenyl Vinyl Ketones

Allenyl vinyl ketones have been shown to be useful precursors for the interrupted Nazarov reaction (0 - 1.3). In many cases the Nazarov reaction of AVKs in the presence

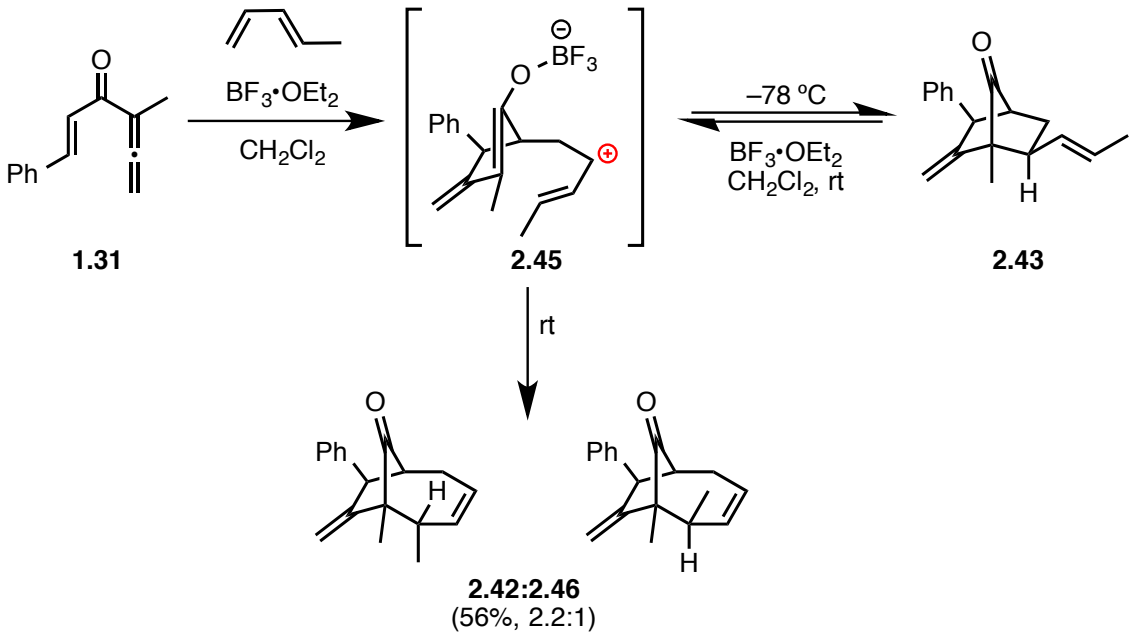
of acyclic 1,3-dienes led to (4+3)-cycloaddition products.[40] However, in some instances mixtures of products were formed. When the Nazarov reaction of AVK **1.31** was intercepted with *trans*-piperylene two products were produced. The (4+3) product **2.42** and the (3+2) product **2.43** were obtained in a 2.7:1 ratio and in a combined yield of 51% (Scheme 2.15). When the same reaction was carried out with *cis*-piperylene only the (3+2) product, **2.44**, was formed in a comparable yield. The stereoselectivity of both the (4+3)- and the (3+2)-cycloaddition was high.



Scheme 2.15 Nazarov reactions of AVK 1.31 in the presence of *trans*-piperylene and of *cis*-piperylene.

The (3+2)-cycloadducts likely arise by a stepwise mechanism. In the reaction between AVK **1.31** and *trans*-piperylene, the initial bond should form between the most electrophilic position of the oxyallyl cation[36] and the less hindered and more electron-rich end of the diene. This would give intermediate **2.45** (Scheme 2.16). Harmata suggested that the allyl cation in intermediate **2.45** could react with the enolate to form either the (3+2) product or the (4+3) product.[43] If the second bond-forming reaction

were reversible, exposure of **2.42** or **2.43** to acidic conditions should equilibrate the compound to the more stable product through intermediate **2.45**. When **2.43** was subjected to BF_3•OEt_2 at room temperature, the (4+3) products **2.42** and **2.46** were formed, as shown in Scheme 2.16.[40]



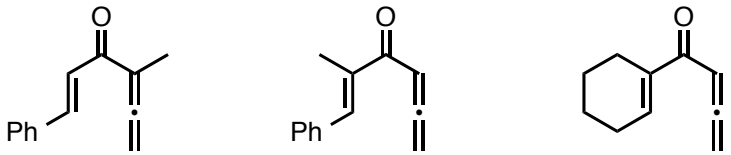
Scheme 2.16 Harmata's proposed stepwise mechanism that would lead to both the (3+2)- and the (4+3)-cycloaddition products.

The reactions shown in Scheme 2.15 highlight the importance of the substitution of the diene in the (3+2)- and (4+3)-cycloadditions. This prompted an investigation into the factors that control the selectivity of cycloaddition reactions with the oxyallyl cations derived from AVKs.[41]

2.2 Results and Discussion

AVKs **1.31**, **2.47** and **2.48**, which are Type I and Type II AVKs, were chosen to test the selectivity of a variety of substituted dienes in the cycloadditions of oxyallyl

cations (Figure 2.1). These AVKs had previously been shown to undergo Nazarov cyclization and subsequent trapping of the oxyallyl cation.[36]

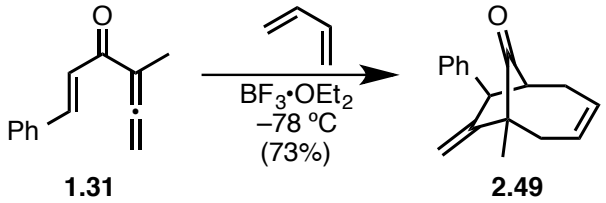


1.31 **2.47** **2.48**

Figure 2.1 AVKs used to determine the (3+2)- vs. (4+3)-cycloaddition selectivity.

2.2.1 Cyclization and Trapping with Substituted Dienes.

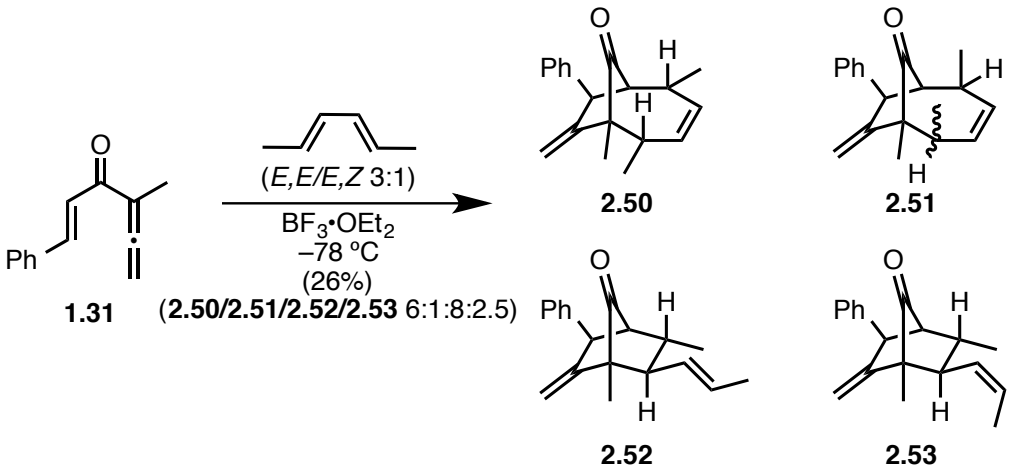
The Nazarov reaction of Type I AVK **1.31** in the presence of 1,3-butadiene led exclusively to the (4+3)-cycloaddition product **2.49** in good yield (Scheme 2.17). No (3+2)-cycloaddition product was detected. This result was consistent with the previous reaction of **1.31** with 2,3-dimethyl-1,3-butadiene, which had intercepted the oxyallyl cation in very high yield by (4+3)-cycloaddition.[40] The result with 1,3-butadiene demonstrated that in the simplest case the energy barrier for (4+3)-cycloaddition was significantly lower than the barrier for (3+2)-cycloaddition and that the oxyallyl cation derived from **1.31** was sufficiently reactive to undergo (4+3)-cycloaddition with an unactivated diene.



1.31 2.49

Scheme 2.17 Nazarov reaction of AVK 1.31 in the presence of 1,3-butadiene.

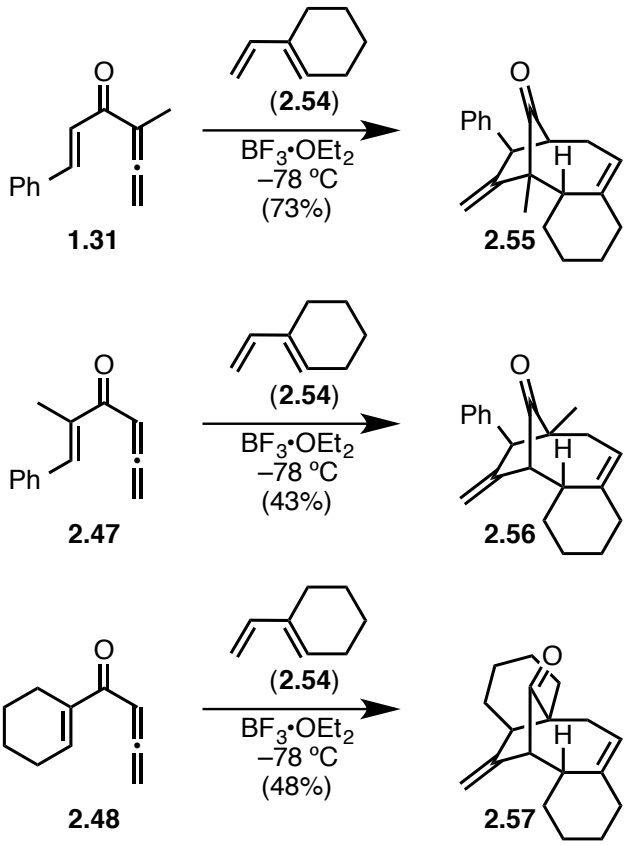
When substitution was placed on both termini of the diene, as in 2,4-hexadiene (available commercially, but only 75% the *E*,*E*-isomer), the result was a mixture of (3+2) and (4+3) products (Scheme 2.18). The overall yield of the reaction was substantially lower than with 1,3-butadiene, which could be rationalized by increased steric interactions between the oxyallyl cation and the diene. The major product was identified as the (4+3)-cycloadduct **2.50**. Its relative stereochemistry was determined using nuclear Overhauser effect (NOE) experiments. The stereochemistry of the other (4+3) product, **2.51**, could not be rigorously determined because it was formed in such a small amount and could not be isolated from the (3+2) products. The (3+2) isomers, **2.52** and **2.53**, were formed with a high degree of stereoselectivity; the relative stereochemistry of both was evident from the NOE data. The (3+2) product **2.53** with a *Z* alkene in the side chain almost certainly formed from the approximately 25% of the 2,4-hexadiene that was the *E,Z* isomer.



Scheme 2.18 Nazarov reaction of AVK 1.31 in the presence of 2,4-hexadiene.

Diene **2.54** is substituted at only one terminus, but because of the vicinal substituent it should be electronically similar to 2,4-hexadiene. Intercepting the oxyallyl cations from AVKs **1.31, 2.47** and **2.48** with **2.54** led exclusively to the (4+3) products **2.55-2.57**. The relative stereochemistry of **2.55** was determined by NOE analysis, and it was confirmed by X-ray crystallography. The trapping reaction occurred with a high degree of stereoselectivity since only one Nazarov product was observed. The stereochemistry for products **2.56** and **2.57** was assigned from the NOE results and showed the same relative orientation as **2.55**. The yields of **2.56** and **2.57** were substantially lower than the yield of **2.55.** This was probably because AVKs **2.47** and **2.48** are significantly less stable than **1.31**. (Attempts to isolate these AVKs had resulted in their almost complete degradation.) These AVKs were prepared from the precursor vinyl homopropargyl alcohols by oxidation and isomerization of the alkyne with base, and then the AVKs were subjected to the Nazarov conditions without purification and without delay. Thus, the yields for the reactions with these AVKs are over the three steps from the alcohols. The regio- and stereochemistry were not affected by the change

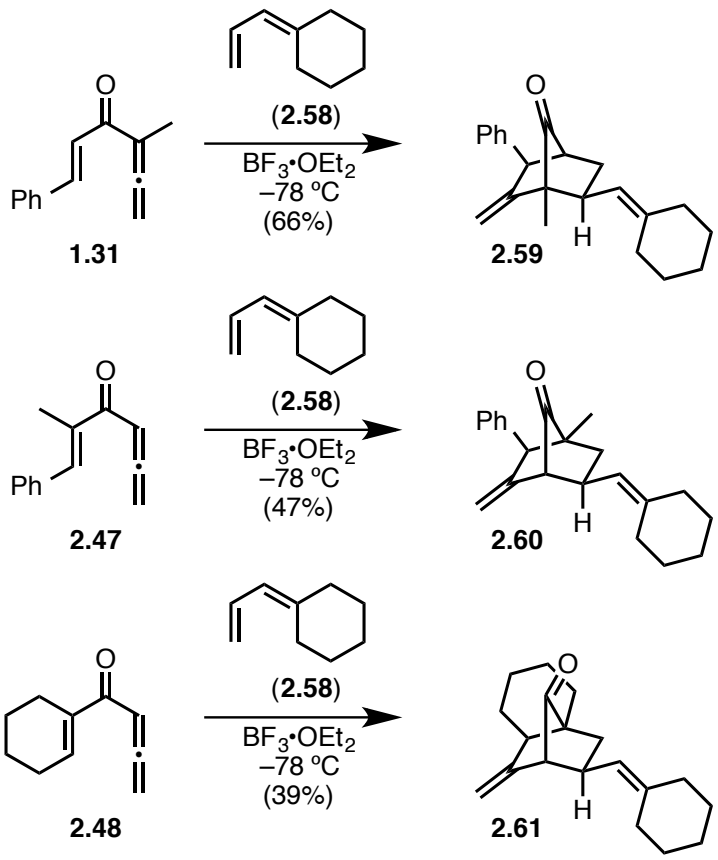
in substitution of the AVKs. All three (4+3)-cycloadditions would have taken place via an extended transition state.



Scheme 2.19 Nazarov reactions of AVKs 1.31, 2.47 and 2.48 in the presence of diene 2.54.

Double substitution on the terminus of the diene, as in diene **2.58**, led to cycloaddition via the (3+2)-cycloaddition pathway, only (Scheme 2.20). The initial bond-forming reaction occurred between the less hindered position on the diene and the most electrophilic position on the oxyallyl cation. The second bond could have formed at either end of the resulting allyl cation moiety, but only products, **2.59**, **2.60** and **2.61**, arising from the addition of the less hindered carbon of the allyl cation, i.e., (3+2) products, were observed. Nevertheless, the (3+2)-cycloaddition occurred with very high

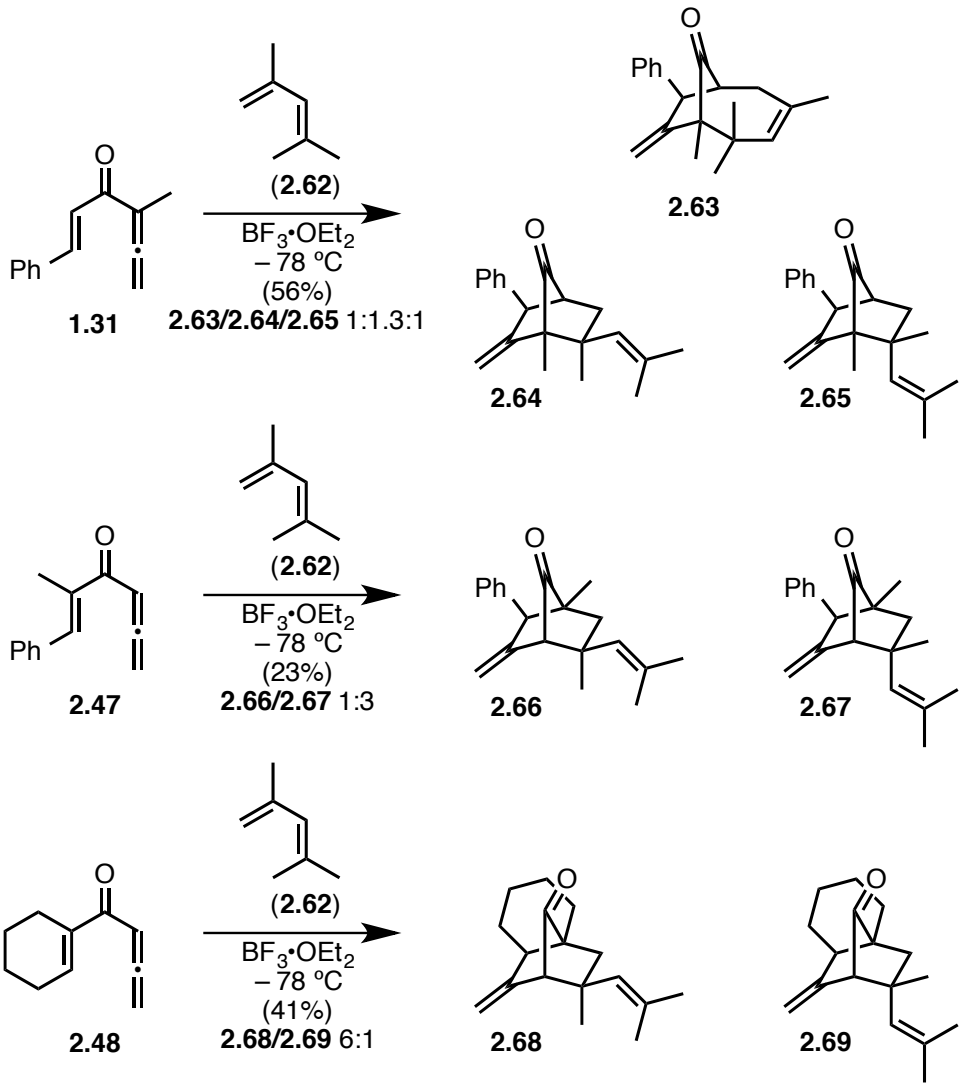
regio- and stereoselectivity with **1.31**, **2.47** and **2.48**; the relative stereochemistry of the products shown in Scheme 2.20 were determined using NOEs. It was clear that completely substituting a terminus of the diene greatly retarded the (4+3) mode of cyclization.



Scheme 2.20 Nazarov reactions of AVKs 1.31, 2.47 and 2.48 in the presence of diene 2.58.

In a previous study it had been demonstrated that the Nazarov cyclization of AVK **1.31** in the presence of 2,3-dimethyl-1,3-pentadiene (**2.62**) led to an inseparable mixture of (4+3) and (3+2) cycloadducts **2.63**-**2.65**, but favoring the (3+2) products (Scheme 2.21).[40] It was hypothesized that intercepting the Nazarov reactions of AVKs **2.47** and **2.48** with diene **2.62** might provide a greater proportion of (4+3) adduct

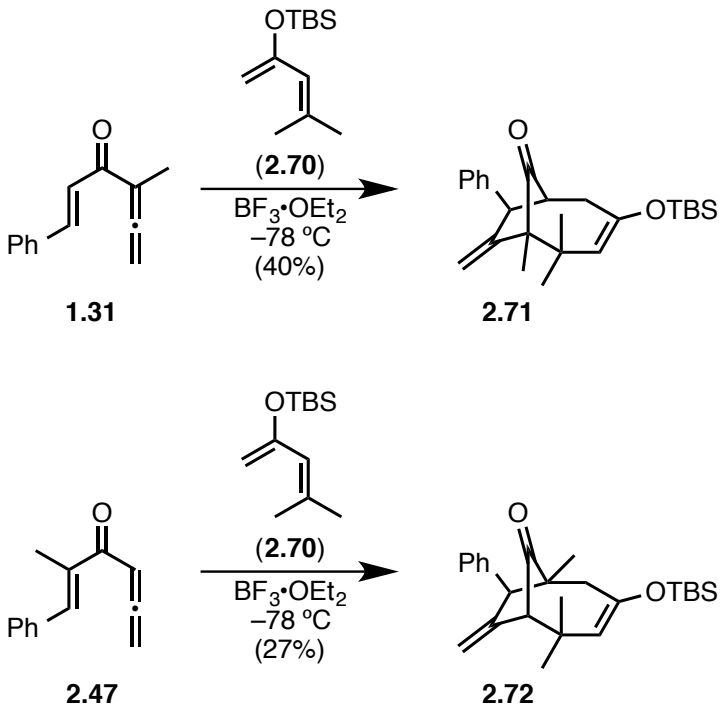
because these (4+3) products would not have contiguous quaternary centers as in **2.63**. However, when AVKs **2.47** and **2.48** were reacted in the presence of **2.62**, only (3+2) products were obtained. In an effort to confirm the earlier result, the Nazarov reaction of **1.31** with **2.62** was repeated several times. The results were mostly consistent with the published result, except in one instance only (3+2) products **2.64** and **2.65** were obtained. The reason for this spurious result was unclear. Nevertheless, the (4+3)-cycloaddition was obviously much more affected than (3+2)-cycloaddition by substitution of the carbon on the diene where the putative second carbon-carbon bond forms. In contrast with the (3+2)-cycloadditions with *trans*- and *cis*-piperylene, with 2,4-hexadiene and with diene **2.58**, (3+2)-cycloadditions with diene **2.62** took place with modest stereoselectivity. With **2.62**, the second carbon-carbon bond formed onto a carbon of the diene that became an annular carbon substituted by two carbons, whereas for the other dienes the corresponding carbon was substituted by a carbon and a hydrogen. The diminished stereoselectivity with **2.62** was thus consistent with the development of stereochemistry in the formation of the second carbon-carbon bond being controlled to a significant extent by steric hindrance.



Scheme 2.21 Nazarov reactions of 1.31, 2.47 and 2.48 in the presence of 2,3-dimethyl-1,3-butadiene.

In a related study it was shown that electron-rich dienes have a preference for (4+3)-cycloadditions over (3+2)-cycloadditions onto the oxyallyl cations derived from AVKs.[42] Diene **2.70** was prepared as an analogue to diene **2.62**. The terminus of **2.70** was doubly substituted, but the oxygen rendered the diene much more electron rich. The Nazarov reactions AVKs **1.31** and **2.47** in the presence of diene **2.70** are shown in Scheme 2.22. The (4+3)-cycloadducts **2.71** and **2.72** were the only Nazarov products

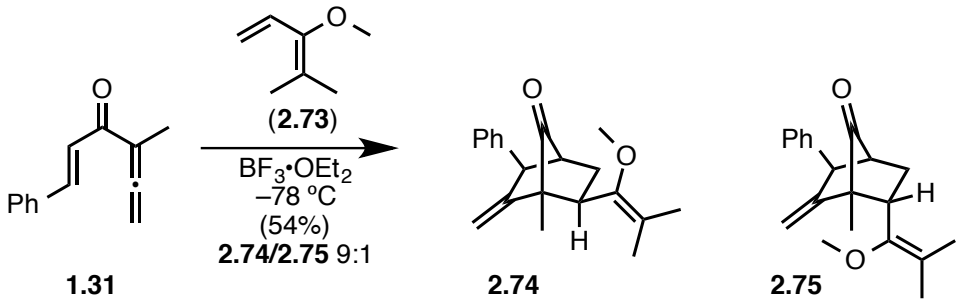
observed. Unfortunately, the attempt to intercept the reaction of AVK **2.48** with diene **2.70** led to no identifiable product.



Scheme 2.22 Nazarov reactions of AVKs 1.31 and 2.47 in the presence of the oxygenated diene 2.70.

Not surprisingly, the more electron-rich and less sterically hindered end of diene **2.70** had added to the most electrophilic position of the oxyallyl cation. To determine if electron donation could overwhelm the steric factor, diene **2.73**, which had a methoxy group donating electron density to the doubly substituted end of the diene, was prepared and tested in a reaction with AVK **1.31** (Scheme 2.23). A trapping reaction occurred, but the electron-rich carbon of the diene had not added to the most electrophilic site of the oxyallyl cation. Instead, the cycloaddition was by a (3+2) process. Therefore, the steric hindrance dominated the selectivity of the reaction with this diene. The regioselectivity of the reaction was once again essentially absolute, and the

stereoselectivity was significantly higher than in the reaction with diene **2.62**. Attempts to intercept the oxyallyl cations from AVKs **2.47** and **2.48** were unsuccessful in the presence of diene **2.73**.

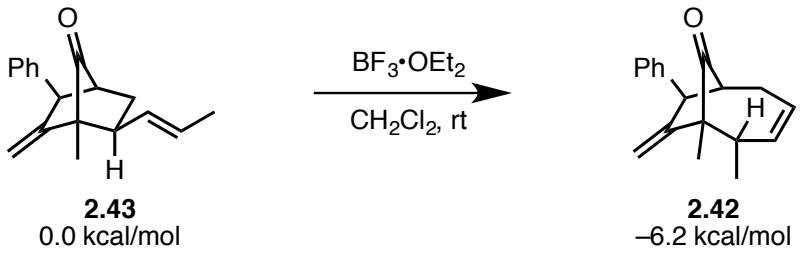


Scheme 2.23 Nazarov reaction of AVK 1.31 in the presence of diene 2.73.

2.2.2 Rearrangements and Computational Results

As mentioned previously, the (3+2) product **2.43** rearranged in the presence of BF_3•OEt_2 at room temperature to form (4+3) products **2.42** and **2.46**. The relative energies of **2.43** and **2.42** were compared computationally as shown in Scheme 2.24. The (4+3) product was found, as expected, to be lower in energy than the (3+2) product. This result prompted a thorough experimental and computational examination of the rearrangements of the (3+2) products that had been produced in this study.[*] In particular, could (3+2) products be equilibrated to (4+3) products?

[*] Dr. Zhe Li, a postdoctoral fellow in the Burnell group, carried out the calculations.

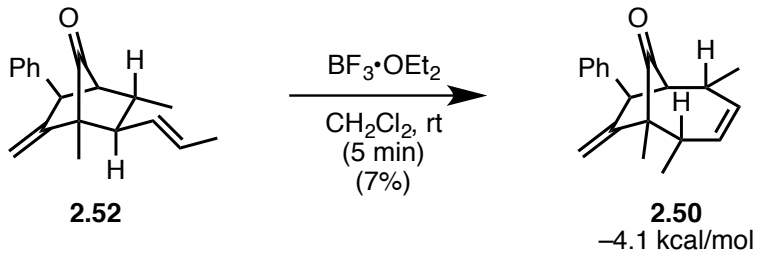


2.43
0.0 kcal/mol

2.42
–6.2 kcal/mol

Scheme 2.24 Rearrangement of (3+2) product 2.43 to (4+3) product 2.42, along with the relative energies computed at ωB97X-D/6-31G(d,p).[67,68]

The mixture of **2.51**, **2.52** and **2.53** was treated with BF_3•OEt_2 at room temperature. Decomposition of the majority of the material occurred rapidly, but a small amount of **2.50** had formed and the proportion of **2.52** decreased. It was hypothesized that **2.52** rearranged in the same way as had **2.43**, but due to the slow conversion at room temperature the isomerization process could not account for the formation of **2.50** under the reaction conditions at –78 ºC. Nonetheless, the Gibbs energy of **2.50** was calculated to be 4.1 kcal/mol lower than that of **2.52**.

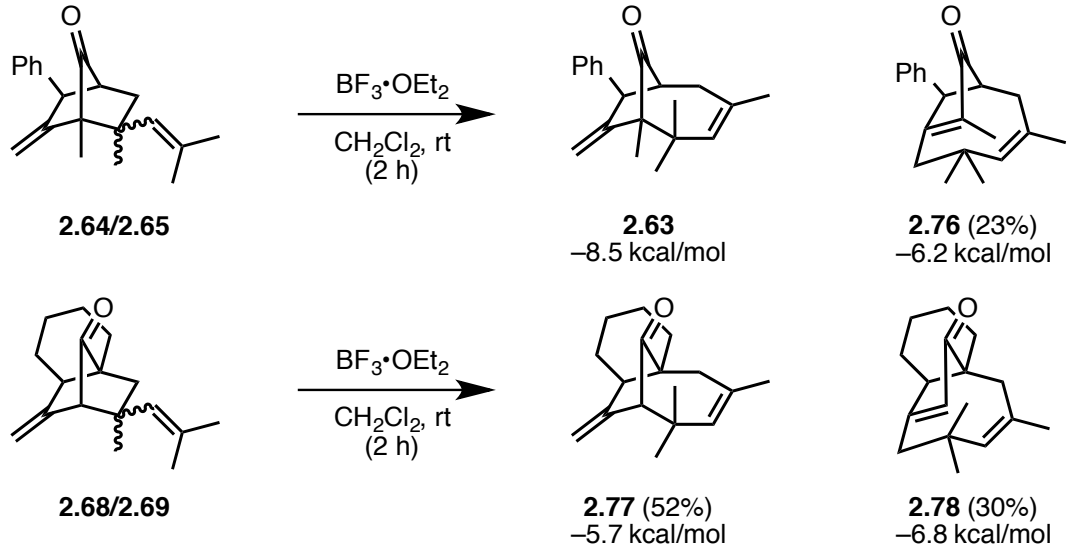


Scheme 2.25 Rearrangement of 2.52 to 2.50, with the relative energies computed at ωB97X-D/6-31G(d,p).

Decomposition was a major competing process in all of the rearrangement experiments. Regardless, in some cases rearranged products could be obtained. When the mixture of 2.64 and 2.65 was exposed to the rearrangement conditions, only bicyclo[5.2.1]decadiene 2.76 was obtained (

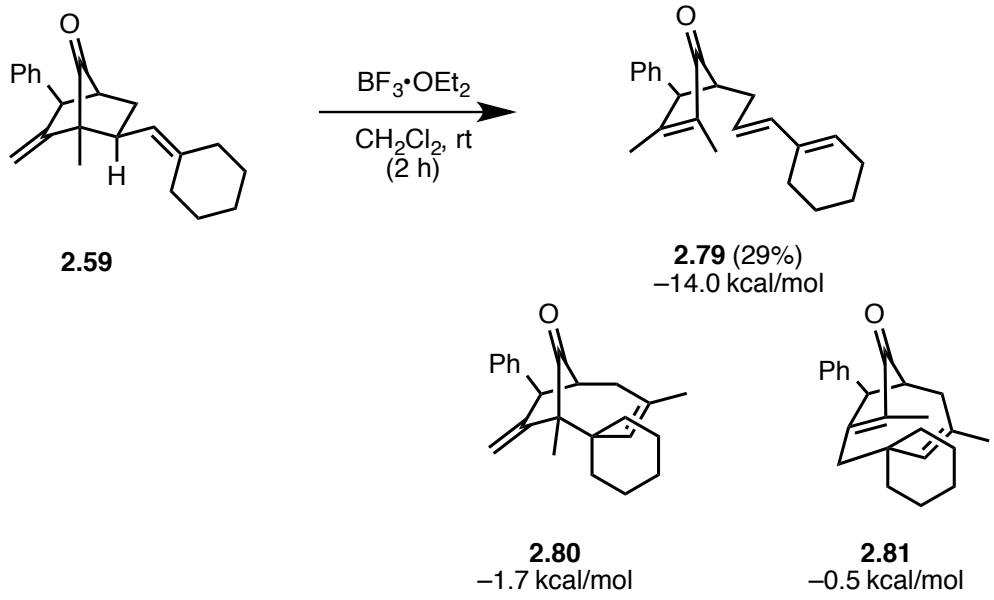
Scheme 2.26). The product **2.76** would arise from breaking of a carbon-carbon bond to reform the allylic cation and the enolate. Closure of the cation onto the exocyclic double bond of the extended enolate would result in the formation of the bicyclo[5.2.1]decadiene skeleton, which represented a formal [5+4] addition of the diene across the oxyallyl cation. This result was surprising because the rearrangement formed a (novel) ten membered ring and it was also surprising because **2.76** was calculated to be 2.3 kcal/mol *less* stable than bicyclo[4.2.1]nonene **2.63.** A similar result was obtained when **2.68** and **2.69** were treated with BF_3•OEt_2. The major product was

the (4+3)-cycloadduct **2.77**, but the bicyclo[5.2.1]decadiene **2.78** was also formed in 30% yield. Once again, the calculations showed that the (4+3) product was thermodynamically more stable, but in this instance the difference was only 0.9 kcal/mol. The rearrangement process was attempted with (3+2) adducts **2.66** and **2.67**, which were derived from AVK **2.47**, but total decomposition occurred.

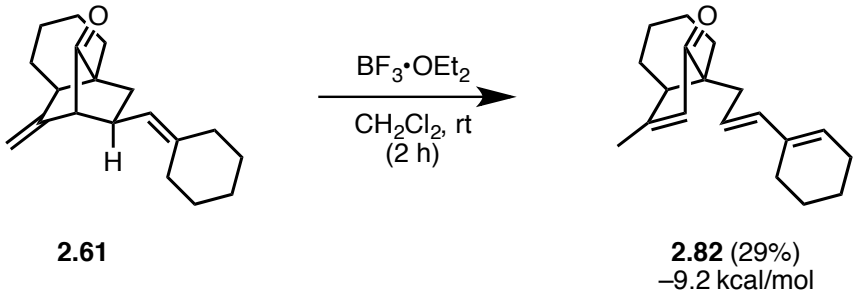


Scheme 2.26 Rearrangement of (3+2) products with the relative energies of the products computed at the ωB97X-D/6-31G(d,p) level of theory.

The rearrangement of the (3+2) product **2.59** did not lead to either bicyclo[4.2.1]nonene **2.80** or bicyclo[5.2.1]decadiene **2.81**. Instead only the ring-opened product **2.79** was isolated (Scheme 2.27). This was consistent with the calculated energies. The ring-opened compound **2.79** was 14.0 kcal/mol lower in energy than **2.59** while the (4+3) and (5+4) products were, respectively, only 1.7 and 0.5 kcal/mol lower energy than **2.59**. The same process occurred with **2.61** (Scheme 2.28). The ring-opened product **2.82** was more stable by 9.2 kcal/mol. Compound **2.60** proved to be unstable to the rearrangement conditions, and complete destruction of the material was the result.



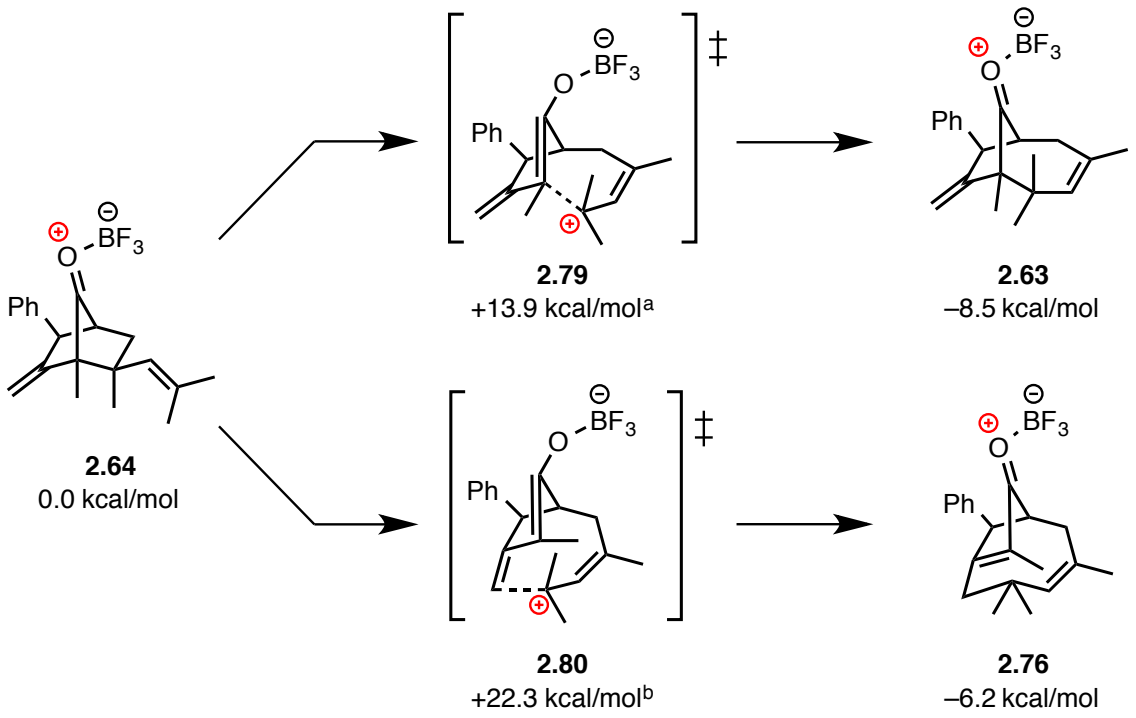
Scheme 2.27 Ring opening of (3+2) products 2.59 with the relative energies computed at ωB97X-D/6-31G(d,p).



Scheme 2.28 Ring opening of (3+2) product 2.61 with the relative energies computed at ωB97X-D/6-31G(d,p).

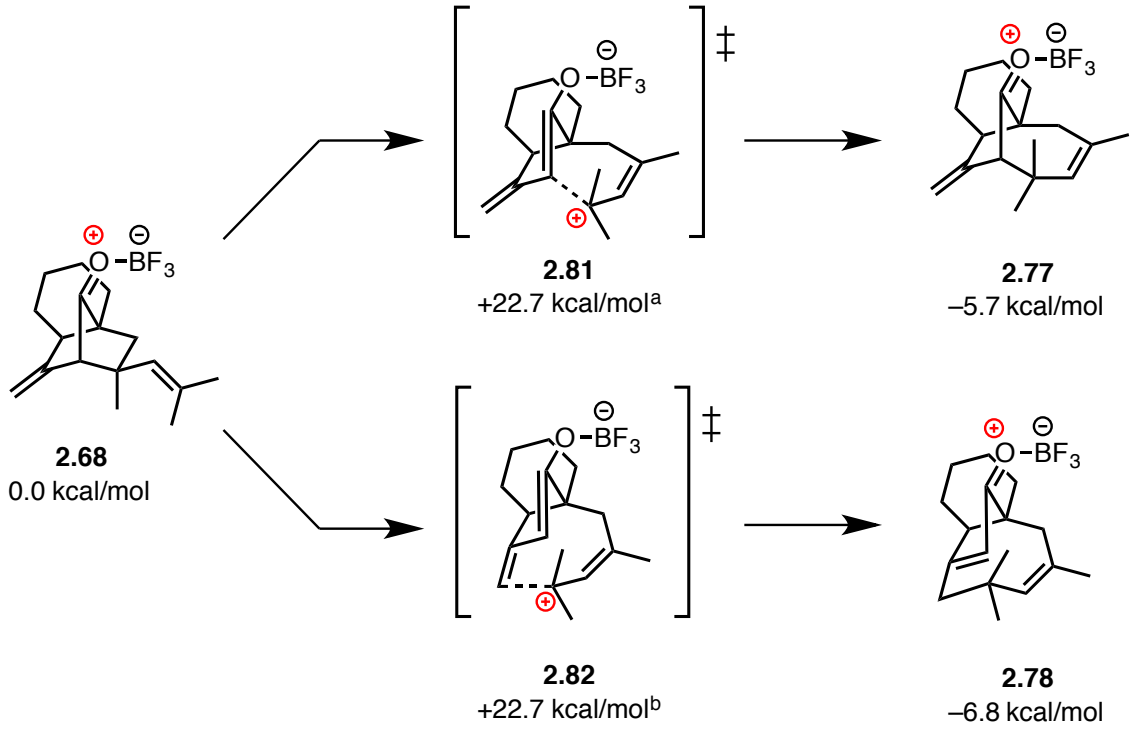
In most cases the major products from the rearrangement experiments were the thermodynamically preferred compounds. The formation of the bicyclo[5.2.1]decadiene products **2.76** and **2.78**, which were not energetically favored, suggested a kinetic preference for those products. Therefore, the transition state energies leading from **2.64** to the (4+3) product **2.63** and the (5+4) product **2.76**; and **2.68** to **2.77** and **2.78**, were calculated. The results of the calculations are summarized in Scheme 2.29 and Scheme

2.30. The barriers to bicyclic compounds **2.77** and **2.78** were essentially the same in energy. Thus, the formation of both bicyclo[4.2.1]nonene and bicyclo[5.2.1]decadiene could be rationalized based on the reaction proceeding through both transition states. However, in the case of **2.64** the transition state energy leading to the (4+3) product, **2.63**, was substantially lower in energy than the transition state energy leading to **2.76** (Scheme 2.29). The computational results suggested, both kinetically and thermodynamically, that the (4+3) compound **2.76** should have been the major product from the rearrangement of **2.64**. This implied that the isolation of only bicyclo[5.2.1]decadiene **2.76** was due to a difference in the stability of the products under the reaction conditions. To test this hypothesis a mixture of **2.64** and **2.65** containing (4+3) product **2.63** was subjected to the rearrangement process. Again, **2.76** was isolated from the reaction mixture but no **2.63** was recovered. In a related experiment, **2.77** was stirred with BF_3•OEt_2 in CH_2Cl_2, after 4 h the compound had been completely destroyed. Overall, it is very likely that the rearrangements occurred only from the (3+2) products and that the bicyclo[5.2.1]decadienes were more stable under the reaction conditions than were the bicyclo[4.2.1]nonenes.



[(a)]ωB97X-D/6-31+G(d,p)//HF/6-31G. [(b)]The energy at ωB97X-D/6-31+G(d,p)//HF/6-31G was +24.7 kcal/mol.

Scheme 2.29 Calculated energies of the transition states for the rearrangements of 2.64 at the ωB97X-D/6-31+G(d,p) level of theory.

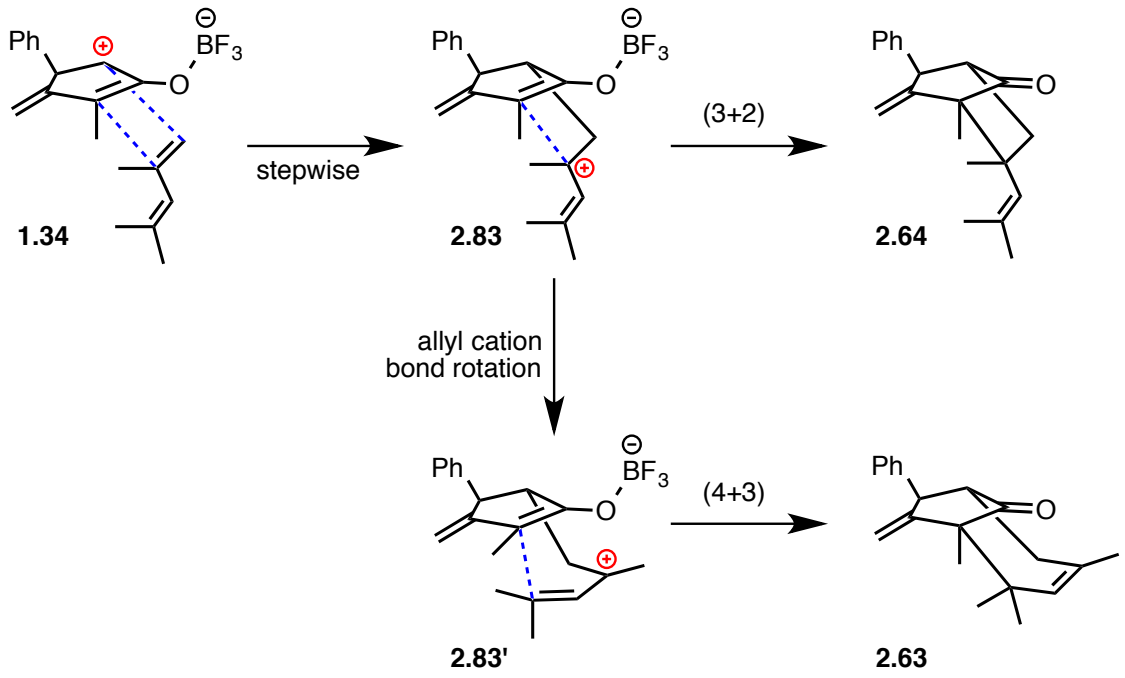


[(a)]ωB97X-D/6-31+G(d,p)//HF/6-31G.[(b)]The energy at ωB97X-D/6-31+G(d,p)//HF/6-31G was +23.2 kcal/mol.

Scheme 2.30 Calculated energies of the transition states for the rearrangements of 2.68 at the ωB97X-D/6-31+G(d,p) level of theory.

2.3 Mechanistic Implications

The formation of (3+2) products from the tandem Nazarov/cycloaddition process had suggested that the (4+3) products might also arise from a stepwise process.[43] The process for the formation of (4+3)-cycloaddition products by a stepwise mechanism is shown in Scheme 2.31. Substituted dienes exist predominantly in the *s-trans* conformation. An initial reaction of an *s-trans* diene with oxyallyl cation **1.34** would lead to intermediate **2.83**. In order for the second bond-forming reaction to occur the allyl cation must undergo isomerization to **2.83′**, which could further cyclize to form **2.63**.



Scheme 2.31 Stepwise formation of (3+2) product 2.64 and (4+3) product 2.63.

The energy required for the rotation of allyl cations like **2.83** has been estimated to be 24 kcal/mol.[69] It is unlikely that this isomerization would occur at a sufficient rate at –78 ºC to account for the formation of the (4+3) products from the interrupted Nazarov reaction. The most likely reason for the formation of (4+3)-cycloaddition products is that the reaction occurs via a concerted mechanism from the *s-cis* conformation of the diene. Thus, the (4+3)-cycloaddition must be significantly faster than (3+2)-cycloaddition in spite of the *s-cis* conformation being higher in energy than the *s-trans* conformation, which would therefore be present is a significantly higher concentration. However, the introduction of a lot of steric hindrance, such as with a geminally disubstituted diene, makes the (4+3)-cycloaddition disfavored and the normally slower (3+2)-cycloaddition then becomes the major pathway.

2.4 Conclusions

The cycloaddition of a series of substituted dienes was tested with oxyallyl cations derived from type I and II allenyl vinyl ketones by Nazarov reactions. (4+3)-Cycloaddition has a lower energy reaction pathway than (3+2)-cycloaddition with unhindered dienes. Nonetheless, both (4+3)- and (3+2)-cycloaddition products were obtained. Substitution of a terminus of the dienes led to a larger proportion of (3+2) products due to steric influences. The results strongly suggest that the (4+3)-cycloaddition occurred through a concerted mechanism and favored an extended transition state. The rearrangement of some of the (3+2)-cycloaddition products led to (4+3) products, but the rate was insufficient to account for the formation of the bicyclo[4.2.1]nonene products at –78 ºC. In other cases bicyclo[5.2.1]decadienes were formed by acid-mediated rearrangement. It appeared that the rearrangements took place from the (3+2)-products but not from the (4+3)-products. Computational analysis showed that the transition states leading to the bicyclo[4.2.1]nonenes were equal or lower in energy than the transition states leading to the bicyclo[5.2.1]decadienes. However, the experimental results showed that the formal (5+4)-cycloaddition products were more stable to the acidic conditions than the (4+3) products.

2.5 Experimental Section

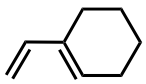
2.5.1 General considerations

Reactions were carried out in oven-dried glassware under an atmosphere of dry nitrogen. Reagents were used as received from commercial sources. Dichloromethane was distilled over calcium hydride. Tetrahydrofuran (THF) was freshly distilled over sodium/benzophenone. EtOAc and hexanes were distilled. Reactions were followed by

TLC analysis using precoated (silica gel 60 F254, 0.25 mm) plates with aluminum backing. Column chromatography was carried out with silica gel (40–63 μm particle size, 230-240 mesh). Evaporation of solvents was under reduced pressure with modest heating. Melting points were uncorrected. IR spectra were recorded on an FT instrument on NaCl or CsI plates as neat liquid films, and only significant absorption bands (in cm^{-1}) are reported. ^{1}H NMR spectra were acquired at 500.1 MHz, and chemical shifts are relative to internal TMS (δ 0.00 ppm). The ^{1}H NMR data are presented as follows: chemical shift in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant(s), *J*, in hertz (Hz), and integration. Diastereomeric ratios were determined by integration of clearly separated ^{1}H NMR signals. ^{13}C NMR spectra were acquired at 125.8 MHz, and chemical shifts are relative to the solvent signal ($CDCl_3$, δ 77.16 ppm). Structural assignments were based on 2-D NMR spectra (COSY, HSQC, HMBC) and nuclear Overhauser effect (NOE) measurements.[70,71] HRMS data were obtained using a TOF mass spectrometer by positive-ion ESI.

2.5.2 Preparation of dienes 2.54, 2.58 and 2.73

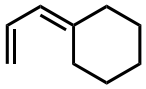
1-Vinylcyclohexene (2.54)



Lindlar catalyst (500 mg) was suspended in Et_2O (50 mL). Quinoline (0.05 mL, 0.4 mmol) and 1-ethynylcyclohexene (5.0 g, 47 mmol) were added, and the flask was flushed with H_2. The mixture was stirred under 1 atm of H_2 for 18 h. The mixture was filtered through Celite and concentrated under vacuum. The residue was purified by

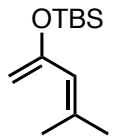
column chromatography (hexanes) to provide **2.54** (2.9 g, 57%) as a clear, colorless liquid: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.36 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.77-5.76 (m, 1H), 5.07 (d, *J* = 17.5 Hz, 1H), 4.90 (d, *J* = 10.7 Hz, 1H), 2.16-2.14 (m, 4H), 1.72-1.59 (m, 4H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 140.3, 136.2, 129.9, 109.7, 25.9, 23.9, 22.7, 22.5. These NMR data are consistent with the literature.[72]

2-Propen-1-ylidenecyclohexane (2.58)



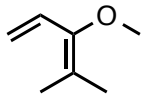
*t*BuOK (12 g, 0.11 mol) in THF (100 mL) was added slowly to a solution of trimethyl-2-propen-1-ylphosphonium bromide[73] (20 g, 0.10 mol) in THF (300 mL) at 0 °C. The mixture was warmed to rt, and it was stirred for 30 min. Cyclohexanone (10.5 mL, 0.10 mol) was added, and the mixture was stirred overnight. The solution was concentrated under vacuum. The residue was purified by column chromatography (hexanes) to give **2.58** (6.5 g, 53%) as a liquid: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.62 (ddd, *J* = 16.8, 10.9, 10.1 Hz, 1H), 5.80 (d, *J* = 11.0 Hz, 1H), 5.10 (d, *J* = 16.8 Hz, 1H), 4.96 (d, *J* = 10.1 Hz, 1H), 2.30-2.27 (m, 2H), 2.15-2.13 (m, 2H), 1.58-1.53 (m, 6 H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 144.3, 132.8, 122.8, 114.6, 37.4, 29.4, 28.6, 27.9, 26.9. These NMR data are consistent with the literature.[74]

2-(*tert*-Butyldimethylsilyloxy)-4-methyl-1,3-pentadiene (2.70)



A solution of 4-methyl-3-penten-2-one (1.2 mL, 10.5 mmol) in THF (10 mL) was cooled to 0 °C. Et_3N (3.5 mL, 25.1 mmol) was added, followed by the slow addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.8 mL, 12.2 mmol). The solution was stirred at 0 °C until reaction was complete, as evidenced by TLC. The solution was then diluted with pentane (80 mL), washed with saturated aqueous $NaHCO_3$ (25 mL), with water (2×25 mL), and with brine (25 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on neutral alumina (GIII) (pentane) to yield **2.70** (1.95 g, 87%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.56 (s, 1H), 4.30 (s, 1H), 4.16 (s, 1H), 1.89 (s, 3H), 1.77 (s, 3H), 0.94 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.8, 136.8, 123.3, 95.0, 27.1, 26.0 (3C), 20.0, 18.5, -4.3 (2C). These NMR data match those in the literature.[75]

Procedure for 3-methoxy-4-methyl-1,3-pentadiene (2.73)

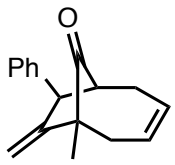


A solution of dimethyl 1-methoxyallylphosphonate (1.7 g, 9.6 mmol) in THF (5 mL) was added to a solution of LDA (11.5 mmol) in THF (20 mL) at –78 °C and stirred for 30 min. A solution of acetone (0.74 mL, 9.6 mmol) in THF (5 mL) was added to the

mixture. The mixture was allowed to warm slowly to rt over 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (25 mL), and the mixture was extracted with Et_2O (25 mL). The organic layer was washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography (10% Et_2O in pentane) to give **2.73** (0.30 g, 28%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.46 (dd, J = 17.1, 10.8 Hz, 1H), 5.33 (d, J = 17.0 Hz, 1H), 5.04 (dd, J = 10.8, 0.4 Hz, 1H), 3.52 (s, 3H), 1.77 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.1, 127.9, 122.0, 112.3, 59.0, 18.5, 18.0. These NMR data match those in the literature.[76]

2.5.3 Nazarov reactions in the presence of 1,3-butadiene and 2,4-hexadiene

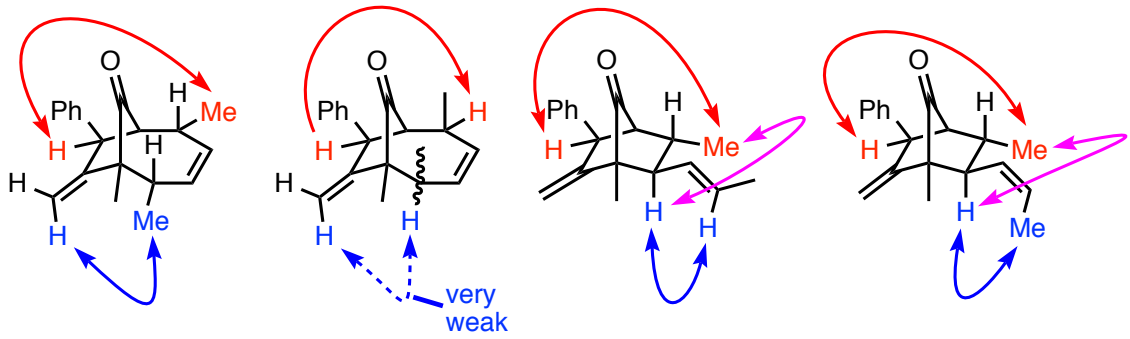
(1*R,6*S**,7*R**)-1-Methyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (2.49)**



BF_3•OEt_2 (0.040 mL, 0.32 mmol) was added drop-wise to a solution of AVK **1.31** (50 mg, 0.27 mmol) and 1,3-butadiene (0.95 mL, 20 wt.-% solution in toluene, 2.7 mmol) in CH_2Cl_2 (30 mL) at –78 °C. The mixture was stirred for 5 min, and then poured into a separatory funnel containing an equal volume of saturated aqueous $NaHCO_3$. The CH_2Cl_2 layer was removed, and additional CH_2Cl_2 (×2) was used to re-extract the aqueous layer. The combined organic layers were dried over Na_2SO_4 and then concentrated under reduced pressure. Chromatography of the residue (2.5% EtOAc in hexanes) yielded **2.49** (0.046 g, 73%) as a colorless oil: IR (film): n = 1744, 1600 cm$^-$

[1]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (m, 2H), 7.19 (m, 1H), 7.04 (m, 2H), 5.68 (m, 1H), 5.63 (m, 1H), 5.09 (d, *J* = 2.4 Hz, 1H), 3.71 (m, 1H), 2.79 (m, 1H), 2.46 (m, 1H), 2.38 (m, 1H), 2.17 (m, 2H), 1.32 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 222.5, 158.4, 146.6, 129.0 (2C), 127.5 (3C), 126.6, 125.8, 110.0, 55.4, 54.0, 52.2, 42.7, 32.2, 21.7; HRMS (ESI) 261.1249, $[C_{17}H_{18}ONa]^+$ requires 261.1250.

(1*R,2*S**,5*R**,6*S**,7*R**)- (2.50) and (1*R**,2*R**,5*S**,6*S**,7*R**)-1,2,5-trimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (2.51), (1*R**,2*R**,3*S**,4*S**,5*R**)-1,3-dimethyl-6-methylene-5-phenyl-2-((*E*)-prop-1-en-1-yl)bicyclo[2.2.1]heptane (2.52) and (1*R**,2*R**,3*S**,4*S**,5*R**)-1,3-dimethyl-6-methylene-5-phenyl-2-((*Z*)-prop-1-en-1-yl)bicyclo[2.2.1]heptane (2.53)**



BF_3•OEt_2 (0.07 mL, 0.55 mmol) was added to a solution of AVK **1.31** (92 mg, 0.50 mmol) and 2,4-hexadiene (*E,E*:*E,Z* = 3:1) (0.27 mL, 2.5 mmol) in CH_2Cl_2 (5.0 mL) at -78 °C. The solution was stirred for 5 min, and then saturated aqueous $NaHCO_3$ (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic solutions were dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue on alumina (3% diethyl ether in pentane) gave **2.50** (12 mg, 9%) and an inseparable 1:8:2.5 mixture of **2.51**, **2.52** and **2.53**, respectively (22 mg,

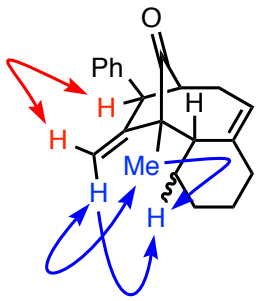
17%). For the mixture of all four cycloaddition products: IR (film): n = 1775, 1743, 1604 cm^{-1}; HRMS (ESI) 289.1557, $[C_{19}H_{22}ONa]^+$ requires 289.1563. For isolated **2.50**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.28 (t, J = 7.9 Hz, 2H), 7.21-7.18 (m, 1H), 7.07 (d, J = 7.0 Hz, 2H), 5.36-5.32 (m, 2H), 4.98 (d, J = 2.9 Hz, 1H), 4.73 (d, J = 2.5 Hz, 1H), 3.70 (dd, J = 2.9, 2.5 Hz, 1H), 2.70-2.69 (m, 1H), 2.61 (td, J = 3.8, 1.1 Hz, 1H), 2.15-2.13 (m, 1H), 1.25 (s, 3H), 1.13 (d, J = 7.3 Hz, 3H), 1.10 (d, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 222.1, 155.1, 146.4, 133.9, 131.3, 128.8, 128.4, 126.4, 112.3, 61.4, 57.8, 48.4, 41.1, 37.7, 20.5, 19.5, 17.1. For **2.51** (from the mixture): ^1H NMR (500 MHz, $CDCl_3$): δ 7.28-7.25 (m, 2H), 7.19 (t, J = 7.3 Hz, 1H), 7.03 (d, J = 7.2 Hz, 2H), 5.59-5.58 (m, 2H), 5.10-5.03 (m, 1H), 4.89 (d, J = 2.0 Hz, 1H), 3.67 (d, J = 1.6 Hz, 1H), 2.58-2.56 (m, 2H), 2.20-2.18 (m, 1H), 1.30 (s, 3H), 1.05 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H) with some signals overlapped; ^{13}C NMR (126 MHz, $CDCl_3$): δ 222.2, 160.0, 148.6, 132.6, 129.5, 128.9, 127.1, 126.4, 109.7, 61.2, 55.5, 53.4, 45.6, 37.9, 20.7, 20.2, 16.6. For **2.52** (from the mixture): ^1H NMR (500 MHz, $CDCl_3$): δ 7.28-7.25 (m, 2H), 7.19 (t, J = 7.3 Hz, 1H), 7.11 (t, J = 6.5 Hz, 2H), 5.43 (dq, J = 14.4, 7.0 Hz, 1H), 5.10-5.08 (m, 1H), 5.03 (d, J = 2.2 Hz, 1H), 4.77 (d, J = 1.7 Hz, 1H), 4.04 (s, 1H), 2.20-2.18 (m, 1H), 1.93-1.86 (m, 2H), 1.68 (d, J = 6.2 Hz, 3H), 1.22 (d, J = 6.7 Hz, 3H), 1.00 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 215.0, 154.0, 143.5, 131.1, 128.7, 127.7, 127.3, 126.7, 107.2, 54.8, 54.5, 53.5, 44.3, 36.4, 18.0, 15.7, 9.9. For **2.53** (from the mixture): ^1H NMR (500 MHz, $CDCl_3$): δ 7.28-7.25 (m, 2 H), 7.19 (t, J = 7.3 Hz, 1H), 7.11 (t, J = 6.5 Hz, 2H), 5.59-5.58 (m, 1H), 5.10-5.03 (m, 2H), 4.81 (d, J = 1.7 Hz, 1H), 4.09 (s, 1H), 2.36 (dd, J = 10.8, 6.0 Hz, 1H), 2.20-2.18 (m, 1H), 1.93-1.86 (m, 1H), 1.64 (dd, J = 6.9, 1.6 Hz, 3H), 1.26 (d, J = 6.9 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$):

δ 214.7, 154.0, 143.4, 130.7, 128.7, 127.7, 126.7, 125.8, 107.2, 54.4, 53.6, 48.4, 44.3, 37.1, 16.2, 13.2, 9.4.

2.5.4 Nazarov reactions in the presence of dienes 2.54, 2.58 and 2.62

The allenyl vinyl ketone (1 equiv) and the diene (usually 2.0 equiv) were dissolved in CH_2Cl_2 (to make a 0.1 M solution of the AVK) and cooled to –78 °C. BF_3•OEt_2 (1.5 equiv) was added. After 5-10 min the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (a volume approximately equal to the volume of CH_2Cl_2) to the rapidly stirred solution, and the reaction flask was removed from the cooling bath. Rapid stirring was continued until the ice crystals melted (usually *ca.* 30 min). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (×2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography with 5% Et_2O in pentane.

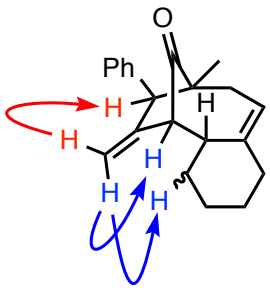
(4a*R,5*S**,7*S**,8*R**)-5-Methyl-6-methylene-7-phenyl-1,2,3,4,4a,5,6,7,8,9-decahydro-5,8-methanobenzo[8]annulen-11-one (2.55)**



AVK **1.31** (50 mg), diene **2.54** (58 mg) and BF_3•OEt_2 (0.05 mL) afforded **2.55** (58 mg, 73%) as a colorless solid: m.p.: 108-111 ºC; IR (film): n = 1743, 1651 cm^{-1}; ^1H NMR

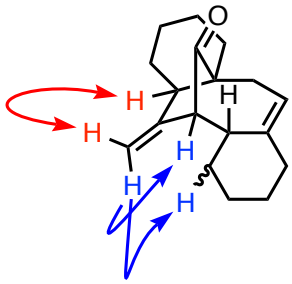
(500 MHz, $CDCl_3$): δ 7.31 (t, *J* = 7.4 Hz, 2H), 7.26-7.22 (m, 1H), 7.16 (d, *J* = 7.0 Hz, 2H), 5.31 (br s, 1H), 4.92 (d, *J* = 3.0 Hz, 1H), 4.60 (d, *J* = 2.7 Hz, 1H), 3.64 (m, 1H), 2.74 (m, 1H), 2.52-2.47 (m, 1H), 2.31-2.24 (m, 2H), 2.07-2.01 (m, 1H), 1.91-1.88 (m, 2H), 1.77-1.73 (m, 2H), 1.48-1.32 (m, 2H), 1.28 (s, 3H), 1.13 (qd, *J* = 12.8, 3.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 218.4, 154.9, 143.6, 140.0, 129.0, 128.7, 126.8, 118.1, 110.8, 59.4, 55.4, 52.0, 47.5, 42.8, 32.5, 30.3, 28.5, 27.6, 19.6; HRMS (ESI) 315.1708, $[C_{21}H_{24}ONa]^+$ requires 315.1719.

(4a*R,5*R**,7*S**,8*R**)-8-Methyl-6-methylene-7-phenyl-1,2,3,4,4a,5,6,7,8,9-decahydro-5,8-methanobenzo[8]annulen-11-one (2.56)**



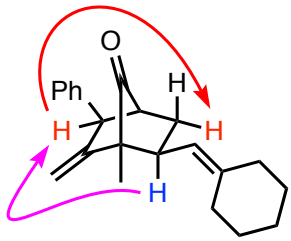
AVK **2.47** (65 mg), diene **2.54** (76 mg) and BF_3•OEt_2 (0.05 mL) gave **2.56** (43 mg, 43%) as an oil: IR (film): *n* = 1741, 1649 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.27 (t, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 7.1 Hz, 2H), 5.35 (d, *J* = 3.0 Hz, 1H), 5.14 (d, *J* = 1.4 Hz, 1H), 4.96 (s, 1H), 3.87 (d, *J* = 1.7 Hz, 1H), 3.17-3.16 (m, 1H), 2.48-2.45 (m, 1H), 2.32-2.28 (m, 2H), 2.13-2.08 (m, 2H), 1.88-1.85 (m, 1H), 1.76-1.66 (m, *J* = 4.2 Hz, 2H), 1.64-1.58 (m, 1H), 1.50-1.41 (m, 1H), 1.35-1.26 (m, 1H), 0.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 221.3, 149.4, 143.4, 139.2, 130.2, 128.7, 127.1, 119.8, 114.3, 60.9, 58.8, 54.2, 44.1, 42.5, 40.1, 31.9, 26.8, 26.5, 20.9; HRMS (ESI) 315.1710, $[C_{21}H_{24}ONa]^+$ requires 315.1719.

(4a*R,10a*S**,11*S**,12a*S**)-12-Methylene-2,3,4,5,7,8,9,10,10a,11,12,12a-dodecahydro-1*H*-4a,11-methanodibenzo[*a*,*e*][8]annulen-13-one (2.57)**



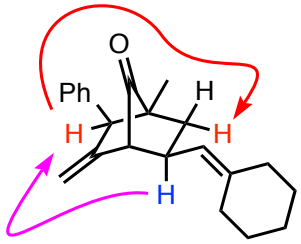
AVK **2.48** (137 mg), diene **2.54** (191 mg) and BF_3•OEt_2 (0.15 mL) yielded **2.57** (111 mg, 48%) as an oil: IR (film): n = 1745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.19-5.17 (m, 1 H), 5.07 (s, 1H), 5.05 (s, 1H), 2.97 (dd, J = 4.1, 2.0 Hz, 1H), 2.46-2.44 (m, 1H), 2.38 (dd, J = 11.7, 5.9 Hz, 1H), 2.19-2.09 (m, 3H), 2.03-1.92 (m, 2H), 1.84-1.73 (m, 4H), 1.66-1.56 (m, 3H), 1.41-1.32 (m, 1H), 1.26-1.10 (m, 4H), 0.98-0.90 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 219.7, 151.2, 136.5, 119.8, 109.5, 55.5, 53.4, 51.3, 43.8, 42.4, 39.1, 34.4, 31.7, 30.7, 26.7, 26.5, 24.1, 23.0; HRMS (ESI) 279.1715, $[C_{18}H_{24}ONa]^+$ requires 279.1719.

(1*R,3*S**,4*R**,6*R**)-6-(Cyclohexylidenemethyl)-1-methyl-2-methylene-3-phenylbicyclo[2.2.1]heptan-7-one (2.59)**



AVK **1.31** (184 mg), diene **2.58** (288 mg) and BF_3•OEt_2 (0.15 mL) provided **2.59** (204 mg, 66%) as an oil: IR (film): n = 1770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.26 (t, J = 7.5 Hz, 2H), 7.18 (t, J = 7.3 Hz, 1H), 7.09 (d, J = 7.5 Hz, 2H), 5.09 (d, J = 2.2 Hz, 1H), 4.82 (d, J = 1.6 Hz, 1H), 4.74 (d, J = 10.6 Hz, 1H), 3.79 (s, 1H), 2.77 (td, J = 10.4, 4.4 Hz, 1H), 2.26 (d, J = 4.7 Hz, 1H), 2.20 (dd, J = 12.9, 10.3 Hz, 1H), 2.16-2.02 (m, 4H), 1.68 (dt, J = 12.9, 4.6 Hz, 1H), 1.58-1.45 (m, 7H), 1.03 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 215.7, 153.8, 143.5, 141.8, 128.7, 127.4, 126.8, 122.8, 107.9, 52.9, 52.5, 48.1, 39.0, 37.4, 33.6, 29.3, 28.8, 28.2, 27.0, 9.6; HRMS (ESI) 329.1864, $[C_{22}H_{26}ONa]^+$ requires 329.1876.

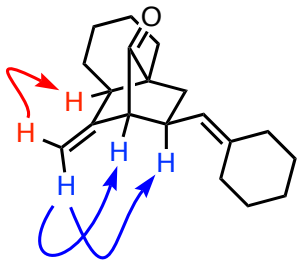
(1*R,2*R**,4*S**,5*R**)-5-(Cyclohexylidenemethyl)-1-methyl-3-methylene-2-phenylbicyclo[2.2.1]heptan-7-one (2.60)**



AVK **2.47** (65 mg), diene **2.58** (88 mg) and BF_3•OEt_2 (0.05 mL) afforded **2.60** (52 mg, 47%) as an oil: IR (film): n = 1768, 1652 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, J = 7.6 Hz, 2H), 7.20-7.17 (m, 1H), 6.97 (d, J = 7.0 Hz, 2H), 5.18 (d, J = 2.6 Hz, 1H), 4.97 (d, J = 9.4 Hz, 1H), 4.71 (d, J = 2.0 Hz, 1H), 3.60-3.59 (m, 1H), 2.93 (ddd, J = 10.4, 9.9, 4.5 Hz, 1H), 2.52 (s, 1H), 2.25 (dd, J = 12.8, 10.4 Hz, 1H), 2.14-2.10 (m, 2H), 2.06-2.04 (m, 2H), 1.53-1.51 (m, 6H), 1.46 (dd, J = 12.8, 4.5 Hz, 1H), 0.67 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 214.9, 149.5, 142.3, 140.9, 128.7, 128.4, 126.9, 124.3,

110.1, 57.7, 57.0, 49.2, 42.1, 37.0, 35.8, 29.4, 28.6, 27.9, 26.9, 12.8; HRMS (ESI) 329.1863, $[C_{22}H_{26}ONa]^+$ requires 329.1876.

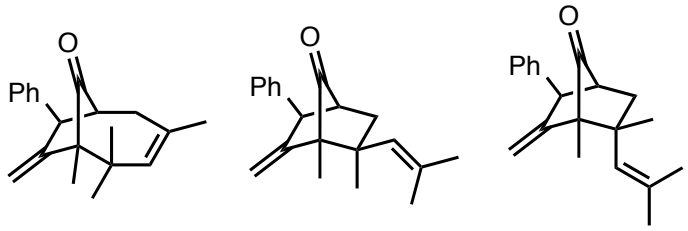
(2*R,3*S**,4a*S**,8a*R**)-3-(Cyclohexylidenemethyl)-1-methyleneoctahydro-1*H*-2,4a-methanonaphthalen-9-one (2.61):**[†]



AVK **2.48** (150 mg), diene **2.58** (244 mg) and BF_3•OEt_2 (0.15 mL) provided **2.61** as an oil: IR (film): n = 1768 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.96 (d, J = 2.0 Hz, 1H), 4.92 (d, J = 9.4 Hz, 1H), 4.82 (s, 1H), 2.74 (td, J = 9.9, 3.8 Hz, 1H), 2.30-2.27 (m, 2H), 2.12-2.02 (m, 4H), 2.00-1.94 (m, 1H), 1.89-1.86 (m, 2H), 1.68-1.64 (m, 1H), 1.56-1.37 (m, 8H), 1.32-1.27 (m, 1H), 1.26-1.19 (m, 1H), 1.17-1.08 (m, 1H), 0.98-0.88 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 214.6, 151.2, 140.7, 124.4, 105.8, 57.0, 47.8, 47.5, 40.6, 37.1, 36.0, 32.6, 29.5, 28.7, 28.0, 27.0, 25.5, 24.9, 22.9; HRMS (ESI) 293.1888, $[C_{19}H_{26}ONa]^+$ requires 293.1876.

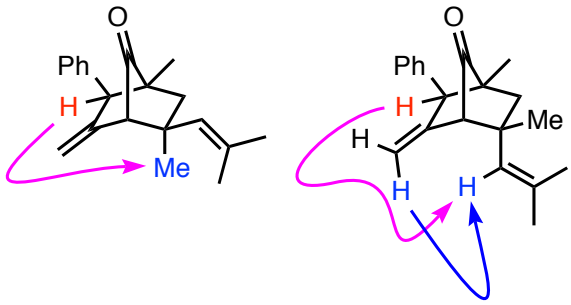
[†] This appeared to contain ca. 10% of the C-3 epimer. Some evident ^1H NMR signals: δ 5.18 (d, J = 8.1 Hz, 1H), 5.07 (d, J = 8.6 Hz, 1H), 4.89 (d, J = 2.0 Hz, 1H), 2.99-2.93 (m, 1 H), 2.20 (dd, J = 12.2, 5.5 Hz, 1H).

(1*R,6*S**,7*R**)-1,2,2,4-Tetramethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (2.63), (1*R**,2*R**,4*R**,5*S**)- (2.64) and (1*R**,2*S**,4*R**,5*S**)-1,2-dimethyl-6-methylene-2-(2-methylprop-1-en-1-yl)-5-phenylbicyclo[2.2.1]heptan-7-one (2.65)**



AVK **1.31** (5.0 mL of a 0.1 M solution in CH_2Cl_2), diene **2.62** (101 mg) and BF_3•OEt_2 (0.10 mL) gave an inseparable mixture of **2.63**, **2.64** and **2.65** (1:1.3:1, respectively) (80 mg, 56%). NMR spectra were as reported previously.[40]

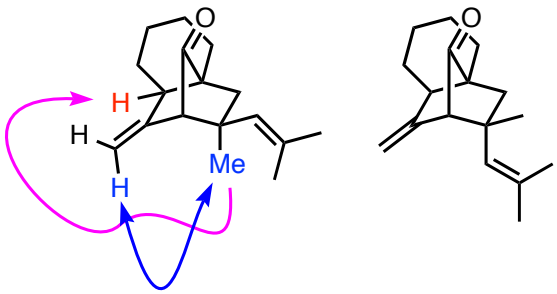
(1*R,2*R**,4*R**,5*R**)- (2.66) and (1*R**,2*S**,4*R**,5*R**)-1,5-dimethyl-3-methylene-5-(2-methylprop-1-en-1-yl)-2-phenylbicyclo[2.2.1]heptan-7-one (2.67)**



AVK **2.47** (214 mg), diene **2.62** (203 mg) and BF_3•OEt_2 (0.15 mL) led to an inseparable mixture of **2.66** and **2.67** (1:3, respectively) (71 mg, 23%). For the mixture: IR (film): *n* = 1772, 1653 cm^{-1}; HRMS (ESI) 303.1718, $[C_{20}H_{24}ONa]^+$ requires 303.1719. For **2.66**: ^1H NMR (500 MHz, $CDCl_3$): δ 5.32 (t, *J* = 1.2 Hz, 1H), 5.19 (d, *J* = 2.7 Hz, 1H), 4.84 (d, *J* = 2.1 Hz, 1H), 3.42 (d, *J* = 2.2 Hz, 1H), 2.59 (s, 1H), 2.08 (d, *J* = 12.3 Hz, 1H),

1.83 (d, J = 12.3 Hz, 1H), 1.70 (overlapped, 3H), 1.67 (d, J = 1.1 Hz, 3H), 1.31 (s, 3H), 0.63 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 214.3, 146.4, 142.3, 134.1, 133.7, 128.4, 126.9, 113.4, 63.2, 57.9, 51.9, 50.9, 36.6, 26.9, 26.0, 20.2, 13.0 (one signal overlapped). For **2.67**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25-7.22 (m, 2H), 7.20-7.16 (m, 1H), 7.00-6.97 (m, 2H), 5.40 (s, 1H), 5.17 (d, J = 2.7 Hz, 1H), 4.79 (d, J = 2.1 Hz, 1H), 3.43 (t, J = 2.2 Hz, 1H), 2.55 (s, 1H), 2.08 (d, J = 12.4 Hz, 1H), 1.83 (d, J = 12.4 Hz, 1H), 1.71 (s, 3H), 1.70 (s, 3H), 1.66 (d, J = 1.1 Hz, 1H), 1.21 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 214.6, 146.7, 142.3, 132.8, 131.9, 128.9, 128.4, 126.9, 113.0, 62.7, 57.7, 51.8, 50.6, 36.9, 28.3, 26.8, 20.0, 12.9.

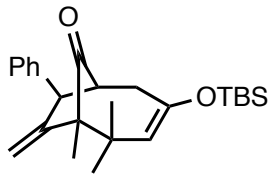
(2*R,3*R**,4a*R**,8a*R**)- (2.68) and (2*R**,3*S**,4a*R**,8a*R**)-3-methyl-1-methylene-3-(2-methylprop-1-en-1-yl)octahydro-1*H*-2,4a-methanonaphthalen-9-one (2.69)**



AVK **2.48** (150 mg), diene **2.62** (192 mg) and BF_3•OEt_2 (0.15 mL) gave an inseparable mixture of **2.68** and **2.69** (6:1, respectively) (100 mg, 41%). For the mixture: IR (film): n = 1775 cm^{-1}; HRMS (ESI) 267.1726, $[C_{17}H_{24}ONa]^+$ requires 267.1719. For **2.68**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.24 (t, J = 1.3 Hz, 1H), 4.97 (d, J = 1.6 Hz, 1H), 4.94 (d, J = 2.2 Hz, 1H), 2.33 (s, 1H), 2.16-2.12 (m, 1H), 1.89-1.81 (m, 2H), 1.83 (dt, J = 14.0, 1.9 Hz, 1H), 1.65 (d, J = 1.1 Hz, 3H), 1.64 (d, J = 1.3 Hz, 3H), 1.56-1.53 (m, 3H), 1.50 (d, J = 12.3 Hz, 1H), 1.45-1.35 (m, 1H), 1.20 (s, 3H), 1.18-1.05 (m, 3H), 0.99-0.90 (m, 1H);

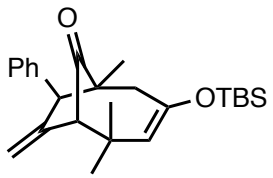
^{13}C NMR (126 MHz, $CDCl_3$): δ 213.9, 147.5, 133.9, 133.7, 109.2, 63.2, 50.3, 49.2, 47.2, 36.2, 32.4, 26.9, 25.8, 25.6, 24.8, 22.8, 20.1; For **2.69**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.29 (t, *J* = 1.2 Hz, 1H), 4.92 (d, *J* = 1.6 Hz, 1H), 2.29 (s, 1H), 1.76 (d, *J* = 12.3 Hz, 1H), 1.67 (d, *J* = 1.3 Hz, 3H) with remaining signals overlapped; ^{13}C NMR (126 MHz, $CDCl_3$): δ 132.1, 108.8, 62.7, 49.9, 48.8, 48.7, 47.1, 32.4, 26.7, 25.5, 24.9, 22.8, 19.8 with remaining signals overlapped.

(1*R,6*S**,7*S**)-4-(*tert*-Butyldimethylsilyloxy)-1,2,2-trimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (2.71)**



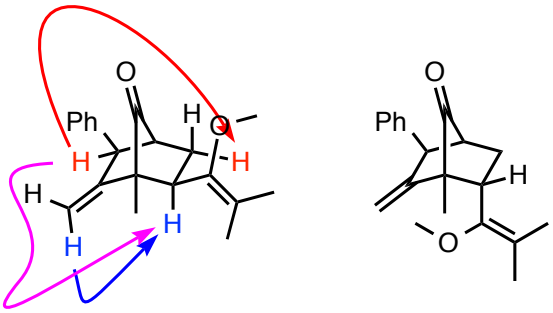
AVK **1.31** (70 mg, 0.40 mmol), **2.70** (0.42 g, 2.0 mmol), and BF_3•OEt_2 (0.05 mL, 0.44 mmol) gave **2.71** (63 mg, 40%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (t, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 2H), 5.04 (d, *J* = 2.7 Hz, 1H), 4.85-4.82 (m, 2H), 3.75 (q, *J* = 2.6 Hz, 1H), 2.62-2.57 (m, 2H), 2.35 (dd, *J* = 17.8, 6.2 Hz, 1H), 1.22 (s, 3H), 1.12 (s, 3H), 1.01 (s, 3H), 0.93 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 220.9, 157.0, 146.6, 146.3, 128.8 (2C), 128.1 (2C), 126.5, 121.8, 113.3, 60.0, 53.6, 51.8, 40.6, 37.5, 26.3, 26.0, 25.9 (3C), 18.2, 17.1, -3.9, -4.3; IR (thin film): 1740 cm^{-1}; HRMS (ESI) calcd for $[C_{25}H_{36}O_2SiNa]^+$: 419.2377, found: 419.2369.

(1*R,6*S**,8*R**)-4-(*tert*-Butyldimethylsilyloxy)-1,5,5-trimethyl-7-methylene-8-phenylbicyclo[4.2.1]non-3-en-9-one (2.72)**



AVK **2.47** (70 mg, 0.40 mmol), **2.70** (0.40 g, 2.0 mmol), and BF_3•OEt_2 (0.05 mL, 0.44 mmol) gave **2.72** (43 mg, 27%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (t, *J* = 7.4 Hz, 2H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 7.3 Hz, 2H), 5.15 (d, *J* = 2.5 Hz, 1H), 4.90 (s, 1H), 4.83 (d, *J* = 1.9 Hz, 1H), 3.95 (d, *J* = 1.7 Hz, 1H), 2.81 (s, 1H), 2.31 (dd, *J* = 16.8, 2.3 Hz, 1H), 2.17 (d, *J* = 16.8 Hz, 1H), 1.25 (s, 3H), 1.17 (s, 3H), 0.94 (s, 9H), 0.63 (s, 3H), 0.17 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 219.3, 149.5, 146.7, 143.1, 130.1, 128.2 (2C), 126.7 (2C), 118.8, 114.4, 65.9, 57.2, 51.1, 47.7, 38.9, 30.6, 29.2, 25.9 (3C), 21.0, 18.2, -4.0, -4.3; IR (thin film): 1742 cm^{-1}; HRMS (ESI) calcd for $[C_{25}H_{36}O_2SiNa]^+$: 419.2377, found: 419.2371.

(1*R,2*S**,4*S**,5*S**)-2-(1-methoxy-2-methylprop-1-en-1-yl)-1-methyl-6-methylene-5-phenylbicyclo[2.2.1]heptan-7-one (2.74) and (1*R**,2*R**,4*S**,5*S**)-2-(1-methoxy-2-methylprop-1-en-1-yl)-1-methyl-6-methylene-5-phenylbicyclo[2.2.1]heptan-7-one (2.75)**



AVK **1** (70 mg, 0.40 mmol), **2.73** (0.52 g, 2.0 mmol) and BF_3•OEt_2 (0.05 mL, 0.44 mmol) gave a 9:1 mixture of **2.74** and **2.75** (64 mg, 54%) as a colorless oil. For **2.74**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (t, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.1 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 5.10 (d, *J* = 2.0 Hz, 1H), 4.81 (s, 1H), 3.78 (s, 1H), 3.55 (s, 3H), 3.04 (dd, *J* = 10.3, 5.1 Hz, 1H), 2.30 (d, *J* = 4.7 Hz, 1H), 2.24 (dt, *J* = 12.4, 5.0 Hz, 1H), 1.96 (dd, *J* = 12.2, 10.7 Hz, 1H), 1.71 (s, 3H), 1.64 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 214.0, 153.3, 150.7, 143.3, 128.6 (2C), 127.5 (2C), 126.7, 117.0, 107.9, 61.3, 52.9, 51.9, 48.1, 43.4, 28.7, 19.7, 18.7, 9.4. For **2.75**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (t, *J* = 7.4 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 4.95 (d, *J* = 2.6 Hz, 1H), 4.77 (d, *J* = 2.1 Hz, 1H), 3.83 (s, 1H), 3.59 (s, 3H), 3.13 (dd, *J* = 10.8, 6.5 Hz, 1H), 2.17-2.08 (m, 2H), 1.95 (d, *J* = 10.4 Hz, 1H), 1.76 (s, 3H), 1.66 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 215.1, 150.4, 149.8, 143.9, 128.7 (2C), 127.7 (2C), 126.7, 119.1, 109.6, 61.9, 55.1, 52.9, 48.2, 41.3, 28.1, 20.1, 19.3, 11.4.

For **2.74** and **2.75**: IR (thin film): 1777, 1767 cm^{-1}; HRMS (ESI) calcd for $[C_{20}H_{24}O_2Na]^+$: 319.1669, found: 319.1670.

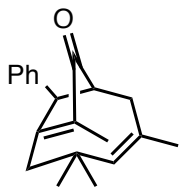
2.5.5 BF_3-mediated rearrangement of 2.52 to 2.50

A 1:10:4 mixture (by ^1H NMR) of **2.51**, **2.52** and **2.53**, respectively, (20 mg, 0.06 mmol) and BF_3•OEt_2 (0.01 mL, 0.09 mmol) in CH_2Cl_2 (6 mL) was stirred at rt for 5 min. A saturated solution of $NaHCO_3$ was added, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (× 2). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was a 1.3:1:7.7:4 mixture (according to the analysis of the ^1H NMR) of **2.50**, **2.51**, **2.52** and **2.53**, respectively, (10 mg, approximately 7% yield of **14**).

2.5.6 BF_3-mediated rearrangement of 2.59, 2.61, 2.64/2.65 and 2.68/2.69

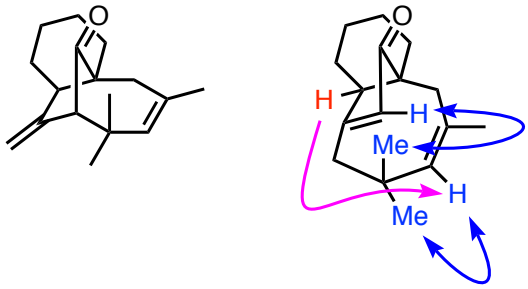
The substrate (1 equiv) in CH_2Cl_2 (sufficient to make a 0.01 M solution) was cooled to 0 °C. BF_3•OEt_2 (5 equiv) was added. The mixture was allowed to warm to rt as it was stirred (2 h). A saturated solution of $NaHCO_3$ was added, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (× 2). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was isolated by column chromatography with 10% Et_2O in pentane.

(7*R,10*S**,4*Z*)-3,3,5,9-tetramethyl-10-phenylbicyclo[5.2.1]deca-1(9),4-dien-8-one (2.76)**



Compounds **2.64/2.65**‡ (4:1, respectively, according to the analysis of the ^{1}H NMR) (70 mg) with BF_3•OEt_2 (0.15 mL) gave **2.76** (16 mg, 23%) as an oil. NMR spectra were as reported in the literature.[40]

(4a*R,9*S**,10a*S**)-6,8,8-Trimethyl-10-methylene-2,3,4,5,8,9,10,10a-octahydro-1*H*-4a,9-methanobenzo[8]annulen-11-one (2.77) and (4a*R**,10a*S**,6*Z*)-6,8,8-trimethyl-1,2,3,4,5,8,9,10a-octahydro-4a,10-(epiethan[2]yl[1]ylidene)benzo[8]annulen-12-one (2.78)**

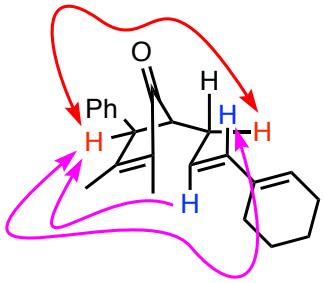


Compounds **2.68/2.69** (45 mg) with BF_3•OEt_2 (0.1 mL) afforded **2.77** (23 mg, 52%) and **2.78** (13 mg, 30%) as oils. For **2.77**: IR (film): n = 1740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.10 (s, 1H), 5.03 (s, 1H), 4.99 (s, 1H), 2.62 (s, 1H), 2.43 (t, J = 7.9 Hz, 1H),

‡ In one experiment only the (3+2)-products **29a,b** were obtained without any of the (4+3)-cycloaddition product **28**.

2.05-2.00 (m, 2H), 1.93 (d, J = 17.0 Hz, 1H), 1.82-1.78 (m, 1H), 1.68 (s, 3H), 1.53-1.49 (m, 2H), 1.22-1.18 (m, 5H), 1.17-1.09 (m, 2H), 1.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 218.8, 151.4, 133.2, 129.4, 109.3, 63.0, 51.7, 46.8, 45.8, 39.1, 31.8, 30.3, 29.7, 29.0, 28.1, 21.8, 20.8; HRMS (ESI) 267.1730, $[C_{17}H_{24}ONa]^+$ requires 267.1719. For **2.78**: IR (film): n = 1713, 1600 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.68 (s, 1H), 5.38 (s, 1H), 2.68 (d, J = 14.2 Hz, 1H), 2.63 (dd, J = 11.3, 5.1 Hz, 1H), 2.59 (d, J = 11.1 Hz, 1H), 2.36 (d, J = 11.1 Hz, 1H), 2.23-2.15 (m, 2H), 1.70 (s, 3H), 1.66-1.63 (m, 3H), 1.60 (d, J = 6.4 Hz, 1H), 1.26-1.21 (m, 2H), 1.23 (s, 3H), 1.09 (s, 3H), 0.88-0.80 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 211.8, 186.8, 135.3, 135.0, 124.9, 56.8, 53.4, 47.4, 43.4, 38.8, 36.6, 34.9, 30.6, 24.3, 24.2 (2C); HRMS (ESI) 267.1722, $[C_{17}H_{24}ONa]^+$ requires 267.1719.

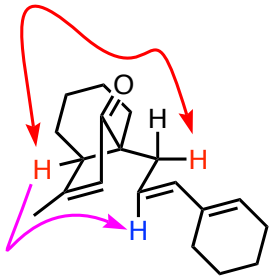
(4*R,5*S**)-5-((*E*)-3-(Cyclohex-1-en-1-yl)allyl)-2,3-dimethyl-4-phenylcyclopent-2-enone (2.79)**



Compound **2.59** (34 mg) with BF_3•OEt_2 (0.1 mL) afforded **2.79** (10 mg, 29%) as an oil: IR (film): n = 1701, 1649, 1602 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (t, J = 7.4 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 7.03 (d, J = 7.2 Hz, 2H), 6.07 (d, J = 15.4 Hz, 1H), 5.64 (s, 1 H), 5.38 (dt, J = 15.4, 7.4 Hz, 1H), 3.48 (s, 1H), 2.62 (dt, J = 13.8, 5.8 Hz, 1H), 2.39-2.36 (m, J = 2.8 Hz, 1H), 2.25 (dt, J = 14.3, 8.2 Hz, 1H), 2.10 (s, 2H), 1.98 (s, 2H), 1.79

(s, 6H), 1.63-1.58 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 210.2, 170.3, 142.1, 136.5, 135.8, 135.6, 128.9, 128.1, 128.0, 127.0, 123.2, 55.7, 55.6, 34.8, 25.9, 24.7, 22.8, 22.7, 15.6, 8.4; HRMS (ESI) 329.1865, $[C_{22}H_{26}ONa]^+$ requires 329.1876.

(3a*R,7a*S**)-7a-((*E*)-3-(Cyclohex-1-en-1-yl)allyl)-3-methyl-3a,4,5,6,7,7a-hexahydro-1*H*-inden-1-one (2.82)**

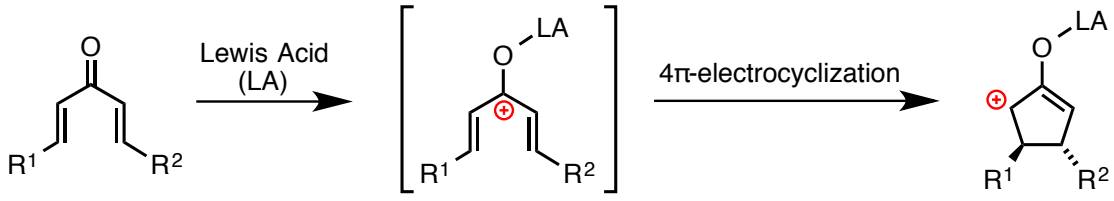


Compound **2.61** (42 mg) with BF_3•OEt_2 (0.1 mL) gave **2.82** (11 mg, 26%) as an oil: IR (film): *n* = 1702, 1601 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.01 (d, *J* = 15.5 Hz, 1H), 5.89 (s, 1H), 5.63 (s, 1H), 5.33 (dt, *J* = 15.3, 7.6 Hz, 1H), 2.58 (t, *J* = 5.4 Hz, 1H), 2.30 (dd, *J* = 13.7, 6.4 Hz, 1H), 2.17 (dd, *J* = 13.7, 8.6 Hz, 1H), 2.11-2.07 (m, 2H), 2.05-1.99 (m, 5H), 1.80-1.73 (m, *J* = 5.0 Hz, 1H), 1.65-1.54 (m, 7H), 1.47-1.43 (m, 3H), 1.33-1.25 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 213.9, 180.3, 136.7, 135.6, 129.6, 128.2, 121.5, 51.9, 48.4, 40.8, 29.7, 25.9, 24.8, 23.6, 22.7, 22.6, 19.0, 18.9, 17.5; HRMS (ESI) 293.1876, $[C_{19}H_{26}ONa]^+$ requires 293.1876.

