New Investigations in the Interrupted Nazarov Reaction

by

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Abstract

The five-membered carbocycle is a structural motif found in a plethora of natural products and bioactive compounds. The Nazarov reaction has emerged as an effective method to synthesize cyclopentenones and acts as a tool for adding structural complexity to molecular frameworks. This dissertation will discuss several projects involving the Nazarov cyclization and its use to build functionality to the cyclopentanoid framework.

Chapter 1 provides a detailed recount of recent advances in Nazarov chemistry. Focus on methods to induce enantioselectivity, the use of alternative substrates as Nazarov reaction precursors, and the use of the Nazarov reaction in total synthesis is presented. Chapter 2 describes the formation of bridged bicyclic compounds via a [3+3]-cycloaddition between organoazides and the Nazarov intermediate. These cycloadducts were also found to thermally decompose to produce ring-enlarged dihydropyridones and 6-methylenepiperidinones.

In Chapter 3, details the attempted development of a domino Nazarov cyclization/Baeyer-Villiger oxidation are provided. While the desired 3,4-dihydropyra-2-one was formed with the use of bis(trimethylsilyl)peroxide as the oxidant, optimization of the transformation failed to produce synthetically useful yields.

Chapter 4 divulges the findings of Nazarov cyclizations of 2-hydroxyalkyl-1,4-diene-3-ones. Originally proposed as substrates that could undergo domino Nazarov cyclization/semipinacol rearrangements, these compounds were found to readily produce alkylidene cyclopentenones under Lewis acid conditions. These

substrates provided insight into the effect that 2-hydroxyalkyl substituents have on the charge density of the oxyallyl cation intermediate of the Nazarov reaction and subsequent alkene formation.

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List of Symbols and Abbreviations

^{1}H	proton
^{13}C	carbon-13
Å	angstrom
Ac	acetyl
Ac_2O	acetic anhydride
Anal.	elemental analysis
app.	apparent (spectral)
aq	aqueous solution
Ar	aryl
Ar_f	3,5-bis(trifluoromethyl)phenyl
B:	unspecified base
Bn	benzyl
br	broad (spectral)
Bu	butyl
°C	degrees Celsius
calcd	calculated
cat.	indicates that the reagent was used in a catalytic amount
cm^{-1}	wave numbers
COSY	H-H correlation spectroscopy
conc.	concentrated
Cy	cyclohexyl
d	day(s); doublet (spectral)

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublets (spectral)
ddd	doublet of doublet of doublets (spectral)
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	density functional theory
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
DMP	Dess-Martin periodinane
dr	diastereomeric ratio
dt	doublet of triplets (spectral)
dtd	doublet of triplets of doublets (spectral)
E^+	unspecified electrophile
EDG	electron-donating group
ee	enantiomeric excess
EI	electron impact (mass spectrometry)
ent	enantiomer

er	enantiomeric ratio
ESI	electrospray ionization (mass spectrometry)
Et	ethyl
EtOAc	ethyl acetate
equiv.	equivalent(s)
EWG	electron-withdrawing group
g	gram(s)
h	hour(s)
Hex	hexyl
HFIP	hexafluoroisopropanol
HMBC	heteronuclear multiple bond coherence (spectral)
HMPA	hexamethylphosphoramide
HSQC	heteronuclear single quantum coherence (spectral)
HRMS	high resolution mass spectrometry
hν	light
Hz	hertz
IPr	1,3-bis(diisopropylphenyl)imidazol-2-ylidene
i-Pr	isopropyl
IR	infrared
J	coupling constant
kcal	kilocalories
KHMDS	potassium bis(trimethylsilyl)amide
L	litre(s); unspecified ligand

LA	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
Ln*	chiral ligand
LUMO	lowest unoccupied molecular orbital
M	molar
m	multiplet (spectral)
M^+	generalized Lewis acid; molecular ion
mCPBA	meta-chloroperbenzoic acid
Me	methyl
Mes	mesityl
mg	milligram(s)
MHz	megahertz
MLn	unspecified metal-ligand pair
µL	microlitre(s)
µW	microwave(s)
min	minute(s)
mL	millilitre(s)
mm	millimeter(s)
mmol	millimole(s)
mol	mole(s)
MOM	methoxymethyl

mp	melting point
MS	molecular sieves
Ms	methanesulfonyl
m/z	mass to charge ratio
n-Bu	normal butyl
nm	nanometer
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
n-Pr	normal propyl
Nuc	unspecified nucleophile
OMOM	methoxymethyl ether
ORTEP	Oak Ridge Thermal-Ellipsoid Plot
PCC	pyridinium chlorochromate
PDC	pyridium dichromate
Ph	phenyl
PMP	para-methoxy phenyl
ppm	parts per million
Pr	propyl
pybox	bixoxazoline ligand
R	generalized alkyl group of substituent
R_f	retention factor (in chromatography)
rOe	rotating-frame Overhauser enhancement
rt	room temperature

s	singlet (spectral)
sat'd	saturated
t	triplet (spectral)
T	temperature
TBAF	tetrabutylammonium fluoride
TBS	tert-butyldimethylsilyl
t-Bu	tert-butyl
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylenediamine
TMS	trimethylsilyl
Tol	tolyl
TROESY	transverse rotating-frame Overhauser enhancement spectroscopy
Ts	p-toluenesulfonyl
TsOH	p-toluenesulfonic acid

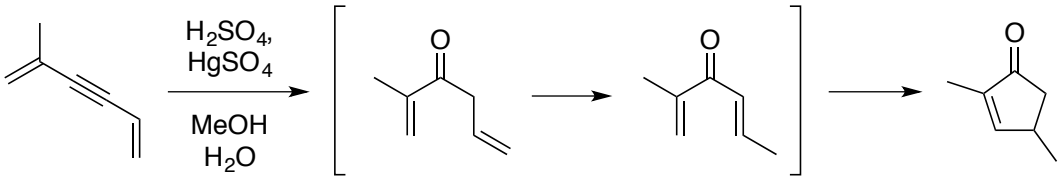
X	unspecified Lewis acid or protic acid
δ	chemical shift
Δ	heat

Chapter 1

The Nazarov Reaction

1.1 The Nazarov Cyclization

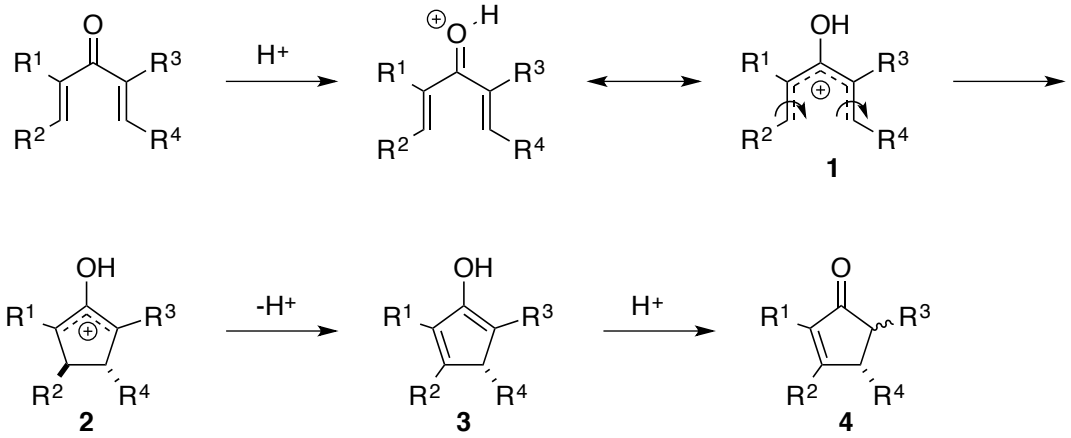
The Nazarov cyclization has long existed as an effective means for the synthesis of cyclopentenones.[1] The first example of a Nazarov reaction was published by Vorländer in 1903,[2] but it remained relatively unexplored until the 1940s. At this time Nazarov and Zaretskaya showed that hydration of dienynes in the presence of mercury salts formed cyclopentenones (Scheme 1.1).[3] The mechanism for this transformation was later elucidated, and 1,4-dien-3-ones were identified as key intermediates in the transformation.[4] Eventually, the conversion of 1,4-dien-3-ones to cyclopentenones would be synonymous with the name Nazarov reaction, and would be heavily investigated for substrate scope.[1,5]



Scheme 1.1 Nazarov's Hydration of Dienynes and Conversion to Cyclopentanones.

The mechanism for the traditional Nazarov reaction employing cross-conjugated dienones (Scheme 1.2) begins with complexation of the carbonyl oxygen with either a Lewis or Brønsted acid, forming a pentadienyl cation **1**. Intermediate **1** then undergoes a conrotatory 4π-electrocyclic ring closure, setting the

stereochemistry of the β- and β'-positions, and forming oxyallyl cation **2**. Deprotonation of intermediate **2** neutralizes the intermediate and forms cyclopentadienol **3**, which tautomerizes to yield cyclopentenone **4**.



Scheme 1.2 Mechanism for the Nazarov Cyclization.

One of the major drawbacks of the Nazarov reaction is the lack of selectivity in the elimination event. There are four possible elimination pathways that could take place to neutralize the oxyallyl cation intermediate and each of these pathways results in two possible diastereomers, making the reaction an unattractive choice for natural product synthesis when stereocontrol is required. However, this problem can be avoided through the use of directing groups that control the elimination step and lead to a predictable outcome of the reaction.

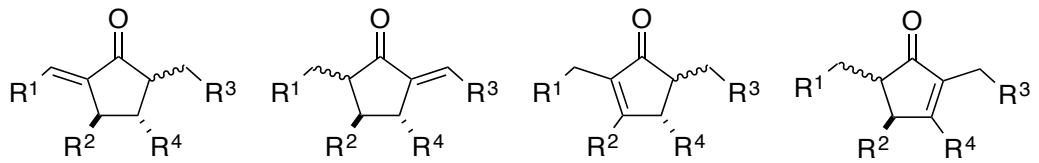
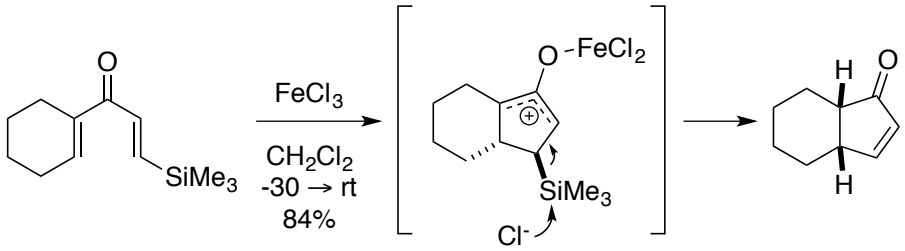


Figure 1.1 Possible Regioisomers Resulting from the Nazarov Reaction.

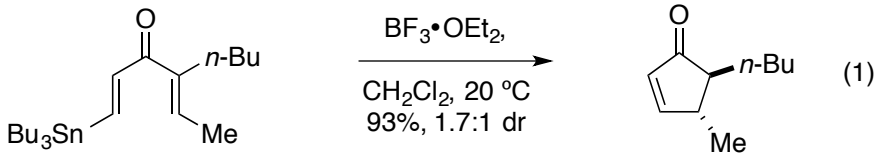
1.1.1 Directed Nazarov Cyclization

The Denmark group found that the regiochemistry of alkene formation could be controlled through the use of silyl-substituted dienones (Scheme 1.3).[5,6] The silyl group stabilizes the oxyallyl cation through the β-silyl effect,[7,8] allowing for a greater charge buildup on the less substituted side of the oxyallyl cation. Upon loss of the silyl group, the enone forms on the less substituted side, without formation of any of the other possible regioisomers.



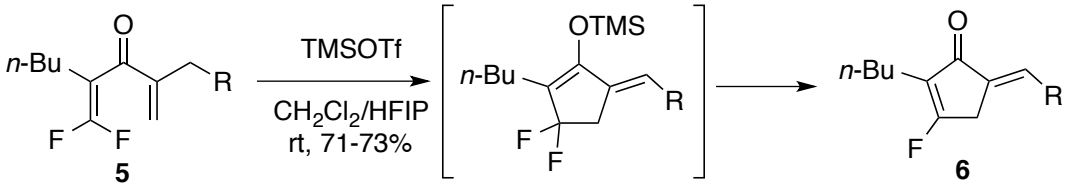
Scheme 1.3 The Silyl-Directed Nazarov Reaction.

Peel and Johnson added to this methodology with their findings on tin-directed Nazarov reactions.[9] β-Tributylstannyl substituted dienones were synthesized and subjected to a Lewis acid. In a manner similar to the silyl group in Denmark's work, the tin substituent effectively stabilizes the cyclopentenyl cation and collapses to form the unsubstituted alkene exclusively.



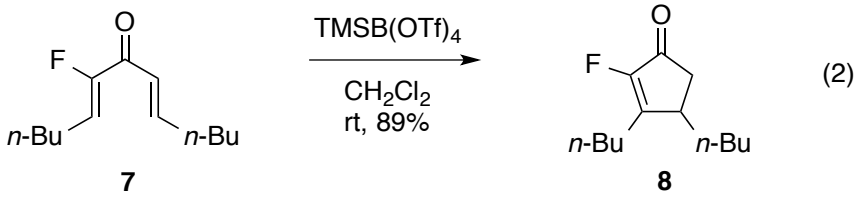
(1)

While silyl and stannyl substituents β-stabilize the oxyallyl cation intermediate, fluorine substitution has a β-destabilizing effect. The Ichikawa group demonstrated the effects of fluorine at the β-position of a dienone with 1,1-difluoro-1,4,diene-3-ones **5** (Scheme 1.4).[10] Exposure of these dienones to TMSOTf resulted in a Nazarov cyclization with exclusive exocyclic deprotonation distal to the fluorine substituents. The silyl enol ether intermediate then eliminated fluoride to provide alkylidene cyclopentenones **6**.



Scheme 1.4 Fluorine Directed Nazarov Reaction.

Fluorine, when at the α-position of a dienone, imparts an α-stabilizing effect, directing proton elimination towards the fluorine, in contrast to the β-substitution examples. Ichikawa and co-workers demonstrated this with dienone **7**, which produced cyclopentenone **8** in excellent yield, as a single regioisomer.[11]

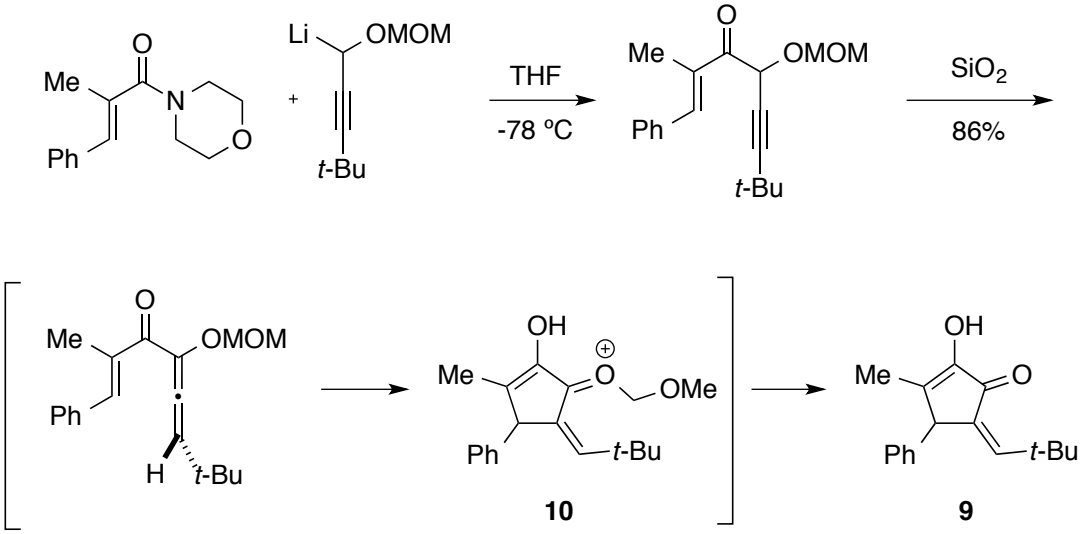


1.1.2 Polarized Dienones

Another drawback of the Nazarov reaction lies in the necessity for strong acids to invoke cyclization. Substitution of electron-donating groups at the α-

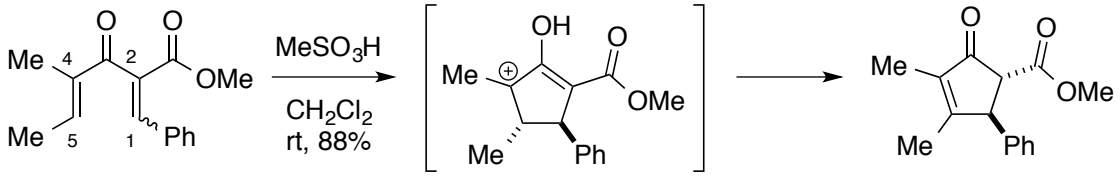
positions has an appreciable effect on both the ease of Nazarov cyclization and on the regioselectivity of the elimination event.[12] These specialized dienones impart partial negative charge on the reaction intermediates, often allowing for milder conditions to induce cyclization.[13] It is rationalized that the oxyallyl cation intermediate is stabilized, lowering the activation barrier for the transformation.

The effect of electron-donating substituents on the Nazarov cyclization is most evident in examples from the Tius group (Scheme 1.5), wherein alkoxy-allene substrates were synthesized via addition of lithiated propargyl ethers into morpholino amides.[14] Upon exposure to mildly acidic conditions, in this case silica gel, the alkyne isomerized to the alkoxy-allene which then underwent Nazarov cyclization to furnish **9**. It is believed that stabilization of the oxyallyl cation, as seen in intermediate **10**, in combination with the release of allenic strain, is the reason why the cyclization occurs under such mild conditions.



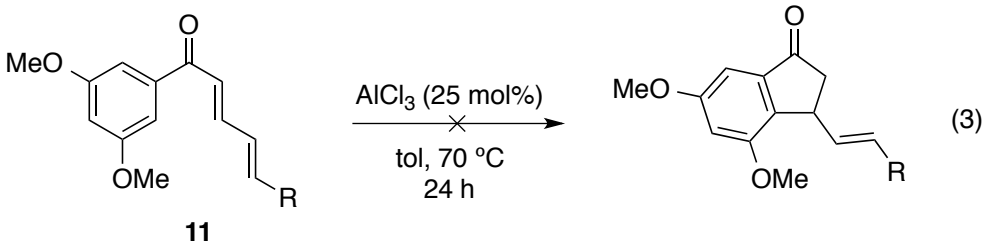
Scheme 1.5 Electron-Releasing Substituents and the Nazarov Reaction.

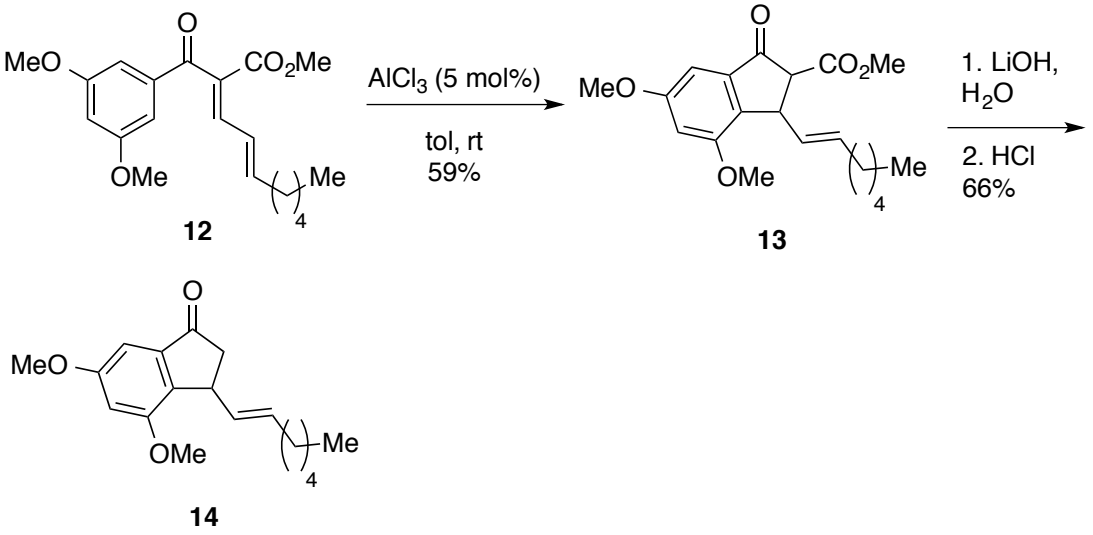
Electron-withdrawing groups at the C-2 position of the dienone have been shown to result in exclusive proton elimination distal to the electron-withdrawing group (Scheme 1.6).[15,16] This is attributed to a destabilization of the oxyallyl cation intermediate, resulting in more cationic character at C-4 and deprotonation at C-5. These dienones have also been used with a variety of catalysts, allowing for milder reaction conditions.[13]



Scheme 1.6 Electron-Withdrawing Groups on Dienones.

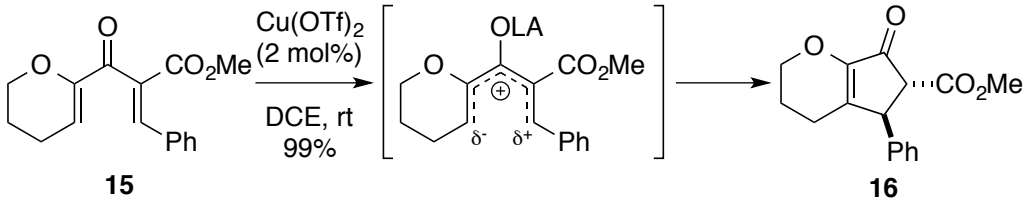
Furthermore, the ester substituent can be easily removed after the Nazarov reaction to provide products that are otherwise difficult to synthesize via conventional Nazarov reaction conditions. This was demonstrated by the Sarpong group, which found that **11** would not cyclize when subjected to a number of different reaction conditions.[17] Instead, **12** was synthesized, and found to form **13** in the presence of aluminum trichloride (Scheme 1.7). The ester group was then removed via base-mediated decarboxylation, allowing access to the desired indanone **14**.





Scheme 1.7 Indanone Synthesis *via* Nazarov Reaction and Decarboxylation.

The Frontier group popularized the combination of electron-donating and electron-withdrawing groups at the C-2 and C-4 positions, respectively (Scheme 1.8).[18,19] They found that these substrates, which they termed 'polarized dienones,' were able to cyclize under remarkably mild conditions. In the case of **15**, only 0.02 equivalents of copper (II) triflate were required to quantitatively covert **15** to **16**, which is a marked improvment from the stoichiometric quantities of initiators typically required for this type of transformation.



Scheme 1.8 Nazarov Cyclization of Polarized Dienones.

1.2 Asymmetric Nazarov Reactions

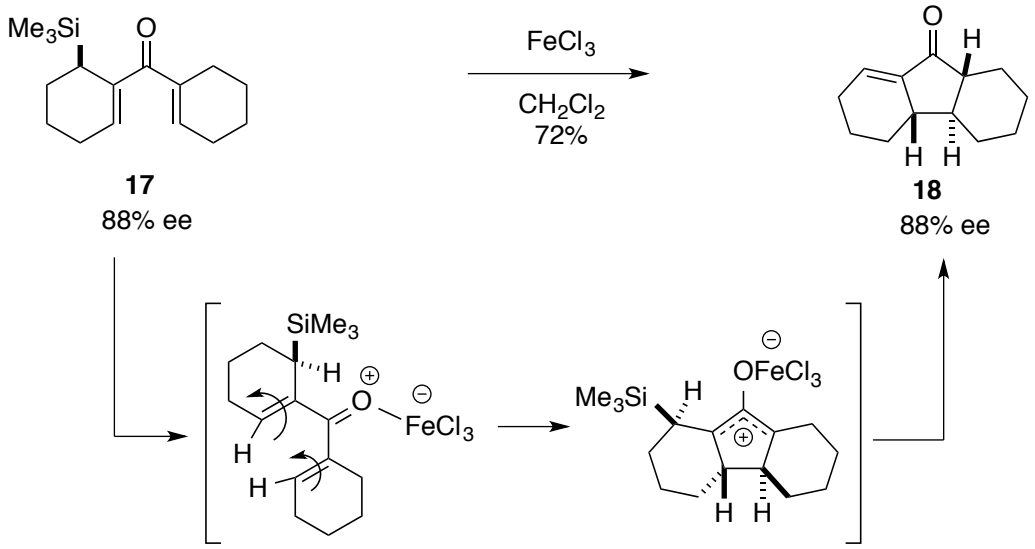
The key electrocyclization step of the Nazarov cyclization effectively translates alkene stereochemistry into aliphatic sp^3 stereogenic centers. As a pericyclic process, this step is stereospecific, and allows for predictability in the relative stereochemistry at the β- and β'- positions. However, without pre-existing stereochemical bias, an equal ratio of clockwise and counterclockwise rotation occurs, resulting in a racemic mixture of products.

