Interrupted Processes and Alternative Substrates for the Nazarov Cyclization

by

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Abstract

This dissertation expands the scope and understanding of the Nazarov electrocyclization and interception of the reactive cyclopentenyl cation intermediate that is formed though a 4π electrocyclization of a pentadienyl cation. An intermolecular process for interrupting the Nazarov is discussed. Also, a new class of alternative substrates, and a new method of activation is presented.

Recent advances in the area of Nazarov chemistry is summarized in Chapter 1. Interrupting the Nazarov reaction from its typical pathway by trapping the reactive cyclopentenyl cation with a nucleophile, or the enol(ate) intermediate with an electrophile enables rapid gains in molecular complexity. Alternative substrates and methods of activation can avoid some of the restrictions faced when using traditional acid activation of cross-conjugated ketones.

Chapter 2 describes the Lewis acid mediated tandem Nazarov cyclization/intermolecular electrophilic aromatic substitution cascade. Our observations suggest that a diquinane is essential in establishing a cyclopentenyl cation that is sufficiently reactive and persistent to be trapped by the arene nucleophile. Importantly, complete regioselectivity and diastereofacial selectivity was observed for arene the trapping.

An oxidation-initiated Nazarov cyclization of 1,4-pentadien-3-yl ethers was developed (Chapter 3). The DDQ oxidation of the 1,4-pentadien-3-yl ether substrates led to a reactive pentadienyl cation intermediate that successfully underwent Nazarov cyclization. The process was terminated by a highly

regioselective elimination to generate cyclopentadienol ethers bearing an exo methylene. The exo elimination was notable, leaving the two new stereocenters formed in the stereospecific cyclization step untouched.

A facile 1,3-transposition of allylic alcohols that was previously observed while preparing substrates for the vinylogous Nazarov reaction has been studied. We were able to expand the scope of this method to include a variety of tertiary propargylic bis(allylic) alcohols, tertiary propargylic allylic alcohols, tertiary bis(propargylic) allylic alcohols, and bis(allylic) cyanohydrins (Chapter 4). Additionally, the vanadium catalyzed transposition was carried out in tandem with a gold catalyzed cycloisomerization to generate tri-substituted furans.

Preface

The research described in Chapter 2 of this dissertation was a joint effort between C. J. Rieder and the author, both under the supervision of Professor F. G. West at the University of Alberta. Compounds **2a, 3a, 7a, 7a', 7b, 7b', 7c, 7c', 7i, 7i'** were first synthesized by C. J. Rieder. The remaining compounds described in sections **2.5**, **3.4**, and **2.6** were synthesized by the author.

Dedication

For Allison and Claire

Mom, Dad, and Dean.

Acknowledgements

I would like to thank all of the people who have helped me get to where I am today, both professionally and personally.

Boss, your chemistry 361 course was a revelation for me, it fostered a passion for synthetic chemistry that led me down this path. I feel fortunate have had your guidance, thank you for giving me a chance.

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All the support staff in the department, analytical, mass spec, NMR, X-ray, glass, machine, and electronics shop, administrative assistants, and stores, thank you for everything you do.

Mom, Dad, and Dean, thanks for all the support over the years. Your belief in what I have been trying to accomplish has been unwavering, I cannot begin express how much that has meant.

Allison, thank you taking this journey with me. I can't thank you enough for all your support and sacrifice. Claire, your arrival was the light at the end of the tunnel, you have been a shinning light in my life ever since.

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List of Symbols and Abbreviations

^{1}H	proton
^{13}C	carbon-13
Å	angstrom
Ac	acetyl
acac	acetylacetonate
app	apparent (spectral)
APT	attached proton test
aq	aqueous solution
Ar	aryl
atm	atmosphere
BAr^{f}	$[B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$
BINOL	1,1'-bi-2-napthol
Bn	benzyl
br	broad (spectral)
ºC	degrees Celsius
calcd	calculated
CAN	ceric ammonium nitrate
cat.	indicates that the reagent was used in a catalytic amount
cm^{-1}	wave numbers
COSY	H-H correlation spectroscopy
conc.	concentrated
d	day(s); doublet (spectral)
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
dd	doublet of doublets (spectral)
ddd	doublet of doublet of doublets (spectral)
dddd	doublet of doublet of doublet of doublets (spectral)
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DFT	density functional theory
DIBAL-H	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMP	Dess-Martin periodinane
dr	diastereomeric ratio
dsept	doublet of septets (spectral)
dt	doublet of triplets (spectral)
$E_{ox}°$	oxidation potential
EAS	electrophilic aromatic substitution
EDG	electron-donating group
EI	electron impact (mass spectrometry)
er	enantiomeric ratio
Et	ethyl
EtOAc	ethyl acetate
equiv.	equivalent(s)
EWG	electron-withdrawing group
g	gram(s)
h	hour(s)
hfacac	hexafluoroacetylacetonate
HMBC	heteronuclear multiple bond coherence (spectral)
HSQC	heteronuclear single quantum coherence (spectral)
HRMS	high resolution mass spectrometry
hν	light
Hz	hertz
IBX	2-iodoxybenzoic acid
IPr	1,3-bis(diisopropylphenyl)imidazol-2-ylidene

i-Pr	isopropyl
IR	infrared
J	coupling constant
J_{AB}	coupling constant between protons A and B
L	liter(s) or unspecified ligand
LA	Lewis acid
LD_{50}	median lethal dose
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LiTMP	lithium tetramethylpiperidide
M	molar or an unspecified metal with unspecified ligands
m	multiplet (spectral)
M^+	molecular ion
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mM	millimolar
mmol	millimole(s)
mol	mole(s)
MS	molecular sieves
Ms	methanesulfonyl
m/*z*	mass to charge ratio
NBS	*N*-bromosuccinimide
n-Bu	butyl
NFIS	*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
Nu	unspedified nucleophile

Ph	phenyl
PMB	*para*-methoxy benzyl
PMP	*para*-methoxy phenyl
ppm	parts per million
Pr	propyl
Py	pyridine
Pybox	bis(oxazoline) ligand
R	generalized alkyl group of substituent
R_f	retention factor (in chromatography)
rOe	rotating-frame Overhauser enhancement
rt	room temperature
s	singlet (spectral)
t	triplet (spectral)
T	temperature
TBCHD	2,4,4,6-tetrabromocyclohexa-2,5-dienone
TBHP	*t*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
tfacac	trifluoroacetylacetonate
TFE	trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TROESY	transverse rotating frame Overhauser enhancement spectroscopy
Ts	*p*-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid

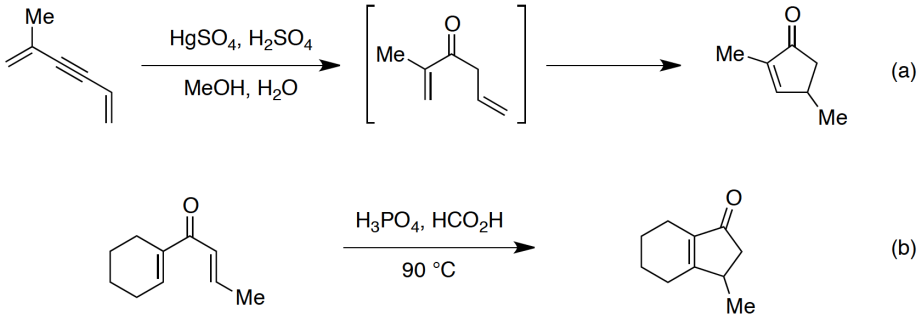
V	volts
δ	chemical shift

Chapter 1

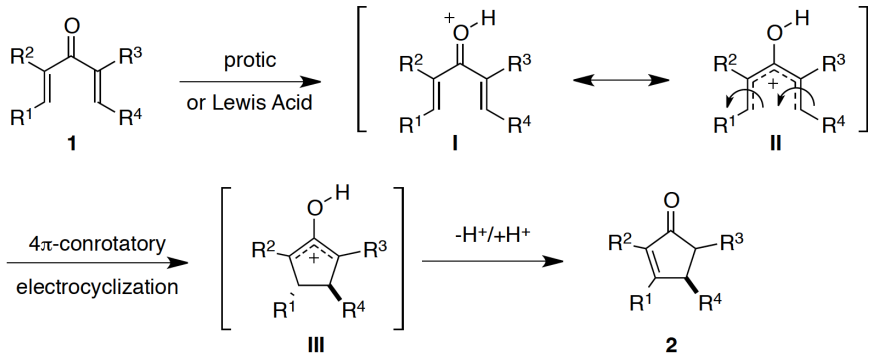
Recent Advances in the Nazarov Cyclization: Interrupted Processes and Alternative Substrates

1.1 Introduction

The Nazarov reaction is an effective method for the synthesis of cyclopentenones from cross-conjugated ketones. In the 1940s and into the 1950s I. N. Nazarov and coworkers undertook extensive investigations into the synthesis of allyl vinyl ketones by hydration of dienynes; their subsequent acid-mediated cyclization yielded 2-cyclopentenones, often directly under the hydration conditions (Scheme 1a).[1] In 1952 Braude and Coles showed the 2-cyclopentenones could be formed from cross-conjugated ketones (Scheme 1b) and correctly implied the involvement of carbocationic intermediates.[2] It was later established that cross-conjugated ketones, when activated by Brønsted or Lewis acid, form a pentadienyl cation **II** (Scheme 2), which undergoes stereospecific 4π-conrotatory cyclization, generating a 2-oxidocyclopentenyl cation **III**. Subsequent elimination and enol tautomerization give the cyclopentenone Nazarov cyclization product **2.**

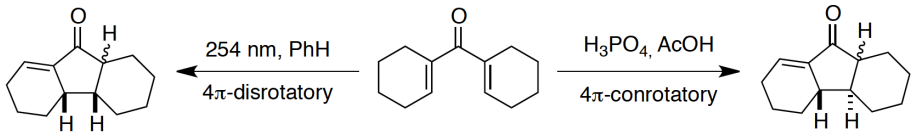


Scheme 1: Early Nazarov Cyclizations.



Scheme 2: Thermal Nazarov Cyclization Mechanism.

The Nazarov reaction can also be initiated photochemically. As demonstrated experimentally by Woodward and coworkers the products are formed with a *cis* relative configuration at the two former dienone β carbons, in the thermal acid-mediated process (Scheme 3). This outcome is consistent with the conservation of orbital symmetry, which favors the conrotation for the thermal process and disrotation for the photochemical one.[3]



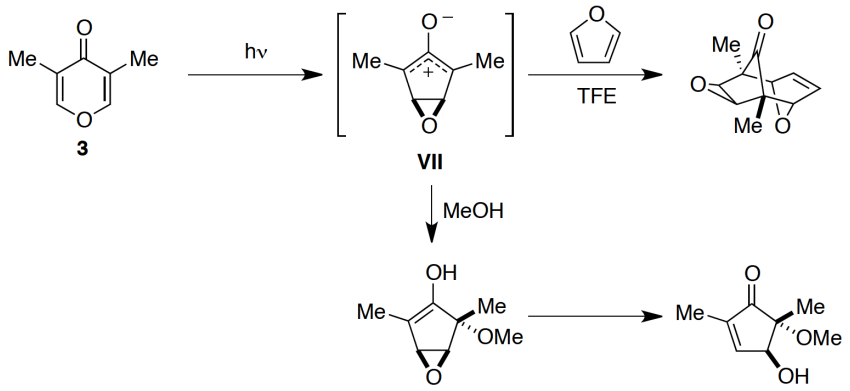
Scheme 3: Photochemical and Thermal Nazarov Reactions.

1.2 The Interrupted Nazarov Reaction[4,5]

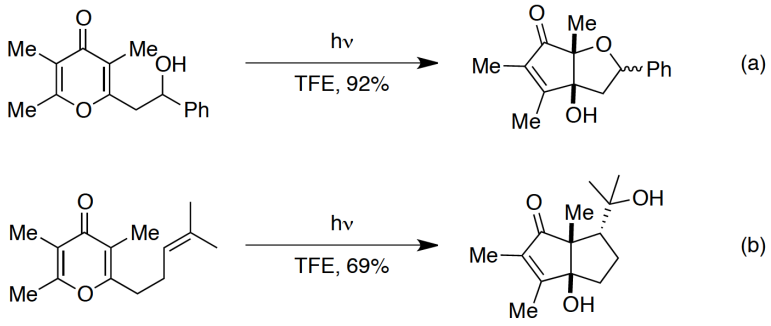
In its own right, the Nazarov reaction has considerable value for the construction of cyclopentenones; however, utilization of the reactive intermediate to form additional strategic bonds has blossomed recently. Specifically, the 2-oxidocyclopentenyl cation **III** (Scheme 2) formed on electrocyclization can participate in a variety of nucleophilic trapping or cycloaddition reactions. This notion of diverting the Nazarov process from its normal elimination pathway using an added reactive moiety (either intra- or intermolecular) has been named the interrupted Nazarov reaction.

1.2.1 Early Interrupted Nazarov Reactions

The first examples, which intentionally exploited 2-oxido-cyclopentenyl cation reactivity were observed during photochemical Nazarov cyclizations. Trapping of the oxyallyl intermediate **VII** generated from photochemical cyclization of 4-pyranone **3** was found to occur in a bimolecular fashion with trapping by hydroxylic solvent[6,7] or in [4+3] cycloadditions with furan (Scheme 4).[6] West and coworkers demonstrated the corresponding intramolecular process using pendent hydroxyl traps[8] to form fused bicyclic products (Scheme 5a). They also found that carbon-based π-nucleophiles such as olefins, arenes, and dienes could be tethered to 4-pyranones to generate bi- and tricyclic ring systems (Scheme 5b).[9-11] The photo-Nazarov methodology had a relatively limited scope and required the use of a hydroxylic solvent with high ionizing power but low nucleophilicity, such as trifluoroethanol.

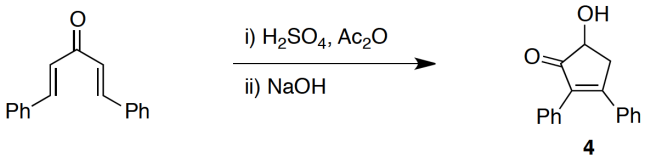


Scheme 4: Interrupted Photo-Nazarov Cyclications.



Scheme 5: Intramolecular Interrupted Photo-Nazarov Cyclization.

The similarity of the intermediate in conventional Nazarov reactions and that formed in the photo-Nazarov process suggested the possibility of expanding this trapping strategy beyond a specialized class of 4-pyranone substrates. In fact, long before the mechanism of the Nazarov reaction was understood, Vorländer and Schroedter in 1903 observed an unknown ketol product from treatment of dibenzylideneacetone with acetic anhydride and sulfuric acid.[12] This product, later proposed to be ketol **4** (Scheme 6),[13] was most likely the result of trapping of the cyclopentenyl cation intermediate with water, bisulfate, or acetate. Although not appreciated at the time as an example of the interrupted Nazarov reaction, this process offered clear evidence in support of the notion that the cationic Nazarov intermediate could be trapped with nucleophiles.

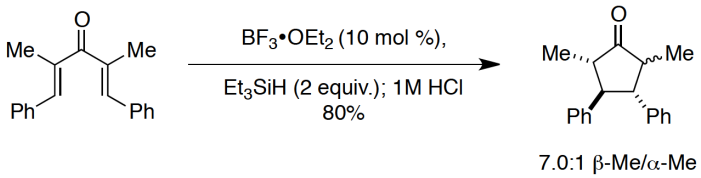


Scheme 6: Vörlander Ketol Formation.

1.2.2 Hydride Trapping - Reductive Nazarov Reaction

An important advantage of the interrupted Nazarov cyclization is the retention of the two stereocenters that are installed stereospecifically in the electrocyclization step to make functionalized cyclopentanones. Giese and West

utilized triethylsilane as a Lewis acid tolerant hydride source to trap the 2-oxidocyclopentenyl cation and form cyclopentanones in good yields (Scheme 7).[14] Nazarov cyclization was followed by a regioselective delivery of hydride at the less substituted end of the 2-oxidocyclopentenyl cation, rationalized by the preferred formation of a more substituted enolate. Hydride addition favors approach from the seemingly more hindered face, resulting from what appears to be a late transition state that forces the α-substituent away from the β-substituent avoiding unfavorable steric interaction to afford the *trans–trans* relative stereochemistry (Figure 1, path A).[15] The reductive Nazarov reaction efficiently captured the oxyallyl cation intermediate conserving the newly formed stereocenters. Another important observation was the capability to achieve the reaction using a catalytic amount of Lewis acid.



Scheme 7: Reductive Nazarov Reaction.

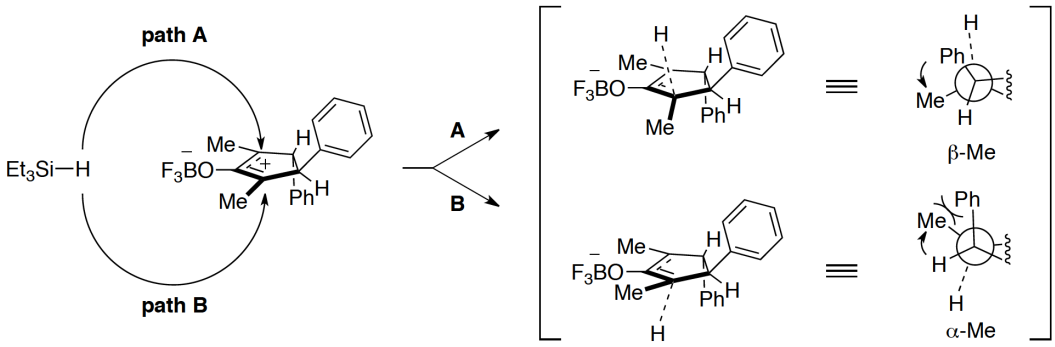
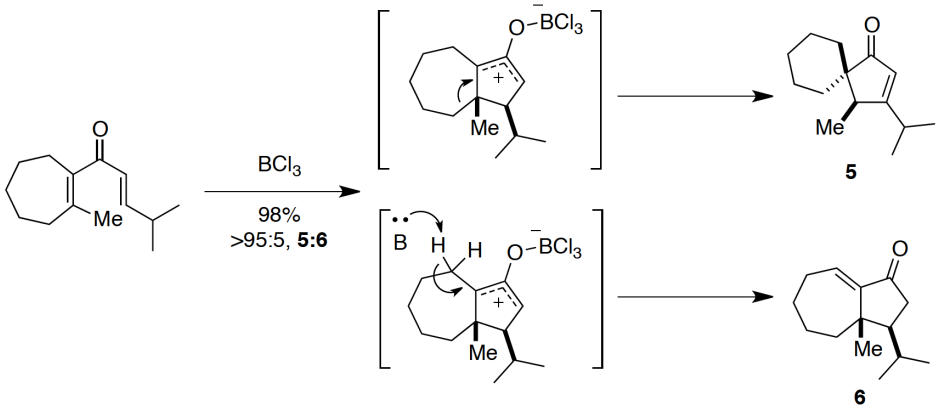


Figure 1: Stereochemistry of the Reductive Nazarov Reaction.

1.2.3 Skeletal Rearrangements

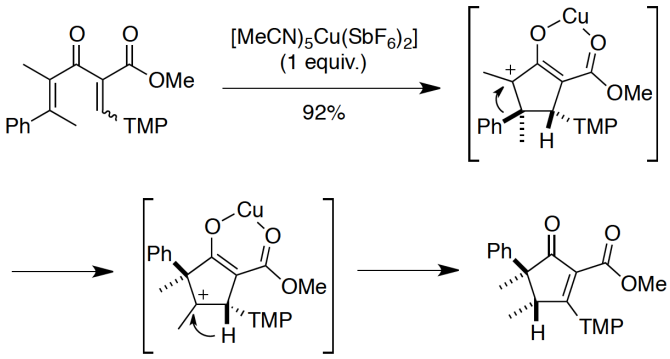
While exploring the synthesis of hydroazulene ring systems using the Nazarov reaction, Chiu and Li found that they could also access spiro[4.5]decanones **5** resulting from Wagner–Meerwein rearrangment of the 2-

oxidocyclopentenyl intermediate (Scheme 8).[16] It appears this method is limited to the formation of spiro[4.5]decanones, as the corresponding spiro[4.4]nonanones are formed as a mixture with the classical Nazarov product.

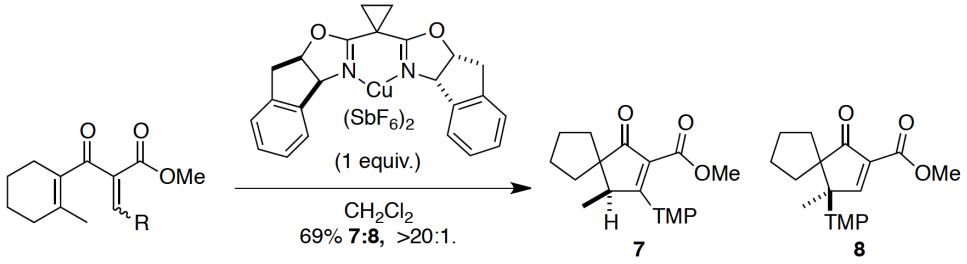


Scheme 8: Tandem Nazarov Spiro[4.5]decanone Synthesis.

Frontier and coworkers have also developed a methodology utilizing [1,2]-shifts to intercept the oxyallyl cation formed following Cu(II) promoted Nazarov cyclization, preparing highly substituted cyclopentanones. Dienones bearing α-ester substituents can undergo Nazarov cyclization followed by two sequential chemoselective and stereospecific [1,2]-migrations to cyclopentenone products.[17] The chemoselectivity of the migrations can be predicted based on the migratory aptitude of the substituents, although steric demand also plays a role, as seen in the preferential migration of hydride rather than the bulky 2,4,6-trimethoxyphenyl (TMP) group (Scheme 9). By employing an asymmetric bis(oxazoline) ligand, the reaction could be performed enantioselectively. Additionally, when one of the dienone alkenes was enclosed in a cyclohexene, the resulting 1,2-shift led to a ring contraction and formation of a spirocyclic ring junction at the α–position (Scheme 10).[18]



Scheme 9: Tandem Nazarov Cyclization – [1,2]-Shift.

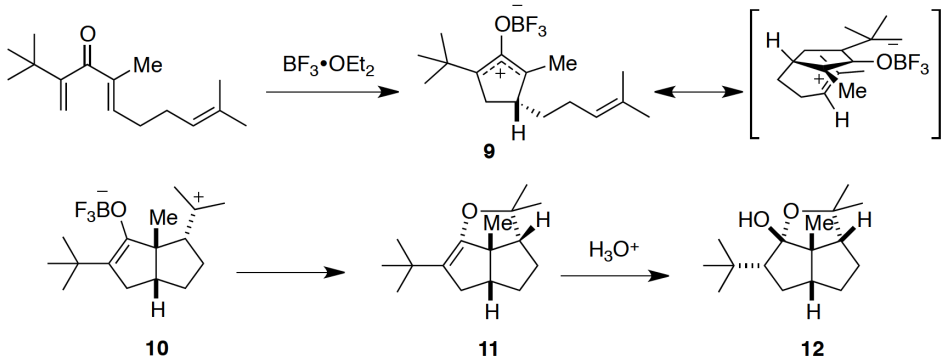


Scheme 10: Spirocycle Synthesis by Tandem Nazarov Cyclization/[1,2]-Shift.

1.2.4 Carbon-Carbon Bond Formations

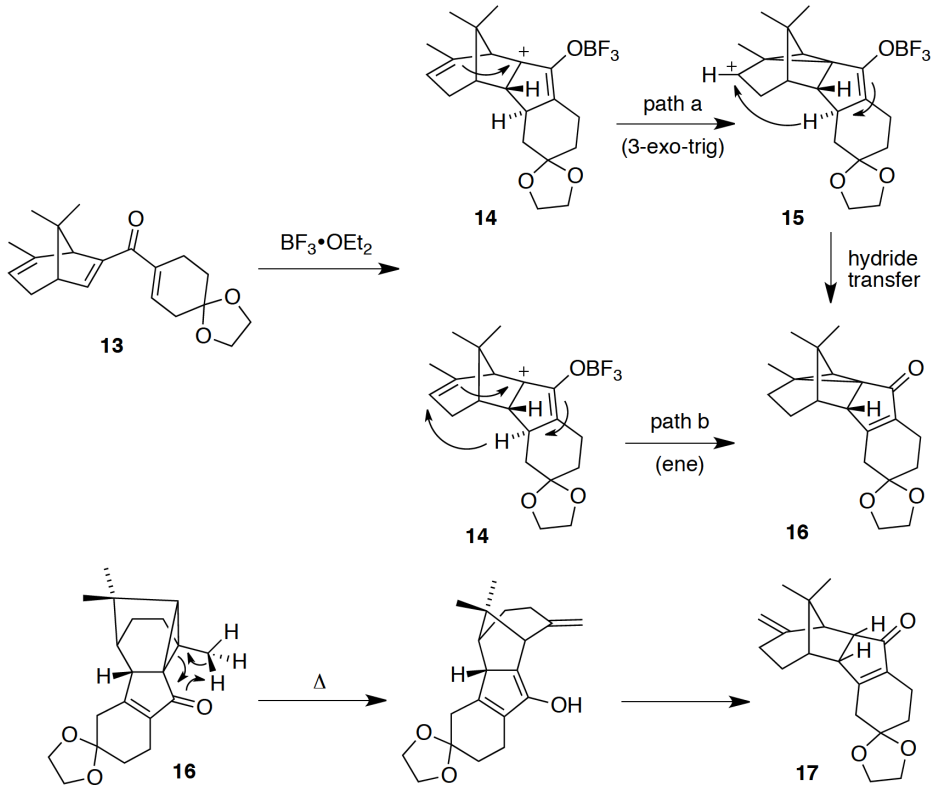
1.2.4.1 Intramolecular Olefin Trapping

In 1998, West and coworkers reported the first deliberate interception of the 2-oxidocyclopentenyl cation intermediate generated by a thermal Nazarov cyclization.[19] In this process, cross-conjugated dienones bearing tethered olefins were treated with $BF_3{\cdot}OEt_2$ to form single polycyclic hemiketal products, with formation of two new carbon–carbon bonds and four or five new stereocenters. The products observed were the result of 4π-conrotatory Nazarov cyclization generating a 2-oxidocyclopentenyl cation intermediate **9** (Scheme 11), which underwent cationic cyclization to the tethered olefin resulting in tertiary carbocation **10**. Trapping of this cation by the boron enolate would lead to strained enol ether **11**, the hydrolysis of which generated the observed hemiketal diquinane product **12**.



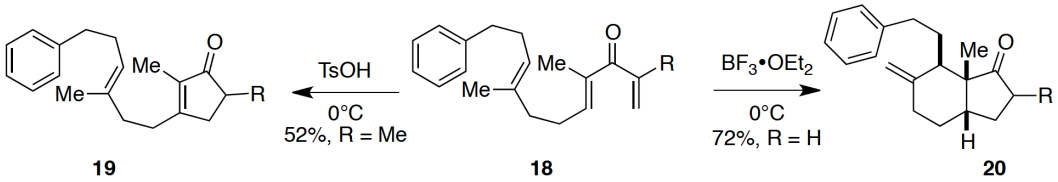
Scheme 11: Intermolecular Olefin Trapping.

Intermolecular trapping of the Nazarov oxyallyl cation intermediate has also been observed for isolated olefins contained in a ridgid bicyclic structure (Scheme 12).[20] In the case of dieneone **13**, Nazarov cyclization formed the 2-oxidocyclopentenyl cation intermediate **14**. The remote olefin intercepted the cation to generate a cyclopropyl ketone product **16**. This mechanistically intriguing process is proposed to occur via a 3-exo-trig cyclization (path a), followed by hydride transfer to form **16**, or alternatively via an ene-like rearrangement (path b). Upon heating, the strained cyclopropyl ketone **16** undergoes isomerization to cyclopentene **17**, most likely via homo-1,5-hydrogen shift followed by tautomerization.

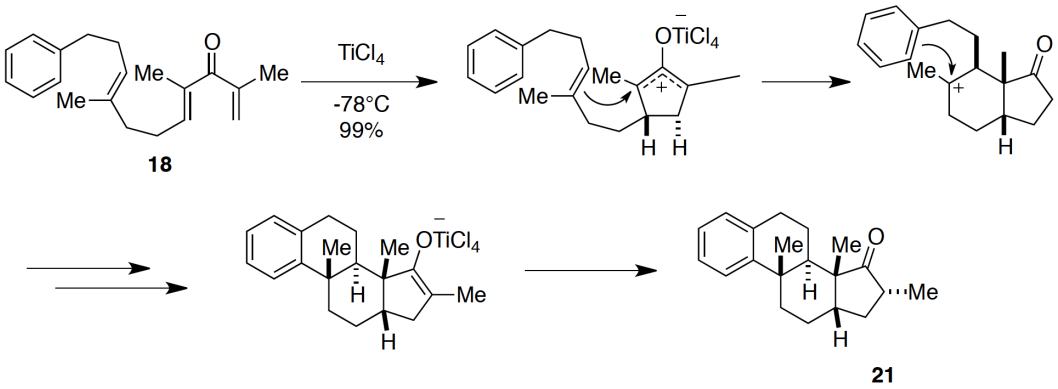


Scheme 12: Isolated Olefin Participation in the Interrupted Nazarov Reaction.

Having observed further cyclization and trapping of carbocations formed *via* interrupted Nazarov reactions. West and co-workers prepared a series of aryl-terminated trienones designed to undergo Nazarov initiated cascade polycyclizations.[21] Initial trials using protic acid generated only the simple cyclopentenone Nazarov product **19** (Scheme 13). When BF_3•OEt_2 was used to initiate the reaction of **18** at 0 °C the hydridenone product **20** was the sole product formed as a result of olefin trapping, followed by elimination of the carbocation rather than a further cyclization event. Lower reaction temperatures along with stronger Lewis acid were used in an effort to increase the lifetime of the carbocation intermediates with hopes of achieving the polycyclization cascade. Use of $TiCl_4$ at -78 °C successfully converted the aryltrienone substrate to the desired tetracyclic product **21** in 99% yield with complete diastereoselectivity (Scheme 14).



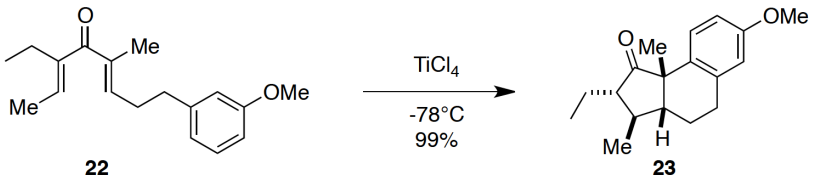
Scheme 13: Premature Termination of Polycyclization Cascade.



Scheme 14: Nazarov Initaited Polycyclization Cascade.

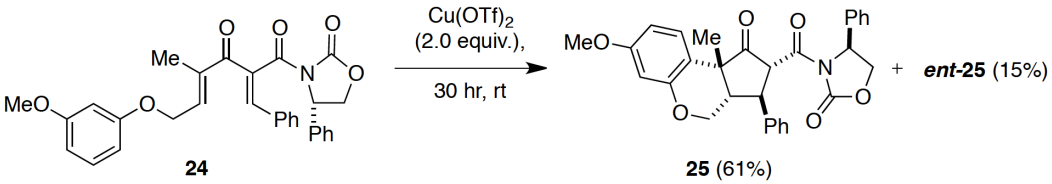
1.2.4.2 Intramolecular Arene Trapping

Work investigating arene trapping of the intermediate cation observed in the Nazarov initiated polycyclization was followed by studies to determine whether a tethered arene could be used to directly trap the Nazarov oxyallyl cation intermediate.[22,23] West and coworkers found that a series of aryl dieneones such as **22** could undergo an interrupted Nazarov reaction to form the desired benzohydrindenones **23** in excellent yield (Scheme 15). A drawback to this method was the failure of a simple phenyl tether to trap the oxyallyl intermediate, instead giving the simple cyclopentenone product.



Scheme 15: Intermolecular Arene Trapping.

Recently, in 2014 Flynn and coworkers reported intermolecular arene trapping of oxyallyl cations derived from α-carboxy dienones bearing electron-rich benzyl ethers attached at the β-position. When α-oxazolidinyl dienone **24** was subjected to $Cu(OTf)_2$ Nazarov cyclization and susbsequent trapping of the incipient oxyallyl cation by the ether tether gave the tricyclic product **25** in good yield, with moderate enantioselectivity (Scheme 16).[24]

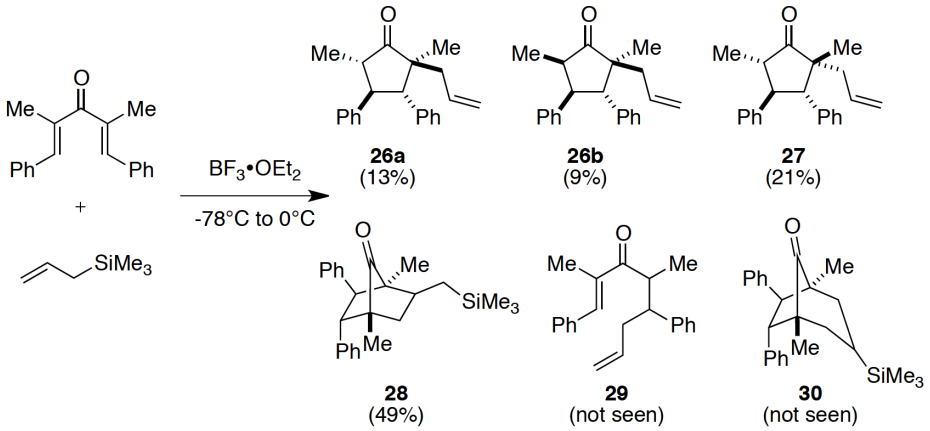


Scheme 16: Enantioselective Intermolecular Arene Trapping.

1.2.4.3 Intermolecular Olefin Trapping

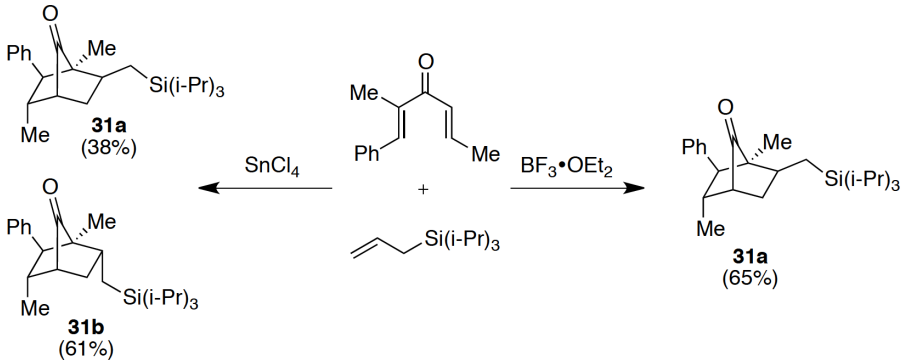
The success of intramolecular interrupted Nazarov processes inspired the investigation of similar bimolecular processes. Initial studies employed simple allylsilanes as nuclophilic trapping reagents, chosen for their known nuclophilic reactivity and Lewis acid stability. Dibenzylidene-3-pentanone was treated with BF_3•OEt_2 in the presence of allyltrimethylsilane to afford a diastereomeric mixture of allylated cyclopentenones **26a**, **26b**, and **27** along with the bicyclo[2.2.1]heptanone product **28** derived from [3+2] cycloaddition (Scheme 17).[25] Products **27** and **28** are thought to arise from the same silicon-stabilized carbocation, which can be trapped by the enolate or undergo silyl elimination. This observation was promising and significant given the number of other

potential pathways. No simple Nazarov products, carbonyl conjugate addition product **29** or bicyclo[3.2.1]octanone products **30** arising from ring closure with concomitant sila-Wagner-Meerwein shift were observed.



Scheme 17: Allylsilane Trapping of the Oxyallyl Cation.

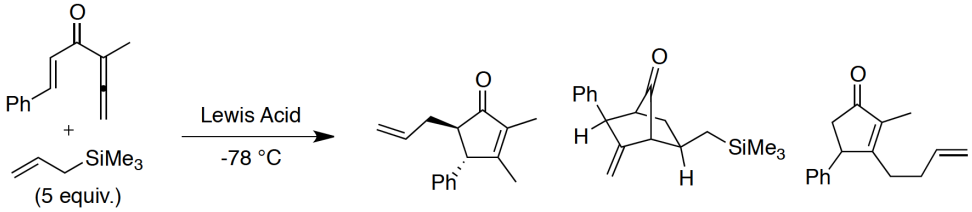
Formation of the [3+2] product could be maximized by using a less labile allylsilane, such as allyltriisopropylsilane. In the case of unsymmetrical dienones, nucleophilic attack occurred exclusively at the less substituted end of the oxyallyl cation intermediate to provide the more stable enolate. Interestingly, complementary diastereoselectivity could be obtained by using different Lewis acids. Use of BF_3•OEt_2 provided exclusively the exo product **31a**, while $SnCl_4$ gave predominantly the endo isomer **31b**.



Scheme 18: Enchanced Selectivity for [3+2] Reactivity.

More recently, an allenyl vinyl ketone substrate was shown by Marx and Burnell to undergo efficient trapping with allylsilanes (Scheme 19).[26] Mixtures of

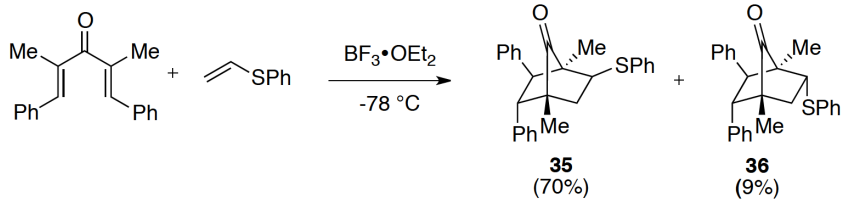
allylated cyclopentenone **32** and [3+2]-adduct **33** were formed using BF_3•OEt_2. However when $Cu(OTf)_2$ or $InCl_3$ were used to promote the Nazarov cyclization, an allylated product **34** arising from trapping at the exocyclic γ-carbon of the extended cationic intermediate was also formed.



	32	**33**	**34**
BF_3•OEt_2 (1.1 equiv)	27%	54%	-
$Cu(OTf)_2$ (5 equiv.)	20%	10%	42%
$InCl_3$ (5 equiv.)	22%	-	56%

Scheme 19: Allylsilane trapping of Allenyl Vinyl Ketones.

Recently a variety of other electron rich olefins with enolate-like reactivity have been used to trap the Nazarov oxyallyl intermediate. In 2007 Mahmoud and West disclosed [3+2] trapping with vinyl sulfides to generate sulfide-substituted bicyclo[2.2.1]heptanones **35** and **36** (Scheme 20) with no evidence of monocyclic trapping products.[27]

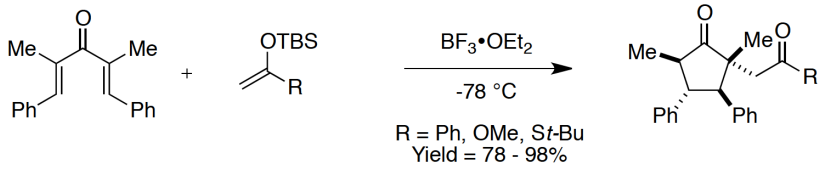


35 (70%) **36** (9%)

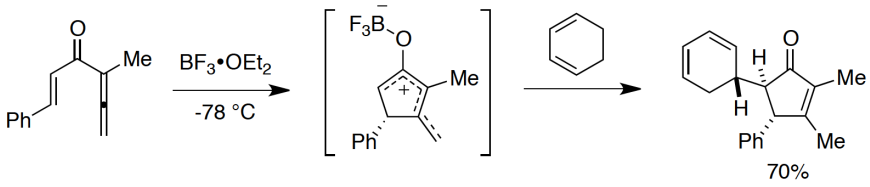
Scheme 20: Vinyl Sulfide Trapping.

In contrast, nucleophilic silyloxyalkenes were used to generate 1,4-dicarbonyl systems containing highly substituted cyclopentanones and up to five new stereocenters in what was termed a 'homologous Mukaiyama reaction'.[28] When simple dienone substrates were treated with BF_3•OEt_2 in the presence of silyl enol ethers, silyl ketene acetals, or mixed ketene *S,O*-acetals, trapping occurred such that the more stable enolate formed on interception of the oxyallyl

cation (Scheme 21). Similarly, in 2010 Marx and Burnell observed efficient trapping of the cationic Nazarov intermediate generated from an allenyl vinyl ketone with enol ethers forming primarily 1,4-dicarbonyls. Notably, unactivated cyclic dienes such as 1,3-cyclohexadiene also successfully trapped the Nazarov intermediate (Scheme 22).[26] This observation is likely owing to the greater conjugative stabilization of the cyclized intermediate generated from Nazarov cyclization of allenyl vinyl ketones, which persists long enough to allow less reactive olefins undergo an interrupted Nazarov reaction.



Scheme 21: Homologous Mukaiyama Reaction.

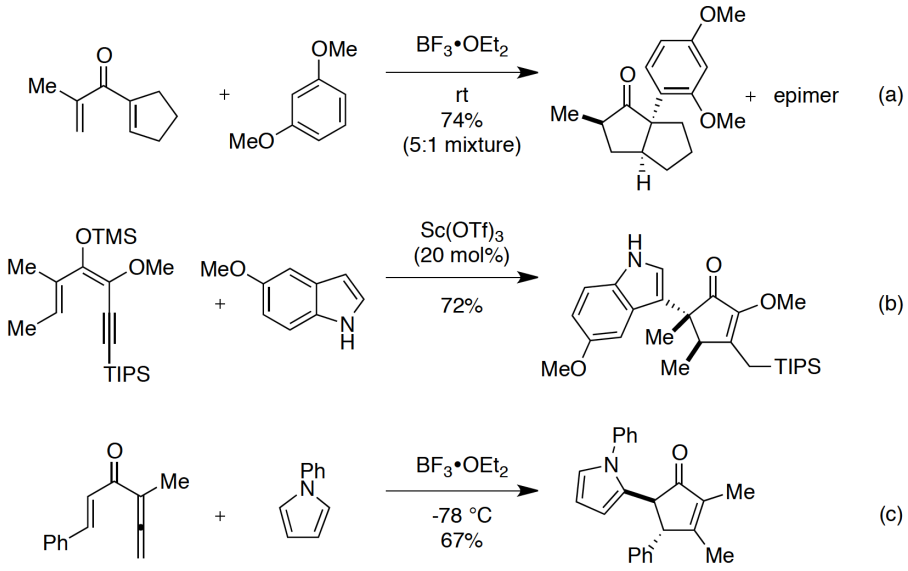


Scheme 22: Diene Trapping of Allenyl Vinyl Ketone.

1.2.4.4 Intermolecular Arene Trapping[29]

West and coworkers found that similar enolonium-type reactivity could be observed for Nazarov intermediates containing at least one fused cyclopentane ring. Treatment of the corresponding dienones with BF_3•OEt_2 in the presence of electron-rich arenes furnished products resulting from electrophilic aromatic substitution onto the cyclized 2-oxidocyclopentenyl Nazarov intermediate.[30] Furans, thiophenes, protected pyrroles, protected indoles,[31] and electron-rich benzene rings were all efficiently trapped (Scheme 23a). Consistent with the intramolecular studies, less electron-rich aromatic rings failed to undergo the domino process, and instead, simple eliminative Nazarov products were isolated.

Shortly after the initial report, Tius and coworkers reported conceptually related work utilizing unprotected indoles as aromatic nucleophiles.[32] In the study, enediyne substrates were cyclized in the presence of catalytic $Sc(OTf)_3$. The resulting cationic Nazarov intermediate was trapped by a variety of indoles at the more nuclophilic C-3 position. The trapping was reasonably efficient, providing the indoles were electron-rich and sterically unencumbered (Scheme 23b). Marx and Burnell have also used heteroaromatic nucleophiles including furan,[26] pyrroles and indoles[33] to trap the cationic Nazarov intermediate generated from Nazarov cyclization of an allenyl vinyl ketone (Scheme 23c).

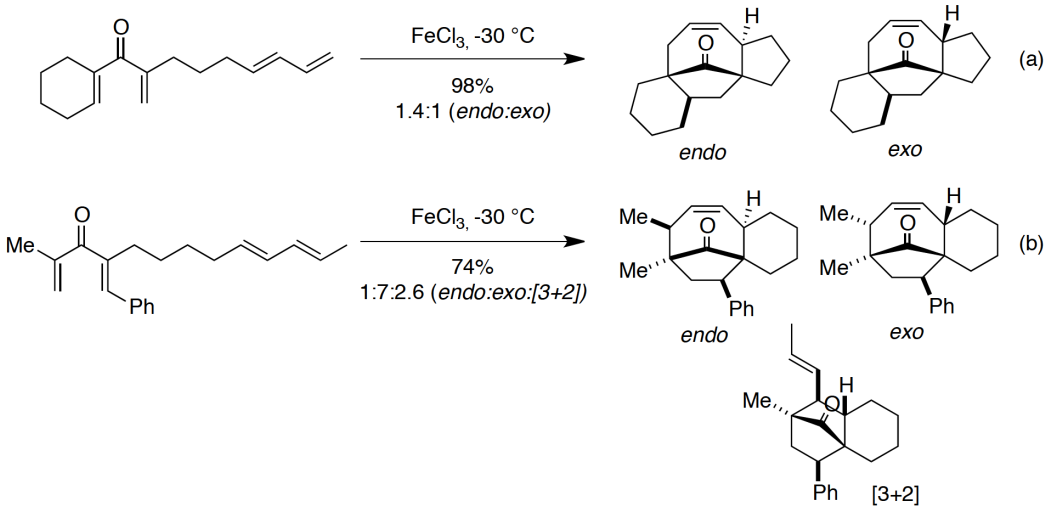


Scheme 23: Intermolecular Arene Trapping.

1.2.4.5 [4+3] Cycloaddition Reactions

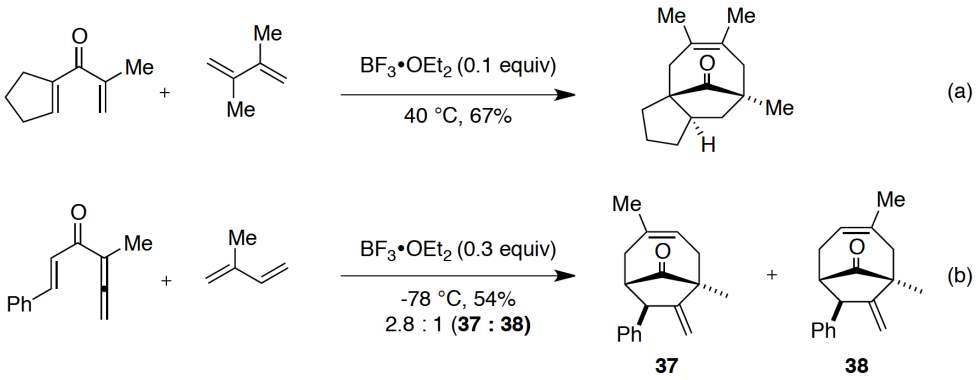
An alternative mode of trapping the oxyallyl intermediate to the nucleophilic processes described above would be through concerted [4+3]-cycloaddition utilizing the oxyallyl intermediate as a dieneophile. This [4+3]-cycloaddition can also be considered to be a formal [4+4]-cycloaddition given that the reactive 2-oxidocyclopentenyl cation intermediate is enclosed within a ring,

furnishing a keto-bridged cyclooctene product. West and coworkers tested this concept using a series of cross-conjugated ketones bearing diene tethers. Treatment with $FeCl_3$ at low temperature led to the desired polycyclic products in excellent yield as a mixture of diastereomers (Scheme 24a).[34] Although exclusive approach of the diene from the more accessible face of the cyclopentenyl cation was seen, reaction via either the *endo* or *exo* transition states were possible, and both products were typically obtained. greater selectivity was observed for 4-carbon tethered tetraenones (Scheme 24b).



Scheme 24: Intermolecular [4+3] Cycloadditions.

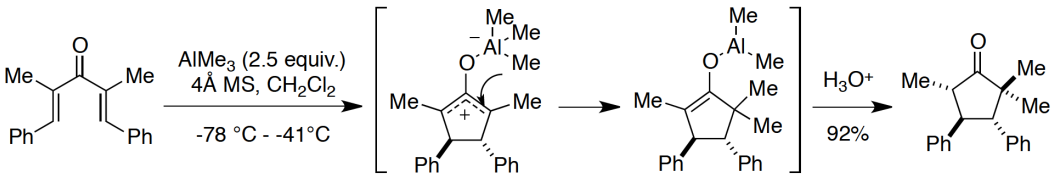
The analogous intermolecular [4+3]-cycloaddition process was also found to be efficient (Scheme 25a).[35] Catalytic activation of simple dienones by BF_3•OEt_2 in the presence of simple cyclic and acyclic dienes formed the [4+3]-cycloadducts in good to excellent yield with complete facial selectivity. Similarly, Marx and Burnell later examined the [4+3] reactivity of an allenyl vinyl ketone. efficient trapping was seen using BF_3•OEt_2 at low temperatures in the presence of simple dienes (Scheme 25b).[26] In cases employing more substituted dienes, [3+2] trapping products were observed as the major products. This was attributed to low populations of the s-*cis* conformation required for a concerted [4+3]-cycloaddition process.



Scheme 25: Intermolecular [4+3] Cycloaddition Reactions.

1.2.4.6 Organoaluminium-Mediated Interrrupted Nazarov Reaction

The first examples of a Nazarov cyclization employing triorganoaluminium reagents was reported by West and coworkers in 2013.[36] In one example, when dibenzylidene-3-pentanone was subjected to Lewis acidic $AlMe_3$, Nazarov cyclization occurred, followed by methyl ligand transfer to the electrophilic oxyallyl cation (Scheme 26). This is notable, because until this report incorporation of an sp^3 alkyl moiety by trapping of a Nazarov generated 2-oxidocyclopentenyl cation had been elusive. In addition to alkyl trapping this powerful method could also be used to transfer cyano, azide, and a simple unactivated phenyl ligands.

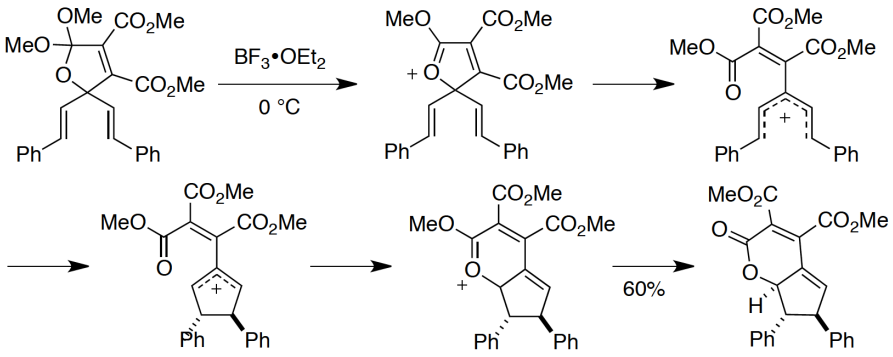


Scheme 26: Organoaluminium-Mediated Interrrupted Nazarov Reaction.

1.2.5 Heteroatom Trapping

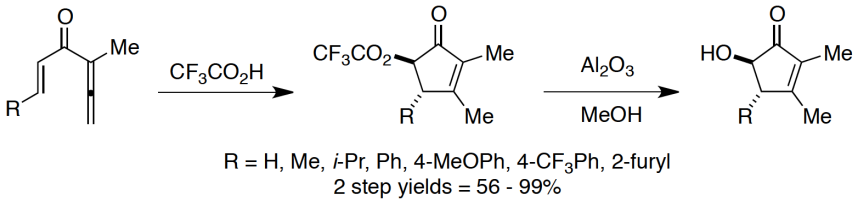
1.2.5.1 Oxygen Nucleophiles

In 2002, Nair et al. used nontraditional *gem*-dialkenyl dihydrofuran substrates in an intramolecular oxygen interrupted Nazarov reaction (Scheme 27).[37] When the substrates were treated with BF_3•OEt_2, a cascade was initiated by dihydrofuran ring opening to generate a pentadienyl cation that underwent Nazarov cyclization to form a cyclopentenyl cation intermediate. Subsequent trapping by oxygen gave the complex bicyclic lactone products and three new stereocenters.



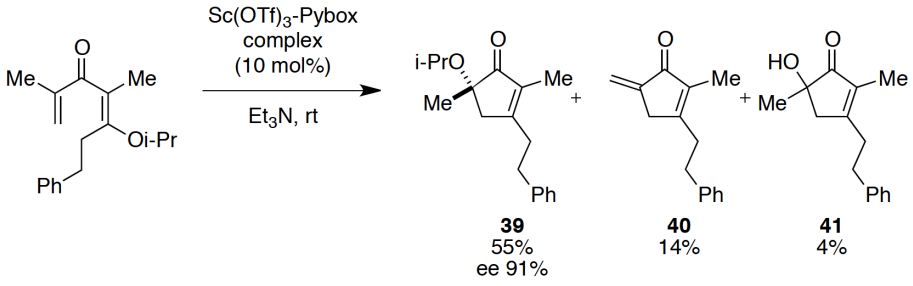
Scheme 27: Oxygen Trapping of *gem*-Dialkenyl Dihydrofurans.

Marx and Burnell observed efficient trapping of the cyclopentenyl cation generated by Brønsted acid promoted Nazarov cyclization of select allenyl vinyl ketones with trifluoroacetic acid. The resulting trifluoroacetate esters could be smoothly converted to α-hydroxycyclopentenones by elution through basic alumina (Scheme 28).[38] Some allenyl vinyl ketones failed to undergo trapping, generating the simple Nazarov product, or underwent premature Michael addition into the allene before Nazarov cyclization could occur.[39]



Scheme 28: Oxygen Trapping of Allenyl Vinyl Ketones.

In 2009, Yaji and Shindo disclosed an asymmetric interrupted Nazarov reaction catalyzed by a $Sc(OTf)_3$–Pybox complex to generate enantioenriched α-alkoxy cyclopentenones such as **39** with good yield and moderate enantiomeric excess. minor amounts of an exocyclic elimination product **40** and α-hydroxy cyclopentenone **41** were also observed (Scheme 29).[40] Intermolecular delivery of the alkoxy nucleophile rather than an intramolecular [1,3]-shift was supported by deuterium labeling experiments.

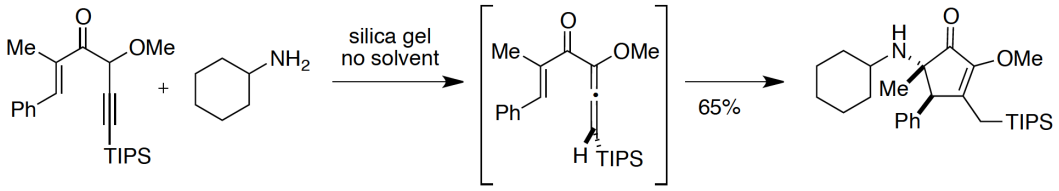


Scheme 29: $Sc(OTf)_3$–Pybox Catalyzed Oxygen Trapping.

1.2.5.2 Nitrogen Nucleophiles

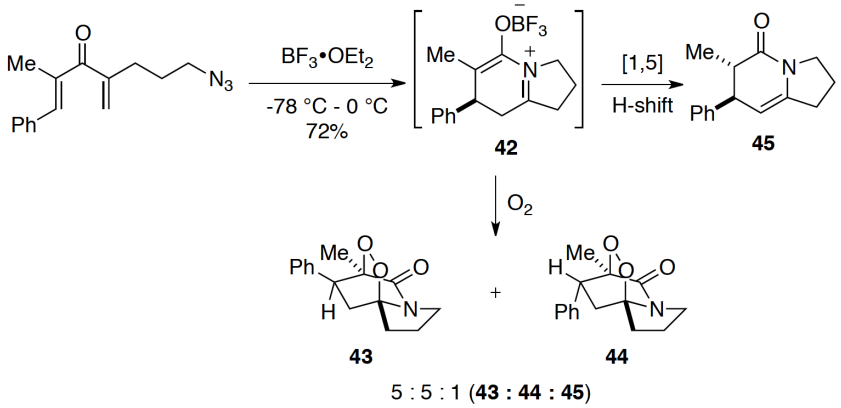
In 2005, Tius and Dhoro reported the first examples of nucleophilic nitrogen trapping for the interrupted Nazarov reaction.[41] Silica gel was sufficiently acidic to promote Nazarov cyclization of allene ethers formed in situ from propargylic enones in the presence of a variety of primary and secondary amines (Scheme 30). Under solvent-free conditions the highly reactive cyclopentenyl cation could be trapped by the amine; this is notable, due to the readily available elimination pathways that are not seen, even in the presence of the basic amine.

The success of this reaction can be attributed to the high reactivity of the allenyl vinyl ketone species, and its close proximity to the nucleophilic amine under solvent-free conditions. By employing a camphor-based chiral auxiliary on the allene ether, control of the torquoselectivity in the conrotatory cyclization was observed.[42]



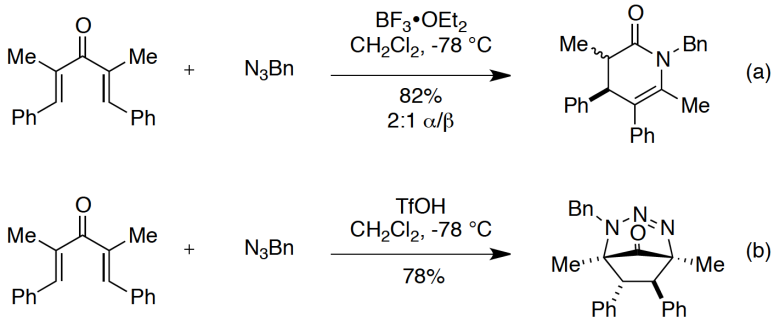
Scheme 30: Amine Interrupted Nazarov Cyclization.

West and co-workers have investigated azides as nucleophiles to intercept the 2-oxidocyclopentenyl cation Nazarov intermediates.[43-45] It was expected that azides would react in a [3+3]-cycloaddition or by direct attack of the oxyallyl cation with the nucleophilic internal nitrogen. Initial studies into trapping with azides focused on intramolecular reactivity using azide tethered dienones.[43] When the substrates were treated with BF_3•OEt_2, starting material was consumed forming a mixture of products. The dihydropyridone **45** was formed as a minor product resulting from Nazarov cyclization, generating an oxyallyl cation intermediate, which underwent nucleophilic attack by the internal azide nitrogen. Subsequent Schmidt rearrangement followed by [1,5]-shift provided the observed product. The major products **43** and **44** were a mixure of intriguing endoperoxide diasteromers, presumably resulting from addition of oxygen to dipolar Schmidt rearrangement intermediate **42**. Dihydropyridone **45** could be formed exclusively by careful exclusion of oxygen; however, the reaction was optimized to favor the peroxy-bridged products by performing the reaction in the presence of oxygen as the endo-peroxide could be a synthetically useful handle for further transformations.



Scheme 31: Intramolecular Azide Trapping.

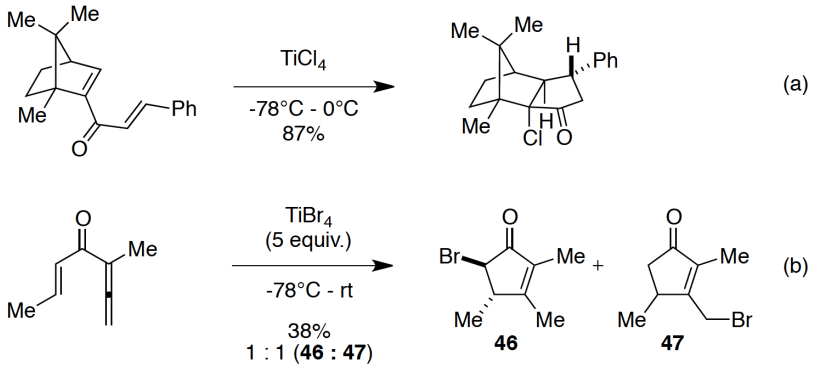
Intermolecular azide trapping of 2-oxidocyclopentenyl cations generated from simple dienones has also been studied.[44] On treatment with BF_3•OEt_2, Nazarov cyclization followed by azide attack and domino ring expansion produced substituted dihydropyridones from simple starting materials (Scheme 32a). *Trans*-dihydropyridones were the major or exclusive product; however, the lack of stereospecificity at the α-carbonyl position was evidence against a concerted [1,5]-hydrogen shift mechanism. In a more recent study an alternative mode of intermolecular azide trapping was observed.[45] When simple dienones were instead treated with strong Brønsted acid in the presence of azides, products resulting from apparent [3+3]-cycloaddition generating bridged bicyclic triazines were observed. This result was in contrast to the Schmidt-type products observed in the earlier Lewis acid mediated report (Scheme 32b).



Scheme 32: Intermolecular Azide Trapping.

1.2.5.3 Halide Nucleophiles

The first examples of nuclophilic halide trapping of the Nazarov oxyallyl cation were reported by White and West in 2005. Bridged bicylic dienones were subjected to a stoichiometric amount of $TiCl_4$. The expected Nazarov cyclization gave the corresponding oxyallyl cation which was intercepted by Lewis acid-derived chloride (Scheme 33a).[46] However, this methodology appears to be limited to hindered bicyclic dienones. Additionally, alkyl shift pathways have been found to compete with the halide trapping step. In 2009, Burnell and Marx reported a low yielding inadvertent halide trapping of the Nazarov 2-oxidocyclopentenyl cation intermediate by incorporation of chloride from $AuCl_3$.[38] A subsequent study sought to generalize the halide trapping process.[47] It was found that allenyl vinyl ketones underwent Lewis acid-mediated Nazarov cyclization, followed by halide trapping in the presence of excess Lewis acid. Moderate to low yields of regioisomeric mono-halogenated cyclopentenones were observed when titanium(IV) halide Lewis acids were used (Scheme 33b), while indium(III) halide activation led to low yields of products resulting from trapping at the terminal position only.



Scheme 33: Lewis Acid Derived Halide Trapping.

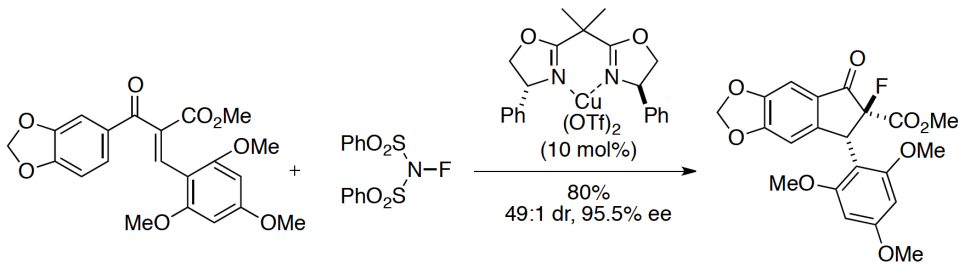
1.2.6 Electrophilic Trapping

All examples of the interrupted Nazarov reaction discussed to this point have involved the trapping of the cyclopentenyl cation formed immediately

following Nazarov cyclization. In the absence of nucleophilic trapping, the enol or enolate species formed upon elimination of the cyclopentenyl cation can also be used in domino processes by interception with suitable electrophiles.

1.2.6.1 Trapping with Electrophilic Halogen

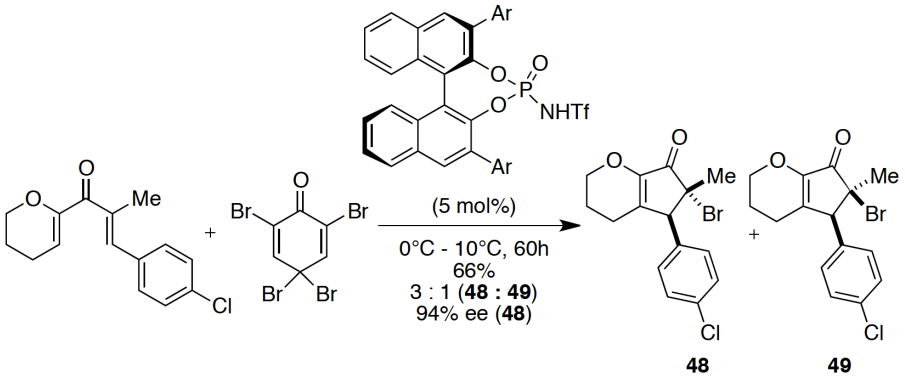
In 2007, Ma and coworkers reported a method for synthesis of fluorinated indanones in a catalytic Nazarov cyclization/electrophilic fluorination sequence.[48] Alkylidine β-ketoesters were treated with a copper(II) Lewis acid in the presence of electrophilic N-fluorobenzenesulfonimide (NFSI). Nazarov cyclization was followed by elimination with rearomatization, and the resulting copper enolate was then captured with electrophilic fluorine to give the fluorinated 1-indanone (Scheme 34). Moderate enantioselectivity was observed when copper(II)-bis (oxazoline) was used to catalyze the reaction. The same group has also developed, a one-pot Knoevenagel condensation/Nazarov cyclization/halogenation sequence to generate the halogenated 1-indanone products from β-ketoesters using electophilic fluorine,[49] chlorine, and bromine.[50] Itoh and coworkers used a Nazarov cyclization/electrophilic fluorination approach analogous to that described previously. α-Ester bearing dienones were treated with $Fe(OTf)_2$ in the presence of NFSI to provide fluorinated cyclopentenones.[51]



Scheme 34: Electrophilic Fluorination.

A conceptually related Brønsted acid-catalyzed Nazarov cyclization/electrophilic bromination method was reported by Rueping and Ieawsuwan giving rise to enantiomerically enriched α-bromocyclopentenones

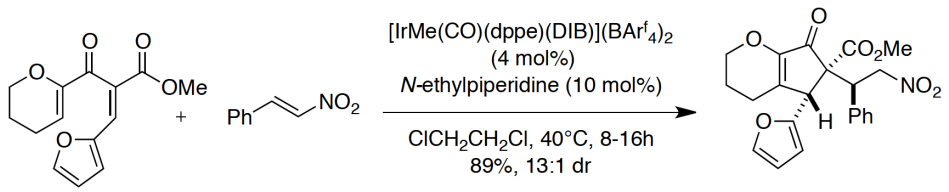
(Scheme 35).[52] Polarized dienones were treated with a chiral BINOL-based *N*-triflylphosphoramide in the presence of the electrophilic bromine source 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCHD). Torquoselective Nazarov cyclization followed by elimination led to an enol that was diastereoselectively captured by bromine from the opposite face to the β-substituent. The process required long reaction times at low temperature; however, the products were isolated in moderate to high yields with synthetically useful enantioselectivity.



Scheme 35: Electrophilic Bromination.

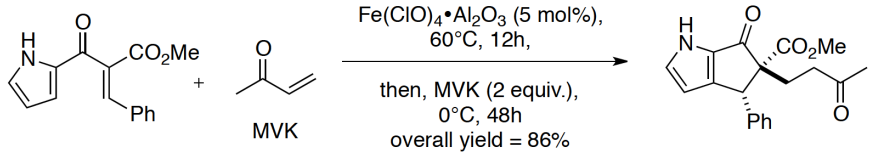
1.2.6.2 Trapping with Michael Acceptors

The enolate intermediate of the Lewis acid mediated Nazarov process has also been successfully employed in conjugate additions. Frontier and coworkers reported the first examples of a tandem Nazarov cyclization/Michael addition (Scheme 36).[53] When polarized push–pull dienones were subjected to catalytic amounts of an iridium(III) complex and amine base in the presence of nitroalkenes, Nazarov cyclization and elimination occurred, followed by Michael addition of the resultant enolate into a nitroalkene. This transformation resulted in the formation of three new stereocenters. The Michael addition is relatively fast, suggesting activation of the nitroalkene by coordination to the Lewis acid.



Scheme 36: Tandem Nazarov Cyclization/Michael Addition.

In a related study, Itoh and coworkers found that pyrrole-containing polarized dienones could undergo Nazarov cyclization in the presence of alumina-supported iron(III) perchlorate. Subsequent Michael addition of the enolate into α,β-unsaturated ketones and aldehydes provided the desired cyclopentenone Michael adducts (Scheme 37).[54] The Michael addition step of the process was slow and required cooling. A subsequent report using an ionic liquid solvent system allowed for increased reaction temperatures, greatly decreasing the reaction time.[55]



Scheme 37: Iron(III) Catalyzed Nazarov Cyclization/Michael Addition.

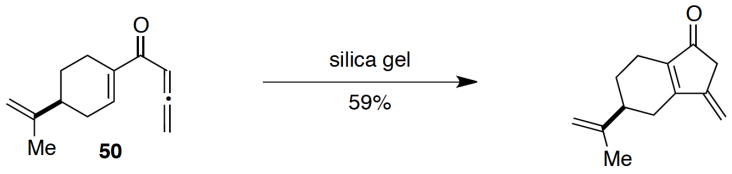
1.3 Alternative Substrates and Activation for the Nazarov Reaction

The classical dienone substrates for the Nazarov reaction are activated through the C-3 carbonyl with Lewis or Brønsted acid, generating the pentadienyl cation that undergoes Nazarov cyclization. In recent years, there has been interest in accessing the reactive pentadienyl cation through alternative substrates that do not involve dienones, or their intermediacy. Alternative Nazarov substrates are capable of providing cyclopentenoid products inaccessible by traditional means. Some alternative substrates can also be activated without the requirement of Lewis or Brønsted acid.

1.3.1 Carbonyl Activation

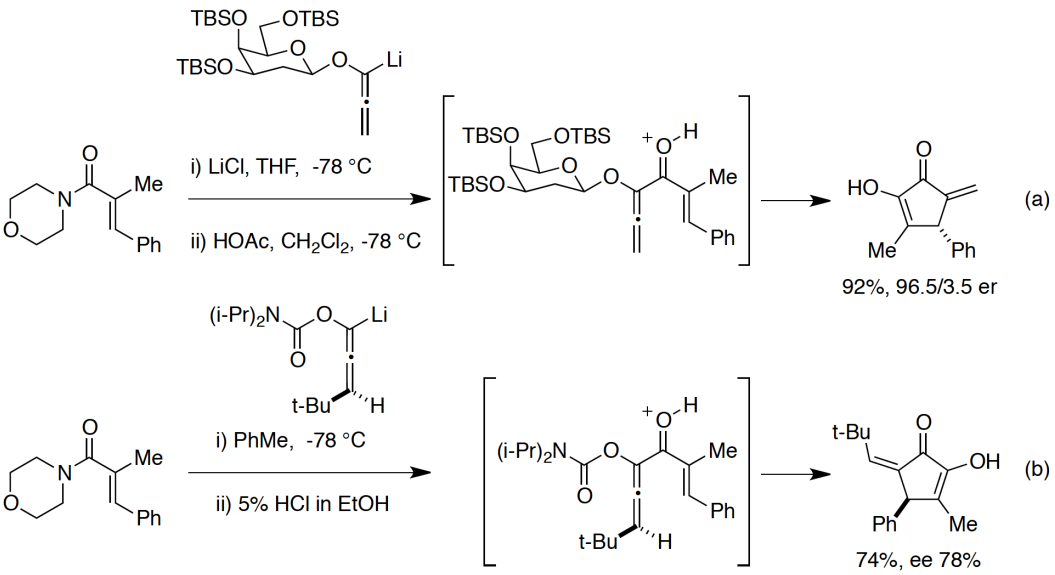
1.3.1.1 Allenyl Vinyl Ketones

Brønsted acid mediated Nazarov cyclization of simple allenyl vinyl ketones was first observed by Hashmi *et al*. They observed that simple allenyl vinyl ketones could undergo acid mediated cyclization to give cyclopentenone products (Scheme 38).[56] The Nazarov cyclization of allenyl vinyl ketones has been shown to be highly facile. For instance, the cyclization of **50** occurs simply in the presence of silica gel. The reactivity of allenyl vinyl ketones has since been studied extensively by Burnell and coworkers in the context of the interrupted Nazarov reaction (Schemes 19, 22, 23c, 25b, 28, 33b).[26,33,38,39,47] These substrates are activated using Lewis or Brønsted acid, in close analogy to the classical dienone substrates.



Scheme 38: Nazarov Cyclization of Allenyl Vinyl Ketone on Silica Gel.

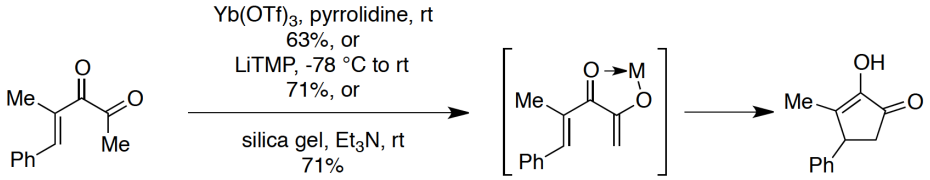
Tius and coworkers have carried out extensive erudite study of the Nazarov cyclizations of allenyl vinyl ketones bearing an α-electron-donating group on the allene.[57,58] These allenyl vinyl ketones are typically generated *in-situ*, normally by lithioallene addition into appropriate morpholino enamides. The α-substituent can be chosen to also serve as a traceless chiral auxiliary, camphor[42,59,60] and carbohydrate[61-64] derived auxiliaries have been well studied in this area, a recent example is shown below (Scheme 39a).[63,64] Additionally, terminally substituted allenyl carbamates have been shown to display axial to tetrahedral chirality transfer (Scheme 39b).[65]



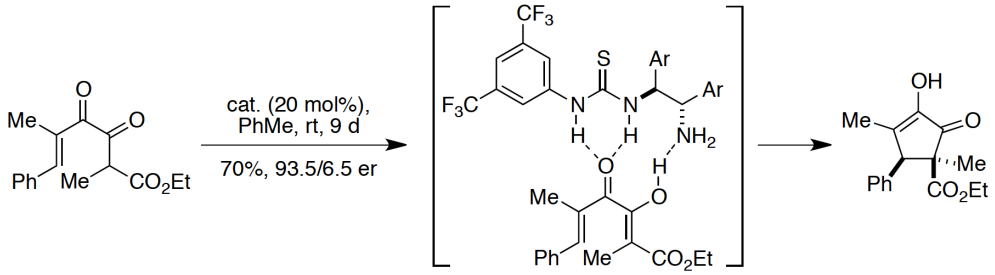
Scheme 39: Enantioselective Nazarov Cyclizations of Allenyl Vinyl Ketones.

1.3.1.2 Activation of α-Diketones

It has long been known that unsaturated α-diketones could be pentadienyl cation precursors. In 1965 Muxfeldt *et al*. reported the formation of α-hydroxycyclopentenones from enediones using magnesium methoxide through a proposed enolate formation/carbonyl activation pathway.[66] More recently Tius and coworkers have found that α-diketones in the presenece of $Yb(OTf)_3$ and pyrrolidine could also generate α-hydroxycyclopentenones. Interestingly lithium tetramethylpiperidide (LiTMP) or silica gel/Et_3N could also successfully mediate the transformation (Scheme 40).[67,68] This is notable because base is used for the enolization, and acid for carbonyl activation of the substrate to generate the reactive pentadienyl intermediate. This led Tius and coworkers to investigate chiral bifunctional thiourea organocatalysts capable of carrying out both the basic catalyzed enolization and acid catalyzed carbonyl activation. The result was an asymmetric organocatalytic Nazarov reaction, giving enantioenriched α-hydroxycyclopentenones in moderate yield with good enantioselectivity over extended reaction times (Scheme 41).[69]

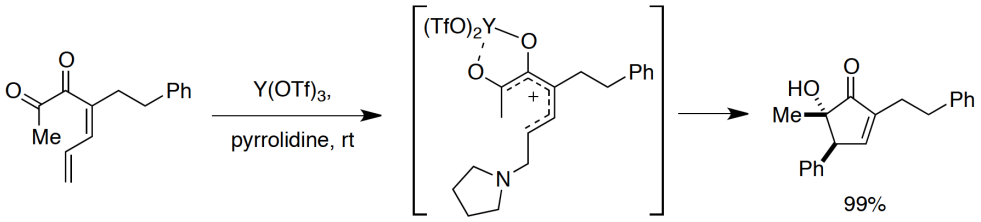


Scheme 40: α-Diketone Nazarov Cyclization.



Scheme 41: Organocatalytic Asymmetric α-Diketone Nazarov Cyclization.

Following the initial report by Tius and coworkers, Frontier *et al*. found that when similar conditions were employed with linearly conjugated dienyl α-diketones 1,6-conjugate addition of pyrrolidine occurred, forming a pentadienyl cation which underwent Nazarov cyclization (Scheme 42).[70] This method could also be applied to nitrogen and malonate nucleophiles.

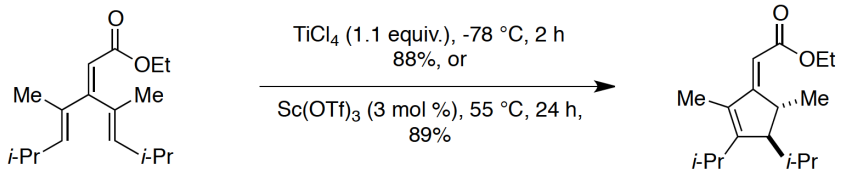


Scheme 42: Conjugate Addition-Initiated Nazarov Cyclization.

1.3.1.3 The Vinylogous Nazarov Reaction

The carbonyl activation discussed to this point involves activation of carbonyl directly attached to the pentadienyl. West and coworkers have developed an alternative [3]dendralene substrate bearing an ester on the C-3 olefin which could be activated by $TiCl_4$ or $Sc(OTf)_3$. This activation generated a pentadienyl

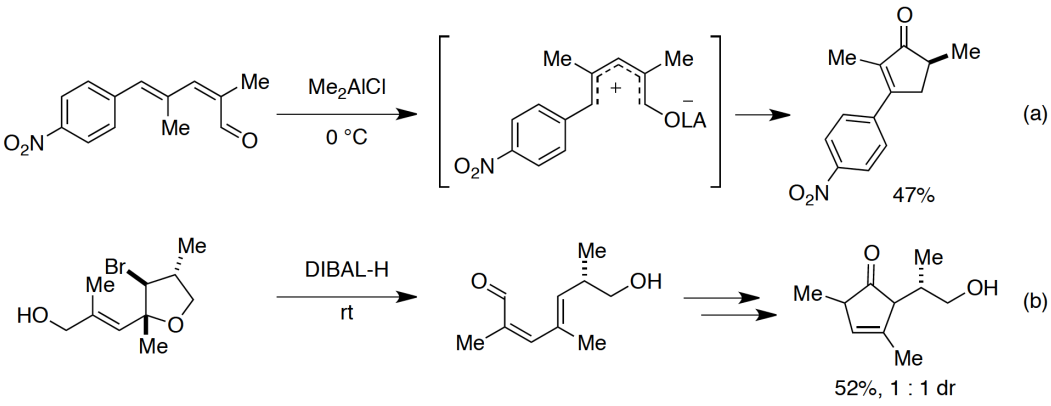
cation that underwent what the authors have named 'the vinylogous Nazarov reaction' (Scheme 43).[71] The ester could be replaced with ketone, aldehyde, or amide functionality with no detriment to the reaction.



Scheme 43: Vinylogous Nazarov Reaction.

1.3.1.4 Iso-Nazarov Reaction

When linearly conjugated carbonyls undergo acid activation and Nazarov cyclization, the intermediate pentadienyl cation is oxygenated at C-1, rather than C-3. This type of iso-Nazarov reactivity was observed by Trauner and coworkers. When a linearly conjugated pentadienal substrate was subjected to Lewis acid activation generating a 1-oxidopentadienyl cation, the activated intermediate underwent electrocyclization to give a cyclopentenone product (Scheme 44a).[72] Jung and Yoo observed similar reactivity in an unexpected rearrangement-cyclization of a 2-alkenyl-3-bromotetrahydrofuran. Under DIBAL-H reduction conditions an intermediate dienal was likely activated by acidic impurities, undergoing iso-Nazarov cyclization to give the cyclopentenone product (Scheme 44b).[73]

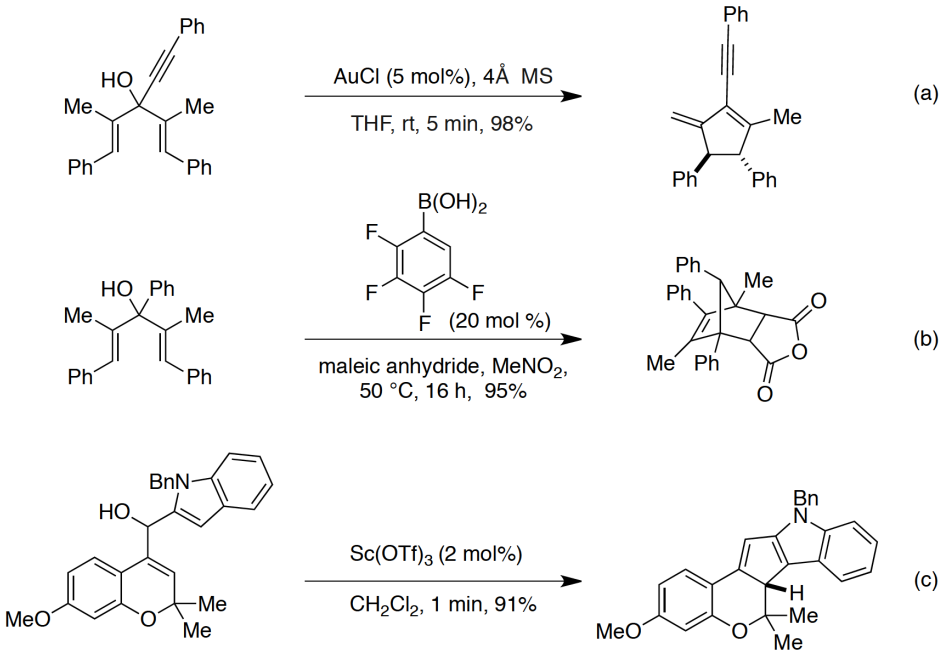


Scheme 44: Iso-Nazarov Reactions.

1.3.2 Activation by Carbon-Oxygen Bond Ionization

1.3.2.1 Alcohol Ionization

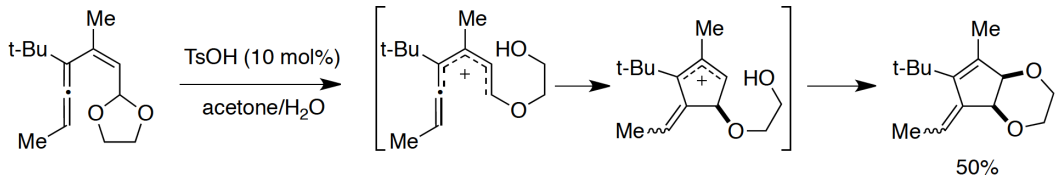
The ionization of cross-conjugated alcohols provides straightforward entry to pentadienyl cations, which can undergo Nazarov cyclization to generate cyclopentenes and cyclopentadienes.[5,74] Several recent examples are highlighted in Scheme 45. During studies of the Meyer-Schuster rearrangement of tertiary alkynyl carbinols West and coworkers observed that under gold(III)-catalyzed conditions, in the presence of molecular sieves, a high yielding dehydrative cyclization was favored (Scheme 45a).[75] The *trans*-relationship of the phenyl substituents provided strong evidence for a Nazarov cyclization. Hall and coworkers used a mild electron-deficient boronic acid catalyst in a high yielding tandem Nazarov cyclization/Diels-Alder method (Scheme 45b).[76] Panda and Singh used the $Sc(OTf)_3$-catalyzed ionization of cross-conjugated alcohols to access a variety of polycyclic scaffolds (Scheme 45c).[77] The reaction of substrates bearing electron-rich arenes were accelerated, relative to simple phenyl substrates.



Scheme 45: Dehydrative Nazarov Reactions.

1.3.2.2 C-O Bond Cleavage

Ionization of ethers and acetals, although less common for formation of the pentadienyl cation, is not without precedent. As discussed in Scheme 26, Nair and coworkers showed that dihydrofuran ring opening of *gem*-dialkenyl dihydrofurans could generate pentadienyl cations which underwent Nazarov cyclization and trapping of the resultant oxyallyl cation in an interrupted Nazarov reactions.[37] Acid-catalyzed ionzation of vinylallene acetals has been used to generate 1-oxidiopentadienyl cations. Following cyclization the allyl cation was trapped by the oxygen tether go give the alkylidenecyclopentene product resulting from an interrupted iso-Nazarov reaction (Scheme 46).[78,79]

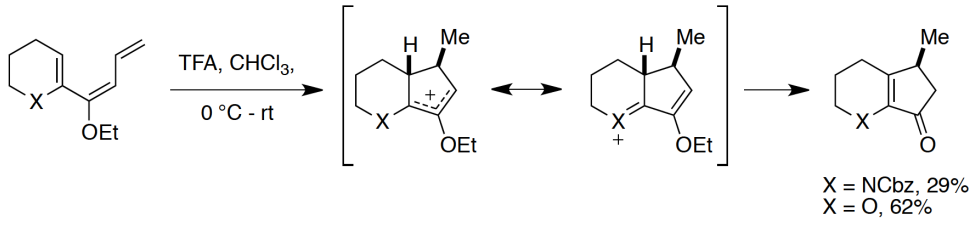


Scheme 46: Acetal Opening-Initiated Nazarov Reaction.

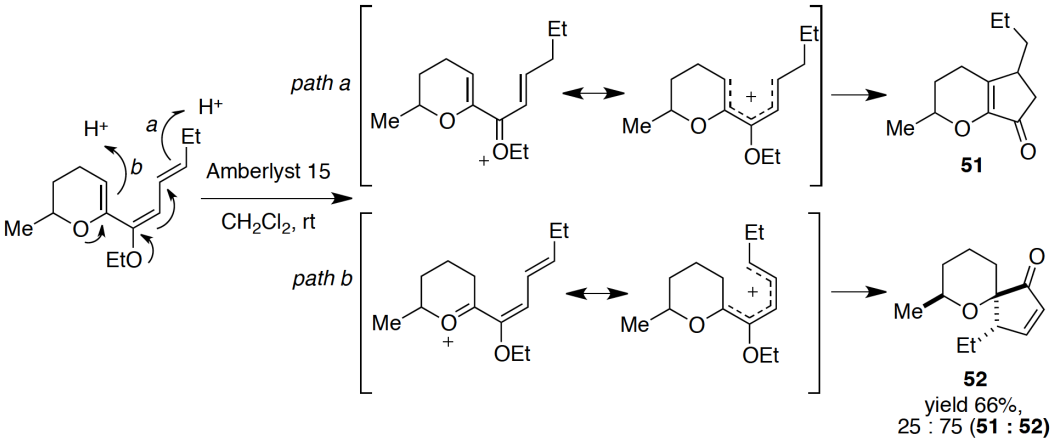
1.3.3 C=C Bond Activation

1.3.3.1 Olefin Activation

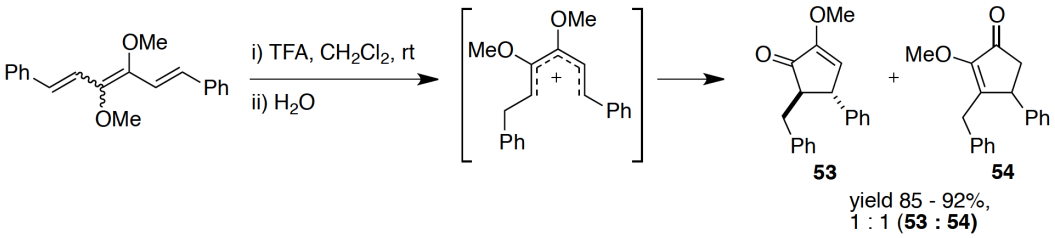
Extensive work by Occhiato and coworkers has demonstrated that alkoxytrienes are valuable pentadienyl cation precursors. Brønsted acid activation of electron-rich trienes derived from lactam or lactone triflates led to pentadienyl cation formation, and highly diastereoselective Nazarov cyclization giving cyclopentenone products (Scheme 47).[80-82] The success of the cyclization was dependant on the ring heteroatom, which stabilized the oxyallyl cation intermediates. The presence of the ring heteroatom was proposed to also help account for successful activation under mildly acidic conditions. When the exocyclic terminal olefin was substituted, the formation of spirocyclic products was a competitive pathway. This was due to protonation of the ring olefin (Scheme 48, path b) rather than the exocyclic terminal olefin (Scheme 48, path a).[83] Following initial reports of triene cyclization by Occhiato and coworkers, Barluenga *et al*. disclosed a similar method for the Nazarov cyclization of dimethoxyhexatrienes. Under acid catalysis, the dimeric dimethoxyhexatrienes were protonated at the terminal olefin forming a pentadienyl cation, which underwent 4π-electrocyclization giving a mixture of regioisomeric methoxycyclopentenones (Scheme 49).[84]



Scheme 47: Alkoxytriene Nazarov Cyclization.

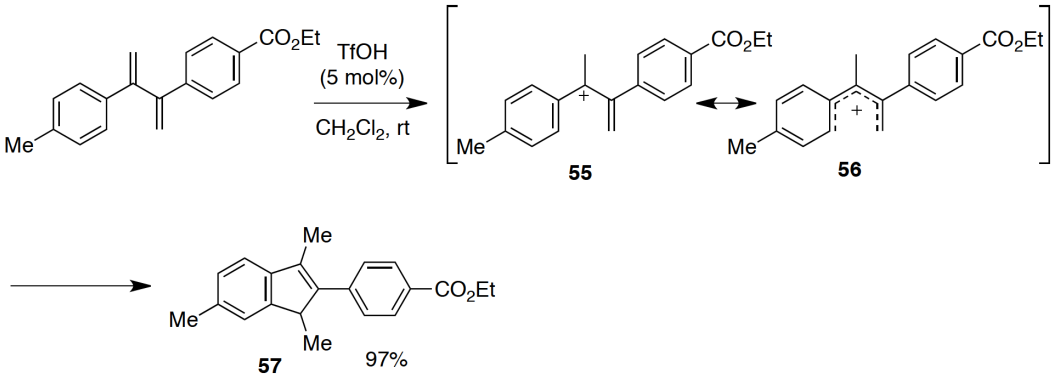


Scheme 48: Competitive Pathways of Alkoxytriene Nazarov Cyclization.



Scheme 49: Dimethoxytriene Nazarov Cyclization.

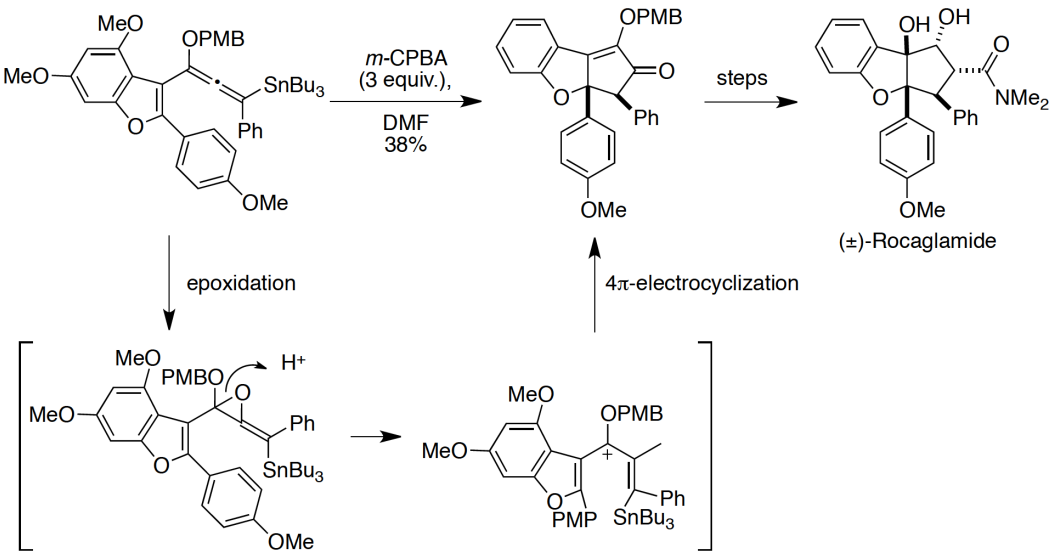
In 2012, Lee and coworkers used 2,3-diaryl-1,3-dienes as pentadienyl cation precursors.[85] The Brønsted acid activation of these substrates is reminiscent of the Lewis acid activation of [3]-dendralenes in the vinylogous Nazarov reaction discussed in Section 1.3.1.3.[71] In these examples, Markovnikov protonation occurred on the olefin leading to the more stabilized 3° benzylic cation, which was in resonance with the pentadienyl cation. Nazarov cyclization and rearomatization gave the indene products (Scheme 50). All unsymmetrical substrates were polarized with a donating group on one aryl substituent, and a withdrawing group on the other, which led to the observed regioselectivity in the products.



Scheme 50: Nazarov Cyclization of 2,3-Diaryl-1,3-dienes.

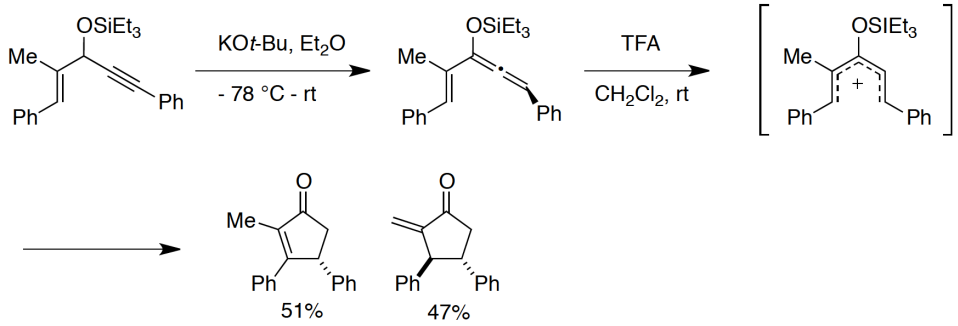
1.3.3.2 Allene Activation

The activation of vinyl allenes by epoxidation/epoxide-opening to generate pentadienyl cations has been previously explored.[86-92] More recently, Frontier and coworkers have exploited this reactivity as a key transformation in their synthesis of rocaglamide.[93,94] Epoxidation of an alkoxyallene, and the subsequent ring opening led to a pentadienyl cation which underwent successful Nazarov cyclization giving a key intermediate towards rocaglamide (Scheme 51). This methodology was later generalized to include a variety of vinyl alkoxyallenes, where DMDO epoxidation gave allene oxides that spontaneously opened to give a pentadienyl cation. The ensuing Nazarov cyclization gave cyclopentenone products, maintaining both of the stereospecifically formed stereocenters.[95]



Scheme 51: Oxidation-Initiated Nazarov Reaction of an Alkoxyallene.

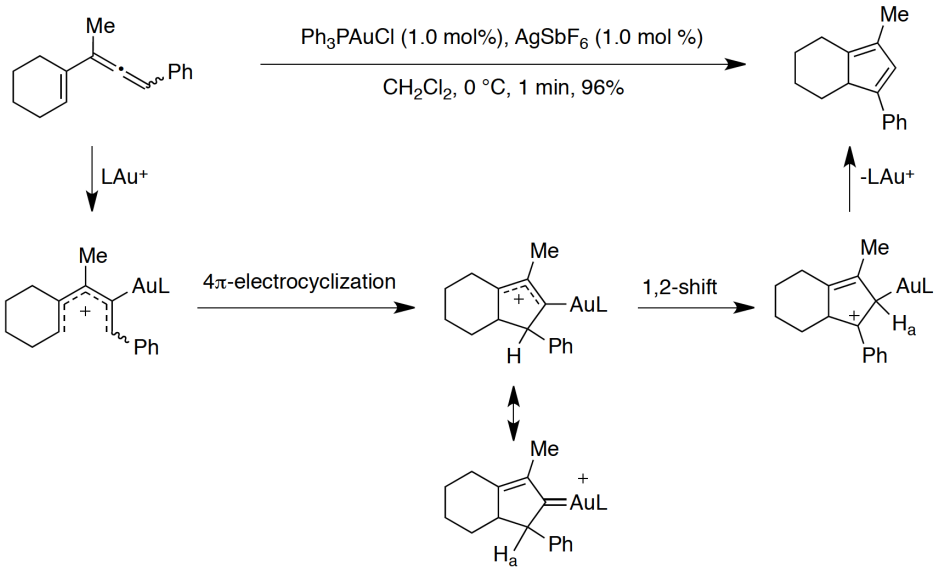
Protonation of vinyl allenes offers another method of accessing pentadienyl cations. Wu and West found that when vinyl siloxyallenes formed *in situ* from siloxyenynes were subjected to Brønsted acid 3-oxidopentadienyl cations were formed and subsequent Nazarov cyclization and elimination led to cyclopentenone products; however, the elimination step suffered from poor regioselectivity (Scheme 52).[96]



Scheme 52: Nazarov Cyclization of Vinyl Siloxyallenes.

Vinyl allenes can also be subjected to transition metal-mediated activation. Toste and Lee used cationic Au(I) to activate allenes. They proposed coordination of the Au(I) to the allene, which led to formation of a pentadienyl cation

intermediate, 4π-electrocyclization then led to an allyl cation which underwent a 1,2-hydrogen shift. Finally elimination gave the cyclopentadiene product (Scheme 53).[97] A contemporaneous report by Iwasawa and coworkers[98] disclosed an analogous Pt(II)-catalyzed reaction.[99]

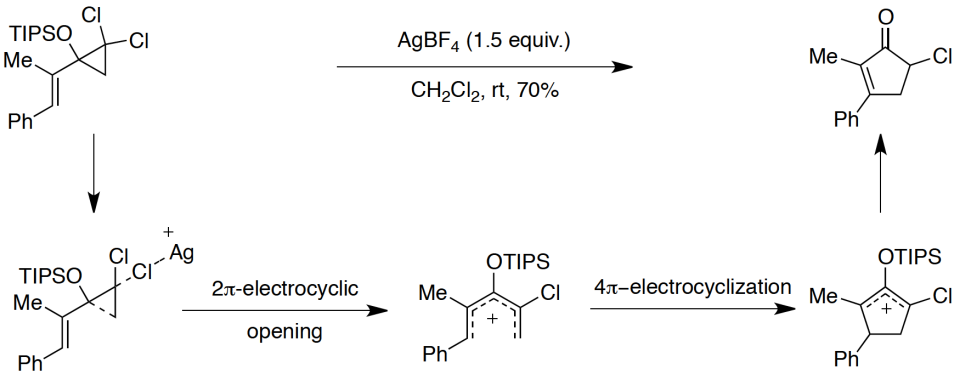


Scheme 53: Gold(I)-Mediated Nazarov Cyclization.

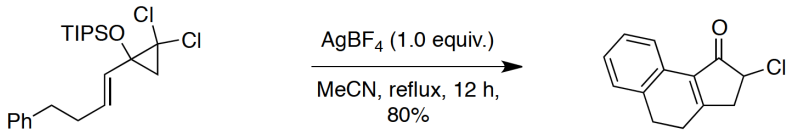
1.3.4 Activation by Ring Opening

The electrocyclic opening of strained small rings as a means of activation for accessing pentadienyl cations for Nazarov cyclization has recently been explored. In 2006, Grant and West found that when alkenyl- and siloxy-substituted *gem*-dichlorocyclopropanes were treated with Ag(I), α-chlorocyclopentenones were formed. This process was proposed to occur by Ag(I)-mediated chloride abstraction, which triggered 2π-electrocyclic cyclopropane opening to generate the 2-siloxypentadienyl cation intermediate, subsequent Nazarov cyclization and elimination gave the observed products (Scheme 54).[100] When arenes were tethered to the alkene, interrupted Nazarov reactions were observed (Scheme 55).[101] Of particular note was the observation

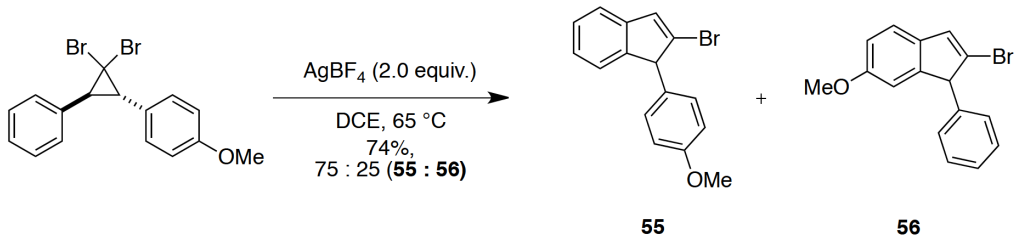
that these substrates could be trapped by a simple phenyl nucleophile. The interrupted Nazarov reaction of an analogous dienone was unsuccessful, requiring a more reactive arene nucleophile (Section 1.2.4.2).[23] In a more recent report, Rosocha and Batey disclosed the related Ag(I) domino 2π-electrocylic ring-opening/4π-electrocyclization of 1,2-diaryl substituted *gem*-dibromocyclopropanes for the synthesis of bromoindenes. This method suffered from poor regioselectivity for unsymmetrical substrates (Scheme 56).[102]



Scheme 54: Dichlorocyclopropane Nazarov Reaction.