Chapter 3
Torquoselectivity in the Nazarov Reactions of Allenyl Vinyl Ketones

3.1 Introduction

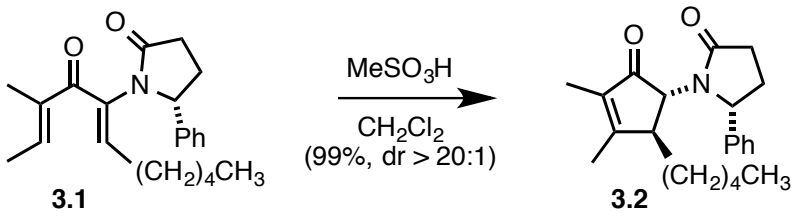
In the classical Nazarov reaction of a divinyl ketone with substituents on the termini, the conrotatory nature of the electrocyclization would determine the relative stereochemistry of the product (Scheme 3.1), but the absolute stereochemistry is the result of torquoselectivity, which is a bias in the direction (clockwise or counterclockwise) of conrotation. Substantial effort has been expended in attempts to develop asymmetric variants of the Nazarov reaction in which a chiral catalyst or auxiliary controls the torquoselectivity.[4]



Scheme 3.1 Acid-mediated reaction of an (*E,E*)-divinyl ketone leading to an oxyallyl cation

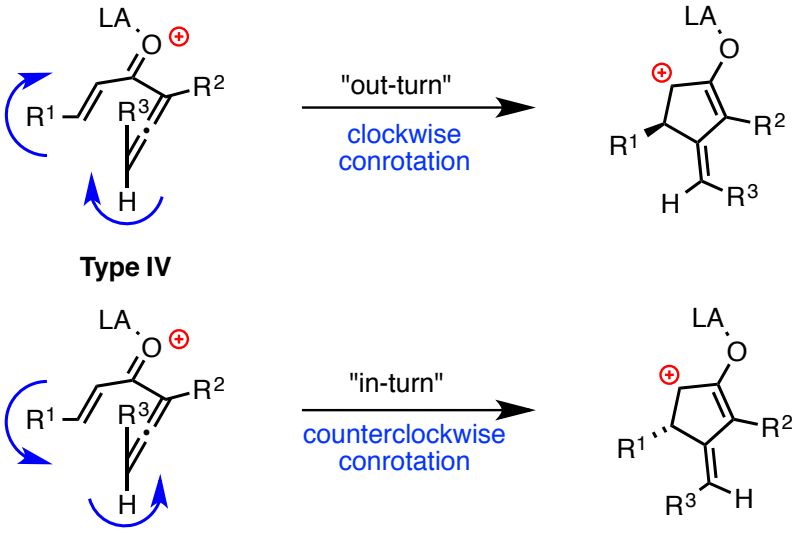
A recent example of a torquoselective Nazarov reaction was developed by Flynn and coworkers using a chiral auxiliary.[77] A series of divinyl ketones bearing chiral oxazolidinones were prepared and tested in the Nazarov reaction, as shown in Scheme 3.2. There were actually three functions for the oxazolidinone auxiliary. First, the auxiliary polarized the divinyl ketone to facilitate cyclization of the otherwise unactivated systems. Secondly, the regioselectivity of the double bond formation in the

products was mediated by the σ-withdrawing nature of the nitrogen. Finally, the chiral oxazolidinone controlled the torquoselectivity of the reaction. The Nazarov reaction of **3.1** occurred with a very high preference for counterclockwise conrotation of the terminal substituents leading to the enantiomerically enriched product **3.2**. The yield for the process was very high, and the diastereoselectivity was > 20:1.



Scheme 3.2 Torquoselective oxazolidinone-mediated Nazarov reaction.

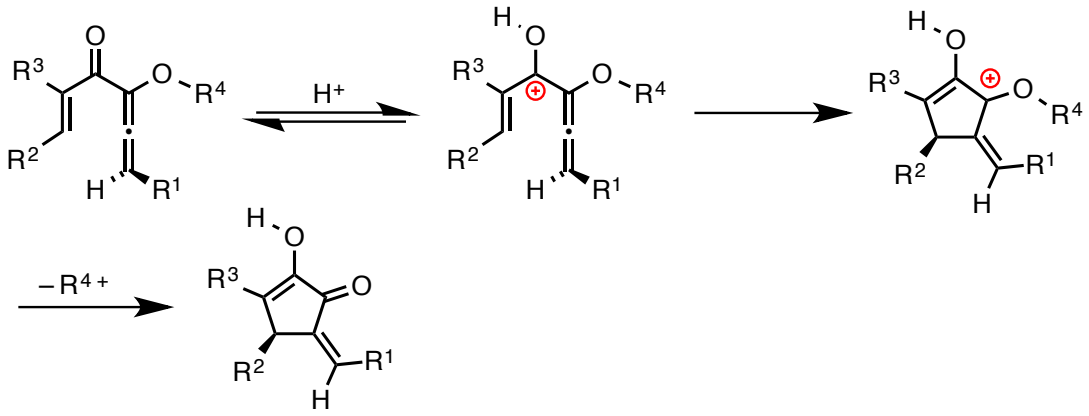
In the case of an allenyl vinyl ketone with a terminally substituted allene, i.e., a Type IV AVK, another effect arises. The geometry of the resulting exocyclic double bond is determined by the torquoselectivity of the reaction. The possible oxyallyl cations arising from the Nazarov reaction of an enantiomerically pure Type IV AVK are shown in Scheme 3.3. The oxyallyl cation in which R^1 and R^3 are *syn*, the result of counterclockwise conrotation, is referred to as the "in-turn" product, and the oxyallyl cation in which R^2 and R^3 are *syn*, the result of clockwise conrotation, is dubbed the "out-turn" product. Thus, the torquoselectivity of the Nazarov reaction of a type IV AVK can be assessed not only by determining the enantiomeric excess at the chiral center but more simply by analyzing the ratio of in-turn versus out-turn products, and the phenomenon can be probed even with a racemic substrate.



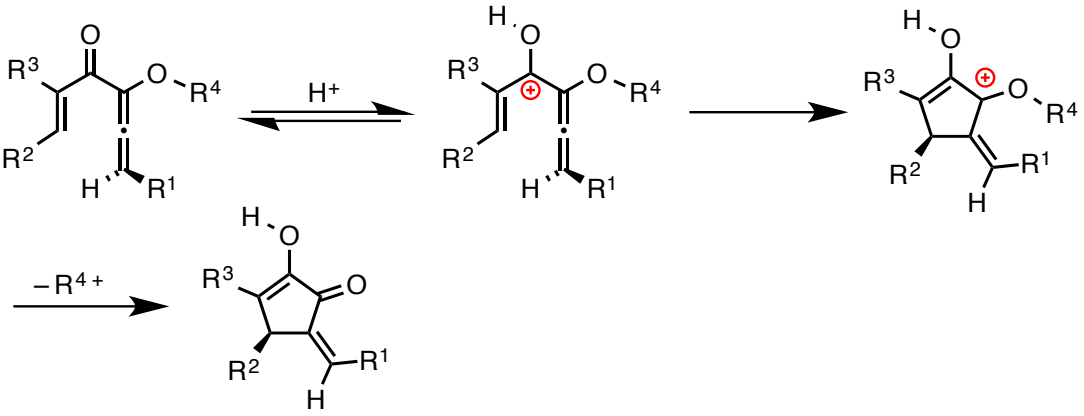
Scheme 3.3 Results of opposite torquoselectivity with a type IV AVK.

3.1.1 Torquoselectivity in the Nazarov Reactions of Allenyl Ethers

The Tius group investigated the torquoselectivity of type IV AVKs bearing an ether substituent on the allene α to the carbonyl, as shown in

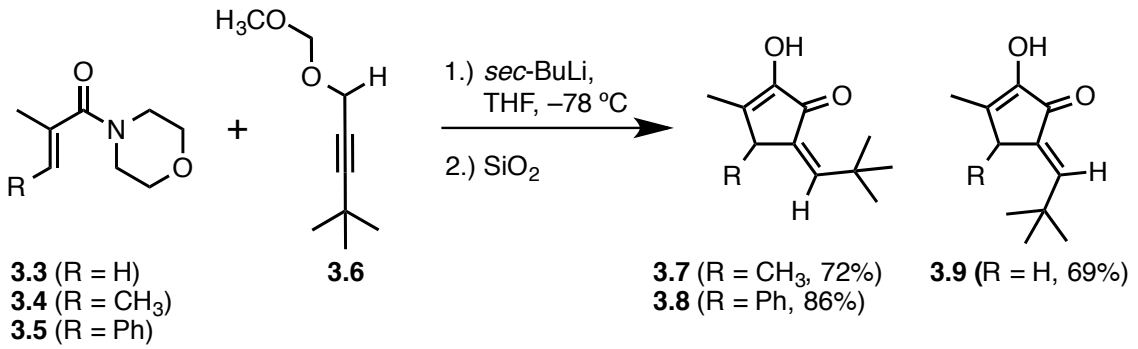


Scheme 3.4. The reaction showed a kinetic preference for the formation of an exocyclic *Z* double bond.[30] Tius suggested that this selectivity arose due to steric interactions between R^1 and R^2.



Scheme 3.4 Nazarov cyclization of allenyl vinyl ketone bearing an allenyl ether.

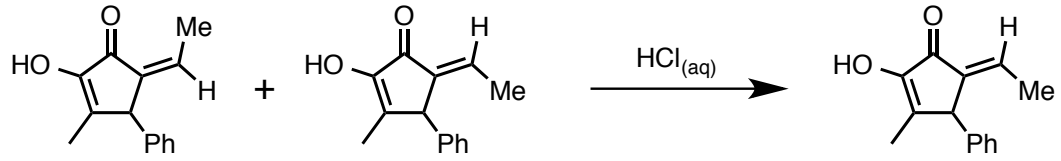
If steric effects controlled the *E/Z* ratio of Nazarov cyclization products, as the sizes of R^1 and R^2 increased so too should the selectivity for the *Z* isomer have increased. This hypothesis appeared to hold true. Addition of propargyl lithium **3.6** to morpholino amides **3.3-3.5** generated homopropargyl ketones that underwent isomerization and cyclization when exposed to SiO_2. When R was a methyl or phenyl group the cyclization produced *Z* isomers **3.7** and **3.8**. However, when R was much smaller, such as hydrogen, the torquoselectivity was reversed and the *E* isomer **3.9** was exclusively isolated (Scheme 3.5).[78]



Scheme 3.5 Torquoselectivity in the Nazarov reaction of AVK ethers.

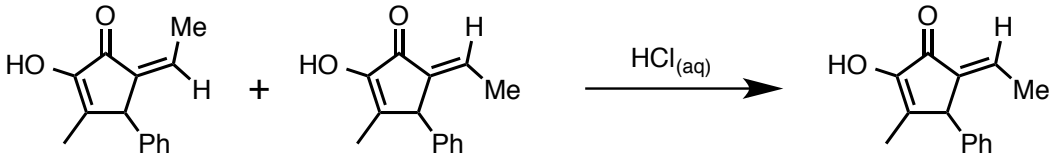
Although the torquoselectivity in many cases was reported to be very high, the results were clouded by the fact that these products also underwent facile isomerization of the exocyclic double bond. Exposure of a mixture of *E/Z* isomers

3.10 **and** 3.11 **to aqueous HCl led to complete isomerization of the double bond to the thermodynamically preferred *E* product**



3.10 **3.11** **3.10**

(Scheme 3.6).[79]

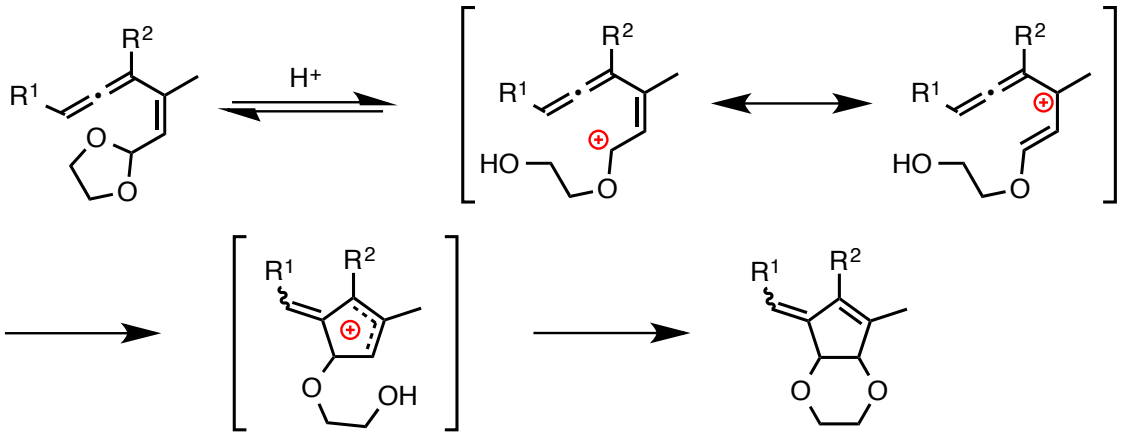


3.10 **3.11** **3.10**

Scheme 3.6 Isomerization of Nazarov products with aqueous acid.

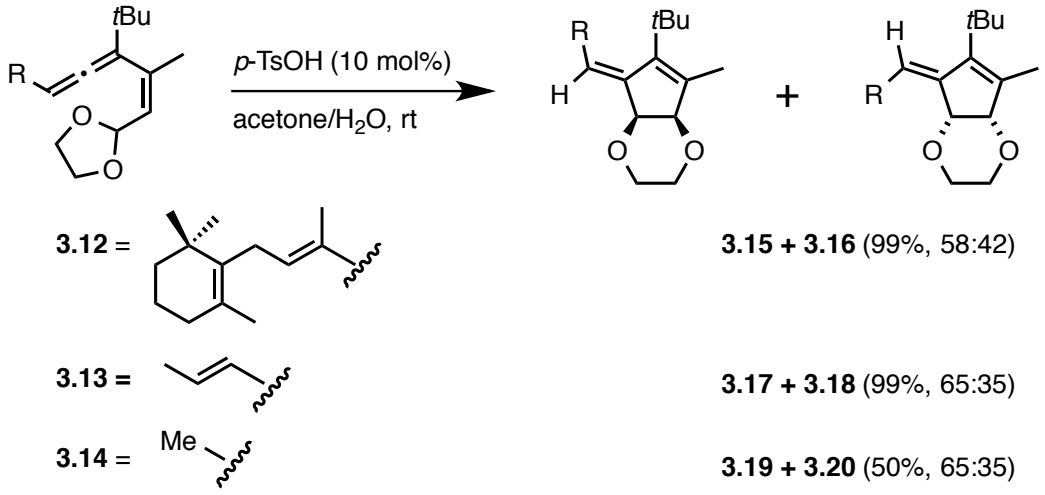
3.1.2 Cyclization of (2*Z*)-Hexa-2,4,5-trienal Acetals

de Lera *et al.* demonstrated that (2*Z*)-hexa-2,4,5-trienal acetals undergo a cyclopentannelation reaction very similar to the Nazarov reaction.[80] The reaction is detailed in Scheme 3.7. Acid-catalyzed opening of the acetal generated a cationic species that underwent a 4π-electrocyclization. The subsequent allyl cation was trapped intramolecularly by the pendent oxygen. The geometry of the exocyclic double bond in the product was the result of the torquoselectivity of the electrocyclization.



Scheme 3.7 Cyclopentannelation of (2*Z*)-hexa-2,4,5-trienal acetals under acidic conditions.

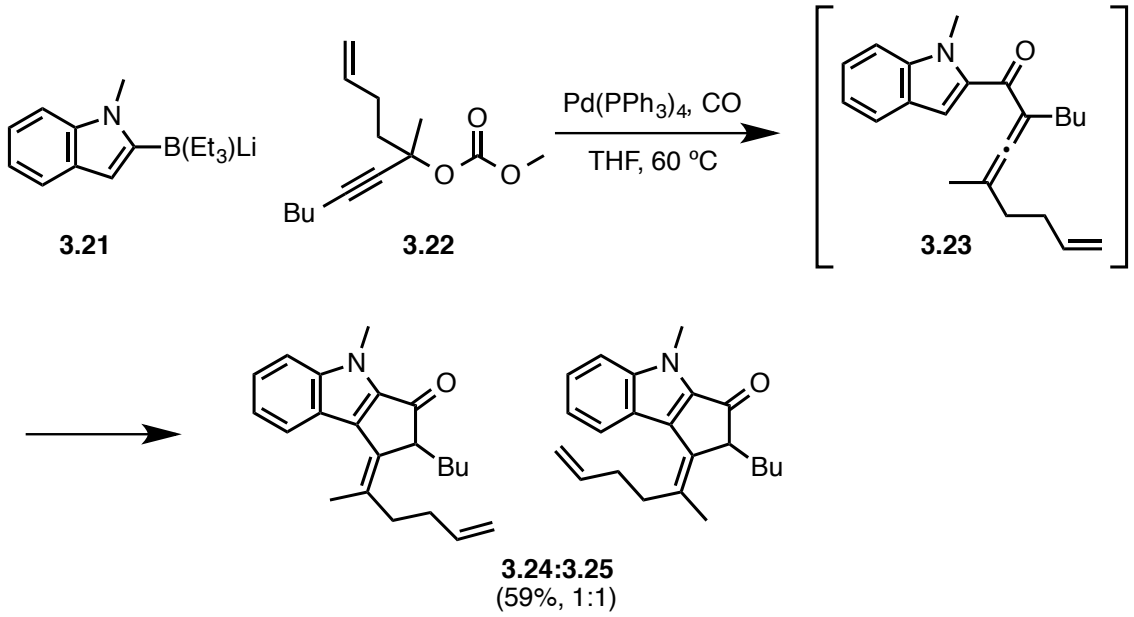
A series of (2*Z*)-hexa-2,4,5-trienal acetals was prepared in order to test the selectivity of this reaction.[81] Acetals **3.12** and **3.13** cyclized in essentially quantitative yield; **3.14** also underwent cyclization but in only 50% yield. In every case the torquoselectivity appeared to be modest. A slight preference for the *E* isomers, **3.15**, **3.17** and **3.19**, was observed (Scheme 3.8). However, the authors noted that the initial results were misleading. When **3.12** was treated with acid at –60 ºC, **3.15** was the only product detected using ^{1}H NMR spectroscopy. The sample was warmed to room temperature and after sitting for 2 weeks **3.15** was completely converted to **3.16**. Thus, the electrocyclization occurred with a high degree of torquoselectivity, but equilibration modified the result.



Scheme 3.8 Cyclization of trienal acetals under catalytic acidic conditions

3.1.3 Apparent Nazarov Cyclization of Allenyl Indolyl Ketones

A process for the synthesis of cyclopenta[*b*]indoles via a palladium-mediated carbonylative cross-coupling was reported by Ishikura *et al.*[82] The one-pot reaction is shown in Scheme 3.9. Treatment of 1-methylindole with *t*-BuLi followed by triethylborane led to the formation of borate **3.21**. In the presence of a palladium catalyst and under an atmosphere of CO, **3.21** was coupled with **3.22**. The products **3.24** and **3.25** arose spontaneously from putative intermediate **3.23**. The authors suggested that the cyclization occurred by nucleophilic attack of the indole onto the central allenic carbon. However, Nazarov reactions of indolyl vinyl ketones have been described in the literature.[83] Regardless of the mechanism by which **3.24** and **3.25** arose, the products were obtained in a 1:1 ratio.

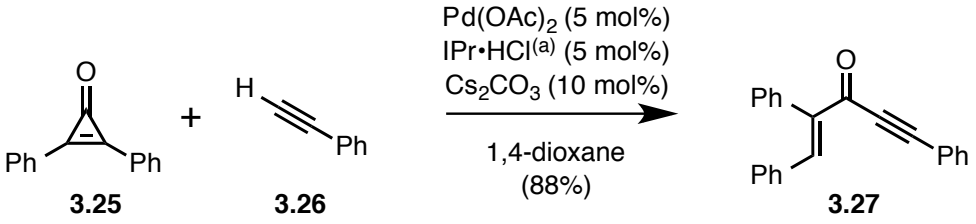


Scheme 3.9 One pot process for the preparation of cyclopenta[*b*]indoles via palladium-catalyzed carbonylative cross-coupling.

3.1.4 Ring-Opening Alkynylation of Cyclopropenones and Subsequent Nazarov-Type Cyclization

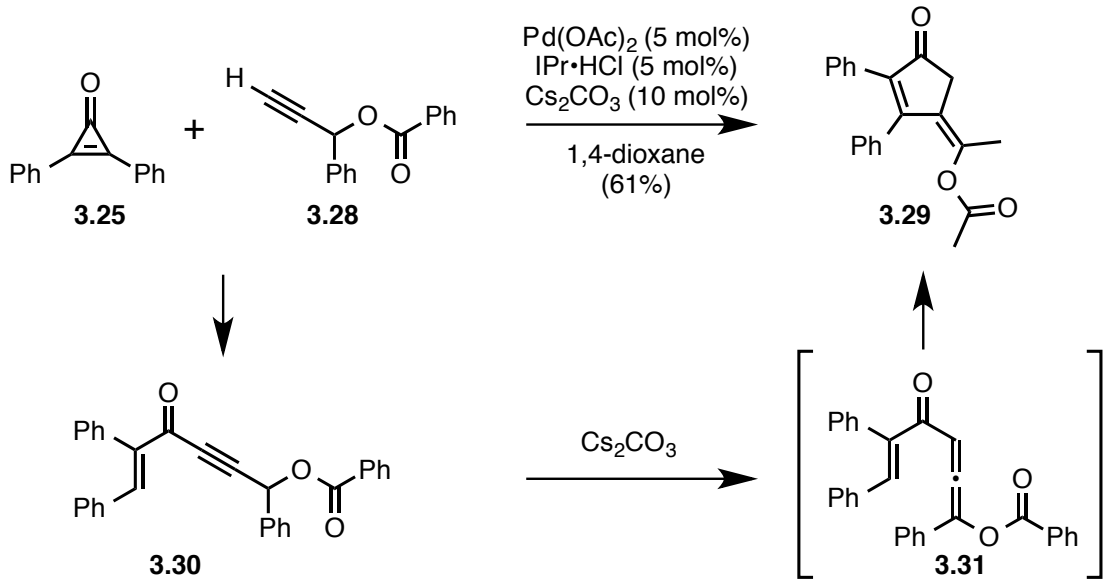
In the course of their studies on the palladium-catalyzed ring opening of cyclopropenones with alkynes, the Sakurai group noted a Nazarov cyclization of a type IV AVK.[84] The general procedure for the ring-opening reaction is shown in Scheme 3.10. In the presence of a palladium catalyst, cyclopropenone **3.25** was opened by the terminal alkyne **3.26** to form the propargyl ketone **3.27**. When an alkyne bearing an ester, such as **3.28**, was subjected to the reaction conditions, cyclopentenone **3.29** was the sole product (Scheme 3.11). The reaction likely initially produced the ketone **3.30**. Upon exposure to a base, such as Cs_2CO_3, the propargyl ketone could isomerize to AVK **3.31**. The AVK was not isolated because it cyclized to form the cyclopentenone **3.29** either during work-up or purification. The geometry of the exocyclic double bond in

3.29 was confirmed using x-ray crystallography. Whether this was the kinetic or the thermodynamic product is not known.



(a) IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole

Scheme 3.10 Palladium mediated ring-opening alkynylation of a cyclopropenone.



Scheme 3.11 Isomerization and Nazarov-type cyclization of propargyl ketone generated from opening of a cyclopropenone with an alkyne.

3.1.5 Nazarov Reaction and Torquoselectivity of Type IV AVKs

The use of allenyl vinyl ketones (AVKs) for the interrupted Nazarov reaction has been the focus a of significant amount of research in the Burnell group.[35,40] One of

the early questions that was addressed was the effect of simple alkyl substitution on the reactivity of AVKs.[36] AVKs of Types I-III were prepared and tested in Nazarov reactions (Figure 3.1). However, AVKs bearing substitution on the terminal end of the allene had not previously been explored. Type IV AVKs are structurally similar to the systems studied by Tius,[79] but they differ by having all carbon substitutents on the allene.

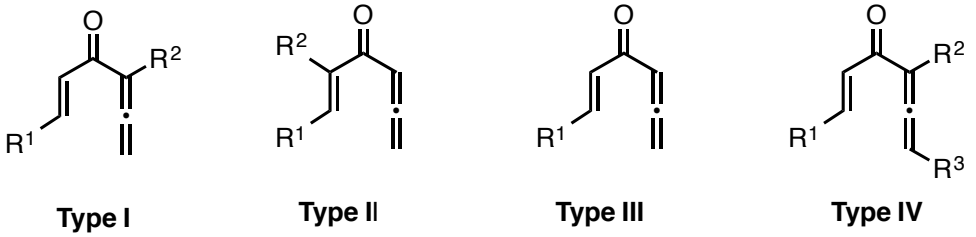


Figure 3.1 Allenyl vinyl ketones with different substitution patterns.

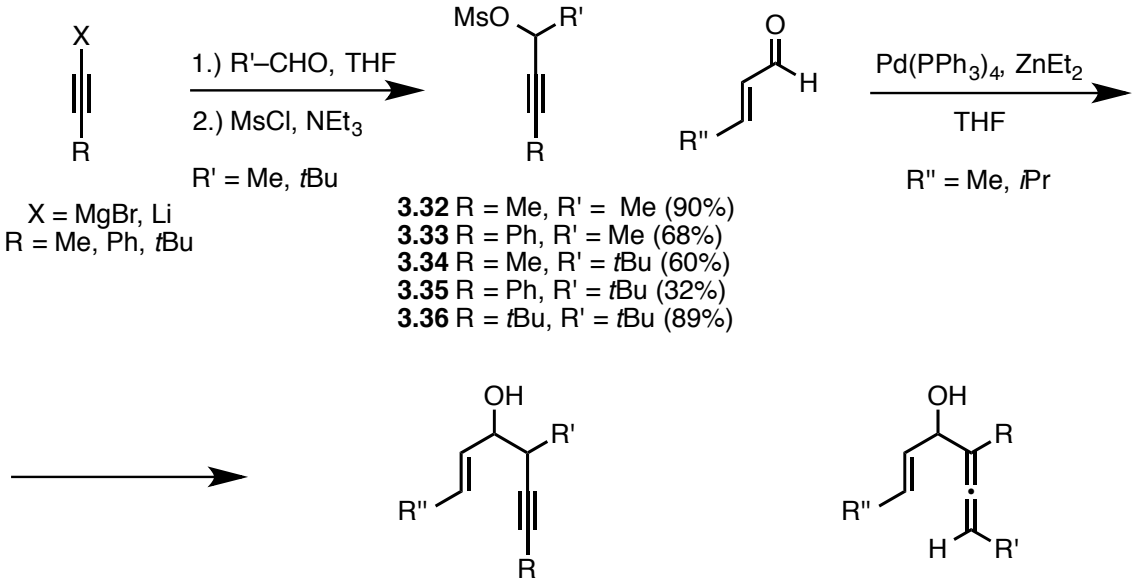
There were three major questions that arose in consideration of Type IV AVKs. First, how would substitution on the terminus of the allene affect the efficiency of the Nazarov reaction and subsequent trapping? Secondly, would the torquoselectivity mirror that observed by Tius, and thirdly would the results of reactions with a series of differently substituted AVKs shed light on the factors that control torquoselectivity?

3.2 Results and Discussion

3.2.1 Synthesis of Terminally Substituted Allenyl Vinyl Ketones

The exploration of Type IV AVKs (in racemic form) began with their synthesis.[85] Propargyl alcohols were assembled by addition of alkynylmagnesium or alkynyllithium reagents to acetaldehyde and trimethylacetaldehyde (Scheme 3.12). The alcohols were then converted into mesylates, **3.32-3.36**, and used without purification due to their limited stability. The mesylates were employed in a palladium-catalyzed

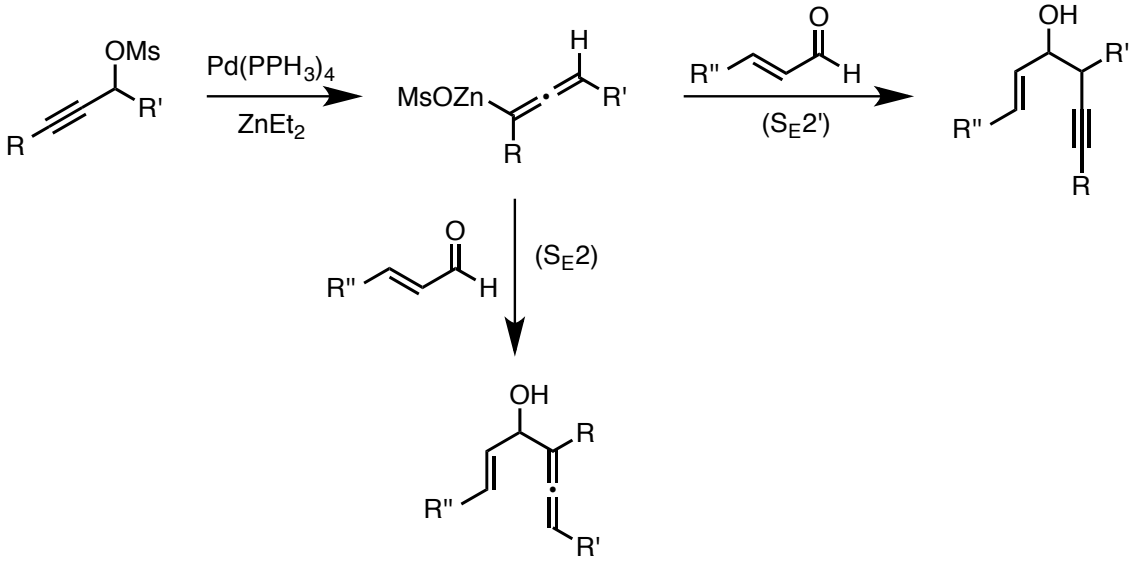
reaction that converted them to organozinc species that were subsequently coupled to α,β-unsaturated aldehydes.[86-88] The coupling reaction predominately produced homopropargyl alcohols **3.37-3.46** with generally high diastereomeric ratios. However, in two cases allenic alcohols **3.47** and **3.48** were also isolated.



Scheme 3.12 Synthesis of homopropargyl alcohols and allenic alcohols.

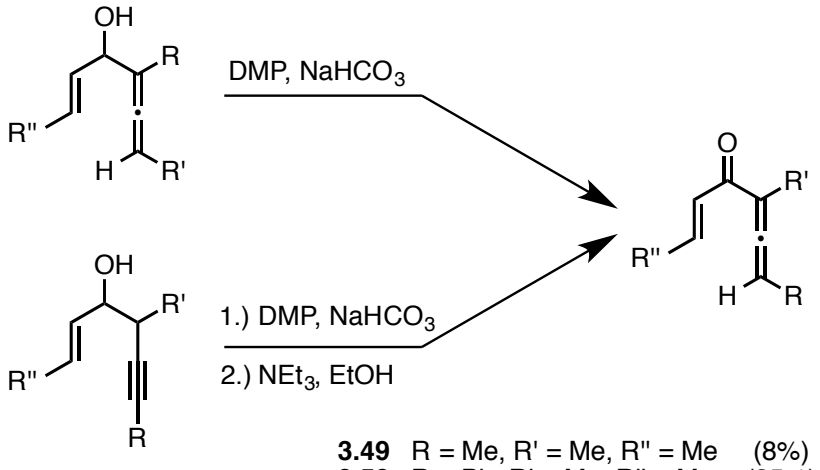
The coupling reaction proceeded through the generation of an allenic zinc species that can react with an electrophile. The allenic zinc could react with an aldehyde through either an S_E2 or S_E2' mechanism.[89] The S_E2' addition was usually preferred, but steric effects might have accounted for the formation of **3.47** and **3.48**. The yields from α,β-unsaturated aldehydes were lower than those reported for similar reactions in the

literature that used saturated aldehydes. It is known that unwanted 1,4-additions of diethylzinc to α,β-unsaturated aldehydes can occur.[88] None of the desired product was obtained when the coupling reaction with acrolein was attempted. Despite the poor yields of homopropargyl and allenic alcohols, sufficient material was produced in order to carry on with the study.



Scheme 3.13 Formation of allenic and homopropargyl alcohols from allenic zinc species via S_E2 and S_E2' mechanisms.

The allenic alcohols were converted to AVKs, **3.49-3.60**, by oxidation with Dess-Martin periodinane buffered with $NaHCO_3$.[90] The homopropargyl ketones were isomerized using NEt_3 in a protic solvent.[91] The isomerization was an equilibration process that relied on the conjugation of the allene with the carbonyl group. The isomerization typically proceeded with modest yield. However, in some cases the isomerization process was very inefficient, for example with **3.49**. The reason for this difference in reactivity was not clear, but none of the homopropargyl alcohol was recovered, which suggested instability of the starting ketone, the allene product, or both.



3.49	R = Me, R' = Me, R'' = Me	(8%)
3.50	R = Ph, R' = Me, R'' = Me	(35%)
3.51	R = Me, R' = *t*Bu, R'' = Me	(13%)
3.52	R = *t*Bu, R' = Me, R'' = Me	(42%)
3.53	R = Ph, R' = *t*Bu, R'' = Me	(69%)
3.54	R = *t*Bu, R' = *t*Bu, R'' = Me	(22%)
3.55	R = Me, R' = Me, R'' = *i*Pr	(49%)
3.56	R = Ph, R' = Me, R'' = *i*Pr	(76%)
3.57	R = Me, R' = *t*Bu, R'' = *i*Pr	(51%)
3.58	R = *t*Bu, R' = *Me*, R'' = *iPr*	(76%)
3.59	R = Ph, R' = *t*Bu, R'' = *i*Pr	(70%)
3.60	R = *t*Bu, R' = *t*Bu, R'' = *i*Pr	(51%)

Scheme 3.14 Oxidation and isomerization of homopropargyl and allenic alcohols to AVKs.

3.2.2 Cyclization of Terminally Substituted AVKs

The oxyallyl cations produced from the Nazarov reaction could not be analyzed directly so it was necessary to trap them. It was important to ensure that the trapping process preserved the exocyclic double bond. Trapping of the oxyallyl cation from type I AVKs with 2,3-dimethyl-1,3-butadiene had been shown to be essentially quantitative.[35,40] Therefore, the AVKs **3.49-3.60** in Figure 3.2 were treated with BF_3•OEt_2 in dichloromethane at –78 ºC in the presence of 2,3-dimethyl-1,3-butadiene. The results of the tandem Nazarov/(4+3)-cycloadditions are summarized in Table 3.1.

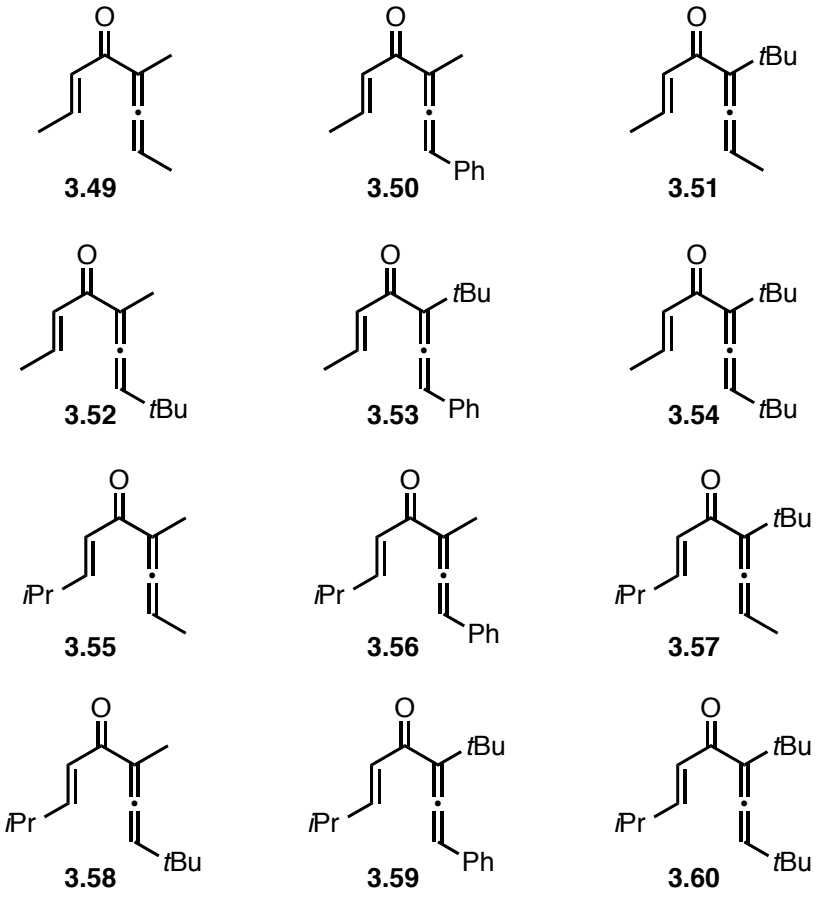


Figure 3.2 Substituted type IV AVKs.

The terminal substitution of the allene had a substantial effect on the tandem process, as the yields in all cases were lower than with type I AVKs.[40] When all of the substituents on the AVK were methyl groups (**3.49**) a mixture of *Z/E* isomers was obtained in a 74:26 ratio. The ratios were determined by integration of the ^{1}H NMR spectra. The isomers were subjected to NOE experiments to determine the geometry of the exocyclic double bond. The NOE contacts for out-turn product **3.61** and in-turn product **3.62** are depicted in Figure 3.3, and these results were typical for the other Nazarov products.

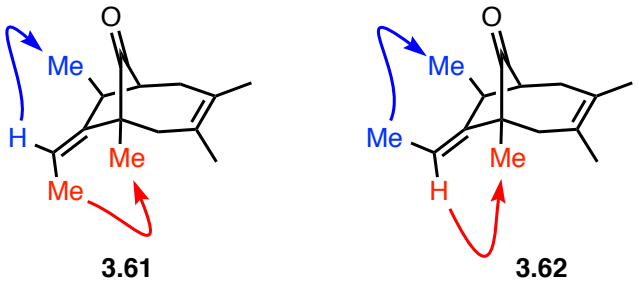
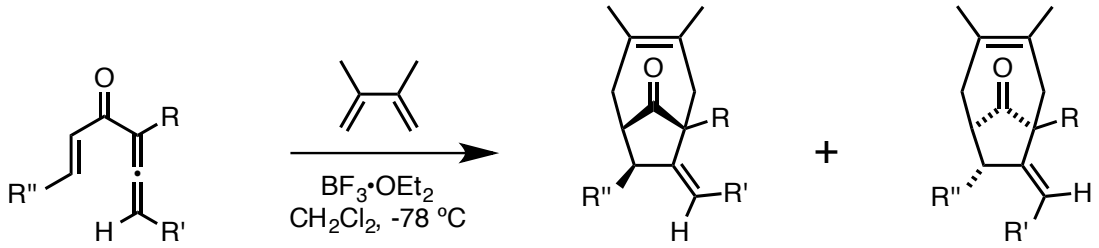


Figure 3.3 NOE contacts for 3.61 and 3.62.

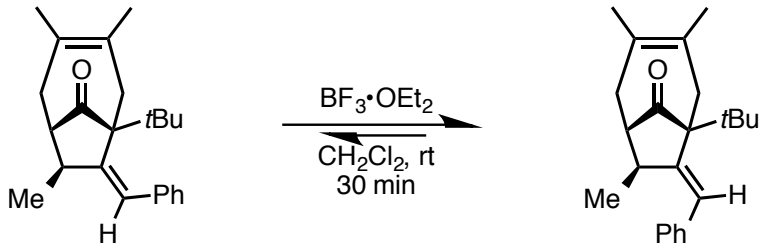
If the steric bulk of *any* substituent was increased, the diastereomeric ratio increased to at least 20:1. When R″ was changed from methyl to isopropyl, i.e., **3.49** to **3.55**, the torquoselectivity increased dramatically. This effect would be reasonable if in the transition state R rotated away from the larger isopropyl group. With this in mind it was expected that increasing the size of R′ might increase the proportion of in-turn products. However, the opposite was true. When the size of R′ was increased from methyl to *tert*-butyl, i.e., **3.49** to **3.52**, the same increase in diastereoselectivity was observed. In this case R rotated toward the *tert*-butyl group and ultimately become coplanar with the large substituent. In an attempt to bias the system as much as possible, AVKs **3.54** and **3.60** were prepared bearing *tert*-butyl groups on both ends of the allene. Unfortunately, no Nazarov products could be isolated from the reactions of these AVKs, but TLC analysis of the reaction mixtures suggested the formation of products similar to those from the other reactions. If AVKs **3.54** and **3.60** followed the same trend as the other AVKs the product may have been highly unstable due to the steric interactions between the *tert*-butyl groups in **3.67** and **3.73**.

Table 3.1 Nazarov Cyclization of AVKs 3.49-3.60 in the Presence of 2,3-Dimethylbutadiene.



AVK	R	R'	R''	Product	Yield (%)
X.4a	Me	Me	Me	**X.5a + X.6a** (74:26)	66
X.4b	Ph	Me	Me	**X.5b**	65
X.4c	Me	*t*Bu	Me	**X.5c**	47
X.4d	*t*Bu	Me	Me	**X.5d**	49
X.4e	Ph	*t*Bu	Me	**X.5e**	56
X.4f	*t*Bu	*t*Bu	Me	**X.5f**	0
X.4g	Me	Me	*i*Pr	**X.5g**	71
X.4h	Ph	Me	*i*Pr	**X.5h**	49
X.4i	Me	*t*Bu	*i*Pr	**X.5i**	59
X.4j	*t*Bu	Me	*i*Pr	**X.5j**	36
X.4k	Ph	*t*Bu	*i*Pr	**X.5k**	77
X.4l	*t*Bu	*t*Bu	*i*Pr	**X.5l**	0

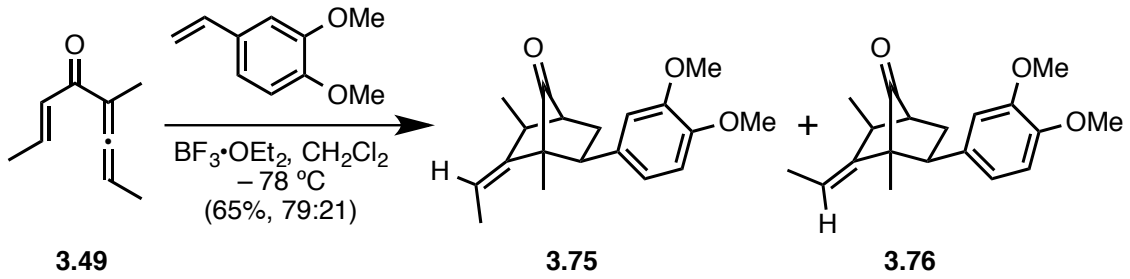
In order to support the idea that the product distributions shown in Table 3.1 represented the torquoselectivity of kinetic reactions, it was helpful to demonstrate that the products were stable under the reaction conditions. Several of the products were resubjected to BF_3•OEt_2 in dichloromethane at room temperature for 30 minutes. (The interrupted Nazarov reactions had taken less than 10 minutes at –78 °C.) Only **3.66**, with a phenyl substituent, underwent any isomerization forming **3.74** (Scheme 3.15). All the other products were recovered unchanged. Thus, no significant isomerization of the exocyclic double bond was occurring with the trapped Nazarov products.



3.66 **3.74**

Scheme 3.15 Isomerization experiment of AVK with phenyl substituent on the allene.

Although the tandem Nazarov/(4+3)-cycloaddition of AVKs has been shown to be one of the most efficient trapping reactions, the oxyallyl cation can also be intercepted by electron-rich styrenes by a (3+2)-cycloaddition.[40] To test whether the trapping process affected the product distribution, AVK **3.49** was exposed to BF_3•OEt_2 in the presence of excess of 3,4-dimethoxystyrene (Scheme 3.16). The (3+2) products **3.75** and **3.76** were produced as an inseparable mixture in a 65% yield. The "out-turn" product was favored in a 79:21 ratio. The structures were assigned using NOE experiments. The isomeric ratio was essentially the same as for the reaction of **3.49** with 2,3-dimethyl-1,3-butadiene. This suggested that the mode of trapping only had a small influence in deciding the apparent torquoselectivity of the reaction, or that a (concerted) (4+3)-cycloaddition has the same steric requirements as a (stepwise) (3+2)-cycloaddition, which would be unlikely.

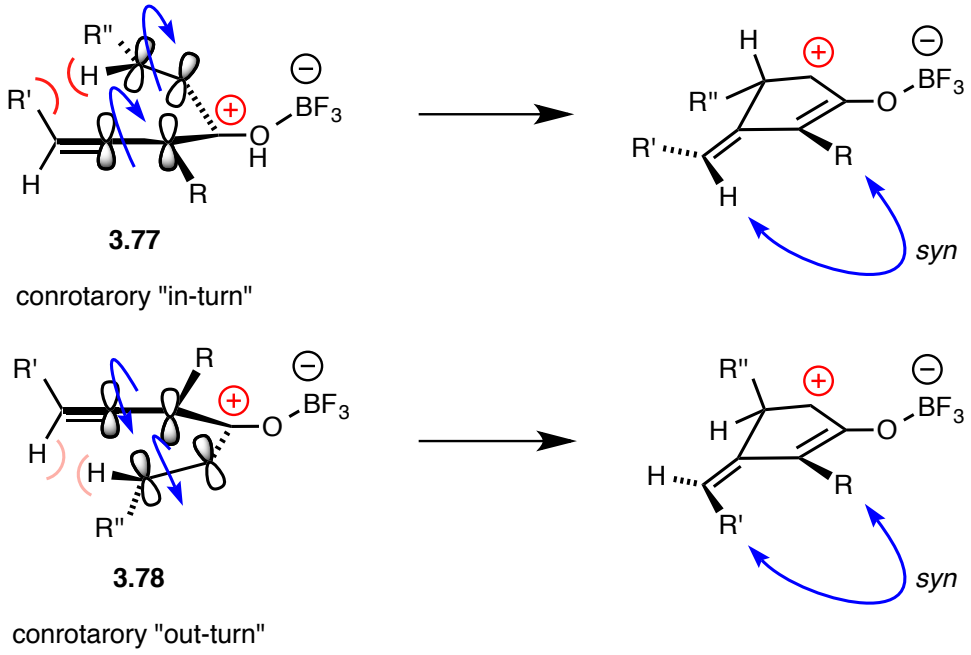


3.49 **3.75** **3.76**

Scheme 3.16 Tandem Nazarov/(3+2)-cycloaddition with 3,4-dimethoxystyrene.

3.2.3 Mechanistic Rationale and Computational Analysis

The experimental results offer some important insights into the factors that control the torquoselectivity of the Nazarov reaction of type IV AVKs. The Nazarov reaction is a 4π-electrocyclization and therefore requires at the transition state a constructive overlap of the HOMO of a pentadienyl cation. At the transition state the newly forming ring is not planar,[92,93] which means two geometries of the allene and vinyl groups are possible. One has the alkene *above* the plane of the allene, as shown in structure **3.77** (Scheme 3.17). In this geometry there would be a significant steric interaction between the vinyl hydrogen and allenic substituent R′. The conrotation of **3.77** would be in-turn and would lead to the product with an *E* exocyclic double bond. The other geometry has the alkene *below* the allene, as shown in structure **3.78**. The steric interactions between the vinyl and allenic substituents would be less in **3.78** than in **3.77**. The Nazarov reaction of **3.78** would lead to the observed major products, which had a *Z* exocyclic double bond. As the size of the allenic substituent R′ increases the preference for structure **3.78** over **3.77** should also increase and lead to the formation of a greater proportion of the out-turn product.



Scheme 3.17 Two geometries for the transition state of the Nazarov reaction of type IV allenyl vinyl ketones.

The mechanistic rationale for the formation of out-turn products from the Nazarov reaction of type IV AVKs presented in Scheme 3.17 provides a convenient explanation of the observed selectivity. However, the effect of increasing the size of R, such as **3.49** to **3.52**, is not obviously explained. This prompted a computational examination of the Nazarov cyclizations of AVKs **3.49-3.60** by another member of the Burnell group.[§] The relative product and transition state energies were calculated using the dispersion-corrected ωB97X-D functional with the 6-31+G(d,p) basis set, and the data are summarized in Table 3.2. In all cases the major product was determined to be the less thermodynamically stable product. However, the transition states leading to the out-turn products were found to be lower in energy for almost every AVK except **3.50** and **3.56**, where the transition state energies for out-turn and in-turn were nearly identical. The

[§] Luc LeBlanc carried out the calculations in the course of his Masters research.[94]

calculations also provided some geometrical information regarding the formation of the in-turn and out-turn Nazarov products. The in-turn product was confirmed to arise from a transition state where the alkene was above the allene as shown in Figure 3.4. This geometry puts R′ and the olefinic hydrogen close to each other at the transition state; the distance was calculated to be approximately 2.4 Å.

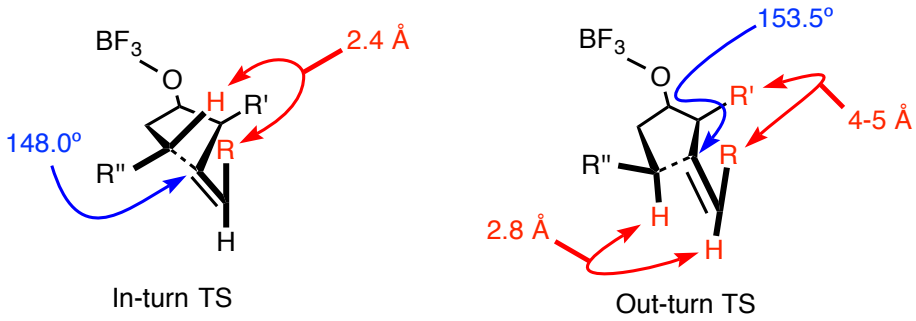
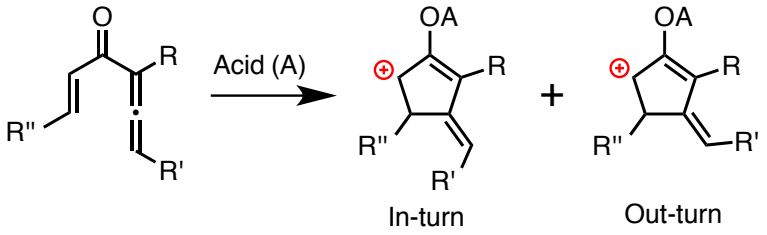


Figure 3.4 Geometrical comparison of the transitions states leading to the in-turn and out-turn Nazarov products.

The calculations showed that the out-turn product was formed via a transition state where the alkene was below the allene (Figure 3.4). The closest steric interaction (approximately 2.8 Å) in that case was between the allenic and olefinic hydrogens. Although it is easy to suggest that the developing steric interaction between R′ and R might contribute to the torquoselectivity of the reaction at the transition state, the distances between these two groups ranged from 4 to 5 Å. The distances between R′ and R were too large for those interactions to be major contributors to the product distribution, but the size of R did appear to have an effect on the degree of torquoselectivity, for instance between **3.49** and **3.52**. This effect appeared to be related to the degree of bending in the allene at the transition state. The allene in the transition state leading to the in-turn product was always more bent than the allene leading to the

out-turn product. The largest energy differences between transition states were also correlated to the largest degree of allene bending.

Table 3.2 Calculated Relative Product and Transition State Energies (ωB97X-D //6-31+G(d,p)) for the Nazarov Cyclization of AVKs 3.49-3.60



AVK	$\Delta E_{\text{In-Out}}$ (kJ·mol^{-1})	$\Delta E_{\text{In-Out}}^{\ddagger}$ (kJ·mol^{-1})
X.4a	– 11.6	4.5
X.4b	– 13.0	1.3
X.4c	– 26.0	6.4
X.4d	– 19.7	20.0
X.4e	– 13.5	4.1
X.4f	– 35.5	19.9
X.4g	– 10.8	3.9
X.4h	– 12.9	– 0.8
X.4i	– 31.5	6.5
X.4j	– 20.1	19.5
X.4k	– 18.0	2.2
X.4l	– 41.5	17.5

The steric interactions between the AVK substituents and the distortion of the allene at the transition state seem to account for the product distribution of most of the products. However, there are some cases where the differences in transition state energy suggested that small amounts of the in-turn product should have been observed, such as with **3.51** and **3.56**. It is possible the (4+3) and (3+2) trapping of the oxyallyl cation is more efficient with the out-turn products than the in-turn products. This effect would artificially enhance the observed product ratios. This will be evaluated computationally.

3.3 Conclusions

The Nazarov reaction of AVKs with terminally substituted allenes has been explored experimentally and computationally. The reaction showed a preference for the formation of the thermodynamically disfavored out-turn products. The products of related reactions have been shown to undergo acid-catalyzed isomerization of the exocyclic double bonds.[79,81] In contrast, the products of the tandem Nazarov/(4+3)-cycloadditions were stable under the reaction conditions. A computational study supported the kinetic control of the reaction and suggested that steric effects primarily control the torquoselectivity. The calculations also showed that a secondary factor affecting the torquoselectivity is the amount of deformation of the allene in the transition state. A transition state with less deformation of the allene is preferred. It is also possible that one oxyallyl cation intermediate is trapped preferentially, which led to the isolation of essentially one product in most cases.

3.4 Experimental Section

3.4.1 General considerations

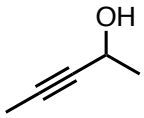
Reactions were carried out in oven-dried glassware under an atmosphere of dry nitrogen. Reagents were used as received from commercial sources. Dichloromethane was distilled over calcium hydride. Tetrahydrofuran (THF) was freshly distilled over sodium/benzophenone. EtOAc and hexanes were distilled. Reactions were followed by TLC analysis using precoated (silica gel 60 F254, 0.25 mm) plates with aluminum backing. Column chromatography was carried out with silica gel (40–63 μm particle size, 230-240 mesh). Evaporation of solvents was under reduced pressure with modest heating. Melting points were uncorrected. IR spectra were recorded on an FT instrument

on NaCl or CsI plates as neat liquid films, and only significant absorption bands (in cm^{-1}) are reported. ^{1}H NMR spectra were acquired at 500.1 MHz, and chemical shifts are relative to internal TMS (δ 0.00 ppm). The ^{1}H NMR data are presented as follows: chemical shift in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant(s), *J*, in hertz (Hz), and integration. Diastereomeric ratios were determined by integration of clearly separated ^{1}H NMR signals. ^{13}C NMR spectra were acquired at 125.8 MHz, and chemical shifts are relative to the solvent signal ($CDCl_3$, δ 77.16 ppm). Structural assignments were based on 2-D NMR spectra (COSY, HSQC, HMBC) and nuclear Overhauser effect (NOE) measurements.[70,71] HRMS data were obtained using a TOF mass spectrometer by positive-ion ESI.

3.4.2 Preparation of propargyl alcohols

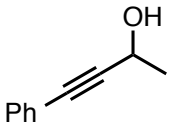
A solution of 1-propynylmagnesium bromide [0.5 M/THF] or phenylethynylmagnesium bromide [1.0 M/THF] (1 equiv) in THF was cooled to 0 °C. Acetaldehyde or 2,2-dimethylpropanal (1 equiv) was added slowly, and the mixture was stirred and warmed to rt over 2 h. The reaction was quenched by the addition of a saturated solution of NH_4Cl, and the phases were separated. The aqueous phase was extracted with Et_2O (×3). The combined organic layers were washed with a saturated solution of NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography.

3-Pentyn-2-ol



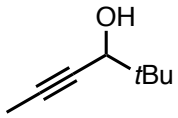
1-Propynylmagnesium bromide solution (40 mL) with acetaldehyde (1.10 mL); chromatography 40% Et_2O/pentane; yield 1.6 g (95%): liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 4.51-4.48 (m, 1H), 1.84 (d, J = 2.1 Hz, 3H), 1.84 (overlapped, 1H), 1.43 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 81.6, 80.3, 58.7, 24.8, 3.6. NMR data are consistent with the literature.[95]

4-Phenyl-3-butyn-2-ol



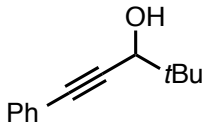
Phenylethynylmagnesium bromide solution (20 mL) with acetaldehyde (1.10 mL); chromatography 40% Et_2O/pentane; yield 2.11 g (72%): liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.43-7.41 (m, 2H), 7.30-7.27 (m, 3H), 4.78-4.73 (m, 1H), 2.84 (d, J = 4.9 Hz, 1H), 1.54 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.7, 128.4, 128.3, 122.7, 91.2, 83.9, 58.7, 24.4; HRMS (ESI) 169.0626, $[C_{10}H_{10}ONa]^+$ requires 169.0624. NMR data are consistent with the literature.[96]

2,2-Dimethyl-4-hexyn-3-ol



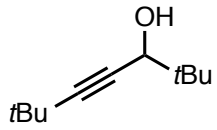
1-Propynylmagnesium bromide solution (50 mL) with 2,2-dimethylpropanal (2.80 mL); chromatography 20% Et_2O/pentane; yield 2.19 g (67%): liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 3.98 (q, J = 2.1 Hz, 1H), 1.86 (d, J = 2.2 Hz, 3H), 1.64 (broad s, 1H), 0.98 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 81.8, 79.0, 71.8, 36.0, 25.4, 3.7; HRMS (ESI) 149.0941, $[C_8H_{14}ONa]^+$ requires 149.0937.

4,4-Dimethyl-1-phenylpentyn-3-ol



Phenylethynylmagnesium bromide solution (15 mL) with 2,2-dimethylpropanal (1.60 mL); chromatography 20% Et_2O/pentane; yield 1.23 g (43%): solid, mp 44-46 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.38 (m, 2H), 7.28-7.25 (m, 3H), 4.19 (d, J = 6.1 Hz, 1H), 1.81 (d, J = 6.2 Hz, 1H), 1.02 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.8, 128.5, 128.4, 122.9, 89.1, 85.8, 72.0, 36.3, 25.5; HRMS (ESI) 211.1095, $[C_{13}H_{16}ONa]^+$ requires 211.1093. NMR data are consistent with the literature.[96]

2,2,6,6-Tetramethyl-4-heptyn-3-ol



A solution of 3,3-dimethyl-1-butyne (2.50 mL, 20 mmol) in THF (25 mL) was cooled to -78 °C. MeLi (19 mL of a 1.6 M solution in Et_2O, 30 mmol) was added over 10 min by use of a syringe pump. After 1 h at -78 °C, 2,2-dimethylpropanal (4.30 mL, 40 mmol) was added dropwise. The temperature was maintained at -78 °C for a further 1 h, and then the reaction mixture was warmed to rt over 2 h. The mixture was cooled to 0 °C before the reaction was quenched by the slow addition of H_2O. The phases were separated, and the organic phase was washed with a saturated solution of NaCl, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by chromatography (40% Et_2O/pentane) to provide the title compound (3.00 g, 90%) as a solid, mp 34-36 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97 (d, J = 6.1 Hz, 1H), 1.63 (d, J = 6.1 Hz, 1H), 1.22 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 94.6, 78.4, 71.6, 36.0, 31.2, 27.5, 25.4; HRMS (ESI) 191.1401, $[C_{11}H_{20}ONa]^+$ requires 191.1406. NMR data are consistent with the literature.[97]

3.4.3 Preparation of propargyl mesylates

Based on a literature procedure,[98] a solution of the propargyl alcohol (1 equiv) in CH_2Cl_2 was cooled to 0 °C. NEt_3 (1.1 equiv) was added, followed by the slow addition of MsCl (1.1 equiv). The reaction mixture was warmed slowly to rt over 1 h. A saturated solution of NH_4Cl was added, and the biphasic mixture was stirred for 30 min. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (×3). The

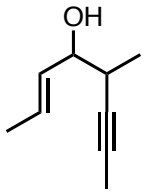
combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. Due to their limited stability, the crude mesylates were used within 24 h without purification. For 3-pentyn-2-yl methanesulfonate (**3.32**): 3-pentyn-2-ol (691 mg) with NEt_3 (1.25 mL) and MsCl (0.68 mL) in CH_2Cl_2 (10 mL) yielded **3.32** (1.26 g, 95%) as an oil. For 4-phenyl-3-butyn-2-yl methanesulfonate (**3.33**): 4-phenyl-3-butyn-2-ol (1.34 g) with NEt_3 (0.85 mL) and MsCl (0.46 mL) in CH_2Cl_2 (10 mL) yielded **3.33** (1.17 g, 95%) as an oil. For 2,2-dimethyl-4-hexyn-3-yl methanesulfonate (**3.34**): 2,2-dimethyl-4-hexyn-3-ol (763 mg) with NEt_3 (1.30 mL) and MsCl (0.46 mL) in CH_2Cl_2 (10 mL) yielded **3.34** (1.10 g, 89%) as an oil. For 4,4-dimethyl-1-phenylpentyn-3-yl methanesulfonate (**3.35**): 4,4-dimethyl-1-phenylpentyn-3-ol (1.06 g) with NEt_3 (1.40 mL) and MsCl (0.78 mL) in CH_2Cl_2 (20 mL) yielded **3.35** (1.10 g, 75%) as a dark orange oil. For 2,2,6,6-tetramethyl-4-heptyn-3-yl methanesulfonate (**3.36**): 2,2,6,6-tetramethyl-4-heptyn-3-ol (1.03 g) with NEt_3 (1.25 mL) and MsCl (0.70 mL) in CH_2Cl_2 (20 mL) yielded **3.36** (1.57 g, 99%) as an off-white solid.

3.4.4 Preparation of (alkynylmethyl) vinyl alcohols

(Alkynylmethyl) vinyl alcohols were synthesized using a procedure based on literature precedent.[86-88] $Pd(PPh_3)_4$ (5 mol%) was dissolved in THF (sufficient to make a 0.2 M solution). Mesylate (1 equiv) was added dropwise followed by the aldehyde (1.3 equiv). The mixture was then cooled to 0 °C, and $ZnEt_2$ (1 M solution in hexane, 2.0 equiv) was added via a syringe pump over 40 min. The reaction mixture was stirred as it warmed to rt over 2 h. The reaction was then quenched with 1 M HCl. A saturated solution of NH_4Cl was added, and the phases were separated. The aqueous phase was extracted with Et_2O (×3). The combined organic layers were washed with a saturated

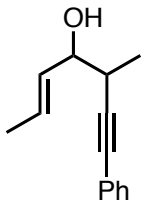
solution of NaCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography.

(*E*)-5-Methyloct-2-en-6-yn-4-ol (3.37)



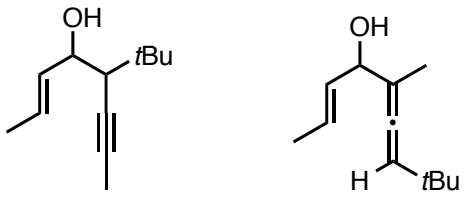
Mesylate **3.32** (417 mg) and crotonaldehyde (0.30 mL) with $Pd(PPh_3)_4$ (120 mg) and $ZnEt_2$ (4.0 mL), and then chromatography (20% Et_2O/pentane) yielded an inseparable mixture (*dr* 8:1 from analysis of the ^1H NMR) of diastereomeric alcohols **3.37** (103 mg, 29%) as an oil. IR (film) 3413 cm^{-1}. NMR signals for the major diastereomer: ^1H NMR (500 MHz, $CDCl_3$) δ 5.68 (dqd, *J* = 15.3, 6.5, 0.9 Hz, 1H), 5.43 (ddq, *J* = 15.3, 7.4, 1.6 Hz, 1H), 3.76 (ddd, *J* = 7.4, 6.5, 4.4 Hz, 1H), 2.42 (qdq, *J* = 7.0, 6.5, 2.4 Hz, 1H), 2.07 (d, *J* = 4.4 Hz, 1H), 1.78 (d, *J* = 2.4 Hz, 3H), 1.67 (dd, *J* = 6.5, 1.6 Hz, 3H), 1.07 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.6, 129.1, 80.1, 78.9, 76.3, 33.9, 17.9, 17.7, 3.7. NMR signals discerned for the minor diastereomer: ^1H NMR (500 MHz, $CDCl_3$) δ 5.54 (ddq, *J* = 15.3, 7.2, 1.6 Hz, 1H), 3.91-3.88 (m, 1H), 2.62-2.57 (m, 1H), 1.03 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 75.6, 33.2, 16.7, 1.7. HRMS (ESI) 161.0934, $[C_9H_{14}ONa]^+$ requires 161.0937.

(*E*)-3-Methyl-1-phenylhept-5-en-1-yn-4-ol (3.38)



Mesylate **3.33** (494 mg) and crotonaldehyde (0.20 mL) with $Pd(PPh_3)_4$ (121 mg) and $ZnEt_2$ (4.0 mL), and then chromatography (20% Et_2O/pentane) yielded **3.38** (136 mg, 31%, *dr* >20:1 from analysis of the ^1H NMR) as an oil. IR (film) 3417, 2314, 1604 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43-7.41 (m, 2H), 7.30-7.29 (m, 3H), 5.79 (dq, *J* = 14.7, 7.1 Hz, 1H), 5.57 (ddd, *J* = 15.3, 7.2, 1.6 Hz, 1H), 3.98 (t, *J* = 6.7 Hz, 1H), 2.76 (quintet, *J* = 6.8 Hz, 1H), 2.11 (s, 1H), 1.75 (dd, *J* = 6.5, 1.1 Hz, 3H), 1.26 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.8, 131.4, 129.3, 128.4, 128.1, 123.4, 90.6, 83.4, 76.1, 34.5, 18.0, 17.3; HRMS (ESI) 223.1089, $[C_{14}H_{16}ONa]^+$ requires 223.1093. NMR data are consistent with the literature.[99]

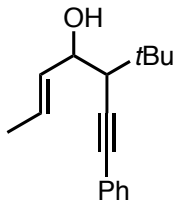
(*E*)-5-*tert*-Butyloct-2-en-6-yn-4-ol (3.39) and (*E*)-5,8,8-trimethylnona-2,5,6-trien-4-ol (3.46)



Mesylate **3.34** (413 mg) and crotonaldehyde (0.30 mL) with $Pd(PPh_3)_4$ (130 mg) and $ZnEt_2$ (4.0 mL), and then chromatography (20% Et_2O/pentane) provided *both* **3.39** (63 mg, 17%, *dr* >20:1 from the analysis of the ^1H NMR) and the allene **3.46** (56 mg,

16%, *dr* >20:1 by ^{1}H NMR) as oils. For **3.39**: IR (film) 3504 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (dq, *J* = 15.3, 6.1 Hz, 1H), 5.59 (ddd, *J* = 15.3, 6.5, 1.1 Hz, 1H), 4.18 (t, *J* = 7.7 Hz, 1H), 2.21 (quintet, *J* = 2.3 Hz, 1H), 1.98 (d, *J* = 9.4 Hz, 1H), 1.88 (d, *J* = 2.5 Hz, 3H), 1.70 (d, *J* = 6.1 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.5, 126.1, 81.8, 76.1, 70.3, 51.3, 33.9, 28.5, 17.8, 3.7; HRMS (ESI) 203.1402, $[C_{12}H_{20}ONa]^+$ requires 203.1406. For **3.46**: IR (film) 3375, 1967 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (dq, *J* = 15.2, 6.5 Hz, 1H), 5.44 (ddq, *J* = 15.2, 7.6, 1.5 Hz, 1H), 5.34 (apparent quintet, *J* = 2.8 Hz, 1H), 4.33-4.30 (m, 1H), 1.79 (d, *J* = 4.9 Hz, 1H), 1.72 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.69 (d, *J* = 2.9 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.8, 132.3, 128.1, 107.5, 105.2, 73.5, 32.4, 30.3, 17.8, 16.0 HRMS (ESI) 203.1413, $[C_{12}H_{20}ONa]^+$ requires 203.1406.

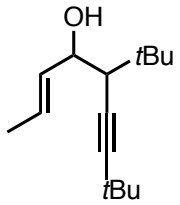
(*E*)-3-*tert*-Butyl-1-phenylhept-5-en-1-yn-4-ol (3.40)



Mesylate **3.35** (524 mg) and crotonaldehyde (0.20 mL) with $Pd(PPh_3)_4$ (174 mg) and $ZnEt_2$ (4.0 mL), and then chromatography (20% Et_2O/pentane) yielded an inseparable mixture (*dr* 10:1 from the analysis of the ^{1}H NMR) of diastereomeric alcohols **3.40** (157 mg, 33%) as an oil. IR (film) 3467, 2233 cm^{-1}. NMR signals for the major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.43 (m, 2H), 7.31-7.30 (m, 3H), 5.76-5.65 (m, 2H), 4.34-4.31 (m, 1H), 2.48 (d, *J* = 1.9 Hz, 1H), 1.95 (d, *J* =9.6 Hz, 1H), 1.73 (d, *J* = 5.7 Hz, 3H), 1.12 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.2, 131.8,

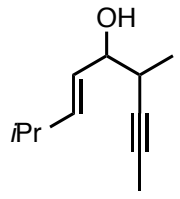
128.4, 128.1, 126.4, 123.5, 87.2, 86.5, 70.6, 51.7, 34.3, 28.6, 17.8. NMR signals discerned for the minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58-5.52 (m, 1H), 4.75-4.72 (m, 1H), 2.44 (d, J = 2.0 Hz, 1H), 1.15 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.8, 125.4, 65.5, 34.5, 13.5. HRMS (ESI) 265.1569, $[C_{17}H_{22}ONa]^+$ requires 265.1563.

(*E*)-5-*tert*-Butyl-8,8-dimethylnon-2-en-6-yn-4-ol (3.41)



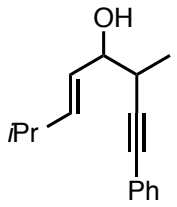
Mesylate **3.36** (503 mg) and crotonaldehyde (0.20 mL) with $Pd(PPh_3)_4$ (130 mg) and $ZnEt_2$ (4.0 mL), and then chromatography (20% Et_2O/pentane) yielded **3.41** (137 mg, 30%, *dr* >20:1 from the analysis of the ^{1}H NMR) as an oil. IR (film) 3488, 2296 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (dq, J = 15.5, 6.2 Hz, 1H), 5.55 (ddd, J = 15.2, 6.5, 1.4 Hz, 1H), 4.19-4.16 (m, 1H), 2.22 (d, J = 1.8 Hz, 1H), 2.03 (d, J = 10.1 Hz, 1H), 1.70 (d, J = 6.2 Hz, 3H), 1.25 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.5, 125.7, 96.0, 75.2, 69.9, 51.1, 33.8, 31.5, 28.4, 27.8, 17.8; HRMS (ESI) 245.1872, $[C_{15}H_{26}ONa]^+$ requires 245.1876.

(*E*)-4,8-Dimethylnon-6-en-2-yn-5-one (3.42)



Mesylate **3.32** (417 mg) and 4-methyl-2-pentenal (0.30 mL) with $Pd(PPh_3)_4$ (130 mg) and $ZnEt_2$ (4.0 mL), and then chromatography (10% Et_2O/pentane) yielded **3.42** (130 mg, 33%, *dr* >20:1 from the analysis of the ^1H NMR) as an oil. IR (film) 3425, 2200 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.68 (ddd, *J* = 15.5, 6.6, 0.9 Hz, 1H), 5.39 (ddd, *J* = 15.5, 7.3, 1.3 Hz, 1H), 3.81 (td, *J* = 6.9, 4.1 Hz, 1H), 2.49-2.43 (m, 1H), 2.31 (sextet of doublets, *J* = 6.7, 1.2 Hz, 1H), 2.15 (d, *J* = 4.2 Hz, 1H), 1.83 (d, *J* = 2.4 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.00 (dd, *J* = 6.8, 1.5 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.3, 127.3, 80.1, 78.8, 76.4, 34.0 31.0, 22.4 (2C), 17.7, 3.7; HRMS (ESI) 189.1250, $[C_{11}H_{18}ONa]^+$ requires 189.1250.

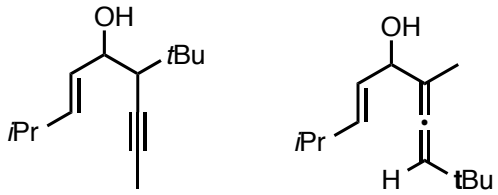
(*E*)-3,7-Dimethyl-1-phenyloct-5-en-1-yn-4-ol (3.43)



Mesylate **3.33** (458 mg) and 4-methyl-2-pentenal (0.30 mL) with $Pd(PPh_3)_4$ (126 mg) and $ZnEt_2$ (4.0 mL), and then chromatography (10% Et_2O/pentane) yielded an inseparable mixture (*dr* 2:1 from the analysis of the ^1H NMR) of diastereomeric alcohols **3.43** (183 mg, 39%) as an oil. IR (film) 3408, 2310 cm^{-1}. NMR signals for the major diastereomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.39 (m, 2H), 7.30-7.28 (dd, 3H), 5.74 (dd, *J* = 15.5, 6.6 Hz, 1H), 5.59 (dd, *J* = 15.5, 7.1 Hz, 1H), 4.06 (ddd, *J* = 7.1, 5.1, 4.2 Hz, 1H), 2.92-2.87 (m, 1H), 2.38-2.31 (m, 1H), 1.90 (d, *J* = 5.2 Hz, 1H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.4, 131.8, 128.3, 128.0, 126.4, 123.6, 91.0, 83.1, 75.8, 34.0, 31.1, 22.5(2C), 16.7. NMR signals

discernable for the minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.48 (dd, J = 16.4, 7.1 Hz, 1H), 4.00-3.97 (m, 1H), 2.77 (quintet, J = 6.8 Hz, 1H), 2.11 (d, J = 4.5 Hz, 1H), 1.25 (d, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.8, 128.4, 128.1, 127.1, 123.4, 90.7, 83.3, 76.2, 34.5, 31.0, 22.4 (2C), 17.3. HRMS (ESI) 251.1397, $[C_{16}H_{20}ONa]^+$ requires 251.1406.

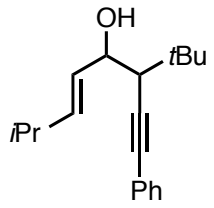
(*E*)-4-*tert*-Butyl-8-methylnon-6-en-2-yn-5-ol (3.44) and (*E*)-2,6,9,9-tetramethyldeca-3,6,7-trien-5-ol (3.48)



Mesylate **3.34** (412 mg) and 4-methyl-2-pentenal (0.23 mL) with $Pd(PPh_3)_4$ (115 mg) and $ZnEt_2$ (4.0 mL), and then chromatography (10% Et_2O/pentane) provided both **3.44** (118 mg, 28%, *dr* >20:1 from the analysis of the ^{1}H NMR) and the allene **3.48** (126 mg, 30%, *dr* >20:1 by ^{1}H NMR) as oils. For **3.44**: IR (film) 3429 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60 (ddd, J = 15.4, 6.5, 0.9 Hz, 1H), 5.49 (ddd, J = 15.4, 6.4, 1.2 Hz, 1H), 4.21-4.17 (m, 1H), 2.29 (sextet, J = 6.7 Hz, 1H), 2.21 (quintet, J = 2.3 Hz, 1H), 1.97 (d, J = 9.3 Hz, 1H), 1.87 (d, J = 2.5 Hz, 3H), 1.03 (s, 9H), 0.99 (dd, J = 6.8, 2.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 130.3, 81.7, 76.2, 70.4, 51.4, 33.9, 30.8, 28.5, 22.4, 3.7; HRMS (ESI) 231.1712, $[C_{14}H_{24}ONa]^+$ 231.1719. For **3.48**: IR (film) 3375, 1963 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (dd, J = 15.4, 6.6 Hz, 1H), 5.39-5.33 (m, 2H), 4.33-4.30 (m, 1H), 2.32 (sextet of doublets, J = 6.7, 0.9 Hz, 1H), 1.78 (d, J = 4.9 Hz, 1H), 1.69 (d, J = 2.9 Hz, 3H), 1.04 (s, 9H), 1.00 (d, J = 6.8 Hz, 6H); ^{13}C

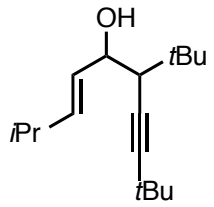
NMR (126 MHz, $CDCl_3$) δ 195.8, 140.2, 128.0, 107.5, 105.2, 73.6, 32.4, 30.9, 30.3, 22.4 (2C), 16.1; HRMS (ESI) 231.1709, $[C_{14}H_{24}ONa]^+$ requires 231.1719.

(*E*)-3-*tert*-Butyl-7-methyl-1-phenyloct-5-en-1-yn-4-ol (3.45)



Mesylate **3.35** (521 mg) and 4-methyl-2-pentenal (0.30 mL) with $Pd(PPh_3)_4$ (121 mg) and $ZnEt_2$ (4.0 mL), and then chromatography (10% Et_2O/pentane) yielded **3.45** (148 mg, 28%, *dr* >20:1 from the analysis of the ^1H NMR) as an oil. IR (film) 3462, 2237 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48-7.46 (m, 2H), 7.35-7.33 (m, 3H), 5.71 (ddd, J = 15.4, 6.4, 1.0 Hz, 1H), 5.61 (ddd, J = 15.4, 6.1, 1.1 Hz, 1H), 4.38 (t, J = 6.6 Hz, 1H), 2.53 (d, J = 2.0 Hz, 1H), 2.36 (sextet, J = 6.7 Hz, 1H), 1.95 (d, J = 9.2 Hz, 1H), 1.17 (s, 9H), 1.05 (dd, J = 6.8, 1.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 131.8, 130.0, 128.4, 128.1, 123.6, 87.4, 86.4, 70.5, 51.8, 34.3, 30.9, 28.7, 22.5; HRMS (ESI) 293.1867, $[C_{19}H_{26}ONa]^+$ requires 293.1876.

(*E*)-6-*tert*-Butyl-2,9,9-trimethyldec-3-en-7-yn-5-ol (3.46)



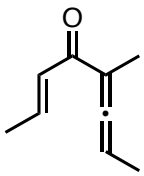
3.46

Mesylate **3.36** (504 mg) and 4-methyl-2-pentenal (0.30 mL) with $Pd(PPh_3)_4$ (119 mg) and $ZnEt_2$ (4.0 mL), and then chromatography (10% Et_2O/pentane) yielded **3.46** (157 mg, 31%, *dr* >20:1 from the analysis of the ^1H NMR) as an oil. IR (film) 3500, 2233 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.60 (ddd, *J* = 15.4, 6.6, 1.0 Hz, 1H), 5.45 (ddd, *J* = 15.4, 6.0, 1.2 Hz, 1H), 4.19 (broad s, 1H), 2.30 (sextet, *J* = 6.7 Hz, 1H), 2.22 (d, *J* = 1.9 Hz, 1H), 1.98 (br s, 1H), 1.24 (s, 9H), 1.03 (s, 9H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8, 130.3, 95.8, 75.2, 69.7, 51.2, 33.8, 31.5, 30.8, 28.4, 27.8, 22.5 (2C); HRMS (ESI) 273.2196, $[C_{17}H_{30}ONa]^+$ requires 273.2189.

3.4.5 Preparation of (alkynylmethyl) vinyl ketones and allenyl vinyl ketones (AVKs)

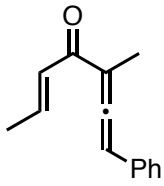
Oxidations were based on the procedure of Marshall and Schaaf.[90] (Alkynylmethyl) vinyl alcohol (1 equiv) was added to a solution of Dess-Martin periodinane (DMP) (1.5 equiv) and $NaHCO_3$ (10 equiv) in CH_2Cl_2 (0.1 M with respect to the alcohol). After 1 h, equal volumes of saturated aqueous $Na_2S_2O_3$ and saturated $NaHCO_3$ were added, and the mixture was stirred until both the organic and the aqueous layers became clear. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (×2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography. (Alkynylmethyl) vinyl ketones were isomerized following the procedure of Harada *et al*.[91] The (alkynylmethyl) vinyl ketone (1 equiv) was dissolved in CH_2Cl_2 (0.1 M) and treated with NEt_3 (1–10 equiv). After stirring for 1–24 h at rt, the solvent was removed under reduced pressure to provide the AVK. (Due to the instability of the AVKs on silica gel, purification by chromatography was not carried out.)

(*E*)-5-Methyloct-2-en-6-yn-4-one and (*E*)-5-methylocta-2,5,6-trien-4-one (3.49)



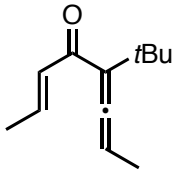
Enynol **3.37** (106 mg) with DMP (493 mg) and $NaHCO_3$ (726 mg), then chromatography (10% Et_2O/pentane) gave the (alkynylmethyl) vinyl ketone (46 mg, 44%) as an oil. IR (film) 2238, 1708, 1638 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.01 (dq, *J* = 15.5, 6.9 Hz, 1H), 6.46 (dq, *J* = 15.5, 1.6 Hz, 1H), 3.41 (qq, *J* = 7.1, 2.4 Hz, 1H), 1.93 (dd, *J* = 6.9, 1.7 Hz, 3H), 1.83 (d, *J* = 2.5 Hz, 3H), 1.32 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.6, 144.0, 128.5, 79.8, 77.6, 37.7, 18.5, 17.2, 3.9; HRMS (ESI) 159.0781, $[C_9H_{12}ONa]^+$ requires 159.0780. The (alkynylmethyl) vinyl ketone (84 mg) with NEt_3 (85 μL) for 2 h provided AVK **3.49** (15 mg, 18%) as an oil. IR (film) 1950, 1667, 1629 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.89 (dq, *J* = 14.9, 7.3 Hz, 1H), 6.72 (dd, *J* = 15.3, 1.5 Hz, 1H), 5.54-5.49 (m, *J* = 2.3 Hz, 1H), 1.88 (dd, *J* = 6.8, 1.4 Hz, 3H), 1.83-1.81 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.7, 190.5, 141.3, 127.0, 104.4, 89.3, 18.2, 13.9, 13.6; HRMS (ESI) 159.0773, $[C_9H_{12}ONa]^+$ requires 159.0780.

(*E*)-3-Methyl-1-phenylhept-5-en-1-yn-4-one and (*E*)-3-methyl-1-phenylhepta-1,2,5-trien-4-one (3.50)



Enynol **3.38** (104 mg) with DMP (304 mg) and $NaHCO_3$ (488 mg), then chromatography (20% Et_2O/pentane) gave 36 mg (35%) of an oil that was an inseparable mixture of the (alkynylmethyl) vinyl ketone and **3.50** in a 1.5:1 ratio (respectively) by ^1H NMR. NMR data for the (alkynylmethyl) vinyl ketone: ^1H NMR (500 MHz, $CDCl_3$) δ 7.43-7.40 (m, 2H), 7.39-7.34 (m, 1H), 7.32-7.28 (m, 2H), 7.07 (dq, J = 15.5, 6.9 Hz, 1H), 6.57-6.53 (m, 1H), 3.67 (q, J = 7.0 Hz, 1H), 1.94 (dd, J = 6.9, 1.7 Hz, 3H), 1.43 (d, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.7, 144.5, 131.8, 129.1, 128.4, 128.4, 128.3, 88.1, 84.1, 38.3, 18.6, 16.9. The 1.5:1 mixture of the (alkynylmethyl) vinyl ketone and **3.50** (25 mg) with NEt_3 (0.10 mL) for 1 h afforded homogeneous AVK **3.50** (25 mg, 99%) as an oil. IR (film) 1938, 1717, 1671, 1629 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.36 (m, 2H), 7.33-7.29 (m, 3H), 6.96 (dq, J = 15.2, 6.9 Hz, 1H), 6.72 (dq, J = 15.2, 1.6 Hz, 1H), 6.57 (q, J = 2.7 Hz, 1H), 1.98 (d, J = 2.8 Hz, 3H), 1.84 (dd, J = 6.9, 1.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.7, 189.6, 142.8, 132.8, 129.5, 128.3, 127.7, 127.4, 108.8, 98.4, 18.6, 14.1; HRMS (ESI) 221.0931, $[C_{14}H_{14}ONa]^+$ requires 221.0937.

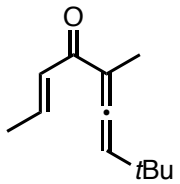
(*E*)-5-*tert*-Butyloct-2-en-6-yn-4-one and (*E*)-5-*tert*-butylocta-2,5,6-trien-4-one (3.51)



Enynol **3.39** (103 mg) with DMP (414 mg) and $NaHCO_3$ (633 mg), then chromatography (10% Et_2O/pentane) provided the (alkynylmethyl) vinyl ketone (73 mg, 72 %) as an oil. IR (film) 2238, 1692, 1629 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.91

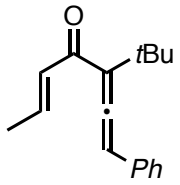
(dq, J = 15.0, 7.3 Hz, 1H), 6.49 (dq, J = 15.4, 1.6 Hz, 1H), 3.17 (q, J = 2.4 Hz, 1H), 1.91 (dd, J = 6.9, 1.5 Hz, 3H), 1.87 (d, J = 2.5 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.9, 143.0, 130.2, 81.5, 75.9, 55.1, 35.0, 28.1, 18.4, 3.9; HRMS (ESI) 201.1242, $[C_{12}H_{18}ONa]^+$ requires 201.1250. The (alkynylmethyl) vinyl ketone (65 mg) with NEt_3 (0.5 mL) for 12 h gave AVK **3.51** (15 mg, 18%) as an oil. IR (film) 1941, 1675, 1629 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (dq, J = 15.2, 6.9 Hz, 1H), 6.65 (d, J = 15.3 Hz, 1H), 5.52 (q, J = 7.2 Hz, 1H), 1.86 (d, J = 7.0 Hz, 3H), 1.81 (d, J = 7.2 Hz, 3H), 1.18 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.0, 190.4, 140.9, 129.5, 117.8, 90.7, 33.7, 29.7, 18.3, 13.9; HRMS 201.1241, $[C_{12}H_{18}ONa]^+$ requires 201.1250.

(*E*)-5,8,8-Trimethylnona-2,5,6-trien-4-one (3.52)



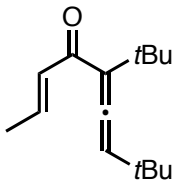
Trienol **3.40** (141 mg) with DMP (489 mg) and $NaHCO_3$ (648 mg), then chromatography (5% Et_2O/pentane) yielded AVK **3.52** (58 mg, 42%) as an oil. IR (film) 1950, 1675, 1629 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (dq, J = 15.2, 6.8 Hz, 1H), 6.76 (dq, J = 15.3, 1.5 Hz, 1H), 5.54 (q, J = 2.7 Hz, 1H), 1.87 (dd, J = 6.8, 1.5 Hz, 3H), 1.85 (d, J = 2.7 Hz, 3H), 1.13 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.1, 194.7, 141.3, 126.9, 106.9, 106.1, 33.5, 30.3, 18.3, 14.1; HRMS (ESI) 201.1241, $[C_{12}H_{18}ONa]^+$ requires 201.1250.

(*E*)-3-*tert*-Butyl-1-phenylhept-5-en-1-yn-4-one and (*E*)-3-*tert*-butyl-1-phenylhepta-1,2,5-trien-4-one (3.53)



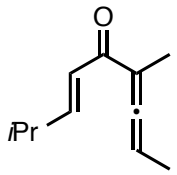
Enynol **3.40** (134 mg) with DMP (395 mg) and $NaHCO_3$ (503 mg), then chromatography (10% Et_2O/pentane) yielded the (alkynylmethyl) vinyl ketone (90 mg, 69%) as an oil. IR (film) 2317, 1692, 1629 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.43 (m, 2H), 7.31-7.30 (m, 3H), 6.97 (dq, *J* = 15.4, 6.9 Hz, 1H), 6.59 (dd, *J* = 15.4, 1.6 Hz, 1H), 3.40 (s, 1H), 1.91 (dd, *J* = 6.9, 1.6 Hz, 3H), 1.12 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.9, 143.5, 131.8, 129.9, 128.4, 128.2, 123.5, 86.7, 86.3, 55.9, 35.5, 28.3, 18.5; HRMS (ESI) 263.1409, $[C_{17}H_{20}ONa]^+$ requires 263.1406. The (alkynylmethyl) vinyl ketone (78 mg) with NEt_3 (50 μL) for 4 h provided AVK **3.53** (77 mg, 99%) as an oil. IR (film) 1925, 1714, 1671, 1625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.5 Hz, 2H), 7.31-7.28 (m, 2H), 7.26-7.25 (m, 1H), 6.87 (dq, *J* = 15.2, 6.8 Hz, 1H), 6.62 (dd, *J* = 15.2, 1.5 Hz, 1H), 6.57 (s, 1H), 1.80 (dd, *J* = 6.9, 1.4 Hz, 3H), 1.27 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.3, 189.1, 142.1, 133.0, 129.5 129.2, 127.9, 127.1, 121.8, 99.4, 34.9, 29.8, 18.3; HRMS (ESI) 263.1397, $[C_{17}H_{20}ONa]^+$ requires 263.1406.

(*E*)-5-*tert*-Butyl-8,8-dimethylnon-2-en-6-yn-4-one and (*E*)-5-*tert*-butyl-8,8-dimethylnona-2,6,7-trien-4-one (3.54)



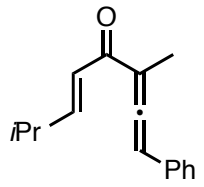
Enynol **3.41** (114 mg) with DMP (328 mg) and $NaHCO_3$ (420 mg), then chromatography (10% Et_2O/pentane) afforded the (alkynylmethyl) vinyl ketone (42 mg, 37%) as an oil. IR (film) 2242, 1692, 1625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (dq, J = 15.4, 6.9 Hz, 1H), 6.55 (dq, J = 15.4, 1.6 Hz, 1H), 3.09 (s, 1H), 1.90 (dd, J = 6.9, 1.7 Hz, 3H), 1.24 (s, 9H), 1.03 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.9, 142.5, 129.8, 95.2, 75.5, 55.4, 34.9, 31.2, 28.1, 27.8, 18.4; HRMS (ESI) 243.1719, $[C_{15}H_{24}ONa]^+$ requires 243.1719. The (alkynylmethyl) vinyl ketone (34 mg) with NEt_3 (0.5 mL) for 15 h yielded AVK **3.54** (20 mg, 59%) as an oil. IR (film) 1942, 1675, 1633 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.81 (dq, J = 15.2, 6.5 Hz, 1H), 6.73 (dq, J = 15.2, 1.3 Hz, 1H), 5.55 (s, 1H), 1.85 (dd, J = 6.5, 1.3 Hz, 3H), 1.19 (s, 9H), 1.13 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.2, 189.8, 140.5, 129.0, 120.0, 107.1, 33.4, 33.2, 30.1, 29.7, 18.2; HRMS (ESI) 243.1708, $[C_{15}H_{24}ONa]^+$ requires 243.1719.

(*E*)-4,8-Dimethylnon-6-en-2-yn-5-one and (*E*)-4,8-dimethylnona-2,3,6-trien-5-one (3.55)



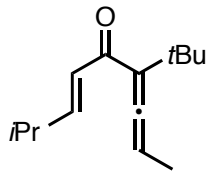
Enynol **3.42** (105 mg) with DMP (414 mg) and $NaHCO_3$ (501 mg), then chromatography (20% Et_2O/pentane) yielded the (alkynylmethyl) vinyl ketone (94 mg, 91%) as an oil. IR (film) 2350, 1704, 1633 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.95 (dd, J = 15.7, 6.7 Hz, 1H), 6.37 (d, J = 15.7 Hz, 1H), 3.45-3.41 (m, 1H), 2.49 (octet, J = 6.8 Hz, 1H), 1.83 (d, J = 1.7 Hz, 3H), 1.32 (d, J = 7.1 Hz, 3H), 1.09 (d, J = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.2, 154.9, 124.1, 79.7, 77.7, 37.7, 31.4, 21.4, 17.2, 3.8; HRMS (ESI) 187.1090, $[C_{11}H_{16}ONa]^+$ requires 187.1093. The (alkynylmethyl) vinyl ketone (81 mg) with NEt_3 (69 μL) for 24 h gave AVK **3.55** (44 mg, 54%) as an oil. IR (film) 1950, 1671, 1625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.84 (dd, J = 15.5, 6.9 Hz, 1H), 6.65 (d, J = 15.5 Hz, 1H), 5.54-5.48 (m, 1H), 2.45 (octet, J = 6.8 Hz, 1H), 1.83-1.81 (m, 6H), 1.06 (d, J = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.7, 191.0, 152.4, 122.7,104.6, 89.3, 31.2, 21.6, 14.0, 13.6; HRMS (ESI) 187.1085, $[C_{11}H_{16}ONa]^+$ requires 187.1093.

(*E*)-3,7-Dimethyl-1-phenyloct-5-en-1-yn-4-one and (*E*)-3,7-dimethyl-1-phenylocta-1,2,5-trien-4-one (3.56)



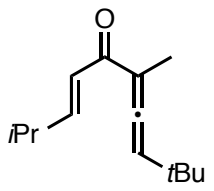
Enynol **3.43** (116 mg) with DMP (298 mg) and $NaHCO_3$ (420 mg), then chromatography (10% Et_2O/pentane) provided the (alkynylmethyl) vinyl ketone (87 mg, 76%) as an oil. IR (film) 2312, 1700, 1638 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.40 (m, 2H), 7.31-7.29 (m, 3H), 7.03 (dd, *J* = 15.7, 6.7 Hz, 1H), 6.47 (dd, *J* = 15.7, 1.3 Hz, 1H), 3.69 (q, *J* = 7.0 Hz, 1H), 2.51 (octet of doublets, *J* = 6.8, 1.3 Hz, 1H), 1.45 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.3, 155.4, 131.7, 128.4, 128.2, 124.1, 123.3, 88.2, 84.1, 38.3, 31.4, 21.4, 16.9; HRMS (ESI) 249.1246, $[C_{16}H_{18}ONa]^+$ requires 249.1250. The (alkynylmethyl) vinyl ketone (74 mg) with NEt_3 (0.5 mL) for 1 h gave AVK **3.56** (74 mg, 99%) as an oil. IR (film) 1938, 1708, 1675, 1629 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.5 Hz, 2H), 7.31-7.26 (m, 3H), 6.88 (dd, *J* = 15.4, 7.1 Hz, 1H), 6.63 (d, *J* = 15.4 Hz, 1H), 6.56 (q, *J* = 2.7 Hz, 1H), 2.40 (octet, *J* = 6.8 Hz, 1H), 1.97 (d, *J* = 2.7 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.4, 189.9, 153.5, 132.5, 129.1, 127.9, 127.3, 122.9, 108.5, 98.0, 31.3, 21.6 (2C), 13.9; HRMS (ESI) 249.1246, $[C_{16}H_{18}ONa]^+$ requires 249.1250.