As interest in the Nazarov cyclization grew, so did interest in the development of methods to influence the absolute stereochemical outcome of the reaction. There now exist two main avenues for inducing absolute stereochemistry in the Nazarov cyclization. The first involves internal asymmetric induction via a pre-existing stereocenter appended to the dienone framework. The second involves external asymmetric induction, whereby the chiral induction is derived from the activating agent, whether that be a chiral Lewis acid or Brønsted acid containing a chiral ionic pair.

1.2.1 Internal Asymmetric Induction

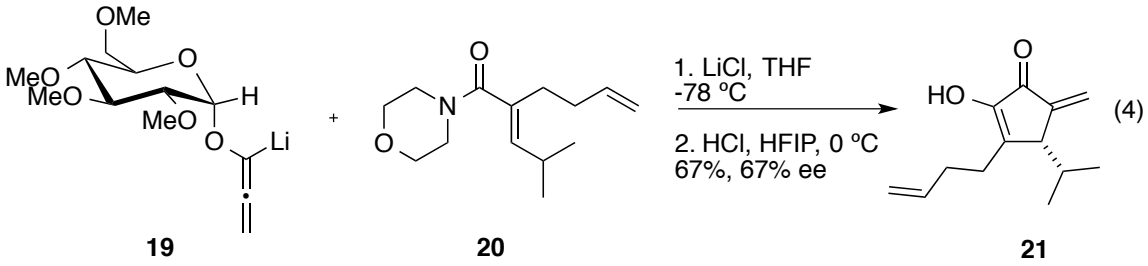
Denmark and co-workers were the first to induce chirality in the Nazarov reaction by using their silyl-directed Nazarov technology in combination with asymmetric induction (Scheme 1.9).[12] Dienone **17** contained a chiral center substituted with a trimethylsilyl substituent adjacent to the α-position. Upon exposure to $FeCl_3$, **17** transfered its chirality to the β- and β'-positions in a highly

torquoselective manor. Loss of the trimethylsilyl group and protonation of the resulting enolate produces **18**. The reaction was found to provide the product with complete chirality transfer.

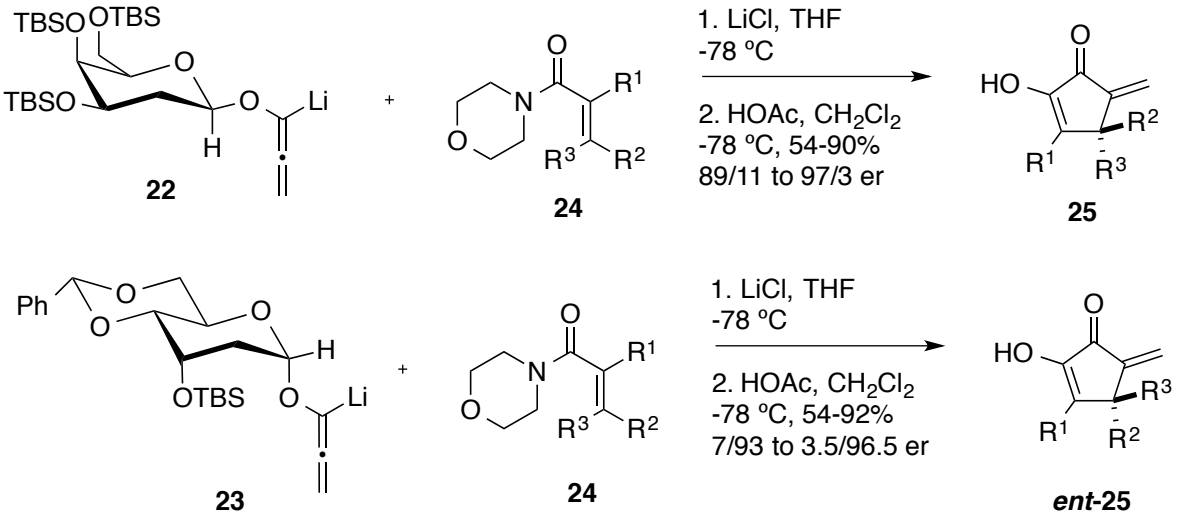


Scheme 1.9 Asymmetric Silyl-Directed Nazarov Reaction

In 2000, the Tius group disclosed their findings on the use of glucose based chiral auxiliaries for asymmetric induction of Nazarov cyclizations.[20] Lithiated allenoates **19**, were added to morpholino amides **20**. Under mildly acidic conditions, the intermediate cyclized to alkylidene cyclopentenone **21** with respectable chirality transfer. Interestingly, when the β-anomer of the carbohydrate was appended to the lithium allenoate the opposite absolute configuration was formed, allowing for easy access to the complimentary configuration. Another attractive feature of this work is that the chiral auxiliary does not require special conditions for removal, but is instead lost in the course of the reaction.



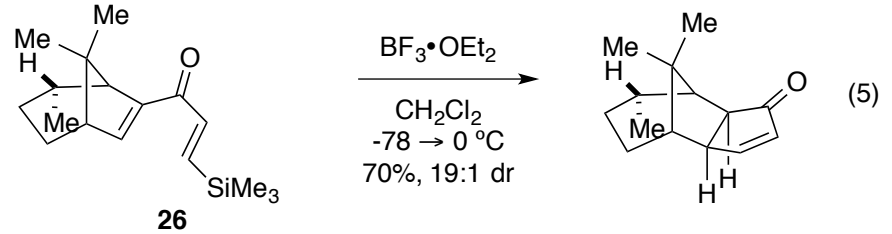
After extensive optimization, the Tius group published a pair of auxiliaries that effectively produce either enantiomer of the Nazarov reaction (Scheme 1.10).[21,22] Addition of glycosylated lithium allenoates **22** and **23** to a variety of morpholino amides **24** successfully produced alkylidene cyclopentenones **25** and ***ent*-25** after exposure to mildly acidic conditions. Quartenary stereocenters were easily accessed via this method, and the ability to make either enantiomer in excess by a simple switch of lithium allenoates, makes this approach particularly attractive.



Scheme 1.10 Sugars as Chiral Auxiliaries in the Nazarov Reaction.

1.2.2 Diastereoselective Nazarov Reactions with Chiral Substrates

In 2005, West and co-workers published their findings on torquoselective Nazarov reactions of dienones appended to bridged bicyclic structures.[23] While investigating silyl directed Nazarov reactions of dienone **26**, it was found that cyclization proceeded to form the *exo* product with excellent dr, which is in agreement with known trends of similar bicyclic alkenes.[24] Interestingly, when dienone **27** was tested, it cyclized to produce the *endo* isomer under the same reaction conditions. The authors attributed this outcome to conformational preferences of the distal portion of the bicyclic system, biasing the rotational preference of the electrocyclization.



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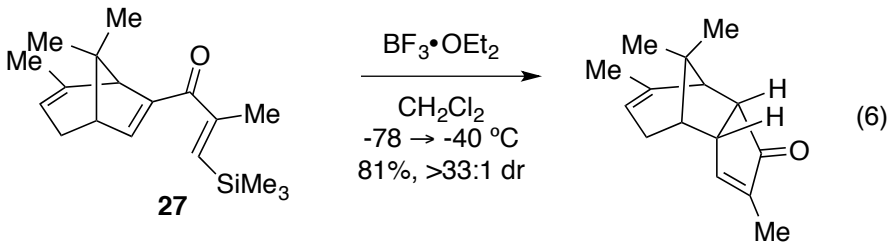

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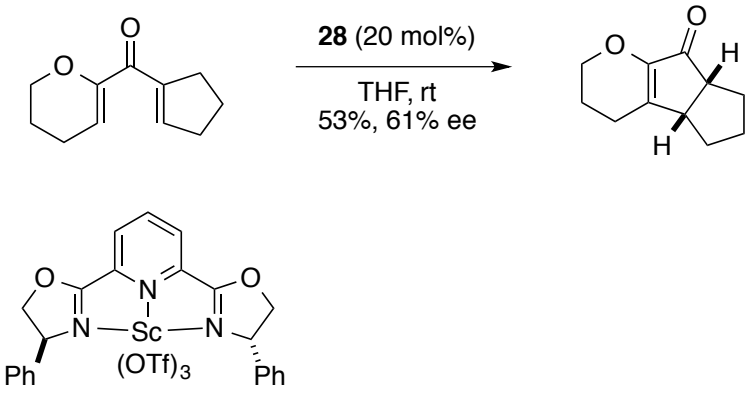
1.2.3 External Asymmetric Induction

Despite the extensive study of the Nazarov reaction dating back to the 1950s, it was not until 2003 that the first method was disclosed for external control of enantioselectivity of the Nazarov reaction. The Trauner group found that 2-alkoxy-1,4-dien-3-ones could be converted to the Nazarov product with moderate

enantioselectivity by using catalytic quantities of the chiral scandium triflate Pybox complex **28** (Scheme 1.11).[25] The alkoxy substitution at C-2 is important to the success of the enantioselectivity as it allows for bidentate binding to the Lewis acid.



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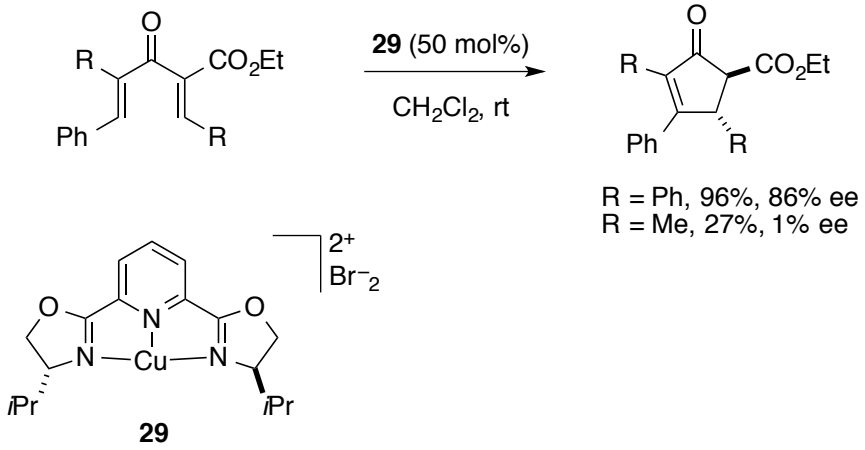
Scheme 1.11 Scandium Triflate Pybox Catalyzed Enantioselective Nazarov Reactions.

Shortly after Trauner's report, Aggarwal and Belfield explored the use of copper bisoxazoline complexes to induce chirality in Nazarov reactions (Scheme 1.12).[26] The placement of esters at the α-position was necessary for bidentate binding to the copper Lewis acid **29**. Unfortunately, the Lewis acid was required in larger quantities than traditionally seen in catalytic reactions. Furthermore, it was found that the size of the β-substituent had a large effect on the enantioselectivity of the reaction, wherein phenyl substitution resulted in 86% enantiomeric excess (ee), and methyl substitution resulted in only 1% ee.



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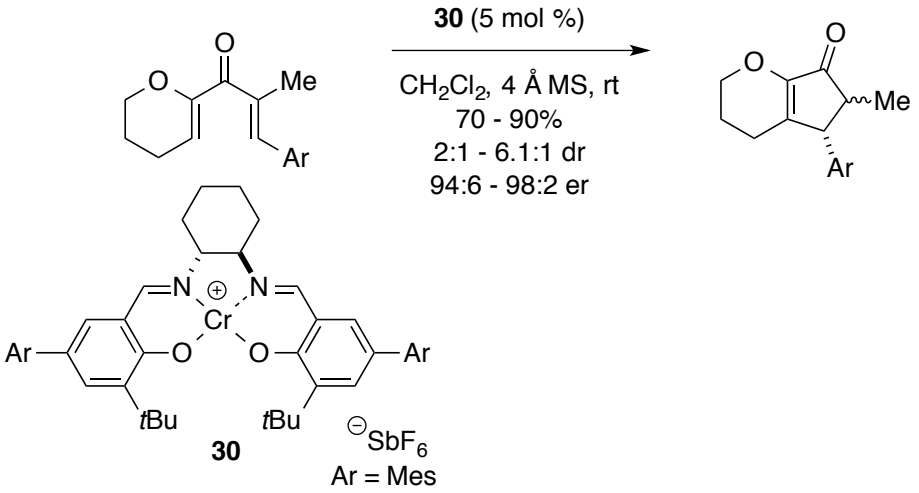
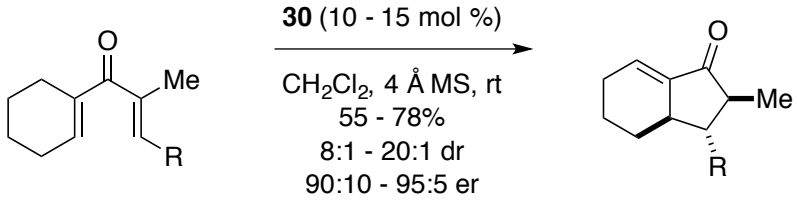
Scheme 1.12 Copper Bisoxazoline Catalyzed Enantioselective Nazarov Reactions.

A number of other catalysts have been designed that are based on the work of the Trauner and Aggarwal groups, including a Fe(II)/Pybox complex,[27] a Cu(II)/ tris(oxazoline) complex,[28] and a chiral V(IV) complex.[29] All of these methods required 2-alkoxy or 2-carboxyl substituted dienones in order to achieve enantioselectivity, which seriously limits the scope of the reactions. Recently, the Rawal group used a novel chromium (III) salen complex to catalyze the Nazarov reaction in excellent enantiomeric excess.[30] In the initial work with dihydropyran substituted dienones, catalyst **30** could be used in 5 mol% to produce the cyclopentenone as a mixture of diastereomers (Scheme 1.13). However, the chromium salen catalyst **30** was also found to induce enantioselectivity in dienones lacking a second binding group (Scheme 1.14). An increase in catalyst loading was required, but good diastereomeric ratios and enantiomeric ratios were achieved with these substrates. To date, this remains the only enantioselective catalytic method to convert "unactivated" dienones to Nazarov products in enantiomeric excesses.



Scheme 1.13 Chromium Salen Chiral Catalyzed Nazarov Reactions.

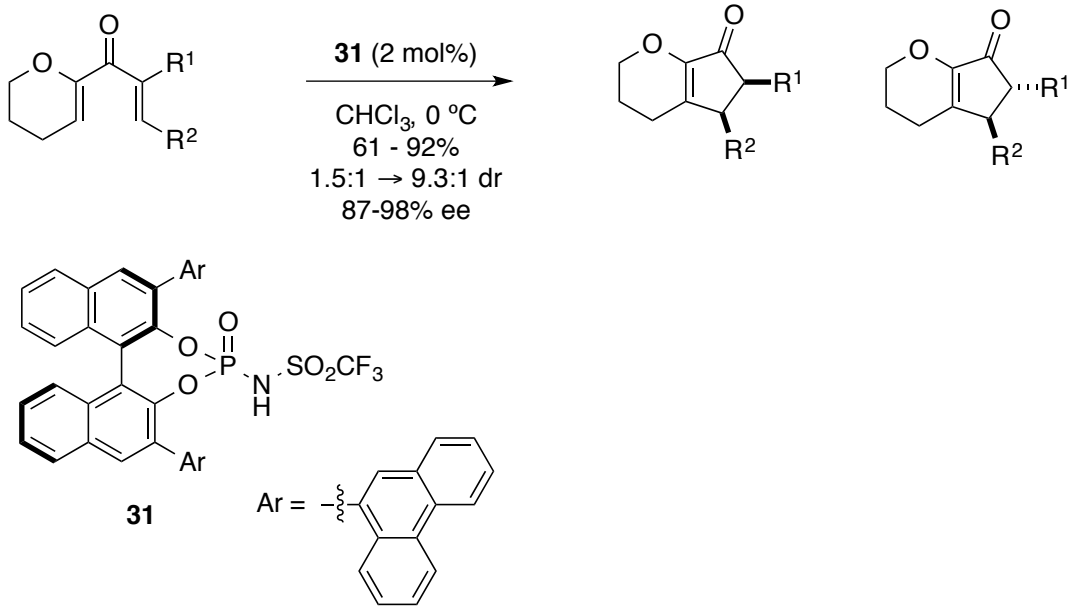


Scheme 1.14 Chiral Catalyzed Nazarov Reactions of Unactivated Dienones.

1.2.4 Organocatalytic Asymmetric Induction

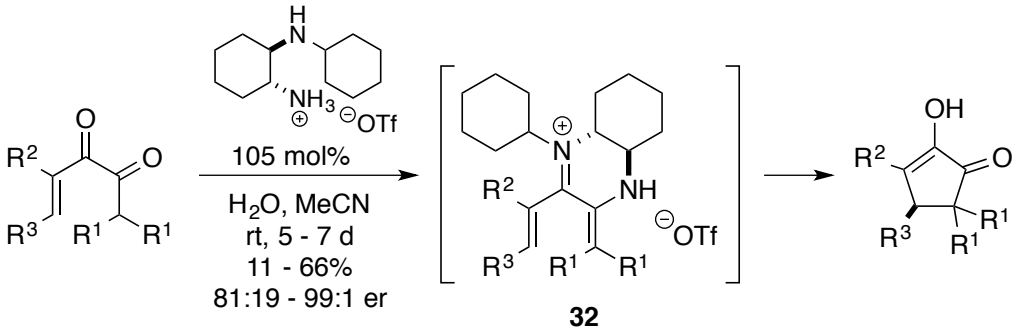
The necessity for strong Brønsted or Lewis acid to initiate the Nazarov cyclization strongly suggests that chiral Brønsted acids may be used as a means to influence the enantioselectivity of the transformation. The Rueping group has shown that a remarkably low catalyst loading of *N*-trifyl phosphoramide **31** was able to effectively convert 2-alkoxy substituted dienones to their respective cyclopentenones in good enantiomeric excess (Scheme 1.15).[31] The enantioselectivity likely arises from a chiral ion-pair association between the pentadienyl cation and the conjugate base of the phosphoramide. However,

enantioselectivity was only seen with dihydropyran containing substrates, and when R^2 was an electron-rich aromatic group.



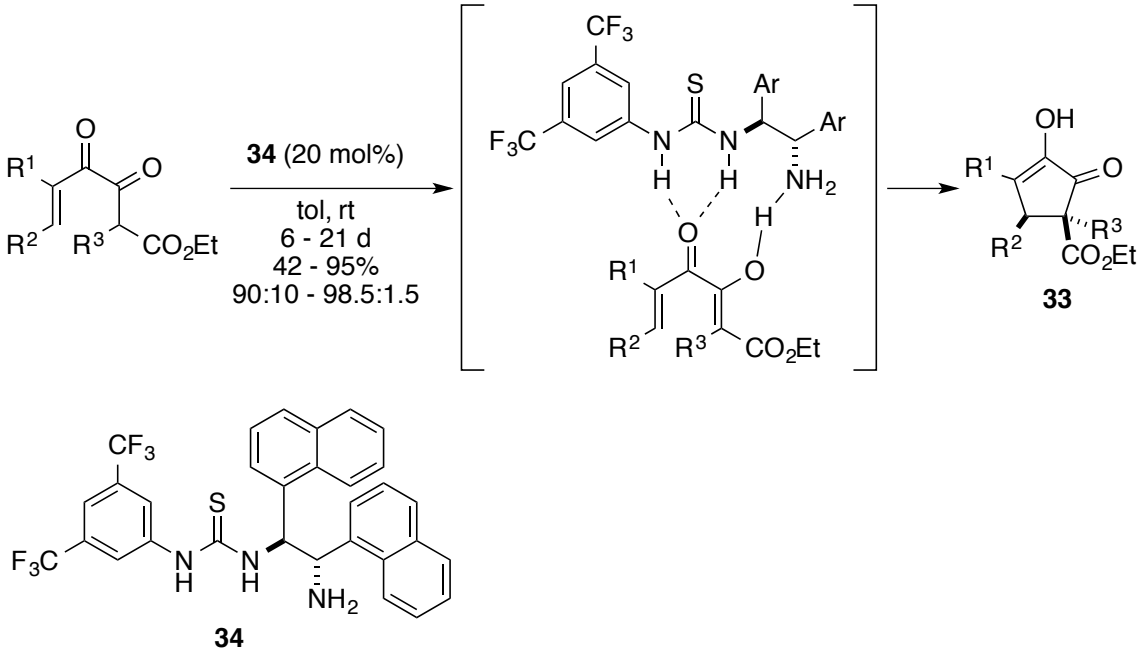
Scheme 1.15 *N*-Trifyl Phosphoramide Catalyzed Enantioselective Nazarov Reactions.

In 2010, the Tius group found that triflate salts of chiral 1,2-diamines were effective for inducing Nazarov cyclizations of α-ketoenones (Scheme 1.16).[32] When used in stoichiometric quantities, the diamine reagent condenses on both the ketone and enone moieties to form the enamine iminium complex **32.** An imino-Nazarov cyclization then occurs, setting the absolute configuration and, after hydrolysis, forms the cyclopentenolone product. Unfortunately, the transformation could not be conducted using catalytic quantities of the diamine due to inefficient turnover, and the reaction time was found to be remarkably long (5 to 7 days). The increased reaction time is likely caused by the ability of the nitrogen to stabilize the pentadienyl cation, reducing the reaction rate of the key 4π electrocyclization step.



Scheme 1.16 Chiral Diamine Initiated Nazarov Reactions of Ketoenones.

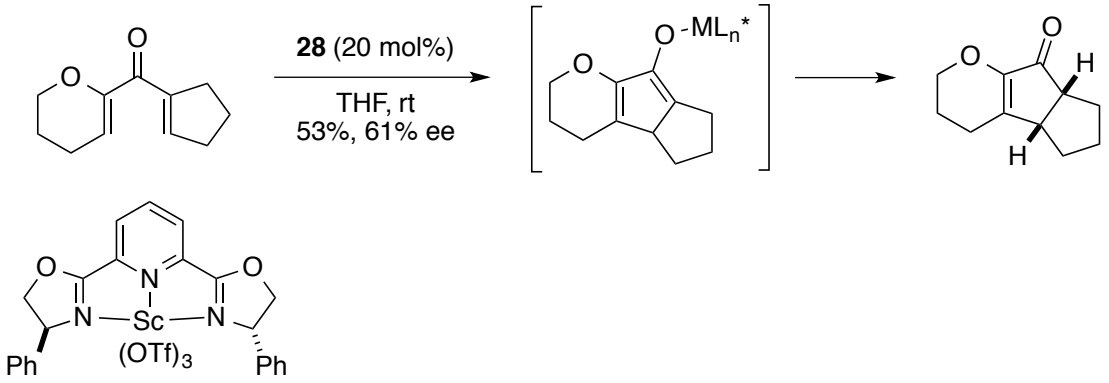
A short while later, the Tius group showcased a thiourea organocatalyst as an effective reagent for asymmetric Nazarov reactions (Scheme 1.17).[33] 2-Ketoenones bearing ester groups are forced to exist mainly as the enol tautomer, and were found to react cleanly with the dual acid/base catalyst **34** to form Nazarov products **33.** This method was able to produce products with quaternary stereocenters in good enantiomeric excess and in good yield, but suffered from long reaction times of up to multiple weeks.



Scheme 1.17 Thiourea Catalyzed Nazarov Cyclizations of Ketoenones.

1.2.5 Enantioselective Protonation

Enantiocontrol over the 4π electrocyclization step is not the only way to achieve enantioselectivity in Nazarov products. Both the Trauner[34] and Rueping groups[35] used chiral catalysts to enantioselectively protonate an achiral enol or enolate produced as an intermediate in the Nazarov reaction (Scheme 1.18). The Trauner study found the chiral scandium indane-pybox **35** to be an effective catalyst for the Nazarov cyclization of a series of dihydropyran-containing dienones. Similarly, the Reuping group found that the chiral *N*-trifylphosphoramide **36** to provide good enantiomeric ratios for dihydropyran-containing dienones (Scheme 1.19).