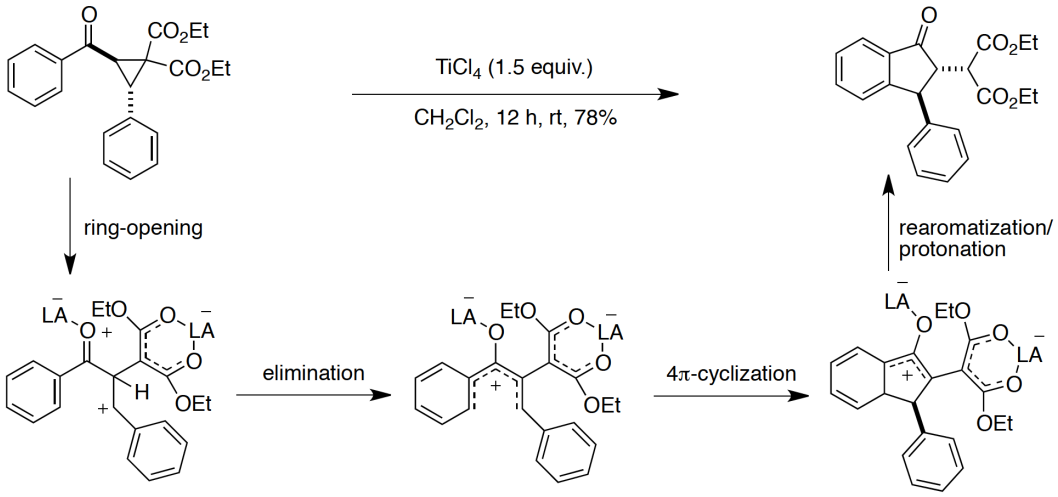


Scheme 55: Interrupted Nazarov Reaction of Dichlorocyclopropanes.



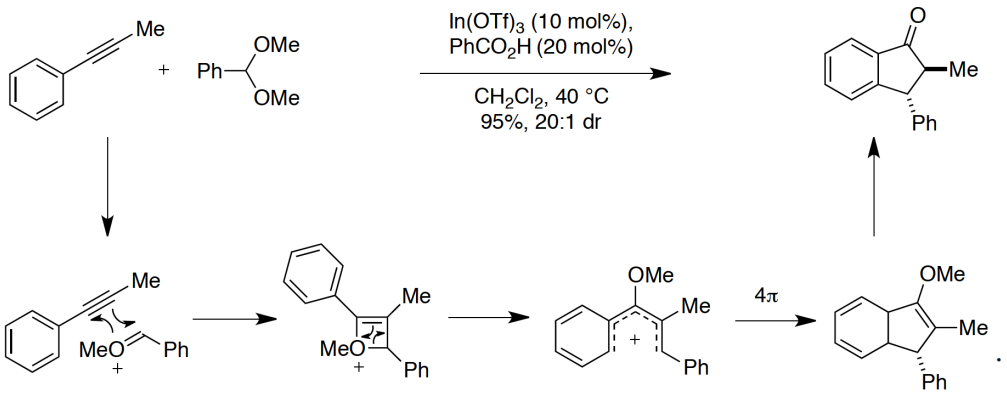
Scheme 56: Dibromocyclopropane Nazarov Reaction.

A recent report by Sathishkannan and Srinivasan exploited the facile Lewis acid ring-opening of donor-acceptor cyclopropanes for the generation of pentadienyl cations. The authors proposed a Lewis acid promoted cyclopropane-opening to generate a 1,3-dipole, which underwent elimination to give the Lewis acid activated 3-oxidopentadienyl cation leading to the observed indanone product (Scheme 57).[103]



Scheme 57: Cyclopropane-Opening Initiated Nazarov Cyclization.

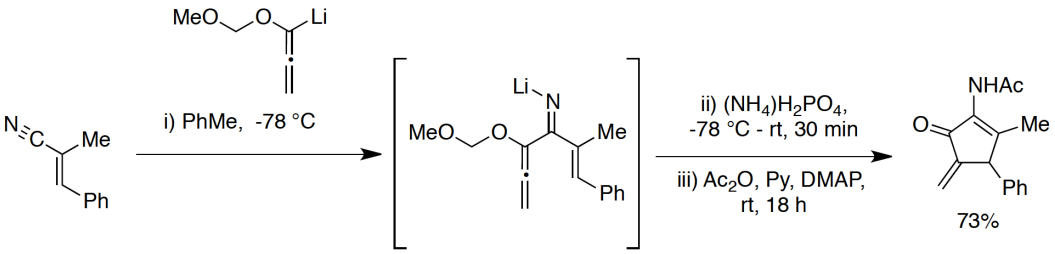
Several examples of alkyne-carbonyl metathesis as entry to Nazarov pentadienyl cations have appeared in recent years.[104-106] One very recent example by Luo and co-workers used acetals and alkynes with catalytic Lewis and Brønsted acid.[106] In the proposed mechanism, the oxocarbenium ion generated under acidic conditons participated in a [2+2]-cycloaddition with the alkyne. The resulting cationic oxetene isomerized to the pentadienyl cation, which underwent Nazarov cyclization leading to indanone products with high diastereoselectivity (Scheme 58).



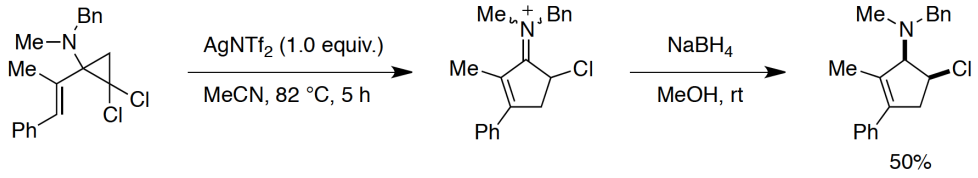
Scheme 58: [2+2]-Cycloaddition-Initiated Nazarov Reaction.

1.3.5 Imino Nazarov Reaction

A classical imino Nazarov reaction, where the C-3 position of the pentadienyl cation is nitrogen substituted has been shown computationally to have an equilibrium favoring the open pentadienyl cation rather than the cyclopentadienyl cation.[107] In 2001, Tius and coworkers reported the formation of α-aminocyclopentenones from imines generated *in situ* by 1,2-addition of allenyl nucleophiles into α,β-unsaturated nitriles.[108] This method worked around the problem of an unfavorable equilibrium through the irreversible loss of a methoxymethyl cation following Nazarov cyclization. The crude products were converted to acetamides for ease of purification and handling (Scheme 59). Recently, West and coworkers expanded the scope of the *gem*-dichlorocyclopropane opening initiated Nazarov reactions (Section 1.3.4). It was found that Ag(I) assisted opening of 1-amino-1-alkenyl-2,2-dichlorocyclopropanes led to pentadienyl cation formation and Nazarov cyclization.[109] Spectral evidence was found for the formation of the cyclized iminium products. Subsequent reduction afforded the neutral amine products (Scheme 60). This method was also applicable to intramolecular arene interrupted Nazarov reactions.



Scheme 59: Imino Allene Nazarov Reaction.



Scheme 60: Dichlorocyclopropane Imino Nazarov Reaction.

1.3.6 Summary

The recent advances in the interrupted Nazarov reaction have provided means for rapidly building molecular complexity. In many cases the stereocenters generated by the stereospecific Nazarov cyclization are maintained as a result of nucleophilic oxyallyl cation trapping. In other cases, the reaction of the enolate intermediate formed after elimination with electrophiles provided another method of interrupting the Nazarov process. Advances in the use of alternative substrates for entry to pentadienyl cations have provided new products that would be inaccessible using traditional dienone substrates. A number of the alternative substrates use alternative methods of activation, which has expanded the conditions that can be used to generate pentadienyl cations beyond Lewis or Brønsted acids. The interrupted Nazarov reaction, and the use of alternative substrates and methods of activation is an area that we hoped to expand. We set out to probe the generality of intermolecular arene trapping. Additionally, we hoped to explore a new type of alternative susbstrate in which the pentadienyl cation is arrived at under oxidative conditions. We also planned to carry out a detailed study of an unexpected isomerization product observed in the attempted formation of vinylogous Nazarov substrates.

1.4 References

(1) Nazarov, I. N.; Yanbikov, Y. M. *Izv. Nauk. SSSR, Ser. Kim,* **1943**; 389-393.

(2) Braude, E. A.; Coles, J. A. *J. Chem. Soc.* **1952**, 1430–1433.

(3) Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed.* **1969**, *8*, 781–932.

(4) A version of this section has been previously published, see the following reference.

(5) West, F. G.; Scadeng, O.; Wu, Y.-K.; Fradette, R. J.; Joy, S. In *Comprehensive Organic Synthesis II*; Elsevier, 2014; pp. 827–866.

(6) Barltrop, J. A.; Day, A. C.; Samuel, C. J. *J. Am. Chem. Soc.* **1979**, *101*, 7521–7528.

(7) West, F. G.; Fisher, P. V.; Gunawardena, G. U.; Mitchell, S. *Tetrahedron Lett.* **1993**, *34*, 4583–4586.

(8) West, F. G.; Fisher, P. V.; Willoughby, C. A. *J. Org. Chem.* **1990**, *55*, 5936–5938.

(9) West, F. G.; Fisher, P. V.; Arif, A. M. *J. Am. Chem. Soc.* **1993**, *115*, 1595–1597.

(10) West, F. G.; Willoughby, D. W. *J. Org. Chem.* **1993**, 3796–3797.

(11) West, F. G.; Hartke-Karger, C.; Koch, D. J.; Kuehn, C. E.; Arif, A. M. *J. Org. Chem.* **1993**, *58*, 6795–6803.

(12) Vorlander, D.; Schroedter, M. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 1409–1407.

(13) Allen, C. F. H.; VanAllan, J. A.; Tinker, J. F. *J. Org. Chem.* **1955**, *20*, 1387–1391.

(14) Giese, S.; West, F. G. *Tetrahedron Lett.* **1998**, *39*, 8393–8396.

(15) Giese, S.; West, F. G. *Tetrahedron,* **2000**, *56*, 10221–10228.

(16) Chiu, P.; Li, S. *Org. Lett.* **2004**, *6*, 613–616.

(17) Lebœuf, D.; Huang, J.; Gandon, V.; Frontier, A. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 10981–10985.

(18) Huang, J.; Lebœuf, D.; Frontier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 6307–6317.

(19) Bender, J. A.; Blize, A. E.; Browder, C. C.; giese, S.; West, F. G. *J. Org. Chem.* **1998**, *63*, 2430–2431.

(20) Giese, S.; Mazzola, R. D.; Amann, C. M.; Arif, A. M.; West, F. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 6546–6549.

(21) Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443–7444.

(22) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033–3035.

(23) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Can. J. Chem.* **2004**, *82*, 375–385.

(24) Chaplin, J. H.; Jackson, K.; White, J. M.; Flynn, B. L. *J. Org. Chem.*

2014, *79*, 3659-3665.
(25) giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem. Int. Ed.* **2000**, 1970–1973.
(26) Marx, V. M.; Burnell, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 1685–1689.
(27) Mahmoud, B.; West, F. G. *Tetrahedron Lett.* **2007**, *48*, 5091–5094.
(28) Yen-Ku, W.; McDonald, R.; West, F. G. *Org. Lett.* **2011**, *13*, 3584-3587.
(29) For further discussion see Chapter 2 of this thesis.
(30) Rieder, C. J.; Fradette, R. J.; West, F. G. *Chem. Commun.* **2008**, 1572–1574.
(31) G West, F.; J Rieder, C.; J Fradette, R. *Heterocycles* **2010**, *80*, 1413–1427.
(32) Basak, A. K.; Tius, M. A. *Org. Lett.* **2008**, *10*, 4073–4076.
(33) Marx, V. M.; LeFort, F. M.; Burnell, D. J. *Adv. Synth. Catal.* **2010**, *353*, 64–68.
(34) Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876–877.
(35) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747–2750.
(36) Kwon, Y.; McDonald, R.; West, F. G. *Angew. Chem. Int. Ed.* **2013**, *52*, 8616–8619.
(37) Nair, V.; Bindu, S.; Sreekumar, V.; Chiaroni, A. *Org. Lett.* **2002**, *4*, 2821–2823.
(38) Marx, V. M.; Burnell, D. J. *Org. Lett.* **2009**, *11*, 1229–1231.
(39) Marx, V. M.; Stoddard, R. L.; Heverly-Coulson, G. S.; Burnell, D. J. *Chem. Eur. J.* **2011**, *17*, 8098–8104.
(40) Yaji, K.; Shindo, M. *Synlett* **2009**, *2009*, 2524–2528.
(41) Dhoro, F.; Tius, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 12472–12473.
(42) Dhoro, F.; Kristensen, T. E.; Stockmann, V.; Yap, G. P. A.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 7256–7257.
(43) Rostami, A.; Wang, Y.; Arif, A. M.; McDonald, R.; West, F. G. *Org. Lett.* **2007**, *9*, 703–706.
(44) Song, D.; Rostami, A.; West, F. G. *J. Am. Chem. Soc.* **2007**, *129*, 12019–12022.
(45) Scadeng, O.; Ferguson, M. J.; West, F. G. *Org. Lett.* **2011**, *13*, 114–117.
(46) White, T. D.; West, F. G. *Tetrahedron Lett.* **2005**, *46*, 5629–5632.
(47) Marx, V. M.; Cameron, T. S.; Burnell, D. J. *Tetrahedron Lett.* **2009**, *50*, 7213–7216.
(48) Nie, J.; Zhu, H.-W.; Cui, H.-F.; Hua, M.-Q.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 3053–3056.
(49) Cui, H.-F.; Dong, K.-Y.; Zhang, G.-W.; Wang, L.; Ma, J.-A. *Chem. Commun.* **2007**, 2284.
(50) Cui, H.-F.; Dong, K.-Y.; Nie, J.; Zheng, Y.; Ma, J.-A. *Tetrahedron Letters* **2010**, *51*, 2374–2377.
(51) Kawatsura, M.; Kajita, K.; Hayase, S.; Itoh, T. *Synlett* **2010**, 1243–1246.

(52) Rueping, M.; Ieawsuwan, W. *Chem. Commun.* **2011**, *47*, 11450.
(53) Janka, M.; He, W.; Haedicke, I. E.; Fronczek, F. R.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2006**, *128*, 5312–5313.
(54) Fujiwara, M.; Kawatsura, M.; Hayase, S.; Nanjo, M.; Itoh, T. *Adv. Synth. Catal.* **2008**, *351*, 123–128.
(55) Ibara, C.; Fujiwara, M.; Hayase, S.; Kawatsura, M.; Itoh, T. *Sci. China Chem.* **2012**, *55*, 1627–1632.
(56) Hashmi, A. S. K.; Bats, J. W.; Choi, J.-H.; Schwarz, L. *Tetrahedron Lett.* **1998**, *39*, 7491–7494.
(57) Tius, M. A. *Chem. Soc. Rev.* **2014**.
(58) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284–290.
(59) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509–8514.
(60) Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 10091–10100.
(61) Harrington, P. E.; Tius, M. A. *Org. Lett.* **2000**, *2*, 2447–2450.
(62) delos Santos, D. B.; Banaag, A. R.; Tius, M. A. *Org. Lett.* **2006**, *8*, 2579–2582.
(63) Banaag, A. R.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 5328–5329.
(64) Banaag, A. R.; Tius, M. A. *J. Org. Chem.* **2008**, *73*, 8133–8141.
(65) Schultz-Fademrecht, C.; Tius, M. A.; Grimme, S.; Wibbeling, B.; Hoppe, D. *Angew. Chem. Int. Ed.* **2002**, *41*, 1532–1535.
(66) Muxfeldt, H.; Weigele, M.; Van Rheenen, V. *J. Org. Chem.* **1965**, *30*, 3573–3574.
(67) Batson, W. A.; Sethumadhavan, D.; Tius, M. A. *Org. Lett.* **2005**, *7*, 2771–2774.
(68) Uhrich, E.; Batson, W.; Tius, M. *Synthesis* **2006**, *2006*, 2139–2142.
(69) Basak, A. K.; Shimada, N.; Bow, W. F.; Vicic, D. A.; Tius, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 8266–8267.
(70) Brooks, J. L.; Caruana, P. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 12454–12457.
(71) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Am. Chem. Soc.* **2009**, *131*, 7504–7505.
(72) Miller, A. K.; Banghart, M. R.; Beaudry, C. M.; Suh, J. M.; Trauner, D. *Tetrahedron* **2003**, *59*, 8919–8930.
(73) Jung, M. E.; Yoo, D. *J. Org. Chem.* **2007**, *72*, 8565–8568.
(74) Spencer, W. T., III; Vaidya, T.; Frontier, A. J. *Eur. J. Org. Chem.* **2013**, *2013*, 3621–3633.
(75) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Org. Chem.* **2011**, *76*, 50–56.
(76) Zheng, H.; Lejkowski, M.; Hall, D. G. *Tetrahedron Lett.* **2013**, *54*, 91–94.
(77) Singh, R.; Panda, G. *Org. Biomol. Chem.* **2011**, *9*, 4782.
(78) de Lera, Á. R.; Rey, J. G.; Hrovat, D.; Iglesias, J.; Lopez, S. *Tetrahedron Lett.* **1997**, *38*, 7425–7428.
(79) Iglesias, B.; de Lera, Á. R.; Rodriguez-Otero, J.; Lopez, S. *Chem. Eur. J.* **2000**, *6*, 4021–4034.

(80) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Deagostino, A.; Venturello, P. *J. Org. Chem.* **2002**, *67*, 7144–7146.
(81) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P. *J. Org. Chem.* **2003**, *68*, 9728–9741.
(82) Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P.; Occhiato, E. G. *J. Org. Chem.* **2004**, *69*, 7705–7709.
(83) Prandi, C.; Deagostino, A.; Venturello, P.; Occhiato, E. G. *Org. Lett.* **2005**, *7*, 4345–4348.
(84) Barluenga, J.; Barrio, P.; Vicente, R.; López, L. A.; Tomás, M. *J. Organomet. Chem.* **2004**, *689*, 3793–3799.
(85) Eom, D.; Park, S.; Park, Y.; Ryu, T.; Lee, P. H. *Org. Lett.* **2012**, *14*, 5392–5395.
(86) Grimaldi, J.; Bertrand, M. *Tetrahedron Lett.* **1969**, 3296–3272.
(87) Bertrand, M.; Dulcere, J. P.; Gil, G. *Tetrahedron Lett.* **1977**, 4403–4406.
(88) Malacria, M.; Roumestant, M. L. *Tetrahedron* **1977**, *33*, 2813–2817.
(89) Doutheau, A.; Gore, J.; Malacria, M. *Tetrahedron* **1977**, *33*, 2393–2398.
(90) Doutheau, A.; Sartoretti, J.; Gore, J. *Tetrahedron* **1983**, *39*, 3059–3065.
(91) Doutheau, A.; Gore, J.; Diab, J. *Tetrahedron* **1985**, *41*, 329–338.
(92) Seong, J. K.; Cha, J. K. *Tetrahedron Lett.* **1988**, *29*, 5613–5616.
(93) Malona, J. A.; Cariou, K.; Frontier, A. J. *J. Am. Chem. Soc.* **2009**, *131*, 7560–7561.
(94) Malona, J. A.; Cariou, K.; Spencer, W. T., III; Frontier, A. J. *J. Org. Chem.* **2012**, *77*, 1891–1908.
(95) Spencer, W. T., III; Levin, M. D.; Frontier, A. J. *Org. Lett.* **2011**, *13*, 414–417.
(96) Yen-Ku, W.; West, F. G. *J. Org. Chem.* **2010**, *75*, 5410–5413.
(97) Lee, J. H.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 912–914.
(98) Funami, H.; Kusama, H.; Iwasawa, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 909–911.
(99) Metal-mediated activation of allenes and alkynes for Nazarov cyclizations is a well studied and growing field, see references 5 and 74 for further examples.
(100) Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348–9349.
(101) Grant, T. N.; West, F. G. *Org. Lett.* **2007**, *9*, 3789–3792.
(102) Rosocha, G.; Batey, R. A. *Tetrahedron* **2013**, *69*, 8758–8768.
(103) Sathishkannan, G.; Srinivasan, K. *Adv. Synth. Catal.* **2014**, *356*, 729–735.
(104) Saito, A.; Umakoshi, M.; Yagyu, N.; Hanzawa, Y. *Org. Lett.* **2008**, *10*, 1783–1785.
(105) Xu, T.; Yang, Q.; Ye, W.; Jiang, Q.; Xu, Z.; Chen, J.; Yu, Z. *Chem. Eur. J.* **2011**, *17*, 10547–10551.
(106) Zhu, L.; Xi, Z.-G.; Lv, J.; Luo, S. *Org. Lett.* **2013**, *15*, 4496–4499.
(107) Smith, D. A.; Ulmer, C. W. I. *J. Org. Chem.* **1997**, *62*, 5110–5115.
(108) Tius, M. A.; Chu, C. C.; Nieves-Colberg, R. *Tetrahedron Lett.* **2001**, *42*, 2419–2422.

(109) Bonderoff, S. A.; Grant, T. N.; West, F. G.; Tremblay, M. *Org. Lett.* **2013**, *15*, 2888–2891.

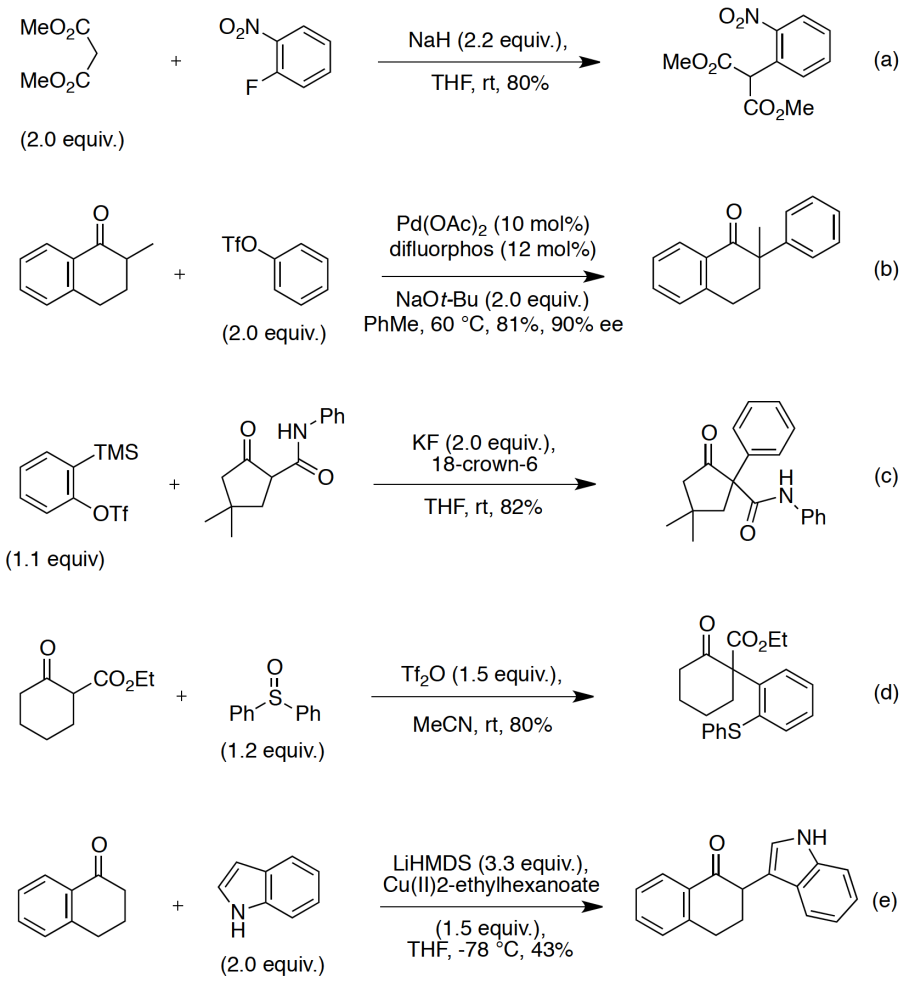
Chapter 2

Heteroaromatic Trapping of Nazarov-derived Oxyallyl Cations [1,2]

2.1 Introduction

Direct arylation adjacent to a ketone carbonyl is a potentially valuable transformation. This would seem to be a straightforward process, which instead presents a significant challenge. The issue lies in the intrinsic nucleophilicity of the ketones via their enol or enolate tautomers, a characteristic that is utilized heavily in aldol chemistry and α-alkylation chemistry. α-Arylation methods using nucleophilic aromatic substitution are known;[3-6] however, highly activated arenes are required (Scheme 1a).[3] This requirement limits the substrate scope to highly electron deficient aromatics. Effective metal-catalyzed cross-coupling protocols have been developed[7-9] (Scheme 1b);[9] additionally, strategies involving arynes have been investigated[10-13] (Scheme 1c).[12] A metal-free sulfoxide-mediated α-arylation protocol has also recently been reported;[14,15] however, the method necessitates the incorporation of an *ortho*-thioether (Scheme 1d). Baran and coworkers have reported an oxidative arene/carbonyl coupling applicable to indoles and pyrroles (Scheme 1e). With the exception of the last case, these methods all require the use of a prefunctionalized arene partner.

Electrophilic aromatic substitution offers an easy method for direct formation of Ar-C bonds from Ar-H precursors. However, with the nucleophilic nature of the ketone enol(ate) in mind (Figure 1), electrophilic aromatic substitution poses an inherent challenge. α-Cationic character is required adjacent to the carbonyl oxygen. This reversal of reactivity, or *umpolung* is most commonly achieved through the formation of oxyallyl cations[16-19] which can be stabilized by delocalization (Figure 2).



Scheme 1: Selected α-Arylation Methods.

Figure 1: Nucleophilicity of Ketone and Enol.

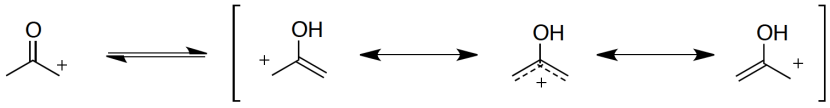


Figure 2: Resonance Stabilized Oxyallyl Cation.

Of the methods used to generate oxyallyl cations (Figure 3), the most common involve ketones with α-halogenation. Ionization of haloketones in a

Favorskii-type process,[20] or the reduction of dihaloketones have both been investigated. Silver(I) promoted heterolysis of methoxyallyl and silyloxyallyl halides has also been successful.[21,22]

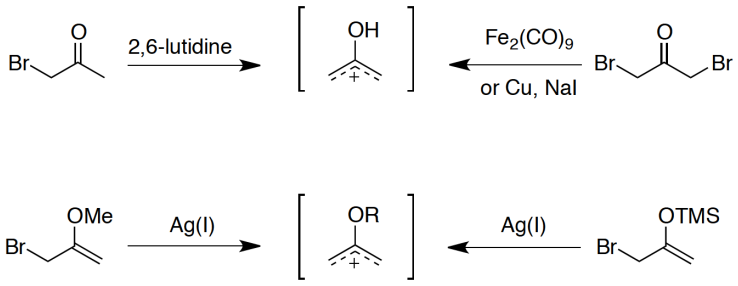
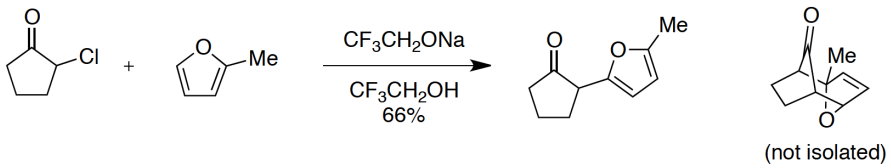


Figure 3: Oxyallyl Cation Generation.

The trapping of oxyallyl cations in direct arylation reactions is dwarfed by their use in [4+3] cycloadditions with cyclic aromatic dienes such as furan for the synthesis of seven-membered rings;[23-25] however, there is precedent for α-arylation of ketones resulting from the interception of oxyallyl cations. Föhlisch and Joachimi observed a mixture of [4+3] cycloaddition and α-arylation products when 2-methylfuran was employed as a nucleophile (Scheme 2).[26] More recently, the groups of Chi and MacMillan have reported indole trapping of oxyallyl cations also generated from haloketones in non-nucleophilic solvents.[27,28]

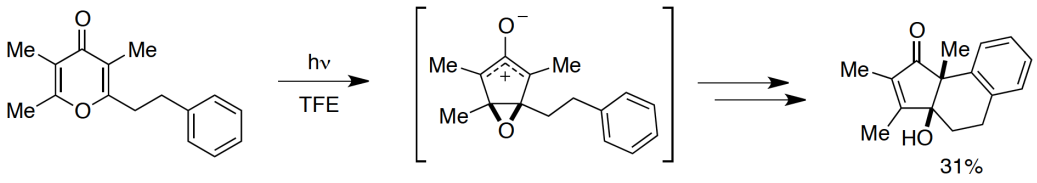


Scheme 2: α-Arylation of the Oxyallyl Cation.

2.2 Background

A major area of interest in the West group has been the study of the Nazarov reaction, in particular trapping the 2-oxidocylopentenyl cation intermediate generated immediately following the cyclization, a process know as an interrupted Nazarov reaction.[29] Early ventures into harvesting reactivity from the oxyallyl cation focused on cross-conjugated dieneones bearing tethered arenes. The use of tethered arenes provided two elements which could help the method succeed. First, the arene tether would allow the process to be unimolecular, and therefore relatively fast in the presence of a high energy oxyallyl cation intermediate. Second, following trapping of the Nazarov intermediate a new cationic intermediate would form; rearomatization was expected to be highly favored leading to stable tricyclic products.

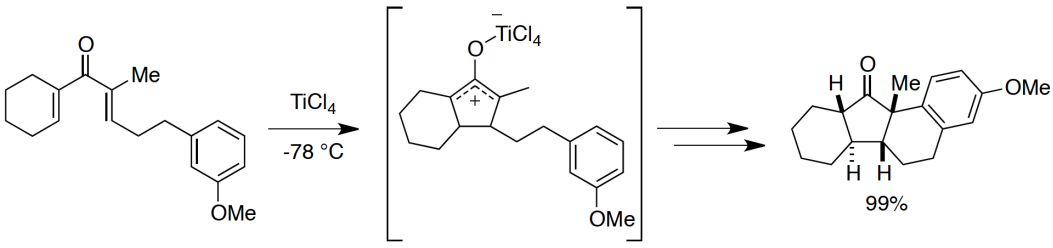
The first studies relied on oxyallyl cations generated from 4-pyranones under photochemical conditions. Following photochemical Nazarov cyclization to a bicyclic oxyallyl cation, successful interception by electrophilic aromatic substitution a simple unactivated phenyl was observed (Scheme 3).[30]



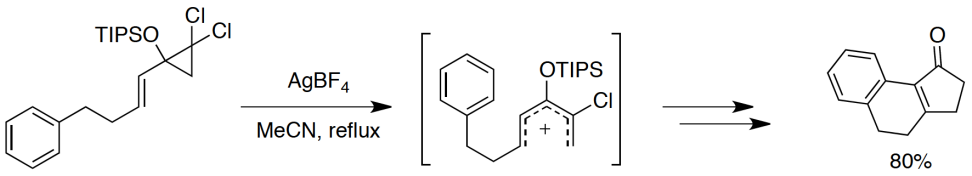
Scheme 3: Photochemical Interrupted Nazarov Reaction.

Yields for the interrupted photo-Nazarov reaction were modest and a non-nucleophilic solvent was required. The methodology was extended to the Nazarov reaction carried out under thermal conditions; however, a simple phenyl tether was not sufficiently nucleophilic to trap the 2-oxidocyclopentenyl cation, so more electron-rich arenes had to be used (Scheme 4).[31,32] More recently, silver(I) was used to promote electrocyclic ring opening of *gem*-dichlorocyclopropanes

forming a pentadienyl cation that could undergo Nazarov cyclization.[33] When a pendant arene was incorporated into the substrate, trapping analogous to the previous work was observed;[34] notably, unactivated arenes could also successfully intercept the oxyallyl cation (Scheme 5).

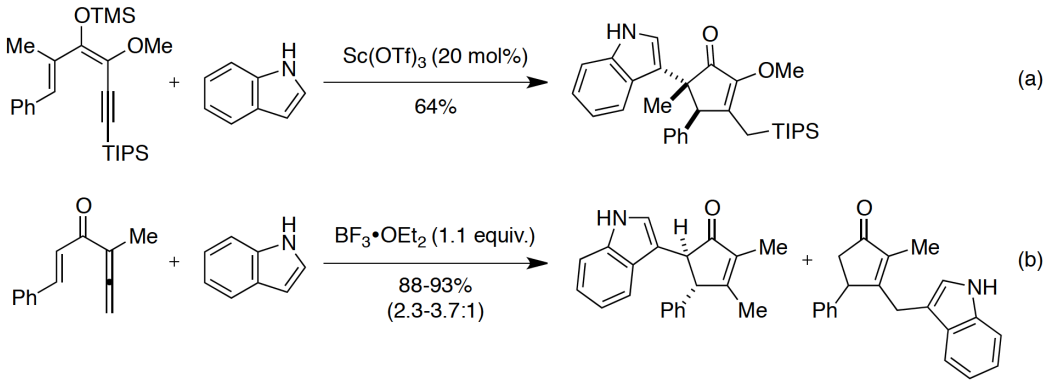


Scheme 4: Intramolecular Arene Trapping of the 2-Oxidocyclopentenyl Cation.



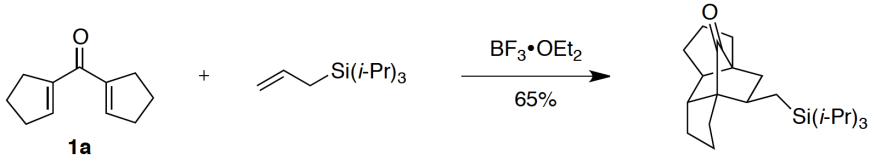
Scheme 5: Silver Mediated Arene Trapping Cascade.

Not long after our initial report of intermolecular arene trapping,[1] Tius and coworkers disclosed a related intermolecular interrupted Nazarov reaction,[35] utilizing allenyl vinyl ketones generated *in situ* from propargyl silyl enol ethers. They were able to trap the 2-oxidocyclopentenyl cation intermediate with indoles at the nucleophilic 3-position (Scheme 6a). More recently the Burnell group has reported the trapping of simple allenyl vinyl ketones with electron rich aromatic heterocycles (Scheme 6b).[36,37]



Scheme 6: Intermolecular Arene Trapping with Allenyl Vinyl Ketones.

Previous and ongoing studies by West and coworkers focus on intermolecular trapping of the Nazarov oxyallyl cation generated under thermal conditions[29] with electron rich π-systems. The earliest examples were [3+2] cycloadditions of the 2-oxidocyclopentenyl cation with allyl silanes, a stepwise process that resulted in bicyclo[2.2.1]heptanones (Scheme 7).[38] The viability of the intermolecular allyl silane method, combined with previous success in intramolecular [4+3] cycloadditions with pendant 1,3-dienes[39] left little doubt that intermolecular [4+3] cycloadditions could be achieved.



Scheme 7: Trapping With Allyl Silane.

Following the report by Wang *et al*. documenting successful [4+3] capture of the Nazarov intermediate with simple 1,3 dienes,[40] West and Rieder sought to expand the scope of this reactivity. Of particular interest was the use of dienone substrates containing a cyclopentenyl unit as exemplified by **1a**, which could react with 1,3-dienes to furnish 5-8, 5-8-5, or 5-8-6 polycyclic ring systems. Initial focus was trapping of oxyallyl intermediates derived from such dienones with furan (Figure 4).

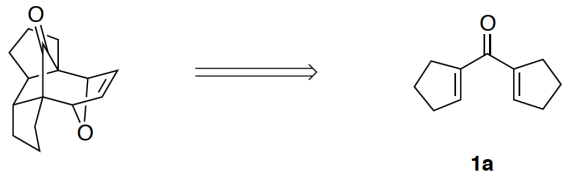
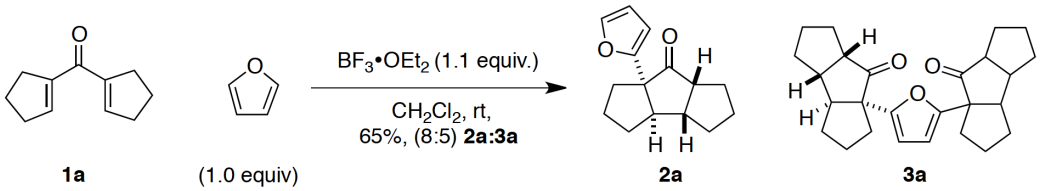


Figure 4: Projected [4+3] Cycloaddition Process.

Using the conditions reported by Wang *et al*. in the initial [4+3] communication,[40] dicyclopentenyl ketone **1a** was subjected to BF_3•OEt_2 in the presence of furan at room temperature. The starting material was consumed, and a mixture of two separable products was cleanly formed. At first inspection of the ^{1}H NMR spectra, the minor product appeared promising as two downfield signals were present as would be expected for the predicted cyclooctene product (Figure 4); however, closer inspection of the proton spectra indicated additional structural elements. When the ^{13}C NMR spectra was analyzed, two downfield resonances (δ 222.5 and 222.2) were found, suggesting the minor product contained two carbonyl carbons. Further confirmation came from the mass spectrometry data. The molecular ion (*m/z* 392.2351, $C_{26}H_{32}O_3$) indicated a product that incorporated two molecules of dicyclopentenyl ketone **1a** ($C_{11}H_{14}O$) and one molecule of furan (C_4H_4O), suggesting the formation of some sort of 2:1 adduct, rather than the expected [4+3] cycloadduct.

When the ^{1}H NMR spectrum of the major product was analyzed, three downfield signals in the same spin system were observed (δ 7.30, 6.26, and 6.10). The observation of more than two signals in the olefin region made it highly unlikely that this was the [4+3] product. Instead, the chemical shift and coupling analysis of the three downfield signals indicated a monosubstituted furan ring. Analysis of two-dimensional NMR data (COSY, HSQC, and HMBC) provided evidence for the triquinane skeleton of product **2a**. The *trans*-relationship was infered by the established conrotatory mechanism of the thermal 4π-electron Nazarov cyclization.[41] The furan nucleophile was proposed to attack the oxyallyl

cation intermediate to generate a *cis* ring-fusion, as the alternative approach would result in a highly strained *trans*-fused bicyclo[3.3.0]octanone system.[42] Finally, it was expected that protonation of the boron enolate would provide the thermodynamically more favorable *cis-anti-cis* triquinane.



Scheme 8: Furan Trapping of Nazarov Intermediate.[43]

After identifying the major product to be **2a**, the result of furan trapping the oxyallyl cation, the minor product with a molecular ion correlating to a 2:1 dienone to furan adduct was examined. The data suggested the minor product to be the result of **2a** reacting with a second oxyallyl cation to give the 2,5-disubstituted furan product **3a**. Due to spectral overlap the stereochemistry of **3a** could not be rigorously assigned. Buoyed by the observation of two carbonyl resonances in the ^{13}C NMR spectra (δ 222.5 and 222.2), and the assumption that both triquinanes had *cis-anti-cis* configuration it was inferred that **3a** was in fact a mixture of two symmetrical 2:1 adducts; one being C_2 and the other being meso (Figure 5).

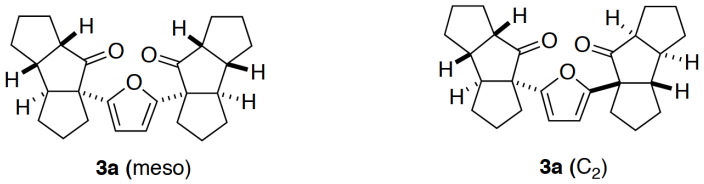
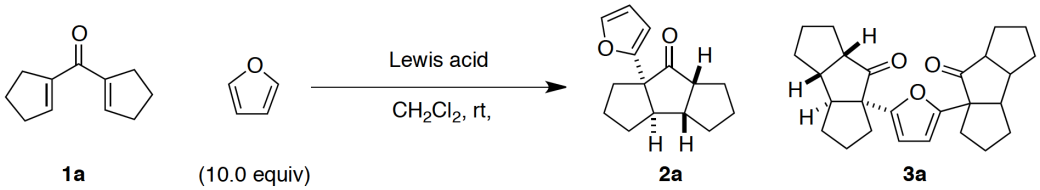


Figure 5: Stereochemistry of Two Proposed Products **3a** and **3b**.

2.3 Results and Discussion[44]

While the [4+3] cycloadduct remained an attractive product, our focus shifted to optimizing the intermolecular arene trapping, reactivity unprecedented in our studies on the interrupted Nazarov reaction. A screen of Lewis acid promoters (Table 1) suggested that BF_3•OEt_2 was the optimum choice. Additionally, the crude reaction mixtures showed no signals in ^{1}H NMR spectra to suggest formation of the [4+3] product. Further optimization of the reaction conditions found that temperature and concentration had little effect on the ratio of products; however, when the amount of furan was increased to 10 equivalents we were able to minimize formation of the 2:1 adduct **3a** (Table 2).

Table 1: Screen of Lewis Acid Promoters.

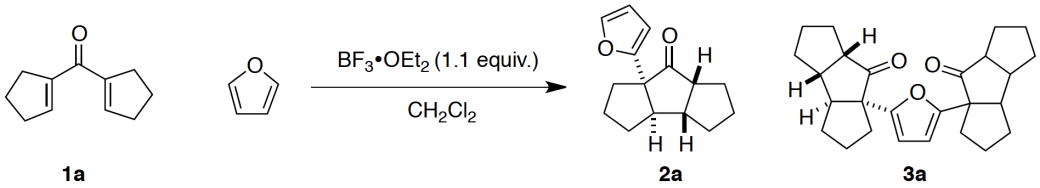


1a (10.0 equiv) **2a** **3a**

Entry	Lewis Acid	Amount	Conversion[b]	**2a : 3a**[b]
1[d]	BF_3•OEt_2[c]	1.1 equiv.	100%	8 : 5
2	$TiCl_4$	1.1 equiv.	100%	7 : 5
3[d]	$TiCl_4$	10 mol%	<5%	n/a
4	$FeCl_3$	1.1 equiv.	100%	14 : 11
5[d]	$FeCl_3$	10 mol%	100%	14 : 11
6[d]	$SnCl_4$	10 mol%	46%	5 : 2
7[d]	$RuCl_3$	10 mol%	70%	10 : 3
8	$AlCl_3$	10 mol%	trace	n/a
9[d]	Et_2AlCl	10 mol%	trace	n/a
10[d]	$Hg(OAc)_2$	10 mol%	trace	n/a
11	$Pb(OAc)_2$	10 mol%	trace	n/a

[a] Conditions: Lewis acid was added to a solution of **1a** (0.05 mmol), and furan (0.1 mmol) in CH_2Cl_2 (10 mM) and allowed to stir for 4 days at rt. Reaction mixtures were quenched by addition of sat. $NaHCO_3$ (aq), extracted with CH_2Cl_2, dried with $MgSO_4$, filtered, and concentrated. [b] Based on ^{1}H NMR integrations of β-furyl protons in the crude reaction mixture. [c] Reaction was complete in 30 min. [d] Reaction carried out by C. J. Rieder.

Table 2: Optimization for Formation of EAS product **2a**.



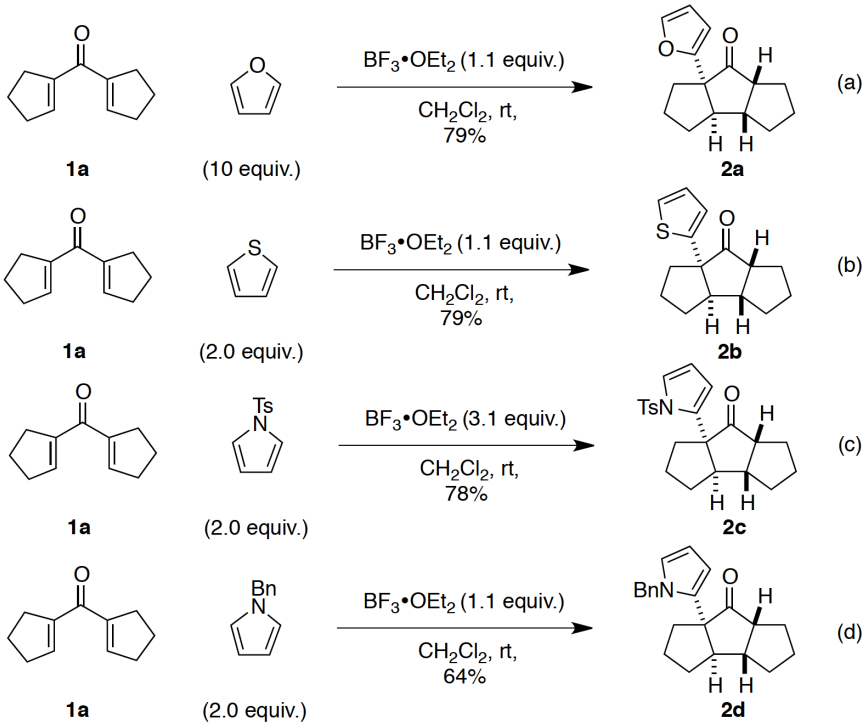
1a **2a** **3a**

Entry	Furan Ratio	Temperature	Time	Concentration	**2a : 3a**[b]
1[a]	2 equiv.	rt	20 min	10 mM	2 : 1
2	2 equiv.	-10 °C	1 h	10 mM	3 : 1
3	2 equiv.	-40 °C	4 h	10 mM	3 : 1
4	1 equiv.	rt	20 min	10 mM	1 : 1
5	5 equiv.	rt	20 min	10 mM	4 : 1
6	10 equiv.	rt	20 min	10 mM	10 : 1
7	2 equiv.	rt	20 min	1 mM	5 : 3
8	2 equiv.	rt	20 min	5 mM	5 : 2
9	2 equiv.	rt	20 min	20 mM	4 : 1
10	2 equiv.	rt	4 h	100 mM	2 : 1

[a] Conditions: BF_3•OEt_2 (1.1 equiv.) was added to a solution of **1a** (0.05 mmol), and furan in CH_2Cl_2. Reaction mixtures were quenched by addition of sat. $NaHCO_3$ (aq), extracted with CH_2Cl_2, dried with $MgSO_4$, filtered, and concentrated. [b] Based on ^{1}H NMR integrations of β-furyl protons in the crude reaction mixture.

Using the optimized conditions (Table 2, entry 6) we were able to favor the formation of α-arylation product **2a** (Scheme 9a), in a synthetically useful yield of 79%. We sought to expand the scope of the reaction to a variety of arenes. When furan was replaced with thiophene, we obtained the arene trapping product **2b** in 79% yield (Scheme 9b), correlations from rOe experiments were used to confirm the *cis-anti-cis* configuration of **2b** (Figure 6). We also found that we were able to reduce the amount of thiophene from 10 equivalents, to 2 equivalents, while observing no traces of a 2:1 adduct. When *N*-tosylpyrrole was used under the standard conditions, the reaction was sluggish and when stirred overnight the

starting material was not consumed. This poor reactivity was thought to be due to the tosyl group interfering with the Lewis acid, and when the amount of BF_3•OEt_2 was increased (3.1 equiv.) the starting dicyclopentenone was rapidly consumed leading to the α-arylation product **2c** in 78% yield (Scheme 9c). In order to avoid the use of superstoichiometric BF_3•OEt_2, we used N-benzylpyrrole as an arene trap; this allowed us to use the standard reaction conditions, yielding the α-arylation product **2d** in good yield (Scheme 9d).



Scheme 9: Heteroarene Trapping.

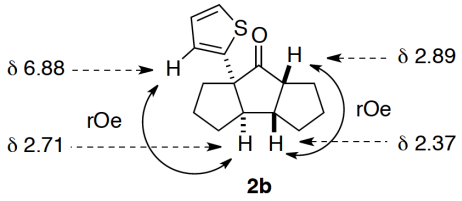
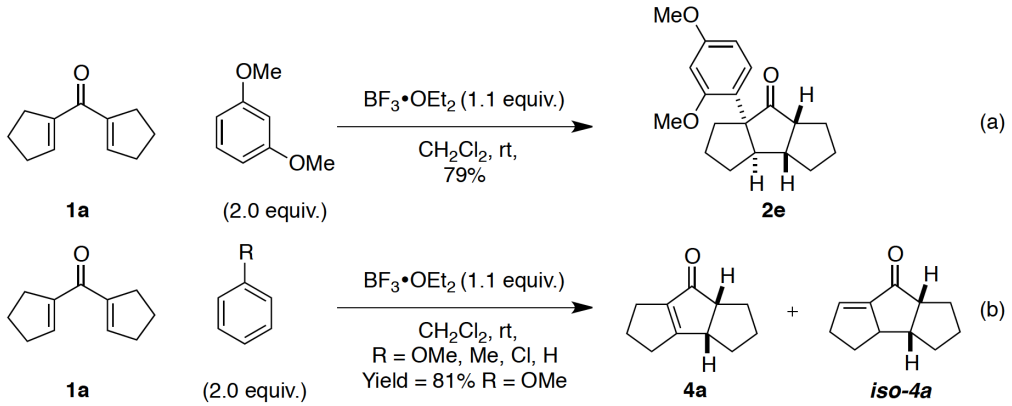


Figure 6: Characteristic rOe Correlations for *cis-anti-cis* Triquinane **2b**.

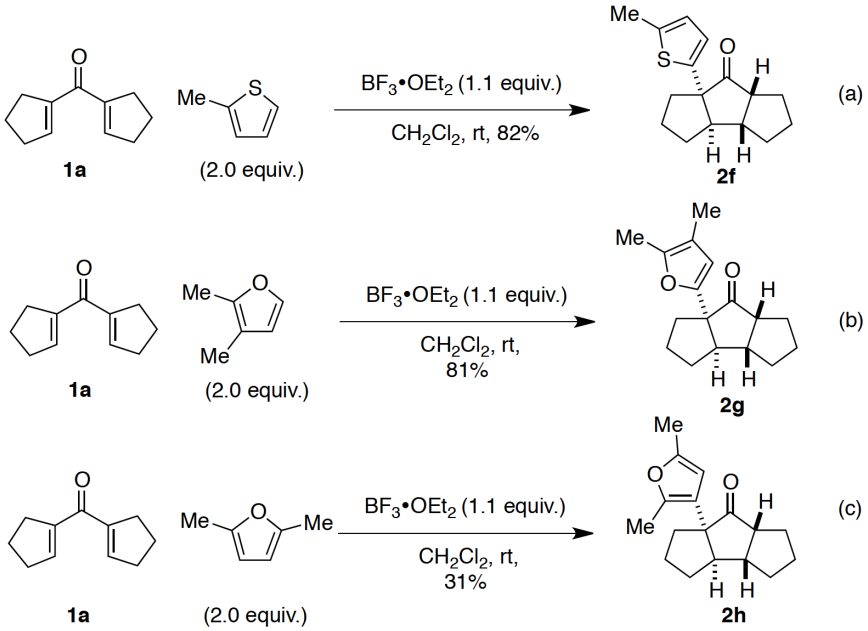
We next explored simple arene nucleophiles for trapping the 2-

oxidocyclopentenyl cation (Scheme 10). 1,3-Dimethoxybenzene proved to be an effective intermolecular trap, giving arene trapped product **2e** in 79% yield. Less electron rich arenes, anisole, toluene, chlorobenzene, and benzene failed to give arene trapped products, instead regioisomers **4a** and ***iso*-4a** of the traditional Nazarov reaction were isolated.



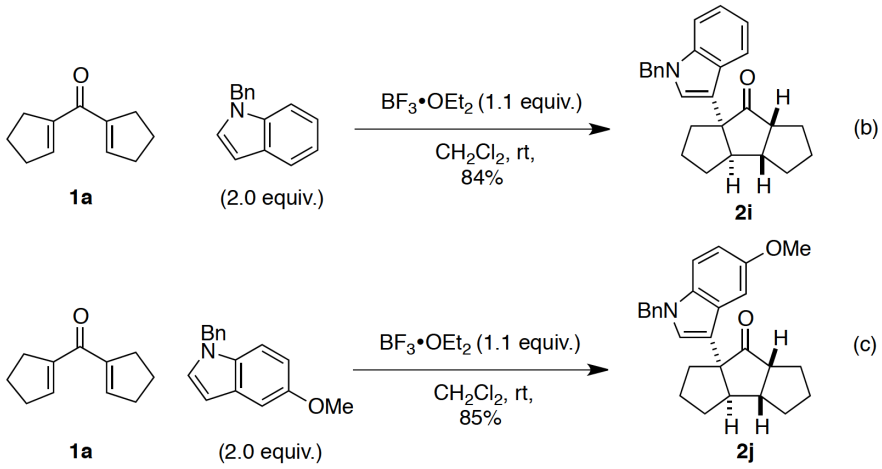
Scheme 10: Electron Rich Arene Trapping.

Given the success of electron rich furan and thiophene trapping the Nazarov oxyallyl cation intermediate we turned our attention to substituted derivatives of these heterocycles. Not surprisingly 2-methylthiophene and 2,3-dimethylfuran successfully underwent the arene trapping reaction giving α-arylated products **2f** and **2g** in good yield (Scheme 11). We were interested to test 2,5-dimethylfuran, considering that the most nucleophilic sites on the furan were blocked by methyl groups; this was a substrate that may be more prone to undergo [4+3] cycloaddition rather than α-arylation. When 2,5-dimethylfuran was subjected to the reaction conditions, the only trapping product observed was α-arylated product **2h**, resulting from reaction at the less reactive 3-position of the furan ring (Scheme 11c).



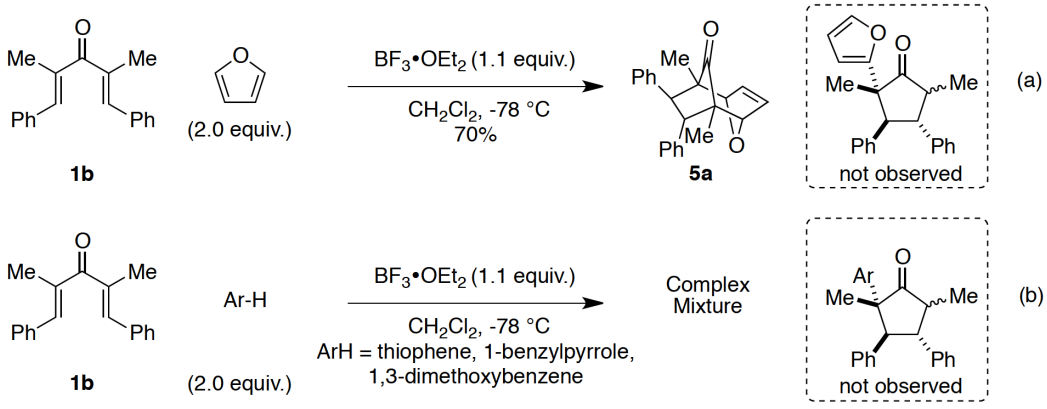
Scheme 11: Substituted Heteroarene Trapping.

We sought to use indoles in our heteroarene trapping protocol, in analogy to Tius' observations (Scheme 6a).[35] When N-protected indoles, 1-benzylindole, and the more electron rich 1-benzyl-5-methoxyindole were subjected to the reaction conditions, indole trapped products **2i** and **2j** were formed in high yield. The indoles selectively reacted at the more nucleophilic 3-position (Scheme 12).



Scheme 12: Indole Trapping.

Given the generality of the arene trapping of dicyclopentenone **1a**, we sought to further understand the reason for this reactivity. The previous investigation by Wang *et al*. into intermolecular [4+3] cycloadditions found that cyclic dienes including furan gave [4+3] cycloadducts with no traces of arene trapping products.[40] We revisited this work, confirming the [4+3] trapping of furan (Scheme 13a), No evidence for the alternative electrophilic aromatic substitution product was seen. We subjected the acyclic divinyl ketone **1b** to the arene trapping conditions using thiophene, 1-benzylpyrrole, and 1,3-dimethoxybenzene, hoping arenes with less 1,3-diene character may be more likely to participate in the α-arylation pathway. In the event, we were unable to observe any products resulting from arene trapping or [4+3] cycloaddition (Scheme 13b).[45] Given the lack of success trapping the oxyallyl cation **II** derived from dienone **1b**, we were forced to rationalize why oxyallyl cation **I** was more able to participate in the arene trapping reaction (Figure 7). One possible reason for the difference in reactivity could be that cation **I** is slow to undergo elimination due to poor conformational mobility. The slow elimination may allow the oxyallyl cation **I** to persist long enough to undergo an otherwise unfavorable electrophilic aromatic substitution.



Scheme 13: Dibenzylidene-3-Pentanone Attempted Arene Trapping.

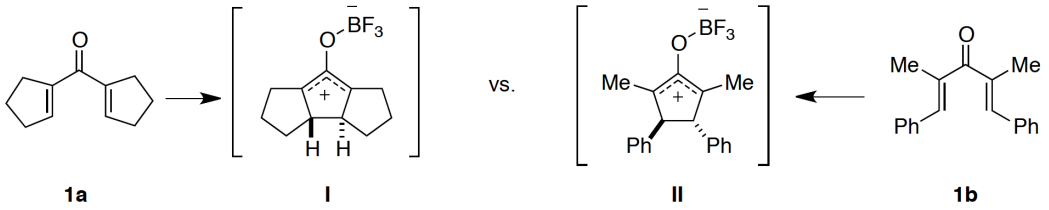
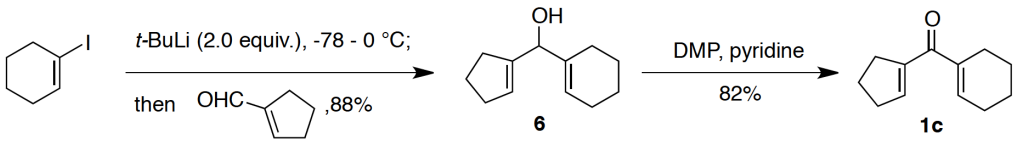


Figure 7: Oxyallyl Cation Comparison.

Since arene trapping was unsuccessful using our standard conditions with dibenzylidine-3-pentanone, we chose to test the higher homologue of dicylopentenyl ketone **1a.** Cyclopentenyl cyclohexenyl ketone **1c** was synthesized from bis(allylic) alcohol **6**, which was derived from 1-iodocyclohexene and 1-cyclopentenecarboxaldehyde (Scheme 14). This unsymmetrical Nazarov substrate was poised to answer several questions about the arene trapping observation (Figure 8). Would the oxyallyl cation **III** derived from **1c** still be competent to undergo arene trapping, or would the increased conformational mobility from the inclusion of a 6-membered ring make arene trapping an uncompetitive pathway? If oxyallyl cation **III** could be successfully trapped, would there be any regioselectivity favoring reaction at the diquinane bridgehead leading to intermediate **IV** or at the hydrindan bridgehead leading to intermediate **V**? Finally, would an increase in conformational mobility lead to erosion of selectivity in the final protonation step leading to a mixture of products or would the *cis-trans-cis* configuration analogous to substrate **1a** be favored?



Scheme 14: Synthesis of Cyclopentenyl Cyclohexenyl Ketone **1c**.

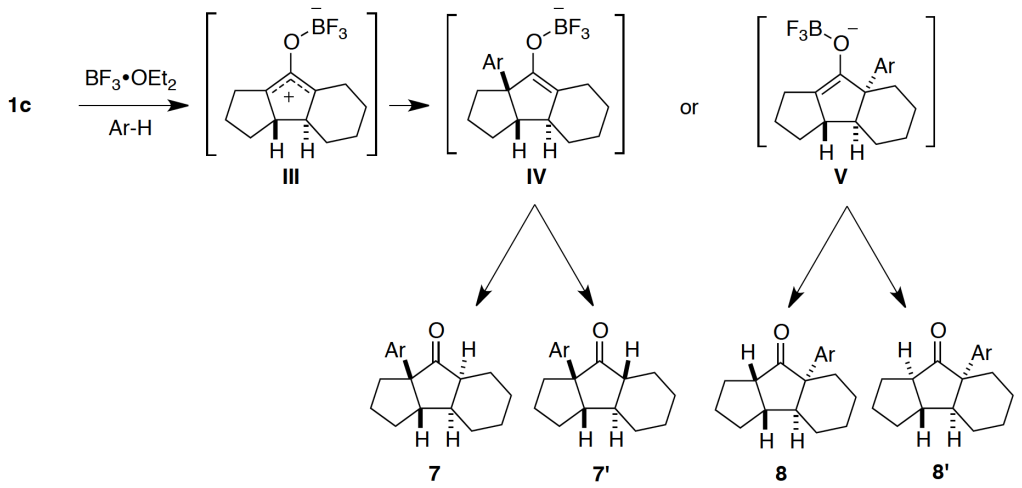
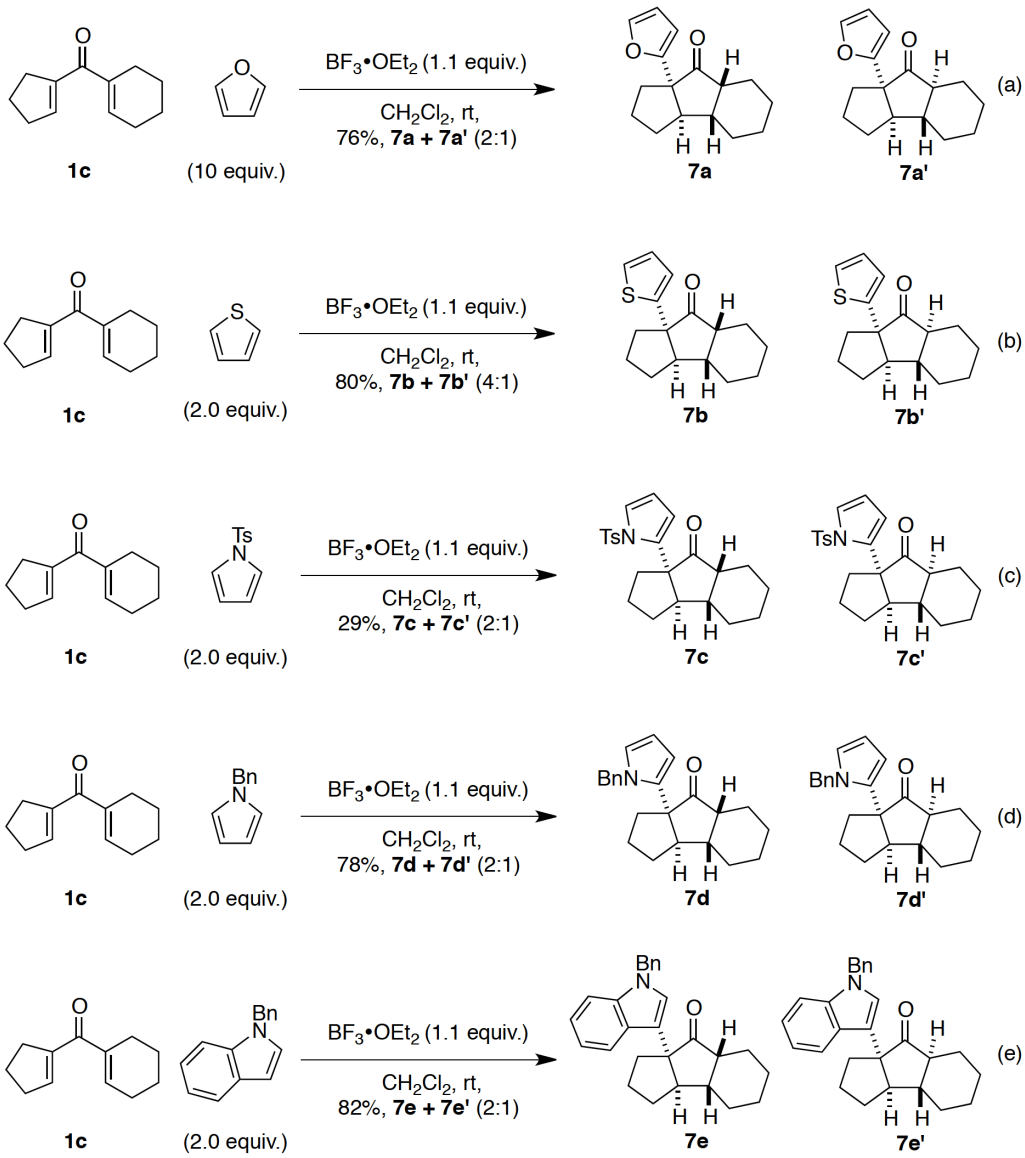


Figure 8: Possible Outcomes of Arene Trapping on Ketone **1c**.

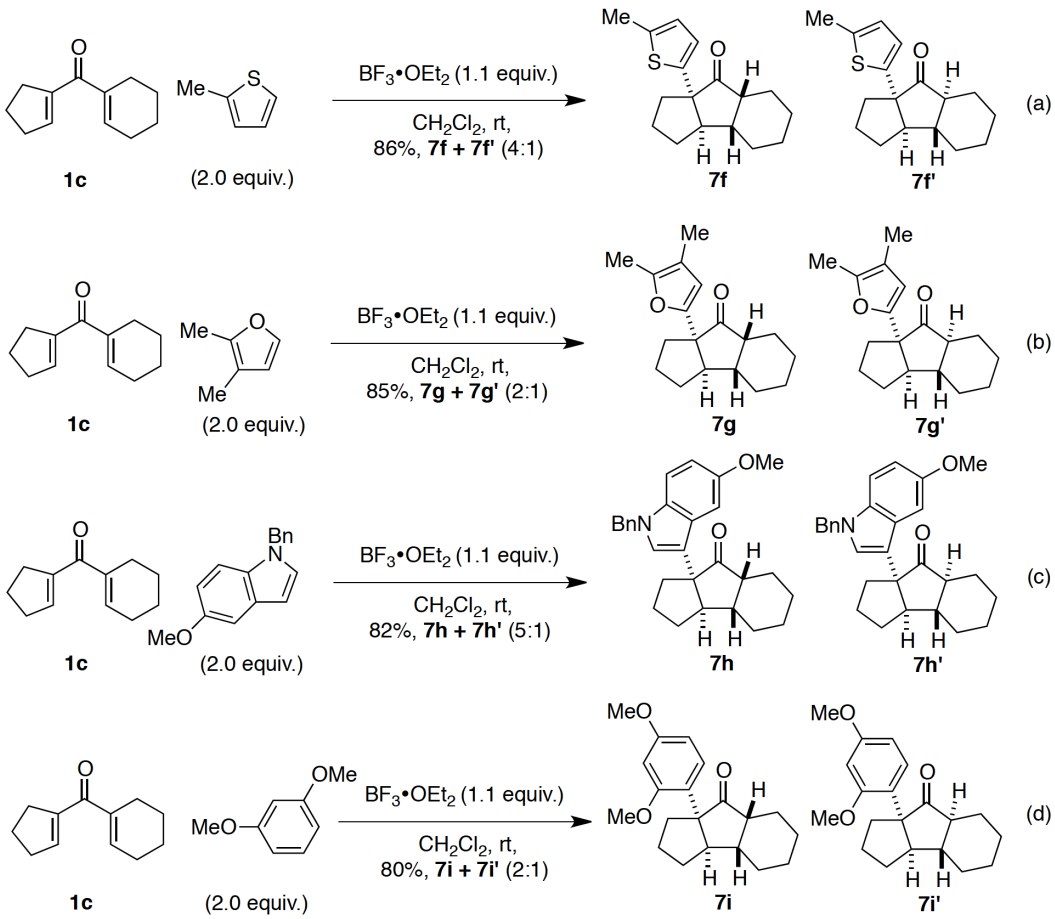
We subjected cyclopentenyl cyclohexenyl ketone **1c** to the optimized conditions using the same series of arenes used with **1a**. α-Arylation products were isolated in high yields (Schemes 15 and 16), with the exception of 2,5-dimethylfuran, for which no trapping products were observed. The α-arylated products were isolated as inseparable mixtures of two products in ratios ranging from 2:1 to 5:1. Two possible sources of the mixtures were suspected. One possibility was the formation of diastereomers with the same regiochemistry such as **7 / 7'** or **8 / 8'**. The mixture of **8** and **8'** was deemed unlikely, as formation of **8'** would require the installation of a highly strained *trans*-diquinane ring-fusion.

Fortunately, careful chromatography allowed us to separate the adducts formed with *N*-benzylpyrrole (**7d** and **7d'**). Characterization using NMR did not allow us to unambiguously determine the regioselectivity of the α-arylation adducts; however, examination of the mass spectral fragmentation revealed an important correlation (Figure 9). Both **7d** and **7d'** displayed the same base peak **VI** in their mass spectra, correlating to loss of a $C_7H_{10}O$ fragment. With the observation of the same *N*-benzylpyrrole containing base peak from both adducts, it can be inferred that both **7d** and **7d'** are arene-substituted at the diquinane bridgehead rather than the hydrindan bridgehead, and thus the mixture of products is inferred to be two diastereomers with the same regiochemistry. This mass

spectral fragmentation was consistent for all α-arylation products derived from dienones **1a** and **1c**.



Scheme 15: Arene Trapping of Unsymmetrical Dieneone.[43]



Scheme 16: Substituted Arene Trapping of Unsymmetrical Dienone.[43]

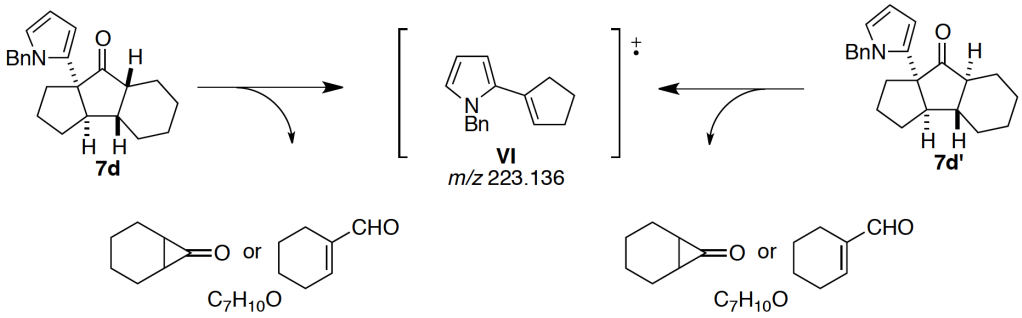


Figure 9: Characteristic Fragmentation of α-Arylated Products.

The observation of apparent diastereomers was presumed to result from low selectivity during protonation of the boron enolate resulting from arene trapping. If this were the case, it might be possible to interconvert **7d** and **7d'** through base-mediated epimerization. Treatment of pure **7d** or **7d'** with DBU resulted in

identical equilibrium mixtures of **7d** or **7d'** (Figure 10), providing further evidence for the structural assignment.

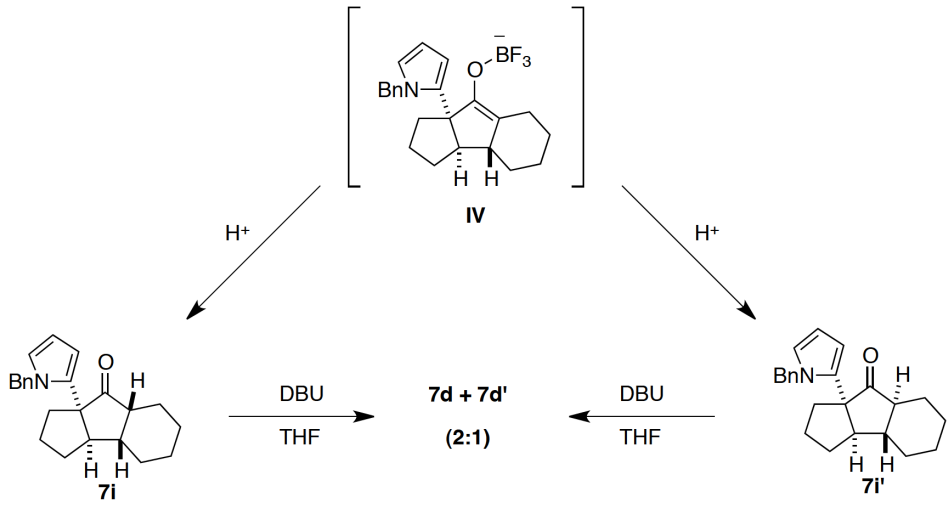


Figure 10: Epimeric Relationship of **7d** and **7d'**

Arene trapped products **7i** and **7i'** were also separable, and 2D NMR experiments were used to establish the *cis* geometry at the hydrindan bridgehead for *cis-trans-cis* major product **7i** (Figure 11). The remaining α-arylated products derived from dienone **1c** were assigned in analogy to this observation.

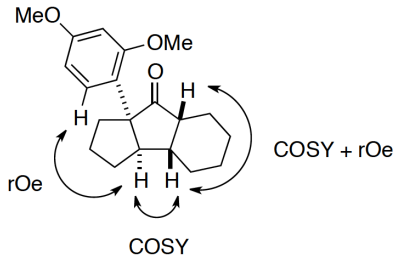
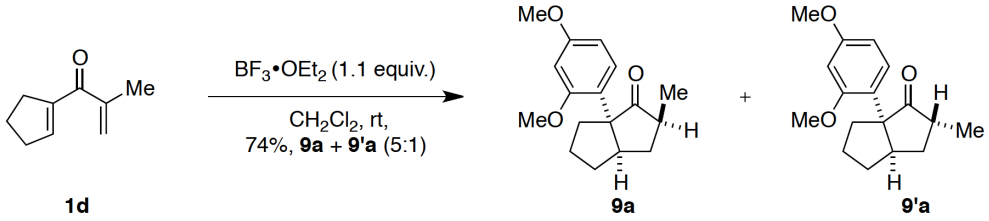


Figure 11: Characteristic NMR Correlations of **7i**.[43]

The arene trapping of dienones **1a** and **1c**, combined with the failure to observe arene trapping under the same conditions with acyclic dienone **1b** suggests the rehybridization of the strained diquinane oxyallyl cation intermediate during arene capture is a driving force of the α-arylation. To test if a bicyclic oxyallyl cation intermediate was sufficient to participate in arene trapping,

cyclopentenyl isopropenyl ketone **1d** was treated with BF_3•OEt_2 and 1,3-dimethoxybenzene. In this experiment the desired aryldiquinane was formed as a 5:1 mixture of isomers (Scheme 17). The major isomer **9** was characterized using vicinal coupling constants, and rOe correlations in the 2D TROESY spectra (Figure 12). Although the minor product **9'** could not be rigorously characterized, it was inferred to be epimeric to **9** at the methyl-susbstituted methine.



Scheme 17: Arene Trapping of Cyclopentenyl Isopropenyl Ketone **1d**.

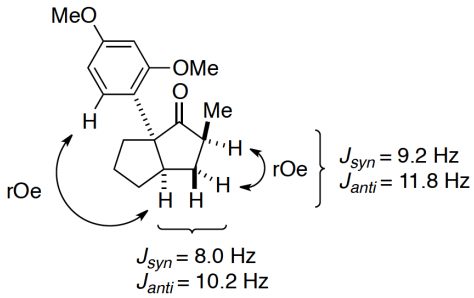


Figure 12: Characterization of Diquinane **9a**.

All of the successful BF_3•OEt_2 mediated intermolecular α-arylation examples we observed occurred exclusively at the diquinane fusion of the oxyallyl cation. Following 4π-conrotatory cyclization, ring strain develops at the diquinane ring junction due to the low conformational mobility in a sp^2 containing five-membered ring. If this were the case, we could expect a discrete cation **VIII** leading to transition state **IX** to be a more realistic representation than the resonance hybrid **VII** with regards to oxyallyl cations derived from cyclopentenyl dienones (Figure 13).

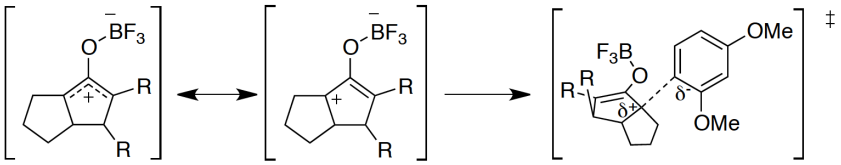


Figure 13: Diquinane Oxyallyl Cation Intermediate.

2.4 Summary

As the earlier studies proved, the oxyallyl cation generated from Nazarov cyclization is able to undergo intramolecular arene trapping with a variety of appropriately substituted dienones.[31,32] In the case of the BF_3•OEt_2 mediated tandem Nazarov cyclization – intermolecular electrophilic aromatic substitution cascade it would appear that a diquinane is essential in creating an oxyallyl cation that is both sufficiently reactive and long lived to undergo the intermolecular trapping process. The failure to trap with methoxybenzene indicates that significant nucleophilicity is required on the part of the arene. For the three successful cyclopentenyl ketone substrates, complete regioselectivity and diastereofacial selectivity was observed in the arene trapping step in all cases.

2.5 Experimental

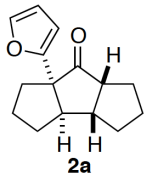
General Information

Reactions were carried out in flame dried glassware under an argon atmosphere. Anhydrous solvents and reagents were transferred using oven dried cannulae or syringes. Solvents were distilled before use: dichloromethane from calcium hydride, tetrahydrofuran and diethyl ether from sodium/benzophenone ketyl. Reactions were monitored with 0.5 mm Kieselgel 60 F254 TLC plates (Merck). Flash chromatography was performed using 230-400 mesh silica gel (Silicycle). Radial chromatography was performed using a Harrison Research Chromatatron Centrifugal Thin Layer Chromatograph Model 7924T. Nuclear

magnetic resonance spectra were recorded at 400 MHz or 500 MHz for ^{1}H NMR and 100 or 125 Hz, for ^{13}C NMR. Coupling constants (*J*) are reported in Hertz (Hz). Chemical shifts are reported on the δ scale (ppm) and spectra are referenced to chloroform (7.26 ppm, ^{1}H; 77.06 ppm, ^{13}C) as an internal standard. Infrared spectra were measured with a Matteson Galaxy Series FT-IR 300 spectrophotometer. Mass spectra were determined on a Kratos MS50 high-resolution mass spectrometer.

Synthesis of 1,4-Dien-3-ones

Dienones **1a, 1b,** and **1d** were synthesized by previously described procedures:
1a and **1b:** Giese, S.; West, F. G. *Tetrahedron* **2000**, *56*, 10221-10228. **1d**: Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003,** *5,* 2747-2750.



2a

Optimized Synthesis of Triquinane 2a. BF_3•OEt_2 (23 μL, 0.16 mmol) was added to a solution of dienone **1a** (24 mg, 0.15 mmol) and furan (110 μL, 1.5 mmol) in CH_2Cl_2 (15 mL) at room temperature. The resulting dark orange mixture was stirred for 30 minutes. The reaction mixture was quenched with sat. $NaHCO_3$(aq) (5 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by flash chromatography gave 23 mg (79%) of **2a** as a colorless oil.

R_f 0.47 (4:1 Hexanes:EtOAc);

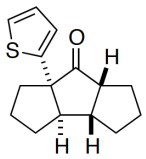
IR (film) 2952, 2868, 1737, 1583, 1503, 1470, 1449 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (dd, 1H, *J* = 1.8, 0.5 Hz), 6.26 (dd, 1H, *J* = 3.2, 1.8 Hz), 6.10 (dd, 1H, *J* = 3.2, 0.5 Hz), 2.84 (app. td, 1H, *J* = 9.2, 4.9 Hz), 2.66 (app. dt, 1H, *J* = 7.9, 3.3 Hz), 2.32 (m,1H), 2.00 – 2.16 (m, 3H), 1.83 – 1.92

(m, 3H), 1.76 (m, 1H), 1.63 – 1.71 (m, 2H), 1.47 – 1.59 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 221.9, 155.9, 141.7, 110.1, 105.5, 62.7, 53.1, 52.3, 47.4, 37.9, 35.1, 34.3, 30.0, 25.8, 25.8;

HRMS calc'd for $C_{15}H_{18}O_2$ (M^+) 230.1307; found 230.1308 (45%), 134.0732 [M – C_6H_8O]$^+$ (100%).



2b

Optimized synthesis of 2b. BF_3•OEt_2 (23 μL, 0.16 mmol) was added to the solution of dienone **1a** (24 mg, 0.15 mmol) and thiophene (12 μL, 0.15 mmol) in CH_2Cl_2 (15 mL) at room temperature. The resulting dark orange reaction mixture was agitated for 30 minutes. The reaction mixture was worked up with sat. $NaHCO_3$(aq) (5 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by flash chromatography gave 29 mg (79%) of **2b** as a pale yellow oil.

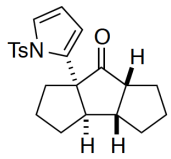
R_f 0.49 (4:1 Hexanes:EtOAc);

IR (film) 2951, 2866, 1734, 1469, 1448 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (dd, 1H, J = 5.1, 1.3 Hz), 6.91 (dd, 1H, J = 5.1, 3.6 Hz), 6.88 (dd, 1H, J = 3.6, 1.3 Hz), 2.89 (app. td, 1H, J = 9.2, 4.2 Hz), 2.71 (app. dt, 1H, J = 7.8, 3.7 Hz), 2.37 (app. tt, 1H, J = 8.2, 4.2 Hz), 2.23 (m, 1H), 2.18 (app. td, 1H, J = 7.8, 4.4 Hz), 2.04 (app. dt, 1H, J = 13.5, 6.9 Hz), 1.83 – 1.92 (m, 3H), 1.80 (m, 1H), 1.67 – 1.78 (m, 2H), 1.48 – 1.56 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 222.2, 147.6, 126.6, 123.7, 123.5, 63.9, 55.3, 52.9, 52.8, 46.5, 42.6, 35.1, 34.5, 30.4, 25.8;

HRMS calc'd for $C_{15}H_{18}OS$ (M^+) 246.1078; found 246.1081 (47%), 150.0500 [M – C_6H_8O]$^+$ (100%).



2c

Optimized synthesis of 2c. BF_3•OEt_2 (70 μL, 0.48 mmol) was added to the solution of dienone **1a** (24 mg, 0.15 mmol) and *N*-tosylpyrrole (66 mg, 0.30 mmol) in CH_2Cl_2 (15 mL) at room temperature. The resulting dark orange reaction mixture was agitated for 30 minutes. The reaction mixture was worked up with sat. $NaHCO_3$(aq) (5 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 ml). The combined organics were dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography gave 30 mg (78%) of **2c** as a pale yellow oil.

R_f 0.27 (4:1 Hexanes:EtOAc);

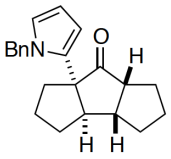
IR (film) *v* 2952, 2868, 1730, 1597, 1473, 1450, 1370 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, 2H, *J* = 8.4 Hz), 7.28 (dd, 2H, *J* = 8.4, 0.7 Hz),

7.07 (dd, 1H, *J* = 3.3, 2.2 Hz), 6.97 (dd, 1H, *J* = 2.2, 1.7 Hz), 6.25 (dd, 1H, *J* = 3.3, 1.7 Hz), 2.80 (app. td, 1H, *J* = 8.9, 4.2 Hz), 2.46 (app. q, 1H, *J* = 3.8 Hz), 2.40 (s, 3H), 2.33 (app. tt, 1H, *J* = 8.4, 4.2 Hz), 2.04 – 2.13 (m, 2H), 1.62 – 1.84 (m, 7H), 1.46 (m, 1H), 1.24 – 1.38 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 223.7, 144.7, 136.0, 131.8, 129.8, 126.7, 121.2, 116.7, 113.1, 61.0, 53.2, 52.7, 46.1, 40.8, 34.9, 34.3, 30.2, 25.7, 25.6, 21.5;

HRMS calc'd for $C_{22}H_{25}O_3NS$ (M^+) 383.1555; found 383.1339 (63%), 287.0979 $[M - C_6H_8O]^+$ (100%).



2d

Synthesis of 2d. This ketone was prepared from **1a** using the procedure described above for **2b**. The product was obtained as a pale yellow oil 20 mg (64%).

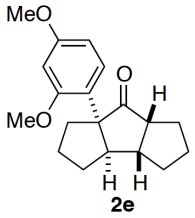
R_f 0.30 (4:1 Hexanes:EtOAc);

IR (film) 3100, 3062, 3029, 2952, 2866, 1730, 1605, 1469, 1477, 1452, 1420, 1329, 1298 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.25 (m, 1H), 7.05 (d, 2H, J = 7.4 Hz), 6.51 (dd, 1H, J = 2.7, 1.9 Hz), 6.07 (dd, 1H, J = 3.5, 3.0 Hz), 6.00 (dd, 1H, J = 3.6, 1.8 Hz), 5.26 (d, 1H, J_{AB} = 16.2 Hz), 5.21 (d, 1H, J_{AB} = 16.2 Hz), 2.91 (ddd, 1H, J = 9.6, 4.9, 4.9 Hz), 2.66 (m, 1H), 2.35 (dddd, 1H, J = 9.0, 9.0, 4.5, 4.5 Hz), 2.13 (m, 1H), 2.04 (m, 2H), 1.84 (m, 3H), 1.74 (m, 3H), 1.57 (m, 2H), 1.46 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 222.0, 139.2, 132.9, 128.6, 127.2, 126.8, 123.7, 107.0, 107.0, 62.9, 53.6, 52.3, 51.9, 45.4, 37.9, 34.1, 33.4, 30.3, 25.8, 25.1;

HRMS calc'd for $C_{22}H_{25}NO$ (M^+) 319.1936; found 319.1932 (68%), 223.1361 [M-C_6H_8O]$^+$ (100%).



2e

Synthesis of 2e. This ketone was prepared from **1a** using the procedure described above for **2b**. The product was obtained as a pale yellow oil 23 mg (78%).

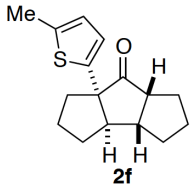
R_f 0.22 (4:1 Hexanes:EtOAc);

IR (film) 2951, 2867, 2836, 1734, 1612, 1584, 1506, 1466, 1208 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, 1H, J = 8.2 Hz), 6.47 (s, 1H), 6.46 (dd, 1H, J =8.2, 2.6 Hz), 3.79 (d, 3H, J = 0.7 Hz), 3.71 (d, 3H, J = 0.7 Hz), 3.05 (ddd, 1H, J = 11.0, 8.3, 4.1 Hz), 2.37 (m, 1H), 2.32 (m, 1H), 2.08 - 1.82 (m, 5H), 1.76 - 1.65 (m, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 222.3, 159.8, 157.2, 128.0, 122.4, 104.0, 99.6, 65.5, 55.7, 55.3, 54.9, 51.6, 45.8, 33.5, 32.8, 30.9, 30.4, 25.1, 23.9;

HRMS calc'd for $C_{19}H_{24}O_3$ (M^+) 300.1726; found 300.1728 (53%), 204.1159 [M – C_6H_8O]$^+$ (100%).



2f

Synthesis of 2f. This ketone was prepared from **1a** using the procedure described above for **2b**. The product was obtained as a pale yellow oil 21 mg (81%).

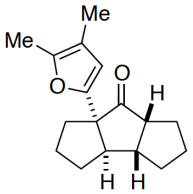
R_f 0.48 (4:1 Hexanes:EtOAc);

IR (film) 3060, 2950, 2866, 1734, 1653, 1552, 1470, 1448, 1230, cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, 1H, *J* = 3.6 Hz), 6.58 (m, 1H), 2.90 (ddd, 1H, *J* = 8.7, 5.6, 5.6 Hz), 2.69 (ddd, 1H, *J* = 7.3, 3.3, 3.3 Hz), 2.44 (s, 3H), 2.38 (dddd, 1H, *J* = 8.1, 8.1, 4.3, 4.3 Hz), 2.19 (m, 2H), 2.04 (ddd, 1H, *J* = 13.6, 7.0, 7.0 Hz), 1.89 (m, 3H), 1.74 (m, 3H), 1.55 (m, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 222.7, 145.0, 138.5, 124.9, 123.6, 64.3, 55.3, 53.1, 46.7, 42.4, 35.2, 34.2, 30.6, 26.1, 26.0, 15.5;

HRMS calc'd for $C_{16}H_{20}OS$ (M^+) 260.1235; found 260.1236 (44%), 164.0660 [M-C_6H_8O]$^+$ (100%).



2g

Synthesis of 2g. This ketone was prepared from **1a** using the procedure described above for **2b**. The product was obtained as a pale yellow oil 21 mg (81%).

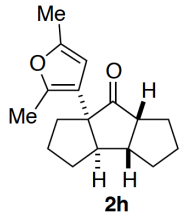
R_f 0.56 (4:1 Hexanes:EtOAc);

IR (film) 2950, 2868, 1736, 1679, 1612, 1448, cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (s, 1H), 2.86 (ddd, 1H, *J* = 9.4, 9.4, 4.6 Hz), 2.67 (ddd, 1H, *J* = 7.3, 3.3, 3.3 Hz), 2.33 (m, 1H), 2.16 (s, 3H), 2.07 (m, 3H), 1.93 (m, 3H), 1.90 (s, 3H), 1.77 (m, 1H), 1.68 (m, 2H), 1.58 (m, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 222.7, 153.4, 146.6, 114.3, 108.9, 62.8, 53.2, 52.4, 46.5, 37.7, 35.1, 34.4, 30.2, 25.9, 25.8, 11.4, 9.9;

HRMS calc'd for $C_{17}H_{22}O_2$ (M^+) 258.1620; found 258.1615 (40%), 162.1045 [M-C_6H_8O]$^+$ (100%).



2h

Synthesis of 2h. This ketone was prepared from **1a** using the procedure described above for **2b**. The product was obtained as a pale yellow oil 16 mg (31%).

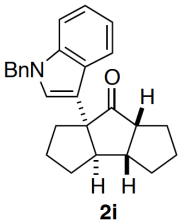
R_f 0.56 (4:1 Hexanes:EtOAc);

IR (film) 2950, 2868, 1732, 1679, 1623, 1577, 1450, cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (s, 1H), 2.89 (app. q, 1H, J = 8.2 Hz), 2.46 (m, 1H), 2.34 (app. tt, 1H, J = 8.7, 4.4 Hz), 2.26 (s, 3H), 2.21 (s, 3H), 2.15 (m, 1H), 2.00 (m, 2H), 1.87 (m, 3H), 1.76 (m, 3H), 1.58 (m, 1H), 1.52 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 223.6, 148.6, 146.0, 121.5, 107.1, 61.1, 54.1, 52.7, 46.0, 39.4, 34.4, 34.3, 30.4, 26.0, 25.5, 14.0, 13.6;

HRMS calc'd for (M^+) $C_{17}H_{22}O_2$ 258.1620; found 258.1615 (56%), 162.1045 [M – C_6H_8O]$^+$ (100%).



2i

Synthesis of 2i. This ketone was prepared from **1a** using the procedure described above for **2b**. The product was obtained as a pale yellow oil 31 mg (84%).

R_f 0.30 (10:1 Hexanes:EtOAc);

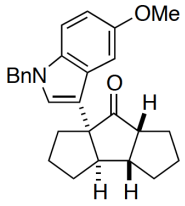
IR (film) 3087, 3061, 3031, 2949, 2865, 1728, 1612, 1542, 1496, 1467, 1453, 1371, 1355, 1335, cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, 1H, J = 7.9 Hz), 7.28 (m, 4H), 7.17 (ddd,

1H, J = 4.2, 6.9, 8.1 Hz), 7.12 (m, 1H), 7.08 (m, 2H), 6.88 (s, 1H), 5.29 (d, 1H, J_{AB} = 16.2 Hz), 5.26 (d, 1H, J_{AB} = 16.2 Hz), 2.91 (m, 2H), 2.46 (dddd, 1H, J = 8.7, 8.7, 4.4, 4.4 Hz), 2.28 (m, 3H), 1.82 (m, 6H), 1.47 (m, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 225.4, 137.9, 137.8, 128.9, 127.7, 126.9, 126.6, 125.8, 122.0, 121.2, 119.2, 117.3, 110.2, 62.2, 53.2, 52.8, 50.2, 46.7, 39.7, 35.4, 34.8, 31.1, 26.2, 26.1;

HRMS calc'd for $C_{26}H_{27}NO$ (M^+) 369.2093; found 369.2096 (50%), 273.1518 [M-C_6H_8O]$^+$ (100%).



2j

Synthesis of 2j. This ketone was prepared from **1a** using the procedure described above for **2b**. The product was obtained as a brown oil 34 mg (85%).

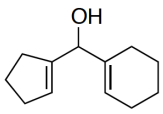
R_f 0.27 (10:1 Hexanes:EtOAc);

IR (film) 3063, 3030, 2948, 2866, 1228, 1621, 1575, 1487, 1451, 1355, 1343, 1288, 1258, 1222, 1180, 1043, 1030, 793, 731, 705 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 3H), 7.13 (m, 2H), 7.07 (m, 2H), 6.87 (s, 1H), 6.84 (dd, 1H, J = 8.9, 2.4 Hz), 5.53 (br s, 2H), 3.88 (s, 3H), 2.93 (ddd, 1H, J = 9.2, 9.2, 5.1 Hz), 2.85 (ddd, 1H, J = 7.3, 3.2, 3.2 Hz), 2.46 (dddd, 1H, J = 8.5, 8.5, 4.2, 4.2 Hz), 2.25 (m, 3H), 1.85 (m, 6H), 1.51 (m, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 225.0, 153.5, 137.7, 133.1, 128.7, 127.5, 126.7, 126.6, 126.3, 116.4, 111.7, 110.7, 103.3, 62.0, 55,9, 52.9, 52.5, 50.2, 46.3, 38.9, 35.0, 34.5, 31.9, 26.2, 25.7;

HRMS calc'd for $C_{27}H_{29}NO_2$ (M^+) 399.2198; found 399.2196 (28%), 303.1623 [M-C_6H_8O]$^+$ (69%), 91.0548 [M-$C_{20}H_{22}NO_2$]$^+$ (100%).



6

(Cyclohexen-1-yl)(cyclopenten-1-yl)methanol 6. *t*-BuLi (4.5 mL, 7.6 mmol, 1.7 M in pentane) was added dropwise to a stirred solution of 1-iodocyclohexene (803 mg, 3.86 mmol) in ethyl ether (5 mL) at –78 °C. The reaction was warmed to 0 °C after 30 min. After 1h, the reaction was cooled to –78 °C and a solution of 1-cyclopentene-1-carboxaldehyde (282 mg, 2.94 mmol) in Et_2O (5 mL) was added via cannula. The reaction was warmed to rt after 30 min. After 1h H_2O (10 mL) was added and the layers were separated. The aqueous layer was neutralized with 1M HCl and extracted with Et_2O (3 x 5 mL). The combined organic phase was washed with H_2O (2 x 5 mL), brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography gave 480 mg (88%) of the desired alcohol as a yellow oil.

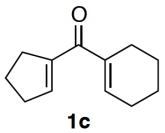
R_f 0.35 (4:1 Hex:EtOAc);

IR (film) 3371 (br), 3049, 2928, 2845, 1635, 1437 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 5.72 (m, 1H), 5.63 (m, 1H), 2.57 (br s, 1H), 2.32–2.38 (m, 2H), 2.15– 2.21 (m, 2H), 1.98 – 2.04 (m, 2H), 1.75 – 1.92 (m, 5H), 1.49 – 1.64 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 138.3, 125.3, 123.3, 75.9, 32.3, 32.0, 25.0, 23.8, 23.4, 22.7, 22.6;

HRMS calc'd for $C_{12}H_{18}O$ (M^+) 178.1359; found 178.1358.



1c

Cyclohexenyl cylopentenyl ketone 1c. To a stirred solution of Dess-Martin periodinane (889 mg, 2.20 mmol) in CH_2Cl_2 (10 mL). A solution of **6** (357 mg, 2.00 mmol) in CH_2Cl_2 (5 mL) was added *via* cannula and allowed to stir for 30 min. The reaction was filtered through a plug of silica gel and eluted with hexanes/EtOAc (4:1 v/v), concentrated. Further purification by flash chromatography gave 268 mg (76%) of the dienone as a colourless oil.

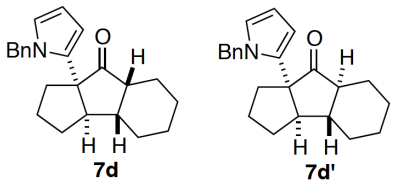
R_f 0.54 (4:1 Hexanes:EtOAc);

IR (film) *v* 3044, 2934, 2859, 1735, 1631, 1434 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 6.64 (tt, 1H, *J* = 3.9, 1.9 Hz), 6.37 (tt, 1H, *J* = 2.6, 1.8 Hz), 2.63 – 2.60 (m, 2H), 2.60 – 2.56 (m, 2H), 2.36 – 2.30 (m, 2H), 2.28 – 2.22 (m, 2H), 1.97 – 1.89 (m, 2H), 1.73 – 1.60 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.9, 143.9, 142.3, 139.44, 139.36, 33.8, 32.2, 25.8, 23.9, 22.7, 22.0, 21.7;

HRMS calc'd for $C_{12}H_{16}O$ (M^+) 176.1201; found 230.1203.



7d **7d'**

Synthesis of 7d and 7'd. These products ware prepared from **1c** using the procedure described above for **2b**. The mixture of diastereomers (**7d : 7d'** 2 : 1) was obtained as a pale yellow oil 58 mg (78%) The diastereomers were separated using radial chromatography.

R_f 0.30 (4 : 1 Hexanes : EtOAc).

7d.

IR (film) 3108, 3037, 2997, 2930, 2861, 1727, 1686, 1498, 1477, 1466, 1457, 1447 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.25 (m, 1H), 7.06 (m, 2H), 6.52 (dd, 1H, *J* = 2.3, 2.3 Hz), 6.07 (d, 2H, *J* = 2.3 Hz), 5.51 (d, 1H, *J* = 16.1 Hz), 5.43 (d, 1H, *J* = 16.1 Hz), 3.07 (ddd, 1H, *J* = 8.3, 4.9, 4.4 Hz), 2.57 (dddd, 1H, *J* = 6.5, 6.5, 6.5, 6.5 Hz), 2.07 (m, 2H), 1.98 (m, 2H), 1.83 (m, 1H), 1.65 (m, 4H), 1.52 (m, 2H), 1.34 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 219.3. 139.7, 134.7, 128.5, 127.0, 126.7, 123.8, 106.8, 106.6, 59.6, 52.2, 50.6, 48.9, 39.3, 39.1, 32.5, 28.3, 26.6, 23.7, 23.4, 23.1;

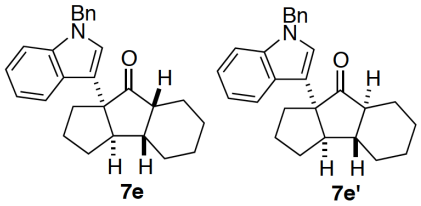
HRMS calc'd for $C_{23}H_{27}NO$ (M^+) 333.2093; found 333.2093 (40%), 223.1364 [m-$C_7H_{10}O$]$^+$ (100%).

7d'

IR (film) 3063, 3030, 2930, 2856, 1733, 1605, 1496, 1476, 1450 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.24 (m, 1H), 7.04 (m, 2H), 6.50 (dd, 1H, *J* = 2.8, 1.8 Hz), 6.10 (dd, 1H, *J* = 3.7, 1.9 Hz), 6.07 (dd, 1H, *J* = 3.7, 2.8 Hz), 5.53 (d, 1H, *J* = 16.1 Hz), 5.28 (d, 1H, *J* = 16.1 Hz), 2.85 (dd, 1H, *J* = 10.1, 7.2 Hz), 2.39 (m, 1H), 2.23 (ddd, 1H, *J* = 14.0, 10.8, 3.4 Hz), 2.11 (m, 1H), 1.91 (m, 1H), 1.81 (m, 2H), 1.68 (m, 4H), 1.47 (m, 1H), 1.16 (m, 4H), 0.90 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.6, 139.4, 134.8, 128.6, 127.1, 126.9, 124.2, 107.0, 106.4, 60.3, 52.4, 52.2, 51.5, 43.4, 35.4, 32.1, 29.7, 26.2, 26.0, 25.2, 25.0; HRMS calc for $C_{23}H_{27}NO$ (M^+) 333.2093; found 333.2093 (40%), 223.1362 [M-$C_7H_{10}O$]$^+$ (100%).



7e **7e'**

Synthesis of 7e and 7e' These products ware prepared from **1c** using the procedure described above for **2b**. The mixture of distereomers (**7e : 7e'** 2 : 1) was obtained as a pale yellow oil 62 mg (82%) The major diastereomer was separated using radial chromatography, while the minor diastereomer was enriched to (**7e : 7e'** 3 : 5).

R_f 0.30 (10:1 Hexanes:EtOAc);

IR (film) *v* 3062, 3031, 2931, 2857, 1730, 1611, 1496, 1480, 1466, 1453, 1356, 1335 cm^{-1};

7e.