(*E*)-4-*tert*-Butyl-8-methylnon-6-en-2-yn-5-one and (*E*)-4-*tert*-butyl-8-methylnona-2,3,6-trien-5-one (3.57)



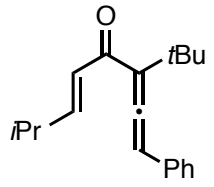
Enynol **3.44** (64 mg) with DMP (168 mg) and $NaHCO_3$ (255 mg), then chromatography (10% Et_2O/pentane) provided the (alkynylmethyl) vinyl ketone (48 mg, 76%) as an oil. IR (film) 2317, 1692, 1629 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.85 (dd, *J* = 15.6, 6.8 Hz, 1H), 6.39 (dd, *J* = 15.6, 1.4 Hz, 1H), 3.20 (q, *J* = 2.5 Hz, 1H), 2.47 (octet of doublets, *J* = 6.8, 1.4 Hz, 1H), 1.86 (d, *J* = 2.5 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.5, 153.8, 126.1, 81.4, 75.9, 55.1, 35.0, 31.3, 28.1, 21.5 (2C), 3.9; HRMS (ESI) 229.1553, $[C_{14}H_{22}ONa]^+$ requires 229.1563. The (alkynylmethyl) vinyl ketone (71 mg) with NEt_3 (0.3 mL) for 2 h yielded AVK **3.57** (71 mg, 99%) as an oil. IR (film) 1946, 1675, 1625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (dd, *J* = 15.5, 6.8 Hz, 1H), 6.58 (dd, *J* = 15.5, 1.3 Hz, 1H), 5.52 (q, *J* = 7.2 Hz, 1H), 2.43 (octet of doublets, *J* = 6.8, 1.3 Hz, 1H), 1.81 (d, *J* = 7.2 Hz, 3H), 1.18 (s, 9H), 1.05 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.9, 190.8, 152.0, 125.1, 117.8, 90.5, 33.6, 31.1, 29.6, 21.6 (2C), 13.8; HRMS (ESI) 229.1555, $[C_{14}H_{22}ONa]^+$ requires 229.1563.

(*E*)-2,6,9,9-Tetramethyldeca-3,6,7-trien-5-one (3.58)



Trienol **3.48** (121 mg) with DMP (365 mg) and $NaHCO_3$ (531 mg), then chromatography (5% Et_2O/pentane) yielded AVK **3.58** (61 mg, 51%) as an oil. IR (film) 1950, 1675, 1629 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.85 (dd, J = 15.5, 6.3 Hz, 1H), 6.70 (dd, J = 15.5, 1.4 Hz, 1H), 5.52 (q, J = 2.7 Hz, 1H), 2.43 (octet of doublets, J = 6.7, 1.3 Hz, 1H), 1.84 (d, J = 2.7 Hz, 3H), 1.12 (s, 9H), 1.05 (d, J = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.1, 190.7, 152.1, 122.5, 106.1, 102.8, 33.4, 31.1, 30.2, 21.5, 21.4, 14.0; HRMS (ESI) 229.1558, $[C_{14}H_{22}ONa]^+$ requires 229.1563.

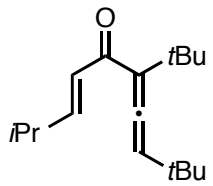
(*E*)-3-*tert*-Butyl-7-methyl-1-phenyloct-5-en-1-yn-4-one and (*E*)-3-*tert*-butyl-7-methyl-1-phenylocta-1,2,5-trien-4-one (3.59)



Enynol **3.45** (138 mg) with DMP (351 mg) and $NaHCO_3$ (591 mg), then chromatography (10% Et_2O/pentane) yielded the (alkynylmethyl) vinyl ketone (119 mg, 87%) as an oil. IR (film) 2213, 1638 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44-7.42 (m, 2H), 7.31-7.30 (m, 3H), 6.92 (dd, J = 15.6, 6.7 Hz, 1H), 6.52 (dd, J = 15.6, 1.3 Hz, 1H), 3.43 (s, 1H), 2.49 (octet of doublets, J = 6.8, 1.3 Hz, 1H), 1.12 (s, 9H), 1.08 (d, J = 6.8

Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.5, 154.3, 131.7, 128.4, 128.2, 125.7, 123.6, 86.8, 86.2, 56.0, 35.5, 31.3, 28.3, 21.5 (2C); HRMS (ESI) 291.1727, $[C_{19}H_{24}ONa]^+$ requires 291.1719. The (alkynylmethyl) vinyl ketone (121 mg) with NEt_3 (69 μL) for 15 h afforded AVK **3.59** (98 mg, 81%) as an oil. IR (film) 1925, 1713, 1675, 1625 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.5 Hz, 2H), 7.31-7.29 (m, 2H), 7.27-7.24 (m, 1H), 6.79 (dd, *J* = 15.4, 7.1 Hz, 1H), 6.57 (s, 1H), 6.52 (dd, *J* = 15.4, 1.2 Hz, 1H), 2.36 (octet of doublets, *J* = 6.8, 1.1 Hz, 1H), 1.27 (s, 9H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.2, 189.8, 153.1, 133.0, 129.1, 127.8, 127.0, 125.3, 121.8, 99.3, 34.8, 31.2, 29.7, 21.6 (2C); HRMS (ESI) 291.1711, $[C_{19}H_{24}ONa]^+$ requires 291.1719.

(*E*)-6-*tert*-Butyl-2,9,9-trimethyldec-3-en-7-yn-5-one and (*E*)-6-*tert*-butyl-2,9,9-trimethyl-deca-3,6,7-trien-5-one (3.60)



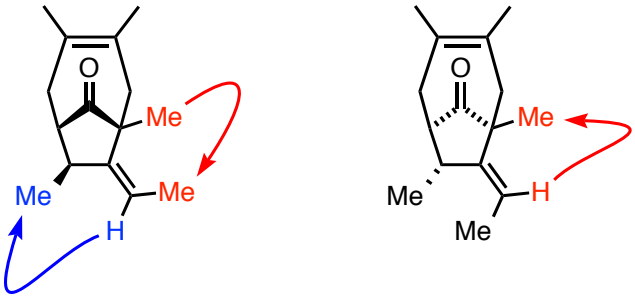
Enynol **3.46** (143 mg) with DMP (460 mg) and $NaHCO_3$ (638 mg), then chromatography (10% Et_2O/pentane) gave the (alkynylmethyl) vinyl ketone (118 mg, 83%) as an oil. IR (film) 2242, 1692, 1629 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (dd, *J* = 15.6, 6.4 Hz, 1H), 6.52 (dd, *J* = 15.6, 1.3 Hz, 1H), 3.09 (s, 1H), 2.47 (octet of doublets, *J* = 6.7, 1.2 Hz, 1H), 1.24 (s, 9H), 1.07 (d, *J* = 6.8 Hz, 6H), 1.03 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.5, 153.3, 125.4, 95.2, 75.7, 55.7, 34.9, 31.2 (2C), 28.1, 27.8, 21.4; HRMS (ESI) 271.2041, $[C_{17}H_{28}ONa]^+$ requires 271.2032. The

(alkynylmethyl) vinyl ketone (104 mg) with NEt_3 (0.5 mL) for 12 h provided AVK **3.60** (64 mg, 61%) as an oil. IR (film) 1942, 1671, 1625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.79 (dd, J = 15.5, 6.1 Hz, 1H), 6.69 (dd, J = 15.5, 1.3 Hz, 1H), 5.55 (s, 1H), 2.43 (octet of doublets, J = 6.6, 1.3 Hz, 1H), 1.20 (s, 9H), 1.13 (s, 9H), 1.04 (d, J = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.3, 190.2, 151.5, 124.6, 120.3, 107.1, 33.4, 33.2, 31.0, 30.1, 29.7, 21.5 (2C); HRMS (ESI) 271.2028, $[C_{17}H_{28}ONa]^+$ requires 271.2032.

3.4.6 Nazarov reactions with (4+3)-cycloadditions

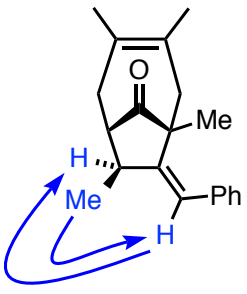
The allenyl vinyl ketone (1 equiv) and 2,3-dimethyl-1,3-butadiene (5 equiv) were dissolved in CH_2Cl_2 (sufficient to make a 0.1 M solution of the AVK) and cooled to –78 °C. BF_3•OEt_2 (1 equiv) was added as a 1 M solution in CH_2Cl_2. After 5-10 min the reaction was quenched by the addition of a saturated solution of $NaHCO_3$, and the mixture was allowed to warm to rt. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (×2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography.

(1*R,6*R**,7*S**,8*Z*)-8-Ethylidene-1,3,4,7-tetramethylbicyclo[4.2.1]bicyclonon-3-en-9-one (3.61) and (1*R**,6*R**,7*S**,8*E*)-8-ethylidene-1,3,4,7-tetramethylbicyclo[4.2.1]bicyclonon-3-en-9-one (3.62)



AVK **3.49** (46 mg) and the diene (0.20 mL) with BF_3•OEt_2 (0.35 mL), then chromatography (3% Et_2O/pentane) yielded **3.61** and **3.62** (49 mg, 66%), an oil, as an inseparable mixture of isomers in a 74:26 ratio (by ^1H NMR), respectively. Data for the mixture: IR (film) 1750 cm^{-1}; HRMS (ESI) 241.1564, $[C_{15}H_{22}ONa]^+$ requires 241.1563. For **3.61**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.37 (q, *J* = 7.2 Hz, 1H), 2.36–2.21 (m, 5H), 2.14 (br d, *J* = 16.4 Hz, 1H), 1.73 (d, *J* = 7.2 Hz, 3H), 1.71 (s, 3H), 1.66 (s, 3H), 1.37 (s, 3H), 0.95 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 224.4, 148.7, 127.7, 125.6, 118.5, 55.1, 51.3, 47.5, 41.3, 39.6, 24.4, 24.1, 23.7, 21.5, 14.0. NMR signals that could be discerned for the minor isomer **3.62**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.27 (qd, *J* = 6.9, 1.7 Hz, 1H), 2.61 (q, *J* = 7.2 Hz, 1H), 1.90 (d, *J* = 15.6 Hz, 1H), 1.60-1.59 (m, 6H), 1.14 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 127.7, 115.3, 55.7, 52.2, 51.9, 39.5, 37.5, 24.0, 23.8, 22.1, 21.2, 13.7.

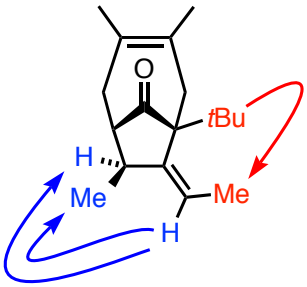
(1*R,6*R**,7*S**,8*Z*)-1,3,4,7-Tetramethyl-8-(phenylmethylene)bicyclo[4.2.1]non-3-en-9-one (3.63)**



AVK **3.50** (13 mg) and the diene (37 μL) with BF_3•OEt_2 (66 μL), then chromatography (3% Et_2O/pentane) gave **3.63** (12 mg, 65%) as an oil. IR (film) 1750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.8 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H),

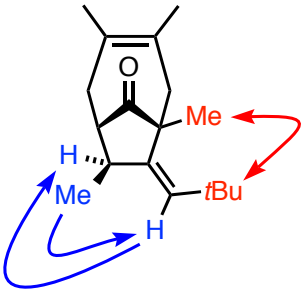
7.18 (d, J = 8.0 Hz, 2H), 6.55 (s, 1H), 2.53 (q, J = 7.2 Hz, 1H), 2.40 (br d, J = 15.5 Hz, 1H), 2.35–2.29 (m, 2H), 2.18 (d, J = 15.8 Hz, 1H), 2.12 (br d, J = 15.8 Hz, 1H), 1.76 (s, 6H), 1.13 (d, J = 7.3 Hz, 3H), 0.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 223.6, 151.3, 137.9, 128.9, 127.9, 127.2, 126.6, 126.5, 125.1, 54.4, 53.2, 50.0, 41.2, 39.7, 24.3, 24.0, 23.7, 21.0; HRMS (ESI) 303.1711, $[C_{20}H_{24}ONa]^+$ requires 303.1719.

(1*R,6*R**,7*S**,8*Z*)-1-*tert*-Butyl-8-ethylidene-3,4,7-trimethylbicyclo[4.2.1]non-3-en-9-one (3.64)**



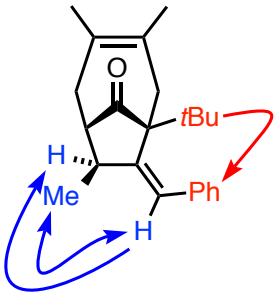
AVK **3.51** (48 mg) and the diene (0.15 mL) with BF_3•OEt_2 (0.30 mL), then chromatography (3% Et_2O/pentane) provided **3.64** (33 mg, 47%) as an oil. IR (film) 1742 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (q, J = 7.5 Hz, 1H), 2.65 (br d, J = 15.7 Hz, 1H), 2.40-2.35 (m, 3H), 2.20-2.16 (m, 2H), 1.72-1.70 (m, 9H), 1.16 (s, 9H), 1.07 (d, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 226.9, 146.5, 126.6, 124.9, 123.7, 61.2, 56.1, 46.4, 41.9, 41.5, 37.5, 28.9, 24.1, 23.9, 22.7, 18.1; HRMS (ESI) 283.2034, $[C_{18}H_{28}ONa]^+$ requires 283.2032. Exposure of a 0.1 M solution of **3.64** (20 mg) in CH_2Cl_2 to BF_3·OEt_2 (0.1 mL) for 30 min at rt returned only **3.64** (16 mg) after the work-up described in the Nazarov procedure.

(1*R,6*R**,7*S**,8*Z*)-8-(2,2-Dimethylpropylidene)-1,3,4,7-tetramethylbicyclo[4.2.1]non-3-en-9-one (3.65)**



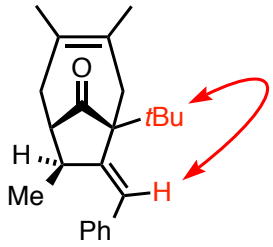
AVK **3.57** (43 mg) and the diene (0.15 mL) with BF_3•OEt_2 (0.24 mL), then chromatography (3% Et_2O/pentane) yielded **3.65** (31 mg, 49%) as an oil. IR (film) 1746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.34 (s, 1H), 2.40 (d, J = 16.0 Hz, 1H), 2.36 (br d, $J \approx$ 15 Hz, 1H), 2.27-2.20 (m, 3H), 2.10 (br d, J = 16.0 Hz, 1H), 1.70 (s, 3H), 1.67 (s, 3H), 1.39 (s, 3H), 1.14 (s, 9H), 0.95 (d, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 224.3, 144.5, 136.9, 126.8, 126.2, 54.0, 51.6, 48.9, 43.5, 39.7, 33.0, 32.4, 25.3, 23.9, 23.8, 23.0; HRMS (ESI) 283.2024, $[C_{18}H_{28}ONa]^+$ requires 283.2032.

(1*R,6*R**,7*S**,8*Z*)-1-*tert*-Butyl-8-(phenylmethylene)-3,4,7-trimethylbicyclo[4.2.1]non-3-en-9-one (3.66)**



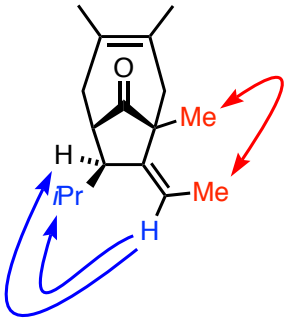
AVK **3.53** (77 mg) and the diene (0.20 mL) with BF_3•OEt_2 (0.35 mL), then chromatography (3% Et_2O/pentane) provided **3.66** (59 mg, 56%) as an oil. IR (film) 1742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.5 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 2H), 6.72 (s, 1H), 2.64 (br d, *J* = 16.3 Hz, 1H), 2.60-2.50 (m, 3H), 2.29 (dd, *J* = 5.1, 3.6 Hz, 1H), 2.26 (br d, *J* = 17.1 Hz, 1H), 1.84 (s, 3H), 1.72 (s, 3H), 1.22 (d, *J* = 7.5 Hz, 3H), 0.85 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 225.4, 149.5, 140.5, 128.6, 128.1, 127.9, 126.3 (2C), 124.9, 62.0, 55.4, 46.9, 45.7, 41.9, 37.5, 28.8, 23.8, 23.7, 23.5; HRMS (ESI) 345.2186, $[C_{23}H_{30}ONa]^+$ requires 345.2189.

(1*R,6*R**,7*S**,8*E*)-1-*tert*-butyl-8-(phenylmethylene)-3,4,7-trimethylbicyclo[4.2.1]non-3-en-9-one (3.74)**



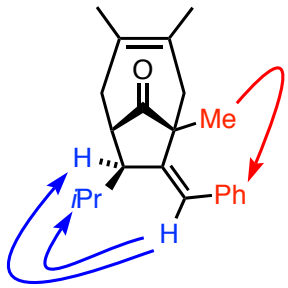
Exposure of a 0.1 M solution of **3.66** (25 mg) in CH_2Cl_2 to BF_3•OEt_2 (0.1 mL) for 30 min at rt returned an inseparable mixture of **3.66** and **3.74** (20:80 by ^1H NMR, 20 mg) after work-up as described in the Nazarov procedure. For **3.74** (from the spectra of the mixture): ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.7 Hz, 2H), 7.27-7.24 (m, 1H), 7.21 (d, *J* = 7.9 Hz, 3H), 6.45 (s, 1H), 2.74 (q, *J* = 7.3 Hz, 1H), 2.45-2.33 (m, 3H), 2.19-2.18 (m, 2H), 1.69 (s, 3H), 1.67 (s, 3H), 1.20 (s, 9H), 1.05 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 225.0, 151.2, 138.3, 128.63, 128.45, 126.4, 125.78, 125.76, 60.7, 56.9, 44.4, 40.2, 38.5, 36.0, 27.6, 24.2, 24.0, 21.1.

(1*R,6*R**,7*S**,8*Z*)-8-Ethylidene-7-isopropyl-1,3,4-trimethylbicyclo[4.2.1]non-3-en-9-one (3.68)**



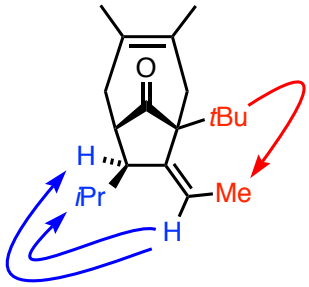
AVK **3.55** (34 mg) and the diene (0.12 mL) with BF_3•OEt_2 (0.21 mL), then chromatography (3% Et_2O/pentane) gave **3.68** (36 mg, 71%) as an oil. IR (film) 1750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.40 (qd, *J* = 7.2, 1.3 Hz, 1H), 2.40-2.37 (m, 2H), 2.35 (d, *J* = 16.0 Hz, 1H), 2.16 (dd, *J* = 16.5, 6.5 Hz, 1H), 2.14-2.10 (m, 2H), 1.76 (dd, *J* = 7.2, 1.2 Hz, 3H), 1.72 (s, 3H), 1.72 (overlapped, 1H), 1.67 (s, 3H), 1.37 (s, 3H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.65 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 225.0, 146.3, 127.8, 125.7, 119.3, 52.9, 52.3, 48.9, 47.7, 40.5, 34.4, 24.2, 23.7, 20.7, 20.4, 17.8, 13.9; HRMS (ESI) 269.1872, $[C_{17}H_{26}ONa]^+$ requires 269.1876.

(1*R,6*R**,7*S**,8*Z*)-7-Isopropyl-1,3,4-trimethyl-8-(phenylmethylene)bicyclo[4.2.1]non-3-en-9-one (3.69)**



AVK **3.56** (74 mg) and the diene (0.20 mL) with BF_3•OEt_2 (0.35 mL), then chromatography (3% Et_2O/pentane) yielded **3.69** (49 mg, 49%) as an oil. IR (film) 1756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 2H), 6.61 (s, 1H), 2.48-2.45 (m, 2H), 2.35 (narrow m, 1H), 2.23 (dd, *J* = 17.0, 6.9 Hz, 1H), 2.18 (d, *J* = 16.1 Hz, 1H), 2.10 (br d, *J* = 16.0 Hz, 1H), 1.99 (m, 1H), 1.78 (s, 6H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.93 (s, 3H), 0.72 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 224.2, 149.1, 138.1, 128.9, 127.9, 127.2, 126.6 (2C), 125.4, 54.2, 52.2, 50.2, 47.7, 40.7, 34.4, 24.2, 23.8, 21.0, 20.1, 17.2; HRMS (ESI) 331.2030, $[C_{22}H_{28}ONa]^+$ requires 331.2032.

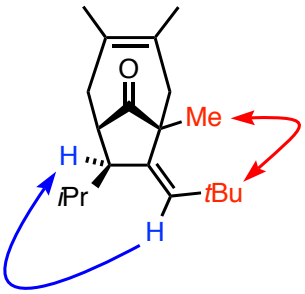
(1*R,6*R**,7*S**,8*Z*)-1-*tert*-Butyl-8-ethylidene-7-isopropyl-3,4-dimethylbicyclo[4.2.1]non-3-en-9-one (3.70)**



AVK **3.57** (23 mg) and the diene (54 μL) with BF_3•OEt_2 (0.10 mL), then chromatography (3% Et_2O/pentane) gave 3.70 (19 mg, 59%) as an oil. IR (film) 1742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.55 (q, *J* = 7.2 Hz, 1H), 2.66 (d, *J* = 16.2 Hz, 1H), 2.45-2.42 (m, 2H), 2.36 (br d, *J* = 16.1 Hz, 1H), 2.10 (br dd, *J* = 17.9, 5.0 Hz, 1H), 1.71-1.66 (m, 10H), 1.39-1.31 (m, 1H), 1.10 (s, 9H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 226.6, 142.8, 127.5, 126.0, 125.1, 61.0, 60.4,

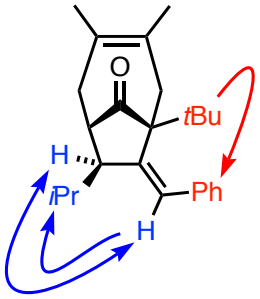
53.5, 42.2, 41.9, 37.8, 30.1, 28.6, 23.8, 23.6, 21.8, 21.0, 17.9; HRMS (ESI) 311.2357, $[C_{20}H_{32}ONa]^+$ requires 311.2345.

(1*R,6*R**,7*S**,8*Z*)-8-(2,2-Dimethylpropylidene)-7-isopropyl-1,3,4-trimethylbicyclo[4.2.1]-non-3-en-9-one (3.71)**



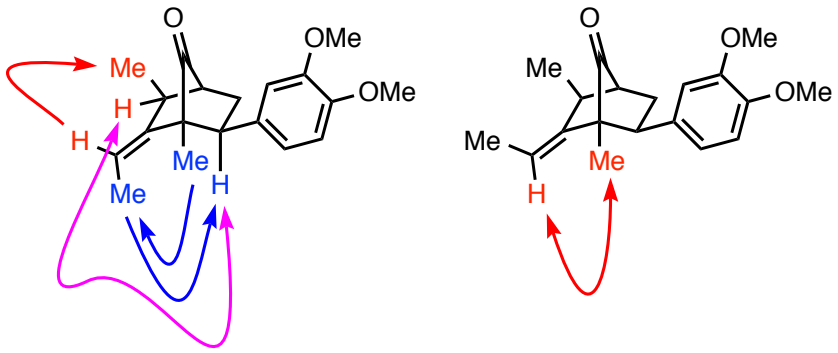
AVK **3.58** (61 mg) and the diene (0.20 mL) with BF_3•OEt_2 (0.30 mL), then chromatography (3% Et_2O/pentane) gave **3.71** (31 mg, 36%) as an oil. IR (film) 1750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.40 (d, *J* = 1.5 Hz, 1H), 2.42-2.36 (m, 3H), 2.14 (dd, *J* = 15.9, 5.8 Hz, 1H), 2.07 (br d, *J* = 16.0 Hz, 1H), 2.03 (narrow m, 1H), 1.79-1.73 (m, 1H), 1.71 (s, 3H), 1.68 (s, 3H), 1.40 (s, 3H), 1.16 (s, 9H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.58 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 224.9, 142.6, 137.0, 127.2, 126.4, 54.0, 52.9, 49.3, 47.2, 40.8, 35.1, 33.1, 32.5, 24.1, 24.0, 21.7, 21.1, 16.9; HRMS (ESI) 311.2358, $[C_{20}H_{32}ONa]^+$ requires 311.2345.

(1*R,6*R**,7*S**,8*Z*)-1-*tert*-Butyl-7-isopropyl-3,4-dimethyl-8-(phenylmethylene)bicyclo[4.2.1]-non-3-en-9-one (3.72)**



AVK **3.59** (25 mg) and the diene (53 μL) with BF_3•OEt_2 (0.10 mL), then chromatography (3% Et_2O/pentane) yielded **3.72** (25 mg, 77%) as an oil. IR (film) 1738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.5 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 2H), 6.67 (s, 1H), 2.61–2.58 (m, 2H), 2.49 (br d, *J* = 16.8 Hz, 1H), 2.22 (br d, *J* = 13.2 Hz, 1H), 2.03-1.97 (m, 2H), 1.80 (s, 3H), 1.71 (s, 3H), 1.52-1.47 (m, 1H), 1.13 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.3 Hz, 3H), 0.85 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 224.8, 145.5, 140.4, 131.5, 128.7, 127.7, 126.5, 126.3, 124.5, 61.8, 61.1, 53.2, 45.8, 42.3, 37.7, 30.5, 28.8, 23.4 (2C), 22.0, 21.2; HRMS (ESI) 373.2497, $[C_{25}H_{34}ONa]^+$ requires 373.2502.

(1*R,2*Z*,3*S**,6*R**)-2-Ethylidene-6-(3,4-dimethoxyphenyl)-1,3-dimethylbicyclo[2.2.1]heptan-7-one (3.75) and (1*R**,2*E*, 3*S**,6*R**)-2-ethylidene-6-(3,4-dimethoxyphenyl)-1,3-dimethylbicyclo[2.2.1]heptan-7-one (3.76).**



AVK **3.49** (30 mg, 0.22 mmol) and 3,4-dimethoxystyrene (0.10 mL, 0.68 mmol) were dissolved in CH_2Cl_2 (2.0 mL). The solution was cooled to -78 ºC, and BF_3•OEt_2 (0.25 mL, 0.22 mmol) was added. After 15 min the reaction was quenched by the addition of a saturated solution of $NaHCO_3$. After warming to rt the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (×2). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (40% Et_2O/pentane) of the residue gave 43 mg (65%) of an oil that was an inseparable mixture (79:21 from the analysis of the ^1H NMR) of diastereomers **3.75** and **3.68**. Data for the mixture: IR (film) 1751 cm^{-1}; HRMS (ESI) 323.1631, $[C_{19}H_{24}O_3Na]^+$ requires 323.1618. For **3.75**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, J = 8.2 Hz, 1H), 6.59-6.55 (m, 1H), 6.50 (d, J = 2.0 Hz, 1H), 5.39-5.34 (m, 1H), 3.85 (s, 6H), 3.02 (dd, J = 10.5, 3.9 Hz, 1H), 2.56 (q, J = 7.1 Hz, 1H), 2.23-2.17 (m, 1H), 2.13-2.09 (m, 2H), 1.75 (dd, J = 7.2 Hz, 1.3 Hz, 3H), 1.04 (d, J = 7.1 Hz, 3H), 0.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 217.2, 149.0, 145.3, 135.8, 120.3, 118.5, 114.9,

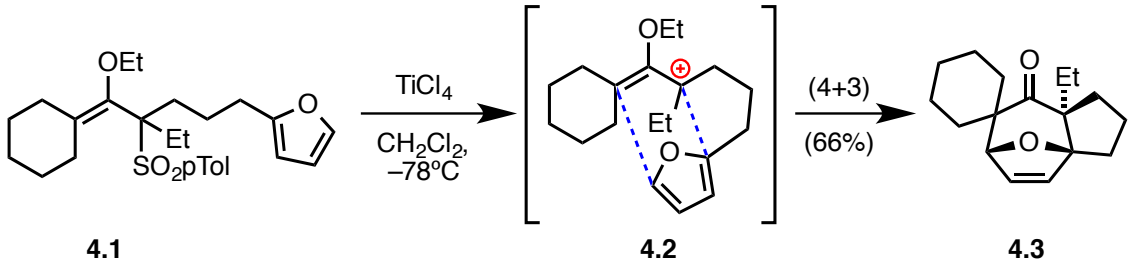
111.2, 111.1, 56.0 (2C), 52.4, 47.8, 47.5, 42.6, 33.4, 21.3, 13.7, 12.4. Discernable NMR signals for **3.78**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.96 (dd, J = 10.7, 4.7 Hz, 1H), 2.84-2.81 (m, 2H), 1.70 (d, J = 6.7 Hz, 3H), 1.07 (d, J = 7.0 Hz, 3H), 0.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 217.5, 148.0, 146.7, 136.3, 120.0, 118.4, 116.3, 111.2, 111.0, 56.0 (2C), 48.8, 48.4, 46.5, 39.6, 33.3, 18.6, 13.5, 10.3.

Chapter 4

Intramolecular Trapping of Allenyl Vinyl Ketones by 1,3-Dienes

4.1 Intramolecular (4+3)-Cycloaddition Reactions

The intermolecular addition of 1,3-dienes to oxyallyl cations has been shown to be an efficient method for the generation of seven-membered rings.[43,44] The intramolecular variants of many reactions are often more efficient than the corresponding intermolecular reactions. An early example of an intramolecular (4+3)-cycloaddition to an oxyallyl cation was demonstrated by Harmata.[100] Treatment of sulfone **4.1** with $TiCl_4$ led to the interception of oxyallyl cation intermediate **4.2** by the pendent furan. Compound **4.3** was formed as a single diastereomer in good yield. The diasteroselective formation of two new rings in a single operation is an efficient method for the generation of cyclic compounds from simple starting materials.

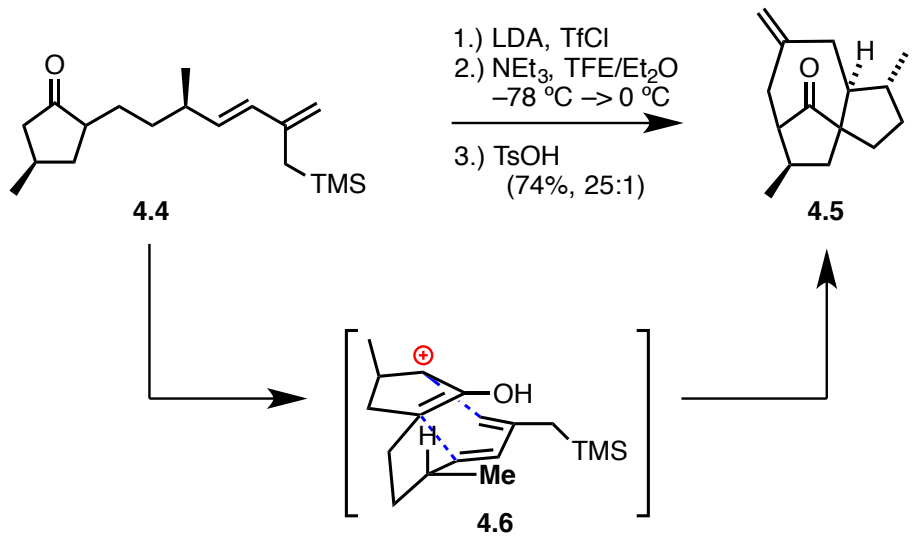


4.1 **4.2** **4.3**

Scheme 4.1 Intramolecular trapping of furan by an oxyallyl cation.

The intramolecular (4+3)-cycloaddition reaction could be carried out with molecules possessing dienes other than furan.[101] In their synthesis of (+)-dactylol, the Harmata group utilized the intramolecular (4+3)-cycloaddition of **4.4** to generate the

requisite ring structure.[102] Treatment of **4.4** with LDA and triflyl chloride led to an α-chloroketone, to which triethylamine in trifluoroethane/Et_2O was added at –78 ºC. Warming to room temperature led to the cyclized product. Partial desilylation occurred during chromatography so the crude cycloadduct was stirred with tosic acid to completely remove the TMS and migrate the alkene into an exocyclic position. Product **4.5**, a 25:1 mixture of diastereomers, was formed in 74% yield over three steps. The transition state geometry can be visualized as **4.6**; the cycloaddition occurred on the less hindered face of the oxyallyl cation and the methyl group on the tether adopted a pseudoequatorial position minimizing steric interactions.[43,103]

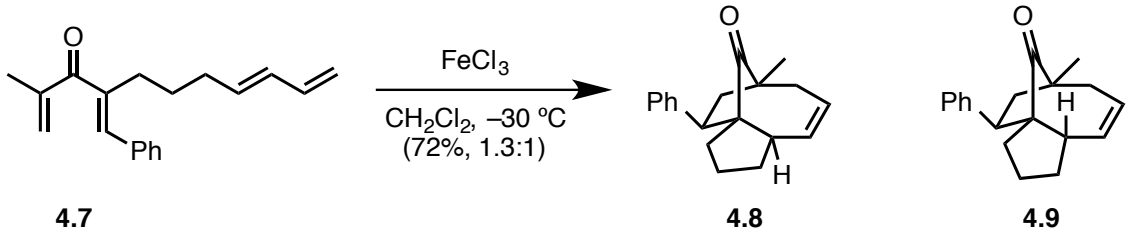


Scheme 4.2 Intramolecular (4+3)-cycloaddition in the total synthesis of (+)-dactylol.

4.1.1 Nazarov Reaction and Intramolecular (4+3)-Cycloaddition

The West group explored the intramolecular trapping of the oxyallyl cations generated from the Nazarov reaction of divinyl ketones with alkenes.[28,104] They have also described the intramolecular trapping of the oxyallyl cation with tethered 1,3-dienes.[105] The tetraenone **4.7** underwent Nazarov cyclization in the presence of $FeCl_3$,

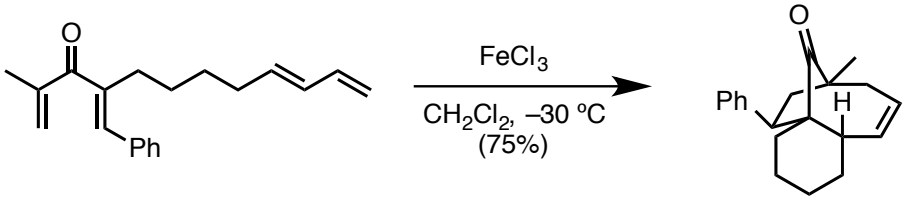
and trapping by the tethered diene led to a mixture of products, **4.8** and **4.9** (Scheme 4.3). The product arising from a compact transition state, **4.8**, was slightly favored, but the diastereoselectivity was low.



4.7 **4.8** **4.9**

Scheme 4.3 Tandem Nazarov/(4+3)-cycloaddition with a tethered 1,3-diene.

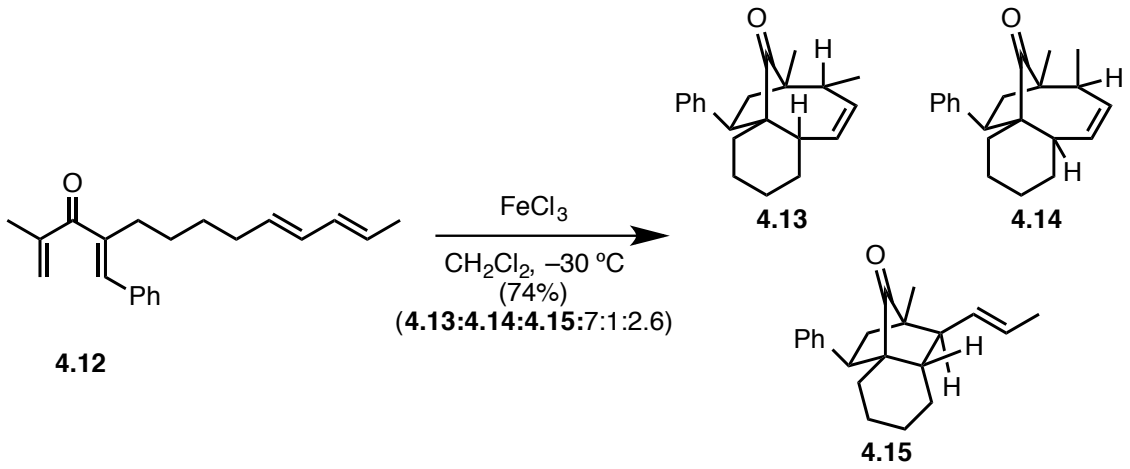
Employing a divinyl ketone bearing a longer tether resulted in much better diastereoselectivity. Cyclization of **4.10** led to the tricyclic compound **4.11** as a single diastereomer in good yield (Scheme 4.4). In this case the product would have arisen from an extended transition state.[105]



4.10 **4.11**

Scheme 4.4 Intramolecular tandem Nazarov reaction/(4+3)-cycloaddition with 4.10.

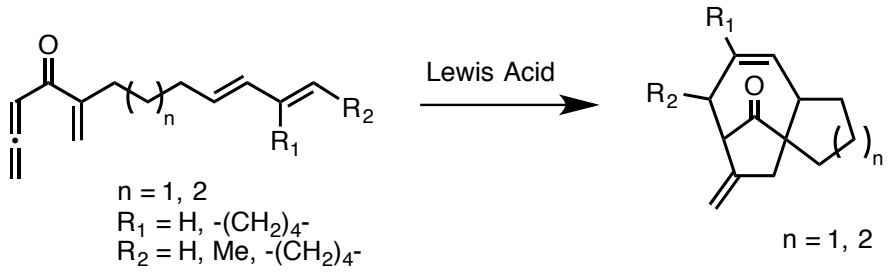
Substitution on the diene also affected the outcome of the reaction. Compound **4.12** gave a mixture of (4+3) products but with good diastereoselectivity (Scheme 4.5). However, (3+2) adduct **4.15** was also formed with high diastereoselectivity. The authors postulated that the (3+2)-cycloaddition product might have arisen due to increased steric demands in the (4+3) transition state.[105]



Scheme 4.5 Formation of (4+3)- and (3+2)-cycloaddition products from the Nazarov reaction of tetraenone 4.12.

4.2 Nazarov Reaction and Intramolecular Trapping with Allenyl Vinyl Ketones

Given the ability of AVKs to undergo Nazarov cyclization followed by (4+3) or (3+2) cyclization it was envisioned that a tethered 1,3-diene could allow the construction of a complex tricyclic skeleton in a single operation (Scheme 4.6). It was also of interest to determine if the diastereoselectivity of the reaction with AVKs would mirror those observed in the intramolecular (4+3)-cycloadditions carried out by West and Harmata.[100,102,105] The initial goal of this project was to develop a general synthetic route towards AVKs with a tethered 1,3-diene. Ideally, the synthetic process would allow for easy variation of the tether length as well as the substitution of the diene. Once a synthetic route was developed the Nazarov reaction could be explored.

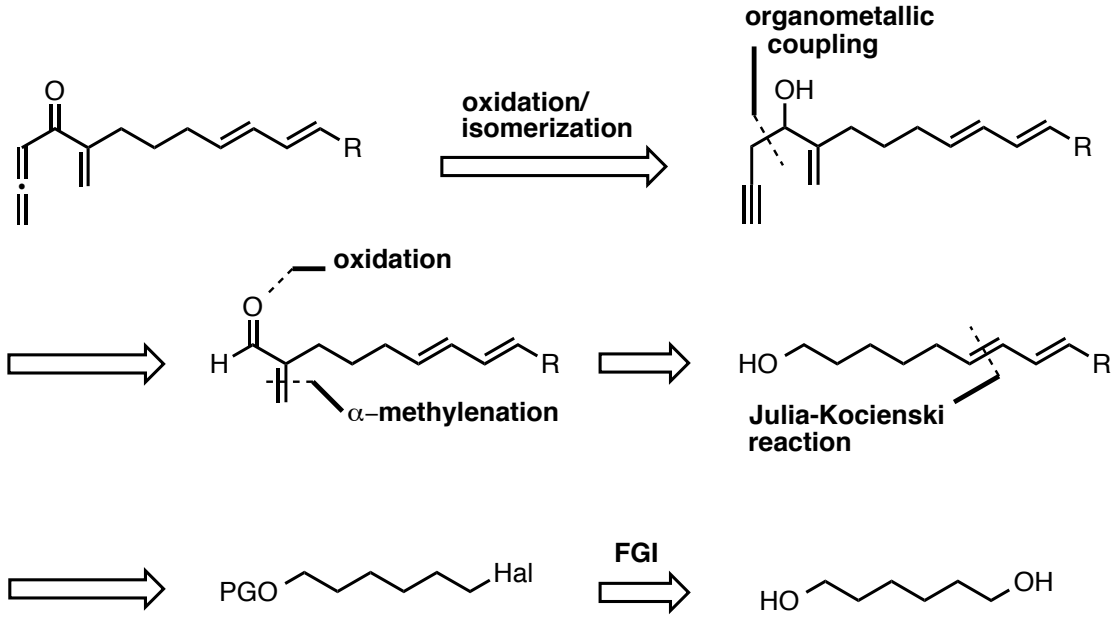


Scheme 4.6 Nazarov reaction of AVK bearing a tethered 1,3-diene.

4.3 Synthesis of Type II Allenyl Vinyl Ketones with Tethered 1,3-dienes

The majority of trapping experiments have been carried out with type I AVKs.[35,37,39] However, synthetic difficulties with type I AVKs bearing tethered 1,3-dienes led to the use of type II AVKs for the intramolecular trapping experiments (Scheme 4.6). Although type II AVKs have been more difficult to handle than their type I counterparts, they could still be synthetically useful.[36] The development of a method to exploit the reactivity of different AVKs is therefore of particular interest.

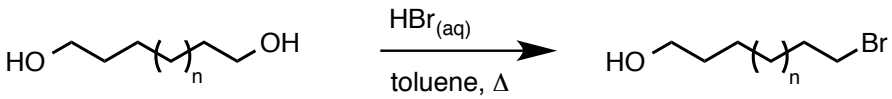
Previous work from the Burnell group involved the synthesis of allenyl vinyl ketones.[35,36] However, the methodology used previously had not been used for the synthesis of AVKs with sensitive functionality attached by a tether. A retrosynthetic analysis for type II AVKs is detailed in Scheme 4.7. It was envisioned that the allenyl vinyl ketone could arise from the corresponding homopropargyl alcohol. The homopropargyl alcohol could be accessed from an α,β-unsaturated aldehyde using the organometallic chemistry used previously by our group. Oxidation and α-methenylation of a primary alcohol would furnish the α,β-unsaturated aldehyde. Preliminary studies suggested that the Julia-Kocienski reaction could be used to prepare a series of olefins that could ultimately give access to a variety of AVKs.



Scheme 4.7 Retrosynthesis of an allenyl vinyl ketone with a tethered 1,3-diene.

4.3.1 Diene Synthesis

The synthesis of the dienes commenced with the preparation of bromoalcohols 4.16 **and** 4.17 **from the corresponding diols using aqueous HBr in toluene.[106] The primary alcohols were then protected as the *tert*-butyldimethylsilyl (TBS) ethers** 4.18 **and** 4.19 **(**



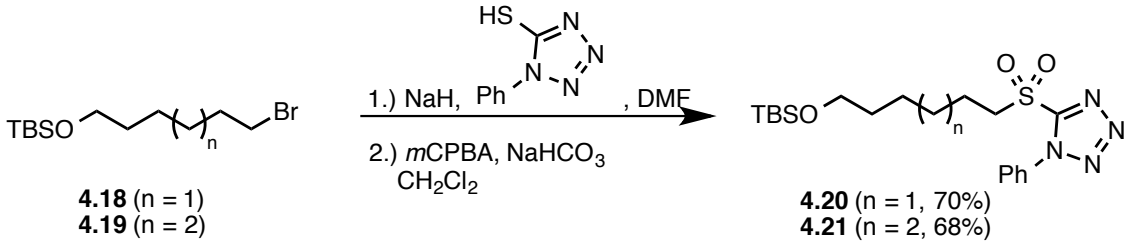
Scheme 4.8). n = 1,2

4.16 (n = 1)
4.17 (n = 2)

4.18 (n = 1, 77%, two steps)
4.19 (n = 2, 88%, two steps)

Scheme 4.8 Preparation of protected bromoalcohols 4.18 and 4.19.

With **4.18** and **4.19** readily available, the synthesis of the requisite dienes could be undertaken. The Julia-Kocienski reaction employs a sulfone that, under sufficiently basic conditions, deprotonates and reacts with an aldehyde to yield predominantly the *E*-alkene.[107] In preparation for the Julia-Kocienski reaction, **4.18** and **4.19** were coupled with 1-phenyl-1*H*-tetrazole-5-thiol using NaH in DMF. Subsequent oxidation of the crude material with buffered *m*CPBA yielded sulfones **4.20** and **4.21** (Scheme 4.9). The $NaHCO_3$ buffer was necessary to inhibit the deprotection of the silyl-protecting group.



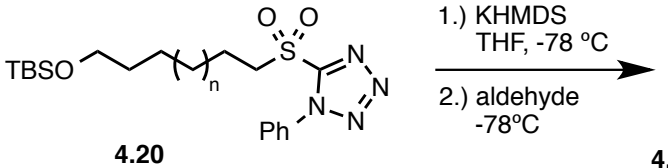
4.18 (n = 1)
4.19 (n = 2)

4.20 (n = 1, 70%)
4.21 (n = 2, 68%)

Scheme 4.9 Preparation of sulfones 4.20 and 4.21.

The sulfones were treated with base followed by addition of an α,β-unsaturated aldehyde to produce the desired diene (Scheme 4.10).[108,109] Three aldehydes were chosen to examine various substitution patterns of the diene in the intramolecular

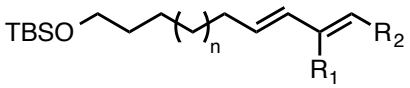
tandem Nazarov/(4+3)-cycloaddition, acrolein, crotonaldehyde, and 1-cyclohexene-1-carboxaldehyde. Each of the dienes **4.22**–**4.26** was produced with a preference for the *E* isomer over the *Z* isomer (Scheme 4.10), but the ratios were disappointing. Separation of the isomers was not achievable by silica gel chromatography. Attempts to improve the *E/Z* selectivity by the addition of 18-crown-6 were unsuccessful.[110] Therefore mixtures were carried forward in the synthesis. Desilylation with tetrabutylammonium fluoride yielded the primary alcohols **4.27-4.31** (Scheme 4.11).



4.20
4.21

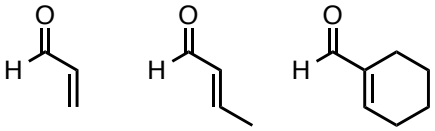
1.) KHMDS
THF, -78 ºC

2.) aldehyde
-78ºC



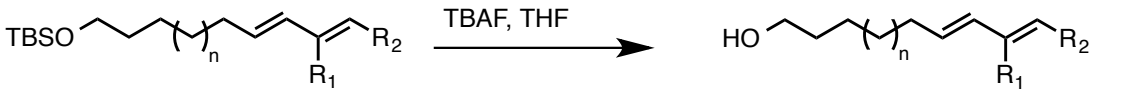
4.22 (n = 1), **4.23** (n = 2): R_1 = H, R_2 = H
4.24 (n = 1), **4.25** (n = 2): R_1 = H, R_2 = Me
4.26 (n = 1): $R_1 = R_2 = -(CH_2)_4-$

Aldehydes



Compound	Yield (%)	*E/Z*
4.22	72	5:1
4.23	58	5:1
4.24	74	3:1
4.25	96	4:1
4.26	51	4:1

Scheme 4.10 Julia-Kocienski reaction to produce 1,3-dienes.



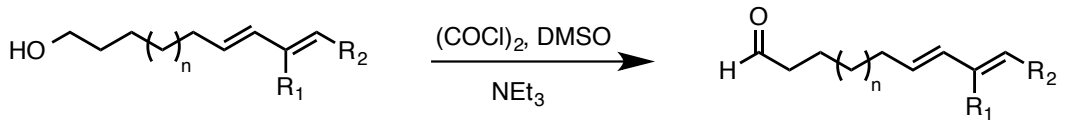
4.22 (n = 1), **4.23** (n = 2)
4.24 (n = 1), **4.25** (n = 2)
4.26 (n = 1)

4.27 (n = 1), **4.28** (n = 2): R_1 = H, R_2 = H
4.29 (n = 1), **4.30** (n = 2): R_1 = H, R_2 = Me
4.31 (n = 1): $R_1 = R_2 = -(CH_2)_4-$

Compound	Yield (%)	*E/Z*
4.27	94	4:1
4.28	85	5:1
4.29	75	3:1
4.30	93	4:1
4.31	88	3:1

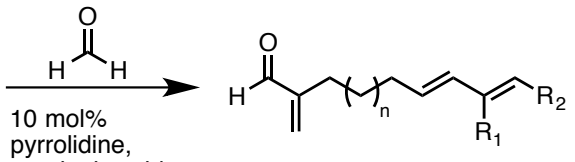
Scheme 4.11 Removal of the *tert*-butyldimethylsilyl protecting group.

The next step was the synthesis of α,β-unsaturated aldehydes required for the organometallic coupling reaction. Oxidation of the primary alcohols, **4.27-4.31**, under Swern conditions led to the formation of the aldehydes **4.32-4.36**. It was envisioned that a Mannich reaction could be used to introduce the α-methylene group. However, classic α-methylenation conditions using Eschenmosher's salt and triethylamine failed to produce sufficient quantities of the desired compounds. Instead the organocatalytic procedure described by Pihko[111,112] utilizing aqueous formaldehyde, propionic acid, and pyrrolidine proved successful and provided the desired α,β-unsaturated aldehydes **4.37-4.41** over two steps from the primary alcohols.



4.27 (n = 1), **4.28** (n = 2): R_1 = H, R_2 = H
4.29 (n = 1), **4.30** (n = 2): R_1 = H, R_2 = Me
4.31 (n = 1): $R_1 = R_2 = -(CH_2)_4-$

4.32 (n = 1), **4.33** (n = 2): R_1 = H, R_2 = H
4.34 (n = 1), **4.35** (n = 2): R_1 = H, R_2 = Me
4.36 (n = 1): $R_1 = R_2 = -(CH_2)_4-$



4.37 (n = 1), **4.38** (n = 2): R_1 = H, R_2 = H
4.39 (n = 1), **4.40** (n = 2): R_1 = H, R_2 = Me
4.41 (n = 1): $R_1 = R_2 = -(CH_2)_4-$

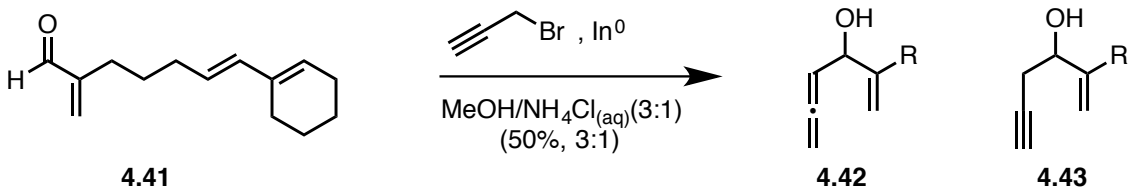
Compound	Yield (%)[a]	*E/Z*
4.37	39	5:1
4.38	32	5:1
4.39	26	4:1
4.40	51	4:1
4.41	42	4:1

[a] Yields are over two steps

Scheme 4.12 Synthesis of α,β-unsaturated aldehydes.

4.4 Synthesis of Allenyl Vinyl Ketones

With a general route to the α,β-unsaturated aldehydes available, conditions for the organometallic coupling reaction could be explored. Initial attempts focused on the methods for the synthesis of homopropargyl/allenyl alcohols used previously in the Burnell group.[36] Treatment of aldehyde **4.41** with In^0 and propargyl bromide in 3:1 $MeOH/NH_4Cl_{(aq)}$ resulted in the formation of a mixture of the desired allenyl alcohol and homopropargyl alcohol in a 3:1 ratio (Scheme 4.13), but the total yield of the alcohols **4.42** and **4.43** was only 50%.

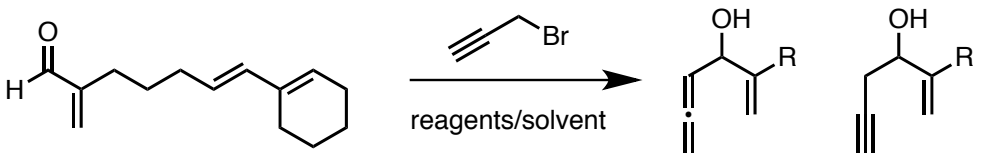


4.41 **4.42** **4.43**

Scheme 4.13 Indium-mediated Barbier-type coupling of α,β-unsaturated aldehyde with propargyl bromide.

A factor contributing to the low yield of the coupling reaction may have been the poor solubility of the aldehyde in the mixed solvent system. Mukaiyama and Harada[113] had reported a procedure for the preparation of α-hydroxy ketones using $SnCl_2$, NaI and propargyl bromide in DMF. More recently the Lee group reported the coupling of a range of aldehydes and propargyl bromides using In^0 and LiI in THF.[114] Both procedures utilized a Finkelstein-type halogen exchange between bromine and iodine to facilitate the metal insertion required for the coupling reaction. Subjecting aldehyde **4.41** to the conditions reported by Lee[114] and Mukaiyama[113] yielded mixtures of the desired allenyl and homopropargyl alcohols with better overall yields. The results are summarized in Table 4.1. The alcohols could not be separated by chromatography. Therefore, the ratios were determined by integration of the ^1H NMR spectra.

Table 4.1 Conditions for the Coupling of α,β-Unsaturated Aldehydes with Propargyl Bromide



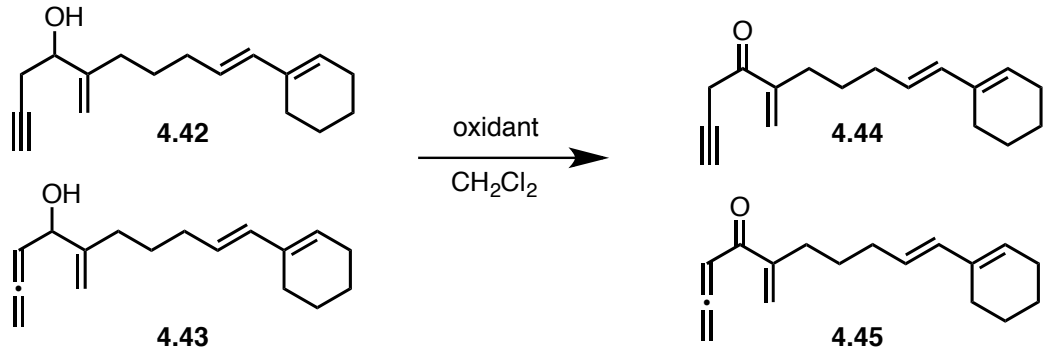
4.41 **4.42** **4.43**

Entry	Reagents	Solvent	Product Yield (**4.42**:**4.43**)
1	In^0	MeOH/NH_4Cl (3:1)	50% (3:1)
2	In^0, LiI	THF	75% (1:2)
3	NaI, $SnCl_2$	DMF	70% (3:1)

Previous studies had shown that the oxidation of homopropargyl and allenyl alcohols was challenging.[36,115] It has been determined that the best oxidants were either MnO_2 (for Type 1 AVKs)[35] or Dess-Martin periodinane (DMP) buffered with $NaHCO_3$ (for Type 2 and 3 AVKs).[36] Yields for these oxidations ranged from 30-80% depending on the substitution on the AVK. Both MnO_2 and DMP were tested with the mixtures of allenyl and homopropargyl alcohols produced from the metal-mediated cross-coupling reactions. The results of this study are described in Table 4.2. MnO_2 was completely ineffective as an oxidant and resulted in recovery of the starting material. Hypervalent iodine oxidants, DMP and 2-iodobenzoic acid (IBX), were the most effective reagents for the oxidation. The yields of the oxidation reaction were difficult to determine because the products were not stable. Silica gel chromatography resulted in a portion of the material undergoing partial Nazarov cyclization. This result had been observed before with Type II AVKs.[29] Subjecting the reaction mixture of **4.42** and **4.43** to chromatography resulted in the isolation of homopropargyl ketone and cyclized

Nazarov product. The combined yield of starting material and product was used to determine the yields of the oxidation reactions.

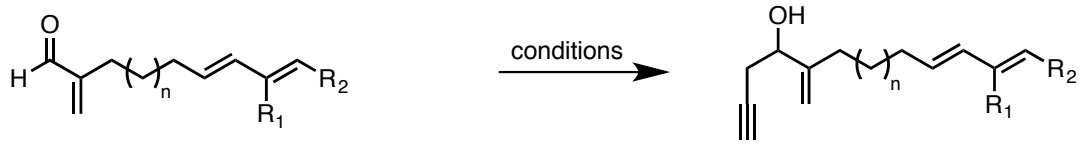
Table 4.2 Oxidation of Allenyl and Homopropargyl Alcohols



Entry	Alcohol Alkyne/Allene Ratio	Conditions	Product Yield
1	1:3	MnO_2, CH_2Cl_2, rt	0%
2	1:3	DMP/$NaHCO_3$, CH_2Cl_2, rt	33%[(a)]
3	2:1	MnO_2, CH_2Cl_2, rt	0%
4	2:1	DMP/$NaHCO_3$, CH_2Cl_2, rt	60%[(a)]

(a) Yields were estimated from the combined yields of allenyl vinyl ketones and Nazarov products after purification of the crude mixture by flash chromatography on SiO_2.

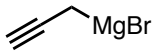
The oxidation results were disappointing. However, the highest yield was for the oxidation of the mixture containing mostly homopropargyl alcohol (Entry 4, Table 4.2). It was hypothesized that perhaps only the homopropargyl alcohol was oxidizing under the reaction conditions. This observation prompted the re-evaluation of the coupling reaction. Since the indium- and tin-mediated coupling reactions are alleged to operate via an S_N2' mechanism[113,114] the allene should be the predominant product. The homopropargyl alcohols were more accessible by Grignard addition of propargyl bromide to the aldehydes **4.37-4.41**.

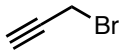


4.37 (n = 1), **4.38** (n = 2): R_1 = H, R_2 = H
4.39 (n = 1), **4.40** (n = 2): R_1 = H, R_2 = Me
4.41 (n = 1): $R_1 = R_2 = -(CH_2)_4-$

4.46 (n = 1), **4.47** (n = 2): R_1 = H, R_2 = H
4.48 (n = 1), **4.49** (n = 2): R_1 = H, R_2 = Me
4.43 (n = 1): $R_1 = R_2 = -(CH_2)_4-$

Conditions

a  , Et_2O

b  , NaI, $SnCl_2$, DMF

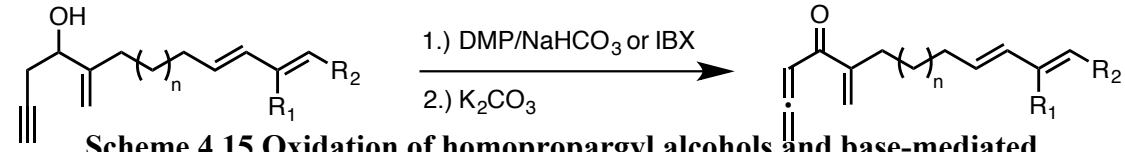
Conditions	Compound	Yield (%)	Ratio
a	**4.46**	64	7:1
b	**4.47***	72	-
a	**4.48**	71	4:1
a	**4.49**	72	4:1
a	**4.43**	56	4:1

*formed as a 2:1 mixture of allene:alkyne

Scheme 4.14 Coupling of propargyl bromide-derived Grignard reagent to α,β-unsaturated aldehydes.

The Grignard addition proceeded smoothly for each of the α,β-unsaturated aldehydes to give only the corresponding homopropargyl alcohols 4.46-4.49 **and** 4.43 **(Scheme 4.14). The alcohols were then oxidized with DMP or IBX, but unfortunately, the yields did not improve. Finally, isomerization of the propargyl ketones with K_2CO_3 resulted in formation of AVKs** 4.50-4.53 **and** 4.45 **(**

Scheme 4.15). The AVKs were prepared directly from the homopropargyl alcohols and used immediately without purification.



4.46 (n = 1), **4.47** (n = 2): R_1 = H, R_2 = H
4.48 (n = 1), **4.49** (n = 2): R_1 = H, R_2 = Me
4.43 (n = 1): $R_1 = R_2 = -(CH_2)_4-$

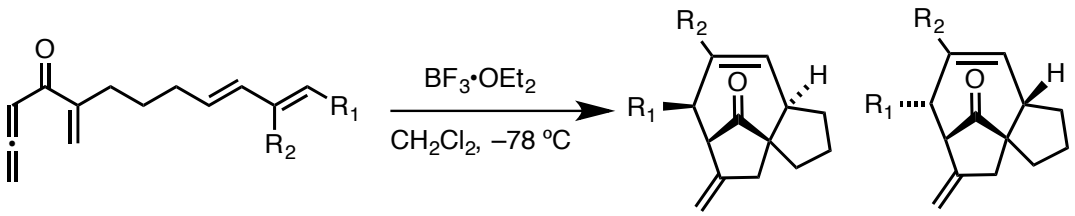
4.50 (n = 1), **4.51** (n = 2): R_1 = H, R_2 = H
4.52 (n = 1), **4.53** (n = 2): R_1 = H, R_2 = Me
4.45 (n = 1): $R_1 = R_2 = -(CH_2)_4-$

Scheme 4.15 Oxidation of homopropargyl alcohols and base-mediated isomerization of propargyl ketones to allenyl vinyl ketones.

4.5 Nazarov Reactions of Allenyl Vinyl Ketones with Tethered 1,3-Butadienes

With a method for the synthesis of allenyl vinyl ketones bearing tethered 1,3-dienes established, intramolecularly trapped Nazarov reactions could be investigated. Treatment of the allenyl vinyl ketones, **4.50**, **4.52**, and **4.45** with BF_3•OEt_2 at –78 ºC led to the formation of a polycyclic ring systems, **4.54-4.58** in which the oxyallyl cations were trapped by the tethered dienes. The (4+3)-cycloaddition can occur via an extended or a compact transition state. In all cases there was a preference for the formation of the products from a compact transition state (Table 4.3). AVK **4.50** led to the formation of a 2:1 mixture of the compact and extended products **4.54** and **4.55**. The selectivity of the cycloaddition improved with the methyl substituted AVK **4.51**. The products were formed in a 6:1 ratio favoring the **4.54**. The diastereomers, **4.54** and **4.55**, were partially separable by flash chromatography. AVK **4.45** gave the best result as only a single diastereomer was formed. These results showed that the substitution pattern of the diene was important in determining the product distribution of the cycloaddition. It is also important to note that only (4+3) cycloadducts were observed.

Table 4.3 Nazarov Cyclization and Intramolecular Trapping by the Tethered 1,3-Diene



Entry	R	compact	extended	Yield[a] ratio[b]
1	$R_1 = R_2 =$ H	**4.54**	**4.55**	52% (2:1)
2	R_1 = Me, R_2 = H	**4.56**	**4.57**	38% (6:1)
3	$R_1 = R_2 = -(CH_2)_4-$	**4.58**	**4.59**	50% (1:0)

[a] Yields over three steps yields from the corresponding homopropargyl alcohols. [b] Ratios were determined from integration of the ^{1}H NMR spectra.

The structure of **4.56** was assigned using NMR spectroscopy. The ^{1}H NMR spectrum was assigned using COSY and HSQC 2D correlation spectroscopy, and the relative stereochemistry was determined based on 1D NOE experiments (Figure 4.1). Positive NOE's were observed between $\mathbf{H_a}$ and $\mathbf{H_b}$ indicating that these hydrogens were *syn*. This contact could only arise if $\mathbf{H_b}$ was down as shown in Figure 4.1. Irradiation of the methyl led to an enhancement of $\mathbf{H_c}$. Finally, irradiating $\mathbf{H_d}$ produced an enhancement of the exocyclic methylene hydrogen $\mathbf{H_e}$. The stereochemical assignment and the important NOE contacts are shown in Figure 4.1. This stereochemistry was consistent with **4.56** having arisen from a concerted reaction with the tethered diene through a compact transition state.

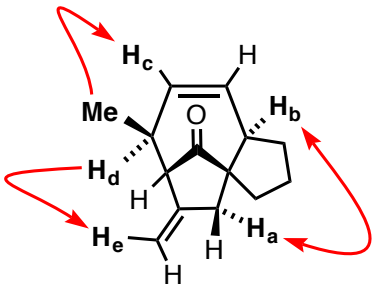


Figure 4.1 Results of NOE experiments on **4.56**.

The relative stereochemistry of **4.54**, and **4.58** were assigned from NOE experiments in a similar manner as **4.56**. Important NOE contacts are shown in Figure 4.2. The relative stereochemistry of the minor compounds, **4.55** and **4.57**, could not be rigorously determined through NOE experiments due to overlapping signals in the ^{1}H NMR spectrum. However, the most likely structures would have arisen through the cycloaddition of the diene via an extended transition state. The suggested relative stereochemistry is shown in Table 4.3.

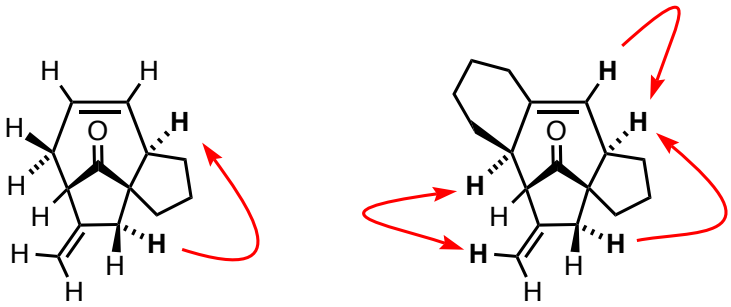
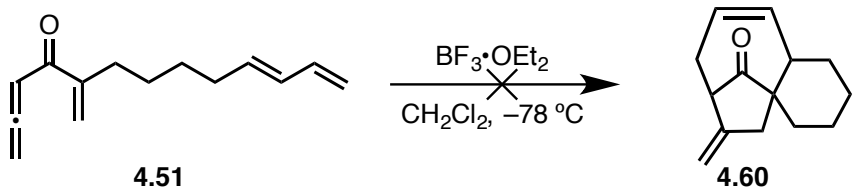


Figure 4.2 Important NOE contacts for the stereochemical assignment of 4.54 and 4.58

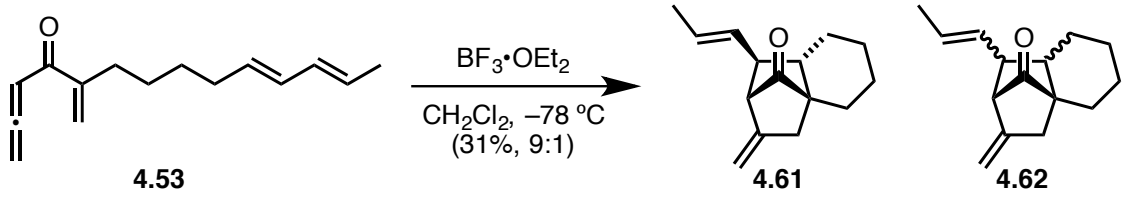
The length of the tether proved to be a very important factor in the tandem Nazarov/intramolecular (4+3) cycloaddition reaction. AVK **4.51**, which is similar to **4.50** except it has one more methylene in the tether, was expected to undergo the Nazarov reaction and then intramolecular trapping to give a tricyclic product such as

4.60 (Scheme 4.16). Exposure of AVK **4.51** to typical Nazarov reaction conditions led to the complete consumption of starting material but no cyclized product was detected.



Scheme 4.16 Attempted tandem Nazarov/cycloaddition reaction of AVK 4.48.

Allenyl vinyl ketone **4.53** underwent Nazarov cyclization when exposed to BF_3•OEt_2 at –78 ºC to produce an inseparable mixture of two products in a 9:1 ratio (Scheme 4.17). However, the products were not (4+3) cycloadducts. The major product was the (3+2)-cycloaddition product **4.61**. The minor product was suggested to be **4.62** based on similarities in the NMR spectra. However, due to the small amount of material the structure of **4.62** could not be assigned with certainty.

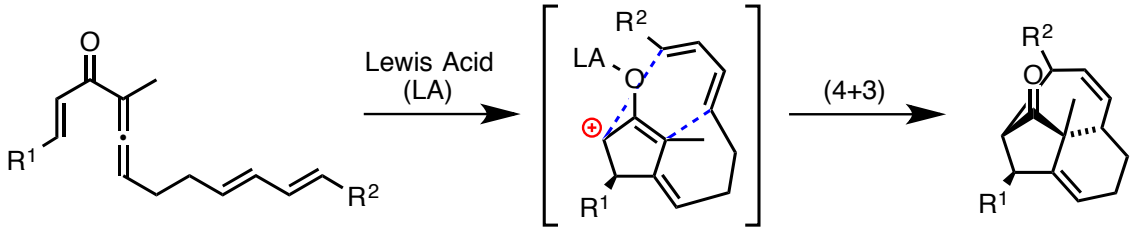


Scheme 4.17 Tandem Nazarov/intramolecular (3+2) trapping.

4.6 Type IV AVKs with Tethered 1,3-Dienes

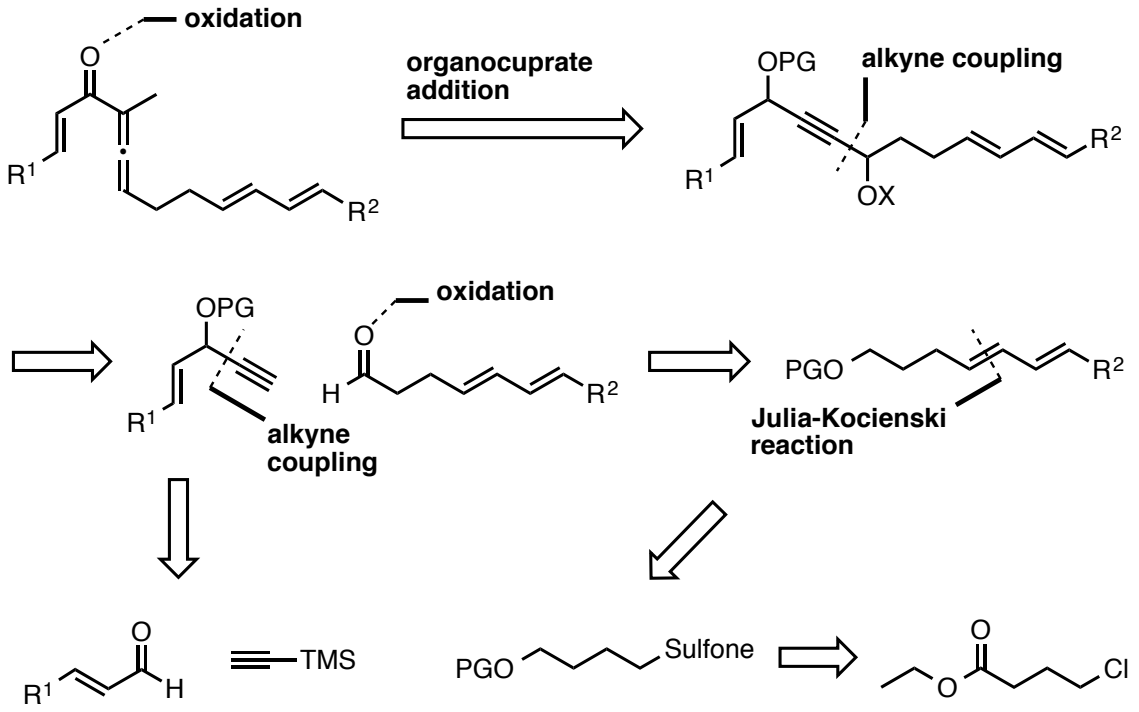
Allenyl vinyl ketones bearing substitution on the terminus of the allene (type IV) have been shown to react in the interrupted Nazarov reactions with a high degree of torquoselectivity.[85] A type IV AVK with a tethered diene on the terminus of the allene should undergo Nazarov cyclization to produce the *E* isomer of the exocyclic double

bond (Scheme 4.18). A tethered 1,3-diene might then be well situated to intercept the oxyallyl cation by a (4+3)-cycloaddition.



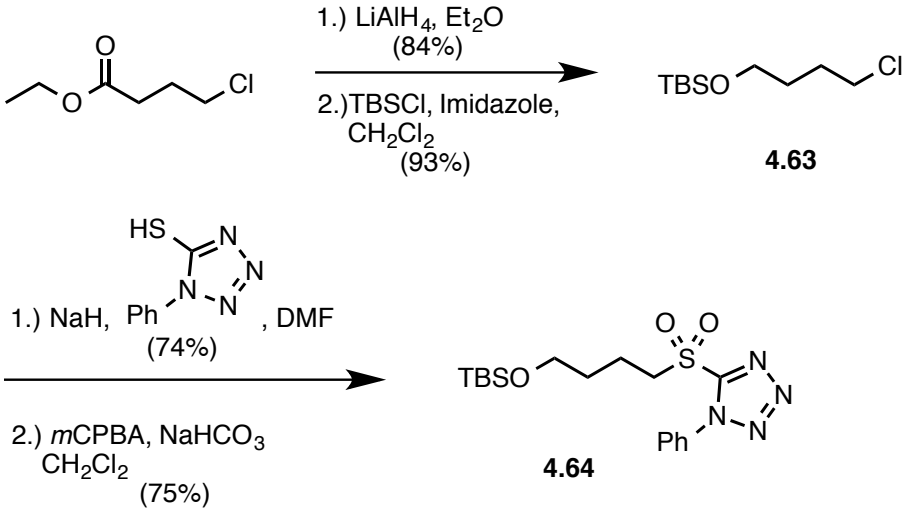
Scheme 4.18 Postulated Nazarov cyclization and intramolecular trapping of a type IV AVK.

A retrosynthetic analysis for type IV AVKs bearing 1,3-tethered dienes is shown in Scheme 4.19. The key step in the synthesis was proposed to be an organocuprate addition to a propargyl alcohol derivative. Conjugate addition of a cuprate to the alkyne and elimination of an oxygen-leaving group (OAc or OMs) would furnish the requisite trisubstituted allene. Simple deprotection and oxidation would give the allenyl vinyl ketone. The propargyl alcohol required for the conjugate addition could be accessed through a base-mediated coupling of an alkyne to a dienal. The dienal was available through chemistry similar to that described previously (Scheme 4.7).



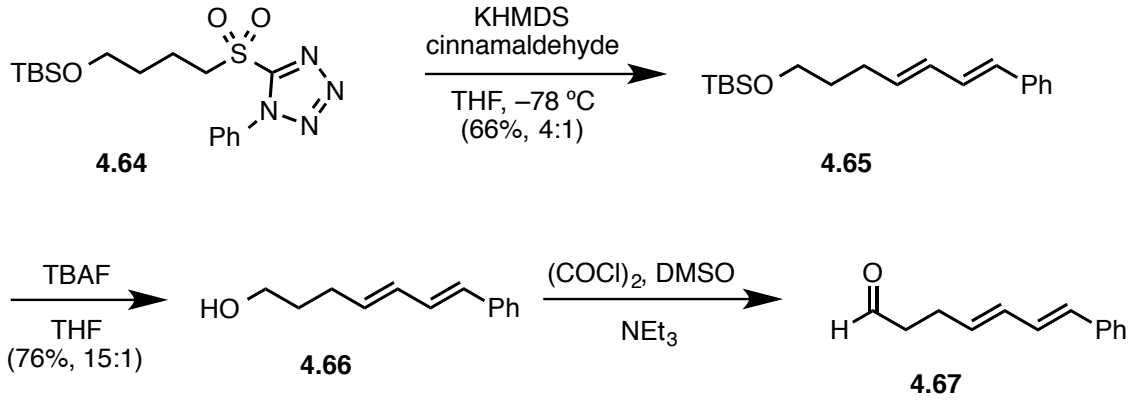
Scheme 4.19 Retrosynthesis of a type IV AVK bearing a tethered 1,3-diene.

The synthesis began with the reduction of ethyl 4-chlorobutyrate using $LiAlH_4$ and subsequent protection of the primary alcohol. The chloride in compound **4.63** was displaced with 1-phenyl-1*H*-tetrazole-5-thiol, and the resulting sulfide was oxidized with *m*CPBA to yield sulfone **4.64** (Scheme 4.20).



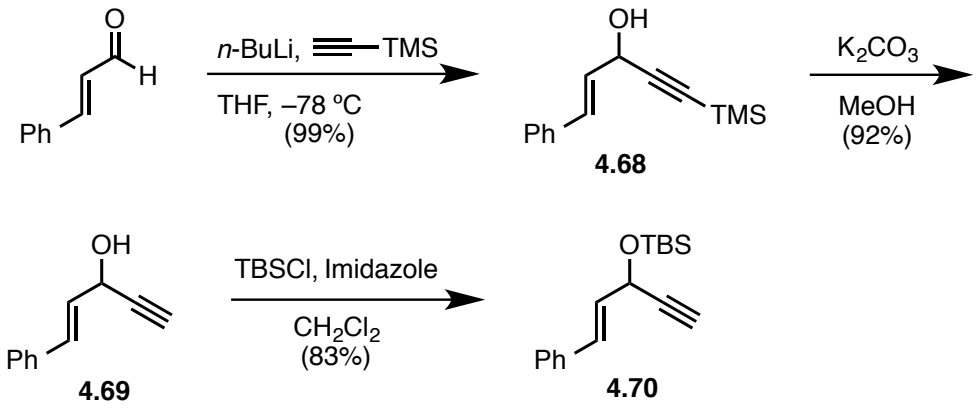
Scheme 4.20 Synthesis of sulfone 4.64 from ethyl 4-chlorobutyrate.

Sulfone **4.64** underwent Julia-Kocienski olefination with *trans*-cinnamaldehyde to produce diene **4.65** with a 4:1 preference for the *E*-alkene. Removal of the silyl protecting group gave alcohol **4.66**. Flash chromatography of the alcohol allowed the partial separation of the *E/Z* isomers and improved the ratio to 15:1. Oxidation of the primary alcohol under Swern conditions led to dienal **4.67,** which was used without purification.



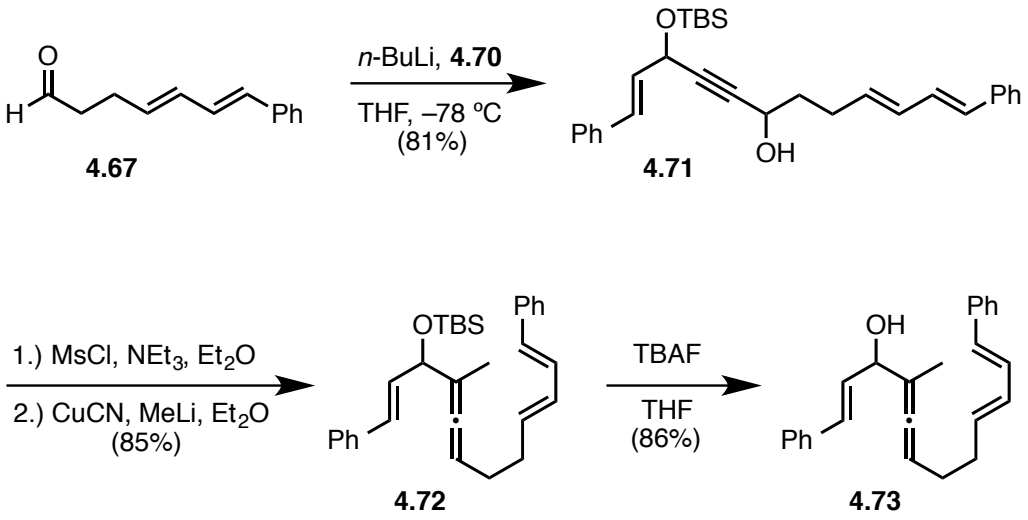
Scheme 4.21 Julia-Kocienski coupling followed by deprotection and oxidation.

The protected propargyl alcohol required for the alkyne coupling shown in Scheme 4.19 was available from *trans*-cinnamaldehyde (Scheme 4.22). Deprotonation of trimethylsilylacetylene with *n*-BuLi led to an anion that could be added to *trans*-cinnamaldehyde in quantitative yield. The TMS group was removed by stirring **4.68** with K_2CO_3 in methanol to provide **4.69**. The alcohol was then protected as a silyl ether, **4.70**.



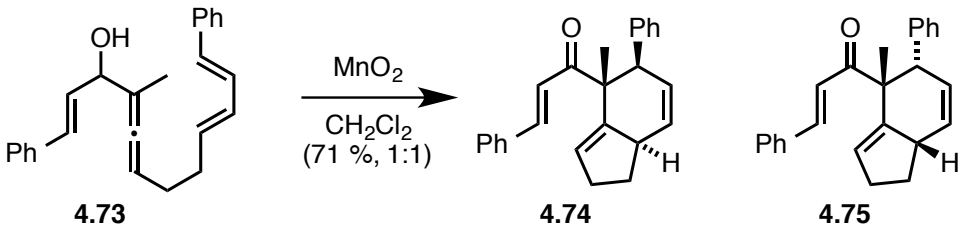
Scheme 4.22 Synthesis of protected propargyl alcohol 4.70 required for alkyne coupling.

The synthesis of the allenyl vinyl alcohol is shown in Scheme 4.23. Addition of **4.70** to dienal **4.67** proceeded smoothly using *n*-BuLi to yield propargyl alcohol **4.71**. The conjugate addition was carried out using a one-pot process.[116] The alcohol was converted to a mesylate using triethylamine and methanesulfonyl chloride, and the cuprate reagent, which was prepared from MeLi and CuCN, was added to the crude mesylate reaction mixture. The two-step procedure produced allene **4.72** in good yield. Deprotection of **4.72** with tetrabutylammonium fluoride yielded allenyl vinyl alcohol **4.73**.



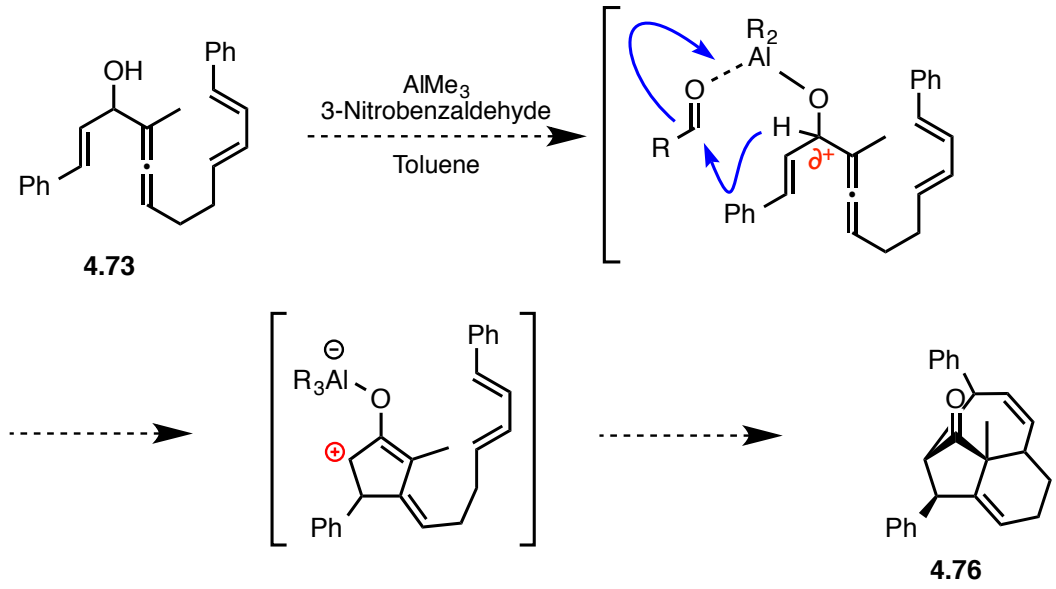
Scheme 4.23 Conjugate addition of an organocuprate to synthesize allenyl vinyl alcohol 4.71.

The oxidation of the allenyl alcohol was followed by an unwanted intramolecular reaction. The allenyl vinyl ketone underwent spontaneous Diels-Alder cyclization to form a mixture of diastereomers **4.74** and **4.75** (Scheme 4.24). When the reaction was carried out with MnO_2 as the oxidant, **4.74** and **4.75** were formed in a 1:1 ratio. When the oxidation was carried out with IBX the yield was substantially lower (32%) but the ratio of products was 2:1 favoring **4.74**. The relative stereochemistry of the adducts were assigned from NOE experiments. The major product arose from an *exo* transition state between the diene and the allene. The minor product was the result of an *endo* transition state.



Scheme 4.24 Oxidation of allenyl vinyl alcohol and intramolecular Diels-Alder.

The West group has shown that the Nazarov reaction of divinyl ketones can be initiated with organoaluminum reagents.[26] Trimethylaluminum has been used in the Oppenauer oxidation of vinyl alcohols.[117] It was hypothesized that trimethylaluminum may be used to promote a tandem oxidation/Nazarov reaction (Scheme 4.25). Initial attempts to carry out the tandem process were unsuccessful.



Scheme 4.25 Proposed tandem oxidation/Nazarov cyclization.

4.7 Conclusions

General methods for the synthesis of Type II and Type IV allenyl vinyl ketones with tethered 1,3-dienes have been developed. The synthetic procedures allowed for variation in the length of the tether, substitution of the diene, and substitution of the allene. The length of the tether had a significant effect on the outcome of the tandem Nazarov/intramolecular trapping reaction of Type II allenyl vinyl ketones. When the diene was attached to the AVK by a three-carbon tether the intermediate oxyallyl cation was intercepted by a (4+3)-cycloaddition. The stereoselectivity of the process was heavily influenced by the substitution of the diene. In one instance a single diastereomer resulted from the tandem process. However, if the tether was increased by a single methylene the trapping occurred exclusively by a (3+2) process. The diastereoselectivity of the (3+2)-cycloaddition was high. The Type IV allenyl vinyl ketone did not undergo the same tandem Nazarov/cycloaddition process as the Type II AVKs. Instead, upon oxidation of the allenyl vinyl alcohol an intramolecular Diels-Alder cyclization occurred. Attempts to suppress this reaction pathway were unsuccessful.

4.8 Experimental Section

4.8.1 General considerations

Reactions were carried out in oven-dried glassware under an atmosphere of dry nitrogen. Reagents were used as received from commercial sources. Dichloromethane was distilled over calcium hydride. Tetrahydrofuran (THF) was freshly distilled over sodium/benzophenone. EtOAc and hexanes were distilled. Reactions were followed by TLC analysis using precoated (silica gel 60 F254, 0.25 mm) plates with aluminum

backing. Column chromatography was carried out with silica gel (40–63 μm particle size, 230-240 mesh). Evaporation of solvents was under reduced pressure with modest heating. ^{1}H NMR spectra were acquired at 500.1 MHz, and chemical shifts are relative to internal TMS (δ 0.00 ppm). The ^{1}H NMR data are presented as follows: chemical shift in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant(s), *J*, in hertz (Hz), and integration. Diastereomeric ratios were determined by integration of clearly separated ^{1}H NMR signals. ^{13}C NMR spectra were acquired at 125.8 MHz, and chemical shifts are relative to the solvent signal ($CDCl_3$, δ 77.16 ppm). Structural assignments were based on 2-D NMR spectra (COSY, HSQC, HMBC) and nuclear Overhauser effect (NOE) measurements.[70,71] HRMS data were obtained using a TOF mass spectrometer by positive-ion ESI.

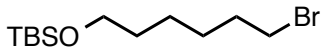
4.8.2 General procedure for the preparation of bromosilyl ethers.

Based on the method of Rabbat and coworkers,[106] diol (1 equiv) was dissolved in toluene and treated with aqueous 48% HBr (1.5 equiv). The heterogeneous mixture was heated under reflux for 24 h. (If the reaction was not complete by TLC analysis a further 0.5-1 equiv of HBr was added, and the mixture was heated under reflux for a further 24 h.) The solution was cooled to room temperature and the phases were separated. The organic phase was diluted with diethyl ether, washed with 1 M aqueous NaOH and brine. The ether layer was then dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum.

The crude bromoalcohol was dissolved in CH_2Cl_2 and cooled to 0 ºC. Imidazole (2-3 equiv) was added, and the solution was stirred for 5 min. TBSCl (1-2 equiv) was added and the mixture was stirred for 2 h. The reaction was quenched with water. The

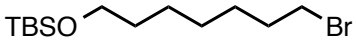
phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (×2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum.

6-Bromo-1-((tert-butyldimethylsilyl)oxy)hexane (4.18)



1,6-Hexanediol (5.0 g, 42 mmol) was reacted with 48% HBr (5 mL + 2 mL, 63 mmol) in toluene (100 mL) to yield 7.5 g of crude bromoalcohol. The bromoalcohol was treated with imidazole (6.8 g, 99 mmol) and TBSCl (10.0 g, 66 mmol) in CH_2Cl_2 (150 mL). The crude material was purified by flash chromatography (5% EtOAc/hexane) to yield **4.18** (9.6 g, 77% over two steps) as a clear colorless oil: ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.62 (t, J = 6.5 Hz, 2H), 3.42 (t, J = 6.9 Hz, 2H), 1.88 (quintet, J = 7.1 Hz, 2H), 1.55-1.51 (m, 2H), 1.49-1.43 (m, 2H), 1.40-1.35 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 63.2, 34.1, 32.96, 32.76, 28.1, 26.1, 25.2, 18.5, –5.1. The spectral data are consistent with the literature.[118]

7-Bromo-1-((tert-butyldimethylsilyl)oxy)heptane (4.19)



1,7-Heptanediol (3.9 g, 30 mmol) was reacted with 48% HBr (4 mL + 2 mL, 54 mmol) in toluene (40 mL) to yield 5.8 g of crude bromoalcohol. The bromoalcohol was treated with imidazole (4.3 g, 63 mmol) and TBSCl (6.1 g, 40 mmol) in CH_2Cl_2 (150 mL). The crude material was purified by flash chromatography (5% Et_2O/pentane) to yield **4.19** (8.2 g, 88% over two steps) as a clear colorless oil. ^{1}H NMR (500 MHz;

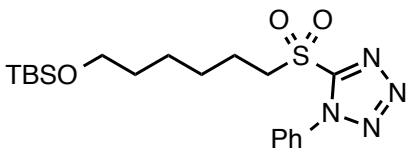
$CDCl_3$): δ 3.60 (t, *J* = 6.5 Hz, 2H), 3.40 (t, *J* = 6.9, 3H), 1.89-1.83 (m, 3H), 1.54-1.50 (m, 2H), 1.46-1.42 (m, 3H), 1.35-1.31 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 63.3, 34.1, 32.94, 32.89, 28.7, 28.3, 26.1, 25.8, 18.5, –5.1. The spectral data are consistent with the literature.[119]

4.8.3 General procedure for the preparation of sulfones

NaH (1.5 equiv) was suspended in DMF and cooled to 0 ºC. 1-Phenyl-1*H*-tetrazole-5-thiol (1 equiv) dissolved in DMF was slowly added to the cold solution, which was stirred for 30 min. The bromosilyl ether **4.18** (1 equiv) was dissolved in DMF and added slowly. The mixture was allowed to gradually come to rt. After 5 h the reaction was complete according to analysis using TLC, and it was quenched by the slow addition of water. The mixture was extracted EtOAc (×3). The combined organic extracts were washed with water followed by brine, then dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum.[120]

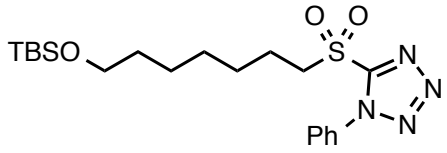
The crude sulfide (1 equiv) was dissolved in CH_2Cl_2. $NaHCO_3$ (5 equiv) and *m*CPBA (2 equiv) were added, and the mixture was stirred for 24 h. The mixture was filtered through Celite, and the organic phase was washed with saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.[120]

(6-(*tert*-Butyldimethylsilanyloxy)hexanesulfonyl)-1-phenyl-5-1*H*-tetrazole (4.20)



NaH (3.7 g, 93 mmol) was suspended in DMF (60 mL). 1-Phenyl-1*H*-tetrazole-5-thiol (9.8 g, 55 mmol) in DMF (20 mL) was added, followed by **4.18** (16.0 g, 54 mmol) in DMF (20 mL). The crude sulfide was oxidized with *m*CPBA (22.1 g, 98 mmol) buffered with $NaHCO_3$ (21.4 g, 255 mmol) in CH_2Cl_2 (200 mL). The crude product was purified by flash chromatography (20% EtOAc/hexane) to yield **4.20** (15.9 g, 70% over two steps) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70-7.68 (m, 2H), 7.64-7.58 (m, 3H), 3.75-3.71 (m, 2H), 3.60 (t, *J* = 6.3 Hz, 2H), 1.99-1.93 (m, 2H), 1.55-1.49 (m, 4H), 1.43-1.39 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 153.5, 133.1, 131.5, 129.8, 125.2, 62.9, 56.0, 32.4, 28.1, 26.1, 25.4, 22.1, 18.5, –5.2; HRMS (ESI): 447.1857, $[C_{19}H_{32}N_4O_3SSiNa]^+$ requires 447.1862.