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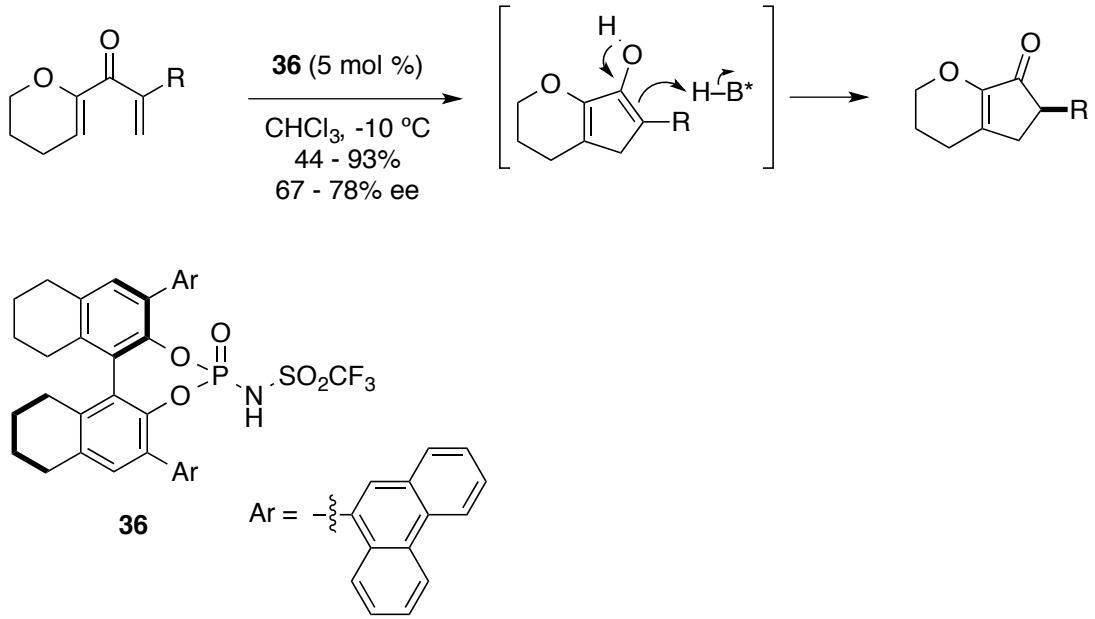
Scheme 1.18 Chiral Scandium Indane-Pybox Catalyzed Enantioselective Protonation of the Nazarov Reaction.



Scheme 1.19 Chiral *N*-Trifyl Phosphoramide Catalyzed Enantioselective Protonation of the Nazarov Reaction.

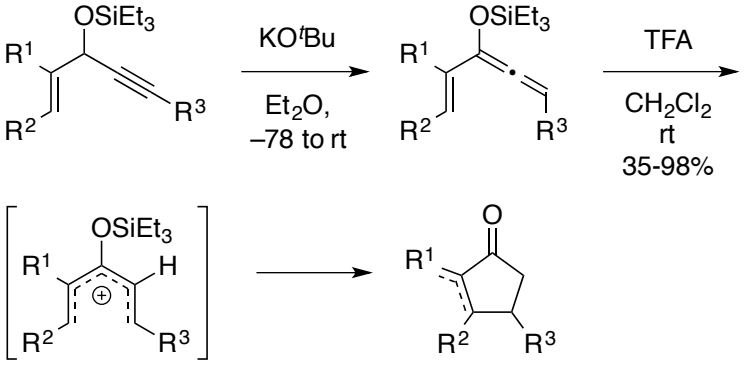
1.3 Alternative Substrates for Nazarov Reactions

The Nazarov cyclization is identified by the formation of a pentadienyl cation that undergoes conrotatory 4π electrocyclic ring closure to form a cyclopentenyl cation. While the pentadienyl cation is traditionally accessed via 1,4-dien-3-ones in the presence of a strong acid, recent attention has focused on alternate substrates to access this intermediate.

1.3.1 Electrophilic Activation of Vinyl Allenes

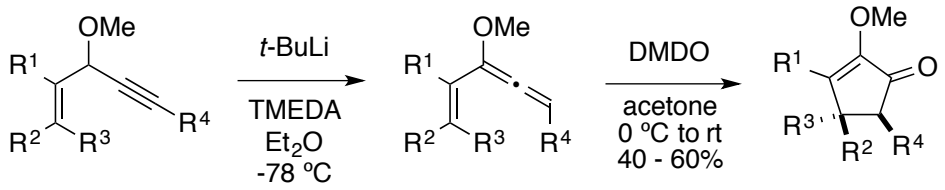
One of the prominent downsides of using dienones as Nazarov precursors lies in the often cumbersome number of steps required to synthesize dienones with the desired substitution patterns. In order to circumvent this problem, both the West[36] and Frontier groups[37] postulated relatively accessible siloxy- and alkoxy-substituted vinyl allenes as Nazarov substrates. By taking advantage of the

nucleophilic character of the internal carbon of the allene, a pentadienyl cation could be produced *in-situ*, and a Nazarov cyclization could occur. The West group's study found that siloxy-vinyl allenes readily cyclize to regioisomeric mixtures of cyclopentenones and alkylidene cyclopentanones in the presence of trifluoroacetic acid (Scheme 1.20). The yields for the transformation were calculated from the starting silyl propargyl ether, as the siloxy vinyl allenes were found to be unstable to chromatographic purification.



Scheme 1.20 Protonation of Vinyl Siloxyallenes.

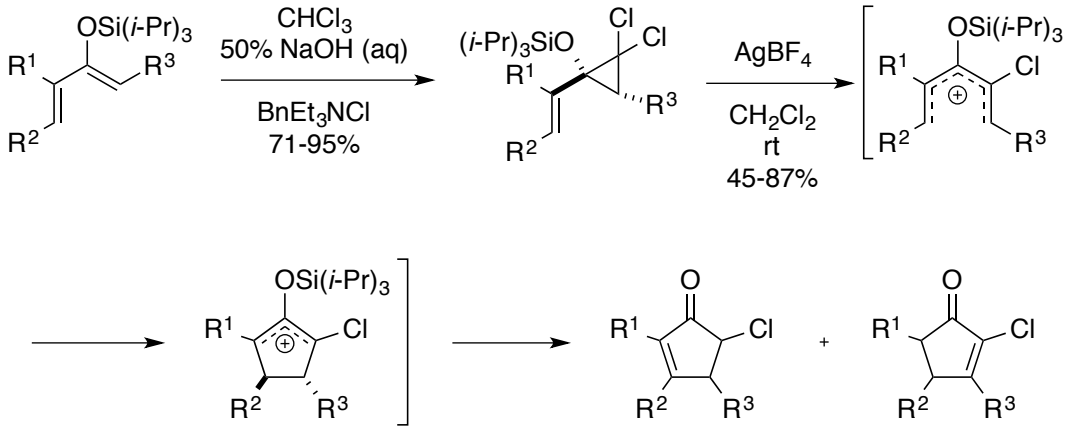
Meanwhile, the Frontier group found that alkoxy-substituted vinyl allenes could be activated with dimethyldioxirane in acetone to produce Nazarov products (Scheme 1.21). Although the Frontier group found that alkoxy vinyl allenes could be purified by chromatography, higher yields were obtained via a two-step process from the propargyl ether without flash chromatographic purification of the intermediate.



Scheme 1.21 Oxidation of Alkoxy Vinyl Allenes.

1.3.2 Vinyl Cyclopropane Opening

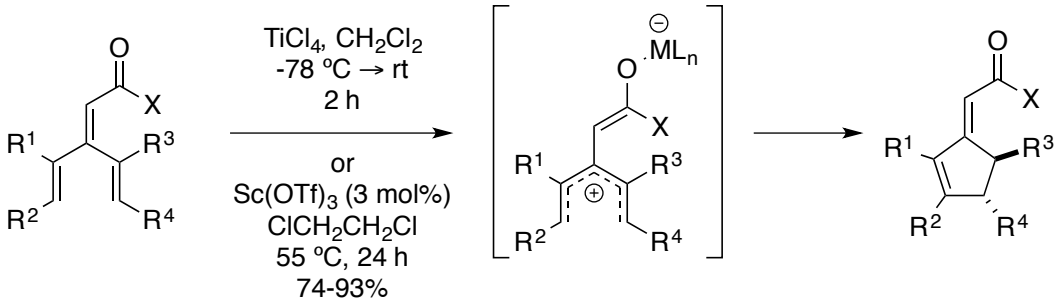
In 2006, Grant and West published an interesting domino ring-opening/ring-closing procedure that incorporated a Nazarov cyclization (Scheme 1.22).[38] Dihalocyclopropanes were synthesized from tri-isopropylsiloxy dienes using phase-transfer conditions. Silver tetrafluoroborate was then added, leading to the abstraction of a chloride from the cyclopropane and a 2π-electrocyclic ring opening to form a pentadienyl cation. This intermediate then underwent Nazarov cyclization, forming mixtures of chloro-substituted cyclopentenones.



Scheme 1.22 Silver-Mediated Opening of Dihalocyclopropanes and Subsequent Nazarov Cyclization.

1.3.3 Vinylogous Nazarov Reactions

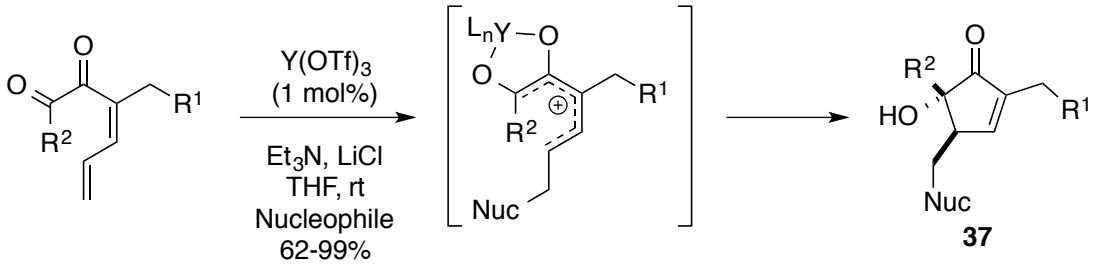
As mentioned previously, the Nazarov reaction is traditionally accomplished by activation of a carbonyl at the C-3 position of a cross-conugated dienone. In 2009, Rieder, Winberg, and West expanded on Nazarov reaction methodology by replacing the ketone moiety at the C-3 position with an electron-deficient alkene (Scheme 1.23).[39] By attaching a carbonyl group to the alkene, it was envisioned that these cross-conjugated trienes could be activated for Nazarov cyclization via complexation of the carbonyl group with a Lewis acid. The methodology was found to be amenable to esters, amides, aldehydes, and ketones producing the cyclized products in good yields and diastereomeric ratios.



Scheme 1.23 The Vinylogous Nazarov Reaction.

The Frontier group was able to access pentadienyl cations by a conjugate addition into dienyl diketones (Scheme 1.24).[40] A variety of nucleophiles were found to add to the dienyl diketones via a 1,6-conjugate addition when the mild Lewis acid $Y(OTf)_3$ was present in catalytic quantities. Subsequent complexation of the Lewis acid with the adjacent ketone resulted in a pentadienyl cation that underwent Nazarov cyclization to form hydroxy-cyclopentenone **37**. This method proved to be

an excellent way to incorporate an amine or malonate nucleophile into a complex structure via a domino process with the Nazarov reaction.

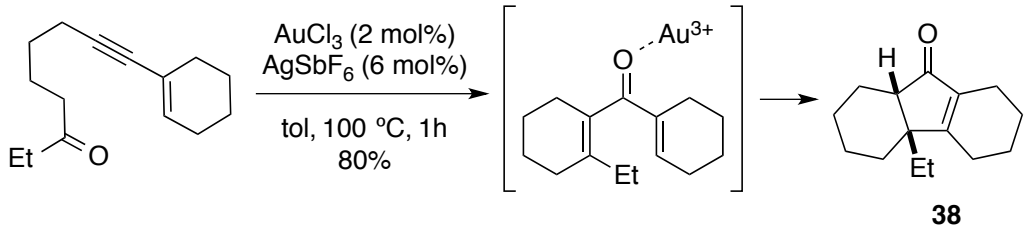


Scheme 1.24 Conjugate Addition Initiated Nazarov Cyclizations.

1.3.4 Domino Gold Catalyzed Rearrangement/Nazarov Cyclization

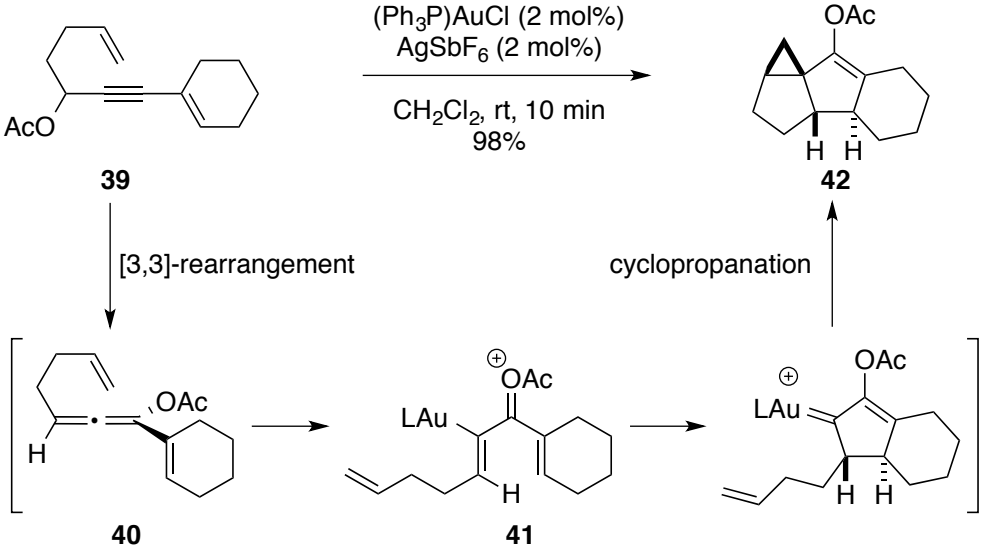
Recently, gold catalysts have attracted attention due to their chemoselectivity and ability to initiate skeletal rearrangements.[41,42] This, combined with non-traditional Nazarov precursors, allows for a method that is both mild and tolerant to functional groups that are otherwise sensitive to Nazarov reaction conditions.

Jin and Yamamoto utilized a gold catalyst to convert ketones tethered to enynes into tricyclic structures in good yields (Scheme 1.25).[43] A cationic gold atom initially catalyzes a hetero-enyne metathesis reaction to produce a dienone *in-situ* that undergoes Nazarov cyclization to yield cyclopentenone **38**.



Scheme 1.25 Gold Catalyzed Domino Hetero-Enyne Metathesis/Nazarov Reaction.

Fensterbank, Malacria, and co-workers utilized a gold catalyst to convert enynyl acetates **39** to polycyclic compounds **42** via a domino process (Scheme 1.26).[44,45] Upon exposure to a mixture of 2 mol% of (PPh_3)AuCl and 2 mol% of $AgSbF_6$, enynyl acetate **39** underwent a [3,3]-sigmatropic rearrangement to form allene **40**, which was activated by the gold catalyst to produce **41.** This intermediate then underwent a metallo-Nazarov reaction, forming a gold carbene, which cyclopropanates the tethered alkene to produce **42**.

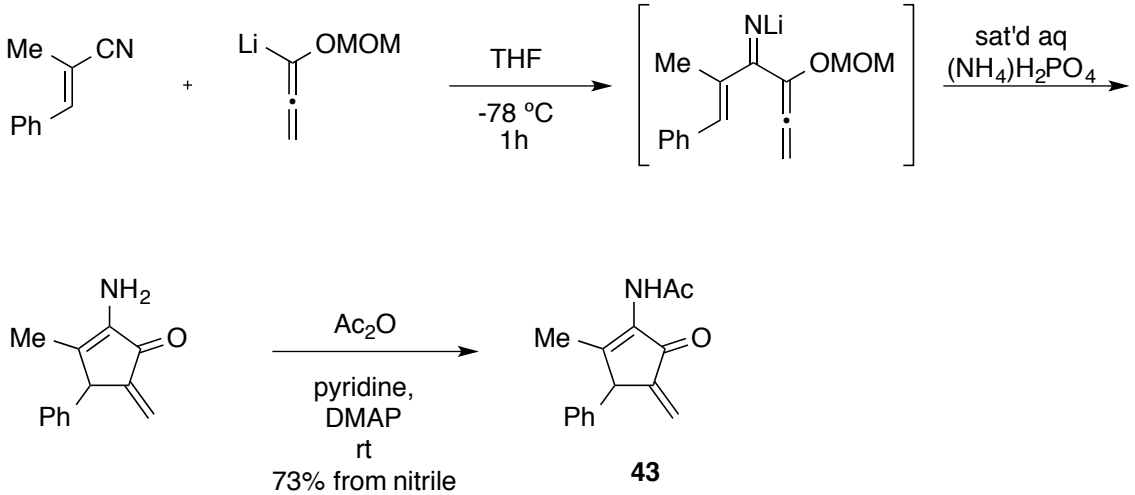


Scheme 1.26 Gold-Catalyzed Domino Isomerization/Nazarov Reaction/Cyclopropanation.

1.3.5 Imino-Nazarov Cyclization

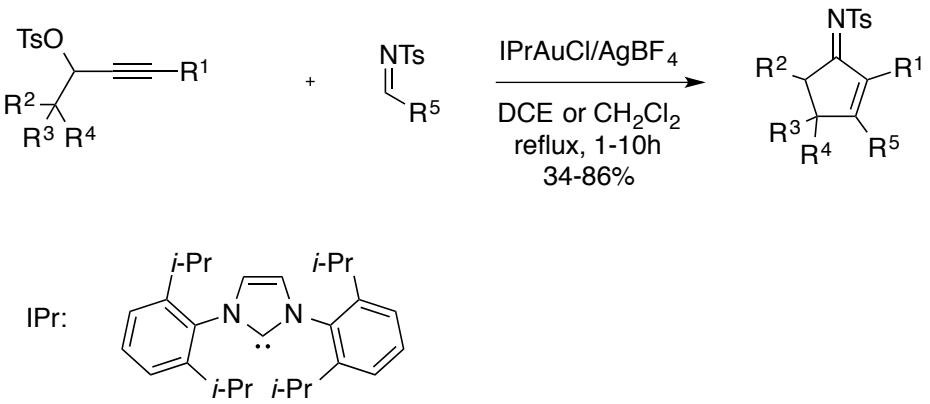
The C-3 imine analogue of the Nazarov cyclization has failed to receive the same level of attention as the traditional oxygen-substituted variant. Methods to synthesize the requisite 1,4-dien-3-imines are limited,[46-50] and most of the reported methods are exclusive to N-tosyl imines; calculations show the key electrocyclization step to be endothermic for the 3-amino-pentadienyl cation.[51]

To date, there have only been five publications featuring imino-Nazarov reactions. The first published account was by the Tius group in 2001 (Scheme 1.27).[52] In this study, *in-situ* generated allenyl-vinyl imines were readily cyclized in an acidic aqueous environment. The driving force for this reaction lies in the relief of allenic strain and the stability imparted on the allyl cation intermediate by the OMOM group. Furthermore, irreversible loss of the MOM protecting group under the reaction conditions acts as a thermodynamic sink for the reaction. In order to purify the resulting product, the amine was acetylated to afford the acetamide **43**. This method is unfortunately limited to substrates lacking N-substitution.



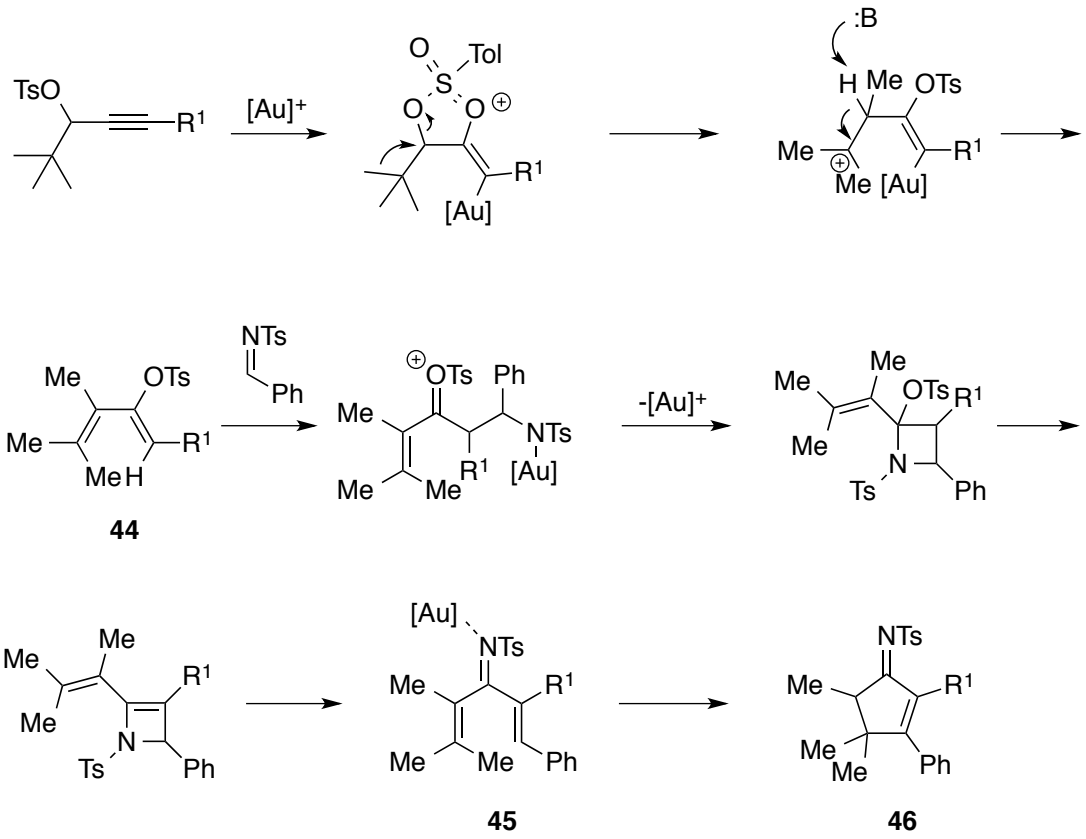
Scheme 1.27 Imino-Nazarov Reaction of Allenylvinylimines.

In 2009, the González group used a gold-catalyzed rearrangement of propargyl tosylates to access imino Nazarov cyclizations (Scheme 1.28).[53] Tosyl imines were required for the reaction, reducing the impact of stabilization from nitrogen on the pentadienyl cation, but preventing the possibility for substrates with more elaborate N-substitution. Regardless of this limitation, the reaction tolerated a diverse range of tosyl imines and internal alkynes.



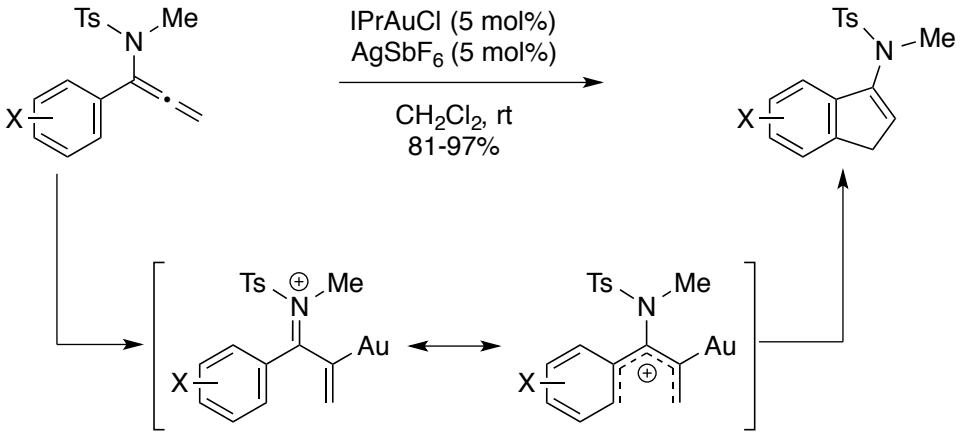
Scheme 1.28 Gold-Catalyzed Imino-Nazarov Reaction.

The mechanism for this transformation (Scheme 1.29) begins with a gold-mediated [1,2]-shift of the tosylate, with migration of one of the substituents and deprotonation to form tosyl diene **44**. A formal [2+2] cycloaddition with the tosyl imine then occurs, followed by loss of the tosylate and ring-opening to form tosyl-dienimine **45**. Nazarov cyclization of **45** then occurs to produce **46**.