^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, 1H, *J* = 8.0 Hz), 7.26 (m, 4H), 7.16 (ddd, 1H, *J* = 7.0, 7.0, 1.2 Hz), 7.11 (ddd, 1H, *J* = 7.0, 7.0, 1.2 Hz), 7.07 (m, 2H), 7.00 (s, 1H), 5.29 (d, 1H, J_{AB} = 16.2 Hz), 5.24 (d, 1H, J_{AB} = 16.2 Hz), 3.03, (ddd, 1H, *J* = 9.3, 3.6, 3.6 Hz), 2.56 (ddd, 1H, *J* = 6.3, 6.3, 6.3 Hz), 2.39 (dddd, 1H, *J* = 13.0, 9.1, 9.1, 7.8 Hz), 2.32 (ddd, 1H, *J* = 13.1, 9.4, 7.1 Hz), 2.21 (ddd, 1H, *J* = 11.6, 6.8, 4.6 Hz), 2.10, (m, 1H), 2.04 (dddd, 1H, *J* = 13.8, 4.6, 4.6, 4.6 Hz), 1.86 (m,

1H), 1.76 (ddd, 1H, J = 11.6, 7.7, 4.2 Hz), 1.63 (m, 2H), 1.50 (dddd, 1H, J = 17.4, 10.7, 6.1, 4.1 Hz), 1.42 (m, 2H), 1.17 (m, 1H), 1.09 (m, 2H);

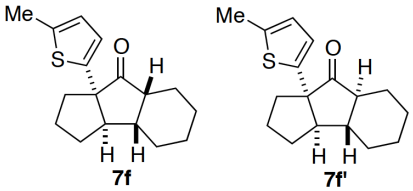
^{13}C NMR (125 MHz, $CDCl_3$) δ 222.9, 138.0, 137.9, 129.0, 127.8, 126.9, 126.8, 125.9, 122.0, 121.4, 119.2, 118.8, 110.3, 59.7, 50.4, 50.3, 49.4, 41.6, 41.4, 34.3, 29.9, 27.5, 24.3, 23.8, 23.8

7e'.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, 1H, J = 8.0 Hz), 7.33-7.21 (m, 4H), 7.16 (m, 1H), 7.11 (m, 2H), 7.07 (m, 1H), 6.92 (s, 1H), 5.29 (d, 1H, J_{AB} = 16.2), 5.24 (d, 1H, J_{AB} = 16.2 Hz), 2.78 (dd, 1H, J = 9.7, 7.6 Hz), 2.56 (m, 1H), 2.23 (m, 1H), 2.11 (m, 1H), 2.06-1.95 (m, 1H), 1.89-1.72 (m, 4H), 1.54-1.37 (m, 2H), 1.29 (m, 1H), 1.25-1.03 (m, 5H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.9, 137.9, 137.8, 128.0, 127.9, 127.0, 126.7, 125.0, 122.3, 121.7, 119.6, 119.4, 110.2, 60.3, 52.9, 51.6, 50.3, 45.2, 36.6, 32.4, 31.2, 26.7, 26.1, 25.6, 25.5;

HRMS calc'd for $C_{27}H_{29}NO$ (M^+) 383.2249; found 383.2247 (82%), 273.1525 [M-$C_7H_{10}O$]$^+$ (100%).



Synthesis of 7f and 7f' These products ware prepared from **1c** using the procedure described above for **2b**. The inseparable mixture of diastereomers (**7f : 7f'** 2 : 1) was obtained as a pale yellow oil 62 mg (82%)

R_f 0.48 (4:1 Hexanes:EtOAc);

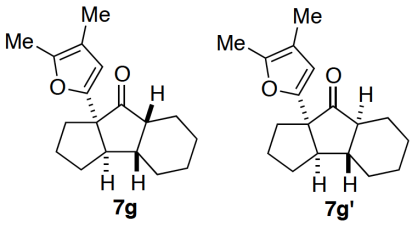
IR (film) 3059, 2930, 2857, 1739, 1551, 1448, cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (d, 1H, J = 3.5 Hz), 6.65 (d, 0.5H, J = 3.5 Hz), 6.57 (m, 1.4H), 2.82 (ddd, 1H, J = 9.0, 4.6, 4.6 Hz), 2.61 (m, 1.6H), 2.45 (d, 3H, J = 1.1 Hz), 2.43 (d, 1.5H, J = 1.1 Hz), 2.37 (ddd, 0.6H, J = 12.2, 7.8, 4.0 Hz), 2.18 (m, 2.2H), 2.04 (m, 3.3H), 1.87 (m, 3.4H), 1.71 (m, 4.6H), 1.52 (m, 1.6H), 1.39 (m, 1H), 1.24 (m, 4.6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 219.0, 215.1, 146.1(two overlapping signals), 138.1, 138.0, 124.9, 124.5, 123.0, 122.7, 62.3, 61.3, 54.5, 53.3, 52.8, 47.9, 44.5, 43.5, 40.0, 38.0, 33.1, 31.8, 30.4, 28.9, 26.8, 26.3, 25.7, 25.3, 25.2, 23.4, 23.3, 23.2, 15.2, 15.2;

HRMS calc'd for $C_{17}H_{22}OS$ (M^+) 274.1391; found 274.1390 (38%), 164.0657[M-$C_7H_{10}O$]$^+$ (100%);

Anal. Calc. for $C_{17}H_{22}OS$: C, 74.40; H, 8.08, S, 11.68. Found: C, 74.48; H, 8.42; S, 11.81.



Synthesis of 7g and 7g' These products ware prepared from **1c** using the procedure described above for **2b**. The inseparable mixture of diastereomers (**7g : 7g'** 2 : 1) was obtained as a pale yellow oil 42 mg (85%).

R_f 0.56 (4:1 Hexanes:EtOAc);

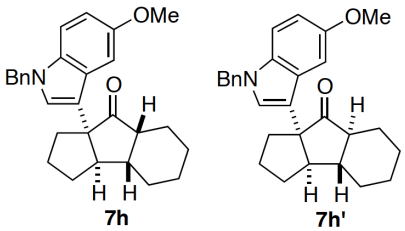
IR (film) 2930, 2858, 1741, 1640, 1561, 1448, cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (s, 1H), 5.84 (s, 0.5H), 2.72 (ddd, 1H, *J* = 8.9, 4.8, 4.8 Hz), 2.59 (ddd, 1H, *J* = 6.1, 6.1, 6.1 Hz), 2.54 (dd, 0.5H, *J* = 10.2, 6.4 Hz), 2.17 (m, 1.9H), 2.15 (s, 3.3H), 2.13 (2, 1.7H), 2.09 (m, 1.3H), 1.97 (m, 2.5H), 1.88 (s, 3.6H), 1.86 (s, 2.0H), 1.72 (m, 6.4H), 1.54 (m, 4H), 1.39 (m, 1H), 1.20 (m, 5.7H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.6, 215.2, 153.7, 153.3, 146.6, 146.3, 114.4, 114.2, 108.6, 108.0, 60.9, 60.0, 54.1, 52.1, 50.5, 47.7, 44.0, 39.8, 38.7, 33.6, 33.3, 31.8, 30.1, 28.8, 26.9, 26.3, 25.4, 25.3, 25.2, 23.6, 23.3, 22.9, 11.4, 11.4, 9.9, 9.8;

HRMS calc'd for $C_{18}H_{24}O_2$ (M^+) 272.1776; found 272.1777 (40%), 162.1043 [M-$C_7H_{10}O$]$^+$ (100%).

Anal. Calc. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88 Found: C, 79.23; H, 8.48;



Synthesis of 7h and 7h' These products ware prepared from **1c** using the procedure described above for **2b**. The inseparable mixture of diastereomers (**7h : 7h'** 5 : 1) was obtained as a pale yellow oil 68 mg (82%).

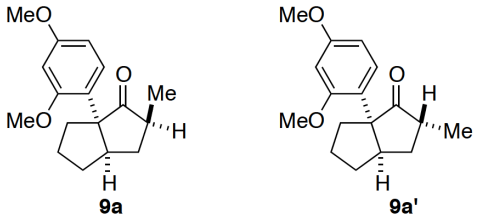
R_f 0.32 (10:1 Hexanes:EtOAc);

IR (film) 3063, 3030, 2933, 2857, 1731, 1621, 1575, 1486, 1450, cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, 0.2H, *J* = 2.4 Hz), 7.34 (d, 1H, *J* = 2.4 Hz), 7.28 (m, 3.3H), 7.13 (d, 1H, *J* = 9.0 Hz), 7.08 (m, 2.4 Hz), 7.00 (s, 1H), 6.93 (s, 2H), 6.85 (m, 1.2H), 5.26 (d, 1H, J = 16.2Hz) 5.21 (d, 1.4H, J = 16.2 Hz), 3.91 (s, 0.6H), 3.90 (s, 3H), 3.03 (ddd, 1H, *J* = 9.0, 3.6, 3.6 Hz), 2.78 (dd, 0.2H, *J* = 9.2, 7.8 Hz), 2.59 (dd, 1.2H, *J* = 11.7, 5.9 Hz), 2.36 (m, 2H), 2.23 (m, 1.2H), 2.16 (m, 0.2H), 2.11 (m, 1H), 2.05 (m, 1.2H), 1.98 (m, 0.6H), 1.86 (m, 1.5H), 1.78 (m, 1.5H), 1.66 (m, 2.6H), 1.48 (m, 3.3), 1.19 (m, 3.9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 222.4, 216.9, 153.8, 153.4, 153.4, 137.8, 137.6, 133.0, 128.7, 128.7, 127.5, 127.5, 126.8, 126.6, 126.5, 126.3, 125.2, 118.4, 117.9, 112.1, 111.4, 110.6, 110.5, 103.7, 103.5, 59.9, 59.4, 56.0, 55.9, 52.6, 51.1, 50.2, 50.1, 49.9, 49.1, 44.9, 41.1, 40.7, 36.0, 33.9, 32.1, 31.6, 30.8, 29.5, 27.1, 26.4, 25.8, 25.3, 25.2, 23.9, 23.5, 23.5;

HRMS calc'd for $C_{28}H_{31}NO_2$ (M^+) 413.2355; found 413.2358 (30%), 303.1628 $[M\text{-}C_7H_{10}O]^+$ (100%).



Synthesis of 9a and 9a' These products ware prepared from **1d** using the procedure described above for **2b**. The inseparable mixture of diastereomers **9a** and what is tentatively assigned as **9a' (**5 : 1) was obtained as a pale yellow oil 17 mg (74%).

IR (film) 2955, 2870, 2837, 1734, 1612, 1584, 1505, 1464 cm^{-1};

^{1}H NMR **9a** (500 MHz, $CDCl_3$) δ 7.06 (d, 1H, *J* = 8.2 Hz), 6.45 (dd, 1H, *J* = 8.2, 2.5 Hz), 6.44 (d, 1H, *J* = 2.5 Hz), 3.79 (s, 3H), 3.71 (s, 3H), 2.74 (m, 1H), 2.68 (ddq, 1H, *J* = 11.8, 9.3, 7.1 Hz), 2.38 (ddd, 1H, *J* = 12.7, 9.2, 8.1 Hz), 2.18 (m, 1H), 1.84 - 1.95 (m, 2H), 1.75 – 1.84 (m, 2H), 1.58 (m, 1H), 1.21 (d, 3H, *J* = 7.1 Hz), 1.18 (ddd, 1H, *J* = 12.8, 11.8, 10.4 Hz);

^{13}C NMR **9a** (125 MHz, $CDCl_3$) δ 221.6, 159.8, 157.4, 127.7, 124.0, 104.0, 99.6, 62.7, 55.3, 55.1, 47.9, 43.8, 36.4, 31.5, 30.5, 24.0, 15.8;

HRMS calc'd for (M^+) $C_{17}H_{22}O_3$ 274.1569; found 274.1568 (23%), 204.1149 [M – $C_4H_6O]^+$ (100%).

Anal. calc'd for $C_{17}H_{22}O_3$ C, 74.42; H, 8.08; found C, 74.28; H, 7.85

4.6 References

(1) Rieder, C. J.; Fradette, R. J.; West, F. G. *Chem. Commun*. **2008**, 1572–1574.

(2) Rieder, C. J.; Fradette, R. J.; West, F. G.; *Heterocycles,* **2010**, *80*, 1413–1427.

(3) Selvakumar, N.; Reddy, B. Y.; Kumar, G. S.; Iqbal, J. *Tetrahedron Lett*. **2001**, *8395-8398*, 1–4.

(4) Snow, R. J.; Butz, T.; Hammach, A.; Kapadia, S.; Morowick, T. M.; Prokpowicz, A. S.; Takahashi, H.; Tan, J.; Tschantz, M. A.; Wang, X.-J. *Tetrahedron Lett*. **2002**, *43*, 7553–7556.

(5) Bella, M.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2005**, *127*, 3670–3671.

(6) Kobbelgaard, S.; Bella, M.; Jørgensen, K. A. *J. Org. Chem*. **2006**, *71*, 4980–4987.

(7) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc*. **1999**, *121*, 1473–1478.

(8) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc*. **2000**, *122*, 1360–1370.

(9) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc*. **2008**, *130*, 195–200.

(10) Tripathy, S.; Reddy, R.; Durst, T. *Can. J. Chem*. **2003**, *81*, 997–1002.

(11) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340–5341.
(12) Mohanan, K.; Coquerel, Y.; Rodriguez, J. *Org. Lett.* **2012**, *14*, 4686–4689.
(13) Goetz, A. E.; Silberstein, A. L.; Corsello, M. A.; Garg, N. K. *J. Am. Chem. Soc.* **2014**, *136*, 3036–3039.
(14) Huang, X.; Maulide, N. *J. Am. Chem. Soc.* **2011**, *133*, 8510–8513.
(15) Huang, X.; Patil, M.; Farès, C.; Thiel, W.; Maulide, N. *J. Am. Chem. Soc.* **2013**, *135*, 7312–7323.
(16) Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **1973**, *12*, 819–835.
(17) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163–344.
(18) Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **1984**, 1–19.
(19) Mann, J. *Tetrahedron* **1986**, *42*, 4611–4659.
(20) Kende, A. S. *Org. React.* **1960**, *11*, 261–291.
(21) Hill, A. E.; Greenwood, G.; Hoffmann, H. M. R. *J. Am. Chem. Soc.* **1973**, *95*, 1338–1340.
(22) Fohlisch, B.; Herter, R.; Wolf, E.; Stezowski, J. J.; Eckle, E. *Chem. Ber.* **1982**, *115*, 355–380.
(23) Harmata, M. *Adv. Synth. Catal.* **2006**, *348*, 2297–2306.
(24) Harmata, M. *Chem. Commun.* **2010**, *46*, 8904-8922.
(25) Lohse, A. G.; Hsung, R. P. *Chem. Eur. J.* **2011**, *17*, 3812–3822.
(26) Fohlisch, B.; Joachimi, R. *Chem. Ber.* **1987**, *120*, 1951–1960.
(27) Tang, Q.; Chen, X.; Tiwari, B.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 1922–1925.
(28) Vander Wal, M. N.; Dilger, A. K.; MacMillan, D. W. C. *Chem. Sci.* **2013**, *4*, 3075-3079.
(29) See Chapter 1 of this thesis for further discussion.
(30) West, F. G.; Willoughby, D. W. *J. Org. Chem.* **1993**, 3796–3797.
(31) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033–3035.
(32) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Can. J. Chem.* **2004**, *82*, 375–385.
(33) Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348–9349.
(34) Grant, T. N.; West, F. G. *Org. Lett.* **2007**, *9*, 3789–3792.
(35) Basak, A. K.; Tius, M. A. *Org. Lett.* **2008**, *10*, 4073–4076.
(36) Marx, V. M.; LeFort, F. M.; Burnell, D. J. *Adv. Synth. Catal.* **2010**, *353*, 64–68.
(37) Marx, V. M.; Burnell, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 1685–1689.
(38) Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem. Int. Ed.* **2000**, 1970–1973.
(39) Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876–877.
(40) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747–2750.
(41) Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed.* **1969**, *8*, 781–932.
(42) Gordon, H. L.; Freeman, S.; Hudlicky, T. *Synlett* **2005**, 2911–2914.

(43) Products **2a, 3a, 7a, 7a', 7b, 7b', 7c, 7c', 7i, 7i'** were first synthesized by C. J. Rieder. For characterization data see references 1, 2, and Rieder, C. J. *Ph.D. Dissertation*, **2010**.

(44) The work discussed herein was a joint effort by C. J. Rieder and the author, disambiguation of contributions are made in reference 43, and throughout Section **2.3.**

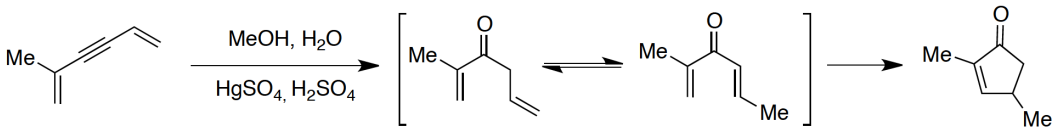
(45) It was observed that acyclic dienones such **1b** could undergo TMSOTf promoted tandem Nazarov cyclization/electrophilic aromatic substitution with arenes possessing sufficient 1,3-diene character. Arenes such as thiophene and 1,3-dimethoxybenzene were unsuccessful. Wu, Y-K. *Ph.D. Dissertation*, **2013**.

Chapter 3

Oxidation-Initiated Nazarov Reaction of 1,4-Pentadien-3-yl Ethers

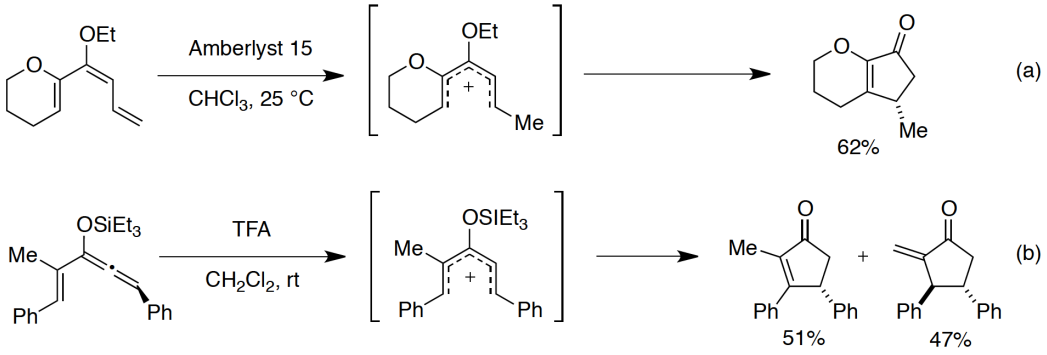
3.1 Introduction

The reactivity of 1,4-dien-3-ones,[1] both as a starting material or as *in situ* generated intermediates from dienynes[2] or allyl vinyl ketones[3] by I. N. Nazarov and cowokers, was the foundation on which the extensive early studies of the reaction bearing his name was built (Scheme 1).[4,5] More recently, many additional methods have been used to generate pentadienyl cations suitable for Nazarov cyclization.[6-12] Alternative substrates from which pentadienyl cations can be generated allow for greater latitude in design of substrates, permitting other substitution than a ketone at C-3.



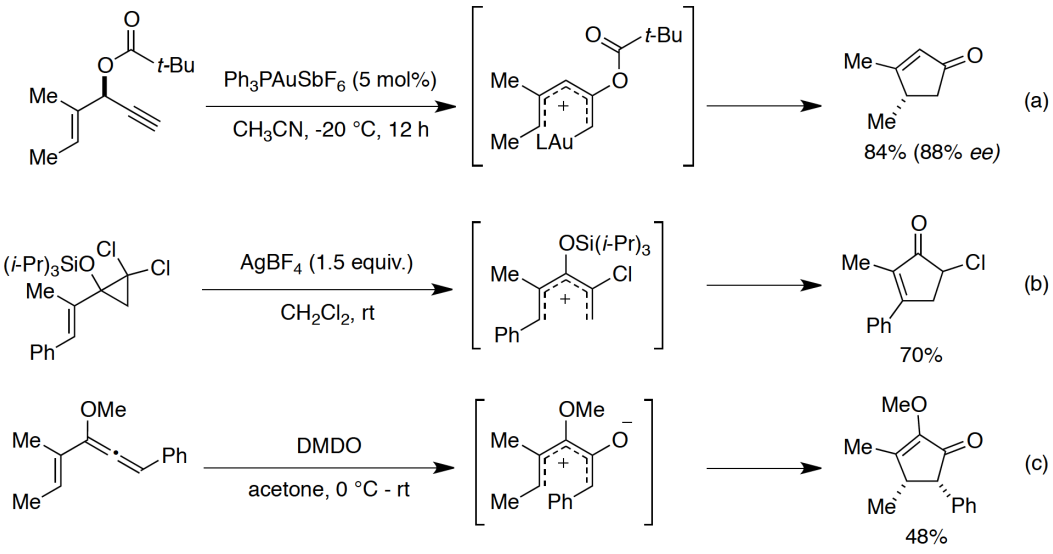
Scheme 1: Nazarov Cyclization of Dienynes.

Oxygenation at the 3-position, used in the traditional Nazarov reaction as the point of activation, also provides additional stabilization to the cyclized 2-oxidocyclopentenyl cation intermediate.[13] Two more recent alternative Nazarov substrates retain the oxygenation at the 3-postion; however, their Brønsted acid activation does not involve protonation on oxygen. Occhiato and coworkers used Brønsted acid activation of electron-rich ethoxytrienes;[14-16] the additional stabilization afforded by the ring heteroatom helps account for the success of these mild conditions (Scheme 2a). Wu and West used trifluoroacetic acid in the protonation of vinylsiloxyallenes to form 3-siloxypentadienyl cations, which could undergo Nazarov cyclization (Scheme 2b).[17]



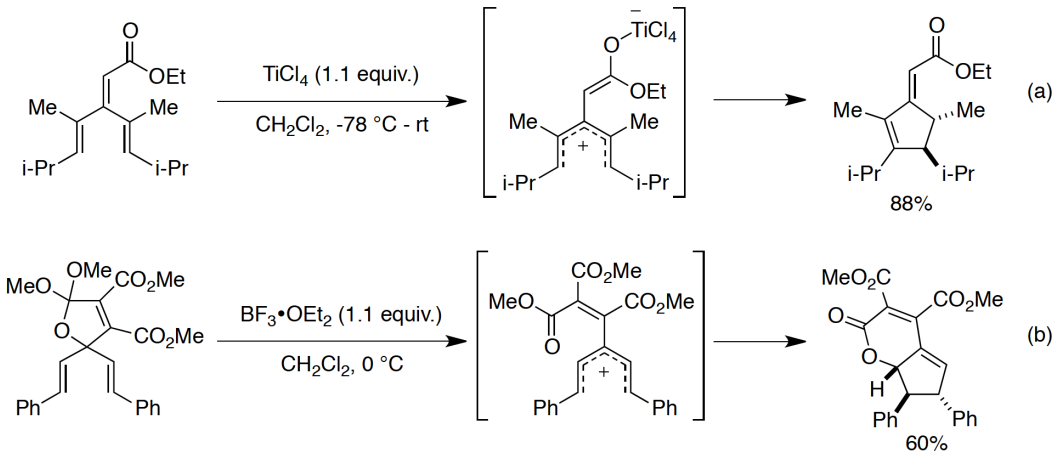
Scheme 2: Alternative Brønsted Acid Activation.

Several recent examples of pentadienyl cation precursors, also oxygenated at the 3-position, could be accessed without the use of strong Lewis or Brønsted acid. In 2005 Toste and co-workers used 1-ethynyl-2-propenyl pivaloates in gold(I) catalyzed cyclizations generating 2-cyclopentenones (Scheme 3a).[18] A benefit of these alternative substrates was the capability of enantioenriched pivaloates to effectively transfer chirality to the products with good enantioselectivity. Grant and West used alkenyldichloropropyl silyl ethers as pentadienyl cation precursors. Silver(I) mediated 2π electrocyclic ring opening lead to pentadienyl cations, which underwent Nazarov cyclization to give α-chlorocyclopentenones in good yield (Scheme 3b).[19,20] Frontier and coworkers utilized an oxidation initiated Nazarov reaction in a recent synthesis of rocaglamide.[21,22] This method has since been generalized to series of vinyl alkoxyallenes. Alkoxyallenes were treated with dimethyldioxirane, forming an allene oxide which opened to a pentadienyl cation that underwent Nazarov cyclization to give the alkoxy cyclopentenone products, retaining both stereospecifically formed stereocenters (Scheme 3c).[23]



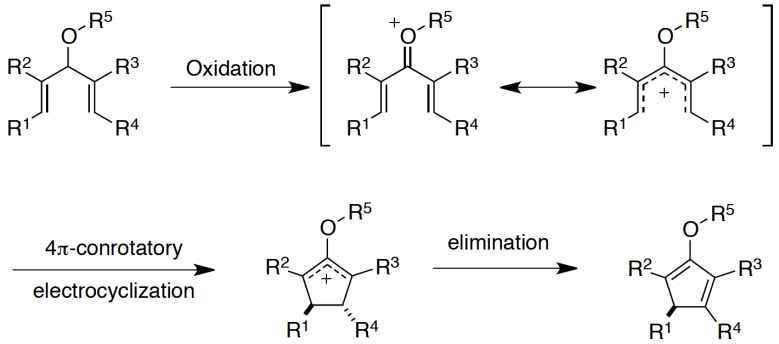
Scheme 3: Alternative Activation Methods.

In only the final case discussed in Scheme 3 is the non-carbonyl functionality on the C-3 oxygen retained; carbon substitution at C-3 of the pentadienyl cation is another alternative that could provide access to substitution patterns not accessible with a carbonyl at C-3. In 2009, West and coworkers described a Nazarov variant where the carbonyl was replaced by an electron deficient alkene. Cross-conjugated trienes could be activated by Lewis acid at the remote carbonyl to generate a pentadienyl cation that underwent subsequent Nazarov cyclization and elimination, leading to alkylidene cyclopentenes; they designated this processes the 'vinylogous Nazarov' reaction (Scheme 4a).[24] In 2002, Nair and coworkers described a Nazarov process with substitution of carbon and oxygen at C-3 in the form of *gem*-dialkenyl dihydrofurans. In this process, Lewis acid mediated C-O bond cleavage led to pentadienyl cation formation and Nazarov cyclization. Interestingly, the resulting allyl cation underwent intramolecular trapping by the tethered ester to give the bicyclic lactone product (Scheme 4b).[25] In this case, it is likely that trapping was aided by the *cis*-alkene geometry of the tether forcing the nucleophile into closer proximity to the reactive allyl cation. The observation of an interrupted Nazarov reaction through C-3 demonstrates another mode of reactivity garnered by non-carbonyl functionality at that position.

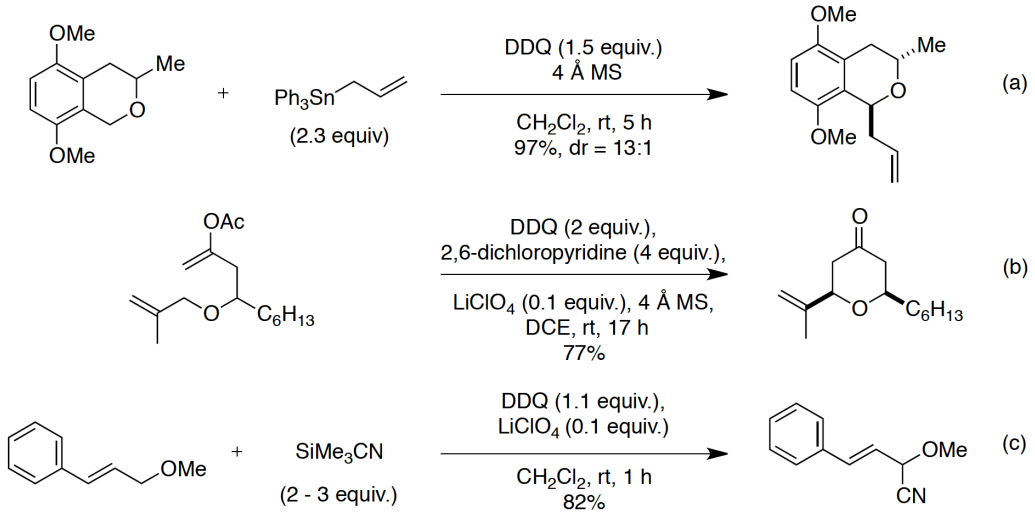


Scheme 4: Activation Through C-3 Carbon Substituent.

As part of a continuing program to develop new alternative Nazarov substrates, we considered the use of skipped dienes substituted with ether moieties at the doubly allylic C-3 position. We envisioned that, under oxidizing conditions, the ether could undergo formal loss of hydride to form an oxocarbenium cation that would be in resonance with a pentadienyl cation capable of undergoing Nazarov cyclization (Scheme 5). Ample precedent exists for the oxidation of benzyl and allyl ethers by single electron oxidation; one of the most widespread examples is in the 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) deprotection of *p*-methoxybenzyl ethers and, to a lesser extent, allyl ethers.[26,27] In addition to simple deprotection, in recent years DDQ has been used as a single electron oxidant to initiate various domino or cascade processes through generation of oxocarbenium ions from benzyl ethers[28-35] (Scheme 6a),[28] allyl ethers[32] (Scheme 6b), and styryl ethers[36-38] (Scheme 6c),[36] which could be trapped with a variety of nucleophiles. With this in mind we set out to study the use of DDQ to initiate Nazarov cyclizations using pentadienyl ether substrates.



Scheme 5: Oxidation-Initiated Nazarov Reaction.

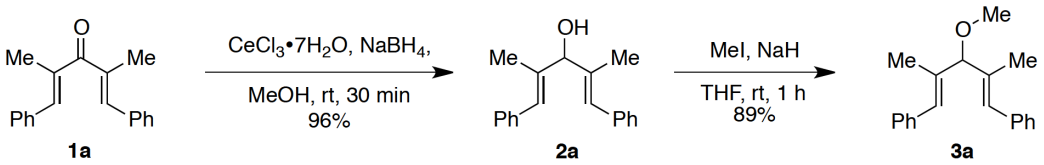


Scheme 6: Selected Examples of Trapping Reactions of DDQ-Generated Oxocarbenium Ions.

3.2 Results and Discussion

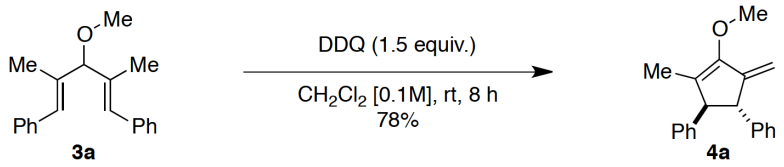
Formation of the initial bis(allylic) ether substrate **3a** was achieved by Luche reduction[39] of dibenzylidiene-3-pentanone **1a** and alkylation of the resulting dienol **2a** to give the bis(allylic) methyl ether product **3a** (Scheme 7). Substrate **3a** was chosen as a test substrate due to the rapidly accessible nature of the starting dienone, the ease with which the parent dienone undergoes Nazarov cyclization, and the expected chemoselectivity of single electron oxidation on the π-systems over the methyl ether. Additionally, employing a symmetrical substrate

could simplify structure elucidation in the event a mixture of products was obtained.



Scheme 7: Synthesis of 3-Methoxypenta-1,4-diene **3a.**

In the initial reaction, the 3-methoxypenta-1,4-diene substrate **3a** was treated with 1.5 equivalents of DDQ in dichloromethane at room temperature. TLC monitoring of the reaction showed consumption of starting material and formation of a single new product. The reaction was quenched by filtration through a short silica gel plug and eluted with dichloromethane. Analysis of the ^{1}H NMR spectrum of the purified product suggested that a single new product had formed. The downfield aromatic protons remained intact, as did the methyl ether singlet. One of the originally allylic methyl groups was no longer apparent, while the other appeared as a multiplet, with chemical shift suggesting that it remained allylic. Four new resonances (δ 5.09, 4.54, 3.66, and 3.57, respectively) each integrating for one proton were observed. The ^{13}C APT NMR spectra confirmed that a single allylic methyl group remained (δ 11.9). Three resonances (δ 59.7, 60.4, and 56.1) corresponded to a methyl ether and two benzylic methines, respectively. Of the remaining 12 carbon resonances, 8 could be accounted for by the two phenyl rings. Three of the remaining 4 carbons were quaternary, and the final carbon (δ 101.6) corresponded to a methylene, an observation supported by the HSQC spectrum. The coupling and connectivity data obtained in COSY (Figure 1) and HSQC spectra, combined with IR and mass spectral data, allowed us to confidently assign the structure of enol ether **4a** (Scheme 8).



Scheme 8: DDQ-Initiated Nazarov Cyclization.

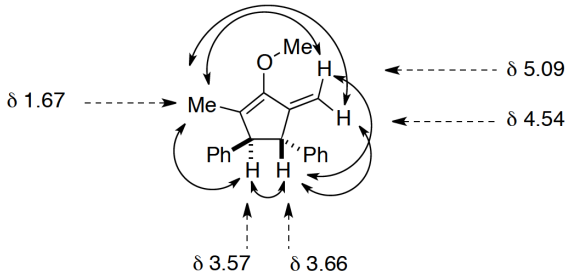
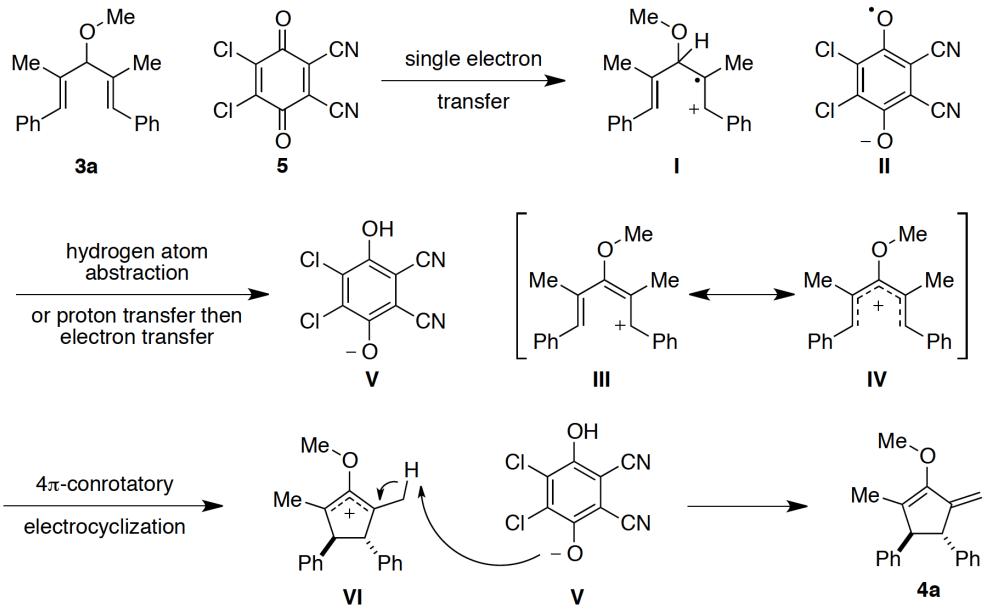


Figure 1: COSY Correlations for Enol Ether **4a**.

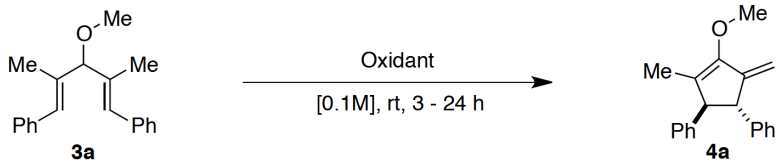
The mechanism of this oxidative Nazarov cyclization likely proceeds via electron transfer from the π-system of bis(allylic) ether **3a**, leading to radical cation **I** and the radical anion of DDQ **II**. Cation **III,** which is in resonance with pentadienyl cation **IV**, is generated by either hydrogen atom abstraction by the radical anion or proton transfer followed by a second electron transfer, either way forming phenolate **V**. Pentadienyl cation **IV** undergoes 4π-electrocylization to give the 2-oxidocyclopentenyl cation **VI**. Elimination occurs regioselectively with exclusive deprotonation at the less hindered methyl rather than the more sterically congested benzylic methine, leading to enol ether **4a** (Scheme 9).



Scheme 9: Proposed DDQ-Initiated Oxidative Nazarov Cyclization Mechanism.

Having observed a successful oxidation initiated Nazarov reaction, we sought to optimize the transformation of bis(allylic) ether **3a** to enol ether **4a** by first carrying out a screen of oxidants (Table 1). Upon careful monitoring of the reaction, we found that reaction using DDQ was in fact complete within 3 h, affording **4a** in 82% yield (Entry 1). Next, we screened ceric ammonium nitrate (CAN). We found that when 1.5 equivalents was used, the reaction failed to go to completion (Entry 2); increasing the loading to 2.5 equivalents allowed for complete consumption of the starting ether, but the isolated yield was lower than observed for DDQ (Entry 3). Potassium ferricyanide was insoluble in CH_2Cl_2, and no reaction was observed (Entry 4); when the reaction was carried out in MeOH, starting material was consumed, leading to an intractable mixture as observed in the ^1H NMR spectrum (Entry 5). Weaker oxidants, benzoquinone and naphthoquinone, failed to consume any of bis(allylic) ether **3a** (Entries 6-7). Hypervalent iodine reagents IBX and $PhI(OAc)_2$ were also unreactive (Entries 8-9).

Table 1: Oxidant Screening.



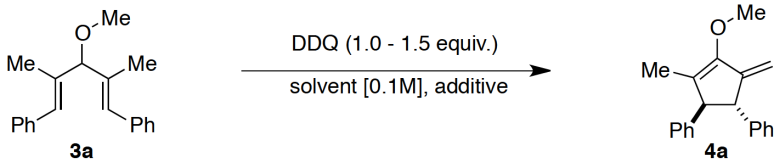
Entry	Oxidant	Loading (equiv.)	Solvent	Time (h)	Yield[a] (%)
1	DDQ	1.5	CH_2Cl_2	3.0	88%
2	CAN	1.5	CH_2Cl_2	20	-[b]
3	CAN	2.5	CH_2Cl_2	6.0	62%
4	$K_3[Fe(CN)_6]$	1.5	CH_2Cl_2	20	-[c]
5	$K_3[Fe(CN)_6]$	1.5	MeOH	12	-[d]
6	Quinone	1.5	CH_2Cl_2	20	-[c]
7	Naphthoquinone	1.5	CH_2Cl_2	20	-[c]
8	IBX	1.5	CH_2Cl_2	20	-[c]
9	$PhI(OAc)_2$	1.5	CH_2Cl_2	20	-[c]

[a]Isolated yield after purification. [b]Reaction incomplete after 24 h. [c]No product formed after 24 h, starting material and baseline impurities observed by TLC. [d]Starting material consumed after 24 h, crude ^{1}H NMR spectra showed intractable material.

Having observed DDQ to be the most reliable oxidant, it was selected as the oxidant of choice for further optimization studies (Table 2). When the loading of DDQ was reduced to 1.0 equivalent, we found that trace amounts of starting material **3a** remained after 24 hours; by increasing the loading of DDQ to 1.2 equivalents, we found that starting material could be cleanly converted into the enol ether **4a** in high yield (Entry 3). A solvent screen indicated that the reaction in DCE (Entry 4) proceeded slightly faster than in CH_2Cl_2; we attributed this to a qualitative observation of DDQ being more soluble in DCE and dissolving more rapidly. The reaction rate appeared to be similar or slower in the additional

solvents screened. The products were not isolated; however, TLC monitoring suggested clean conversion of **3a** to **4a** (Entries 4-7). Moving forward, CH_2Cl_2 was retained as the solvent of choice. Various additives were also screened. Molecular sieves were employed to remove any water that may be present in our reaction mixture; however, we saw no improvement in reaction time or yield, leading us to believe our reaction conditions were sufficiently anhydrous. The addition of Brønsted acid additives has been reported to increase the activity of DDQ,[40] and we hoped this may improve the yield or rate of our test reaction; however, after 2 hours, we found that the starting material was consumed and the ^{1}H NMR spectrum showed only intractable material. $LiClO_4$ has been reported to form a more reactive cation in the context of DDQ-initiated oxocarbenium formation;[36,38,41] we hoped that a similar effect would increase the rate of pentadienyl cation formation and decrease reaction time. In practice, the addition of 10 mol% $LiClO_4$ reduced the reaction time from 4 to 3 hours, a small improvement, with no effect on yield. The simplicity of the DDQ activation in a common solvent without the requirement of additional additives was attractive, so the conditions used in Entry 3 were chosen moving forward.

Table 2: DDQ-Initiated Nazarov Optimization.



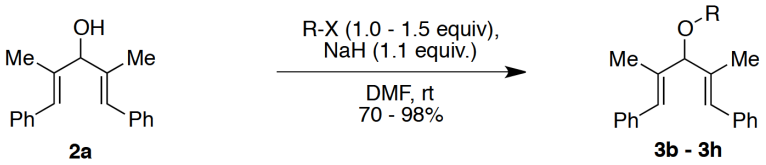
Entry	DDQ (equiv.)	Solvent	Additive	Temp. (°C)	Time (h)	Yield[a] (%)
1	1.5	CH_2Cl_2	-	rt	3.0	88
2	1.0	CH_2Cl_2	-	rt	24	-[b]
3	1.2	CH_2Cl_2	-	rt	4.0	92
4	1.2	DCE	-	rt	3.5	-[c]
5	1.2	MeCN	-	rt	8.0	-[c]
6	1.2	PhH	-	rt	4.0	-[c]
7	1.2	THF	-	rt	5.5	-[c]
8	1.2	CH_2Cl_2	4 Å MS	rt	4.0	92
9	1.2	CH_2Cl_2	MsOH	rt	2.0	-[d]
10	1.2	CH_2Cl_2	$LiClO_4$	rt	3.0	90

[a]Isolated yield after purification. [b]Reaction incomplete after 24 h. [c]Reactions were complete by TLC, but were not purfied as no significant improvement in reaction time was observed. [d]Starting material consumed, crude ^{1}H NMR spectra showed intractable material.

With optimized conditions for the DDQ initiated oxidative Nazarov reaction selected, we sought to expand the scope of this reaction beyond the methyl ether used in substrate **3a**. Substrate synthesis was straightforward, using the Williamson ether synthesis to provide bis(allylic) ethers **3b** to **3h** from dienol **2a** and the corresponding halides (Scheme 10). When selecting ether substituents, we were careful to use functional groups that would be unlikely to be oxidized in the presence of the bis(allylic) ether based on the reported oxidation potential of a comparable compound (cinnamyl alcohol $E_{ox}° = 1.36$ V).[42] We suspected that the

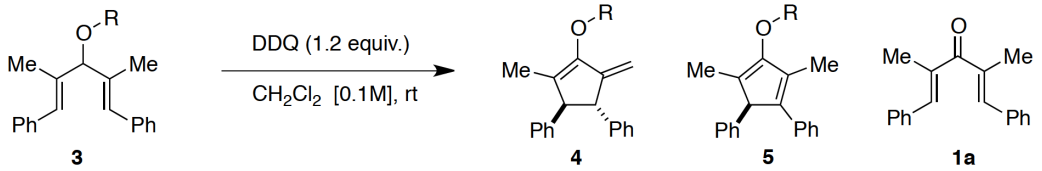
corresponding dienol **2a** would have an oxidation potential equal to, or lower than, cinnamyl alcohol. Our first test substrate was, in fact, dienol **2a**, which was rapidly oxidized by DDQ to dibenzylidiene-3-pentanone **1** (Table 3, Entry 2). This was not unexpected, as the DDQ oxidation of allylic alcohols is well precedented.[43-46] The second bis(allylic) ether we tested, **3b** was the *n*-butyl homologue of the methyl ether test substrate. The reaction proceeded cleanly and in high yield using the optimized conditions. Next, we investigated the allyl ether-bearing substrate **3c**; based on the observations of Lund,[42] the oxidation potential of allyl alcohol is greater than 2.0 V, convincing us that the DDQ oxidation would be regioselective and lead to the desired pentadienyl cation. In practice, the reaction generating **4c** was high yielding with no evidence of allyl ether cleavage, a process that has been shown to occur with DDQ.[27] In a similar fashion, propargyl ether **3d** was a successful substrate. Next, we looked to test a series of benzyl ether derivatives. Unsubstituted benzyl ether **3e** was a viable substrate, so we set out to test several *para*-substituted derivatives. Resonance donating *p*-bromobenzyl substrate **3f** and inductively donating *p*-methylbenzyl substrate **3g**, while both weakly donating, were expected to have greater oxidation potentials than the bis(allylic) ether; therefore, we expected they would be successful Nazarov substrates. This was the case with *p*-bromobenzyl substrate **3f**, which gave exclusively the Nazarov product; however, while the *p*-methylbenzyl substrate **3g** gave a moderate yield of the Nazarov product **4g**, traces of *p*-tolualdehyde and dienol **2a** were observed in the crude ^{1}H NMR spectrum, resulting from oxidation of the *p*-tolyl tether. We tested the *p*-methoxybenzyl derivative **3h** knowing that the reaction conditions were likely to deprotect the *p*-methoxybenzyl ether, given the low oxidation potential of *p*-methoxybenzyl alcohol ($E_{ox}°$ = 1.22 V)[42] and ample precedent for DDQ-mediated removal of *p*-methoxybenzyl ethers.[26] In this event we obtained a mixture of products, observing resonances corresponding to *p*-anisaldehyde, dienol **2a**, dibenzylidiene-3-pentanone **1a**, unreacted bis(allylic) ether **3h**, as well as signals characteristic of the exocyclic olefin observed for previous enol ether products **4a** to **4g**; however, despite our efforts, we were unable to isolate pure enol ether **4h**. Regardless of the

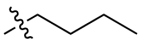
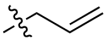
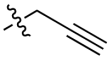
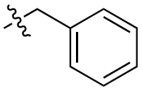
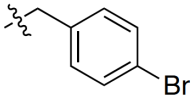
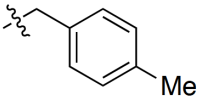
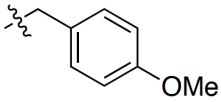
nature of the R-group, all Nazarov cyclization products **4** possessed an exocyclic methylene moiety resulting from exclusive elimination towards one of the methyl groups, with no evidence for the corresponding cyclopentenones **5**.



Scheme 10: Bis(allylic) Ether Synthesis.

Table 3: Reaction Scope of Ether Substituent.

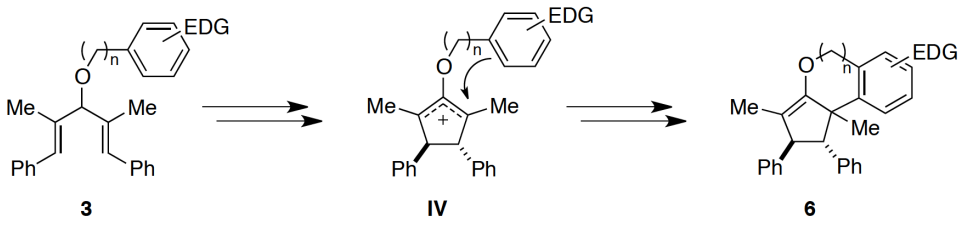


Entry	Bis(allylic) Ether	R	Time (h)	Product	Yield[a] (%)
1	**3a**	Me	4.0	**4a**	92
2	**2a**	H	2.0	**1a**	94
3	**3b**		4.0	**4b**	88
4	**3c**		4.0	**4c**	85
5	**3d**		4.0	**4d**	90
6	**3e**		4.0	**4e**	82
7	**3f**		4.0	**4f**	89
8[b]	**3g**		4.0	**4g**	67
9[c,d]	**3h**		3.0	-	-

[a]Isolated yield after purification. [b]Traces of alcohol **2a** and ketone **1a** and *p*-tolualdehyde were present in the crude ^{1}NMR spectra. [c]Traces of alcohol **2a** and ketone **1a** and *p*-anisaldehyde were present in the crude ^{1}NMR spectra. [d]Characteristic signals corresponding to the desired oxidative Nazarov product were observed in the crude ^{1}NMR spectra; however, the pure product could not be isolated.

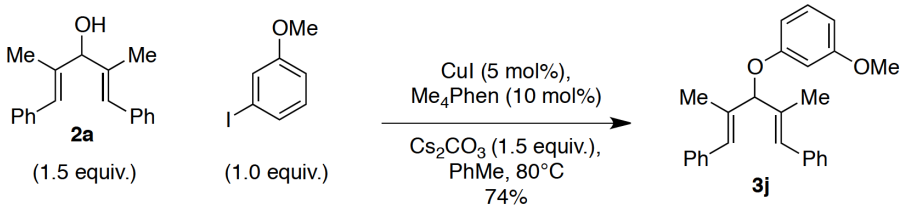
Given our ongoing interest in interrupting the Nazarov reaction with arenes,[6] we turned our focus towards ether substrates with electron rich arene

tethers that could be suitable for intercepting the cyclized oxyallyl cation Nazarov intermediate. Interrupted Nazarov reactions through the 3-position of the Nazarov precursor are rare but not unprecedented, as shown in the studies by Nair and coworkers above (Scheme 4b).[25] Previous studies by West and co-workers indicated that trapping of the 2-oxidocyclopentenyl cation moieties tethered by an ethylene linker to one of the pentadienyl termini was efficient.[47,48] We were interested to learn if a similar arene trap at the central carbon could also be a competent trap for an interrupted Nazarov reaction (Scheme 11).



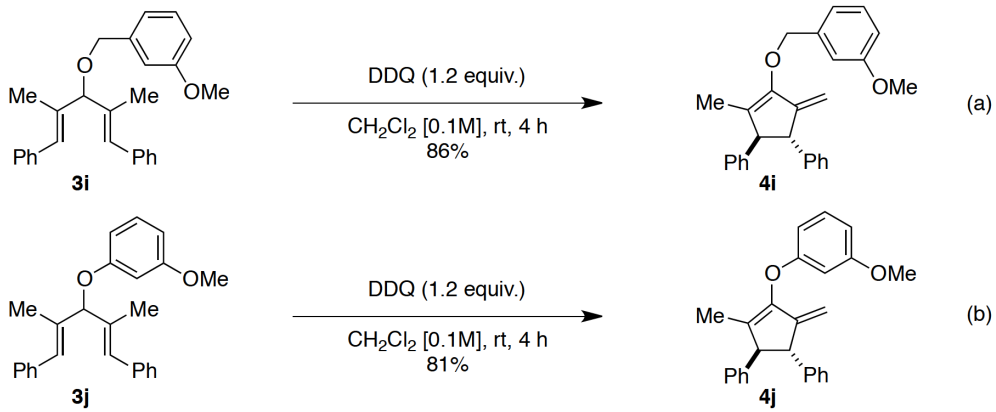
Scheme 11: Proposed Interrupted Oxidative Nazarov Reaction.

We prepared *m*-methoxybenzyl bis(allylic) ether **3i** using the Williamson ether synthesis described previously (Scheme 10). We were concerned that deprotection of *m*-methoxybenzyl ether **3i** would compete with any Nazarov process; however, we expected the *m*-methoxybenzyl ether to be less susceptible to deprotection than the corresponding *para*-substituted derivative. Additionally, we targeted *m*-methoxyphenyl bis(allylic) ether **3j** which would not be susceptible to the same deprotection pathway. Methoxyphenyl bis(allylic) ether **3j** was synthesized using the Cu(I)-catalyzed aryl ether methodology described by Buchwald and co-workers in 2008 (Scheme 12).[49].

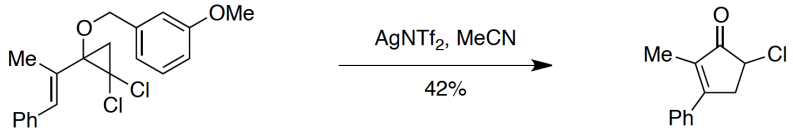


Scheme 12: Synthesis of Aryl Bis(allylic) Ether **3j.**

When *m*-methoxybenzyl bis(allylic) ether **3i** was subjected to the optimized conditions, the starting material was consumed, leading to clean formation of the eliminative Nazarov product **4i** only (Scheme 13a), with no traces of interrupted Nazarov products. While the lack of trapped products was discouraging, we were pleased to find that deprotection was not a competitive pathway for the *m*-methoxybenzyl ether. We attempted to favor the interrupted Nazarov reaction by lowering the reaction temperature, hoping that this would allow the reactive 2-oxidocyclopentenyl cation to persist long enough to allow trapping by the arene nucleophile to occur. Lowering the reaction temperature first to 0 °C and then further to -10 °C failed to provide any product other than **4i** in 7 and 10 hours respectively. Next, we attempted the interrupted Nazarov reaction with aryl bis(allylic) ether **3j**, at both rt and -10 °C. We obtained only the standard Nazarov product **4j** (Scheme 13b), with no evidence of an interrupted Nazarov product. When both substrates **3i** and **3j** were subjected to further reduced temperatures of -40 °C and -78 °C with hopes of observing the interrupted reaction, only mixtures of unreacted starting materials **3i** and **3j** and standard Nazarov reaction products **4i** and **4j** were observed in the ^{1}H NMR spectra of the sluggish reactions, which were quenched after 8 hours. An arene-interrupted Nazarov reaction tethered through oxygen at the 3-position was unsuccessful, mirroring previous studies by West and Bonderoff in which alkoxy vinyl dihalocyclopropanes also failed to participate in the interrupted Nazarov reaction, instead giving only the simple Nazarov product (Scheme 14).[50] It is possible that the geometry for nucleophilic trapping is unfavorable, as the previously successful example by Nair and coworkers[25] may have been assisted by the *cis* geometry and greater rigidity of the alkene tether bringing the allyl cation and nucleophile into closer proximity for trapping (Scheme 4a).

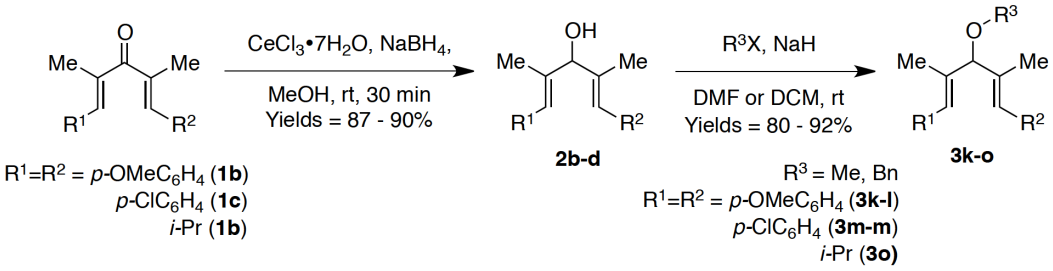


Scheme 13: Attempted Interrupted Oxidative Nazarov Reactions.

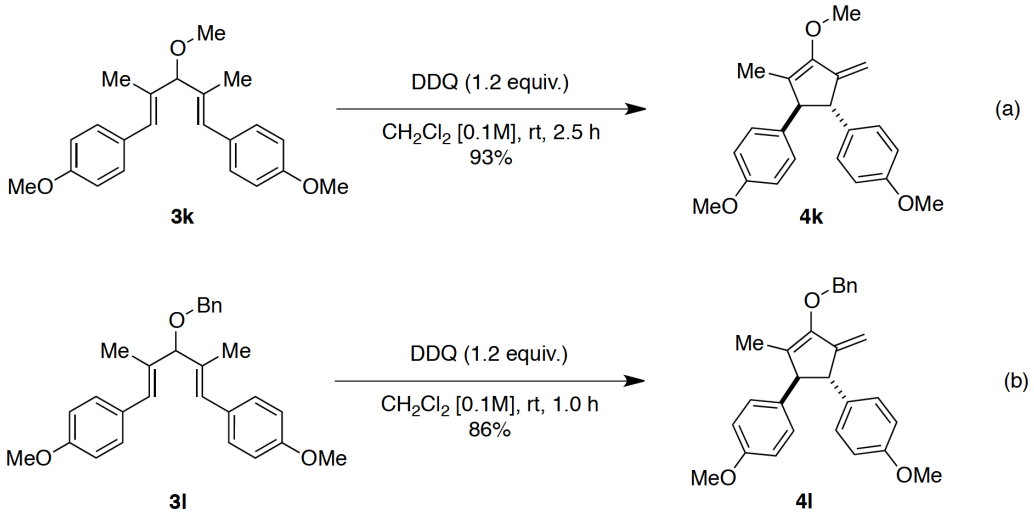


Scheme 14: Attempted Interrupted Dihalocyclopropane Nazarov Reaction.

Although the interrupted version of the oxidative Nazarov process was not successful, we wanted to evaluate the scope of the basic reaction by exploring the role of substitution using additional symmetrical substrates derived from dienones **1a-c** (Scheme 15). Moving forward, we planned to use methyl and benzyl ethers as representative ether substrates. Bis(allylic) ether substrates **3k** and **3l** bearing electron donating aryl substituents on both vinyl termini were expected to undergo facile DDQ oxidation, and, when they were subjected to the optimized conditions, the expected Nazarov products were formed in high yield, with the reaction running to completion giving products **4k** and **4l** in 2.5 and 1.0 hours, respectively (Scheme 16). Incorporating a strongly donating *p*-methoxy group on the arene served to increase the reaction rate, suggesting that the DDQ oxidation step forming the pentadienyl cation is slower than the Nazarov cyclization step.

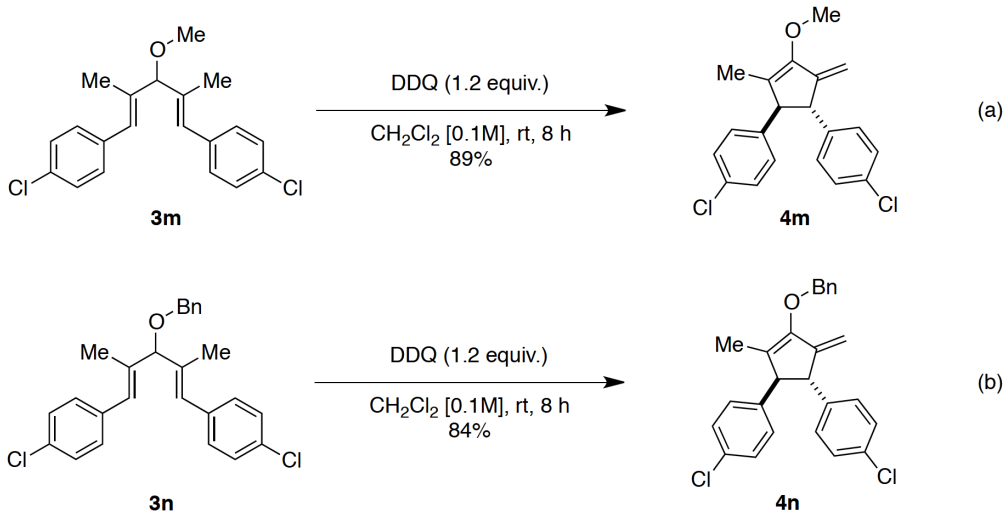


Scheme 15: Synthesis of Symmetrical Bis(allylic) Ether Substrates **3k-o**.



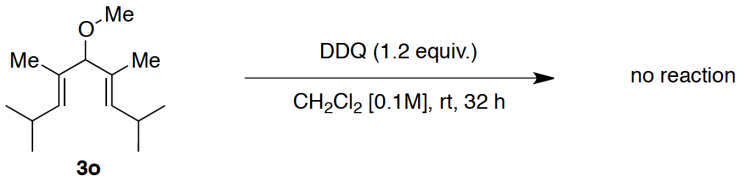
Scheme 16: Nazarov Reaction of *p*-Methoxy Bis(allylic) Ether Substrates.

In the case of substrates **3m** and **3n**, we expected introduction of a *p*-chloro group on the arene termini to either slow the reaction down as a poor substrate for single electron transfer or shut down the reaction completely. When these substrates were subjected to the standard conditions, the reactions were slowed considerably; however, the products **4m** and **4n** were still formed in high yields (Scheme 17).



Scheme 17: Nazarov Reactions of *p*-Chloro Bis(allylic) Ether Substrates.

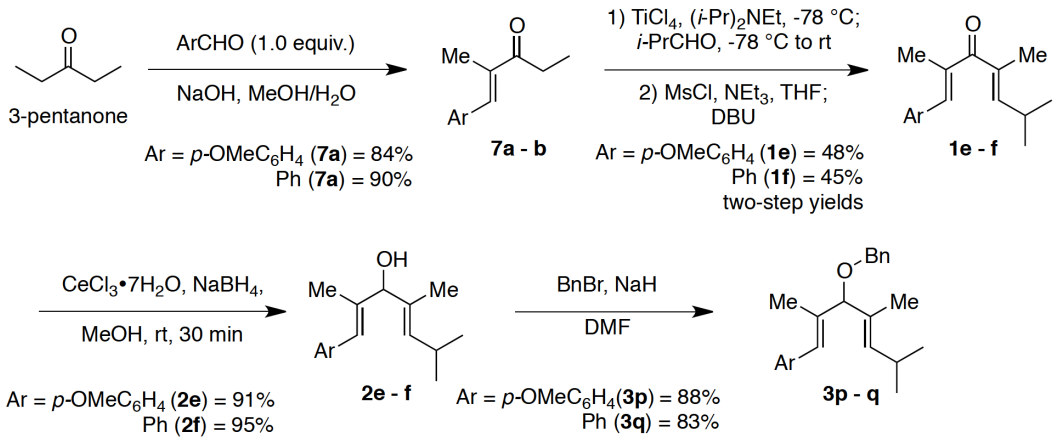
Finally, we tested substrate **3o** bearing *i*-Pr groups rather than arenes at the termini. When we subjected this substrate to the standard conditions, no reaction was observed upon extended stirring for 32 hours (Scheme 18). Changing the solvent to CH_3CN, DCE, and benzene, as well as heating to reflux temperatures in all solvents, had no effect; only unreacted starting material and varying amounts of decomposition products were observed in crude ^{1}H NMR spectra. We suspected that this lack of reactivity was a direct result of the inaccessibly high oxidation potential of the simple, trisubstituted olefins in **3o** as compared with the styryl cases discussed above. It should be noted that Nazarov cyclization has been demonstrated for pentadienyl cations bearing *i*-Pr groups on their termini,[51] again suggesting that the problem lies with the initial single electron-transfer step.



Scheme 18: Attempted Nazarov Reaction of *i*-Pr Bis(allylic) Ether Substrate **3o**.

To further probe the role of terminal substituents, we targeted unsymmetrical substrates **3p** and **3q**. These compounds, bearing an arene at one end and an *i*-Pr group at the other, were expected to be competent substrates,

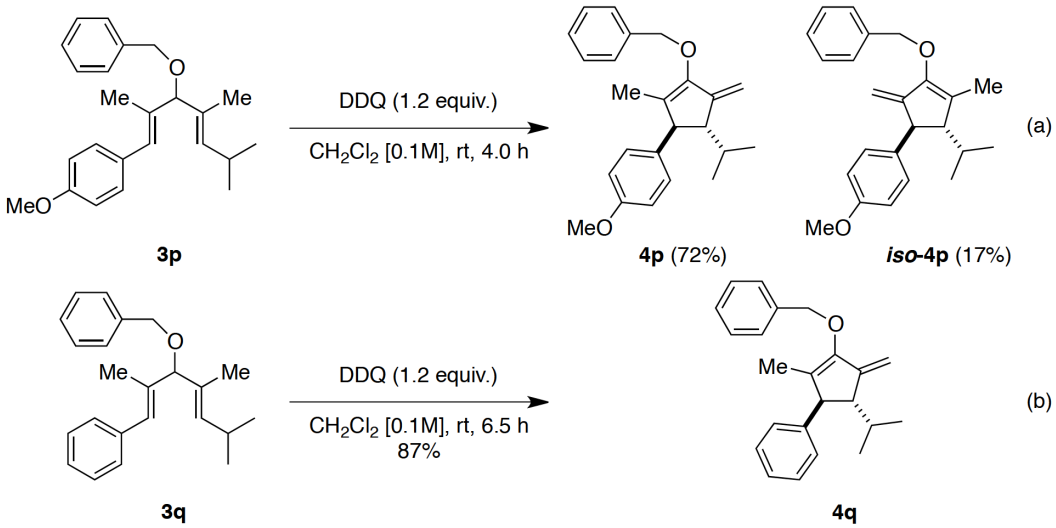
since only one styryl group should be required for the initial oxidative step that leads to the pentadienyl cation necessary for electrocyclization. These unsymmetrical substrates would also serve to answer questions about the regioselectivity of the elimination step; would exocyclic elimination still be observed, and would there be any differentiation between the β-*i*-Pr or the β-aryl side of the oxyallyl cation? Bis(allylic) ethers **3p** and **3q** were synthesized using a five-step sequence from 3-pentanone. Base-catalyzed mono aldol condensation using the desired aldehyde provided enones **7a** and **7b**. A second titanium(IV) mediated aldol reaction gave the hydroxy ketones, followed by a one-pot mesylation/elimination sequence, which gave rise to the parent dienones **1e** and **1f**.[52] Luche reduction to the dienols **2e** and **2f** was followed by Williamson etherification to provide the desired pentadien-3-yl ethers **3p** and **3q** (Scheme 19).



Scheme 19: Unsymmetrical Bis(allylic) Ether Synthesis.

Substrate **3p** was chosen because we knew that a *p*-methoxy substituent would increase the rate of a reaction that may otherwise be slow. When subjected to the standard reaction conditions, bis(allylic) ether **3p** was consumed in 4 hours, leading to the formation of two new spots as observed by TLC. Upon examination of the crude ^{1}H NMR spectrum, it appeared that two products had formed in a 2.3 : 1 ratio. Fortunately, the two products were separable by radial chromatography. Spectroscopic characterization revealed the mixture to be two regioisomers **4p**

and ***iso*-4p**; the major isomer proved to be enol ether **4p,** resulting from exocyclic elimination at the methyl group adjacent to the *i*-Pr group, while the minor product was enol ether ***iso*-4p** from elimination at the methyl group adjacent to the aryl moiety. As in previous cases, no endocyclic elimination products were observed (Scheme 20a). Next, bis(allylic) ether **3q** was treated under the optimized conditions. The starting material was consumed, leading to a single spot by TLC. Given the mixture isolated in the previous unsymmetrical case, we were concerned that the single spot might be coeluting isomers; however, to our surprise, we observed only a single product in the crude ^{1}H NMR spectrum. Following purification and full spectroscopic characterization we determined that the single product was **4q**, resulting from exocyclic elimination on the same side as the *i*-Pr substituent, mirroring the selectivity observed for bis(allylic) ether **3p** (Scheme 20b). Key 2D-NMR correlations used to identify the regioisomers **4p** and ***iso*-4p** appear below (Figure 2); 2D NMR correlations for enol ether **4q** were analogous to **4p**.



Scheme 20: Reactions of Unsymmetrical Bis(allylic) Ethers **3p** and **3q**.

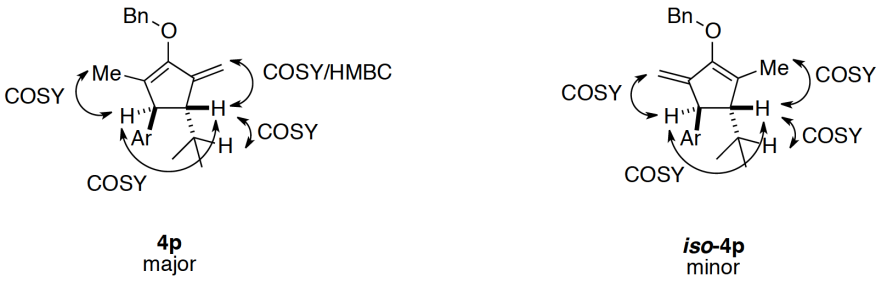
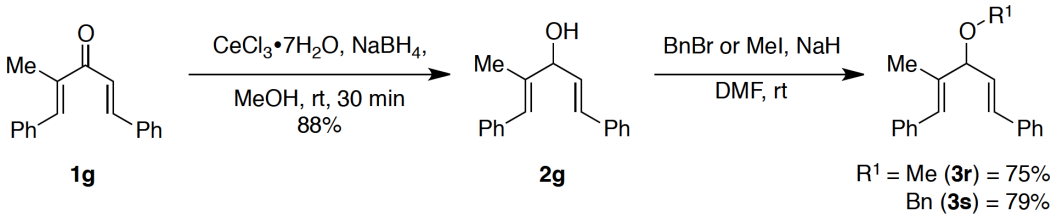


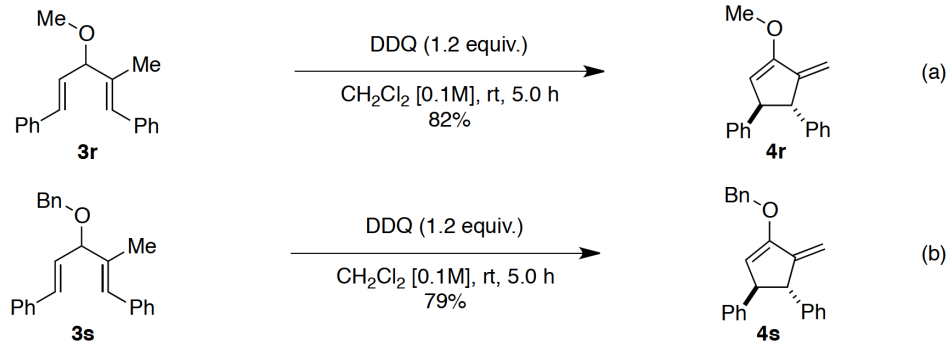
Figure 2: Key 2D NMR Correlations for Nazarov Products **4p** and ***iso*-4p.**

For both substrates **3p** and **3q**, the major products resulted from regioselective elimination on the same side as the *i*-Pr substituent. The reason(s) for this selectivity are unclear. One possible explanation is that reduced steric encumberance of deprotonation from the same side as the smaller *i*-Pr is kinetically favorable; however, the (aryl and *i*-Pr) β-substituents are fairly far away from the α-methyl protons that are removed. A second possible basis for the selectivity is a π-stacking interaction between the β-aryl substituent and the benzyl tether, causing the methyl group on the same side as the aryl group to be more sterically hindered, allowing for a more facile elimination on the same side as the *i*-Pr substituent.

Having observed regioselectivity in the elimination step for bis(allylic) ether substrates varying at the β-position, we sought to probe the regioselectivity for substrates differently substituted at the α-position. Bis(allylic) ethers **3r** and **3s** in which one of the pentadienyl 2 / 4 positions was unsubstituted were prepared (Scheme 21) and examined to determine the effect of methyl substitution on reaction efficiency. Moreover, the possibility of endocyclic elimination of the cyclized intermediate might arise with the removal of one of the methyl groups. When bis(allylic) ethers **3r** and **3s** were subjected to the optimized conditions, single products were formed in both cases, resulting from regioselective exocyclic elimination to give products **4r** and **4s** in high yield (Scheme 22).

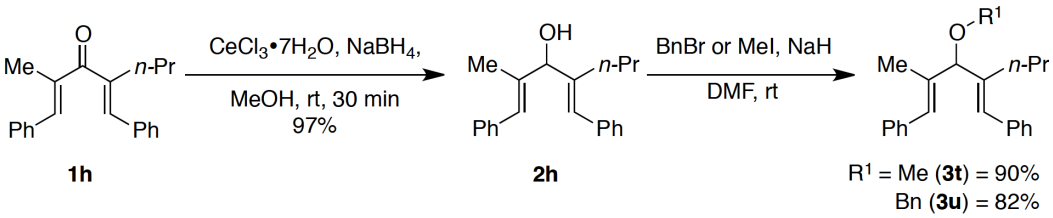


Scheme 21: Synthesis of Unsymmetrical Bis(allylic) Ethers **3r** and **3s**.

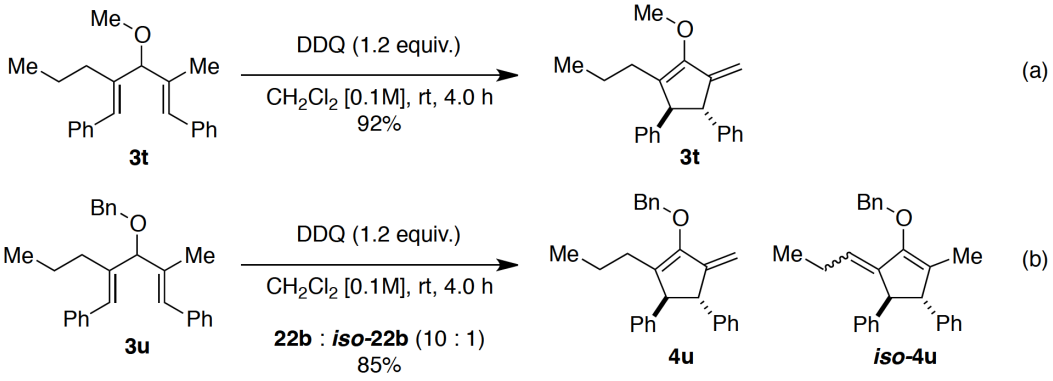


Scheme 22: Reactions of Unsymmetrical Bis(allylic) Ethers **3r** and **3s**.

Bis(allylic) ethers **3t** and **3u** with an α-methyl group on one side and a larger *n*-propyl on the other were prepared using the sequence described in Scheme 23. Based on our observations to this point we expected that an exocyclic elimination would occur; however, we wanted to determine if any selectivity for deprotonation of one of the methyl protons over the more hindered methylene protons of the *n*-propyl chain would be observed. Substrate **3t** underwent a clean and high yielding oxidation initiated Nazarov reaction to provide **4t** resulting from a highly regioselective elimination at the methyl group. Substrate **3u** also successfully underwent Nazarov cyclization; however an inseparable 10 : 1 mixture of regiosomers **4u**, and what is tentatively assigned as ***iso*-4u** were observed (Scheme 24). Diagnostic COSY correlations for the regioisomer tentatively assigned as ***iso*-4u** are shown in Figure 3.



Scheme 23: Synthesis of Unsymmetrical Bis(allylic) Ethers **3t** and **3u**.



Scheme 24: Reactions of Unsymmetrical Bis(allylic) Ethers **3t** and **3u**.

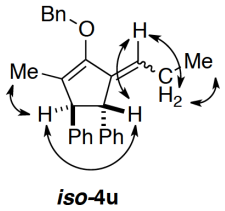
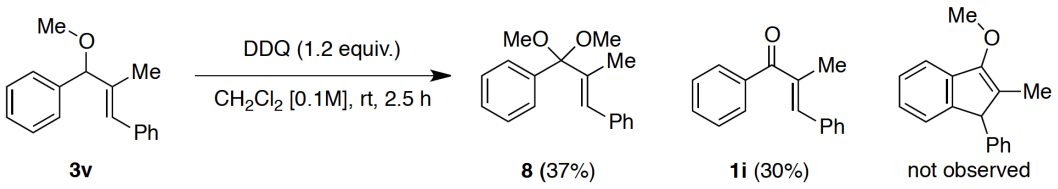


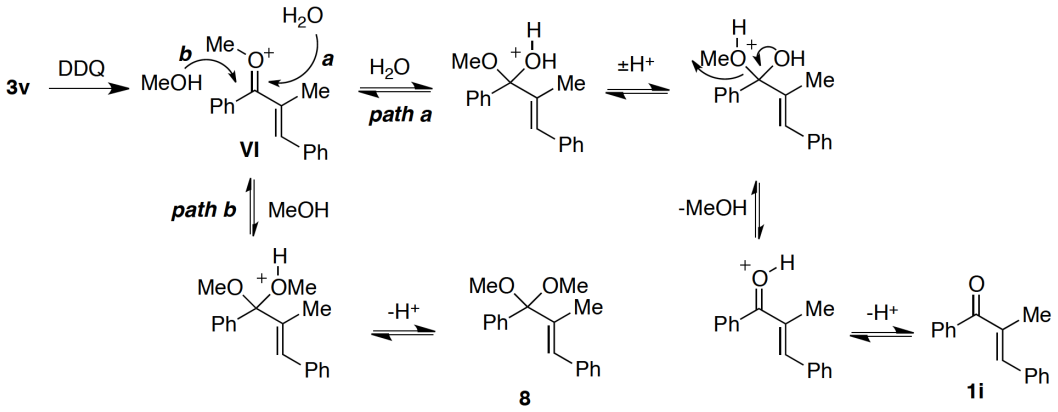
Figure 3: Diagnostic COSY Correlations for ***iso*-4u**.

To this point, all the successful DDQ initiated Nazarov reaction we had observed proceeded with complete selectivity towards the formation of an exocyclic olefin in the elimination step. We sought to test benzyl ether **3v**, where one styryl group was replaced by phenyl; we expected that, if this substrate underwent oxidation and Nazarov cyclization, the elimination would be highly likely or occur endocyclically to rearromatize the arene. When we subjected the ether **3v** to the standard reaction conditions, the starting material was consumed, and two new spots were observed by TLC. Neither of the new products were the result of Nazarov cyclization (Scheme 25). Instead, the acetal **8** and ketone **1i**,

both resulting from oxidation at the ether metine, were obtained. We presume that these compounds arise from trapping of the oxocarbenium ion intermediate **VI** by adventitious nucleophiles, either water or methanol (Scheme 26). Any methanol present was assumed to come from hydrolysis (path a), suggesting that removal of water would prolong the lifetime of **VI**. In fact, running the reaction in the presence of molecular sieves suppressed the formation of **8** and **1i**, but none of the desired indene Nazarov cyclization product was isolated, even when the reaction was carried out in DCE at reflux. The parent ketone of ether **3v** is reported to be a poor Nazarov substrate, requiring forcing conditions, as the cyclization step requires dearomatization.[53]



Scheme 25: Attempted Oxidation-Initiated Nazarov Reaction of Ether **3v**.



Scheme 26: Formation of Acetal **8** and Enone **1i**.

The use of stochiometric DDQ for the oxidation initiated Nazarov reaction had been shown to be effective for generating the reactive pentadienyl cation intermediate and allowing the Nazarov reaction to proceed unhindered. The moderate toxicity of DDQ (LD_{50} = 83 mg/kg),[54] in addition to the potential for

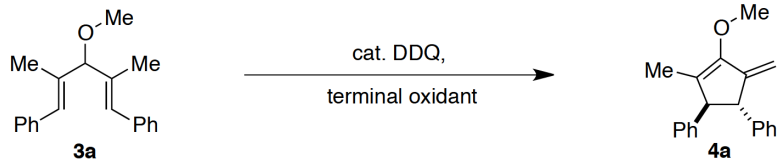
HCN liberation in the presence of moisture, led us to explore the use of catalytic DDQ with a stoichiometric terminal oxidant with ether substrate **3a**. Both HNO_3[55] and $FeCl_3$[56] are known to regenerate DDQ from its reduced hydroquinone form; however, one goal of this oxidative approach to the Nazarov reaction was to avoid the use of strong Brønsted or Lewis acids. Inspired by a recent report by Floreancig and Liu[57] successfully employing catalytic DDQ with MnO_2 as a stoichiometric oxidant for oxidative cyclizations, dehydrogenations, and cross dehydrogenative couplings, as well as an account reported by Helquist and coworkers[46] using catalytic DDQ with $Mn(OAc)_3$ as terminal oxidant for benzylic and allylic oxidations, we hoped to apply these manganese oxidants for regenerating DDQ to our oxidation-initiated Nazarov reaction.

In theory, one equivalent of MnO_2 would be sufficient for stoichiometric oxidation of the ether substrate via regeneration of catalytic DDQ, However, past experience with MnO_2 oxidations of allylic alcohols had required several equivalents for complete consumption of starting material. As a starting point, we used 0.2 equivalents of DDQ, with 5.0 equivalents of terminal oxidant MnO_2. While the reaction was successful, the reaction time and yields were highly variable (Table 4, Entry 1). Lowering either the MnO_2 loading or DDQ loading independently resulted in reactions that were incomplete after 48 hours (Entries 2 and 3). Doubling the MnO_2 loading to 10.0 equiv while reducing DDQ loading to 0.1 equiv resulted in extended reaction times and variable yields (Entry 4). When 10.0 equivalents of MnO_2 were used, the reaction mixture was a thick slurry; we suspected that inadequate magnetic stirring was a possible cause of the variable reaction times. We found that by adding half of the MnO_2 at the outset and adding the remaining half after 8 hours, the yields and reaction times were much more reproducible (Entry 6). A second solution was to dilute the reaction mixture two fold. The resulting slurry was significantly thinner and less prone to difficulties with magnetic agitation. Again the yields and reaction times were more reproducible (Entry 7). While both methods were successful in ensuring the reaction conditions were reproducible, we preferred the method described in Entry

7 for operational simplicity; however, the method described in Entry 6 may be more amenable to larger scale reactions where high dilution is less desirable.

With what was learned from optimization using MnO_2, we tested $Mn(OAc)_3$ as a terminal oxidant for regenerating DDQ. Although 2 equivalents of $Mn(OAc)_3$ are required to reoxidize 2,3-dichloro-5,6-dicyanohydroquinone to DDQ,[58] we chose to use the 5.0 equivalents previously optimized for MnO_2, which we hoped would be a sufficiently large excess. $Mn(OAc)_3$ is commercially available as $Mn(OAc)_3 \bullet 2H_2O$; and we worried that the water of hydration might interfere by hydrolysis of the intermediate pentadienyl cation. Accordingly, 4 Å MS were added to the reaction mixture to sequester any water released from the manganese acetate. The reaction was high yielding and proceeded more rapidly than with MnO_2 (Entry 9); we also found that the exclusion of molecular sieves had little effect on the reaction (Entry 10). While $Mn(OAc)_3$ was successful in reoxidizing DDQ, allowing us to use it catalytically, it is actually more expensive on a per mol basis than DDQ,[59] making it a less than ideal choice of oxidant. Finally, we investigated the use of a catalytic *t*-BuONO/O_2 system reported by Hu and coworkers for the reoxidation of DDQ.[60] This system could allow us to avoid the use of a superstoichiometric terminal oxidant; however, after 48 hours, large amounts of starting material remained as observed by TLC. The yield of 16% corresponds closely to the 20 mol% of DDQ in the reaction mixture, suggesting that DDQ was not regenerated after 48 hours under these reaction conditions (Entry 11).

Table 4: Use of Catalytic DDQ With Stoichiometric Terminal Oxidants.



Entry[a]	DDQ (equiv.)	Oxidant (equiv.)	Solvent	Conc. [M]	Time (h)	Yield (%)[b]
1	0.2	MnO_2 (5.0)	CH_2Cl_2	[0.1]	20-44	60-84
2	0.2	MnO_2 (2.0)	CH_2Cl_2	[0.1]	48	-[c]
3	0.1	MnO_2 (5.0)	CH_2Cl_2	[0.1]	48	-[c]
4	0.1	MnO_2 (10.0)	CH_2Cl_2	[0.1]	32-48	53-80
5	0	MnO_2 (5.0)	CH_2Cl_2	[0.1]	48	-[c]
6	0.2	MnO_2 (5.0)[d]	CH_2Cl_2	[0.1]	28	79-84
7	0.2	MnO_2 (5.0)	CH_2Cl_2	[0.05]	28	84-86
8	0.2	MnO_2 (5.0)	CH_3NO_2	[0.05]	16	82
9[e]	0.2	$Mn(OAc)_3$ (5.0)	CH_2Cl_2	[0.05]	20	84
10	0.2	$Mn(OAc)_3$ (5.0)	CH_2Cl_2	[0.05]	20	80
11[f]	0.2	*t*-BuONO/O_2 (0.2)	DCE	[0.05]	48	16

[a]All crude reaction mixtures were slurried with celite before quenching to speed filtration. [b]Isolated yield after purification. [c]Reaction incomplete after 48 h. [d]2.5 equiv. MnO_2 were added at the beginning of the reaction, and a second dose of 2.5 equiv. was added at 8 h. [e]Reaction run with 4 Å MS. [f]Reaction run at 80 °C under an O_2 atmosphere in a sealed tube.

3.3 Summary

We were able to develop an oxidation initiated Nazarov reaction of bis(allylic) ethers. This process involved the DDQ oxidation of the bis(allylic) ether substrates, generating a reactive 3-oxidopentadienyl cation intermediate that successfully underwent Nazarov cyclization. The final products were enol ethers

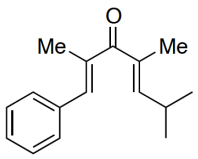
bearing an exo methylene, resulting from a highly regioselective elimination step. This exo elimination was notable, as it left the two new stereocenters formed in the stereospecific cyclization step untouched. We attempted arene trapping with electron rich arenes tethered through the C-3 ether; however, these attempted interrupted Nazarov reactions were unsuccessful, leading instead to the simple Nazarov products. At present, it appears that arene substitution is required at one terminus of the bis(allylic) ether in order for the oxidation step to proceed, as indicated by the failure of bis(allylic) ether **3v** to undergo Nazarov reaction. The DDQ initiated Nazarov cyclization of bis(allylic) ethers permits the use of a new class of alternative substrates, a new and minld method of activation, and affords a new type of Nazarov products (dienol ethers).

3.4 Experimental

General Information

Reactions were carried out in flame dried glassware under an argon atmosphere. Anhydrous solvents and reagents were transferred using oven dried cannulae or syringes. Solvents were distilled before use: dichloromethane, dichloroethane and acetonitrile from calcium hydride, benzene, tetrahydrofuran and diethyl ether from sodium/benzophenone ketyl. Reactions were monitored with 0.5 mm Kieselgel 60 F254 TLC plates (Merck). Flash chromatography was performed using 230-400 mesh silica gel (Silicycle). Radial chromatography was performed using a Harrison Research Chromatatron Centrifugal Thin Layer Chromatograph Model 7924T. Nuclear magnetic resonance spectra were recorded at 400 MHz or 500 MHz for ^{1}H NMR and 100 or 125 Hz, for ^{13}C NMR. Coupling constants (*J*) are reported in Hertz (Hz). Chemical shifts are reported on the δ scale (ppm) and spectra are referenced to chloroform (7.26 ppm, ^{1}H; 77.06 ppm, ^{13}C) as an internal standard. Infrared spectra were measured with a Matteson Galaxy Series FT-IR 300 spectrophotometer. Mass spectra were determined on a

Kratos MS50 high-resolution mass spectrometer. Known dienones, and dienols **1a**,[61] **1b**,[52] **1c**,[62] **1d**,[52] **1e**,[51] **1g**,[63] **1h**[52], **2a**[51] were prepared by literature procedures.



1f

(*E,E*)-2,4,6-Trimethyl-1-phenylhepta-1,4-dien-3-one 1f. $TiCl_4$ (0.89 mL, 8.0 mmol) was added dropwise to a solution of benzylidene-3-pentanone[64] (1.39 g, 8.00 mmol) in CH_2Cl_2 (32 mL) at -78 °C followed by dropwise addition of *i*Pr_2NEt (1.67 mL, 9.60 mmol). The resulting dark brown solution was stirred at -78 °C for 1 h. Isobutyraldehyde (1.10 mL, 12.0 mmol) was added dropwise, and the reaction mixture was stirred at -78 °C for 2 h, then warmed to rt. The reaction was quenched with water (30 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by flash chromatography gave hydroxy ketones (1.16 g, 4.7 mmol) that were carried directly forward to the next step. The hydroxy ketones were taken up in CH_2Cl_2 (20 mL) and cooled to 0 °C. triethylamine (1.0 mL, 7.1 mmol) was added to the solution, followed by dropwise addtion of methanesulfonyl chloride (0.47 mL, 6.1 mmol). The reaction was stirred for 5 h at rt. DBU (2.1 mL, 14.1 mmol) was added dropwise, and the mixture was stirred overnight. The reaction was quenched with 1 M HCl (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with water (2 x 20 mL), brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by flash chromatography gave 0.82 g (45%) of the desired dienone **1f** as a yellow oil.

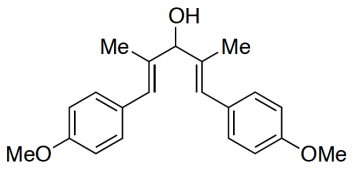
R_f 0.47 (10:1 Hexane : EtOAc);

IR (film) 3026, 2961, 2928, 2870, 1637, 1492, 1448 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 4H), 7.36 – 7.30 (m, 1H), 7.04 (m, 1H), 6.13 (dq, 1H, *J* = 9.5, 1.4 Hz), 2.75 (dsept, 1H, *J* = 9.4, 6.6 Hz), 2.13 (d, 3H, *J* = 1.4 Hz), 1.92 (d, 3H, *J* = 1.4 Hz), 1.06 (d, 6H, *J* = 6.6 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 149.9, 138.2, 137.1, 136.2, 133.6, 129.5, 128.4, 128.1, 28.2, 22.1, 14.9, 12.8;

HRMS calc'd for $C_{16}H_{20}O$ (M^+) 228.1514; found 228.1514.



2b

***(E,E)*-1,5-Bis(4-methoxyphenyl)penta-1,4-dien-3-ol 2b**. 1,5-Bis(4-methoxyphenyl) penta-1,4-dien-3-one **1b** (1.29 g, 4.0 mmol) and $CeCl_3 \bullet 7H_2O$ (1.49 g, 4.0 mmol) were dissolved in MeOH (10 mL) at rt. $NaBH_4$ (151 mg, 4.0 mmol) was added, and rapid evolution of gas was observed. The reaction mixture was stirred for 30 min. The reaction was quenched with 1M HCl (10 mL), and the mixture was extracted with diethyl ether (3 x 15 mL), the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude dienol was purified by flash chromatography (10 : 1 hexane : EtOAc) to give 1.19 g (92%) of **2b** as a pale orange oil.

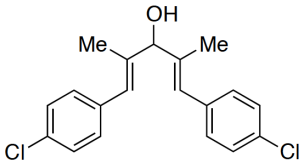
R_f 0.32 (5:1 Hexane : EtOAc);

IR (film) 3474, 3031, 2956, 2911, 1607, 1511, 1463, 1442, 1250, 1178, 1034 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.26 (m, 4H), 6.90 – 6.88 (m, 4H), 6.64 (br s, 2H), 4.68 (m, 1H), 3.82 (s, 6H), 1.87 (d, 1H, *J* = 3.2 Hz), 1.83 (d, 6H, *J* = 1.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 136.4, 130.3, 130.2, 125.9, 113.6, 82.6, 55.3, 14.1;

HRMS calc'd for $C_{21}H_{24}O_3$ (M^+) 324.1725; found 324.1725.



2c

(*E,E*)-1,5-Bis(4-chlorophenyl)penta-1,4-dien-3-ol 2c. (*E,E*)-1,5-Bis(4-chlorophenyl)penta-1,4-dien-3-ol was prepared from 1,5-bis(4-chlorophenyl)penta-1,4-dien-3-one **1c** (1.25 g, 4.0 mmol) according to the procedure described for **2b**. Purification by flash chromatography (10:1 hexane : EtOAc) furnished 1.16 g (87%) of dienol **2c** as a colorless oil.

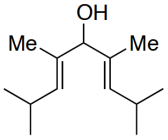
R_f 0.44 (5:1 Hexane : EtOAc)

IR (film) 3373, 3028, 2958, 2915, 1491, 1092, 1013 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.30 (m, 4H), 7.25 – 7.23 (m, 4H), 6.65 (br s, 2H), 4.69 (m, 1H), 1.86 (d, 1H, J = 3.2 Hz), 1.81 (d, 6H, J = 1.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 136.0, 132.4, 130.3, 128.4, 125.6, 82.2, 14.1;

HRMS calc'd for $C_{19}H_{18}{}^{35}Cl_2O$ (M^+) 332.0735; found 332.0728.



2d

(*E,E*)-1,5-Bis(isopropyl)penta-1,4-dien-3-ol 2d. (*E,E*)-1,5-Bis(isopropyl)penta-1,4-dien-3-ol **2d** was prepared from diisopropylidene-3-pentanone **1d** (785 mg, 4.0 mmol) according to the procedure described for **2b**. Purification by flash chromatography (10:1 hexane : EtOAc) furnished 730 g (93%) of dienol **2c** as a colorless oil.

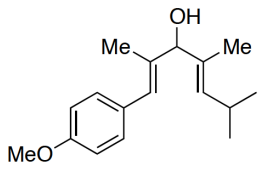
R_f 0.49 (5:1 Hexane : EtOAc);

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.33 (m, 2H), 4.28 (br s, 1H), 2.55 (dsept, 2H, *J* = 9.2, 6.6 Hz), 1.51 (br s, 1H), 1.48 (d, 6H, *J* = 1.3 Hz), 0.97 (d, 6H, *J* = 6.6 Hz), 0.96 (d, 6H, *J* = 6.6 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 133.9, 131.0, 83.5, 27.1, 23.0, 22.9, 12.3;

IR (film) 3379, 3025, 2962, 2924, 1465, 1051 cm^{-1};

HRMS calc'd for $C_{13}H_{24}O$ (M^+) 196.1827; found 196.1826.



2e

(*E,E*)-1-(4-Methoxyphenyl)-2,4,6-trimethylhepta-1,4-dien-3-ol 2e. (*E,E*)-1-(4-Methoxyphenyl)-2,4,6-trimethylhepta-1,4-dien-3-ol **2e** was prepared from 1-(4-methoxyphenyl)-2,4,6-trimethylhepta-1,4-dien-3-one **1e** (1.03 g, 4.0 mmol) according to the procedure described for **2b**. Purification by flash chromatography (10:1 hexane : EtOAc) furnished 948 g (91%) of dienol **2e** as an orange oil.

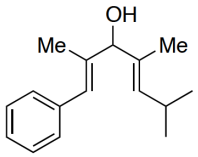
R_f 0.35 (5:1 Hexane : EtOAc);

IR (film) 3436, 3031, 2956, 2934, 2866, 1608, 1511, 1465, 1250, 1177, 1037 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.23 (m, 2H), 6.89 – 6.87 (m, 2H), 6.57 (m, 1H), 5.41 (m, 1H), 4.48 (s, 1H), 3.81 (s, 3H), 2.58 (dsept, 1H, *J* = 9.0, 6.6 Hz), 1.74 (d, 3H, *J* = 1.2 Hz), 1.70 (d, 1H, *J* = 3.1 Hz), 1.57 (d, 3H, *J* = 1.3 Hz), 1.00 (d, 3H, *J* = 6.6 Hz), 0.98 (d, 3H, *J* = 6.6 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 136.6, 134.8, 132.6, 130.5, 130.2, 125.1, 113.6, 82.0, 55.3, 27.1, 23.0, 14.1, 12.0;

HRMS calc'd for $C_{17}H_{24}O_2$ (M^+) 260.1776; found 260.1777.



2f

(*E,E*)-2,4,6-Trimethyl-1-phenylhepta-1,4-dien-3-ol 2f. (*E,E*)-2,4,6-Trimethyl-1-phenylhepta-1,4-dien-3-ol **2f** was prepared from (*E,E*)-2,4,6-Trimethyl-1-phenylhepta-1,4-dien-3-one(685 mg, 3.0 mmol) according to the procedure described for **2b**. Purification by flash chromatography (10:1 hexane : EtOAc) furnished 656 g (95%) of dienol **2f** as a yellow oil.

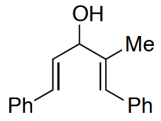
R_f 0.46 (10:1 Hexane : EtOAc);

IR (film) 3372, 3056, 3024, 2957, 2926, 2867, 1492, 1465, 1446, 1054 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 4H), 7.24 – 7.20 (m, 1H), 6.65 (br s, 1H), 5.42 (m, 1H), 4.51 (s, 1H), 2.59 (dsept, 1H, J = 9.1, 6.7 Hz), 1.75 (d, 3H, J = 1.4 Hz), 1.74 (br s, 1H), 1.59 (d, 3H, J = 1.4 Hz), 1.00 (d, 3H, J = 6.9 Hz), 0.9 (d, 3H, J = 6.9 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 137.9, 135.1, 132.6, 129.0, 128.1, 126.3, 125.5, 81.9, 27.1, 22.9, 14.2, 11.9;

HRMS calc'd for $C_{16}H_{22}O$ (M^+) 230.1671; found 230.1669.



2g

***(E,E)*-2-Methyl-1,5-diphenyl-1,4-pentadien-3-ol 2g.** (*E,E*)-2-Methyl-1,5-diphenyl-1,4-pentadien- 3-ol **2g** was prepared from 2-methyl-1,5-diphenyl-1,4-pentadien-3-one **1g** (1.24 g, 5.0 mmol) according to the procedure described for

2b. Purification by flash chromatography (10:1 hexane : EtOAc) furnished 1.10 g (88%) of dienol **2g** as a pale yellow oil.

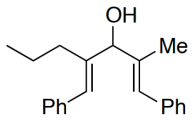
R_f 0.43 (5:1 Hexane : EtOAc)

IR (film) 3381, 3055, 3023, 2977, 2921, 2819, 1601, 1490, 1446, 1055 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.37 (m, 2H), 7.35 – 7.331 (m, 6H), 7.27 – 7.23 (m, 2H), 6.68 (d, 1H, J = 16.4 Hz), 6.63 (s, 1H), 6.22 (dd, 1H, J = 16.4, 6.2 Hz), 4.76 (s, 1H), 1.84 (br s, 1H), 1.98 (d, 3H, J = 1.2 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 137.0, 136.8, 131.5, 128.9, 128.8, 128.6, 128.1, 127.7, 127.6, 126.7, 126.5, 81.3, 13.4;

HRMS calc'd for $C_{18}H_{28}O$ (M^+) 250.1358; found 250.1358.



2h

(*E,E*)-2-Methyl-1-phenyl-4-(phenylmethylidene)hept-1-en-3-ol 2h. (*E,E*)-2-Methyl-1-phenyl-4-(phenylmethylidene)hept-1-en-3-ol **2h** was prepared from 2-methyl-1-phenyl-4-(phenylmethylene)-1-hepten-3-one **1h** (1.45 g, 5.0 mmol) according to the procedure described for **2b**. Purification by flash chromatography (10:1 hexane : EtOAc) furnished 1.42 g (97%) of dienol **2g** as a pale yellow oil.

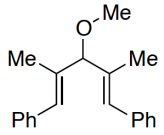
R_f 0.49 (5:1 Hexane : EtOAc);

IR (film) 3369, 3055, 3024, 2958, 2930, 1600, 1493, 1445, 1075 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 8H), 7.27 – 7.22 (m, 2H), 6.73 (s, 1H), 6.72 (s, 1H), 4.80 (m, 1H), 2.34 (m, 1H), 2.14 (m, 1H), 1.86 (d, 3H, J = 1.4 Hz), 1.82 (m, 1H); 1.55 (m, 2H), 0.93 (t, 3H, J = 7.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 138.4, 137.8, 137.7, 129.0, 128.7, 128.3, 128.2, 127.1, 126.6, 126.5, 126.4, 81.0, 30.8, 22.3, 14.5, 13.9;

HRMS calc'd for $C_{21}H_{24}O$ (M^+) 292.1827; found 292.1825.



3a

(*E,E*)-3-Methoxy-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene 3a. (*E,E*)-2,4-Dimethyl-1,5-diphenyl-1,4-pentadien-3-ol **2a** (2.64 g, 10.0 mmol) was dissolved in DMF (10 mL) and cooled to 0 °C. Sodium hydride 60% in mineral oil (0.6 g, 15 mmol), was added, and vigorous gas evolution was observed. Iodomethane (0.93 mL, 15 mmol) was added dropwise. The reaction mixture was warmed to rt and stirred until starting material was consumed as observed by TLC (1 h). The reaction mixture was quenched by addition of water (100 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with water (2 x 50 mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (20 : 1 hexane : EtOAc) furnished 2.50 g (90 %) of ether **3a** as a colorless oil.

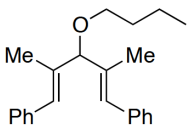
R_f 0.52 (10:1 Hexane : EtOAc);

IR (film) 3081, 3056, 3023, 2980, 2930, 1600, 1492, 1445, 1094 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 8H), 7.24 – 7.20 (m, 2H), 6.67 (m, 2H), 4.13 (s, 1H), 3.40 (s, 3H), 1.81 (d, 6H, J = 1.3 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 136.2, 129.1, 128.2, 127.2, 126.5, 91.4, 56.2, 14.1;

HRMS calc'd for $C_{20}H_{22}O$ (M^+) 278.1671; found 278.1671.



3b

(*E,E*)-3-Butoxy-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene 3b. (*E,E*)-3-Butoxy-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene **3b** was prepared from (*E,E*)-*2*,4-dimethyl-1,5-diphenyl-1,4-pentadien-3-ol **2a** (528 mg, 2.0 mmol) and bromobutane (0.22 mL, 4.0 mmol) according to the procedure described for **3a**. Purification by flash chromatography (10:1 hexane : EtOAc) furnished 557 mg (87%) of ether **3b** as a colorless oil.

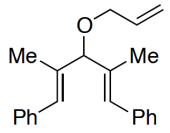
R_f 0.54 (10:1 Hexane : EtOAc);

IR (film) 3081, 3056, 3024, 2957, 2932, 2870, 1599, 1492, 1446, 1095 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 8H), 7.30 – 7.26 (m, 2H), 6.73 (s, 2H), 4.27 (s, 1H), 3.53 (t, 2H, J = 6.5 Hz), 1.88 (m, 6H), 1.74 – 1.69 (m, 2H), 1.55 – 1.48 (m, 2H), 1.02 (t, 3H, J = 7.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 136.7, 129.1, 128.1, 126.9, 126.4, 89.5, 68.2, 32.1, 19.7, 14.2, 14.1;

HRMS calc'd for $C_{23}H_{28}O$ (M^+) 320.2140; found 320.2140.



3c

(*E,E*)-3-Allyloxy-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene 3c. (*E,E*)-3-Allyloxy-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene **3b** was prepared from (*E,E*)-*2*,4-dimethyl-1,5-diphenyl-1,4-pentadien-3-ol **2a** (528 mg, 2.0 mmol) and allyl bromide (0.35 mL, 4.0 mmol) according to the procedure described for **3a**. Purification by flash chromatography (10:1 hexane : EtOAc) furnished 559 mg (92%) of ether **3c** as a colorless oil.

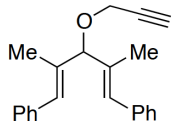
R_f 0.51 (10:1 Hexane : EtOAc);

3081, 3056, 3024, 2980, 2919, 2853, 1600, 1492, 1445, 1078 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 8H), 7.30 – 7.26 (m, 2H), 6.74 (m, 2H), 6.06 (app ddt, 1H, *J* = 17.2, 10.6, 5.4 Hz), 5.41 (app dq, 1H, *J* = 17.1, 1.7 Hz), 5.26 (app dq, 1H, *J* = 10.5, 1.7 Hz), 4.35 (s, 1H), 4.11 (app t, 1H, *J* = 1.4 Hz), 4.10 (app t, 1H, *J* = 1.4 Hz), 1.88 (d, 6H, *J* = 1.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 136.3, 135.1, 129.1, 128.2, 127.3, 126.5, 116.6, 88.8, 69.1, 14.2;

HRMS calc'd for $C_{22}H_{24}O$ (M^+) 304.1827; found 304.1829.