(7-(*tert*-Butyldimethylsilanyloxy)heptanesulfonyl)-1-phenyl-5-1*H*-tetrazole (4.21)



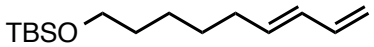
NaH (1.7 g, 42 mmol) was suspended in DMF (30 mL). 1-Phenyl-1*H*-tetrazole-5-thiol (9.8 g, 55 mmol) in DMF (15 mL) was added, followed by **4.19** (16.0 g, 54 mmol) in DMF (15 mL). The crude sulfide was oxidized with *m*CPBA (14.1 g, 63 mmol) buffered with $NaHCO_3$ (14.5 g, 173 mmol) in CH_2Cl_2 (250 mL). Purification by flash chromatography (20% EtOAc/Hexane) yielded **4.21** (9.6 g, 68% over two steps) as a pale yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.74-7.72 (m, 2H), 7.67-7.62 (m, 3H), 3.78-3.75 (m, 2H), 3.63 (t, *J* = 6.5 Hz, 2H), 2.03-1.97 (m, 2H), 1.56-1.52 (m, 4H), 1.41-1.38 (m, 4H), 0.93 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 153.7, 133.2,

131.6, 129.9, 125.2, 63.2, 56.2, 32.8, 28.9, 28.3, 26.1, 25.6, 22.1, 18.5, –5.1; HRMS (ESI): 461.2132, $[C_{20}H_{34}N_4O_3SSiNa]^+$ requires 461.2019.

4.8.4 General procedure for the Julia-Kocienski olefination reaction for the synthesis of 1,3-dienes

Following a literature procedure,[109] the sulfone (1 equiv) and an aldehyde (1.5 equiv) were dissolved in THF and cooled to –78 ºC (EtOAc/$N_{2(l)}$ bath). KHMDS (2.0 equiv) was then added slowly to the cold stirring solution. The mixture was maintained at a temperature of –78 ºC for 1 h. The mixture was warmed to rt, and the reaction was quenched with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted Et_2O (×3). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum.

(6*E*,8-Nonadienyl-1-oxy)-*tert*-butyldimethylsilane (4.22)



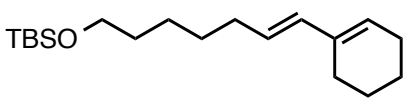
Sulfone **4.20** (2.1 g, 5.0 mmol) and acrolein (0.5 ml, 7.5 mmol) in THF (50 mL) with KHMDS (15 mL, 7.5 mmol) gave a crude product that was purified by flash chromatography (5% Et_2O/pentane) to yield **4.22** (908 mg, 72%, *E:Z*/5:1) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.31 (dt, *J* = 17.0, 10.3 Hz, 1H), 6.05 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.70 (dt, *J* = 14.9, 7.4 Hz, 1H), 5.08 (d, *J* = 16.8 Hz, 1H), 4.95 (d, *J* = 10.0 Hz, 1H), 3.60 (t, *J* = 6.6 Hz, 2H), 3.60 (t, *J* = 6.6 Hz, 2H), 2.09 (q, *J* = 7.0 Hz, 2H), 1.55-1.49 (2H, m), 1.43-1.38 (m, 3H) 1.36-1.31 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 137.5, 135.5, 131.1, 114.8, 63.4, 32.87, 32.67, 29.1, 26.1, 25.5, 18.5, –5.1; NMR signals discerned for the minor isomer: ^{1}H NMR (500

MHz; $CDCl_3$): δ 6.64 (dt, *J* = 16.9, 10.6 Hz, 1H), 5.45 (q, *J* = 8.9 Hz, 1H), 5.17 (d, *J* = 16.9 Hz, 1H), 2.19 (q, *J* = 7.1 Hz, 2H). HRMS (ESI): 277.1950, $[C_{15}H_{30}OSiNa]^+$ requires 277.1958.

(6*E*,8*E*-Decadienyl-1-oxy)-*tert*-butyldimethylsilane (4.24)

Sulfone **4.20** (2.3 g, 5.4 mmol) and crotonaldehyde (0.6 mL, 7.3 mmol) in THF (50 mL) with KHMDS (15 mL, 7.5 mmol) gave a crude product that was purified by flash chromatography (5% Et_2O/pentane) to yield **4.24** (1.0 g, 74%, *E:Z*/3:1) as a clear slightly yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.02-5.96 (m, 2H), 5.59-5.52 (m, 2H), 3.60 (m, 2H), 2.05 (q, *J* = 7.1 Hz, 2H), 1.73-1.72 (d, *J* = 7.0 Hz, 3H), 1.51 (quintet, *J* = 7.0 Hz, 2H), 1.42-1.30 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (126 MHz; $CDCl_3$): δ 132.0, 131.7, 130.3, 126.7, 63.3, 32.75, 32.56, 29.3, 26.0, 25.4, 18.4, 18.0, –5.2; NMR signals discerned for the minor isomer: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.39-6.33 (m, 1H), 5.70 (dq, *J* = 14.6, 7.1 Hz, 1H), 5.32 (dt, *J* = 10.5, 7.8 Hz, 1H), 2.20 (q, *J* = 7.0 Hz, 2H), 1.81 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 129.7, 129.0, 128.6, 127.0, 32.8, 29.6, 27.7, 25.5, 18.3; HRMS (ESI): 291.2113, $[C_{16}H_{32}OSiNa]^+$ requires 291.2120.

((6*E*)-7-(1-Cyclohexene)-6-hexadienyl-1-oxy)*tert*-butyldimethylsilane (4.26)



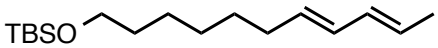
Sulfone **4.20** (1.2 g, 2.8 mmol) and 1-cyclohexene-1-carboxaldehyde (0.48 mL, 4.2 mmol) in THF (50 mL) with KHMDS (11 mL, 5.5 mmol) gave a crude product that was purified by flash chromatography (5% Et_2O/pentane) to yield **4.26** (450 mg, 51%, *E:Z*/4:1) as a clear yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.02 (d, *J* = 15.7 Hz, 1H), 5.63-5.62 (m. 1H), 5.54 (dt, *J* = 15.6 Hz, 6.9 Hz, 1H), 3.60 (m, 2H), 2.13-2.07 (m, 5H), 1.68-1.62 (m, 2H), 1.61-1.56 (m, 3H), 1.53-1.49 (m, 2H), 1.41-1.31 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 135.8, 133.6, 127.2, 126.7, 63.4, 32.97, 32.90, 29.7, 26.1, 25.9, 25.5, 24.8, 22.8, 22.7, 18.5, –5.1; NMR signals discerned for the minor isomer: ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.73 (d, *J* = 11.8 Hz, 1H), 5.26 (dt, *J* = 11.8, 7.4 Hz, 1H), 2.24 (q, *J* = 6.6 Hz, 2H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 135.6, 131.8, 129.7, 127.3, 30.3, 29.9, 29.2, 29.1, 25.8, 25.7, 23.1, 22.3; HRMS (ESI): 331.2414, $[C_{19}H_{36}OSiNa]^+$ requires 331.2433.

((7*E*,9*E*)-Deca-7,9-dienyl-1-oxy)-*tert*-butyldimethylsilane (4.23)

Sulfone **4.21** (3.9 g, 9.0 mmol) and acrolein (0.48 mL, 4.2 mmol) in THF (50 mL) with KHMDS (11.0 mL, 5.5 mmol) gave a crude product that was purified by flash chromatography (5% Et_2O/pentane) to yield **4.23** (450 mg, 51%, *E:Z*/4:1) as a clear colorless oil: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.31 (dt, *J* = 17.0, 10.3 Hz, 1H), 6.04 (dd, *J* = 15.2, 10.3 Hz, 1H), 5.70 (dt, *J* = 14.8, 7.3 Hz, 1H), 5.08 (d, *J* = 16.9 Hz, 1H), 4.95 (d, *J* = 10.1 Hz, 1H), 3.60 (t, *J* = 6.6 Hz, 2H), 2.08 (q, *J* = 7.2 Hz, 2H), 1.53-1.48 (m, 2H), 1.41-1.38 (m, 2H), 1.33-1.31 (m, 4H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 137.5, 135.7, 131.1, 114.7, 63.4, 33.0, 32.6, 29.33, 29.14, 26.1, 25.8,

18.5, -5.1; NMR signals discerned for the minor isomer: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.64 (dt, *J* = 17.0, 10.6 Hz, 1H), 5.45 (q, *J* = 9.2 Hz, 1H), 5.17 (d, *J* = 17.3 Hz, 1H), 2.18 (q, *J* = 7.3 Hz, 2H); HRMS (ESI): 291.2111, $[C_{16}H_{32}OSiNa]^+$ requires 291.2120.

((7*E*,9*E*)-Undeca-7,9-dienyl-1-oxy)-*tert*-butyldimethylsilane (4.25)



Sulfone **4.21** (2.1 g, 4.8 mmol) and crotonaldehyde (0.6 mL, 7.3 mmol) in THF (50 mL) with KHMDS (15.0 mL, 7.5 mmol) gave a crude product that was purified by flash chromatography (5% Et_2O/pentane) to yield **4.25** (1.3 g, 96%, *E:Z*/4:1) as a clear colorless oil: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.09-5.98 (m, 2H), 5.64-5.55 (m, 2H), 3.63 (t, *J* = 6.6 Hz, 2H), 2.08 (q, *J* = 7.2 Hz, 2H), 1.76 (d, *J* = 6.6 Hz, 3H), 1.56-1.51 (m, 2H), 1.43-1.40 (m, 2H), 1.37-1.33 (m, 4H), 0.93 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 132.3, 131.9, 130.4, 126.8, 63.4, 33.0, 32.7, 29.6, 29.1, 26.1, 25.8, 18.5, 18.1, -5.1; NMR signals discerned for the minor isomer: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.39-6.33 (m, *J* = 1.4 Hz, 1H), 5.70 (dq, *J* = 14.7, 7.2 Hz, 1H), 5.32 (q, *J* = 9.4 Hz, 1H), 2.19 (q, *J* = 7.0 Hz, 2H), 1.81 (d, *J* = 6.8 Hz, 3H) ^{13}C NMR (126 MHz; $CDCl_3$): δ 129.2, 128.4, 125.5, 25.9, 14.3; HRMS (ESI): 305.2283, $[C_{17}H_{34}OSiNa]^+$ requires 305.2277. The spectral data for the minor compound are consistent with the literature.[121]

4.8.5 General procedure for the removal of *tert*-butyldimethyl silyl protecting group

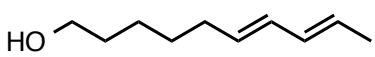
The silylether (1 equiv) was dissolved in THF and treated with a 1M solution of TBAF (2 equiv) in THF. The reaction mixture was stirred for 1 h, and then the reaction was quenched with saturated $NH_4Cl_{(aq)}$. The phases were separated and the aqueous

phase was extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum.

(*E*)-6,8-Nonadien-1-ol (4.27)

Silylether **4.22** (908 mg, 3.56 mmol) with TBAF (7.0 mL, 7.0 mmol) in THF (20 mL) gave a crude product that was purified by flash chromatography (30% EtOAc/hexane) to yield **4.27** (472 mg, 94%, *E:Z*/5:1) as a clear colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.26 (dt, *J* = 16.9, 10.2 Hz, 1H), 6.00 (1H, dd, *J* = 15.2, 10.4 Hz), 5.66 (1H, dt, *J* = 15.2, 7.0 Hz,), 5.04 (1H, d, *J* = 15.8 Hz,), 4.91 (1H, d, *J* = 10.0 Hz), 3.66 (2H, t, *J* = 6.6 Hz), 2.12 (2H, quintet, *J* = 6.6 Hz), 1.63-1.57 (2H, m), 1.49-1.36 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 137.3, 135.3, 131.1, 114.9, 63.0, 32.7, 32.5, 29.0, 25.4. NMR signals discerned for the minor isomer: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.67 (dtd, *J* = 16.9, 10.2, 1.0 Hz, 1H), 5.49 (q, *J* = 9.1 Hz, 1H), 5.22 (d, *J* = 16.9 Hz, 1H), 2.24 (q, *J* = 6.9 Hz, 2H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 132.7, 132.2, 129.4, 116.9, 29.4, 27.7; HRMS (ESI): 163.1094, $[C_9H_{16}ONa]^+$, requires 163.1093. The spectral data are consistent with the literature.[122]

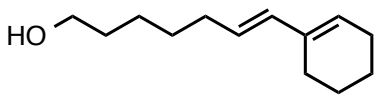
6*E*,8*E*-Decadien-1-ol (4.29)



Silylether **4.24** (1.0 g, 3.7 mmol) with TBAF (5.0 mL, 5.0 mmol) in THF (10 mL) gave a crude product that was purified by flash chromatography (20% EtOAc/hexane) to yield **4.29** (427 mg, 75%, *E:Z*/3:1) as a clear, slightly yellow, oil: ^{1}H

NMR (500 MHz, $CDCl_3$): δ 6.04-5.92 (m, 2H), 5.60-5.51 (m, 2H), 3.60 (t, *J* = 6.6 Hz, 2H), 2.05 (q, *J* = 7.1 Hz, 2H), 1.73-1.72 (d, *J* = 6.5 Hz, 3H), 1.52 (dt, *J* = 14.7, 7.3 Hz, 2H), 1.42-1.29 (m, 4H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 131.9, 131.7, 130.6, 127.0, 63.1, 32.8, 32.6, 29.3, 25.4, 18.2; NMR signals discerned for the minor isomer: ^1H NMR (500 MHz; $CDCl_3$): δ 6.38-6.32 (m, *J* = 1.6, 1.2 Hz, 1H), 5.71 (dq, *J* = 14.5, 7.1 Hz, 1H), 5.32 (dt, *J* = 10.8, 7.6 Hz, 1H), 2.21 (q, *J* = 6.8 Hz, 2H), 1.81 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 129.6, 129.3, 128.8, 127.1, 32.8, 29.6, 27.7, 25.5, 18.5 HRMS (ESI): 177.1257, $[C_{10}H_{18}ONa]^+$ requires 177.1255. The spectral data are consistent with the literature.[123]

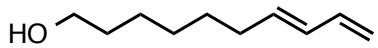
(6*E*)-7-(1-Cyclohexene)-6-heptene-1-ol (4.31)



Silylether **4.26** (450 mg, 1.46 mmol) with TBAF (2.0 mL, 2.0 mmol) in THF (5 mL) gave a crude product that was purified by flash chromatography (20% EtOAc/hexane) to yield **4.31** (250 mg, 88%) as a clear yellow oil: ^1H NMR (500 MHz, $CDCl_3$): δ 6.02 (d, *J* = 15.6 Hz, 1H), 5.63 (m, 1H), 5.53 (dt, *J* = 15.6, 7.0 Hz, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.13-2.08 (m, 5H), 1.67-1.64 (m, 2H), 1.61-1.55 (m, 5H), 1.44-1.35 (m, 4H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 135.7, 133.7, 127.3, 126.5, 63.0, 32.9, 32.7, 29.6, 25.8, 25.4, 24.7, 22.7, 22.7; NMR signals discerned for the minor isomer: ^1H NMR (500 MHz; $CDCl_3$): δ 5.72 (d, *J* = 11.7 Hz, 1H), 5.24 (dt, *J* = 11.8, 7.3 Hz, 1H), 2.24 (q, *J* = 6.5 Hz, 2H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 135.5, 131.9, 129.4, 127.3,

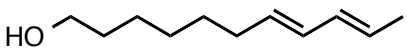
30.2, 29.13, 28.96, 25.69, 25.53, 23.0, 22.2; HRMS (ESI): 217.1565, $[C_{13}H_{22}ONa]^+$ requires 217.1568.

(*E*)-7,9-Decadien-1-ol (4.28)



Silylether **4.23** (908 mg, 3.38 mmol) with TBAF (7.0 mL, 7.0 mmol) in THF (20 mL) gave a crude product that was purified by flash chromatography (30% EtOAc/hexane) to yield **4.28** (472 mg, 94%, *E:Z*/5:1) as a clear colorless oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.34 (dt, *J* = 17.0, 10.2 Hz, 1H), 6.08 (dd, *J* = 15.0, 10.3 Hz, 1H), 5.73 (dt, *J* = 14.9, 7.3 Hz, 1H), 5.12 (d, *J* = 16.9 Hz, 1H), 4.99 (d, *J* = 10.1 Hz, 1H), 3.69-3.66 (m, 2H), 2.12 (q, *J* = 7.1 Hz, 2H), 1.64-1.58 (m, 2H), 1.48-1.30 (m, 6H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 137.3, 135.4, 131.0, 114.7, 63.0, 32.7, 32.5, 29.13, 28.96, 25.6; NMR signals discerned for the minor isomer: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.67 (dt, *J* = 16.8, 10.6 Hz, 1H), 5.48 (q, *J* = 9.2 Hz, 1H), 5.21 (d, *J* = 16.7 Hz, 1H), 2.23 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 132.8, 132.3, 129.2, 116.8, 29.5, 27.6; HRMS (ESI): 177.1260, $[C_{10}H_{18}ONa]^+$ requires 177.1255.

7*E*,9*E*-Undecadien-1-ol (4.30)



Silylether **4.25** (1.3 g, 4.6 mmol) with TBAF (10.0 mL, 10.0 mmol) in THF (15 mL) gave a crude product that was purified by flash chromatography (30% Et_2O/pentane) to yield **4.30** (723 mg, 93%, *E:Z*/4:1) as a clear colorless oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.08-5.96 (m, 2H), 5.64-5.55 (m, *J* = 6.7 Hz, 2H), 3.67 (t, *J* = 6.4

Hz, 2H), 2.09 (q, *J* = 7.0 Hz, 2H), 1.76 (d, *J* = 6.5 Hz, 3H), 1.61-1.57 (m, 2H), 1.47-1.34 (m, 6H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 132.1, 131.8, 130.5, 126.9, 63.2, 32.9, 32.6, 29.5, 29.1, 25.8, 18.1 NMR signals discerned for the minor isomer: ^{1}H NMR (500 MHz; CDCl3): δ 6.38-6.33 (m, 1H), 5.74-5.66 (m, 1H), 5.34-5.29 (m, 1H), 2.22-2.17 (m, 2H), 1.81 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 129.8, 129.7, 128.7, 127.2, 29.8, 29.2, 27.7, 18.4. HRMS (ESI): 191.1414, $[C_{11}H_{20}ONa]^+$ requires 191.1412. The spectral data are consistent with the literature.[105]

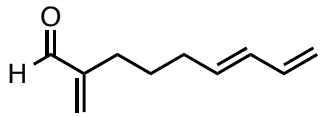
4.8.6 General procedure for the preparation of α,β-unsaturated aldehydes.

Oxalyl chloride (3 equiv) was dissolved in CH_2Cl_2 (0.3 M wrt oxalyl chloride) and cooled to –78 ºC (EtOAc/$N_{2(l)}$ bath). Dimethylsulfoxide (DMSO) (4 equiv) was added slowly to the cold solution, which was stirred for 15 minutes. The diene was dissolved in CH_2Cl_2 (0.5 M) and added to the cold stirring mixture. After stirring for 30 min at –78 ºC, NEt_3 (10 equiv) was added, the mixture was stirred for a further 5 min at –78 ºC, then warmed to 0 ºC and stirred for 20 min. The reaction was quenched by addition of saturated aqueous NH_4Cl and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (×3), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was used immediately in the next step without further purification.

Following the procedure of Pihko, aldehyde (1 equiv) and aqueous formaldehyde (>1 equiv) were dissolved in *i*-PrOH[111] or CH_2Cl_2.[112] Catalytic amounts of propionic acid or 4-dimethylaminobenzoic acid (0.10 equiv) and pyrrolidine (0.10 equiv) were added, and the mixture was stirred at 45 ºC for 45 min. The reaction was

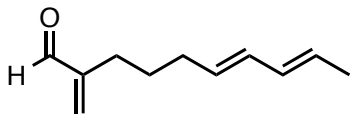
quenched with a saturated $NaHCO_{3(aq)}$, and the solution was extracted with CH_2Cl_2 (×3). The combined organic extracts were dried over anhydrous $NaSO_4$, filtered and concentrated under vacuum.

(6*E*)-2-Methylene-6,8-nonadien-1-al (4.37)



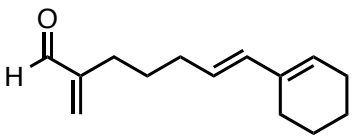
Alcohol **4.27** (304 mg, 2.17 mmol) was oxidized to the corresponding aldehyde using oxalyl chloride (0.55 mL, 6.4 mmol), DMSO (0.60 mL, 8.4 mmol), and triethylamine (1.5 mL, 10.8 mmol). The crude material was treated with 38% aqueous formaldehyde (0.2 mL, 2.8 mmol), 4-dimethylaminobenzoic acid (40 mg, 0.24 mmol), and pyrrolidine (25 μL, 0.24 mmol). Purification by flash chromatography (10% Et_2O/pentane) yielded **4.37** (173 mg, 55% over two steps) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.54 (1H, s), 6.31 (1H, dt, *J* = 17.0, 10.3 Hz), 6.26 (1H, d, *J* = 0.6 Hz), 6.06 (1H, dd, *J* = 15.2, 10.4 Hz), 6.01 (1H, d, *J* = 0.4 Hz), 5.69 (1H, dt, *J* = 14.9, 7.3 Hz), 5.10 (1H, d, *J* = 16.5 Hz), 4.97 (1H, d, *J* = 10.2 Hz), 2.26 (2H, t, *J* = 7.7 Hz), 2.11 (2H, q, *J* = 7.1 Hz), 1.57 (2H, m); ^{13}C NMR (126 MHz; $CDCl_3$): δ 194.8, 150.2, 137.3, 134.5, 134.2, 131.7, 115.2, 32.2, 27.5, 27.4; NMR signals discerned for the minor isomer: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.65-6.57 (m, 1H), 5.46-5.41 (m, 1H), 5.19 (d, *J* = 16.9 Hz, 1H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 150.2, 134.2, 132.3, 132.0, 129.9, 117.3, 27.8, 27.5; HRMS (ESI): 173.0931, $[C_{10}H_{14}ONa]^+$ 173.0937. The spectral data are consistent with the literature.[105]

(6*E*,8*E*)-2-Methylene-6,8-decadien-1-al (4.39)



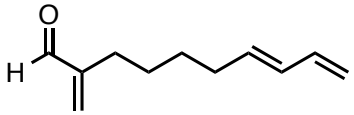
Alcohol **4.29** (762 mg, 4.9 mmol) was oxidized to the corresponding aldehyde using oxalyl chloride (1.3 mL, 15.0 mmol), DMSO (1.4 mL, 20.0 mmol), and triethylamine (3.5 mL, 25.1 mmol). The crude material was treated with 38% aqueous formaldehyde (0.4 mL, 5.5 mmol), 4-dimethylaminobenzoic acid (59 mg, 0.36 mmol), and pyrrolidine (27 μL, 0.33 mmol). Purification by flash chromatography (10% Et_2O/pentane) yielded **4.39** (215 mg, 40% over two steps) as a clear colorless oil: ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.53 (s, 1H), 6.24 (s, 1H), 6.04-5.94 (m, 3H), 5.61-5.49 (m, 2H), 2.25 (t, *J* = 7.9 Hz, 2H), 2.07 (q, *J* = 7.2 Hz, 2H), 1.72 (d, *J* = 6.6 Hz, 3H), 1.54 (quintet, *J* = 7.5 Hz, 2H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 194.8, 150.3, 134.1, 131.7, 131.1 (2C), 127.3, 32.2, 27.65, 27.48, 18.1; NMR signals discerned for the minor isomer: ^{1}H NMR (500 MHz; CDCl3): δ 5.67 (dd, *J* = 15.0, 7.2 Hz, 1H), 5.26 (q, *J* = 9.1 J Hz, 1H), 2.18 (q, *J* = 7.5 Hz, 3H), 1.77 (d, *J* = 6.7 Hz, 3H) ^{13}C NMR (126 MHz; $CDCl_3$): δ 150.3, 134.2, 129.3, 128.8, 127.0, 28.0, 27.55, 27.37, 18.4; HRMS (ESI): 187.1096, $[C_{11}H_{16}ONa]^+$ requires 187.1093.

(6*E*)-7-(1-Cyclohexene)-2-methylene-6-hepten-1-al (4.41)



Alcohol **4.31** (810 mg, 4.17 mmol) was oxidized to the corresponding aldehyde using oxalyl chloride (1.1 mL, 12.8 mmol), DMSO (1.2 mL, 16.9 mmol), and triethylamine (5.8 mL, 41.6 mmol). The crude material was treated with 38% aqueous formaldehyde (0.3 mL, 4.2 mmol), propionic acid (30 μL, 0.40 mmol), and pyrrolidine (30 μL, 0.37 mmol). Purification by flash chromatography (5% EtOAc/hexane) yielded **4.41** (546 mg, 64% over two steps) as a clear yellow oil: ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.53 (s, 1H), 6.24 (d, *J* = 0.8 Hz, 1H), 6.02 (d, *J* = 15.7 Hz, 1H), 5.99 (s, 1H), 5.51 (dt, *J* = 15.4, 7.4 Hz, 1H), 2.25 (t, *J* = 7.4 Hz, 2H), 2.12-2.07 (m, 6H), 1.66-1.63 (m, 2H), 1.60-1.51 (m, 4H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 194.8, 150.3, 135.6, 134.20 (2C), 127.6, 125.7, 32.5, 27.8, 27.4, 25.9, 24.7, 22.8, 22.7; NMR signals discerned for the minor isomer: ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.75 (d, *J* = 12.3 Hz, 1H), 5.60 (s, 1H), 5.24 (dt, *J* = 11.7, 7.3 Hz, 1H) ^{13}C NMR (126 MHz; $CDCl_3$): δ 194.8, 150.3, 135.4, 132.4, 128.7, 127.5, 29.1, 28.58, 28.47, 27.5, 25.7, 23.0, 22.2 HRMS (ESI): 227.1406, $[C_{14}H_{20}ONa]^+$ requires 227.1412.

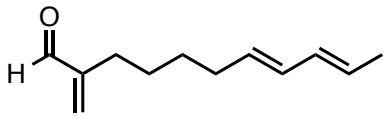
(7*E*)-2-Methylene-7,9-decadien-1-al (4.38)



Alcohol **4.28** (680 mg, 4.41 mmol) was oxidized to the corresponding aldehyde using oxalyl chloride (1.2 mL, 14.0 mmol), DMSO (1.6 mL, 22.5 mmol), and triethylamine (3.1 mL, 22.2 mmol). The crude material was treated with 38% aqueous formaldehyde (0.24 mL, 3.31 mmol), propionic acid (21 μL, 0.28 mmol), and pyrrolidine (23 μL, 0.28 mmol) in *i*PrOH (0.3 mL). Purification by flash

chromatography (10% Et_2O/pentane) yielded **4.38** (217 mg, 34% over two steps) as a clear colorless oil: ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.57 (s, 1H), 6.34 (dt, *J* = 17.0, 10.2 Hz, 1H), 6.28 (s, 1H), 6.08 (dd, *J* = 15.1, 10.4 Hz, 1H), 6.02 (s, 1H), 5.72 (dt, *J* = 14.9, 7.3 Hz, 1H), 5.12 (d, *J* = 16.7 Hz, 1H), 4.99 (d, *J* = 10.2 Hz, 1H), 2.29 (t, *J* = 7.3, 2H), 2.14 (q, *J* = 7.0, 2H), 1.54-1.42 (m, 4H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 194.8, 150.4, 137.4, 135.1, 134.1, 131.3, 115.0, 32.4, 29.0, 27.8, 27.5; NMR signals discerned for the minor isomer: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.66 (dt, *J* = 16.9, 10.6 Hz, 1H), 5.47 (q, *J* = 9.2 Hz, 1H), 5.22 (d, *J* = 16.8 Hz, 1H), 2.23 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 132.53, 132.35, 129.6, 117.1, 29.3, 27.6; HRMS (ESI): 187.1204, $[C_{11}H_{16}ONa]^+$ requires 187.1099.

(7*E*,9*E*)-2-Methylene-7,9-undecadien-1-al (4.40)

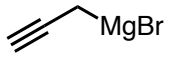


Alcohol **4.30** (855 mg, 5.08 mmol) was oxidized to the corresponding aldehyde using oxalyl chloride (0.88 mL, 10.3 mmol), DMSO (1.1 mL, 15.5 mmol), and triethylamine (3.6 mL, 25.8 mmol). The crude material was treated with 38% aqueous formaldehyde (0.40 mL, 5.5 mmol), 4-dimethylaminobenzoic acid (127 mg, 0.77 mmol), and pyrrolidine (27 μL, 0.33 mmol). Purification by flash chromatography (10% Et_2O/pentane) yielded **4.40** (465 mg, 51% over two steps) as a clear colorless oil: ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.53 (s, 1H), 6.23 (s, 1H), 6.04-5.94 (m, 3H), 5.60-5.49 (m, *J* = 7.0 Hz, 2H), 2.24 (t, *J* = 7.4 Hz, 2H), 2.06 (q, *J* = 7.1 Hz, 2H), 1.72 (d, *J* = 6.5 Hz, 3H), 1.50-1.36 (m, 4H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 194.8, 150.4, 134.1, 131.7

(2C), 130.7, 127.1, 32.4, 29.2, 27.8, 27.4, 18.1; NMR signals discerned for the minor isomer: ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.54 (s, 1H), 6.31-6.28 (m, 1H), 5.67 (td, J = 14.2, 7.4, 1H), 5.26 (dt, J = 10.7, 7.7, 1H), 2.17 (q, J = 7.0, 2H), 1.77 (d, J = 6.7, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 134.1, 129.4, 129.0, 127.1, 32.7, 29.5, 27.8, 27.5, 18.4. HRMS (ESI): 201.1249, $[C_{12}H_{18}ONa]^+$ requires 201.1255.

4.8.7 General procedure for the synthesis of homopropargyl alcohols

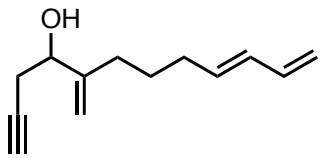
2-Propynyl Magnesium Bromide



Following the procedure of Sondheimer *et al.*,[124] magnesium turnings (0.486 g, 19.99 mmol) and $HgCl_2$ (30 mg, 0.11 mmol) were combined and stirred in Et_2O (3 mL). Propargyl bromide (0.30 mL, 2.7 mmol) was added to the reaction vessel, which was gently warmed until commencement of the reaction (vigorous bubbling of the solution). Another 0.70 mL of propargyl bromide (7.3 mmol) were dissolved in Et_2O (7 mL) and added dropwise to the stirring mixture. After stirring for 2 h the solution was diluted with Et_2O (10 mL) and was used without purification.

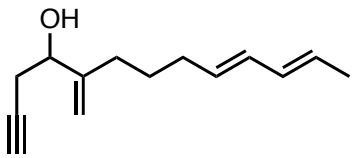
The aldehyde (1 equiv) was dissolved in Et_2O, cooled to 0 ºC and treated with 1.0 mL aliquots of the previously prepared Grignard reagent every 15 min until complete consumption of the aldehyde was observed by TLC. The reaction was quenched with saturated aqueous NH_4Cl. The phases were separated and the aqueous layer was extracted Et_2O (×3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum.

(9*E*)-5-Methylene-9,11-dodecadien-1-yn-4-ol (4.46)



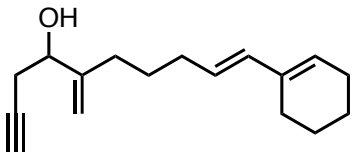
Aldehyde **4.37** (173 mg, 1.15 mmol) was treated with the Grignard reagent (1.5 mL) in Et_2O (10 mL). The crude product was purified by flash chromatography (20% EtOAc/hexane) to yield **4.46** (134 mg, 64%, *E:Z*/7:1) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.30 (dt, *J* = 17.0, 10.3 Hz, 1H), 6.05 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.69 (dt, *J* = 15.2, 7.0 Hz, 1H), 5.13 (s, 1H), 5.09 (d, *J* = 16.4 Hz, 1H), 4.96 (d, *J* = 10.6 Hz, 1H), 4.93 (s, 1H), 4.24 (m, 1H), 2.53 (ddd, *J* = 16.8, 4.9, 2.7 Hz, 1H), 2.45 (ddd, *J* = 16.7, 7.3, 2.6 Hz, 1H), 2.11 (m, 4H), 2.06 (t, *J* = 2.6 Hz, 1H), 1.59 (quintet, *J* = 7.6 Hz, 2H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 149.5, 137.3, 134.8, 131.5, 115.1, 110.7, 80.8, 72.8, 71.0, 32.3, 31.3, 27.5, 26.5; NMR signals discerned for the minor isomer: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.66-6.58 (m, *J* = 10.2, 1.0 Hz, 1H), 5.44 (q, *J* = 9.0 Hz, 1H), 5.18 (d, *J* = 16.8 Hz, 1H), 2.22 (q, *J* = 7.5 Hz, 2H) ^{13}C NMR (126 MHz; $CDCl_3$): δ 149.5, 132.3, 129.8, 117.2, 31.3, 27.8; HRMS (ESI): 213.1242, $[C_{13}H_{18}O]^+$ requires 213.1250.

(9*E*,11*E*)-5-Methylene-9,11-tridecadien-1-yn-4-ol (4.48)



Aldehyde **4.39** (207 mg, 1.26 mmol) was treated with the Grignard reagent (3 mL) in Et_2O (15 mL). Purification by flash chromatography (20% Et_2O/pentane) yielded **4.48** (188 mg, 71%, *E:Z*/4:1) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.03-5.99 (m, 2H), 5.60-5.52 (m, 2H), 5.13 (s, 1H), 4.93 (s, 1H), 4.24 (m, 1H), 2.53 (ddd, *J* = 16.8, 4.9, 2.7 Hz, 1H), 2.45 (ddd, *J* = 16.8, 7.4, 2.7 Hz, 1H), 2.11-2.06 (m, 3H), 2.03 (t, *J* = 2.3 Hz, 1H), 1.73 (d, *J* = 6.4 Hz, 3H), 1.61-1.54 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.7, 131.7, 131.4, 131.0, 127.3, 110.6, 80.8, 72.9, 71.0, 32.4, 31.4, 27.8, 26.5, 18.2; NMR signals discerned for the minor isomer: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.33-6.28 (m, 1H), 5.68 (dq, *J* = 14.6, 7.1 Hz, 1H), 5.28 (dt, *J* = 10.7, 7.6 Hz, 1H), 5.14 (s, 1H), 4.94 (s, 1H), 2.20 (q, *J* = 7.2 Hz, 2H), 1.77 (d, *J* = 7.7 Hz, 3H) ^{13}C NMR (126 MHz; $CDCl_3$): δ 149.6, 129.6, 129.20, 129.12, 127.0, 72.9, 28.0, 27.5, 18.5; HRMS (ESI): 227.1414, $[C_{14}H_{20}ONa]^+$ requires 227.1406.

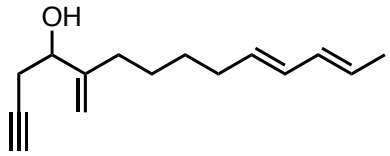
(9*E*)-10-(1-Cyclohexene)-5-methylene-9-decen-1-yn-4-ol (4.43)



Aldehyde **4.41** (60 mg, 0.29 mmol) was treated with the Grignard reagent (1 mL) in Et_2O (3 mL). Purification by flash chromatography (20% EtOAc/hexane) yielded **4.43** (41 mg, 56%, *E:Z*/4:1) as a clear yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.02 (d, *J* = 15.6 Hz, 1H), 5.63-5.61 (m, 1H), 5.52 (dt, *J* = 15.7, 6.9 Hz, 1H), 5.12 (s, 1H), 4.93 (s, 1H), 4.23 (m, 1H), 2.52 (ddd, *J* = 16.7, 4.9, 2.7 Hz, 1H), 2.44 (ddd, *J* = 16.8, 7.3, 2.6 Hz, 1H), 2.11 (m, 8H), 2.06 (t, *J* = 2.7 Hz, 1H), 1.65 (m, 2H), 1.60-1.53

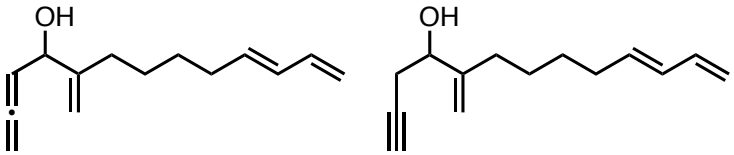
(m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.8, 135.6, 134.1, 127.5, 126.0, 110.5, 80.8, 72.8, 71.0, 32.7, 31.4, 28.0, 26.5, 25.9, 24.7, 22.7 (2C); NMR signals discerned for the minor isomer: ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.74 (t, *J* = 10.5 Hz, 1H), 5.28-5.22 (m, 1H), 3.78-3.72 (m, 2H), 2.33-2.23 (m, 4H); ^{13}C NMR (126 MHz; CDCl3): δ 135.7, 133.8, 127.3, 126.4, 81.0, 70.9, 69.9, 36.2, 32.8, 29.7, 27.5, 25.3; HRMS (ESI): 267.1731, $[C_{17}H_{24}ONa]^+$ requires 267.1719.

(10*E*,12*E*)-5-Methylene-10,12-tetradecadien-1-yn-4-ol (4.49)



Aldehyde **4.39** (207 mg, 1.16 mmol) was treated with the Grignard reagent (3 mL) in Et_2O (15 mL). Purification by flash chromatography (20% Et_2O/pentane) yielded **4.49** (188 mg, 71%, *E:Z*/4:1) as a clear colorless oil: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.08-5.97 (m, 2H), 5.65-5.55 (m, 2H), 5.15 (s, 1H), 4.96 (s, 1H), 4.28 (dt, *J* = 7.7, 4.1 Hz, 1H), 2.57 (ddd, *J* = 16.7, 4.8, 2.6 Hz, 1H), 2.49 (ddd, *J* = 16.7, 7.4, 2.6 Hz, 1H), 2.15-2.09 (m, 3H), 2.07-2.03 (m, 2H), 1.78-1.76 (m, 3H), 1.57-1.50 (m, 2H), 1.49-1.43 (m, 2H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 149.9, 131.80, 131.78, 130.7, 127.0, 110.5, 80.9, 72.8, 71.0, 32.5, 31.9, 29.4, 27.6, 26.6, 18.1; NMR signals discerned for the minor isomer: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.39-6.33 (m, 1H), 5.75-5.69 (m, 1H), 5.34-5.28 (m, 1H), 2.24-2.20 (m, 2H), 1.81 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 129.50, 129.37, 128.9, 127.1, 125.8, 31.9, 29.6, 27.7, 18.4; 241.1678, HRMS (ESI): $[C_{15}H_{22}ONa]^+$ requires 241.1568.

(10*E*)-5-Methylene-1,2,10,12-tridecatetraen-4-one (4.47a) and (10*E*)-5-methylene-10,12-tridecadien-1-yn-4-ol (4.47b)



Propargyl bromide (0.15 mL, 1.3 mmol) was added to a solution of $SnCl_2$ (281 mg, 1.48 mmol) and NaI (216 mg, 1.44 mmol) in DMF (3 mL), and the mixture was stirred for 1 h. The mixture was cooled to 0 ºC, and the aldehyde **4.38** (213 mg, 1.29 mmol) in DMF (1 mL) was added, and it was stirred 12 h. The reaction was quenched with water and the phases were separated. The aqueous phase was extracted with Et_2O (×2). The combined organic extracts were washed with water (×3), 5% aqueous LiCl, and brine, dried over Mg_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (10 % Et_2O/pentane) to yield **4.47a/b** as a mixture (192 mg, 72 %, 2:1 by 1H NMR integration). NMR signals for allene **4.47a**: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.31 (dt, *J* = 17.0, 10.2 Hz, 1H), 6.05 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.70 (dt, *J* = 14.9, 7.3 Hz, 1H), 5.24 (q, *J* = 6.6 Hz, 1H), 5.12 (s, 1H), 5.09 (d, *J* = 16.7 Hz, 1H), 4.96 (d, *J* = 10.1 Hz, 1H), 4.91 (dd, *J* = 2.4, 1.3 Hz, 1H), 4.90 (dt, *J* = 2.6, 1.4 Hz, 2H), 4.63-4.62 (m, 1H), 2.14-2.09 (m, 4H), 1.52-1.47 (m, 2H), 1.46-1.42 (m, 2H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 207.4, 150.5, 137.4, 135.3, 131.2, 114.9, 110.0, 94.0, 78.1, 72.9, 32.5, 31.7, 29.1, 27.6; NMR signals for homopropargyl alcohol **4.47b**: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.34 (dt, *J* = 17.0, 10.2 Hz, 1H), 6.09 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.73 (dt, *J* = 14.9, 7.3 Hz, 1H), 5.16 (s, 1H), 5.13 (d, *J* = 16.9 Hz, 1H), 4.99 (d, *J* = 10.1 Hz, 1H), 4.97 (s, 1H), 4.28 (dt, *J* = 7.7, 4.2 Hz, 1H), 2.57 (ddd, *J*

= 16.7, 4.9, 2.6 Hz, 1H), 2.49 (ddd, *J* = 16.7, 7.3, 2.6 Hz, 1H), 2.18-2.18 (m, 2H), 2.10 (t, *J* = 2.6 Hz, 1H), 2.08-2.02 (m, 2H), 1.57-1.51 (m, 2H), 1.50-1.45 (m, 2H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 149.8, 137.4, 135.2, 131.3, 114.9, 110.6, 80.8, 72.8, 71.0, 32.5, 31.8, 29.1, 27.6, 26.6; HRMS (ESI): 227.1410, $[C_{14}H_{20}ONa]^+$ requires 227.1412

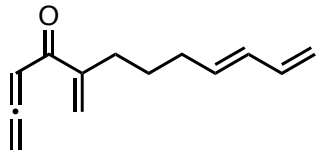
4.8.8 General procedures for the oxidation of homopropargyl alcohols to allenyl vinyl ketones

Procedure 1: The alcohol (1 equiv) was dissolved in CH_2Cl_2 (0.1 M) along with $NaHCO_{3(s)}$ (10 equiv). Dess-Martin periodinane (DMP) (1.3 equiv) was added, and the reaction mixture was stirred. After 1 hour the mixture was diluted with equal volumes of saturated solutions of $NaHCO_{3(aq)}$ and $Na_2S_2O_{3(aq)}$ and stirred until both layers were clear. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (×3). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was used without purification.

Procedure 2: The alcohol (1 equiv) was added to a stirring solution of IBX (2 equiv) in DMSO (1 M). After stirring for 1 h, water was added and the mixture was filtered. The filtrate was partitioned between EtOAc and water. The organic phase was washed with water (×3), and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was used without further purification.

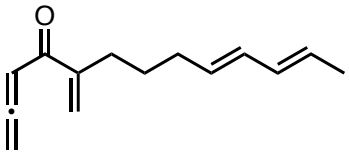
The crude ketone (1 equiv) was dissolved in CH_2Cl_2 (0.1 M) and treated with $K_2CO_{3(s)}$ (1.1 equiv). The mixture was stirred for 30 min then filtered. The residue was washed with CH_2Cl_2 and the combined organic filtrate was concentrated. The crude product was used without further purification.

(9*E*)-5-Methylene-1,2,9,11-dodecatetraen-4-one (4.50)



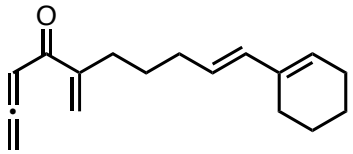
Following **Procedure 1**, **4.46** (80 mg, 0.42 mmol) was treated with $NaHCO_{3(s)}$ (336 mg, 4.00 mmol) and DMP (231 mg, 0.54 mmol). The resulting propargyl ketone was isomerized to **4.50** with K_2CO_3 (64 mg, 0.46 mmol). The crude product was used immediately in the next reaction.

(9*E*,11*E*)-5-Methylene-1,2,9,11-tridecatetraen-4-one (4.52)



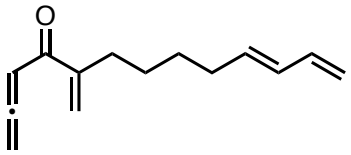
Following **Procedure 1**, **4.48** (80 mg, 0.39 mmol) was treated with $NaHCO_{3(s)}$ (386 mg, 4.59 mmol) and DMP (289 mg, 0.68 mmol). The resulting propargyl ketone was isomerized to **4.52** with K_2CO_3 (60 mg, 0.43 mmol). The crude product was used immediately in the next reaction.

(9*E*)-10-(1-Cyclohexene)-5-methylene-1,2,9-decatrien-4-one (4.45)



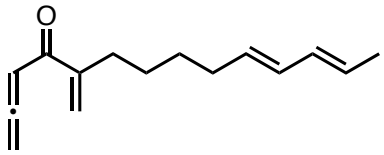
Following **Procedure 1**, **4.43** (14 mg, 0.05 mmol) was treated with $NaHCO_{3(s)}$ (42 mg, 0.50 mmol) and DMP (28 mg, 0.07 mmol). The resulting propargyl ketone was isomerized to **4.45** with K_2CO_3 (8 mg, 0.06 mmol). The crude product was used immediately in the next reaction.

(10*E*)-5-Methylene-1,2,10,12-tridecatetraen-4-one (4.51)



Following **Procedure 2**, **4.47a/b** (63 mg, 0.38 mmol) was oxidized with IBX (177 mg, 0.63 mmol). The resulting propargyl ketone was isomerized to **4.51** with K_2CO_3 (58 mg, 0.42 mmol).

(10*E*,12*E*)-5-Methylene-1,2,10,12-tetradecatetraen-4-one (4.53)



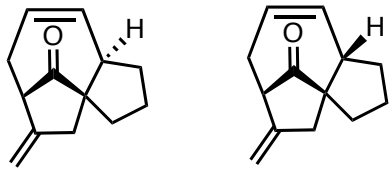
Following **Procedure 2**, **4.49** (76 mg, 0.37 mmol) was oxidized with IBX (196 mg, 0.70 mmol). The resulting propargyl ketone was isomerized to **4.53** with K_2CO_3 (54 mg, 0.39 mmol).

The isomerization products were identified from analysis of the crude NMR. Disappearance of the propargylic protons α to the ketone and the appearance of two new signals in the olefinic region confirmed the presence the allene.

4.8.9 General procedures for the Nazarov cyclization of AVKs with tethered 1,3-dienes

The AVK was dissolved in CH_2Cl_2 (0.1 M) and cooled to –78 ºC. BF_3•OEt_2 (2.0 equiv) was added, and the reaction mixture was stirred for 5 min. The reaction was quenched at –78 ºC by addition of saturated aqueous $NaHCO_3$, and it was allowed to come to rt. The phases were then separated and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

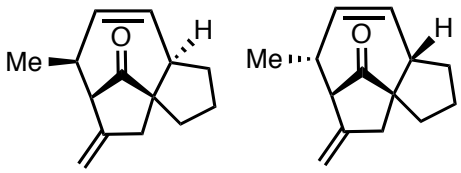
(3a*R,6*R**,9a*R**)-5-Methylene-1,2,3,4,5,6,7,9a-octahydro-3a,6-methanocyclopenta[8]annulen-10-one (4.54) and (3a*R**,6*R**,9a*R**)-5-methylene-1,2,3,4,5,6,7,9a-octahydro-3a,6-methanocyclopenta[8]annulen-10-one (4.55)**



Crude **4.50** (< 0.4 mmol) was treated with BF_3•OEt_2 (0.1 mL, 0.8 mmol). Purification by flash chromatography (3% EtOAc/hexane) yielded a **4.54** and **4.55** (2:1 mixture) (41 mg, 52% over three steps): NMR signals for the major isomer **4.54**: ^{1}H NMR (500 MHz; CDCl3): δ 5.63 (dddd, *J* = 12.9, 4.3, 2.6, 1.8 Hz, 1H), 5.39-5.34 (m, 1H), 5.10-5.09 (m, 1H), 5.04 (dt, *J* = 3.2, 1.5 Hz, 1H), 3.08-3.07 (m, 1H), 2.81-2.76 (m, 1H), 2.64 (ddd, *J* = 16.2, 3.0, 1.5 Hz, 1H), 2.58 (dddd, *J* = 17.9, 5.3, 2.7, 2.6 Hz, 1H), 2.42-2.35 (m, 2H), 2.33-2.28 (m, 1H), 1.94-1.84 (m, 2H), 1.65-1.61 (m, 2H), 1.36-1.27 (m, 1H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 219.3, 146.8, 129.7, 122.9, 107.6, 59.6, 51.4, 50.2, 44.2, 34.6, 33.6, 31.9, 23.4; NMR signals discerned for the minor isomer **4.55**: ^{1}H

NMR (500 MHz; $CDCl_3$): δ 5.73-5.66 (m, 2H), 4.94-4.93 (m, 1H), 4.90 (dd, *J* = 3.8, 1.9 Hz, 1H), 2.68-2.63 (m, 1H), 2.15-2.04 (m, 2H), 1.74-1.67 (m, 1H), 1.46 (ddd, *J* = 13.0, 8.7, 4.1 Hz, 1H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 221.6, 146.7, 131.3, 127.8, 107.8, 60.2, 54.4, 49.4, 39.7, 34.1, 33.1, 31.7, 22.4; HRMS (ESI): 211.095, $[C_{13}H_{16}ONa]^+$ requires 211.1099.

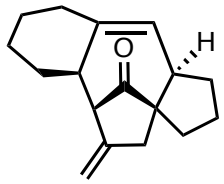
(3a*R,6*R**,7*R**,9a*S**)-7-Methyl-5-methylene-1,2,3,4,5,6,7,9a-octahydro-3a,6-methanocyclopenta[8]annulen-10-one (4.56) and (3a*R**,6*R**,7*S**,9a*R**)-7-methyl-5-methylene-1,2,3,4,5,6,7,9a-octahydro-3a,6-methanocyclopenta[8]annulen-10-one (4.57)**



Crude **4.49** (< 0.4 mmol) was treated with BF_3•OEt_2 (0.1 mL, 0.8 mmol). Purification by flash chromatography (3% EtOAc/hexane) yielded **4.56** and **4.57** (6:1 mixture) (30 mg, 38% over three steps). Pure **4.56** was obtained by careful flash chromatography using a 3% Et_2O/pentane elution system: NMR signals for the major isomer **4.56**: ^1H NMR (500 MHz; C_6D_6): δ 5.37 (ddd, *J* = 12.9, 4.5, 1.7 Hz, 1H), 5.18 (dddd, *J* = 12.9, 4.6, 2.0, 1.1 Hz, 1H), 4.91-4.89 (m, 1H), 4.83 (dt, *J* = 3.2, 1.6 Hz, 1H), 2.70 (d, *J* = 1.5 Hz, 1H), 2.40-2.34 (m, 2H), 2.32-2.27 (m, 1H), 2.21 (ddd, *J* = 16.4, 3.1, 1.6 Hz, 1H), 1.89-1.85 (m, 1H), 1.82-1.75 (m, 1H), 1.65-1.61 (m, 1H), 1.40-1.30 (m, 2H), 1.29-1.23 (m, 1H), 1.16 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz; C_6D_6): δ 215.8, 147.7, 129.8, 128.4, 107.4, 58.8, 55.9, 51.8, 43.6, 40.5, 35.1, 32.2, 23.3, 20.5; NMR

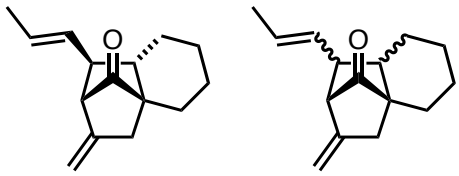
signals discerned for the minor isomer **4.57**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.63 (1H, dt, *J* = 11.7, 2.7 Hz), 5.42-5.38 (1H, m), 4.93-4.91 (2H, m), 2.77 (1H, br s), 2.60 (1H, dq, *J* = 17.6, 2.2 Hz), 2.41-2.35 (2H, m), 2.23 (1H, dt, *J* = 17.7, 2.5 Hz), 2.20-1.40 (4H, unresolved multiplets), 1.25 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (126 MHz; $CDCl_3$): δ 135.6, 130.7, 109.5, 61.6, 60.2, 50.5, 36.8, 32.9, 32.1, 29.8, 22.5, 21.3; HRMS 225.1260, (ESI): $[C_{14}H_{18}ONa]^+$ requires 225.1255.

(3a*R,6*R**,6a*S**,11a*S**)-5-Methylene-1,2,3,4,5,6,6a,7,8,9,10,11a-dodecahydro-3a,6-methanobenzo[*a*]cyclopenta[*d*][8]annulen-12-one (4.58)**



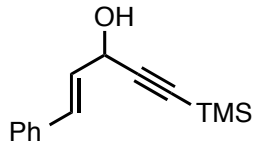
Crude **4.45** (< 0.05 mmol) was treated with BF_3•OEt_2 (0.01 mL, 0.08 mmol). Purification by flash chromatography (3% EtOAc/hexane) yielded a **4.58** (7 mg, 50% over three steps): ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.38 (d, *J* = 4.1 Hz, 1H), 5.07 (ddd, *J* = 3.5, 2.5, 1.6 Hz, 1H), 5.05 (dt, *J* = 3.4, 1.7 Hz, 1H), 2.78-2.76 (m, 1H), 2.76-2.71 (m, 1H), 2.62 (ddd, *J* = 16.2, 2.9, 1.5 Hz, 1H), 2.38-2.28 (m, 3H), 2.16-2.12 (m, 1H), 2.07-2.01 (m, 1H), 1.93-1.77 (m, 5H), 1.64-1.57 (m, 3H), 1.53-1.46 (m, J = 8.7, 4.0, 1H), 1.32-1.24 (m, 2H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 217.7, 147.2, 137.6, 122.2, 107.3, 59.5, 56.1, 52.4, 48.7, 44.2, 41.2, 35.8, 34.5, 31.9, 29.3, 27.3, 23.3. HRMS (ESI): 265.1565, $[C_{17}H_{22}ONa]^+$ requires 265.1568.

(1*R,2*R**,4a*R**,8a*R**)-3-Methylene-1-((*E*)-prop-1-en-1-yl)octahydro-1*H*-2,4a-methanonaphthalen-9-one (4.61) and (1ξ,2*R**,4a*R**,8aξ)-3-methylene-1-((*E*)-prop-1-en-1-yl)octahydro-1*H*-2,4a-methanonaphthalen-9-one (4.62)**



Crude **4.53** (< 0.3 mmol) was treated with BF_3•OEt_2 (0.1 mL, 0.8 mmol). Purification by flash chromatography (3% Et_2O/pentane) yielded **4.61** and **4.62** (9:1 mixture) (20 mg, 31% over three steps). ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.47 (dq, *J* = 15.1, 6.4 Hz, 1H), 5.33 (ddq, *J* = 15.1, 8.4, 1.5 Hz, 1H), 4.95 (t, *J* = 2.6 Hz, 1H), 4.75 (t, *J* = 2.1 Hz, 1H), 2.95 (dt, *J* = 17.0, 2.5 Hz, 1H), 2.40 (s, 1H), 2.21-2.13 (m, 2H), 1.86-1.78 (m, 2H), 1.69-1.62 (m, 5H), 1.56-1.45 (m, 2H), 1.42-1.37 (m, 1H), 1.29-1.14 (m, 2H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 212.8, 143.9, 132.7, 125.3, 105.5, 57.2, 49.5, 48.7, 45.8, 32.2, 26.9, 26.3, 25.3, 21.9, 17.9; HRMS (ESI): Submitted, $[C_{15}H_{20}ONa]^+$ requires 239.1412.

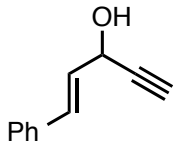
(1*E*)-1-Phenyl-5-(trimethylsilyl)-1-penten-4-yn-3-ol (4.68)



Ethynyltrimethylsilane (2.0 mL, 14.2 mmol) was dissolved in THF (20 mL) and cooled to –78 ºC. *n*-BuLi [2.5 M/Hexane] (5.7 mL, 14.3 mmol) was added slowly, and the mixture was stirred for 15 min. Cinnamaldehyde (1.6 mL, 12.7 mmol) was added

slowly and the mixture was allowed to warm slowly for 1 h. The reaction was quenched with saturated aqueous NH_4Cl. The phases were separated, and the organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to yield **4.68** (3.0 g, 99%). The crude material was used without further purification. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.41 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 15.8 Hz, 1H), 6.29 (dd, *J* = 15.8, 6.0 Hz, 1H), 5.04 (t, *J* = 5.7 Hz, 1H), 0.21 (s, 9H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 136.3, 132.2, 128.8, 128.26, 128.07, 127.0, 104.4, 91.5, 63.5, 0.0. The spectral data are consistent with the literature.[125]

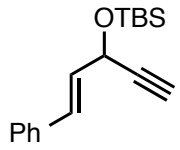
(1*E*)-1-Phenyl-1-penten-4-yn-3-ol (4.69)



Compound **4.68** (3.0 g, 13.0 mmol) was dissolved in MeOH (30 mL). K_2CO_3 (551 mg, 3.99 mmol) was added and the mixture was stirred for 1 h. The solvent was removed under reduced pressure, and the residue was partitioned between Et_2O and saturated aqueous NH_4Cl. The phases were separated, and the organic phase was washed with water, and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to yield **4.69** (1.9 g, 92%). The product was used without further purification. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.42 (d, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 6.81 (d, *J* = 15.8 Hz, 1H), 6.31 (dd, *J* = 15.8, 5.9 Hz, 1H), 5.07 (s, 1H), 2.65 (d, *J* = 2.0 Hz, 1H), 2.12 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (126 MHz;

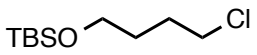
$CDCl_3$): δ 136.1, 132.4, 128.8, 128.4, 127.6, 127.0, 82.9, 74.8, 62.9. The spectral data was consistent with the literature.[126]

(1*E*)-3-(*tert*-Butyldimethylsilyloxy)-1-phenyl-1-penten-4-yne (4.70)



Compound **4.69** (1.9 g, 12.0 mmol) was dissolved in CH_2Cl_2 (30 mL). Imidazole (1.9 g, 27.9 mmol) and TBSCl (2.4 g, 15.9 mmol) were added, and the mixture was stirred for 2 h. The reaction was quenched with water. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (×2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude material was purified by flash chromatography (10% Et_2O/pentane) to yield **4.70** (2.9 g, 92 %). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.40 (d, J = 7.7 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.3 Hz, 2H), 6.72 (d, J = 15.8 Hz, 1H), 6.24 (dd, J = 15.7, 5.6 Hz, 1H), 5.08 (d, J = 5.1 Hz, 1H), 2.55 (s, 1H), 0.95 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 136.6, 130.7, 129.0, 128.7, 128.0, 126.9, 83.7, 73.7, 63.5, 26.0, 18.5, –4.4, –4.6.

4-Chloro-1-((tert-butyldimethylsilyl)oxy)butane (4.63)

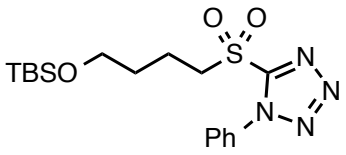


$LiAlH_4$ (4.0 g, 105.4 mmol) was suspended in Et_2O (140 mL), and the mixture was cooled to 0 ºC. Ethyl 4-chlorobutyrate (10.0 mL, 71.3 mmol) in Et_2O (10 mL) was

added slowly, and the mixture was stirred for 30 min. The reaction was quenched by the slow addition of water (4 mL), 1M NaOH (4 mL), and a further 12 mL of water. The mixture was filtered through Celite, and the filtrate was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude product was used without further purification.

The crude oil (6.5 g, 59.9 mmol) was dissolved in CH_2Cl_2 (130 mL). Imidazole (8.0 g, 117.5 mmol) and TBSCl (12.7 g, 84.3 mmol) were added, and the mixture was stirred for 2 h. The reaction was quenched with water. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (×2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude material was purified by flash chromatography (10% Et_2O/pentane) to yield **4.63** (12.5 g, 93 %). ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.65 (t, J = 6.2 Hz, 2H), 3.57 (t, J = 6.7 Hz, 2H), 1.85 (quintet, J = 6.9 Hz, 2H), 1.65 (quintet, J = 6.1 Hz, 2H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (126 MHz; $CDCl_3$): δ 62.4, 45.2, 30.2, 29.5, 26.1, 18.5, -5.2. The spectral data are consistent with the literature.[127]

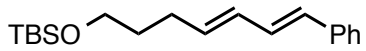
(6-(*tert*-Butyldimethylsilanyloxy)butanesulfonyl)-1-phenyl-5-1*H*-tetrazole (4.64)



Following the general procedure for sulfone synthesis: NaH (60% dispersion in mineral oil) (2.7 g, 67.5 mmol) was suspended in DMF (60 mL), 1-phenyl-1*H*-tetrazole-5-thiol (10.0 g, 56.1 mmol) in DMF (20 mL) was added, followed by **4.63** (12.5 g, 56.1

mmol) in DMF (20 mL). The crude sulfide was oxidized with *m*CPBA (≤ 77% purity, 18 g) in CH_2Cl_2 (200 mL). Purification by flash chromatography (20% EtOAc/Hexane) yielded **4.64** (8.0 g, 49% over two steps) as a pale yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.70-7.68 (m, 2H), 7.63-7.58 (m, 3H), 3.82-3.79 (m, 2H), 3.67 (t, *J* = 5.9 Hz, 2H), 2.09-2.03 (m, 2H), 1.74-1.69 (m, 2H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 153.7, 133.2, 131.6, 129.8, 125.2, 62.2, 56.1, 31.0, 26.07, 26.04, 19.3, 18.4, -5.2 HRMS (ESI): Submitted, $[C_{17}H_{28}N4O_3SSiNa]^+$ requires 419.1549.

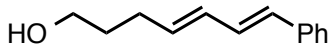
((4*E*,6*E*)-7-Phenyl-4,6-heptadienyl-1-oxy)-*tert*-butyldimethylsilane (4.65)



Sulfone **4.64** (2.1 g, 5.0 mmol) and *trans*-cinnamaldehyde (0.73 ml, 5.8 mmol) in THF (50 mL) were subjected to the general procedure for diene synthesis using KHMDS (15.0 mL, 7.5 mmol). The crude product was purified by flash chromatography (5% Et_2O/pentane) to yield **4.65** (1.1 g, 66%, *E:Z*/4:1) as a clear colorless oil. NMR signals for the major compound: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.38 (d, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 6.75 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.44 (d, *J* = 15.7 Hz, 1H), 6.22 (dd, *J* = 15.1, 10.5 Hz, 1H), 5.83 (dt, *J* = 14.8, 7.3 Hz, 1H), 3.64 (t, *J* = 6.4 Hz, 2H), 2.21 (q, *J* = 7.3 Hz, 2H), 1.66 (quintet, *J* = 7.0 Hz, 2H), 0.91 (s, 11H), 0.06 (s, 7H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 137.8, 135.4, 131.0, 130.2, 129.5, 128.7, 127.2, 126.3, 62.7, 32.6, 29.3, 26.1, 18.5, -5.1; NMR signals discerned for the minor compound: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.08 (dd, *J* = 15.6, 11.1, 1H), 6.53 (d, *J* = 15.6, 1H), 5.56-5.51 (m, 1H), 2.37 (q, *J* = 7.3, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 132.7, 132.2, 129.2, 127.5, 126.5, 24.5; Submitted, HRMS (ESI):

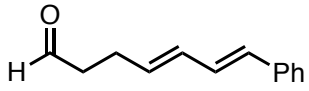
$[C_{19}H_{30}OSiNa]^+$ requires 325.1964. The spectral data was consistent with the literature.[128]

(4*E*,6*E*)-7-Phenyl-4,6-heptadien-1-ol (4.66)



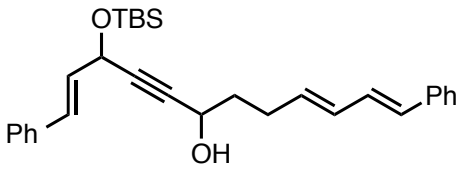
Silylether **4.65** (1.2 g, 3.7 mmol) was deprotected with TBAF (8.0 mL, 8.0 mmol) in THF (20 mL) following the general procedure. The crude product was purified by flash chromatography (30% EtOAc/hexane) to yield **4.66** (530 mg, 76%, *E:Z*/15:1) as a clear colorless oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.38 (d, *J* = 7.8 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.75 (dd, *J* = 15.7, 10.4 Hz, 1H), 6.46 (d, *J* = 15.7 Hz, 1H), 6.25 (dd, *J* = 14.9, 10.6 Hz, 1H), 5.84 (dt, *J* = 14.9, 7.3 Hz, 1H), 3.69 (t, *J* = 6.5 Hz, 2H), 2.26 (q, *J* = 7.3 Hz, 2H), 1.75-1.69 (m, 2H), 1.32 (s, 1H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 137.7, 134.8, 131.3, 130.6, 129.3, 128.7, 127.3, 126.3, 62.6, 32.4, 29.3. The spectral data was consistent with the literature.[128]

(4*E*,6*E*)-7-Phenyl-4,6-heptadien-1-al (4.67)



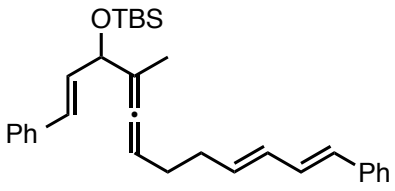
According to the general procedure for Swern oxidation: **4.66** (530 mg, 2.82 mmol) was oxidized using oxalyl chloride (0.70 mL, 8.2 mmol), DMSO (0.80 mL, 11.3 mmol), and triethylamine (2.0 mL, 14.3 mmol) provided **4.67** (468 mg, 90%). Product used without further purification.

(1*E*,9*E*,11*E*)-3-(*tert*-Butyldimethylsiloxy)-1,12-diphenyl-1,9,11-dodecatrien-4-yn-6-ol (4.71)



Compound **4.70** (768 mg, 2.82 mmol) was dissolved in THF (15 mL) and cooled to –78 ºC. *n*-BuLi [2.5 M/Hexane] (5.7 mL, 14.3 mmol) was added slowly and stirred for 15 min. **4.67** (468 mg, 2.51 mmol) was added slowly, and the mixture was allowed to warm slowly for 1 h. The reaction was quenched with saturated aqueous NH_4Cl. The phases were separated, and the organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (20% Et_2O/pentane) yielded **4.71** (967 mg, 81%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.40 (d, *J* = 7.7 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 6.9 Hz, 2H), 7.25 (t, *J* = 6.6 Hz, 1H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.77-6.68 (m, 2H), 6.44 (d, *J* = 15.7 Hz, 1H), 6.28-6.22 (m, 2H), 5.82 (dt, *J* = 14.8, 7.3 Hz, 1H), 5.13 (d, *J* = 5.5 Hz, 1H), 4.48 (d, *J* = 5.4 Hz, 1H), 2.35 (q, *J* = 7.4 Hz, 2H), 1.91-1.83 (m, 3H), 0.96 (s, 9H), 0.19 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (126 MHz; CDCl3): δ 137.6, 136.5, 134.0, 131.6, 130.8, 130.4, 129.2, 128.7, 128.0, 127.3, 126.9, 126.3, 86.3, 85.1, 63.7, 62.1, 37.2, 28.6, 26.0, 18.5, –4.3, –4.5; Submitted, HRMS (ESI): $[C_{30}H_{38}O_2SiNa]^+$ requires 481.2539.

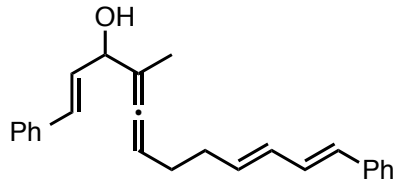
(1*E*,9*E*,11*E*)-3-(*tert*-Butyldimethylsiloxy)-1,12-diphenyl-1,4,5,9,11-dodecapentaene (4.72)



Propargyl alcohol **4.71** (637 mg, 1.39 mmol) was dissolved in Et_2O (15 mL) and cooled to 0 ºC. Triethylamine (0.4 mL, 2.9 mmol) and MsCl (0.25 mL, 3.2 mmol) were added dropwise, and the mixture was stirred for 1 h. CuCN (688 mg, 7.68 mmol) in Et_2O (10 mL) was cooled to 0 ºC, and MeLi [1.6 M/Et_2O] (5.0 mL, 8.0 mmol) was then added. The cuprate was then added dropwise to the mesylate solution. The mixture was allowed to warm to rt over 1 h and was then quenched with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted with Et_2O (×3). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography (10% Et_2O/pentane) provided **4.72** (540 mg, 85%, mixture of diastereomers) as a colorless oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ (two diastereomers) 7.40-7.35 (m, 4H), 7.32-7.27 (m, 4H), 7.24-7.18 (m, 2H), 6.77-6.72 (m, 1H), 6.59 (dd, *J* = 15.8, 7.0 Hz, 1H), 6.44 (dd, *J* = 15.7, 7.1 Hz, 1H), 6.25-6.18 (m, 2H), 5.84 (dq, *J* = 14.6, 7.1 Hz, 1H), 5.18-5.14 (m, 1H), 4.80-4.79 (m, 1H), 2.27 (q, *J* = 6.9 Hz, 2H), 2.17-2.12 (m, 2H), 1.67-1.65 (m, 3H), 0.94 (two s, 9H), 0.12-0.09 (m, 6H); ^{13}C NMR (126 MHz; $CDCl_3$): δ (two diastereomers) 201.47, 201.35, 137.79, 137.77, 137.3, 134.98, 134.96, 131.83, 131.75, 131.27, 131.23, 130.45, 130.44, 129.48, 129.45, 129.38, 129.36, 128.69, 128.67, 127.45, 127.26, 126.6, 126.3, 90.9, 90.6, 75.36, 75.16,

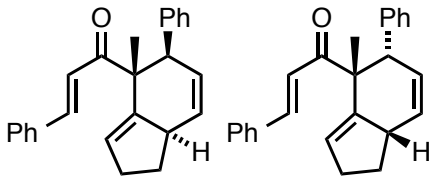
32.8, 32.5, 28.97, 28.87, 26.0, 18.56, 18.52, 14.0, 13.8, –4.57, –4.59, –4.62, –4.68; HRMS (ESI): 479.2758, $[C_{31}H_{40}OSiNa]^+$ requires 479.2741.

(1*E*,9*E*,11*E*)-1,12-Diphenyl-1,4,5,9,11-dodecapentaen-3-ol (4.73)



Silylether **4.71** (266 mg, 0.58 mmol) was deprotected with TBAF (1.0 mL, 1.0 mmol) in THF (5 mL) following the general procedure. The crude product was purified by flash chromatography (30% Et_2O/pentane) to yield **4.73** (171 mg, 86%, a mixture of diastereomers) as a clear colorless oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.40-7.36 (m, 4H), 7.33-7.28 (m, 4H), 7.24-7.18 (m, 2H), 6.75 (dd, *J* = 15.6, 10.5 Hz, 1H), 6.63 (d, *J* = 15.8 Hz, 1H), 6.45 (d, *J* = 15.7 Hz, 1H), 6.26-6.18 (m, *J* = 5.4 Hz, 2H), 5.84 (dt, *J* = 14.8, 7.2 Hz, 1H), 5.40-5.37 (m, 1H), 4.63 (dd, *J* = 17.5, 6.2 Hz, 1H), 2.30 (q, *J* = 7.0 Hz, 2H), 2.19 (q, *J* = 7.0 Hz, 2H), 1.93 (br s, 1H), 1.75 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ (two diastereomers) 199.80, 199.66, 137.7, 136.9, 134.67, 134.62, 131.48, 131.30, 131.22, 130.7, 130.35, 130.26, 129.3, 128.76, 128.69, 127.85, 127.83, 127.3, 126.72, 126.53, 126.34, 103.54, 103.42, 94.4, 94.2, 73.77, 73.68, 32.38, 32.34, 28.85, 28.81, 15.68, 15.54; Submitted, HRMS (ESI): $[C_{25}H_{26}ONa]^+$ requires 365.1881.

(*E*)-1-((4*R,5*R**,7a*R**)-4-Methyl-5-phenyl-2,4,5,7a-tetrahydro-1*H*-inden-4-yl)-3-phenylprop-2-en-1-one (4.74) and (*E*)-1-((4*R**,5*S**,7a*S**)-4-methyl-5-phenyl-2,4,5,7a-tetrahydro-1*H*-inden-4-yl)-3-phenylprop-2-en-1-one (4.75)**



Allene **4.73** (55 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (1.5 mL). MnO_2 (533 mg, 6.13 mmol) was added and the mixture was stirred for 2.5 h. The mixture was then filtered, and the filtrate was concentrated under vacuum. Purification by flash chromatography (10% Et_2O/pentane) yielded a mixture of **4.74** and **4.75** (39 mg, 71%, 1:1).

Following **procedure 2** for the oxidation of homopropargyl alcohols: **4.73** (63 mg, 0.38 mmol) was oxidized with IBX (145 mg, 0.52 mmol) in DMSO (2 mL). Purification by flash chromatography (10% Et_2O/pentane) yielded a mixture of **4.74** and **4.75** (42 mg, 32%, 2:1).

Spectroscopic data for the mixture: NMR signals from major compound **4.74**: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.75 (d, *J* = 15.7 Hz, 1H), 7.54-7.53 (m, 1H), 7.39-7.37 (m, 2H), 7.33-7.12 (m, 7H), 7.03 (d, *J* = 15.7 Hz, 1H), 5.78 (dd, *J* = 9.9, 2.5, 1H), 5.71 (ddd, *J* = 9.8, 5.1, 2.2 Hz, 1H), 5.64 (d, *J* = 1.8, 1H), 4.34 (d, *J* = 5.0, 1H), 3.17 (apparent t, *J* = 8.2, 1H), 2.55-2.51 (m, 2H), 2.39-2.33 (m, 1H), 1.74-1.63 (m, 1H), 0.95 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 200.4, 54.6, 48.1, 44.0, 32.09, 32.02, 20.7; NMR signals from minor compound **4.75**: ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.50 (d, *J* = 15.7 Hz, 1H),

5.97 (d, J = 9.8 Hz, 1H), 5.59 (s, 1H), 3.58 (d, J = 4.7, 1H), 3.41-3.38 (m, 1H), 2.49-2.42 (m, 2H), 1.54 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 200.4, 54.6, 53.3, 44.2, 32.5, 30.6, 24.1. Carbon signals for the aromatic and double bonds of both compounds. ^{13}C NMR (126 MHz; $CDCl_3$): δ 143.9, 143.3, 143.0, 140.73, 140.57, 139.7, 135.3, 134.9, 130.33, 130.25, 130.0, 129.81, 129.75, 128.65, 128.58, 128.40, 128.2, 127.9, 127.6, 127.01, 126.95, 126.5, 125.8, 125.1, 121.2; Submitted, HRMS (ESI): $[C_{25}H_{24}ONa]^+$ requires 363.1725.

Chapter 5
Conclusion

5.1 Summary and Future Work

The research presented in this thesis has been directed towards developing a better understanding of the different selectivities that arise from the interrupted Nazarov reaction of allenyl vinyl ketones. Chapter 2 and Chapter 4 were mainly concerned with the interception of the oxyallyl cation intermediate of the Nazarov reaction whereas Chapter 3 was focused on the Nazarov reaction itself.

5.2 (3+2)- Versus (4+3)-Cycloadditions

The oxyallyl cation derived from the Nazarov reaction of allenyl vinyl ketones could be trapped by substituted dienes by (3+2)- and (4+3)-cycloaddition. The trapping process was significantly affected by the substitution pattern of the dienes. The oxyallyl cation showed a general preference for (4+3)-cycloaddition reactions. However, when the terminus of the diene was geminally disubstituted (3+2)-cycloadducts dominated the product mixture. In some cases an electron-donating group on the diene was sufficient to overcome the steric bias of terminally substituted dienes.

The experimental evidence presented in Chapter 2 suggested that the (4+3)-cycloaddition proceeded by a concerted mechanism. It would be informative to compare computationally the (4+3)- and (3+2)-cycloaddition reactions. It would be particularly helpful to confirm that the addition of an *s-cis* diene to the oxyallyl cation, leading to the (4+3) product, occurs with a lower barrier than the addition of an *s-trans* diene, which would lead to a (3+2) product. The factors that control the *endo/exo* addition of

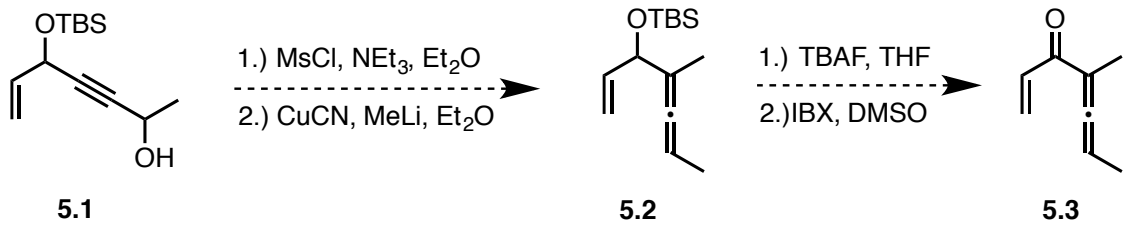
dienes to cyclic oxyallyl cations are not well understood. A computational study could be carried out to discern what factors that control this selectivity. The results of the calculations could be used to guide experiments that would corroborate the findings.

An ongoing study in the Burnell group involves the exploration of Nazarov reactions of allenyl aryl ketones.[129] Recent results have shown that the nature of the Lewis acid used to initiate the Nazarov reaction has a profound effect on the efficiency of those cyclizations. Some previous studies on the reactivity of oxyallyl cations have shown that the method of generating the cation plays a role in its selectivity for (3+2)- versus (4+3)-cycloadditions.[43,50,51,62] It would be instructive to explore the effect of using different Lewis acids to initiate the Nazarov reaction on the selectivity of (3+2)- versus (4+3)-cycloaddition.

5.3 Torquoselectivity in the Nazarov Reaction of AVKs

Allenyl vinyl ketones with terminally substituted allenes were prepared, and they were employed in Nazarov reactions that were intercepted by (4+3)-cycloaddition. The products obtained showed a strong preference in the Nazarov step for the conrotation of the termini to give the thermodynamically less stable *Z* exocyclic double bond, even when the *cis* substituents were encumbered in the product. The results of this research indicated that the torquoselectivity arose primarily from the substituent on the allene turning away from the vinyl group to the minimize steric interaction in the transition state. The hypothesis regarding basis of the torquoselectivity has been supported with a computational analysis.

AVKs without a terminal vinyl substituent were not available due to synthetic complications. This was unfortunate because such AVKs should have had the best chance to display the opposite torquoselectivity. However, the reactions of these AVKs could be examined computationally. If the opposite torquoselectivity is predicted, the Nazarov reaction of such AVKs should then be tested experimentally. Some of the chemistry developed in Chapter 4 might be used for the synthesis of AVK **5.3** (Scheme 5.1). Alkyl cuprate addition to a mesylate derived from propargyl alcohol **5.1** could furnish allene **5.2**.[116] Deprotection and oxidation using established procedures might allow access to the AVKs with no vinyl substitution.[36,85]



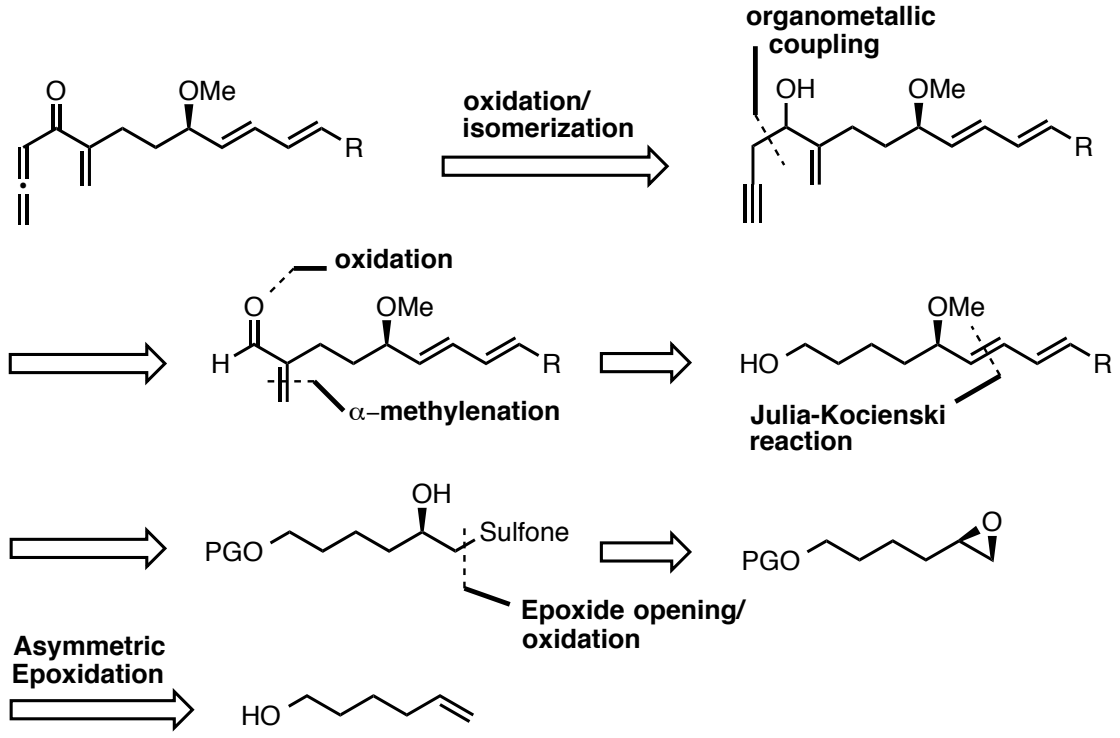
Scheme 5.1 Possible synthesis of type IV AVK with no terminal vinyl substituent.

5.4 Intramolecular Trapping of Allenyl Vinyl Ketones

The intramolecular interrupted Nazarov reaction was explored with allenyl vinyl ketones bearing tethered 1,3-dienes. The length of the tether and substitution on the diene both played important roles in terms of selectivity in the trapping process. The diene's substitution controlled the diastereoselectivity of the cycloaddition. When the diene was connected to a type II AVK by a three-carbon tether only (4+3)-cycloaddition products were isolated. When the length of the tether was increased by a single methylene the selectivity changed and (3+2) products were formed. A Type IV allenyl vinyl alcohol was synthesized bearing a tethered diene on the terminus of the allene.

When the alcohol was oxidized to the AVK the diene underwent spontaneous Diels-Alder cyclization onto the allene rather than a tandem Nazarov/cycloaddition process.

Previous work by Giguere and Harmata had shown that substitution on the tether can control the diastereoselectivity of the intramolecular (4+3)-cycloaddition to allyl cations.[102,103] Allenyl vinyl ketones bearing a chiral center on the tether should be available through a reaction sequence similar to that used to synthesize the Type II AVKs. The starting material could be available from the asymmetric epoxidation of 5-hexene-1-ol.[130] The epoxide could be opened with a thiol and oxidized to produce a sulfone that could be used in a Julia-Kocienski olefination.[131] Elaboration of the diene to the allenyl vinyl ketone would follow the same sequence as described previously. It would be of great interest to see how substitution on the tether would affect the yield and selectivity of the tandem Nazarov/cycloaddition reaction.



Scheme 5.2 Retrosynthesis of an allenyl vinyl ketone bearing a chiral center on the tether.

Initial attempts to develop the intramolecular (4+3)-cycloaddition of allenyl vinyl ketones focused on the synthesis of type I AVKs. However, synthetic difficulties resulted in the study being suspended. In light of new methodologies disclosed in this thesis for the synthesis of allenyl vinyl ketones, it would be worth revisiting the project. Two type I AVKs are shown in Figure 5.1.

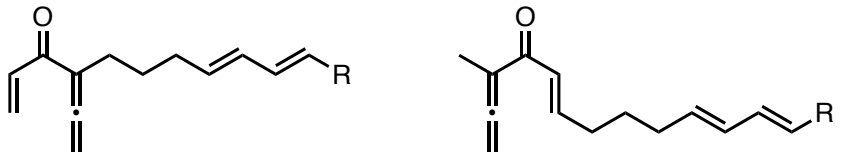
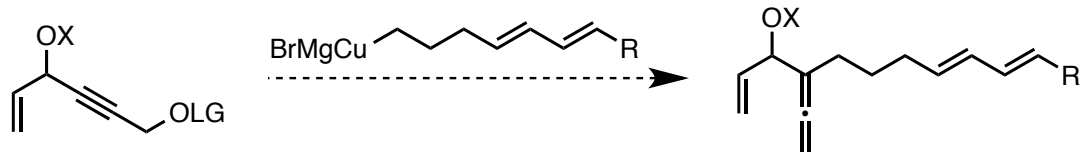


Figure 5.1 Type I allenyl vinyl ketones bearing tethered 1,3-dienes.

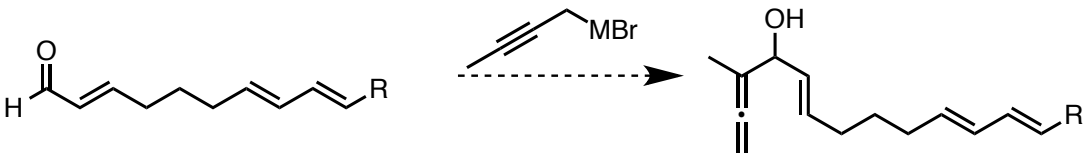
Type I AVKs with the diene tethered to the top of the allene may be available using organocuprate chemistry. The diene tether could be synthesized as previously

described and then converted to the necessary organocuprate from the corresponding Grignard reagent. The organocuprate could be added to a propargyl alcohol derivative to generate the substructure of the allenyl vinyl ketone (Scheme 5.3).



Scheme 5.3 Proposed organocuprate addition for the synthesis of type I AVKs with tethered dienes α to the ketones.

The allenyl vinyl ketones bearing a tethered 1,3-diene on the vinyl group could be synthesized using known chemistry. A metal-mediated Barbier type addition of 1-bromo-2-propyne to an α,β-unsaturated aldehyde would provide allenic alcohols as shown in Scheme 5.4.[113,114] Oxidation of the alcohol would generate the allenyl vinyl ketone.



Scheme 5.4 Proposed synthesis of type I AVK with a vinyl tethered diene.