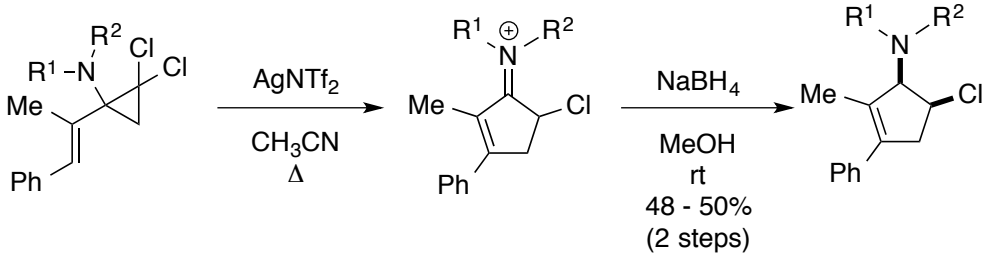
Scheme 1.29 Mechanism for Gold-Catalyzed Nazarov Reaction.

In 2012, the Hsung group disclosed the conversion of α-aryl-substituted allenamides to aromatic-ring fused cyclopentenamides using a gold (I) catalyst (Scheme 1.30).[54] The methodology effectively built upon findings of both the West group[36] and the Frontier group[37] on Nazarov reactions of alkoxy vinyl allenes and the various gold-catalyzed Nazarov reactions[44,45,53] described above. While the reaction was tolerant of various substituted aryl groups, it was limited to unsubstituted allenes and N-tosyl amides.



Scheme 1.30 Nazarov Cyclization of α-Aryl-Substituted Allenamides.

In 2013, the West group published the first imino-Nazarov process containing N-alkylated substrates[55] by using the silver-mediated opening of substituted dichlorocyclopropanes[38] described previously (Scheme 1.31). A variety of tertiary amines, including morpholino, N-methyl benzyl, and N-methyl phenyl, were shown work, unlike the imino-Nazarov reports discussed above. In order to effectively purify the products, the iminium ion was immediately reduced to the tertiary amine with sodium borohydride in methanol.



Scheme 1.31 Silver-Mediated Imino-Nazarov of Aminodihalocyclopropanes.

The other instance of an imino-Nazarov reaction is the previously described enantioselective Nazarov reaction of α-ketoenones with chiral diamines by the Tius

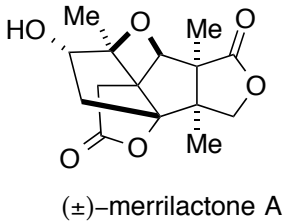
group.[32] This method fails to incorporate nitrogen into the final product despite using stoichiometric quantities of a diamine reagent.

1.4 Nazarov Cyclizations in Total Synthesis

The Nazarov reaction has been used as an effective tool for the construction of cyclopentenones and their derivatives in a variety of total syntheses. The ability to construct a ring in tandem with multiple stereogenic centers makes the method attractive, as does the formation of the synthetically useful enone functional group.

1.4.1 Synthesis of (±)-Merrilactone A

The sesquiterpene natural product merrilactone A was first isolated in 2000 by the Fukuyama group[56,57] and has been shown to promote neurite outgrowth in fetal rat neurons. The natural product is not only promising as a biological target, but its complex, congested structure makes it highly appealing to the synthetic community. In 2007, the Frontier group disclosed their synthesis of (±)-merrilactone A, utilizing a Nazarov cyclization to form the C-ring, as one of their key steps.[58,59]

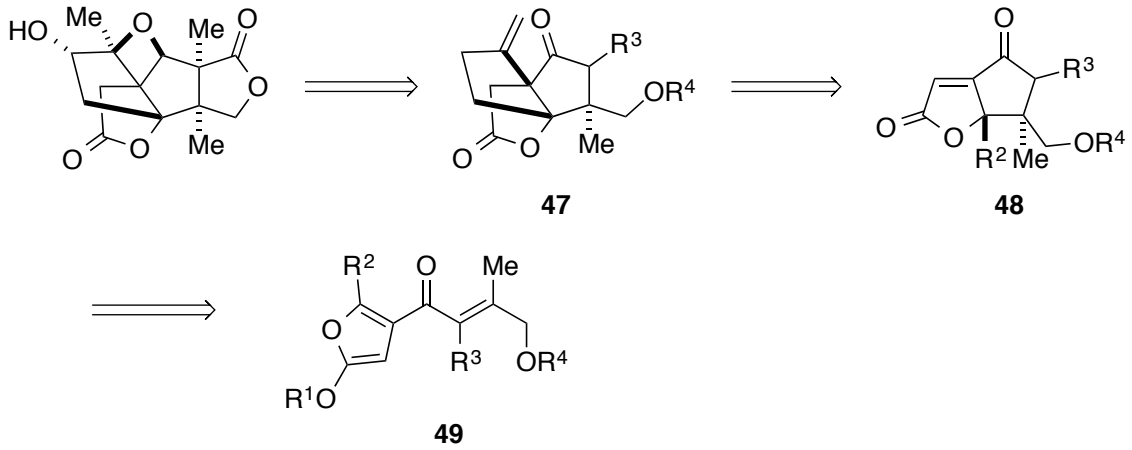


(±)–merrilactone A

Figure 1.2 (±)-Merrilactone A

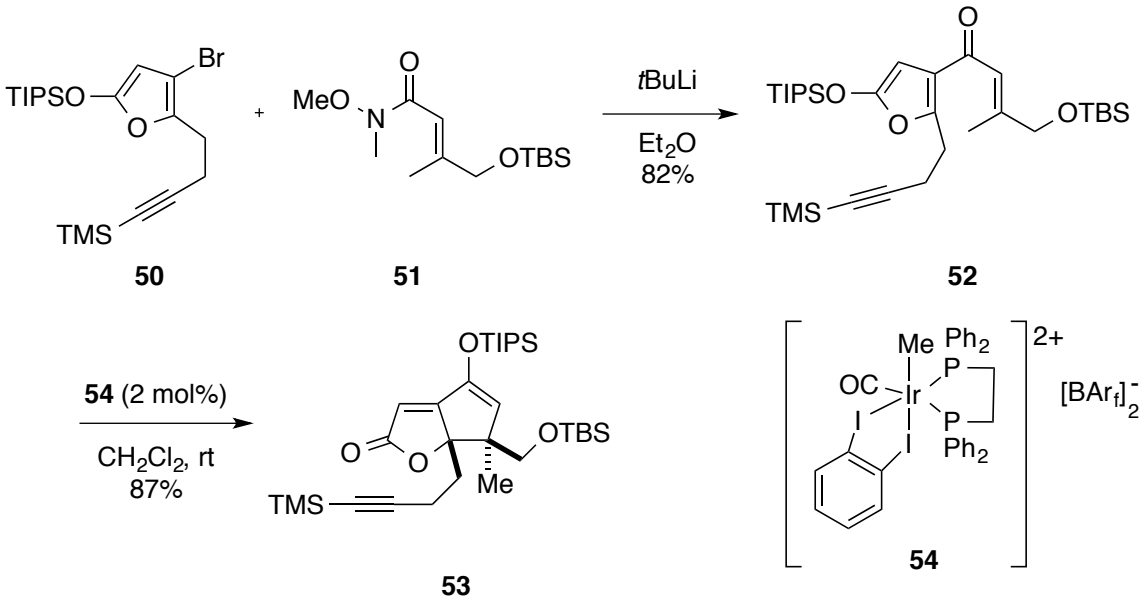
Retrosynthetically, the Frontier group proposed that merrilactone A could come from tricyclic compound **47,** an intermediate in the Danishefsky group's

synthesis.[60,61] This intermediate could be broken down to the cyclopentanone **48**, which would be accessed via Nazarov cyclization of a furanyl substituted enone such as **49** (Scheme 1.32).



Scheme 1.32 Retrosynthesis of (±)-Merrilactone A.

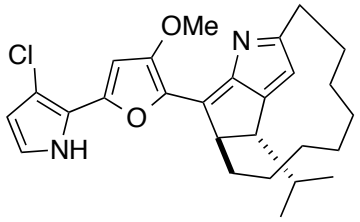
The key Nazarov precursor was obtained via a lithium-halogen exchange of furanyl bromide **50**, followed by nucleophilic addition of the resulting organolithium into Weinreb amide **51** (Scheme 1.33). With Nazarov substrate **52** in hand, various acids were tested for the annulation process. Copper (II) triflate and triisopropylsilyl triflate failed to consume **52** when used in catalytic quantities. However, the iridium Lewis acid **54** successfully converted **52** into bicycle **53** in 87% yield with only a 2% catalytic loading of the iridium complex. Additionally, the reaction converted the siloxy furan moiety to a lactone due to the migration of the triisopropyl silyl group. After six more steps to elaborate the molecular framework, Danishefsky's intermediate **53** was produced, and the Frontier group's formal synthesis of (±)-merrilactone A was finalized.



Scheme 1.33 Synthesis of 54.

1.4.2 Synthesis of (+)-Roseophilin

Roseophilin has been shown to have activity against K562 human erythroid leukemia cells and human nasopharyngeal carcinoma cells.[62] The intriguing structure, including an azafulvene, a pyrrolylfuran, and an ansa macrocycle, makes it an attractive target for total synthesis.

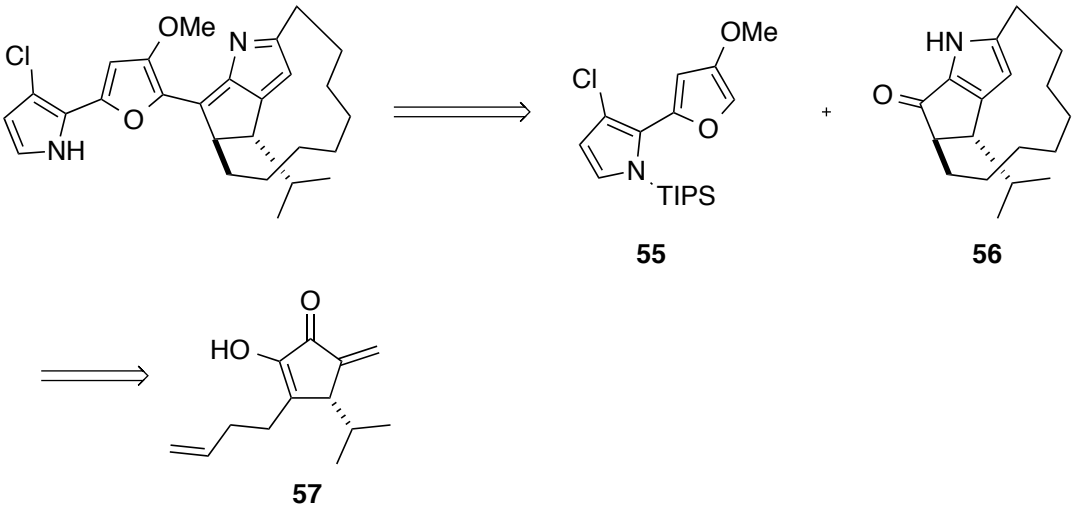


(+)-roseophilin

Figure 1.3 (+)-Roseophilin

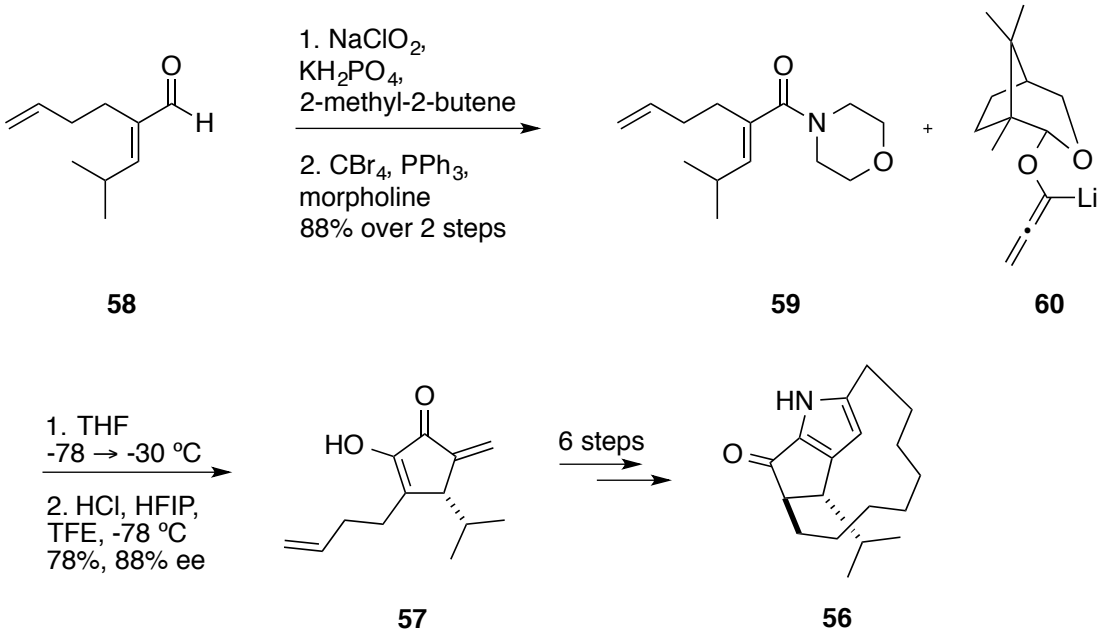
In 2001, the Tius group disclosed their total synthesis of (+)-roseophilin.[63] Retrosynthetically, they envisioned a disconnection that would produce protected

azafulvene **55** and ketopyrrole **56**, which could be formed from alkylidene cyclopentenone **57** (Scheme 1.34).



Scheme 1.34 Retrosynthesis of (+)-Roseophilin.

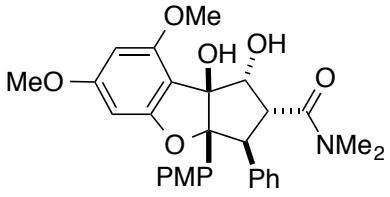
The Tius group's synthesis of (+)-roseophilin began with oxidation of enal **58** to the corresponding carboxylic acid, followed by conversion to the morpholino amide **59** via the acid bromide (Scheme 1.35). Amide **59** was then combined with the chiral lithioallene **60,** derived from (+)-camphoric acid. After warming to –30 °C, hydrochloric acid was added in a mixture of hexafluoroisopropanol and trifluorethanol, furnishing **57**. The camphor derived chiral auxiliary **60** effectively induced an enantiomeric excess of 88% in the transformation, while the four sugar based auxiliaries that were also tested failed to produce a comparable enantiomeric excess. Subsequently, a six-step sequence was used to produce macrocycle **56,** which was combined with **55** to form (+)-roseophilin.



Scheme 1.35 Synthesis of 57.

1.4.3 Synthesis of (±)-Rocaglamide

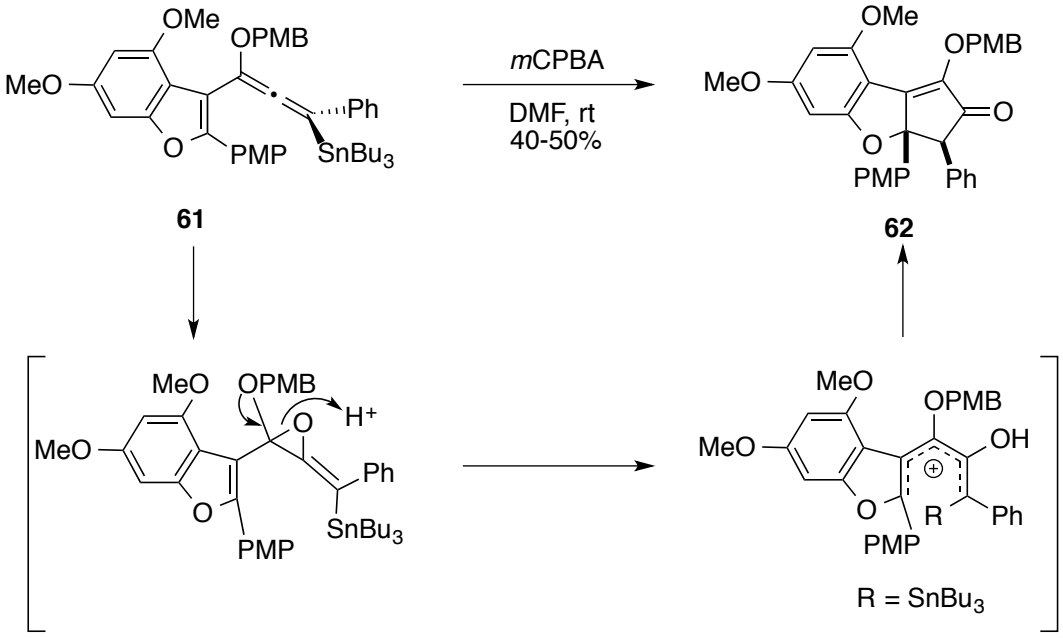
Rocaglamide, a metabolite isolated from the roots and stems of *Aglia elliptifolia*,[64] has been shown to have cytostatic and cytotoxic activity against a number of human cancer cell lines.[65] The Frontier group approached the synthesis of the natural product with the idea that a Nazarov cyclization could be used to form the densely substituted cyclopentanol ring.[66]



(±)-rocaglamide

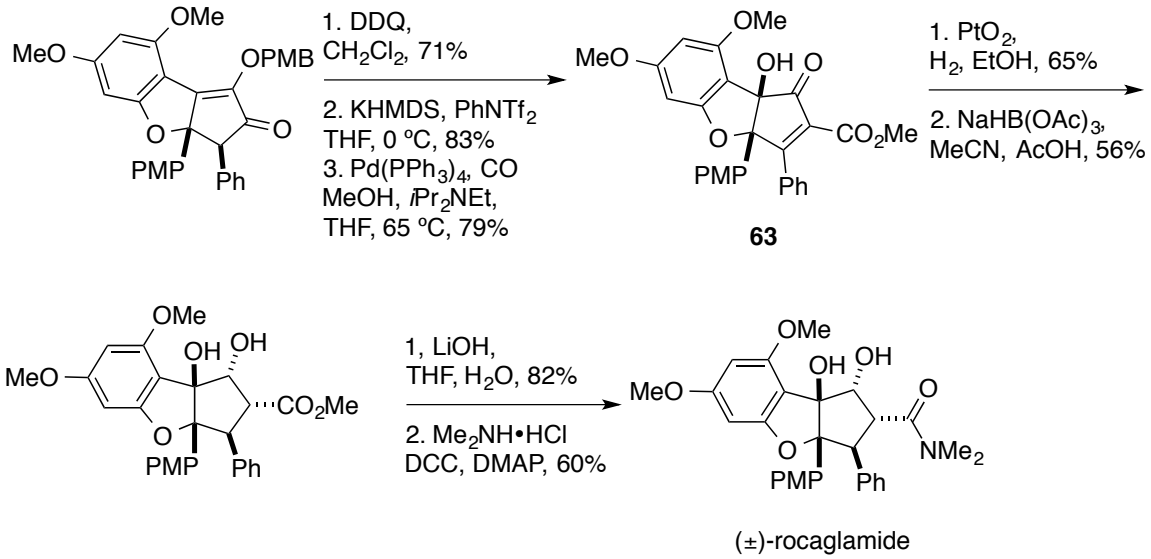
Figure 1.4 (±)-Rocaglamide

After initial attempts to perform a Nazarov cyclization on a fully substituted polarized dienone failed to produce the desired hydroxy intercepted cyclopentanone, the Frontier group rethought their strategy. Alternatively, tributylstannyl substituted allene **61** was proposed as a suitable substrate (Scheme 1.36). Oxidation of the allene and subsequent opening of the vinyl epoxide successfully produced the pentadienyl cation necessary for Nazarov cyclization and, upon collapse of the stannyl substituent, produced cyclopentenone **62** in moderate yield.



Scheme 1.36 Retrosynthesis of (±)-Rocaglamide.

The cyclopentenone was further elaborated via removal of the *p*-methoxy benzyl group and oxidation of the resulting enol with excess DDQ (Scheme 1.37). Conversion of the ketone to the enoate was then carried out in good yield. A final series of steps was conducted to convert the functional groups of **63** to those found in (±)-rocaglamide.



Scheme 1.37 Synthesis of (±)-Rocaglamide.

1.4.4 Synthesis of (+)-Mandinoline A and B

In 2007, the Tius group utilized a Nazarov cyclization in their strategy towards the natural products (+)-mandinoline A and its diastereomer (+)-mandinoline B.[67] The natural products are of particular interest as they are no longer available from natural sources, making synthesis a requirement for investigating their use as pharmaceutical compounds. Furthermore, these compounds have been shown to be selective inhibitors of interleukin-6 (IL-6).[68,69]

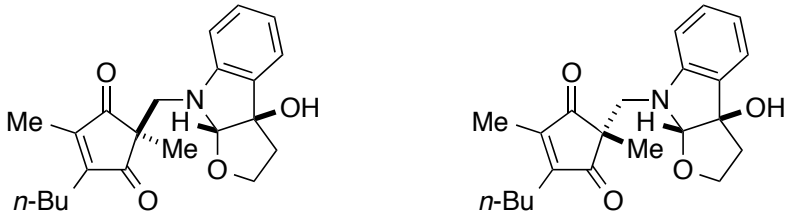
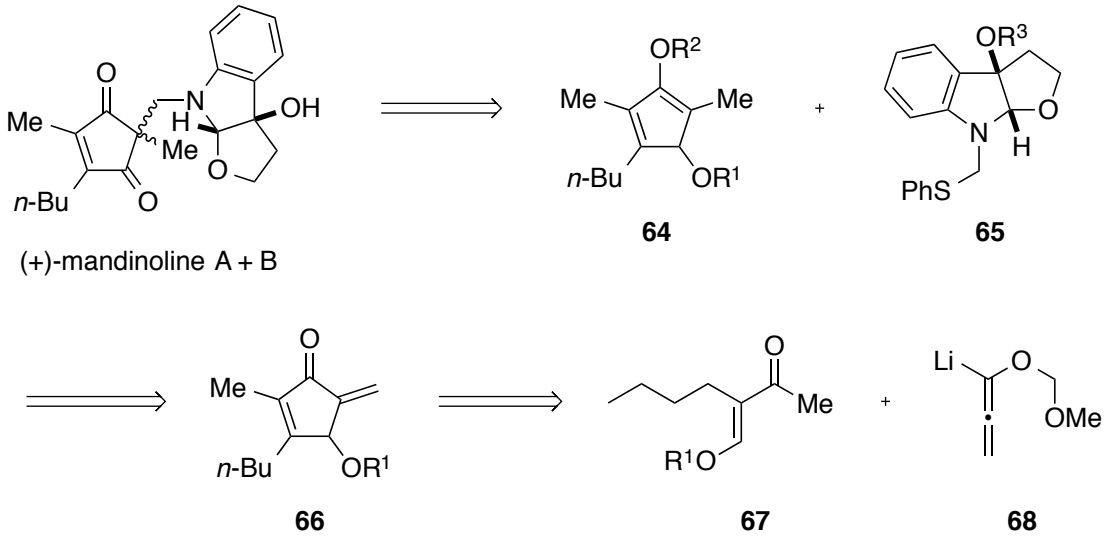


Figure 1.5 (+)-Mandinoline A and B

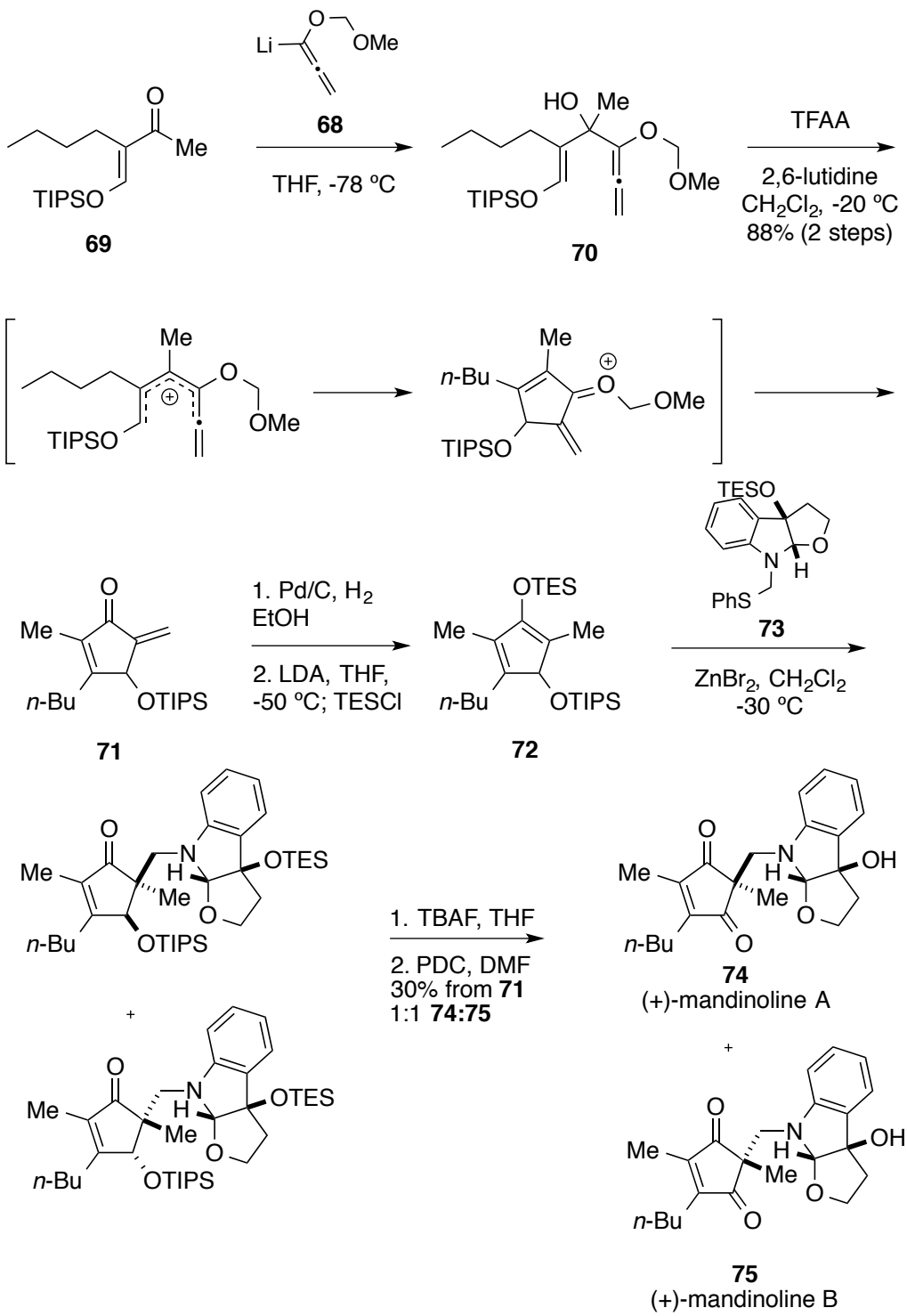
Retrosynthetically, the Tius group envisioned a disconnection that would produce cyclopentadienol **64** and hydroxyfuroindoline **65** (Scheme 1.38). They saw **65** coming from alkylidene cyclopentenone **66**, which would result from an *in-situ* Nazarov cyclization after combination of enolone **67** and lithiated alkoxy allene **68**.