3d

(*E*,*E*)-2,4-Dimethyl-1,5-diphenyl-3-(2-propynyloxy)-1,4-pentadiene 3d. (*E*,*E*)-2,4-Dimethyl-1,5-diphenyl-3-(2-propynyloxy)-1,4-pentadiene **3d** was prepared from (*E*,*E*)-2,4-dimethyl-1,5-diphenyl-1,4-pentadien-3-ol **2a** (528 mg, 2.0 mmol) and propargyl bromide (0.30 mL, 4.0 mmol) according to the procedure described for **3a**. Purification by flash chromatography (20:1 hexane : EtOAc) furnished 492 mg (81%) of ether **3d** as a colorless oil.

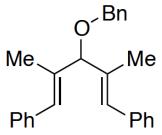
R_f 0.45 (10:1 Hexane : EtOAc);

IR (film) 3292, 3081, 3055, 3024, 2949, 2914, 2855, 2117, 1599, 1491, 1443, 1078 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 8H), 7.25 – 7.22 (m, 2H), 6.70 (m, 2H), 4.52 (s, 1H), 4.24 (d, 2H, *J* = 2.4 Hz), 2.46 (t, 1H, *J* = 2.4 Hz), 1.83 (d, 6H, *J* = 1.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 135.3, 129.1, 128.2, 127.9, 126.6, 88.0, 80.1, 74.3, 55.3, 14.2;

HRMS calc'd for $C_{22}H_{22}O$ (M^+) 302.1671; found 302.1670.



3e

(*E*,*E*)-3-Benzyloxy-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene 3e. (*E*,*E*)-3-Benzyloxy-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene **3e** was prepared from (*E*,*E*)-*2*,4-dimethyl-1,5-diphenyl-1,4-pentadien-3-ol **2a** (528 mg, 2.0 mmol) and benzyl bromide (0.26 mL, 2.2 mmol) according to the procedure described for **3a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 588 mg (83%) of ether **3e** as a colorless oil.

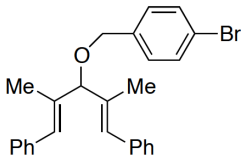
R_f 0.53 (10:1 Hexane : EtOAc);

IR (film) 3082, 3059, 3025, 2940, 2913, 2858, 1599, 1493, 1452, 1091, 1073 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.43 (m, 2H), 7.40 – 7.35 (m, 10H), 7.33 – 7.30 (m, 1H), 7.27 – 7.23 (m, 2H), 6.74 (m, 2H), 4.62 (s, 2H), 4.37 (s, 1H), 1.87 (d, 6H, J = 1.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 137.8, 136.2, 129.1, 128.4, 128.2 (2 overlapping signals), 127.6, 127.5, 126.5, 88.8, 70.0, 14.2;

HRMS calc'd for $C_{26}H_{26}O$ (M^+) 354.1984; found 354.1993.



3f

(*E*,*E*)-3-(*p*-Bromobenzyloxy)-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene 3f. (*E*,*E*)-3-(*p*-Bromobenzyloxy)-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene **3f** was prepared from (*E*,*E*)-*2*,4-dimethyl-1,5-diphenyl-1,4-pentadien-3-ol **2a** (528 mg, 2.0 mmol) and 4-bromobenzyl bromide (550 mg, 2.2 mmol) according to the

procedure described for **3a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 667 mg (77%) of ether **3e** as a yellow oil.

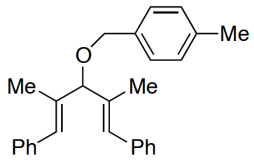
R_f 0.50 (10:1 Hexane : EtOAc);

IR (film) 3081, 3054, 3023, 2947, 2913, 2856, 1599, 1489, 1446, 1072, 1011, 752 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.48 (m, 2H), 7.37 – 7.28 (m, 10H), 7.26 – 7.22 (m, 2H), 6.70 (s, 2H), 4.54 (s, 2H), 4.32 (s, 1H), 1.84 (d, 6H, *J* = 1.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 137.7, 136.0, 131.5, 129.2, 129.1, 128.2, 127.6, 126.6, 121.3, 88.9, 69.2, 14.2;

HRMS calc'd for $C_{26}H_{25}{}^{79}BrO$ (M^+) 432.1089; found 432.1089.



3g

(*E*,*E*)-3-(*p*-Methylbenzyloxy)-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene 3g. (*E*,*E*)-3-(*p*-Methylbenzyloxy)-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene **3g** was prepared from (*E*,*E*)-2,4-dimethyl-1,5-diphenyl-1,4-pentadien-3-ol **2a** (528 mg, 2.0 mmol) and 4-methylbenzyl bromide (407 mg, 2.2 mmol) according to the procedure described for **3a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 633 mg (86%) of ether **3g** as an orange oil.

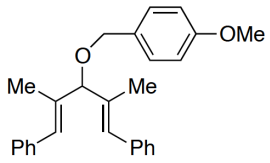
R_f 0.52 (10:1 Hexane : EtOAc);

IR (film) 3081, 3053, 3023, 2918, 2858, 1599, 1491, 1445, 1077 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 10H), 7.28 – 7.21 (m, 4H), 6.76 (m, 2H), 4.59 (s, 2H), 4.37 (m, 1H), 2.40 (s, 3H), 1.89 (d, 6H, *J* = 1.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 137.1, 136.3, 135.7, 129.1, 129.1, 128.1, 127.7, 127.4, 126.4, 88.6, 69.8, 21.2, 14.2;

HRMS calc'd for $C_{27}H_{28}O$ (M^+) 368.2140; found 368.2140.



3h

(*E*,*E*)-3-(*p*-Methoxybenzyloxy)-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene 3h. (*E*,*E*)-3-(*p*-Methoxybenzyloxy)-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene **3h** was prepared from (*E*,*E*)-*2*,4-dimethyl-1,5-diphenyl-1,4-pentadien-3-ol **2a** (528 mg, 2.0 mmol) and 4-methoxybenzyl chloride (0.30 mL, 2.2 mmol) according to the procedure described for **3a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 676 mg (88%) of ether **3h** as an orange oil.

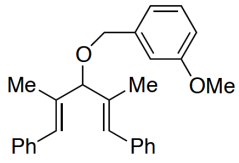
R_f 0.37 (10:1 Hexane : EtOAc);

3080, 3054, 3023, 3023, 2953, 2935, 2857, 2835, 1612, 1600, 1513, 1442, 1248, 1076, 1036 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 10H), 7.25 – 7.21 (m, 2H), 6.92 – 6.89 (m, 2H), 6.70 (s, 2H), 4.52 (s, 2H), 4.32 (s, 1H), 3.82 (s, 3H), 1.84 (d, 6H, *J* = 1.2 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 137.8, 136.3, 130.8, 129.2, 129.1, 128.2, 127.4, 126.5, 113.8, 88.5, 69.7, 55.3, 14.3;

HRMS calc'd for $C_{27}H_{28}O_2$ (M^+) 384.2089; found 384.2089.



3i

(*E*,*E*)-3-(*m*-Methoxybenzyloxy)-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene 3i. (*E*,*E*)-3-(*m*-Methoxybenzyloxy)-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene **3i** was prepared from (*E*,*E*)-2,4-dimethyl-1,5-diphenyl-1,4-pentadien-3-ol **2a** (528 mg,

2.0 mmol) and 3-methoxybenzyl chloride (0.32 mL, 2.2 mmol) according to the procedure described for **3a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 607 mg (79%) of ether **3i** as an orange oil.

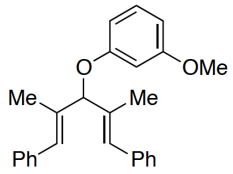
R_f 0.42 (10:1 Hexane : EtOAc);

IR (film) 3081, 3054, 3023, 2953, 2857, 2835, 1600, 1587, 1490, 1266, 1076, 1053 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, 8H), 7.34 – 7.26 (m, 3H), 7.04 – 7.02 (m, 2H), 6.89 – 6.87 (m, 1H), 6.76 (m, 2H), 4.62 (s, 2H), 4.38 (s, 1H), 3.86 (s, 3H), 1.89 (d, 6H, J = 1.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 140.5, 137.8, 136.2, 129.4, 129.1, 128.2, 127.5, 126.5, 119.8, 113.0, 112.9, 88.8, 69.8, 55.3, 14.3;

HRMS calc'd for $C_{27}H_{28}O_2$ (M^+) 384.2089; found 384.2099.



3j

(*E*,*E*)-3-(*m*-Methoxyphenoxy)-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene 3j. A 10 mL Biotage microwave reaction vial was charged with (*E*,*E*)-2,4-dimethyl-1,5-diphenyl-1,4-pentadien-3-ol **2a** (1.59 g, 6.0 mmol), 3-iodoanisole (0.48 mL, 4.0 mmol), CuI (38 mg, 0.2 mmol), 3,4,7,8-tetramethyl-1,10-phenanthroline (95 mg, 0.4 mmol), and Cs_2CO_3 (1.96 g, 6.0 mmol). The reaction vial was sealed, evacuated, and back-filled with argon. Toluene (4.0 mL) was added via syringe, and the reaction mixture was heated at 110 °C for 24 h. The reaction was cooled to rt, diluted with EtOAc (20 ml), filtered through a silica gel plug, and eluted with additional EtOAc (100 mL). The filtrate was concentrated and further purification by flash chromatography (40:1 hexane : EtOAc) furnished 0.90 g (61%) of ether **3j** as a colorless oil.

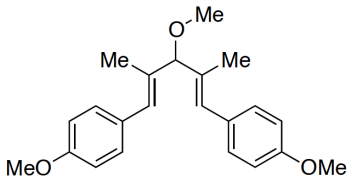
R_f 0.40 (10:1 Hexane : EtOAc);

IR (film) 3055, 3023, 2919, 2835, 1598, 1490, 1148, 1047 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 8H), 7.25 – 7.21 (m, 2H), 7.17 (t, 1H, *J* = 8.1 Hz), 6.73 (s, 2H), 6.63 – 6.60 (m, 2H), 6.53 – 6.51 (m, 1H), 5.07 (s, 1H), 3.80 (s, 3H), 1.94 (d, 6H, *J* = 1.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 159.4, 137.5, 135.3, 129.8, 129.1, 128.2, 127.8, 126.7, 108.5, 106.7, 102.6, 88.0, 55.31, 14.4;

HRMS calc'd for $C_{26}H_{26}O_2$ (M^+) 370.1933; found 370.1933.



3k

(*E*,*E*)-3-Methoxy-2,4-dimethyl-1,5-bis(*p*-methoxyphenyl)-1,4-pentadiene 3k. (*E*,*E*)-3-Methoxy-2,4-dimethyl-1,5-bis(4-methoxyphenyl)-1,4-pentadiene **3k** was prepared from (*E*,*E*)-1,5-bis(4-methoxyphenyl)penta-1,4-dien-3-ol **2b** (649 mg, 2.0 mmol) and iodomethane (0.19 mL, 3.0 mmol) according to the procedure described for **3a**. Purification by flash chromatography (10:1 hexane : EtOAc) furnished 623 mg (92%) of ether **3k** as an orange oil.

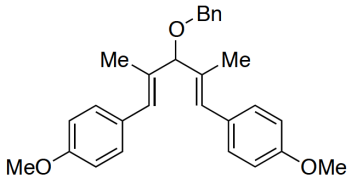
R_f 0.38 (10:1 Hexane : EtOAc);

IR (film) 3032, 2953, 2934, 2835, 1607, 1510, 1464, 1249, 1094, 1037 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 4H), 6.90 – 6.88 (m, 4H), 6.59 (m, 2H), 4.10 (s, 1H), 3.82 (s, 6H), 3.38 (s, 3H), 1.80 (m, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 134.6, 130.4, 130.4, 126.5, 113.6, 91.6, 56.2, 55.3, 14.1;

HRMS calc'd for $C_{22}H_{26}O_3$ (M^+) 338.1882; found 388.1880.



3l

(*E*,*E*)-3-Benzyloxy-2,4-dimethyl-1,5-bis(*p*-methoxyphenyl)-1,4-pentadiene 3l. (*E*,*E*)-3-Benzyloxy-2,4-dimethyl-1,5-bis(*p*-methoxyphenyl)-1,4-pentadiene **3l** was prepared from (*E*,*E*)-1,5-bis(*p*-methoxyphenyl)penta-1,4-dien-3-ol **2b** (649 mg, 2.0 mmol) and benzyl bromide (0.26 mL, 2.2 mmol) according to the procedure described for **3a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 705 mg (85%) of ether **3l** as a yellow oil.

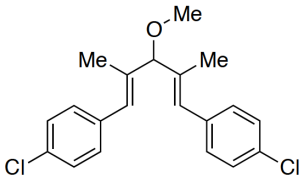
R_f 0.35 (10:1 Hexane : EtOAc);

IR (film) 3061, 3031, 2953, 2933, 2835, 1607, 1510, 1464, 1454, 1249, 1072, 1036 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 4H), 7.32 – 7.28 (m, 5H), 6.93 – 6.89 (m, 4H), 6.65 (s, 2H), 4.85 (s, 2H), 4.32 (s, 1H), 3.83 (s, 6H), 1.84 (m, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 138.9, 134.6, 130.5, 130.3, 128.3, 127.6, 127.4, 126.8, 113.6, 89.1, 69.9, 55.3, 14.3;

HRMS calc'd for $C_{28}H_{30}O_3$ (M^+) 414.2195; found 414.2195.



3m

(*E*,*E*)-3-Methoxy-2,4-dimethyl-1,5-bis(*p*-chlorophenyl)-1,4-pentadiene 3m. (*E*,*E*)-3-Methoxy-2,4-dimethyl-1,5-bis(*p*-chlorophenyl)-1,4-pentadiene **3m** was prepared from (*E*,*E*)-1,5-bis(*p*-chlorophenyl)penta-1,4-dien-3-ol **2c** (649 mg, 2.0 mmol) and iodomethane (0.19 mL, 3.0 mmol) according to the procedure

described for **3a**. . Purification by flash chromatography (20:1 hexane : EtOAc) furnished 604 mg (94%) of ether **3m** as a colorless oil.

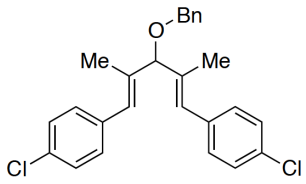
R_f 0.50 (10:1 Hexane : EtOAc);

IR (film) 3027, 2980, 2932, 2822, 1490, 1445, 1093, 1013 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 4H), 7.26 – 7.23 (m, 4H), 6.60 (s, 2H), 4.10 (s, 1H), 3.38 (s, 3H), 1.77 (d, 6H, J = 1.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 136.1, 132.3, 130.3, 128.3, 126.2, 91.1, 56.3, 14.0;

HRMS calc'd for $C_{20}H_{20}{}^{35}Cl_2O$ (M^+) 346.0891; found 346.0889.



3n

(*E*,*E*)-3-Benzyloxy-2,4-dimethyl-1,5-bis(*p*-chlorophenyl)-1,4-pentadiene 3n. (*E*,*E*)-3-Benzyloxy-2,4-dimethyl-1,5-bis(*p*-chlorophenyl)-1,4-pentadiene **3n** was prepared from (*E*,*E*)-1,5-Bis(*p*-chlorophenyl)penta-1,4-dien-3-ol **2c** (649 mg, 2.0 mmol) and benzyl bromide (0.26 mL, 2.2 mmol) according to the procedure described for **3a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 677 mg (80%) of ether **3m** as a pale yellow oil.

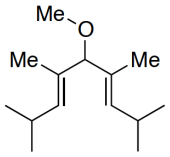
R_f 0.44 (10:1 Hexane : EtOAc);

IR (film) 3087, 3064, 3030, 3029, 2955, 2919, 2857, 1490, 1454, 1092, 1073, 1013 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 5H), 7.36 – 7.34 (m, 4H), 7.30 – 7.27 (m, 4H), 6.69 (s, 2H), 4.91 (s, 2H), 4.35 (s, 1H), 1.84 (d, 6H, J = 1.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 136.9, 136.1, 132.3, 130.3, 128.4, 128.3, 127.6, 127.6, 126.4, 88.6, 70.1, 14.2;

HRMS calc'd for $C_{26}H_{24}{}^{35}Cl_2O$ (M^+) 422.1204; found 422.1199.



3o

(*E,E*)-3-Methoxy-2,4-dimethyl-1,5-bis(isopropyl)-1,4-pentadiene 3o. (*E,E*)-3-Methoxy-2,4-dimethyl-1,5-bis(isopropyl)-1,4-pentadiene **3o** was prepared from (*E,E*)-1,5-bis(isopropyl)penta-1,4-dien-3-ol **2d** (197 mg, 1.0 mmol) and iodomethane (0.094 mL, 32 mmol) according to the procedure described for **3a**. Purification by flash chromatography (20:1 hexane : EtOAc) furnished 191 mg (92%) of ether **3m** as colorless oil.

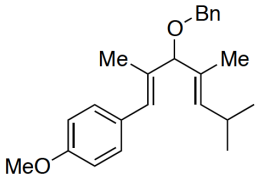
R_f 0.56 (10:1 Hexane : EtOAc);

IR (film) 2961, 2930, 2867, 1464, 1290, 1089, 1071 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 5.29 (m, 2H), 3.71 (br s, 1H), 3.22 (s, 3H), 2.55 (dsept, 2H, *J* = 9.4, 6.6 Hz), 1.44 (d, 6H, *J* = 1.2 Hz), 0.97 (d, 6H, *J* = 6.6 Hz), 0.96 (d, 6H, *J* = 6.6 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 134.8, 130.5, 90.5, 55.7, 27.1, 23.1, 23.0, 12.0;

HRMS calc'd for $C_{14}H_{26}O$ (M^+) 210.1984; found 210.1983.



3p

(*E,E*)-3-(*p*-Methoxybenzyloxy)-2,4,6-trimethyl-1-phenylhepta-1,4-diene 3p. (*E,E*)-3-(*p*-Methoxybenzyloxy)-2,4,6-trimethyl-1-phenylhepta-1,4-diene **3p** was prepared from (*E,E*)-1-(4-methoxyphenyl)-2,4,6-trimethylhepta-1,4-dien-3-ol **2e** (521 mg, 2.0 mmol) and benzyl bromide (0.26 mL, 2.2 mmol) according to the procedure described for **3a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 617 mg (88%) of ether **3p** as an orange oil.

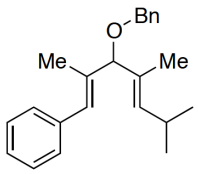
R_f0.43 (10:1 Hexane : EtOAc);

IR (film) 3088, 3063, 3031, 2956, 2933, 2866, 1608, 1511, 1465, 1454, 1299, 1250, 1091, 1072, 1038 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 4H), 7.30 – 7.25 (m, 3H), 6.90 – 6.88 (m, 2H), 6.59 (s, 1H), 5.42 (m, 1H), 4.52 (d, 1H, J_{AB} = 12.1 Hz), 4.49 (d, 1H, J_{AB} = 12.1 Hz), 4.16 (s, 1H), 3.86 (s, 3H), 2.62 (m, 1H), 1.75 (m, 3H), 1.57 (m, 3H), 1.06 (dd, 3H, *J* = 6.6, 1.2 Hz), 1.04 (dd, 3H, *J* = 6.6, 1.2 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 139.1, 136.2, 134.9, 130.7, 130.5, 130.2, 128.3, 127.5, 127.3, 125.8, 113.6, 88.5, 69.6, 55.3, 27.2, 23.1, 23.0, 14.5, 12.1;

HRMS calc'd for $C_{24}H_{30}O_2$ (M^+) 350.2246; found 350.2246.



3q

(*E*,*E*)-3-Benzyloxy-2,4,6-trimethyl-1-phenylhepta-1,4-diene 3q. (*E*,*E*)-3-Benzyloxy-2,4,6-trimethyl-1-phenylhepta-1,4-diene **3q** was prepared from (*E*,*E*)-2,4,6-trimethyl-1-phenylhepta-1,4-dien-3-ol **2f** (461 mg, 2.0 mmol) and benzyl bromide (0.26 mL, 2.2 mmol) according to the procedure described for **3a**. Purification by flash chromatography (60:1 hexane : EtOAc) furnished 532 mg (83%) of ether **3q** as a yellow oil.

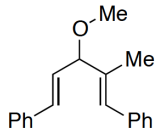
R_f0.50 (10:1 Hexane : EtOAc);

IR (film); 3062, 3027, 2957, 2925, 2867, 1495, 1454, 1072, 1029;

^1H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 9H), 7.23 – 7.19 (m, 1H), 6.67 (m, 1H), 5.41 (m, 1H), 4.53 (d, 1H, J_{AB} = 12.0 Hz) 4.48 (d, 1H, J_{AB} = 12.0 Hz), 4.13 (s, 1H), 2.62 (dsept, 1H, *J* = 9.3, 6.7 Hz), 1.76 (d, 3H, *J* = 1.4 Hz), 1.58 (d, 3H, *J* = 1.4 Hz), 1.02 (d, 3H, *J* = 6.7 Hz), 0.99 (d, 3H, *J* = 6.7 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 138.1, 136.6, 136.5, 130.4, 129.1, 128.3, 128.1, 127.5, 127.3, 126.3, 126.2, 88.4, 69.7, 27.2, 23.1, 23.0, 14.6, 11.9;

HRMS calc'd for $C_{23}H_{28}O$ (M^+) 320.2140; found 320.2135.



3r

(*E,E*)-3-Methoxy-2-methyl-1,5-diphenyl-1,4-pentadiene 3r. (*E,E*)-3-Methoxy-2-methyl-1,5-diphenyl-1,4-pentadiene **3r** was prepared from (*E,E*)-2-methyl-1,5-diphenyl-1,4-pentadien-3-ol **2g** (501 mg, 2.0 mmol) and iodomethane (0.19 mL, 3.0 mmol) according to the procedure described for **3a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 379 mg (75%) of ether **3r** as an orange oil.

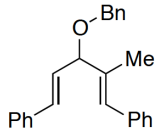
R_f 0.43 (10:1 Hexane : EtOAc);

IR (film) 3080, 3056, 3023, 2976, 2921, 2819, 1600, 1492, 1446, 1103 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.42 (m, 2H), 7.37 – 7.32 (m, 6H), 7.28 – 7.23 (m, 2H), 6.69 (d, 1H, J = 16.5 Hz), 6.63 (s, 1H), 6.25 (dd, 1H, J = 16.5, 6.3 Hz), 4.33 (m, 1H), 3.41 (s, 3H), 1.90 (d, 3H, J = 1.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 137.2, 136.9, 131.5, 129.1, 128.8, 128.6, 128.2, 127.7, 127.6, 126.6, 126.6, 87.7, 56.1, 13.6;

HRMS calc'd for $C_{19}H_{20}O$ (M^+) 264.1514; found 264.1514.



3s

(*E,E*)-3-Benzyloxy-2-methyl-1,5-diphenyl-1,4-pentadiene 3s. (*E,E*)-3-Benzyloxy-2-methyl-1,5-diphenyl-1,4-pentadiene **3r** was prepared from (*E,E*)-2-methyl-1,5-diphenyl-1,4-pentadien-3-ol **2g** (250 mg, 1.0 mmol) and benzyl bromide (0.23 mL, 1.1 mmol) according to the procedure described for **3a**.

Purification by flash chromatography (60:1 hexane : EtOAc) furnished 269 mg (79%) of ether **3s** as an orange oil.

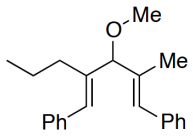
R_f 0.46 (10:1 Hexane : EtOAc);

IR (film) 3082, 3059, 3026, 2917, 2858, 1599, 1494, 1449, 1093, 1012 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.23 (m, 15H), 6.70 (d, 1H, J = 16.0 Hz), 6.63 (s, 1H), 6.03 (dd, 1H, J = 16.0, 6.2 Hz), 4.63 (d, 1H, J_{AB} = 12.2 Hz), 4.56 (d, 1H, J_{AB} = 12.2 Hz), 4.54 (m, 1H), 1.93 (d, 3H, J = 1.2 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 137.5, 137.3, 136.9, 131.5, 129.1, 128.9, 128.6, 128.4, 128.2, 127.9, 127.8, 127.7, 127.6, 126.7, 126.6, 85.2, 69.9, 13.8;

HRMS calc'd for $C_{25}H_{24}O$ (M^+) 340.1827; found 340.1826.



3t

(*E*,*E*)-3-Methoxy-2-methyl-1-phenyl-4-(phenylmethylene)-1-heptene 3t. (*E*,*E*)-3-Methoxy-2-methyl-1-phenyl-4-(phenylmethylene)-1-heptene **3t** was prepared from (*E*,*E*)-2-Methyl-1-phenyl-4-(phenylmethylidene)hept-1-en-3-ol **2h** (585 mg, 2.0 mmol) and iodomethane (0.19 mL, 3.0 mmol) according to the procedure described for **3a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 552 mg (90%) of ether **3t** as a yellow oil.

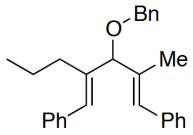
R_f 0.49 (10:1 Hexane : EtOAc);

IR (film) 3081, 3056, 3023, 2958, 2930, 2871, 1600, 1493, 1446, 1097 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 7H), 7.26 – 7.20 (m, 3H), 6.68 (br s, 1H), 6.64 (br s, 1H), 4.19 (s, 1H), 3.39 (s, 3H), 2.31 (m, 1H), 2.07 (m, 1H), 1.80 (m, 3H), 1.59 – 1.46 (m, 2H), 0.90 (t, 3H, J = 7.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 138.0, 136.5, 129.0, 128.8, 128.2, 128.1, 126.7, 126.6, 90.0, 56.4, 30.8, 22.1, 14.5, 13.5;

HRMS calc'd for $C_{22}H_{26}O$ (M^+) 306.1984; found 306.1981.



21b

(*E,E*)-3-Benzyloxy-2-methyl-1-phenyl-4-(phenylmethylene)-1-heptene 3u. (*E,E*)-3-Benzyloxy-2-methyl-1-phenyl-4-(phenylmethylene)-1-heptene **3u** was prepared from (*E,E*)-2-Methyl-1-phenyl-4-(phenylmethylidene)hept-1-en-3-ol **2h** (585 mg, 2.0 mmol) and benzyl bromide (0.26 mL, 2.2 mmol) according to the procedure described for **3a**. Purification by flash chromatography (60:1 hexane : EtOAc) furnished 627 mg (82%) of ether **3t** as a pale yellow oil.

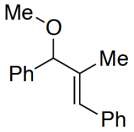
R_f 0.54 (10:1 Hexane : EtOAc);

IR (film); 3081, 3057, 3025, 2958, 2869, 1599, 1493, 1453, 1091, 1074 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.42 (m, 2H), 7.39 – 7.30 (m, 11H), 7.27 – 7.23 (m, 2H), 6.78 (s, 1H), 6.69 (s, 1H), 4.64 (d, 1H, J_{AB} = 12.3 Hz), 4.59 (d, 1H, J_{AB} = 12.3 Hz), 4.42 (s, 1H), 2.34 (m, 1H), 2.12 (m, 1H), 1.87 (d, 3H, J = 1.2 Hz), 1.58 – 1.48 (m, 2H), 0.90 (t, 3H, J = 7.2 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 138.8, 138.0, 137.7, 136.6, 129.1, 128.8, 128.5, 128.4, 128.2, 128.2, 127.6, 127.4, 127.0, 126.6, 126.4, 87.5, 70.1, 30.8, 22.1, 14.5, 13.9;

HRMS calc'd for $C_{28}H_{30}O$ (M^+) 382.2297; found 328.2299.



23

***E*-1-Methoxy-2-methyl-1,3-diphenyl-2-propene 3v**. *E*-1-Methoxy-2-methyl-1,3-diphenyl-2-propene **3v** was prepared from α-1-methyl-2-phenylethenyl-benzenemethanol[65] (449 mg, 2.0 mmol) and iodomethane (0.19 mL, 3.0 mmol) according to the procedure described for **3a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 415 mg (87%) of ether **3v** as a pale yellow oil.

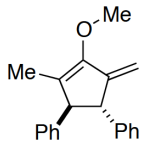
R_f 0.44 (10:1 Hexane : EtOAc);

3084, 3059, 3026, 2981, 2932, 2820, 1492, 1449, 1096 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.47 (m, 2H), 7.42 – 7.38 (m, 6H), 7.35 – 7.26 (m, 2H), 6.78 (m, 1H), 4.79 (s, 1H), 3.47 (s, 3H), 1.78 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 137.9, 137.5, 129.1, 128.2, 128.1, 127.6, 127.3, 126.6, 126.6, 88.8, 56.4, 13.4;

HRMS calc'd for $C_{17}H_{18}O$ (M^+) 238.1358; found 238.1355.



4a

Enol ether 4a. (*E,E)*-3-Methoxy-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene **3a** (56 mg, 0.20 mmol) was dissolved in CH_2Cl_2, 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (55 mg, 0.24 mmol) was added, and the reaction mixture immediately turned a deep purple color. The reaction was stirred at rt until starting material was consumed as observed by TLC (4 h). The reaction mixture was then filtered through a silica gel plug and eluted with CH_2Cl_2 (50 mL). The filtrate was concentrated, and further purification by flash chromatography (5 : 1 hexane : CH_2Cl_2) gave 51 mg (92%) of the enol ether **4a** as a colorless oil.

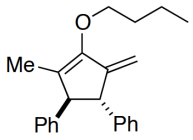
R_f 0.52 (2:1 Hexane : CH_2Cl_2);

IR (film) 3084, 3061, 3027, 2922, 2851, 1634, 1492, 1453, 1140 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 4H), 7.25 – 7.20 (m, 2H), 7.14 – 7.09 (m, 4H), 5.08 (m, 1H), 4.54 (m, 1H), 3.87 (s, 3H), 3.66 (m, 1H), 3.57 (m, 1H), 1.67 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 150.7, 144.9, 143.9, 129.2, 128.6, 128.5, 127.8, 127.6, 126.6, 126.4, 101.6, 60.4, 59.7, 56.2, 11.9;

HRMS calc'd for $C_{20}H_{20}O$ (M^+) 276.1514; found 276.1512.



4b

Enol ether 4b. Enol ether **4b** was prepared (*E,E)*-3-butoxy-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene **3b** (64 mg, 0.20 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 56 mg (88%) of enol ether **4b** as a pale yellow oil.

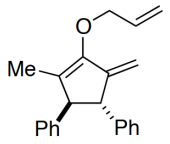
R_f 0.52 (10:1 Hexane : EtOAc);

IR (film) 3084, 3060, 3027, 2959, 2932, 2872, 1702, 1633, 1601, 1493, 1452, 1156 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.32 (m, 3H), 7.28 – 7.24 (m, 3H), 7.18 – 7.13 (m, 4H), 5.12 (m, 1H), 4.57 (s, 1H), 4.05 (t, 2H, *J* = 6.6 Hz), 3.70 (m, 1H), 3.61 (m, 1H), 1.84 – 1.77 (m, 2H), 1.70 (s, 3H), 1.63 – 1.55 (m, 2H), 1.05 (t, 3H, *J* = 7.2 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 151.2, 145.0, 144.0, 129.9, 128.6, 128.5, 127.8, 127.6, 126.6, 126.3, 101.5, 71.8, 60.3, 56.2, 32.6, 19.3, 14.0, 12.0;

HRMS calc'd for $C_{23}H_{26}O$ (M^+) 318.1984; found 318.1982.



4c

Enol ether 4c. Enol ether **4c** was prepared from (*E,E)*-3-allyloxy-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene **3c** (64 mg, 0.20 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 51 mg (85%) of enol ether **4c** as a colorless oil.

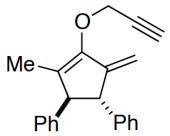
R_f 0.49 (10:1 Hexane : EtOAc);

IR (film) 3083, 3061, 3027, 2927, 2859, 1628, 1634, 1601, 1492, 1453, 1324, 1156 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 4H), 7.25 – 7.21 (m, 2H), 7.14 – 7.09 (m, 4H), 6.11 (m, 1H), 5.43 (m, 1H), 5.30 (m, 1H), 5.09 (m, 1H), 4.54 (m, 2H), 4.53 (m, 1H), 3.67 (m, 1H), 3.59 (m, 1H), 1.66 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 151.0, 144.9, 143.8, 134.5, 130.7, 128.6, 128.5, 127.8, 127.6, 126.6, 126.4, 117.6, 101.7, 72.6, 60.3, 56.2, 12.1;

HRMS calc'd for $C_{22}H_{22}O$ (M^+) 302.1671; found 302.1669.



4d

Enol ether 4d. Enol ether **4d** was prepared from (*E,E)*-2,4-dimethyl-1,5-diphenyl-3-(2-propynyloxy)-1,4-pentadiene **3d** (60 mg, 0.20 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 54 mg (90%) of enol ether **4d** as a colorless oil.

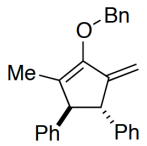
R_f 0.44 (10:1 Hexane : EtOAc);

IR (film) 3298, 3085, 3061, 3029, 2931, 2123, 1718, 1655, 1633, 1601, 1494, 1453, 1140 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 4H), 7.30 – 7.26 (m, 2H), 7.19 – 7.15 (m, 4H), 5.11 (d, 1H, *J* = 2.1 Hz), 4.72 (d, 2H, *J* = 2.5 Hz), 4.60 (m, 1H), 3.72 (m, 1H), 3.65 (m, 1H), 2.58 (t, 1H, *J* = 2.5 Hz), 1.75 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 150.3, 144.6, 143.5, 132.8, 128.7, 128.5, 127.8, 127.6, 126.7, 126.4, 101.9, 79.7, 75.2, 60.3, 58.9, 56.3, 12.2;

HRMS calc'd for $C_{22}H_{20}O$ (M^+) 300.1514; found 300.1513.



4e

Enol ether 4e. Enol ether **4e** was prepared from (*E,E)*-3-benzyloxy-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene **3e** (142 mg, 0.40 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 116 mg (82%) of enol ether **4e** as a colorless oil.

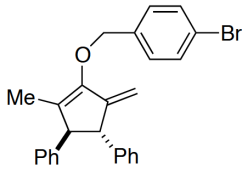
R_f 0.48 (10:1 Hexane : EtOAc)

IR (film) 3086, 3061, 3029, 2934, 1703, 1649, 1633, 1601, 1495, 1453, 1138 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.51 (m, 2H), 7.45 – 7.34 (m, 3H), 7.34 – 7.22 (m, 6H), 7.14 – 7.12 (m, 2H), 7.03 – 7.01 (m, 2H), 5.17 (m, 1H), 5.08 (m, 2H), 4.59 (m, 1H), 3.67 (m, 1H), 3.58 (m, 1H), 1.56 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 150.9, 144.7, 143.7, 137.7, 131.2, 128.6, 128.5, 128.4, 128.4, 128.1, 127.8, 127.6, 126.6, 126.3, 101.8, 73.4, 60.2, 56.3, 12.0;

HRMS calc'd for $C_{26}H_{24}O$ (M^+) 352.1827; found 352.1827.



4f

Enol ether 4f. Enol ether **4f** was prepared from (*E,E)*-3-(*p*-bromobenzyloxy)-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene **3f** (87 mg, 0.20 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 77 mg (89%) of enol ether **4f** as a pale yellow oil.

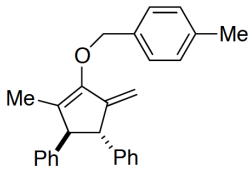
R_f 0.46 (10:1 Hexane : EtOAc);

IR (film) 3083, 3060, 3027, 2932, 1701, 1633, 1600, 1489, 1453, 1148 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.52 (m, 2H), 7.36 – 7.34 (m, 2H), 7.31 – 7.20 (m, 6H), 7.09 – 7.07 (m, 2H), 6.97 – 6.95 (m, 2H), 5.09 (d, 1H, *J* = 2.4 Hz); 5.00 (s, 2H), 4.55 (s, 1H), 3.62 (m, 1H), 3.54 (m, 1H), 1.54 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 150.9, 144.6, 143.6, 136.7, 131.6, 131.4, 130.0, 128.7, 128.5, 127.8, 127.6, 126.7, 126.4, 122.1, 101.9, 72.5, 60.2, 56.3, 12.1;

HRMS calc'd for $C_{26}H_{23}{}^{79}BrO$ (M^+) 430.0932; found 430.0929.



4g

Enol ether 4g. Enol ether **4g** was prepared from (*E,E)*-3-(*p*-methylbenzyloxy)-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene **3g** (74 mg, 0.20 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 49 mg (67%) of enol ether **4f** as an orange oil.

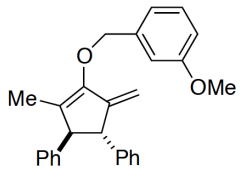
R_f 0.50 (10:1 Hexane : EtOAc);

IR (film) 3084, 3059, 3026, 2957, 2927, 2872, 1720, 1633, 1601, 1492, 1453, 1139 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.38 (m, 2H), 7.31 – 7.22 (m, 8H), 7.13 – 7.10 (m, 2H), 7.01 – 6.99 (m, 2H), 5.15 (d, 1H, J = 2.2 Hz), 5.03 (s, 2H), 4.57 (m, 1H), 3.64 (m, 1H), 3.56 (m, 1H), 2.41 (s, 3H), 1.54 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 151.0, 144.8, 143.8, 137.9, 134.7, 131.2, 129.1, 128.6, 128.5, 128.5, 127.9, 127.6, 126.6, 126.3, 101.8, 73.3, 60.3, 56.3, 21.3, 12.0;

HRMS calc'd for $C_{27}H_{26}O$ (M^+) 366.1984; found 366.1983.



4i

Enol ether 4i. Enol ether **4i** was prepared from (*E,E)*-3-(*m*-methoxybenzyloxy)-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene **3i** (77 mg, 0.20 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 66 mg (86%) of enol ether **4f** as a yellow oil.

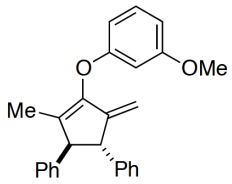
R_f 0.39 (10:1 Hexane : EtOAc);

IR (film) 3083, 3060, 3026, 2936, 2908, 1633, 1601, 1587, 1491, 1453, 1267, 1147 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 5H), 7.30 – 7.26 (m, 2H), 7.19 – 7.16 (m, 2H), 7.14 – 7.12 (m, 2H), 7.08 – 7.06 (m, 2H), 6.98 – 6.96 (m, 1H), 5.21 (d, 1H, J = 2.3 Hz), 5.10 (s, 2H), 4.63 (m, 1H), 3.90 (s, 3H), 3.71 (m, 1H), 3.62 (m, 1H), 1.62 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 152.7, 150.9, 144.7, 143.7, 139.3, 131.1, 129.5, 128.6, 128.5, 127.8, 127.6, 126.6, 126.4, 120.5, 113.7, 113.6, 101.8, 73.2, 60.3, 56.3, 55.3, 12.0;

HRMS calc'd for $C_{27}H_{26}O_2$ (M^+) 382.1933; found 382.1932.



4j

Enol ether 4j. Enol ether **4j** was prepared from (*E,E)*-3-(*m*-methoxyphenoxy)-2,4-dimethyl-1,5-diphenyl-1,4-pentadiene **3j** (74 mg, 0.20 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 60 mg (81%) of enol ether **4f** as a yellow oil.

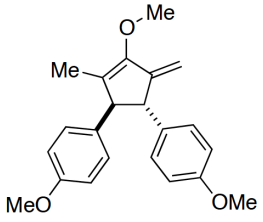
R_f 0.38 (10:1 Hexane : EtOAc);

IR (film) 3061, 3027, 2937, 2835, 1635, 1602, 1489, 1452, 1282, 1151 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 4H), 7.32 – 7.27 (m, 3H), 7.23 – 7.20 (m, 4H), 6.75 – 6.73 (m, 1H), 6.71 (m, 1H), 6.65 – 6.63 (m, 1H), 4.96 (d, 1H, *J* = 2.2 Hz), 4.59 (s, 1H), 3.87 (m, 1H), 3.86 (s, 3H), 3.78 (m, 1H), 1.67 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 158.6, 149.5, 148.5, 144.3, 143.3, 133.9, 130.0, 128.8, 128.6, 127.9, 127.7, 126.9, 126.5, 107.8, 107.5, 103.3, 101.6, 60.4, 56.2, 55.3, 11.8;

HRMS calc'd for $C_{26}H_{24}O_2$ (M^+) 368.1776; found 368.1774.



4k

Enol ether 4k. Enol ether **4k** was prepared from (*E,E)*-3-methoxy-2,4-dimethyl-1,5-bis(*p*-methoxyphenyl)-1,4-pentadiene **3k** (68 mg, 0.20 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 63 mg (93%) of enol ether **4k** as a pale yellow oil.

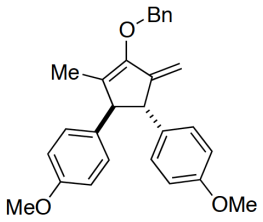
R_f 0.33 (10:1 Hexane : EtOAc);

IR (film) 3031, 2997, 2955, 2955, 2934, 2836, 1695, 1609, 1512, 1463, 1250, 1177, 1035 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 7.05 – 6.98 (m, 4H), 6.85 – 6.81 (m, 4H), 5.04 (m, 1H), 4.50 (m, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.56 (m, 1H), 3.47 (m, 1H), 1.67 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 158.1, 154.1, 151.0, 137.0, 136.0, 129.3, 128.7, 128.5, 114.0, 113.8, 101.2, 59.7, 59.7, 55.7, 55.2, 55.2, 11.8;

HRMS calc'd for $C_{22}H_{24}O_3$ (M^+) 336.1725; found 336.1728.



4l

Enol ether 4l. Enol ether **4l** was prepared from (*E,E)*-3-benzyloxy-2,4-dimethyl-1,5-bis(*p*-methoxyphenyl)-1,4-pentadiene **3l** (83 mg, 0.20 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 71 mg (86%) of enol ether **4l** as a yellow oil.

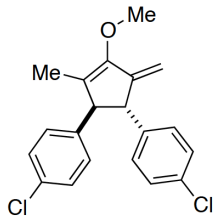
R_f 0.34 (10:1 Hexane : EtOAc);

IR (film) 3088, 3064, 3031, 2997, 2952, 2932, 2834, 1632, 1611, 1511, 1462, 1248, 1175, 1036 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.47 (m, 2H), 7.42 – 7.35 (m, 3H), 7.03 – 7.00 (m, 2H), 6.90 – 6.88 (m, 2H), 6.84 – 6.79 (m, 4H), 5.10 (app d, 1H, J = 2.2 Hz), 5.04 (d, 1H, J_{AB} = 11.7 Hz), 5.03 (d, 1H, J_{AB} = 11.7 Hz), 4.53 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.54 (m, 1H), 3.46 (m, 1H), 1.51 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 158.1, 152.4, 151.2, 137.7, 136.9, 135.9, 131.3, 128.8, 128.6, 128.5, 128.4, 128.1, 113.9, 113.8, 101.4, 73.4, 59.7, 55.9, 55.3 (2 overlapping signals), 11.9;

HRMS calc'd for $C_{28}H_{28}O_3$ (M^+) 412.2038; found 412.2038.



4m

Enol ether 4m. Enol ether **4m** was prepared from (*E,E)*-3-methoxy-2,4-dimethyl-1,5-bis(*p*-chlorophenyl)-1,4-pentadiene **3m** (69 mg, 0.20 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 61 mg (89%) of enol ether **4l** as a colorless oil.

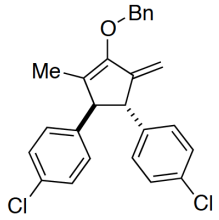
R_f 0.47 (10:1 Hexane : EtOAc);

IR (film) 3086, 3027, 2933, 2852, 1703, 1643, 1490, 1090, 1014 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 4H), 7.07 – 7.01 (m, 4H), 5.11 (m, 1H), 4.54 (m, 1H), 3.88 (s, 3H), 3.59 (m, 1H), 3.51 (m, 1H), 1.67 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 150.0, 142.8, 142.0, 132.5, 132.3, 129.2, 128.9, 128.7, 128.7, 128.1, 101.2, 59.9, 59.8, 55.7, 11.8;

HRMS calc'd for $C_{20}H_{18}{}^{35}Cl_2O$ (M^+) 344.0735; found 344.0733.



4n

Enol ether 4n. Enol ether **4n** was prepared from (*E,E)*-3-benzyloxy-2,4-dimethyl-1,5-bis(*p*-chlorophenyl)-1,4-pentadiene **3n** (85 mg, 0.20 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 71 mg (84%) of enol ether **4l** as a pale yellow oil.

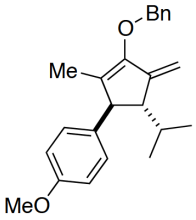
R_f 0.43 (10:1 Hexane : EtOAc);

IR (film) 3088, 3064, 3030, 2932, 2907, 1647, 1634, 1490, 1140, 1090 cm^{-1};

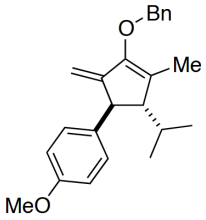
^1H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.50 (m, 2H), 7.47 – 7.41 (m, 3H), 7.30 – 7.26 (m, 4H), 7.05 – 7.02 (m, 2H), 6.91 – 6.88 (m, 2H), 5.18 (app d, 1H, J = 2.6 Hz), 5.09 (d, 1H, J_{AB} = 11.5 Hz), 5.07 (d, 1H, J_{AB} = 11.5 Hz), 4.57 (m, 1H), 3.56 (m, 1H), 3.49 (m, 1H), 1.54 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 150.3, 142.7, 141.9, 137.4, 132.5, 132.3, 130.4, 129.3, 128.9, 128.8, 128.7, 128.5 (2 overlapping signals), 128.3, 102.3, 73.3, 59.7, 55.9, 11.9;

HRMS calc'd for $C_{26}H_{22}{}^{35}Cl_2O$ (M^+) 420.1048; found 420.1045.



4p



***iso*-4p**

Enol ethers 4p and *iso*-4p. Enol ethers **4p** and ***iso*-4p** were prepared from (*E,E)*-3-(*p*-methoxybenzyloxy)-2,4,6-trimethyl-1-phenylhepta-1,4-diene **3p** (70 mg, 0.20 mmol) according to the procedure described for **4a**. The corresponding mixture of enol ethers **4p** and ***iso*-4p** (**4p** : ***iso*-4p** – 2.3 : 1) were obtained as a yellow oil, 62 mg (89%). Small amounts of both isomers were obtained by radial chromatography (80:1 to 20:1 gradient, Hexane : EtOAc).

R_f 0.40 (10:1 Hexane : EtOAc)

Enol ether 4p

IR (film) 3030, 2960, 2922, 2851, 1700, 1632, 1512, 1496, 1252;

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.44 (m, 2H), 7.39 – 7.31 (m, 3H), 7.00 – 6.98 (m, 2H), 6.81 – 6.78 (m, 2H), 5.10 (m, 1H), 4.98 (d, 1H, *J* = 11.4 Hz), 4.88 (d, 1H, *J* = 11.4 Hz), 4.72 (m, 1H), 3.78 (m, 3H), 3.25 (m, 1H), 2.52 (app ddt, 1H, *J* = 4.1, 2.1, 2.1 Hz) 1.92 (dsept, 1H, *J* = 6.9, 4.5 Hz), 1.46 (m, 3H), 0.94 (d, 3H, *J* = 6.9 Hz), 0.88 (d, 3H, *J* = 6.9 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 152.9, 150.1, 137.9, 137.5, 132.6, 128.5, 128.4, 128.2, 128.0, 113.9, 100.2, 73.4, 55.3, 55.0, 51.6, 32.7, 19.9, 17.4, 11.4;

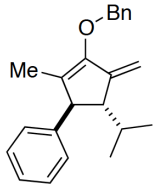
HRMS calc'd for $C_{24}H_{28}O_2$ (M^+) 348.2089; found 348.2089.

Enol ether *iso*-4p-partial

IR (film) 3031, 2962, 2931, 2872, 1700, 1609, 1512, 1253, 1179, 1035 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.43 (m, 2H), 7.39 – 7.31 (m, 3H), 7.07 – 7.04 (m, 2H), 6.83 – 6.80 (m, 2H), 4.95 (m, 1H), 4.92 (d, 1H, J_{AB} = 11.4 Hz) 4.90 (d, 1H, J_{AB} = 11.4 Hz), 4.43 (m, 1H), 3.79 (s, 3H), 3.44 (m, 1H), 2.48 (m, 1H), 1.99 (dsept, 1H, *J* = 6.9, 3.5 Hz), 1.67 (m, 3H), 0.89 (d, 3H, *J* = 6.9 Hz), 0.74 (d, 3H, *J* = 6.9 Hz);

HRMS calc'd for $C_{24}H_{28}O_2$ (M^+) 348.2089; found 348.2091.



4q

Enol ether 4q. Enol ether **4q** was prepared from *(E,E)*-3-benzyloxy-2,4,6-trimethyl-1-phenylhepta-1,4-diene **3q** (96 mg, 0.30 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 83 mg (87%) of enol ether **4q** as a pale yellow oil.

R_f 0.46 (10:1 Hexane : EtOAc);

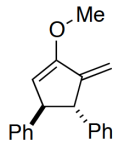
IR (film) 3086, 3028, 2958, 2930, 2872, 1701, 1652, 1631, 1453, 1150 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.44 (m, 2H), 7.39 – 7.31 (m, 3H), 7.27 – 7.24 (m, 2H), 7.19 – 7.16 (m, 1H), 7.09 – 7.07 (m, 2H), 5.11 (m, 1H), 4.99 (d, 1H,

J = 11.5 Hz), 4.89 (d, 1H, J = 11.5 Hz), 4.73 (m, 1H), 3.30 (m, 1H), 2.56 (app ddt, 1H, J = 4.1, 2.0, 2.0 Hz), 1.93 (dsept, 1H, J = 6.9, 4.4 Hz), 1.47 (m, 3H), 0.95 (d, 3H, J = 6.9 Hz); 0.89 (d, 3H, J = 6.9 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 150.1, 145.4, 137.9, 132.4, 128.5, 128.4, 128.2, 128.0, 127.6, 126.2, 100.3, 73.4, 54.9, 52.5, 32.8, 19.8, 17.4, 11.9;

HRMS calc'd for $C_{23}H_{26}O$ (M^+) 318.1984; found 318.1985.



4r

Enol ether 4r. Enol ether **4r** was prepared from (*E,E)*-3-methoxy-2-methyl-1,5-diphenyl-1,4-pentadiene **3r** (53 mg, 0.20 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 43 mg (82%) of enol ether **4r** as a yellow oil.

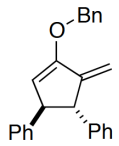
R_f 0.40 (10:1 Hexane : EtOAc);

IR (film) 3082, 3057, 3025, 2980, 2930, 2819, 1600, 1493, 1447, 1098 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 4H), 7.25 – 7.21 (m, 2H), 7.16 – 7.14 (m, 4H), 5.22 (m, 1H), 5.12 (m, 1H), 4.58 (m, 1H), 3.85 (m, 1H), 3.83 (m, 3H), 3.69 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 151.1, 145.5, 144.3, 128.5, 128.2, 128.2, 127.2, 126.5, 126.4, 106.2, 103.6, 57.6, 56.9, 55.4;

HRMS calc'd for $C_{19}H_{18}O$ (M^+) 262.1358; found 262.1358.



4s

Enol ether 4s. Enol ether **4s** was prepared from (*E,E)*-3-benzyloxy-2-methyl-1,5-diphenyl-1,4-pentadiene **3s** (68 mg, 0.20 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 53 mg (79%) of enol ether **4s** as a yellow oil.

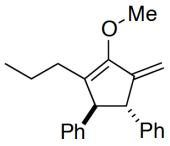
R_f 0.42 (10:1 Hexane : EtOAc);

IR (film) 3062, 3027, 2920, 2851, 1632, 1610, 1453, 1164 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.48 (m, 2H), 7.45 – 7.42 (m, 2H), 7.39 – 7.22 (m, 7H), 7.20 – 7.18 (m, 2H), 7.14 – 7.12 (m, 2H), 5.35 (m, 1H), 5.20 (m, 1H), 5.11 (d, 1H, J_{AB} = 12.0 Hz), 5.08 (d, 1H, J_{AB} = 12.0 Hz), 4.64 (m, 1H), 3.89 (m, 1H), 3.72 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 151.1, 145.4, 144.4, 137.0, 128.6, 128.5 (2 overlapping signals), 128.2, 128.0, 127.4, 127.2, 126.5, 126.5, 107.5, 104.0, 71.2, 57.4, 55.8;

HRMS calc'd for $C_{25}H_{22}O$ (M^+) 338.1671; found 338.1670.



4t

Enol ether 4t. Enol ether **4t** was prepared from (*E,E)*-3-methoxy-2-methyl-1-phenyl-4-(phenylmethylene)-1-heptene **3t** (61 mg, 0.20 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 56 mg (79%) of enol ether **4t** as a yellow oil.

R_f 0.41 (10:1 Hexane : EtOAc);

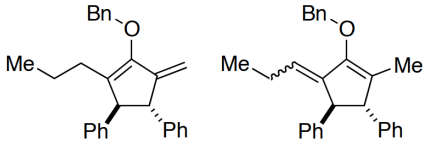
IR (film) 3084, 3061, 3026, 2958, 2933, 2870, 1632, 1601, 1493, 1453, 1138 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 4H), 7.24 – 7.20 (m, 2H), 7.13 – 7.08 (m, 4H), 5.07 (d, 1H, J = 2.2 Hz), 4.55 (m, 1H), 3.84 (s, 3H), 3.64 (m, 2H),

2.37 (app. dt, 1H, J = 13.9, 8.1, 8.1 Hz), 1.78 (app. dt, 1H, J = 13.9, 8.7, 5.1 Hz), 1.45 – 1.35 (m, 1H), 1.34 – 1.24 (m, 1H), 0.85 (t, 3H, J = 7.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 150.7, 145.2, 144.0, 134.5, 128.6, 128.5, 127.6, 127.6, 126.6, 126.3, 101.9, 60.0, 57.9, 56.1, 27.7, 20.5, 14.1;

HRMS calc'd for $C_{22}H_{24}O$ (M^+) 304.1827; found 304.1826.



4u ***iso*-4u**

Enol ethers 4u and *iso*-4u. Enol ethers **4u** and what is tentatively assigned as ***iso*-4u** were prepared from (*E,E)*-3-benzyloxy-2-methyl-1-phenyl-4-(phenylmethylene)-1-heptene **3u** (153 mg, 0.40 mmol) according to the procedure described for **4a**. Purification by flash chromatography (60:1 hexane : EtOAc) furnished an inseparable mixture of enol ethers **4u** and ***iso*-4u** (**4b** : ***iso*-4b** 10 : 1 as determined by integration of benzylic methine protons in the ^{1}H NMR spectrum) as a yellow oil, 129 mg (89%).

R_f 0.50 (10:1 Hexane : EtOAc);

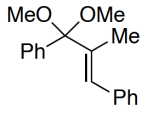
IR (film) 3085, 3062, 3028, 2959, 2931, 2871, 1631, 1601, 1493, 1453, 1144 cm^{-1};

4u ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.51 (m, 2H), 7.45 – 7.22 (m, 9H), 7.15 – 7.13 (m, 2H), 7.04 – 7.03 (m, 2H), 5.16 (m, 1H), 5.07 (d, 1H, J = 11.5 Hz) 5.04 (d, 1H, J = 11.5 Hz), 4.61 (s, 1H), 3.68 (m, 1H), 3.65 (m, 1H), 2.32 (ddd, 1H, J = 16.0, 8.2, 8.2 Hz), 1.68 (ddd, 1H, J = 14.1, 9.1, 5.3 Hz), 1.41 – 1.31 (m, 1H), 1.24 – 1.13 (m, 1H), 0.82 (t, 3H, J = 7.3 Hz);

4u ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 150.9, 145.1, 143.9, 137.7, 136.1, 128.6, 128.6, 128.5, 128.4, 128.1, 127.7, 127.6, 126.6, 126.4, 102.1, 73.6, 57.8, 56.4, 27.9, 20.4, 14.2;

Partial data for unobscured signals of ***iso*-4u** ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (app. t, 1H, J = 7.6 Hz), 3.76 (s, 1H), 3.42 (s, 1H), 1.88 (m, 1H), 1.78 (m, 1H), 1.57 (s, 3H), 0.77 (t, 3H, J = 7.5 Hz);

HRMS calc'd for $C_{28}H_{28}O$ (M^+) 380.2140; found 380.2141.



8

***E*-1,1-dimethoxy-2-methyl-1,3-diphenyl-2-propene 8**. 1,1-Dimethoxy-2-methyl-1,3-diphenyl-2-propene **8** was prepared from *E*-1-methoxy-2-methyl-1,3-diphenyl-2-propene **3v** (48 mg, 0.20 mmol) according to the procedure described for **4a**. Purification by flash chromatography (40:1 hexane : EtOAc) furnished 27 mg (37%) of **8** and 13 mg (30%) of 2-methyl-1,3-diphenyl-2-propen-1-one[64] **1i** as colorless oils.

R_f 0.48 (10:1 Hexane : EtOAc);

IR (film); 3083, 3057, 3025, 2954, 2940, 1447, 1096, 1063 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.54 (m, 2H), 7.36 – 7.33 (m, 6H), 7.30 – 7.22 (m, 2H), 7.21 (m, 1H), 3.16 (s, 6H), 1.59 (d, 3H, J = 1.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 137.9, 137.1, 129.2, 128.1, 127.9, 127.7, 127.6, 126.2, 103.4, 49.2, 14.3;

HRMS calc'd for $C_{18}H_{20}O_2$ (M^+) 268.1463; found 268.1463.

3.5 References

(1) Nazarov, I. N.; Zaretskaya, I. I.; Sorkina, T. I. *Zh. Obshch. Khim.* **1960**, *30*, 746-754.
(2) Nazarov, I. N.; Yanbikov, Y. M. *Bull. Acad. Sci. URSS. Classe Sci. Chim.* **1943**, 389-393.
(3) Nazarov, I. N.; Yanbikov, Y. M. *Bull. Acad. Sci. URSS. Sci, Chim.* **1946**, 633-646.
(4) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429–444.
(5) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React.* **1994**, *45*, 1–158.
(6) See the following six references and Chapter 1 of this thesis for more detailed discussion.
(7) Tius, M. A. *Eur. J. Org. Chem.* **2005**, *2005*, 2193–2206.
(8) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676–5688.
(9) Nakanishi, W.; West, F. G. *Curr. Opin. Drug. Discovery Dev.* **2009**, *12*, 732–751.
(10) Spencer, W. T., III; Vaidya, T.; Frontier, A. J. *Eur. J. Org. Chem.* **2013**, *2013*, 3621–3633.
(11) Tius, M. A. *Chem. Soc. Rev.* **2014**, DOI: 10.1039/c3cs60333d
(12) West, F. G.; Scadeng, O. S.; Wu, Y-K; Fradette, R. J.; Joy S. in *Comprehensive Organic Synthesis II*; Knochel, P; Molander, G. A.; Eds.; Elsevier: Oxford, **2014**.
(13) Smith, D. A.; Ulmer, C. W. I. *J. Org. Chem.* **1997**, *62*, 5110–5115.
(14) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Deagostino, A.; Venturello, P. *J. Org. Chem.* **2002**, *67*, 7144–7146.
(15) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P. *J. Org. Chem.* **2003**, *68*, 9728–9741.
(16) Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P.; Occhiato, E. G. *J. Org. Chem.* **2004**, *69*, 7705–7709.
(17) Wu, Y-K.; West, F. G. *J. Org. Chem.* **2010**, *75*, 5410–5413.
(18) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802–5803.
(19) Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348–9349.

(20) Grant, T. N.; West, F. G. *Org. Lett.* **2007**, *9*, 3789–3792.
(21) Malona, J. A.; Cariou, K.; Frontier, A. J. *J. Am. Chem. Soc.* **2009**, *131*, 7560–7561.
(22) Malona, J. A.; Cariou, K.; Spencer, W. T., III; Frontier, A. J. *J. Org. Chem.* **2012**, *77*, 1891–1908.
(23) Spencer, W. T., III; Levin, M. D.; Frontier, A. J. *Org. Lett.* **2011**, *13*, 414–417.
(24) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Am. Chem. Soc.* **2009**, *131*, 7504–7505.
(25) Nair, V.; Bindu, S.; Sreekumar, V.; Chiaroni, A. *Org. Lett.* **2002**, *4*, 2821–2823.
(26) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wiley-Interscience, **2006**.
(27) Yadav, J. S.; Chandrasekhar, S.; Sumithra, G.; Kache, R. *Tetrahedron Lett.* **1996**, *37*, 6603–6606.
(28) Xu, Y.-C.; Roy, C.; Lebeau, E. *Tetrahedron Lett.* **1993**, *34*, 8189–8192.
(29) Xu, Y.-C.; Kohlman, D. T.; Liang, S. X.; Erikkson, C. *Org. Lett.* **1999**, *1*, 1599–1602.
(30) Ying, B.-P.; Trogden, B. G.; Kohlman, D. T.; Liang, S. X.; Xu, Y.-C. *Org. Lett.* **2004**, *6*, 1523–1526.
(31) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242–4243.
(32) Tu, W.; Liu, L.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2008**, *47*, 4184–4187.
(33) Park, S. J.; Price, J. R.; Todd, M. H. *J. Org. Chem.* **2012**, *77*, 949–955.
(34) Han, X.; Floreancig, P. E. *Org. Lett.* **2012**, *14*, 3808–3811.
(35) Meng, Z.; Sun, S.; Yuan, H.; Lou, H.; Liu, L. *Angew. Chem. Int. Ed.* **2013**, *53*, 543–547.
(36) Hayashi, Y.; Mukaiyama, T. *Chem. Lett.* **1987**, 1811–1814.
(37) Liu, L.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2010**, *49*, 5894–5897.
(38) Clausen, D. J.; Floreancig, P. E. *J. Org. Chem.* **2012**, *77*, 6574–6582.
(39) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.
(40) Zhai, L.; Shukla, R.; Wadumethrige, S. H.; Rathore, R. *J. Org. Chem.* **2010**, *75*, 4748–4760.
(41) Cui, Y.; Villafane, L. A.; Clausen, D. J.; Floreancig, P. E. *Tetrahedron* **2013**, *69*, 7618–7626.
(42) Lund, H. *Acta Chem. Scand.* **1957**, *11*, 491–498.
(43) Satoh, T.; Nakamura, A.; Iriuchijima, A.; Hayashi, Y.; Kubota, K.-I. *Tetrahedron* **2001**, *57*, 9689–9696.
(44) Sinha, A. K.; Sharma, A.; Swaroop, A.; Kumar, V. *Tetrahedron* **2007**, *63*, 1000–1007.
(45) Liu, S.-W.; Hsu, H.-C.; Chang, C.-H.; Tsai, H.-H. G.; Hou, D.-R. *Eur. J. Org. Chem.* **2010**, *2010*, 4771–4773.
(46) Cosner, C. C.; Cabrera, P. J.; Byrd, K. M.; Thomas, A. M. A.; Helquist, P. *Org. Lett.* **2011**, *13*, 2071–2073.
(47) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033–3035.

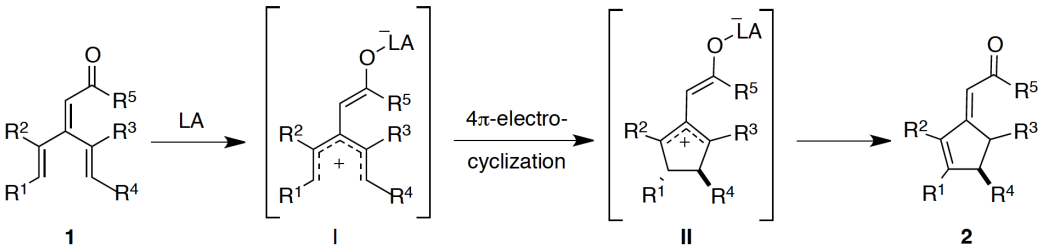
(48) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Can. J. Chem.* **2004**, *82*, 375–385.
(49) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284–286.
(50) Bonderoff, S. A. *Ph.D Dissertation*, 2012.
(51) Kwon, Y.; McDonald, R.; West, F. G. *Angew. Chem. Int. Ed.* **2013**, *52*, 8616–8619.
(52) Scadeng, O.; Ferguson, M. J.; West, F. G. *Org. Lett.* **2011**, *13*, 114–117.
(53) Braude, E. A.; Forbes, W. F. *J. Chem. Soc.* **1953**, 2208–2216.
(54) Toxicity data was obtained from the MSDS sheet.
(55) Newman, M. S.; Khanna, V. K. *Organic Preparations and Procedures International* **1985**, *17*, 422–423.
(56) Chandrasekhar, S.; Sumithra, G.; Yadav, J. S. *Tetrahedron Lett.* **1996**, *37*, 1645–1646.
(57) Liu, L.; Floreancig, P. E. *Org. Lett.* **2010**, *12*, 4686–4689.
(58) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339–363.
(59) Based on the price of 100 g bottles of reagent grade material from Sigma-Aldrich, 2014.
(60) Shen, Z.; Dai, J.; Xiong, J.; He, X.; Mo, W.; Hu, B.; Sun, N.; Hu, X. *Adv. Synth. Catal.* **2011**, *353*, 3031–3038.
(61) Rampal, J. B.; Berlin, D.; Edasery, J. P.; Satyamurthy, N.; van der Helm, D. *J. Org. Chem.* **1981**, *46*, 1166–1172.
(62) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Org. Chem.* **2011**, *76*, 50–56.
(63) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747–2750.
(64) Lu, S.-M.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 8920–8923.
(65) Smith, C. D.; Rosocha, G.; Mui, L.; Batey, R. A. *J. Org. Chem.* **2010**, *75*, 4716–4727.

Chapter 4

Vanadium Catalyzed 1,3-Transposition of Tertiary Propargylic Allylic Alcohols

4.1 Introduction

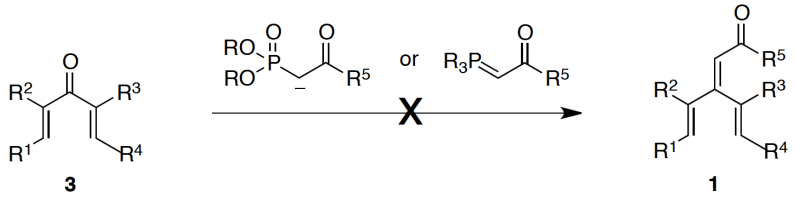
Due to the strength of the Nazarov 4π electrocyclization as a method for synthesizing cyclopentanones there is interest in exploring alternative substrates for the Nazarov reaction.[1-5] The pentadienyl cation intermediates necessary for Nazarov cyclization, traditionally generated from 1,4-diene-3-ones can also be accessed from a number of alternative substrates.[6] Looking to modify the traditional dienone at the 3-position, it was envisioned that the carbonyl could be replaced by an olefin. By replacing the carbonyl functionality at the 3-position with an α,β-unsaturated carbonyl moiety, the resulting electron deficient [3]dendralene **1** would be homologous to the traditional 1,4-diene-3-ones. We predicted that these vinylogus substrates could be activated by Lewis or Brønsted acid in a similar manner to traditional divinyl ketone substrates (Scheme 1).



Scheme 1: Proposed [3]dendralene Nazarov Substrates.

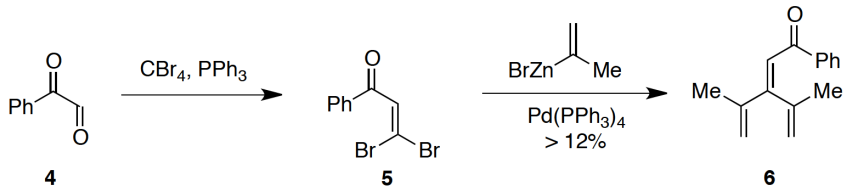
In order to investigate the vinylogus Nazarov reaction, a method to construct the requisite [3]dendralene substrates was required. At first glance the most straightforward approach for the synthesis of [3]dendralenes would be Wittig or Horner-Wadsworth-Emmons olefination of the corresponding readily

available 1,4-diene-3-ones (Scheme 2). However, the steric hindrance and electronic deactivation of the ketone doomed such a direct olefination protocol.



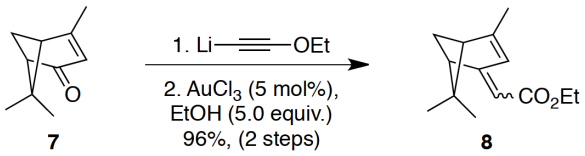
Scheme 2: Proposed Ylide Route to [3]Dendralenes.

Cross-coupling protocols for *gem*-dibromoolefins have been previously reported with vinyl metal coupling partners.[7] The *trans*-bromide reacted selectively, allowing for a variety of symmetrical and unsymmetrical [3]dendralene substrates. In practice the *gem*-dibromoolefin **5** could be generated from the corresponding aldehyde. However in the cross-coupling step the non-polar product of Negishi coupling was isolated in low yield (Scheme 3).[8] Neither the ylide approach or the cross-coupling approach appeared to be viable methods to access a library of [3]dendralenes for the vinylogous Nazarov reaction.



Scheme 3: Negishi Coupling Route to [3]Dendralenes.

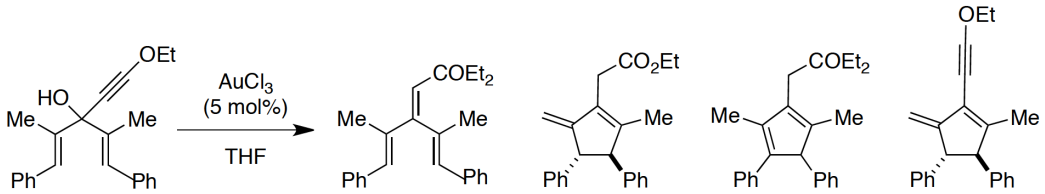
Synthesizing the desired [3]dendralenes from 1,4-diene-3-ones remained an attractive approach, and the literature provided a promising result. In 2006 Dudley and Engel reported the synthesis of a hindered α,β,γ,δ-unsaturated ester from the hindered α,β-unsaturated ketone, verbenone by a 2-step sequence.[9,10] An initial 1,2-lithium acetylide addition followed by a gold-catalyzed Meyer-Schuster rearrangement, gave the desired α,β,γ,δ-unsaturated ester in excellent yield (Scheme 4).



Scheme 4: 1,2-Addition – Gold-Catalyzed Rearrangement of Verbenone.

We concluded that the Meyer-Schuster rearrangement,[11,12] converting a propargylic alcohol to an α,β-unsaturated carbonyl compound, was an attractive route to the desired [3]dendralenes. It would have greater atom-economy, avoiding the use of stoichiometric vinyl metal, and stiochiometric phosphorus(V) oxide waste. When the gold(III) catalyzed Meyer-Schuster rearrangement was applied to 3° propargylic alcohols derived from 1,4-diene-3-ones (Table 1), the desired [3]dendralenes were formed; however, the results were inconsistent and varying amounts of cycloisomerized products were observed. Addition of water, or base was of some benefit, at the expense of yield and increased reaction times.

Table 1: Additive Effects on $AuCl_3$ Catalyzed Meyer-Schuster Rearrangement.[13]

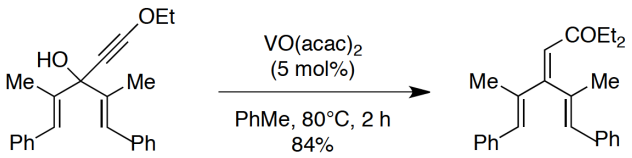


9a **1a** **10a** **11a** **12a**

	Additive	Loading (equiv.)	Temp (°C)	Time (h)	Yield (%)[a] **1a**	**10a**	**11a**	**12a**
1	None	–	rt	16		62		
2	None	–	50	2 min			63	
3	EtOH	10	rt	30 min	10[b]	90[b]		
4	H_2O	1	rt	5 min	70			
5	*i*-Pr_2NEt	0.15	rt	24	53			
6	Lutidine	0.15	rt	24	51			
7	4Å MS		rt	5 min				93

[a]Isolated yield after purification. [b]Yields based on ratios measured in crude NMR.

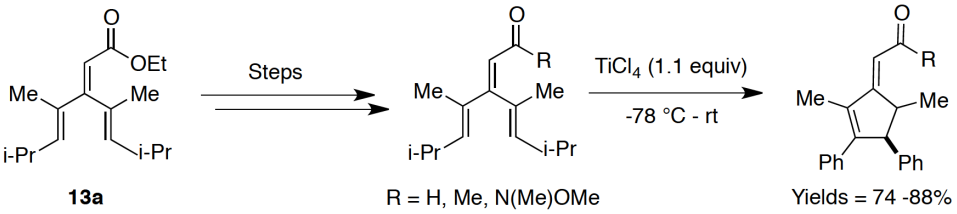
At this juncture focus was shifted to the use of metal oxo catalysts for the Meyer-Schuster rearrangement. A brief survey of metal oxo catalysts revealed $VO(acac)_2$ to be the optimal choice. While these conditions required longer reaction times and higher temperature, the desired cross-conjugated trienoates were reliably obtained in high yield.[13,14]



9a **1a**

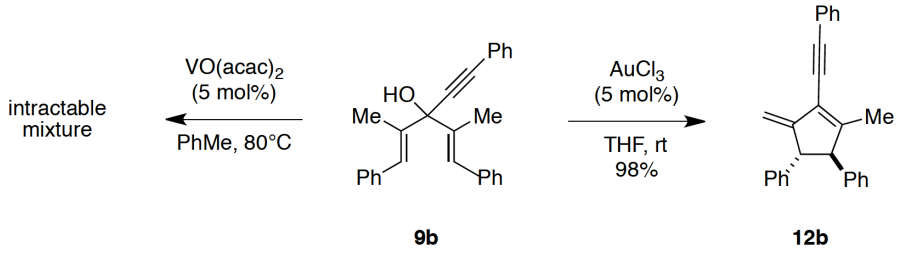
Scheme 5: $VO(acac)_2$ Catalyzed Meyer-Schuster Rearrangement.

With a reliable method to prepare [3]dendralene **1a**, the vinylogous Nazarov reaction could be tested. The Nazarov cyclization was found to be facile at low temperatures under Lewis acid activation, giving good to excellent yields. The ester could be successfully derivatized to alternative carbonyl functionality;[14] however, multiple steps were required to transform the enoate to the corresponding ketone, aldehyde or Weinreb amide (Scheme 6).



Scheme 6: Carbonyl Functionalization and the Vinylogous Nazarov Reaction.

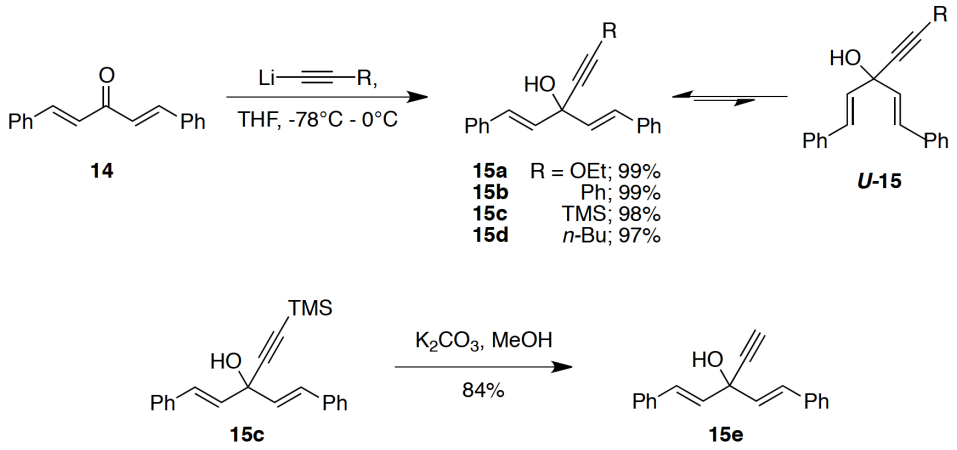
Ideally, these substrates could be prepared by Meyer-Schuster rearrangement of the corresponding propargylic alcohols. When propargylic alcohol **9b**, analogous to **9a** but bearing a phenyl on the alkyne terminus, was treated under the optimized vanadium-catalyzed reaction conditions the starting material was consumed giving an intractable mixture. Given the lack of success with the vanadium conditions, the previously successful Au(III) conditions were revisited. For standard reaction conditions, or in the presence of water or 4Å MS the product formed was a methylenecyclopentene resulting from dehydration and subsequent Nazarov cyclization of the resulting pentadienyl cation.[13]



Scheme 7: Dehydrative Nazarov Cyclization.

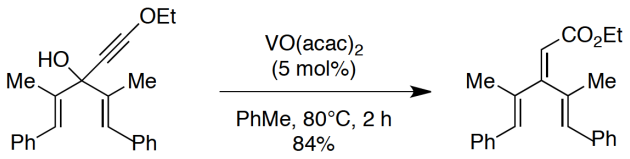
With this result in mind, substrates **15a** – **15e** that were less likely to undergo cyclization were prepared from dibenzylideneacetone **14**.[15] Substrates

lacking substitution at the 2- and 4- positions are known to be less active Nazarov substrates, resulting from a low probability of existing in the U-shaped conformation ***U*-15** required for Nazarov cyclization.



Scheme 8: Synthesis of Dibenzylideneacetone Analogues.

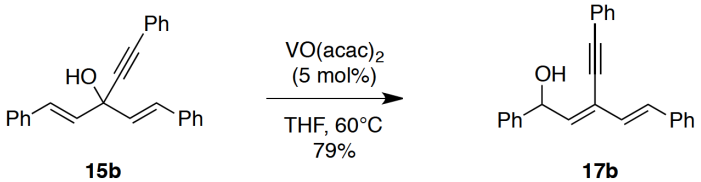
When these substrates were treated under the previously successful conditions using $AuCl_3/H_2O$, $AuCl_3$/*i*-PrNEt, $VO(acac)_2$, and $VO(Oi\text{-}Pr)_3$, either there was no consumption of starting materials, or decomposition to intractable mixtures occured. The one exception to these observations was substrate **15a**, which unsurprisingly underwent Meyer-Schuster rearrangement under all conditions tested. When propargylic alcohol **15b** was used to screen the vanadium catalysts, this time using dry THF rather than toluene, a new product was formed that was slightly more polar by TLC. This observation came as a surprise, due to the less polar nature of the Meyer-Schuster and cyclization products observed to this point. [15]



9a **1a**

Scheme 9: Meyer-Schuster Rearrangement of Dibenzylideneacetone Analogue.

Subjected to spectral analysis the product's ^{13}C NMR indicated that the new compound lacked the symmetry of compound **15b**, as 19 distinct carbon resonances were observed rather than 13. Examination of ^{13}C NMR and IR spectra suggested that no carbonyl functionality was introduced, additionally, the IR spectrum revealed that the alcohol functionality was maintained, indicated by a broad O-H stretching signal. Also, the alkyne was maintained; indicated by the C-C sp stretching and ^{13}C NMR resonances (δ 97.1, 83.7 ^{13}C NMR). In the ^{1}H NMR spectra a spin-system of two doublets with large coupling constants (J = 15.8 Hz), resulting from a *trans*-1,2-disubstituted alkene, similar to the starting material was observed (δ 7.12, 6.77 ^{1}H NMR). A second spin-system of coupled doublets, also integrating for one proton each, but with smaller coupling constants (J = 8.9 Hz), and an upfield shift (δ 6.23, 6.03 ^{1}H NMR) was also observed. When the HSQC spectra was analyzed, a diagnostic cross-peak correlating a carbon at 72.7 ppm to the methine proton at 6.03 ppm was found (Figure 1). This suggested that the hydroxyl group had undergone 1,3-transpostion, moving the 1,4-diene into conjugation, giving the 2° allylic alcohol **17b** as a single olefin isomer (Scheme 10).



15b **17b**

Scheme 10: 1,3-Transposition of **15b**.

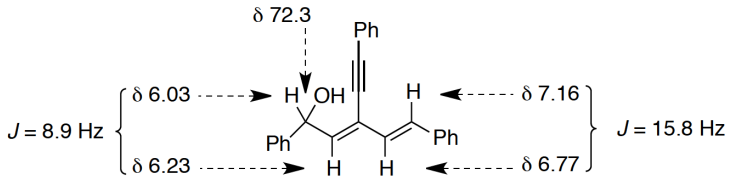
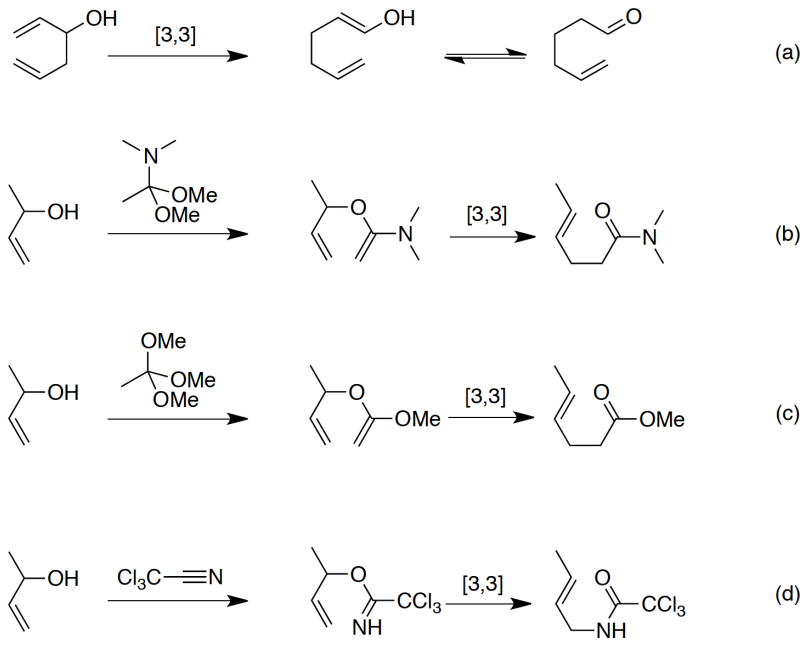


Figure 1: Characteristic Coupling Constants and Chemical Shifts.

With this unexpected, but facile 1,3-transposition it was now possible to obtain both a 2° and 3° isomer of the allylic alcohol. If generalized, this method would be useful for accessing a variety of allylic alcohol building blocks.

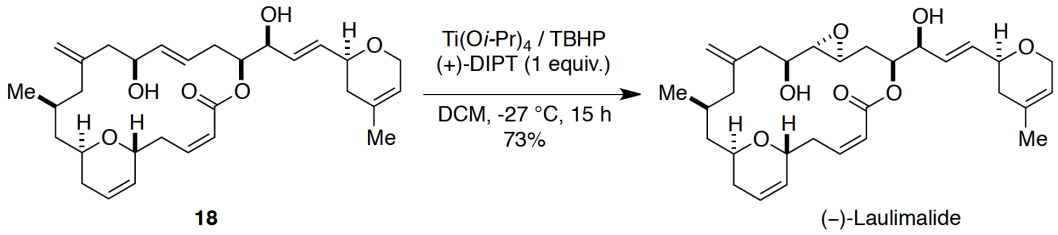
4.2 Synthetic Utility of Allylic Alcohols

Allylic alcohols are valuable substrates used in an array of powerful synthetic methods. Several [3,3] sigmatropic rearrangements require allylic alcohols as substrates. The oxy-Cope and anion accelerated oxy-Cope utilize allylic homoallylic alcohols[16,17] (Scheme 11a). Eschenmoser (Scheme 11b) and Johnson (Scheme 11c) variants of the Claisen rearrangement[18,19] provide γ,δ-unsaturated esters and amides using allylic alcohols as starting material. Similarly, the Overman rearrangement[20] (Scheme 11d) can be used to generate allylic trichloroacetamides from corresponding allylic alcohols.

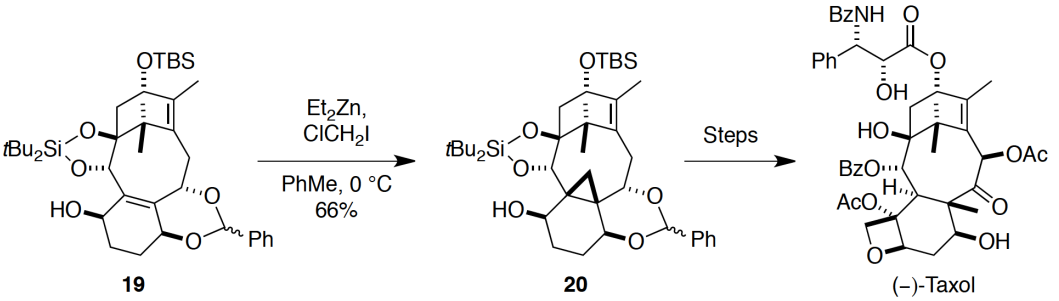


Scheme 11: [3,3] Sigmatropic Rearrangements.

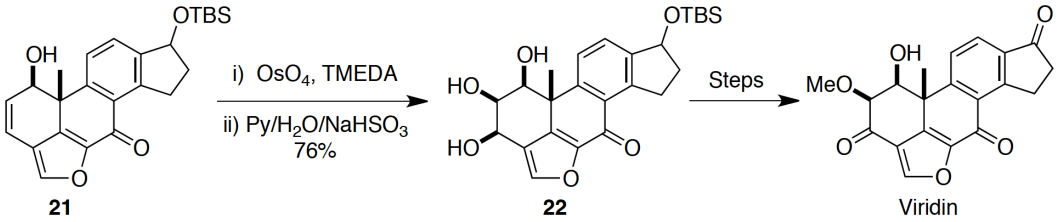
Allylic alcohols also serve as important directing groups by preassociating to reagents allowing for regio- and stereochemically controlled functionalization of the substrates. This is especially notable in the context of total synthesis. Examples of this include a highly selective Sharpless epoxidation; the final step in Paterson and co-workers synthesis of (-)-laulimalide (Scheme 12) .[21] A hydroxyl directed Simmons-Smith cyclopropanation of a highly functionalized intermediate used by the Kuwajima group for the synthesis of (–)-taxol.[22] Sorensen and coworkers used a hydroxyl-directed dihydroxylation to access the *all-syn* triol **22** on route to viridin.[23] Having tools to rapidly access an array of these synthetically useful building blocks is highly desirable given the powerful methodology in place to exploit the allylic alcohol functionality.



Scheme 12: Directed Shaprless Epoxidaion.



Scheme 13: Directed Simmons-Smith Cyclopropanation.

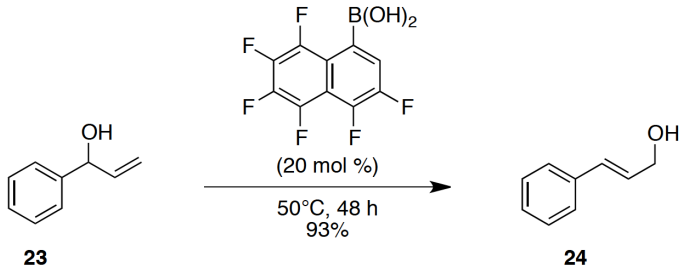


Scheme 14: Directed Dihydroxylation.

4.3 1,3-Transpositions of Allylic Alcohols

Classical conditions[24] for allylic alcohol 1,3-transposition require the use of excess strong Brønsted acid for ionization to form a free carbocation which will rearrange to the thermodynamic product(s). Recently conditions using methanesulfonic acid[25] and catalytic benzoic acids[26] have appeared in the literature. Hall and coworkers recently reported the use of catalytic polyfluoro arylboronic acids to effect 1,3-transposition of allylic alcohols (Scheme 15).[27] Although the process is acid catalyzed; mechanistic studies suggest an ordered transition state with a substantial degree of concertedness similar to that of metal oxo catalysis. Stoichiometric activating agents have been utilized for 1,3-allylic

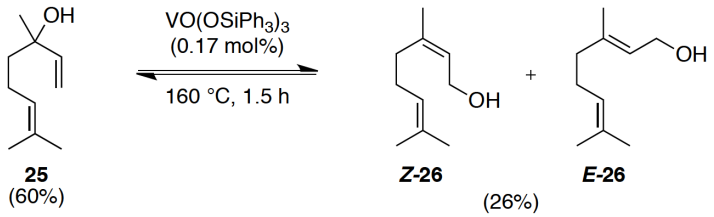
inversions of parent allylic alcohols; silyl ethers,[28,29] esters,[30] *ortho* esters, [31]and carbonates[32] have been reported. While these methods are useful, they do require at least a full equivalent of the functionalizing reagent.



23 **24**

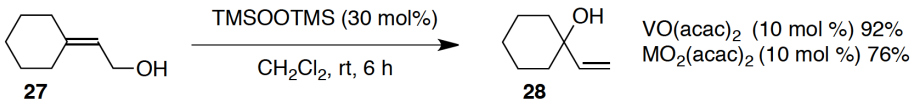
Scheme 15: Boronic Acid Catalyzed 1,3-Transposition.

1,3-allylic alcohol transpositions have been explored previously using catalytic metal oxo species. The earliest reports by Chabardes and coworkers found that using catalytic triphenylsilyl orthovanadate required high temperatures to effect isomerization, and led to equilibrium mixtures (Scheme 16).[33] $WO(OMe)_4$•Py was used at even lower catalyst loading, however improvements in product distribution were minimal.[34] Later, catalytic $VO(acac)_2$ and $MO_2(acac)_2$ were combined with substoichiometric trimethylsilyl peroxide to efficently isomerize 2° and 1° allylic alcohols to 3° allylic alcohols (Scheme 17).[35] These early metal oxo isomerizations using vanadium, molybdenum and tungsten are proposed to first undergo ligand exchange with the allylic alcohol, followed by [3,3]-rearrangement; closely resembling a Claisen rearrangement. Ligand exchange then releases the product alcohol (Figure 2).



25 (60%) ***Z*-26** ***E*-26** (26%)

Scheme 16: Early Orthovanadate Isomerization.



Scheme 17: Silyl Peroxide Activated Metal Oxo Catalysis.

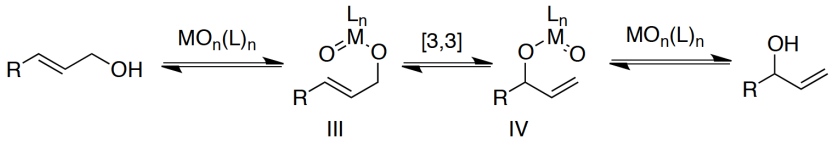
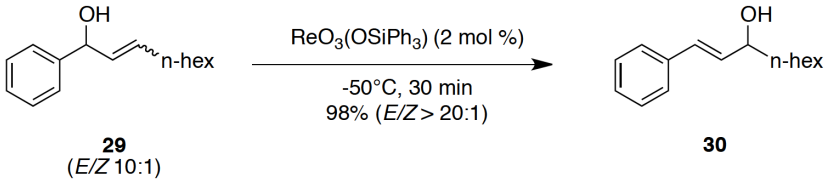


Figure 2: Metal Oxo [3,3]- Rearrangement Mechanism

More recently, rhenium(VII) oxo complexes have been used as effective transposition catalysts; active at ambient temperature and below (Scheme 18).[29,36-41] The triphenylsilyl perrhennate isomerization is proposed to be mechanistically similar to the vanadate mechanism first suggested by Chabardes, however the highly polarized nature of the six-membered transition structure is also prone to competitive formation of an ion-pair or complete ionization.[29] In 1995 Li and coworkers used catalytic $RuCl_2(PPh_3)_2$ in aqueous media to effect a 1,3-allylic alcohol transposition. The use of water as a solvent is attractive, however this reaction differs from previous examples in that it likely proceeds via a dehydrative/rehydrative mechanism.[42]

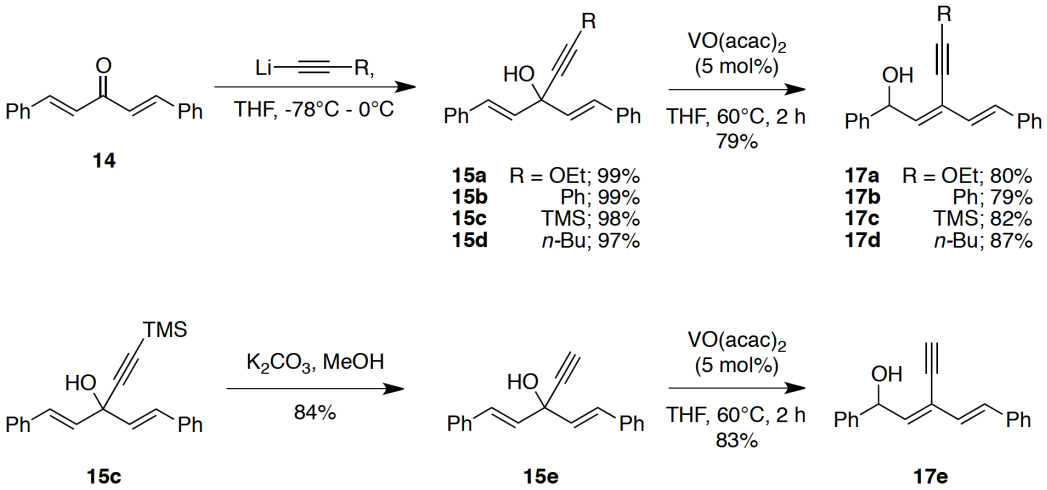


Scheme 18: $ReO_3(OSiPh_3)$ Catalyzed Allylic Alcohol Isomerization.

4.4 Results and Discussion

4.4.1 Reactions with Propargylic Bis(allylic) Alcohols

After observing the vanadium catalyzed 1,3-transposition of 3° allylic alcohol **15b** to 2° allylic alcohol **17b** (Scheme 10), the value of a process that would allow us to access both of these allylic alcohol isomers from easily accessible starting materials was clear. This method also contrasts many of the earlier examples, as a 2° benzylic alcohol is formed, moving out of conjugation with a phenyl, rather than being driven by styrene formation. Several additional propargylic alcohols derived from dibenzylideneacetone, differing at the alkyne terminus were screened under the originally successful conditions. In all five cases, the 1,3-transposition product was isolated in high yield (Scheme 19). Notably, at 60 °C **15a** undergoes 1,3-transposition to **17a** with complete selectivity, rather than Meyer-Schuster rearrangement.



Scheme 19: 1,3-Transposition of Dibenzylideneacetone Analogues.

We presumed that the mechanism of the transposition was analogous to that proposed by Chabardes and co-workers in their early work using $VO(O\textit{i}\text{-}Pr)_3$.[33] $VO(acac)_2$ first undergoes ligand exchange with the 3° allylic alcohol starting material **15**, and then the vanadium oxo bond is then involved in a [3,3]

rearrangement to transpose the vanadyl oxygen. Finally another ligand exchange releases the isomerized 2° allylic alcohol product (Figure 3). All of these steps are reversible, and the driving force is the formation of a thermodynamically favorable linearly conjugated aryl 1,3-diene system. Evidence for the reversibility of this process is shown when 2° allylic alcohol **17a** is treated using the previously successful Meyer-Schuster rearrangement conditions, the triene **16a** is formed in the same yield (84%) as from **15a (** Figure 4).

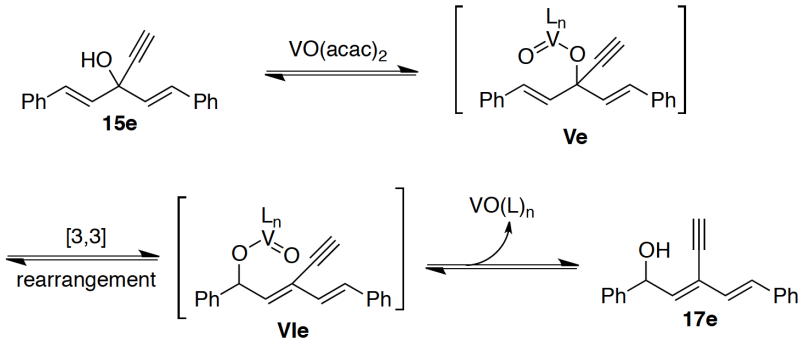


Figure 3: $VO(acac)_2$ Catalyzed 1,3-Transposition Mechanism.

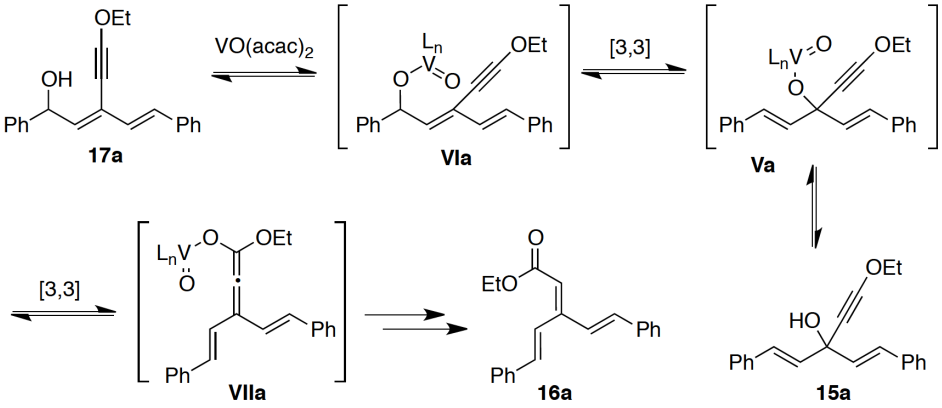
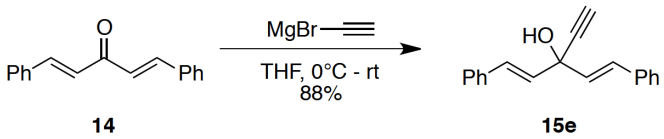


Figure 4: Formation of Meyer-Schuster Product from 2° Allylic Alcohol.

With a small set of successful substrates observed we sought to optimize the reaction conditions. Tertiary allylic alcohol **15e** was chosen as a test substrate due to practical considerations; **15e** and **17e** are reasonably well separated on TLC allowing for easier reaction monitoring and product purification. Additionally, 3° allylic alcohol **15e** could be accessed more readily using the corresponding commercially available Grignard reagent in high yield (Scheme 20).

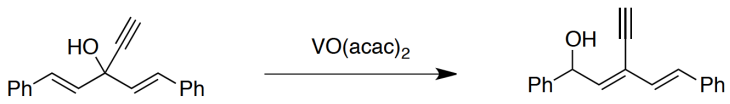


14 15e

Scheme 20: Ethynylmagnesium Bromide Addition.

For the optimization (Table 2), we began in toluene, the solvent of choice for the previous Meyer-Schuster reaction, in order to screen the effect of temperature. At high temperatures (entries 1-2), although the starting material was consumed inside of one hour, low yields were obtained along with varying amounts of unidentified impurities. Lower temperatures (entries 3-4) were also tested. At 60 °C the reaction was complete in one hour in excellent yield, while at ambient temperature the reaction was sluggish, but completed in high yield. A reaction temperature of 60 °C was chosen going forward as it gave high yield in reduced reaction time as compared to the room temperature conditions. Next, catalyst loading was examined; at 2.5 mol% catalyst loading no change was observed in yield or reaction time; however, further reduction to 1 mol% resulted in trace amounts starting material remaining in the crude NMR spectrum even after 2.5 hours. Finally, a brief solvent screen showed more polar solvents (entries 8-10) THF, acetonitrile and dichloroethane provided comparable yields; however, the reaction times were increased. Although toluene and benzene provided similar results, toluene was used as the solvent of choice due to the toxicity associated with benzene.

Table 2: Optimization $VO(acac)_2$ Catalyzed 1,3-Transposition.



15e **17e**

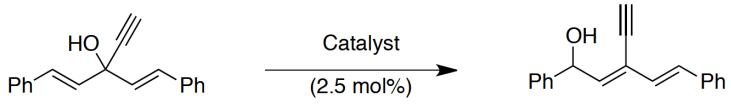
	$VO(acac)_2$ (mol %)	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	5.0	PhMe	80	1	44
2	5.0	PhMe	110	1	36
3	5.0	PhMe	60	1	91
4	5.0	PhMe	rt	3	82[b]
5	2.5	PhMe	60	1	91
6	1.0	PhMe	60	1.5	86[b]
7	2.5	PhH	60	1	90
8	2.5	THF	60	2	90
9	2.5	MeCN	60	3.5	76
10	2.5	DCE	60	1	88

[a]Isolated yield after purification. [b]Trace starting material remained in crude NMR.

The conditions optimized for $VO(acac)_2$ were then applied to several different metal oxo catalysts (Table 3). $VO(O\textit{i}\text{-Pr})_3$ was successful in catalyzing the isomerization; however, the yield was slightly reduced. $VO(tfacac)_2$ and $VO(hfcac)_2$ were prepared using the method described by Dilli and Patsalides.[43] We expected the fluorinated vanadium(IV) catalysts to be more active. In practice the reactions using $VO(tfacac)_2$ and $VO(hfacac)_2$ were completed faster, even at room temperature; however, in both cases slightly lower yields were observed. When $MO_2(acac)_2$ was employed, the starting material was consumed in 1 h; however, crude ^1H NMR spectra showed that the desired isomerized product was a minor component in an otherwise intractable mixture of products. When

$TiO_2(acac)_2$ was tested, no reaction was observed after 1 h, and after 24 h the crude ^1H NMR spectra showed only starting material with a trace of the isomerized product. Although the fluorinated vanadium(IV) catalysts and VO(O*i*-Pr)$_3$ successfully catalyzed the reaction, $VO(acac)_2$ was selected as the catalyst of choice, thanks to its superior yield, at the cost of slightly increased reaction time and temperature. $VO(acac)_2$ is also commercially available at a lower cost than the fluorinated catalysts that must be synthesized, and unlike VO(O*i*-Pr)$_3$ it is not moisture sensitive.

Table 3: Metal Oxo Catalyst Screening.