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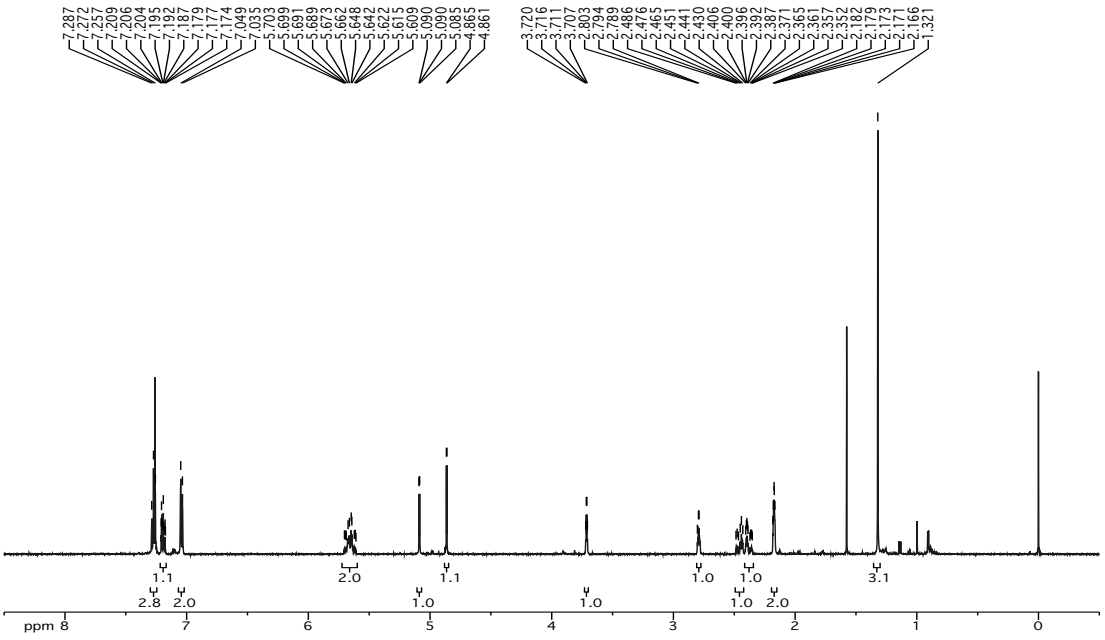
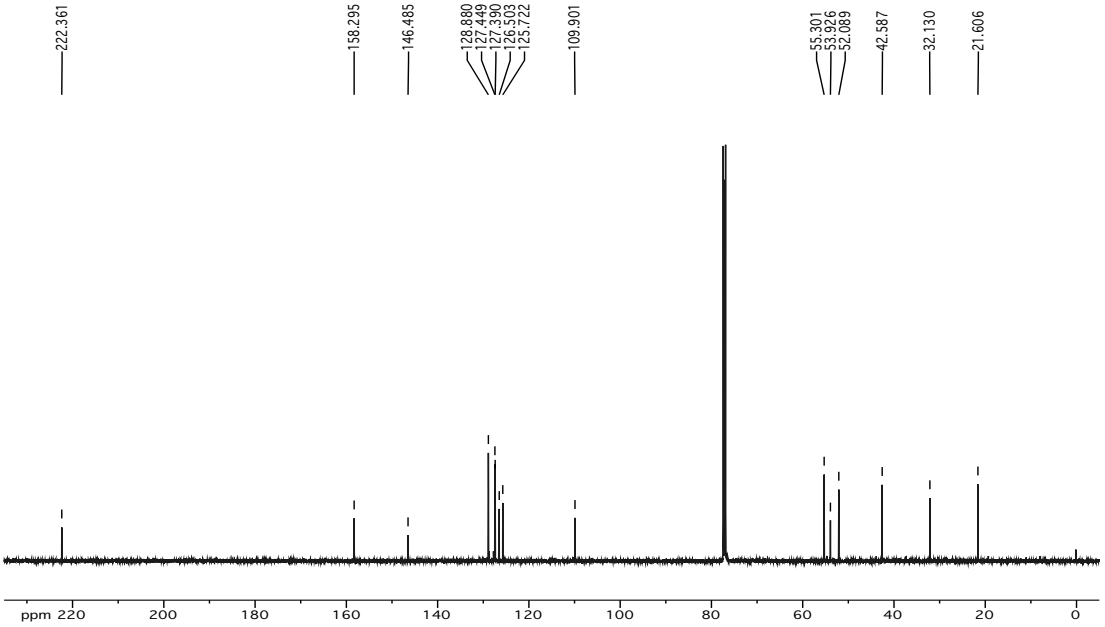
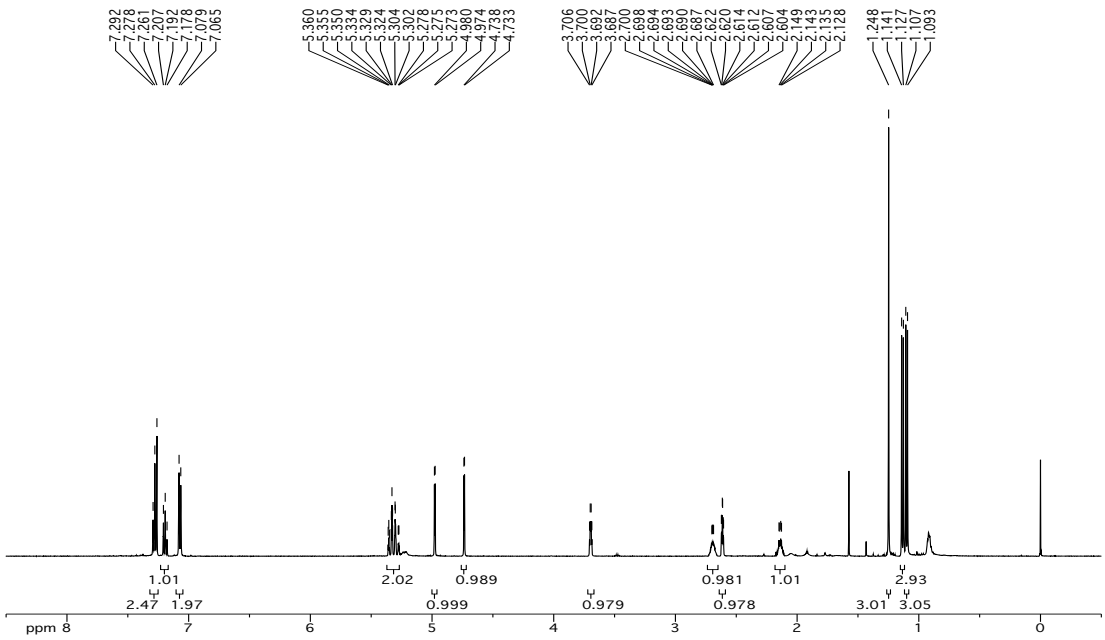
Appendix A NMR Spectra for Chapter 2

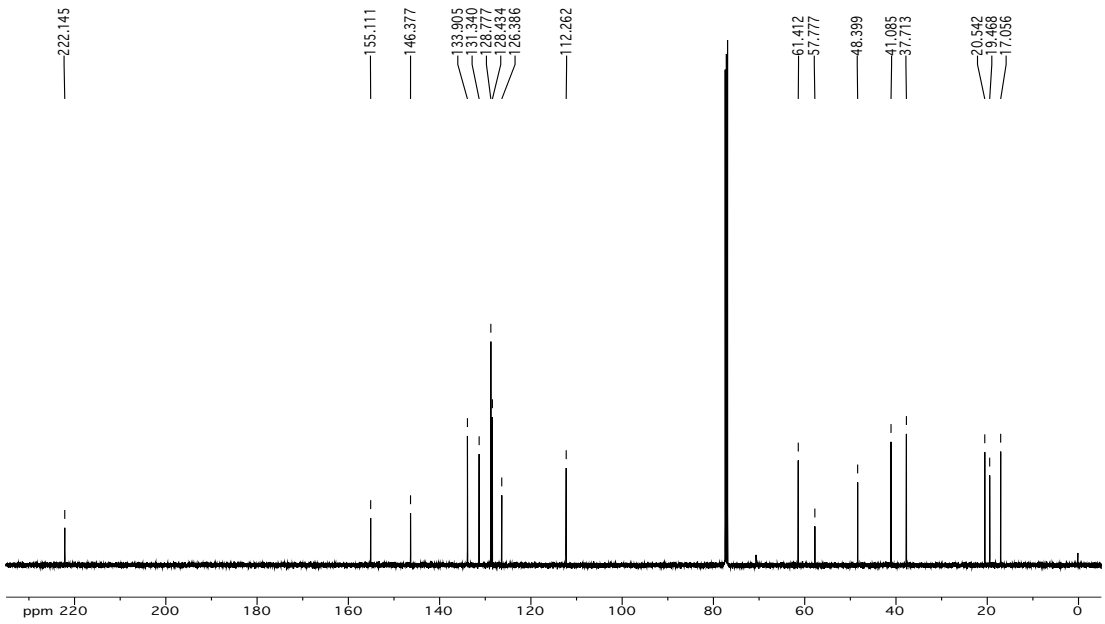
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,6*S**,7*R**)-1-Methyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (2.49)**



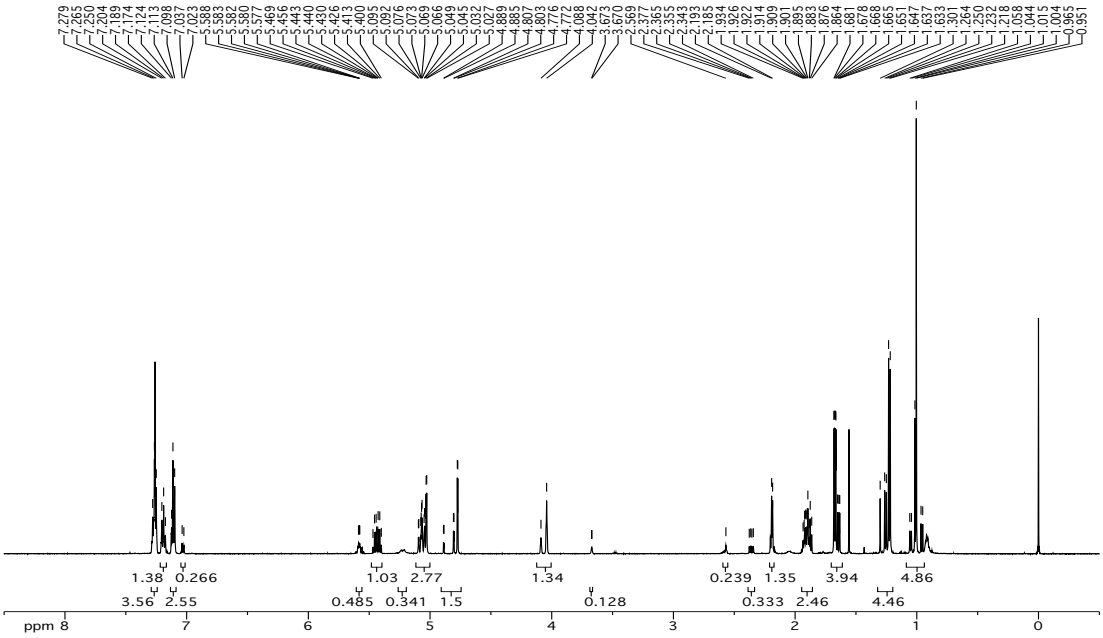


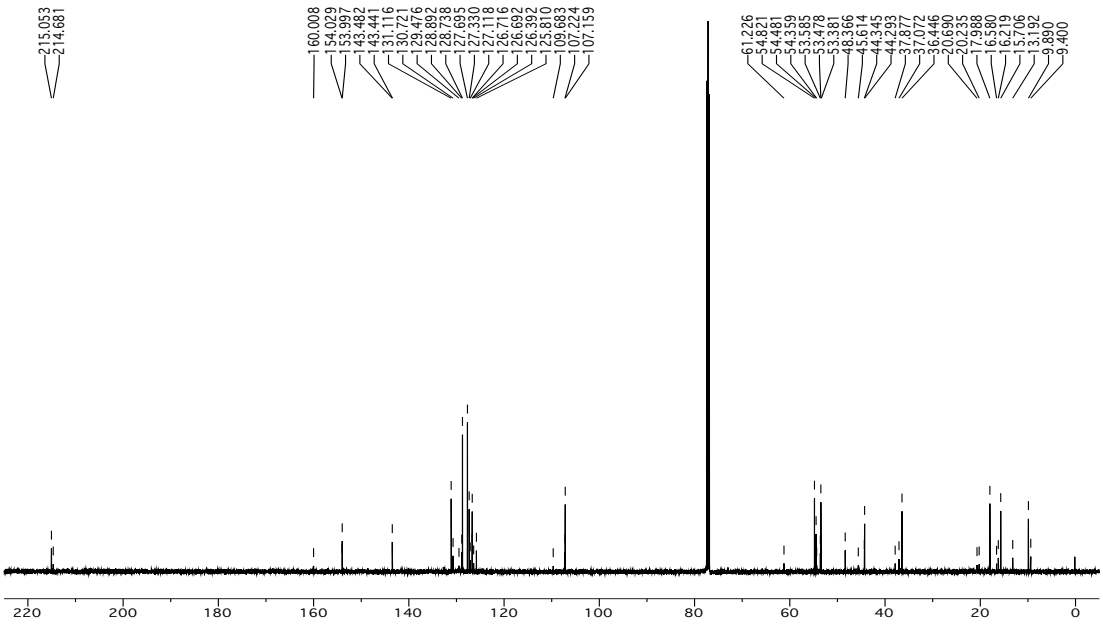
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,2*S**,5*R**,6*S**,7*R**)-*)-1,2,5-trimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (2.50)**



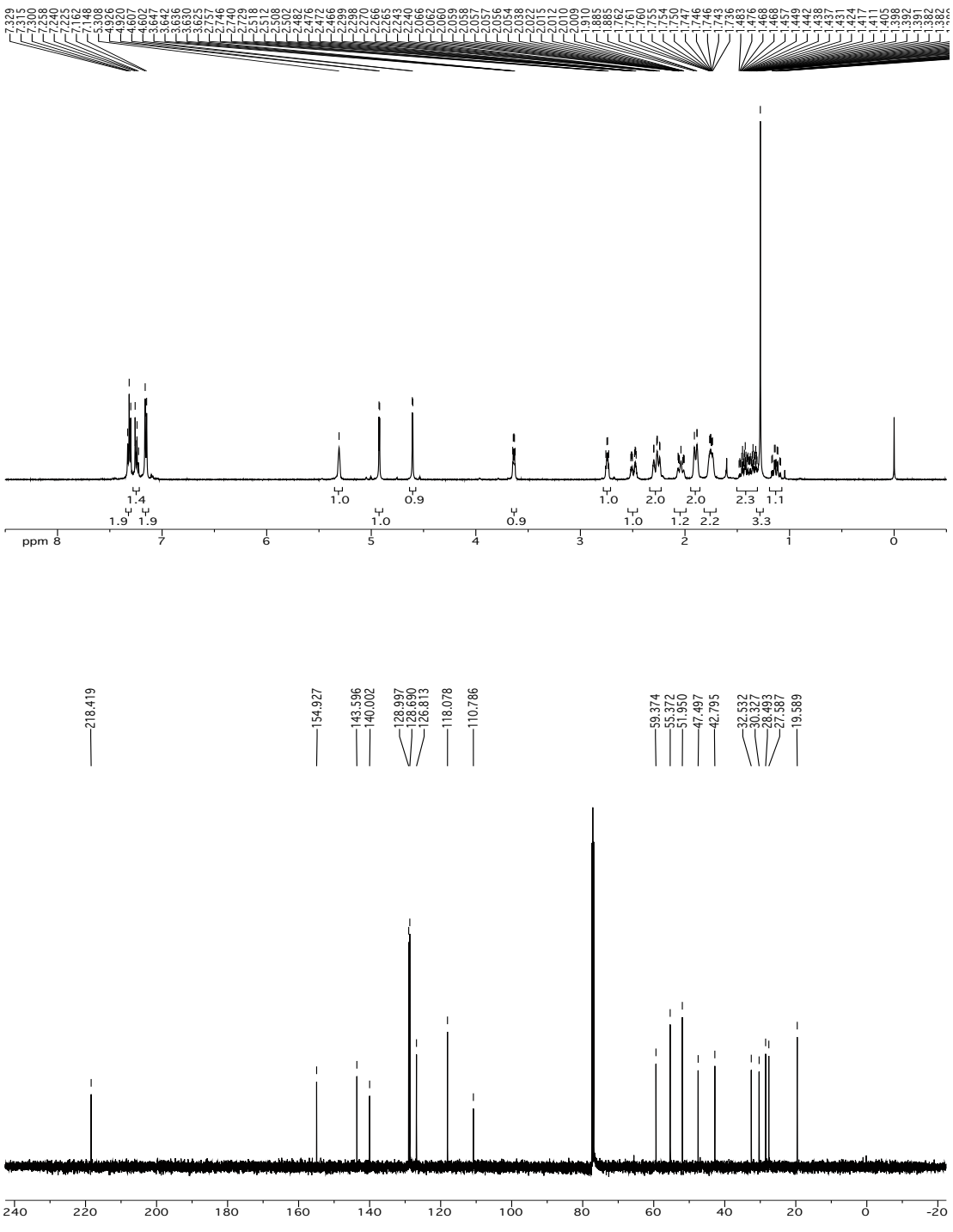


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,2*R**,5*S**,6*S**,7*R**)-1,2,5-trimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (2.51), (1*R**,2*R**,3*S**,4*S**,5*R**)-1,3-dimethyl-6-methylene-5-phenyl-2-((*E*)-prop-1-en-1-yl)bicyclo[2.2.1]heptane (2.52) and (1*R**,2*R**,3*S**,4*S**,5*R**)-1,3-dimethyl-6-methylene-5-phenyl-2-((*Z*)-prop-1-en-1-yl)bicyclo[2.2.1]heptane (2.53)**

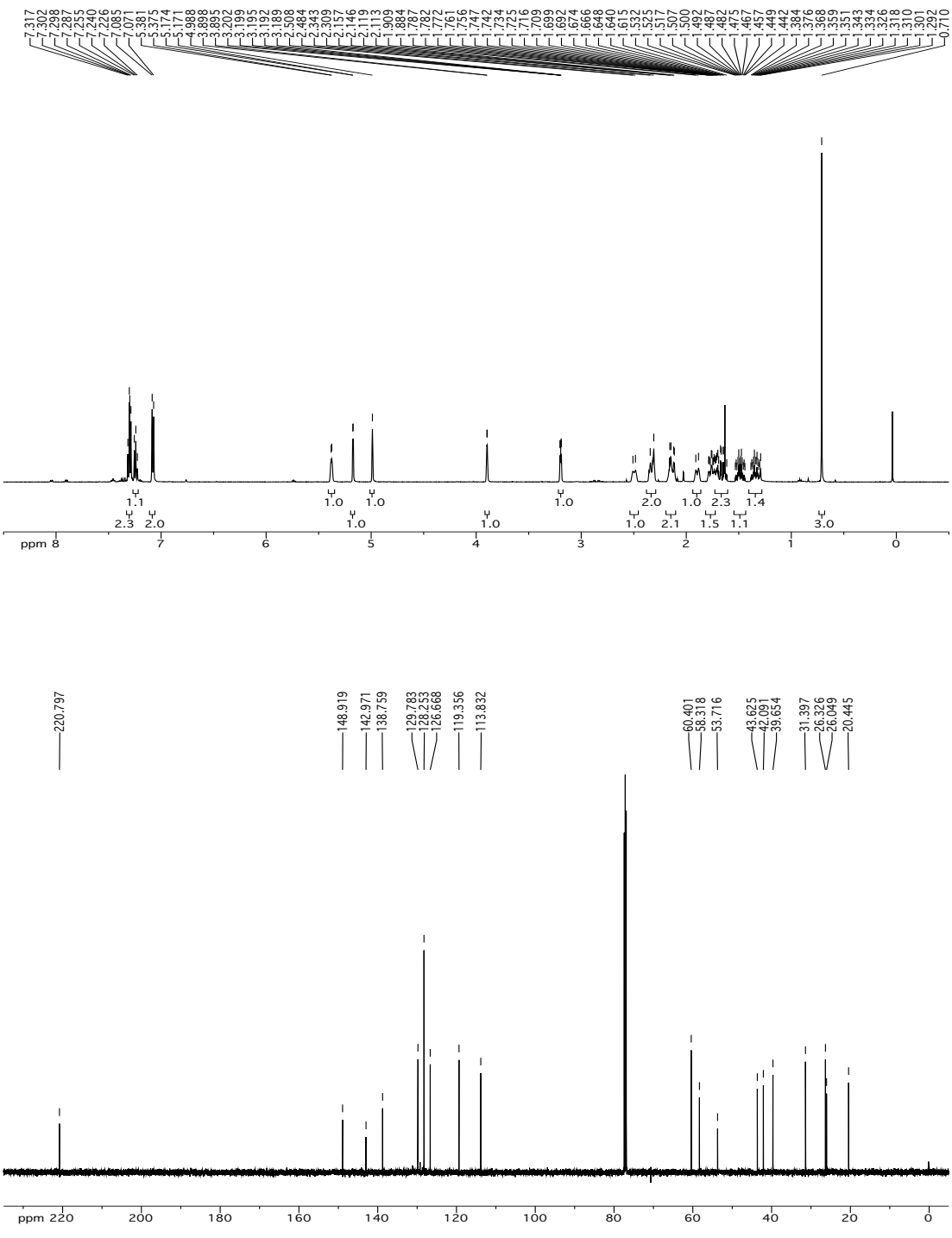




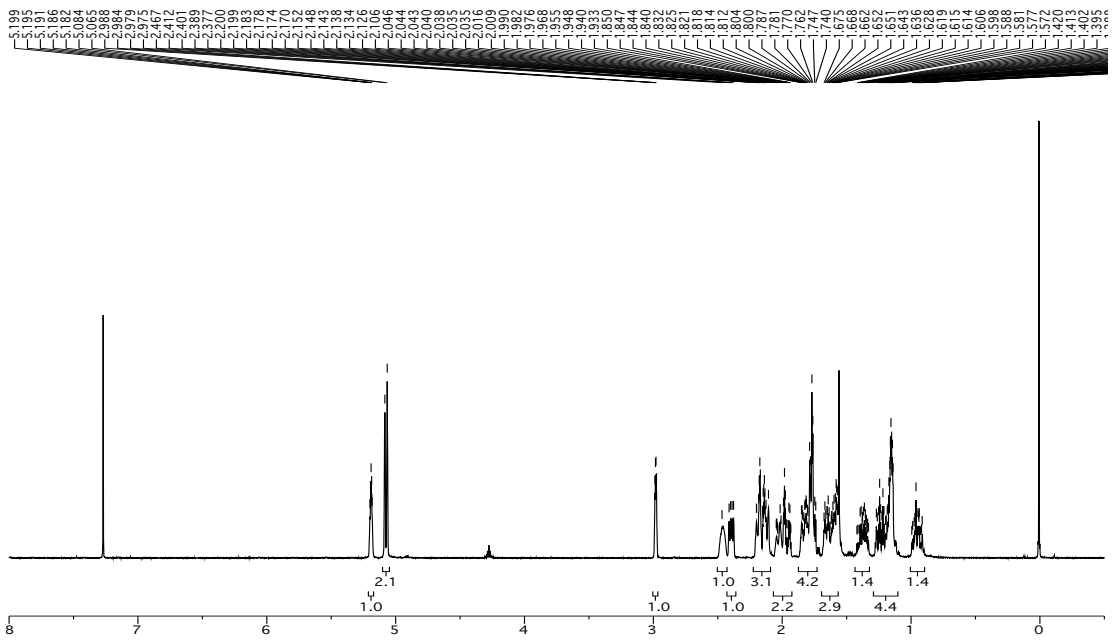
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (4a*R,5*S**,7*S**,8*R**)-5-Methyl-6-methylene-7-phenyl-1,2,3,4,4a,5,6,7,8,9-decahydro-5,8-methanobenzo[8]annulen-11-one (2.55)**

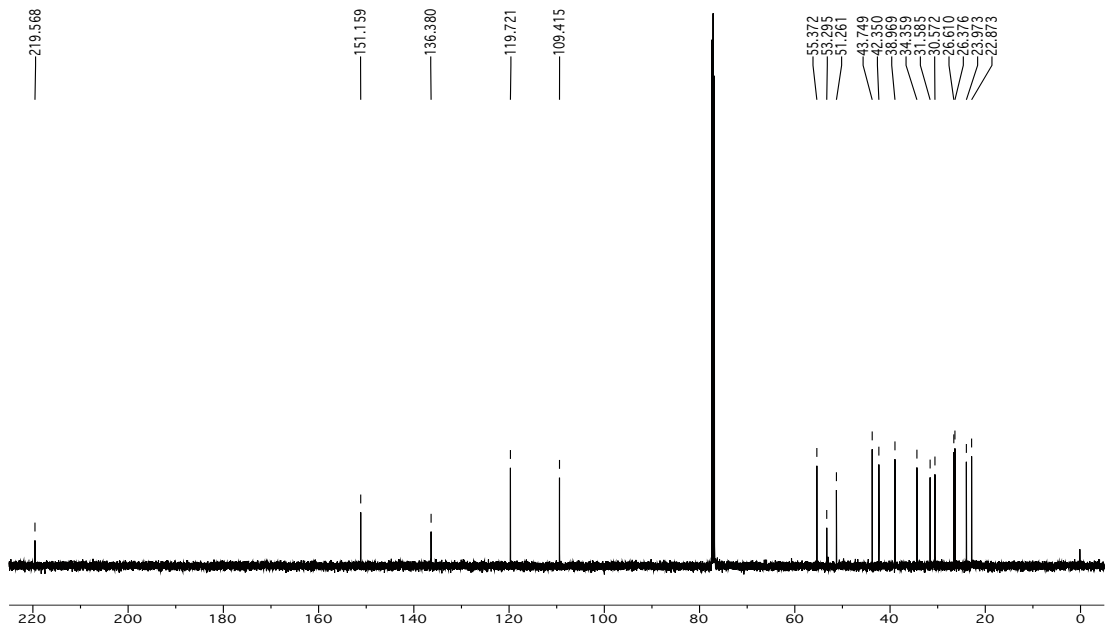


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (4a*R,5*R**,7*S**,8*R**)-8-Methyl-6-methylene-7-phenyl-1,2,3,4,4a,5,6,7,8,9-decahydro-5,8-methanobenzo[8]annulen-11-one (2.56)**

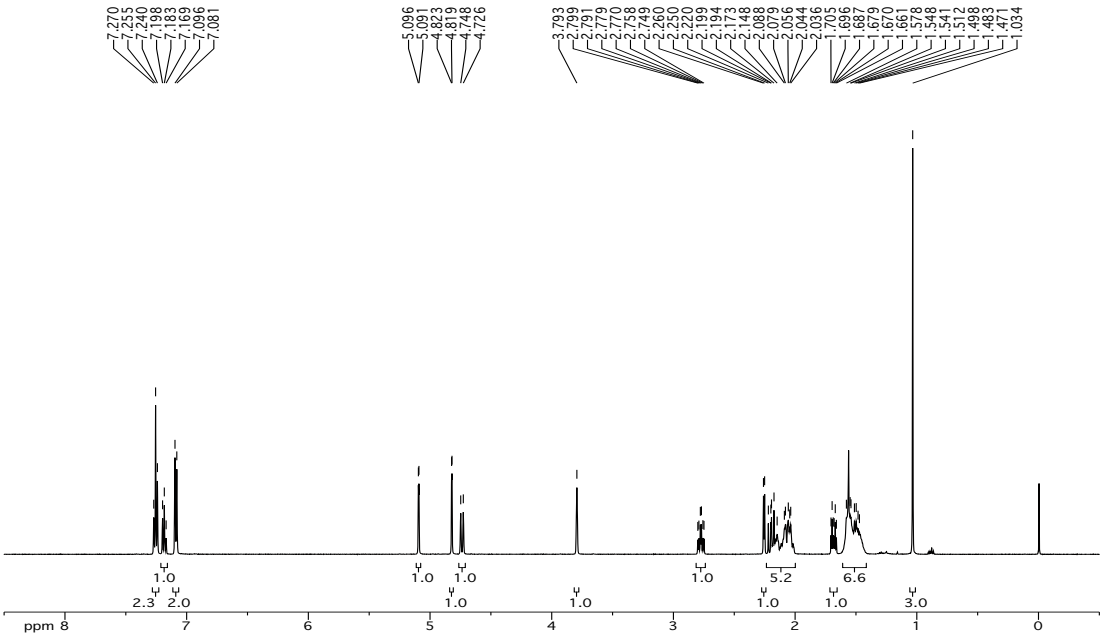


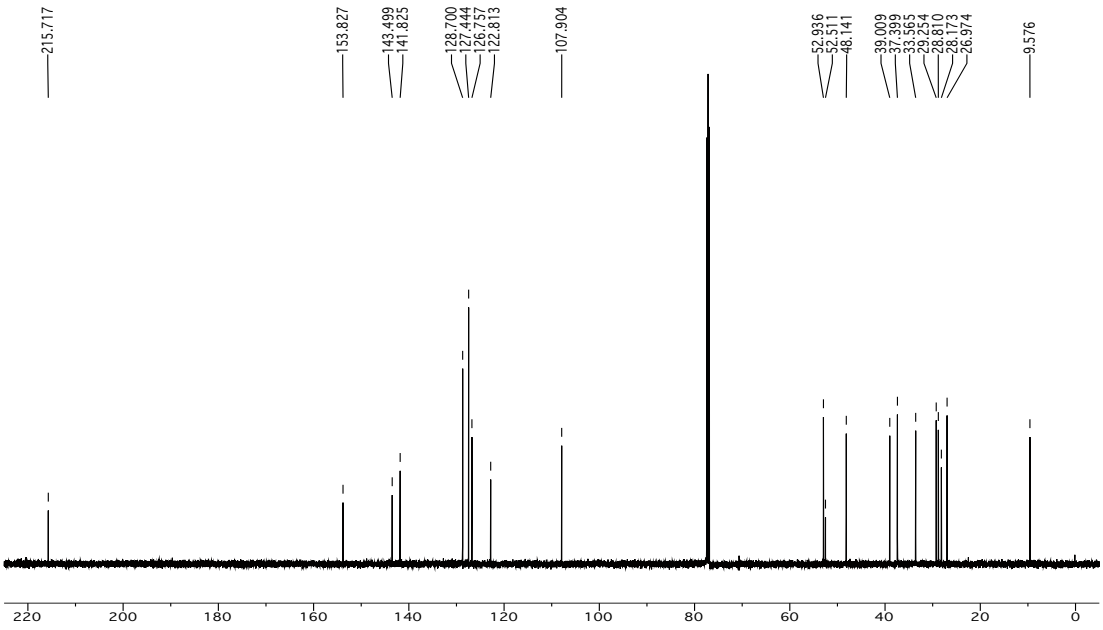
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (4a*R,10a*S**,11*S**,12a*S**)-12-Methylene-2,3,4,5,7,8,9,10,10a,11,12,12a-dodecahydro-1*H*-4a,11-methanodibenzo[*a*,*e*][8]annulen-13-one (2.57)**



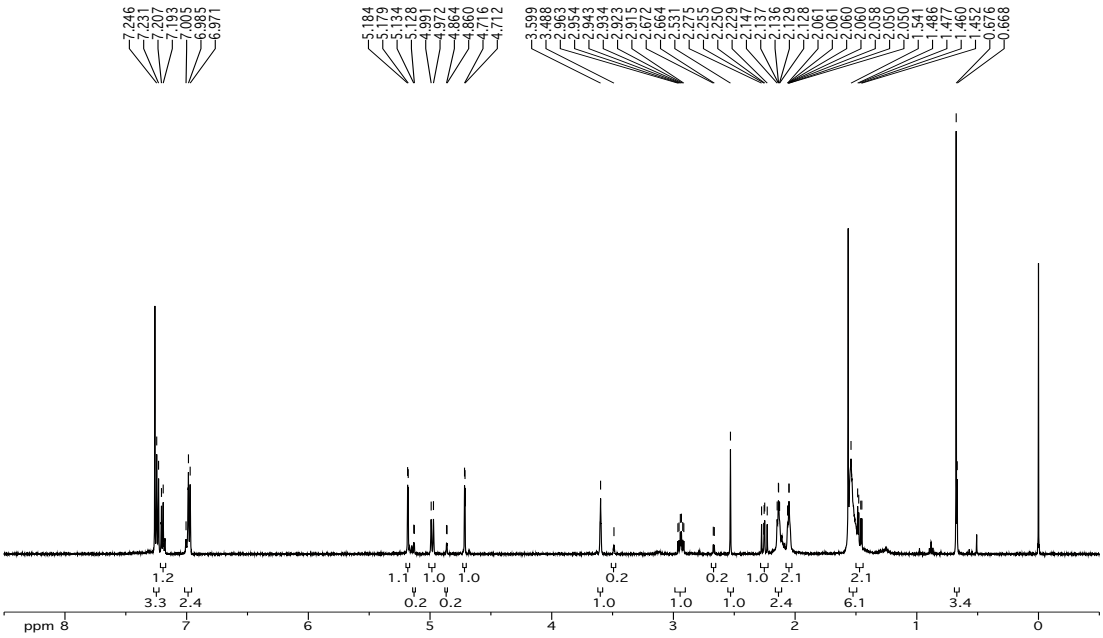


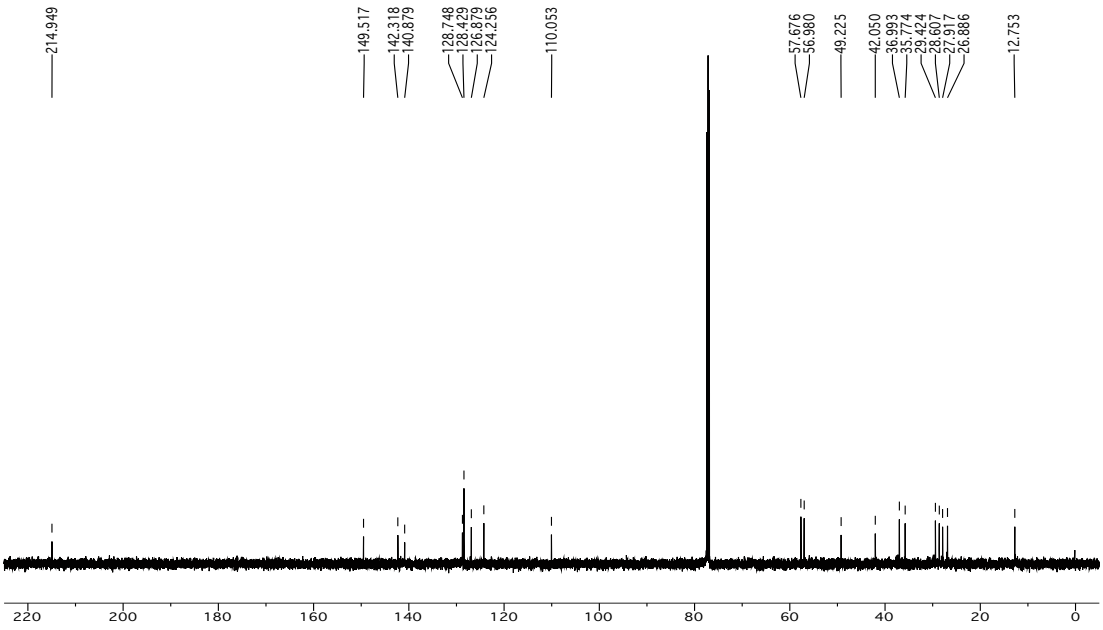
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,3*S**,4*R**,6*R**)-6-(Cyclohexylidenemethyl)-1-methyl-2-methylene-3-phenylbicyclo[2.2.1]heptan-7-one (2.59)**



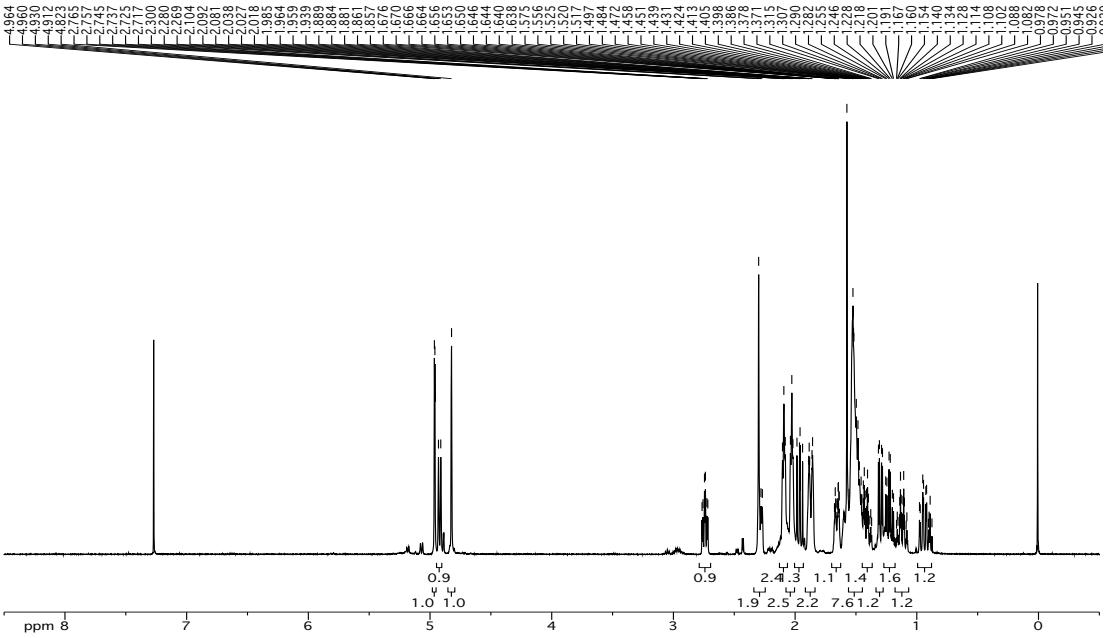


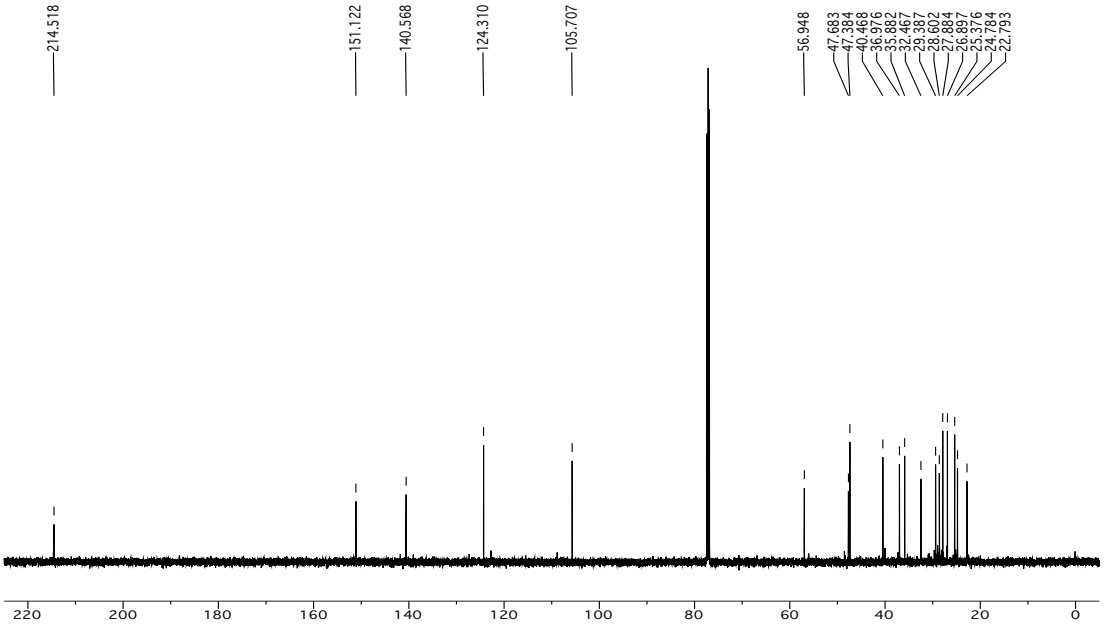
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,2*R**,4*S**,5*R**)-5-(Cyclohexylidenemethyl)-1-methyl-3-methylene-2-phenylbicyclo[2.2.1]heptan-7-one (2.60)**



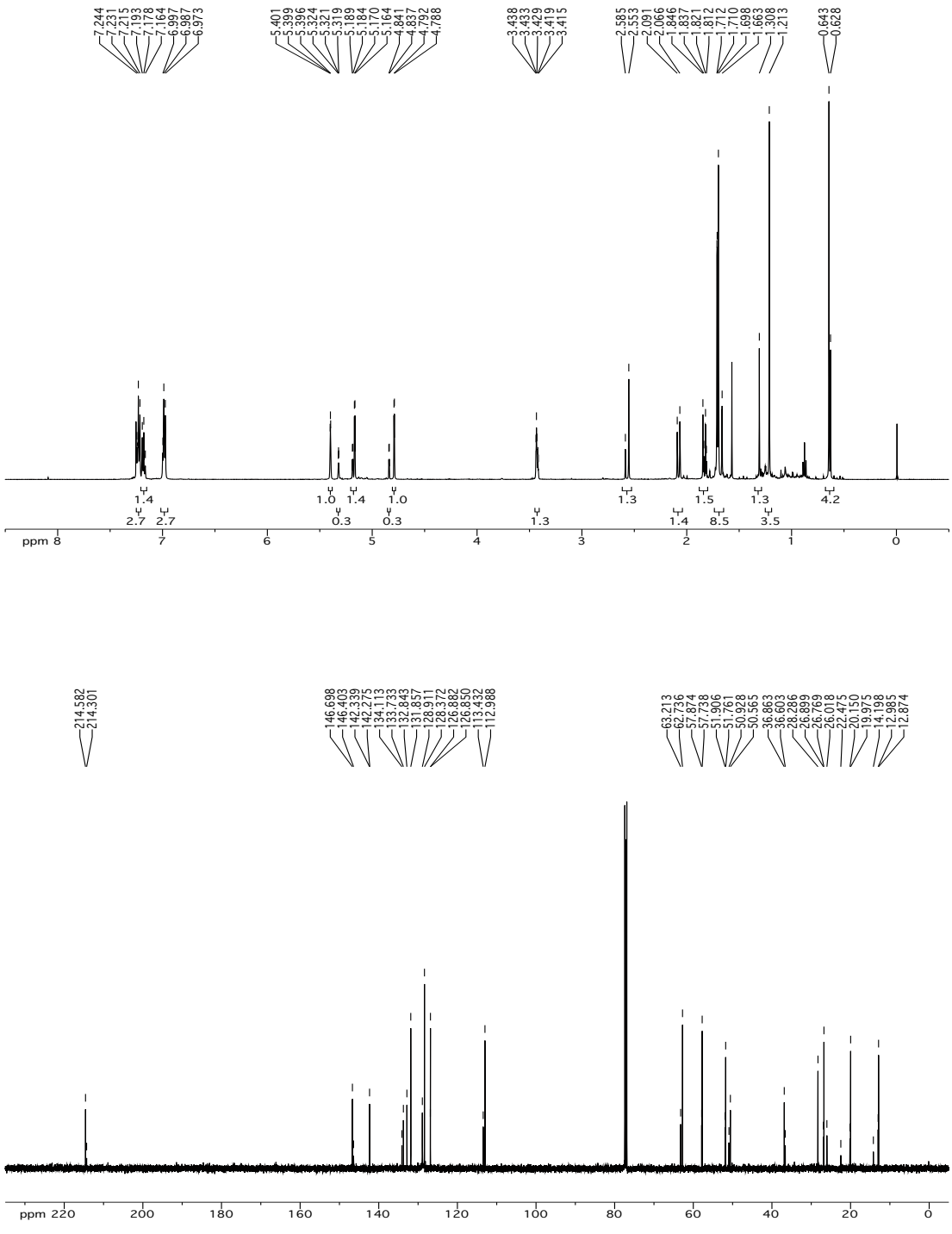


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (2*R,3*S**,4a*S**,8a*R**)-3-(Cyclohexylidenemethyl)-1-methyleneoctahydro-1*H*-2,4a-methanonaphthalen-9-one (2.61)**

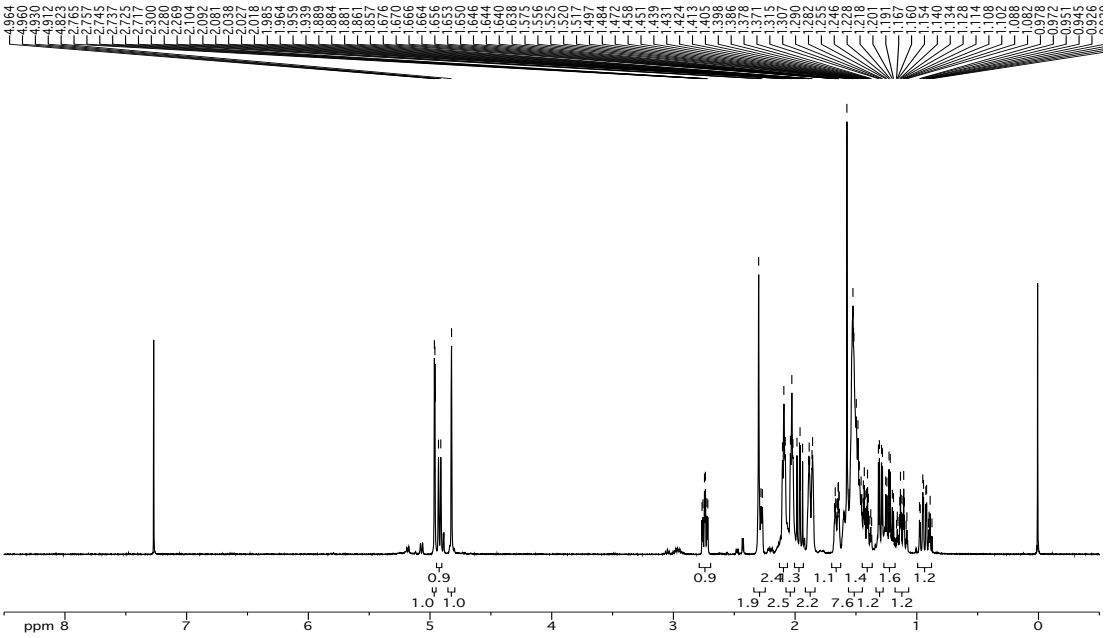


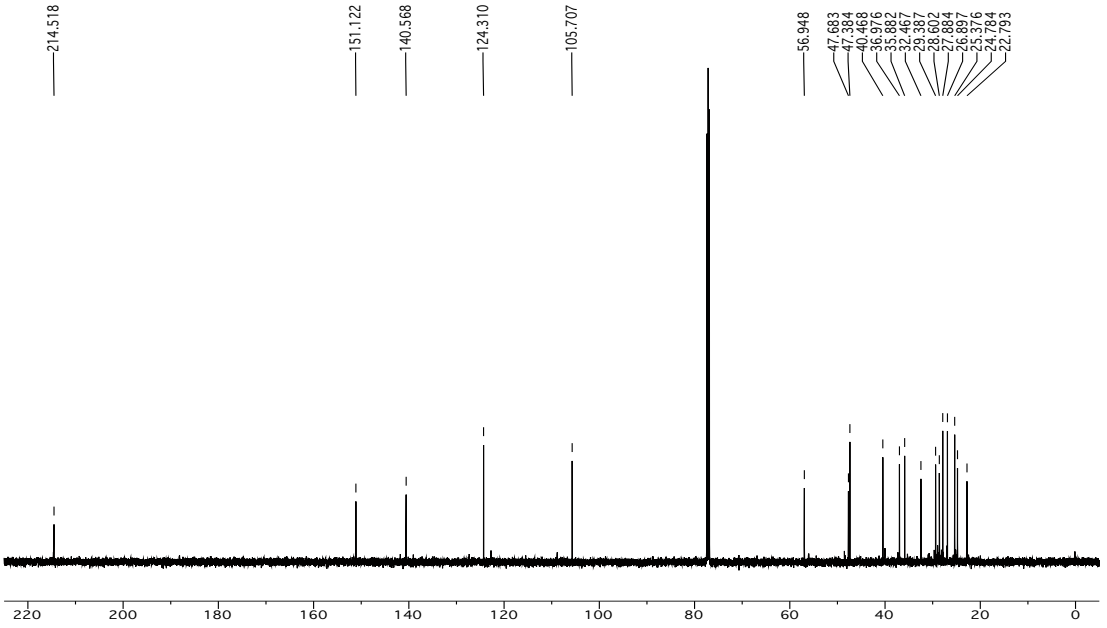


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,2*R**,4*R**,5*R**)- (2.66) and (1*R**,2*S**,4*R**,5*R**)-1,5-dimethyl-3-methylene-5-(2-methylprop-1-en-1-yl)-2-phenylbicyclo[2.2.1]heptan-7-one (2.67)**

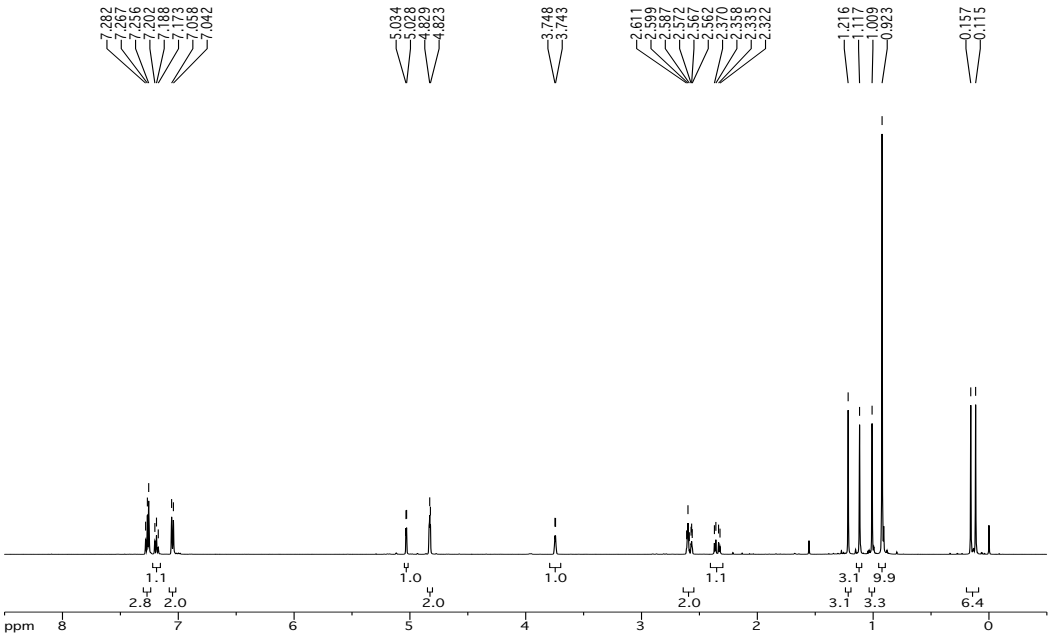


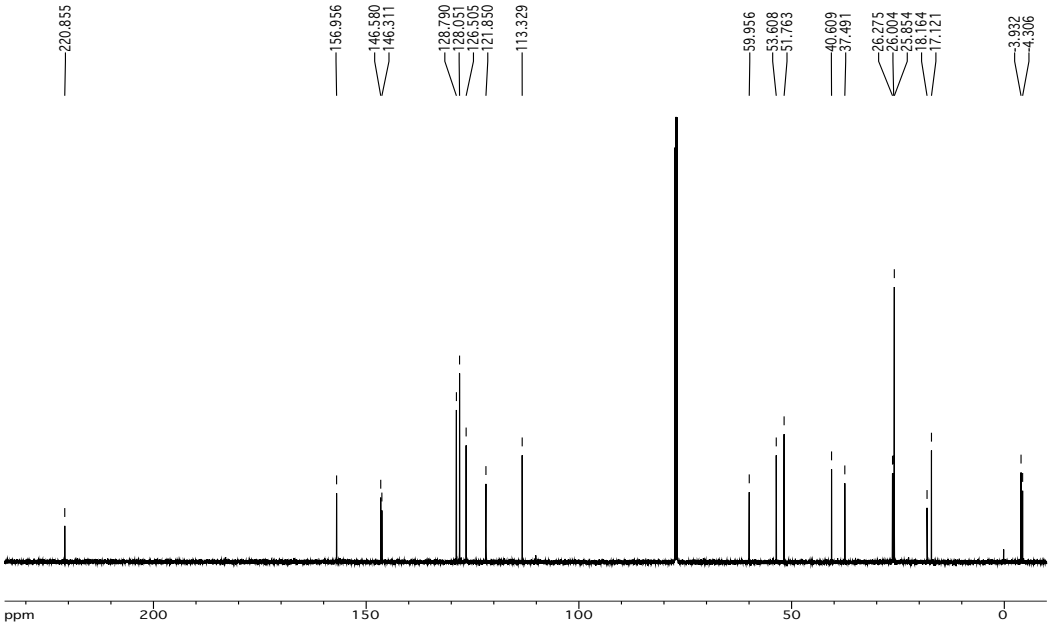
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (2*R,3*R**,4a*R**,8a*R**)- (2.68) and (2*R**,3*S**,4a*R**,8a*R**)-3-methyl-1-methylene-3-(2-methylprop-1-en-1-yl)octahydro-1*H*-2,4a-methanonaphthalen-9-one (2.69)**



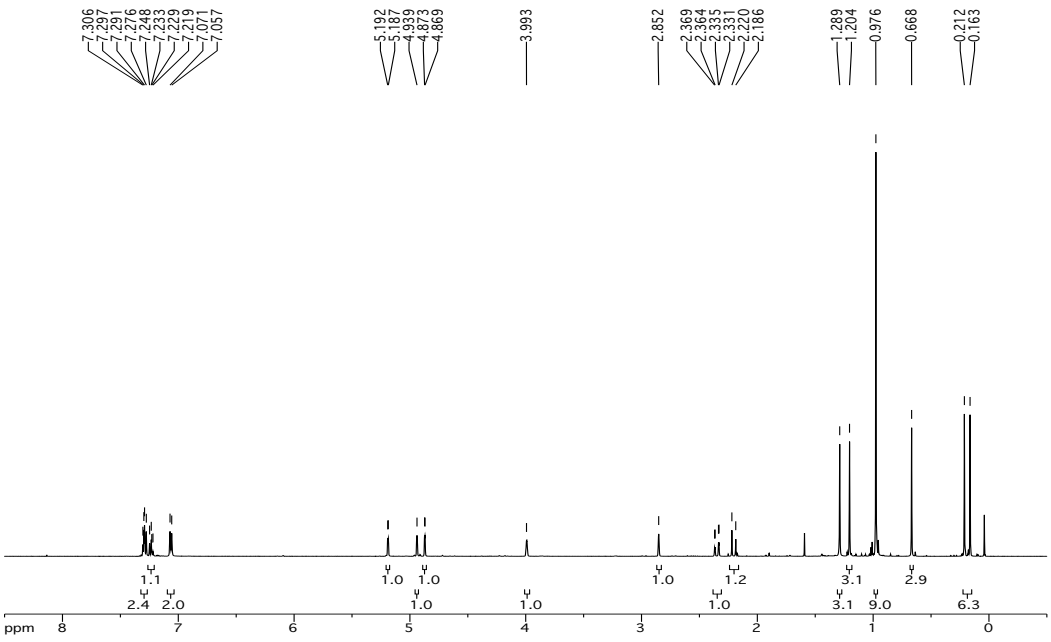


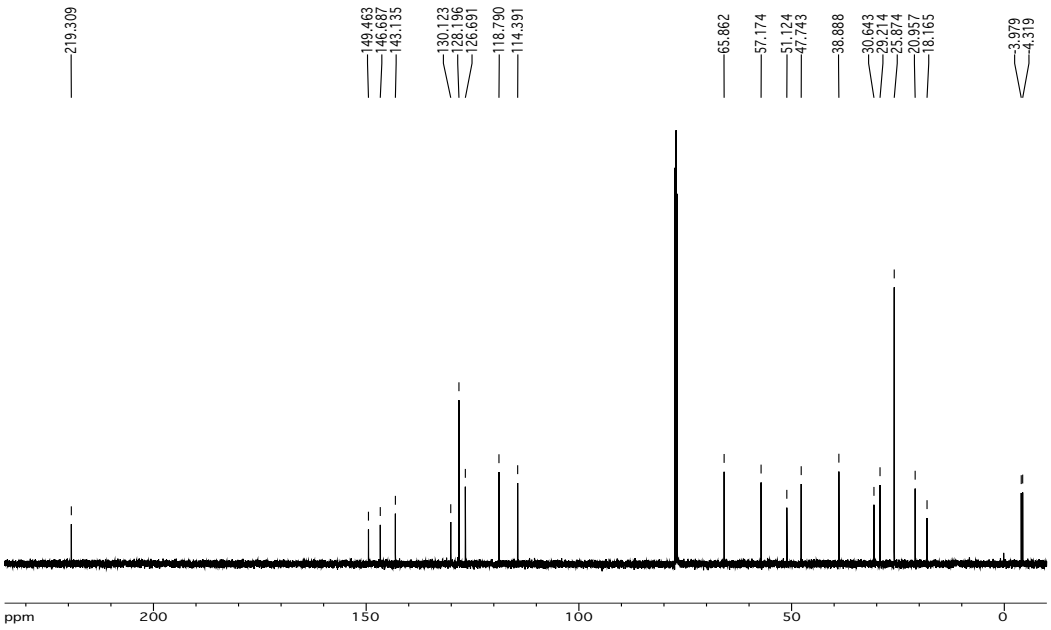
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,6*S**,7*S**)-4-(*tert*-Butyldimethylsilyloxy)-1,2,2-trimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (2.71)**



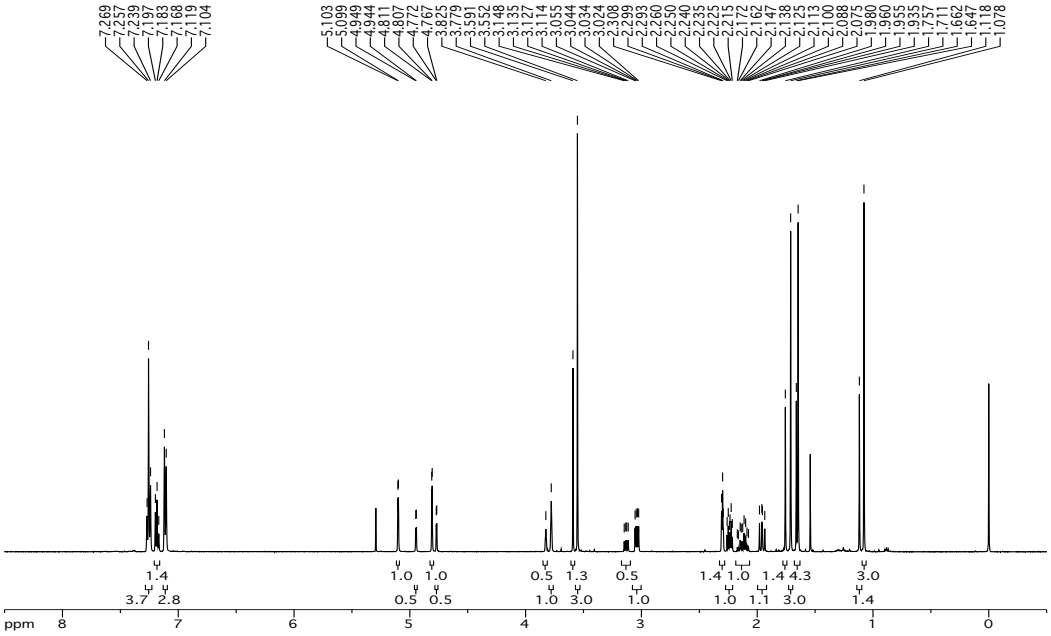


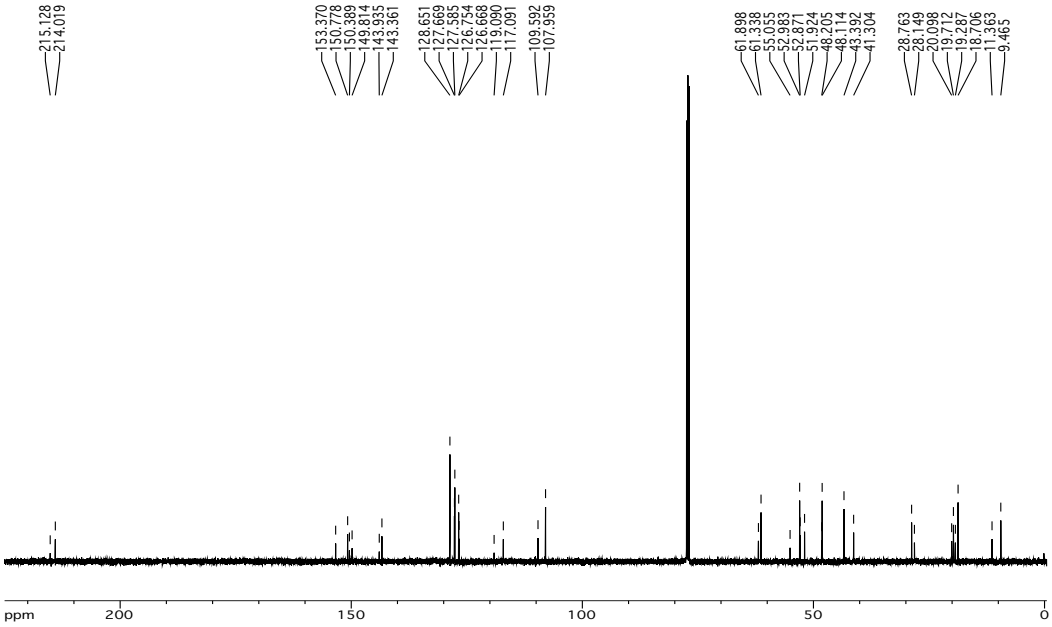
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,6*S**,8*R**)-4-(*tert*-Butyldimethylsilyloxy)-1,5,5-trimethyl-7-methylene-8-phenylbicyclo[4.2.1]non-3-en-9-one (2.72)**



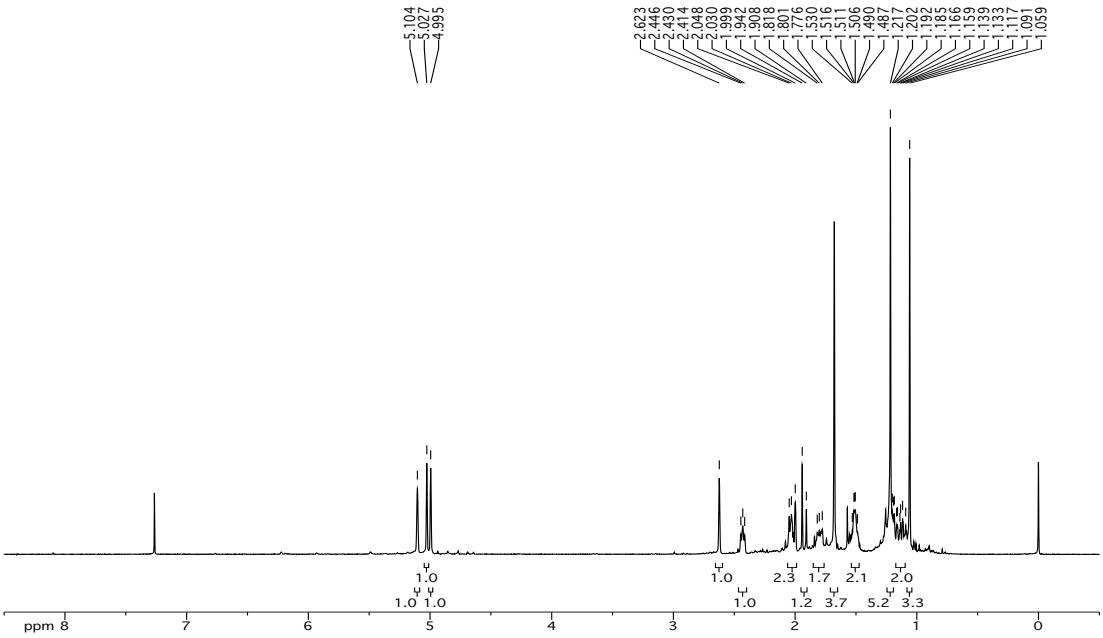


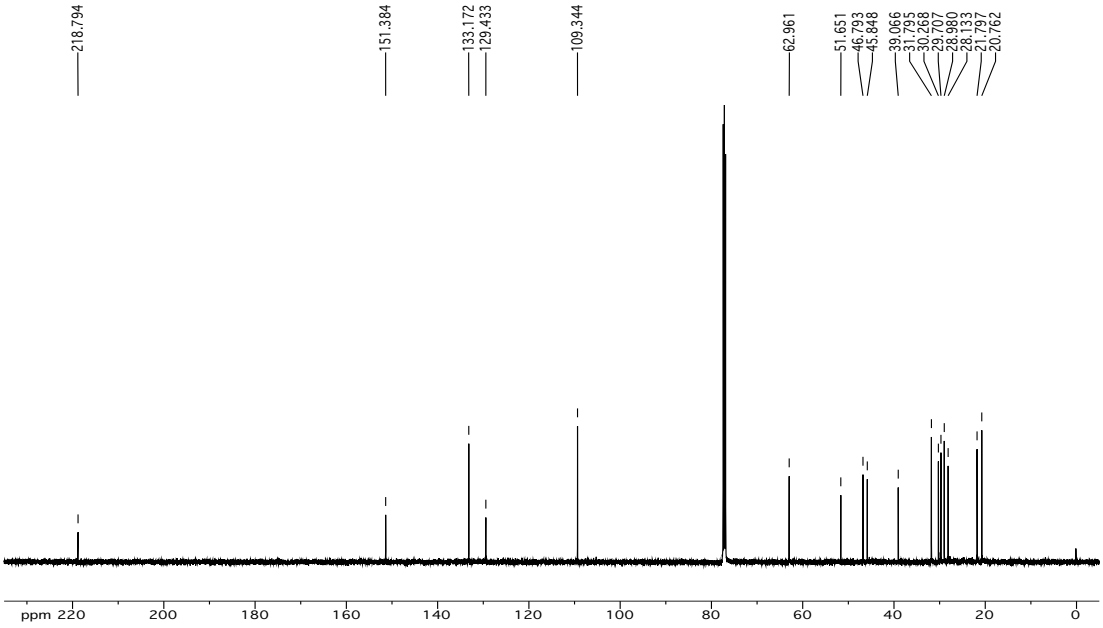
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,2*S**,4*S**,5*S**)-2-(1-methoxy-2-methylprop-1-en-1-yl)-1-methyl-6-methylene-5-phenylbicyclo[2.2.1]heptan-7-one (2.74), and (1*R**,2*R**,4*S**,5*S**)-2-(1-methoxy-2-methylprop-1-en-1-yl)-1-methyl-6-methylene-5-phenylbicyclo[2.2.1]heptan-7-one (2.75)**



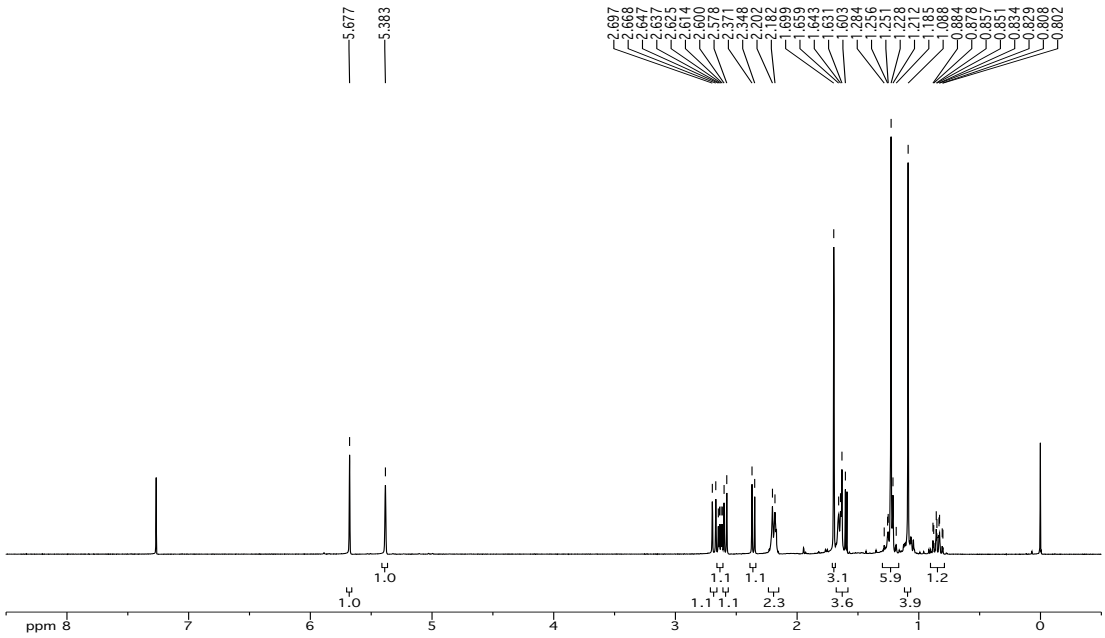


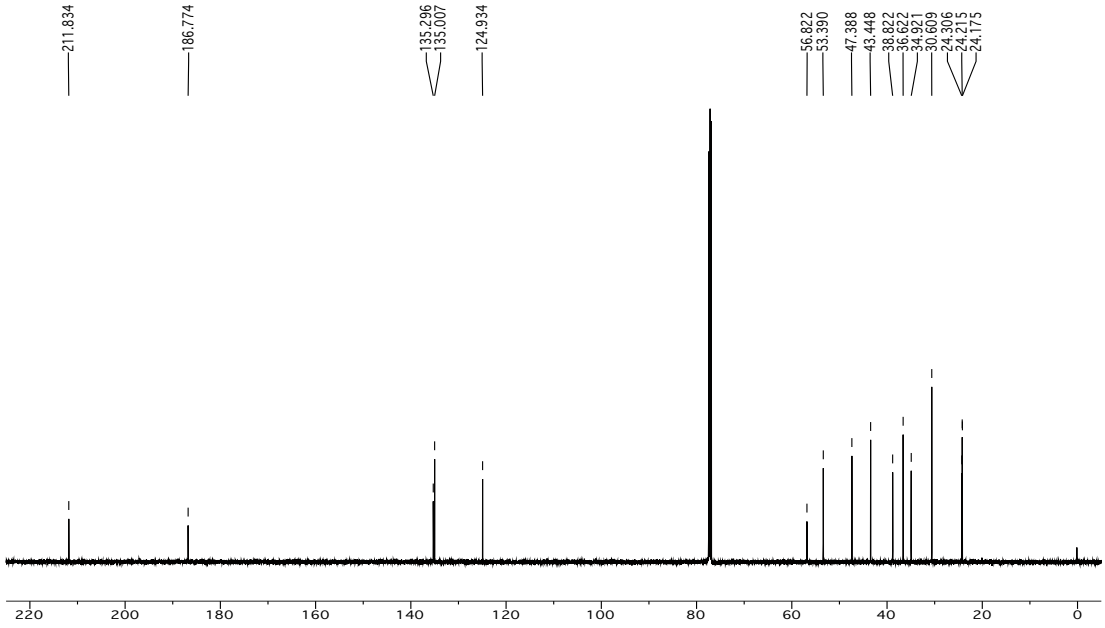
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (4a*R,9*S**,10a*S**)-6,8,8-Trimethyl-10-methylene-2,3,4,5,8,9,10,10a-octahydro-1*H*-4a,9-methanobenzo[8]annulen-11-one (2.77)**



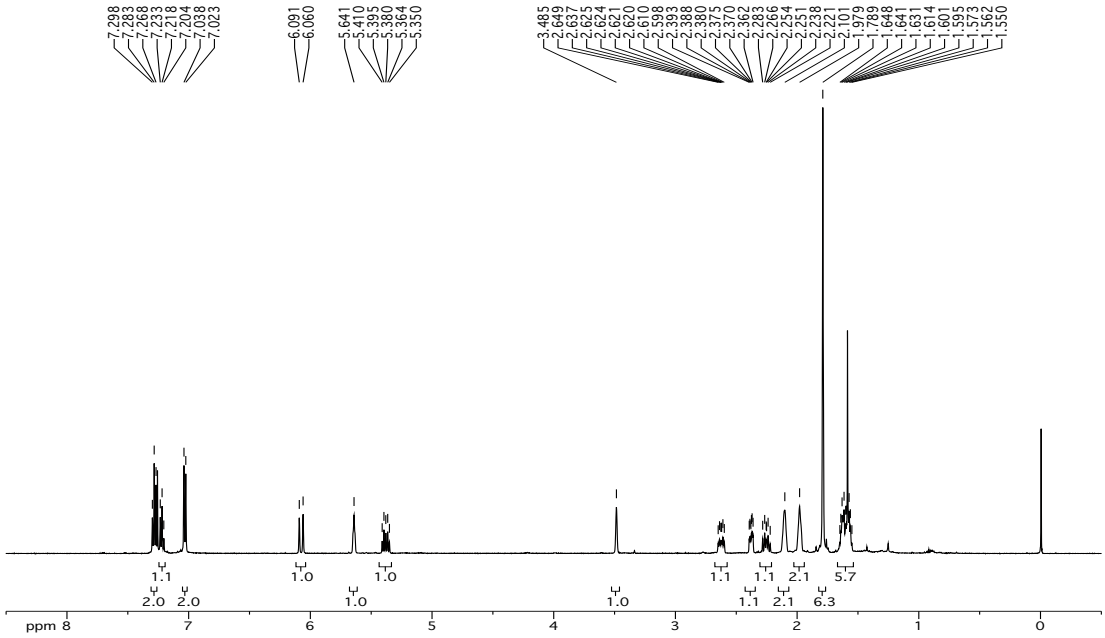


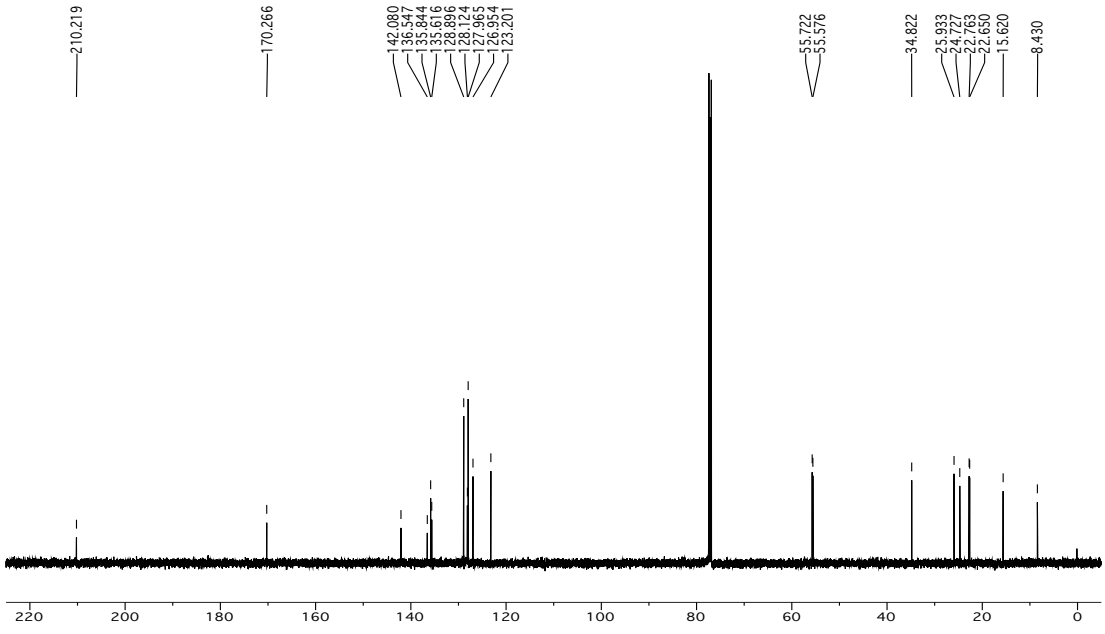
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (4a*R,10a*S**,6*Z*)-6,8,8-trimethyl-1,2,3,4,5,8,9,10a-octahydro-4a,10-(epiethan[2]yl[1]ylidene)benzo[8]annulen-12-one (2.78)**



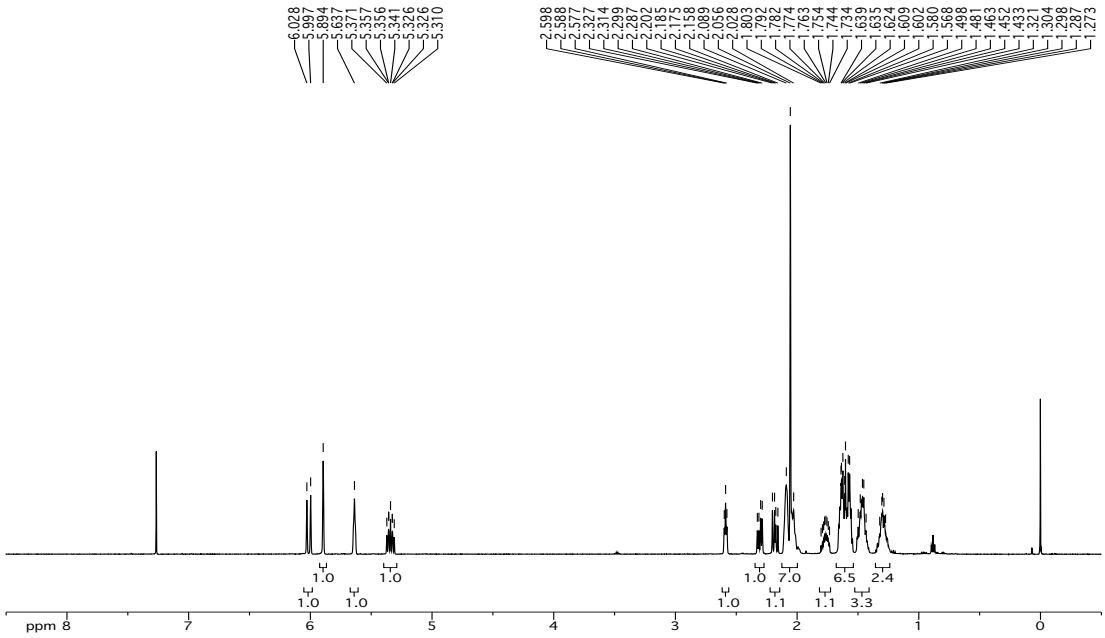


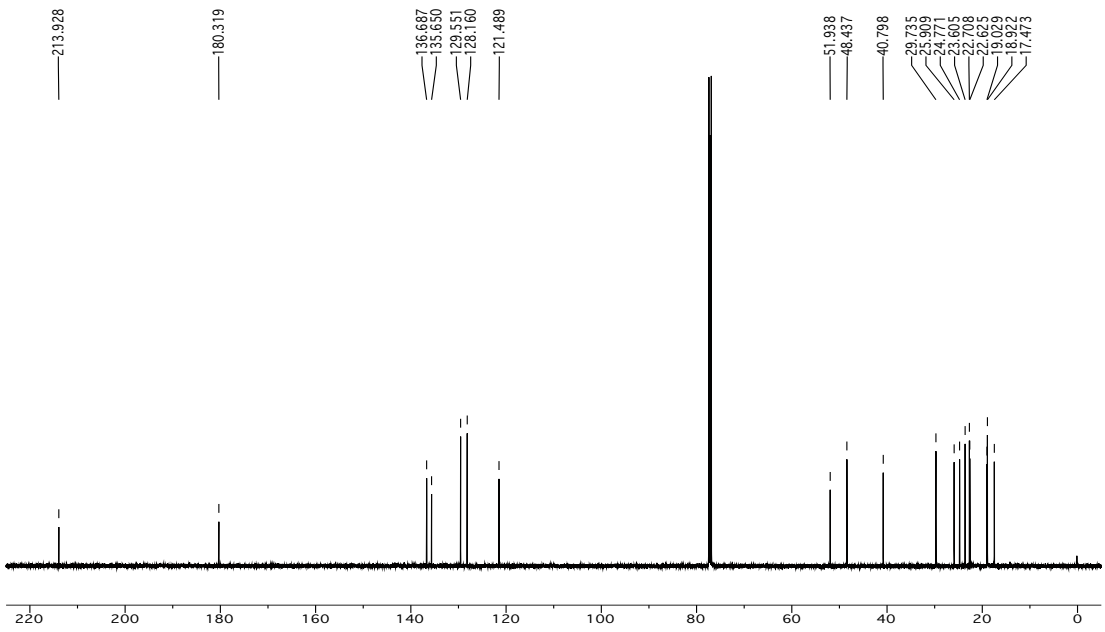
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (4*R,5*S**)-5-((*E*)-3-(Cyclohex-1-en-1-yl)allyl)-2,3-dimethyl-4-phenylcyclopent-2-enone (2.79)**





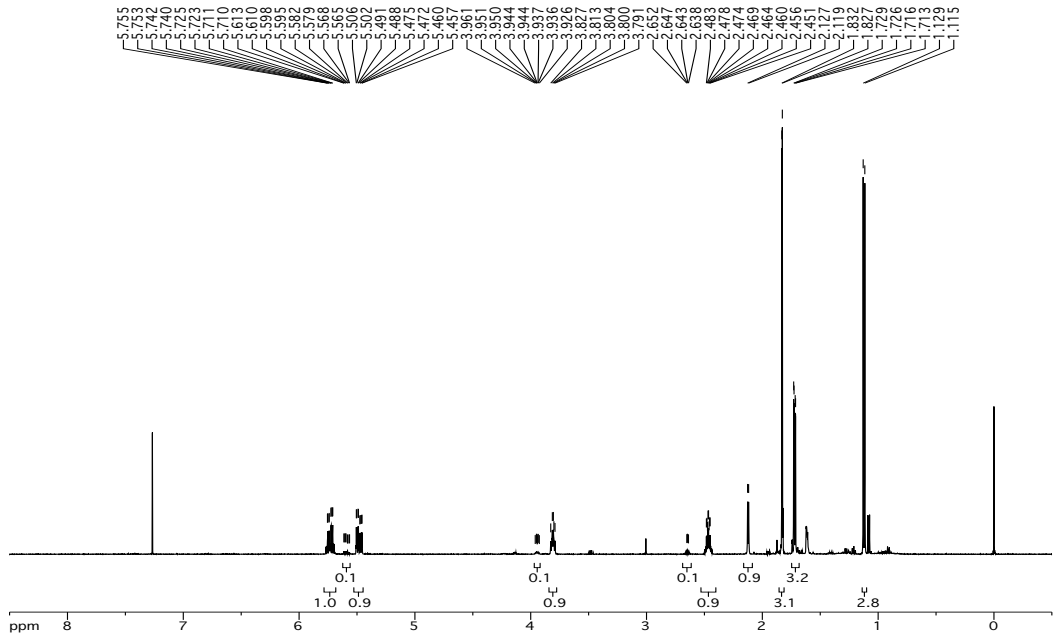
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (3a*R,7a*S**)-7a-((*E*)-3-(Cyclohex-1-en-1-yl)allyl)-3-methyl-3a,4,5,6,7,7a-hexahydro-1*H*-inden-1-one (2.82)**

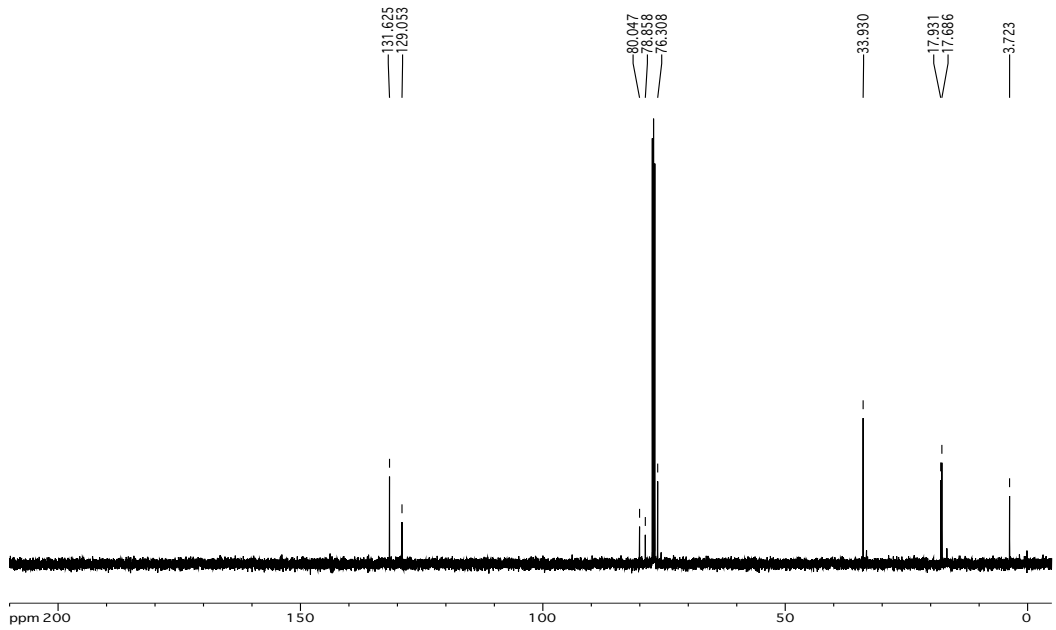




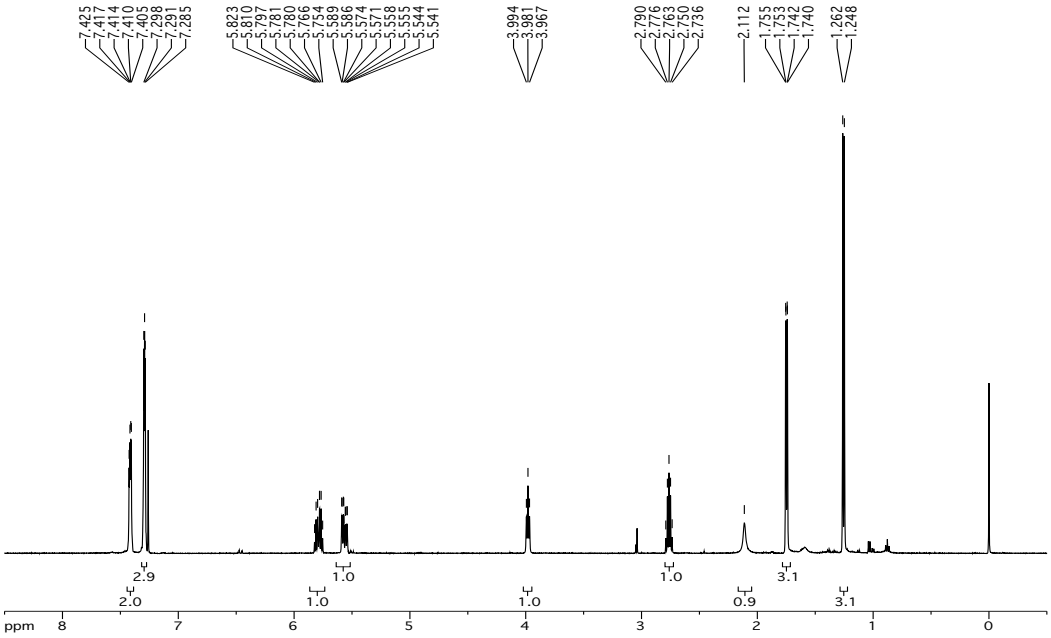
Appendix B NMR Spectra for Chapter 3

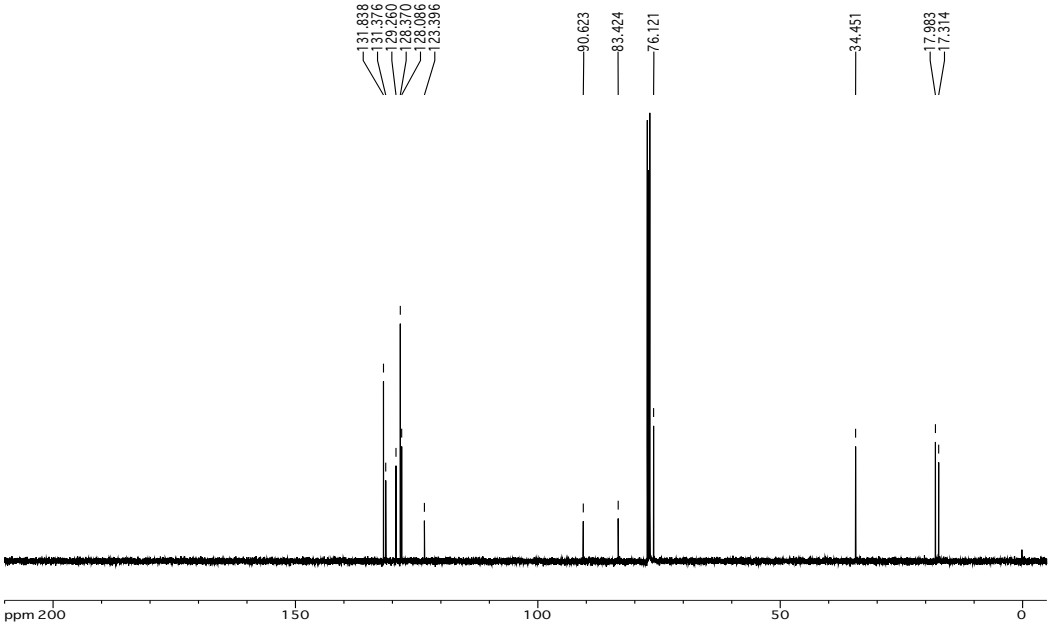
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-5-Methyloct-2-en-6-yn-4-ol (3.37)



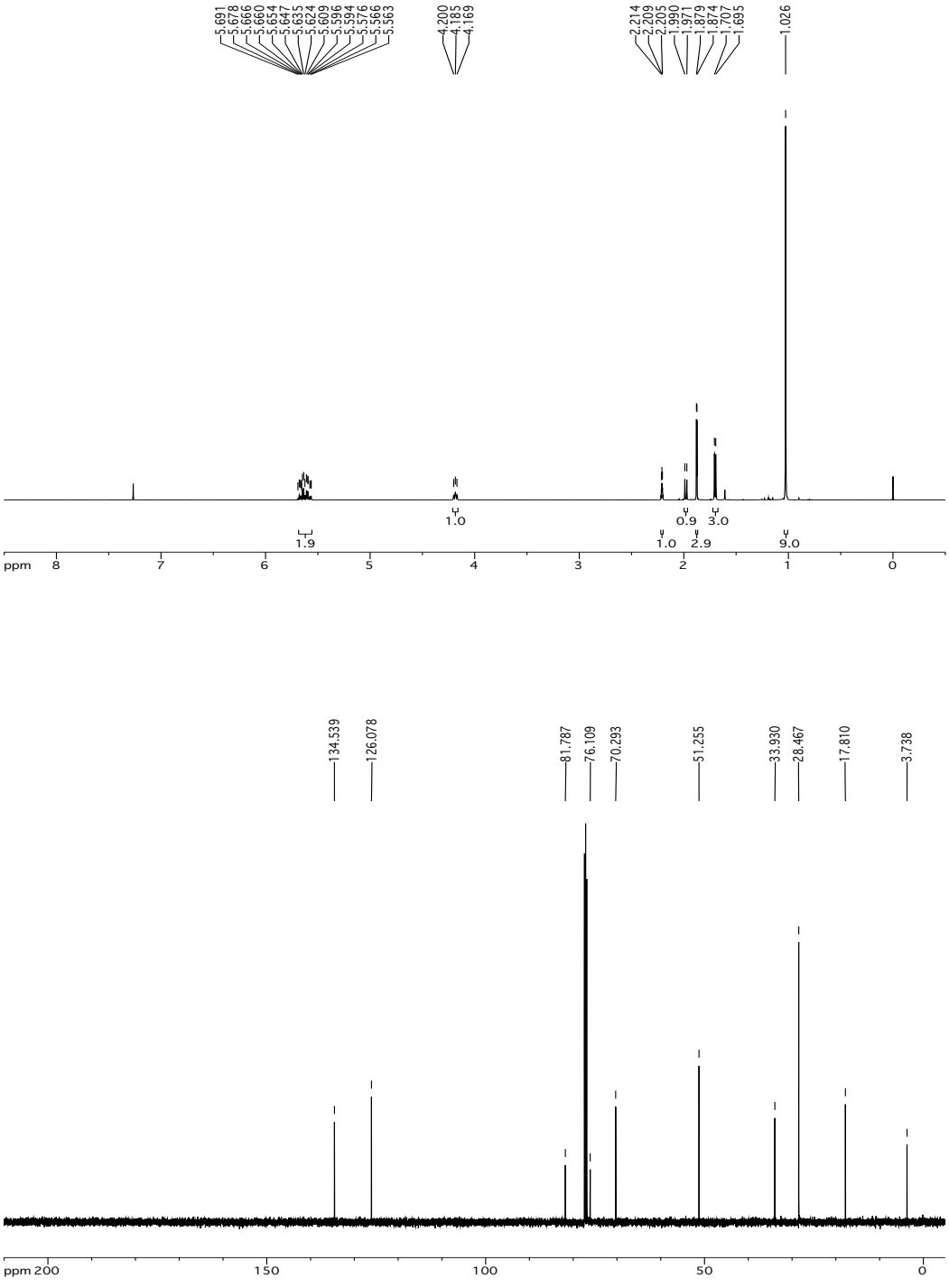


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-3-Methyl-1-phenylhept-5-en-1-yn-4-ol (3.38)

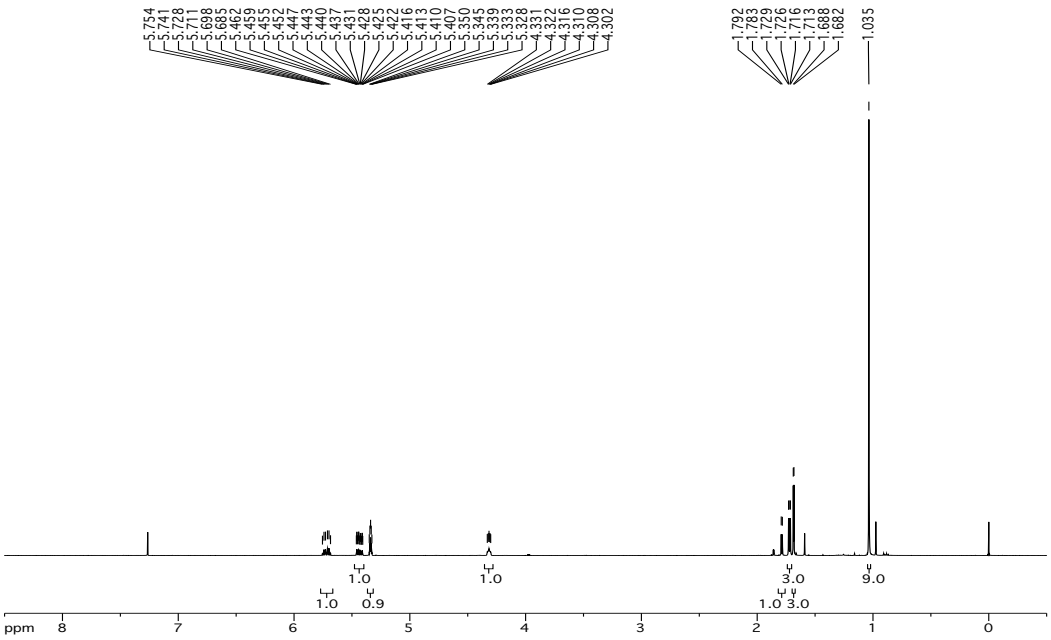


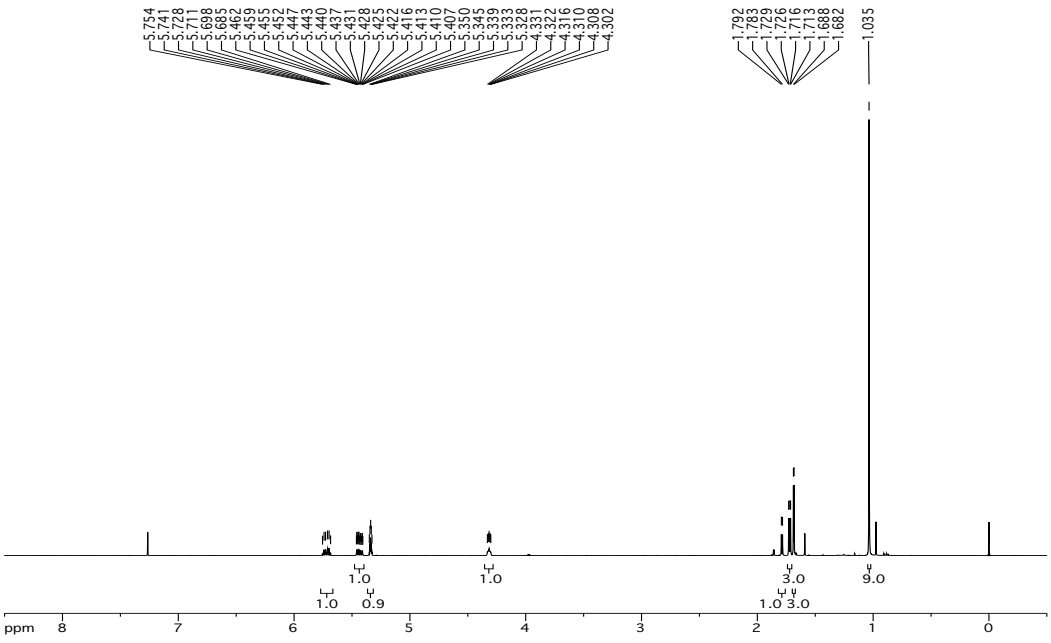


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-5-*tert*-Butyloct-2-en-6-yn-4-ol (3.39)

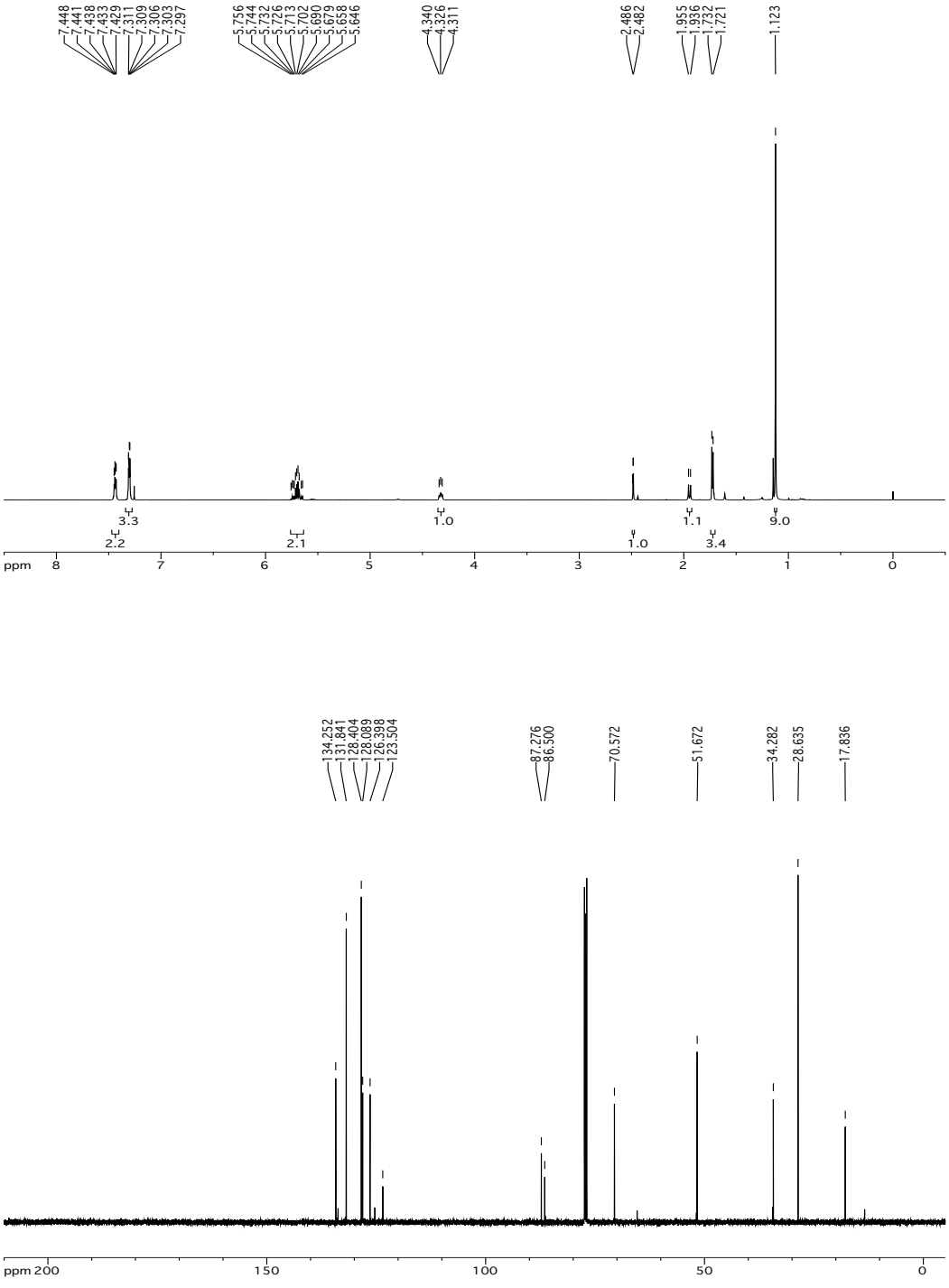


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-5,8,8-trimethylnona-2,5,6-trien-4-ol (3.46)