Scheme 1.38 Retrosynthesis of (+)-Mandinoine A and B

The Tius group's synthesis of (+)-mandinoine A and B began with the butyl-substituted enone **69** (Scheme 1.39). Addition of lithiated alkoxy allene **68** to **69** produced tertiary alcohol **70**. Trifluoroacetic anhydride was added, which created a cyclopentadienyl cation that underwent an iso-Nazarov cyclization whereby the oxygen substitution is at C-4 rather than at C-3. This efficiently produced **71** in a 88% yield over two steps. Alkylidene cyclopentenone **71** was then prepared via the reduction of the exocyclic alkene and formation of silylenol ether **72**. Alkylation of **72** was accomplished with chiral aminal **73**, producing a mixture of diastereomers. The synthesis was then completed by deprotection of the secondary alcohol with

TBAF, and subsequent oxidation with PDC, producing (+)-mandinoline A and (+)-mandinoline B in a 1:1 ratio and 30% yield from **71**.



Scheme 1.39 Synthesis of (+)-Mandinoline A and (+)-Mandinoline B.

1.5 The Interrupted Nazarov Reaction

A substantial amount of research has been conducted into intercepting the oxyallyl cation intermediate of the Nazarov reaction with a number of different nucleophiles.[4i] The oxyallyl cation has been shown to undergo cycloadditions with dienes,[70,71] electron-rich alkenes,[72,73] and azides.[74] It has also been shown to react with various nucleophiles at a single terminus of the oxyallyl cation to produce different *umpolung* products.[75-79] Details of these reactions are covered in Chapter 2.1.

1.6 Conclusion

The Nazarov reaction has seen a substantial amount of improvement since its first documented occurrence by Vorländer[1] in 1903 and its expansion by Nazarov in the 1950s.[2,5a-c] Investigations into substitution effects, development of milder reaction conditions, and ways to impart enantioselectivity into the reaction have made the Nazarov reaction more popular in organic chemistry. Furthermore, interrupting the Nazarov reaction (Chapter 2.1) has allowed for rapid development of skeletal complexity and formation of novel structures. In Chapters 2, 3, and 4, new developments in the interrupted Nazarov reaction are discussed. This includes the discovery of [3+3] cycloadditions between alkyl azides and the Nazarov intermediate in Chapter 2, a domino Nazarov cyclization/Baeyer-Villiger reaction in Chapter 3, and a double eliminative Nazarov reaction in Chapter 4.

1.7 References

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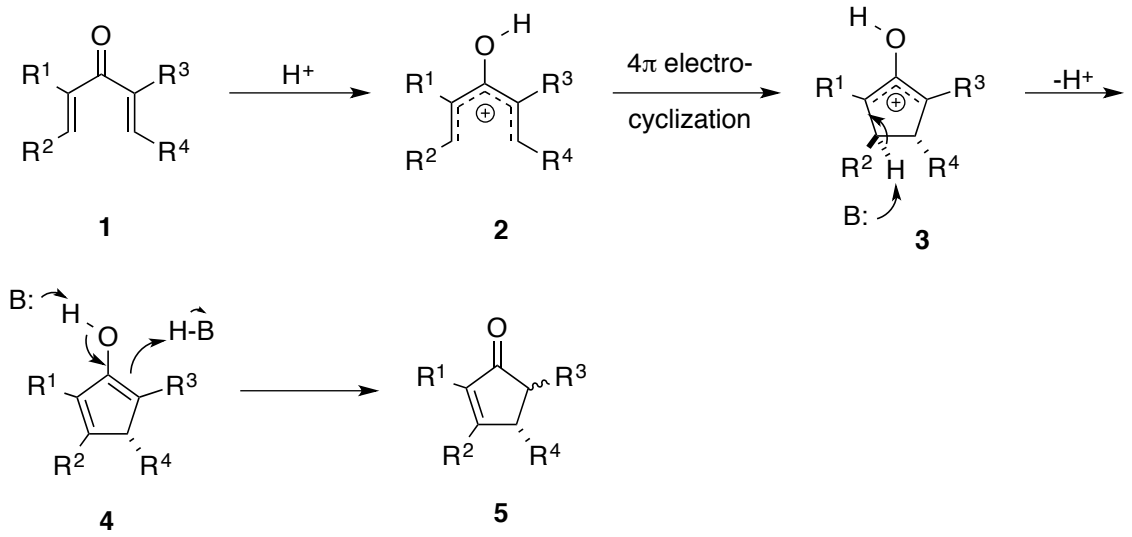
Chapter 2

[3+3] Cycloadditions Between Organoazides and the Nazarov Intermediate and the Thermolysis of Their Cycloadducts

2.1 The Nazarov Reaction

The Nazarov reaction is well established as an effective means to produce cyclopentenones from simple 1,4-diene-3-ones (Scheme 2.1).[1-3] The mechanism of the Nazarov cyclization begins with complexation of the oxygen of dienone **1** with a strong Lewis or Brønsted acid, creating pentadienyl cation **2**. Subsequent annulation occurs *via* a concerted stereospecifc 4π-conrotatory electrocyclization, setting the stereochemistry at the two β positions. The ring closure produces oxyallyl cation **3** that undergoes proton elimination to produce a dienol or a dienolate **4**, which will undergo either tautomerization or protonation to give cyclopentenone **5**.



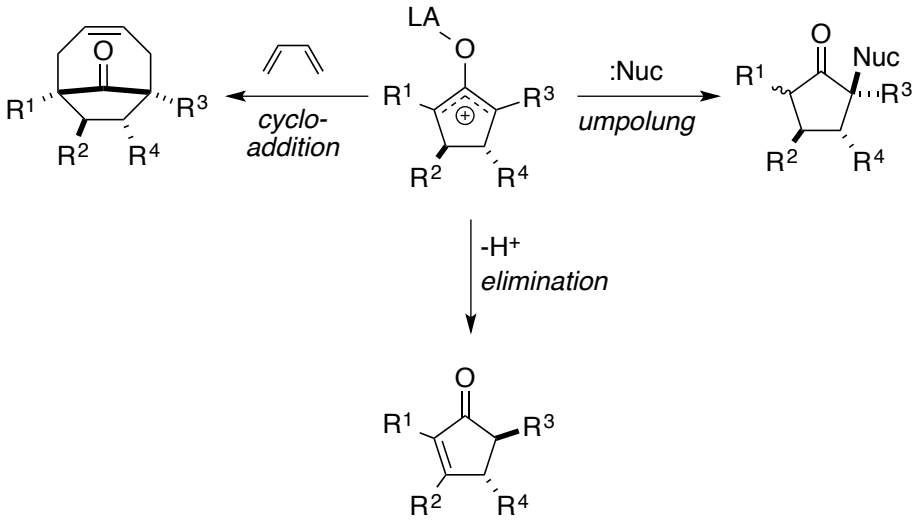
Scheme 2.1 The Nazarov Cyclization.

Recent developments in the Nazarov reaction have focused on asymmetric induction,[3,4] catalytic activation methods,[2,4-8] alternate substrates to the traditional dienones,[9-11], and trapping of the oxyallyl cation intermediate to add molecular complexity.[12] Most of these themes were covered in detail throughout Chapter 1, and will not be repeated. Trapping of the oxyallyl cation intermediate, however, was not covered in Chapter 1, and will be discussed below.

2.1.1 The Interrupted Nazarov Reaction

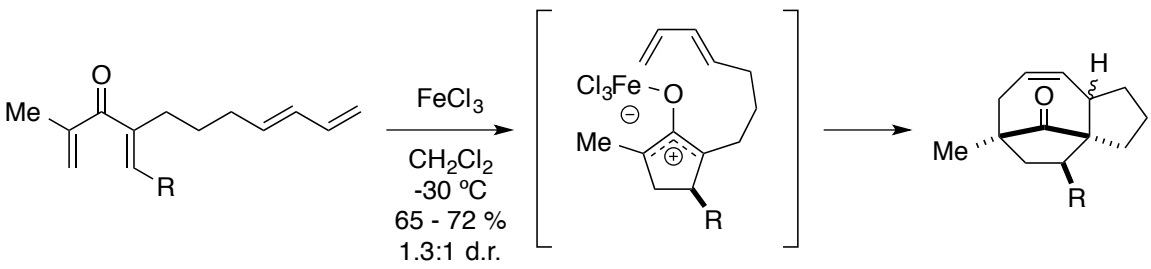
Trapping of the oxyallyl cation intermediate of the Nazarov cyclization with various nucleophiles has been termed the "interrupted Nazarov reaction."[13] By intercepting the oxyallyl cation with a nucleophile the proton elimination step is prevented, allowing for the stereocenters formed during the electrocyclization to be preserved. Furthermore, reactivity can be harnessed at both α-positions

(cycloadditions) or at a single α-position (direct nucleophilic attack) – reactivity that would otherwise be cumbersome to accomplish (Scheme 2.2).



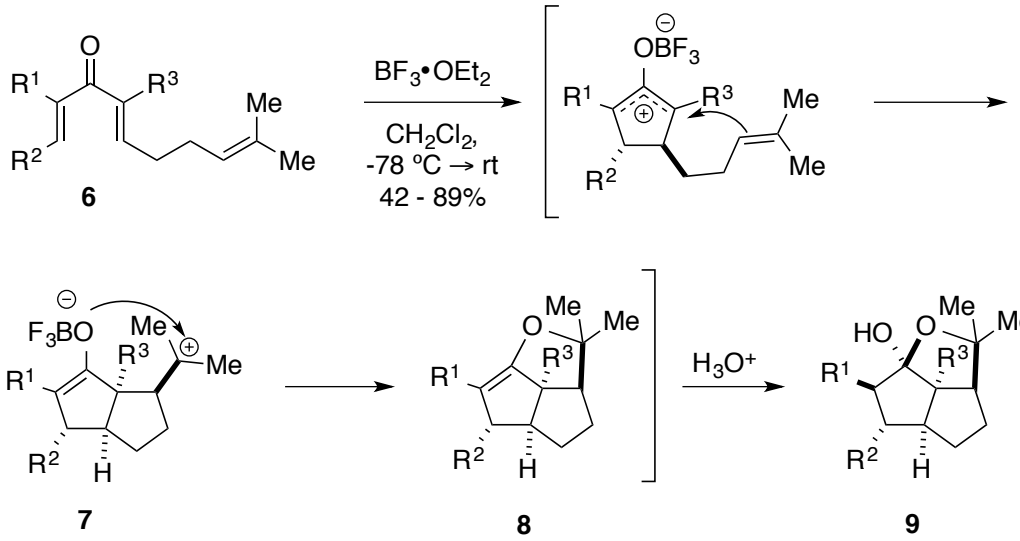
Scheme 2.2 The Interrupted Nazarov Reaction.

The first instance of an interrupted Nazarov reaction involving a cycloaddition was accomplished by tethering dienes to the substrate, which then trapped the oxyallyl cation in an intramolecular [4+3] fashion (Scheme 2.3).[14] A variety of keto-bridged cyclooctenes were synthesized *via* this method as mixtures of diastereomers. This methodology was later built upon using simple dienes in intermolecular reactions.[15] Additionally, allylsilanes[16] and vinyl sulfides[17] were found to undergo intermolecular [3+2] cycloadditions with the Nazarov intermediate.

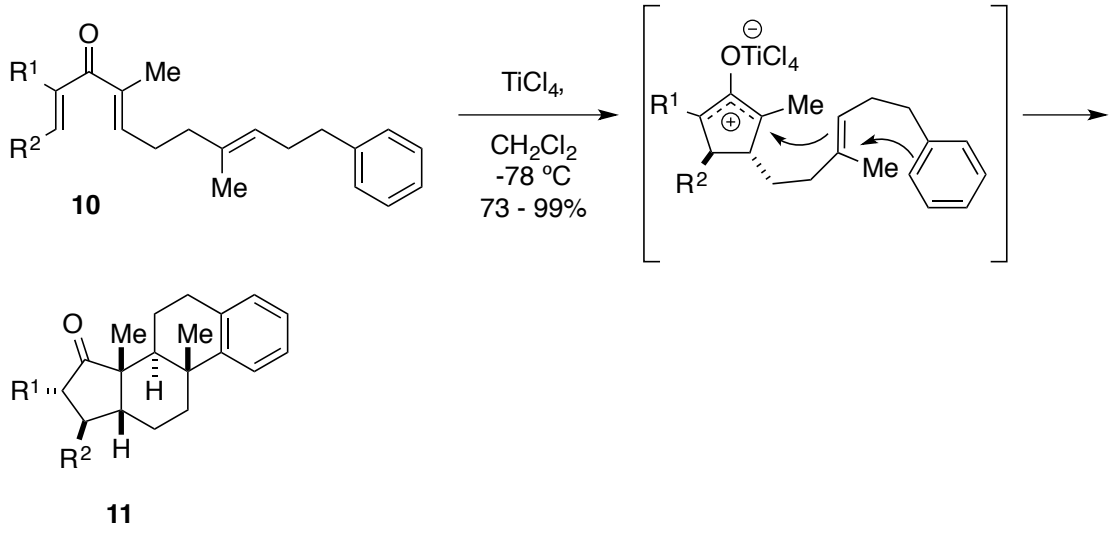


Scheme 2.3 First Example of an Intramolecular [4+3] Cycloaddition of a Diene and the Nazarov Intermediate.

The oxyallyl intermediate can also be used to initiate sequences of cationic trapping events to form polycyclic carbon skeletons. This was displayed in two separate publications by the West group.[13,18] Trienones **6** underwent Nazarov cyclization followed by nucleophilic trapping by the pendant alkene to form a new cation **7** when exposed to BF_3•OEt_2 (Scheme 2.4). This cation was subsequently trapped by the oxygen of the metallo-enolate to form **8**, which was converted to **9** upon acidic workup. Furthermore, if an aromatic group was tethered through the alkene, as in **10**, the aromatic group can trap the tertiary cation, effectively forming tetracyclic compound **11** with six contiguous stereocenters (Scheme 2.5).



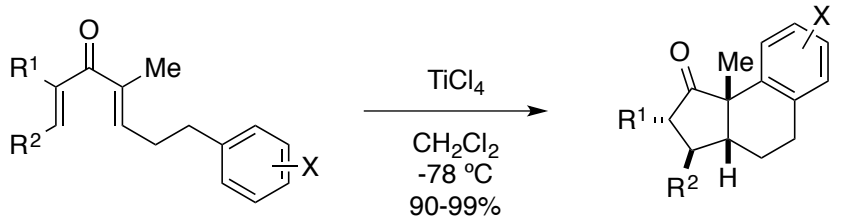
Scheme 2.4 Intramolecular Prins Trapping of the Nazarov Intermediate.



Scheme 2.5 Cascade Trapping of the Nazarov Intermediate.

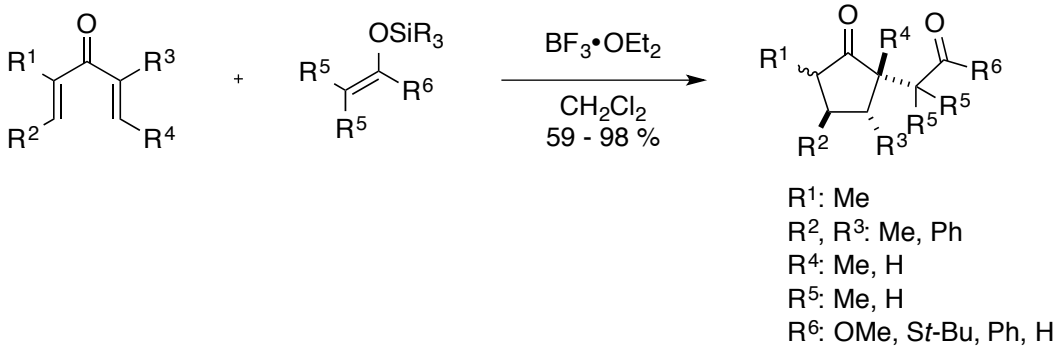
A variety of nucleophiles have been shown to interrupt the Nazarov reaction in a net *umpolung* fashion, producing cyclopentanones with new functionalities attached at the α-position. Dienones with tethered electron rich aromatic ring systems undergo domino Nazarov cyclization/intramolecular Friedel-Crafts reactions when exposed to Lewis acids (Scheme 2.6).[19] Similarly, when bicyclic

dienones were mixed with electron-rich aromatics and BF_3•OEt_2 they underwent the analogous process in an intermolecular fashion.[20,21]



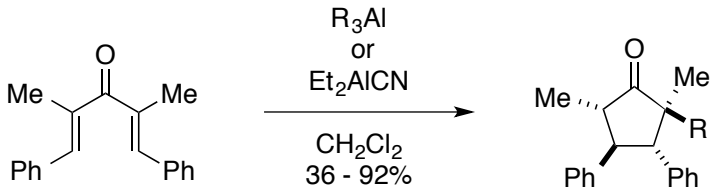
Scheme 2.6 Intramolecular Friedel-Crafts Trapping of the Nazarov Intermediate.

The use of electron-rich carbon nucleophiles as trapping agents allows for functionality to be added to the cyclopentanone quickly and provides new handles for further synthetic manipulations. This is especially evident in the case of silyl enol ethers and silyl ketene acetals (Scheme 2.7).[22] By trapping with these enolate-like carbonyls, homo-Mukaiyama products are formed, notably with a minimal amount of Mukaiyama-Michael addition products.



Scheme 2.7 *Umpolung* Trapping of the Nazarov Intermediate.

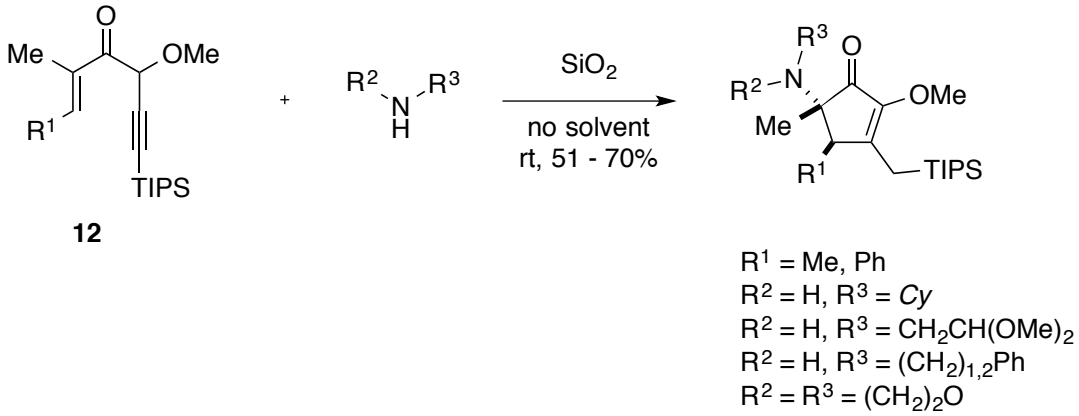
Recently, the incorporation of *sp*^{3}- and *sp*- nucleophiles into the Nazarov framework was showcased (Scheme 2.8).[23] By utilizing aluminum based Lewis acids, nucleophiles were introduced at the α-position in an intramolecular fashion, avoiding direct 1,2-addition onto the ketone. Methyl, ethyl, phenyl, and cyano groups were all successfully incorporated using this method.



Scheme 2.8 Organoaluminum-Mediated Trapping of the Nazarov Intermediate.

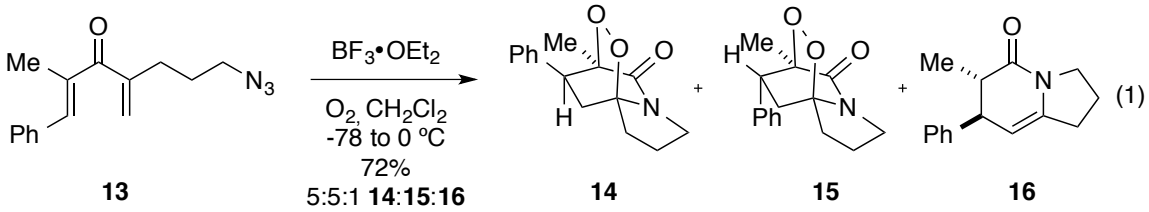
2.1.2 Interrupted Nazarov Reactions with Nitrogen-Based Nucleophiles

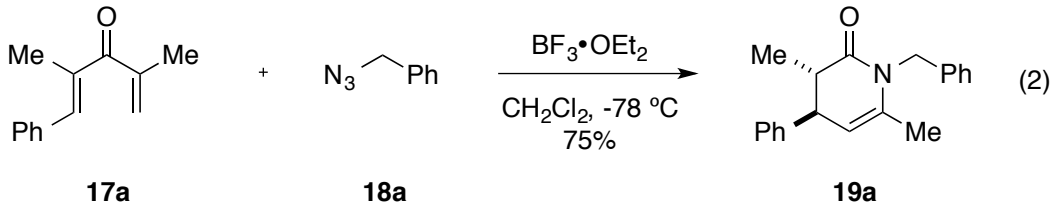
The majority of methods for interrupting the Nazarov cyclization involve carbon-based nucleophiles,[12] while only a few methods exist employing heteroatom-based nucleophiles.[24-27] The only examples of amine nucleophiles intercepting the Nazarov intermediate were published by the Tius group in 2005, and an asymmetric variant in 2007.[28,29] The authors showed that a variety of primary and secondary amines were readily incorporated into the cyclopentenone product when enone **12** was stirred with activated silica gel and a slight excess of amine. Modifying the enone by replacing the methyl ether at the α-position with a camphor-derived variant allowed for the Nazarov cyclization to occur with torqueoselectivity, setting the absolute configuration of the stereocenters of the cyclopentenone.