15e **17e**

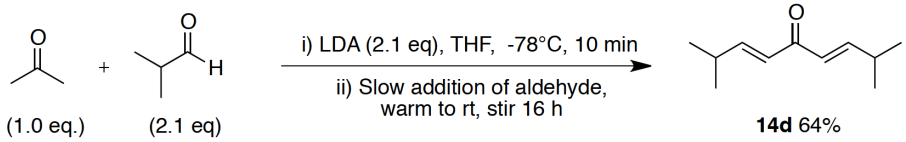
	Catalyst	Loading (mol%)	Solvent	Temp (°C)	Time (hr)	Yield[a] (%)
1	$VO(O\textit{i}\text{-}Pr)_3$	2.5	PhMe	60	1	86
2	$VO(O\textit{i}\text{-}Pr)_3$	2.5	THF	60	1	-[b]
3	$VO(O\textit{i}\text{-}Pr)_3$	2.5	PhMe	rt	1.5	80
4	$VO(tfacac)_2$	2.5	PhMe	60	1	79
5	$VO(tfacac)_2$	2.5	PhMe	rt	1	-[b]
6	$VO(hfacac)_2$	2.5	PhMe	60	1	74
7	$VO(hfacac)_2$	2.5	PhMe	rt	1	76[b]
8	$MO_2(acac)_2$	2.5	PhMe	60	1	Trace[c]
9	$TiO(acac)_2$	2.5	PhMe	60	24	Trace[d]

[a]Isolated yield. [b]Reaction incomplete after 1 hr. [c]Starting material consumed, trace product observed in crude NMR spectra. [d]Unreacted starting material with trace product and uncharacterized impurities in crude NMR spectra.

Tertiary allylic alcohol dibenzylideneacetone derivatives **15a-15e** were then subjected to the optimized conditions. Fortunately, the reactions were high yielding, similar to the initial findings. A series of 3° propargyl bis(allylic) alcohols were then prepared to further test the scope of the 1,3-transposition. The aryl substituents on the allylic termini were altered, *p*-Chloro derivatives **15f** and **15g**, and *p*-methoxy derivatives **15h** and **15i** were prepared from the corresponding divinyl ketones to see if withdrawing or donating groups affected the reaction. Under the standard isomerization conditions the expected 1,3-transposition products were formed in high yields (entries 6-9). The donating or withdrawing aryl substituents appeared to have little effect on the rate or yield of

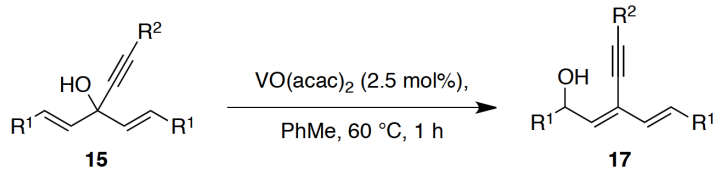
the reaction itself; however, we did note slow decomposition of compounds bearing donating aryl substituents (**15h**, **15i**, **17h** and **17i**) upon sitting in $CDCl_3$ likely due to acid catalyzed ionization and subsequent side reactions in the mildly acidic $CDCl_3$.

Next, the aryl substituent on the allylic termini was replaced with an aliphatic group. When standard base-catalyzed aldol condensation conditions were used to prepare divinyl ketone **14d**, none of the desired double aldol condensation product was observed in the crude NMR. Suspecting possible interference by the acidic isobutyraldehyde α-proton, a bulkier base was chosen. When LDA was used as the base, ketone **14d** was formed in a synthetically useful yield (Scheme 21). With ketone **14d** in hand, the corresponding 3° allylic alcohols were prepared under the standard conditions and the subsequent 1,3-transposition was high yielding (entries 10-11). All products in Table 4 led to the observation of single olefin isomers **17**, with complete consumption of starting materials **15.**



Scheme 21: Preparation of Divinyl Ketone **14d**.

Table 4: Tertiary Propargylic Bis(allylic) Alcohol Substrate Scope.



15 17

	3° Alcohol	R^1	R^2	Product (Yield(%))[a]
1	**15a**	Ph	OEt	**17a** (84)
2	**15b**	Ph	Ph	**17b** (82)
3	**15c**	Ph	TMS	**17c** (80)
4	**15d**	Ph	*n*-Bu	**17d** (87)
5	**15e**	Ph	H	**17e** (91)
6	**15f**	*p*-ClC_6H_4	H	**17f** (87)
7	**15g**	*p*-ClC_6H_4	*n*-Bu	**17g** (83)
8	**15h**	*p*-$OMeC_6H_4$	H	**17h** (79)
9	**15i**	*p*-$OMeC_6H_4$	*n*-Bu	**17i** (86)
10	**15j**	*i*-Pr	H	**17j** (89)
11	**15k**	*i*-Pr	*n*-Bu	**17k** (91)

[a]Isolated yields after purification.

It was important to determine the double bond geometry of the products. Once the connectivity was established, and proton signals assigned, 2D TROESY could be used to observe rOe correlations that could be used to confirm the double bond geometry. 2D TROESY spectrum was collected for 2° allylic alcohol product **17f**. The diagnostic rOe was observed between the lone proton on the transposed trisubstituted olefin, and the β-proton on the unchanged styryl moiety (Figure 5). This rOe was convincing evidence to confirm *E*-geometry of the transposed double bond.

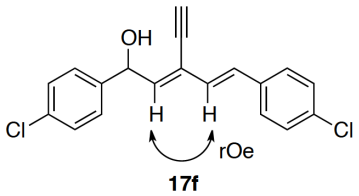
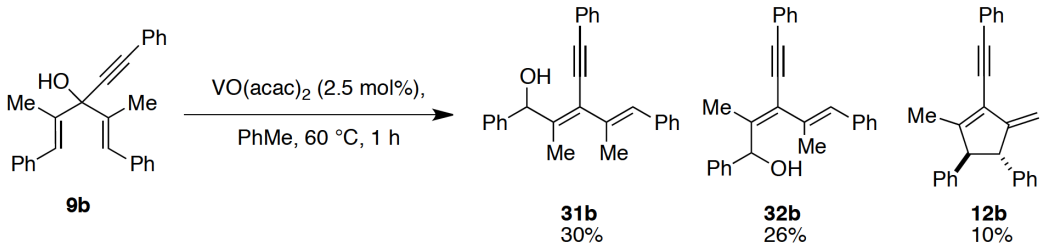


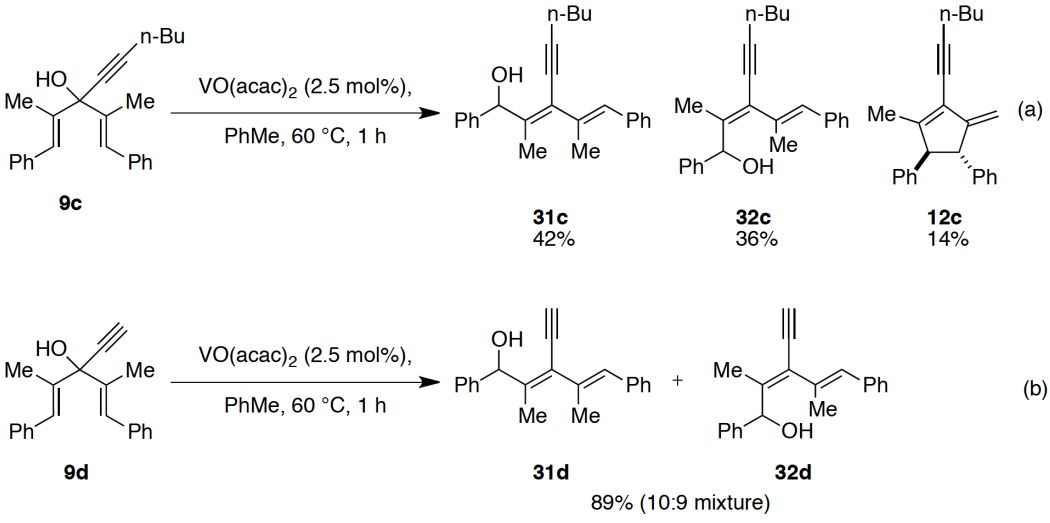
Figure 5: Olefin Geometry Determination of 2° Allylic Alcohol **17f**.

We were interested in testing the vanadium(IV) catalyzed 1,3-transposition on 3° propargylic bis(allylic) alcohols derived from dibenzylidene-3-pentanone. These substrates would lead to tetrasubstituted olefins if the isomerization were successful providing an opportunity to further probe the selectivity of this process. Tertiary propargylic bis(allylic) alcohols **9b** and **9c** were prepared using the standard lithium acetylide procedure, while **9d** was prepared by the standard Grignard addition protocol. When 3° propargylic alcohol **9b** was subjected to the optimized 1,3-transposition conditions three products were isolated (Scheme 22). The major products **31b** and **32b** resulted from the 1,3-transposition. The *Z*-isomer **31b** was isolated in 30% yield, in slight excess to the *E*-isomer **32b** that was isolated in 26% yield. This almost 1:1 ratio of olefin isomers is surprising at first as it would seem that the equilibrium mixture would be more likely to favor the isomer **31b** where the larger allylic and 2° benzyl alcohol substituents are *trans* to one another on the tetrasubstituted olefin. However, when the *A*-value[44] of methyl (1.74) is compared to that of isopropyl (2.21) which is a reasonable comparison to the 2° benzyl alcohol based on *A*-values of hydroxymethyl, benzyl, and ethyl substituents (1.76, 1.68, and 1.79 respectively), the mixture of the two isomeric 1,3-transposition products is more easily accounted for given the small difference in size, but remains somewhat surprising. The minor product **12b** resulted from a dehydrative Nazarov-type cyclization, indicating some degree of asynchronicity in the $VO(acac)_2$ catalyzed transposition, as any pentadienyl cation formed would be likely to undergo rapid cyclization.[13]



Scheme 22: 1,3-Transposition of Dibenzylidene-3-Pentanone Derivative.

Dibenzylidene-3-pentanone derivatives **9c** and **9d** were synthesized by the standard lithium acetylide and ethynyl Grignard addition procedures respectively. Tertiary propargylic alcohol **9c** successfully underwent the 1,3-transposition giving a similar mixture of *Z* and *E* olefin isomers **31c** and **32c**, as well as a small amount of the cyclized minor product **12c** (Scheme 23a). Tertiary propargylic alcohol **9d** also gave a mixture of *E* and Z olefin isomers; however, in this case the isomers were not separable and the geometry was assigned based on analogy to the previous examples (Scheme 23b). Notably, in the vanadium catalyzed reaction of **9d**, no formation of the dehydrative Nazarov cyclization product was observed.



Scheme 23: 1,3-Transposition of Dibenzylidene-3-Pentanone Derivatives.

The *Z* and *E* geometries of tetrasubstituted olefin products **31** and **32** were assigned by way of nOe correlations from 1D-NOESY experiments. In the case of compound **31c** (Figure 6), when the methyl group adjacent to the hydroxyl was irradiated, an nOe was observed for the β-methyl on the unchanged styryl moiety. Next, the β-methyl group was irradiated, and nOe was observed for the methyl adjacent to the hydroxyl. These observations allowed us to confidently assign **31c** as the *Z*-isomer. Compound **32c**, which had the same connectivity as **31c**, was suspected to be the other olefin isomer. The β-methyl on the unchanged styryl moiety was irradiated in a 1D-NOESY experiment, and a nOe was observed for the benzylic proton, offering support for its assignment as the *E*-isomer.

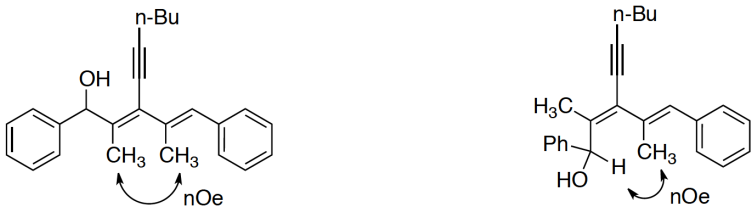
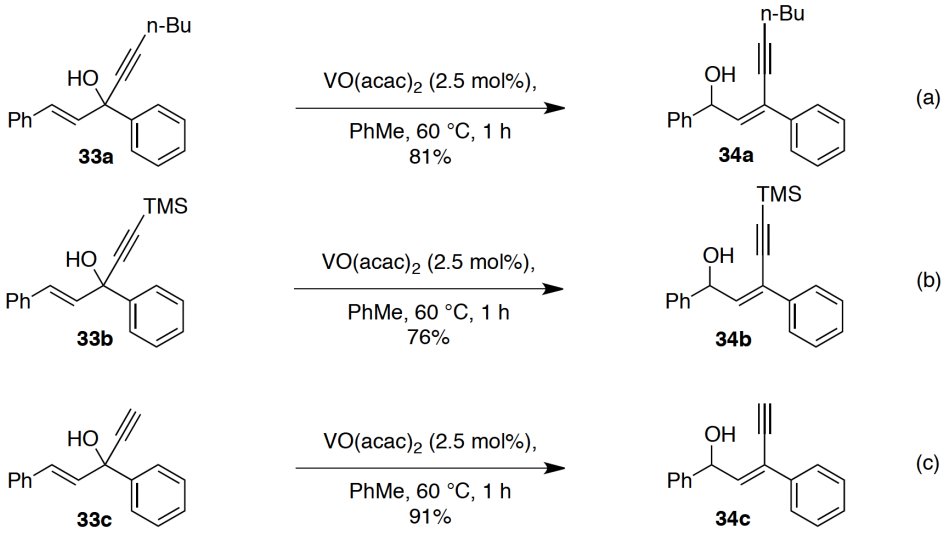


Figure 6: Olefin Geometry Determination of 2° Allylic Alcohols **31c** and **32c**.

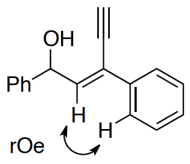
4.4.2 Reactions with Tertiary Propargylic Allylic Alcohols

Next, we planned to investigate the 1,3-transposition on 3° propargylic alcohols derived from chalcone. Once again the standard lithium acetylide and ethynyl Grignard addition procedures were successful in preparing the required 3° propargylic alcohol substrates **33a-c**. When these compounds were subjected to the optimized conditions, the desired 1,3-transposition products were formed in high yields. As was the case with previous substrates (Table 4), no Meyer-Schuster rearrangement products were observed. Preferential transposition of **33** to **34** converts one styrene to another. We presume the driving force in these cases is the extra stabalization provided by the cross-conjugated alkyne.



Scheme 24: 1,3-Transposition of Chalcone Derivatives.

We observed single olefin diastereomers in the reactions of **33a-c**. Correlations from a 2D TROESY spectrum of compound **34c** were used to confirmed the expected *E*-olefin geometry. An rOe correlation between the proton of the tri-substiuted olefin and the *ortho* protons of the phenyl on the same olefin was used as evidence to assign the *E*-olefin geometry, consistent with the much bulkier phenyl substituent being situated *trans* to the bulky benzylic alcohol. The geometry of compounds **34a** and **34b** were assigned based on analogy to **34c**.

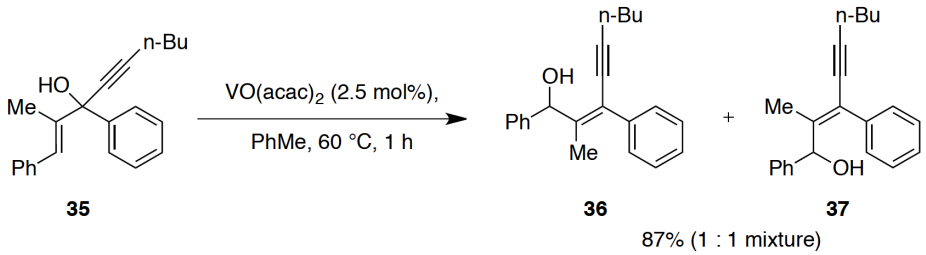


34c

Figure 7: Olefin Geometry Determination of 2° Allylic Alcohol **34c**.

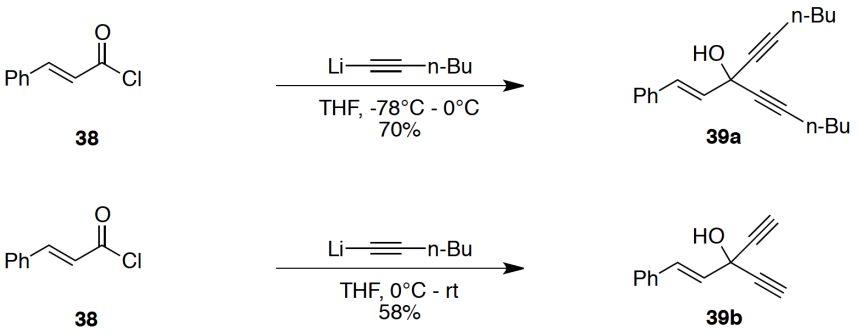
Tertiary propargylic alcohol **35**, prepared from α-methyl chalcone, was synthesized to draw a parallel to the selectivity of substrates **9b** to **9d**. We were interested to see if the *E*/*Z* selectivity would be any greater for this class of substrate. The reaction proved high yielding, albeit with a 1 : 1 *E*/*Z* ratio of the 1,3-transposition products **36** and **37** (Scheme 25). This observation again

suggests that the steric bulk of the methyl and 2° benzyl alcohol groups is too similar, therefore the equilibrium mixture of products does not favor either isomer.

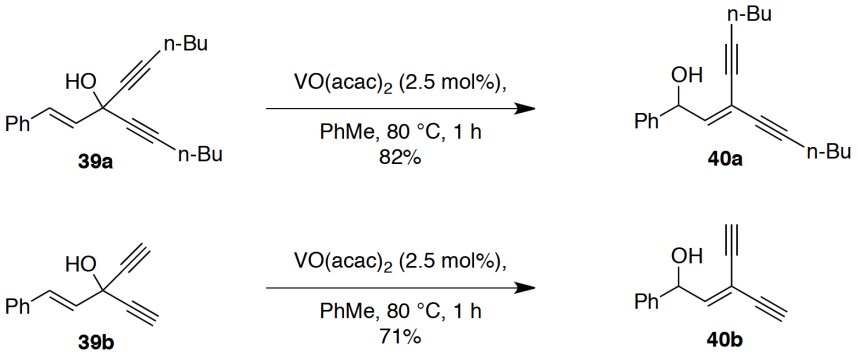


Scheme 25: 1,3-Transposition of α-Methyl Chalcone Derivative **35**.

Further testing the 1,3-transposition selectivity, we prepared bis(propargylic) allylic alcohols **39a** and **39b** by double addition of the corresponding acetylide nucleophile to the corresponding acid chloride **38** (Scheme 26). The presence of two alkynes potentially capable of undergoing a competitive Meyer-Schuster reaction could serve to further validate our methodology. When the bis(propargylic) allylic alcohols were subjected to the optimized reaction conditions, the reaction proved to be sluggish. After 2 hours, NMR indicated only trace products had formed, with large amounts of starting material remaining. We resubmitted the starting materials to our reaction conditions, but increased the catalyst loading to 5%. After 8 hours the crude NMR indicated that only trace starting material (>10%) remained, however the product was difficult to separate from this unreacted material. Next we examined increased reaction temperatures, although we were reluctant to do so based upon our previous observations (Table 2). Gratifyingly, when the reaction temperature was increased to 80 °C the starting materials were completely consumed within 1 h, and products **40a** and **40b** were formed in high yields (Scheme 27).



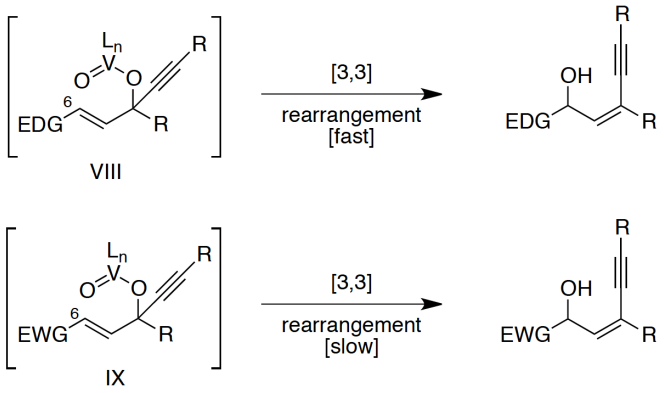
Scheme 26: Synthesis of Bis(propargylic) Allylic Alcohols.



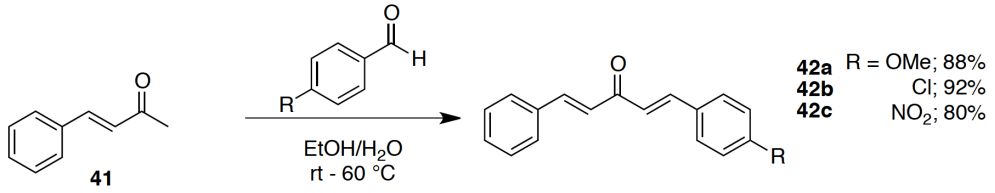
Scheme 27: 1,3-Transposition of Bis(propargylic) Allylic Alcohols.

4.4.3 Reactions with Unsymmetrical Propargylic Bis(allylic) Alcohols

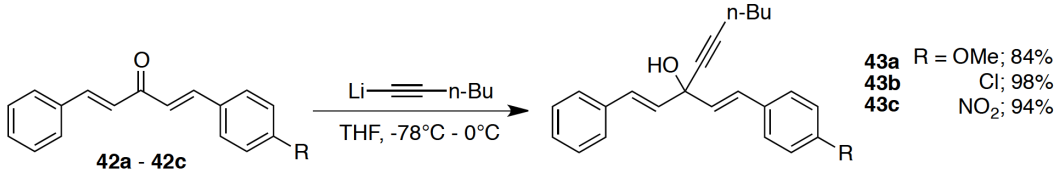
We were interested to see if unsymmetrical bis(allylic) propargyl alcohols would undergo a selective 1,3-transposition, differentiating between the two olefins either electronically or by steric encumbrance. Using the Claisen rearrangement as a model, when a donating group is placed at the allylic terminus (in our case the 6-position of the proposed oxo vanadium intermediate **VIII** (Scheme 28) the rate of the [3,3]-rearrangement should increase;[45] a correspondingly withdrawing substituent should decelerate the reaction.[46] To test this, three unsymmetrical divinyl ketones **41a** – **41c** were prepared from benzylideneacetone and the corresponding substituted benzaldehydes using standard base catalyzed aldol condensation conditions (Scheme 29). Addition of hexynyl lithium under the optimized conditions to the aforementioned divinyl ketones gave the required unsymmetrical bis(allylic) propargyl alcohols (Scheme 30).



Scheme 28: Expected Substituent Effects on [3,3] Rearrangement.

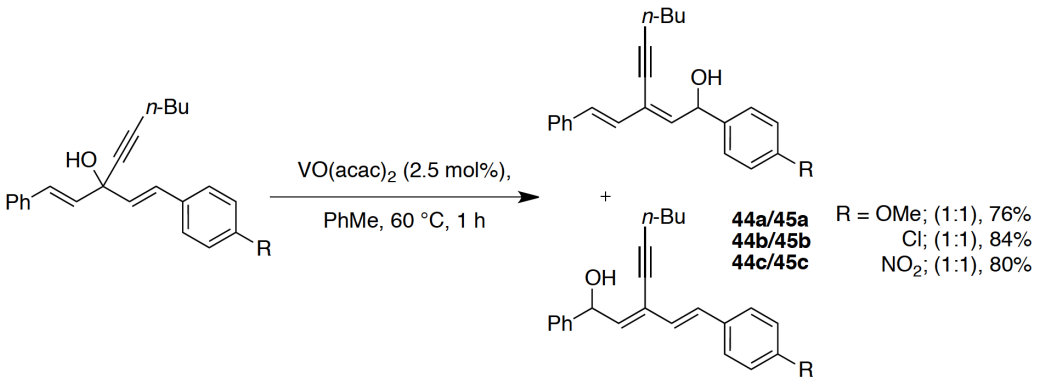


Scheme 29: Synthesis of Unsymmetrical Divinyl Ketones.

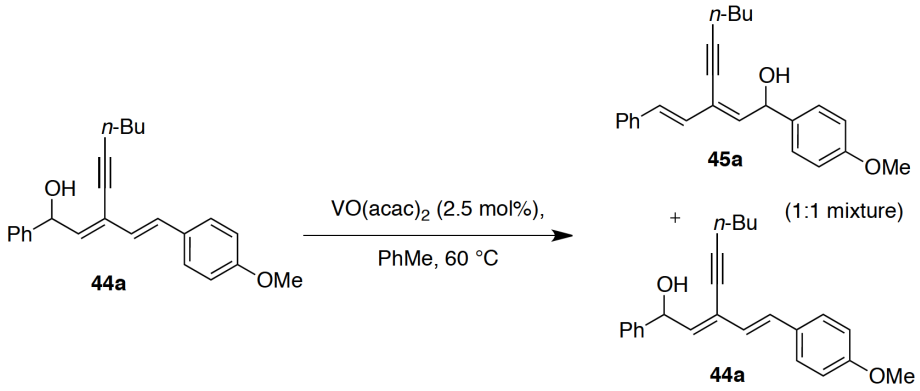


Scheme 30: Synthesis of Unsymmetrical Bis(allylic) Propargyl Alcohols.

With unsymmetrical bis(allylic) propargyl alcohols **43a** – **43c** in hand we were able to test the selectivity of the 1,3-transposition using the standard catalytic $VO(acac)_2$ conditions. For all three substrates the vanadium catalyzed 1,3-transposition was high yielding using the optimized conditions; however, the isomerization gave 1:1 mixtures of the two expected regioisomers which were inseparable by flash chromatography (Scheme 31). We suspected that this was a result of the isomerization being under thermodynamic control. To test this, we were able to isolate small amounts of pure **44a** using radial chromatography. When **44a** was subjected to the reaction conditions, we observed equilibration back to a 1:1 mixture (Scheme 32), indicating that the reaction is most likely a reversible thermodynamic equilibrium.



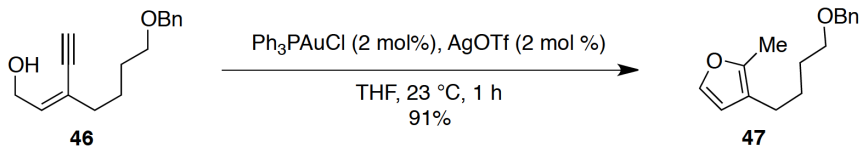
Scheme 31: 1,3-Transposition of Unsymmetrical Bis(allylic) Propargyl Alcohols.



Scheme 32: Equilibration of Allylic Alcohol **44a**.

4.4.4 Tandem Reactions with Propargylic Bis(allylic) Alcohols

We hoped to further exploit this 1,3-transposition by taking advantage of the remaining alkyne functionality. Inspired by a high yielding gold catalyzed enynol cyclization (Scheme 33) used by Nicolaou and co-workers in their 2010 synthesis of Englerin A,[47] we sought to apply this to our 1,3-transposition products. Gold catalyzed cyclization of 2-en-4-yn-1-ols has been previously investigated, with both Au(I) and Au(III) being reported as catalysts.[48,49] Given our interest in tandem reactions we hoped to perform the 1,3-transposition, followed by the enynol cycloisomerization in one pot to generate highly substituted furans (Figure 8).



Scheme 33: Gold Catalyzed Cycloisomerization.

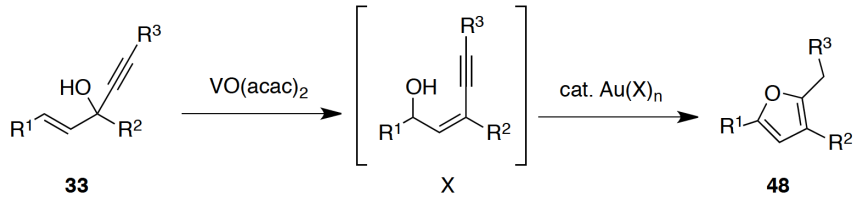
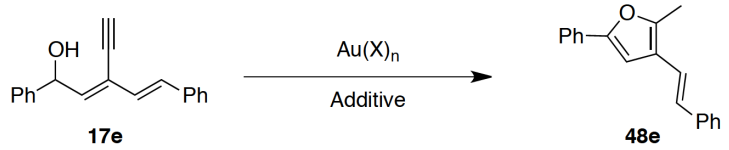


Figure 8: Proposed Tandem 1,3-Transposition/Cycloisomerization.

In order to study a possible tandem reaction we first sought to validate the gold catalyzed cycloisomerization. The 1,3-transposition product **17e** was chosen as the test substrate to screen the gold cycloisomerization conditions. First, we looked to the standard Au(I) conditions used by Liu and co-workers.[49] Gold(I) catalyst Ph_3PAuCl, combined with AgOTf additive in DCM, resulted in the complete consumption of **17e** within 1 h, yielding the expected tri-substituted furan product **48e** in good yield (Table 5, entry 1). The reaction was run with different Ag(I) salts, as well as in the absence of any silver additive (entry 2 – entry 4), however AgOTf proved to be the most effective silver additive. We switched the solvent from DCM to toluene, the preferred solvent for the 1,3-transposition and found the effect on yield was minimal, which was encouraging for a 1-pot procedure (entry 5). Au(III) has also been successfully used for this type of cyclization. When **17e** was subjected to catalytic $AuCl_3$ (entry 6), the desired product was formed in 82% yield, higher than observed for any of the Au(I) trials. The addition of AgOTf did not improve the yield of the reaction. A brief screen of solvents (entry 7 – entry 10) indicated that DCM and toluene were the best choices, with toluene giving us the ability to raise the reaction temperature to a greater degree if required. When the reaction was run at elevated temperatures (60 °C), the reaction was complete in 30 minutes; however, a small decrease in yield was observed (entry 13). $AuCl_3$ appeared to be the optimum

catalyst, and toluene, our previous solvent of choice was compatible with the cyclization conditions.

Table 5: Validation and Optimization of Gold Catalyzed Cycloisomerization.



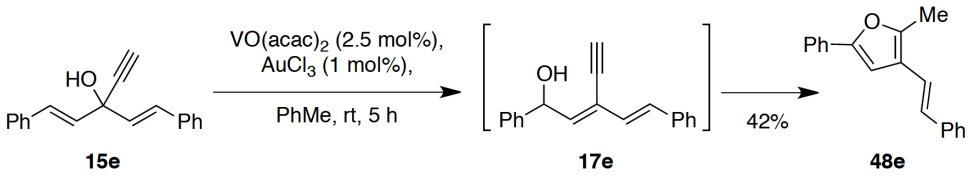
17e 48e

	Catalyst (1 mol%)	Additive (1 mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	Ph_3PAuCl	AgOTf	DCM	rt	1	68
2	Ph_3PAuCl	$AgNTf_2$	DCM	rt	1	52
3	Ph_3PAuCl	$AgBF_4$	DCM	rt	1	-[b]
4	Ph_3PAuCl	-	DCM	rt	2.5	-[b]
5	Ph_3PAuCl	AgOTf	PhMe	rt	1	66
6	$AuCl_3$	-	DCM	rt	1	82
7	$AuCl_3$	AgOTf	DCM	rt	1	-[b]
8	$AuCl_3$	-	THF	rt	1	66
9	$AuCl_3$	-	MeCN	rt	1	-[b]
10	$AuCl_3$	-	PhMe	rt	1	82
11	$AuCl_3$	-	THF	60	1	-[b]
12	$AuCl_3$	-	MeCN	60	0.5	-[b]
13	$AuCl_3$	-	PhMe	60	0.5	74

[a]Isolated yields after purification. [b]When reactions were run in parallel the cleanest crude reaction mixture was purified for isolated yield.

Once we had satisfied ourselves that our substrate **17e** was suitable for the known gold chemistry, we set about carrying out the 1,3-transposition and cycloisomerization in tandem. Using a combination of the $VO(acac)_2$ transposition conditions optimized in Table 2, and the $AuCl_3$ cycloisomerization conditions optimized in Table 5 we tested our proposed one pot method using propargylic bis(allylic) alcohol **15e** (Scheme 34). After 4 hours TLC showed formation of the

furan product, with small amounts of intermediate **17e** remaining. Upon stirring the reaction mixture for an additional hour impurities began to appear by TLC, therefore the reaction was quenched, and the crude mixture was purified. The isolated yield after purification was 42%. When compared to the overall yield of 75% for the two-step process, the tandem reaction was inferior, and would require further optimization.

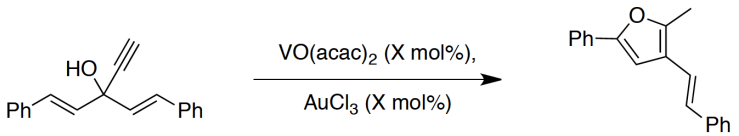


Scheme 34: Tandem 1,3-Transposition/Cycloisomerization.

We compared the effect of changing solvent, and a switch from toluene to DCM elicited no change in the reaction time or yield (Table 6, entry 2). Increasing the temperature did lead to more rapid consumption of starting material; however, isolated yield was negatively affected (Table 6, entry 3). Next, we looked to increasing the gold catalyst loading (entry 4) and were pleased to see an increase in yield, but this was not ideal, due to the high cost of $AuCl_3$. We knew from previous optimization (Table 2) that the 1,3-transposition was also successful at lower catalyst loading, so we retained the 1:1 ratio of catalysts, but reduced the loading to 1 mol% (Table 6, entry 6). The result was a slightly increased reaction time, but a comparable yield. It seemed that avoiding having excess $VO(acac)_2$ relative to $AuCl_3$ led to an improvement in the reaction yield. It seemed possible that the π-acid $AuCl_3$ could be associating to the $VO(acac)_2$, in effect poisoning the gold catalysis. To remedy this we attempted to add $AuCl_3$ in excess relative to $VO(acac)_2$ (Table 6, entry 7). We found that excess gold did not improve the reaction yield, and only provided a modest improvement in the reaction rate. Given the low solubility of $AuCl_3$ in toluene we diluted the reaction mixtures, to see if this would improve the reaction. Diluting by an order of magnitude slowed the reaction, to the point where it was not complete after 6

hours. A more modest two-fold dilution did not change the reaction time, but gave a slight improvement in yield. Still seeking to avoid any negative deactivating interactions of the catalysts we set up the reaction with $VO(acac)_2$ as the only catalyst in the reaction mixture. When **15e** was consumed by TLC, we then added the $AuCl_3$ catalyst. This method provided a yield almost identical to the two-step procedure, and required only a single purification step.

Table 6: Optimization of Tandem 1,3-Transposition/Cycloisomerization.



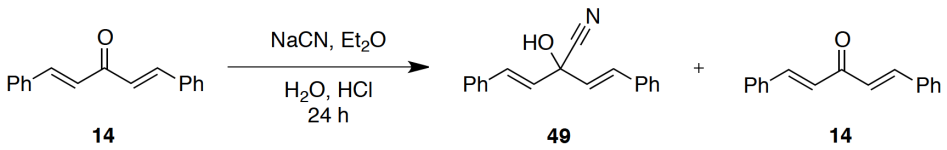
15e **48e**

	$VO(acac)_2$ (mol %)	$AuCl_3$ (mol %)	Solvent	Conc. [M]	Temp. (°C)	Time (h)	Yield (%)[a]
1	2.5	1.0	PhMe	0.1	rt	5	42
2	2.5	1.0	DCM	0.1	rt	5	40
3	2.5	1.0	PhMe	0.1	60	3	31
4	2.5	2.5	PhMe	0.1	rt	3.5	64
5	2.5	2.5	PhMe	0.1	60	2	-[b]
6	1.0	1.0	PhMe	0.1	rt	4	61
7	1.0	2.5	PhMe	0.1	rt	3.5	60
8	1.0	1.0	PhMe	0.05	rt	4	66
9	1.0	1.0	PhMe	0.01	rt	6	-[c]
10	1.0	1.0[d]	PhMe	0.05	rt	4	77
11	1.0	1.0[d]	PhMe	0.05	60	3	63

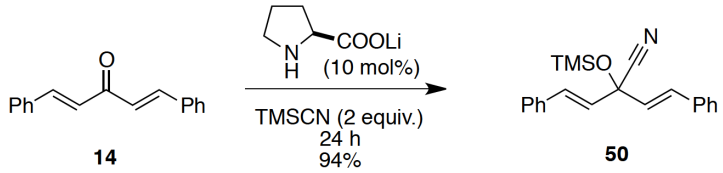
[a]Isolated yields after purification. [b]When reactions were run in parallel the cleanest crude reaction mixture was purified for isolated yield. [c]Reaction incomplete. [d]$AuCl_3$ was added after **15e** was deemed to be consumed by TLC.

4.4.5 Reactions with Bis(allylic) Cyanohydrins

Having successfully used 3° propargylic allylic alcohols in our vanadium catalyzed 1,3-transpositions, we hoped to extend this methodology by replacing the alkyne with a nitrile. Catalytic Re(VII) 1,3-transposition of allylic cyanohydrins is precedented[29] and related rearrangements of functionalized allylic cyanohydrins in the form of acetates[50] and carbonates[51] have also appeared in the literature. We turned our attention to preparing the required cyanohydrin. Bis(allylic) cyanohydrin **49**, which could be derived from dibenzylideneacetone was our substrate of choice. We chose classical cyanohydrin formation conditions employing sodium cyanide and concentrated hydrochloric acid.[52] Under these conditions we observed the formation of the desired cyanohydrin **49**, however after 24 hours the reaction had not gone to completion (Scheme 35). Following work-up we attempted to purify the cyanohydrin; however, the product was unstable to chromatographic purification, undergoing reversion to the dibenzylideneacetone starting material. If the reaction could be forced to completion, the crude cyanohydrin could be carried forward to the vanadium catalyzed 1,3-transposition step. We explored the use of crown ethers to increase the nucleophilicity of cyanide, using catalytic 15-crown-5 combined with sodium cyanide, as well as 18-crown-6 with potassium cyanide. In both cases significant amounts of starting material remained. Given the difficulty in isolating adequately pure cyanohydrin **49** using classical methods, we switched our attention to the synthesis of the corresponding TMS protected cyanohydrin **50**. Even if the cyanosilylation also failed to go to completion, we had more confidence in our ability to purify the *O*-silylated cyanohydrin **50**. Using the proline salt catalyzed cyanosilylation method disclosed by Shen and Ji in 2009[53] we were able to obtain the desired *O*-silylated cyanohydrin **50** with complete conversion in excellent yield (Scheme 36).



Scheme 35: Classical Cyanohydrin Synthesis.



Scheme 36: Proline Salt Catalyzed Cyanosilylation.

With pure *O*-silylated cyanohydrin **50** in hand we turned our attention to the 1,3-transposition. In order to attempt the isomerization we would first have to reveal the hydroxyl group. To that effect we subjected the *O*-silyl cyanohydrin **50** to acidic deprotection conditions, and after work-up and concentration used cyanohydrin **49** directly without further purification. When the previously optimized conditions were used we found that the reaction was sluggish, and we observed significant decomposition by TLC. After 4 hours the incomplete reaction was quenched; however, the desired nitrile **51** was isolated in 18% yield (entry 1, Table 7). Increasing catalyst loading again consumed the starting material but the isolated yield was low. Increasing the reaction temperature led to increased decomposition, and intractable mixtures (entries 3 and 4, Table 7). We turned to the more active VO(O*i*-Pr)$_3$ catalyst in hopes of avoiding extensive decomposition of the starting material back to ketone **14**, gratifyingly the reaction was completed in 2 or 3 hours depending on the catalyst loading (entries 5 and 6, Table 7) giving the nitrile 1,3-transposition product **51** in good yield, with only trace ketone appearing in the crude ^{1}H NMR spectra.

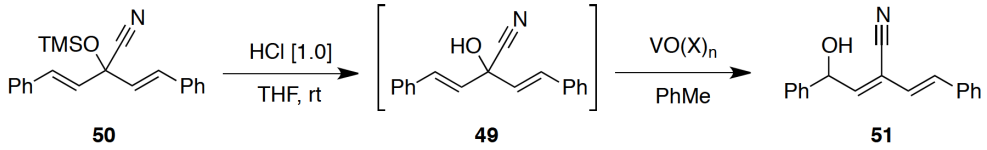


Table 7: Optimization of Vanadium Catalyzed Cyanohydrin Isomerization.

	Catalyst	Loading (mol %)	Temp. (°C)	Time (h)	Yield (%)[a]
1	$VO(acac)_2$	2.5	60	4	18[b]
2	$VO(acac)_2$	5	60	5	42
3	$VO(acac)_2$	2.5	80	4	-[c]
4	$VO(acac)_2$	2.5	110	2	-[d]
5	$VO(O\textit{i}\text{-}Pr)_3$	2.5	60	3	74
6	$VO(O\textit{i}\text{-}Pr)_3$	5	60	2	82

[a]Isolated yields after purification. [b]Reaction incomplete, crude contained **49** and **14**. [c]When reactions were run in parallel the cleanest crude reaction mixture was purified for isolated yield. [d]Intractable mixture.

4.5 Summary

During the development of a vanadium catalyzed Meyer-Schuster reaction for the synthesis of [3]dendralenes, a facile 1,3-transposition of allylic alcohol was observed. We were able to expand this method to a variety of tertiary propargylic bis(allylic) alcohols, tertiary propargylic allylic alcohols, and tertiary bis(propargylic) allylic alcohols. The vanadium catalyzed transposition could also be carried out in tandem with a gold catalyzed cycloisomerization to form tri-substituted furans. Finally, our vanadium catalyzed transposition method could also be applied to a bis(allylic) cyanohydrin for the synthesis of an α,β-unsaturated nitrile.

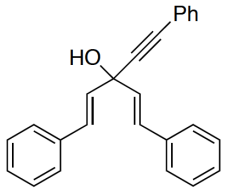
4.6 Experimental

General Information

Reactions were carried out in flame dried glassware under an argon atmosphere. Anhydrous solvents and reagents were transferred using oven dried cannulae or syringes. Solvents were distilled before use: dichloromethane and acetonitrile from calcium hydride, tetrahydrofuran from sodium/benzophenone ketyl, toluene from sodium. Reactions were monitored with 0.5 mm Kieselgel 60 F254 TLC plates (Merck). Flash chromatography was preformed using 230-400 mesh silica gel (Silicycle). Nuclear magnetic resonance spectra were recorded at 400 MHz, 500 MHz or 700 MHz for ^{1}H NMR and 100 or 125 Hz, for ^{13}C NMR. Coupling constants (*J*) are reported in Hertz (Hz). Chemical shifts are reported on the δ scale (ppm) and spectra are referenced to chloroform (7.26 ppm, ^{1}H; 77.06 ppm, ^{13}C) as internal standard. Infrared spectra were measured with a Matteson Galaxy Series FT-IR 300 spectrophotometer. Mass spectra were determined on a Kratos MS50 high-resolution mass spectrometer.

Previously Reported Alcohols.

15a, 9b, 9c[13]



15b

Propargylic Alcohol 15b. ^{n}BuLi (1.0 mL, 2.0 M in hexanes, 2.0 mmol) was added to a stirred solution of phenylaceteylene (241 μL, 2.2 mmol) in THF (6 mL) at -78 °C. The reaction was warmed to 0 °C for 1 h. The mixture was cooled to at -78 °C and dibenzylideneacetone (469mg, 2.0 mmol) in THF (10 mL) was

added via cannula. The rection mixture was warmed to 0 °C. The reaction was quenched with 1M HCl (10mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash chromatography (10 : 1 hexane : EtOAc) gave 592 mg (88%) of the desired alcohol as a pale yellow oil.

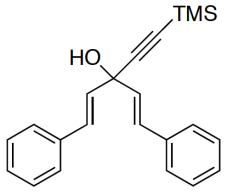
R_f 0.40 (4:1 Hexane : EtOAc);

IR (film) 3329 (br), 3082, 3058, 3027, 2229, 1599, 1491, 1448, 965, 754, 733, 691 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.54 (m, 2H), 7.48 – 7.45 (m, 4H), 7.38 – 7.32 (m, 7H), 7.30 – 7.25 (m, 2H), 7.02 (d, 2H, *J* = 15.8 Hz), 6.41 (d, 2H, *J* = 15.8 Hz), 2.47 (s, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 131.8, 131.1, 130.1, 128.7, 128.6, 128.4, 128.0, 126.9, 122.3, 88.6, 87.6, 71.7;

HRMS calc'd for $C_{25}H_{20}O$ (M^+) 336.1514; found 336.1497.



15c

Propargylic Alcohol 15c. Propargylic alcohol **15c** was prepared from dibenzylideneacetone (469mg, 2.0 mmol) and trimethylsilylacetylene (310 μL, 2.2 mmol) using the procedure described above for **15b**. Purification by flash chromatography (10 : 1 hexane : EtOAc) furnished (91%) of alcohol **15c** as a colorless oil.

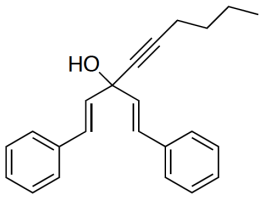
R_f 0.40 (4:1 Hexane: EtOAc)

IR (film) 3352 (br), 3083, 3060, 2959, 2168, 1600, 1578, 1495, 1449, 1250, 1069 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.44 (m, 4H), 7.37 – 7.34 (m, 4H), 7.30 – 7.27 (m, 2H), 6.96 (d, 2H, *J* = 15.8 Hz), 6.33 (d, 2H, *J* =15.8 Hz), 2.45 (s, 1H), 0.29 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 131.0, 130.1, 128.6, 128.1, 126.9, 104.8, 92.4, 71.5, 0.0;

HRMS calc'd for $C_{22}H_{24}OSi$ (M^+) 332.1596; found 332.1589.



15d

Propargylic Alcohol 15d. Propargylic alcohol **15d** was prepared from dibenzylideneacetone (469mg, 2.0 mmol) and 1-hexyne (310 μL, 2.2 mmol) using the procedure described above for **15b**. Purification by flash chromatography (20 : 1 hexane : EtOAc) furnished 570 mg (90%) of alcohol **15d** as a yellow oil.

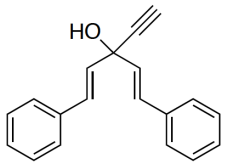
R_f 0.42 (4:1 Hexane: EtOAc)

IR (film) 3339 (br), 3082, 3059, 3026, 3001, 2957, 2932, 2862, 2237, 1495, 1448, 966 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.43 (m, 4H), 7.36 – 7.32 (m, 4H), 7.29 – 7.25 (m, 2H), 6.94 (d, 2H, *J* = 15.8 Hz), 6.33 (d, 2H, *J* = 15.8 Hz), 2.39 (t, 2H, *J* = 7.2 Hz), 2.34 (s, 1H), 1.66 – 1.59 (m, 2H), 1.56 – 1.48 (m, 2H), 0.98 (t, 3H, *J* = 7.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 131.8, 129.7, 128.6, 128.0, 126.9, 88.8, 79.9, 71.4, 30.8, 22.1, 18.6, 13.7;

HRMS calc'd for $C_{24}H_{23}O$ (M^+) 316.1827; found 316.1840.



15e

Propargylic Alcohol 15e. Ethynylmagnesium bromide (8.8 mL, 0.5 M in THF, 4.4 mmol) was added to a stirred solution of dibenzylideneacetone (937 mg, 4.0 mmol) in THF (8 mL) at 0 °C. The reaction was warmed to rt and stirred for 1 h. The reaction was quenched with sat. NH_4Cl (10 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash chromatography (10 : 1 hexane : EtOAc) furnished 867 mg (78%) of **15e** as a colorless oil.

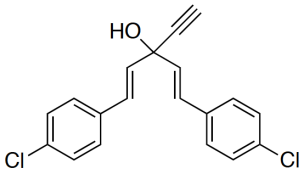
R_f 0.30 (4:1 Hexane: EtOAc)

IR (film) 3350 (br), 3293, 3083, 3059, 3027, 2113, 1600, 1577, 1493, 1448, 1070, cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.44 (m, 4H), 7.38 – 7.34 (m, 4H), 7.31 – 7.27 (m, 2H), 6.69 (d, 2H, J = 15.8 Hz), 6.35 (d, 2H, J = 15.8 Hz), 2.88 (s, 1H), 2.56 (s, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 130.6, 130.3, 128.6, 128.2, 126.6, 83.6, 75.9, 71.2;

HRMS calc'd for $C_{19}H_{16}O$ (M^+) 260.1201; found 260.1194.



15f

Propargylic Alcohol 15f. Propargylic alcohol **15f** was prepared from *p*-chlorodibenzylideneacetone (606 mg, 2.0 mmol) and Ethynylmagnesium bromide

(4.4 mL, 0.5 M, 2.2 mmol) using the procedure described for **15e**. Flash chromatography (10 : 1 hexane : EtOAc) furnished 527 mg (80%) of alcohol **15f** as a colorless oil.

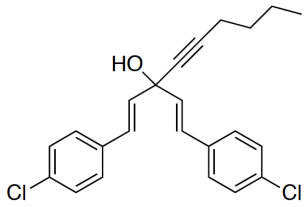
R_f 0.36 (4:1 Hexane: EtOAc)

IR (film) 3300 (br), 3286, 3100, 3031, 2119, 1647, 1592, 1492, 1405, 1091, 1013, 977, 970 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.34 (m, 4H), 7.31 – 7.29 (m, 4H), 6.91 (d, 2H, *J* = 15.9 Hz), 6.26 (d, 2H, *J* = 15.8 Hz), 2.87 (s, 1H), 2.43 (s, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 134.5, 134.0, 131.0, 129.2, 128.9, 128.2, 83.2, 76.2, 71.1;

HRMS calc'd for $C_{19}H_{14}{}^{35}Cl_2O$ (M^+) 328.0422; found 328.0422.



15g

Propargylic Alcohol 15g. Propargylic alcohol **15g** was prepared from *p*-chlorodibenzylideneacetone (606 mg, 2.0 mmol) and 1-hexyne (310 μL, 2.2 mmol) using the procedure described above for **15b**. Flash chromatography (20 : 1 hexane : EtOAc) furnished 724 mg (94%) of alcohol **15g** as a yellow oil.

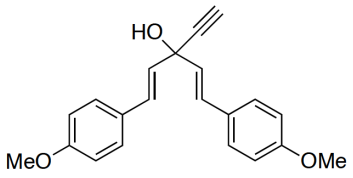
R_f 0.40 (4:1 Hexane: EtOAc)

IR (film) 3352 (br), 3030, 2958, 2932, 2238, 1620, 1593, 1491, 1404, 1328, 1091, 1013, 967 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.33 (m, 4H), 7.30 – 7.27 (m, 4H), 6.86 (d, 2H, *J* =15.8 Hz), 6.27 (d, 2H, *J* = 15.8 Hz), 2.43 (s, 1H), 2.36 (t, 2H, *J* = 7.1 Hz), 1.63 – 1.57 (m, 2H), 1.53 – 1.45 (m, 2H), 0.96 (t, 3H, *J* = 7.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 134.8, 133.6, 132.2, 128.8, 128.5, 128.1, 89.1, 79.6, 71.3, 30.7, 22.1, 18.6, 13.6;

HRMS calc'd for $C_{23}H_{22}{}^{35}Cl_2O$ (M^+) 384.1048; found 384.1048.



15h

Propargylic Alcohol 15h. Propargylic alcohol **15h** was prepared from *p*-methoxydibenzylideneacetone (589 mg, 2.0 mmol) and ethynylmagnesium bromide (4.4 mL, 0.5 M, 2.2 mmol) using the procedure described for **15e**. Flash chromatography (10 : 1 hexane : EtOAc) furnished 474 mg (74%) of alcohol **15h** as an orange oil.

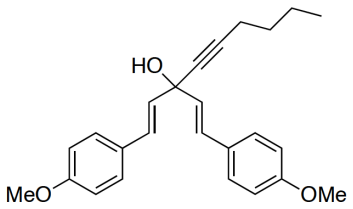
R_f 0.28 (4:1 Hexane: EtOAc)

IR (film) 3436 (br), 3287, 3033, 3003, 2956, 2934, 2910, 2837, 1607, 1512, 1464, 1442, 1304, 1249, 1176, 1032, 970 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.36 (m, 4H), 6.89 (d, 2H, *J* = 15.9 Hz), 6.87 – 6.85 (m, 4H), 6.18 (d, 2H, *J* = 15.9 Hz), 3.81 (s, 6H), 2.84 (s, 1H), 2.37 (s, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 129.7, 128.9, 128.7, 114.1, 83.9, 75.6, 71.4, 55.3;

HRMS calc'd for $C_{21}H_{20}O_3$ (M^+) 320.1412; found 320.1412.



15i

Propargylic Alcohol 15i. Propargylic alcohol **15i** was prepared from *p*-methoxydibenzylideneacetone (589 mg, 2.0 mmol) and 1-hexyne (310 μL, 2.2 mmol) using the procedure described above for **15b**. Flash chromatography (20 : 1 hexane : EtOAc) furnished 602 mg (80%) of alcohol **15i** as an orange oil.

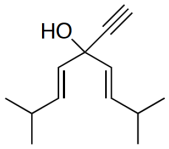
R_f 0.32 (4:1 Hexane: EtOAc)

IR (film) 3455 (br), 3032, 3003, 2957, 2933, 2836, 1607, 1512, 1464, 1303, 1248, 1174, 1085, 968 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.35 (m, 4H), 6.87 – 6.85 (m, 4H), 6.86 (d, 2H, *J* = 15.8 Hz), 6.18 (d, 2H, *J* = 15.8 Hz), 3.81 (s, 6H), 2.37 (t, 2H, *J* = 7.0 Hz), 2.26 (s, 1H), 1.64 – 1.46 (m, 4H), 0.96 (t, 3H, *J* = 7.2 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 129.8, 129.0, 128.1, 114.0, 88.6, 80.2, 71.6, 55.3, 30.8, 22.1, 18.6, 13.7;

HRMS calc'd for $C_{25}H_{28}O_3$ (M^+) 376.2038; found 376.2043



15j

Propargylic Alcohol 15j. Propargylic alcohol **15j** was prepared from diisopropylideneacetone (333 mg, 2.0 mmol) and ethynylmagnesium bromide (4.4 mL, 0.5 M, 2.2 mmol) using the procedure described for **15e**. Flash chromatography (20 : 1 hexane : EtOAc) furnished 269 mg (70%) of alcohol **15j** as a pale yellow oil.

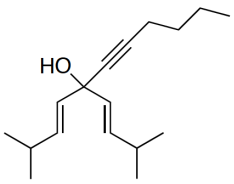
R_f 0.32 (4:1 Hexane: EtOAc)

IR (film) 3462 (br), 3311, 2960, 2927, 2167, 1692, 1624, 1465, 1384, 1367, 1028, 973, cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 5.96 (dd, 2H, *J* = 15.4, 6.5 Hz), 5.48 (dd, 2H, *J* = 15.4, 1.4 Hz), 2.68 (s, 1H), 2.34 (app octet of doublets, 2H, *J* = 6.7, 1.5 Hz) 2.12 (s, 1H), 1.01 (d, 12H, *J* = 6.7 Hz);

^{13}C NMR (125 MHz, C_6D_6) δ 137.5, 130.7, 85.4, 74.5, 70.9, 30.8, 22.3

HRMS calc'd for $C_{13}H_{20}O$ (M^+) 192.1514; found 192.1512.



15k

Propargylic Alcohol 15k. Propargylic alcohol **15k** was prepared from diisopropylideneacetone (333 mg, 2.0 mmol) and 1-hexyne (310 μL, 2.2 mmol) using the procedure described above for **15b**. Flash chromatography (20 : 1 – 10 :1 hexane : EtOAc) furnished 368 mg (74%) of alcohol **15k** as a yellow oil.

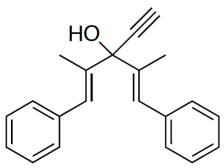
R_f 0.38 (4:1 Hexane: EtOAc)

IR (film) 3393 (br), 3025, 2959, 2932, 2230, 1662, 1599, 1466, 1382, 1364, 970 cm^{-1};

^1H NMR (500 MHz, C_6D_6) δ 6.17 (dd, 2H, *J* = 15.4, 6.7 Hz), 5.74 (dd, 2H, *J* = 15.4, 1.4 Hz), 2.24 (app octet of doublets, 2H, *J* = 6.7, 1.4 Hz), 2.08 (t, 2H, *J* = 7.0 Hz), 1.39- 1.27 (m, 4H), 0.95 (dd, 12H, *J* = 6.7, 1.3 Hz), 0.78 (t, 3H, *J* = 7.0 Hz);

^{13}C NMR (125 MHz, C_6D_6) δ 136.8, 131.8, 86.8, 82.4, 71.2, 31.1, 30.8, 22.5, 22.4, 22.2, 18.8, 13.7;

HRMS calc'd for $C_{17}H_{28}O$ (M^+) 248.2140; found 248.2140.



9d

Propargylic Alcohol 9d. Propargylic alcohol **9d** was prepared from dibenzylidene-3-pentanone (1.05 g, 4.0 mmol) and ethynylmagnesium bromide (8.8 mL, 0.5 M, 4.4 mmol) using the procedure described for **15e**. Flash chromatography (20 : 1 hexane : EtOAc) furnished 807 mg (70%) of alcohol **9d** as a colorless oil.

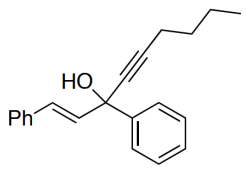
R_f 0.40 (4:1 Hexane: EtOAc)

IR (film) 3546, 3445 (br), 3292, 3082, 3056, 3024, 2955, 2922, 2856, 2108, 1600, 1491, 1443, 1381, 1090, 1023 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 8H), 7.27 – 7.32 (m, 2H), 7.13 (s, 2H), 2.80 (s, 1H), 2.83 (br s, 1H), 1.90 (s, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 137.3, 129.1, 128.2, 127.0, 126.8, 84.7, 78.3, 75.8, 13.7;

HRMS calc'd for $C_{21}H_{20}O$ (M^+) 288.1514; found 288.1513.



33a

Propargylic Alcohol 33a. Propargylic alcohol **33a** was prepared from chalcone (416mg, 2.0 mmol) and 1-hexyne (310 μL, 2.2 mmol) using the procedure described above for **15b**. Flash chromatography (20 : 1: EtOAc) furnished 488 mg (84%) of alcohol **15k** as a yellow oil.

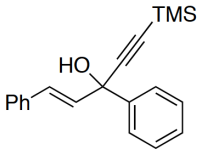
R_f 0.36 (4:1 Hexane: EtOAc);

IR (film) 3414(br), 3083, 3060, 3027, 2958, 2932, 1600, 1492, 1448 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.73 (m, 2H), 7.44 – 7.38 (m, 2H), 7.35 – 7.30 (m, 6H), 6.96 (d, 1H, J = 15.7 Hz), 6.41 (d, 1H, J = 15.7 Hz), 2.56 (s, 1H), 2.39 (t, 2H, J = 7.2 Hz), 1.66 – 1.59 (m, 2H), 1.56 – 1.48 (m, 2H), 0.99 (t, 3H, J = 7.2 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ144.0, 136.4, 133.6, 128.7, 128.6, 128.4, 127.9, 127.8, 126.9, 125.8, 88.7, 81.2, 73.0, 30.7, 22.1, 18.6, 13.7;

HRMS calc'd for $C_{21}H_{22}O$ (M^+) 290.1671; found 290.1670.



33b

Propargylic Alcohol 33b. Propargylic alcohol **33b** was prepared from chalcone (416 mg, 2.0 mmol) and trimethylsilylacetylene (310 μL, 2.2 mmol) using the procedure described above for **15b**. Purification by flash chromatography (10 : 1 hexane : EtOAc) furnished 272 mg (91%) of alcohol **15c** as a colorless oil.

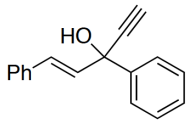
R_f 0.43 (4:1 Hexane: EtOAc)

IR (film) 3352 (br), 3083, 3060, 2959, 2168, 1600, 1578, 1495, 1449, 1250, 1069 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.66 – 7.63 (m, 2H), 7.53 – 7.50 (m, 2H), 7.39 – 7.26 (m, 6H), 6.91 (d, 1H, *J* = 16.0 Hz), 6.48 (dd, 1H, *J* = 16.0 Hz), 2.35 (br s, 1H), 0.30 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 139.7, 136.5, 128.67 128.5, 128.3, 127.8, 126.1, 126.0, 124.2, 104.2, 92.4, 72.6, 0.0;

HRMS calc'd for $C_{20}H_{22}OSi$ (M^+) 306.1440; found 306.1438.



33c

Propargylic Alcohol 33c. Propargylic alcohol **33c** was prepared from chalcone (416 mg, 2.0 mmol) and ethynylmagnesium bromide (4.4 mL, 0.5 M, 2.2 mmol) using the procedure described for **15e**. Flash chromatography (20 : 1 hexane : EtOAc) furnished 421 mg (70%) of alcohol **15j** as a pale yellow oil.

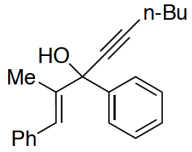
R_f 0.36 (4:1 Hexane: EtOAc)

IR (film) 3415, 3291, 3060, 3027, 2925, 1599, 1491, 1448, 1028 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.69 (m, 2H), 7.43 – 7.38 (m, 4H), 7.35 – 7.31 (m, 3H), 7.28 – 7.29 (m, 1H), 6.99 (d, 1H, *J* = 15.8 Hz), 6.39 (d, 1H, *J* = 15.8 Hz), 2.88 (s, 1H), 2.62 (s, 1H);

^{13}C NMR (125 MHz, C_6D_6) δ 142.9, 136.1, 132.3, 129.6, 128.6, 128.5, 128.2, 128.1, 127.0, 125.7, 84.8, 72.8;

HRMS calc'd for $C_{17}H_{14}O$ (M^+) 234.1045; found 234.1044.



35

Propargylic Alcohol 35. Propargylic alcohol **35** was prepared from α-methyl chalcone (445 mg, 2.0 mmol) and 1-hexyne (310 μL, 2.2 mmol) using the procedure described above for **15b**. Flash chromatography (20 : 1: EtOAc) furnished 524 mg (86%) of alcohol **35** as a yellow oil.

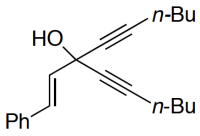
R_f 0.37 (4:1 Hexane: EtOAc);

IR (film) 3414(br), 3083, 3060, 3027, 2958, 2932, 1600, 1492, 1448 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.55 (m, 2H), 7.38 – 7.28 (m, 2H), 7.25 – 7.21 (m, 1H), 7.17 (m, 1H), 2.47 (s, 1H), 2.35 (t, 2H, *J* = 7.1 Hz), 1.62 – 1.56 (m, 2H), 1.51 – 1.44 (m, 2H), 0.95 (t, 3H, *J* = 7.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) 143.4, 140.2, 137.8, 129.2, 128.2, 128.1, 127.7, 126.6, 126.2, 125.0, 88.4, 81.9, 76.5, 30.7, 22.1, 18.6, 14.6, 13.6;

HRMS calc'd for $C_{22}H_{24}O$ (M^+) 304.1827; found 304.1826.



39a

Propargylic Alcohol 39a. ^{n}BuLi (2.0 mL, 2.0 M in hexanes, 4.0 mmol) was added to a stirred solution of 1-hexyne (454 μL, 4.0 mmol) in THF (6 mL) at -78 °C. The reaction was warmed to 0 °C for 1 hr. The mixture was cooled to at -78 °C and cinnamoyl chloride (333 mg, 2.0 mmol) in THF (10 mL) was added via

cannula. The reaction mixture as warmed to 0 °C. The reaction was quenched with 1M HCl (10 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over magnesium sulfate, filtered, and concentrated. Flash chromatography (20 : 1 – 10 : 1 hexane : EtOAc) furnished 459 mg (78%) of alcohol **39a** as a pale yellow oil (78%).

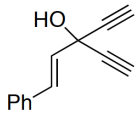
R_f 0.42 (4:1 Hexane: EtOAc)

IR (film) 3428 (br), 3083, 2060, 3027, 2958, 2933, 2872, 2234, 1700, 1493, 1466, 1449, 1328, 964 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.42 (m, 2H), 7.35 – 7.25 (m, 3H), 6.98 (d, 1H, J = 15.6 Hz), 6.34 (d, 1H, J = 15.6 Hz), 2.49 (s, 1H), 2.29 (t, 4H, J = 7.0 Hz), 1.59 – 1.40 (m, 8H), 0.93 (t, 6H, J = 7.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 130.7, 130.1, 128.6, 128.1, 127.1, 85.8, 79.7, 63.5, 30.5, 22.0, 18.6, 13.6;

HRMS calc'd for $C_{21}H_{26}O$ (M^+) 294.1984; found 294.1981.



39b

Propargylic Alcohol 39b. Ethynylmagnesium bromide (8.0 mL, 0.5 M in THF, 4.0 mmol) was added to a stirred solution of cinnamoyl chloride (333 mg, 2.0 mmol) in THF (10 mL) at 0 °C. The reaction was warmed to rt and stirred for 1 h. The reaction was quenched with sat. NH_4Cl (10 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over magnesium sulfate, filtered, and concentrated. Flash chromatography (10 : 1 hexane : EtOAc) furnished 226 mg (62 %) of alcohol **39b** as a colorless oil.

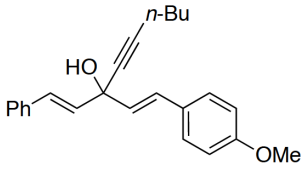
R_f 0.38 (4:1 Hexane: EtOAc)

IR (film) 3384 (br), 3291, 3084, 3060, 2028, 2120, 1712, 1677, 1633, 1600, 1493, 1449, 1012, 966 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.43 (m, 2H), 7.37 – 7.27 (m, 3H), 7.06 (d, 1H, *J* = 15.7 Hz), 6.35 (d, 1H, *J* = 15.7 Hz), 2.76 (s, 2H), 2.73 (br s, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 131.7, 128.7, 128.6, 128.3, 127.2, 82.2, 73.6, 63.0;

HRMS calc'd for $C_{13}H_{10}O$ (M^+) 182.0732; found 182.0728.



43a

Propargylic Alcohol 43a. Propargylic alcohol **43a** was prepared from 1-(4-methoxyphenyl)-5-phenyl-1,4-pentadiene-3-one[54] (529 mg, 2.0 mmol) and 1-hexyne (310 μL, 2.2 mmol) using the procedure described above for **15b**. Flash chromatography (10 : 1 hexane : EtOAc) furnished 582 mg (84 %) of alcohol **43a** as an orange oil.

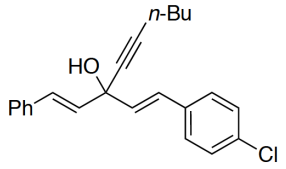
R_f 0.36 (4:1 Hexane: EtOAc)

IR (film) *v* 3445 (br), 3057, 2926, 2852, 2209, 1721, 1599, 1490, 1449 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.43 (m, 2H), 7.38 – 7.32 (m, 4H), 7.28 – 7.24 (m, 1H), 6.92 (d, 1H, *J* = 15.8 Hz), 6.88 (d, 1H, *J* = 15.8 Hz), 6.88 – 6.86 (m, 2H), 6.33 (d, 1H, *J* = 15.8 Hz), 6.20 (d, 1H, *J* = 15.8 Hz), 3.82 (s, 3H), 2.38 (t, 2H, *J* = 7.0 Hz), 2.37 (s, 1H), 1.65 – 1.59 (m, 2H), 1.55 – 1.48 (m, 2H), 0.98 (t, 3H, *J* = 7.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 136.5, 132.0, 129.6, 129.4, 129.2, 129.1, 128.6, 128.1, 127.9, 126.9, 114.0, 88.6, 80.1, 71.5, 55.3, 30.8, 22.1, 18.6, 13.7;

HRMS calc'd for $C_{24}H_{26}O_2$ (M^+) 346.1933; found 346.1938.



43b

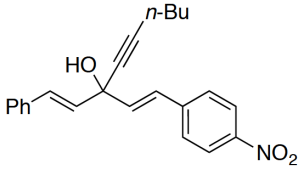
Propargylic Alcohol 43b. Propargylic alcohol **43b** was prepared from 1-(4-chlorophenyl)-5-phenyl-1,4-pentadiene-3-one[54] (537 mg, 2.0 mmol) and 1-hexyne (310 μL, 2.2 mmol) using the procedure described above for **15b**. Flash chromatography (20 : 1 hexane : EtOAc) furnished 660 mg (94 %) of alcohol **43b** as a colorless oil.

R_f 0.43 (4:1 Hexane : EtOAc);

IR (film) 3352 (br), 3028, 2960, 2234, 1620, 1594, 1421, 1091 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.42 (m, 9H), 6.92 (d, 1H, *J* = 15.8 Hz), 6.86 (d, 1H, *J* = 15.8 Hz), 6.29 (d, 1H, *J* = 15.8 Hz), 6.28 (d, 1H, *J* = 15.8 Hz), 2.37 (t, 2H, *J* = 7.0 Hz), 2.34 (s, 1H), 1.63 – 1.46 (m, 4H), 0.96 (t, 3H, *J* = 7.4 Hz);

HRMS calc'd for $C_{23}H_{23}{}^{35}ClO$ (M^+) 350.1437 found 350.1437.



43c

Propargylic Alcohol 43c. Propargylic alcohol **43c** was prepared from 1-(4-nitrophenyl)-5-phenyl-1,4-pentadiene-3-one[54] (559 mg, 2.0 mmol) and 1-hexyne (310 μL, 2.2 mmol) using the procedure described above for **15b**. Flash chromatography (20 : 1 – 5 : 1 hexane : EtOAc) furnished 665 mg (92 %) of alcohol **43c** as a light brown oil.

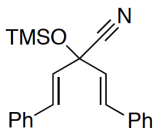
R_f 0.32 (4:1 Hexane : EtOAc)

IR (film) *v* 3459 (br), 3108, 3029, 3958, 2932, 2222, 1597, 1518, 1344 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 – 8.18 (m, 2H), 7.56 – 7.54 (m, 2H), 7.44 – 7.42 (m, 2H), 7.35 – 7.32 (m, 2H), 7.29 – 7.26 (m, 1H), 6.96 (d, 1H, *J* = 15.8 Hz), 6.95 (d, 1H, *J* = 15.8 Hz), 6.46 (d, 1H, *J* = 15.8 Hz), 6.28 (d, 1H, *J* = 15.8 Hz), 2.37 (t, 2H, *J* = 7.2 Hz), 2.35 (s, 1H), 1.63 – 1.56 (m, 2H), 1.53 – 1.45 (m, 2H), 0.96 (t, 3H, *J* = 7.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 136.3, 136.0, 130.9, 130.4, 128.6, 128.2, 127.4, 127.2, 126.9, 124.0, 89.4, 79.3, 71.3, 30.8, 22.2, 18.7, 13.7 (one missing sp^2 carbon, possibly overlapping);

HRMS calc'd for $C_{23}H_{23}NO_3$ (M^+) 361.1678; found 361.1675.



50

***O*-TMS-cyanohydrin 50.** Dibenzylideneacetone (937 mg, 0.4 mmol) was added to a flask containing the lithium salt of L-proline (48 mg, 0.04 mmol), trimethylsilyl cyanide (500 μL 0.4 mmol) was added, and the mixture was stirred at rt for 12 h solvent free. A second portion of trimethylsilyl cyanide (500 μL 0.4 mmol) was added and the reaction was stirred for an additional 12 h. Upon completion the reaction mixture was taken up in Et_2O (10 mL) and washed with water (10 mL) in the fumehood. The aqueous layer was back-extracted with Et_2O (2 x 10 mL). The combined organic extracts were dried with $MgSO_4$ and $NaHCO_3$, filtered, and concentrated to give **50** as an orange oil (92%).

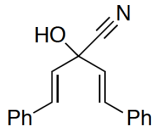
R_f 0.48 (4:1 Hexane: EtOAc)

IR (film) 3083, 3061, 3028, 2959, 2921, 2851, 2239, 1656, 1606, 1495, 1450, 1254 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.43 (m, 4H), 7.37 – 7.29 (m, 6H), 6.95 (d, 2H, *J* = 15.9 Hz), 6.17 (d, 2H, *J* = 15.9 Hz), 0.29 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.3, 131.6, 128.8, 128.7, 128.2, 127.1, 118.9, 73.7, 1.6;

HRMS calc'd for $C_{21}H_{23}NOSi$ (M^+) 333.1549; found 333.1548.



49-partial data

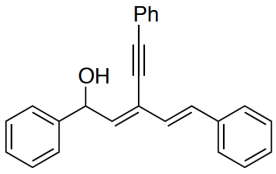
Cyanohydrin 49. *O*-TMS-cyanohydrin **50** (167 mg, 0.5 mmol) was dissolved in THF (5 mL) and stirred with 1M HCl (1 mL) for 1 h at rt. Following hydrolysis the reaction mixture was extracted with Et_2O (10 mL) and water (10 mL), the aqueous layer was back-extracted with Et_2O (10 mL). The organic layers were dried with $MgSO_4$ and several mg of sodium bicarbonate, filtered, and concentrated. The cyanohydrin **49** was used immediately without further purification.

R_f 0.24 (4:1 Hexane: EtOAc)

IR (film) 3390 (br), 3084, 3060, 3028, 2243, 1600, 1578, 1494, 1449, 1071, 1033, 966 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.44 (m, 4H), 7.39 – 7.31 (m, 6H), 7.04 (d, 2H, *J* = 15.9 Hz), 6.27 (d, 2H, *J* = 15.9 Hz), (OH proton not detected);

HRMS calc'd for $C_{18}H_{15}NO$ (M^+) 261.1154; found 261.1153.



17b

Propargylic Alcohol 17b. $VO(acac)_2$ (3.4 mg, 0.013 mmol) was added to a solution of tertiary allylic alcohol **15b** (168 mg, 0.50 mmol) in toluene (5 mL). The mixture was stirred for 1 h at 60 °C and allowed to cool to rt. The reaction mixture was quenched by filtration through a silica gel plug eluted with CH_2Cl_2

(50 mL), and concentrated. Purification by flash chromatography (30 :1 hexane : EtOAc) gave 138 mg (82 %) of the desired alcohol as a pale yellow oil.

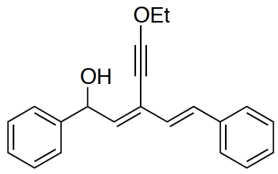
R_f 0.40 (4:1 Hexane: EtOAc)

IR (film) 3367, 3081, 3060, 3030, 2208, 1699, 1599, 1490, 1450, 1070, 1027, 1015, 960, cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.59 (m, 2H), 7.54 – 7.52 (m, 2H), 7.47 – 7.24 (m, 11H), 7.12 (d, 1H, *J* = 15.8 Hz), 6.77 (d, 1H, *J* = 15.8 Hz), 6.23 (d, 1H, *J* = 8.9 Hz), 6.03 (d, 1H, *J* = 8.9 Hz), 2.26 (br s, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.7, 141.3, 136.7, 132.8, 131.7, 128.8, 128.7, 128.7, 128.5, 128.0, 128.0, 127.8, 126.8, 126.0, 123.5, 122.8, 97.1, 83.7, 72.7;

HRMS calc'd for $C_{25}H_{20}O$ (M^+) 336.1514; found 336.1513.



17a

Propargylic Alcohol 17a. Propargylic alcohol **17a** was prepared from tertiary alcohol **15a** (152 mg, 0.50 mmol) using the procedure described above for **17b**. Flash chromatography (20 : 1 hexane : EtOAc) furnished 127 mg (84 %) of alcohol **17a** as a yellow oil.

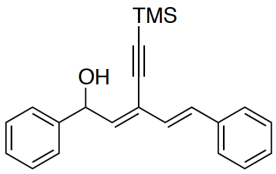
R_f 0.30 (4:1 Hexane: EtOAc)

IR (film) 3396 (br), 3082, 3059, 3027, 2982, 2261, 1723, 1701, 1599, 1495, 1448, 1390, 1239, 1090, 1068, 1003, 966 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.46 (m, 2H), 7.42 – 7.40 (m, 2H), 7.38 – 7.21 (m, 6H), 6.97 (d, 1H, *J* = 15.6 Hz), 6.72 (d, 1H, *J* = 15.6), 6.04 (d, 1H, *J* = 8.7 Hz), 5.88 (dd, 1H, *J* = 8.7, 1.8 Hz), 4.30 (q, 2H, *J* = 7.2 Hz), 2.13 (br s, 1H), 1.50 (t, 3H, *J* = 7.1 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 138.8, 137.0, 132.0, 129.3, 128.7, 128.6, 127.8, 127.6, 126.7, 125.9, 124.1, 105.6, 75.4, 72.6, 34.5, 14.6;

HRMS calc'd for $C_{21}H_{20}O_2$ (M^+) 304.1463; found 304.1463.



17c

Propargylic Alcohol 17c. Propargylic alcohol **17c** was prepared from tertiary alcohol **15c** (166 mg, 0.50 mmol) using the procedure described above for **17b**. Flash chromatography (20 : 1 hexane : EtOAc) furnished 133 mg (80 %) of alcohol **17c** as a yellow oil.

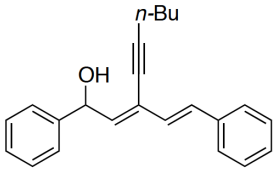
R_f 0.40 (4:1 Hexane: EtOAc)

IR (film) 3381, 3082, 3061, 3030, 2959, 2899, 2148, 1702, 1602, 1494, 1449, 1250, 1030, 1015, 902 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.25 (m, 10H), 7.06 (d, 1H, *J* = 15.7), 6.70 (d, 1H, *J* = 15.7), 6.21 (d, 1H, *J* = 8.8 Hz), 5.97 (d, 1H, *J* = 8.8 Hz), 2.37 (s, 1H), 0.36 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 142.0, 136.7, 132.9, 128.7, 128.7, 128.0, 127.8, 127.8, 126.8, 125.9, 123.6, 103.1, 99.3, 72.6, 0.0;

HRMS calc'd for $C_{22}H_{24}OSi$ (M^+) 332.1596; found 332.1588.



17d

Propargylic Alcohol 17d. Propargylic alcohol **17d** was prepared from tertiary alcohol **15d** (158 mg, 0.50 mmol) using the procedure described above for **17b**.

Flash chromatography (20 : 1 hexane : EtOAc) furnished 138 mg (87 %) of alcohol **17d** as a yellow oil.

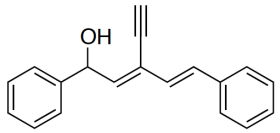
R_f 0.42 (4:1 Hexane: EtOAc)

IR (film) 3352 (br), 3082, 3061, 3029, 3004, 2958, 2931, 2224, 1602, 1494, 1449, 1379, 1189, 1030, 1011, 960 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.48 (m, 2H), 7.44 – 7.24 (m, 8H), 7.03 (d, 1H, *J* = 15.7), 6.71 (d, 1H, *J* = 15.7), 6.10 (d, 1H, *J* = 8.7 Hz) 5.93 (d, 1H, *J* = 8.7 Hz), 2.54 (t, 2H, *J* = 7.1 Hz), 1.72 – 1.65 (m, 2H), 1.60 – 1.53 (m, 2H), 1.01 (t, 3H, *J* = 7.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 140.2, 136.9, 132.4, 128.7, 128.6, 128.6, 127.8, 127.6, 126.7, 125.9, 124.3, 98.7, 74.9, 72.5, 30.9, 22.1, 19.3, 13.7;

HRMS calc'd for $C_{21}H_{20}O_2$ (M^+) 316.1827; found 316.1833.



17e

Propargylic Alcohol 17e. Propargylic alcohol **17e** was prepared from tertiary alcohol **15e** (130 mg, 0.50 mmol) using the procedure described above for **17b**. Flash chromatography (20 : 1 – 10 : 1 hexane : EtOAc) furnished 118 mg (91 %) of alcohol **17e** as a colorless oil.

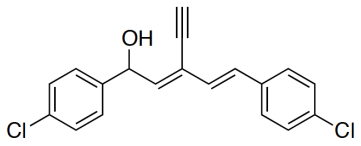
R_f 0.30 (4:1 Hexane: EtOAc)

IR (film) *v* 3392 (br), 3290, 3083, 3061, 3030, 1699, 1601, 1493, 1449, 1071, 1030, 1013, 961, 752, 697 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.23 (m, 10H), 7.05 (d, 1H, *J* = 15.7 Hz), 6.70 (dd, 1H, *J* = 15.7, 0.7 Hz), 6.23 (dd, 1H, *J* = 8.9, 0.7 Hz), 5.94 (dd, 1H, 8.9, 2.6 Hz), 3.64 (d, 1H, J = 0.7 Hz), 2.15 (d, 1H, J = 3.1 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 142.4, 136.9, 133.0, 128.7, 128.7, 128.1, 127.9, 127.6, 126.8, 125.9, 122.7, 85.1, 78.1, 72.4

HRMS calc'd for $C_{19}H_{16}O$ (M^+) 260.1201; found 260.1198.



17f

Propargylic Alcohol 17f. Propargylic alcohol **17f** was prepared from tertiary alcohol **15f** (165 mg, 0.50 mmol) using the procedure described above for **17b**. Flash chromatography (20 : 1 hexane : EtOAc) furnished 143 mg (87 %) of alcohol **17f** as a yellow oil.

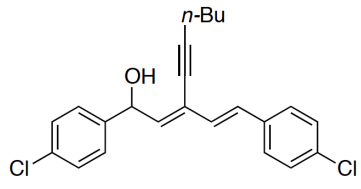
R_f 0.36 (4:1 Hexane: EtOAc)

IR (film) 3568, 3350 (br), 3274, 3080, 3052, 2286, 1903, 1983, 1652, 1591, 1491, 1406, 1094, 1012, 964 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 8H), 6.99 (d, 1H, *J* = 15.9 Hz), 6.64 (d, 1H *J* = 15.9 Hz), 6.16 (d, 1H, *J* = 8.9 Hz), 5.90 (d, 1H, *J* = 8.9 Hz), 3.47 (s, 1H), 2.23 (br s, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 140.8, 135.0, 133.8, 133.6, 131.9, 128.9, 128.8, 128.0, 128.0, 127.3, 122.8, 85.5, 77.8, 71.8;

HRMS calc'd for $C_{19}H_{14}{}^{35}Cl_2O$ (M^+) 328.0422; found 328.0421.



17g

Propargylic Alcohol 17g. Propargylic alcohol **17g** was prepared from tertiary alcohol **15g** (193 mg, 0.50 mmol) using the procedure described above for **17b**. Flash chromatography (30 : 1 hexane : EtOAc) furnished 160 mg (83 %) of alcohol **17g** as a yellow oil.

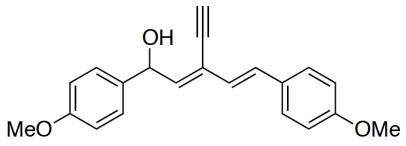
R_f 0.40 (4:1 Hexane: EtOAc)

IR (film) 3409 (br), 3032, 3003, 2956, 2932, 2836, 2236, 1607, 1577, 1512, 1464, 1303, 1247, 1174, 1033, 968 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.38 (m, 2H), 7.35 – 7.27 (m, 6H), 6.95 (d, 1H, *J* = 15.6 Hz), 6.64 (d, 1H, *J* = 15.6 Hz), 6.02 (d, 1H, *J* = 8.7 Hz), 5.87 (d, 1H, 8.7 Hz), 2.51 (t, 2H, *J* = 7.1 Hz) 2.18 (br s, 1H), 1.68 – 1.62 (m, 2H), 1.56 – 1.50 (m, 2H), 0.98 (t, 3H, *J* = 7.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1, 140.1, 135.3, 133.6, 133.4, 131.4, 129.1, 128.9, 128.7, 127.9, 127.2, 124.4, 99.1, 74.6, 71.9, 30.8, 22.1, 19.3, 13.7;

HRMS calc'd for $C_{23}H_{22}{}^{35}Cl_2O$ (M^+) 384.1048; found 384.1042.



17h

Propargylic Alcohol 17h. Propargylic alcohol **17h** was prepared from tertiary alcohol **15h** (160 mg, 0.50 mmol) using the procedure described above for **17b**. Flash chromatography (20 : 1 hexane : EtOAc) furnished 127 mg (79 %) of alcohol **17h** as a yellow oil.

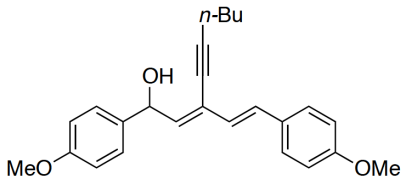
R_f 0.28 (4:1 Hexane: EtOAc)

IR (film) 3437 (br), 3286, 3032, 3003, 2956, 2935, 2909, 2836, 2252, 1696, 1608, 1514, 1464, 1304, 1258, 1177 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 4H), 6.99 (d, 1H, *J* = 15.8 Hz), 6.92 – 6.84 (m, 4H), 6.57 (d, 1H, *J* = 15.7 Hz), 6.17 (d, 1H, *J* = 8.9 Hz), 5.87 (d, 1H, *J* = 8.9 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 3.43 (s, 1H), 2.28 (br s, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 159.2, 141.9, 134.8, 132.2, 129.4, 128.0, 127.2, 125.7, 122.4, 114.1, 114.0, 84.9, 78.3, 72.0, 55.3, 55.3;

HRMS calc'd for $C_{21}H_{20}O_3$ (M^+) 320.1412; found 320.1411.



17i

Propargylic Alcohol 17i. Propargylic alcohol **17i** was prepared from tertiary alcohol **15i** (188 mg, 0.50 mmol) using the procedure described above for **17b**. Flash chromatography (40 : 1 hexane : EtOAc) furnished 161 mg (86 %) of alcohol **17i** as an orange oil.

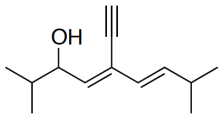
R_f 0.32 (4:1 Hexane: EtOAc)

IR (film) 3390 (br), 3081, 3059, 3027, 2921, 2853, 2199, 1671, 1598, 1490, 1448, 1443, 1028, 1009 cm^{-1};

H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 4H), 6.95 (d, 1H, *J* = 15.6 Hz), 6.91 – 6.85 (m, 4H), 6.57 (d, 1H, *J* = 15.6 Hz), 6.04 (d, 1H, *J* = 8.7 Hz), 5.85 (d, 1H, *J* = 8.7 Hz), 3.81 (s, 3H), 3.81 (s, 3H), 2.52 (t, 2H, *J* = 7.0 Hz), 2.10 (br s, 1H), 1.69 – 1.50 (m, 4H), 0.99 (t, 3H, *J* = 7.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 159.1, 139.5, 135.2, 131.8, 129.7, 128.0, 127.2, 126.8, 124.1, 114.1, 114.0, 98.4, 75.1, 72.2, 55.3, 55.3, 30.9, 22.1, 19.3, 13.7;

HRMS calc'd for $C_{25}H_{28}O_3$ (M^+) 376.2038; found 376.2043



17j

Propargylic Alcohol 17j. Propargylic alcohol **17i** was prepared from tertiary alcohol **15i** (96 mg, 0.50 mmol) using the procedure described above for **17b**.

Flash chromatography (20 : 1 hexane : EtOAc) furnished 86 mg (89 %) of alcohol **17j** as a yellow oil.

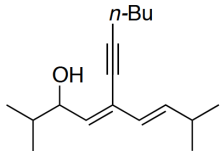
R_f 0.32 (4:1 Hexane: EtOAc)

IR (film) 3350 (br), 3311, 2960, 2930, 2871, 2098, 1646, 1600, 1466, 1383, 1365, 1011, 966 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 6.12 (dd, 1H, *J* = 15.4, 6.9 Hz), 5.96 (d, 1H, *J* = 15.4 Hz), 5.86 (d, 1H, *J* = 8.9 Hz) 4.45 (m, 1H), 3.25 (s, 1H), 2.39 (app octet of doublets, 1H, *J* =7.0, 1.3 Hz), 1.80 (app oct 1H, *J* = 6.7 Hz), 1.71 (br s, 1H), 1.03 (d, 6H, *J* = 6.8 Hz), 0.98 (d, 3H, *J* = 6.8 Hz), 0.91 (d, 3H, *J* = 6.8 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 140.3, 126.3, 123.6, 84.1, 78.7, 75.3, 34.1, 31.0, 22.3, 22.2, 18.2, 18.1;

HRMS calc'd for $C_{13}H_{20}O$ (M^+) 192.1514; found 192.1514.



17k

Propargylic Alcohol 17k. Propargylic alcohol **17k** was prepared from tertiary alcohol **15k** (74 mg, 0.30 mmol) using the procedure described above for **17b**. Flash chromatography (20 : 1 hexane : EtOAc) furnished 68 mg (91 %) of alcohol **17k** as a yellow oil.

R_f 0.38 (4:1 Hexane: EtOAc)

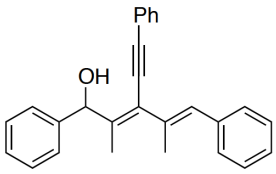
IR (film) 3370, 2959, 2932, 2872, 2224, 1600, 1466, 1381, 1365, 1011, 965 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (dd, 1H, *J* = 15.4, 7.0 Hz), 5.95 (d, 1H, *J* = 15.4 Hz), 5.73 (d, 1H, J = 8.8 Hz), 4.42 (m, 1H), 2.41 (t, 2H, *J* = 7.1 Hz), 2.38 (app octet of doublets, 1H, *J* = 6.7, 1,3 Hz), 1.79 (app oct, 1H, *J* = 6.8 Hz), 1.61 – 1.55 (m, 2H), 1.54 – 1.44 (m, 2H), 1.03 (d, 6H, *J* = 6.7 Hz), 0.98 (d, 3H, *J* = 6.7 Hz), 0.94 (t, 3H, *J* = 7.2 Hz), 0.91 (d, 3H, *J* = 6.9 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1, 137.7, 127.2, 125.1, 97.6, 75.5, 75.4, 34.1, 30.9, 30.9, 22.4, 22.3, 22.0, 19.2, 18.2 (2 carbons), 13.6;

HRMS calc'd for $C_{17}H_{28}O$ (M^+) 248.2140; found 248.2137.

Propargylic alcohols 31b, 32b, and cyclopentene 12b. Propargylic alcohol **9b** (182 mg, 0.50 mmol) was subjected to the procedure described above for **17b**. Purification by flash chromatography (60 : 1 - 10 :1 hexane : EtOAc) furnished 47 mg (30%) of alcohol **31b,** 55 mg (26%) of alcohol **32b**, and 17 mg (10%) of **12b** as a colorless oils. Sperctal data for **12b** matched previously reported values.[13]



31b

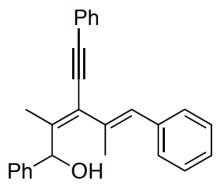
R_f 0.38 (4:1 Hexane: EtOAc)

IR (film) 3431 (br), 3082, 3060, 3027, 2924, 2853, 2186, 1693, 1598, 1490, 1449, 1376, 1027 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.57-7.56 (m, 2H), 7.47 – 7.45 (m, 2H), 7.40 – 7.22 (m, 11H), 6.40 (s, 1H), 6.38 (d, 1H, *J* = 3.4 Hz), 2.14 (s, 3H), 2.11 (d, 1H, *J* = 3.8 Hz), 1.79 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.4, 142.2, 137.5, 135.1, 131.4, 130.1, 129.0, 128.4, 128.3, 128.2, 128.2, 127.2, 126.7, 125.4, 123.5, 93.9, 87.9, 74.8, 17.8, 13.2;

HRMS calc'd for $C_{27}H_{24}O$ (M^+) 364.1827; found 364.1825.



32b

R_f 0.37 (4:1 Hexane: EtOAc)

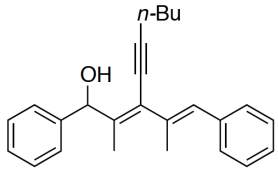
IR (film) 3426 (br), 3082, 3060, 3027, 2978, 2917, 2853, 2200, 1693, 1598, 1584, 1490, 1449, 1028, 1010 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.45 (m, 2H), 7.42- 7.24 (m, 13H), 6.55 (s, 1H), 6.00 (d, 1H, *J* = 3.2 Hz), 2.21 (s, 3H, *J* = 1.4 Hz), 1.98 (s, 3H), 1.91 (d, 1H, *J* = 3.8 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 142.1, 137.3, 135.2, 131.5, 129.7, 129.1, 128.4, 128.3, 128.3, 128.2, 127.3, 126.9, 126.6, 126.0, 123.6, 94.8, 88.1, 72.5, 18.6, 15.5;

HRMS calc'd for $C_{27}H_{24}O$ (M^+) 364.1827; found 364.1826.

Propargylic alcohols 31c, 32c, and cyclopentene 12c. Propargylic alcohol **9c** (172 mg, 0.50 mmol) was subjected to the procedure described above for **17b**. Purification by flash chromatography (80 : 1 - 20 :1 hexane : EtOAc) furnished 62 mg (42%) of alcohol **31c,** 72 mg (36%) of alcohol **32c**, and 23 mg (14%) of **12c** as a colorless oils. Sperctal data for **12c** matched previously reported values.[13]



31c

R_f 0.42 (4:1 Hexane: EtOAc)

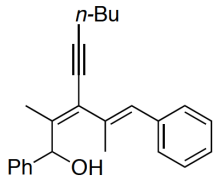
IR (film) 3412 (br), 3084, 3059, 3026, 2958, 2930, 2872, 2859, 2212, 1722, 1708, 1600, 1493, 1449, 1262, 1102, 1018 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.50 (m, 2H), 7.38 – 7.27 (m, 7H), 7.23 – 7.21 (m, 1H), 6.32 (s, 1H), 6.26 (s, 1H), 2.41 (t, 2H, *J* = 7.1 Hz), 2.10 (s, 1H),

2.06 (d, 3H, J = 1.5 Hz), 1.71 (s, 3H), 1.59 – 1.54 (m, 2H), 1.47 – 1.42 (m, 2H), 0.92 (t, 3H, J = 7.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 142.4, 137.7, 135.9, 129.4, 129.0, 128.3, 128.2, 127.1, 126.6, 125.4, 125.3, 95.1, 78.9, 74.7, 31.0, 22.1, 19.4, 17.6, 13.7, 13.0;

HRMS calc'd for $C_{25}H_{28}O$ (M^+) 344.2140; found 344.2136.



32c

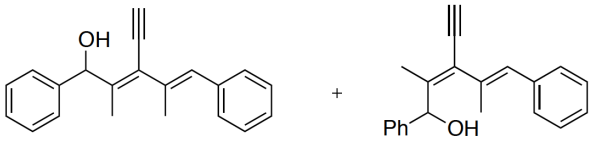
R_f 0.39 (4:1 Hexane: EtOAc)

IR (film) 3390 (br), 3083, 3059, 3026, 2957, 2931, 2872, 2859, 2212, 1600, 1493, 1449, 1376, 1029, 1012 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, 10H), 6.48 (s, 1H), 5.95 (s, 1H), 2.42 (t, 2H, J = 7.1 Hz), 2.15 (d, 3H, J = 1.5 Hz), 1.88 (br s, 1H), 1.87 (s, 3H), 1.60-1.55 (m, 2H), 1.50 – 1.44 (m, 2H), 0.94 (t, 3H, J = 7.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 142.3, 137.4, 135.9, 129.1, 129.0, 128.3, 128.2, 127.2, 127.1, 126.7, 125.9, 96.2, 79.1, 72.5, 31.0, 22.1, 19.4, 18.4, 15.2, 13.7;

HRMS calc'd for $C_{25}H_{28}O$ (M^+) 344.2140; found 344.2142.



31d/32d

Propargylic Alcohol 31d/32d. Propargylic alcohol **9d** (144 mg, 0.50 mmol) was subjected to the procedure described above for **17b**. Purification by flash chromatography (60 : 1 - 20 :1 hexane : EtOAc) furnished an inseparable mixture

128 mg (89%, **31d : 32d** 10 : 9 determined by integration of methine ^{1}H NMR signals) as a colorless oil.

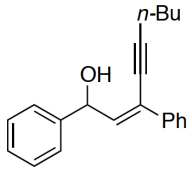
R_f 0.32 (4:1 Hexane: EtOAc)

IR (film) 3394 (br), 3285, 3084, 3059, 3026, 2980, 2946, 2916, 2855, 2085, 1600, 1493, 1448, 1376, 1175, 1075, 1029, 1011, 920 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.51 (m, 2H), 7.39 – 7.22 (m, 16H), 6.50 (s, 1H), 6.36 (s, 1H), 6.29 (d, 1H, *J* = 3.8 Hz), 5.94 (d, 1H, *J* = 4.2 Hz), 3.27 (s, 1H), 3.26 (s, 1H), 2.14 (d, 3H, *J* = 1.5 Hz), 2.10 (m, 1H), 2.08 (d, 3H, *J* = 1.5 Hz), 1.95 (s, 3H), 1.91 (m, 1H), 1.75 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.2, 146.0, 142.0, 141.9, 137.3, 137.1, 134.8, 134.8, 130.3, 129.9, 129.0, 128.9, 128.4, 128.3, 128.2, 128.2, 127.4, 127.3, 126.9, 126.8, 125.9, 125.5, 125.4, 123.7, 82.5, 82.2, 82.2, 81.8, 74.5, 72.3, 18.3, 17.5, 15.3, 13.0;

HRMS calc'd for $C_{21}H_{20}O$ (M^+) 288.1514; found 288.1516.



33a

Propargylic Alcohol 34a. Propargylic alcohol **34a** was prepared from tertiary alcohol **33a** (145 mg, 0.50 mmol) using the procedure described above for **17b**. Flash chromatography (20 : 1 hexane : EtOAc) furnished 118 mg (81 %) of alcohol **34a** as a yellow oil.

R_f 0.42 (4:1 Hexane: EtOAc)

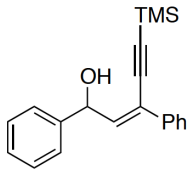
IR (film) 3355 (br), 3084, 3061, 3029, 2958, 2932, 2872, 2224, 1600, 1494, 1448, 1020 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.61 (m, 2H), 7.52 – 7.50 (m, 2H), 7.39 – 7.27 (m, 6H), 6.47 (d, 1H, *J* = 8.7 Hz), 5.99 (dd, 1H, *J* = 8.7, 2.5 Hz), 2.51 (t, 2H,

J = 7.1 Hz), 2.24 (d, 1H, J = 2.7 Hz), 1.68 – 1.62 (m, 2H), 1.58 – 1.49 (m, 2H), 0.98 (t, 3H, J = 7.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 137.7, 137.0, 128.6, 128.3, 128.1, 127.6, 126.4, 125.9, 125.0, 98.2, 77.2, 73.0, 30.9, 22.2, 19.4, 13.7;

HRMS calc'd for $C_{21}H_{22}O$ (M^+) 290.1671; found 290.1668.



34b

Propargylic Alcohol 34b. Propargylic alcohol **34b** was prepared from tertiary alcohol **33b** (153 mg, 0.50 mmol) using the procedure described above for **17b**. Flash chromatography (20 : 1 hexane : EtOAc) furnished 116 mg (76 %) of alcohol **34b** as a pale yellow oil.

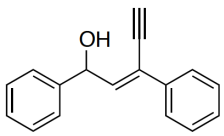
R_f 0.40(4:1 Hexane: EtOAc)

IR (film) 3532, 3344 (br), 3084, 3062, 3031, 2960, 2899, 2148, 1601, 1494, 1448, 1250, 1038, 1023 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.61 (m, 2H), 7.55 – 7.52 (m, 2H), 7.41 – 7.28 (m, 6H), 6.58 (d, 1H, J = 8.7 Hz), 6.03 (dd, 1H, J = 8.7, 2.7 Hz), 2.35 (m, 1H), 0.32 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.7, 139.4, 136.8, 128.6, 128.4, 128.3, 127.8, 126.3, 126.0, 124.2, 102.5, 101.4, 73.0, 0.0;

HRMS calc'd for $C_{20}H_{22}OSi$ (M^+) 306.1440; found 306.1440.



34c

Propargylic Alcohol 34c. Propargylic alcohol **34b** was prepared from tertiary alcohol **33c** (117 mg, 0.50 mmol) using the procedure described above for **17b**. Flash chromatography (10 : 1 hexane : EtOAc) furnished 107 mg (91 %) of alcohol **34c** as colorless oil.

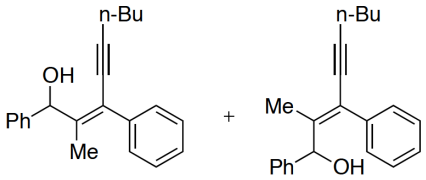
R_f 0.30 (4:1 Hexane: EtOAc)

IR (film) 3384 (br), 3289, 3085, 3061, 3030, 2098, 1676, 1599, 1493, 1448, 1035, 1022 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.62 (m, 2H), 7.54 – 7.51 (m, 2H), 7.41 – 7.29 (m, 6H), 6.62 (d, 1H, *J* = 8.9 Hz), 6.02 (d, 1H, *J* = 8.9 Hz), 3.47 (s, 1H), 2.33 (s, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 139.9, 136.6, 128.7, 128.5, 128.4, 127.8, 126.3, 125.9, 123.3, 84.6, 80.2, 72.8;

HRMS calc'd for $C_{17}H_{14}O$ (M^+) 234.1045; found 234.1044.



36/37

Propargylic Alcohol 36/37. Propargylic alcohol **35** (152 mg, 0.50 mmol) was subjected to the procedure described above for **17b**. Purification by flash chromatography (40 : 1 hexane : EtOAc) furnished an inseparable mixture 132 mg (87%, **36 : 37** 1 : 1 determined by integration of methine ^1H NMR signals) as a colorless oil.