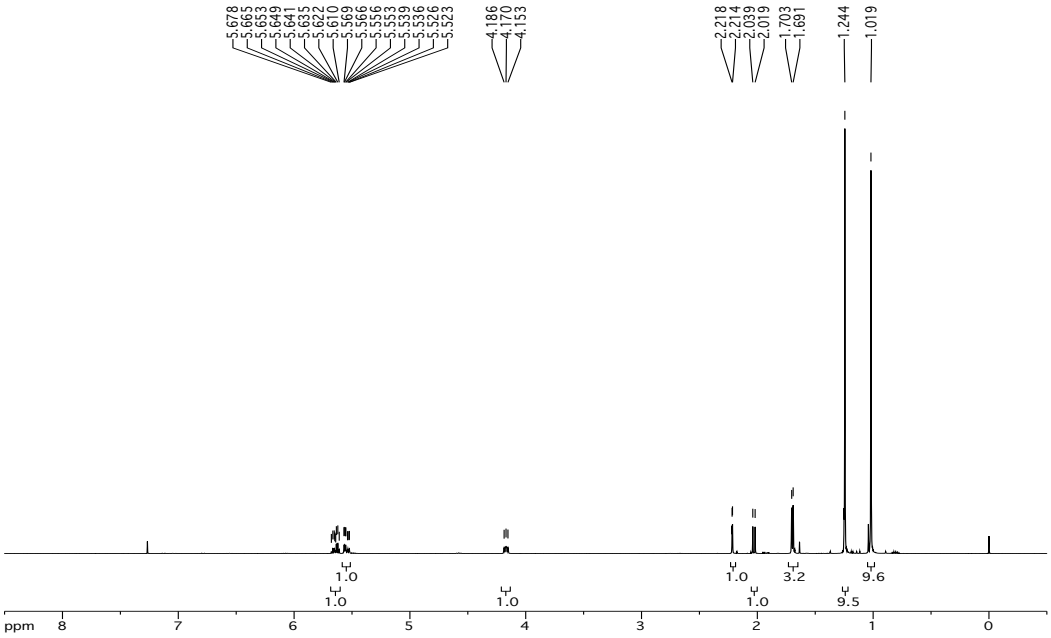


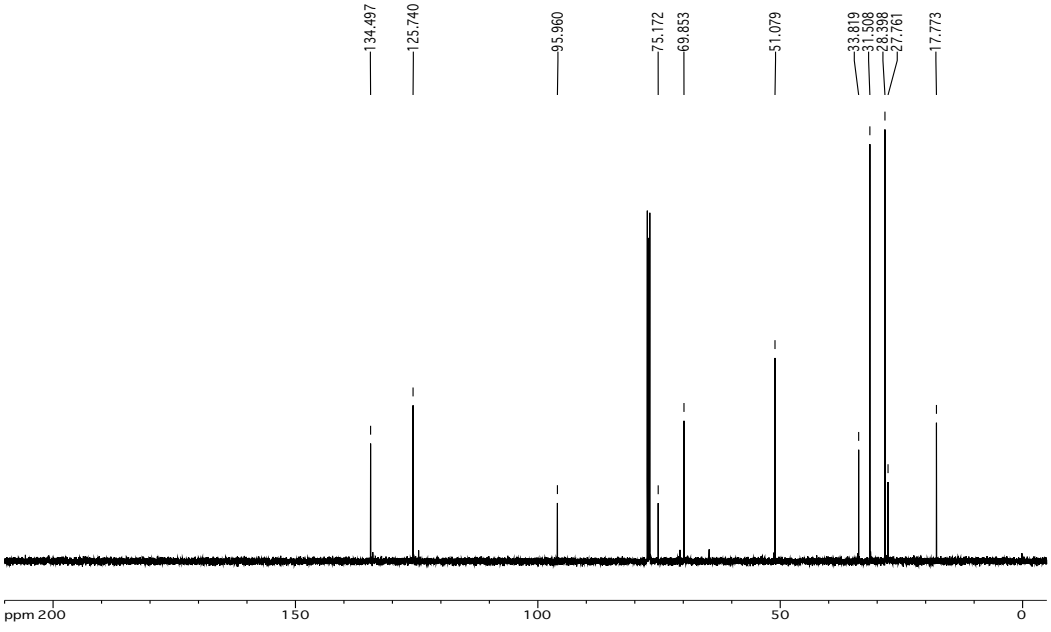


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-3-*tert*-Butyl-1-phenylhept-5-en-1-yn-4-ol (3.40)

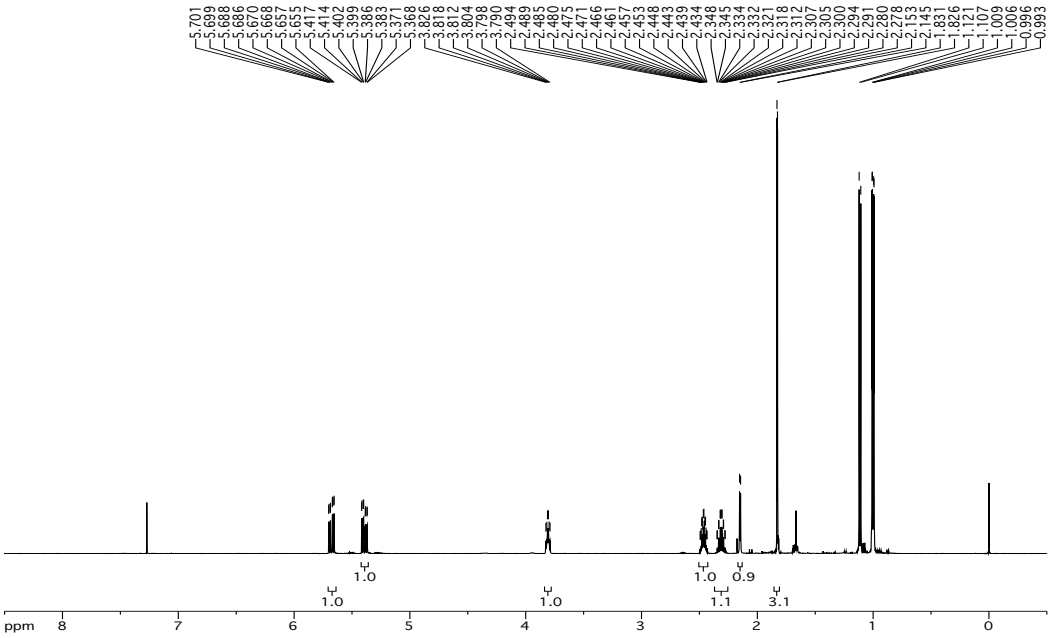


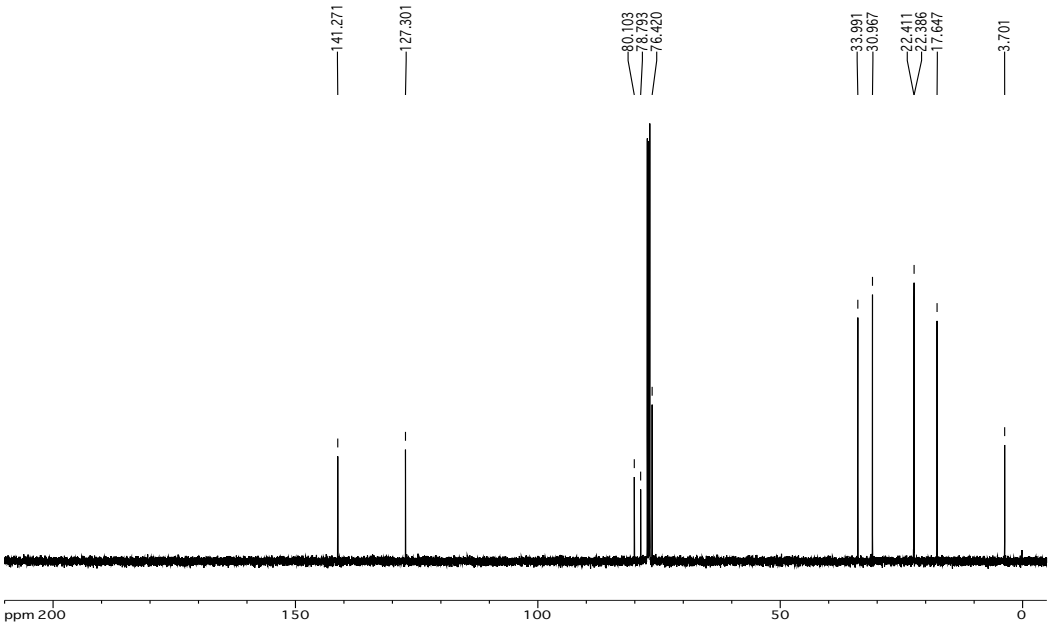
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of 8,8-dimethylnon-2-en-6-yn-4-ol (3.41)



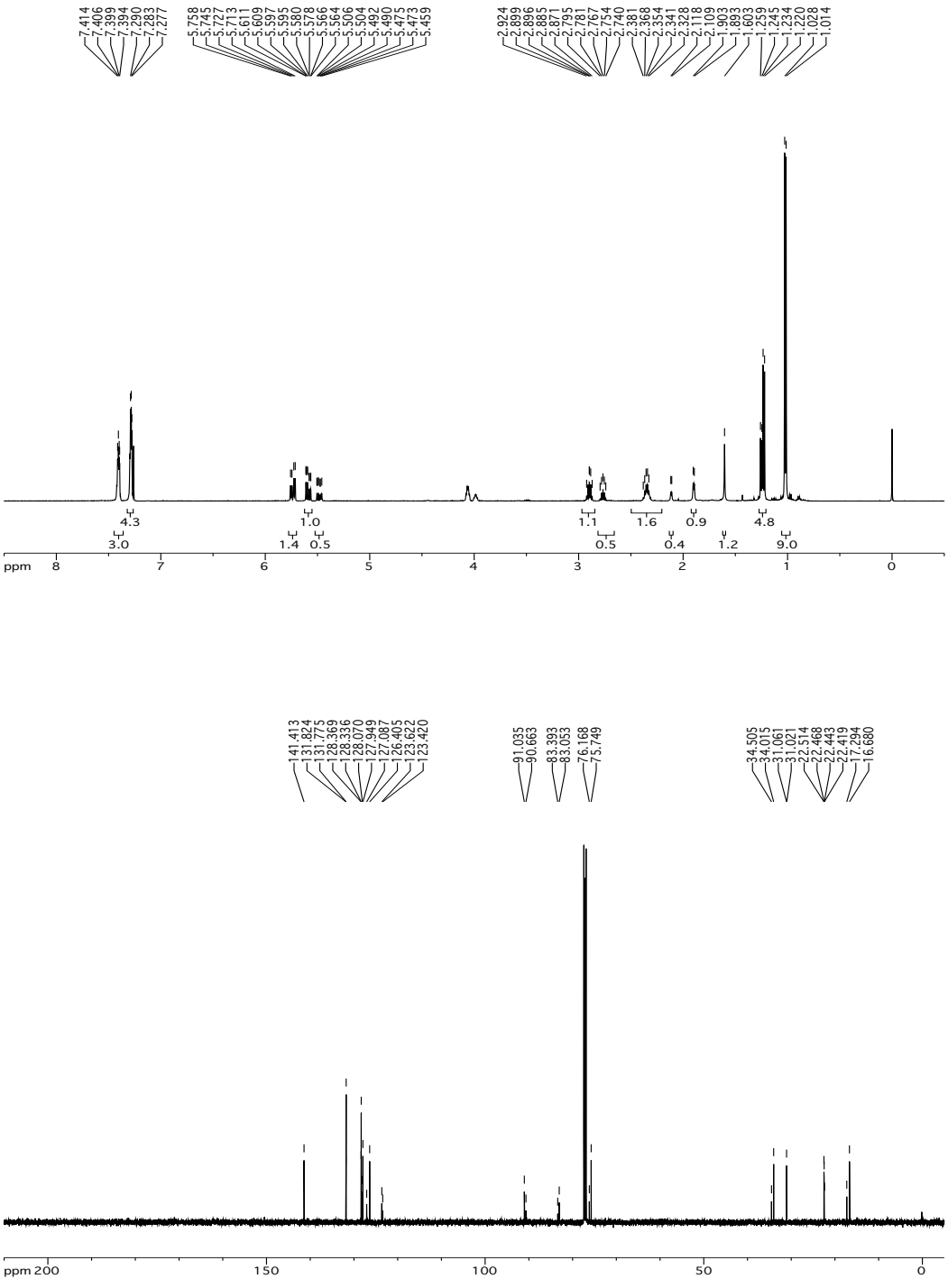


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-4,8-Dimethylnon-6-en-2-yn-5-one (3.42)

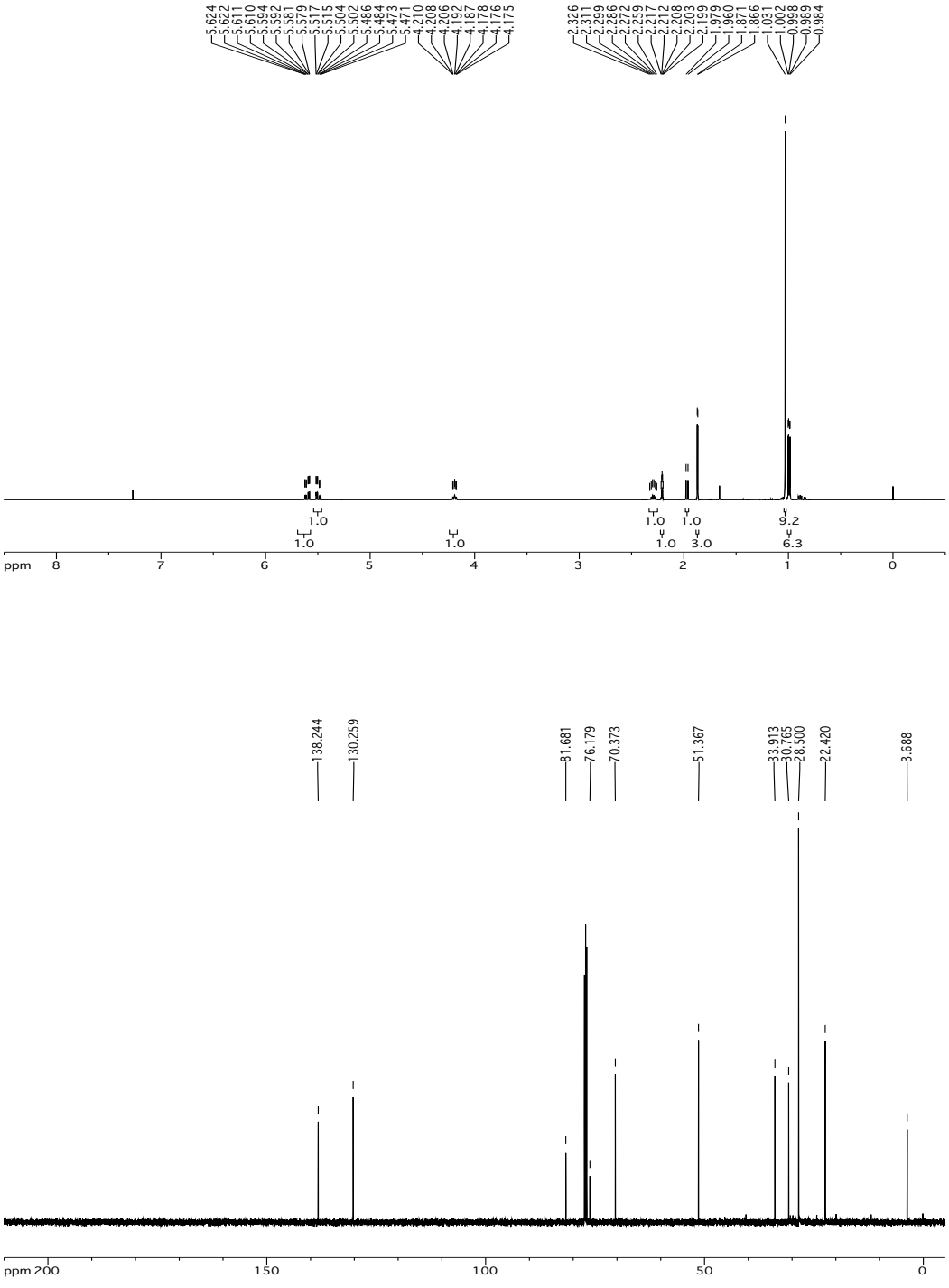




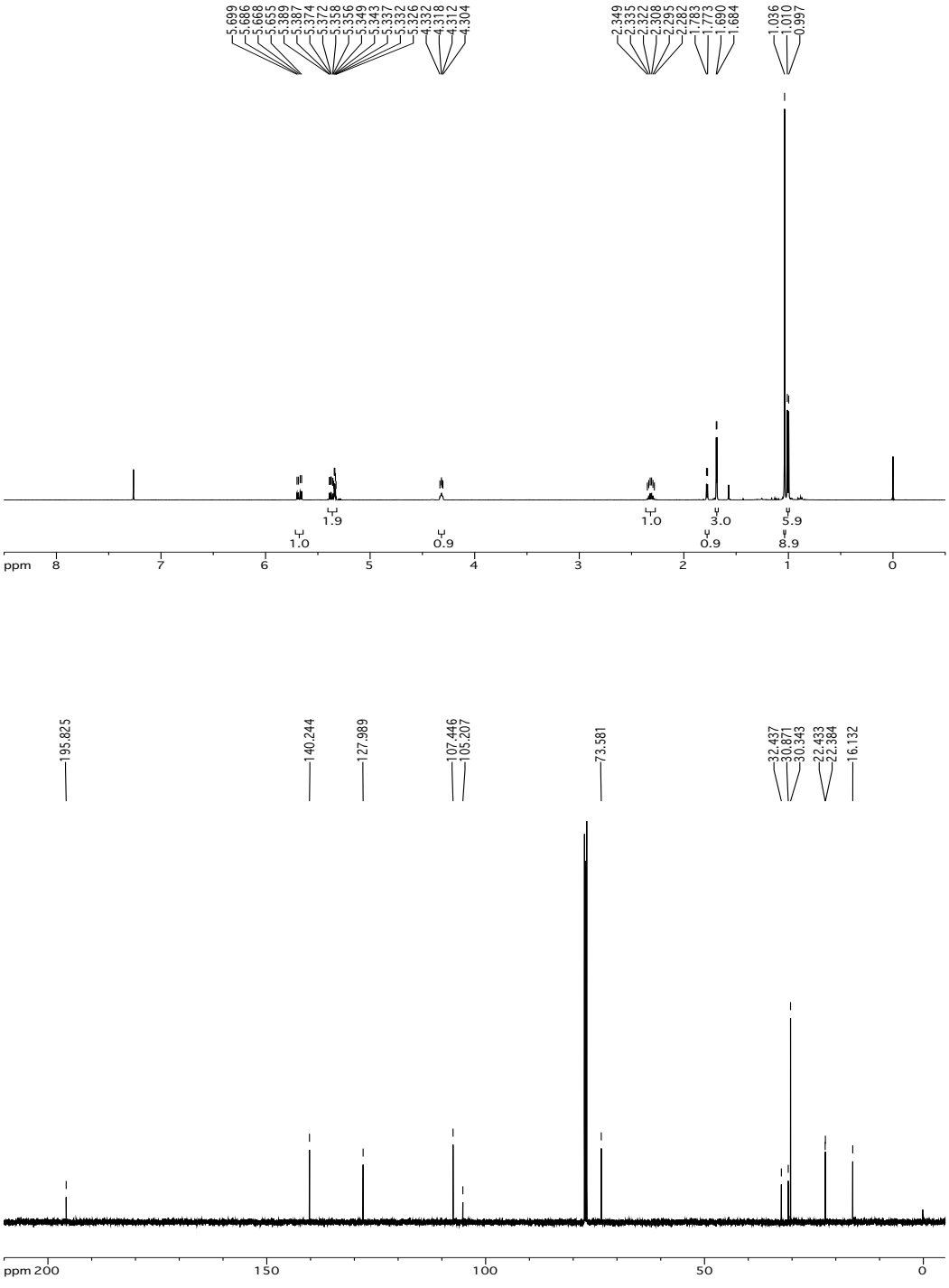
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-3,7-Dimethyl-1-phenyloct-5-en-1-yn-4-ol (3.43)



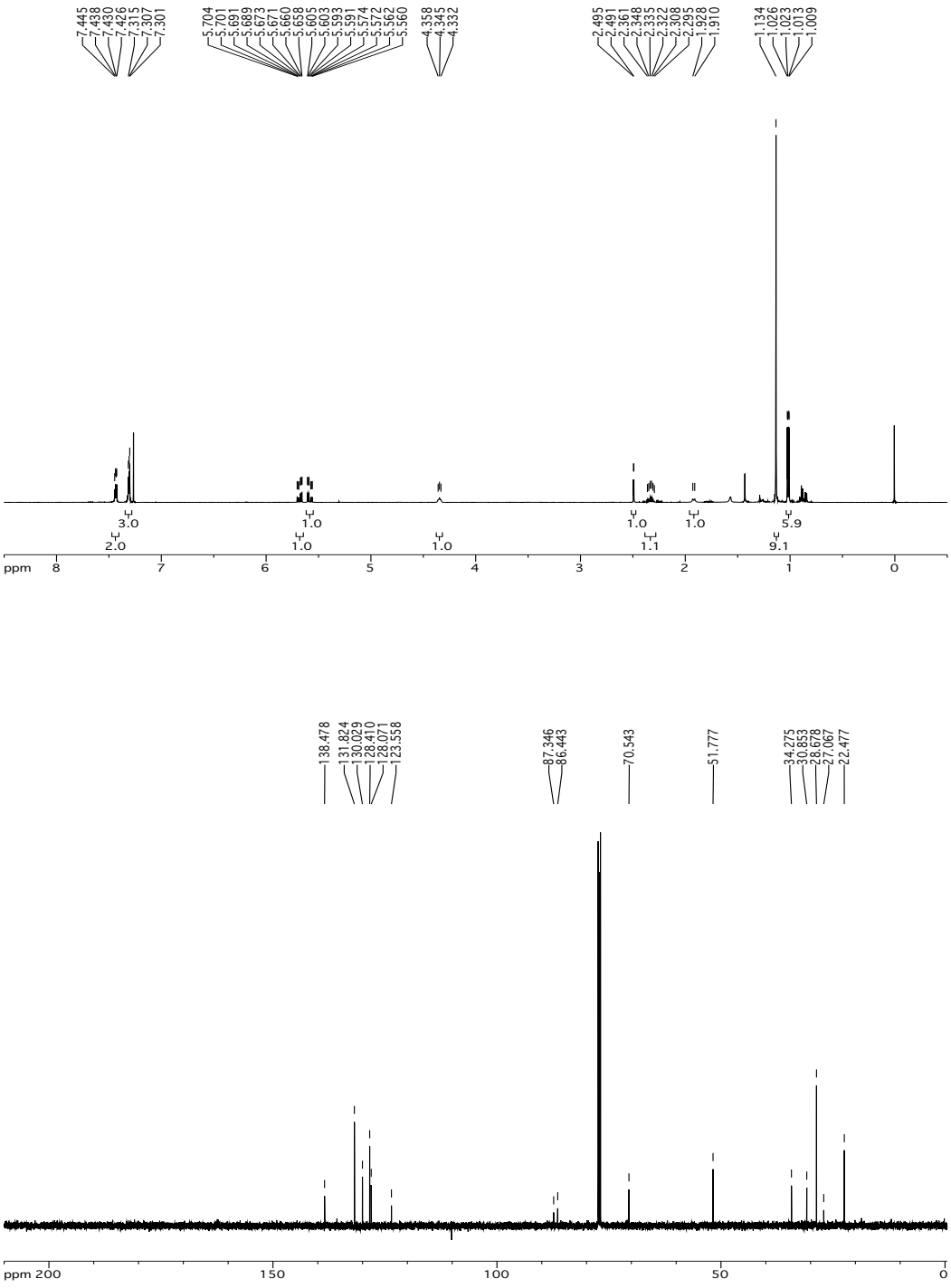
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-4-*tert*-Butyl-8-methylnon-6-en-2-yn-5-ol (3.44)



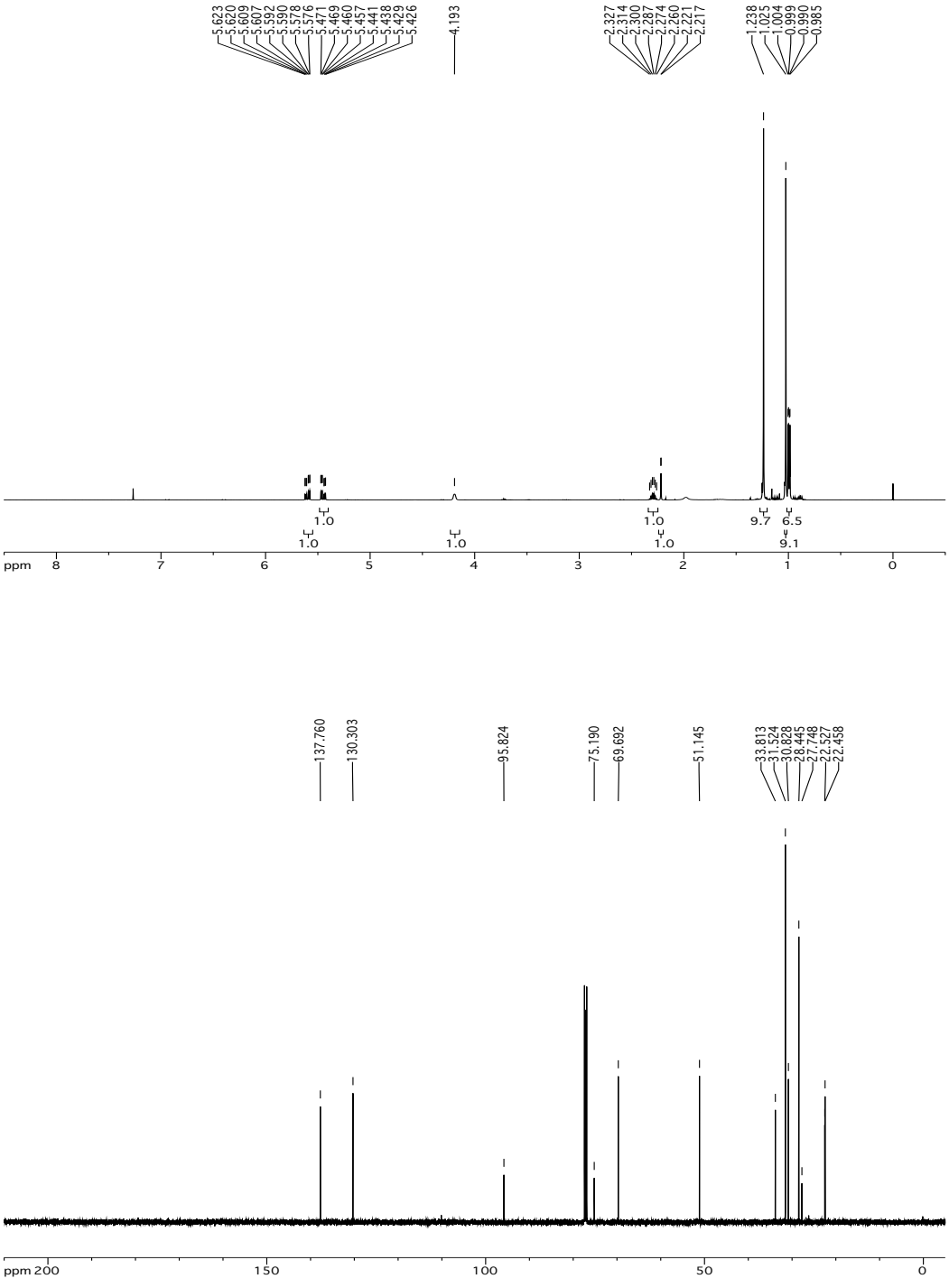
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-2,6,9,9-tetramethyldeca-3,6,7-trien-5-ol (3.48)



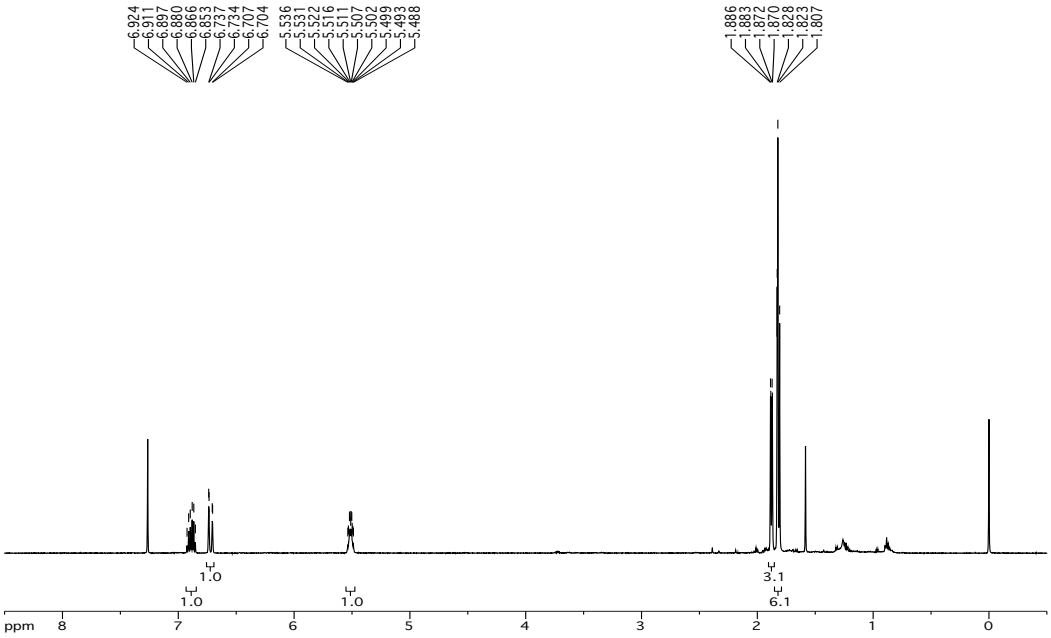
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-3-*tert*-Butyl-7-methyl-1-phenyloct-5-en-1-yn-4-ol (3.45)

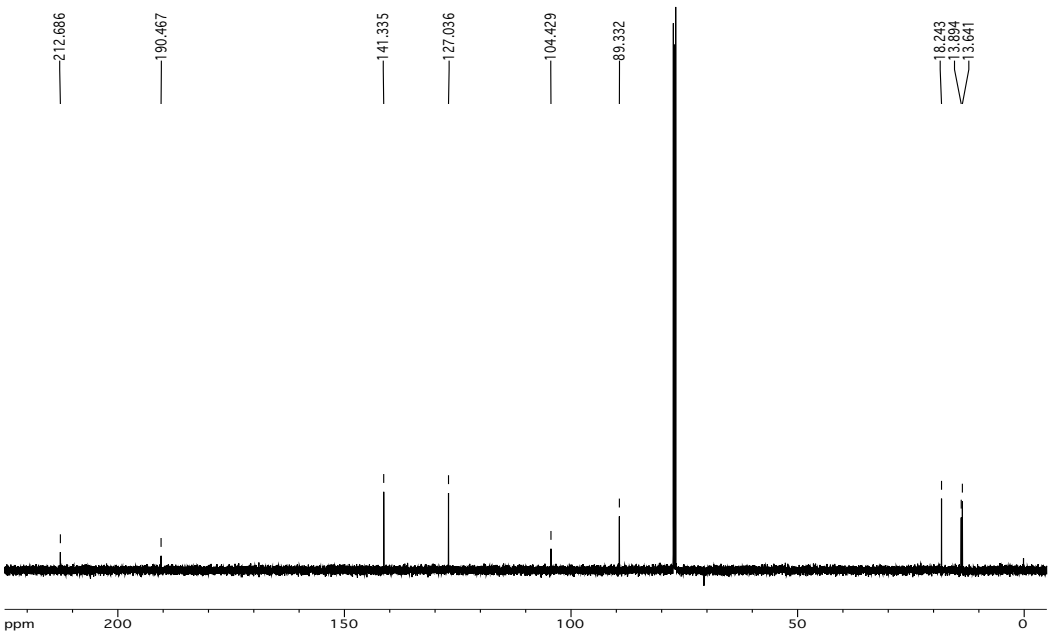


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-6-*tert*-Butyl-2,9,9-trimethyldec-3-en-7-yn-5-ol (3.46)

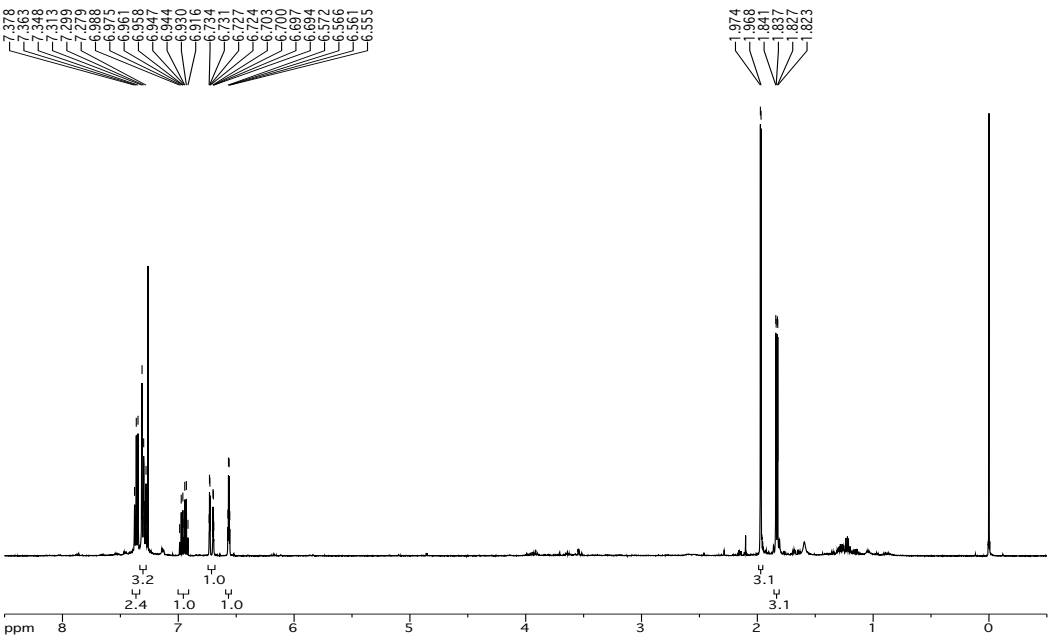


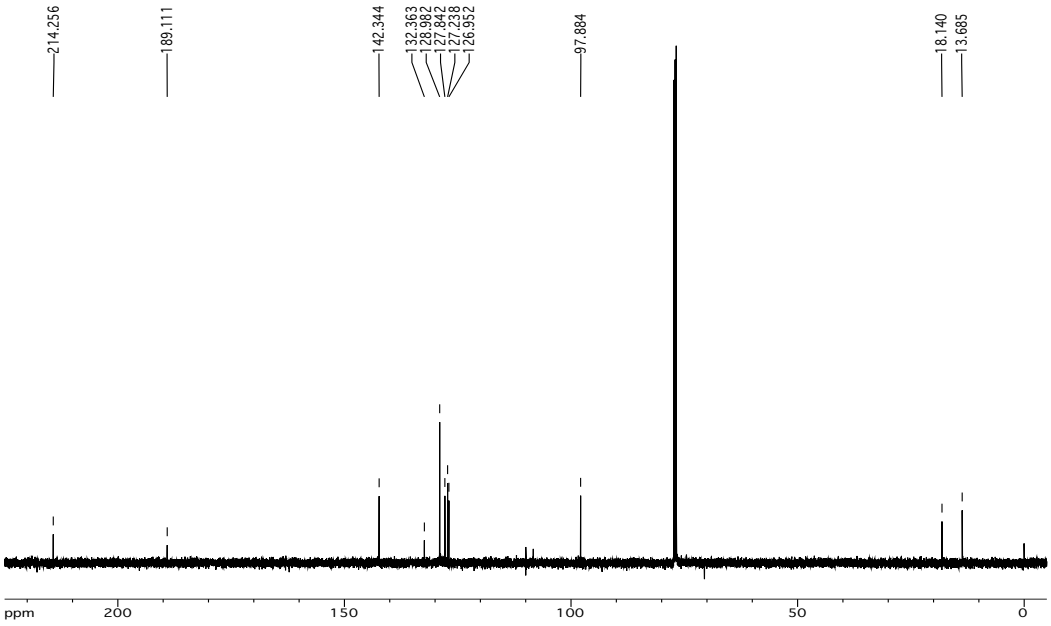
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-5-Methyloct-2-en-6-yn-4-one and (*E*)-5-methylocta-2,5,6-trien-4-one (3.49)



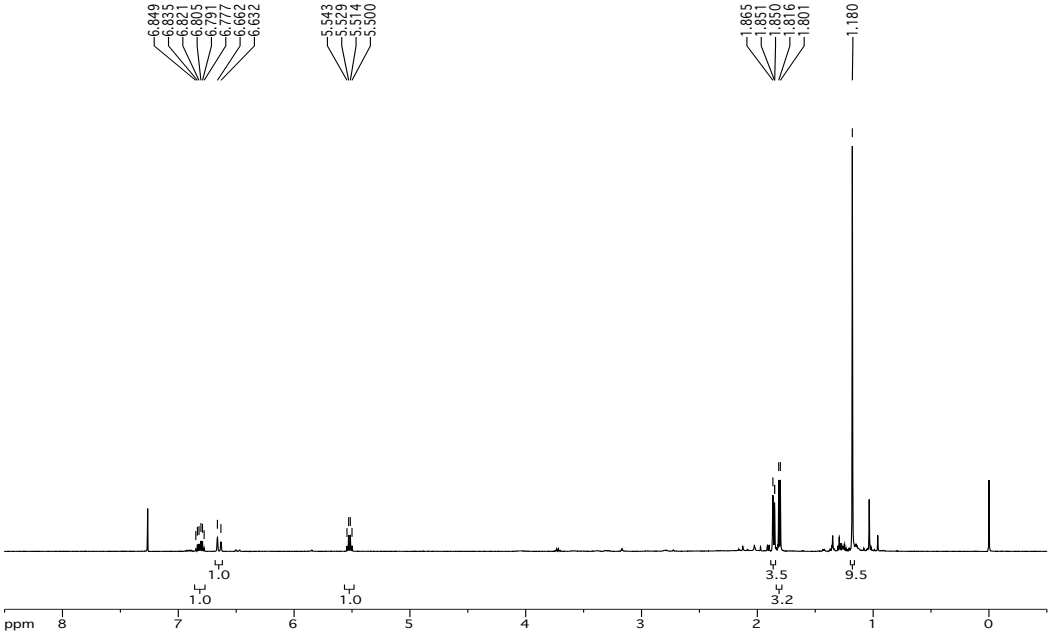


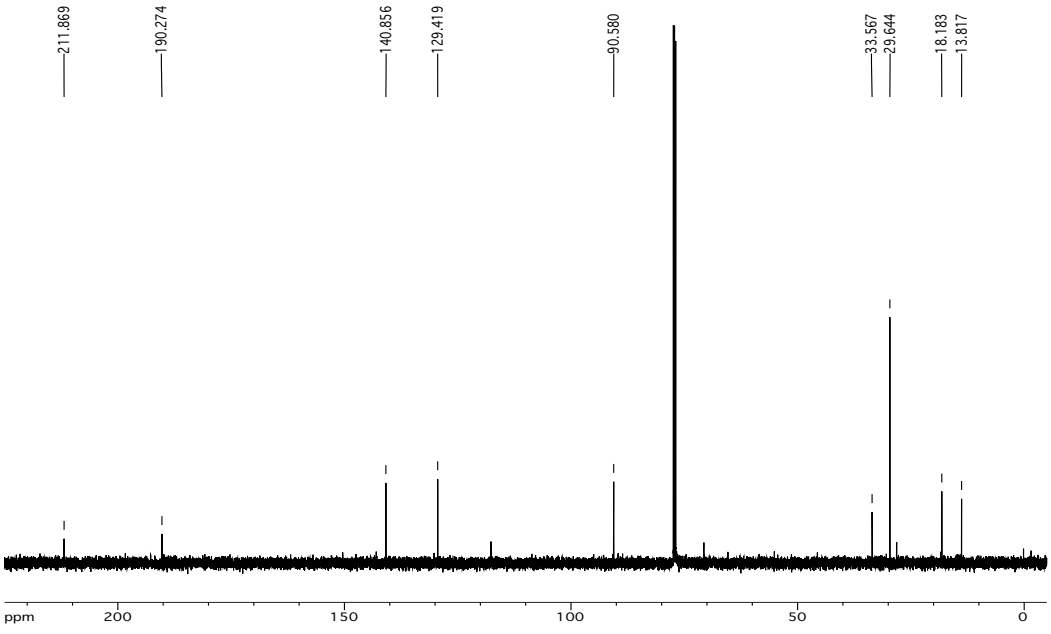
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-3-Methyl-1-phenylhept-5-en-1-yn-4-one and (*E*)-3-methyl-1-phenylhepta-1,2,5-trien-4-one (3.50)



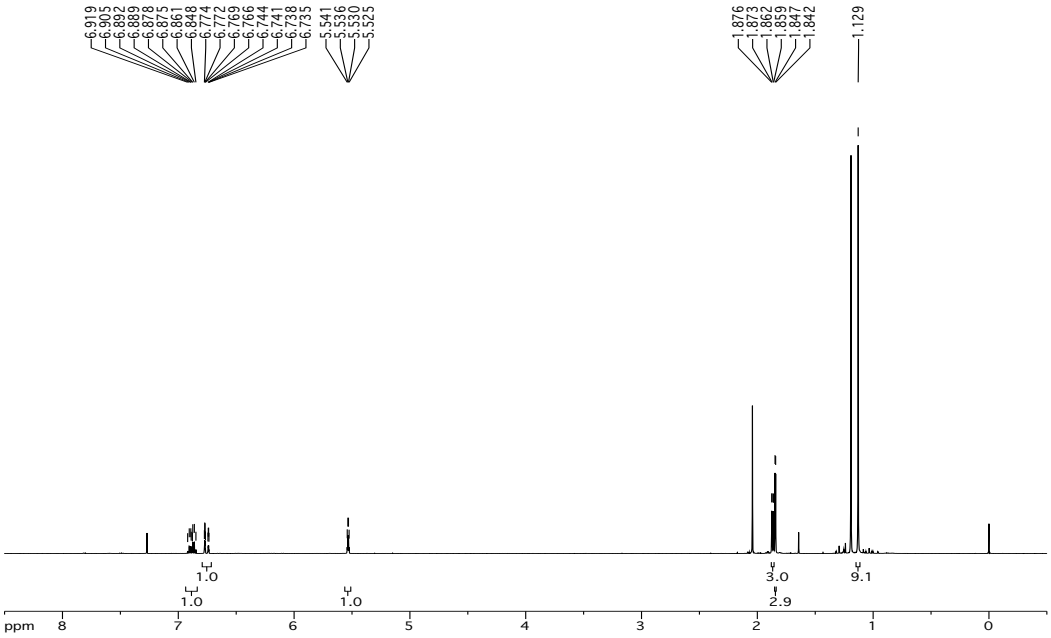


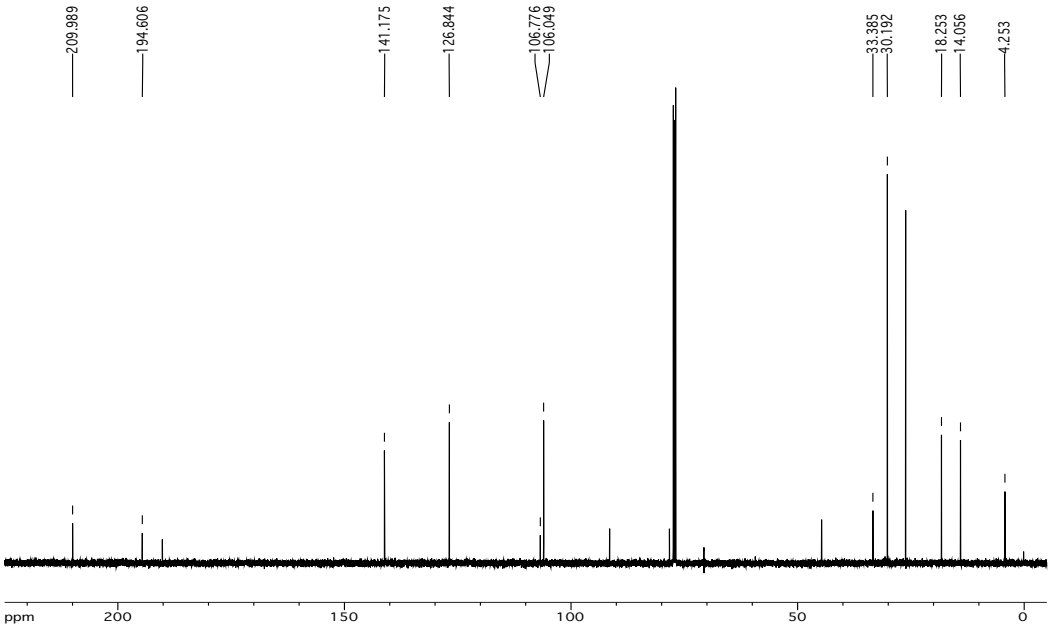
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-5-*tert*-Butyloct-2-en-6-yn-4-one and (*E*)-5-*tert*-butylocta-2,5,6-trien-4-one (3.51)



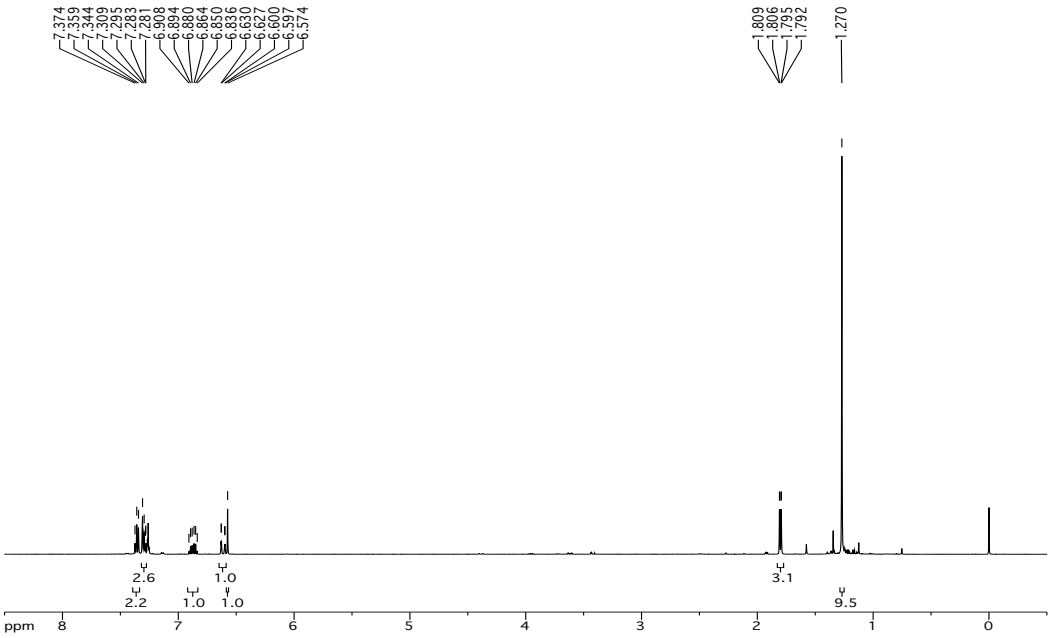


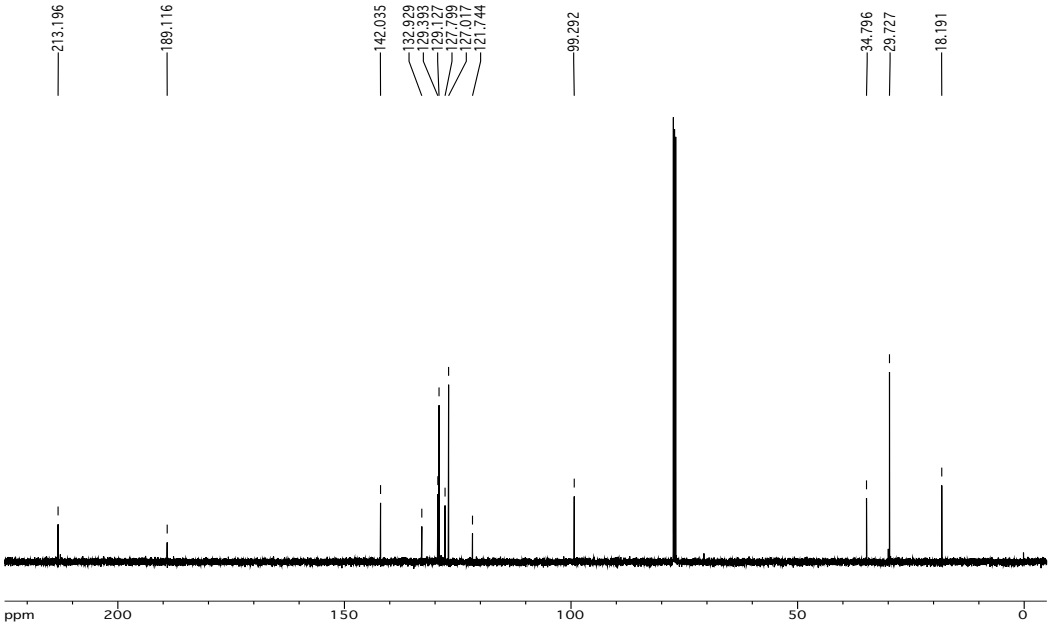
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-5,8,8-Trimethylnona-2,5,6-trien-4-one (3.52)



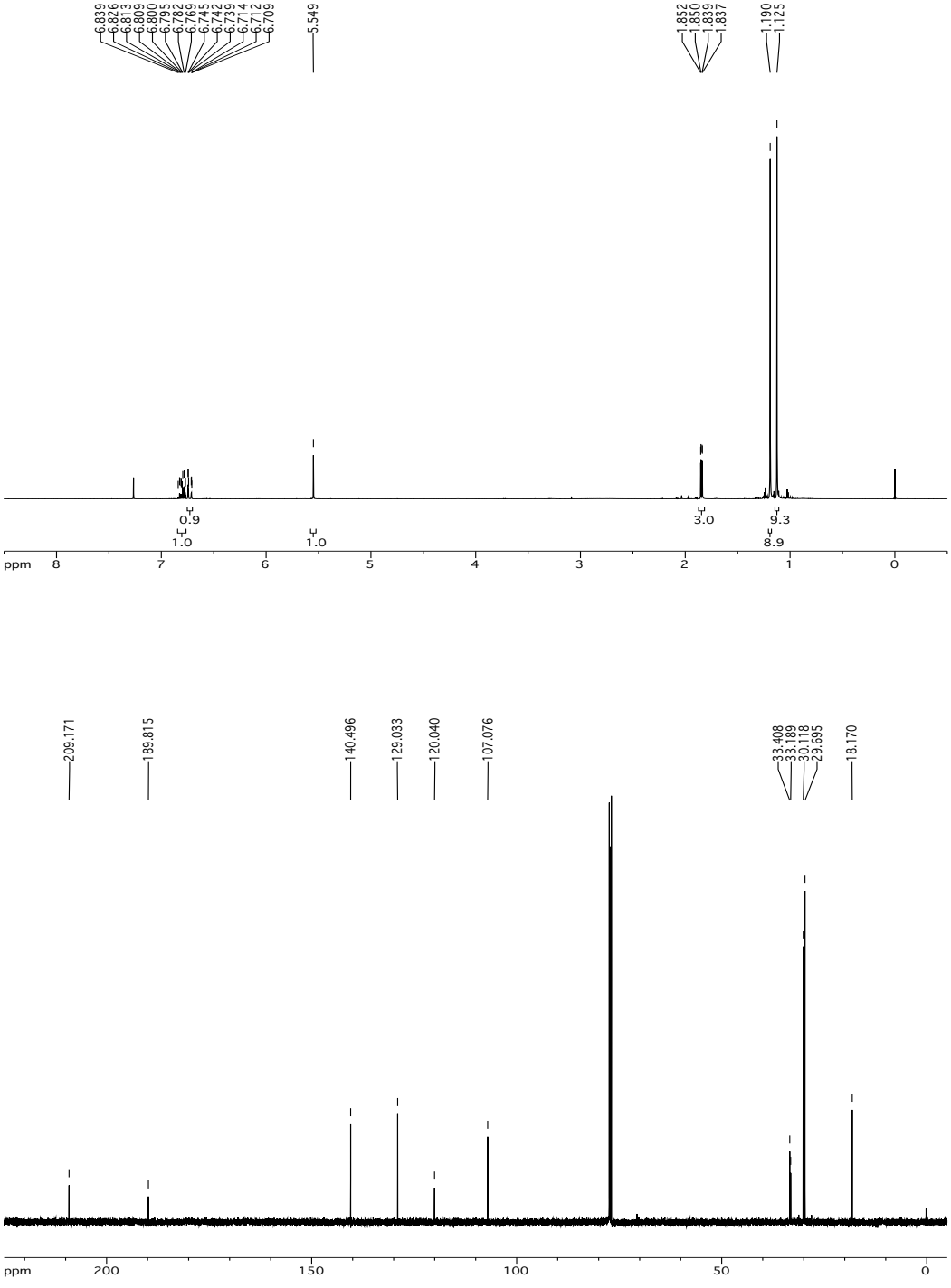


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-3-*tert*-Butyl-1-phenylhept-5-en-1-yn-4-one and (*E*)-3-*tert*-butyl-1-phenylhepta-1,2,5-trien-4-one (3.53)

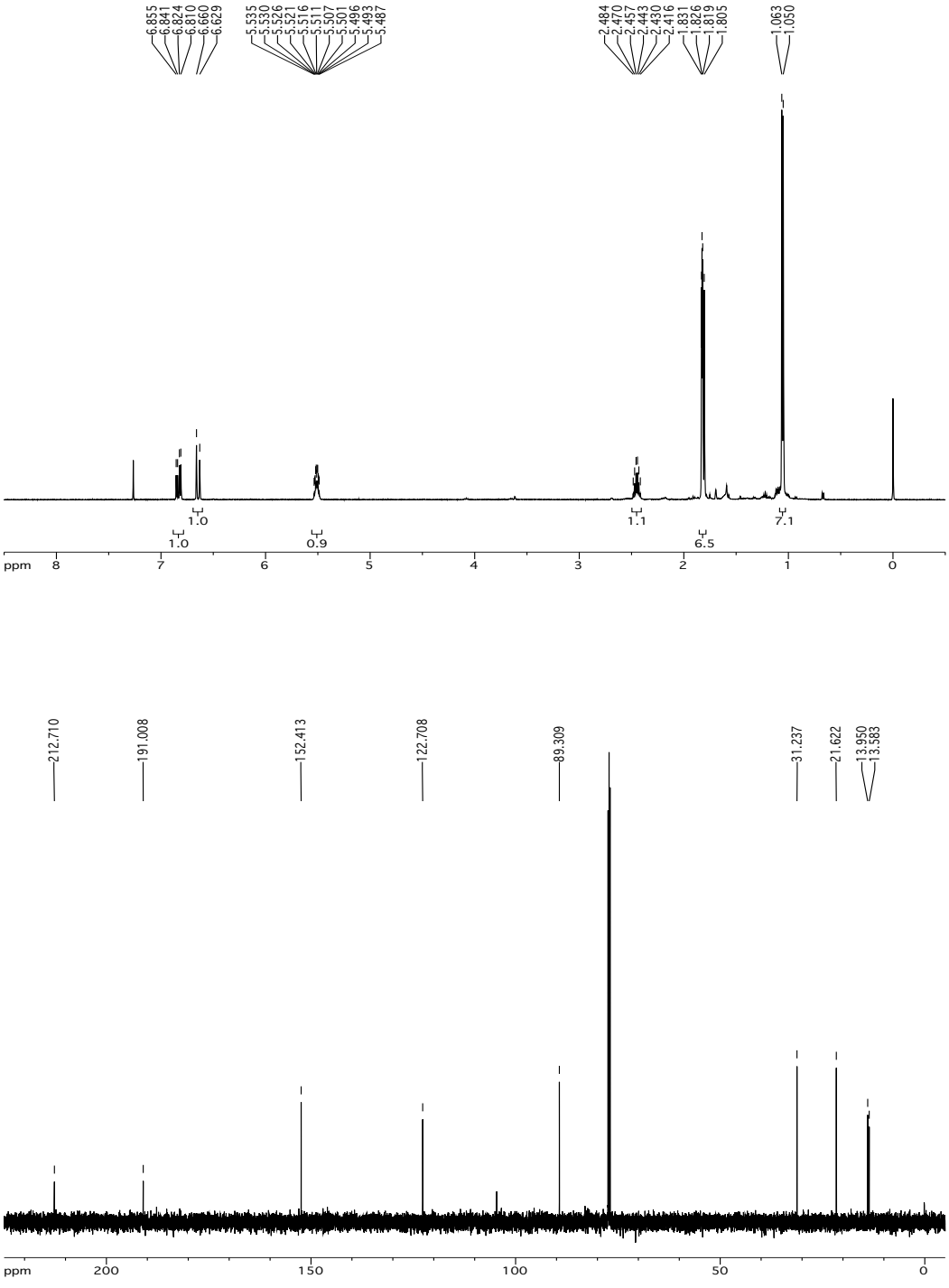




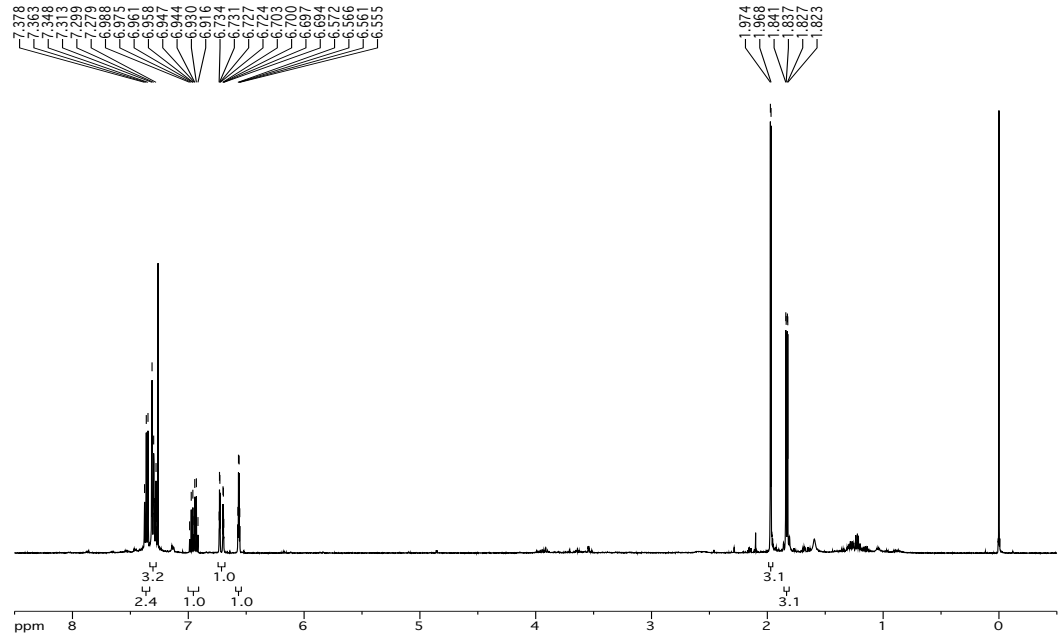
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-5-*tert*-butyl-8,8-dimethylnona-2,6,7-trien-4-one (3.54)

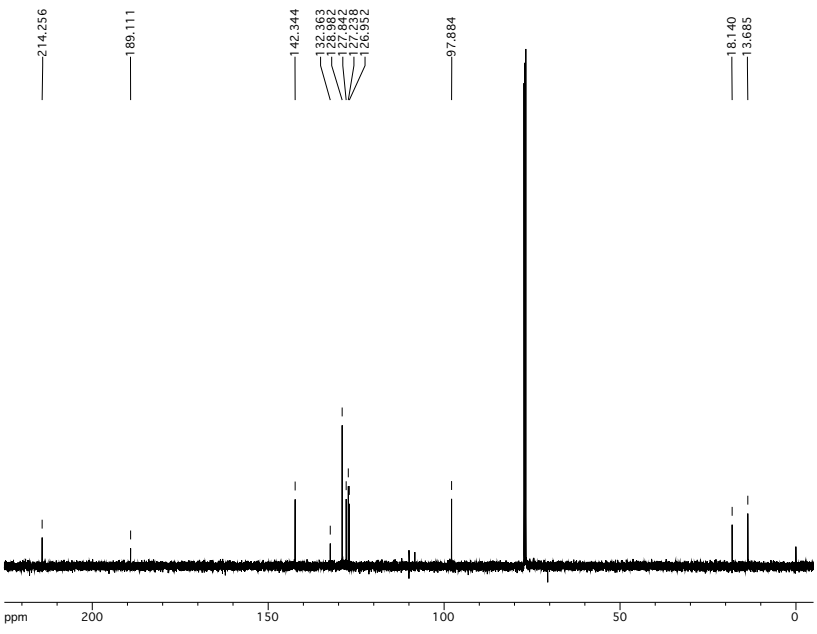


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-4,8-dimethylnona-2,3,6-trien-5-one (3.55)

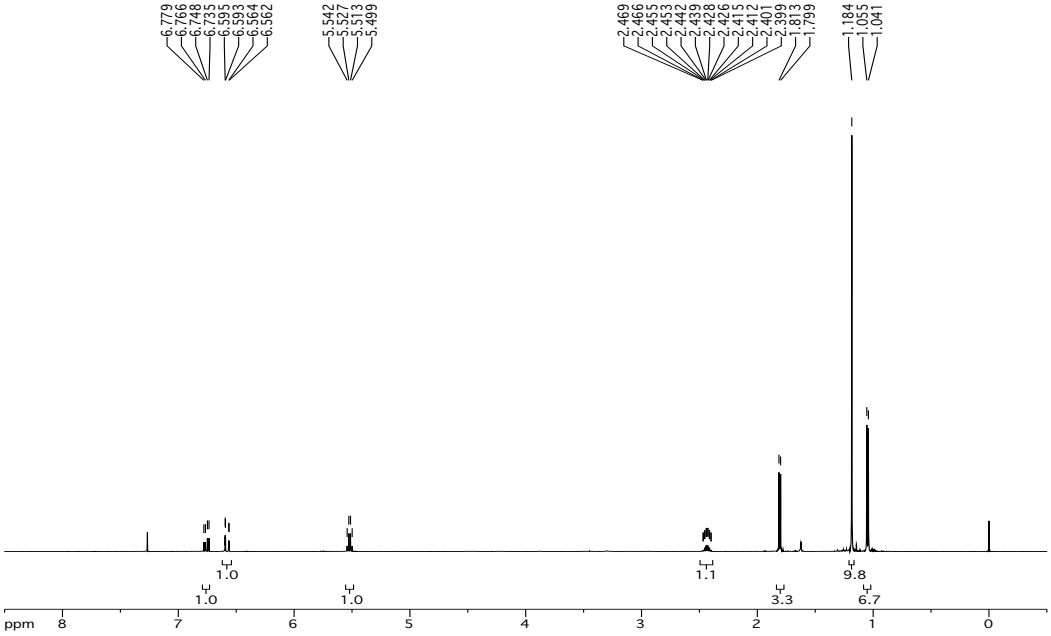


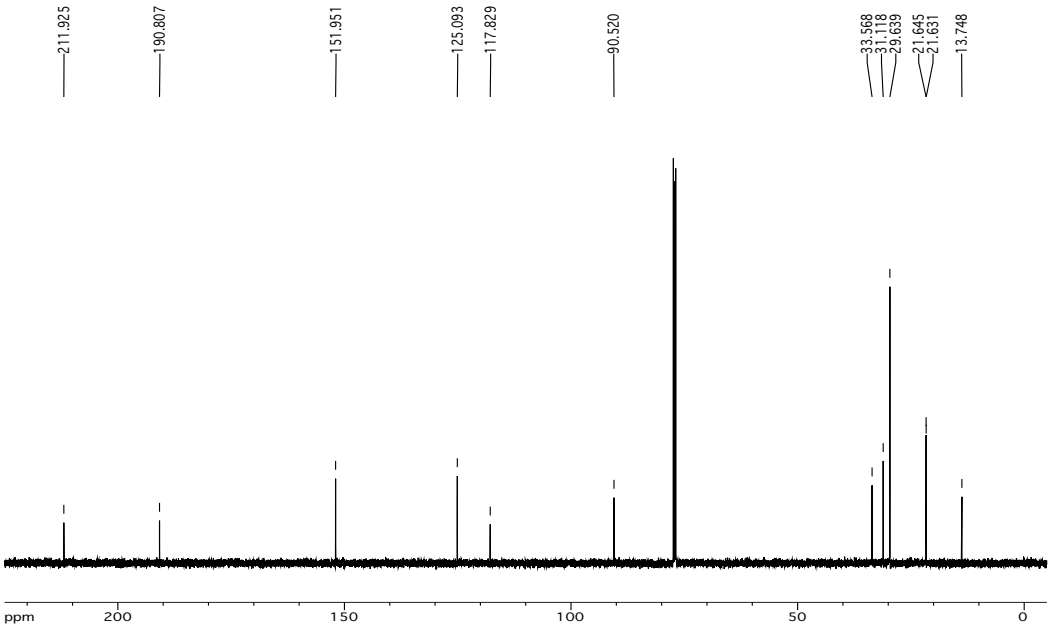
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-3,7-dimethyl-1-phenylocta-1,2,5-trien-4-one (3.56)



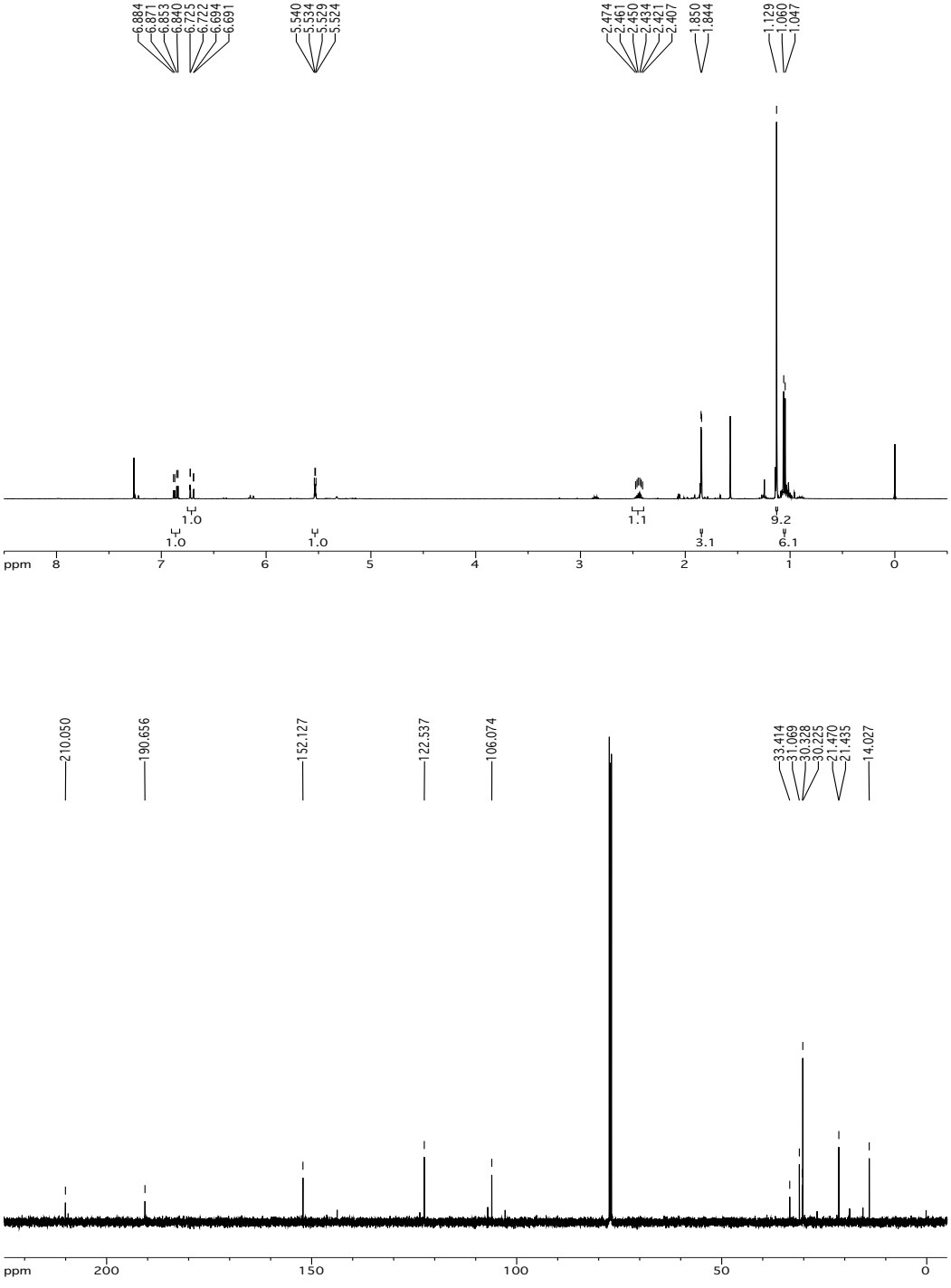


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-4-*tert*-butyl-8-methylnona-2,3,6-trien-5-one (3.57)

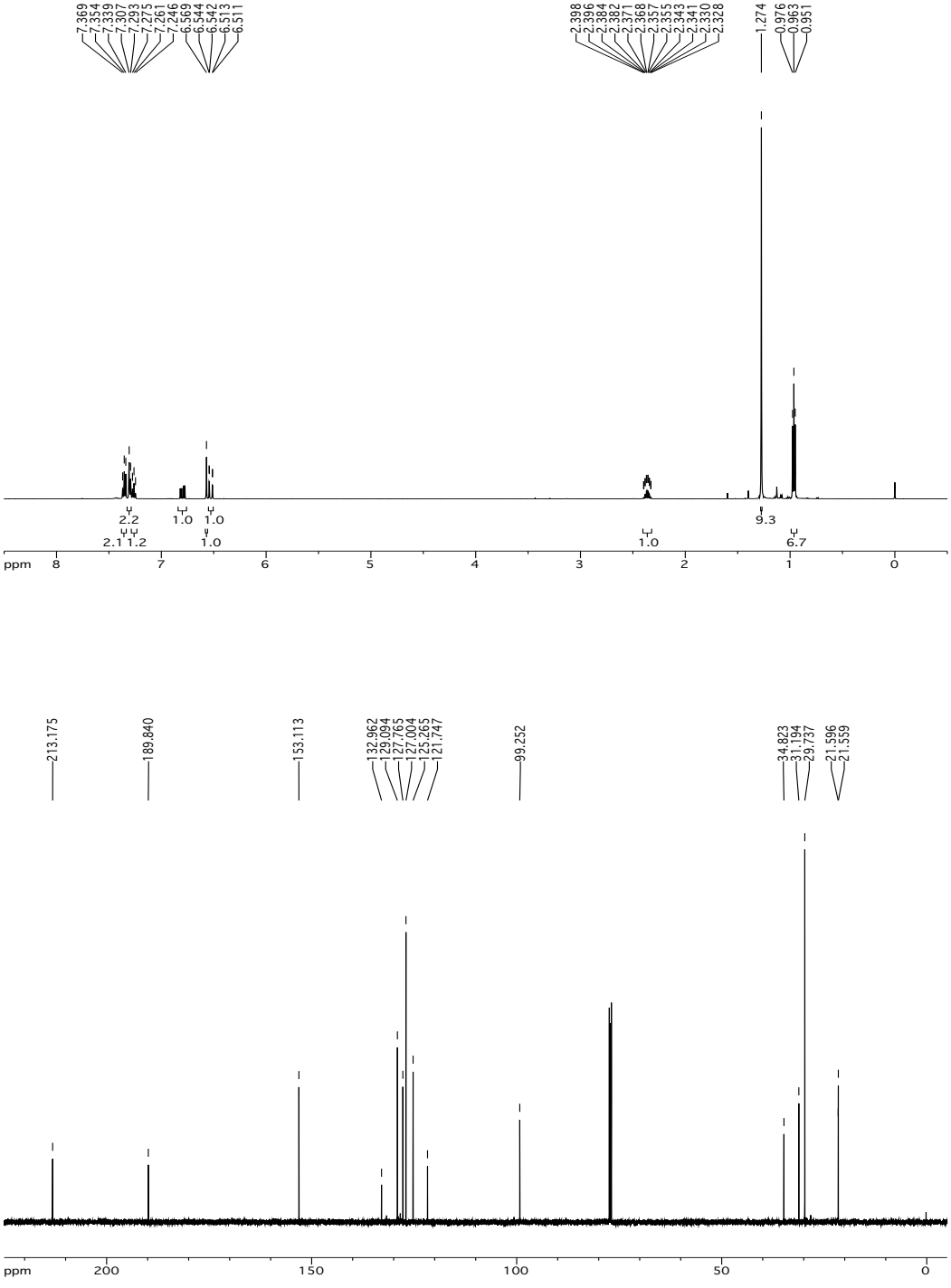




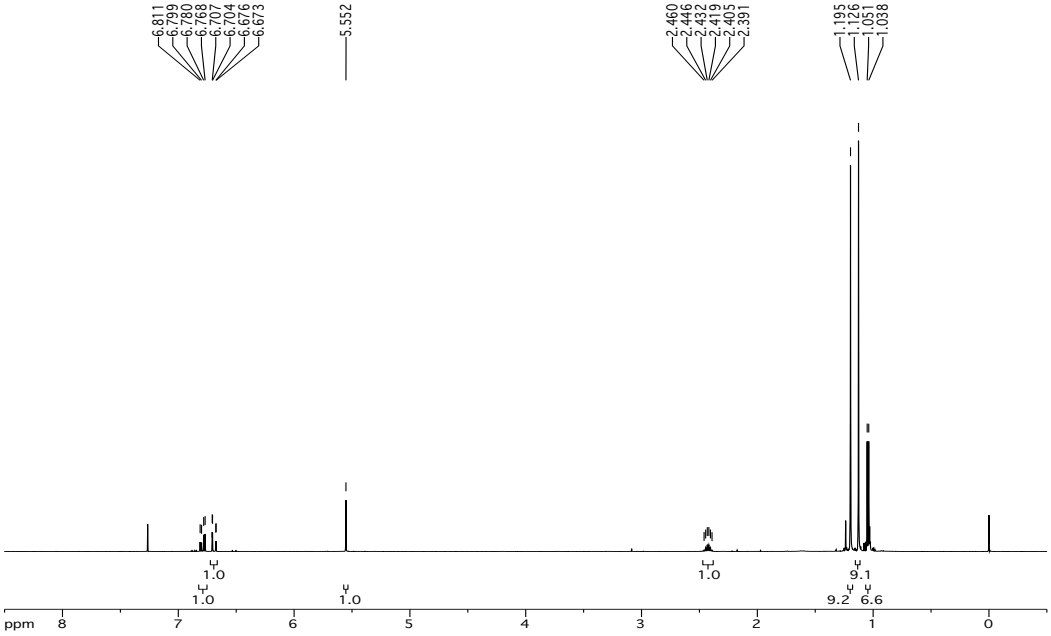
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-2,6,9,9-Tetramethyldeca-3,6,7-trien-5-one (3.58)

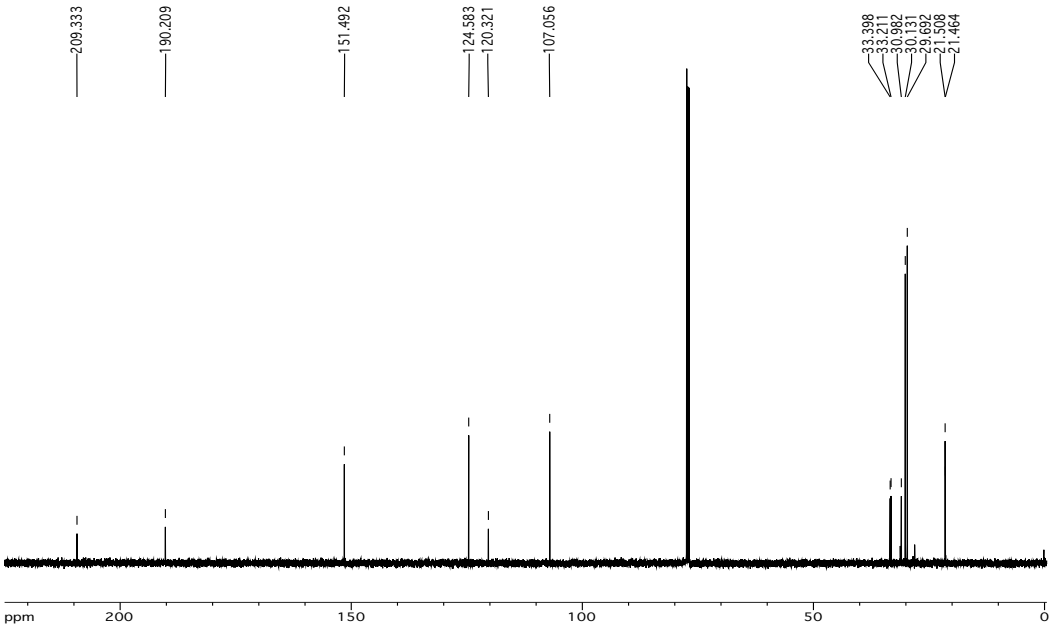


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-3-*tert*-butyl-7-methyl-1-phenylocta-1,2,5-trien-4-one (3.59)

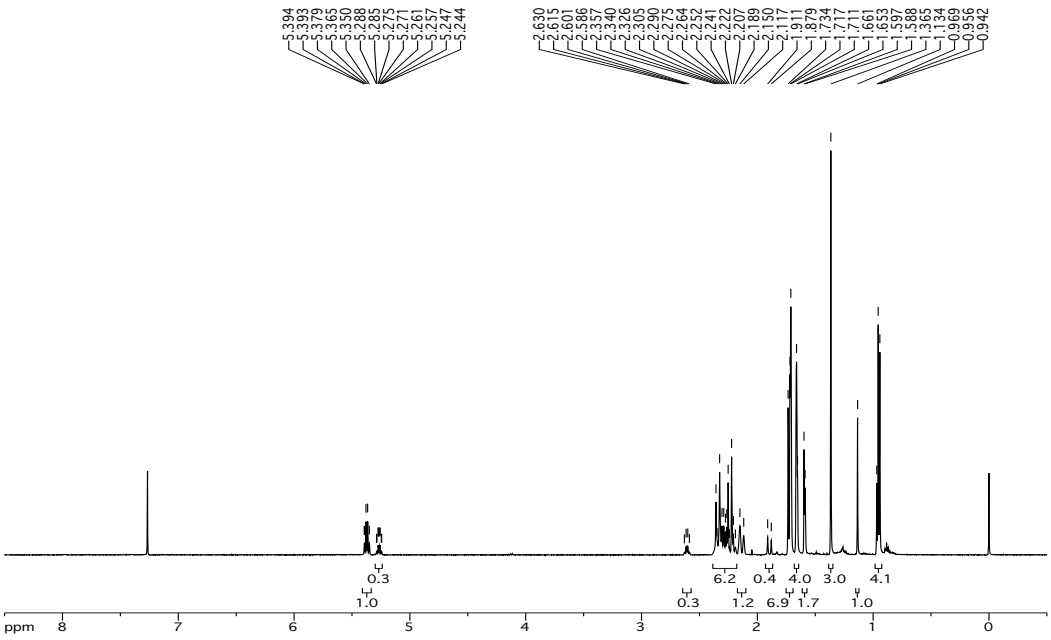


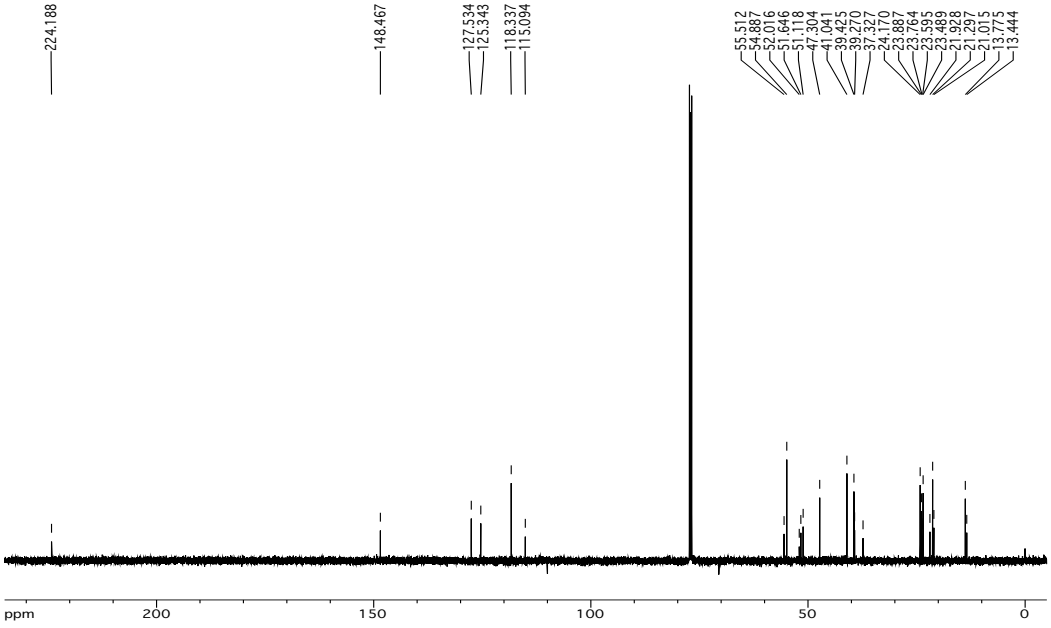
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-6-*tert*-butyl-2,9,9-trimethyl-deca-3,6,7-trien-5-one (3.60)



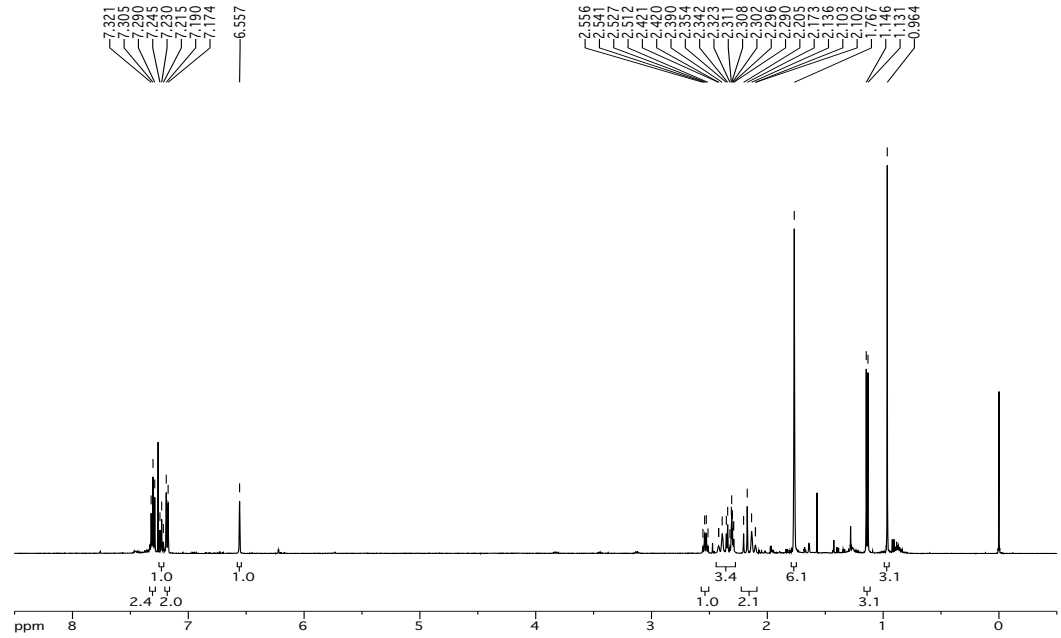


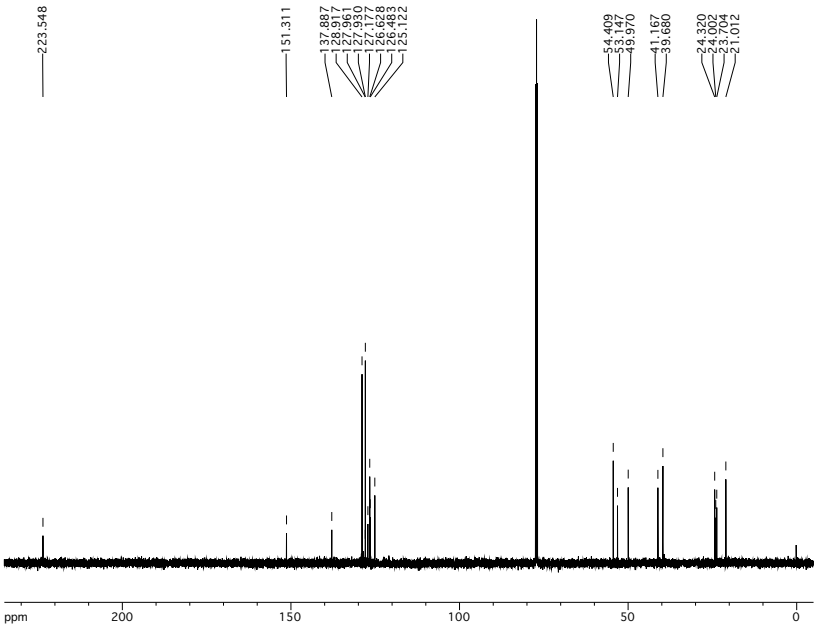
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,6*R**,7*S**,8*Z*)-8-Ethylidene-1,3,4,7-tetramethylbicyclo[4.2.1]bicyclonon-3-en-9-one (3.61) and (1*R**,6*R**,7*S**,8*E*)-8-ethylidene-1,3,4,7-tetramethylbicyclo[4.2.1]bicyclonon-3-en-9-one (3.62)**



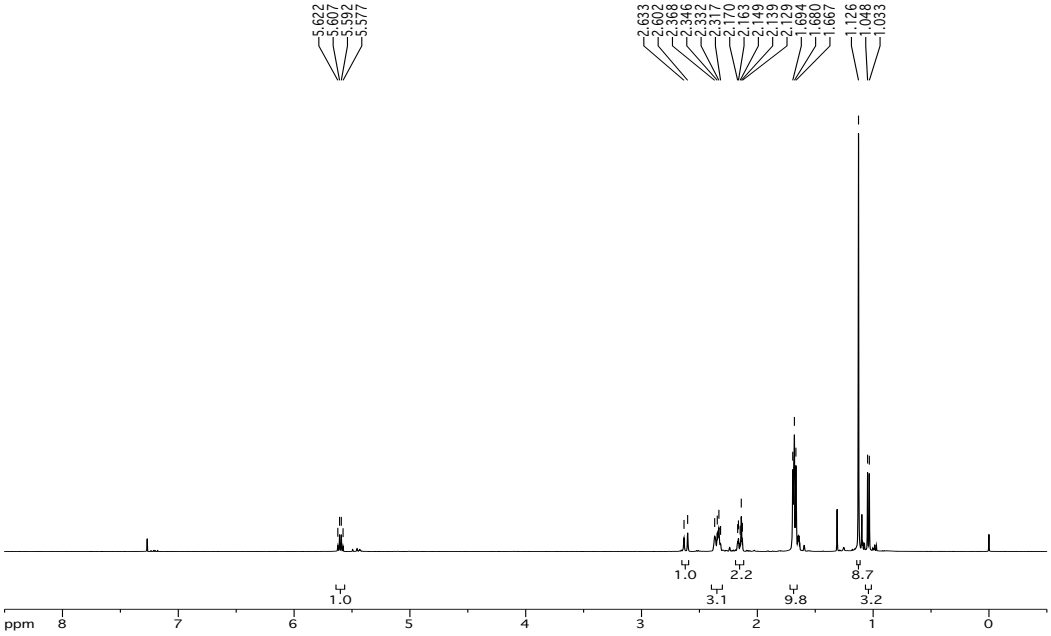


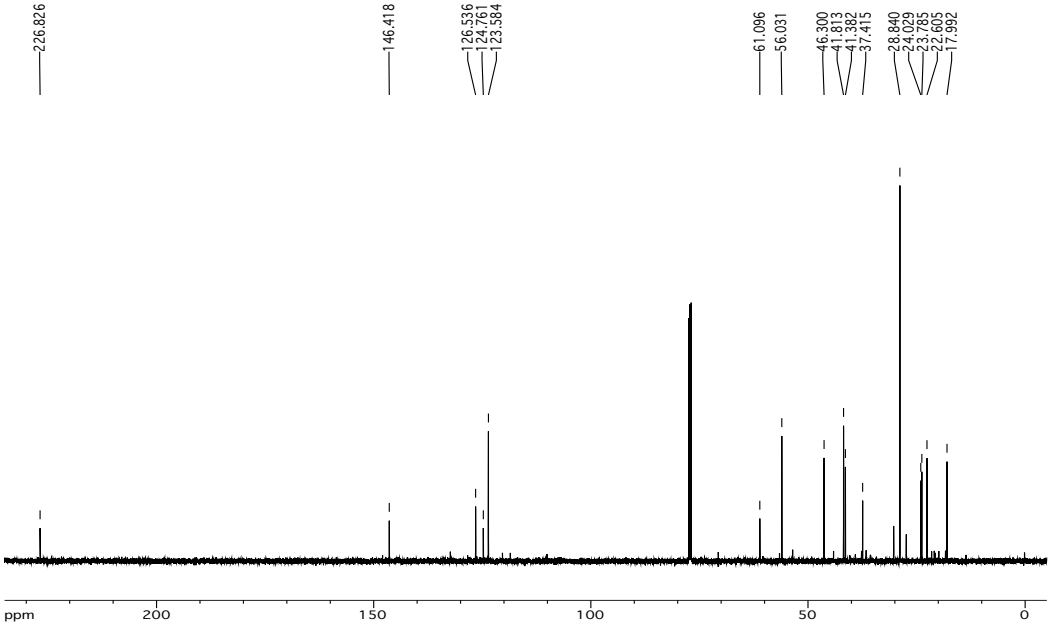
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,6*R**,7*S**,8*Z*)-1,3,4,7-Tetramethyl-8-(phenylmethylene)bicyclo[4.2.1]non-3-en-9-one (3.63)**