Scheme 2.9 Amine Intercepted Nazarov Reaction.

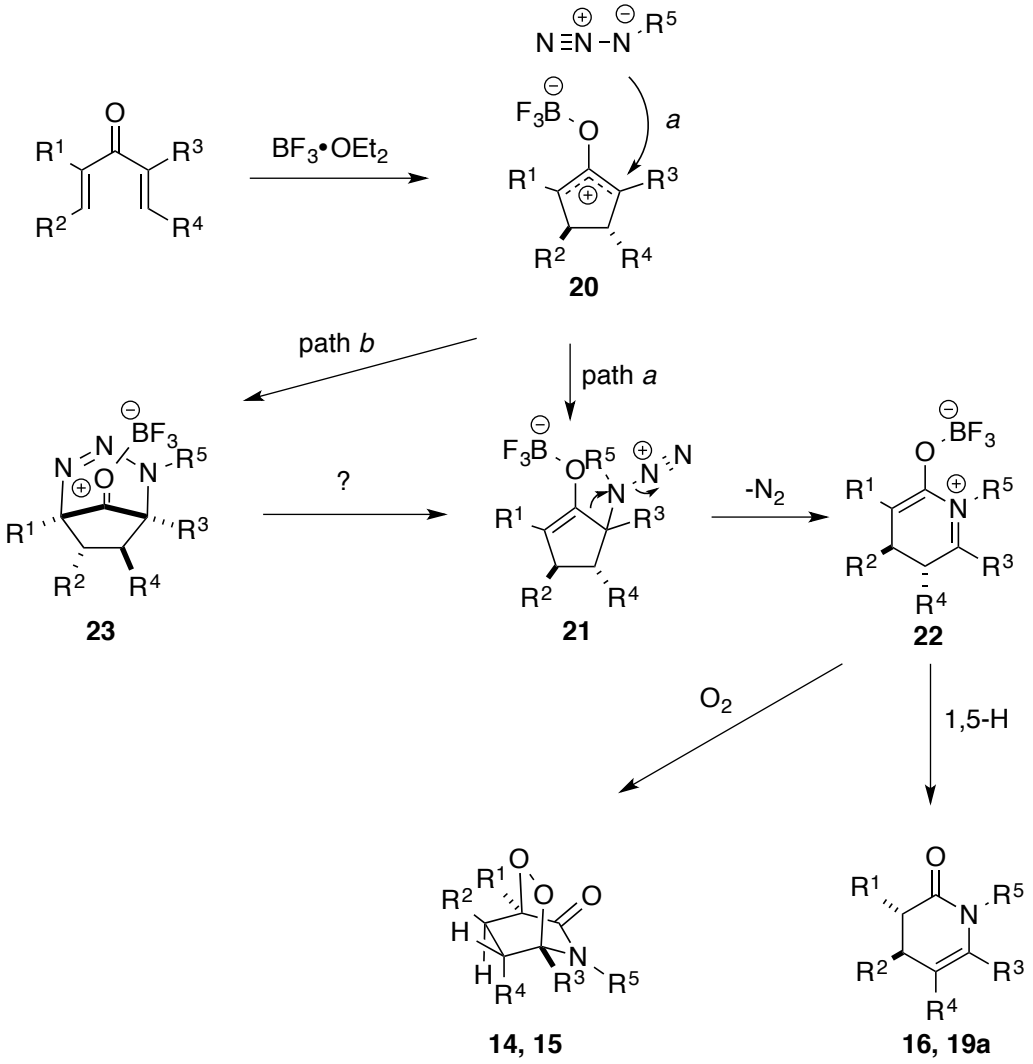
Alkyl azides, when used as nucleophiles to intercept the Nazarov reaction, undergo a remarkably different reaction pathway than other nucleophilic traps. While most trapping agents result in cycloaddition or direct nucleophilic attack pathway, azides lead to a ring-expanded product and the formation of a new amide bond.[30,31] The first example of an azide-captured Nazarov reaction mediated by Lewis acid was an intramolecular variant published by the West group.[30] In this study adventitious oxygen trapped a late stage intermediate, leading to a diastereomeric mixture of endoperoxides **14** and **15**, as seen in eq 1. A smaller quantity of the intermediate, which was not trapped by oxygen, led to dihydropyridone **16**. In a later study, azides and dienones were combined intermolecularly and only dihydropyridone **19a** was observed.[31]





The mechanism for this transformation is postulated to begin with Nazarov cyclization of the dienone to form cyclopentenyl cation **20**, which is attacked by the azide to form intermediate **21** (Scheme 2.10). A subsequent Schmidt-like rearrangement and loss of molecular nitrogen provides zwitterionic intermediate **22**, the common intermediate for the formation of **14**, **15**, and the dihydropyridones **16** and **19a**. If oxygen is present, a single electron transfer pathway resulting in the net [4+2] cycloaddition products **14** and **15** can occur**.** Otherwise, a 1,5-hydride shift or proton exchange occurs to form **16** and **19a**.

It is worth noting that the initial incorporation of the azide potentially occurs via a [3+3] cycloaddition with the oxyallyl cation. This reaction pathway has been observed by both Aubé,[32,33] Schultz,[34,35] and Pearson,[36] on oxyallyl cations generated by different means. The cycloadduct **23** could then cleave to form **21** and rearrange to key intermediate **22**.

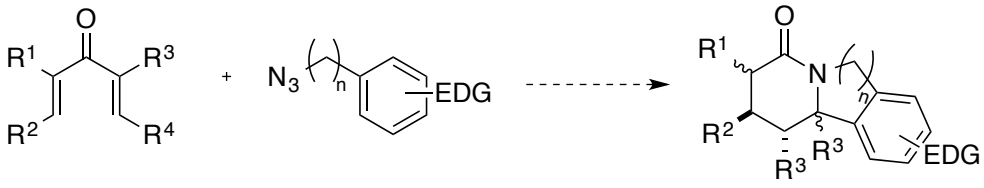


Scheme 2.10 Mechanism for the Azide Captured Nazarov/Schmidt Process.

2.2 [3+3] Cycloadditions Between Organoazides and the Nazarov Intermediate

The interception of intermediate **22** by molecular oxygen led to the hypothesis that **22** could be intercepted by other nucleophiles, allowing for rapid development of molecular complexity.[37] Initial focus was on tethering potential nucleophiles to the azide to form indolizidine and quinolizidine backbones (Scheme

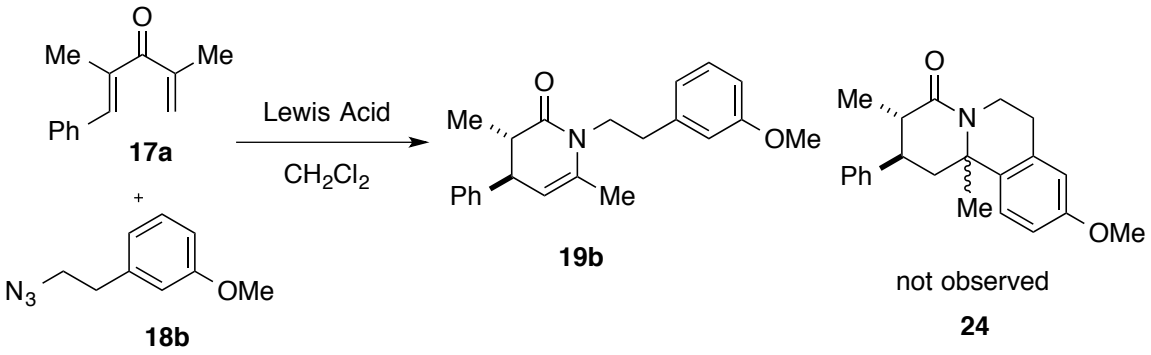
2.11). This method would combine the advantages of both the *intra-* and *inter-*molecular cases; the formation of bicyclic products with the potential for rapid diversity. It is also important to note the significant reduction in synthetic steps compared to the intramolecular methodology, which required multiple steps to produce the azide-tethered dienones.



Scheme 2.11 Proposed Trapping of the Nazarov/Schmidt Process.

Studies began with aryl-tethered azide **18b** and dienone **17a**. Subjecting the reactants to the standard reaction conditions of BF_3•OEt_2 at low temperature, established in the intermolecular studies,[31] led to dihydropyridone **19b.** Unfortunately, none of the desired bicyclic product **24** was observed. Increasing the temperature or the reaction time failed to influence the reactivity. The examination of other Lewis acids was also uneventful, with $TiCl_4$ also producing **19b** (40% yield) and both $SnCl_4$ and TMSOTf producing intractable mixtures.

Table 2-1 Survey of Lewis Acids for the Formation of 21.

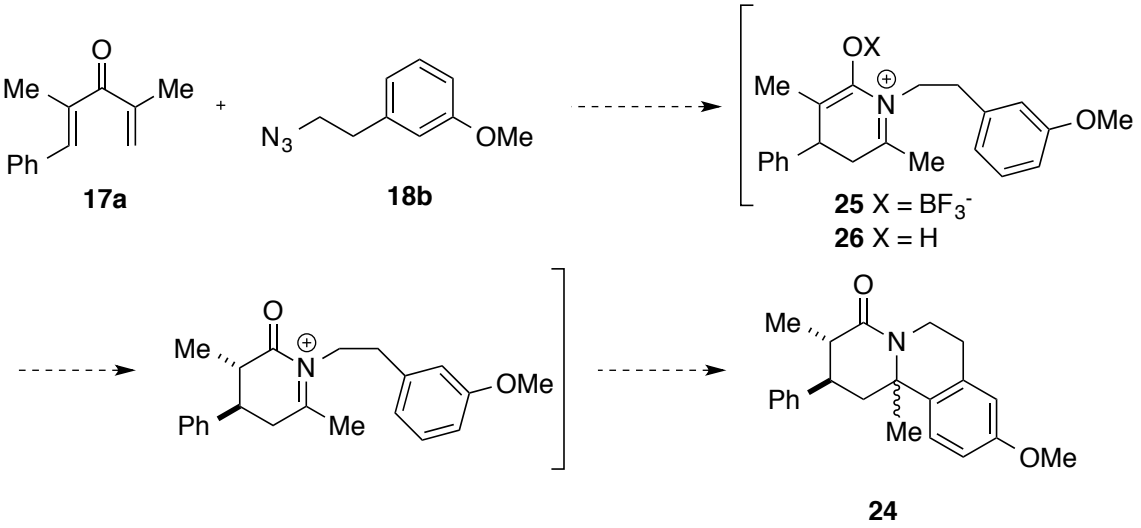


Entry	Lewis Acid	Conditions	Product	Yield[b]
1	BF_3•OEt_2	–78 to -40 °C	**19b**	40 %
2	BF_3•OEt_2	0 °C	**19b**	65 %
3	BF_3•OEt_2	rt	**19b**	55 %
4	$TiCl_4$	–78 to -40 °C	**19b**	40 %
5	$SnCl_4$	–78 to -40 °C	Intractable material	
6	TMSOTf	–78 to -40 °C	Intractable material	

[a] Dienone **17a** (1.0 equiv) and azide **18b** (2.0 equiv) were dissolved in CH_2Cl_2 (0.1 M), flushed with Ar and cooled to the appropriate temperature. Lewis acid (1.2 equiv) was then added slowly and the reaction stirred until complete by TLC. [b]All yields are of purified product after flash chromatography.

With the Lewis acids tested producing either **19b** or an intractable mixture, the approach to forming **24** was re-examined. The zwitterionic intermediate **25** could undergo either proton exchange or a [1,5]-H shift to neutralize the individual ionic components. One possible approach to increase the chance of aryl trapping would be to employ an excess of strong Brønsted acid, which could both initiate the Nazarov cyclization and tautermerize the enol portion of intermediate **26** (Scheme

2.12). This would leave an N-acyl iminium ion that could be trapped by the aromatic group to produce **24**.

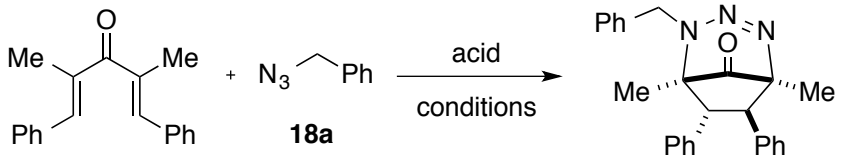


Scheme 2.12 Formation of N-Acyl Iminium Ion to Encourage Aromatic Trapping.

A series of Brønsted acids were tested with dienone **17b** and benzyl azide **18a** (Table 2-2), and their ability to initiate the Nazarov cyclization and permit the original azide capture/Schmidt rearrangement process was assessed. Trifluoroacetic acid failed to consume any of the starting dienone, even upon warming to 0 °C. A stronger Brønsted acid, *p*-toluenesulfonic acid, consumed the starting material, but produced an intractable mixture. Noting the consumption of starting material, other strong acids were analyzed and bis(trifluoromethane)sulfonimide was found to produce one main product. Upon characterization, it was revealed that the product was not the expected dihydropyridone, but instead the [3+3]-cycloadduct **27a** formed as a single diastereomer in 57% yield. The cycloadduct, being a crystalline solid, was analyzed

by single crystal X-ray diffraction to confirm the structural assignment as **27a**. Further optimization found trifluoromethanesulfonic acid to yield **27a** in 78% after only five minutes at –78 °C.

Table 2-2 Survey of Brønsted Acids for Formation of 27a.



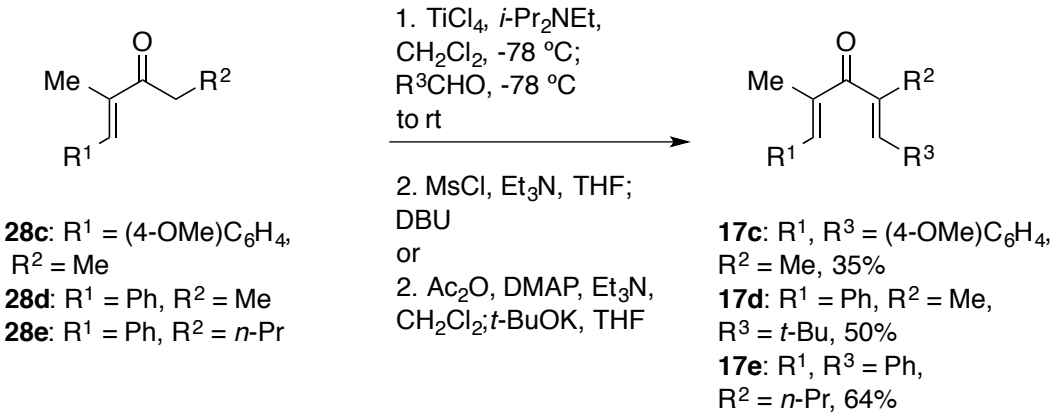
17b **18a** **27a**

Entry	Acid	Conditions	Yield 27a[b]
1	trifluoroacetic acid	CH_2Cl_2, –78 °C 2h; then 0 °C, 2h	no conversion
2	*p*-toluenesulfonic acid	CH_2Cl_2, –78 °C, 0.5 h	intractable mixture
3	bis(trifluoromethane)sulfonimide	CH_2Cl_2, –78 °C, 0.25 h	57 %
4	trifluormethanesulfonic acid	CH_2Cl_2, –78 °C, 5 min	78 %

[a]**17b** and **18a** (2.0 equiv) stirred with 2.2 equiv of the indicated acid at the temperature indicated. [b]Yields are provided for isolated product after chromatographic purification.

In order to investigate the generality of this unexpected [3+3] cycloaddition, a number of symmetrical and unsymmetrical dienones were synthesized for use in this reaction. Dienones **17c-e**, substituted with groups of sufficient steric bulk to diminish potential 1,4-additions in the [3+3] chemistry, were prepared from the

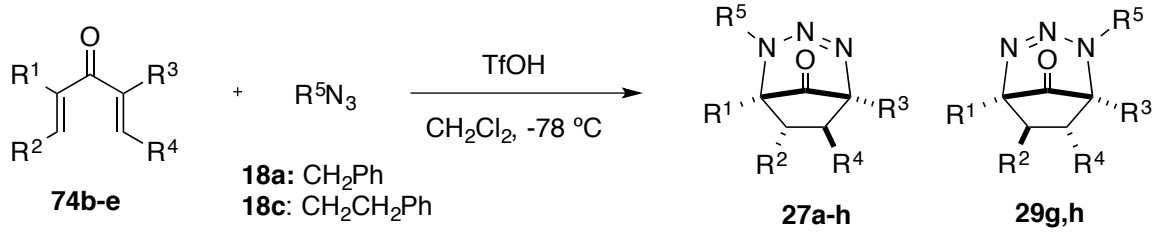
corresponding enones **28c-e**. Aldol addition to the appropriate aldehyde followed by elimination of the activated alcohol furnished **17c-e**.



Scheme 2.13 Synthesis of Dienones 17c-e.

Dienone **17b** reacted in a similar fashion as with azide **18c**, producing **27b** in good yield as a single diastereomer. Symmetrical dienone **17c**, with *p*-methoxyphenyl groups at the β- and β'-positions also reacted well, forming cycloadducts **27c** and **27d** in good yield. The regioselectivity of the reaction was tested with dienones **17d** and **17e**. Dienone **17d**, substituted with phenyl at the β-position and *t*-butyl group at the β'-position, produced a single regioisomer upon reaction with **18a** and **18c**, respectively. Upon careful analysis of the HMBC correlations, it was found that the alkyl group of the azide is positioned on the side distal to the bulky *tert*-butyl group. Alternatively, **17e** was found to produce a mixture of regioisomers, forming **27g** and **29g** in a ratio of 1:2.2, and **27h** and **29h** in a ratio of 1:2.1. In both cases, the ratio showed slight preference for the alkyl group on the azide to align with the side substituted with the *n*-propyl substituent rather than the methyl group.

Table 2-3[3+3] Cycloaddition of Azides and the Nazarov Intermediate.

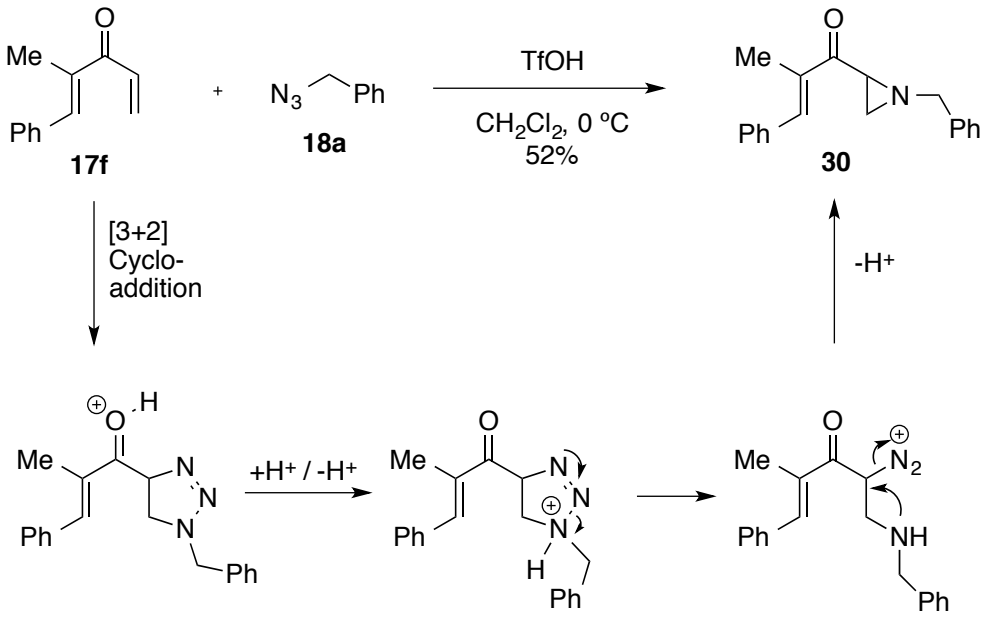


Entry	Dienone	R^1	R^2	R^3	R^4	Azide	Product yield (%)[b]
1	**17b**	Me	Ph	Me	Ph	**18a**	**27a** (78)
2	**17b**	Me	Ph	Me	Ph	**18c**	**27b** (70)
3	**17c**	Me	(4-OMe)C_6H_4	Me	(4-OMe)C_6H_4	**18a**	**27c** (81)
4	**17c**	Me	(4-OMe)C_6H_4	Me	(4-OMe)C_6H_4	**18c**	**27d** (64)
5	**17d**	Me	Ph	Me	*t*-Bu	**18a**	**27e** (75)[c]
6	**17d**	Me	Ph	Me	*t*-Bu	**18c**	**27f** (62)[c]
7	**17e**	Me	Ph	*n*-Pr	Ph	**18a**	**27g/29g** (81, 1:2.2)
8	**17e**	Me	Ph	*n*-Pr	Ph	**18c**	**27h/29h** (61, 1:2.1)

[a]Dienone (1 equiv) and azide (2 equiv) were dissolved in CH_2Cl_2 (0.2 M) and cooled to −78 °C. TfOH (2.2 equiv) was added slowly and the reaction was stirred until disappearance of dienone as indicated by TLC (5-30 min). The reaction was quenched with saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, concentrated, and purified by flash chromatography. [b]All yields indicate isolated product after flash chromatography. [c]Reactions with dienone **17d** were conducted at -40 °C.

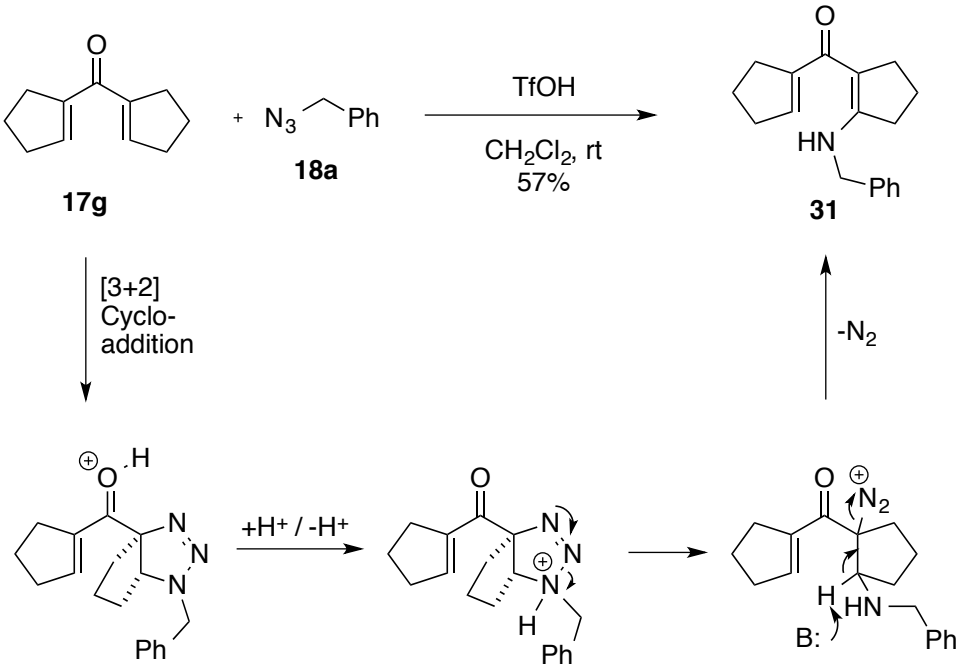
The [3+3] methodology was further probed with dienones **17f and 17g**, which were synthesized according to literature methods.[31,38] These two dienones

require higher temperatures to cyclize, 0 °C and room temperature, respectively.[20,31] Under the reaction conditions, **17f** produced aziridine **30** as the only identifiable product in 52% yield. The elevated temperature required for the reaction is believed to allow for the competing aziridination to occur prior to electrocyclization. This is analogous to the work of the Johnston group, whereby enones were shown to undergo aziridination with azides under Brønsted acid conditions.[39] In their work, the Johnston group identified a [3+2] cycloadduct that decomposes to extrude molecular nitrogen, and form the product aziridine.[40] While no [3+2] cycloadduct was observed in the reaction of **17f** with benzyl azide, this mechanism cannot be ruled out.



Scheme 2.14 Formation of Aziridine 30.