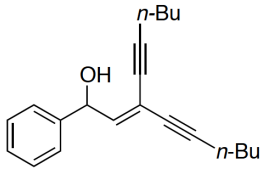
R_f 0.37 (4:1 Hexane: EtOAc)

IR (film) *v* 3405, 3083, 3060, 3028, 2245, 1645, 1578, 1494, 1449, 965 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.58 (m, 2H), 7.43 – 7.26 (m, 18H), 6.42 (s, 1H), 5.64 (s, 1H), 2.43 (t, 2H, *J* = 6.7 Hz), 2.42 (t, 2H, *J* = 6.9 Hz), 2.27 (d, 1H, *J* = 3.2 Hz), 1.97 (s, 3H), 1.94 (s, 1H), 1.67 (s, 3H), 1.62 – 1.54 (m, 4H), 1.51 – 1.43 (m, 4H), 0.95 (t, 3H, *J* = 7.4 Hz), 0.94 (t, 3H, *J* = 7.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 143.8, 142.3, 142.0, 139.4, 139.1, 129.0, 128.8, 128.4, 128.3 (2 overlapping signals), 128.1, 127.3, 127.1, 127.1, 127.1, 125.8, 125.4, 123.3, 121.5, 96.6, 95.2, 80.6, 80.4, 74.9, 72.1, 30.9, 30.9, 22.1, 22.0, 19.4, 19.4, 15.4, 13.6, 13.6, 13.5;

HRMS calc'd for $C_{22}H_{24}O$ (M^+) 304.1827; found 304.1814.



40a

Propargylic Alcohol 40a. $VO(acac)_2$ (3.4 mg, 0.013 mmol) was added to a solution of tertiary allylic alcohol **39a** (147 mg, 0.50 mmol) in toluene (5 mL). The mixture was stirred for 2 h at 80 °C and allowed to cool to rt. The reaction mixture was quenched by filtration through a silica gel plug eluted with CH_2Cl_2 (50 mL). Purification by flash chromatography (20 : 1 hexane : EtOAc) furnished 121 mg (82 %) of the desired alcohol as a pale yellow oil.

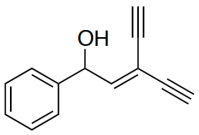
R_f 0.42 (4:1 Hexane: EtOAc)

IR (film) 3411 (br), 3086, 3062, 3030, 2958, 2933, 2872, 2221, 1697, 1602, 1454, 1021 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.41 (m, 2H), 7.36 – 7.33 (m, 2H), 7.29 (m, 1H), 6.23 (d, 1H, J = 8.9 Hz), 5.76 (dd, 1H, J = 8.9, 2.3 Hz), 2.40 (t, 2H, J = 7.1 Hz), 2.29 (d, 2H, J = 7.1 Hz), 2.06 (d, 1H, J = 2.9 Hz), 1.60 – 1.36 (m, 8H), 0.93 (t, 3H, J = 7.3 Hz), 0.90 (t, 3H, J = 7.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.6, 142.2, 128.6, 127.8, 125.9, 107.3, 95.3, 89.6, 78.6, 76.2, 72.1, 30.6, 30.6, 22.1, 22.0, 19.3, 19.0, 13.6, 13.6;

HRMS calc'd for $C_{21}H_{26}O$ (M^+) 294.1984; found 294.1978.



40b

Propargylic Alcohol 40b. Propargylic alcohol **40b** was prepared from the tertiary alcohol **39b** (36 mg, 0.20 mmol) using the procedure described above for **40a**. Flash chromatography (10 : 1 hexane : EtOAc) furnished 29 mg (80 %) of alcohol **40b** as colorless oil.

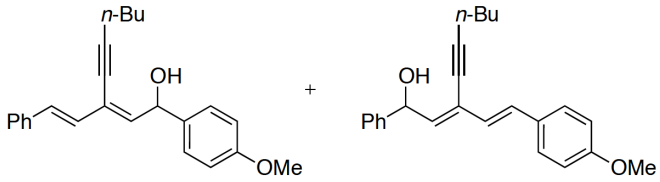
R_f 0.38 (4:1 Hexane: EtOAc)

IR (film) 3413 (br), 3290, 3085, 3062, 3031, 2105, 1701, 1634, 1599, 1494, 1451, 1017 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.42 (m, 2H), 7.40 – 7.35 (m, 2H), 7.33 – 7.29 (m, 1H), 6.56 (d, 1H, *J* = 9.0 Hz), 5.80 (dd, 1H, *J* = 8.9 Hz, 3.1 Hz), 3.28 (s, 1H), 2.92 (s, 1H), 2.15 (d, 1H, *J* = 3.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 141.3, 128.8, 128.2, 126.0, 104.4, 82.7, 80.4, 78.0, 77.1, 72.0;

HRMS calc'd for $C_{13}H_{10}O$ (M^+) 182.0732; found 182.0731.



44a/45a – partial data

Propargylic Alcohols 44a/45a. Propargylic alcohol **43a** (173 mg, 0.50 mmol) was subjected to the procedure described above for **17b**. Purification by flash chromatography (40 : 1 hexane : EtOAc) furnished an inseparable mixture 132 mg (76%, **44a : 45a** 1 : 1 determined by integration of methine ^1H NMR signals) as yellow oil. Small amounts of pure **44a** were isolated by further purification using radial chromatography (80 :1 – 10:1 hexane : EtOAc), ^1H NMR data

reported for **45a** were taken from the spectrum of the mixture by discounting the resonances known to arise from **44a**.

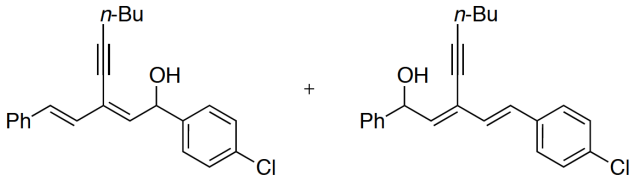
R_f 0.40 (4:1 Hexane: EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) **44a** δ 7.47 – 7.45 (m, 2H), 7.38 – 7.33 (m, 4H), 7.29 – 7.26 (m, 1H), 6.96 (d, 1H, 15.7 Hz), 6.87 – 6.85 (m, 2H), 6.57 (d, 1H, 15.7 Hz), 6.03 (d, 1H, 8.8 Hz), 5.90 (dd, 1H, 8.8, 3.0 Hz), 3.81 (s, 3H), 2.52 (t, 2H, *J* = 7.0 Hz), 2.12 (d, 1H, *J* = 3.1 Hz), 1.69 – 1.63 (m, 2H), 1.58 – 1.50 (m, 2H), 0.98 (t, 3H, *J* = 7.3 Hz);

^{1}H NMR (500 MHz, $CDCl_3$) **45a** δ 7.41 – 7.30 (m, 6H), 7.25 – 7.21 (m, 1H), 6.99 (d, 1H, 15.8 Hz), 6.91 – 6.88 (m, 2H), 6.69 (d, 1H, 15.8 Hz), 6.09 (d, 1H, 8.8 Hz), 5.85 (d, 1H, 8.7, 2.3 Hz), 3.80 (s, 3H), 2.51 (t, 2H, *J* = 7.0 Hz), 2.08 (br s, 1H), 1.68 – 1.62 (m, 2H), 1.57 – 1.49 (m, 2H), 0.98 (t, 3H, *J* = 7.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) **44a** δ 159.5, 142.9, 139.2, 132.0, 129.7, 128.6, 128.0, 127.6, 126.7, 125.9, 124.5, 114.1, 98.5, 75.1, 72.6, 55.3, 30.9, 22.2, 19.3, 13.7;

HRMS calc'd for $C_{24}H_{26}O_2$ (M^+) 346.1933; found 346.1942.



44b/45b – partial data

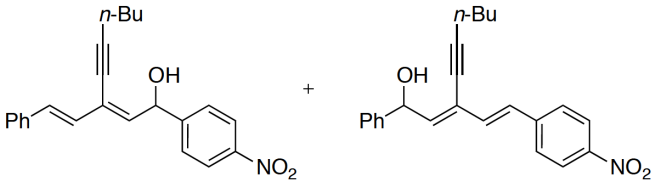
Propargylic Alcohols 44b/45b. Propargylic alcohol **43b** (175 mg, 0.50 mmol) was subjected to the procedure described above for **17b**. Purification by flash chromatography (40 : 1 hexane : EtOAc) furnished an inseparable mixture 147 mg (84%, **44b : 45b** 1 : 1 determined by integration of methine ^{1}H NMR signals) as pale yellow oil.

R_f 0.40 (4:1 Hexane: EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.45 (m, 2H), 7.42 – 7.22 (m, 16H), 7.01 (d, 1H, *J* = 15.8 Hz), 6.94 (d, 1H, *J* = 15.8 Hz), 6.68 (d, 1H, *J* = 15.8 Hz), 6.65 (d,

1H, J = 15.8 Hz), 6.09 (d, 1H, J = 9.0 Hz), 6.01 (d, 1H, J = 9.0 Hz), 5.90 (d, 1H, J = 9.0 Hz), 5.88 (d, 1H, J = 9.0 Hz), 2.52 two overlapping signals (t, 4H, J = 7.0 Hz), 2.20 (s, 1H), 2.18 (s, 1H), 1.69 – 1.50 (m, 8H), 0.98 two overlapping signals (t, 6H, J = 7.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.7, 141.3, 140.8, 139.6, 136.8, 135.4, 133.4, 133.3, 132.8, 131.1, 129.3, 128.8, 128.7, 128.7, 128.6, 128.5, 128.0, 127.9, 127.7, 127.3, 126.8, 125.9, 124.7, 124.0, 99.0, 98.8, 74.8, 74.8, 72.5, 71.9, 30.9, 30.8, 22.1, 22.1, 19.3 (2 overlapping signals), 13.7 (2 overlapping signals).



44c/45c

Propargylic Alcohols 44c/45c. Propargylic alcohol **43c** (181 mg, 0.50 mmol) was subjected to the procedure described above for **17b**. Purification by flash chromatography (20 : 1 hexane : EtOAc) furnished an inseparable mixture 145 mg (80%, **44c : 45c** 1 : 1 determined by integration of methine ^{1}H NMR signals) as an orange oil.

R_f 0.32 (4:1 Hexane: EtOAc)

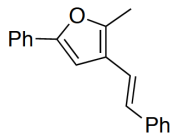
IR (film) 3388 (br), 3061, 3029, 2958, 2931, 2872, 2223, 1597, 1517, 1342 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 – 8.16 (m, 4H), 7.65 – 7.63 (m, 2H), 7.52 – 7.50 (m, 2H), 7.48 – 7.46 (m, 2H), 7.42 – 7.24 (m, 8H), 7.04 (d, 1H, J = 15.6 Hz), 7.02 (d, 1H, J = 15.6 Hz), 6.82 (d, 1H, J = 15.6 Hz), 6.68 (d, 1H, J = 15.6 Hz), 6.21 (d, 1H, J = 8.8 Hz), 6.02 (d, 1H, J = 8.8 Hz), 5.97 (d, 1H, J = 8.8 Hz), 5.91 (d, 1H, J = 8.8 Hz), 2.54 (t, 2H, J = 7.1 Hz), 2.53 (t, 2H, J = 7.1 Hz), 2.41 (s, 1H),

2.26 (s, 1H), 1.70 – 1.67 (m, 4H), 1.58 – 1.51 (m, 4H), 1.00 (t, 3H, J = 7.3 Hz), 0.99 (t, 3H, J = 7.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 147.3, 146.9, 143.4, 143.0, 142.4, 138.3, 136.5, 133.5, 133.2, 129.9, 128.7, 128.7, 128.1, 128.1, 127.9, 127.1, 126.8, 126.6, 125.9, 125.6, 124.1, 123.8, 123.5, 99.4, 99.4, 74.7, 74.3, 72.5, 71.7, 30.8, 30.8, 22.1, 22.1, 19.3, 19.3, 13.6, 13.6;

HRMS calc'd for $C_{23}H_{23}NO_3$ (M^+) 361.1678; found 361.1675.



48e

Furan 48e. $VO(acac)_2$ (1.3 mg, 0.005 mmol) was added to a solution of tertiary allylic alcohol **15e** (139 mg, 0.5 mmol) in toluene (9 mL). The mixture was stirred for 2 h at rt. When starting material was deemed consumed by TLC, $AuCl_3$ (1.0 mL, 0.005 M in toluene, 0.005 mmol) was added and the reaction stirred for 2 h. The reaction mixture was quenched by filtration through a silica gel plug eluted with CH_2Cl_2 (50 mL). and concentrated. Purification by flash chromatography (40 : 1 hexane : EtOAc) furnished 107 mg (77%) of furan **48e** as a colorless oil.

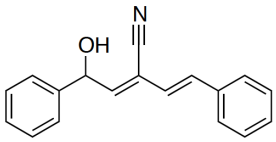
R_f 0.70 (4:1 Hexane: EtOAc)

IR (film) 2926, 2852, 1683, 1614, 1449, 984 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.68 (m, 2H), 7.51 – 7.49 (m, 2H), 7.42 – 7.35 (m, 4H), 7.29 – 7.24 (m, 2H), 6.94 (d, 1H, J = 16.1 Hz), 6.87 (s, 1H), 6.81 (d, 1H, J = 16.1 Hz), 2.48 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 149.9, 137.8, 130.7, 128,7, 128.7, 127.2, 127.2, 127.1, 126.0, 123.6, 120.9, 118.9, 102.9, 12.1;

HRMS calc'd for $C_{19}H_{16}O_3$(M^+) 260.1201; found 260.1194.



51

Nitrile 51. $VO(O\textit{i-Pr})_3$ (7 μL, 0.03 mmol) was added to a solution of cyanohydrin **49** (131 mg, 0.50 mmol) in toluene (5 mL). The mixture was stirred for 1 h at 60 °C and allowed to cool to rt. The reaction mixture was quenched by filtration through a silica gel plug eluted with CH_2Cl_2 (50 mL), and concentrated. Purification by flash chromatography (10 : 1 hexane : EtOAc) furnished 107 mg (82%) of the desired alcohol as an orange oil.

R_f 0.22 (4:1 Hexane: EtOAc)

IR (film) *v* 3419 (br), 3084, 3061, 3030, 2919, 2850, 2229, 1630, 1601, 1493, 1450, 1032, 1018, 958 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.47 (m, 2H), 7.43 – 7.27 (m, 8H), 7.03 (d, 1H, *J* = 16.0 Hz), 6.64 (d, 1H, *J* = 16.0 Hz), 6.51 (d, 1H, *J* = 8.9 Hz), 5.82 (dd, 1H, *J* = 8.9, 2.2 Hz), 2.33 (d, 1H, *J* = 3.0 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.1, 141.1, 135.4, 135.1, 129.1, 129.0, 128.9, 128.7, 127.0, 126.3, 123.4, 115.0, 114.8, 73.1;

HRMS calc'd for $C_{18}H_{15}NO$ (M^+) 261.1154; found 261.1151.

4.7 References

(1) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676–5688.

(2) Nakanishi, W.; West, F. G. *Curr. Opin. Drug. Discovery Dev.* **2009**, *12*, 732–751.

(3) Spencer, W. T., III; Vaidya, T.; Frontier, A. J. *Eur. J. Org. Chem.* **2013**, *2013*, 3621–3633.

(4) Tius, M. A. *Chem. Soc. Rev.* **2014**, DOI: 10.1039/c3cs60333d

(5) West, F. G.; Scadeng, O. S.; Wu, Y-K; Fradette, R. J.; Joy S. in *Comprehensive Organic Synthesis II*; Knochel, P; Molander, G. A.; Eds.; Elsevier: Oxford, **2014**.

(6) See Chapter 1 of this thesis for more detailed discussion.

(7) Miller, N. A.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *Angew. Chem. Int. Ed.* **2007**, *46*, 937–940.

(8) Winberg, K. J. University of Alberta, *Unpublished results*.

(9) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027–4029.

(10) Engel, D. A.; Lopez, S. S.; Dudley, G. B. *Tetrahedron* **2008**, *64*, 6988–6996.

(11) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429–438.

(12) Cadierno, V.; Crochet, P.; García-Garrido, S. E.; Gimeno, J. *Dalton Trans.* **2010**, *39*, 4015-4031.

(13) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Org. Chem.* **2011**, *76*, 50–56.

(14) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Am. Chem. Soc.* **2009**, *131*, 7504–7505.

(15) Rieder, C. J. *Ph.D. Dissertation*, **2010**.

(16) Hill, R. K. *Comp. Org. Synth.* **1991**, *5*, 785–826.

(17) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13972–14020.

(18) Wipf, P. *Comp. Org. Synth.* **1991**, *5*, 827–873.

(19) Martín Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939–3002.

(20) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218–224.

(21) Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149–3152.

(22) Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811–3820.

(23) Anderson, E. A.; Alexanian, E. J.; Sorensen, E. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 1998–2001.

(24) Young, W. G.; Nozaki, K.; Warner, R. *J. Am. Chem. Soc.* **1939**, 2564–2565.

(25) Leleti, R. R.; Hu, B.; Prashad, M.; Repič, O. *Tetrahedron Lett.* **2007**, *48*, 8505–8507.

(26) McCubbin, J. A.; Voth, S.; Krokhin, O. V. *J. Org. Chem.* **2011**, *76*, 8537–8542.

(27) Zheng, H.; Lejkowski, M.; Hall, D. G. *Chem. Sci.* **2011**, *2*, 1305.

(28) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2006**, *128*, 8142–8143.

(29) Morrill, C.; Beutner, G. L.; Grubbs, R. H. *J. Org. Chem.* **2006**, *71*, 7813–7825.
(30) Serra-Muns, A.; Guérinot, A.; Reymond, S.; Cossy, J. *Chem. Commun.* **2010**, *46*, 4178.
(31) Conrow, R. E. *Org. Lett.* **2006**, *8*, 2441–2443.
(32) Shekhar, S.; Trantow, B.; Leitner, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 11770–11771.
(33) Chabardes, P.; Kuntz, E.; Varagnat, J. *Tetrahedron* **1977**, *33*, 1775–1783.
(34) Hosogai, T.; Fujita, Y.; Ninagawa, Y.; Nishida, T. *Chem. Lett.* **1982**, 357–360.
(35) Matsubara, S.; Okazoe, T.; Oshima, K.; Takai, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 844–849.
(36) Bellemin-Laponnaz, S.; Gisie, H.; Le Ny, J. P.; Osborn, J. A. *Angew. Chem. Int. Ed.* **1997**, *36*, 976–979.
(37) Jacob, J.; Espenson, J. H.; Jensen, J. H.; Gordon, M. S. *Organometallics* **1998**, *17*, 1835–1840.
(38) Bellemin-Laponnaz, S.; Le Ny, J. P.; Osborn, J. A. *Tetrahedron Lett.* **2000**, *41*, 1549–1552.
(39) Morrill, C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 2842–2843.
(40) Herrmann, A. T.; Saito, T.; Stivala, C. E.; Tom, J.; Zakarian, A. *J. Am. Chem. Soc.* **2010**, *132*, 5962–5963.
(41) Xie, Y.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2013**, *52*, 625–628.
(42) Li, C.-J.; Wang, D.; Chen, D.-L. *J. Am. Chem. Soc.* **1995**, 12867–12868.
(43) Dilli, S.; Patsalides, E. *Aust. J. Chem.* **1976**, *29*, 2369–2379.
(44) Boiadjiev, S. E.; Lightner, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 11328–11339.
(45) Curran, D. P.; Suh, Y.-G. *J. Am. Chem. Soc.* **1984**, *106*, 5002–5004.
(46) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6984–6986.
(47) Nicolaou, K. C.; Kang, Q.; Ng, S. Y.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2010**, *132*, 8219–8222.
(48) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2285–2288.
(49) Du, X.; Song, F.; Lu, Y.; Chen, H.; Liu, Y. *Tetrahedron* **2009**, *65*, 1839–1845.
(50) Mandai, T.; Hashio, S.; Goto, J.; Kawada, M. *Tetrahedron Lett.* **1981**, *22*, 2187–2190.
(51) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3021–3024.
(52) Eliel, E. L.; Freeman, J. P. *Org. Synth.* **1953**, *33*, 7–10.
(53) Shen, Z.-L.; Ji, S.-J. *Synth. Commun.* **2009**, *39*, 775–791.
(54) Weber, W. M.; Hunsaker, L. A.; Abcouwer, S. F.; Deck, L. M.; Vander Jagt, D. L. *Bioorg. Med. Chem.* **2005**, *13*, 3811–3820.

Chapter 5

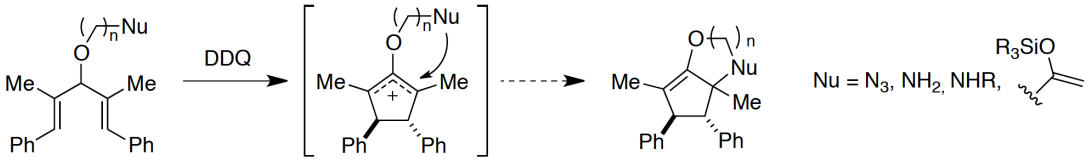
Concluding Remarks and Future Directions

In previous attempts to furnish a 5,8,5-tricycle through the Lewis acid mediated intermolecular Nazarov cyclization/[4+3]-cycloaddition, novel arene trapped products were observed. [1]As earlier studies showed, the oxyallyl cation generated from Nazarov cyclization is able to undergo intramolecular arene trapping with a variety of appropriately substituted dienones.[2,3] In the case of the BF_3•OEt_2 mediated tandem Nazarov cyclization/intermolecular electrophilic aromatic substitution cascade our observations suggest that a diquinane is essential in establishing a 2-oxidiocyclopentenyl cation that is sufficiently reactive and long lived to undergo the bimolecular trapping process. The failure of anisole to trap the 2-oxidiocyclopentenyl cation indicates that significant nucleophilicity is required on the part of the arene. Complete regioselectivity and diastereofacial selectivity was observed for arene trapping step in all cases for the cyclopentenyl ketone substrates (Chapter 2).

We were able to develop an oxidation initiated Nazarov reaction of bis(allylic) ethers. This process involved the DDQ oxidation of the bis(allylic) ether substrates, generating a reactive 3-oxidopentadienyl cation intermediate that successfully underwent Nazarov cyclization. The final products were enol ethers bearing an exo methylene, resulting from a highly regioselective elimination step. This exo elimination was notable, as it left the two new stereocenters formed in the stereospecific cyclization step untouched. We attempted arene trapping with electron rich arenes tethered through the C-3 ether; however, these attempted interrupted Nazarov reactions were unsuccessful, leading instead to the simple Nazarov products. At present, it appears that arene substitution is required at one terminus of the bis(allylic) ether in order for the oxidation step to proceed. The DDQ initiated Nazarov cyclization of bis(allylic) ethers permits the use of a new

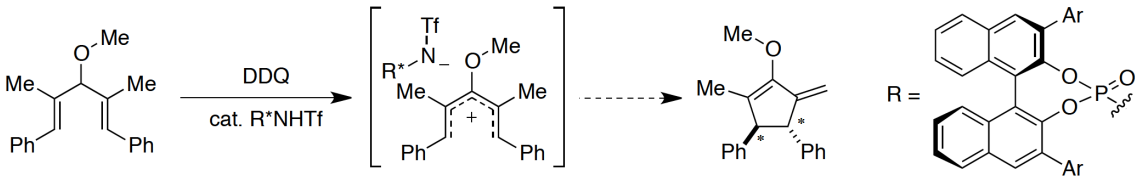
class of alternative substrates, a new and mild method of activation, and affords a new type of Nazarov products (dienol ethers).

Our preliminary studies of the DDQ-initiated Nazarov reaction showed that a variety of ether moieties were tolerated under the reaction conditions. We attempted to intercept the oxyallyl cation intermediate using electron-rich arenes through this ether moiety. While the initial attempts failed to provide the arene interrupted Nazarov products, there are many other functional groups that could be viable carbon or heteroatom nucleophiles to attach through the C-3 ether, which have been previously used in interrupted Nazarov reactions. Azides,[4-6] amines,[7,8] and silyl enol ethers[9] are possible nucleophilic tethers to further probe an interrupted Nazarov reaction of 1,4-pentadien-3-yl ethers (Scheme 1).



Scheme 1: Interrupted DDQ-Initiated Nazarov Reaction.

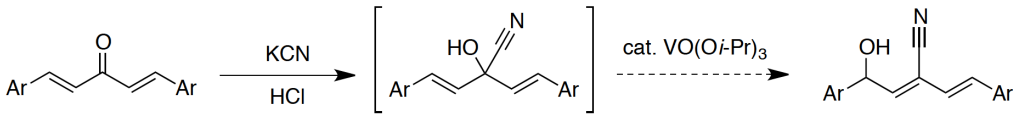
We envision an asymmetric version of the DDQ-initiated Nazarov reaction. Reuping and coworkers used chiral *N*-triflyl phosphoramides as Brønsted acid catalysts to control the conrotation of the Nazarov cyclization, presumably via a chiral ion-pair mechanism.[10] Floreancig and co-workers used a related chiral *N*-triflyl phosphoramide to carry out enantioselective DDQ-initiated oxidative coupling reactions.[11] We propose a related chiral ion pair between the phosphoramide and pentadienyl cation to control the torquoselectivity of the Nazarov cyclization to furnish enantioenriched Nazarov products (Scheme 2).



Scheme 2: Asymmetric DDQ-Initiated Nazarov Reaction.

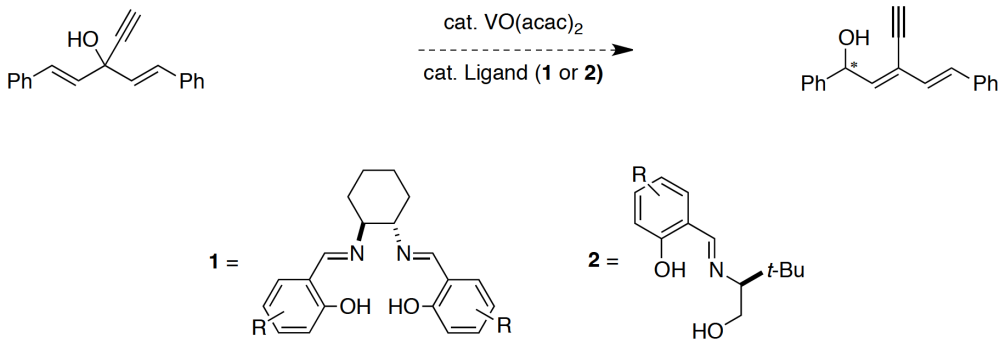
During the development of a vanadium catalyzed Meyer-Schuster reaction for the synthesis of [3]dendralenes[12] that were used in the vinylogous Nazarov reaction,[13] a facile 1,3-transposition of allylic alcohols was observed. We were able to expand the scope of this method to include variety of tertiary propargylic bis(allylic) alcohols, tertiary propargylic allylic alcohols, and tertiary bis(propargylic) allylic alcohols (Chapter 4). The vanadium catalyzed transposition method was also successfully applied to a bis(allylic) cyanohydrin for the synthesis of an α,β-unsaturated nitrile. Additionally, the vanadium catalyzed transposition was carried out in tandem with a gold catalyzed cycloisomerization to generate tri-substituted furans.

Further work to expand the scope of the tandem 1,3-transposition/cycloisomerization to additional tertiary propargylic bis(allylic) alcohols, tertiary propargylic allylic alcohols, and tertiary bis(propargylic) allylic alcohols is required. Additionally, expanding the cyanohydrin 1,3-transposition method by carrying out cyanohydrin formation in tandem with the vanadium catalyzed 1,3-transposition is an attractive method (Scheme 3). This would avoid the use of a protected *O*-TMS-cyanohydrin or handling of the labile bis(allylic) cyanohydrin.



Scheme 3: One-pot Cyanohydrination/1,3-Transposition.

The use of chiral vanadium catalysts in the 1,3-transposition methodology may allow for the generation of enantioenriched 2° allylic alcohols. $VO(acac)_2$ in the presence of tetradentate salen ligands **1** or bidentate Schiff base ligands **2** has been used for catalytic asymmetric processes.[14] We imagine that these systems could be applied to the vanadium-catalyzed 1,3-transposition of allylic alcohols (Scheme 4).



Scheme 4: Catalytic Asymmetric 1,3-Transposition.

References

(1) Rieder, C. J. *Ph.D. Dissertation*, **2010**.
(2) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033–3035.
(3) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Can. J. Chem.* **2004**, *82*, 375–385.
(4) Song, D.; Rostami, A.; West, F. G. *J. Am. Chem. Soc.* **2007**, *129*, 12019–12022.
(5) Rostami, A.; Wang, Y.; Arif, A. M.; McDonald, R.; West, F. G. *Org. Lett.* **2007**, *9*, 703–706.
(6) Scadeng, O.; Ferguson, M. J.; West, F. G. *Org. Lett.* **2011**, *13*, 114–117.
(7) Dhoro, F.; Tius, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 12472–12473.
(8) Dhoro, F.; Kristensen, T. E.; Stockmann, V.; Yap, G. P. A.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 7256–7257.
(9) Yen-Ku, W.; McDonald, R.; West, F. G. *Org. Lett.* **2011**, *13*, 3584–3587.
(10) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2097–2100.
(11) Cui, Y.; Villafane, L. A.; Clausen, D. J.; Floreancig, P. E. *Tetrahedron* **2013**, *69*, 7618–7626.
(12) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Org. Chem.* **2011**, *76*, 50–56.
(13) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Am. Chem. Soc.* **2009**, *131*, 7504–7505.
(14) Bolm, C. *Coordination Chemistry Reviews,* **2003**, *237*, 245–256.

Bibliography

Chapter 1

(1) Nazarov, I. N.; Yanbikov, Y. M. *Izv. Nauk. SSSR, Ser. Kim,* **1943**; 389-393.

(2) Braude, E. A.; Coles, J. A. *J. Chem. Soc.* **1952**, 1430–1433.

(3) Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed.* **1969**, *8*, 781–932.

(4) A version of this section has been previously published, see the following reference.

(5) West, F. G.; Scadeng, O.; Wu, Y.-K.; Fradette, R. J.; Joy, S. In *Comprehensive Organic Synthesis II*; Elsevier, 2014; pp. 827–866.

(6) Barltrop, J. A.; Day, A. C.; Samuel, C. J. *J. Am. Chem. Soc.* **1979**, *101*, 7521–7528.

(7) West, F. G.; Fisher, P. V.; Gunawardena, G. U.; Mitchell, S. *Tetrahedron Lett.* **1993**, *34*, 4583–4586.

(8) West, F. G.; Fisher, P. V.; Willoughby, C. A. *J. Org. Chem.* **1990**, *55*, 5936–5938.

(9) West, F. G.; Fisher, P. V.; Arif, A. M. *J. Am. Chem. Soc.* **1993**, *115*, 1595–1597.

(10) West, F. G.; Willoughby, D. W. *J. Org. Chem.* **1993**, 3796–3797.

(11) West, F. G.; Hartke-Karger, C.; Koch, D. J.; Kuehn, C. E.; Arif, A. M. *J. Org. Chem.* **1993**, *58*, 6795–6803.

(12) Vorlander, D.; Schroedter, M. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 1409–1407.

(13) Allen, C. F. H.; VanAllan, J. A.; Tinker, J. F. *J. Org. Chem.* **1955**, *20*, 1387–1391.

(14) Giese, S.; West, F. G. *Tetrahedron Lett.* **1998**, *39*, 8393–8396.

(15) Giese, S.; West, F. G. *Tetrahedron,* **2000**, *56*, 10221–10228.

(16) Chiu, P.; Li, S. *Org. Lett.* **2004**, *6*, 613–616.

(17) Lebœuf, D.; Huang, J.; Gandon, V.; Frontier, A. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 10981–10985.

(18) Huang, J.; Lebœuf, D.; Frontier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 6307–6317.

(19) Bender, J. A.; Blize, A. E.; Browder, C. C.; giese, S.; West, F. G. *J. Org. Chem.* **1998**, *63*, 2430–2431.

(20) giese, S.; Mazzola, R. D.; Amann, C. M.; Arif, A. M.; West, F. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 6546–6549.

(21) Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443–7444.

(22) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033–3035.

(23) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Can. J. Chem.* **2004**, *82*, 375–385.

(24) Chaplin, J. H.; Jackson, K.; White, J. M.; Flynn, B. L. *J. Org. Chem.* **2014**, *79*, 3659-3665.
(25) Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem. Int. Ed.* **2000**, 1970–1973.
(26) Marx, V. M.; Burnell, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 1685–1689.
(27) Mahmoud, B.; West, F. G. *Tetrahedron Lett.* **2007**, *48*, 5091–5094.
(28) Yen-Ku, W.; McDonald, R.; West, F. G. *Org. Lett.* **2011**, *13*, 3584-3587.
(29) For further discussion see Chapter 2 of this thesis.
(30) Rieder, C. J.; Fradette, R. J.; West, F. G. *Chem. Commun.* **2008**, 1572–1574.
(31) G West, F.; J Rieder, C.; J Fradette, R. *Heterocycles* **2010**, *80*, 1413–1427.
(32) Basak, A. K.; Tius, M. A. *Org. Lett.* **2008**, *10*, 4073–4076.
(33) Marx, V. M.; LeFort, F. M.; Burnell, D. J. *Adv. Synth. Catal.* **2010**, *353*, 64–68.
(34) Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876–877.
(35) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747–2750.
(36) Kwon, Y.; McDonald, R.; West, F. G. *Angew. Chem. Int. Ed.* **2013**, *52*, 8616–8619.
(37) Nair, V.; Bindu, S.; Sreekumar, V.; Chiaroni, A. *Org. Lett.* **2002**, *4*, 2821–2823.
(38) Marx, V. M.; Burnell, D. J. *Org. Lett.* **2009**, *11*, 1229–1231.
(39) Marx, V. M.; Stoddard, R. L.; Heverly-Coulson, G. S.; Burnell, D. J. *Chem. Eur. J.* **2011**, *17*, 8098–8104.
(40) Yaji, K.; Shindo, M. *Synlett* **2009**, *2009*, 2524–2528.
(41) Dhoro, F.; Tius, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 12472–12473.
(42) Dhoro, F.; Kristensen, T. E.; Stockmann, V.; Yap, G. P. A.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 7256–7257.
(43) Rostami, A.; Wang, Y.; Arif, A. M.; McDonald, R.; West, F. G. *Org. Lett.* **2007**, *9*, 703–706.
(44) Song, D.; Rostami, A.; West, F. G. *J. Am. Chem. Soc.* **2007**, *129*, 12019–12022.
(45) Scadeng, O.; Ferguson, M. J.; West, F. G. *Org. Lett.* **2011**, *13*, 114–117.
(46) White, T. D.; West, F. G. *Tetrahedron Lett.* **2005**, *46*, 5629–5632.
(47) Marx, V. M.; Cameron, T. S.; Burnell, D. J. *Tetrahedron Lett.* **2009**, *50*, 7213–7216.
(48) Nie, J.; Zhu, H.-W.; Cui, H.-F.; Hua, M.-Q.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 3053–3056.
(49) Cui, H.-F.; Dong, K.-Y.; Zhang, G.-W.; Wang, L.; Ma, J.-A. *Chem. Commun.* **2007**, 2284.
(50) Cui, H.-F.; Dong, K.-Y.; Nie, J.; Zheng, Y.; Ma, J.-A. *Tetrahedron Letters* **2010**, *51*, 2374–2377.

(51) Kawatsura, M.; Kajita, K.; Hayase, S.; Itoh, T. *Synlett* **2010**, 1243–1246.
(52) Rueping, M.; Ieawsuwan, W. *Chem. Commun.* **2011**, *47*, 11450.
(53) Janka, M.; He, W.; Haedicke, I. E.; Fronczek, F. R.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2006**, *128*, 5312–5313.
(54) Fujiwara, M.; Kawatsura, M.; Hayase, S.; Nanjo, M.; Itoh, T. *Adv. Synth. Catal.* **2008**, *351*, 123–128.
(55) Ibara, C.; Fujiwara, M.; Hayase, S.; Kawatsura, M.; Itoh, T. *Sci. China Chem.* **2012**, *55*, 1627–1632.
(56) Hashmi, A. S. K.; Bats, J. W.; Choi, J.-H.; Schwarz, L. *Tetrahedron Lett.* **1998**, *39*, 7491–7494.
(57) Tius, M. A. *Chem. Soc. Rev.* **2014**.
(58) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284–290.
(59) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509–8514.
(60) Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 10091–10100.
(61) Harrington, P. E.; Tius, M. A. *Org. Lett.* **2000**, *2*, 2447–2450.
(62) delos Santos, D. B.; Banaag, A. R.; Tius, M. A. *Org. Lett.* **2006**, *8*, 2579–2582.
(63) Banaag, A. R.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 5328–5329.
(64) Banaag, A. R.; Tius, M. A. *J. Org. Chem.* **2008**, *73*, 8133–8141.
(65) Schultz-Fademrecht, C.; Tius, M. A.; Grimme, S.; Wibbeling, B.; Hoppe, D. *Angew. Chem. Int. Ed.* **2002**, *41*, 1532–1535.
(66) Muxfeldt, H.; Weigele, M.; Van Rheenen, V. *J. Org. Chem.* **1965**, *30*, 3573–3574.
(67) Batson, W. A.; Sethumadhavan, D.; Tius, M. A. *Org. Lett.* **2005**, *7*, 2771–2774.
(68) Uhrich, E.; Batson, W.; Tius, M. *Synthesis* **2006**, *2006*, 2139–2142.
(69) Basak, A. K.; Shimada, N.; Bow, W. F.; Vicic, D. A.; Tius, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 8266–8267.
(70) Brooks, J. L.; Caruana, P. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 12454–12457.
(71) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Am. Chem. Soc.* **2009**, *131*, 7504–7505.
(72) Miller, A. K.; Banghart, M. R.; Beaudry, C. M.; Suh, J. M.; Trauner, D. *Tetrahedron* **2003**, *59*, 8919–8930.
(73) Jung, M. E.; Yoo, D. *J. Org. Chem.* **2007**, *72*, 8565–8568.
(74) Spencer, W. T., III; Vaidya, T.; Frontier, A. J. *Eur. J. Org. Chem.* **2013**, *2013*, 3621–3633.
(75) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Org. Chem.* **2011**, *76*, 50–56.
(76) Zheng, H.; Lejkowski, M.; Hall, D. G. *Tetrahedron Lett.* **2013**, *54*, 91–94.
(77) Singh, R.; Panda, G. *Org. Biomol. Chem.* **2011**, *9*, 4782.
(78) de Lera, Á. R.; Rey, J. G.; Hrovat, D.; Iglesias, J.; Lopez, S.

Tetrahedron Lett. **1997**, *38*, 7425–7428.
(79) Iglesias, B.; de Lera, Á. R.; Rodriguez-Otero, J.; Lopez, S. *Chem. Eur. J*. **2000**, *6*, 4021–4034.
(80) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Deagostino, A.; Venturello, P. *J. Org. Chem*. **2002**, *67*, 7144–7146.
(81) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P. *J. Org. Chem*. **2003**, *68*, 9728–9741.
(82) Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P.; Occhiato, E. G. *J. Org. Chem*. **2004**, *69*, 7705–7709.
(83) Prandi, C.; Deagostino, A.; Venturello, P.; Occhiato, E. G. *Org. Lett*. **2005**, *7*, 4345–4348.
(84) Barluenga, J.; Barrio, P.; Vicente, R.; López, L. A.; Tomás, M. *J. Organomet. Chem*. **2004**, *689*, 3793–3799.
(85) Eom, D.; Park, S.; Park, Y.; Ryu, T.; Lee, P. H. *Org. Lett*. **2012**, *14*, 5392–5395.
(86) Grimaldi, J.; Bertrand, M. *Tetrahedron Lett*. **1969**, 3296–3272.
(87) Bertrand, M.; Dulcere, J. P.; Gil, G. *Tetrahedron Lett*. **1977**, 4403–4406.
(88) Malacria, M.; Roumestant, M. L. *Tetrahedron* **1977**, *33*, 2813–2817.
(89) Doutheau, A.; Gore, J.; Malacria, M. *Tetrahedron* **1977**, *33*, 2393–2398.
(90) Doutheau, A.; Sartoretti, J.; Gore, J. *Tetrahedron* **1983**, *39*, 3059–3065.
(91) Doutheau, A.; Gore, J.; Diab, J. *Tetrahedron* **1985**, *41*, 329–338.
(92) Seong, J. K.; Cha, J. K. *Tetrahedron Lett*. **1988**, *29*, 5613–5616.
(93) Malona, J. A.; Cariou, K.; Frontier, A. J. *J. Am. Chem. Soc*. **2009**, *131*, 7560–7561.
(94) Malona, J. A.; Cariou, K.; Spencer, W. T., III; Frontier, A. J. *J. Org. Chem*. **2012**, *77*, 1891–1908.
(95) Spencer, W. T., III; Levin, M. D.; Frontier, A. J. *Org. Lett*. **2011**, *13*, 414–417.
(96) Yen-Ku, W.; West, F. G. *J. Org. Chem*. **2010**, *75*, 5410–5413.
(97) Lee, J. H.; Toste, F. D. *Angew. Chem. Int. Ed*. **2007**, *46*, 912–914.
(98) Funami, H.; Kusama, H.; Iwasawa, N. *Angew. Chem. Int. Ed*. **2007**, *46*, 909–911.
(99) Metal-mediated activation of allenes and alkynes for Nazarov cyclizations is a well studied and growing field, see references 5 and 74 for further examples.
(100) Grant, T. N.; West, F. G. *J. Am. Chem. Soc*. **2006**, *128*, 9348–9349.
(101) Grant, T. N.; West, F. G. *Org. Lett*. **2007**, *9*, 3789–3792.
(102) Rosocha, G.; Batey, R. A. *Tetrahedron* **2013**, *69*, 8758–8768.
(103) Sathishkannan, G.; Srinivasan, K. *Adv. Synth. Catal*. **2014**, *356*, 729–735.
(104) Saito, A.; Umakoshi, M.; Yagyu, N.; Hanzawa, Y. *Org. Lett*. **2008**, *10*, 1783–1785.
(105) Xu, T.; Yang, Q.; Ye, W.; Jiang, Q.; Xu, Z.; Chen, J.; Yu, Z. *Chem. Eur. J*. **2011**, *17*, 10547–10551.
(106) Zhu, L.; Xi, Z.-G.; Lv, J.; Luo, S. *Org. Lett*. **2013**, *15*, 4496–4499.

(107) Smith, D. A.; Ulmer, C. W. I. *J. Org. Chem.* **1997**, *62*, 5110–5115.
(108) Tius, M. A.; Chu, C. C.; Nieves-Colberg, R. *Tetrahedron Lett.* **2001**, *42*, 2419–2422.
(109) Bonderoff, S. A.; Grant, T. N.; West, F. G.; Tremblay, M. *Org. Lett.* **2013**, *15*, 2888–2891.

Chapter 2

(1) Rieder, C. J.; Fradette, R. J.; West, F. G. *Chem. Commun.* **2008**, 1572–1574.
(2) Rieder, C. J.; Fradette, R. J.; West, F. G.; *Heterocycles,* **2010**, *80*, 1413–1427.
(3) Selvakumar, N.; Reddy, B. Y.; Kumar, G. S.; Iqbal, J. *Tetrahedron Lett.* **2001**, *8395-8398*, 1–4.
(4) Snow, R. J.; Butz, T.; Hammach, A.; Kapadia, S.; Morowick, T. M.; Prokpowicz, A. S.; Takahashi, H.; Tan, J.; Tschantz, M. A.; Wang, X.-J. *Tetrahedron Lett.* **2002**, *43*, 7553–7556.
(5) Bella, M.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 3670–3671.
(6) Kobbelgaard, S.; Bella, M.; Jørgensen, K. A. *J. Org. Chem.* **2006**, *71*, 4980–4987.
(7) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478.
(8) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370.
(9) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195–200.
(10) Tripathy, S.; Reddy, R.; Durst, T. *Can. J. Chem.* **2003**, *81*, 997–1002.
(11) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340–5341.
(12) Mohanan, K.; Coquerel, Y.; Rodriguez, J. *Org. Lett.* **2012**, *14*, 4686–4689.
(13) Goetz, A. E.; Silberstein, A. L.; Corsello, M. A.; Garg, N. K. *J. Am. Chem. Soc.* **2014**, *136*, 3036–3039.
(14) Huang, X.; Maulide, N. *J. Am. Chem. Soc.* **2011**, *133*, 8510–8513.
(15) Huang, X.; Patil, M.; Farès, C.; Thiel, W.; Maulide, N. *J. Am. Chem. Soc.* **2013**, *135*, 7312–7323.
(16) Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **1973**, *12*, 819–835.
(17) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163–344.
(18) Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **1984**, 1–19.
(19) Mann, J. *Tetrahedron* **1986**, *42*, 4611–4659.
(20) Kende, A. S. *Org. React.* **1960**, *11*, 261–291.
(21) Hill, A. E.; Greenwood, G.; Hoffmann, H. M. R. *J. Am. Chem. Soc.* **1973**, *95*, 1338–1340.
(22) Fohlisch, B.; Herter, R.; Wolf, E.; Stezowski, J. J.; Eckle, E. *Chem. Ber.* **1982**, *115*, 355–380.
(23) Harmata, M. *Adv. Synth. Catal.* **2006**, *348*, 2297–2306.
(24) Harmata, M. *Chem. Commun.* **2010**, *46*, 8904-8922.

(25) Lohse, A. G.; Hsung, R. P. *Chem. Eur. J.* **2011**, *17*, 3812–3822.
(26) Fohlisch, B.; Joachimi, R. *Chem. Ber.* **1987**, *120*, 1951–1960.
(27) Tang, Q.; Chen, X.; Tiwari, B.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 1922–1925.
(28) Vander Wal, M. N.; Dilger, A. K.; MacMillan, D. W. C. *Chem. Sci.* **2013**, *4*, 3075-3079.
(29) See Chapter 1 of this thesis for further discussion.
(30) West, F. G.; Willoughby, D. W. *J. Org. Chem.* **1993**, 3796–3797.
(31) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033–3035.
(32) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Can. J. Chem.* **2004**, *82*, 375–385.
(33) Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348–9349.
(34) Grant, T. N.; West, F. G. *Org. Lett.* **2007**, *9*, 3789–3792.
(35) Basak, A. K.; Tius, M. A. *Org. Lett.* **2008**, *10*, 4073–4076.
(36) Marx, V. M.; LeFort, F. M.; Burnell, D. J. *Adv. Synth. Catal.* **2010**, *353*, 64–68.
(37) Marx, V. M.; Burnell, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 1685–1689.
(38) Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem. Int. Ed.* **2000**, 1970–1973.
(39) Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876–877.
(40) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747–2750.
(41) Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed.* **1969**, *8*, 781–932.
(42) Gordon, H. L.; Freeman, S.; Hudlicky, T. *Synlett* **2005**, 2911–2914.
(43) Products **2a, 3a, 7a, 7a', 7b, 7b', 7c, 7c', 7i, 7i'** were first synthesized by C. J. Rieder. For characterization data see references 1, 2, and Rieder, C. J. *Ph.D. Dissertation*, **2010**.
(44) The work discussed herein was a joint effort by C. J. Rieder and the author, disambiguation of contributions are made in reference 43, and throughout Section **2.3.**
(45) It was observed that acyclic dienones such **1b** could undergo TMSOTf promoted tandem Nazarov cyclization/electrophilic aromatic substitution with arenes possessing sufficient 1,3-diene character. Arenes such as thiophene and 1,3-dimethoxybenzene were unsuccessful. Wu, Y-K. *Ph.D. Dissertation*, **2013**.

Chapter 3

(1) Nazarov, I. N.; Zaretskaya, I. I.; Sorkina, T. I. *Zh. Obshch. Khim.* **1960**, *30*, 746-754.
(2) Nazarov, I. N.; Yanbikov, Y. M. *Bull. Acad. Sci. URSS. Classe Sci. Chim.* **1943**, 389-393.
(3) Nazarov, I. N.; Yanbikov, Y. M. *Bull. Acad. Sci. URSS. Sci, Chim.* **1946**,

633-646.
(4) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429–444.
(5) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React.* **1994**, *45*, 1–158.
(6) See the following six references and Chapter 1 of this thesis for more detailed discussion.
(7) Tius, M. A. *Eur. J. Org. Chem.* **2005**, *2005*, 2193–2206.
(8) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676–5688.
(9) Nakanishi, W.; West, F. G. *Curr. Opin. Drug. Discovery Dev.* **2009**, *12*, 732–751.
(10) Spencer, W. T., III; Vaidya, T.; Frontier, A. J. *Eur. J. Org. Chem.* **2013**, *2013*, 3621–3633.
(11) Tius, M. A. *Chem. Soc. Rev.* **2014**, DOI: 10.1039/c3cs60333d
(12) West, F. G.; Scadeng, O. S.; Wu, Y-K; Fradette, R. J.; Joy S. in *Comprehensive Organic Synthesis II*; Knochel, P; Molander, G. A.; Eds.; Elsevier: Oxford, **2014**.
(13) Smith, D. A.; Ulmer, C. W. I. *J. Org. Chem.* **1997**, *62*, 5110–5115.
(14) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Deagostino, A.; Venturello, P. *J. Org. Chem.* **2002**, *67*, 7144–7146.
(15) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P. *J. Org. Chem.* **2003**, *68*, 9728–9741.
(16) Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P.; Occhiato, E. G. *J. Org. Chem.* **2004**, *69*, 7705–7709.
(17) Wu, Y-K.; West, F. G. *J. Org. Chem.* **2010**, *75*, 5410–5413.
(18) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802–5803.
(19) Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348–9349.
(20) Grant, T. N.; West, F. G. *Org. Lett.* **2007**, *9*, 3789–3792.
(21) Malona, J. A.; Cariou, K.; Frontier, A. J. *J. Am. Chem. Soc.* **2009**, *131*, 7560–7561.
(22) Malona, J. A.; Cariou, K.; Spencer, W. T., III; Frontier, A. J. *J. Org. Chem.* **2012**, *77*, 1891–1908.
(23) Spencer, W. T., III; Levin, M. D.; Frontier, A. J. *Org. Lett.* **2011**, *13*, 414–417.
(24) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Am. Chem. Soc.* **2009**, *131*, 7504–7505.
(25) Nair, V.; Bindu, S.; Sreekumar, V.; Chiaroni, A. *Org. Lett.* **2002**, *4*, 2821–2823.
(26) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wiley-Interscience, **2006**.
(27) Yadav, J. S.; Chandrasekhar, S.; Sumithra, G.; Kache, R. *Tetrahedron Lett.* **1996**, *37*, 6603–6606.
(28) Xu, Y.-C.; Roy, C.; Lebeau, E. *Tetrahedron Lett.* **1993**, *34*, 8189–8192.
(29) Xu, Y.-C.; Kohlman, D. T.; Liang, S. X.; Erikkson, C. *Org. Lett.* **1999**, *1*, 1599–1602.

(30) Ying, B.-P.; Trogden, B. G.; Kohlman, D. T.; Liang, S. X.; Xu, Y.-C. *Org. Lett.* **2004**, *6*, 1523–1526.
(31) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242–4243.
(32) Tu, W.; Liu, L.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2008**, *47*, 4184–4187.
(33) Park, S. J.; Price, J. R.; Todd, M. H. *J. Org. Chem.* **2012**, *77*, 949–955.
(34) Han, X.; Floreancig, P. E. *Org. Lett.* **2012**, *14*, 3808–3811.
(35) Meng, Z.; Sun, S.; Yuan, H.; Lou, H.; Liu, L. *Angew. Chem. Int. Ed.* **2013**, *53*, 543–547.
(36) Hayashi, Y.; Mukaiyama, T. *Chem. Lett.* **1987**, 1811–1814.
(37) Liu, L.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2010**, *49*, 5894–5897.
(38) Clausen, D. J.; Floreancig, P. E. *J. Org. Chem.* **2012**, *77*, 6574–6582.
(39) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.
(40) Zhai, L.; Shukla, R.; Wadumethrige, S. H.; Rathore, R. *J. Org. Chem.* **2010**, *75*, 4748–4760.
(41) Cui, Y.; Villafane, L. A.; Clausen, D. J.; Floreancig, P. E. *Tetrahedron* **2013**, *69*, 7618–7626.
(42) Lund, H. *Acta Chem. Scand.* **1957**, *11*, 491–498.
(43) Satoh, T.; Nakamura, A.; Iriuchijima, A.; Hayashi, Y.; Kubota, K.-I. *Tetrahedron* **2001**, *57*, 9689–9696.
(44) Sinha, A. K.; Sharma, A.; Swaroop, A.; Kumar, V. *Tetrahedron* **2007**, *63*, 1000–1007.
(45) Liu, S.-W.; Hsu, H.-C.; Chang, C.-H.; Tsai, H.-H. G.; Hou, D.-R. *Eur. J. Org. Chem.* **2010**, *2010*, 4771–4773.
(46) Cosner, C. C.; Cabrera, P. J.; Byrd, K. M.; Thomas, A. M. A.; Helquist, P. *Org. Lett.* **2011**, *13*, 2071–2073.
(47) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033–3035.
(48) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Can. J. Chem.* **2004**, *82*, 375–385.
(49) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284–286.
(50) Bonderoff, S. A. *Ph.D Dissertation*, 2012.
(51) Kwon, Y.; McDonald, R.; West, F. G. *Angew. Chem. Int. Ed.* **2013**, *52*, 8616–8619.
(52) Scadeng, O.; Ferguson, M. J.; West, F. G. *Org. Lett.* **2011**, *13*, 114–117.
(53) Braude, E. A.; Forbes, W. F. *J. Chem. Soc.* **1953**, 2208–2216.
(54) Toxicity data was obtained from the MSDS sheet.
(55) Newman, M. S.; Khanna, V. K. *Organic Preparations and Procedures International* **1985**, *17*, 422–423.
(56) Chandrasekhar, S.; Sumithra, G.; Yadav, J. S. *Tetrahedron Lett.* **1996**, *37*, 1645–1646.
(57) Liu, L.; Floreancig, P. E. *Org. Lett.* **2010**, *12*, 4686–4689.
(58) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339–363.
(59) Based on the price of 100 g bottles of reagent grade material from Sigma-Aldrich, 2014.

(60) Shen, Z.; Dai, J.; Xiong, J.; He, X.; Mo, W.; Hu, B.; Sun, N.; Hu, X. *Adv. Synth. Catal.* **2011**, *353*, 3031–3038.
(61) Rampal, J. B.; Berlin, D.; Edasery, J. P.; Satyamurthy, N.; van der Helm, D. *J. Org. Chem.* **1981**, *46*, 1166–1172.
(62) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Org. Chem.* **2011**, *76*, 50–56.
(63) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747–2750.
(64) Lu, S.-M.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 8920–8923.
(65) Smith, C. D.; Rosocha, G.; Mui, L.; Batey, R. A. *J. Org. Chem.* **2010**, *75*, 4716–4727.

Chapter 4

(1) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676–5688.
(2) Nakanishi, W.; West, F. G. *Curr. Opin. Drug. Discovery Dev.* **2009**, *12*, 732–751.
(3) Spencer, W. T., III; Vaidya, T.; Frontier, A. J. *Eur. J. Org. Chem.* **2013**, *2013*, 3621–3633.
(4) Tius, M. A. *Chem. Soc. Rev.* **2014**, DOI: 10.1039/c3cs60333d
(5) West, F. G.; Scadeng, O. S.; Wu, Y-K; Fradette, R. J.; Joy S. in *Comprehensive Organic Synthesis II*; Knochel, P; Molander, G. A.; Eds.; Elsevier: Oxford, **2014**.
(6) See Chapter 1 of this thesis for more detailed discussion.
(7) Miller, N. A.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *Angew. Chem. Int. Ed.* **2007**, *46*, 937–940.
(8) Winberg, K. J. University of Alberta, *Unpublished results*.
(9) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027–4029.
(10) Engel, D. A.; Lopez, S. S.; Dudley, G. B. *Tetrahedron* **2008**, *64*, 6988–6996.
(11) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429–438.
(12) Cadierno, V.; Crochet, P.; García-Garrido, S. E.; Gimeno, J. *Dalton Trans.* **2010**, *39*, 4015-4031.
(13) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Org. Chem.* **2011**, *76*, 50–56.
(14) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Am. Chem. Soc.* **2009**, *131*, 7504–7505.
(15) Rieder, C. J. *Ph.D. Dissertation*, **2010**.
(16) Hill, R. K. *Comp. Org. Synth.* **1991**, *5*, 785–826.
(17) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13972–14020.
(18) Wipf, P. *Comp. Org. Synth.* **1991**, *5*, 827–873.
(19) Martín Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939–3002.
(20) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218–224.
(21) Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149–3152.
(22) Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811–3820.

(23) Anderson, E. A.; Alexanian, E. J.; Sorensen, E. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 1998–2001.
(24) Young, W. G.; Nozaki, K.; Warner, R. *J. Am. Chem. Soc.* **1939**, 2564–2565.
(25) Leleti, R. R.; Hu, B.; Prashad, M.; Repič, O. *Tetrahedron Lett.* **2007**, *48*, 8505–8507.
(26) McCubbin, J. A.; Voth, S.; Krokhin, O. V. *J. Org. Chem.* **2011**, *76*, 8537–8542.
(27) Zheng, H.; Lejkowski, M.; Hall, D. G. *Chem. Sci.* **2011**, *2*, 1305.
(28) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2006**, *128*, 8142–8143.
(29) Morrill, C.; Beutner, G. L.; Grubbs, R. H. *J. Org. Chem.* **2006**, *71*, 7813–7825.
(30) Serra-Muns, A.; Guérinot, A.; Reymond, S.; Cossy, J. *Chem. Commun.* **2010**, *46*, 4178.
(31) Conrow, R. E. *Org. Lett.* **2006**, *8*, 2441–2443.
(32) Shekhar, S.; Trantow, B.; Leitner, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 11770–11771.
(33) Chabardes, P.; Kuntz, E.; Varagnat, J. *Tetrahedron* **1977**, *33*, 1775–1783.
(34) Hosogai, T.; Fujita, Y.; Ninagawa, Y.; Nishida, T. *Chem. Lett.* **1982**, 357–360.
(35) Matsubara, S.; Okazoe, T.; Oshima, K.; Takai, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 844–849.
(36) Bellemin-Laponnaz, S.; Gisie, H.; Le Ny, J. P.; Osborn, J. A. *Angew. Chem. Int. Ed.* **1997**, *36*, 976–979.
(37) Jacob, J.; Espenson, J. H.; Jensen, J. H.; Gordon, M. S. *Organometallics* **1998**, *17*, 1835–1840.
(38) Bellemin-Laponnaz, S.; Le Ny, J. P.; Osborn, J. A. *Tetrahedron Lett.* **2000**, *41*, 1549–1552.
(39) Morrill, C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 2842–2843.
(40) Herrmann, A. T.; Saito, T.; Stivala, C. E.; Tom, J.; Zakarian, A. *J. Am. Chem. Soc.* **2010**, *132*, 5962–5963.
(41) Xie, Y.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2013**, *52*, 625–628.
(42) Li, C.-J.; Wang, D.; Chen, D.-L. *J. Am. Chem. Soc.* **1995**, 12867–12868.
(43) Dilli, S.; Patsalides, E. *Aust. J. Chem.* **1976**, *29*, 2369–2379.
(44) Boiadjiev, S. E.; Lightner, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 11328–11339.
(45) Curran, D. P.; Suh, Y.-G. *J. Am. Chem. Soc.* **1984**, *106*, 5002–5004.
(46) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6984–6986.
(47) Nicolaou, K. C.; Kang, Q.; Ng, S. Y.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2010**, *132*, 8219–8222.
(48) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2285–2288.
(49) Du, X.; Song, F.; Lu, Y.; Chen, H.; Liu, Y. *Tetrahedron* **2009**, *65*, 1839–1845.
(50) Mandai, T.; Hashio, S.; Goto, J.; Kawada, M. *Tetrahedron Lett.* **1981**, *22*,

2187–2190.
(51) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3021–3024.
(52) Eliel, E. L.; Freeman, J. P. *Org. Synth.* **1953**, *33*, 7–10.
(53) Shen, Z.-L.; Ji, S.-J. *Synth. Commun.* **2009**, *39*, 775–791.
(54) Weber, W. M.; Hunsaker, L. A.; Abcouwer, S. F.; Deck, L. M.; Vander Jagt, D. L. *Bioorg. Med. Chem.* **2005**, *13*, 3811–3820.

Chapter 5

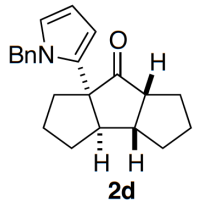
(1) Rieder, C. J. *Ph.D. Dissertation*, **2010**.
(2) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033–3035.
(3) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Can. J. Chem.* **2004**, *82*, 375–385.
(4) Song, D.; Rostami, A.; West, F. G. *J. Am. Chem. Soc.* **2007**, *129*, 12019–12022.
(5) Rostami, A.; Wang, Y.; Arif, A. M.; McDonald, R.; West, F. G. *Org. Lett.* **2007**, *9*, 703–706.
(6) Scadeng, O.; Ferguson, M. J.; West, F. G. *Org. Lett.* **2011**, *13*, 114–117.
(7) Dhoro, F.; Tius, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 12472–12473.
(8) Dhoro, F.; Kristensen, T. E.; Stockmann, V.; Yap, G. P. A.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 7256–7257.
(9) Yen-Ku, W.; McDonald, R.; West, F. G. *Org. Lett.* **2011**, *13*, 3584–3587.
(10) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2097–2100.
(11) Cui, Y.; Villafane, L. A.; Clausen, D. J.; Floreancig, P. E. *Tetrahedron* **2013**, *69*, 7618–7626.
(12) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Org. Chem.* **2011**, *76*, 50–56.
(13) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Am. Chem. Soc.* **2009**, *131*, 7504–7505.
(14) Bolm, C. *Coordination Chemistry Reviews,* **2003**, *237*, 245–256.

Appendix A: Selected NMR Spectra

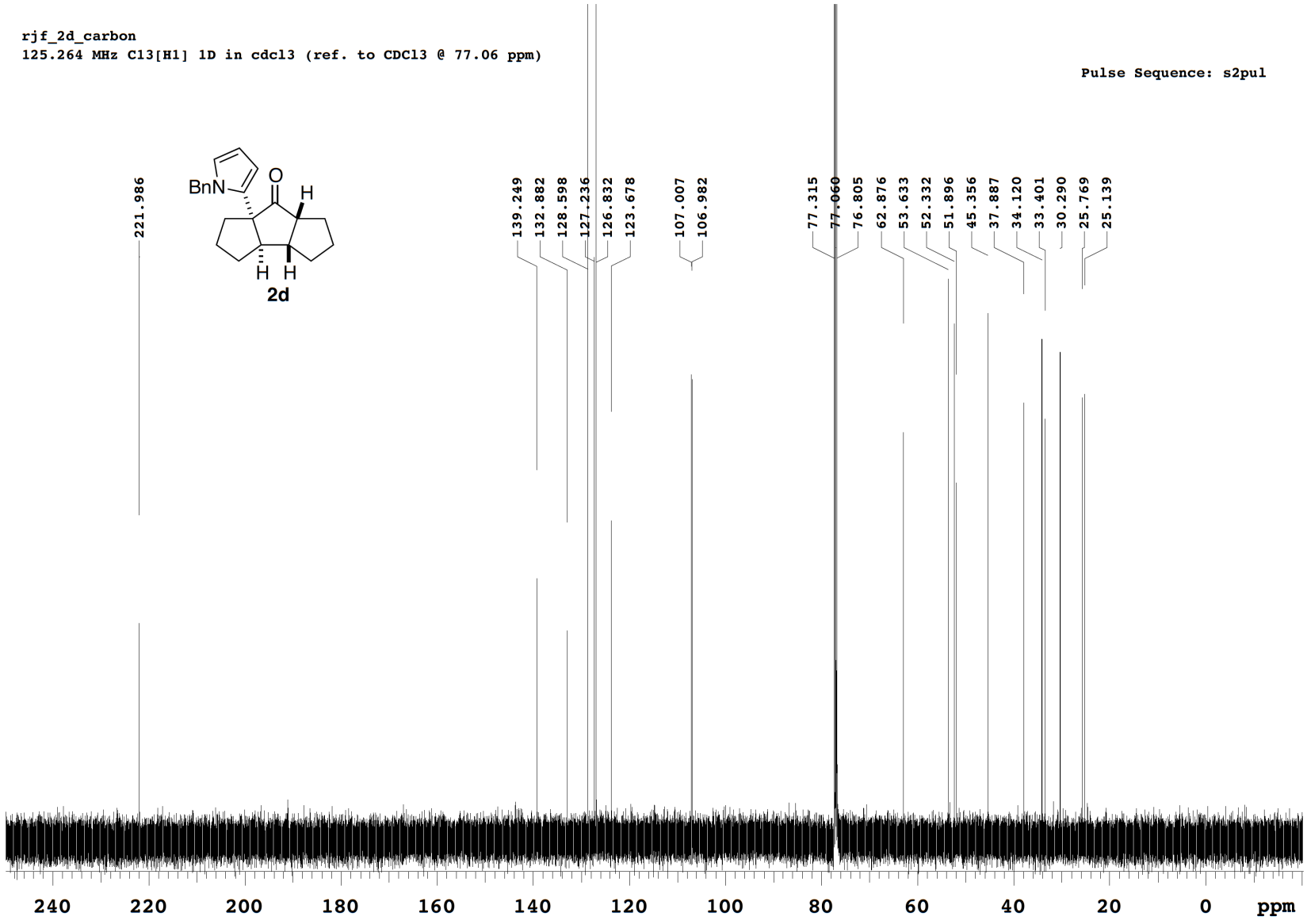
(Chapter 2)

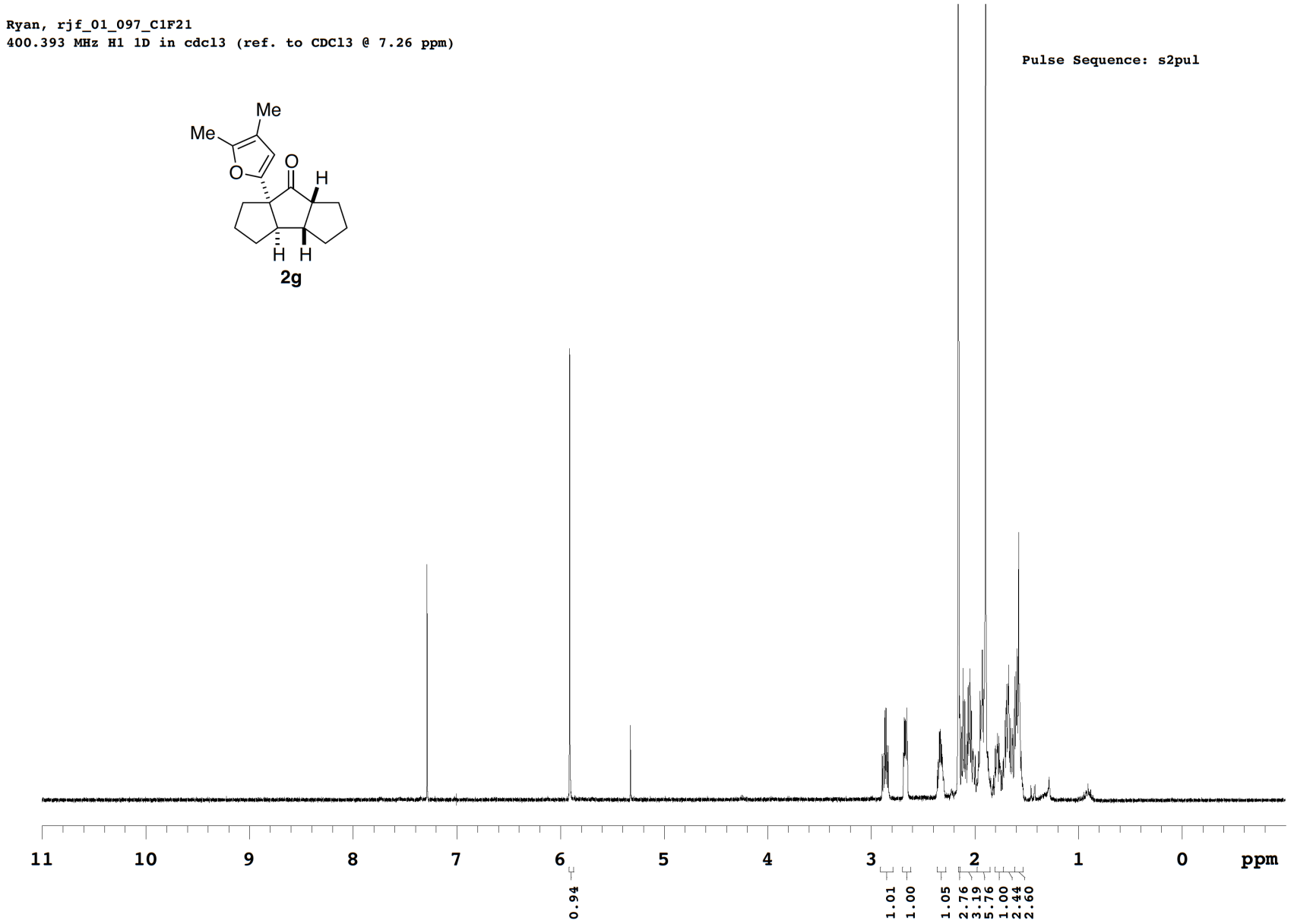
rjf_2d_proton
498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

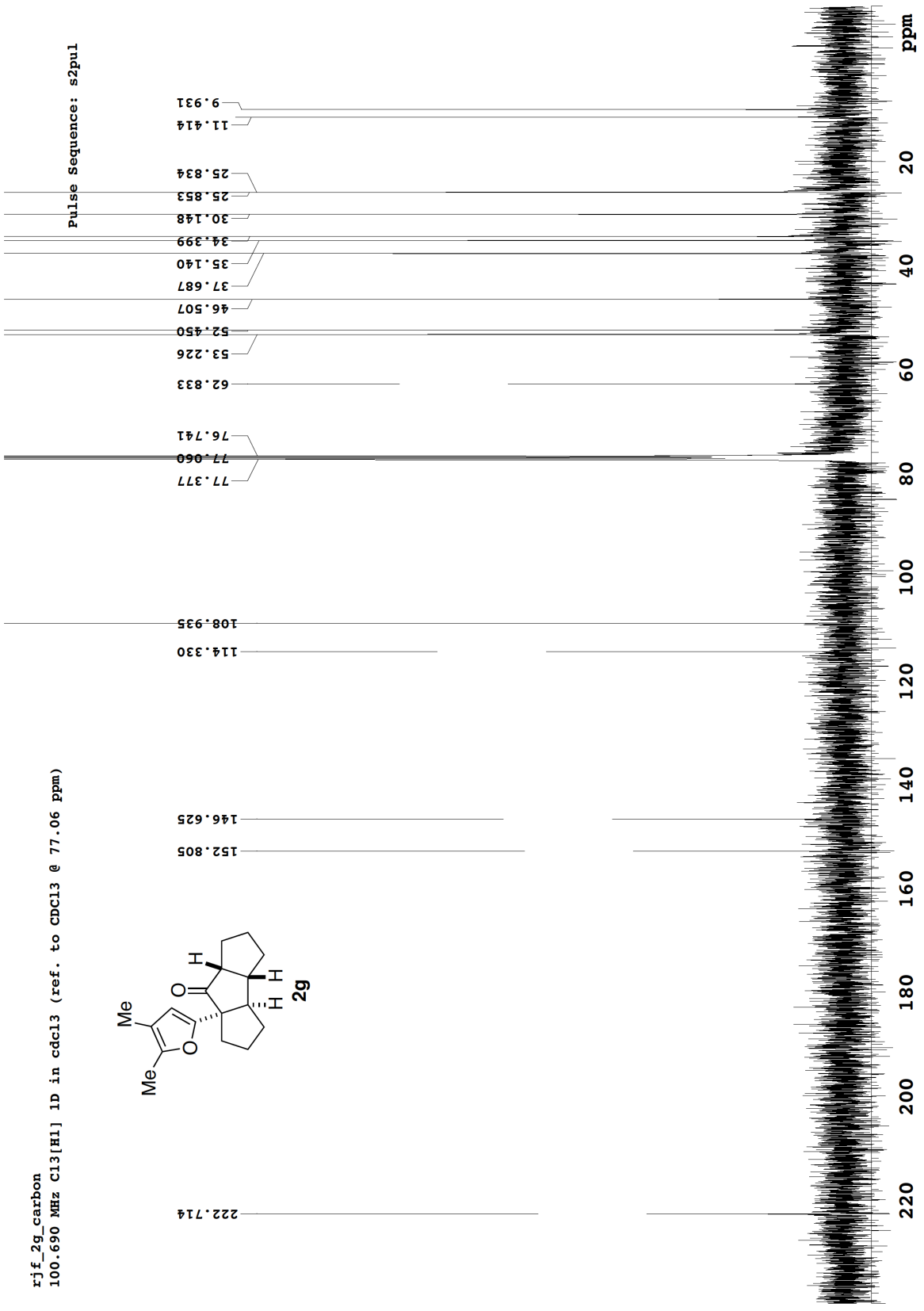
Pulse Sequence: s2pul



2d

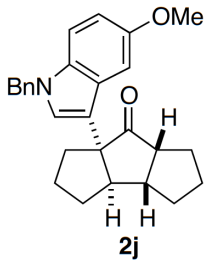

rjf_2d_carbon
125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: s2pul
BnN
O
H
H H
2d
221.986
139.249
132.882
128.598
127.236
126.832
123.678
107.007
106.982
77.315
77.060
76.805
62.876
53.633
52.332
51.896
45.356
37.887
34.120
33.401
30.290
25.769
25.139
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Ryan, rjf_01_097_C1F21
400.393 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
Pulse Sequence: s2pul
Me
Me
O
O
H
H H
2g
11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.94
1.01 1.00 1.05 2.76 3.19 5.76 1.00 2.44 2.60

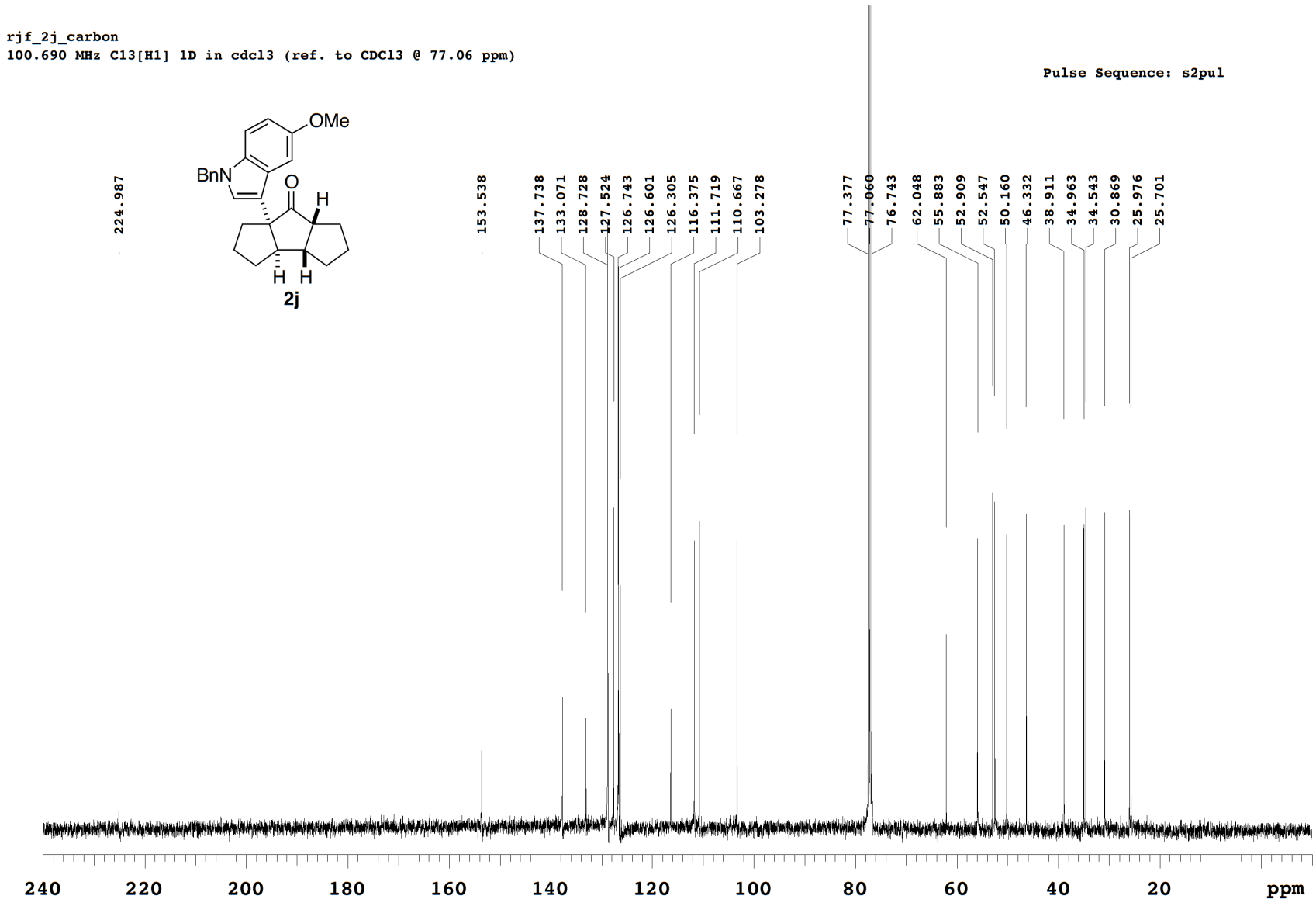

rjf_2g_carbon
100.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: s2pul
222.714
152.805
146.625
114.330
108.935
77.377
77.060
76.741
62.833
53.226
52.450
46.507
37.687
35.140
34.399
30.148
25.853
25.834
11.414
9.931
Me
Me
O
O
H
H
H
2g
ppm
220
200
180
160
140
120
100
80
60
40
20

rjf_2j_proton
400.393 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: s2pul

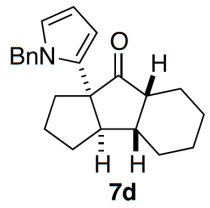


2j

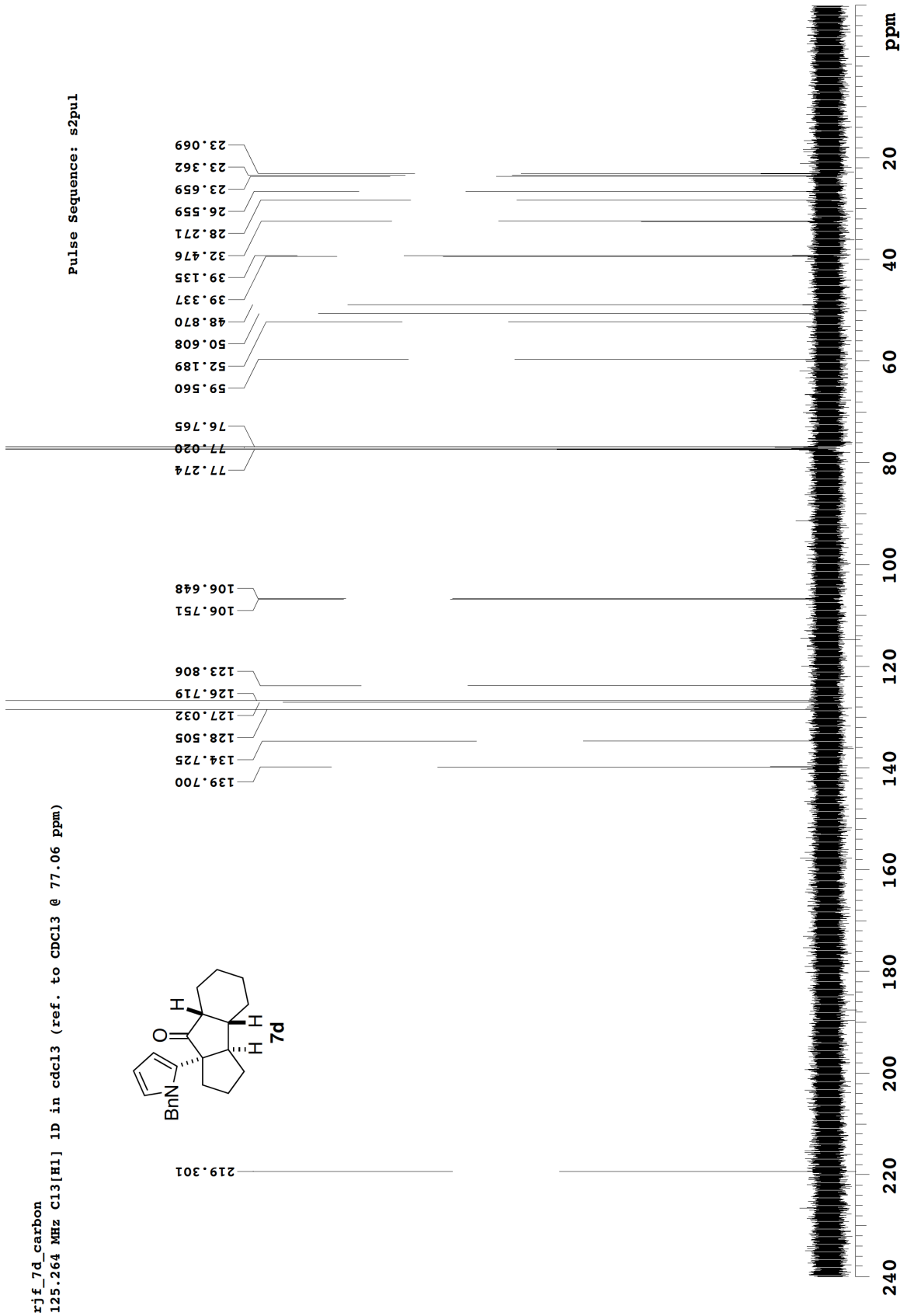

rjf_2j_carbon
100.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: s2pul
OMe
BnN
O
H
H H
2j
224.987
153.538
137.738
133.071
128.728
127.524
126.743
126.601
126.305
116.375
111.719
110.667
103.278
77.377
77.060
76.743
62.048
55.883
52.909
52.547
50.160
46.332
38.911
34.963
34.543
30.869
25.976
25.701
240
220
200
180
160
140
120
100
80
60
40
20
ppm

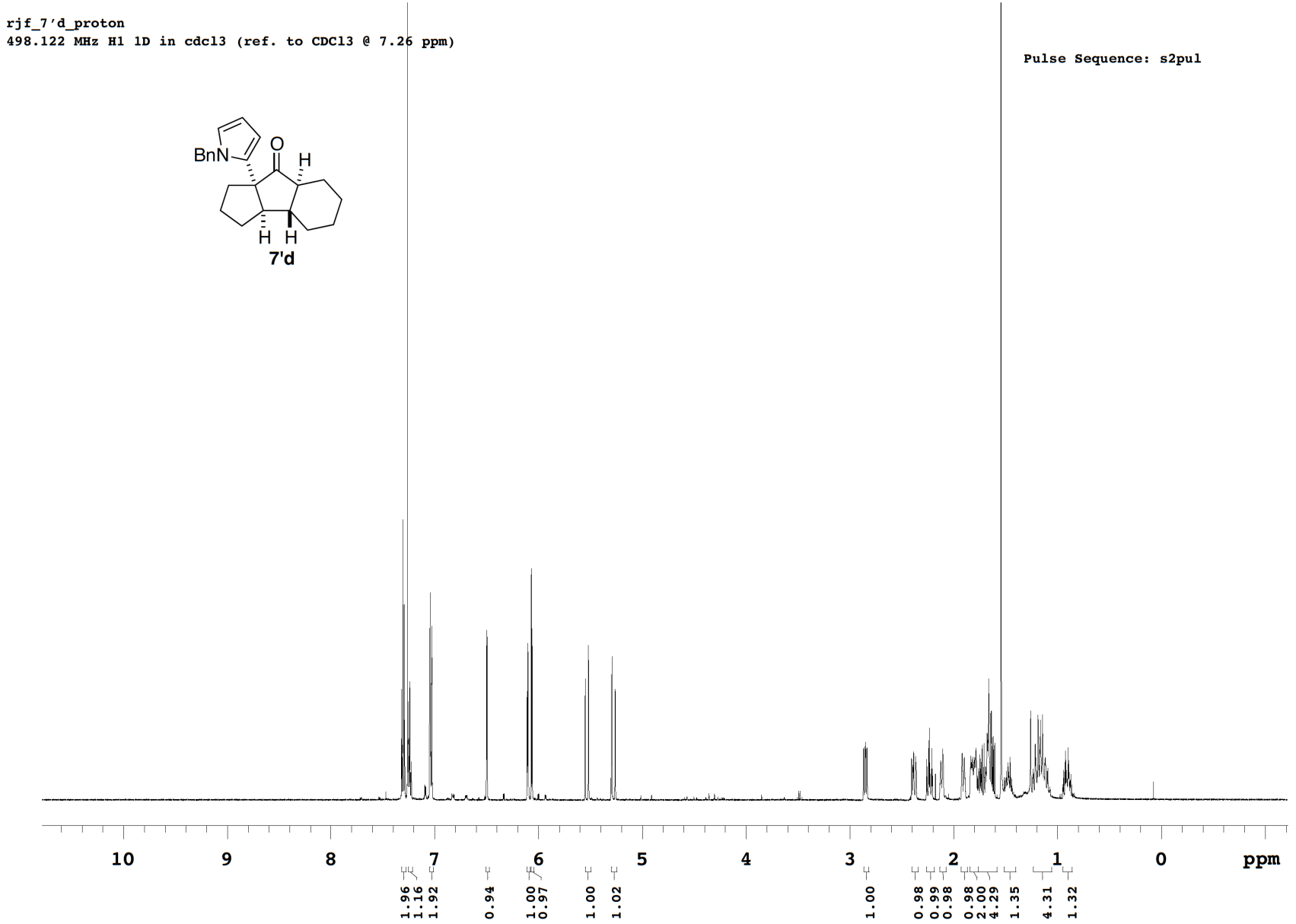
rjf_7d_proton
498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: s2pul



7d


rjf_7d_carbon
125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: s2pul
219.301
139.700
134.725
128.505
127.032
126.719
123.806
106.751
106.648
77.274
77.020
76.765
59.560
52.189
50.608
48.870
39.337
39.135
32.476
28.271
26.559
23.659
23.362
23.069
BnN
O
H
H
H
7d
ppm
240
220
200
180
160
140
120
100
80
60
40
20


rjf_7'd_proton
498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
Pulse Sequence: s2pul
BnN
O
H
H H
7'd
10 9 8 7 6 5 4 3 2 1 0 ppm
1.96 1.16 1.92 0.94 1.00 0.97 1.00 1.02 1.00 0.98 0.99 0.98 0.98 2.00 4.29 1.35 4.31 1.32

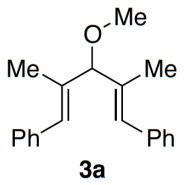
rjf_7'd_carbon
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: s2pul
215.566
139.355
134.757
128.507
127.053
126.824
124.111
106.352
106.967
77.254
77.000
76.746
60.195
52.372
52.124
51.486
43.376
35.387
32.073
29.659
26.218
25.909
25.115
24.959
BnN
O
H
H
H
7'd

Appendix B: Selected NMR Spectra

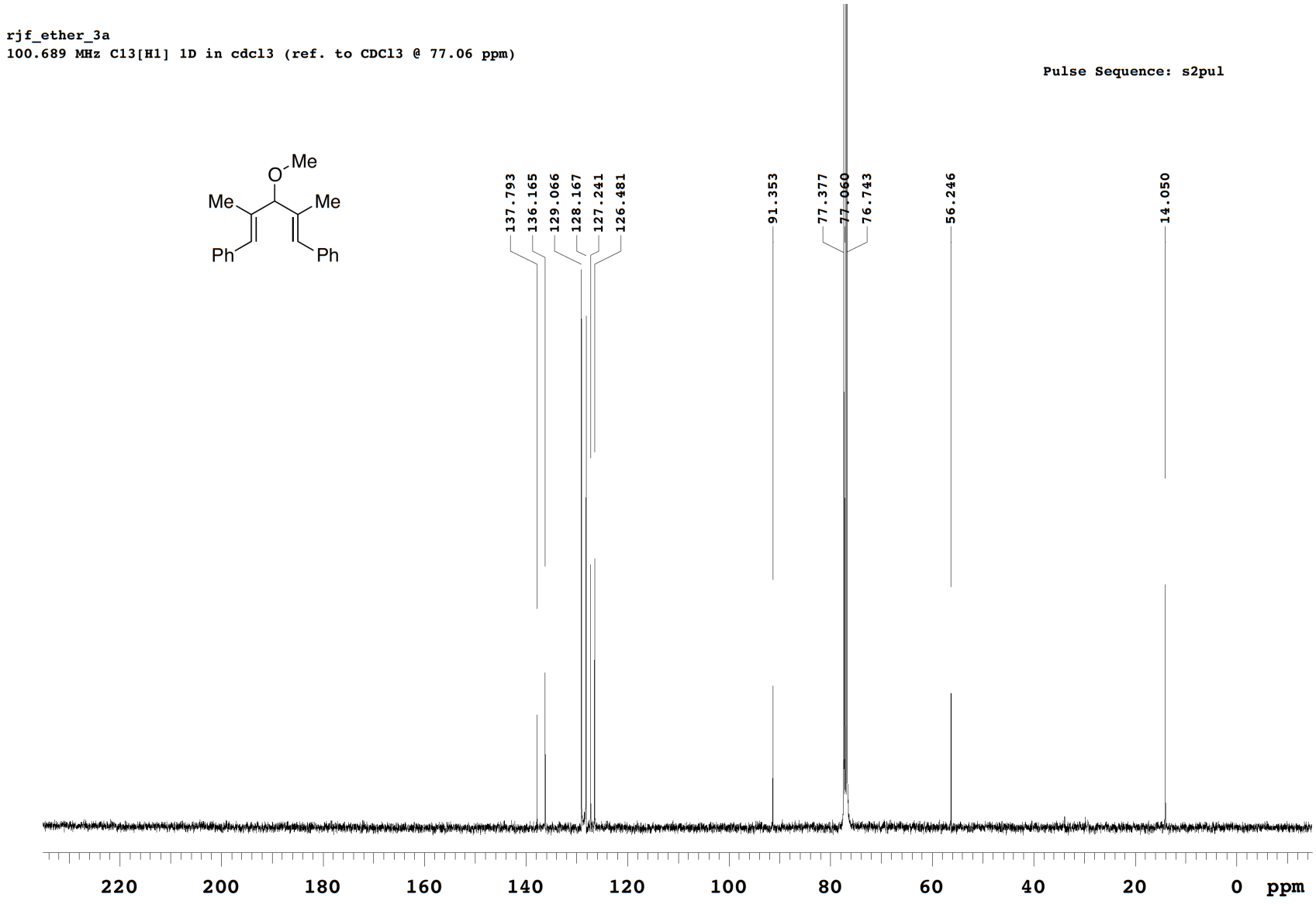
(Chapter 3)

rjf_ether_3a
400.392 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: PRESAT

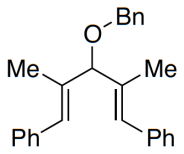


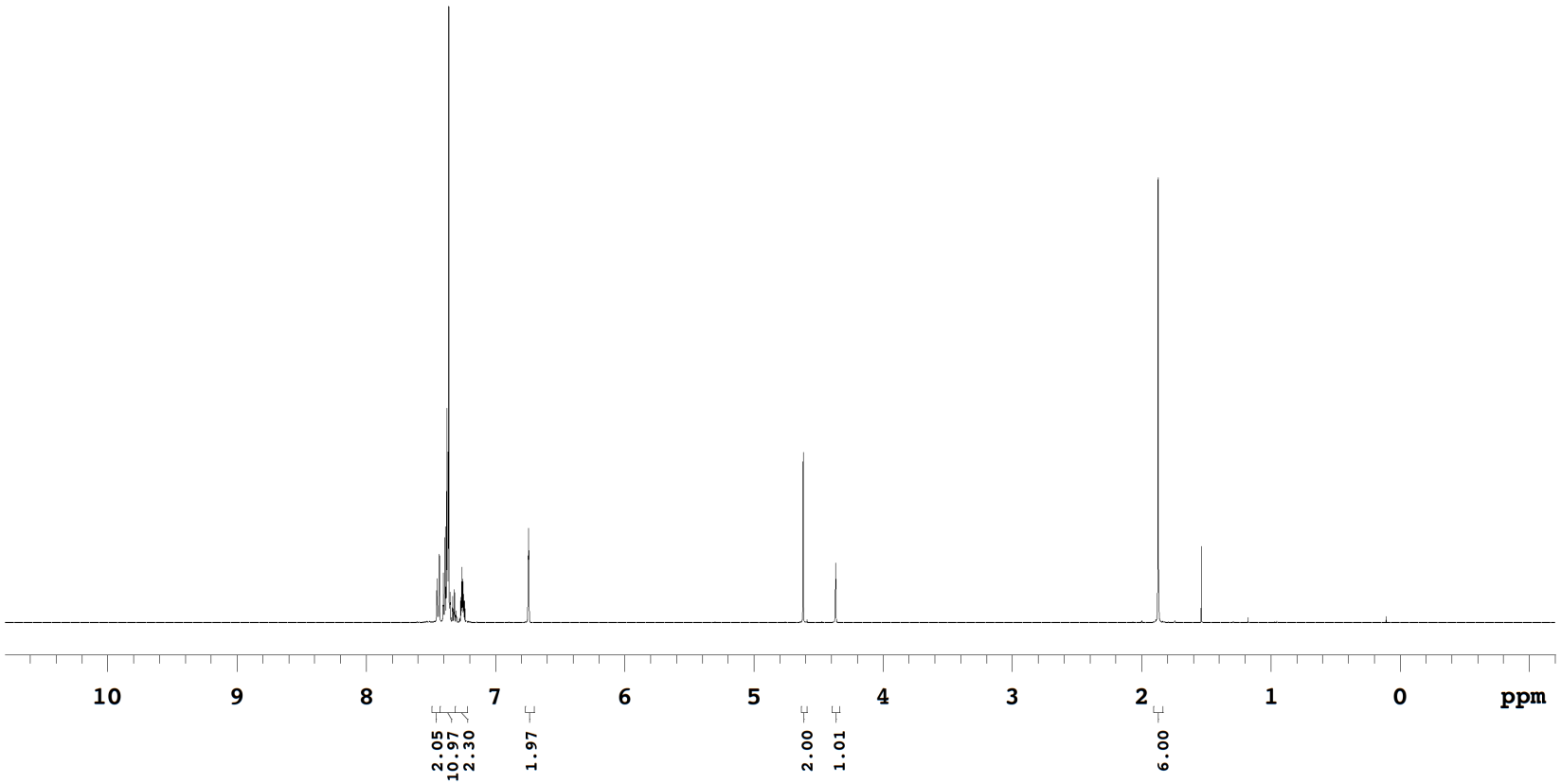
3a


rjf_ether_3a
100.689 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: s2pul
Me
O
Me
Me
Ph
Ph
137.793
136.165
129.066
128.167
127.241
126.481
91.353
77.377
77.060
76.743
56.246
14.050
220
200
180
160
140
120
100
80
60
40
20
0
ppm

rjf_ether_3e
498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

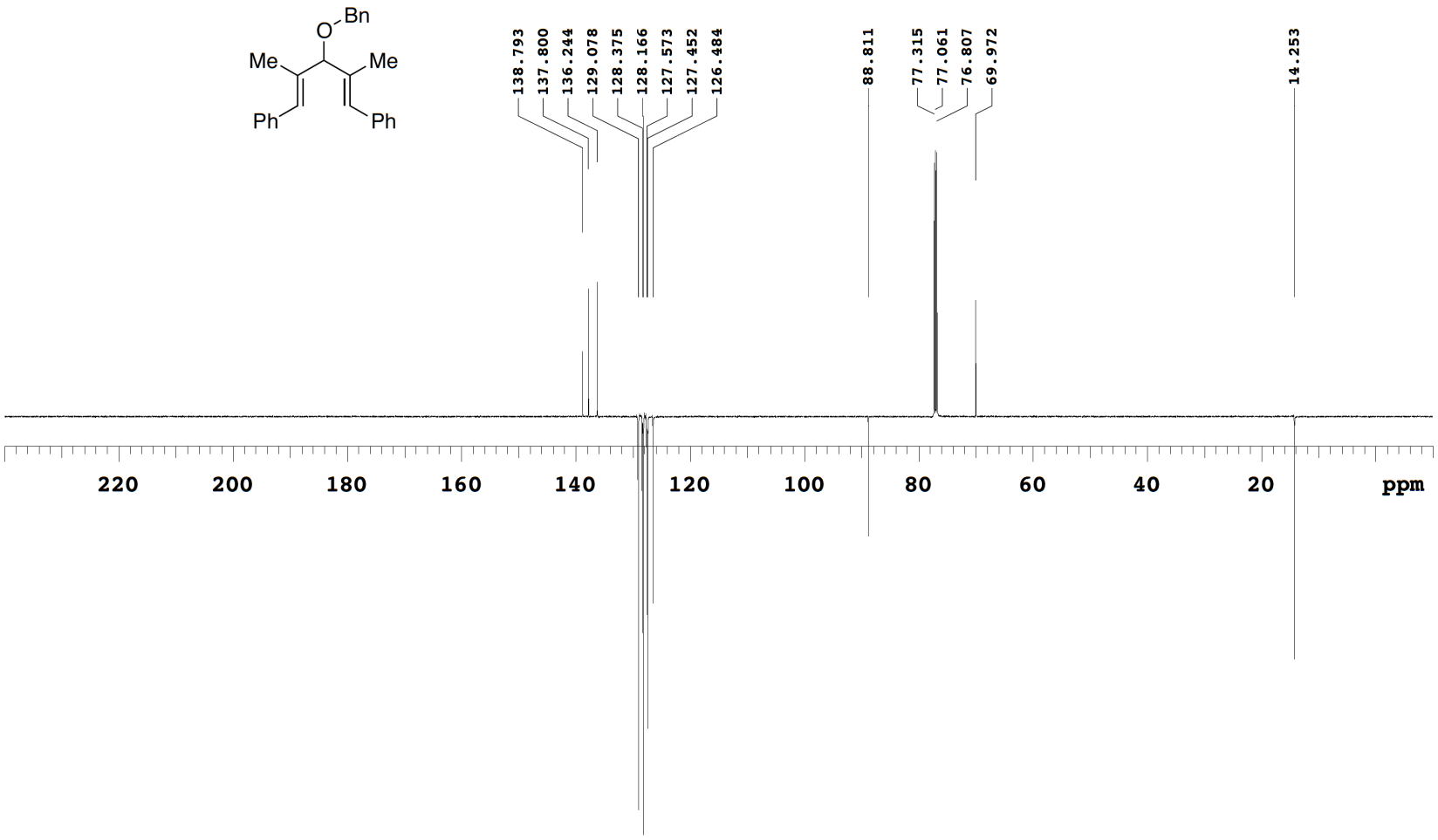
Pulse Sequence: s2pul





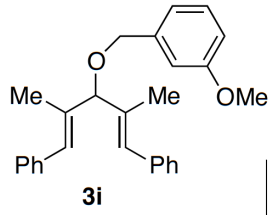
rjf_ether_3e
125.690 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal

Pulse Sequence: APT_ad

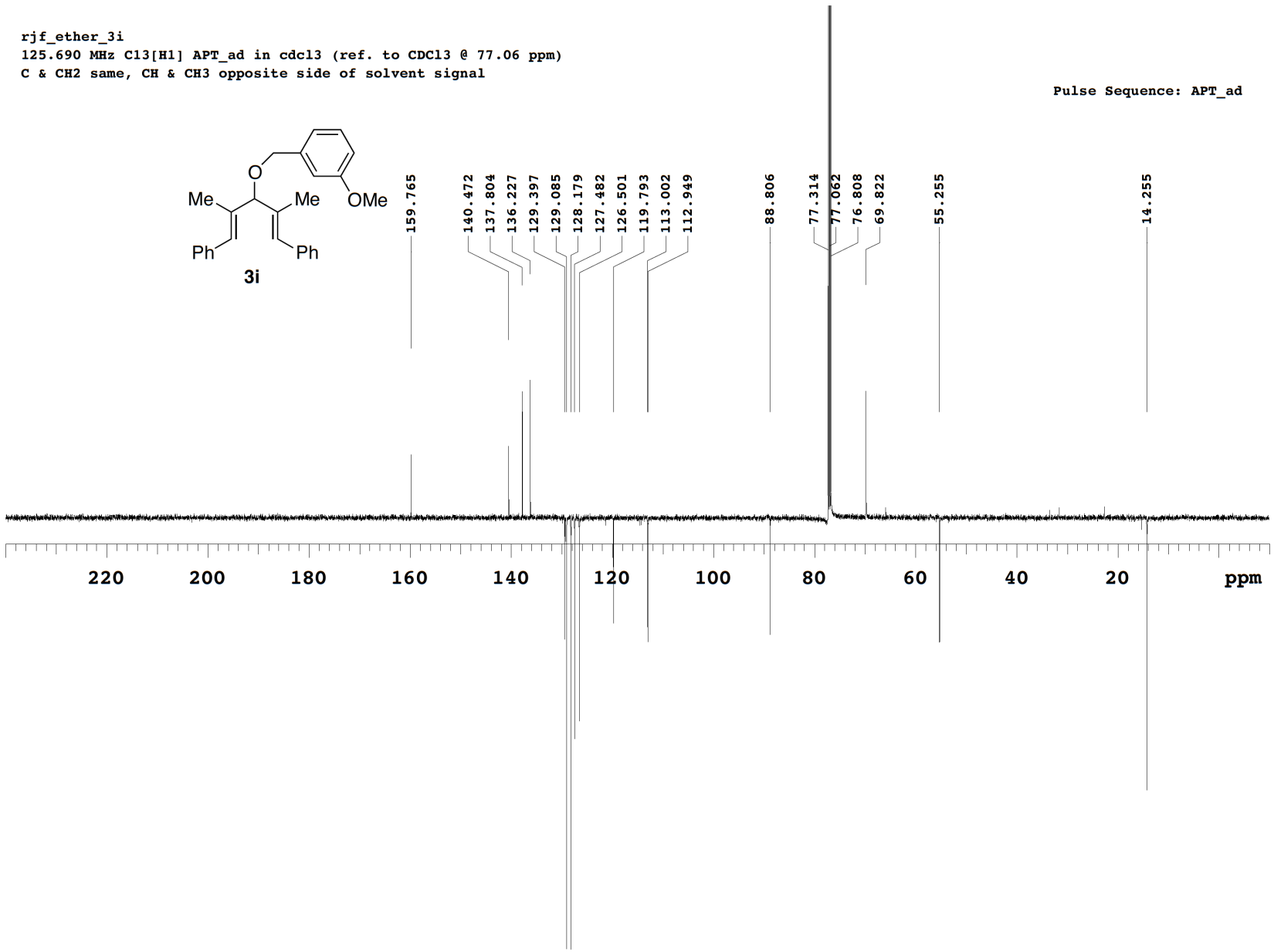


rjf_ether_3i
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: PRESAT

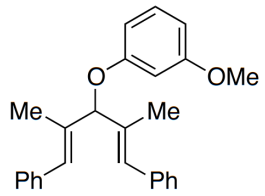


3i

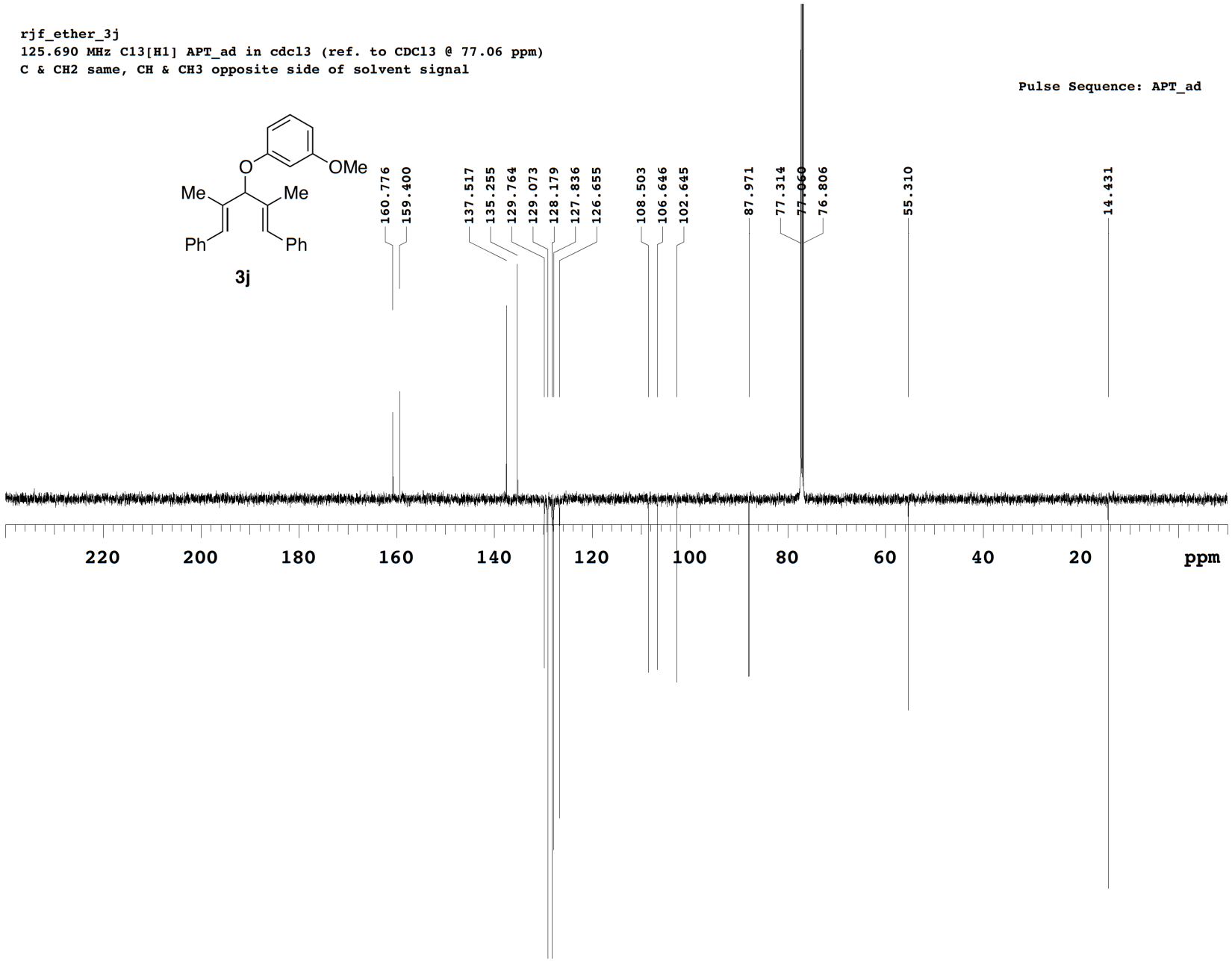

rjf_ether_3i
125.690 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal
Pulse Sequence: APT_ad
O
Me
Me
OMe
Ph
Ph
3i
159.765
140.472
137.804
136.227
129.397
129.085
128.179
127.482
126.501
119.793
113.002
112.949
88.806
77.314
77.062
76.808
69.822
55.255
14.255
220
200
180
160
140
120
100
80
60
40
20
ppm

rjf_ether_3j
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: PRESAT

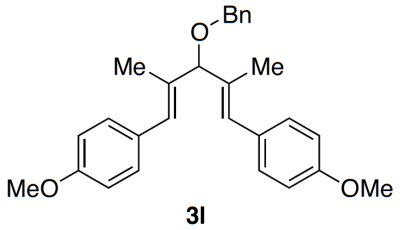


3j

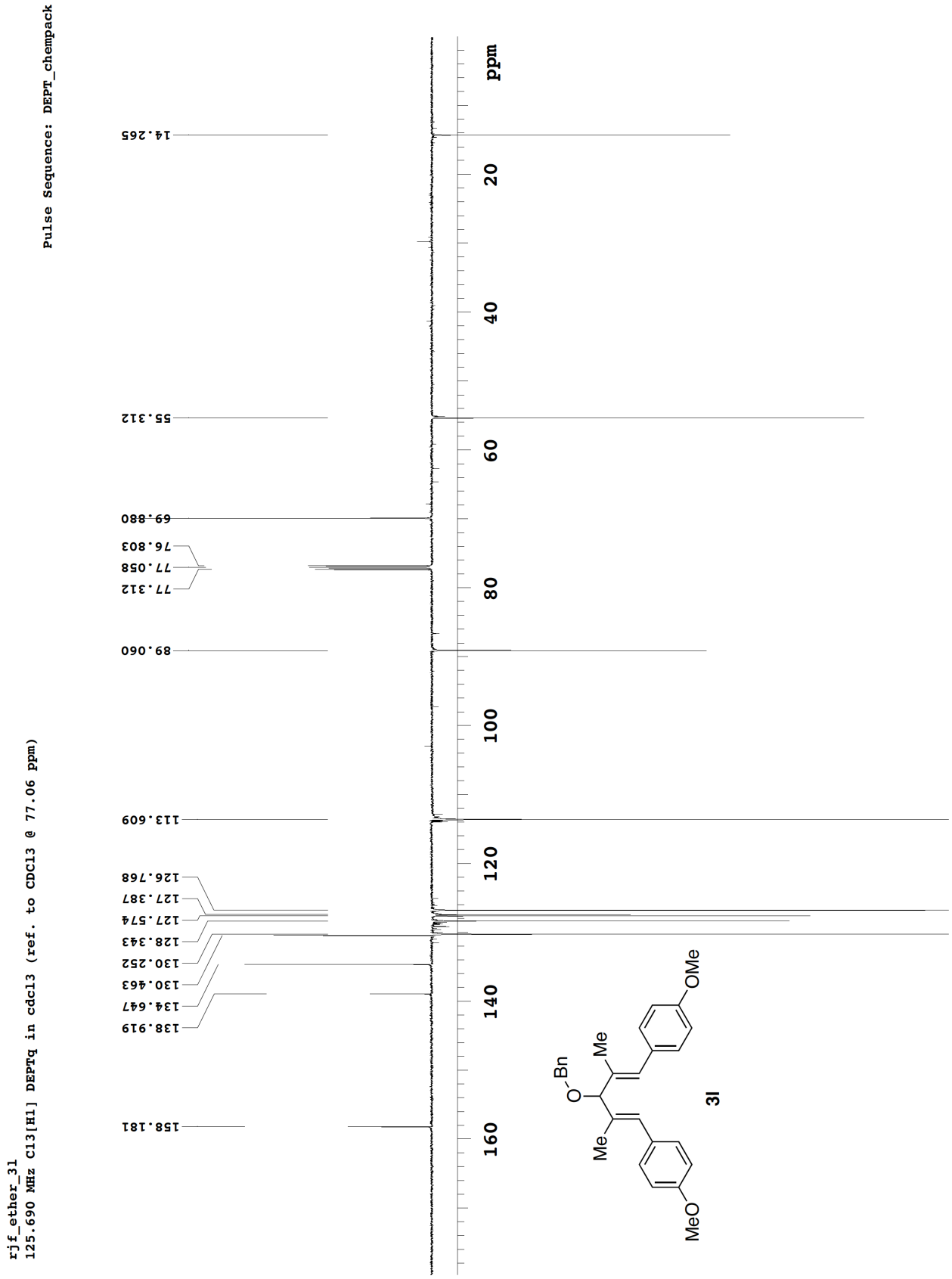

rjf_ether_3j
125.690 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal
Pulse Sequence: APT_ad
O
OMe
Me
Me
Ph
Ph
3j
160.776
159.400
137.517
135.255
129.764
129.073
128.179
127.836
126.655
108.503
106.646
102.645
87.971
77.314
77.060
76.806
55.310
14.431
220
200
180
160
140
120
100
80
60
40
20
ppm

rjf_ether_3l
399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: s2pul

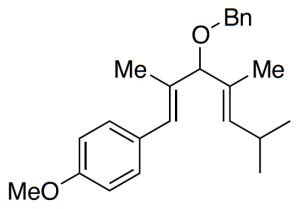


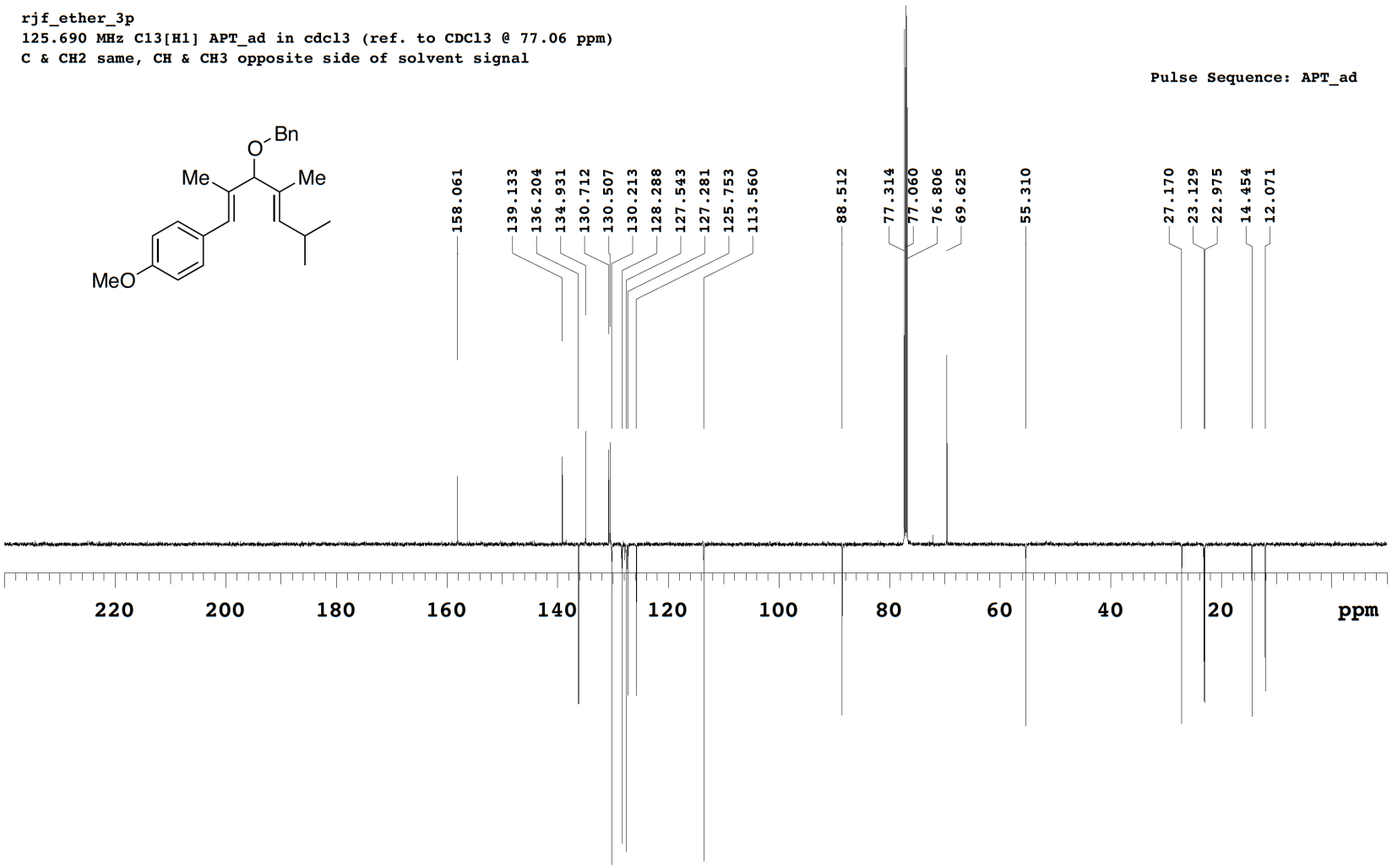
3l


rjf_ether_31
125.690 MHz C13[H1] DEPTq in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: DEPT_chempack
14.265
55.312
69.880
76.803
77.058
77.312
89.060
113.609
126.768
127.387
127.574
128.343
130.252
130.463
134.647
138.919
158.181
ppm
20
40
60
80
100
120
140
160
OMe
Me
O
Bn
Me
MeO
3l

rjf_ether_3p
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

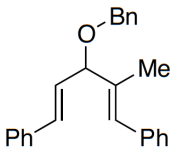
Pulse Sequence: PRESAT



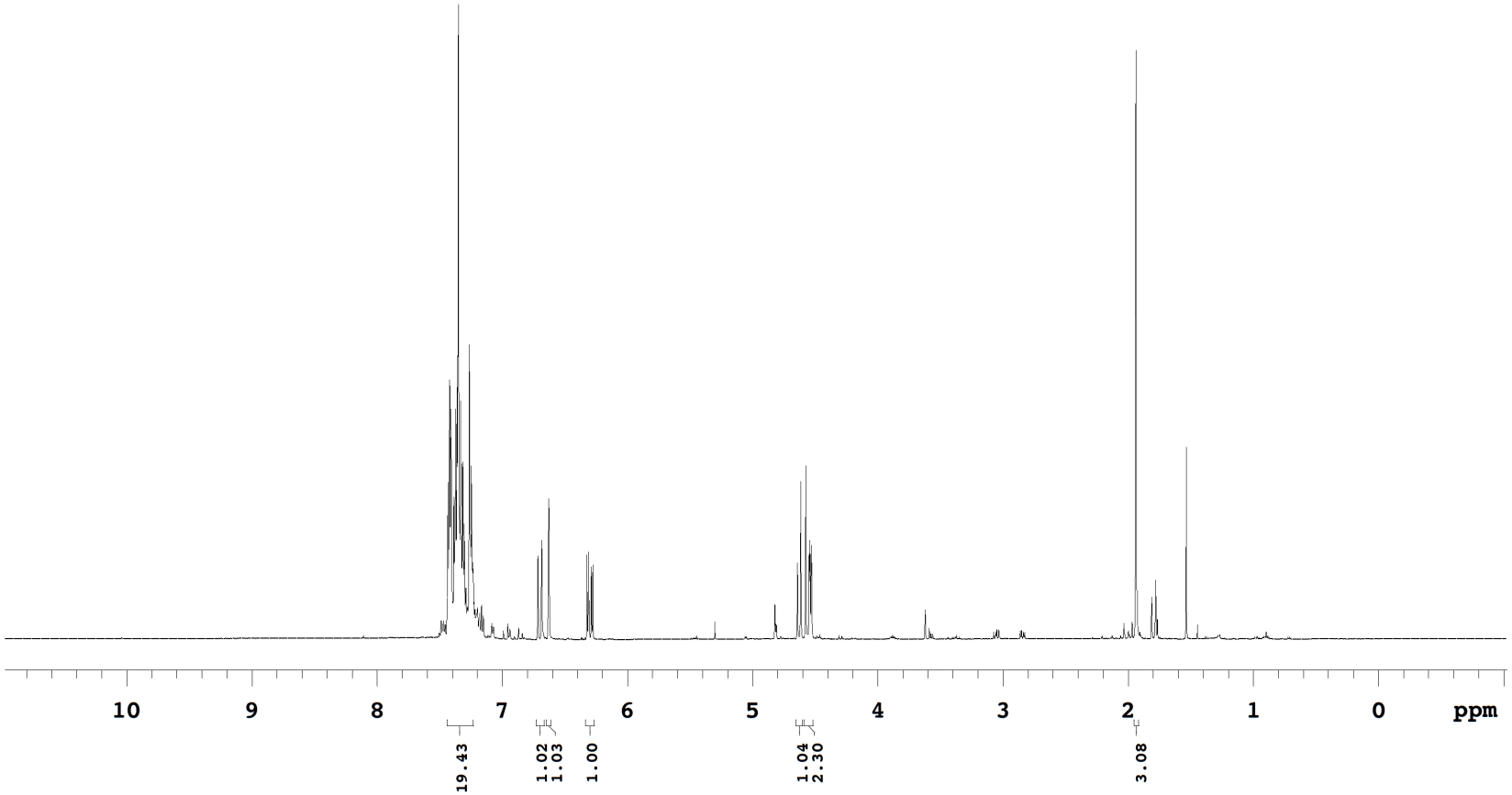

rjf_ether_3p
125.690 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal
Pulse Sequence: APT_ad
O
Bn
Me
Me
MeO
158.061
139.133
136.204
134.931
130.712
130.507
130.213
128.288
127.543
127.281
125.753
113.560
88.512
77.314
77.060
76.806
69.625
55.310
27.170
23.129
22.975
14.454
12.071
220
200
180
160
140
120
100
80
60
40
20
ppm

rjf_ether_3s
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: PRESAT

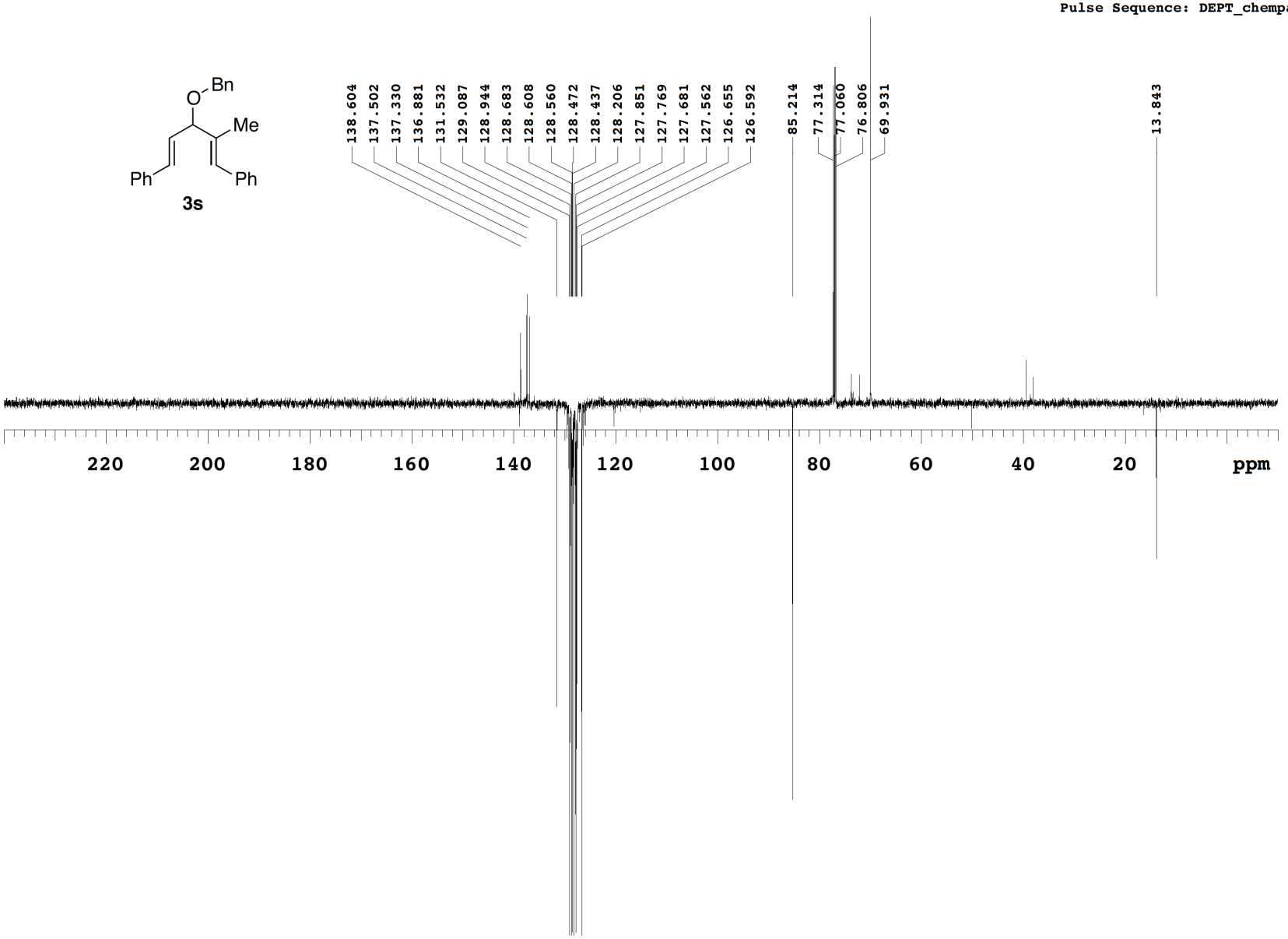


3s



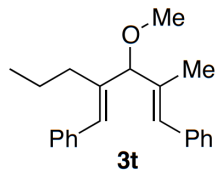
rjf_ether_3s
125.690 MHz C13[H1] DEPTq in cdcl3 (ref. to CDCl3 @ 77.06 ppm)

Pulse Sequence: DEPT_chempack

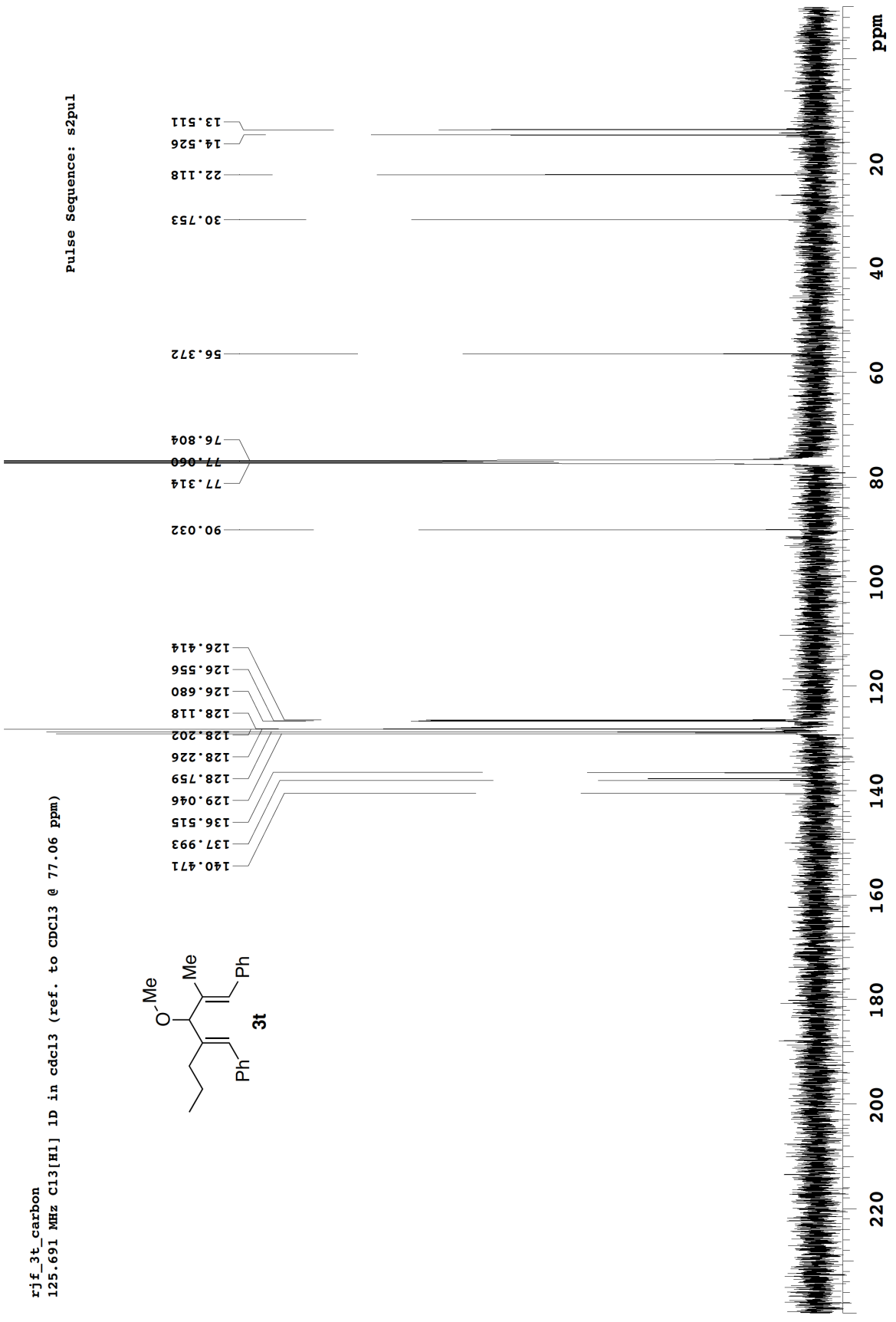


rjf_3t_proton
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: PRESAT

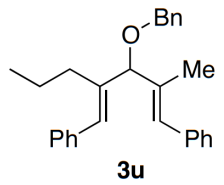


3t

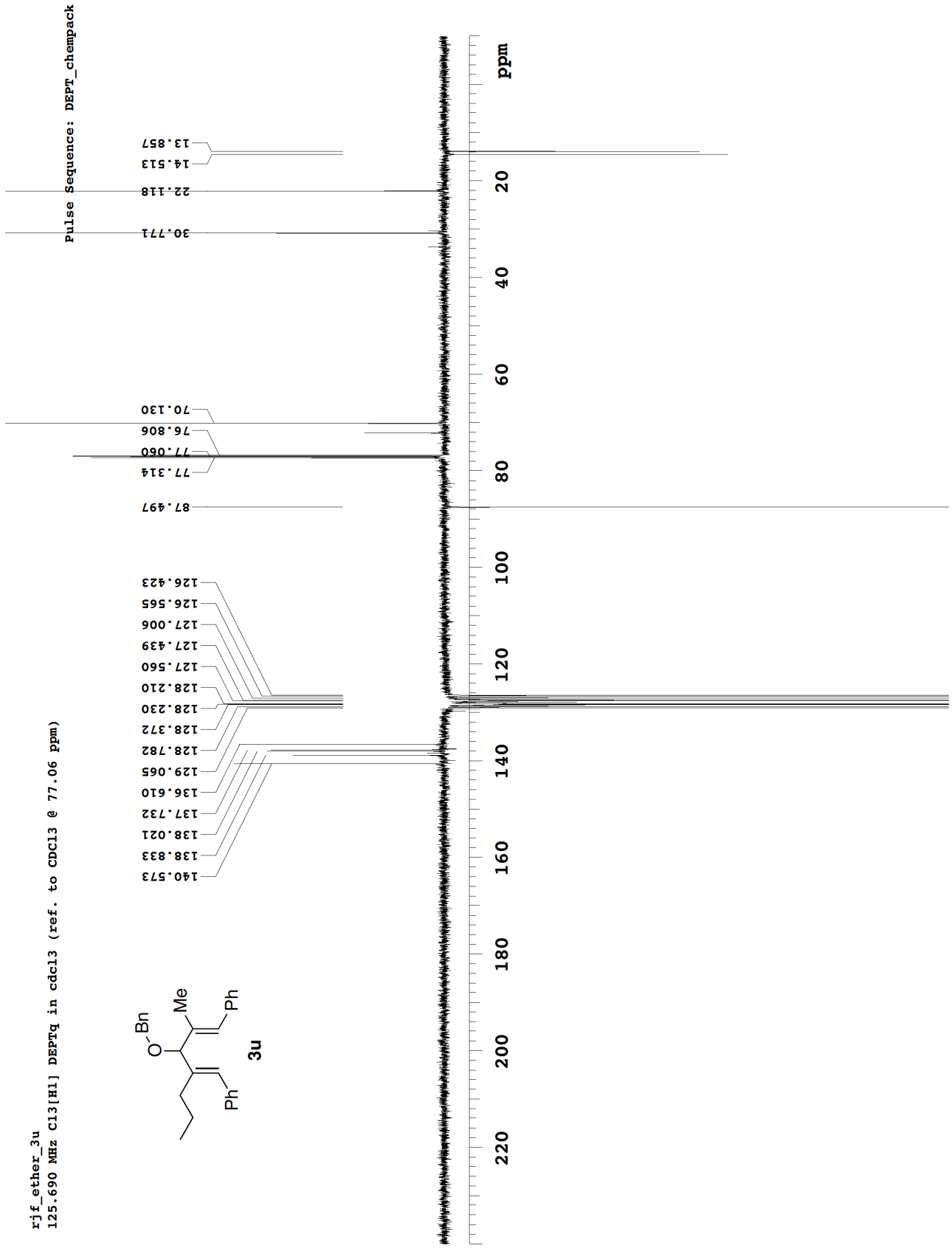

rjf_3t_carbon
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: s2pul
13.511
14.526
22.118
30.753
56.372
76.804
77.060
77.314
90.032
126.414
126.556
126.680
128.118
128.202
128.226
128.759
129.046
136.515
137.993
140.471
Me
O
Me
Ph
Ph
3t
ppm
220
200
180
160
140
120
100
80
60
40
20

rjf_ether_3u
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: PRESAT

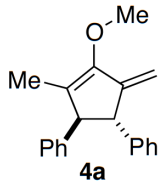


3u


rjf_ether_3u
125.690 MHz C13[H1] DEPTq in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: DEPT_chempack
13.857
14.513
22.118
30.771
70.130
76.806
77.060
77.314
87.497
126.423
126.565
127.006
127.439
127.560
128.210
128.230
128.372
128.782
129.065
136.610
137.732
138.021
138.833
140.573
Bn
O
Me
Ph
Ph
3u
ppm
20
40
60
80
100
120
140
160
180
200
220

rjf_enolether_4a
498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

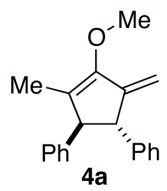
Pulse Sequence: s2pul



4a

rjf_enolether_4a
125.692 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal

Pulse Sequence: APT_ad

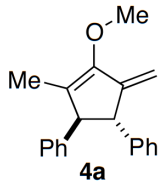


4a

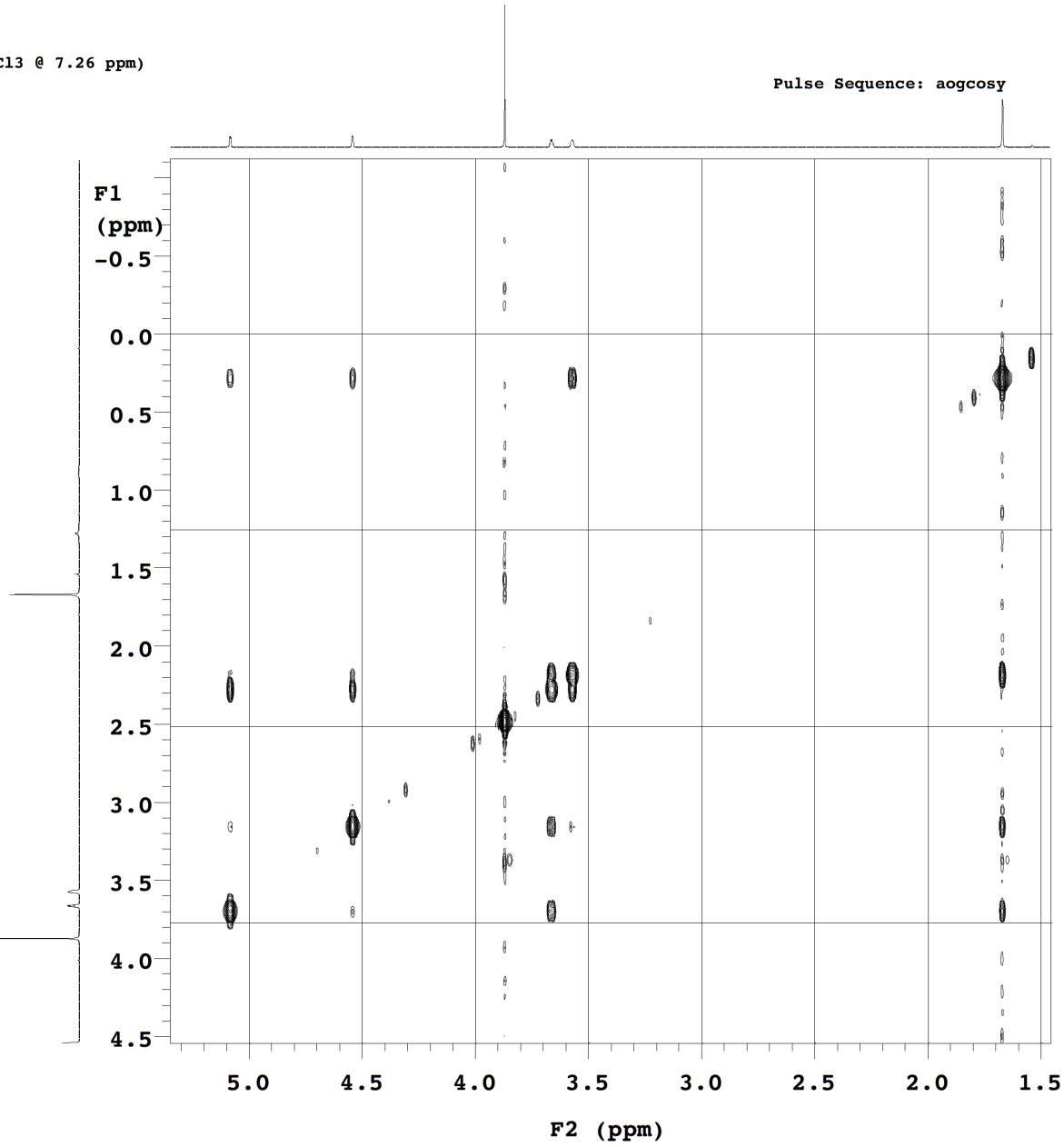
rjf_enolether_4a
499.815 MHz H1 aogcosy in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Temp. 27.7 C / 300.9 K
Operator: westnmr
INOVA-500 "d602"

Relax. delay 1.000 sec
Acq. time 1.000 sec
Width 6009.6 Hz
2D Width 6009.6 Hz
Single scan
365 increments
OBSERVE H1, 499.8124105 MHz
DATA PROCESSING
Sq. sine bell 0.160 sec
F1 DATA PROCESSING
Sq. sine bell 0.026 sec
FT size 8192 x 1024
Total time 12 min



4a

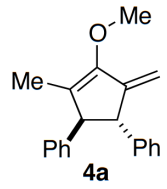


rjf_enolether_4a
499.814 MHz H1 gHSQC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm)

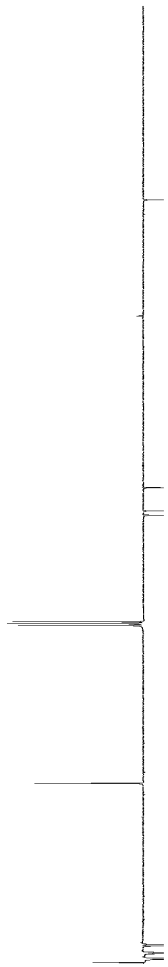
Pulse Sequence: gHSQC

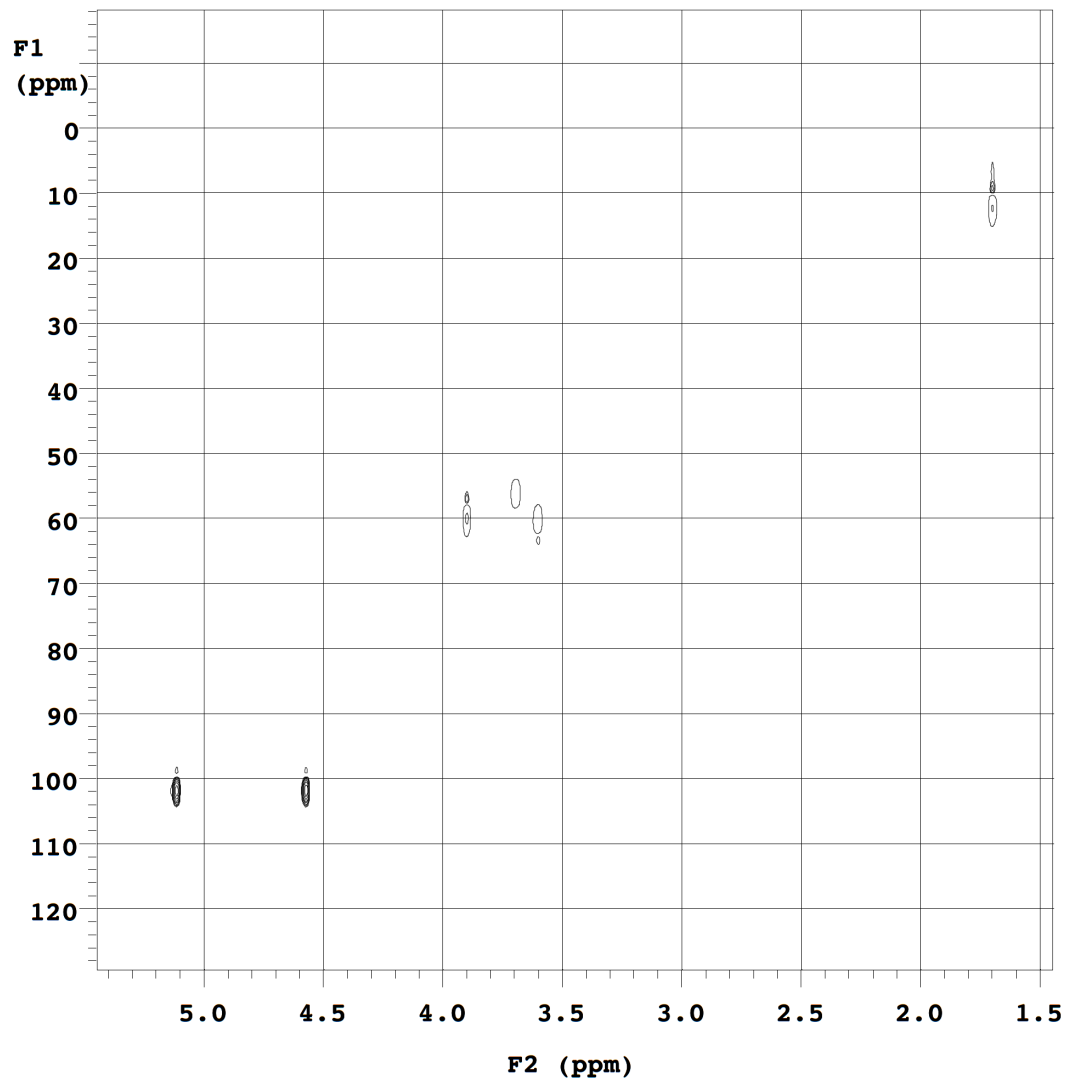
Temp. 27.7 C / 300.9 K
Operator: westnmr
INOVA-500 "d602"

Relax. delay 1.750 sec
Acq. time 0.250 sec
Width 6009.6 Hz
2D Width 33755.3 Hz
2 repetitions
2 x 106 increments
OBSERVE H1, 499.8123944 MHz
DECOUPLE C13, 125.6923360 MHz
Power 34 dB
on during acquisition
off during delay
W40_colddual modulated
DATA PROCESSING
Sq. sine bell 0.125 sec
Shifted by -0.125 sec
F1 DATA PROCESSING
Sq. sine bell 0.003 sec
Shifted by -0.003 sec
FT size 8192 x 1024
Total time 14 min



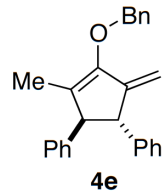
4a



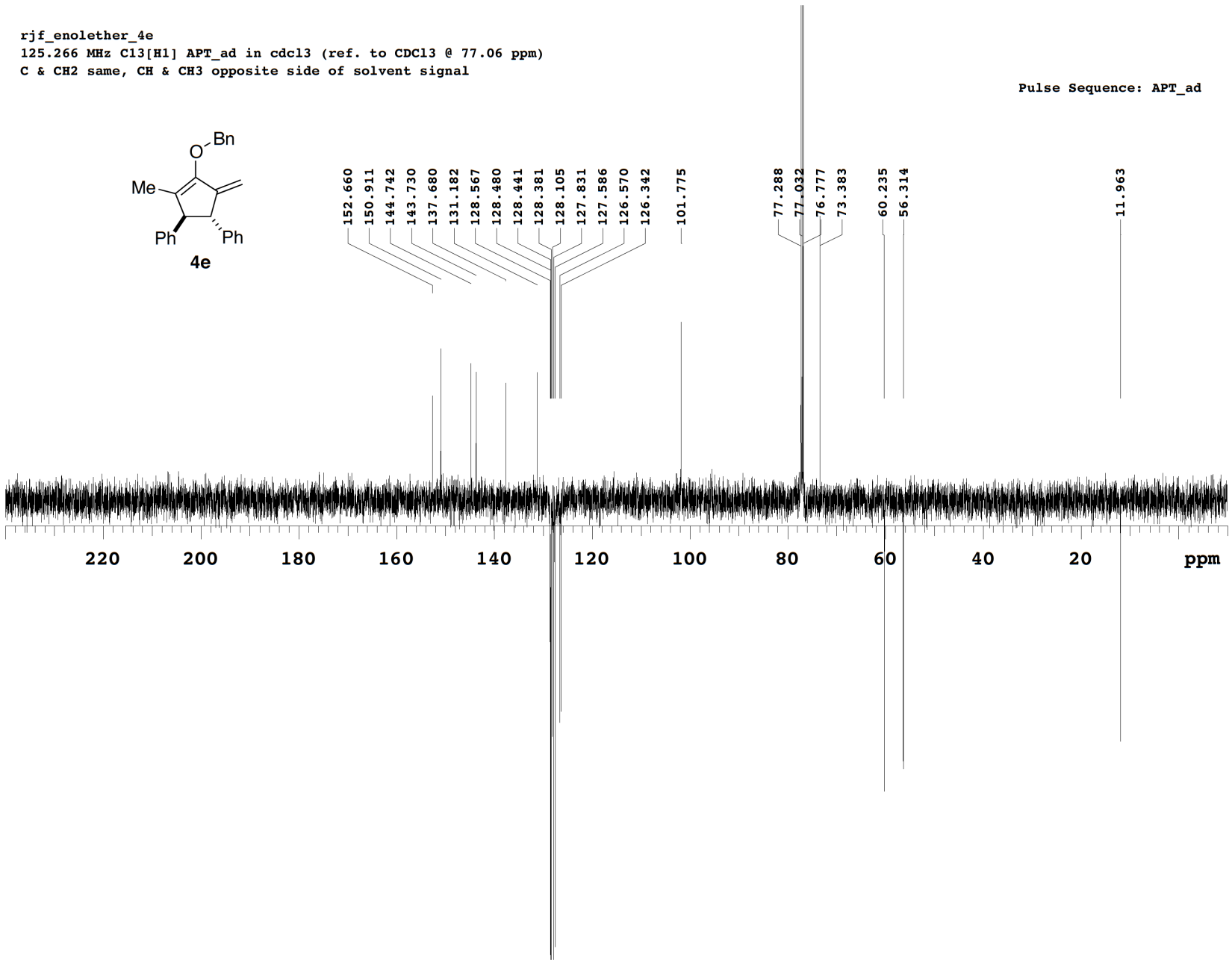


rjf_enolether_4e
498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: s2pul

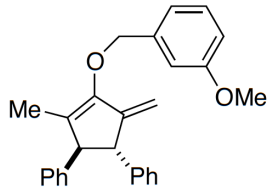


4e


rjf_enolether_4e
125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal
Pulse Sequence: APT_ad
Bn
O
Me
Ph
Ph
4e
152.660
150.911
144.742
143.730
137.680
131.182
128.567
128.480
128.441
128.381
128.105
127.831
127.586
126.570
126.342
101.775
77.288
77.032
76.777
73.383
60.235
56.314
11.963
220
200
180
160
140
120
100
80
60
40
20
ppm

rjf_enolether_4i
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

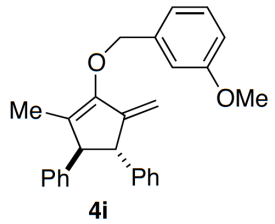
Pulse Sequence: PRESAT



4i

rjf_enolether_4i
125.690 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal

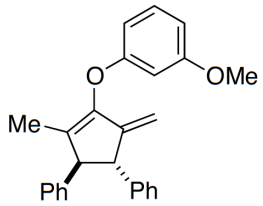
Pulse Sequence: APT_ad



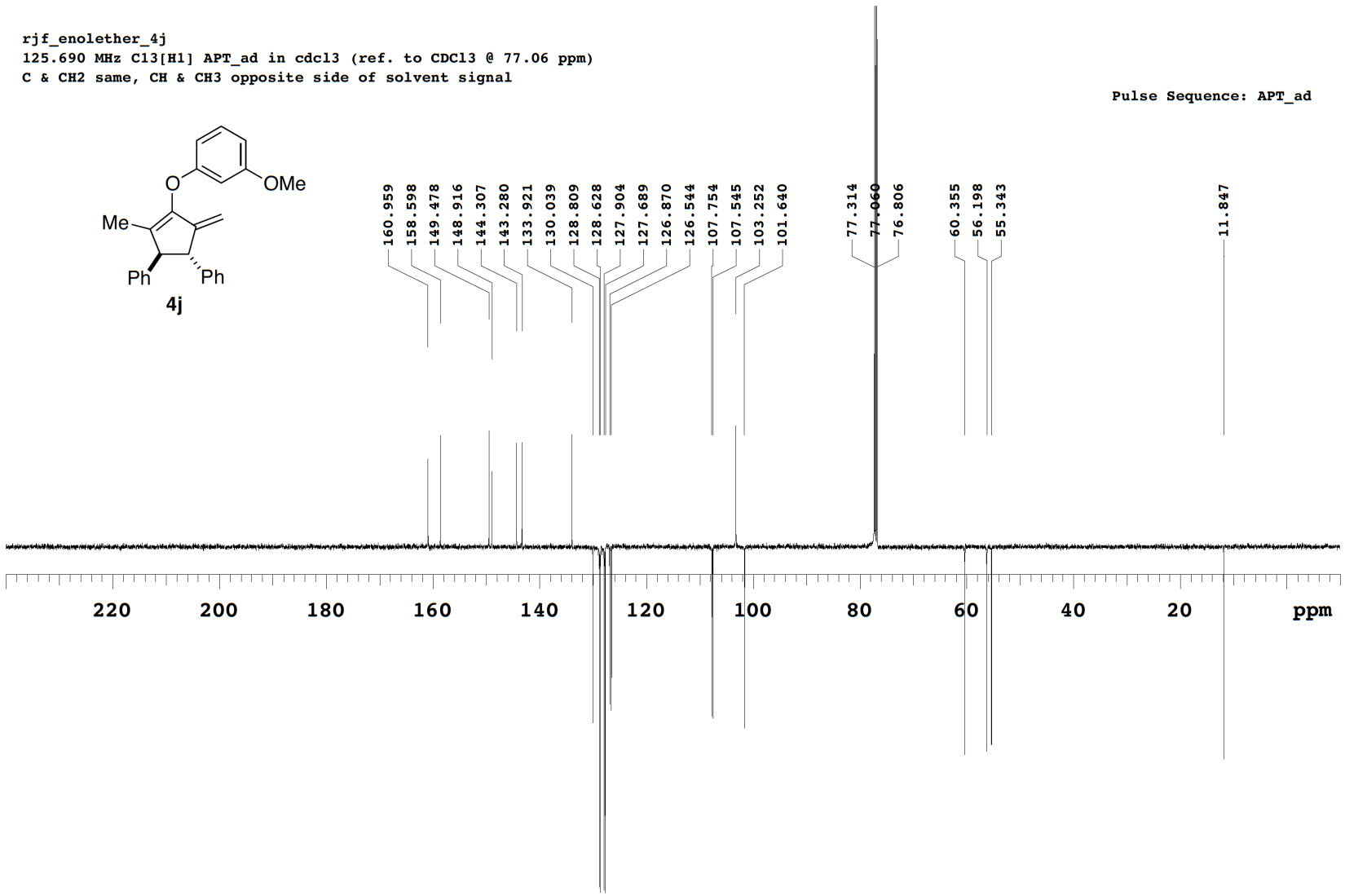
4i

rjf_enolether_4j
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: PRESAT

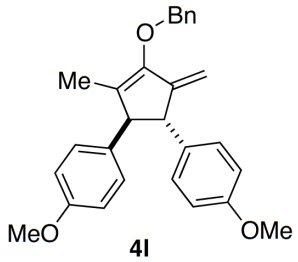


4j

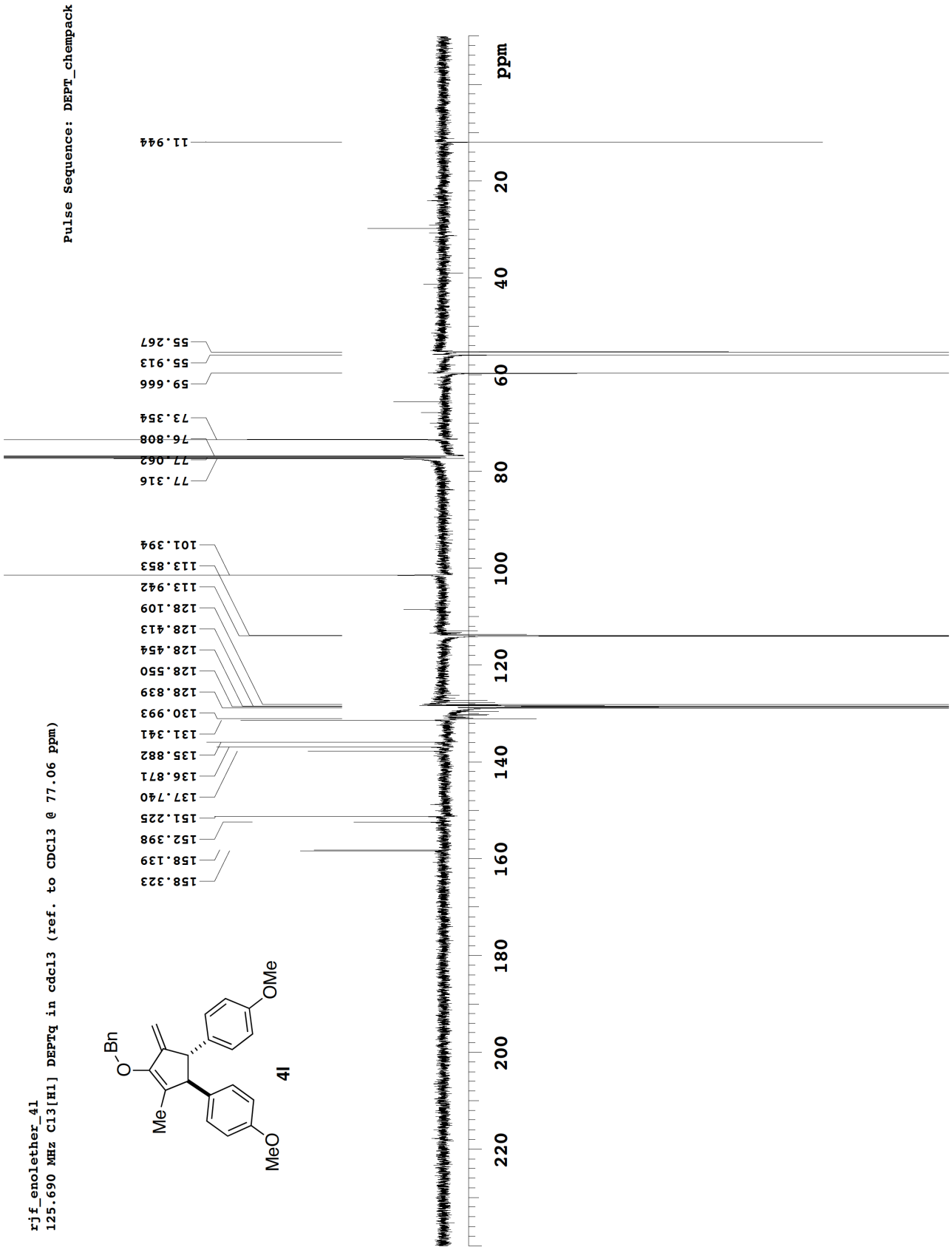

rjf_enolether_4j
125.690 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal
Pulse Sequence: APT_ad
O
OMe
Me
Ph
Ph
4j
160.959
158.598
149.478
148.916
144.307
143.280
133.921
130.039
128.809
128.628
127.904
127.689
126.870
126.544
107.754
107.545
103.252
101.640
77.314
77.060
76.806
60.355
56.198
55.343
11.847
220
200
180
160
140
120
100
80
60
40
20
ppm

rjf_enolether_4l
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: PRESAT

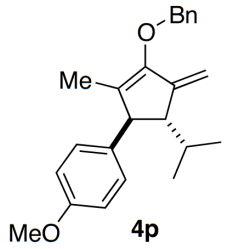


4l

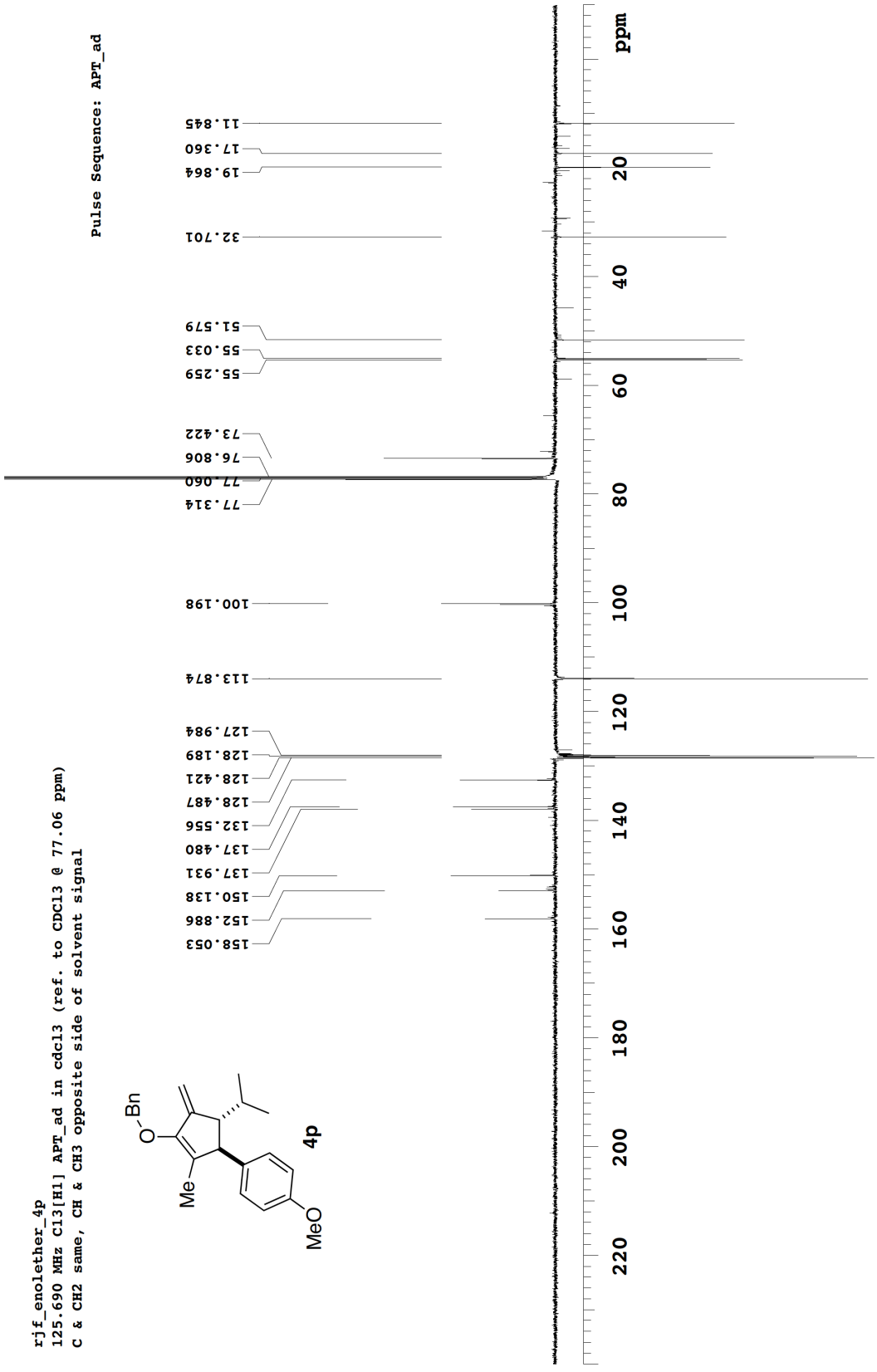

rjf_enolether_41
125.690 MHz C13[H1] DEPTq in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: DEPT_chempack
11.944
55.267
55.913
59.666
73.354
76.808
77.062
77.316
101.394
113.853
113.942
128.109
128.413
128.454
128.550
128.839
130.993
131.341
135.882
136.871
137.740
151.225
152.398
158.139
158.323
ppm
20
40
60
80
100
120
140
160
180
200
220
Bn
O
Me
OMe
MeO
4l

rjf_enolether_4p
498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: s2pul



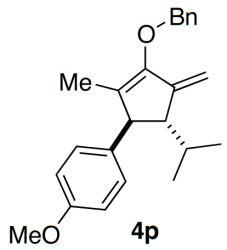
4p


rjf_enolether_4p
125.690 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal
Pulse Sequence: APT_ad
11.845
17.360
19.864
32.701
51.579
55.033
55.259
73.422
76.806
77.060
77.314
100.198
113.874
127.984
128.189
128.421
128.487
132.556
137.480
137.931
150.138
152.886
158.053
ppm
Bn
O
Me
MeO
4p

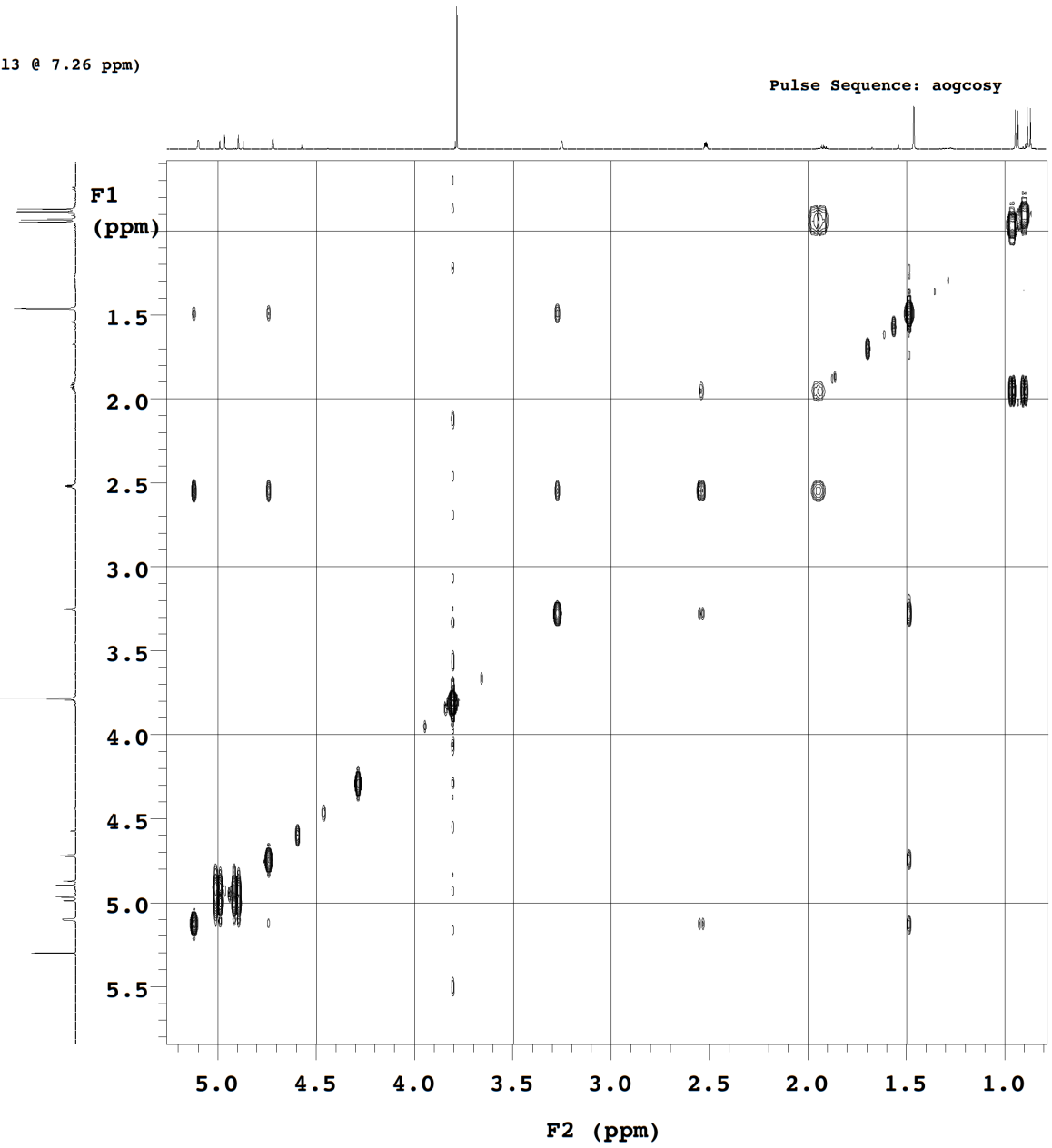
rjf_enolether_4p
498.118 MHz H1 aogcosy in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Temp. 26.3 C / 299.4 K
Operator: nmrlab
INOVA-500 "d602"

Relax. delay 1.000 sec
Acq. time 1.000 sec
Width 3734.8 Hz
2D Width 3734.8 Hz
Single scan
199 increments
OBSERVE H1, 498.1154023 MHz
DATA PROCESSING
Sq. sine bell 0.160 sec
F1 DATA PROCESSING
Sq. sine bell 0.027 sec
FT size 8192 x 1024
Total time 6 min 52 sec



4p

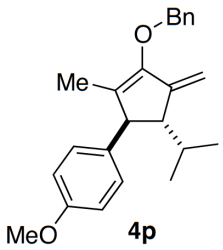


rjf_enolether_4p
499.806 MHz H1 gHMBC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm

Pulse Sequence: gHMBC

Temp. 27.6 C / 300.8 K
Sample #4, Operator: WEST

Relax. delay 1.500 sec
Acq. time 0.500 sec
Width 6009.6 Hz
2D Width 33755.3 Hz
8 repetitions
170 increments
OBSERVE H1, 499.8039202 MHz
DATA PROCESSING
Sq. sine bell 0.250 sec
F1 DATA PROCESSING
Sq. sine bell 0.003 sec
FT size 8192 x 1024
Total time 47 min



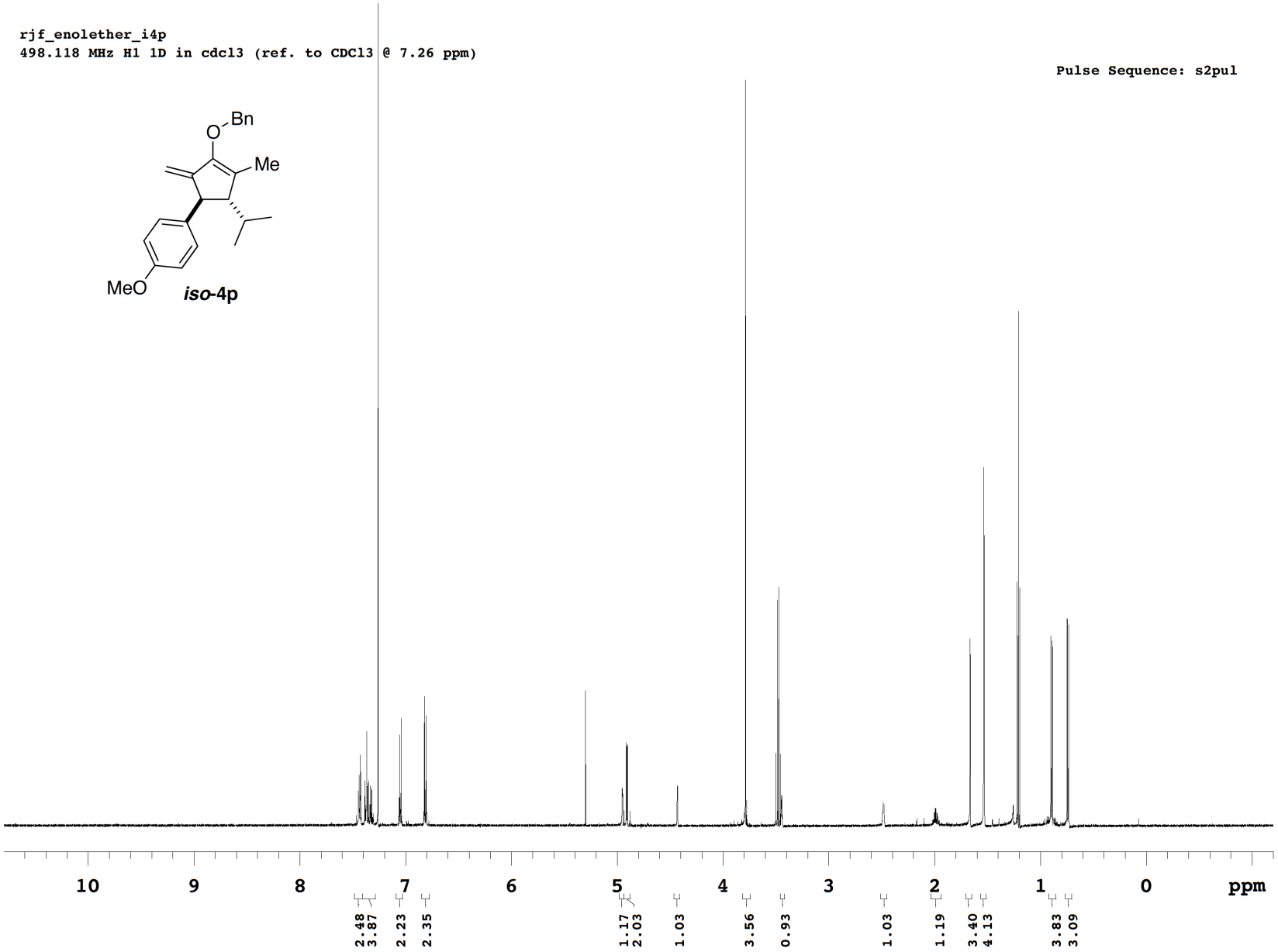
4p

F1 (ppm)

20
40
60
80
100
120
140
160
180

7 6 5 4 3 2 1

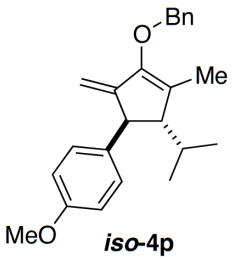
F2 (ppm)


rjf_enolether_i4p
498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
Pulse Sequence: s2pul
Bn
O
Me
MeO
iso-4p
10
9
8
7
6
5
4
3
2
1
0
ppm
2.48
3.87
2.23
2.35
1.17
2.03
1.03
3.56
0.93
1.03
1.19
3.40
4.13
3.83
3.09

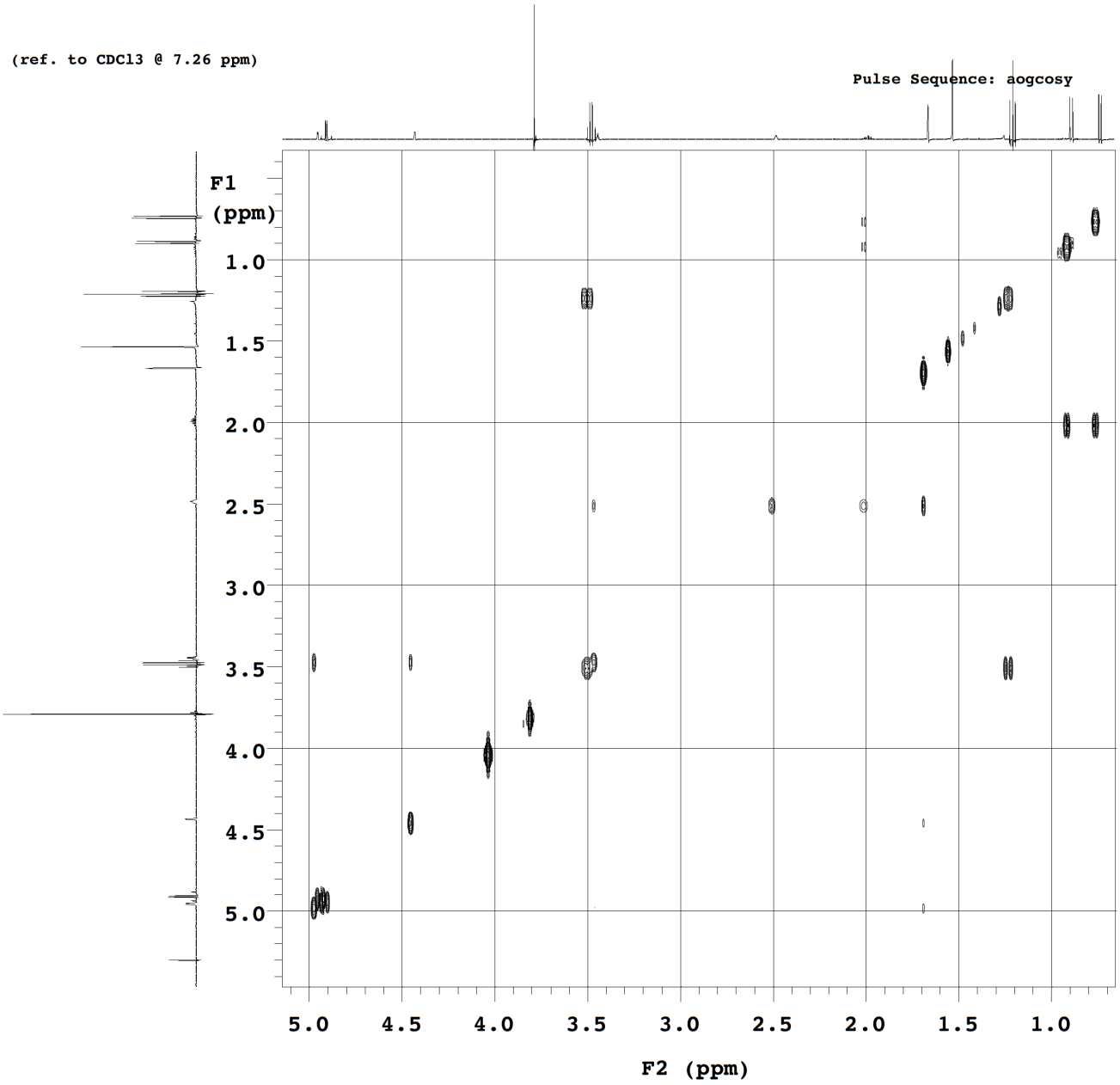
rjf_enolether_i4p
498.118 MHz H1 aogcosy in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Temp. 26.3 C / 299.4 K
Operator: nmrlab
INOVA-500 "d602"

Relax. delay 1.000 sec
Acq. time 0.999 sec
Width 3988.0 Hz
2D Width 3988.0 Hz
Single scan
213 increments
OBSERVE H1, 498.1154023 MHz
DATA PROCESSING
Sq. sine bell 0.160 sec
F1 DATA PROCESSING
Sq. sine bell 0.027 sec
FT size 8192 x 1024
Total time 7 min 20 sec

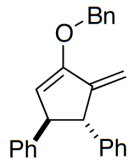


iso-4p

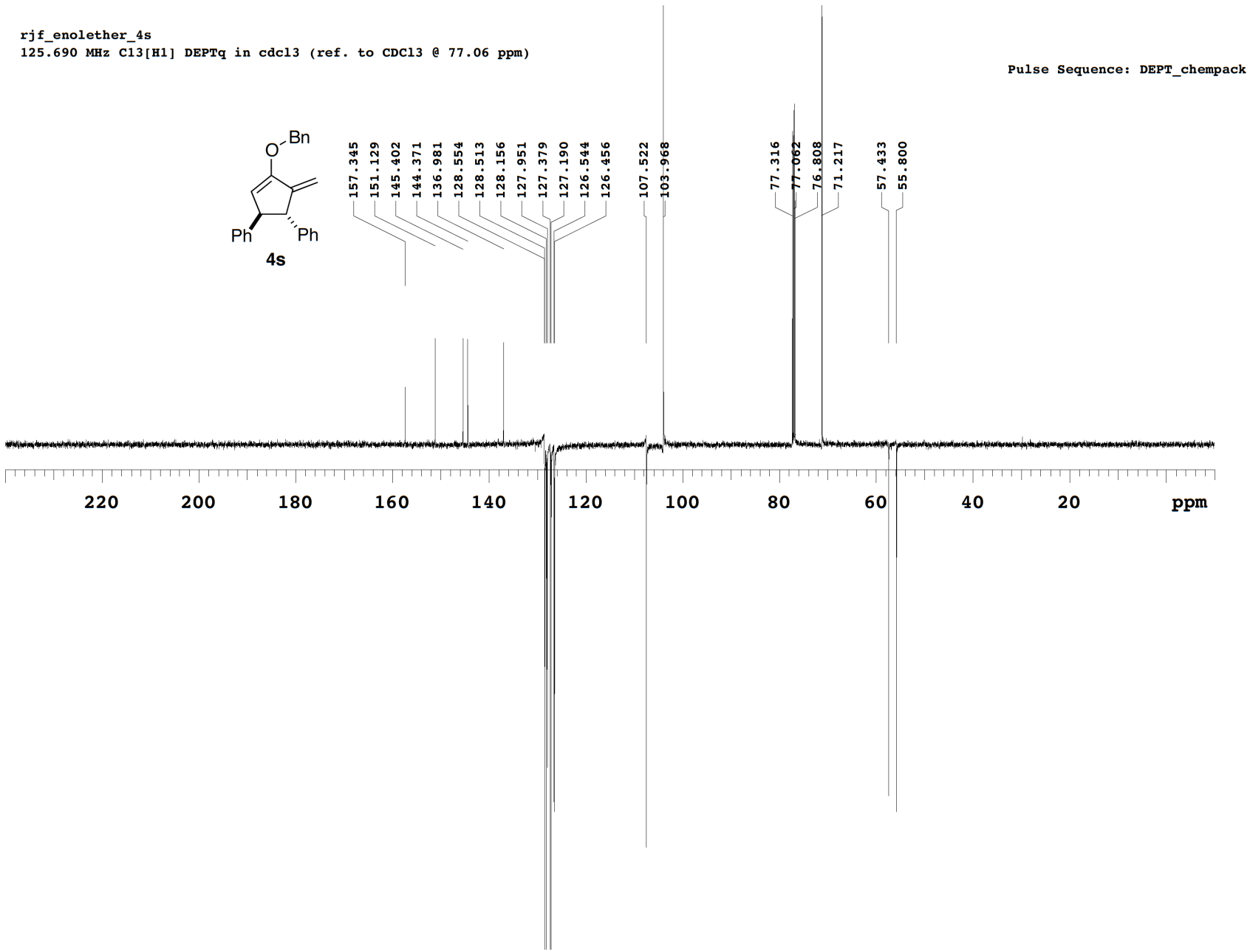


rjf_enolether_4s
498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: s2pul

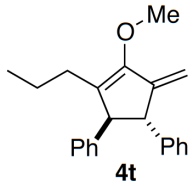


4s

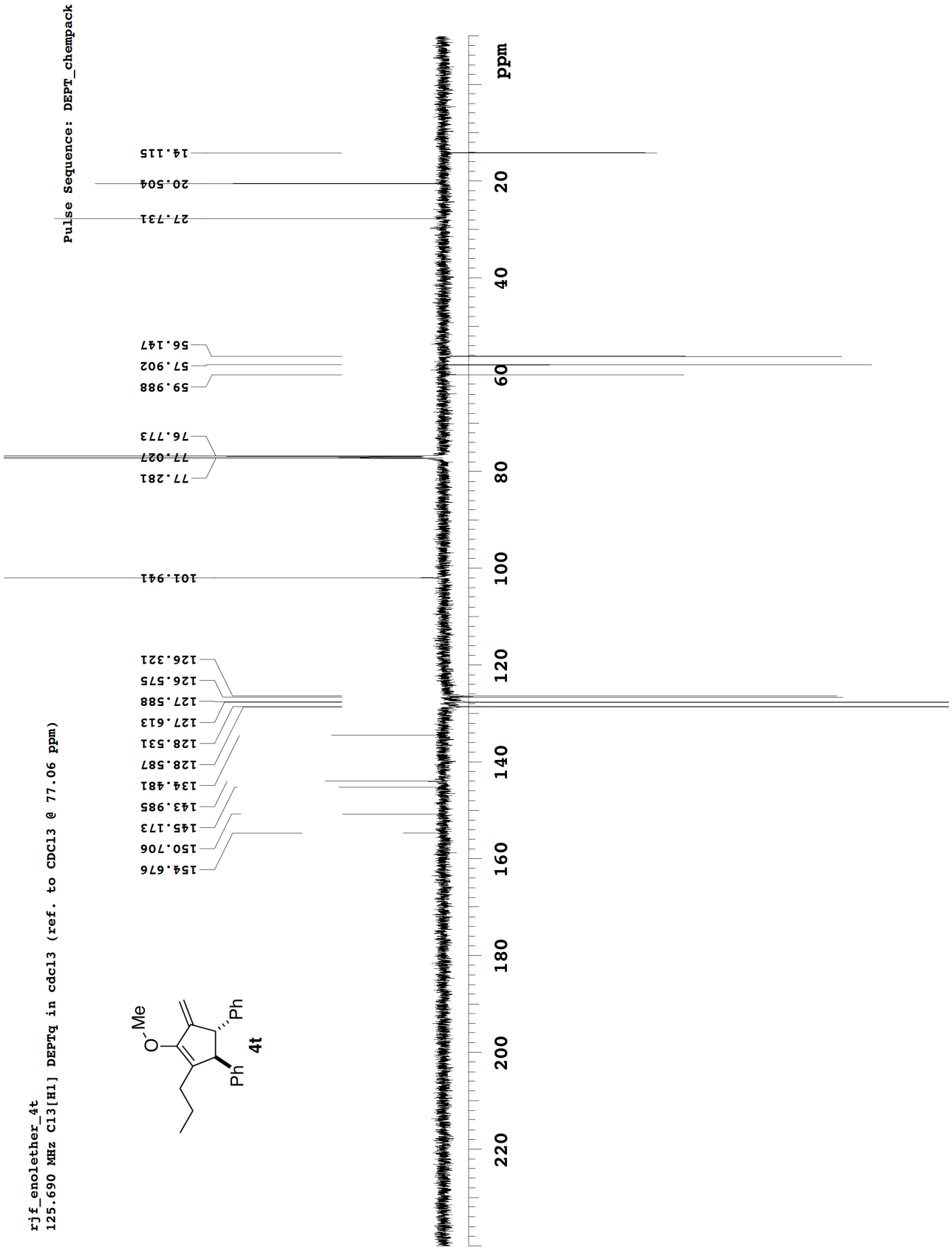

rjf_enolether_4s
125.690 MHz C13[H1] DEPTq in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: DEPT_chempack
Bn
O
Ph
Ph
4s
157.345
151.129
145.402
144.371
136.981
128.554
128.513
128.156
127.951
127.379
127.190
126.544
126.456
107.522
103.968
77.316
77.062
76.808
71.217
57.433
55.800
220
200
180
160
140
120
100
80
60
40
20
ppm

rjf_enolether_4t
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: PRESAT

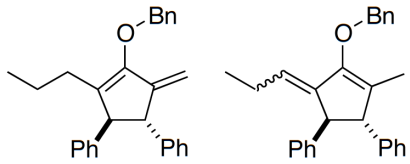


4t


rjf_enolether_4t
125.690 MHz C13[H1] DEPTq in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: DEPT_chempack
14.115
20.504
27.731
56.147
57.902
59.988
76.773
77.027
77.281
101.941
126.321
126.575
127.588
127.613
128.531
128.587
134.481
143.985
145.173
150.706
154.676
ppm
20
40
60
80
100
120
140
160
180
200
220
Me
O
Ph
Ph
4t

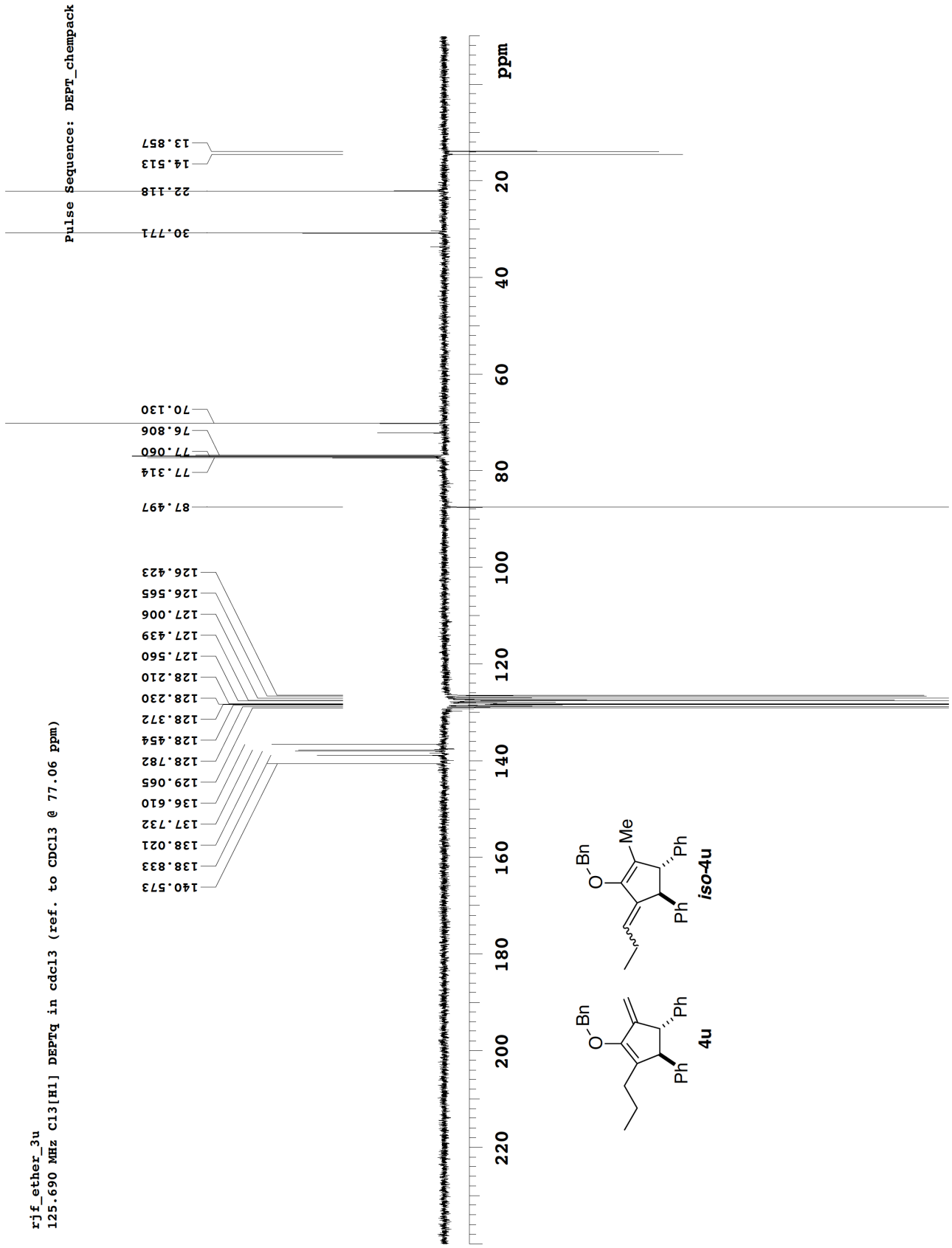
rjf_enolether_4u/i4u
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

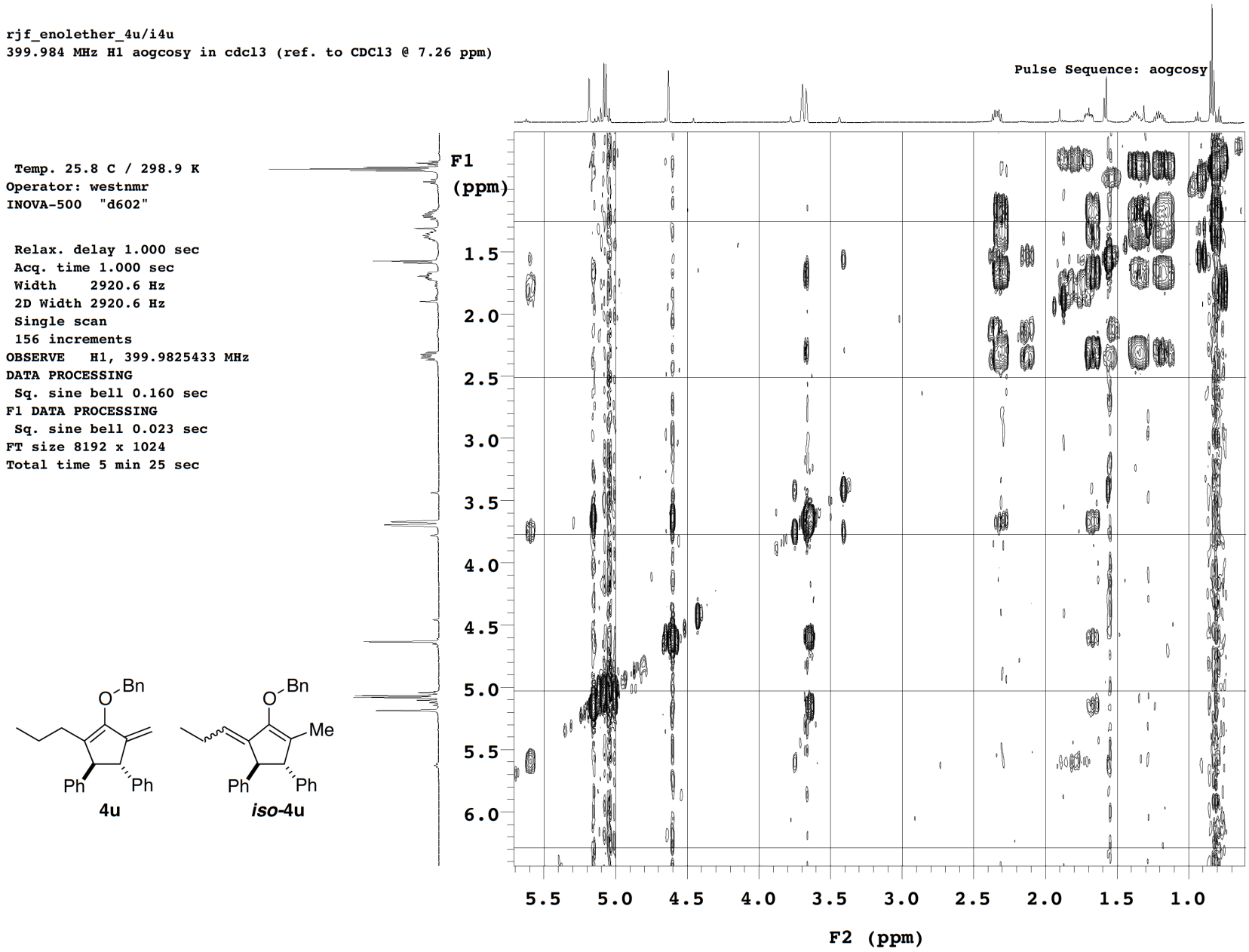
Pulse Sequence: PRESAT



4u

***iso*-4u**


rjf_ether_3u
125.690 MHz C13[H1] DEPTq in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: DEPT_chempack
13.857
14.513
22.118
30.771
70.130
76.806
77.060
77.314
87.497
126.423
126.565
127.006
127.439
127.560
128.210
128.230
128.372
128.454
128.782
129.065
136.610
137.732
138.021
138.833
140.573
ppm
20
40
60
80
100
120
140
160
180
200
220
Bn
O
Me
Ph
Ph
iso-4u
Bn
O
Ph
Ph
4u

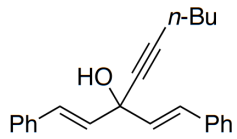

rjf_enolether_4u/i4u
399.984 MHz H1 aogcosy in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
Pulse Sequence: aogcosy
Temp. 25.8 C / 298.9 K
Operator: westnmr
INOVA-500 "d602"
Relax. delay 1.000 sec
Acq. time 1.000 sec
Width 2920.6 Hz
2D Width 2920.6 Hz
Single scan
156 increments
OBSERVE H1, 399.9825433 MHz
DATA PROCESSING
Sq. sine bell 0.160 sec
F1 DATA PROCESSING
Sq. sine bell 0.023 sec
FT size 8192 x 1024
Total time 5 min 25 sec
F1 (ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
F2 (ppm)
O Bn
Ph Ph
4u
O Bn
Me
Ph Ph
iso-4u

Appendix C: Selected NMR Spectra

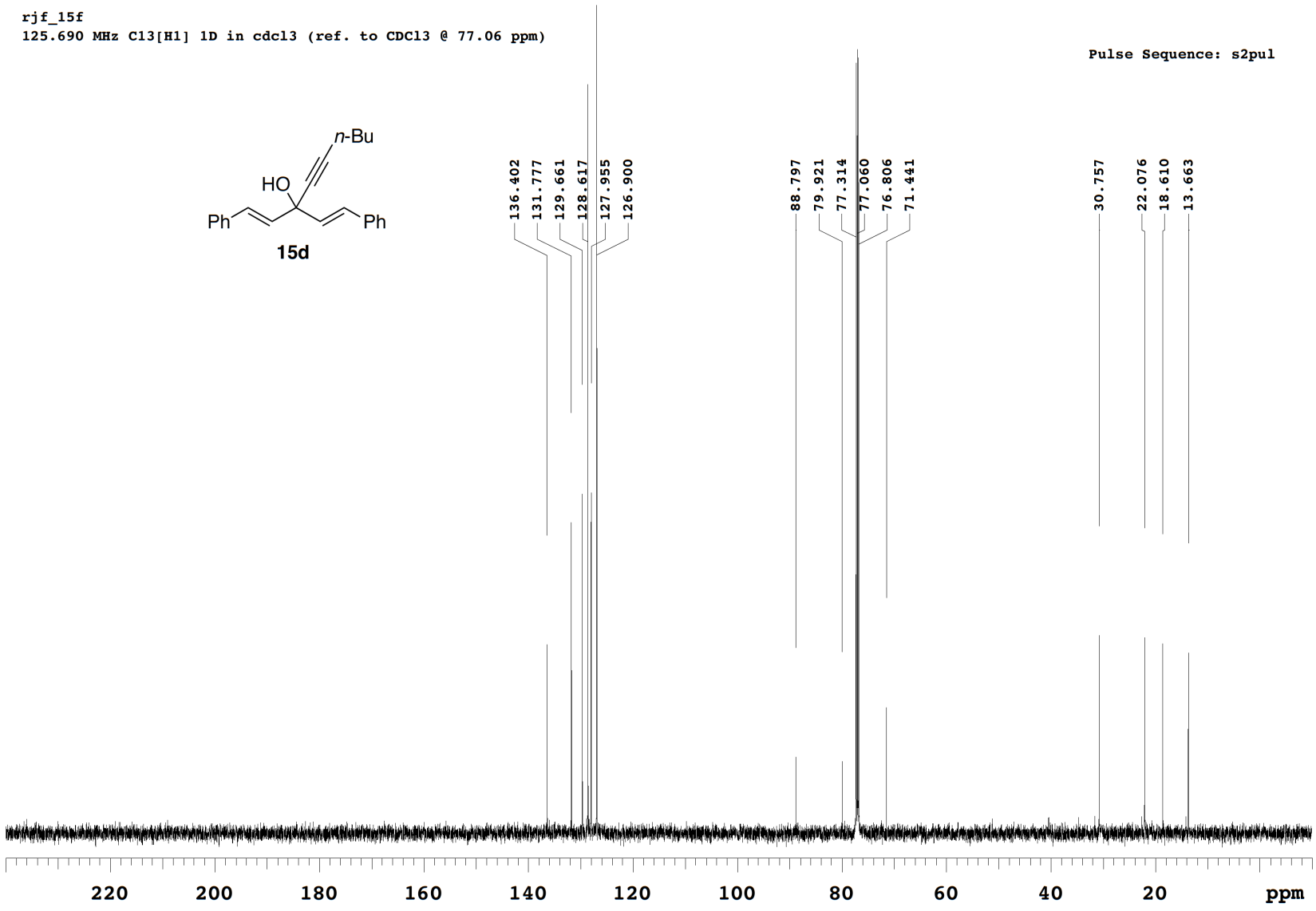
(Chapter 4)

rjf_15d
499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: s2pul

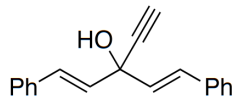


15d

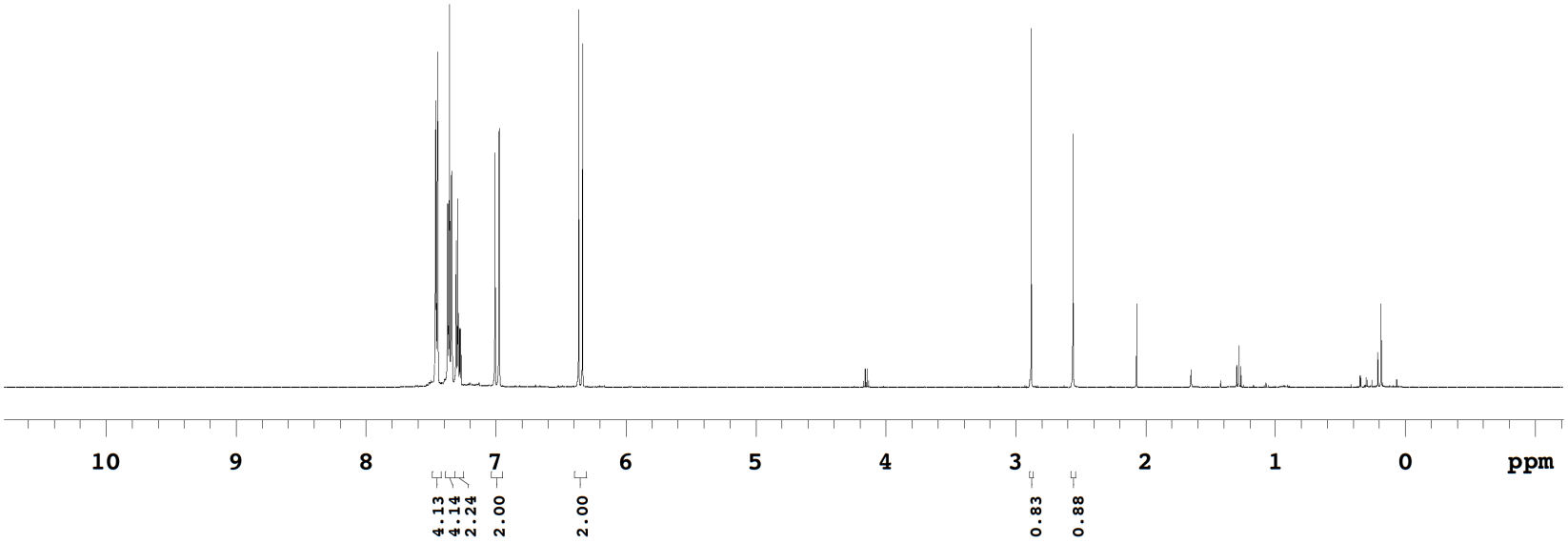

rjf_15f
125.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: s2pul
n-Bu
HO
Ph
Ph
15d
136.402
131.777
129.661
128.617
127.955
126.900
88.797
79.921
77.314
77.060
76.806
71.441
30.757
22.076
18.610
13.663
220
200
180
160
140
120
100
80
60
40
20
ppm

rjf_15e
499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: s2pul

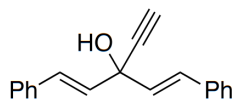


15e



rjf_15e
125.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)