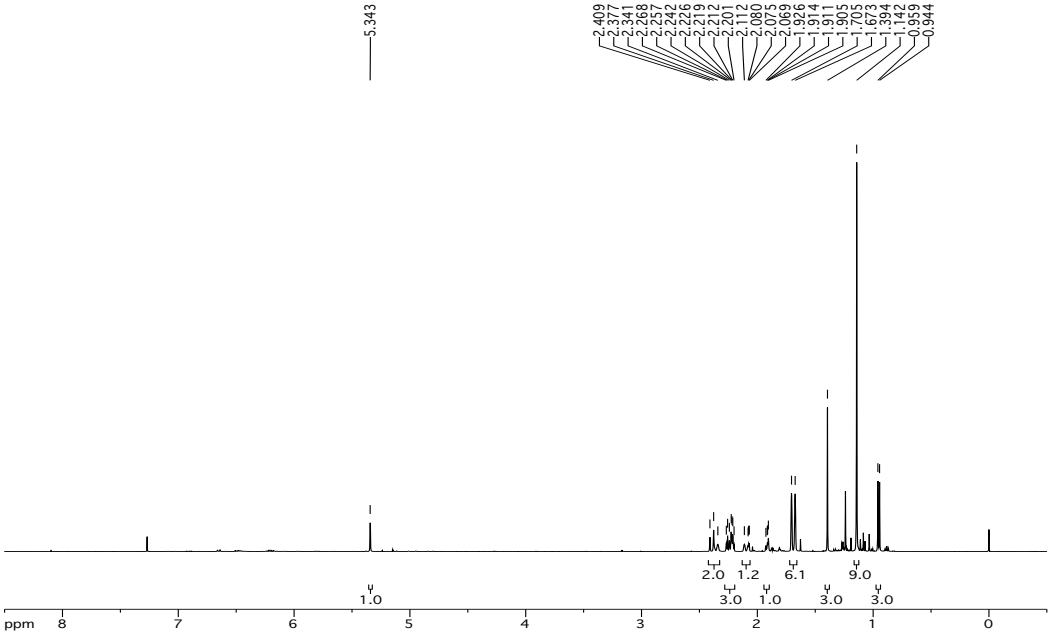


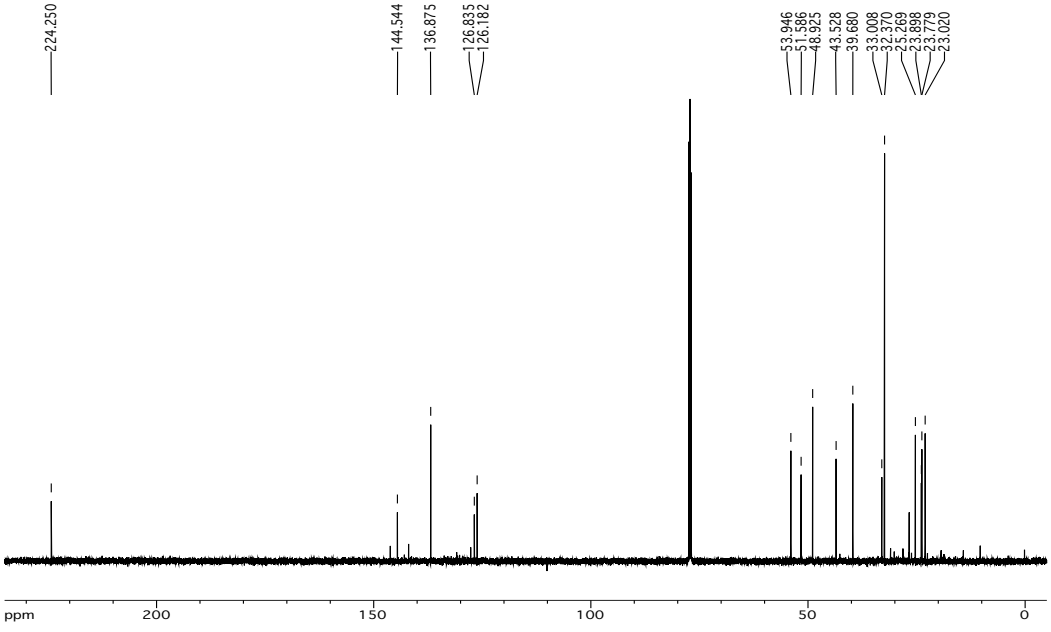
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,6*R**,7*S**,8*Z*)-1-*tert*-Butyl-8-ethylidene-3,4,7-trimethylbicyclo[4.2.1]non-3-en-9-one (3.64)**



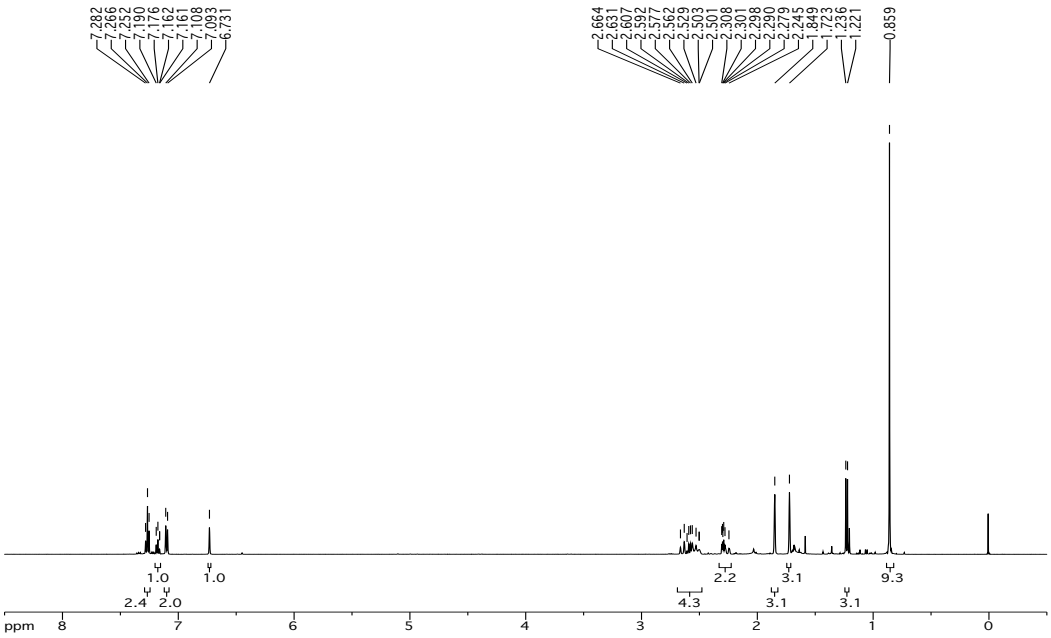


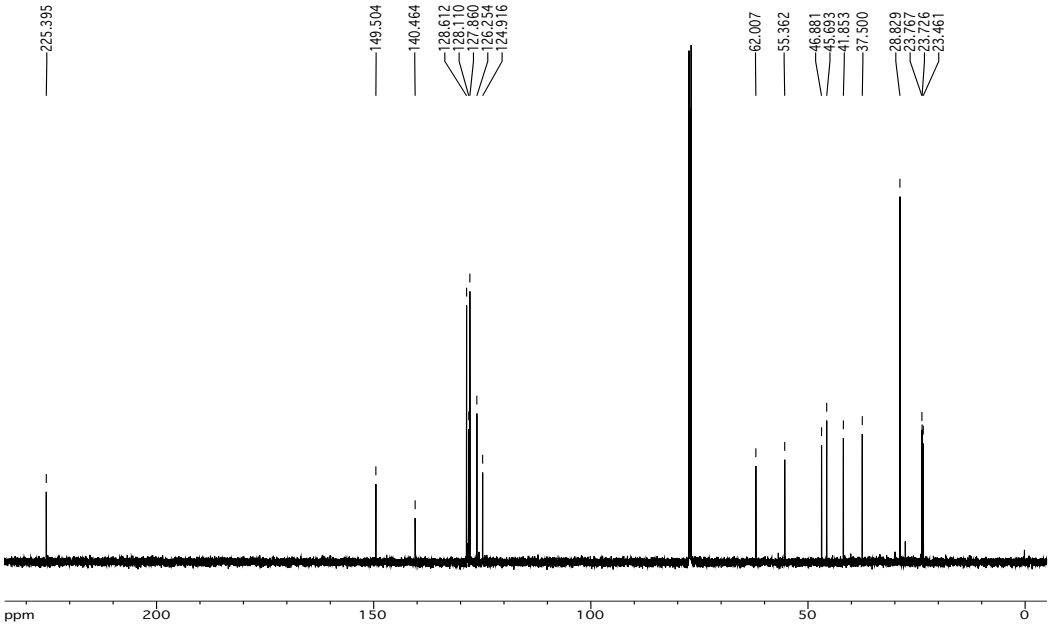
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,6*R**,7*S**,8*Z*)-8-(2,2-Dimethylpropylidene)-1,3,4,7-tetramethylbicyclo[4.2.1]non-3-en-9-one (3.65)**



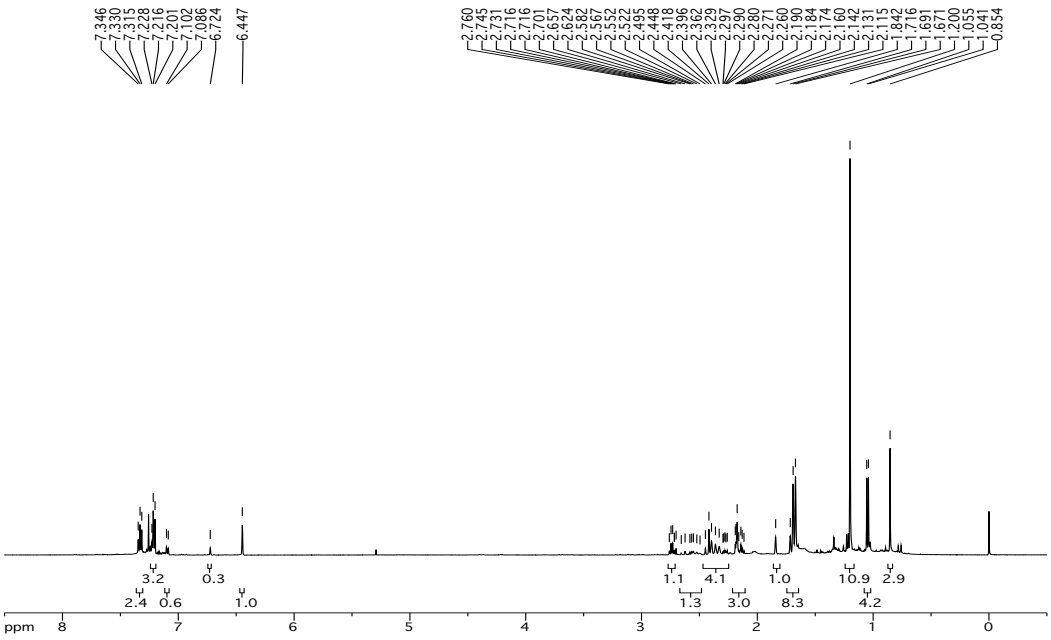


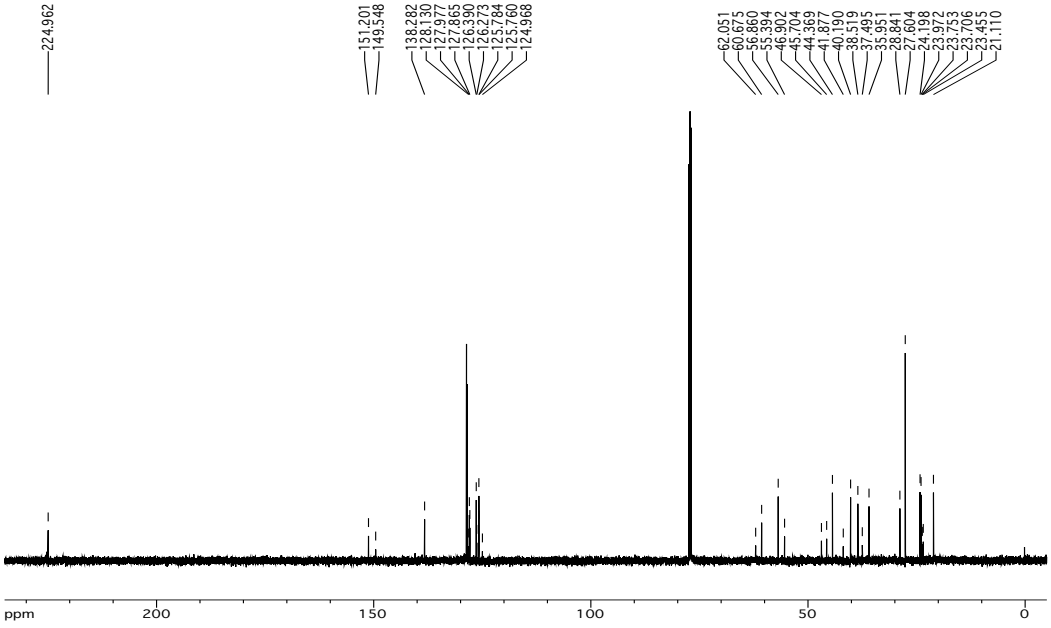
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,6*R**,7*S**,8*Z*)-1-*tert*-Butyl-8-(phenylmethylene)-3,4,7-trimethylbicyclo[4.2.1]non-3-en-9-one (3.66)**



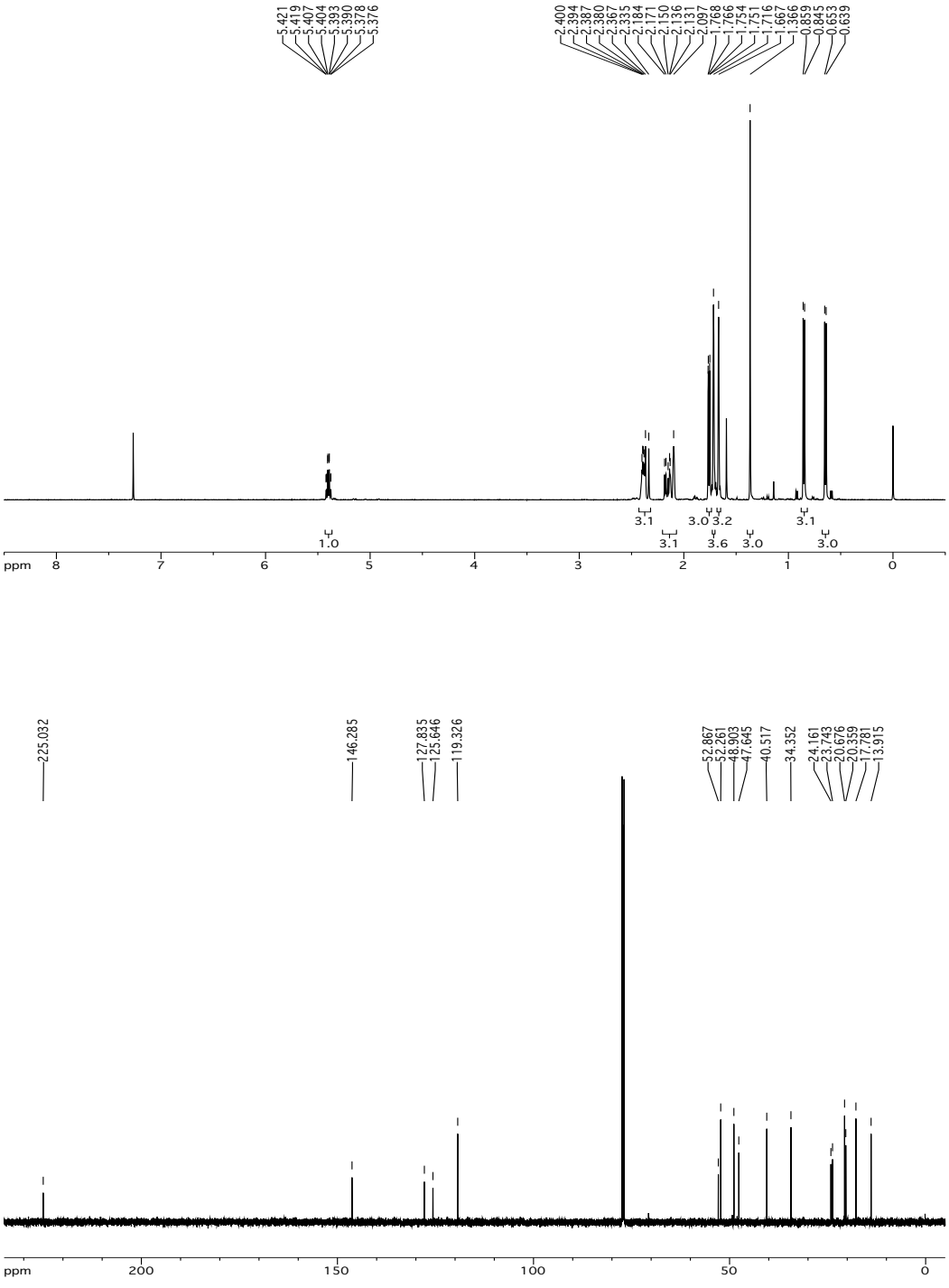


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,6*R**,7*S**,8*Z*)-1-*tert*-Butyl-8-(phenylmethylene)-3,4,7-trimethylbicyclo[4.2.1]non-3-en-9-one (3.66) and (1*R**,6*R**,7*S**,8*E*)-1-*tert*-butyl-8-(phenylmethylene)-3,4,7-trimethylbicyclo[4.2.1]non-3-en-9-one (3.74)**

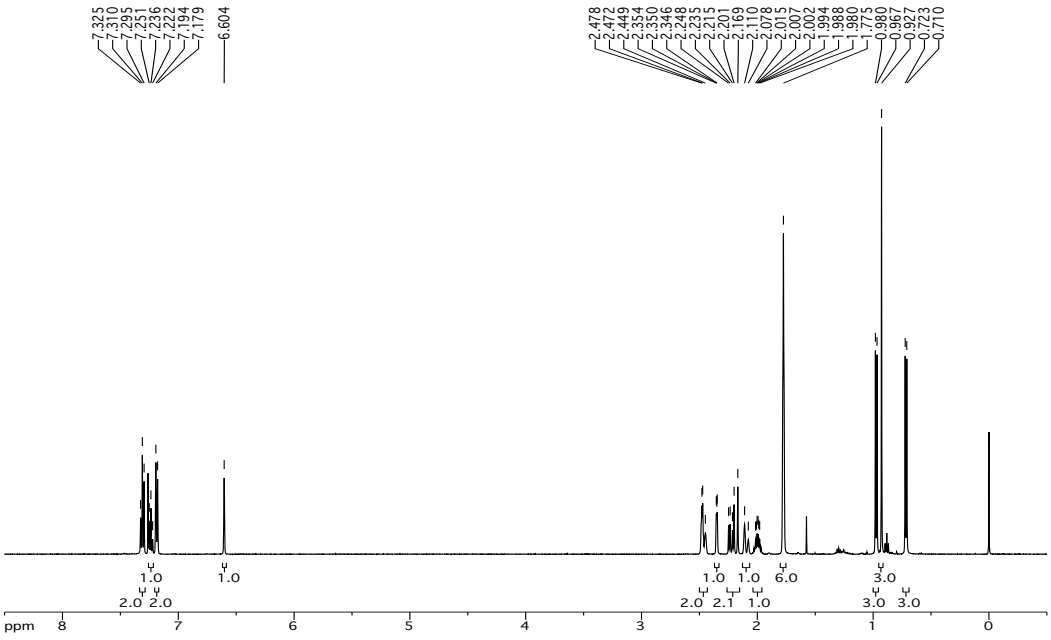


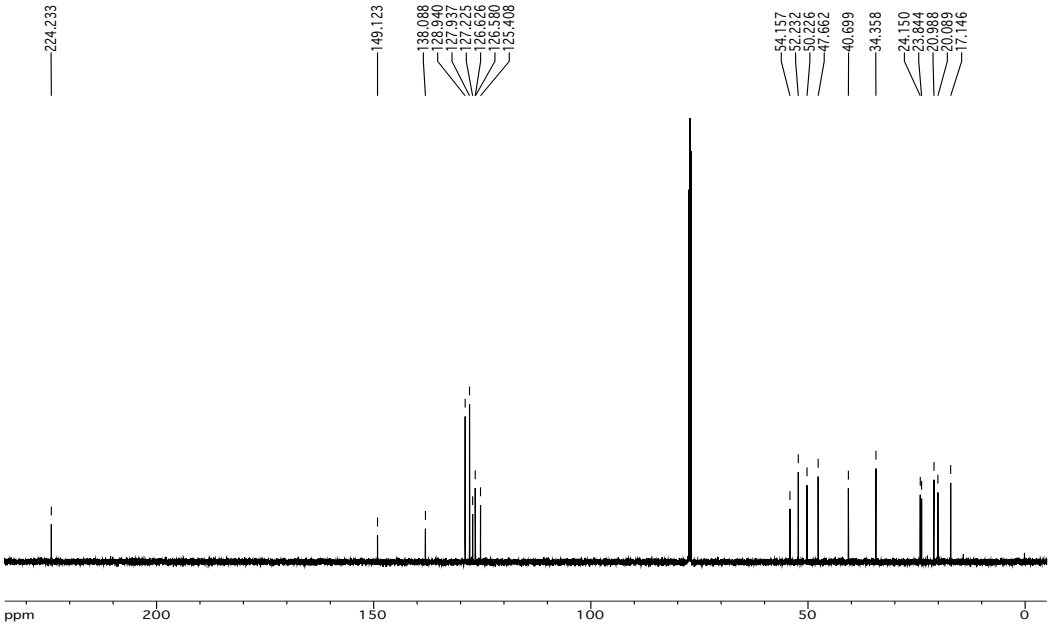


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,6*R**,7*S**,8*Z*)-8-Ethylidene-7-isopropyl-1,3,4-trimethylbicyclo[4.2.1]non-3-en-9-one (3.68)**

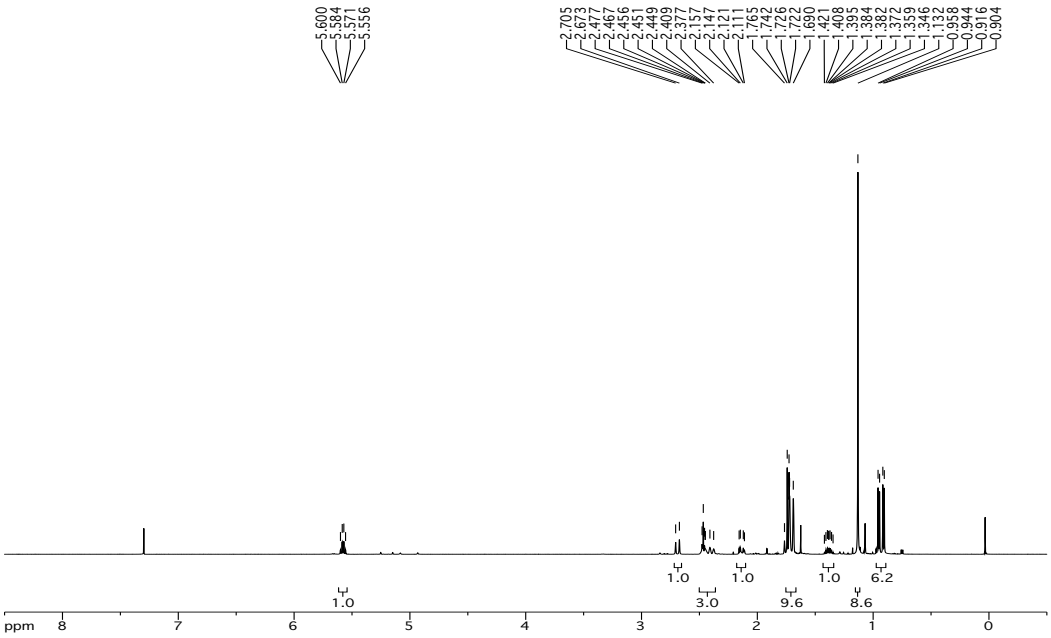


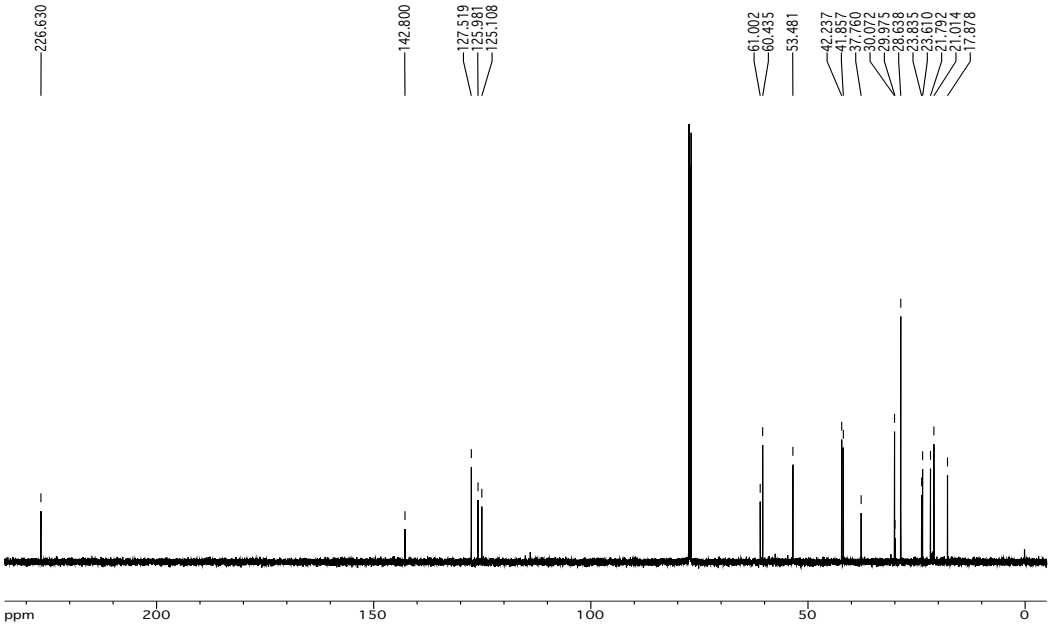
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,6*R**,7*S**,8*Z*)-7-Isopropyl-1,3,4-trimethyl-8-(phenylmethylene)bicyclo[4.2.1]non-3-en-9-one (3.69)**



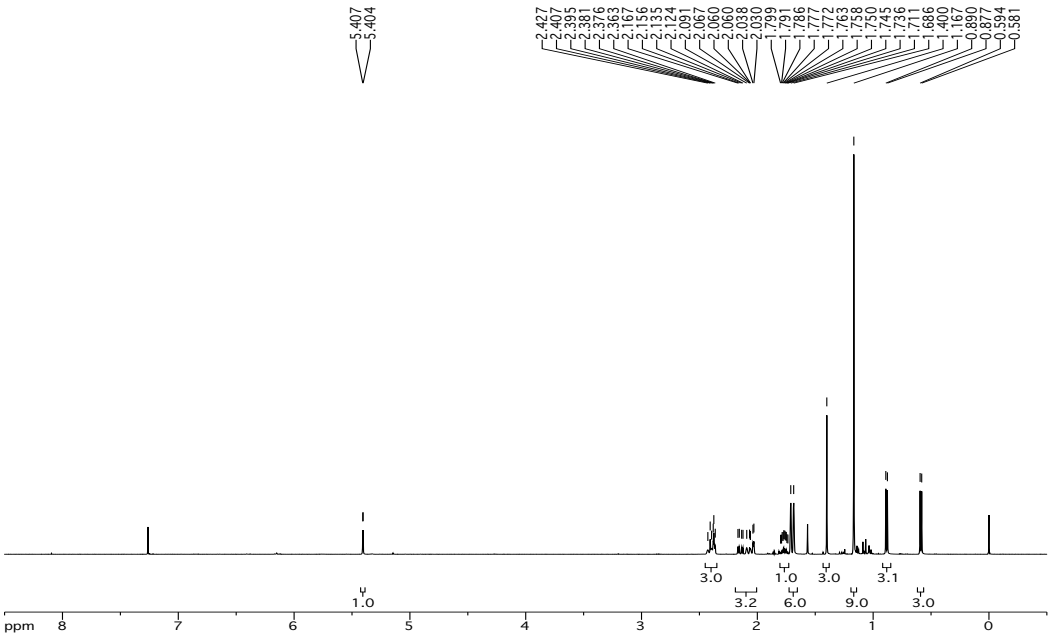


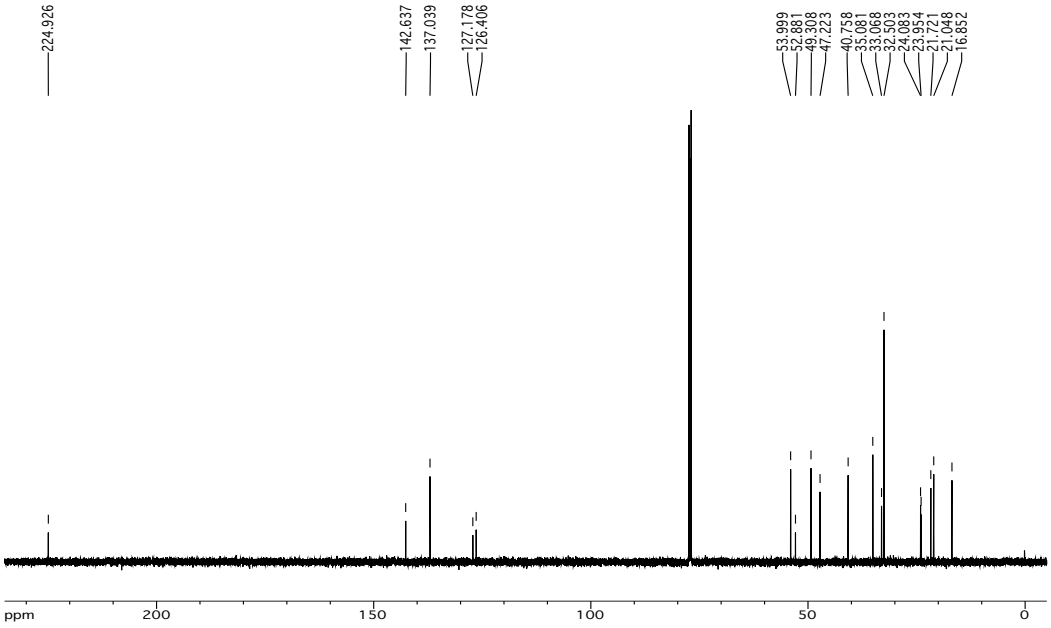
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,6*R**,7*S**,8*Z*)-1-*tert*-Butyl-8-ethylidene-7-isopropyl-3,4-dimethylbicyclo[4.2.1]non-3-en-9-one (3.70)**



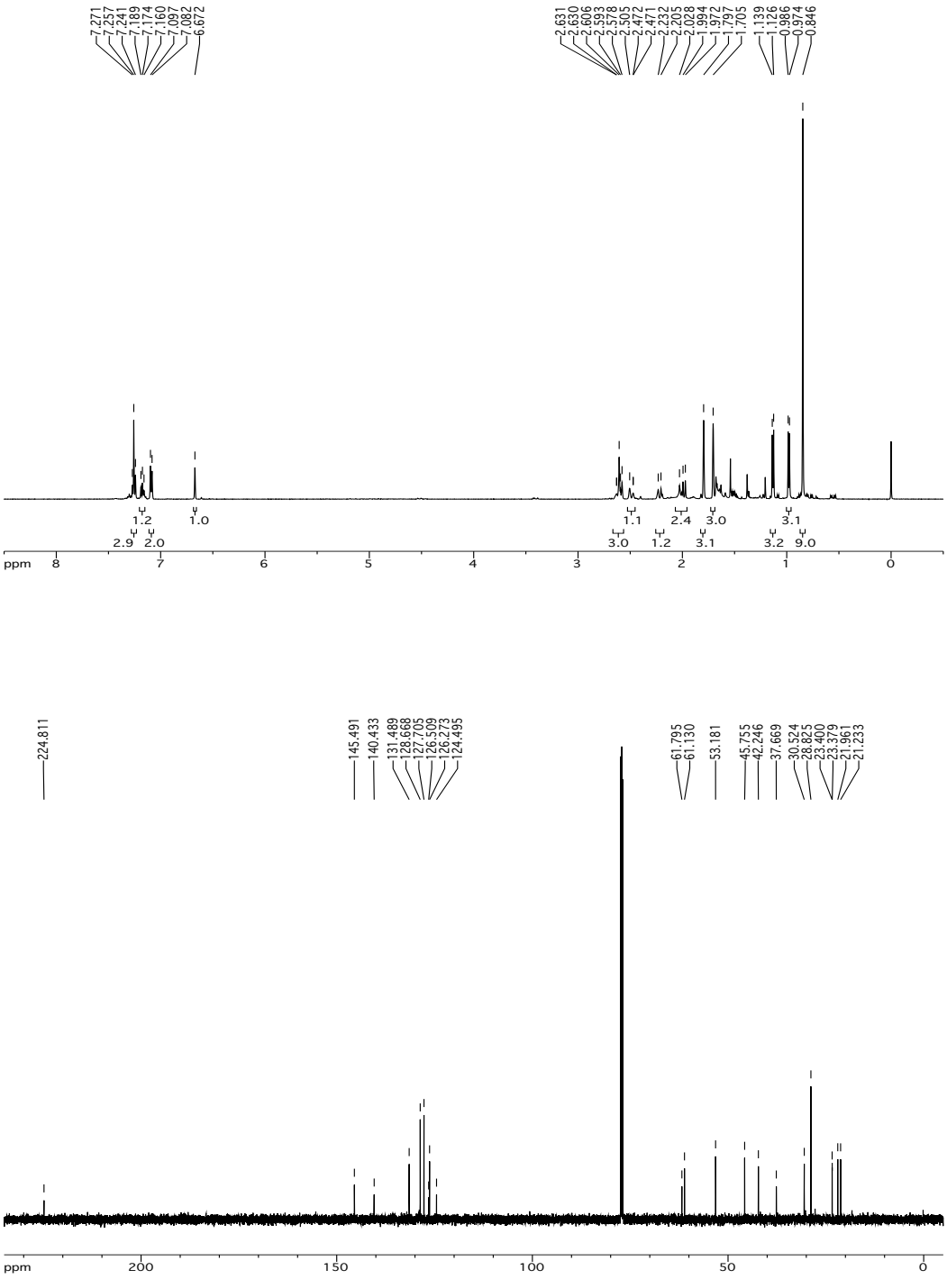


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,6*R**,7*S**,8*Z*)-8-(2,2-Dimethylpropylidene)-7-isopropyl-1,3,4-trimethylbicyclo[4.2.1]-non-3-en-9-one (3.71)**

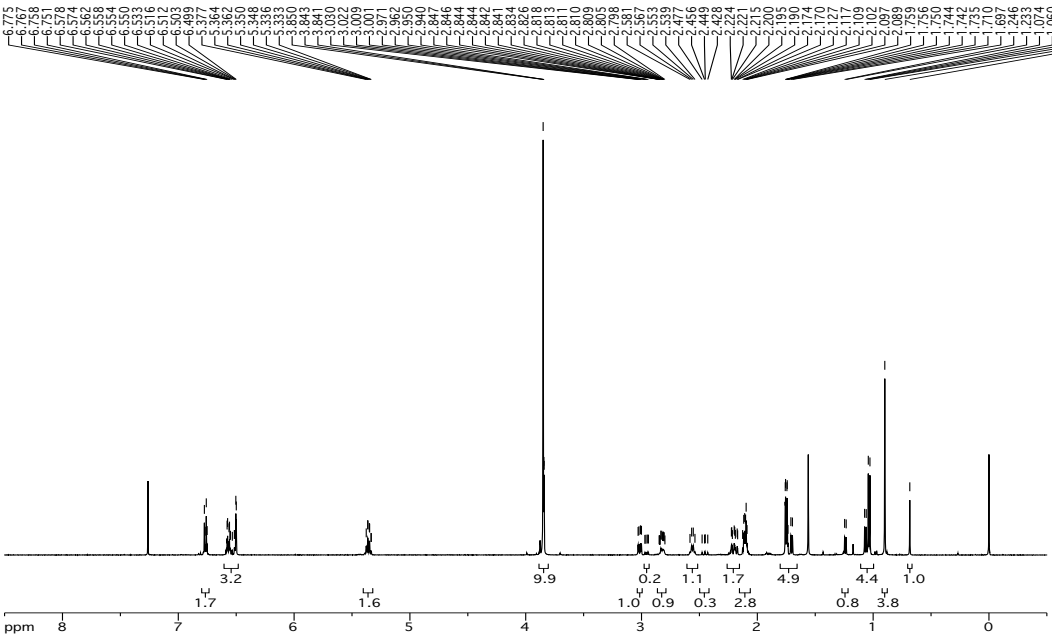


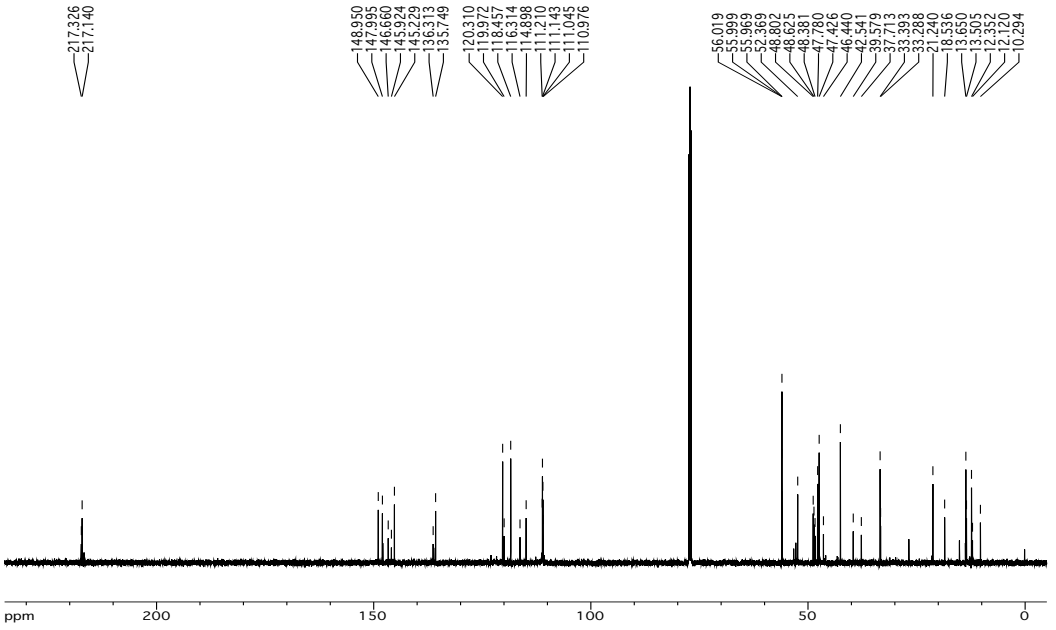


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,6*R**,7*S**,8*Z*)-1-*tert*-Butyl-7-isopropyl-3,4-dimethyl-8-(phenylmethylene)bicyclo[4.2.1]-non-3-en-9-one (3.72)**



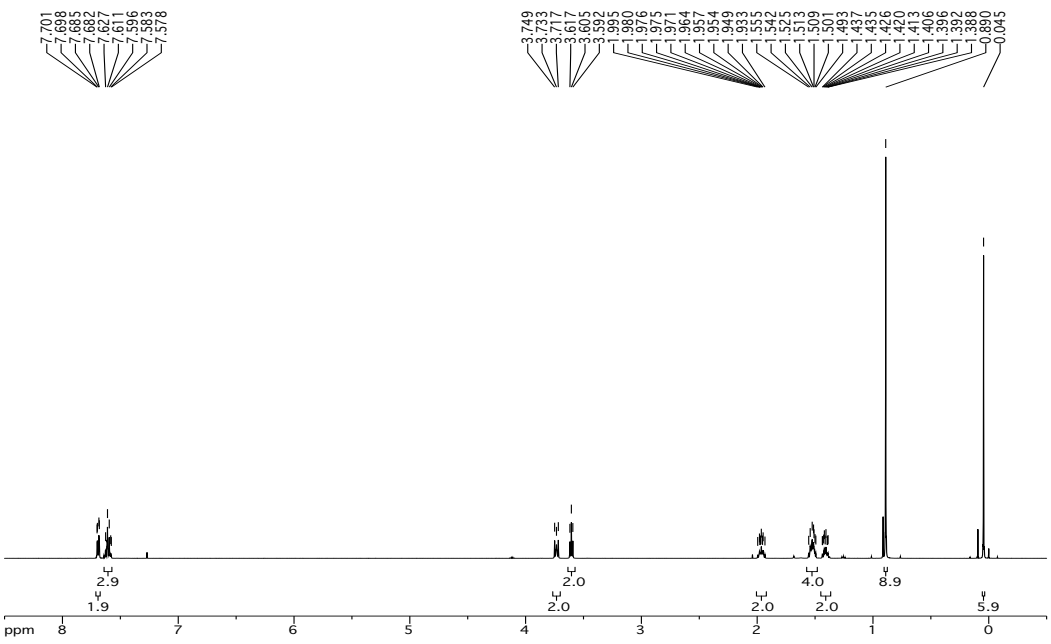
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,2*Z*,3*S**,6*R**)-2-Ethylidene-6-(3,4-dimethoxyphenyl)-1,3-dimethylbicyclo[2.2.1]heptan-7-one (3.75) and (1*R**,2*E*, 3*S**,6*R**)-2-ethylidene-6-(3,4-dimethoxyphenyl)-1,3-dimethylbicyclo[2.2.1]heptan-7-one (3.76).**

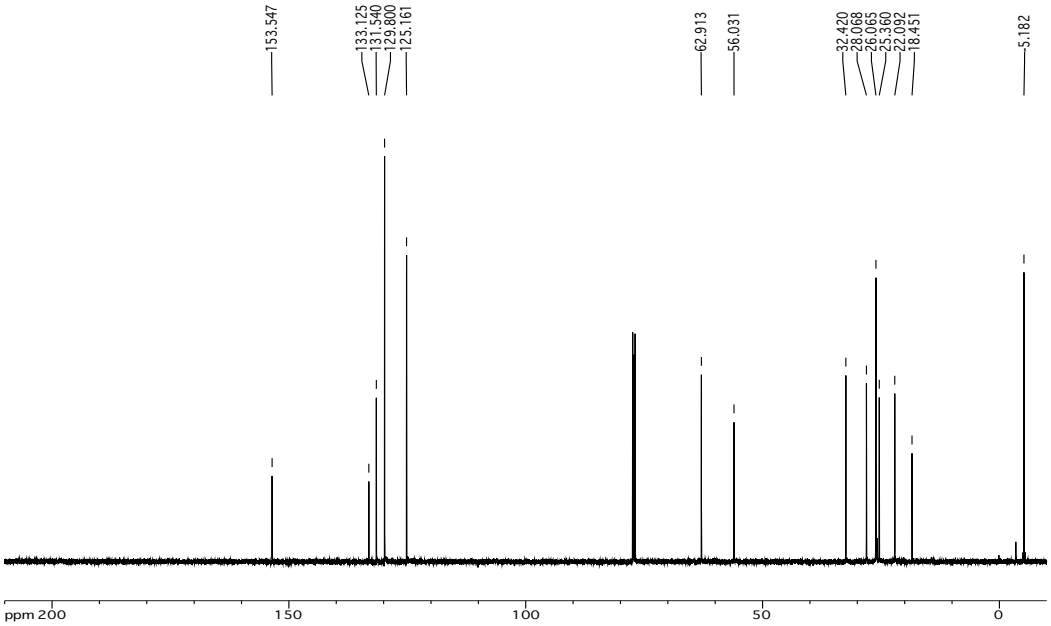




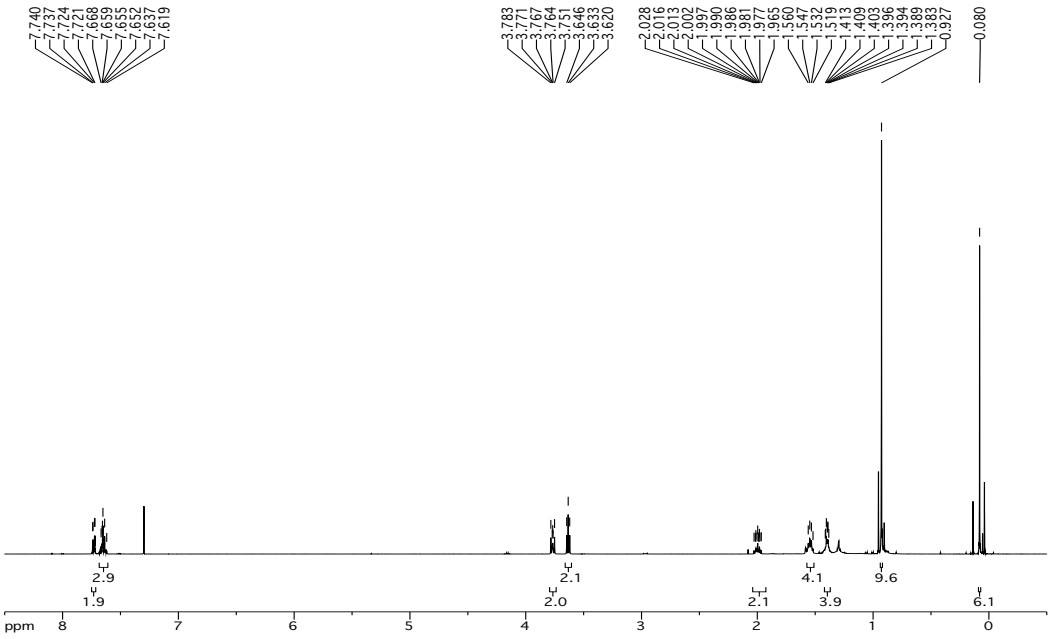
Appendix C NMR Spectra for Chapter 4

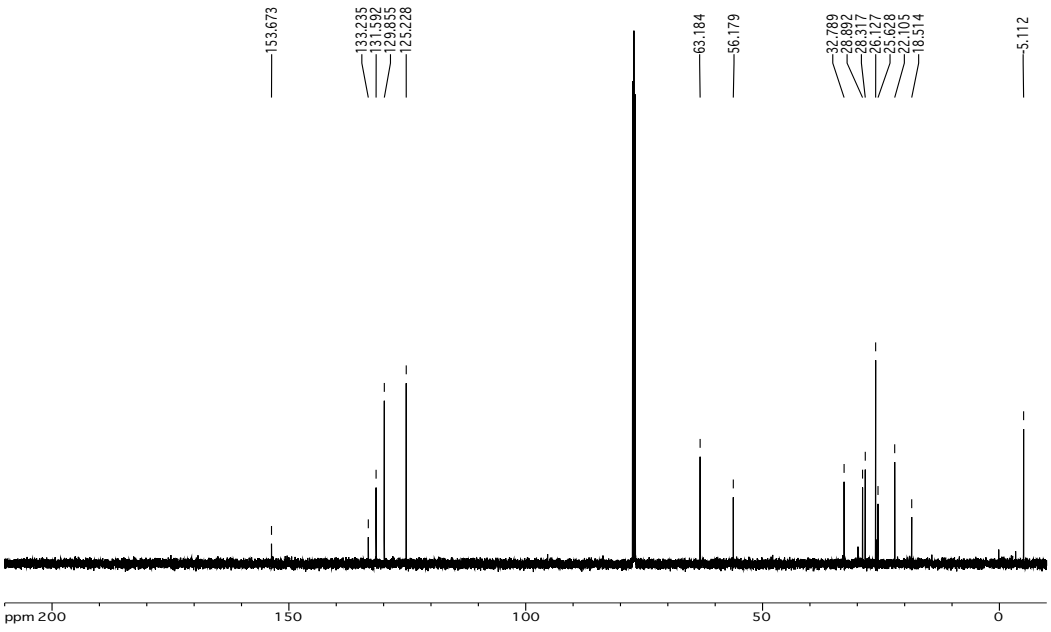
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (6-(*tert*-Butyldimethylsilanyloxy)hexanesulfonyl)-1-phenyl-5-1*H*-tetrazole (4.20)



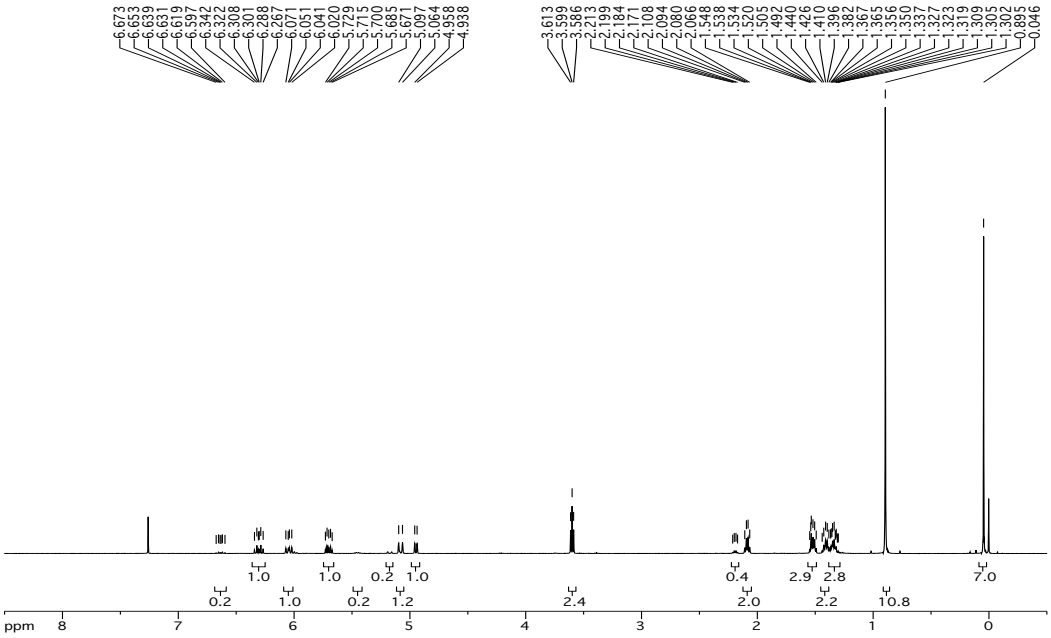


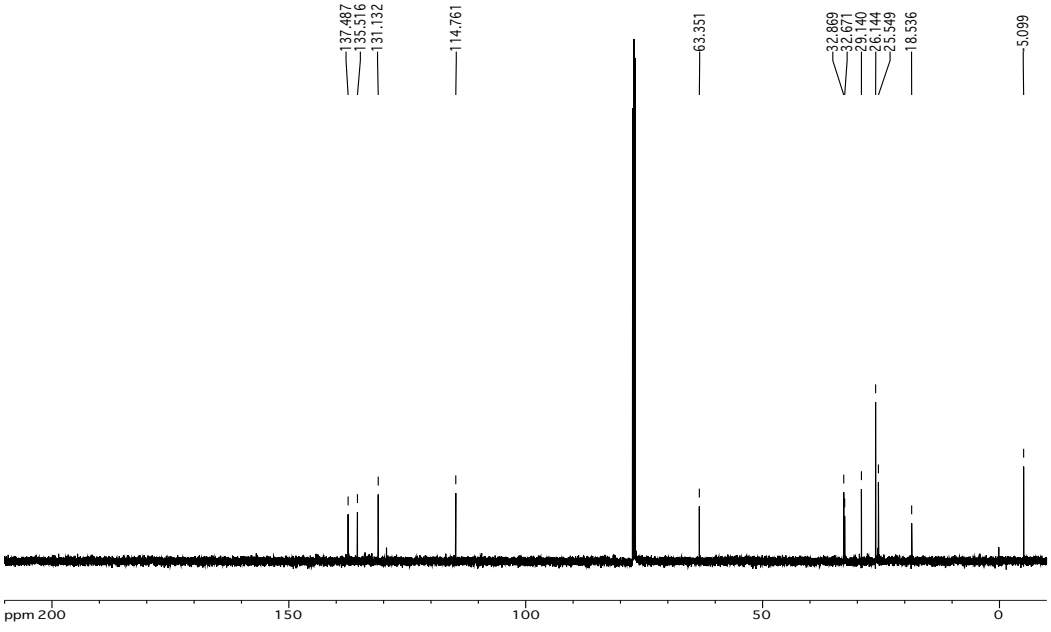
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (7-(*tert*-Butyldimethylsilanyloxy)heptanesulfonyl)-1-phenyl-5-1*H*-tetrazole (4.21)



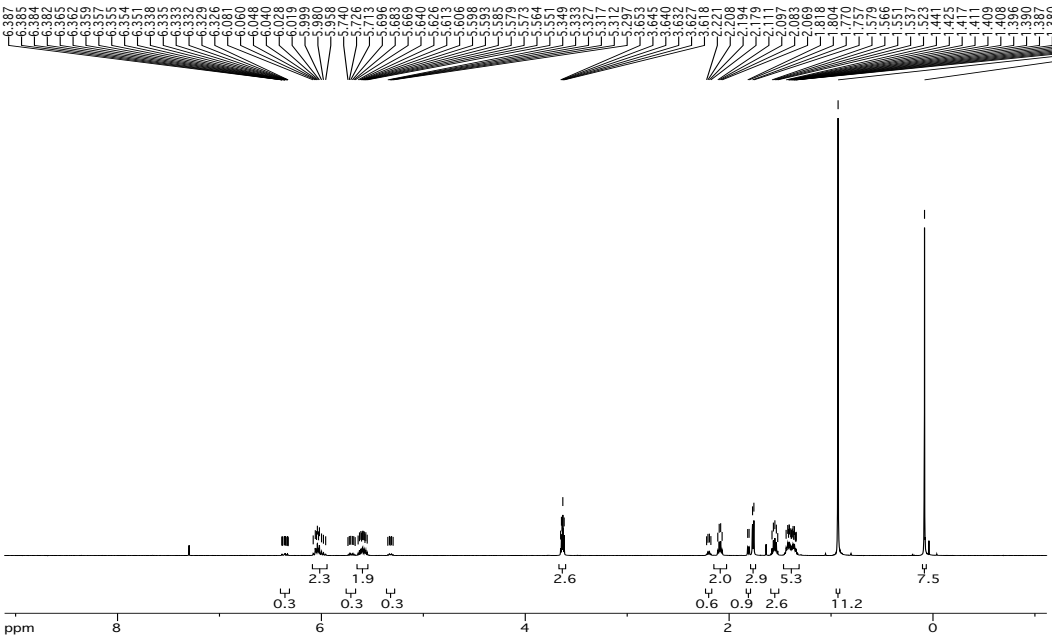


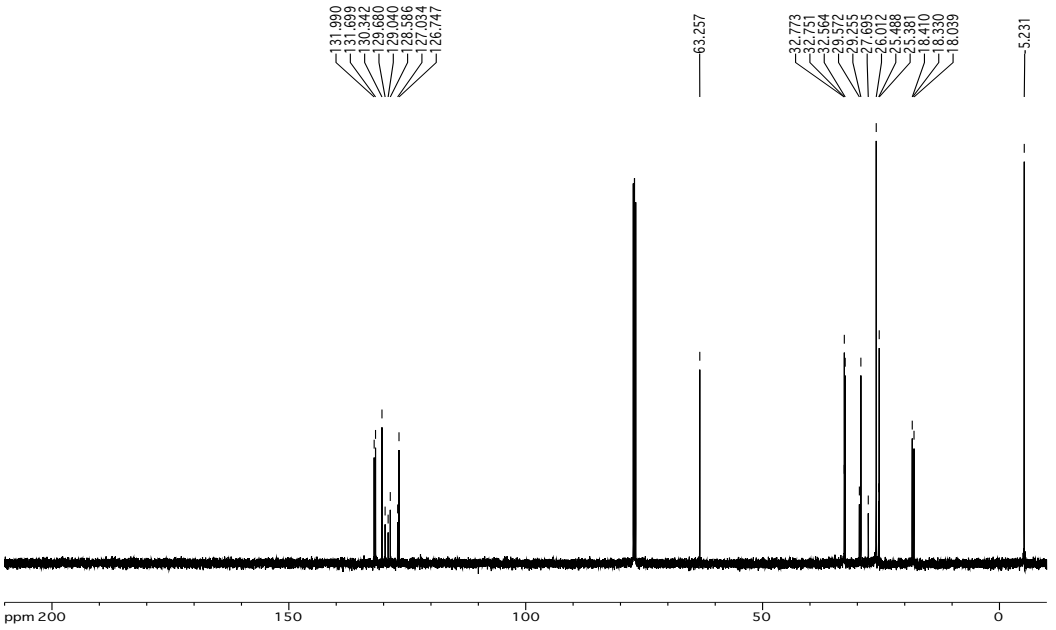
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (6*E*,8-Nonadienyl-1-oxy)-*tert*-butyldimethylsilane (4.22)



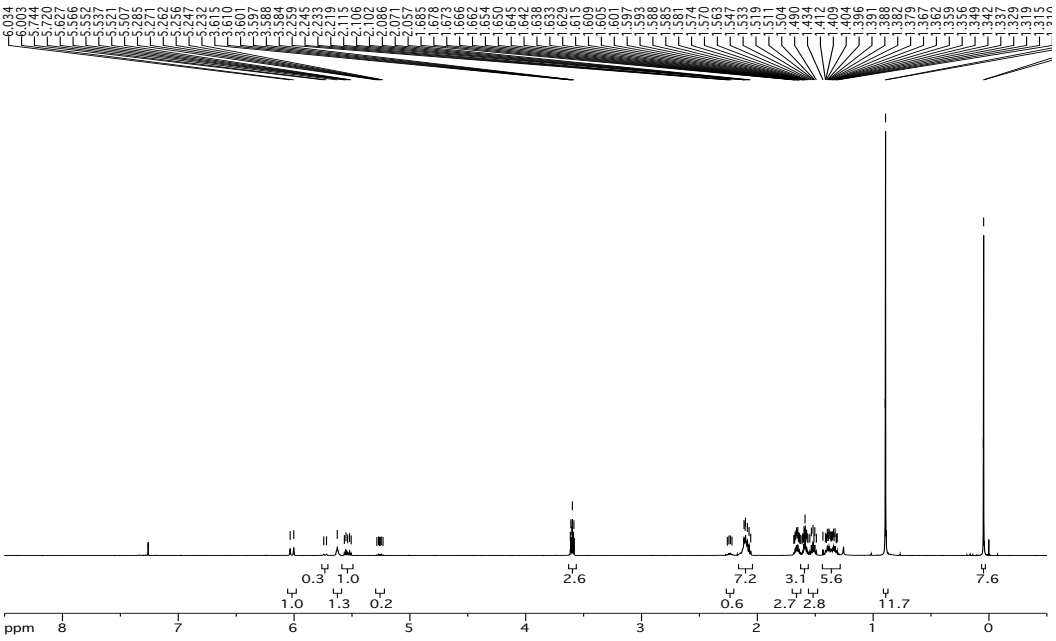


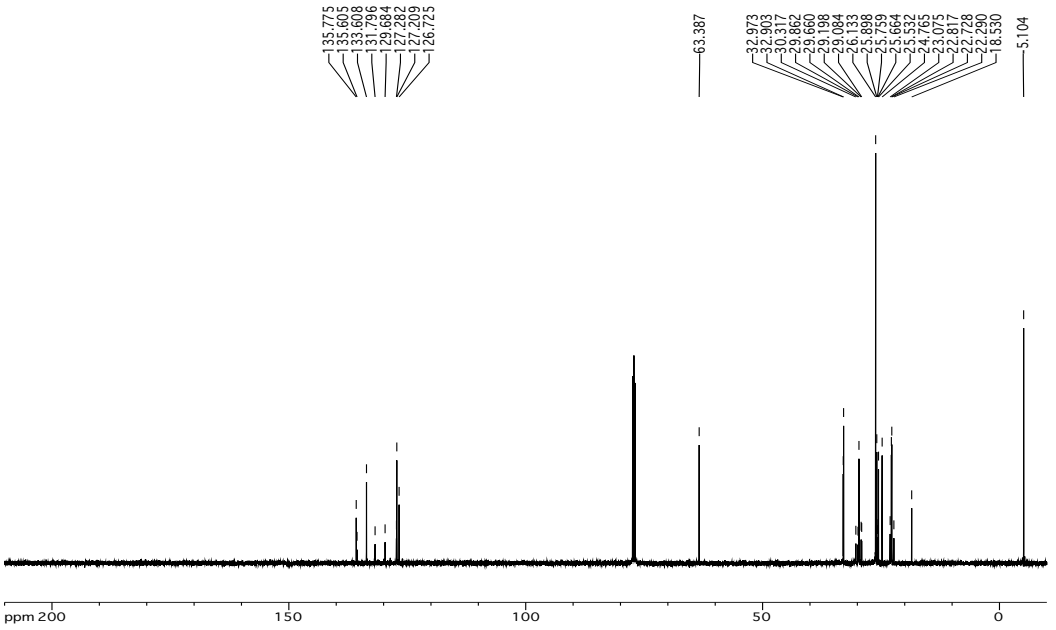
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (6*E*,8*E*-Decadienyl-1-oxy)-*tert*-butyldimethylsilane (4.24)



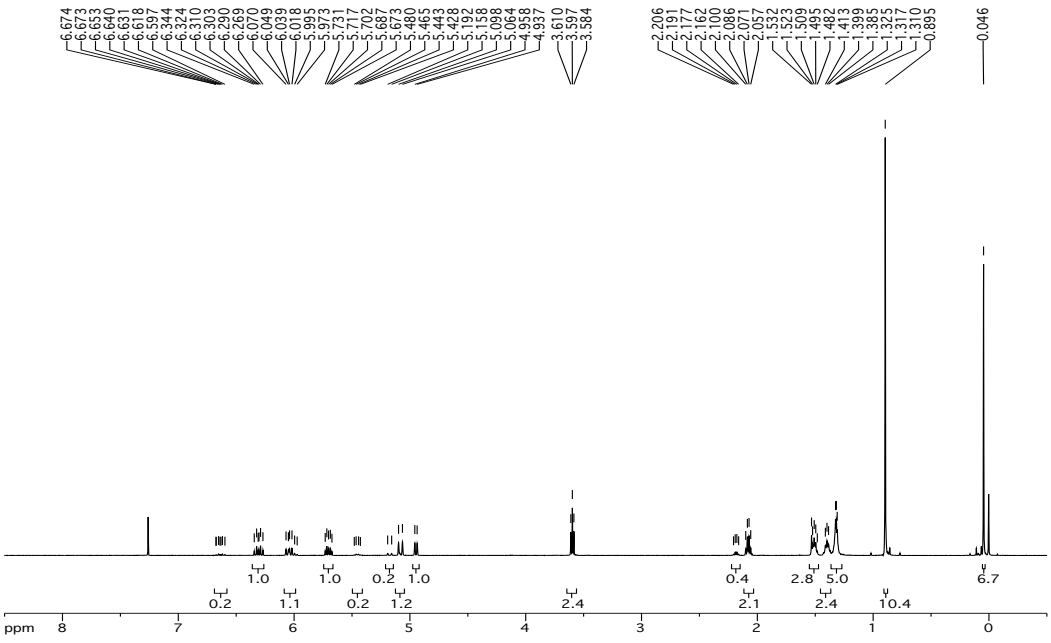


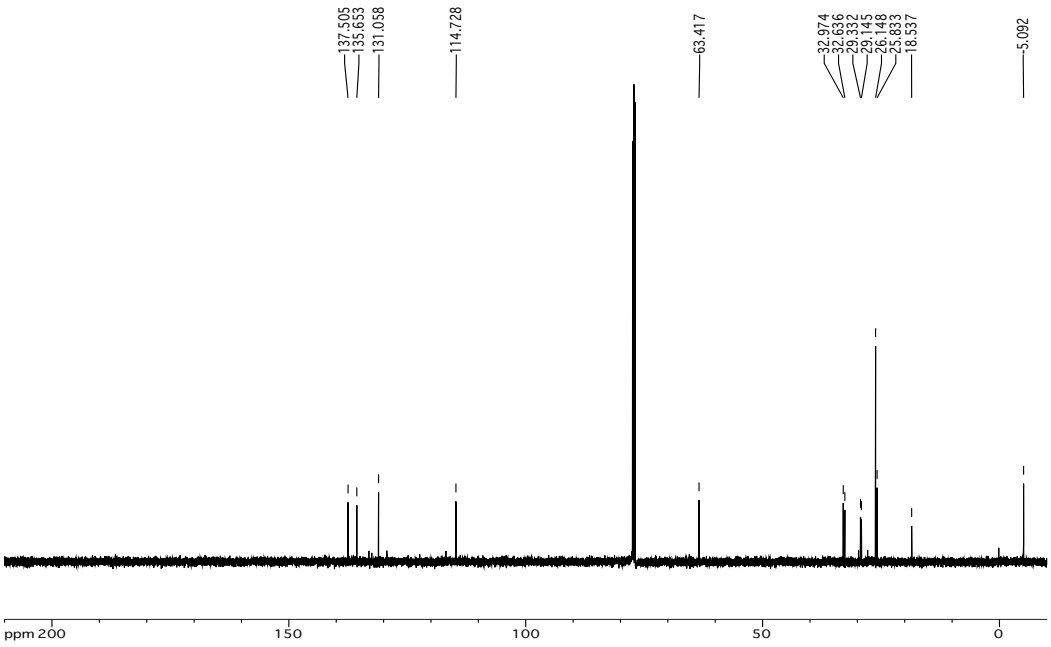
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of ((6*E*)-7-(1-Cyclohexene)-6-hexadienyl-1-oxy)*tert*-butyldimethylsilane (4.26)



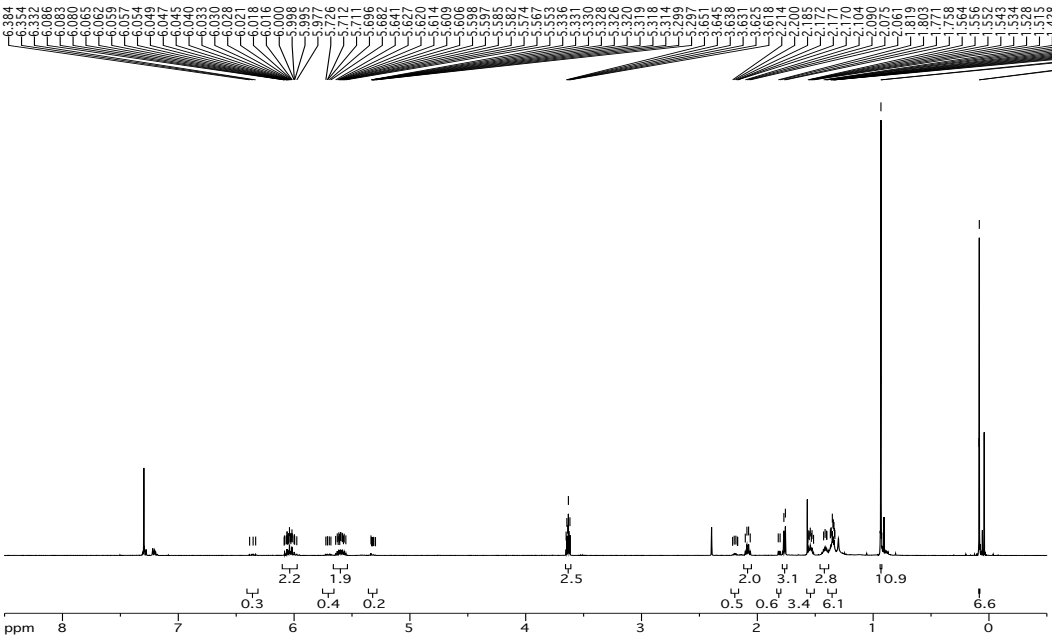


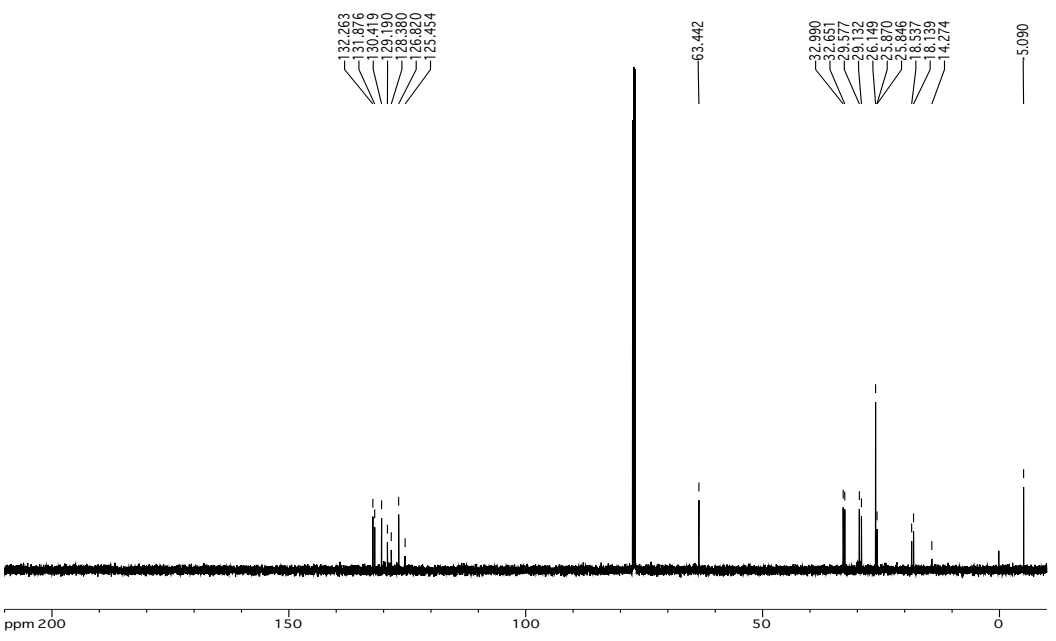
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of ((7*E*,9*E*)-Deca-7,9-dienyl-1-oxy)-*tert*-butyldimethylsilane (4.23)



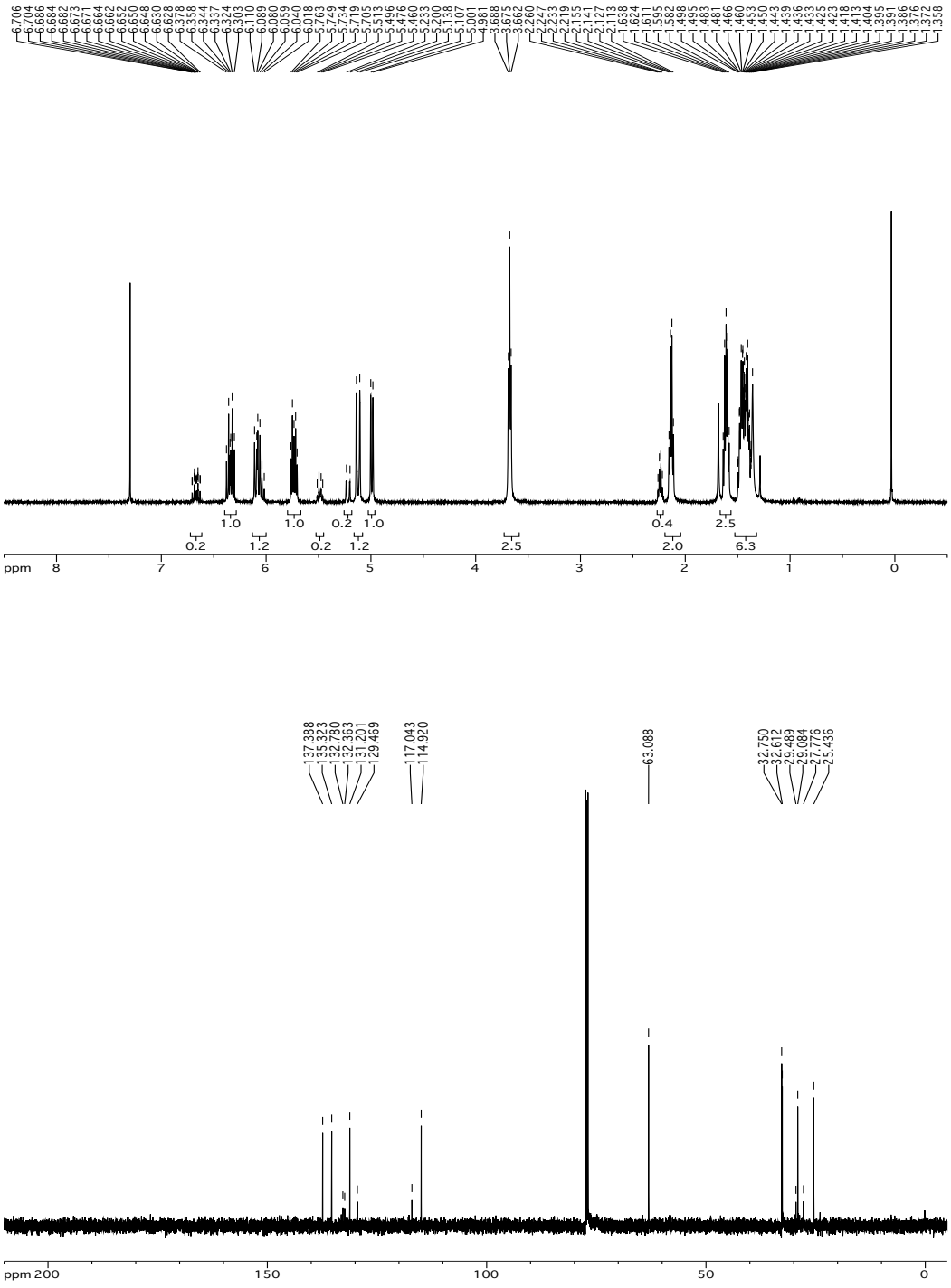


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of ((7*E*,9*E*)-Undeca-7,9-dienyl-1-oxy)-*tert*-butyldimethylsilane (4.25)

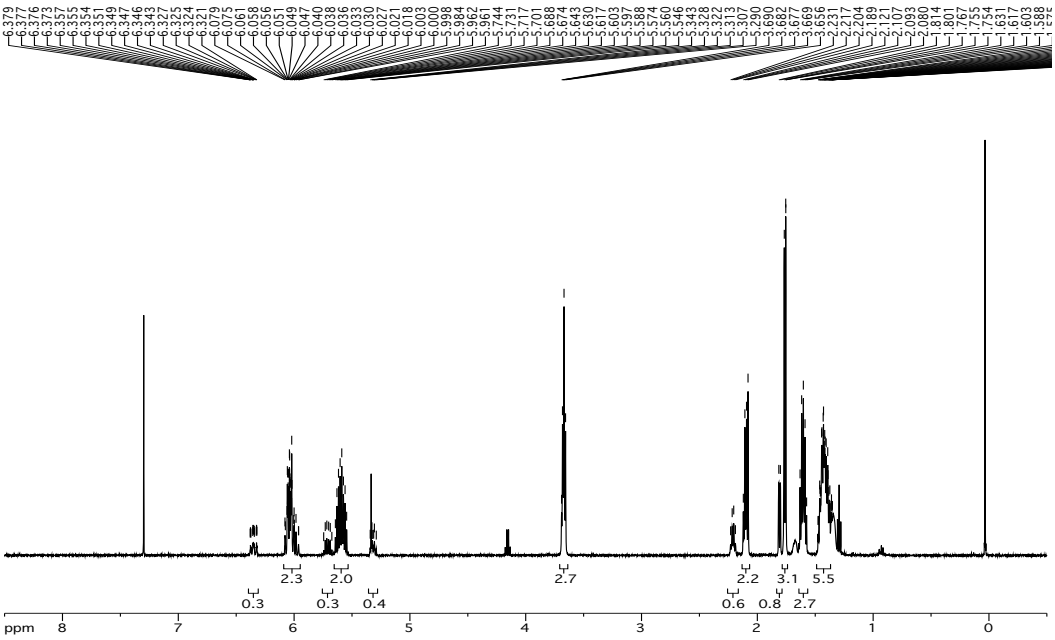


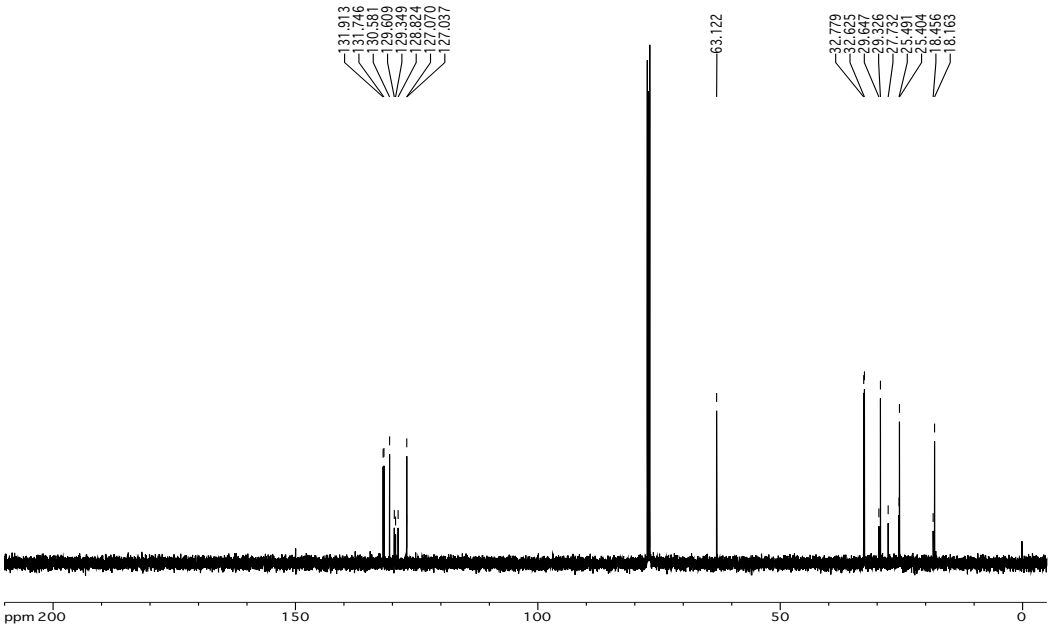


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-6,8-nonadien-1-ol (4.27)

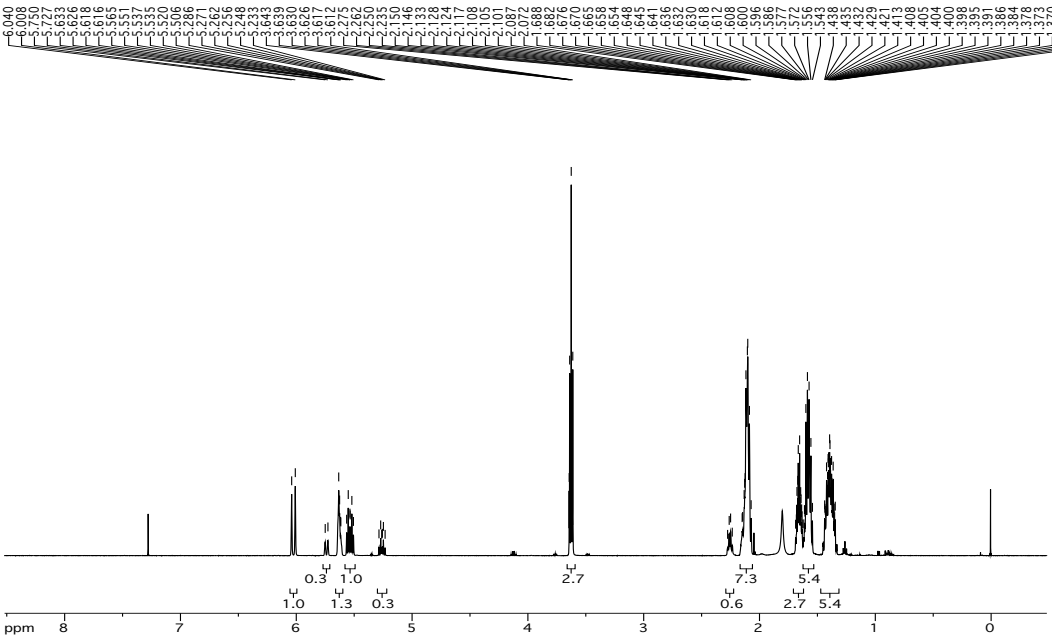


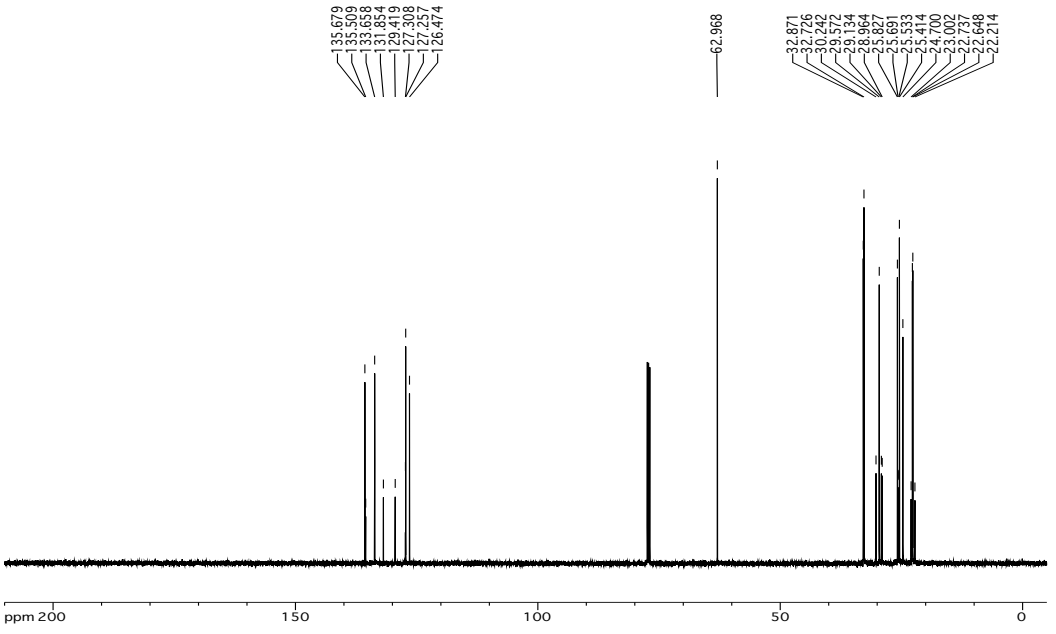
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of 6*E*,8*E*-Decadien-1-ol (4.29)



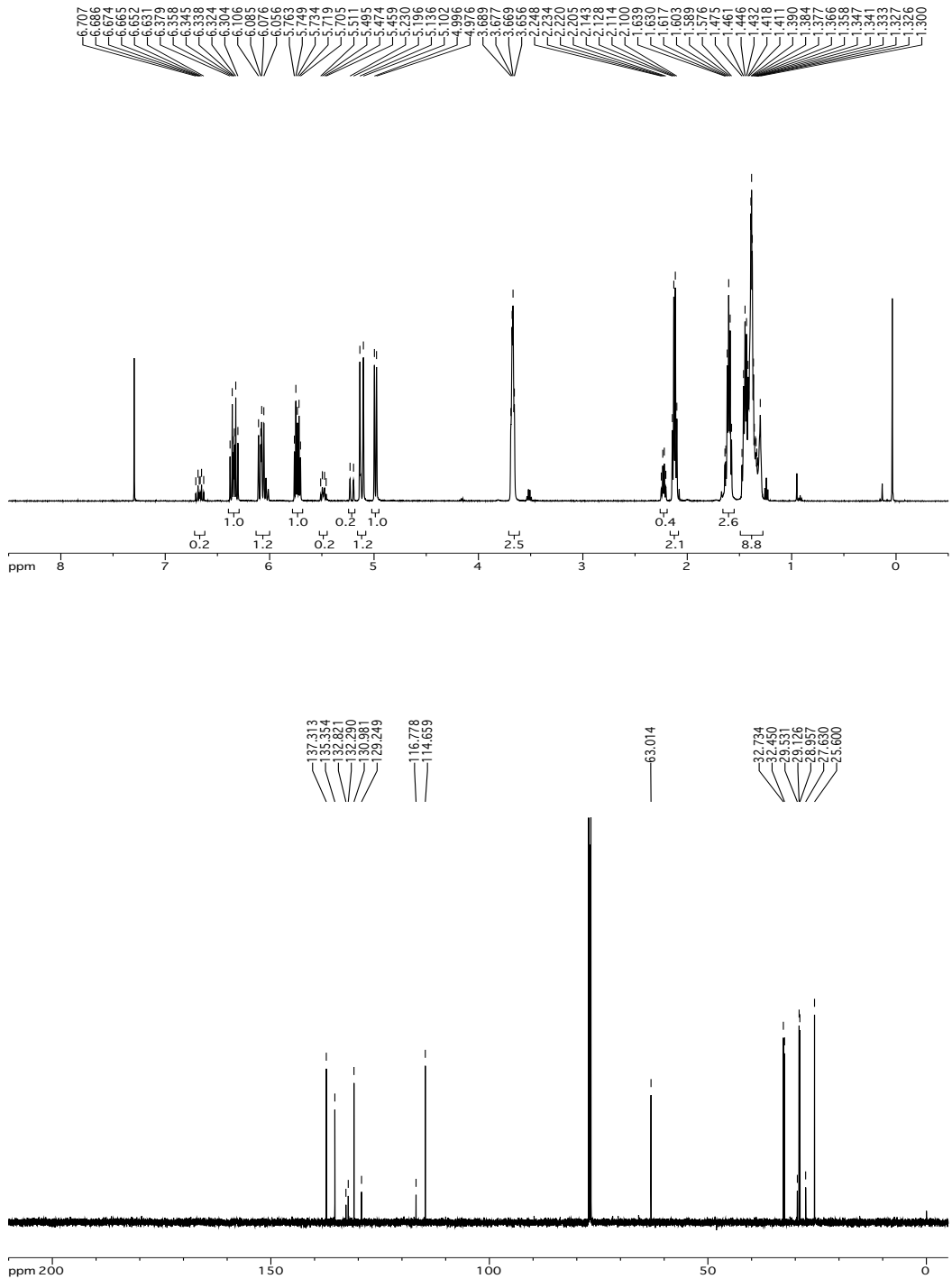


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (6*E*)-7-(1-Cyclohexene)-6-heptene-1-ol (4.31)

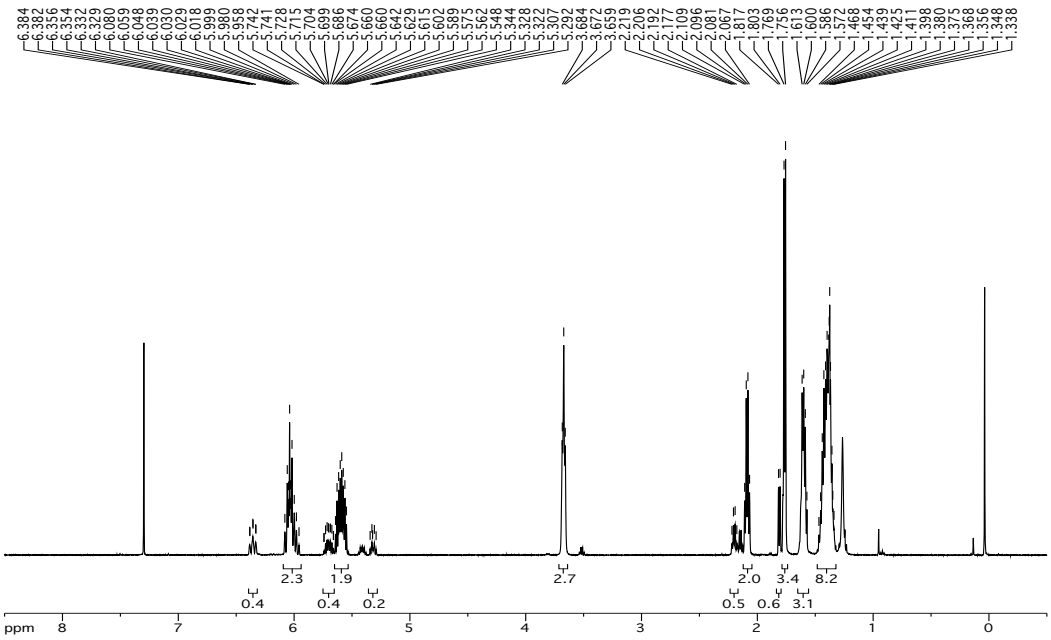


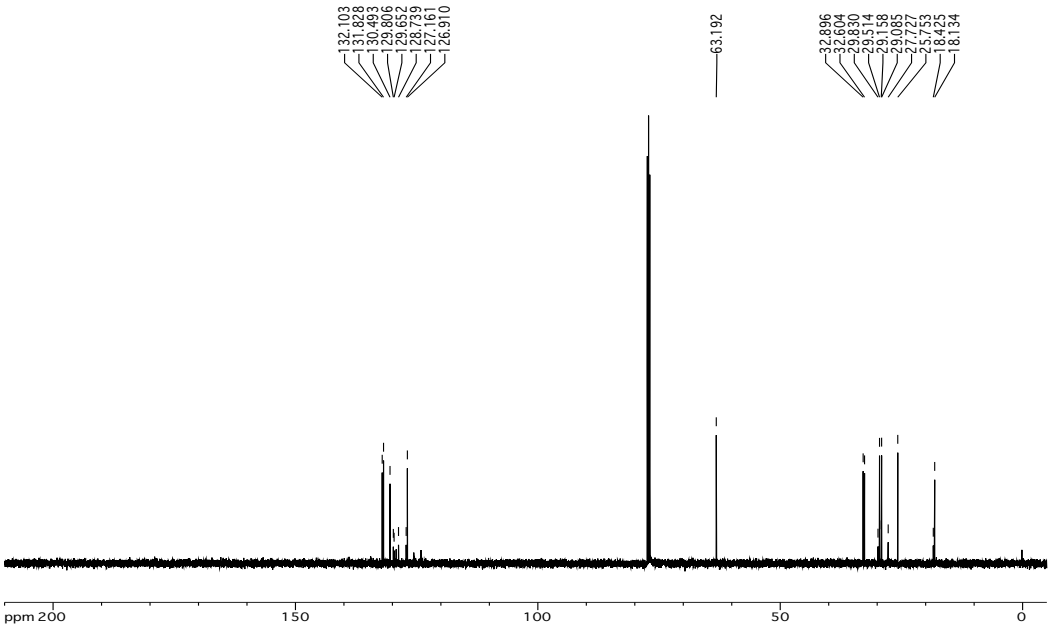


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-7,9-Decadien-1-ol (4.28)

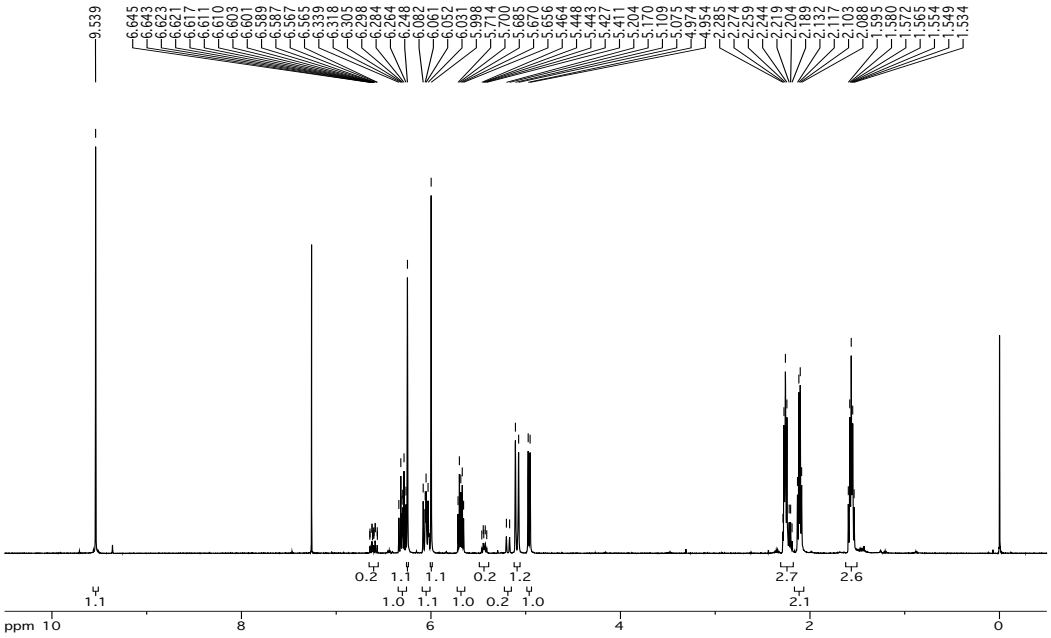


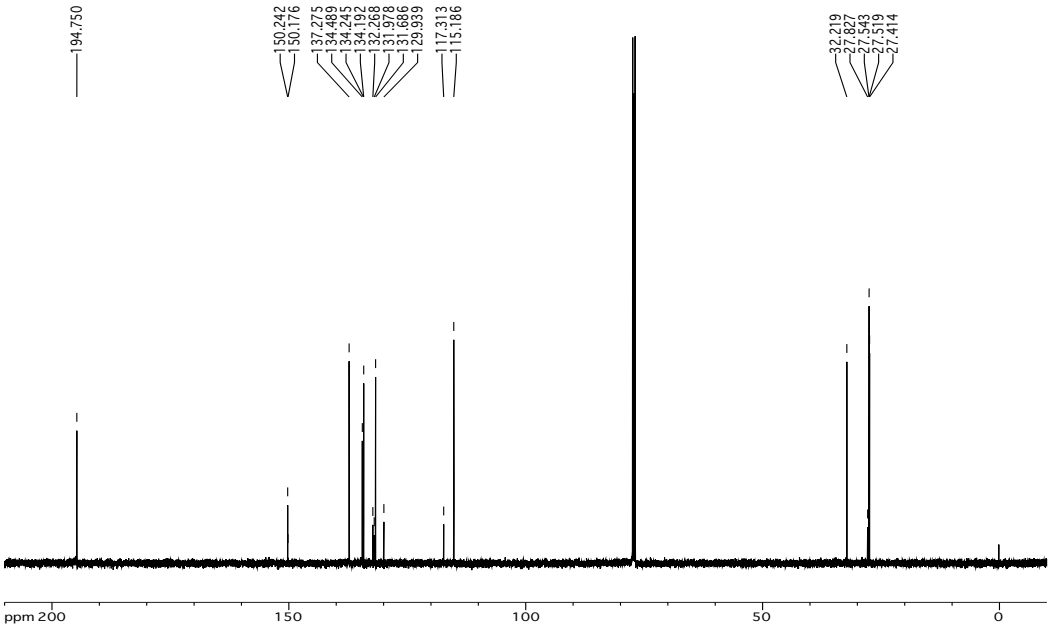
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of 7*E*,9*E*-Undecadien-1-ol (4.30)