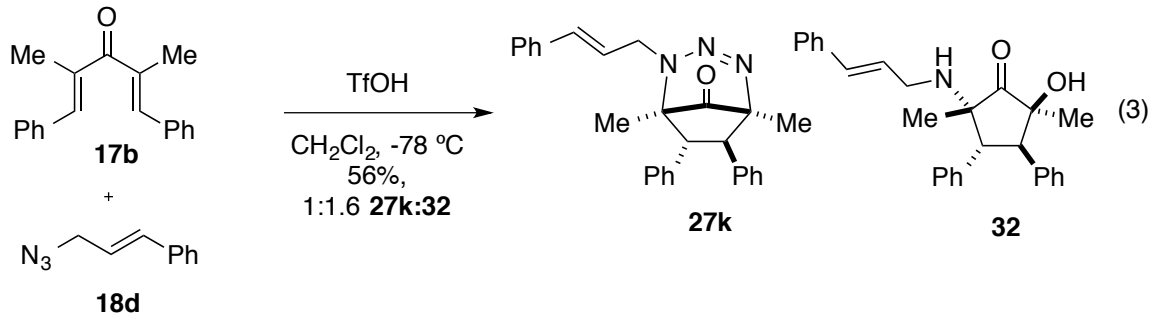
Dienone **17g** required the reaction with azide **18a** to be conducted at room temperature in order to consume the starting material. Similar to **17f**, the electrocyclization failed to occur. The resulting product was found to be enaminone **31**. This is presumed to form *via* a similar mechanism as aziridine **30**; initial [3+2] cycloaddition followed by cleavage of the nitrogen-nitrogen bond.[41] The rigid configuration around the transient cyclopentane unit hinders formation of the aziridine, instead nitrogen is extruded *via* either proton elimination or a nitrogen-assisted 1,2-hydride shift, followed by tautomerization, to provide **31**.

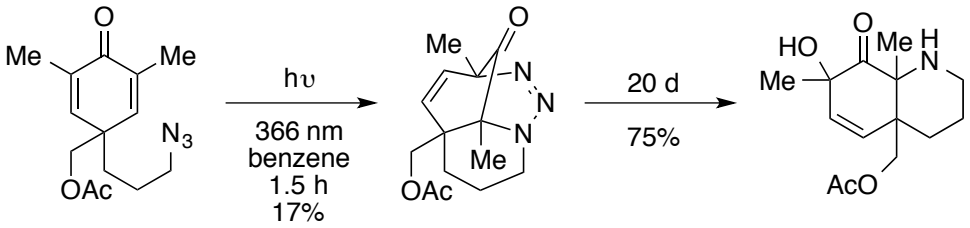


Scheme 2.15 Formation of Enaminone 31.

Dienone **17b** was also subjected to the standard reaction conditions with cinnamyl azide **18d**. This combination was reported to form the dihydropyridone product in the presence of Lewis acid[31] and was expected to furnish the [3+3]

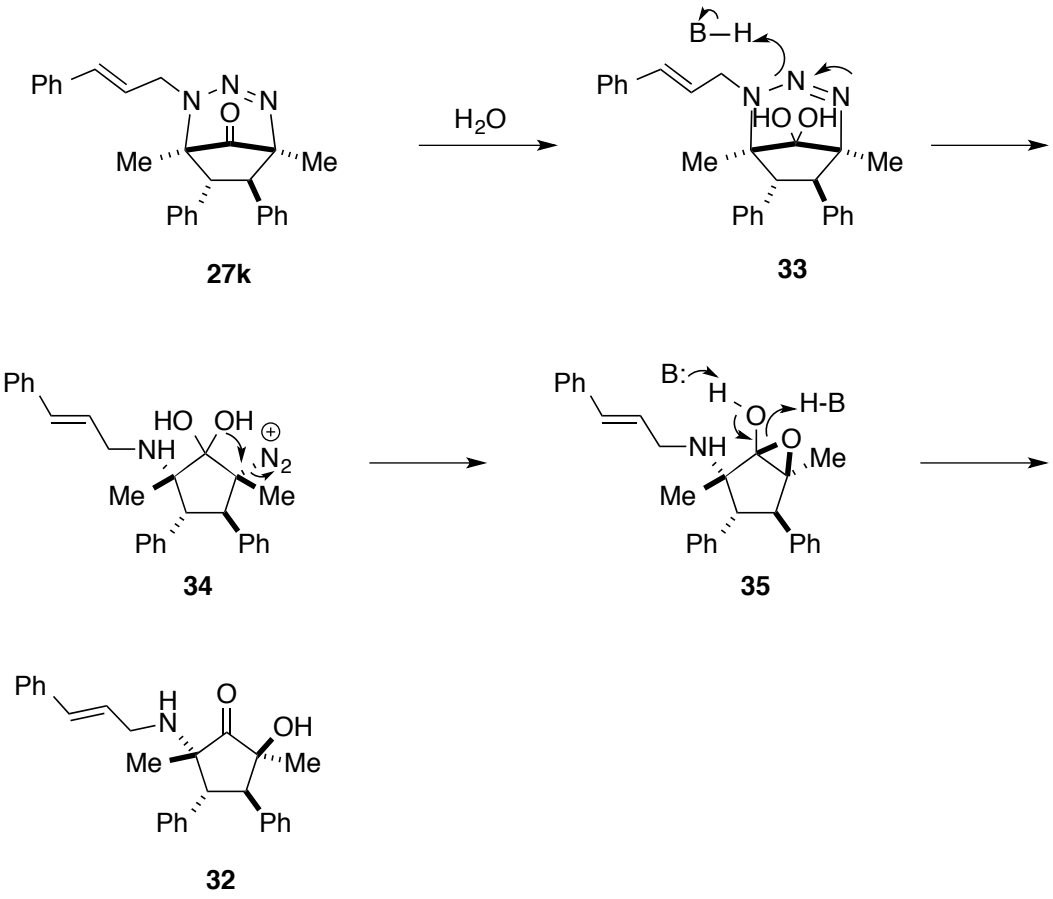
cycloadduct under Brønsted acid conditions. Although the crude reaction mixture indicated that cycloadduct **27k** was the primary product, chromatographic purification resulted in a 1:1.6 mixture of **27k** and a new product. This new product's molecular formula indicated a loss of N_2 and incorporation of H_2O. Qualitative analysis of the compound's spectra led to the structural assignment of the product as 2-hydroxy-5-aminocyclopentanone **32**. A crystal suitable for X-ray diffraction analysis confirmed the structure as **32**, and established the stereochemical relationship of the amino and hydroxyl groups as being *trans*. This hydrolysis product is analogous to the one reported by the Schultz group in their intramolecular [3+3]-photocycloaddition publication (Scheme 2.16).[34,35] In their work, the hydrolysis product was observed upon prolonged storage, upwards of 20 days. Interestingly, cycloadducts **27a-h** and **29g-h** did not hydrolyze to the corresponding 2-hydroxy-5-aminocylcopentanones after extended storage. Furthermore, attempts to drive **27k** to **32** by stirring **27k** with silica gel failed to consume the cycloadduct completely.





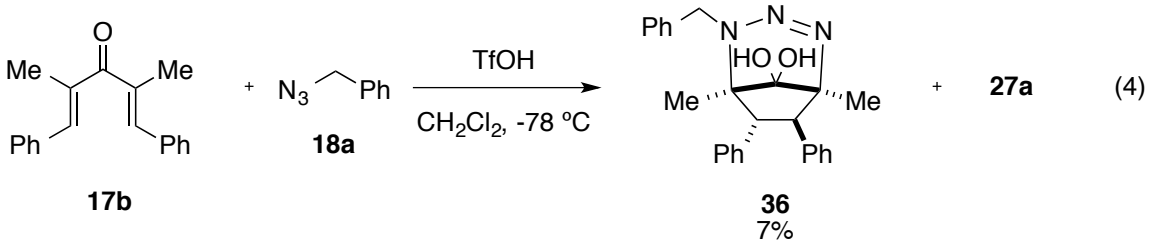
Scheme 2.16 Schultz's Photochemical [3+3] Cycloaddition and Decomposition.

The mechanism for the conversion of **27k to 32** is proposed to begin with hydration of the ketone to generate hydrate **33** (Scheme 2.17). The triazene bridge is then fragmented to form **34**. The hydroxyl group anti to the diazonium would then attack to form epoxide **35**, with the necessary orientation of the oxygen at C-2. This intermediate could then open to form the 2-hydroxy-5-aminocyclopentanone product.



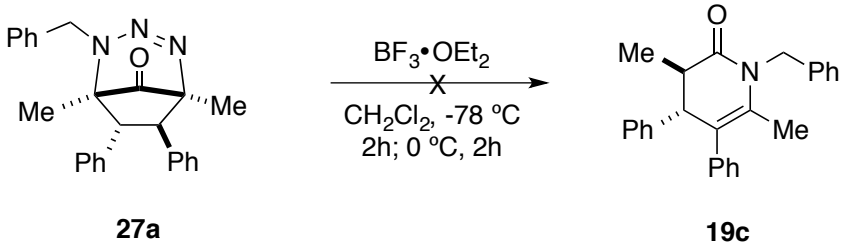
Scheme 2.17 Formation of 2-Hydoxy-5-aminocyclopentanone 32.

Confidence that the first intermediate in the hydrolysis of **27k** to **32** is hydrate **33** stems from previous findings in the reaction between dienone **17b** and azide **18a**. When this process was conducted on a larger scale a moderate quantity of insoluble solid formed during work-up. NMR analysis of the product mixture found the ketone moiety to have disappeared and the mass spectrum indicated that hydrate **36** had formed. The hydrate could be converted back into **27a** by stirring in a basic solution.



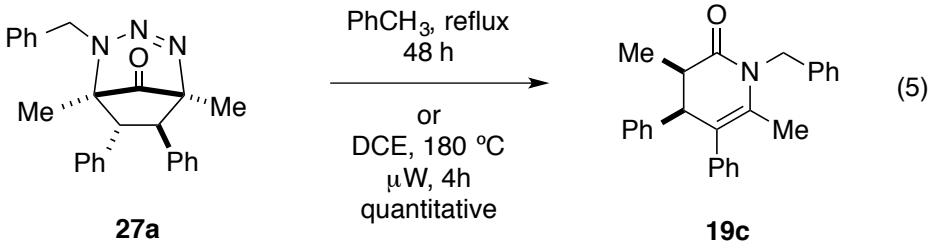
2.3 Reactivity of [3+3] Cycloadducts

The hydrolysis of **27k** to **32** suggested that the [3+3]-cylcoadducts are potentially labile, and might be reactive under other conditions. As was noted above, it was considered possible that the domino Nazarov/Schmidt methodology could proceed via a transient [3+3]-cyclcoadduct (Scheme 2.10, path *b*). To test this hypothesis, cycloadduct **27a** was subjected to the standard Lewis acidic conditions (BF_3•OEt_2, –78 °C) that had been used in the originally reported reaction.[31] No consumption of **27a** was observed at this temperature, nor upon warming to 0 °C for two hours (Scheme 2.18). This suggests that path *b* is not a key pathway in the domino Nazarov cyclization/Schmidt rearrangement methodology.



Scheme 2.18 Attempted Conversion of 27a to 19c.

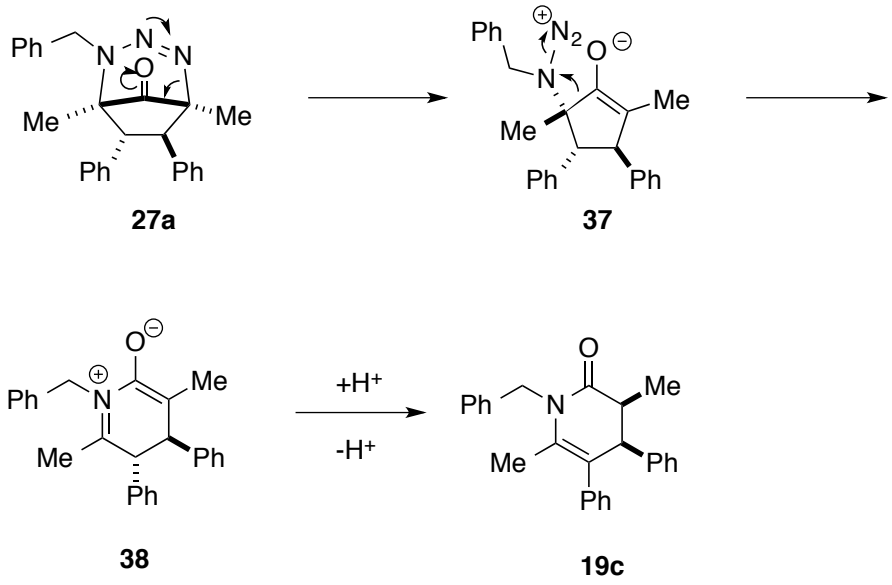
To investigate the thermal stability of the [3+3] cycloadducts **27a** was heated at 90 °C in toluene for two days, at which time the complete consumption of the starting material. The lone compound produced was determined to be **19c**, formed in quantitative yield and as a single diastereomer. Of note, in the Lewis acid methodology compound **19c** was formed in a 2:1 ratio of *trans* to *cis* diastereomers.[31] Furthermore, the reaction time could be reduced to four hours if the reaction was conducted at 180 °C in 1,2-dichloroethane under microwave conditions.



27a **19c** (5)

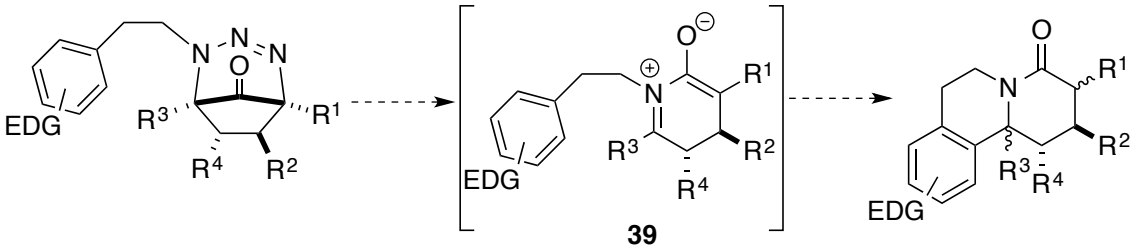
The proposed mechanism for the thermal decomposition of **27a** to **19c** begins with cleavage of the C-N bond of the triazene bridge, breaking the bicyclic structure and forming the zwitterion **37** (Scheme 2.19). This intermediate can then undergo a ring enlargement, ejecting molecular nitrogen and forming **38**. Subsequent proton exchange would produce dihydropyridone **19c**. The formation of a single diastereomer in this reaction is likely attributed to the lack of Lewis acid, reducing the likelihood of tautermerization and subsequent epimerization of the α-carbon. The formation of exclusively the *cis* isomer suggests that under these

reaction conditions the [1,5]-hydride shift is not a contributing pathway for the production of **19c** from **38**.



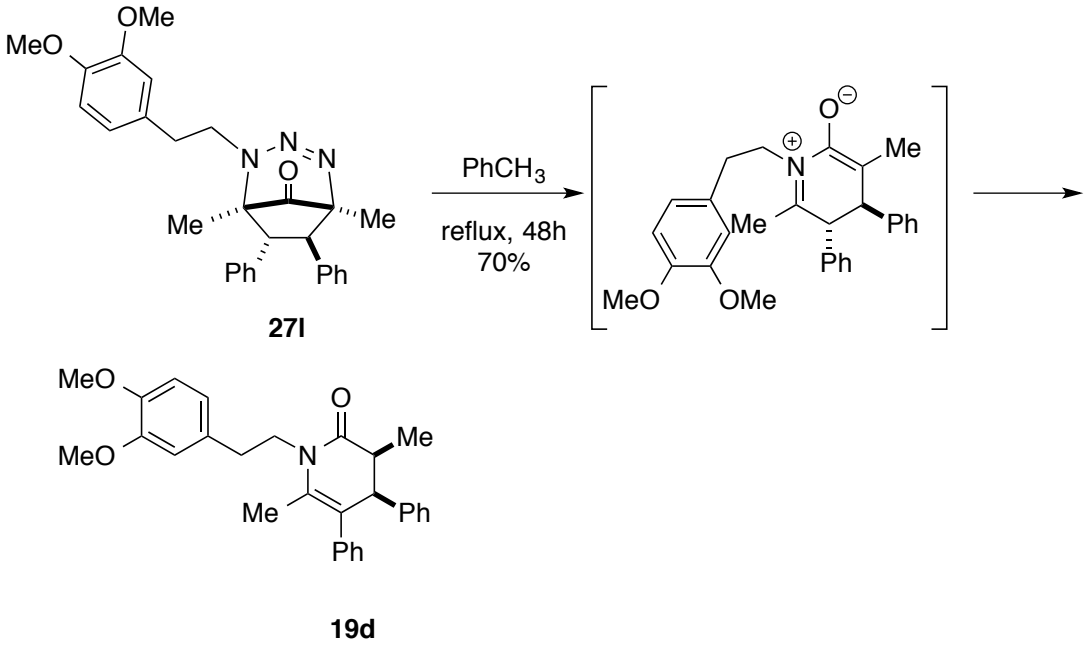
Scheme 2.19 Thermal Decomposition of Cycloadduct 27a.

The thermal decomposition of cycloadduct **27a** to form **19c** renewed our interest in diverting the 1,4-dipole precursor to the dihydropyridone products via an intramolecular nucleophilic trapping reaction (Scheme 2.20). The lack of Lewis acid in the reaction and the use of elevated temperatures inspired optimism that a suitable aromatic group could close onto the cationic portion of intermediate **39** and produce the tricyclic structures discussed earlier in section 2.2.



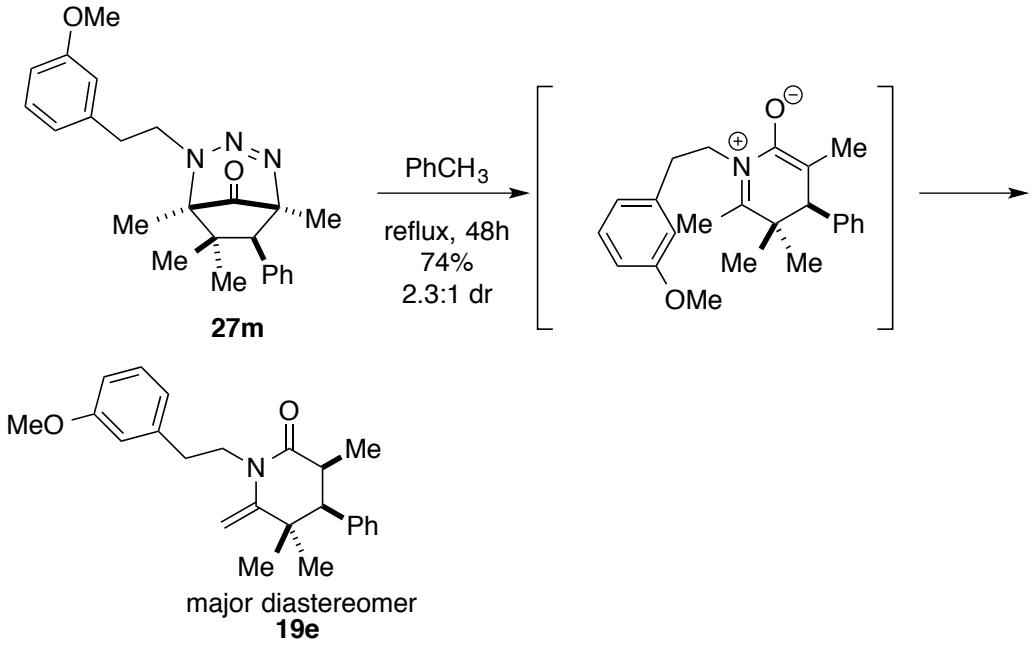
Scheme 2.20 Potential Trapping of Zwitterion 39.

To test the viability of this reaction, cycloadduct **27l** was heated in toluene at reflux for 48 hours. Unfortunately, the only product isolated was the simple untrapped dihydropyridone **19d**, in a 70% yield (Scheme 2.21). This result suggested that the proton exchange was too facile to allow for the desired aromatic trapping event to occur. Iodomethane and bis(trifluoromethane)sulfonimide were both tested as agents that could capture the enolate portion of the zwitterionic intermediate and facilitate the production of an N-acyl iminium intermediate. In both cases, however, presence of the additives produced an intractable mixture.



Scheme 2.21 Thermal Decomposition of 27l to Dihydropyridone 19d.

Cycloadduct **27m** was also tested for potential aromatic trapping. This cycloadduct was synthesized with a quartenary *geminal*-dimethyl group in place of the tertiary benzylic group, effectively preventing the endocyclic alkene from forming. Unfortunately, thermolysis of **27m** led to the formation of **19e**, with the olefin exocyclic to the ring, in a 2.3:1 ratio of diastereomers (Scheme 2.22). The lack of diastereocontrol indicates a diminished stereoselectivity in the protonation of the enolate component of the zwitterion. The lack of aromatic trapping further supports the findings that the iminium component of the zwitterion is not reactive enough to be trapped by the tethered aromatic group.



Scheme 2.22 Thermal Decomposition of 27m.

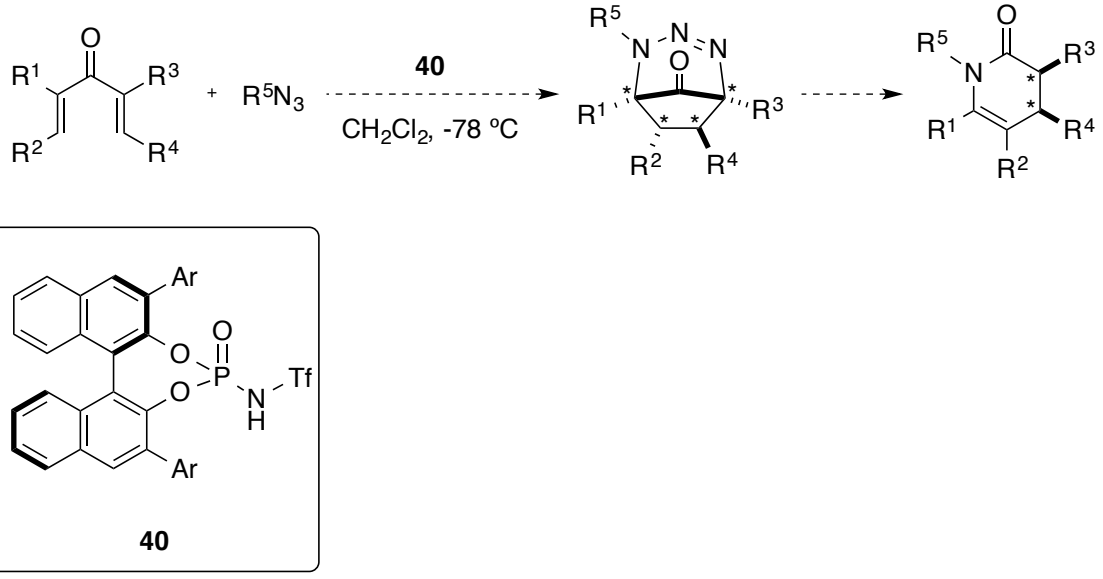
2.4 Conclusion

A series of 1,4-diene-3-ones was found to undergo Nazarov cyclization, followed by [3+3] cylcoaddition with organoazides in the presence of the strong Brønsted acid trifluoromethanesulfonic acid. The majority of the cycloadducts were stable and obtained in good yield with excellent stereochemistry and modest to complete regiocontrol. These cycloadducts were shown to undergo thermolysis under microwave conditions, losing molecular nitrogen and rearranging to form dihydropyridones; the same structures were produced when dienones and azides were combined under Lewis acidic conditions.

2.5 Future Directions

The discovery of the [3+3] cycloaddition of alkyl azides with the Nazarov intermediate and the subsequent thermolysis of these products leads us to believe that this methodology could be expanded on to include other fruitful endeavors.

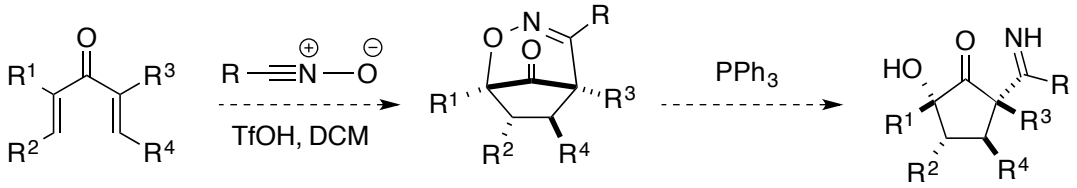
It is conceivable that through the use of strong chiral Brønsted acids, such as N-trifyl phosphoramides **40**, torquoselectivity could be introduced into the Nazarov cyclization. The addition of a chiral Brønsted acid to a solution of dienone and alkyl azide would ideally lead chiral cycloadducts. Thermolysis of these chiral cycloadducts would produce chiral dihydropyridones.