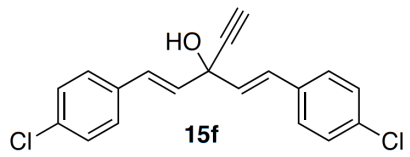
Pulse Sequence: s2pul



15e

rjf_15f
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: PRESAT

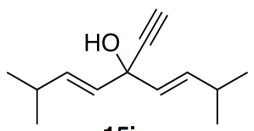


15f

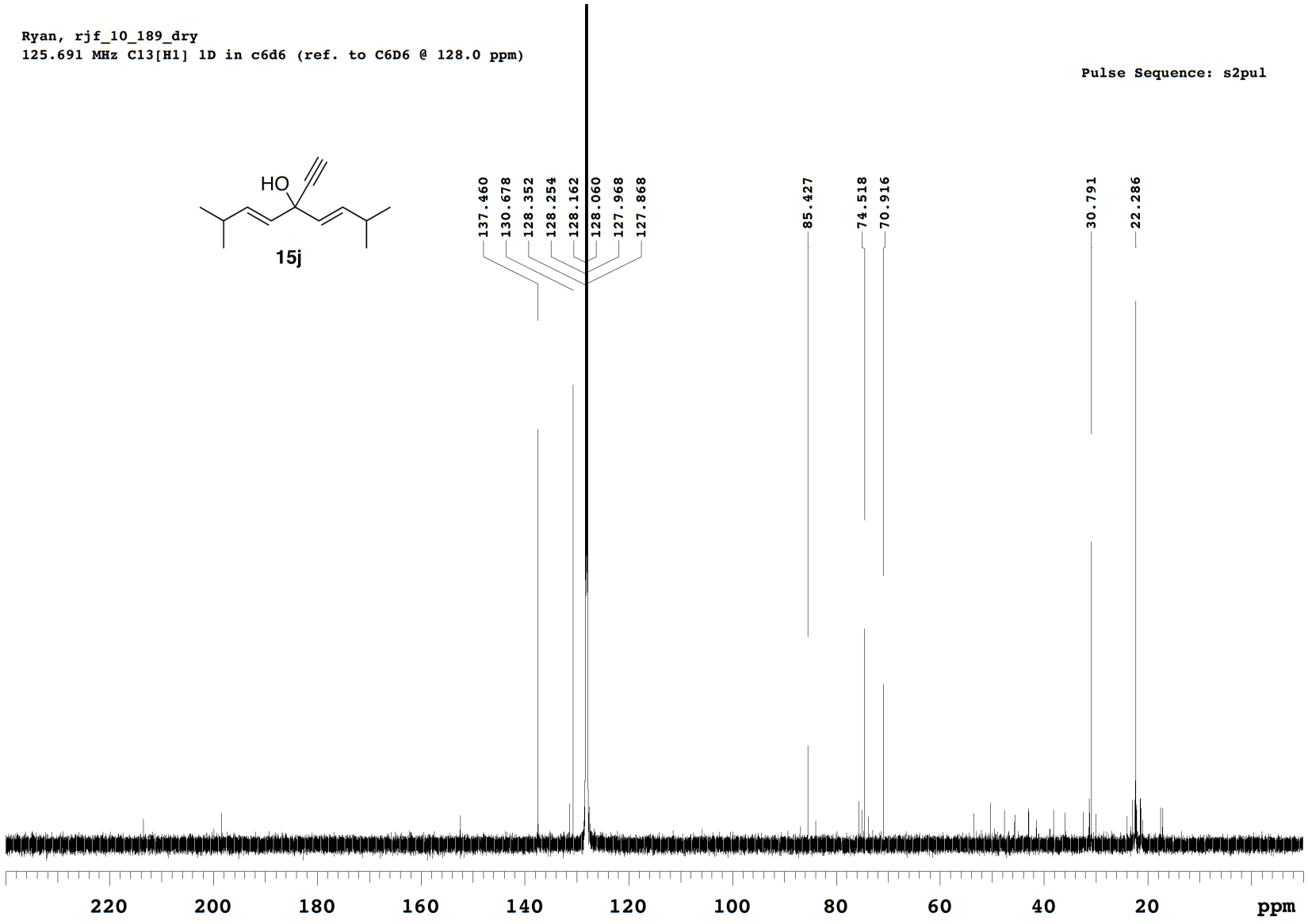

rjf_15f
125.690 MHz C13[H1] DEPTq in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: DEPT_chempack
HO
Cl
Cl
15f
134.508
133.954
131.017
129.235
128.878
128.156
83.178
77.312
77.060
76.806
76.184
71.100
220
200
180
160
140
120
100
80
60
40
20
ppm

rjf_15j
499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: s2pul

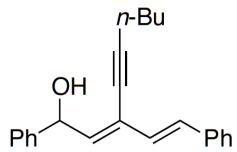


15j

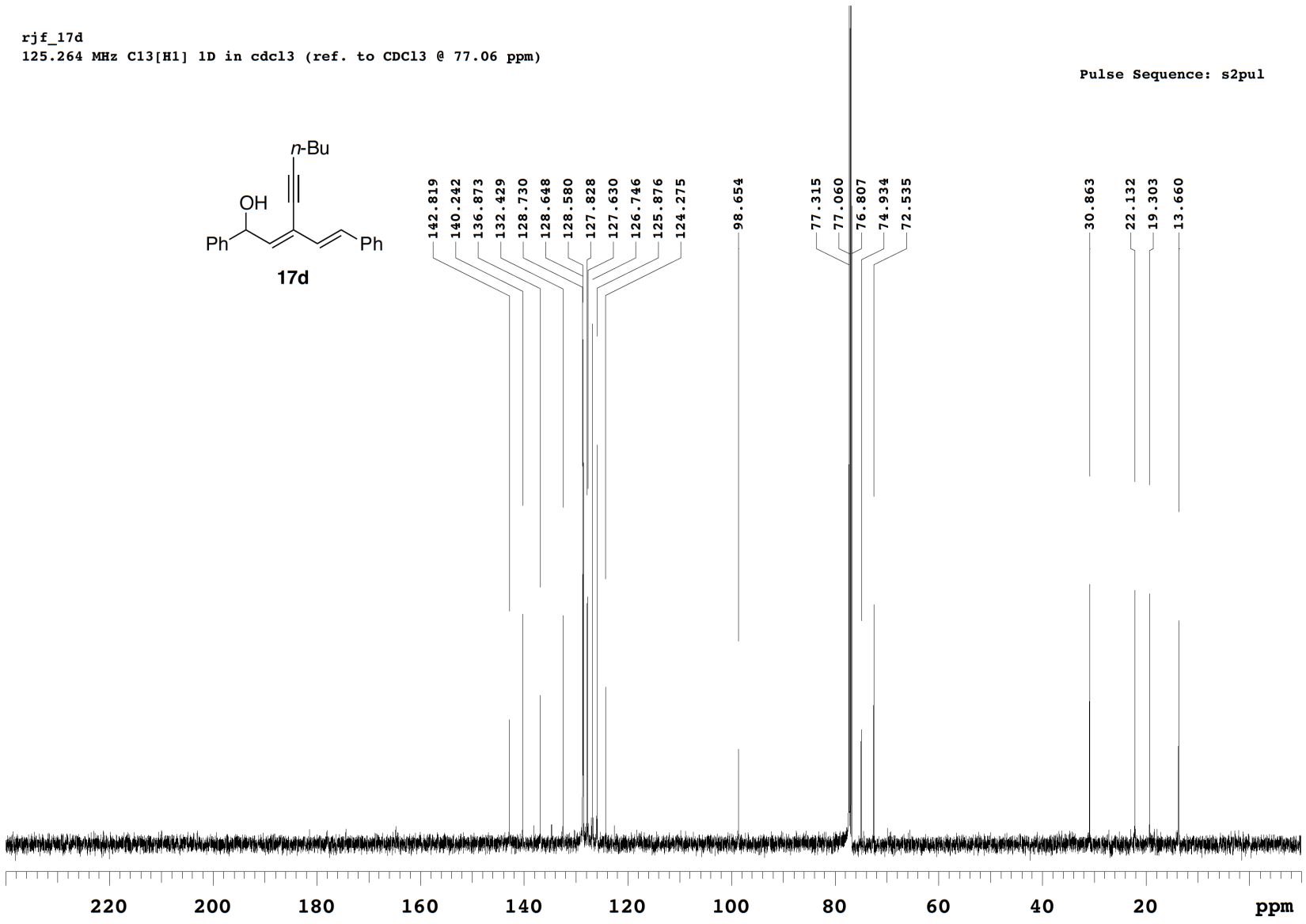

Ryan, rjf_10_189_dry
125.691 MHz C13[H1] 1D in c6d6 (ref. to C6D6 @ 128.0 ppm)
Pulse Sequence: s2pul
HO
15j
137.460
130.678
128.352
128.254
128.162
128.060
127.968
127.868
85.427
74.518
70.916
30.791
22.286
220
200
180
160
140
120
100
80
60
40
20
ppm

rjf_17d
498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: s2pul

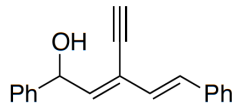


17d

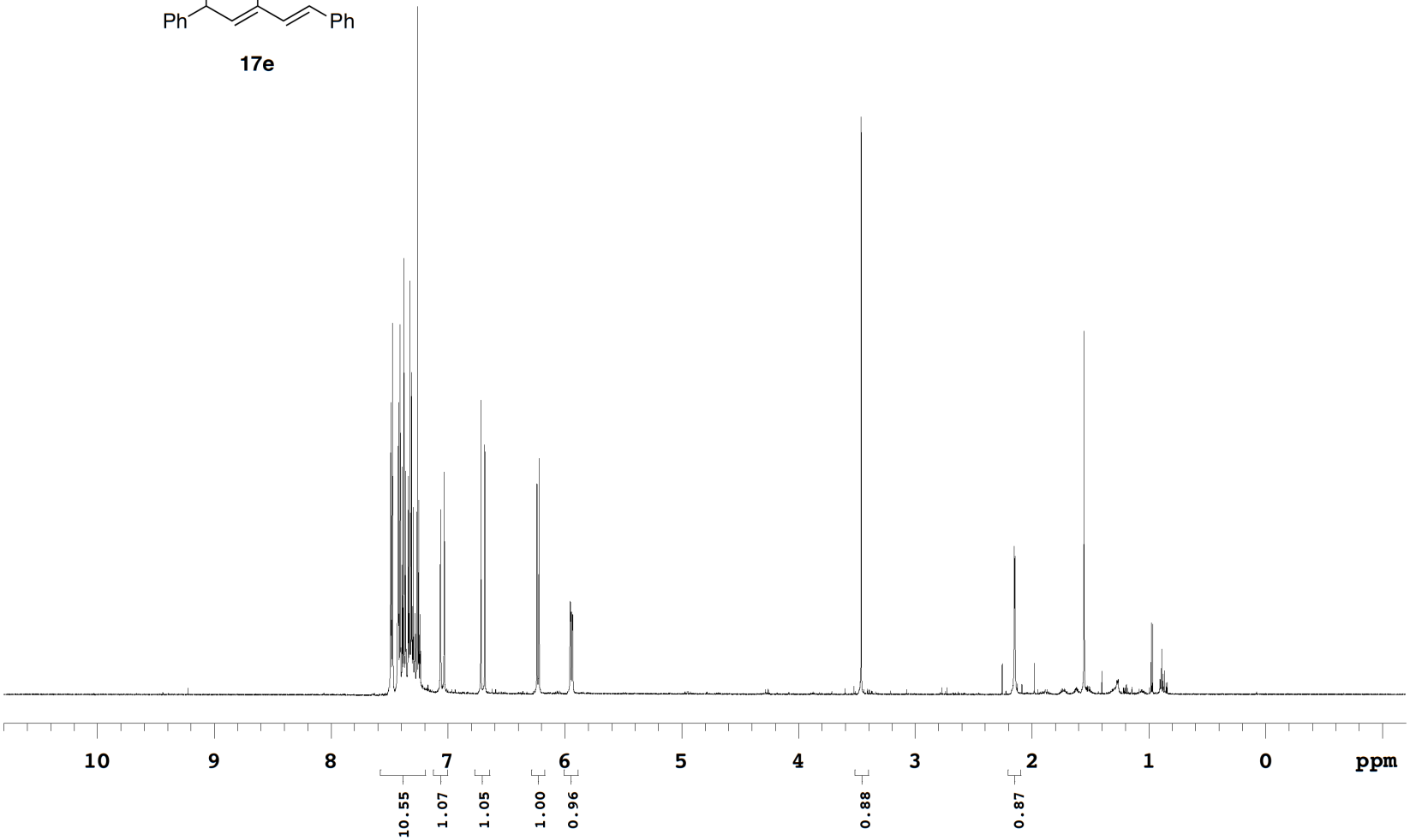

rjf_17d
125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: s2pul
n-Bu
OH
Ph
Ph
17d
142.819
140.242
136.873
132.429
128.730
128.648
128.580
127.828
127.630
126.746
125.876
124.275
98.654
77.315
77.060
76.807
74.934
72.535
30.863
22.132
19.303
13.660
220
200
180
160
140
120
100
80
60
40
20
ppm

rjf_17e
499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: s2pul

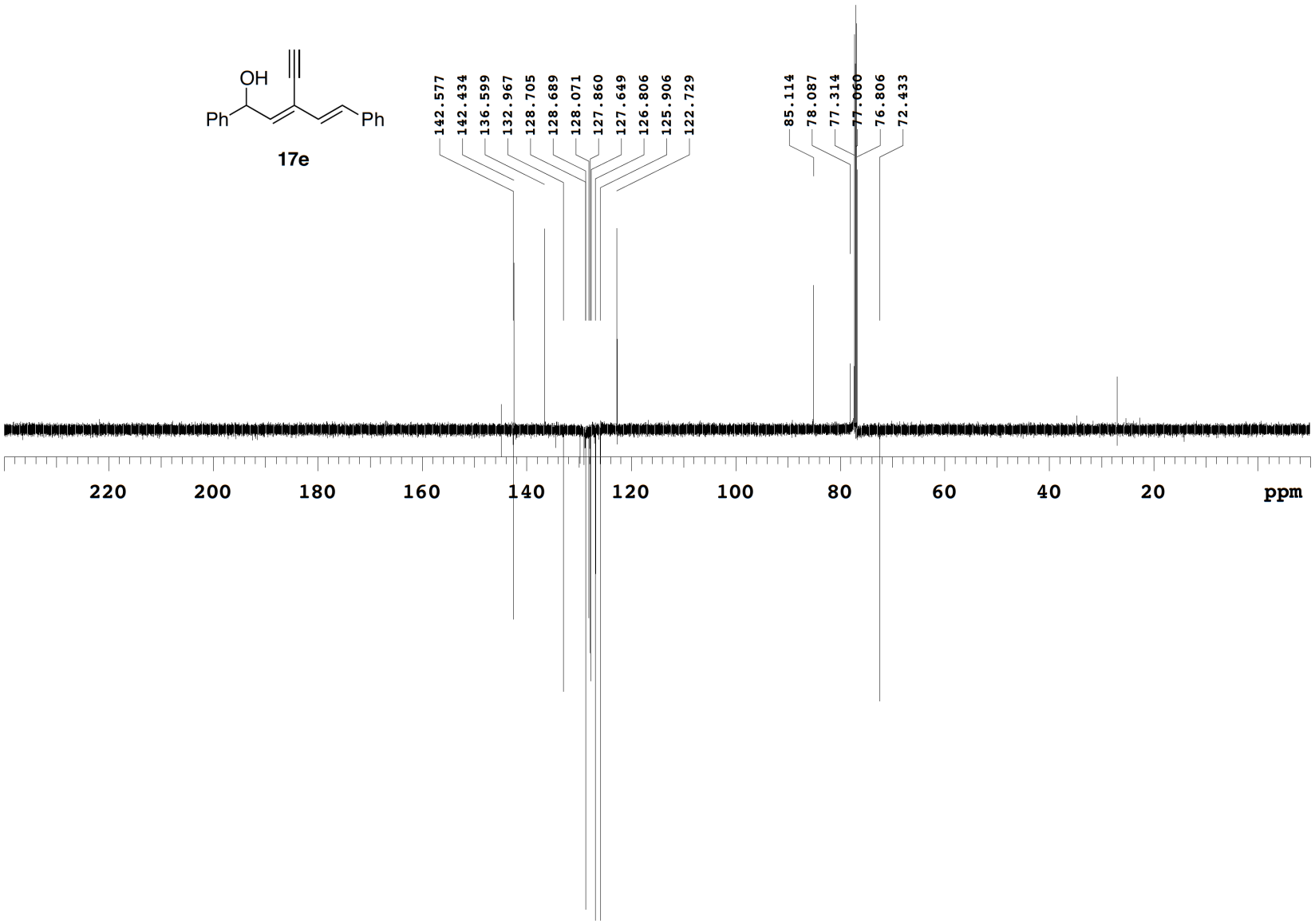


17e



rjf_17e
125.692 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal

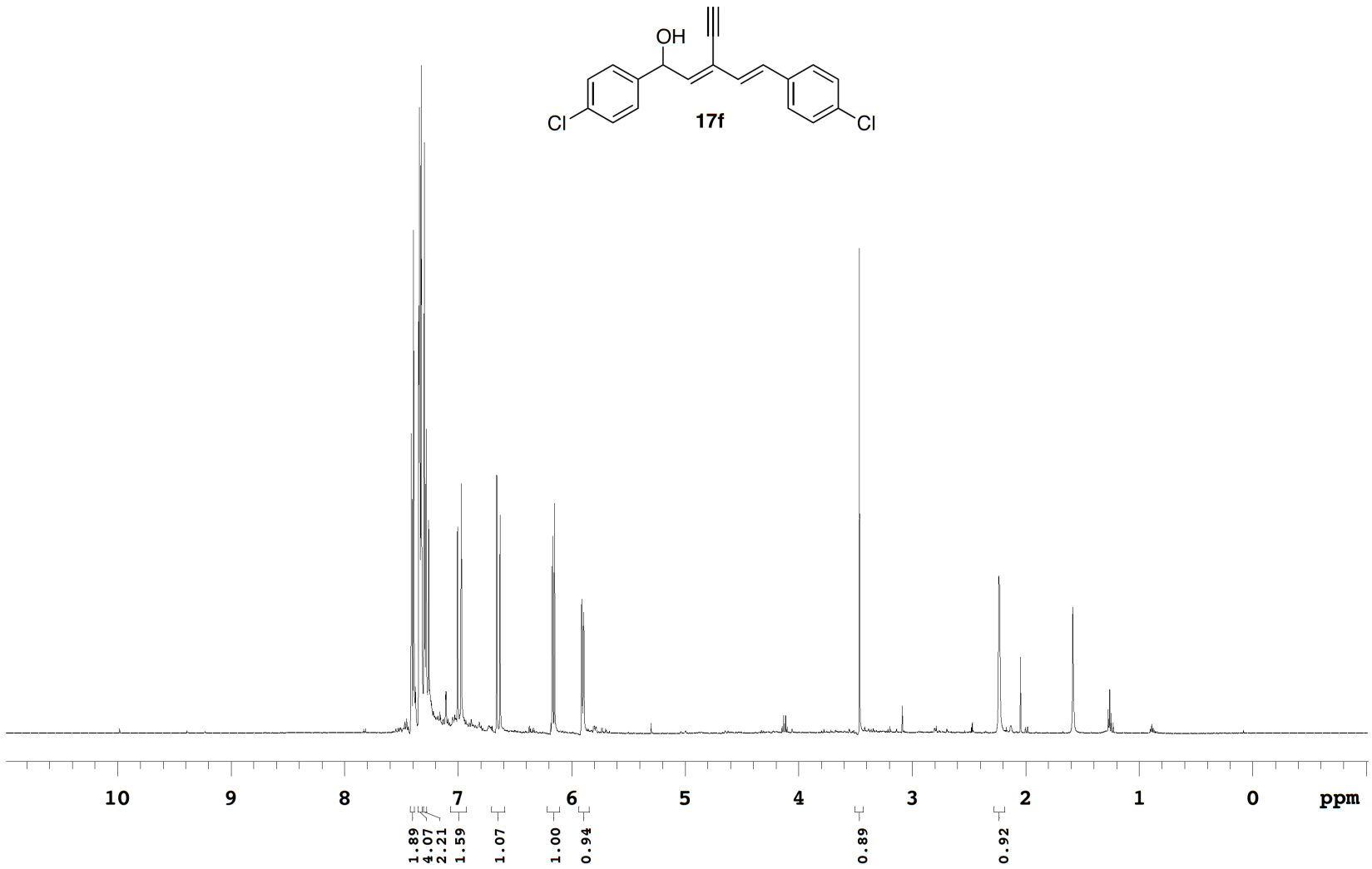
Pulse Sequence: APT_ad

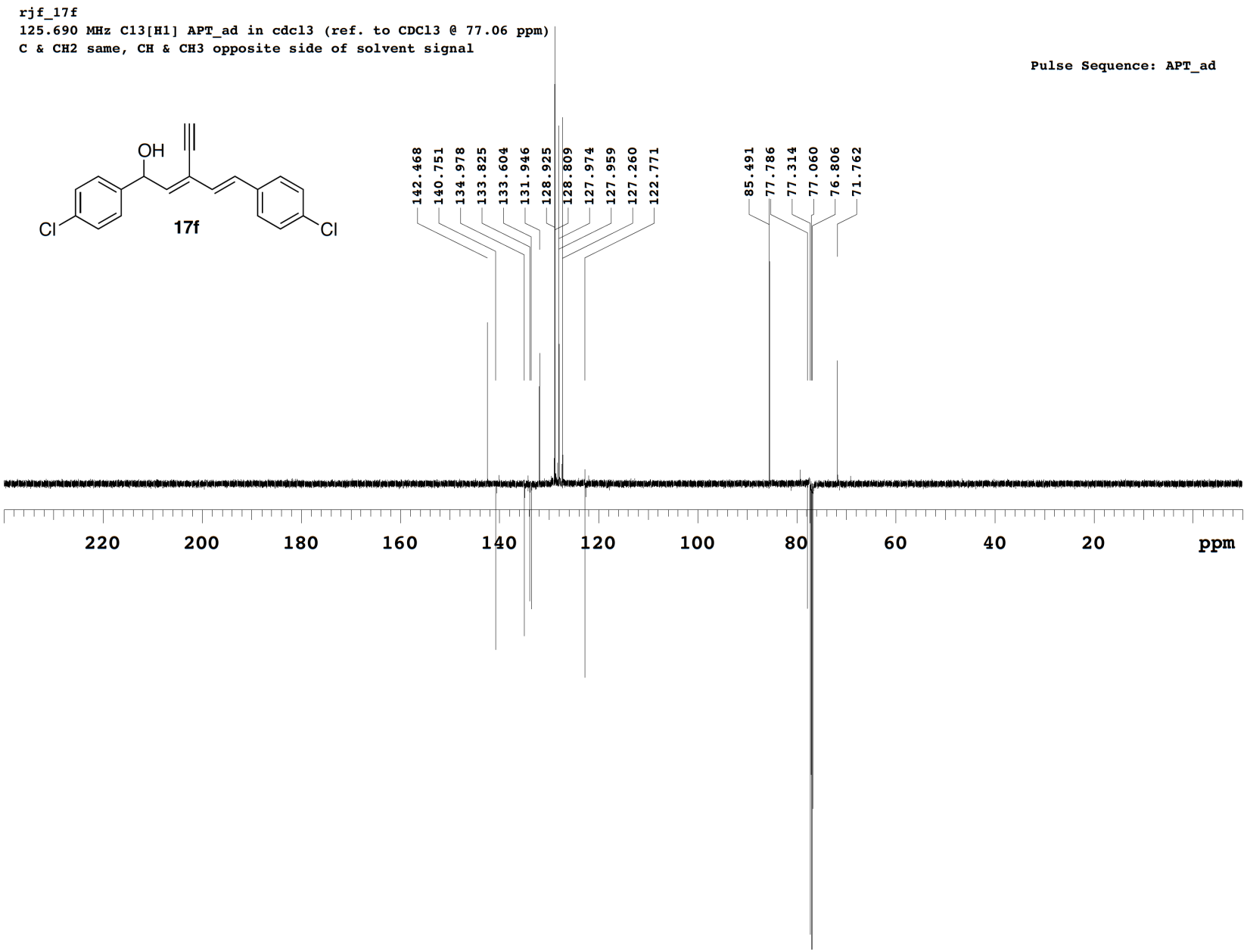


17e

rjf_17f
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: PRESAT

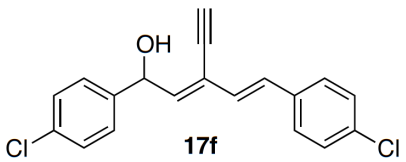



rjf_17f
125.690 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal
Pulse Sequence: APT_ad
OH
Cl
Cl
17f
142.468
140.751
134.978
133.825
133.604
131.946
128.925
128.809
127.974
127.959
127.260
122.771
85.491
77.786
77.314
77.060
76.806
71.762
220
200
180
160
140
120
100
80
60
40
20
ppm

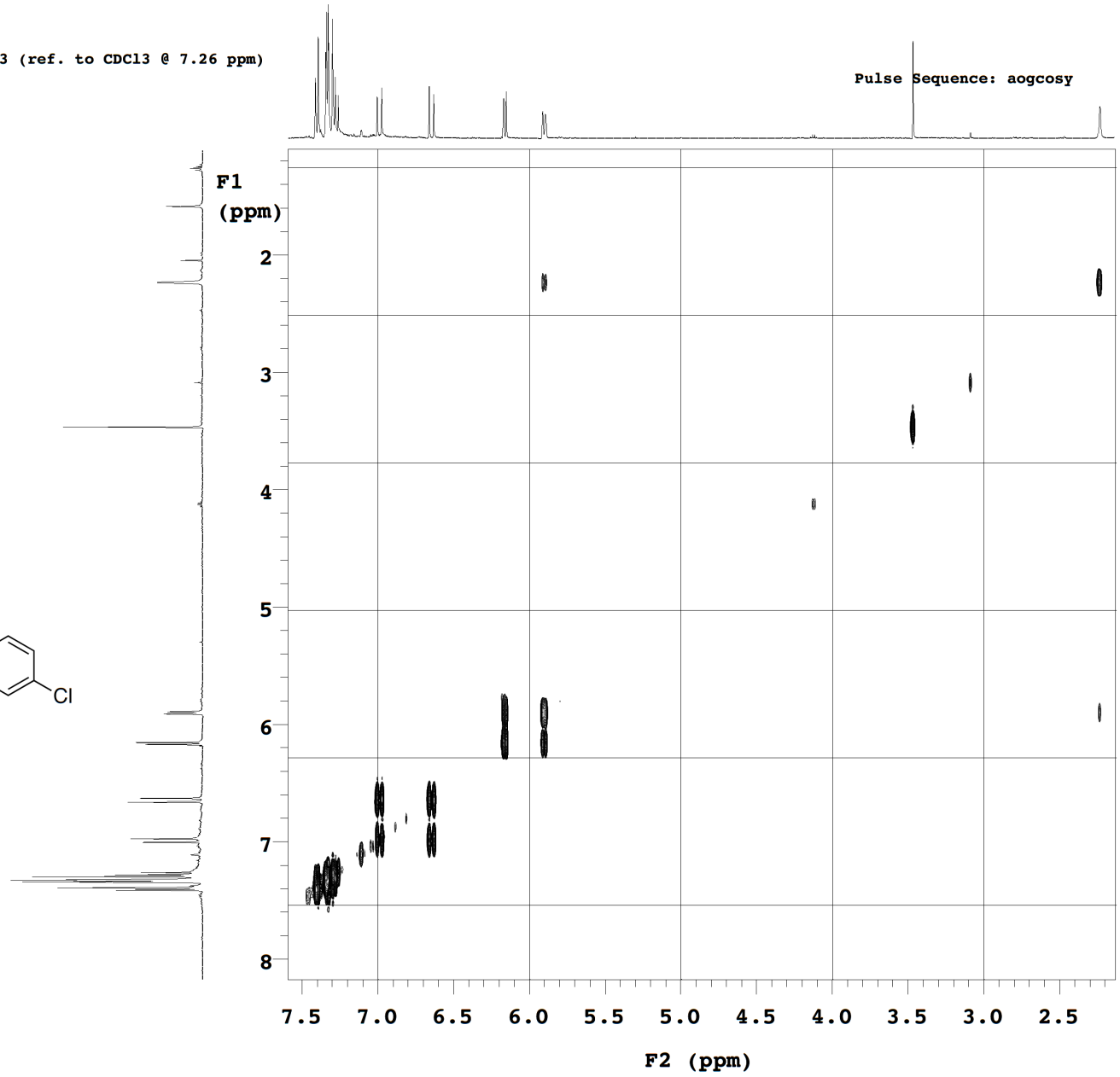
rjf_17f
499.806 MHz H1 aogcosy in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Temp. 27.7 C / 300.9 K
Sample #2, Operator: WEST

Relax. delay 1.000 sec
Acq. time 1.000 sec
Width 6009.6 Hz
2D Width 6009.6 Hz
Single scan
170 increments
OBSERVE H1, 499.8039345 MHz
DATA PROCESSING
Sq. sine bell 0.160 sec
F1 DATA PROCESSING
Sq. sine bell 0.014 sec
FT size 8192 x 1024
Total time 5 min 51 sec



17f

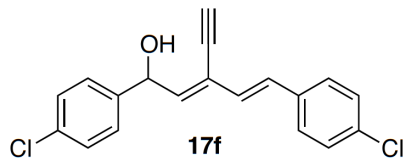


17f_HMBC
499.806 MHz H1 gHMBC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm)

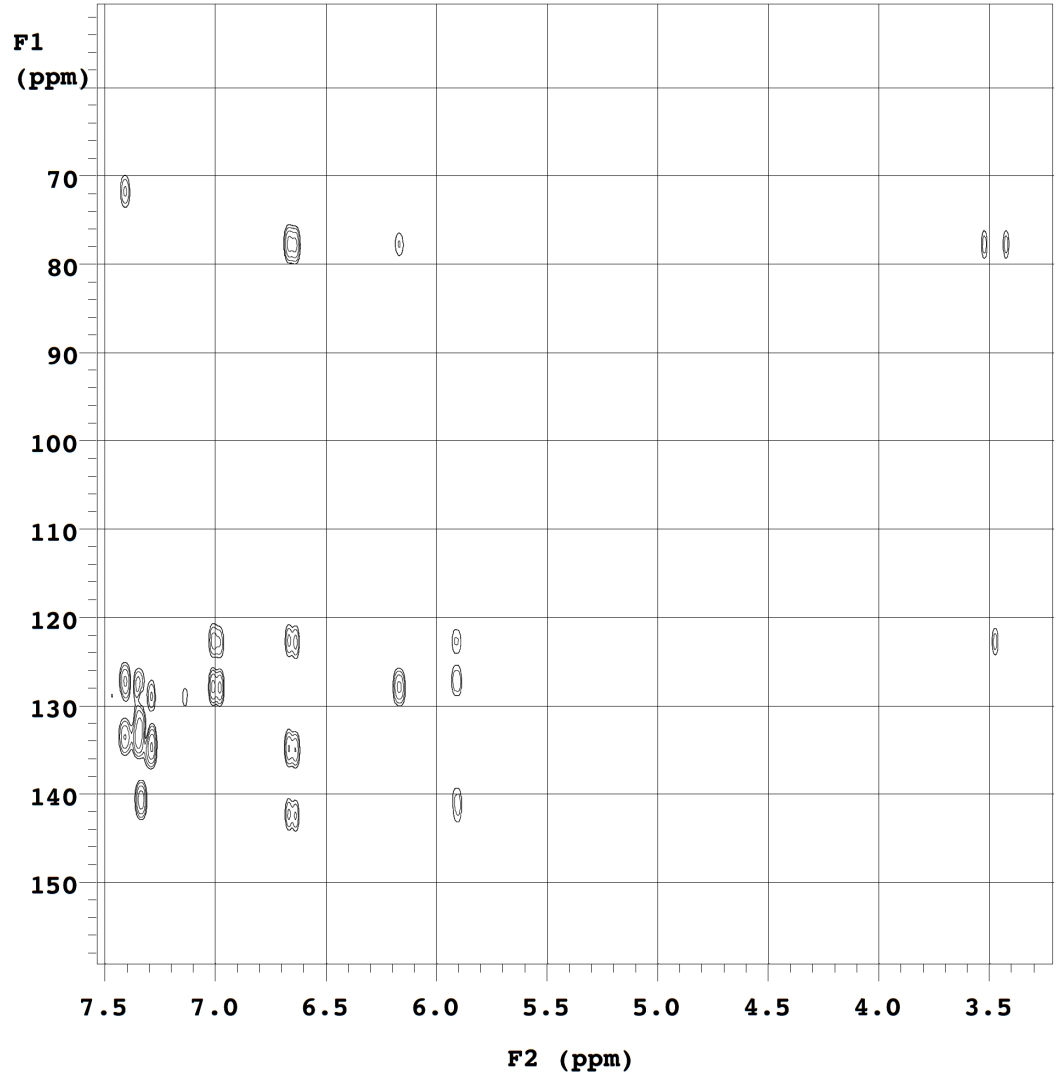
Pulse Sequence: gHMBC

Temp. 27.7 C / 300.9 K
Sample #12, Operator: WEST

Relax. delay 1.500 sec
Acq. time 0.500 sec
Width 6009.6 Hz
2D Width 33755.3 Hz
2 repetitions
170 increments
OBSERVE H1, 499.8039363 MHz
DATA PROCESSING
Sq. sine bell 0.100 sec
Shifted by -0.070 sec
F1 DATA PROCESSING
Sq. sine bell 0.003 sec
FT size 8192 x 1024
Total time 12 min



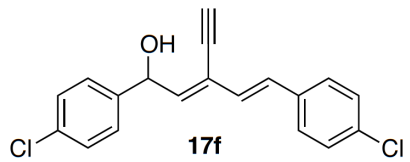
17f



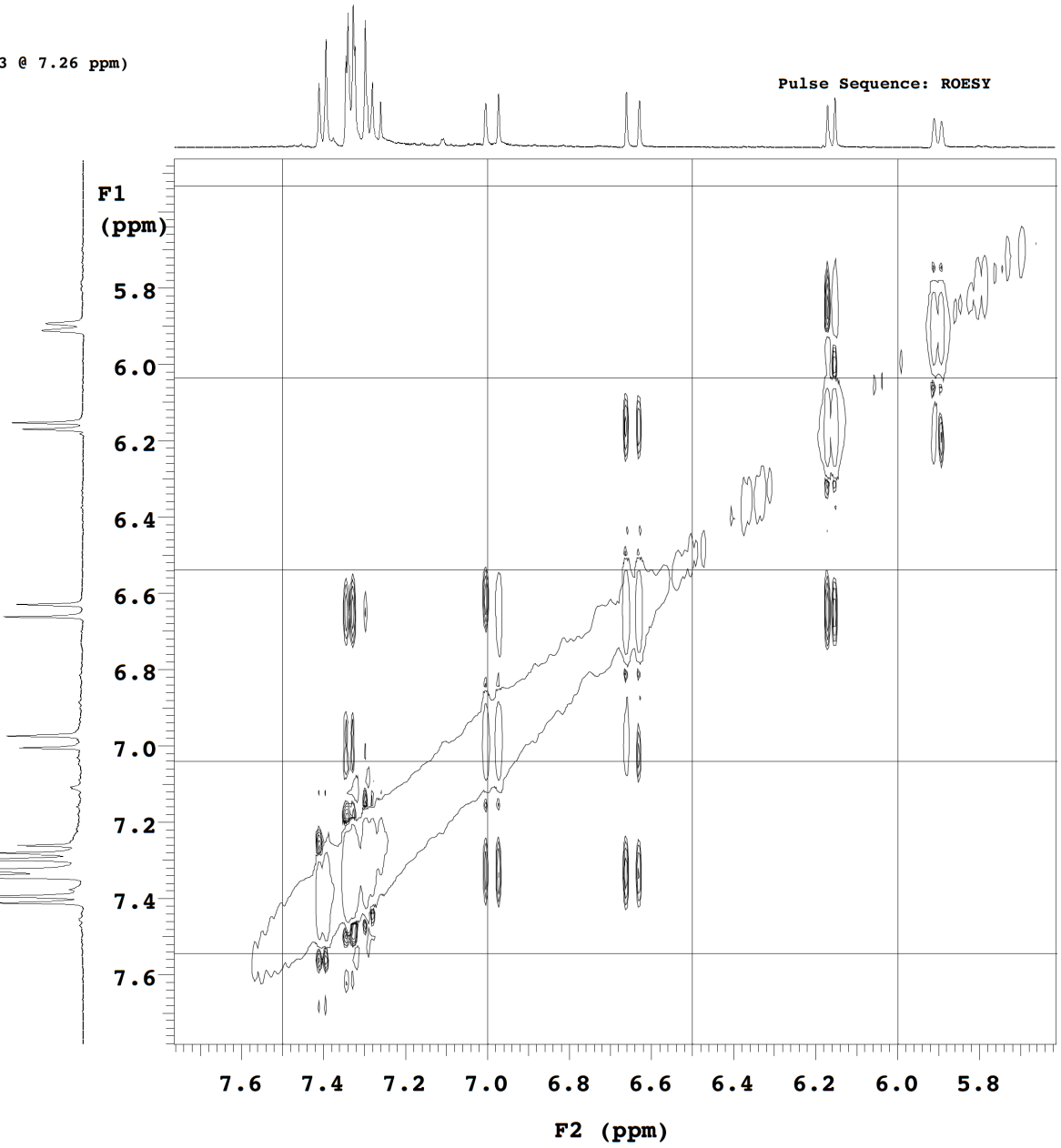
17f_ROESY
499.807 MHz H1 ROESY in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Temp. 27.7 C / 300.9 K
Sample #12, Operator: WEST

Relax. delay 1.000 sec
Acq. time 1.000 sec
Width 8012.8 Hz
2D Width 8012.8 Hz
16 repetitions
2 x 170 increments
OBSERVE H1, 499.8039391 MHz
DATA PROCESSING
Sq. sine bell 0.250 sec
Shifted by -0.250 sec
F1 DATA PROCESSING
Sq. sine bell 0.017 sec
Shifted by -0.017 sec
FT size 8192 x 1024
Total time 3 hr, 39 min

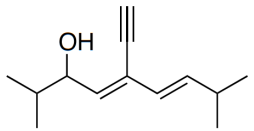


17f

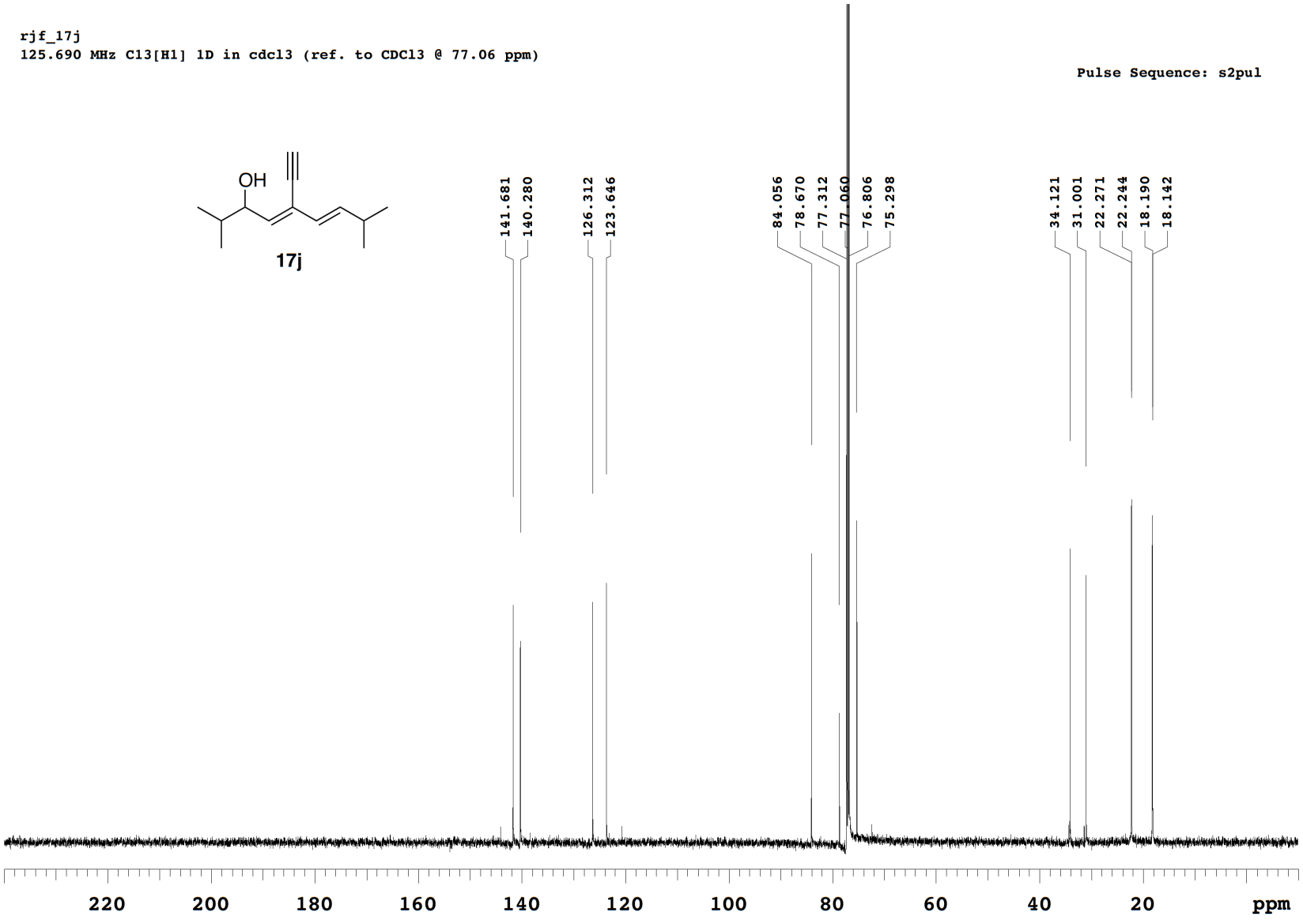


rjf_17j
499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: s2pul

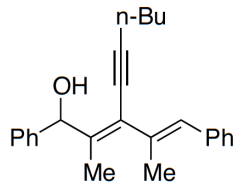


17j

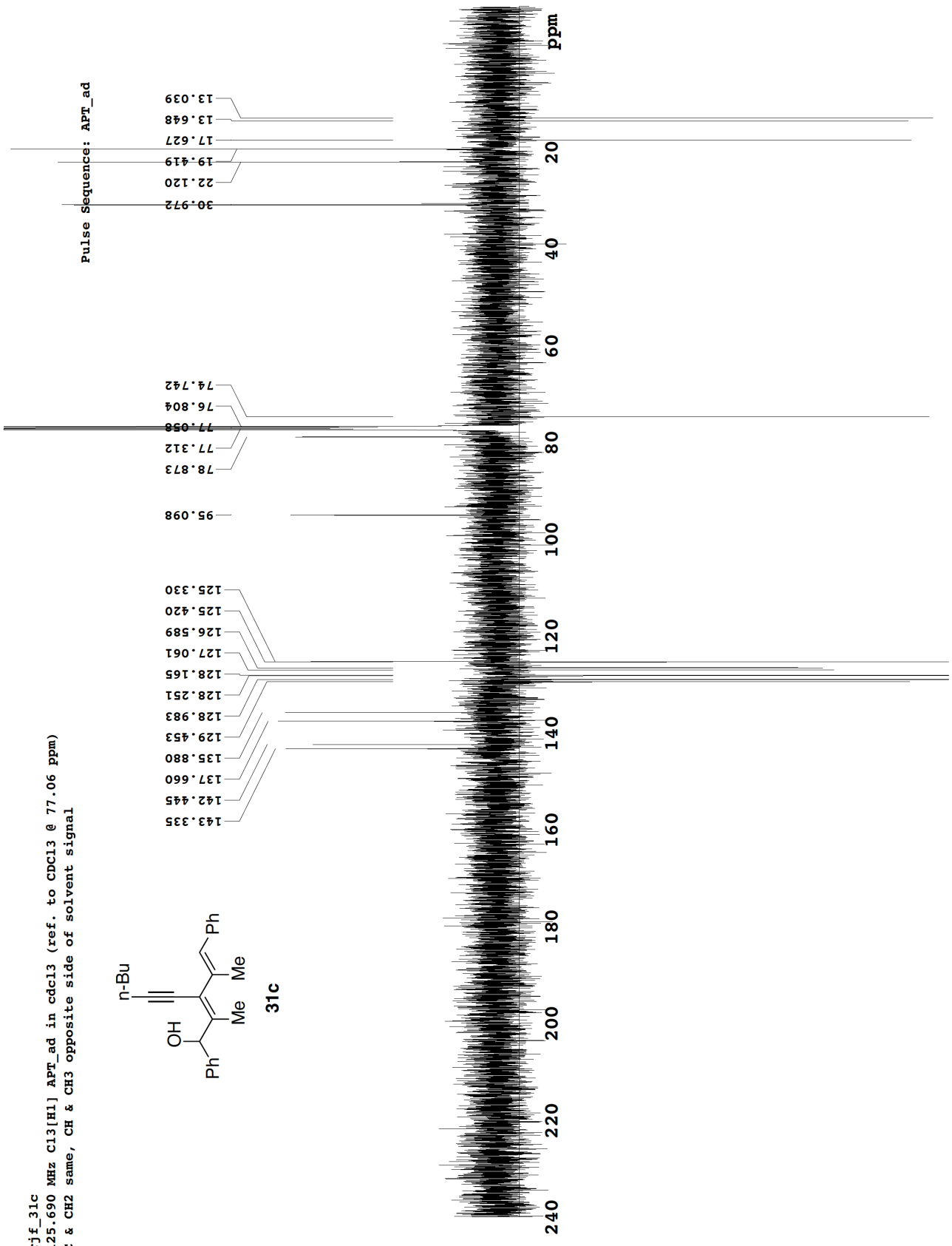

rjf_17j
125.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: s2pul
OH
17j
141.681
140.280
126.312
123.646
84.056
78.670
77.312
77.060
76.806
75.298
34.121
31.001
22.271
22.244
18.190
18.142
220
200
180
160
140
120
100
80
60
40
20
ppm

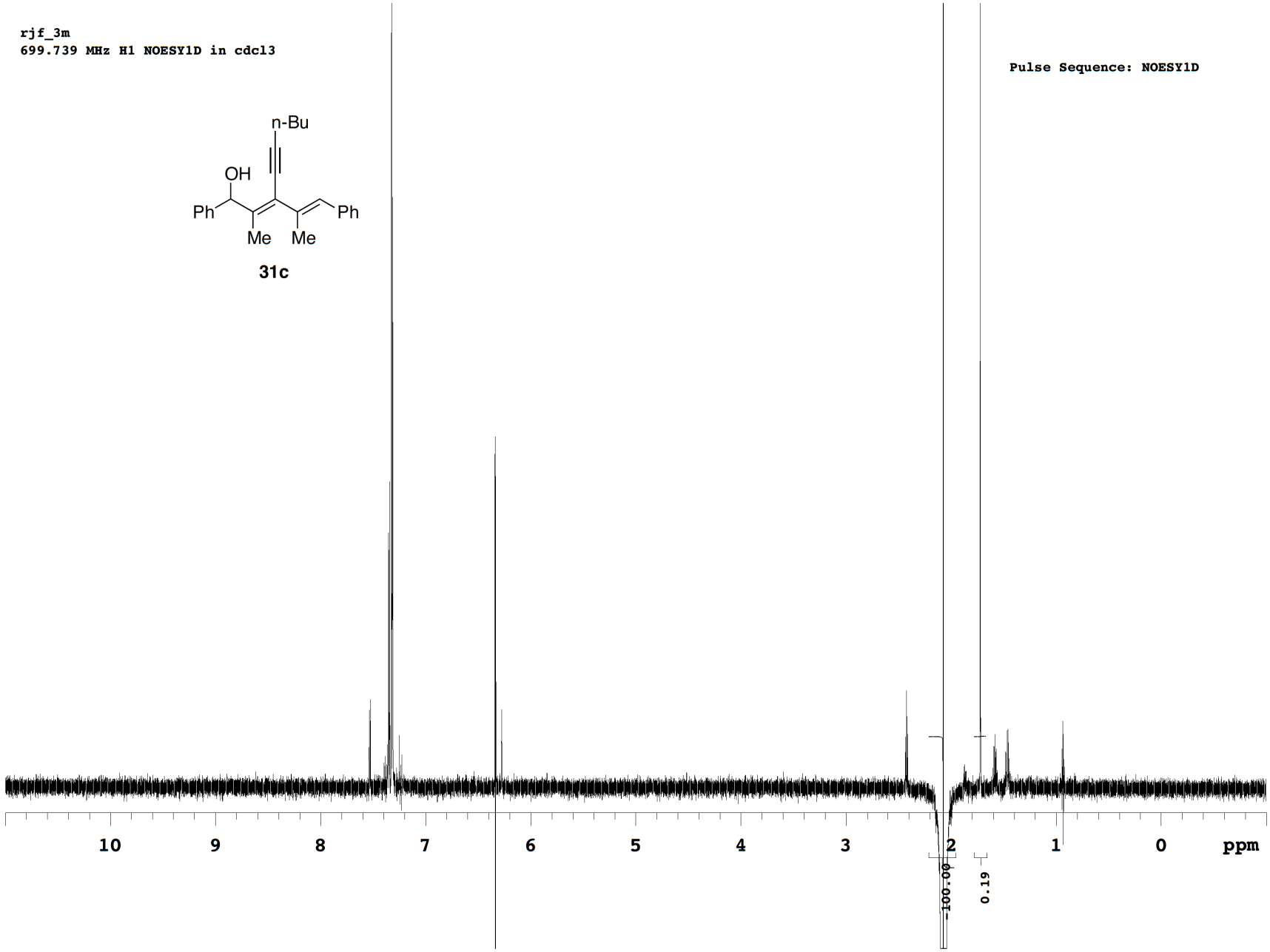
rjf_31c
699.738 MHz H1 1D in cdcl3

Pulse Sequence: s2pul



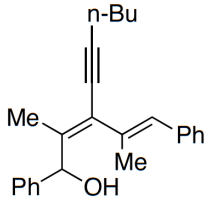
31c


rjf_31c
125.690 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal
Pulse Sequence: APT_ad
13.039
13.648
17.627
19.419
22.120
30.972
74.742
76.804
77.058
77.312
78.873
95.098
125.330
125.420
126.589
127.061
128.165
128.251
128.983
129.453
135.880
137.660
142.445
143.335
ppm
n-Bu
OH
Ph
Me
Me
Ph
31c

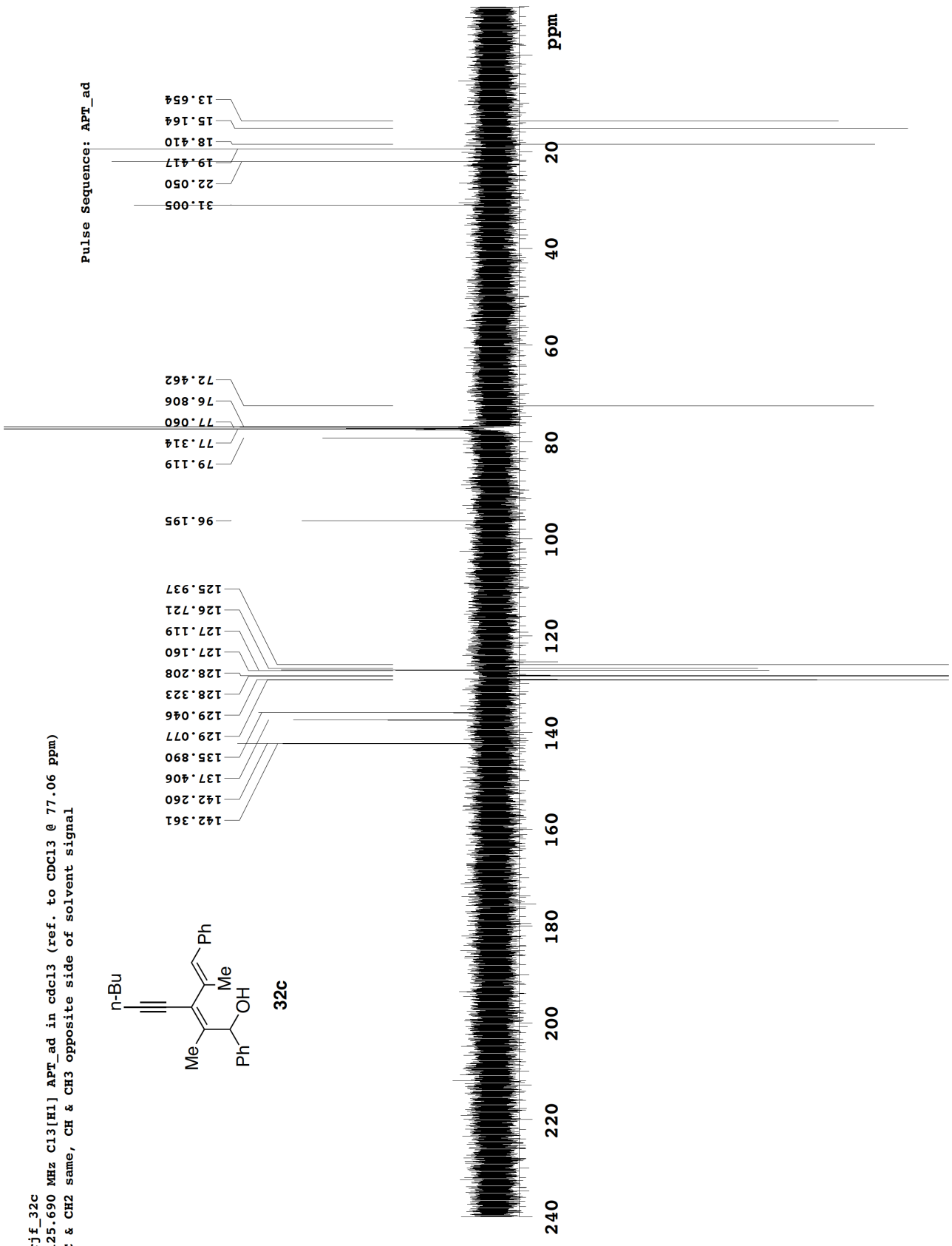

rjf_3m
699.739 MHz H1 NOESY1D in cdcl3
Pulse Sequence: NOESY1D
n-Bu
OH
Ph
Ph
Me
Me
31c
10
9
8
7
6
5
4
3
2
1
0
ppm
100.00
0.19

rjf_32c
699.738 MHz H1 1D in cdcl3

Pulse Sequence: s2pul

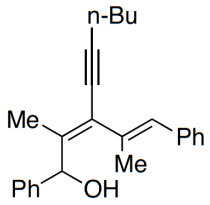


32c


rjf_32c
125.690 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal
Pulse Sequence: APT_ad
13.654
15.164
18.410
19.417
22.050
31.005
72.462
76.806
77.060
77.314
79.119
96.195
125.937
126.721
127.119
127.160
128.208
128.323
129.046
129.077
135.890
137.406
142.260
142.361
ppm
n-Bu
Me
Ph
OH
Me
Ph
32c

rjf_32c
699.739 MHz H1 NOESY1D in cdcl3

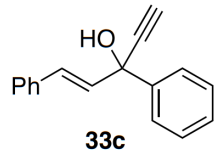
Pulse Sequence: NOESY1D



32c

rjf_33c
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

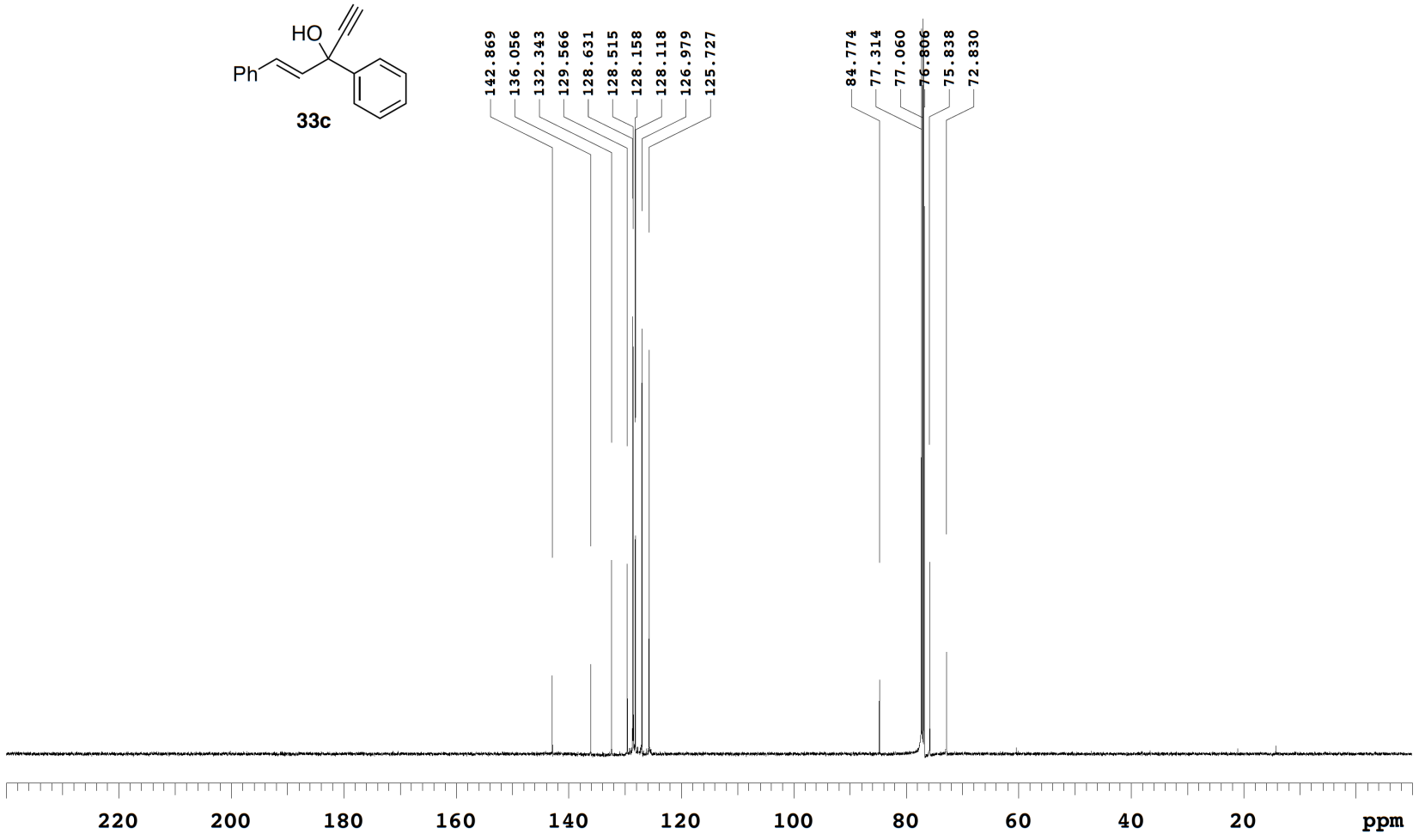
Pulse Sequence: PRESAT



33c

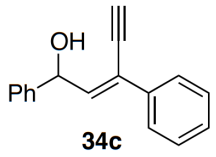
rjf_33c
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)

Pulse Sequence: s2pul

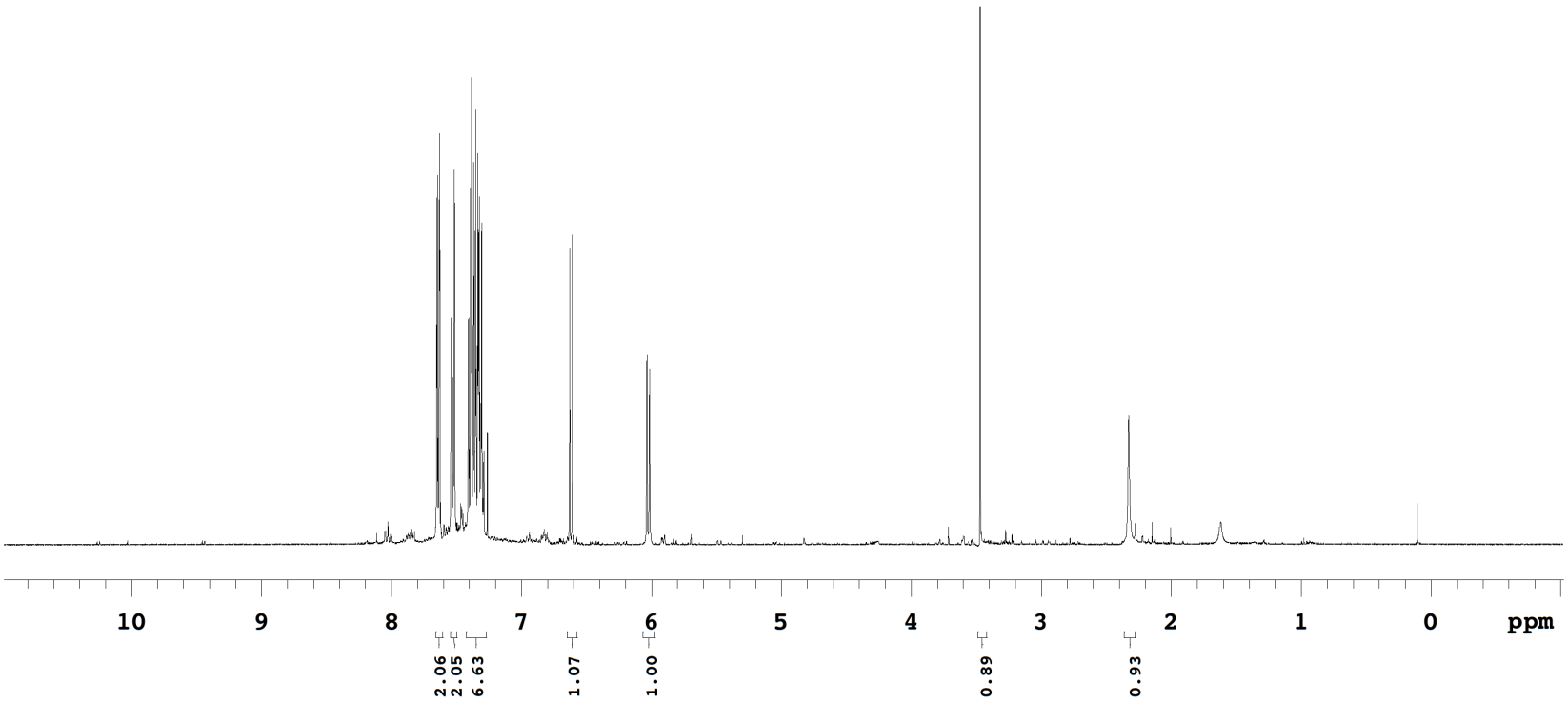


rjf_34c
400.392 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: PRESAT

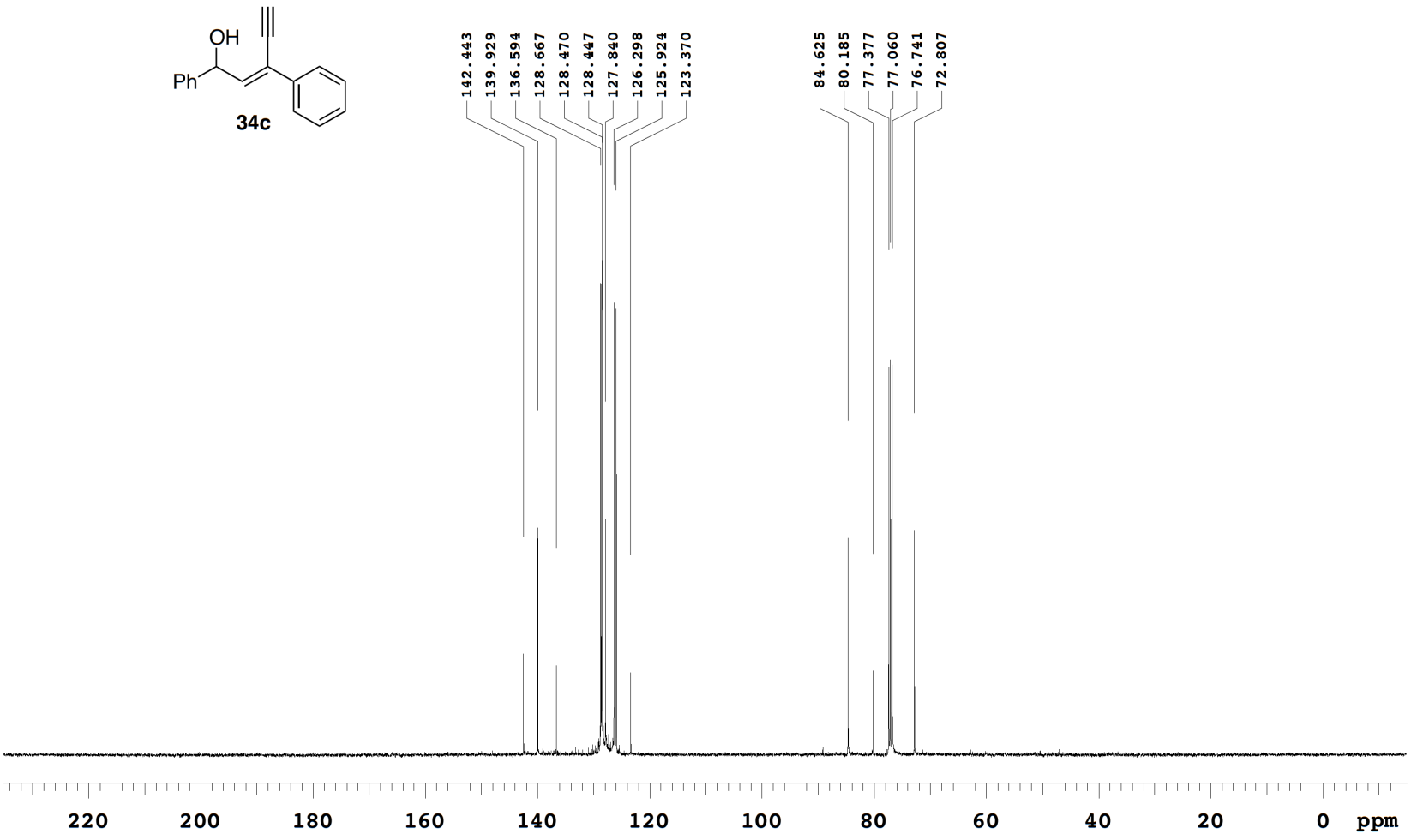


34c

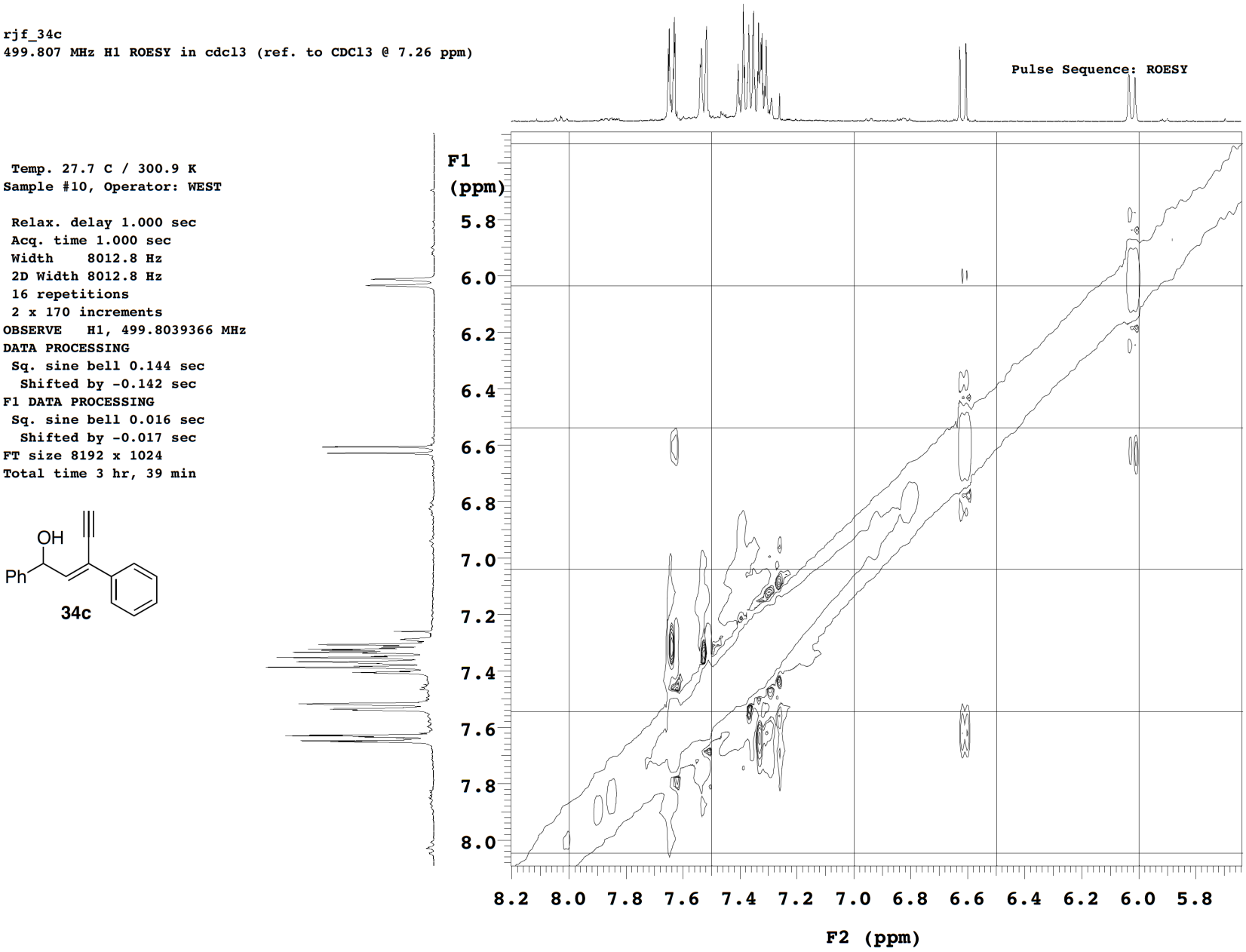


rjf_34c
100.689 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)

Pulse Sequence: s2pul



rjf_34c
499.807 MHz H1 ROESY in cdcl3 (ref. to CDCl3 @ 7.26 ppm)



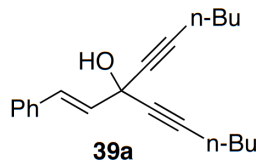
Temp. 27.7 C / 300.9 K
Sample #10, Operator: WEST

Relax. delay 1.000 sec
Acq. time 1.000 sec
Width 8012.8 Hz
2D Width 8012.8 Hz
16 repetitions
2 x 170 increments
OBSERVE H1, 499.8039366 MHz
DATA PROCESSING
Sq. sine bell 0.144 sec
Shifted by -0.142 sec
F1 DATA PROCESSING
Sq. sine bell 0.016 sec
Shifted by -0.017 sec
FT size 8192 x 1024
Total time 3 hr, 39 min

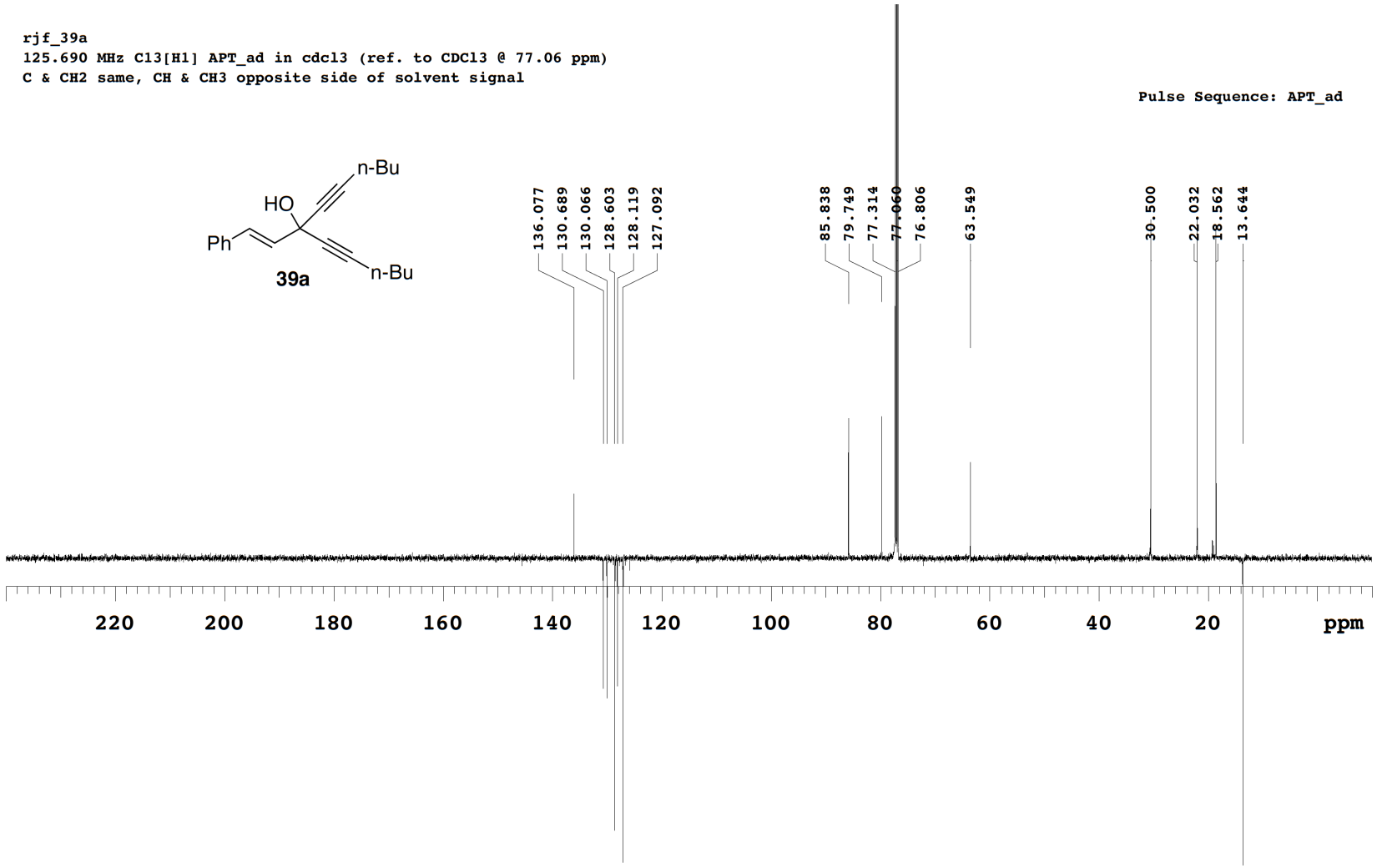
34c

rjf_39a
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: PRESAT

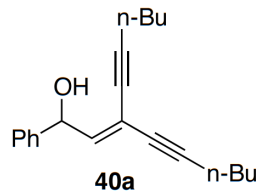


39a

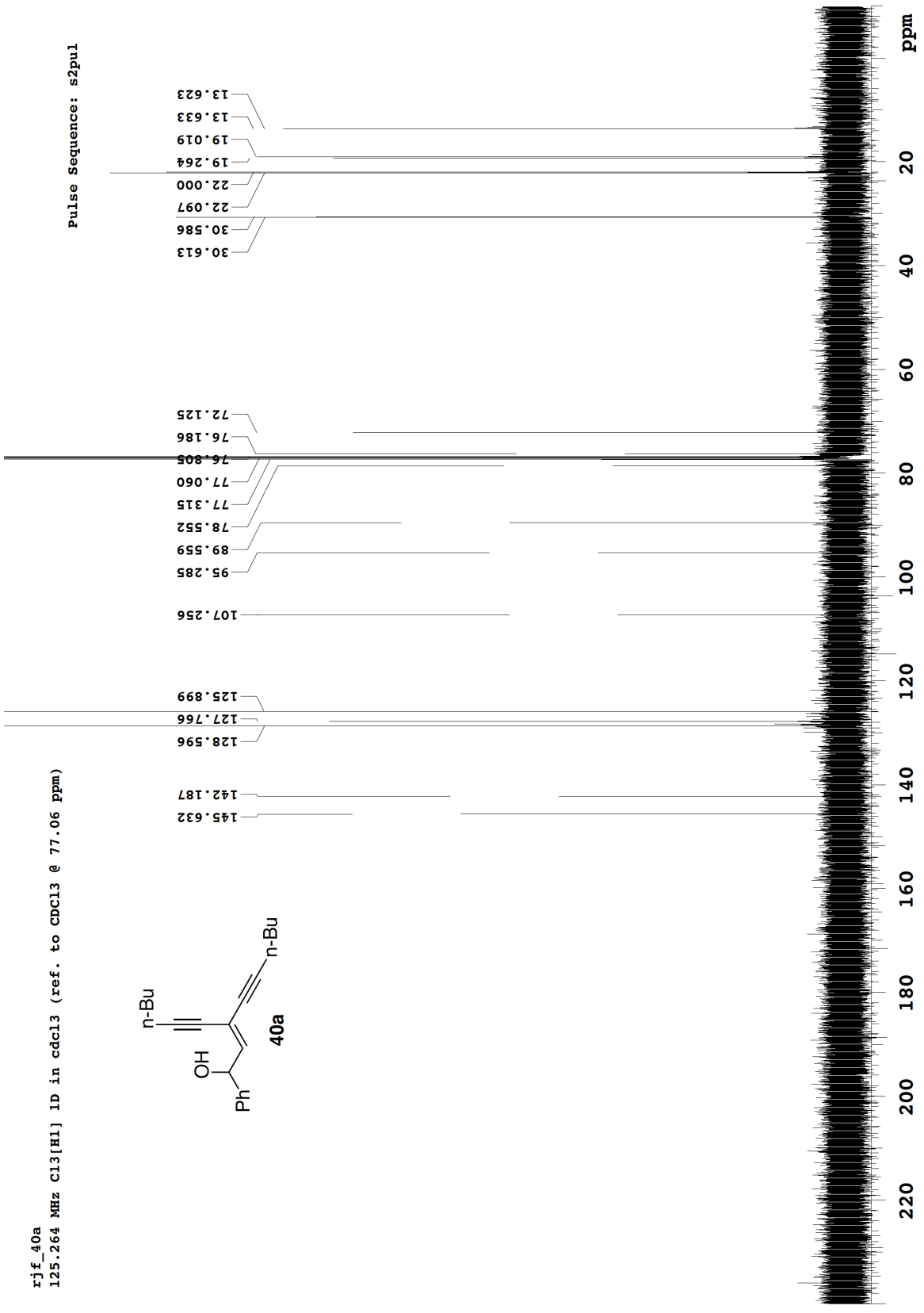

rjf_39a
125.690 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal
Pulse Sequence: APT_ad
n-Bu
HO
Ph
n-Bu
39a
136.077
130.689
130.066
128.603
128.119
127.092
85.838
79.749
77.314
77.060
76.806
63.549
30.500
22.032
18.562
13.644
220
200
180
160
140
120
100
80
60
40
20
ppm

rjf_40a
498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: s2pul

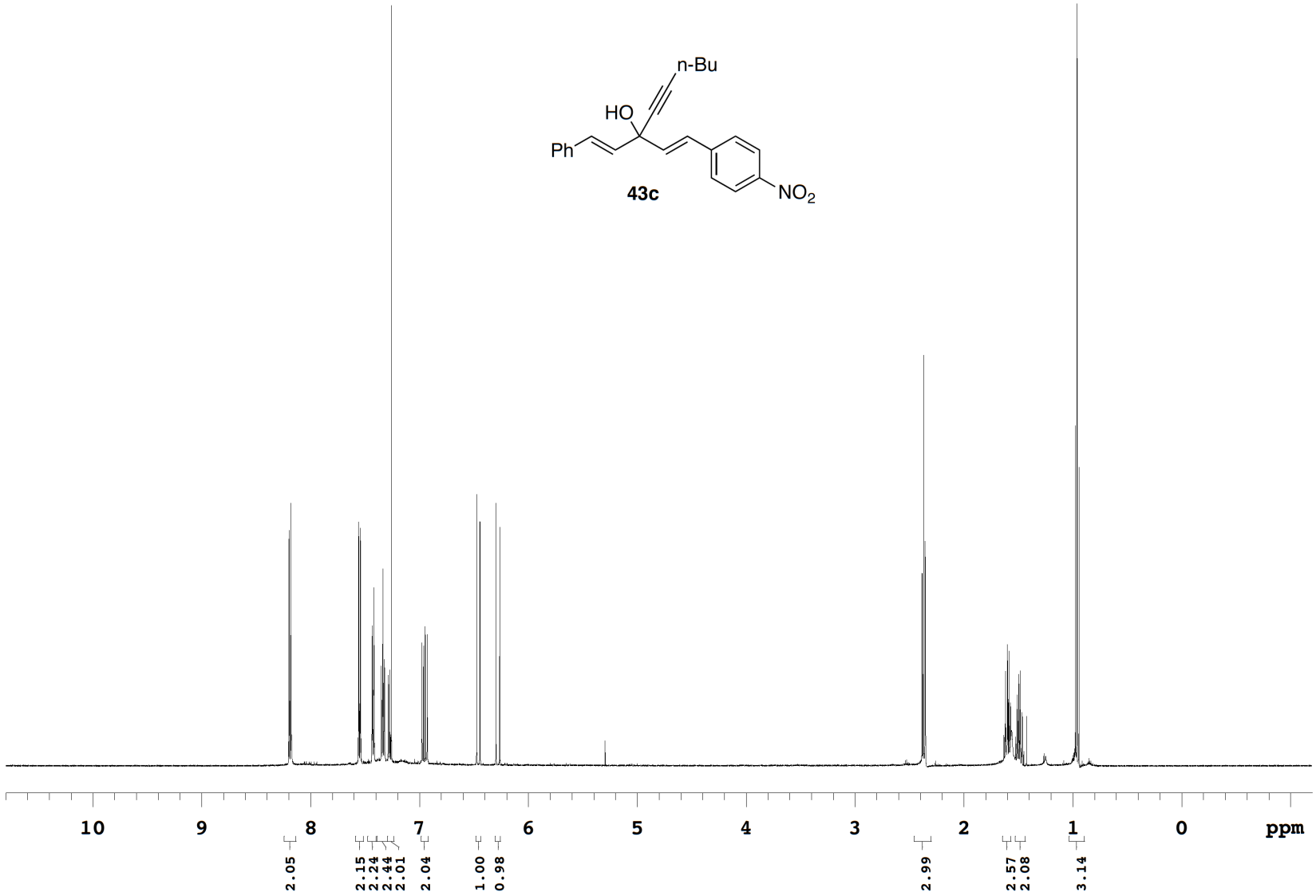


40a

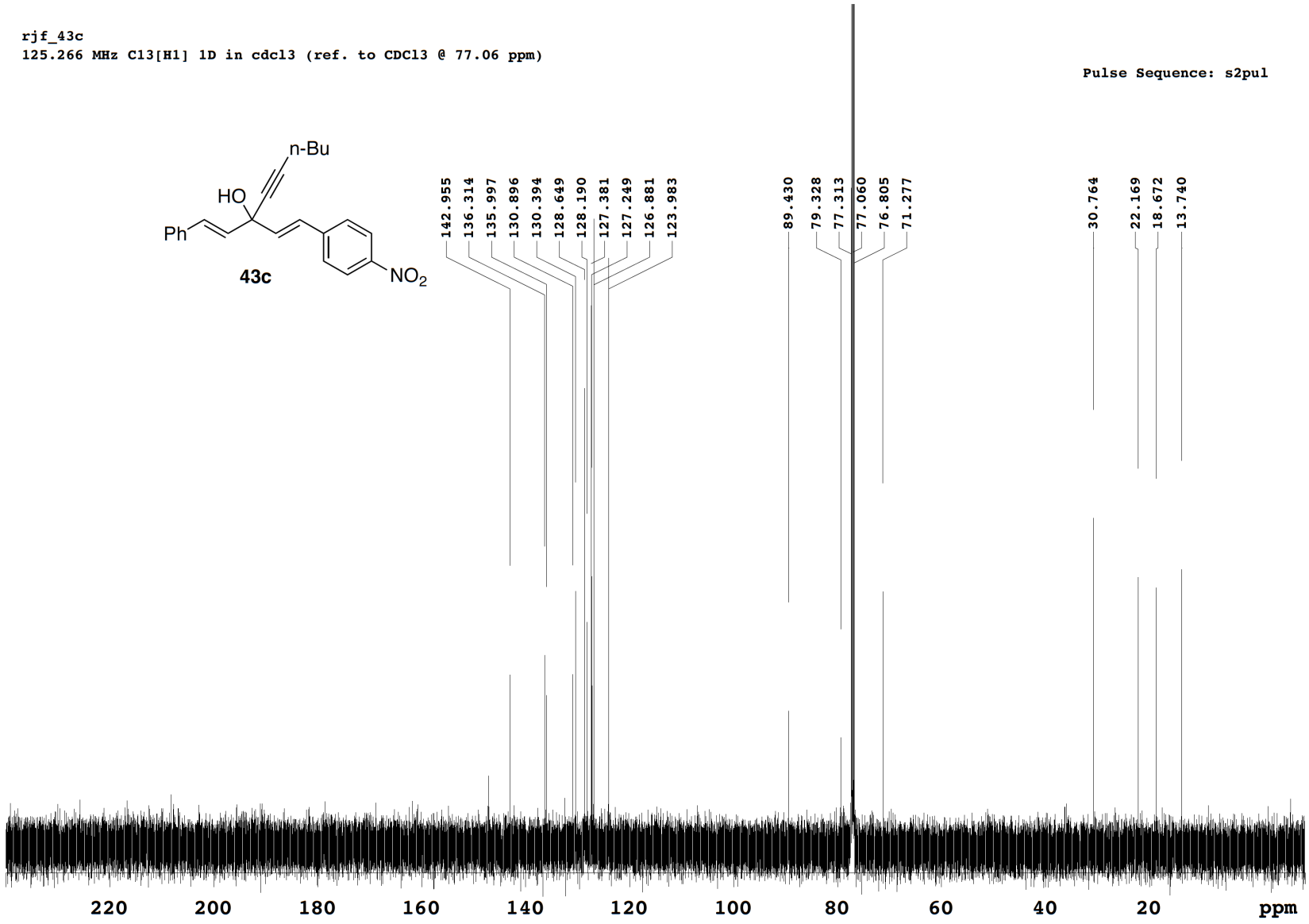

rjf_40a
125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: s2pul
n-Bu
n-Bu
OH
Ph
40a
145.632
142.187
128.596
127.766
125.899
107.256
95.285
89.559
78.552
77.315
77.060
76.805
76.186
72.125
30.613
30.586
22.097
22.000
19.264
19.019
13.633
13.623
ppm
220
200
180
160
140
120
100
80
60
40
20

rjf_43c
498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

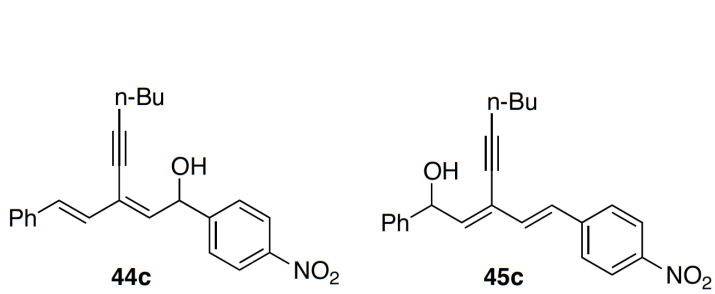
Pulse Sequence: s2pul



43c

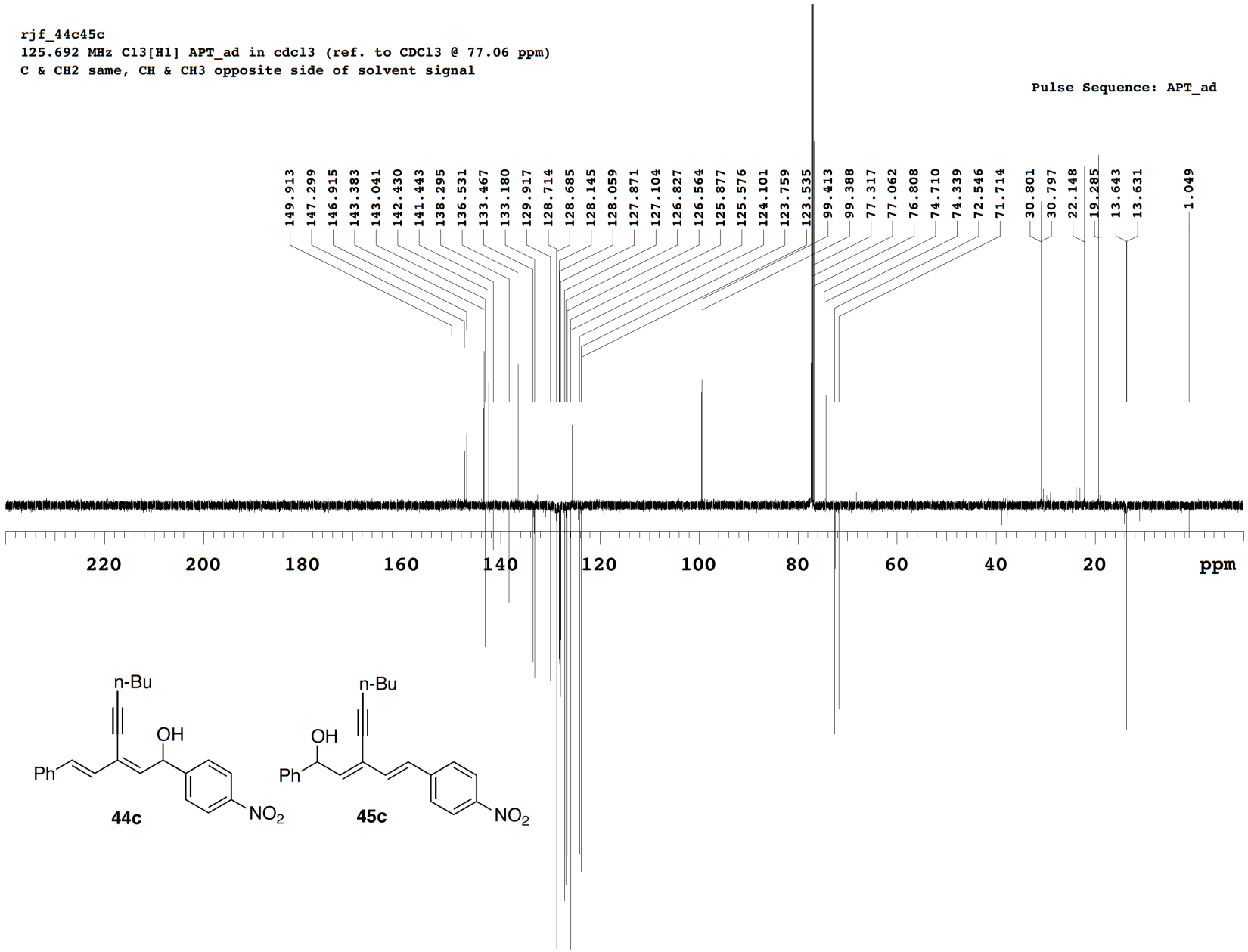

rjf_43c
125.266 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
Pulse Sequence: s2pul
n-Bu
HO
Ph
NO2
43c
142.955
136.314
135.997
130.896
130.394
128.649
128.190
127.381
127.249
126.881
123.983
89.430
79.328
77.313
77.060
76.805
71.277
30.764
22.169
18.672
13.740
220
200
180
160
140
120
100
80
60
40
20
ppm

rjf_44c45c
499.815 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)



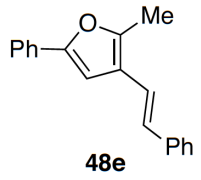
44c

45c


rjf_44c45c
125.692 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal
Pulse Sequence: APT_ad
149.913
147.299
146.915
143.383
143.041
142.430
141.443
138.295
136.531
133.467
133.180
129.917
128.714
128.685
128.145
128.059
127.871
127.104
126.827
126.564
125.877
125.576
124.101
123.759
123.535
99.413
99.388
77.317
77.062
76.808
74.710
74.339
72.546
71.714
30.801
30.797
22.148
19.285
13.643
13.631
1.049
220
200
180
160
140
120
100
80
60
40
20
ppm
n-Bu
OH
Ph
NO2
44c
n-Bu
OH
Ph
NO2
45c

rjf_48e
499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

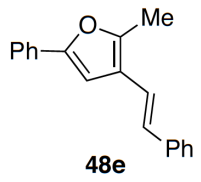
Pulse Sequence: s2pul



48e

rjf_48e
125.692 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal

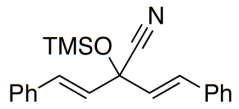
Pulse Sequence: APT_ad



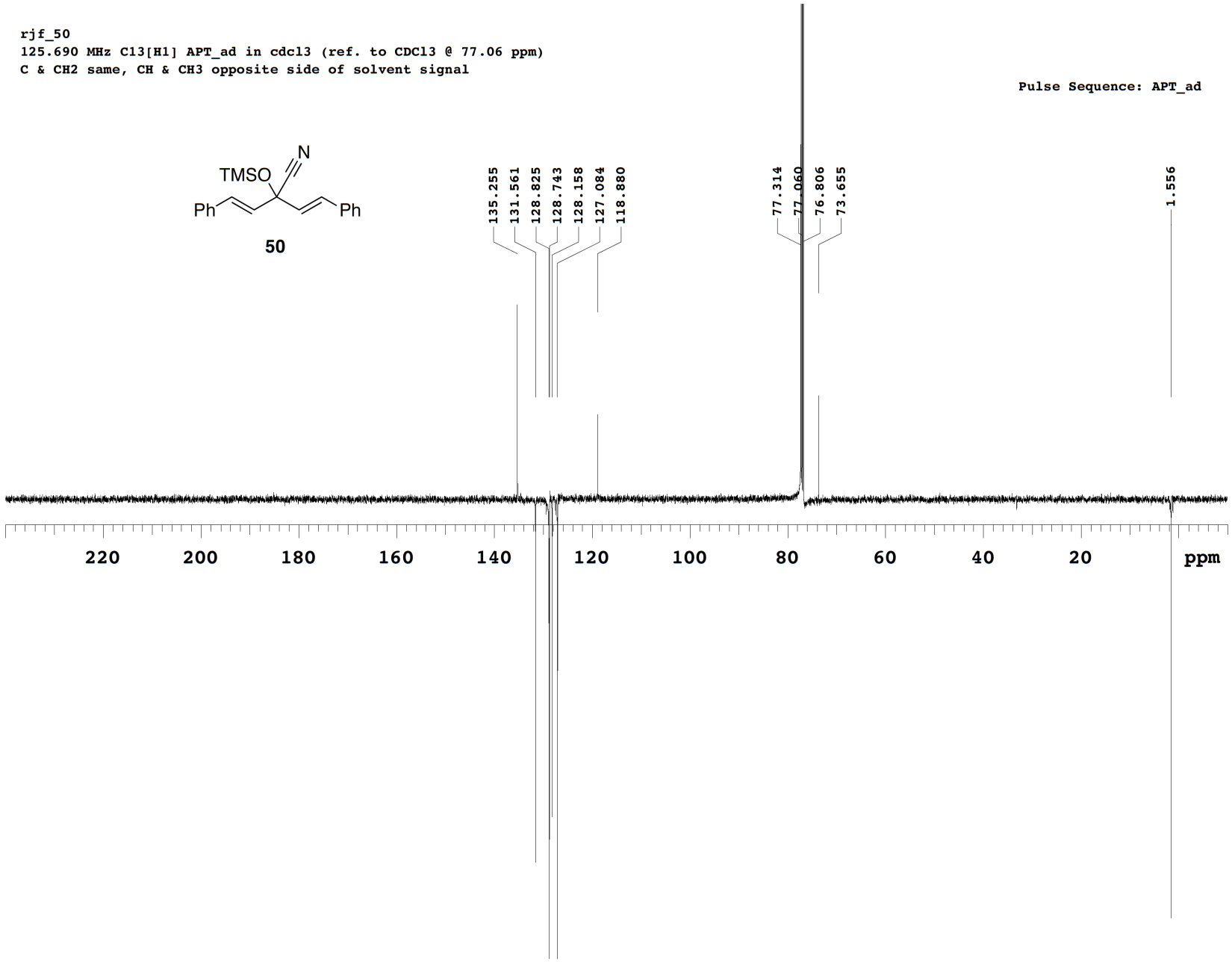
48e

rjf_50
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: PRESAT

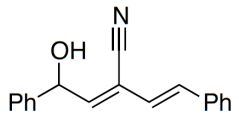


50

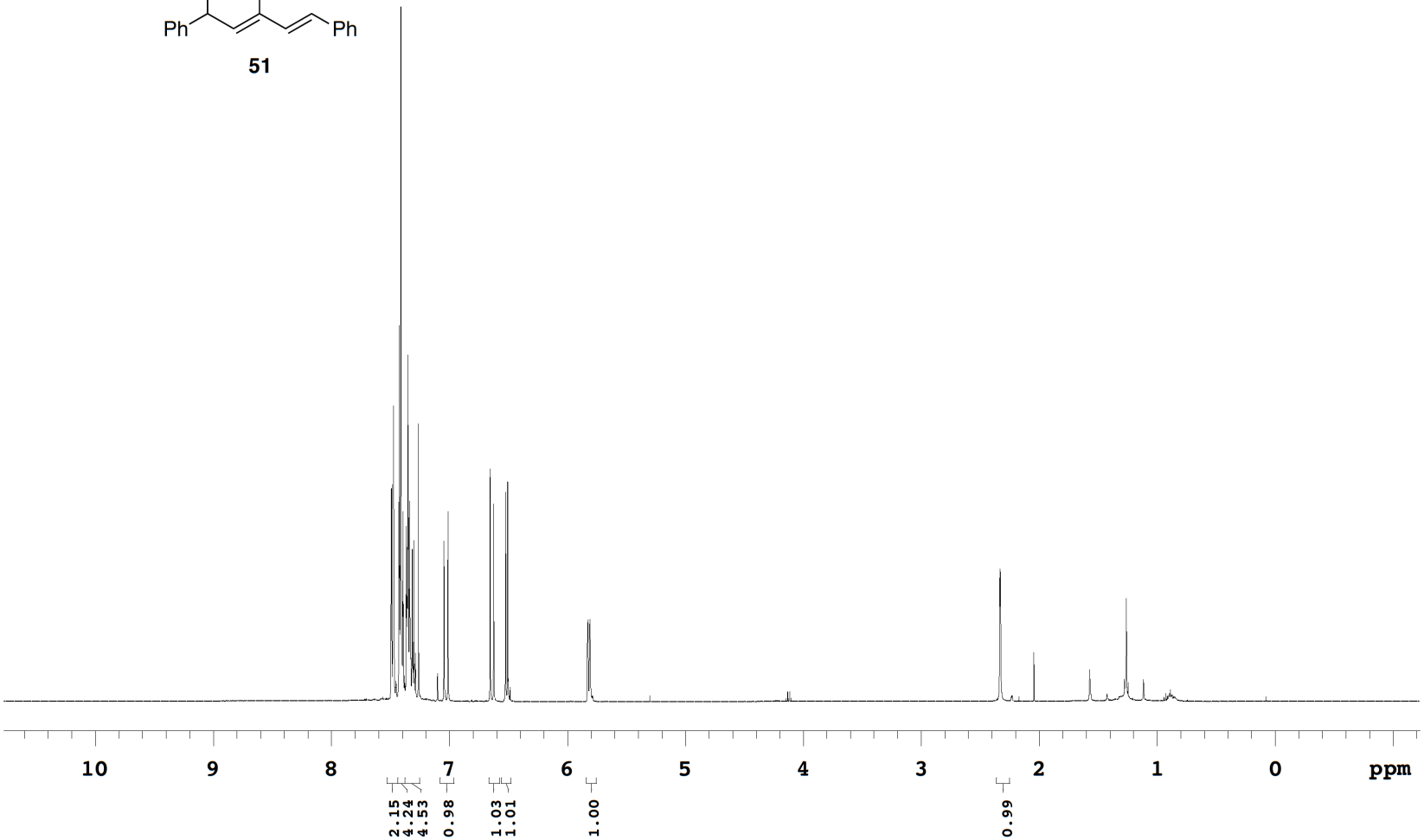

rjf_50
125.690 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal
Pulse Sequence: APT_ad
TMSO
N
Ph
Ph
50
135.255
131.561
128.825
128.743
128.158
127.084
118.880
77.314
77.060
76.806
73.655
1.556
220
200
180
160
140
120
100
80
60
40
20
ppm

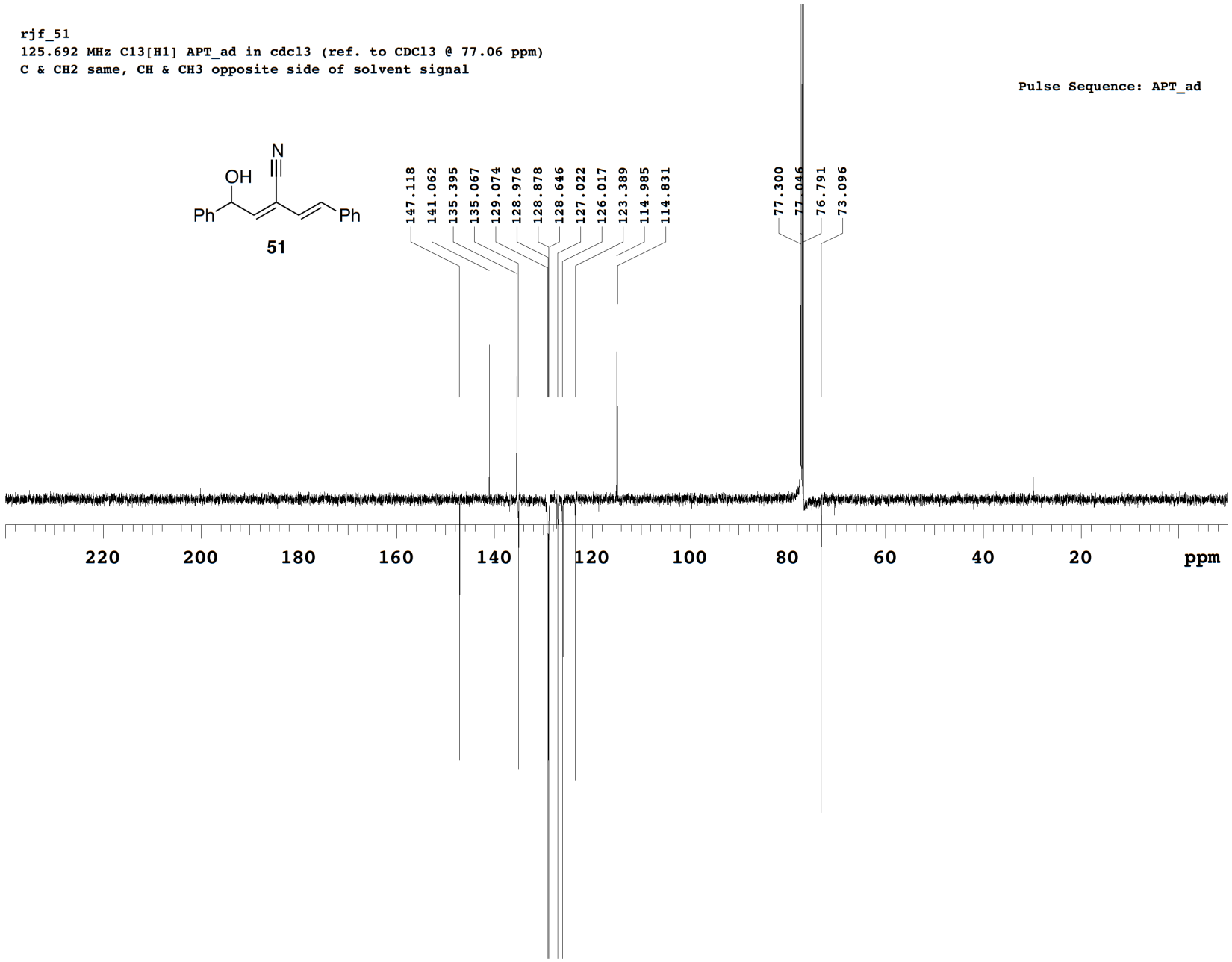
rjf_51
499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

Pulse Sequence: s2pul



51




rjf_51
125.692 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
C & CH2 same, CH & CH3 opposite side of solvent signal
Pulse Sequence: APT_ad
N
OH
Ph
Ph
51
147.118
141.062
135.395
135.067
129.074
128.976
128.878
128.646
127.022
126.017
123.389
114.985
114.831
77.300
77.046
76.791
73.096
220
200
180
160
140
120
100
80
60
40
20
ppm