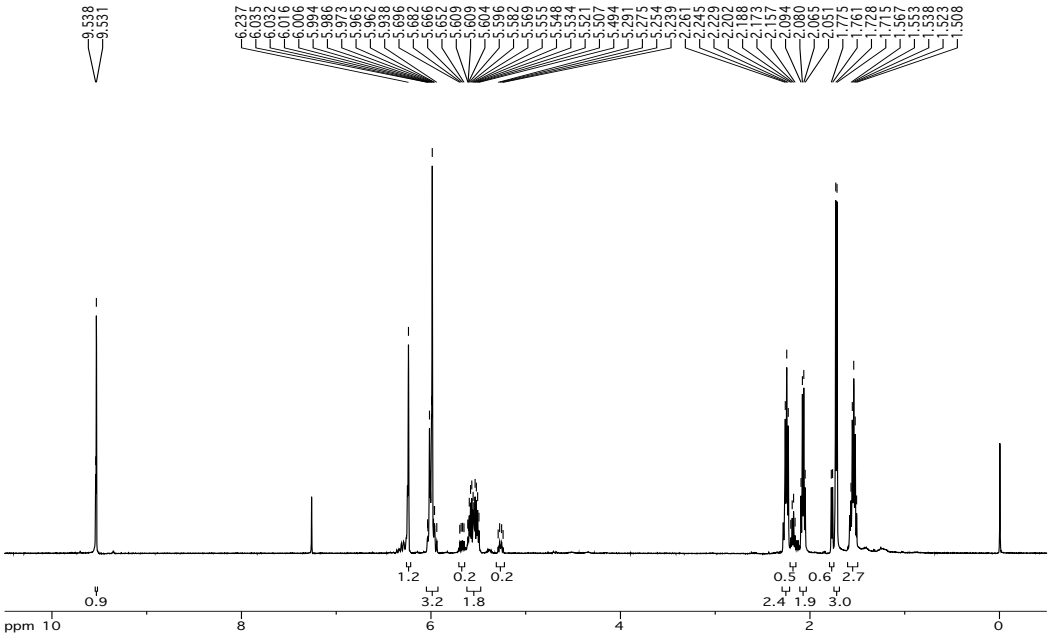


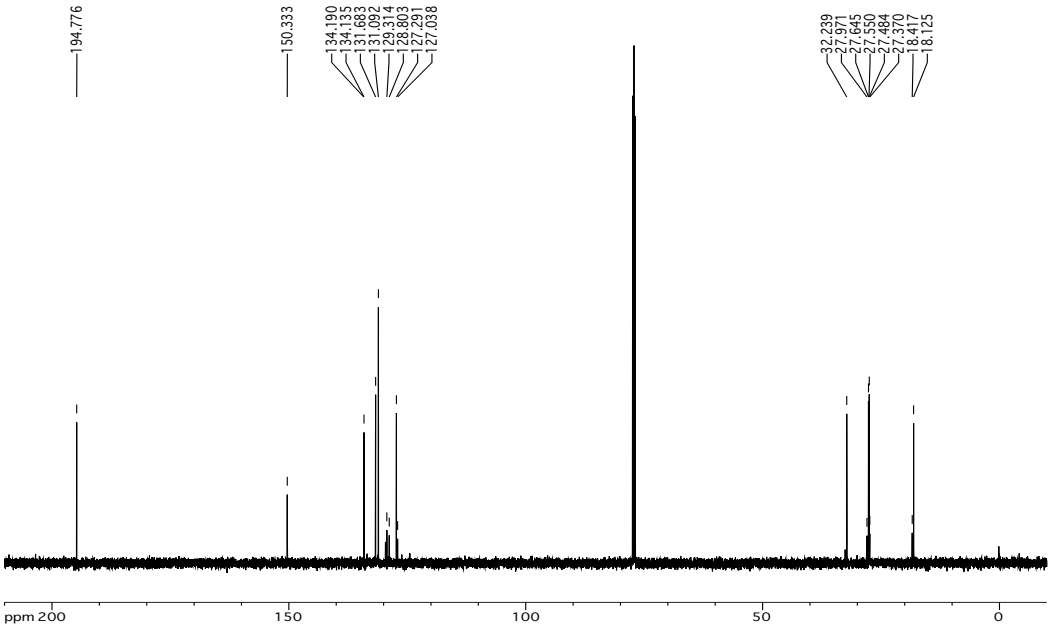
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (6*E*)-2-Methylene-6,8-nonadien-1-al (4.37)



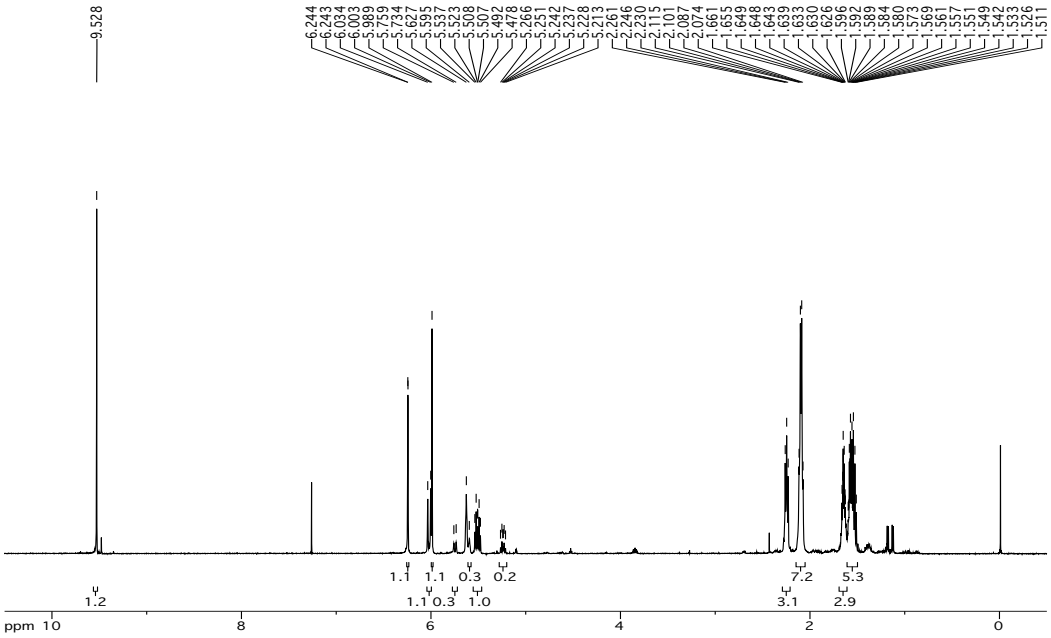


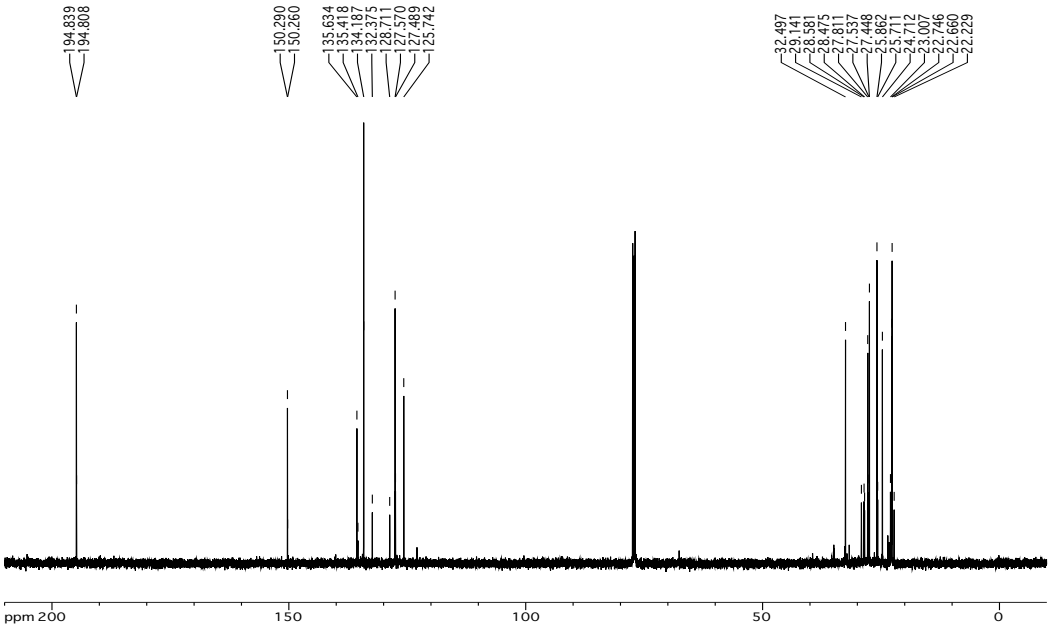
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (6*E*,8*E*)-2-Methylene-6,8-decadien-1-al (4.39)



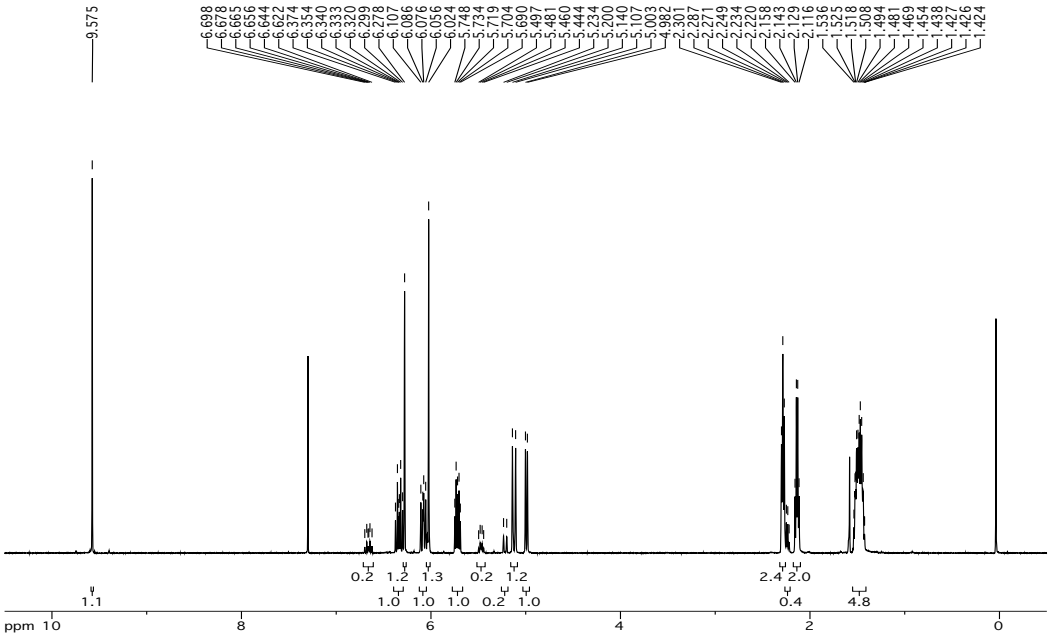


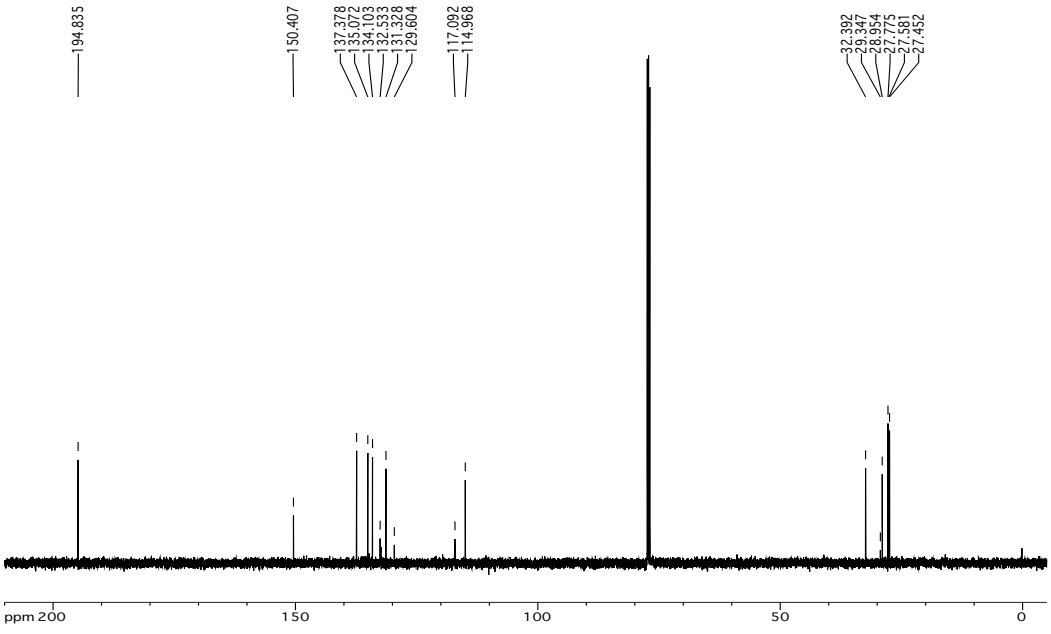
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (6*E*)-7-(1-Cyclohexene)-2-methylene-6-hepten-1-al (4.41)



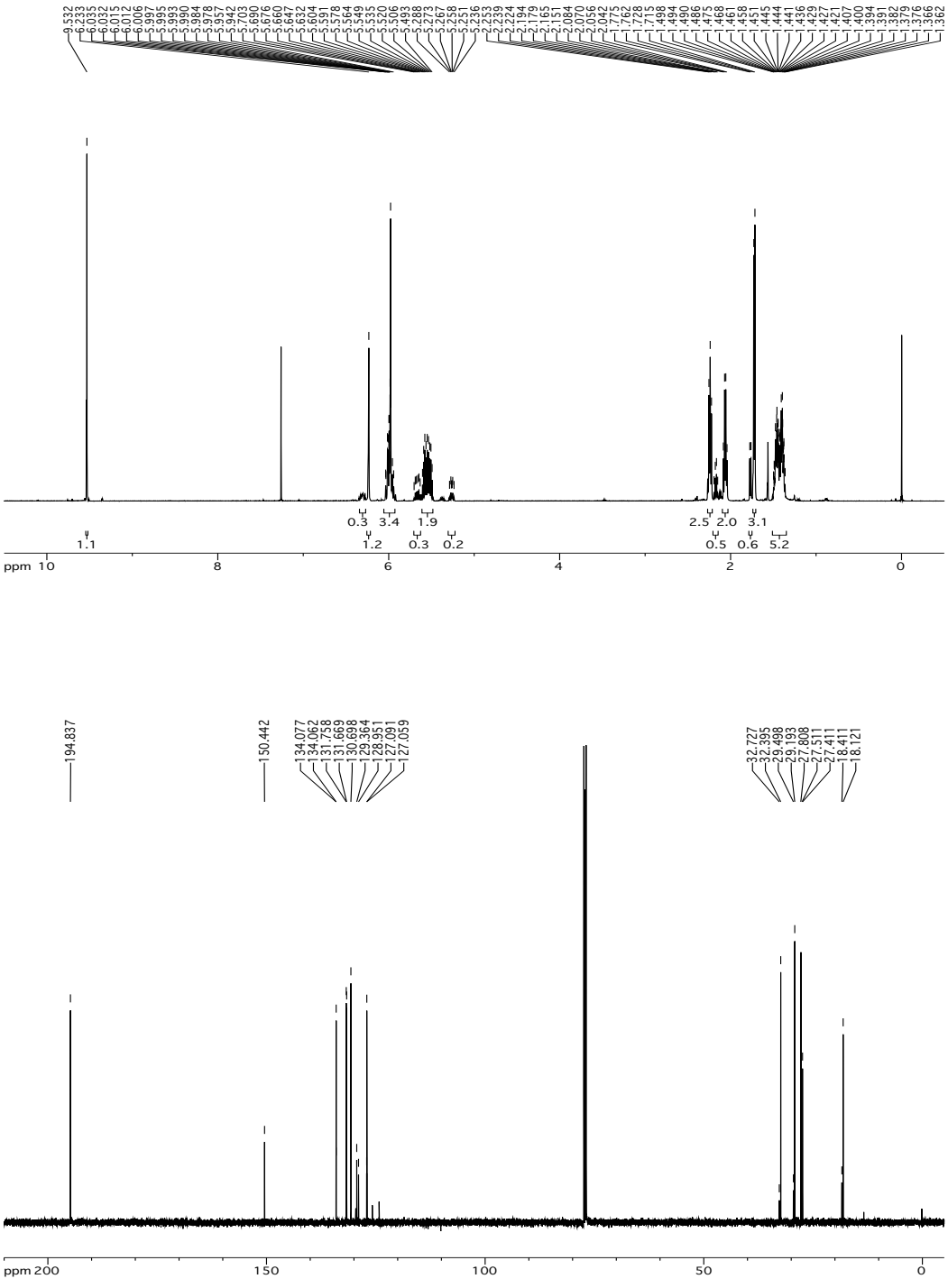


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (7*E*)-2-Methylene-7,9-decadien-1-al (4.38)

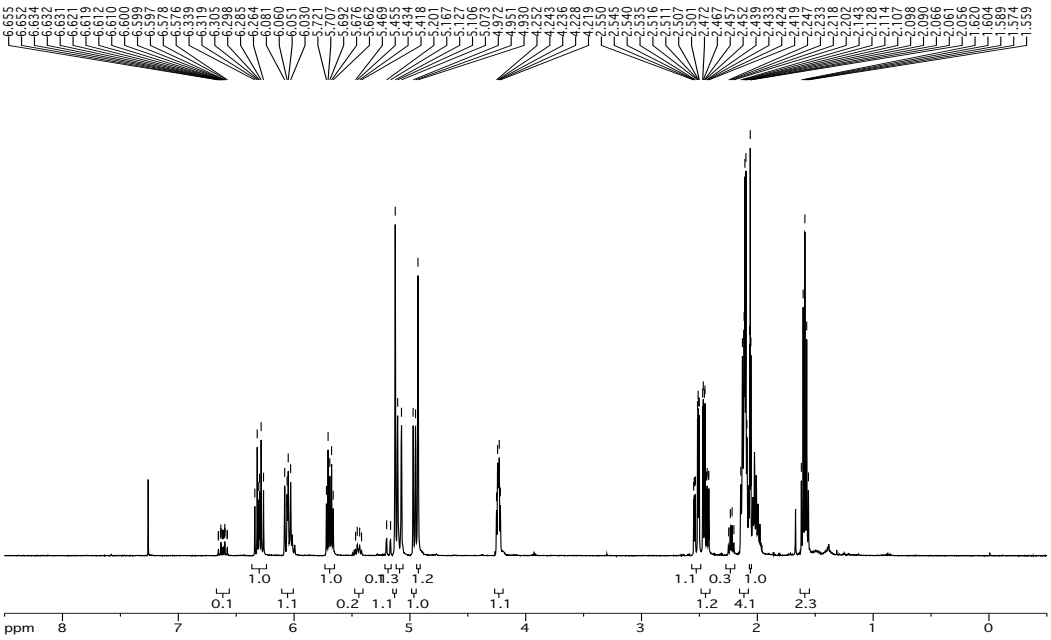


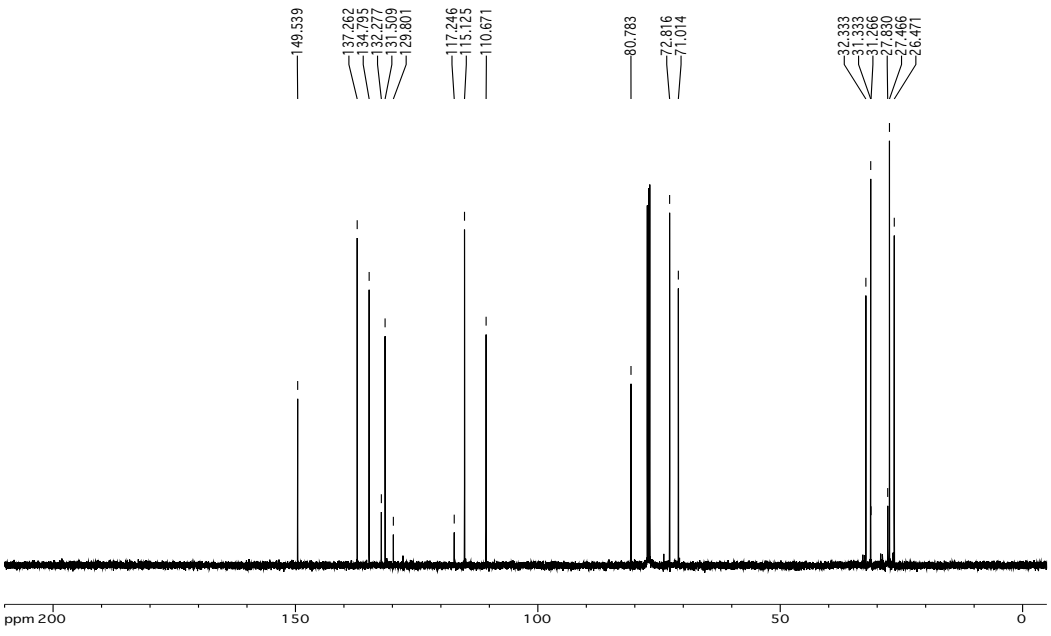


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (7*E*,9*E*)-2-Methylene-7,9-undecadien-1-al (4.40)

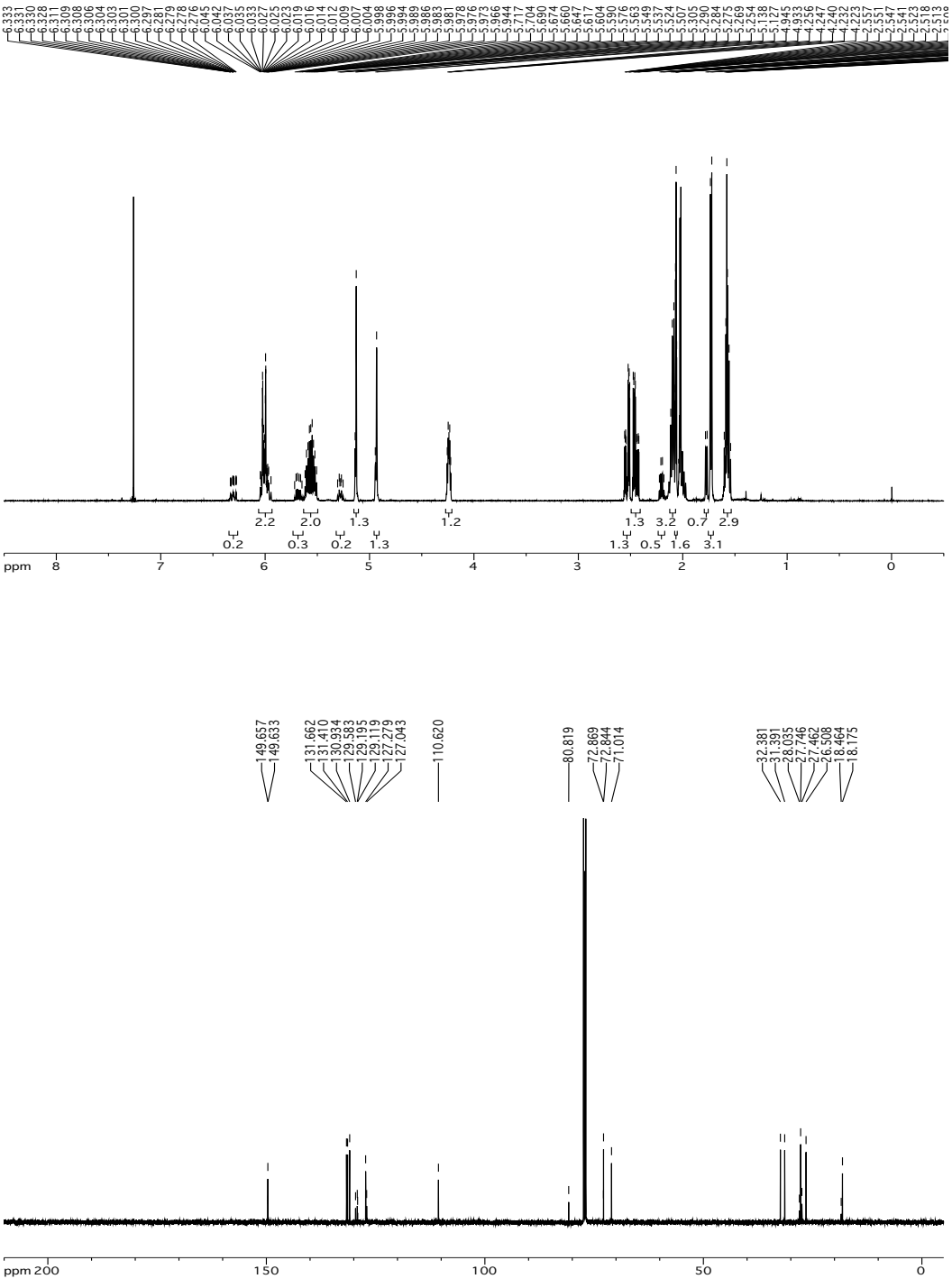


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (9*E*)-5-Methylene-9,11-dodecadien-1-yn-4-ol (4.46)

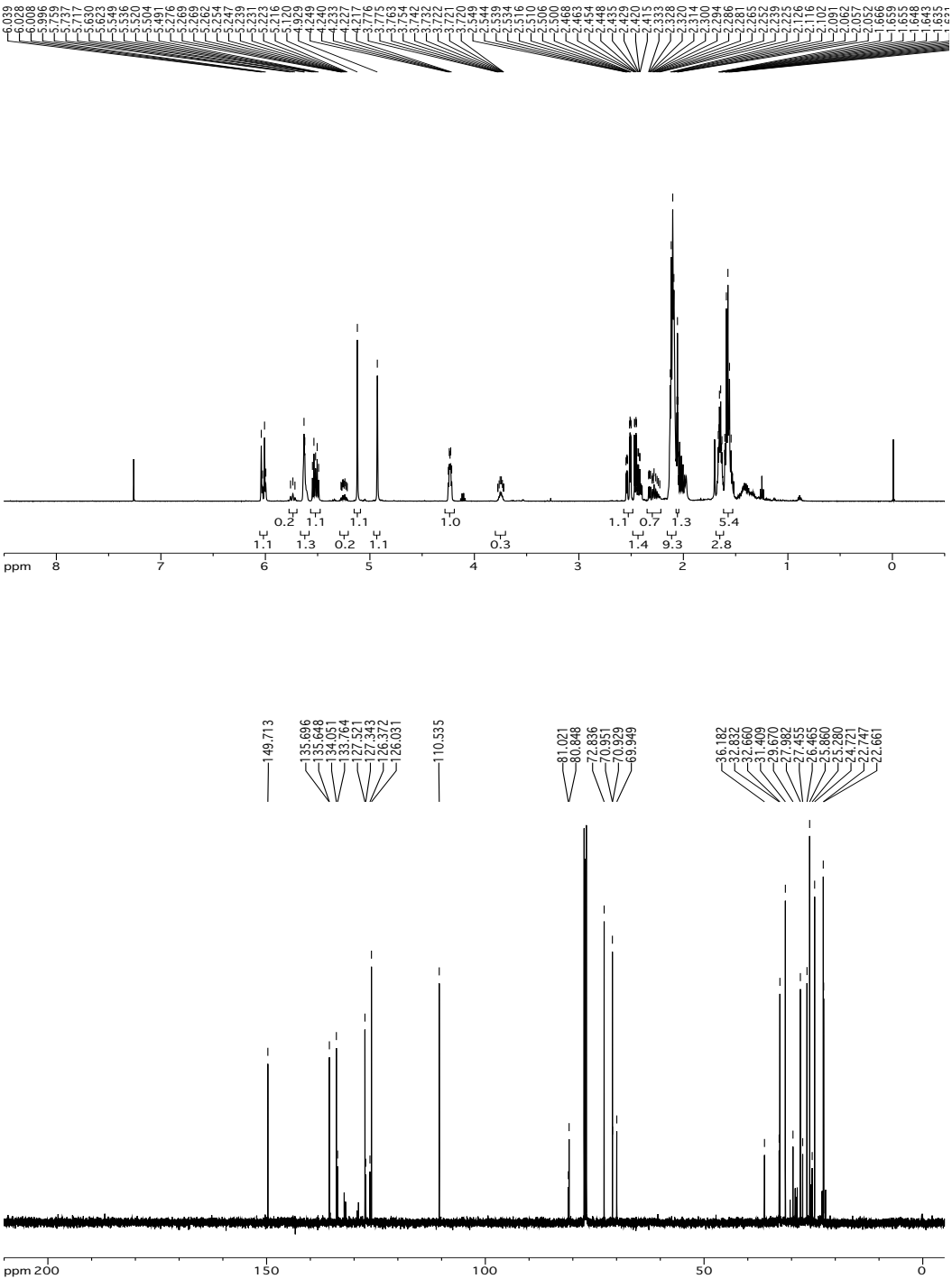




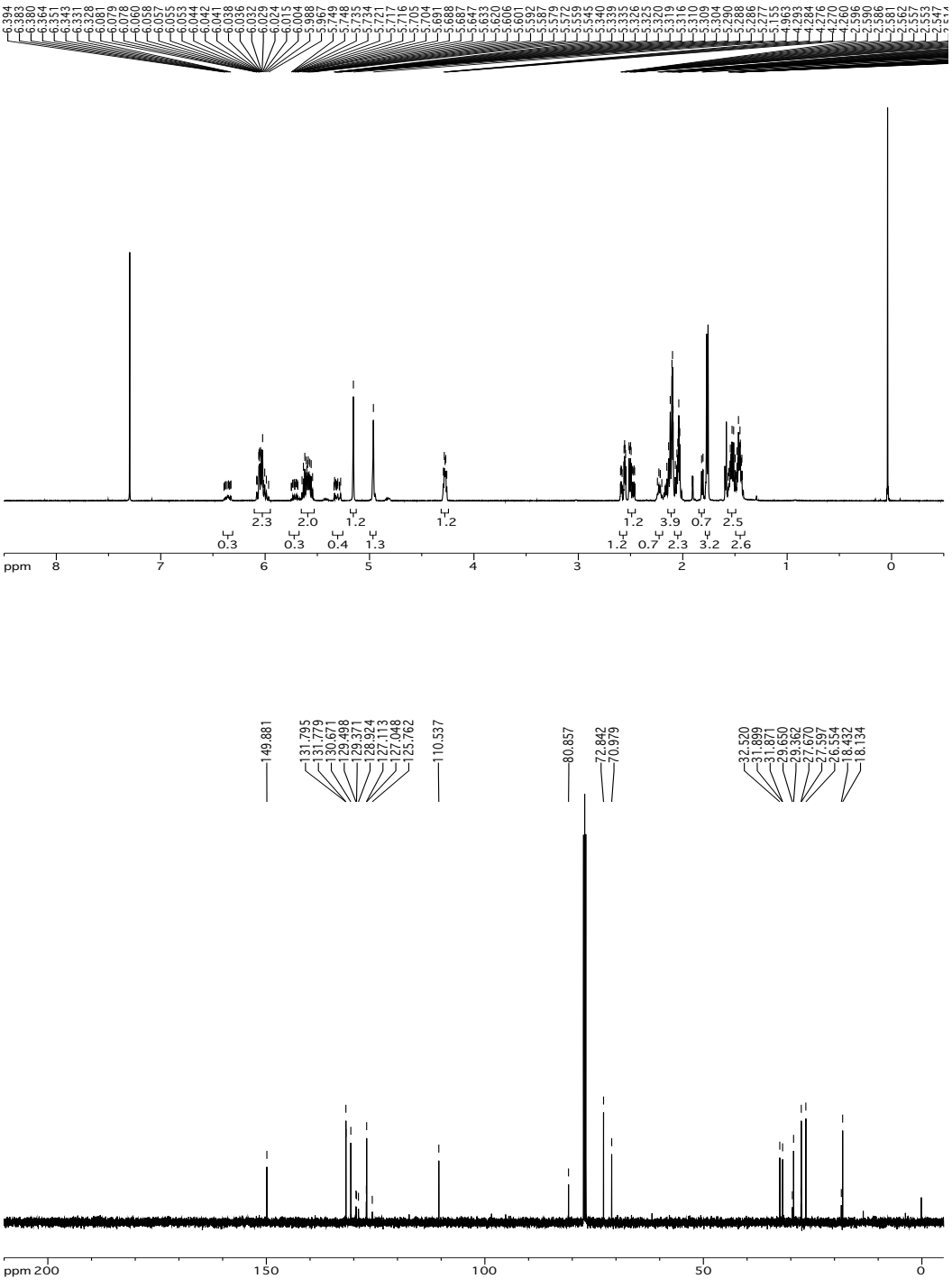
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (9*E*,11*E*)-5-Methylene-9,11-tridecadien-1-yn-4-ol (4.48)



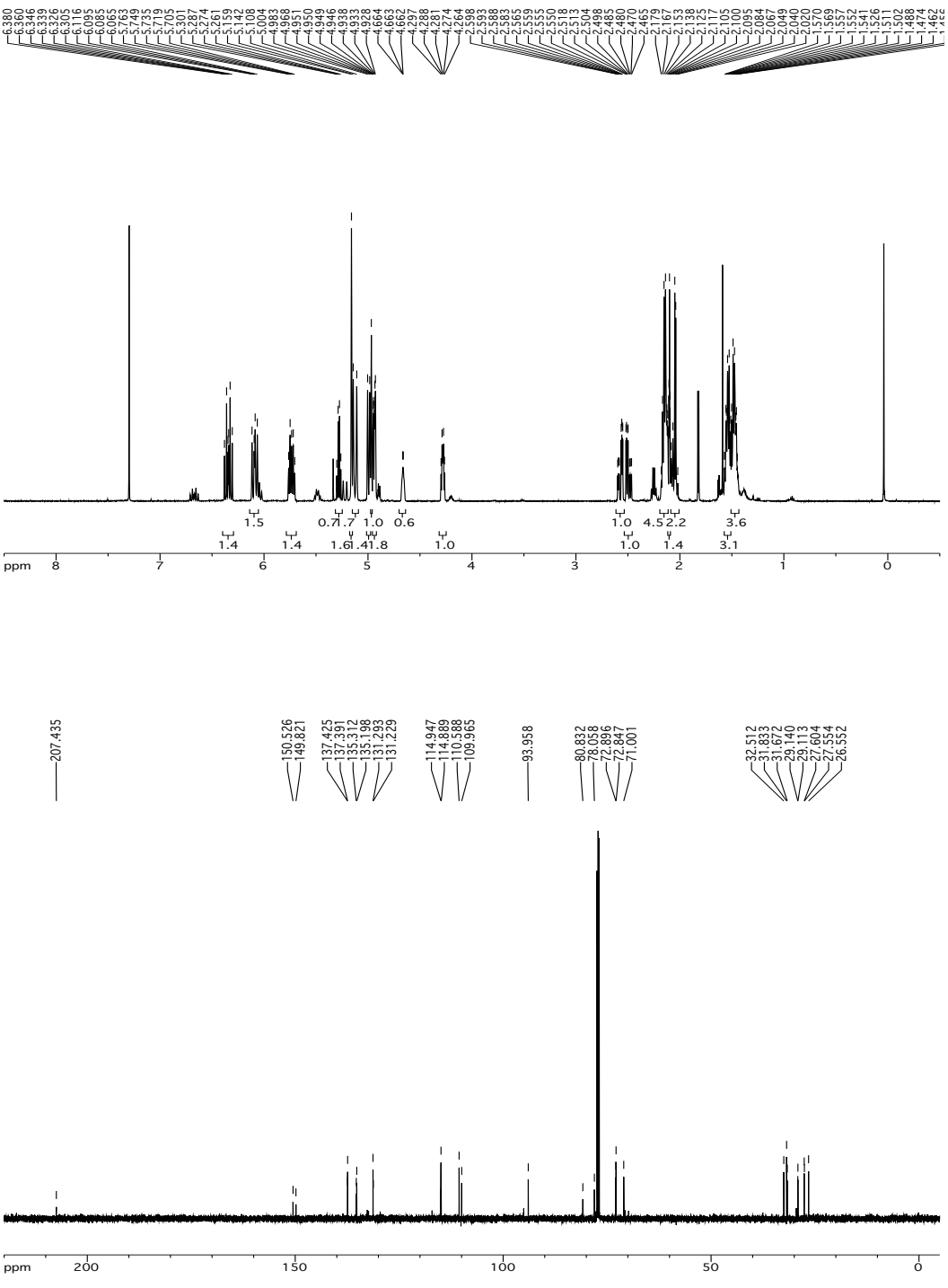
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (9*E*)-10-(1-Cyclohexene)-5-methylene-9-decen-1-yn-4-ol (4.43)



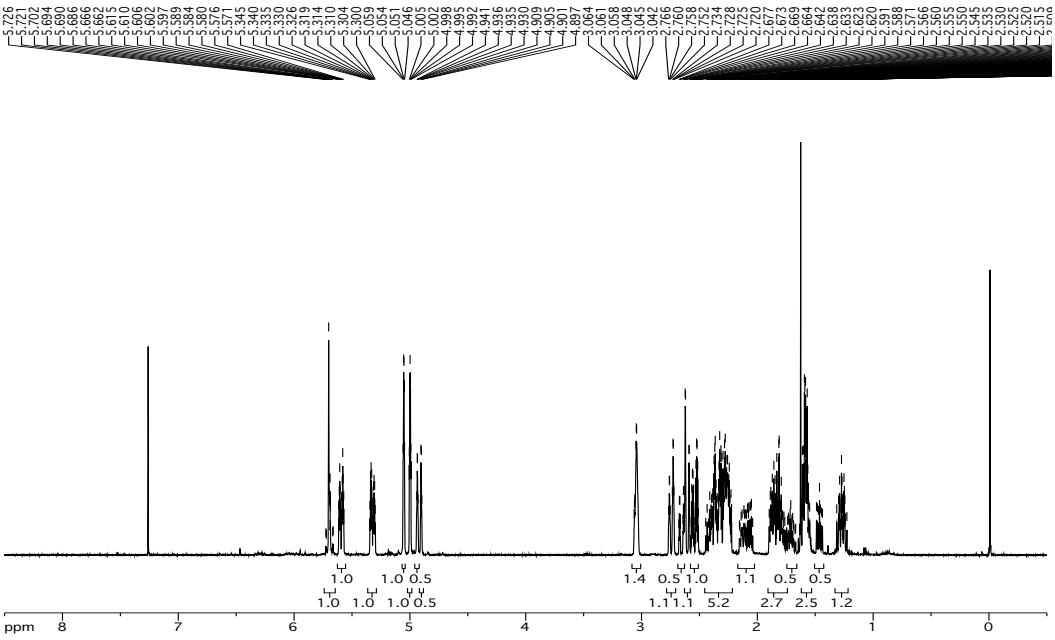
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (10*E*,12*E*)-5-Methylene-10,12-tetradecadien-1-yn-4-ol (4.49)

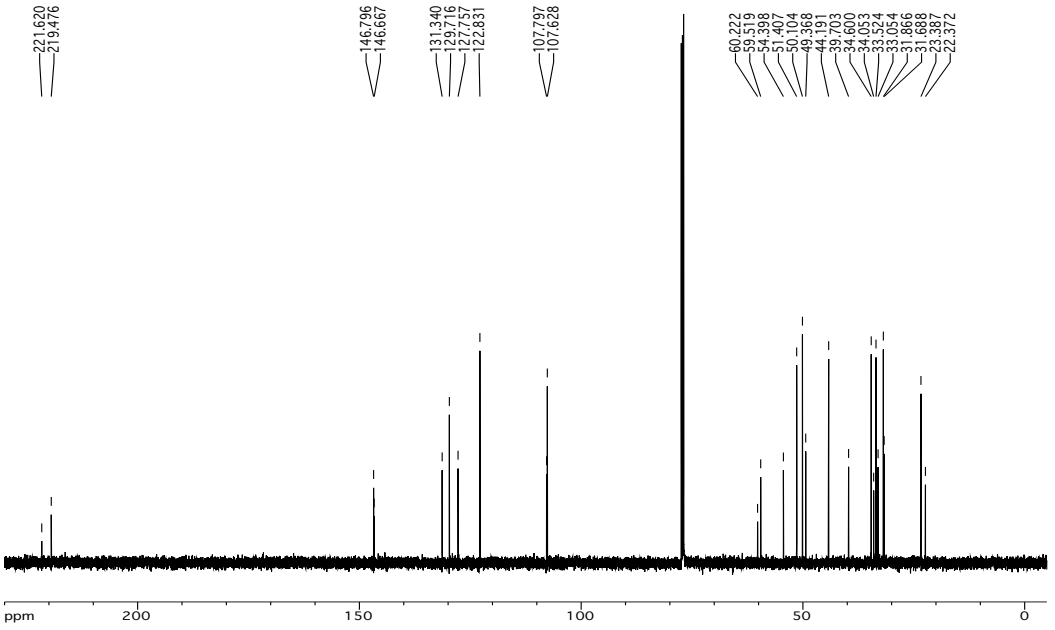


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (10*E*)-5-Methylene-1,2,10,12-tridecatetraen-4-one (4.47a) and (10*E*)-5-Methylene-10,12-tridecadien-1-yn-4-ol (4.47b)

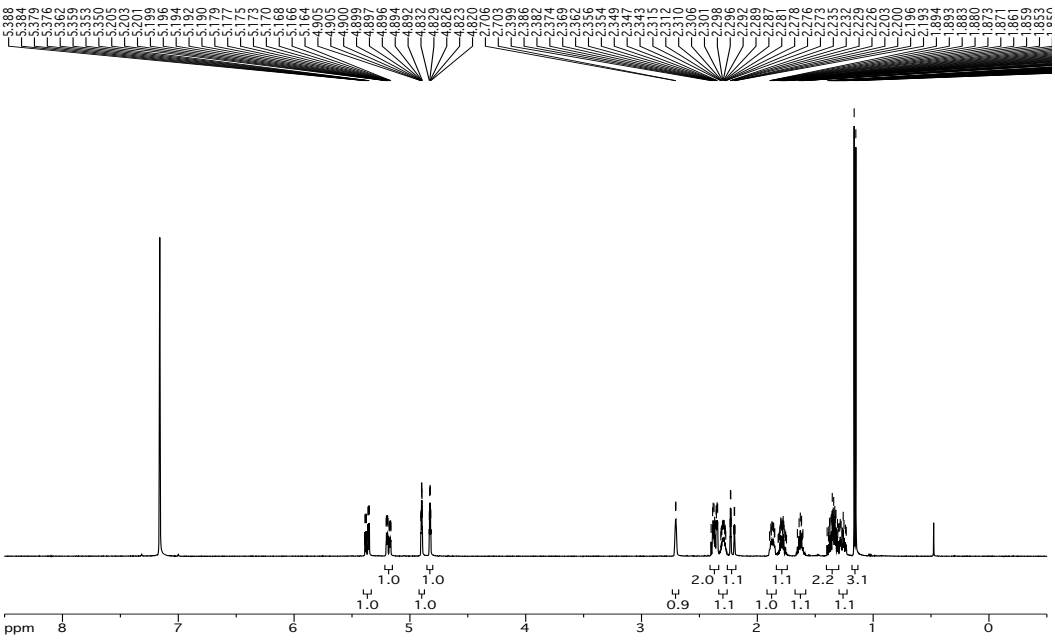


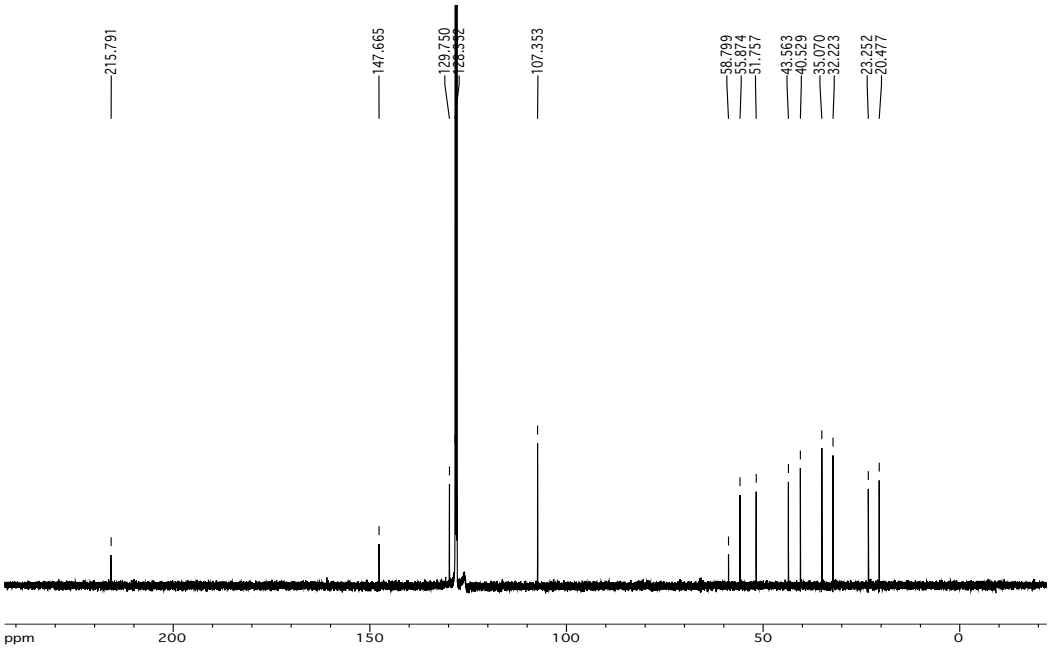
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (3a*R,6*R**,9a*R**)-5-methylene-1,2,3,4,5,6,7,9a-octahydro-3a,6-methanocyclopenta[8]annulen-10-one (4.54) and (3a*R**,6*R**,9a*R**)-5-methylene-1,2,3,4,5,6,7,9a-octahydro-3a,6-methanocyclopenta[8]annulen-10-one (4.55)**



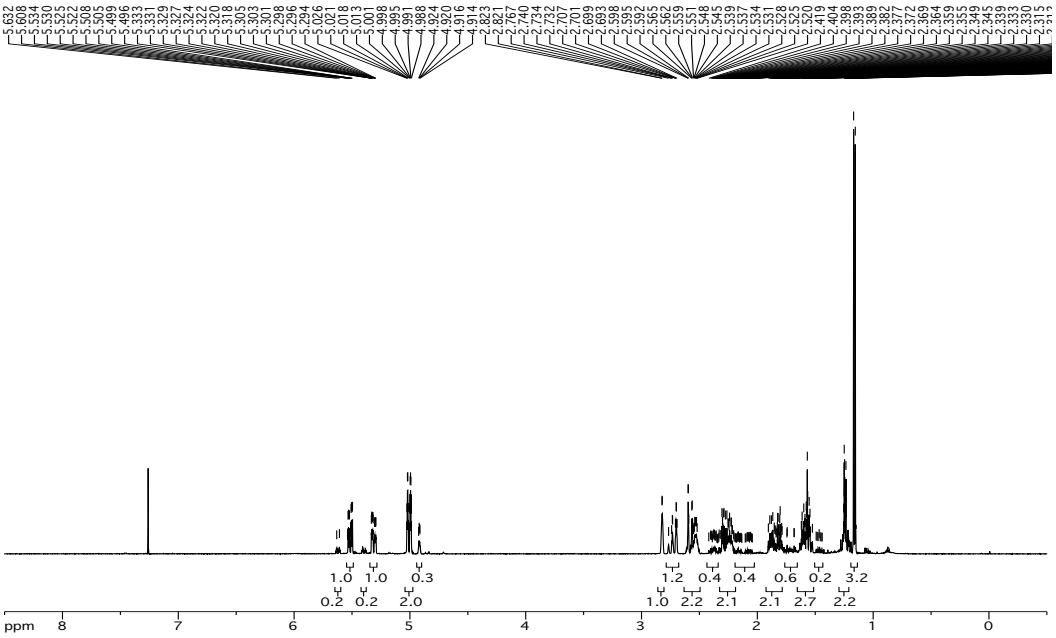


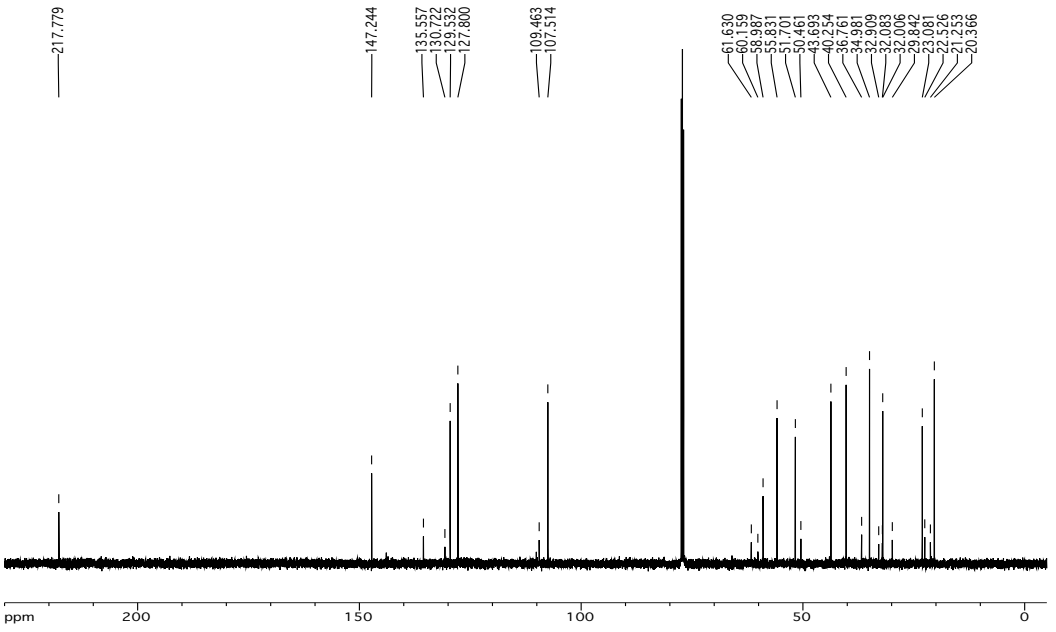
^{1}H NMR (500 MHz, C_6D_6) and ^{13}C NMR (126 MHz, C_6D_6) of (3a*R,6*R**,7*R**,9a*S**)-7-methyl-5-methylene-1,2,3,4,5,6,7,9a-octahydro-3a,6-methanocyclopenta[8]annulen-10-one (4.56)**



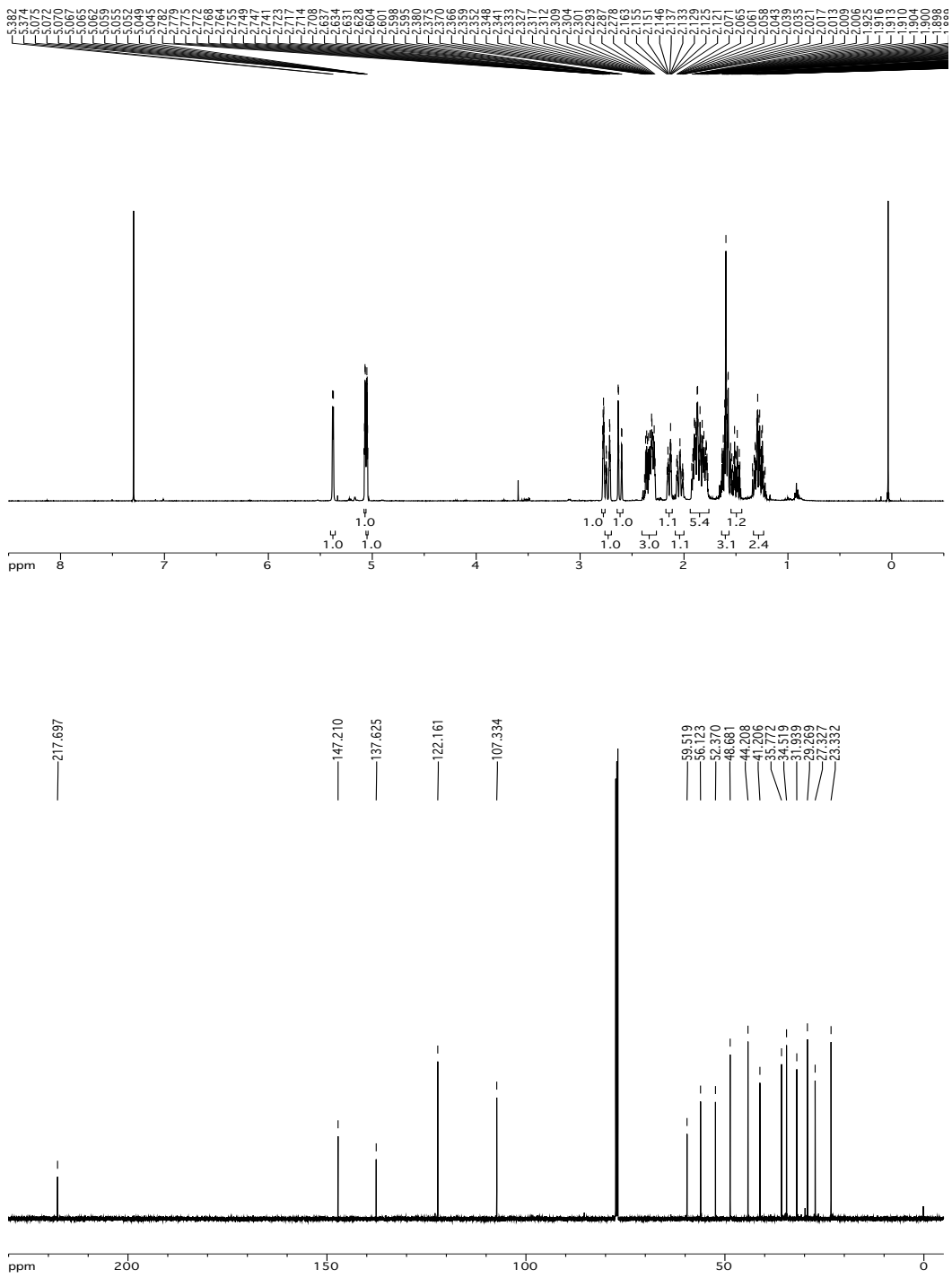


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (3a*R,6*R**,7*R**,9a*S**)-7-methyl-5-methylene-1,2,3,4,5,6,7,9a-octahydro-3a,6-methanocyclopenta[8]annulen-10-one (4.56) and (3a*R**,6*R**,7*S**,9a*R**)-7-methyl-5-methylene-1,2,3,4,5,6,7,9a-octahydro-3a,6-methanocyclopenta[8]annulen-10-one (4.57)**

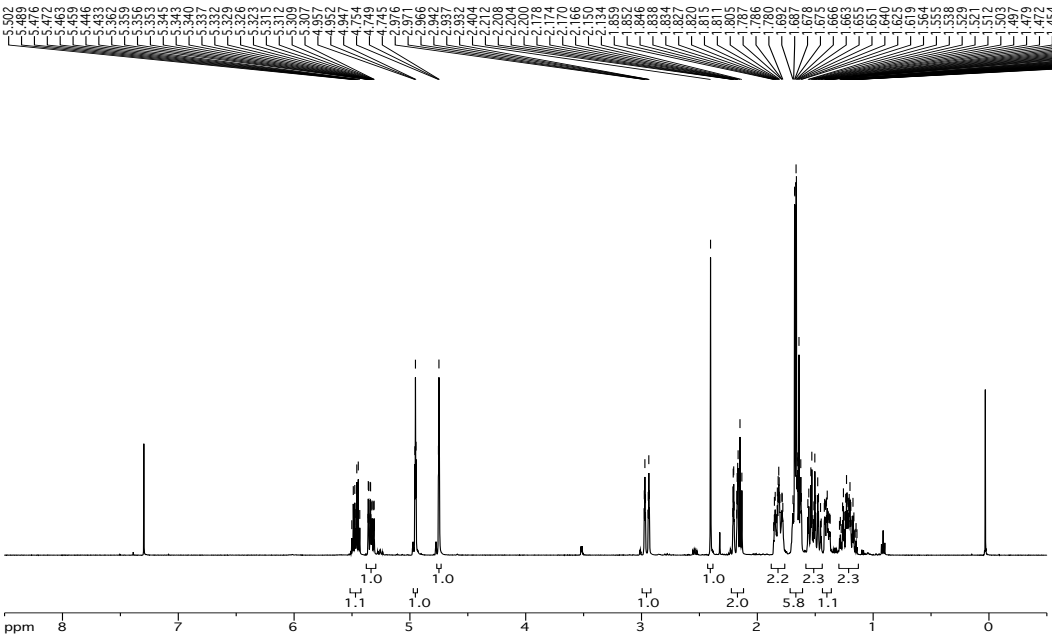


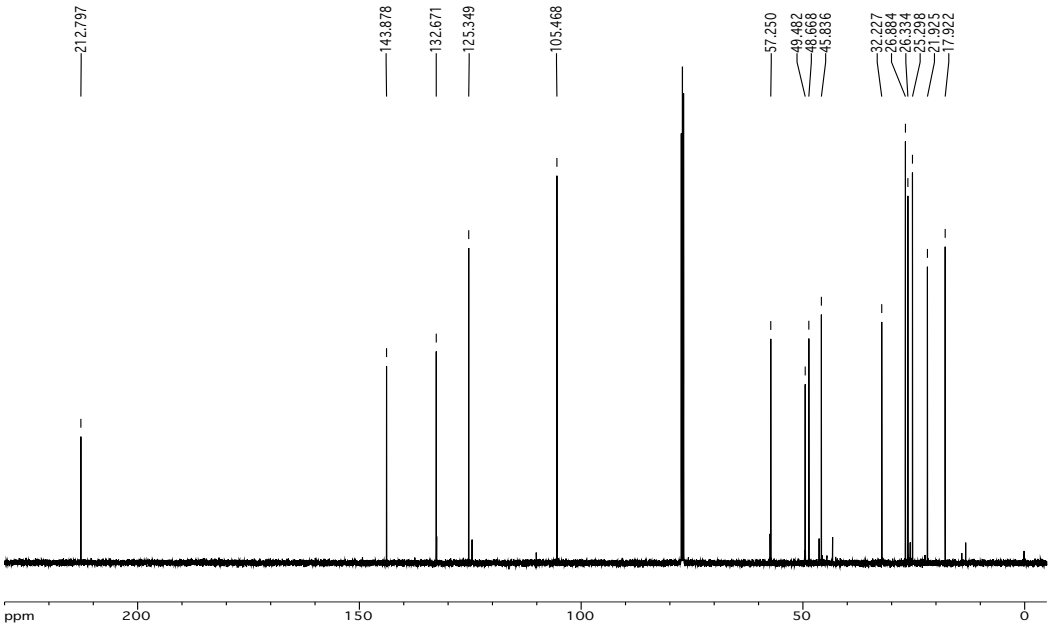


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (3a*R,6*R**,6a*S**,11a*S**)-5-methylene-1,2,3,4,5,6,6a,7,8,9,10,11a-dodecahydro-3a,6-methanobenzo[*a*]cyclopenta[*d*][8]annulen-12-one (4.58)**

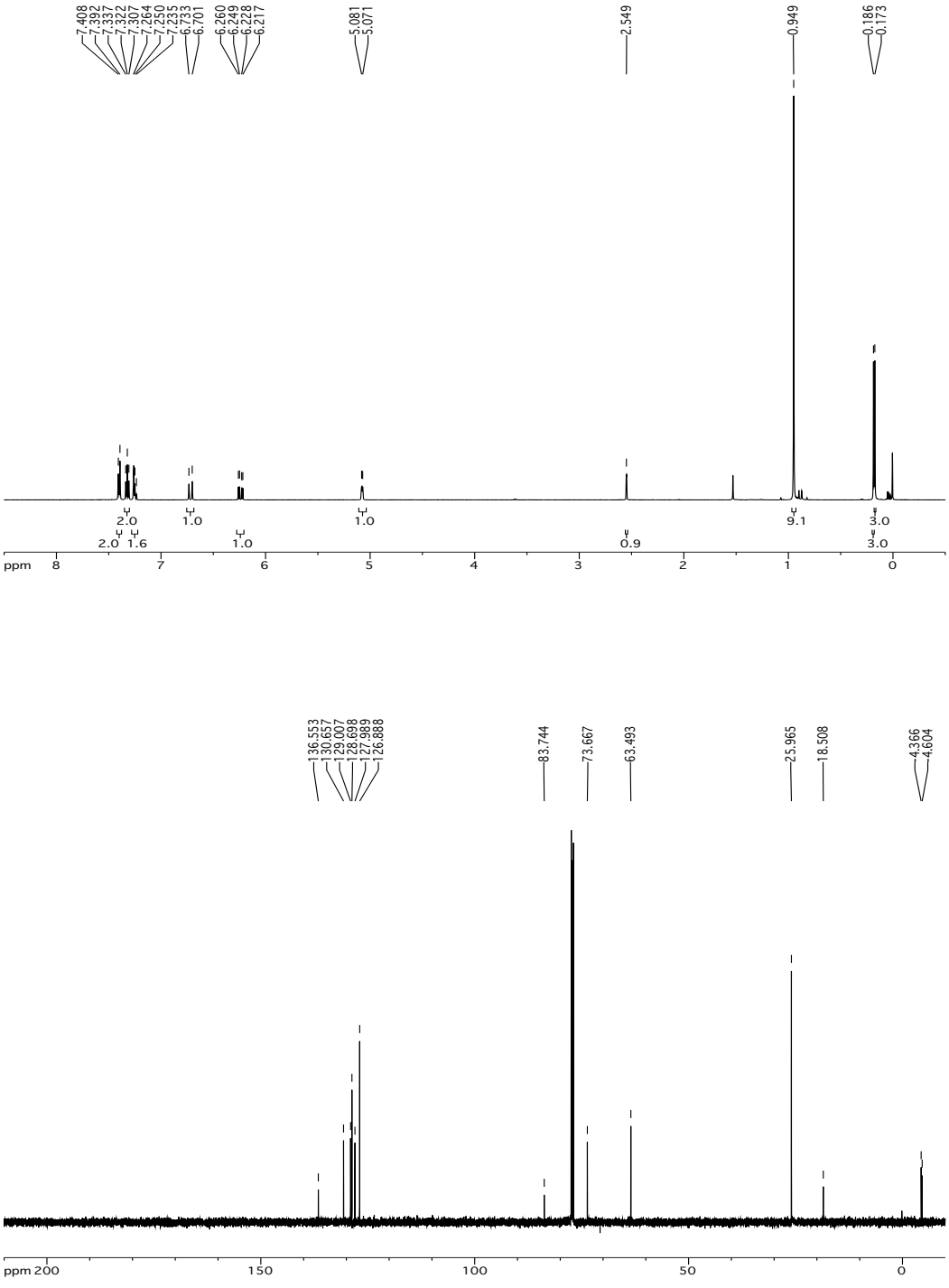


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R,2*R**,4a*R**,8a*R**)-3-methylene-1-((*E*)-prop-1-en-1-yl)octahydro-1*H*-2,4a-methanonaphthalen-9-one (4.61) and (1ξ,2*R**,4a*R**,8aξ)-3-methylene-1-((*E*)-prop-1-en-1-yl)octahydro-1*H*-2,4a-methanonaphthalen-9-one (4.62)**

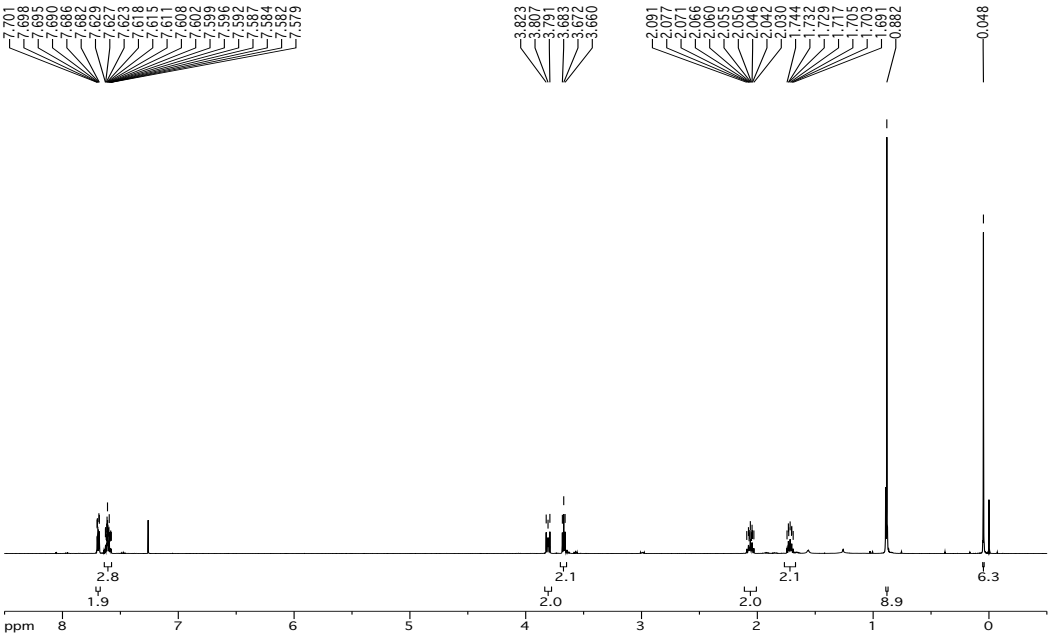


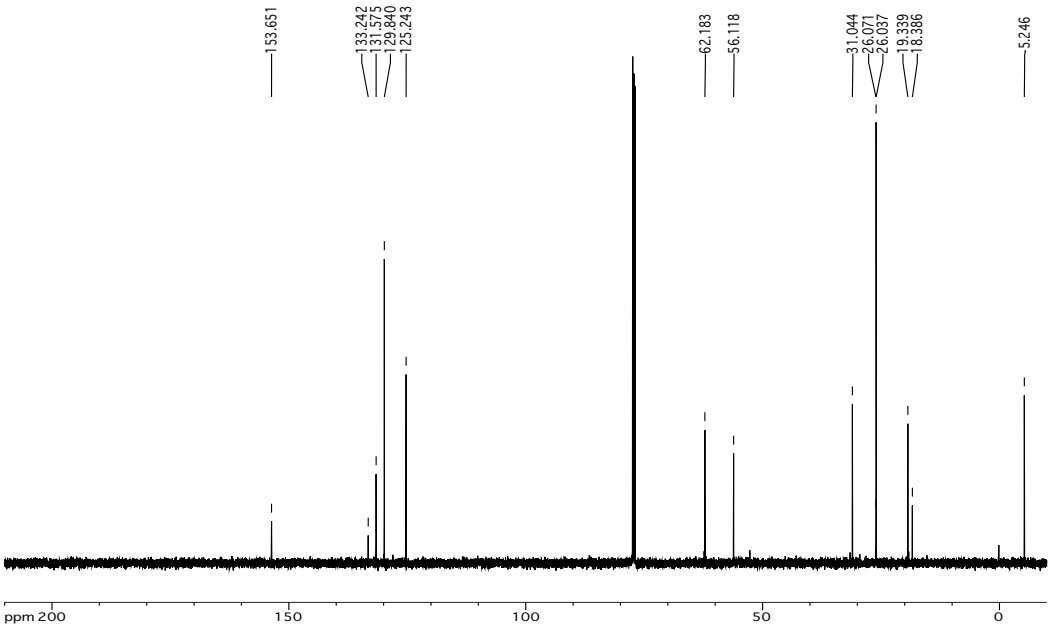


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*E*)-3-(*tert*-butyldimethylsilyloxy)-1-phenyl-1-penten-4-yne (4.70)

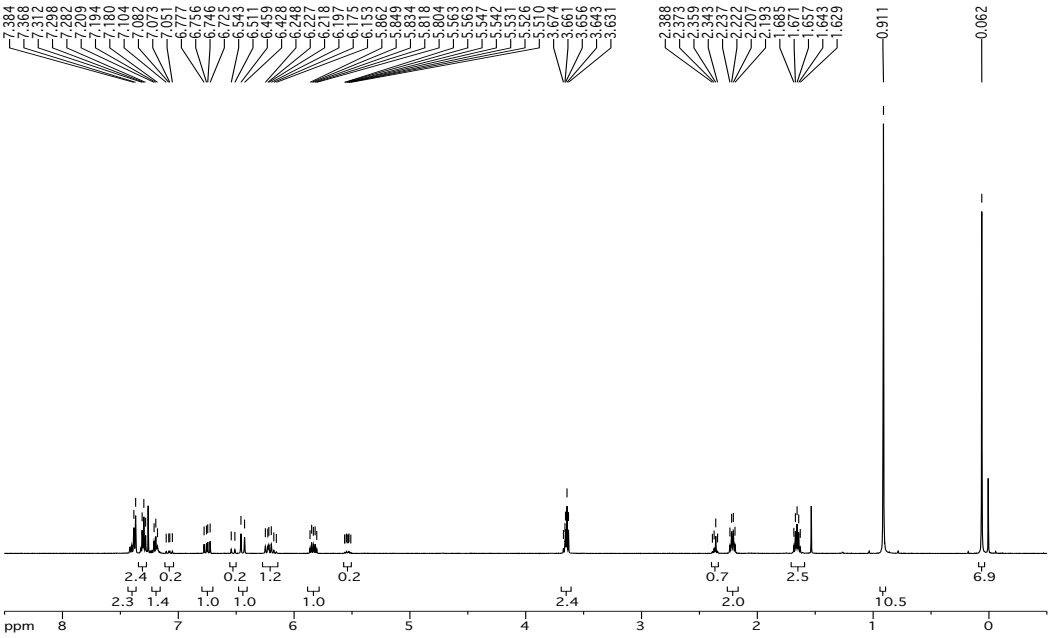


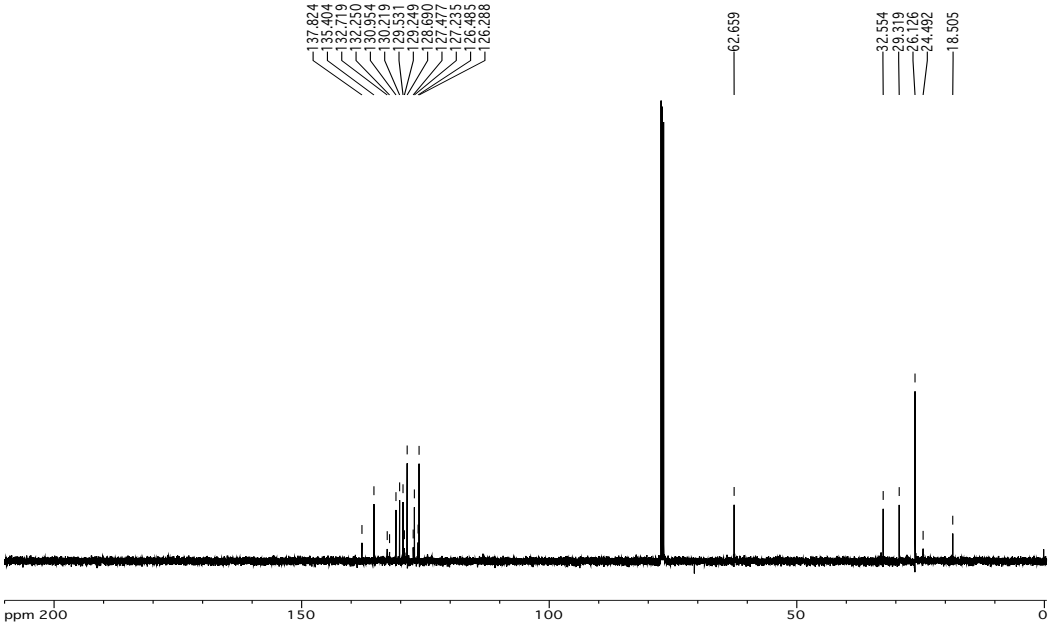
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (6-(*tert*-Butyldimethylsilanyloxy)butanesulfonyl)-1-phenyl-5-1*H*-tetrazole (4.64)



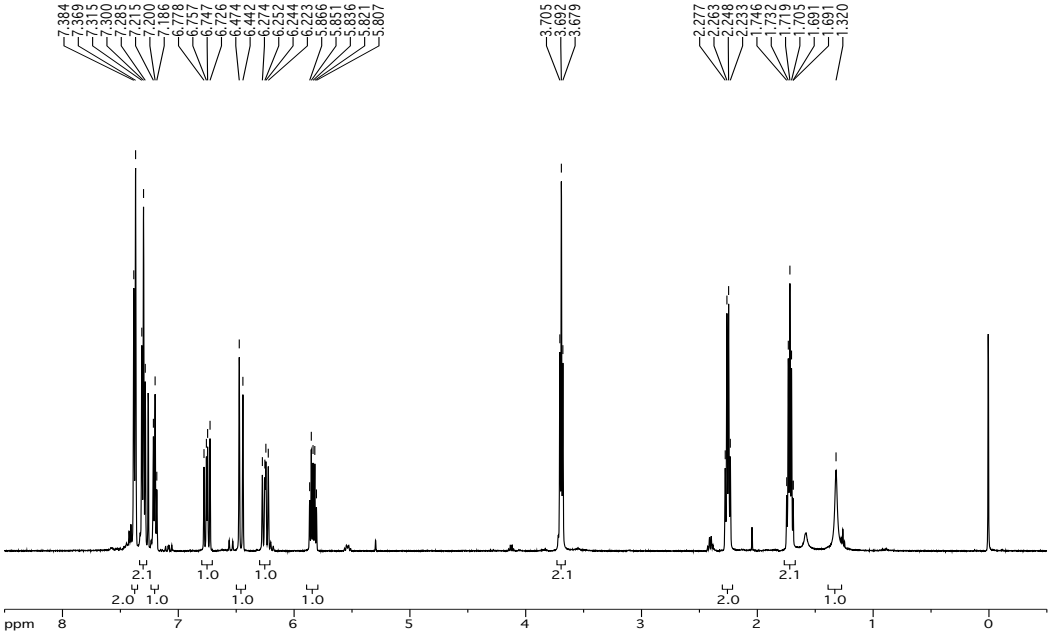


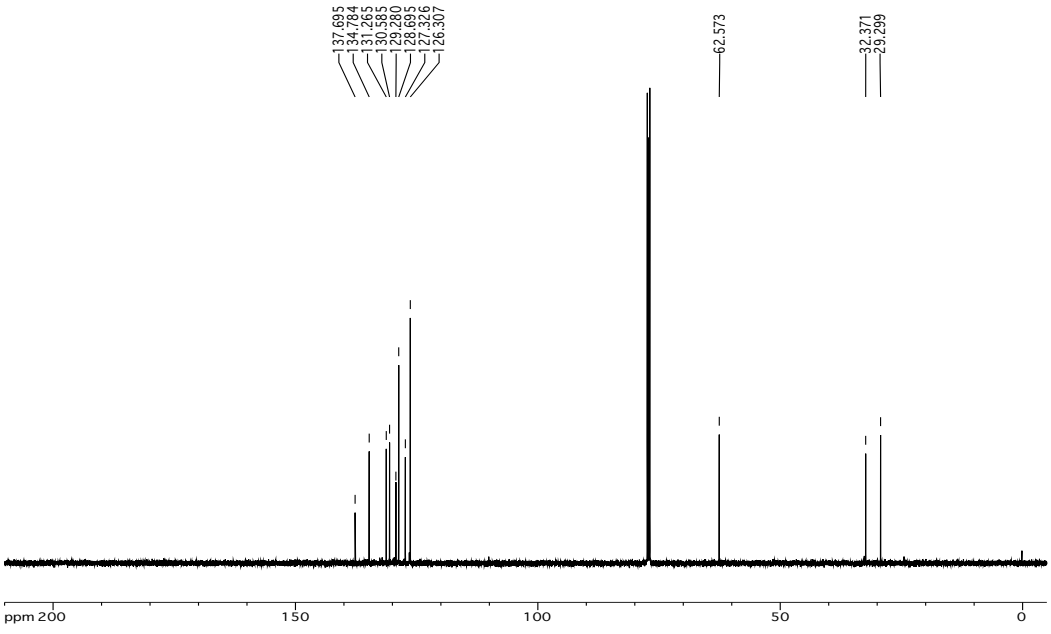
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of ((4*E*,6*E*)-7-Phenyl-4,6-heptadienyl-1-oxy)-*tert*-butyldimethylsilane (4.65)



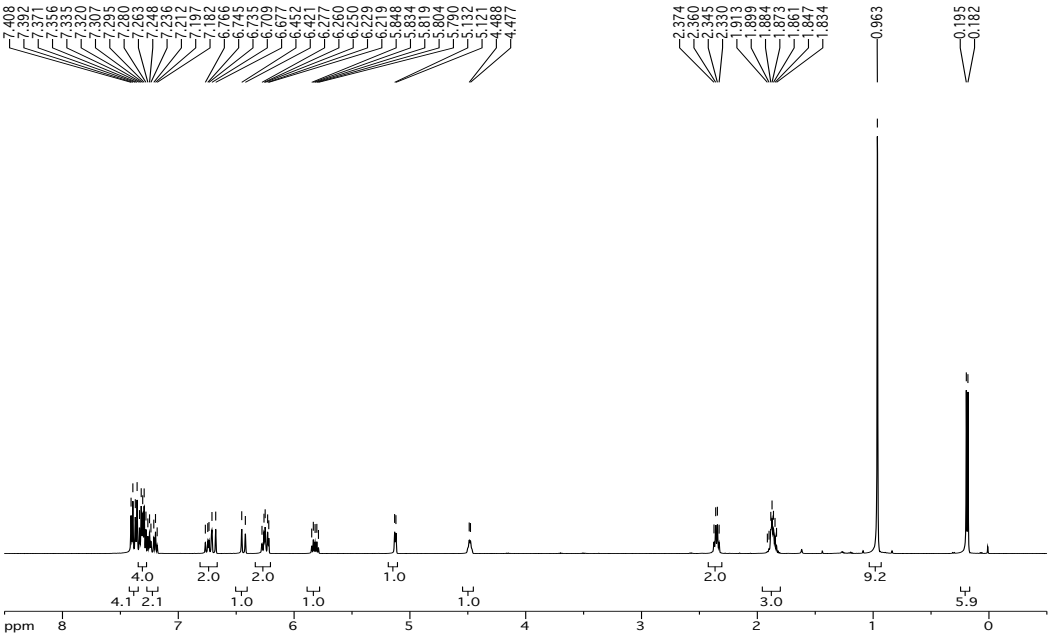


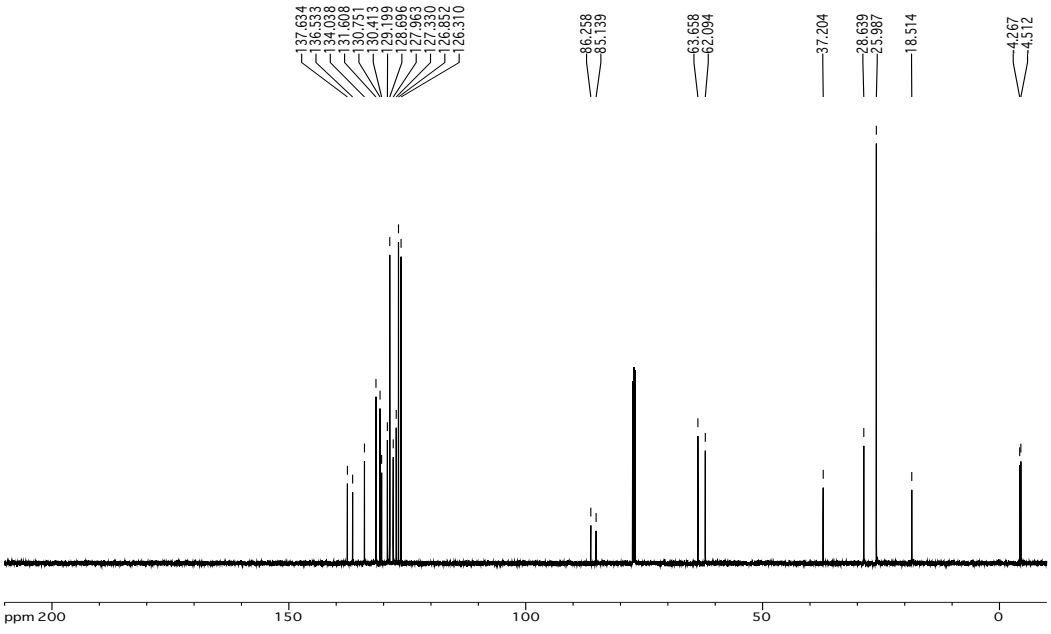
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (4*E*,6*E*)-7-Phenyl-4,6-heptadien-1-ol (4.66)



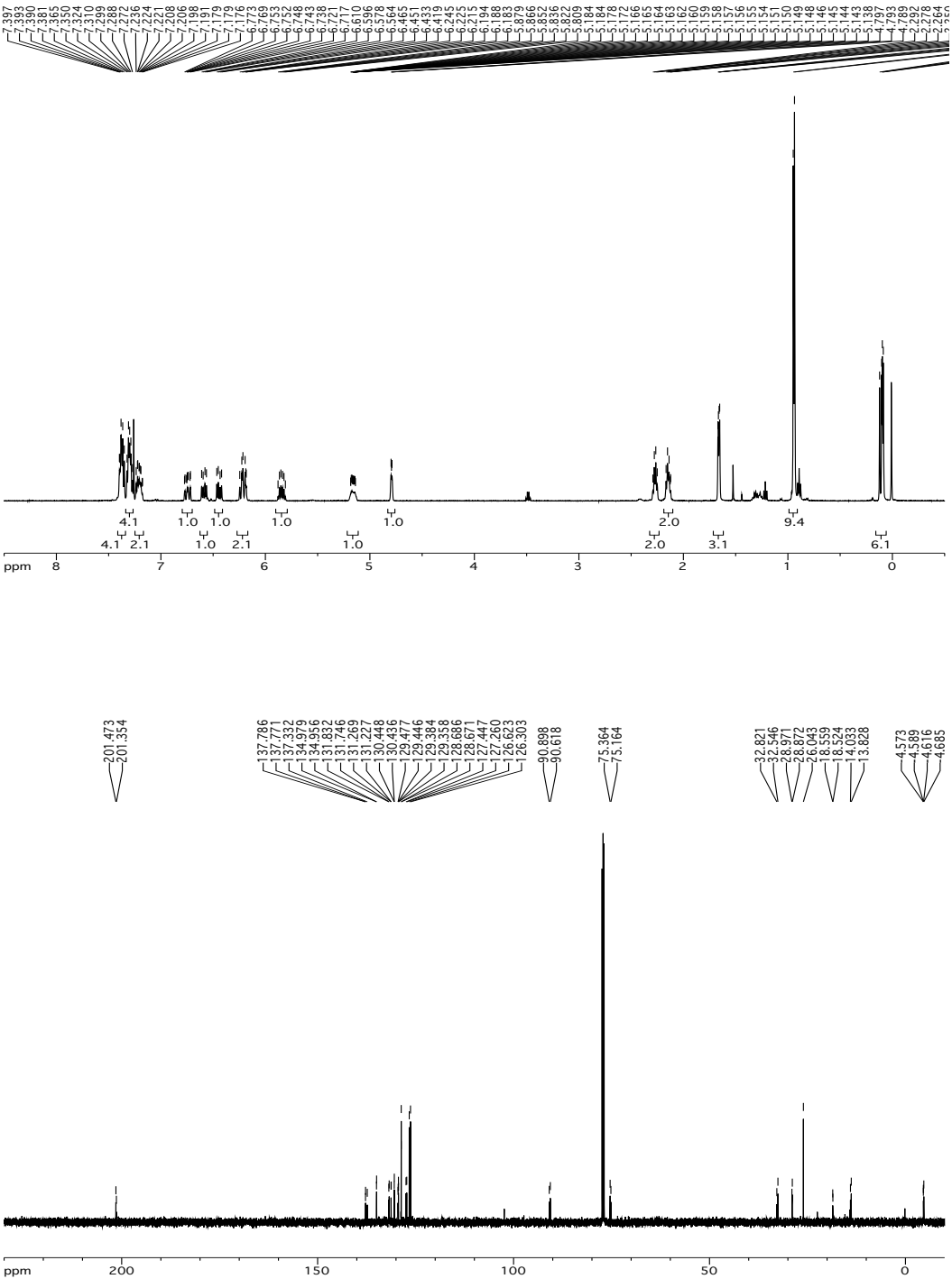


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*E*,9*E*,11*E*)-3-(tert-Butyldimethylsiloxy)-1,12-diphenyl-1,9,11-dodecatrien-4-yn-6-ol (4.71)

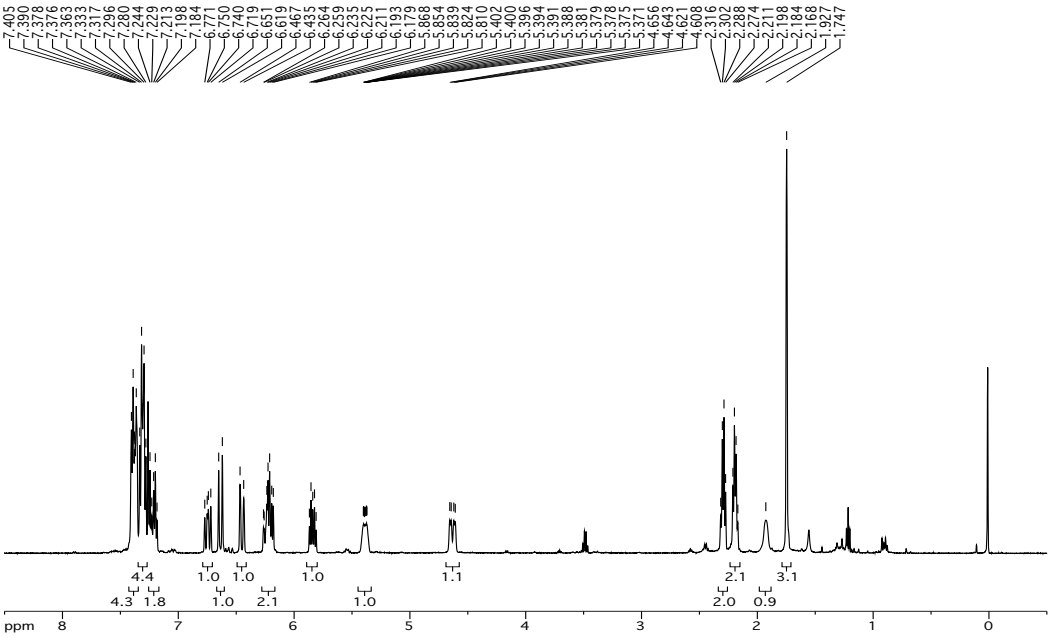


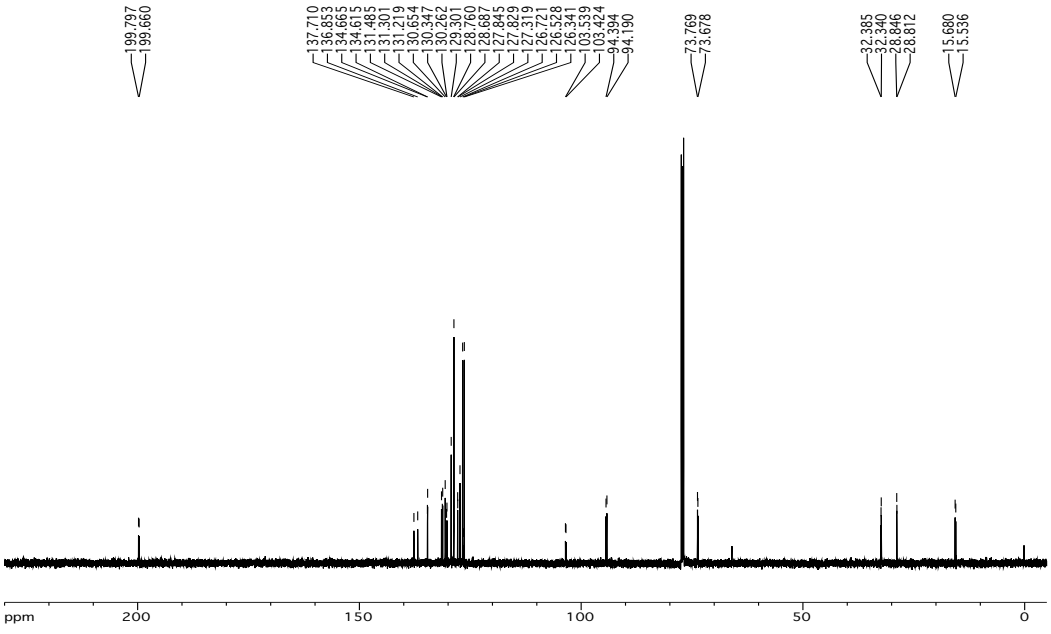


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*E*,9*E*,11*E*)-3-(tert-Butyldimethylsiloxy)-1,12-diphenyl-1,4,5,9,11-dodecapentaene (4.72)

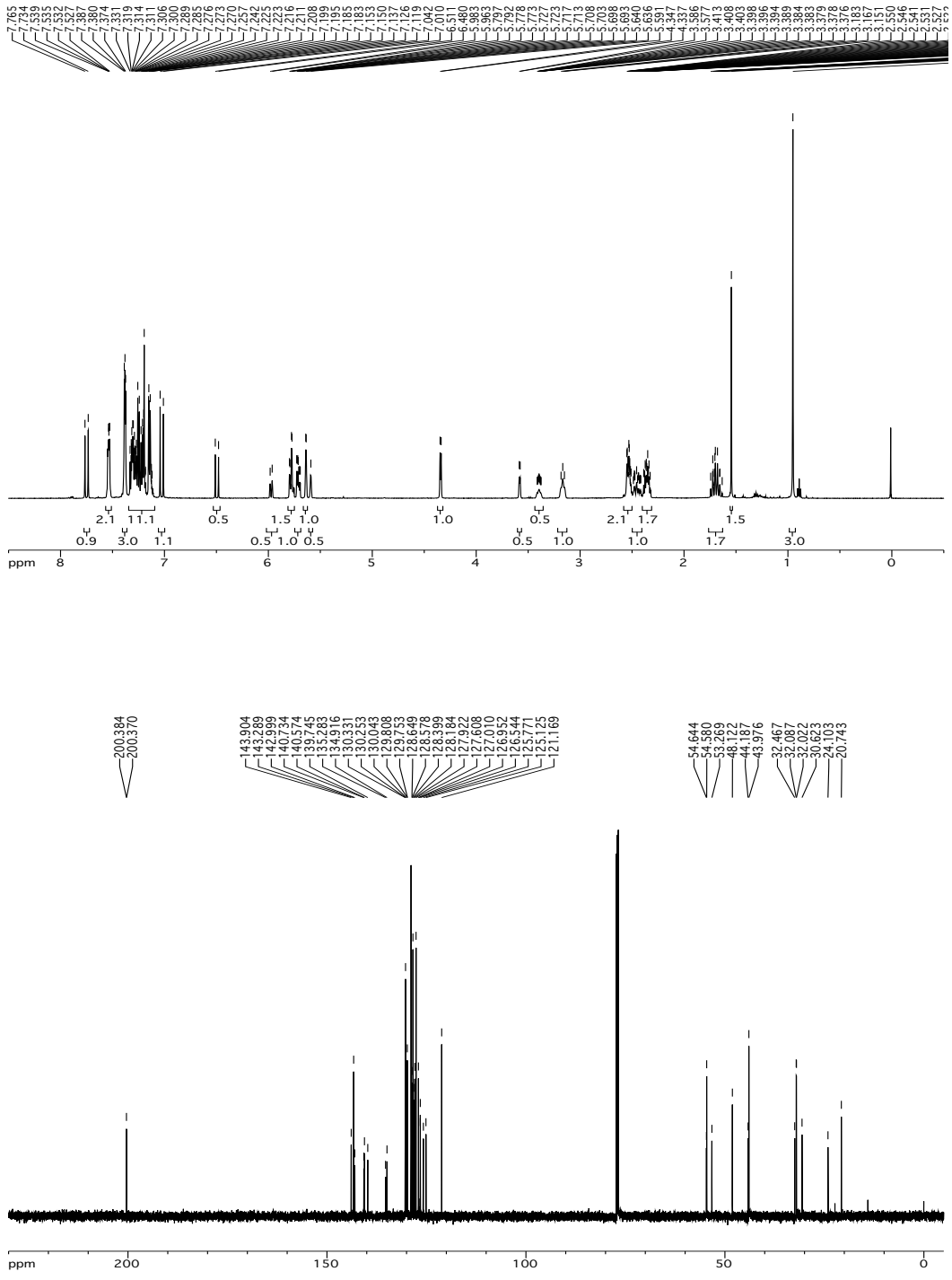


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (1*E*,9*E*,11*E*)-1,12-diphenyl-1,4,5,9,11-dodecapentaen-3-ol (4.73)





^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-1-((4*R,5*R**,7a*R**)-4-methyl-5-phenyl-2,4,5,7a-tetrahydro-1*H*-inden-4-yl)-3-phenylprop-2-en-1-one (4.74) and (*E*)-1-((4*R**,5*S**,7a*S**)-4-methyl-5-phenyl-2,4,5,7a-tetrahydro-1*H*-inden-4-yl)-3-phenylprop-2-en-1-one (4.75)**



Appendix D Computational Details

The Gaussian 09 software package was employed to perform quantum mechanical calculations on the cationic products of the BF3-mediated Nazarov reaction of each AVK (3.49-3.60) via both inward rotation and outward rotation and the transition states leading to these products were located. Stationary points were fully optimized in their ground states at the ωB97X-D/6-31+G(d,p) level of theory. Initial calculations at the B3LYP/6-31G(d) level of theory had initially located the same products and transition states, and the intrinsic reaction coordinate method was used to connect those transition states to the corresponding starting material and product minima. Minima and first-order saddle points were characterized by their number of imaginary frequencies following normal-mode vibrational analysis, i.e., 0 and 1, respectively. All geometries and thermodynamic data were obtained from calculations done in the gas phase at 298.15 K and 1.0 atm. Experimental detail and Cartesian coordinates for the compounds and transition states in Chapter 2 and Chapter 3 can be found in the supplementary information of the respective publications.[**]

[**] Morgan, T. D. R.; LeFort, F. M.; Li, Z.; Marx, V. M.; Boyd, R. J.; Burnell, D. J. *Eur. J. Org. Chem.* **2015***, 2015*, 2952-2959; Morgan, T. D.; LeBlanc, L. M.; Ardagh, G. H.; Boyd, R. J.; Burnell, D. J. *J. Org. Chem.* **2015***, 80*, 1042-1051.