Scheme 2.23 Chiral Brønsted Acid Induced Enantioselectivity in [3+3] Cycloaddition

It is conceivable that other 1,3-dipoles could undergo [3+3] cycloadditions with the Nazarov intermediate under the reaction conditions. Nitrile oxides would

produce interesting bridged bicyclic structures, and cleavage of the nitrogen-oxygen bond would produce cyclopentanones with both hydroxyl and imine functionality at the α-positions.



Scheme 2.24 Nitrile Oxides as 1,3-Dipoles in [3+3] Cycloaddtions with the Nazarov Intermediate

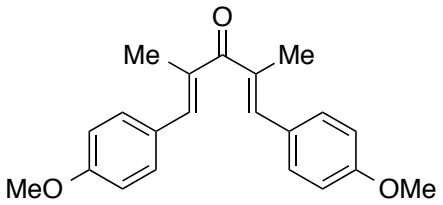
These methods would nicely compliment the [3+3] cycloaddition of alkyl azides and the Nazarov intermediate methodology mentioned above. Furthermore, these methods would provide ways to access unique structures in short order.

2.6 Experimental

2.6.1 General Information

Reactions were carried out in flame-dried glassware under a positive argon atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannulae. Solvents were distilled before use: methylene chloride from calcium hydride, tetrahydrofuran, and diethylether from sodium/benzophenone ketyl. Thin layer chromatography was performed on glass plates precoated with 0.25 mm Kieselgel 60 F254 (Merck). Flash chromatography column were packed with 230-400 mesh silica gel (Silicycle). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz or 500 MHz and coupling constants (*J*) are reported in Hertz (Hz). Standard notation was used to describe the multiplicity of signals observed in ^{1}H NMR spectra: broad (br), apparent (app), multiplet (m), singlet (s), doublet (d), triplet (t), etc. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz or 125 MHz and are reported (ppm) relative to the center line of the triplet from chloroform-*d* (77.26 ppm). Infrared (IR) spectra were measured with a Mattson Galaxy Series FT-IR 3000 spectrophotometer. Mass spectra were determined on a PerSeptive Biosystem Mariner high-resolution electrospray spectrometer in the positive mode.

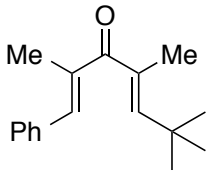
2.6.2 Experimental Procedures and Characterization



Dienone 17c. To a solution of **28c**[42] (1.4 g, 6.9 mmol) in DCM (50 mL, 0.15 M) at –78 °C, $TiCl_4$ (751 μL, 6.85 mmol, 1.0 equiv) was added dropwise, followed by $^{i}Pr_2NEt$ (1.43 mL, 8.22 mmol, 1.2 equiv) dropwise, turning the solution dark brown in color. After stirring at –78 °C for 1.5 hours, *p*-methoxybenzaldehyde (1.24 mL, 10.3 mmol, 1.5 equiv) was added dropwise. The solution was stirred at –78 °C for 2 hours, and then allowed to slowly warm to room temperature overnight. The reaction was then quenched with water (30 mL). The aqueous layer was extracted (2 x 30 mL), and the organic layers were combined and washed with water (2 x 30 mL) and brine (1 x 30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The crude material was then purified by flash column chromatography (silica gel, hexanes:EtOAc 2:1) and carried directly to the next step.

To a solution of hydroxy ketones, and DMAP (83 mg, 0.68 mmol, 0.1 equiv) in DCM (50 mL) was added TEA (1.4 mL, 10 mmol, 1.5 equiv) followed by Ac_2O (777 μL, 8.22 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 2 hours and then quenched with 1N HCl solution. The aqueous layer was extracted with DCM (2 x 20 mL). The organic layers were combined and washed with 1N HCl (2 x 20 mL), water (1 x 20 mL), sat'd $NaHCO_3$ solution (1 x 20 mL), and brine (1 x 20 mL). The organic layer was then filtered and concentrated by rotary evaporation.

^{t}BuOK (1.54 g, 13.7 mmol, 2.0 equiv) was then added to a solution of the crude material in THF (50 mL). The reaction mixture was then brought to reflux overnight. The reaction was quenched with sat'd NH_4Cl solution. The aqueous layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, washed with water (2 x 20 mL) and brine (1 x 20 mL), and dried ($MgSO_4$). The organic layer was filtered, concentrated by rotary evaporation and purified by column chromatography (silica gel, hexanes:EtOAc 8:1) to yield **17c** (35%) as a white solid: R_f 0.30 (hexanes:EtOAc 5:1); mp 89-90 °C; IR (solid cast) 3096, 3032, 3007, 2964, 2935, 2916, 2839, 1606, 1570, 1514, 1466, 1459 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.39 (m, 4H), 7.14 (br s, 2H), 6.92-6.96 (m, 4H), 3.85 (s, 6H), 2.21 (d, *J* = 1.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 159.6, 138.6, 135.1, 131.3, 128.7, 113.9, 55.4, 15.0; HRMS (EI, M^+) Calcd for $C_{21}H_{22}O_3$ 322.1569; Found m/z 322.1572; Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.39; H, 6.87.

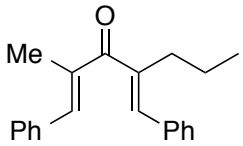


Dienone 17d. To a solution of **28d**[43] (1.5 g, 8.6 mmol) in DCM (50 mL, 0.2 M) at –78 °C was added $TiCl_4$ (943 μL, 8.6 mmol, 1.0 equiv) dropwise, followed by $^{i}Pr_2NEt$ (1.8 mL, 10 mmol, 1.2 equiv) dropwise. The brown solution was stirred at –78 °C for 1.5 hours before trimethylacetaldehyde (4.68 mL, 43 mmol, 5 equiv) was added dropwise. The solution was stirred at –78 °C for 1.5 hours before being warmed to room temperature over 4 hours. The reaction mixture was quenched with H_2O (20 mL). The aqueous layer was extracted with DCM (2 x 20 mL) and the organic layers

were combined, washed with water (2 x 20 mL) and brine (1 x 20 mL), and dried ($MgSO_4$). The organic layer was filtered, concentrated by rotary evaporation and purified by flash column chromatography (silica gel, hexanes:EtOAc column volumes of 12:1→8:1→4:1). The crude material was then carried on to the next step.

The mixture of hydroxy ketones and DMAP (105 mg, 0.86 mmol, 0.10 equiv) was dissolved in DCM (50 mL). To the mixture was added TEA (1.8 mL, 13 mmol, 1.5 equiv), followed by Ac_2O (976 μL, 10.2 mmol, 1.2 equiv) and stirred for 2 hours. The mixture was quenched with 1N HCl (20 mL). The aqueous layer was extracted with DCM (1 x 20mL) and the organic layers were combined, washed with 1N HCl (2 x 20 mL), water (1 x 20 mL), sat'd $NaHCO_3$ (1 x 20 mL), and brine (1 x 20 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The crude material was then dissolved in THF (50 mL), and ^{t}BuOK (1.93 g, 17.2 mmol, 2.0 equiv) was added. The reaction mixture was brought to reflux overnight. The reaction was quenched with sat'd NH_4Cl solution and the aqueous layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, washed with water (2 x 20 mL) and brine (1 x 20 mL), dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The crude material was then purified by flash column chromatography (silica gel, hexanes:EtOAc 20:1) to yield **17d** (50%) as a thick yellow oil: R_f 0.33 (hexanes:EtOAc 19:1); IR (film) 3082, 3056, 3025, 2959, 2868, 1695, 1640, 1492 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.30 (m, 5H), 7.06 (d, *J*=1.5 Hz, 1H), 6.24 (q, *J*=1.4 Hz, 1H), 2.11 (d, *J*=1.4 Hz, 3H), 2.02 (d, *J*=1.4 Hz, 3H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 151.5, 138.7, 137.4, 136.4,

134.7, 129.7, 128.7, 128.3, 33.8, 30.5, 15.1, 14.1; HRMS (EI, M^+) Calcd for $C_{17}H_{22}O$ 242.1671; Found m/z 242.1667.



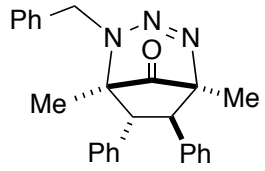
Dienone 17e. To a solution of **28e**[44] (2.02 g, 10 mmol) in DCM (100 mL, 0.10 M) at –78 °C was added $TiCl_4$ (1.32 mL, 12 mmol, 1.2 equiv) dropwise followed by $^iPr_2NEt$ (2.08 mL, 12 mmol, 1.2 equiv). The dark brown solution was stirred for 1.5 hours at –78 °C before benzaldehyde (1.5 mL, 15 mmol, 1.5 equiv) was added dropwise. The solution was stirred at –78 °C for 1.5 hours, then allowed to warm up slowly to room temperature overnight. The reaction was quenched with water (40 mL) and the aqueous layer was extracted with DCM (2 x 40 mL). The organic layers were combined, washed with water (2 x 40 mL) and brine (1 x 40 mL), dried ($MgSO_4$) and concentrated by rotary evaporation. The crude material was purified by flash column chromatography (silica gel, hexanes:EtOAc 8:1) to give 870 mg of hydroxy ketones, carried directly to the next step.

To a mixture of hydroxy ketones in THF (25 mL) at 0° C was added TEA (590 μL, 4.23 mmol, 1.5 equiv), followed by methanesulfonyl chloride (240 μL, 3.10 mmol, 1.1 equiv) dropwise. The mixture was stirred for 15 min, during which a white precipitate appeared. DBU (2.1 mL, 14 mmol, 5.0 equiv) was added dropwise and the mixture was stirred overnight. The reaction was quenched with 1 N HCl (10 mL). The aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were

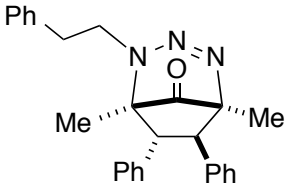
combined and washed with 1 N HCl (2 x 10 mL), water (1 x 10 mL), and brine (1 x 10 mL). The organic layer was then dried ($MgSO_4$), concentrated by rotary evaporation and purified by flash column chromatography (silica gel, hexanes:EtOAc 21:1) to yield **17e** (64%) as a yellow oil: R_f 0.33 (hexanes: EtOAc 15:1); IR (film) 3056, 3025, 2960, 2930, 2871, 1638, 1447 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.32 (m, 11H), 7.10 (s, 1H), 2.68 (m, 2H) 2.23 (d, *J*=1.5 Hz, 3H), 1.59 (2H, m), 1.01 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 142.6, 140.1, 137.9, 137.7, 136.2, 136.2, 129.9, 129.4, 128.7, 128.7, 128.6, 128.3, 30.5, 22.2, 14.9, 14.6; HRMS (EI, M^+) Calcd for $C_{21}H_{22}O$ 290.1671; Found m/z 290.1672; Anal. Calcd for $C_{21}H_{22}O$: C, 86.85; H, 7.64. Found: C, 86.51; H, 7.59.

Tandem Nazarov Cyclization/[3+3] Cycloaddition Reactions:

Standard Procedure:
Dienone **17a-e**(0.20 mmol) and azide **18a,c,d**(0.40 mmol, 2.0 equiv) was dissolved in DCM (5 mL, 0.04M), flushed with argon and cooled to –78 °C. Trifluoromethanesulfonic acid (39 μL, 0.44 mmol, 2.2 equiv) was added dropwise, resulting in a bright yellow solution. The reaction mixture was stirred until dienone was consumed according to TLC analysis. The reaction was quenched with sat'd $NaHCO_3$ (10 mL) and warmed to room temperature. The aqueous layer was extracted with DCM (2 x 15 mL), the combined organic layers were washed with brine solution (1 x 15 mL) and dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation providing a semi-solid that was purified by flash column chromatography (silica gel) to afford the desired cycloadduct.

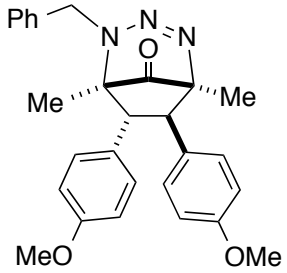


Cycloadduct 27a. The standard procedure was used to yield **27a** (78%) after purification by flash chromatography (silica gel, hexanes:EtOAc 8:1) as a white solid: R_f 0.35 (hexanes:EtOAc 5:1); mp (dec) 148-150 °C; IR (solid cast) 3057, 3042, 3026, 2997, 2930, 1751, 1600, 1495, 1452, 1468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51-7.45 (m, 5H), 7.30-7.23 (m, 6H), 7.02-6.96 (m, 4H), 4.81 (d, *J* = 16.6 Hz, 1H), 4.08 (d, *J* = 6.8 Hz, 1H), 3.41 (d, *J* = 6.8 Hz, 1H), 3.27 (d, *J* = 16.7 Hz, 1H), 1.26 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 141.4, 138.6, 136.5, 129.6, 129.3, 129.0, 128.9, 128.6, 128.4, 127.7, 127.6, 126.6, 73.4, 73.0, 64.3, 56.7, 54.7, 14.8, 14.1; HRMS (ESI, M^+) Calcd for $C_{26}H_{25}N_3O$ 396.1998; Found m/z 396.2076; Anal. Calcd for $C_{26}H_{25}N_3O$: C, 78.96; H, 6.37; N, 10.62. Found: C, 78.87; H, 6.38; N, 10.51.

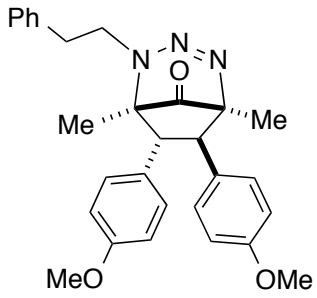


Cyloadduct 27b. The standard procedure was used to yield **27b** (70%) after purification by flash chromatography (silica gel, hexanes:EtOAc 8:1) as a white solid: R_f 0.36 (hexanes:EtOAc 5:1); mp 144-146 °C; IR (solid cast) 3058, 3029, 2979, 2944, 2933, 1751, 1602, 1494, 1471, 1452 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H), 7.26-7.15 (m, 6H), 6.98-6.95 (m, 2H), 6.92-6.89 (m, 2H), 3.98 (d, *J*=6.8 Hz, 1H), 3.31 (d, *J*=6.8 Hz, 1H), 3.22 (ddd, *J*=13.8, 9.2, 5.6 Hz, 1H), 2.73 (m, 2H), 2.61 (ddd, *J*=13.8, 8.7, 7.3 Hz, 1H), 1.26 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.2,

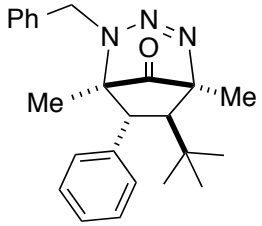
141.2, 138.2, 136.2, 129.7, 129.4, 128.9, 128.7, 128.5, 128.3, 128.2, 127.4, 126.5, 73.1, 72.3, 63.8, 56.2, 51.7, 36.9, 14.6, 13.6; HRMS (ESI, M^+) Calcd for $C_{27}H_{27}N_3O$ 410.2154; Found m/z 410.2228.



Cycloadduct 27c. The standard procedure was used to yield **27c** (81%) after purification by flash chromatography (silica gel, hexanes:EtOAc 4:1) as a white solid: R_f 0.13 (hexanes:EtOAc 5:1); mp (dec) 138-140 °C; IR (solid cast) 3063, 3031, 2996, 2957, 2934, 2837, 1751, 1612, 1514, 1496 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J*=8.7 Hz, 2H) 7.25-7.19 (m, 3H), 7.00-6.96 (m, 4H), 6.83 (d, *J*=8.7Hz, 2H), 6.77 (d, *J*=8.6 Hz, 2H), 4.80 (d, *J*=16.4 Hz, 1H), 3.91 (d, *J*=6.7 Hz, 1H), 3.85 (s, 3H), 3.74 (s, 3H), 3.31 (d, *J*=16.6 Hz, 1H), 3.25 (d, *J*=6.7 Hz, 1H), 1.19 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.2, 159.5, 158.8, 138.4, 133.5, 130.3, 129.3, 128.6, 128.0, 127.3, 126.3, 114.4, 114.0, 73.2, 72.6, 63.8, 56.3, 55.3, 55.2, 54.4, 14.6, 13.8; HRMS (ESI, M^+) Calcd for $C_{28}H_{29}N_3O_3$ 456.2209; Found m/z 456.2282; Anal. Calcd for $C_{28}H_{29}N_3O_3$: C, 73.82; H, 6.42; N, 9.22. Found: C, 73.64; H, 6.41; N, 9.16.

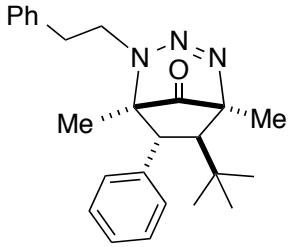


Cycloadduct 27d. The standard procedure was used to yield **27d** (64%) after purification by flash chromatography (silica gel, hexanes:EtOAc 4:1) as a white solid: R_f 0.14 (hexanes:EtOAc 5:1); mp (dec) 146-148 °C; IR (solid cast) 3062, 3029, 2995, 2934, 2837, 1751, 1612, 1514, 1454 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25-7.18 (m, 5H), 7.00 (m, 2H), 6.90 (m, 2H), 6.81 (m, 2H), 6.75 (m, 2H), 3.84 (d, *J*=6.9 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.29 (ddd, *J*=13.5, 7.1, 7.1 Hz, 1H), 3.20 (d, *J*=7.0 Hz, 1H), 2.76 (app t, *J*=8.0, 7.5 Hz, 2H), 2.65 (ddd, *J*=13.8, 8.9, 7.0 Hz, 1H), 1.22 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.5, 159.6, 158.9, 138.4, 133.6, 130.4, 129.4, 128.9, 128.7, 128.2, 126.7, 114.4, 114.2, 73.4, 72.3, 63.7, 56.2, 55.4, 55.3, 51.9, 37.2, 14.7, 13.7; HRMS (ESI, M^+) Calcd for $C_{29}H_{31}N_3O_3$ 470.2365; Found m/z 470.2438; Anal. Calcd for $C_{29}H_{31}N_3O_3$: C, 74.18; H, 6.65; N, 8.95. Found: C, 74.17; H, 6.65; N, 9.00.



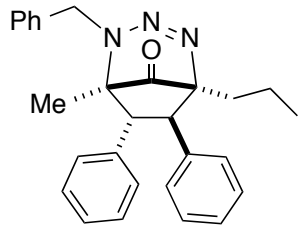
Cycloadduct 27e. The standard procedure was carried out at -40 °C to yield **27e** (75%) after purification by flash chromatography (silica gel, hexanes:EtOAc 8:1) as a white solid: R_f 0.36 (hexanes:EtOAc 5:1); mp (dec) 122-125 °C; IR (solid cast) 3087, 3029, 3004, 2964, 2871, 1753, 1602, 1473 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47-

7.38 (m, 5H), 7.21-7.14 (m, 3H), 6.90 (d, *J*=7.3 Hz, 2H), 4.52 (d, *J*=16.6 Hz, 1H), 3.06 (d, *J*= 16.7 Hz, 1H), 3.03 (d, *J*=6.5 Hz, 1H), 2.90 (d, *J*=6.5 Hz, 1H), 1.67 (s, 3H), 1.14 (s, 3H), 0.82 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.2, 139.0, 138.4, 129.0, 128.5, 128.4, 127.6, 127.2, 126.3, 74.2, 71.6, 58.4, 57.9, 54.0, 36.0, 28.4, 17.0, 13.9; HRMS (ESI, M^+) Calcd for $C_{24}H_{29}N_3O$ 376.2311; Found m/z 376.2378; Anal. Calcd for $C_{24}H_{29}N_3O$: C, 76.76; H, 7.78; N, 11.19. Found: C, 76.72; H, 7.73; N, 11.12.

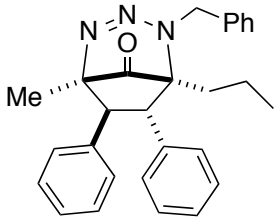


Cycloadduct 27f. The standard procedure was carried out at -40 °C to yield **27f** (62%) after purification by flash chromatography (silica gel, hexanes:EtOAc 8:1) as a white solid: R_f 0.39 (hexanes:EtOAc 5:1); mp (dec) 116-118 °C; IR (solid cast) 3061, 3032, 2998, 2977, 2941, 2913, 1751, 1602, 1499 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H), 7.22-7.14 (m, 3H), 6.93-6.90 (m, 2H), 3.03-2.96 (m, 2H) 2.75 (d, *J*=6.4 Hz, 1H), 2.50 (ddd, *J*=13.6, 8.9, 7.1 Hz, 1H), 1.64 (s, 3H), 1.19 (s, 3H) 0.803 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 139.4, 138.6, 129.2, 128.9, 128.9, 128.7, 127.8, 126.7, 74.5, 71.4, 58.4, 58.0, 51.5, 37.1, 36.2, 36.2, 17.3, 13.9; HRMS (ESI, M^+) Calcd for $C_{25}H_{31}N_3O$ 390.2467; Found m/z 390.2535.

Cycloadduct 27g and 29g. The standard procedure was used to yield **27g** and **29g** (81%) in a 1:2.2 ratio of **27g**:**29g** after purification by flash chromatography (silica gel, hexanes:EtOAc 8:1).



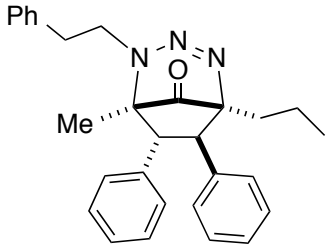
Cycloadduct 27g. White solid, R_f 0.24 (hexanes:EtOAc 8:1); mp (dec) 129-130 °C; IR (solid cast) 3087, 3062, 3029, 2961, 2932, 2872, 1752, 1698, 1602, 1495, 1453; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.38 (m, 5H), 7.30-7.28 (m, 6H), 6.97 (d, *J*=7.3 Hz, 2H), 6.92 (d, *J*=7.1 Hz, 2H), 4.71 (d, *J*=16.5 Hz, 1H), 4.00 (d, *J*=6.4 Hz, 1H), 3.27 (d, *J*=6.4 Hz, 1H), 3.20 (d, *J*=16.6 Hz, 1H), 1.78 (m, 1H), 1.61 (ddd, *J*=14.5, 12.0, 4.6 Hz, 1H), 1.41 (ddd, *J*=14.2, 12.0, 4.2 Hz, 1H), 1.29 (m, 1H), 1.20 (s, 3H), 0.74 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.6, 141.5, 138.4, 136.4, 129.3, 129.0, 128.6, 128.6, 128.2, 128.1, 127.3, 127.3, 126.4, 75.0, 72.7, 64.4, 55.9, 54.3, 30.8, 15.6, 14.7, 14.0; HRMS (ESI, M^+) Calcd for $C_{28}H_{29}N_3O$ 424.2311; Found m/z 424.2383.



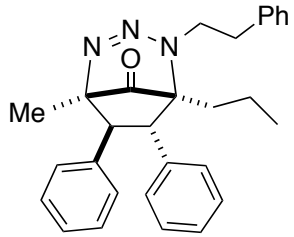
Cycloadduct 29g. White solid, R_f 0.20 (hexanes:EtOAc 8:1); mp (dec) 138-140 °C; IR (solid cast) 3087, 3063, 3029, 3004, 2965, 2932, 2874, 1749, 1602, 1472, 1453; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.38 (m, 5H), 7.29-7.18 (m, 6H), 6.98 (d, *J*=7.2 Hz, 2H), 6.91 (d, *J*=7.0 Hz, 2H), 4.61 (d, *J*=16.7 Hz, 1H), 4.00 (d, *J*=6.2 Hz, 1H), 3.78 (d, *J*=6.1 Hz, 1H), 3.27 (d, *J*=16.7 Hz, 1H), 1.64-1.40 (m, 4H), 1.14 (s, 3H), 0.91 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9, 142.2, 138.9, 137.1, 129.5, 129.3, 129.1,

128.8, 128.5, 128.3, 127.6, 127.5, 126.6, 77.1, 74.7, 59.0, 56.2, 54.2, 29.2, 18.1, 14.9, 14.8; HRMS (ESI, M^+) Calcd for $C_{28}H_{29}N_3O$ 424.2311; Found m/z 424.2380.

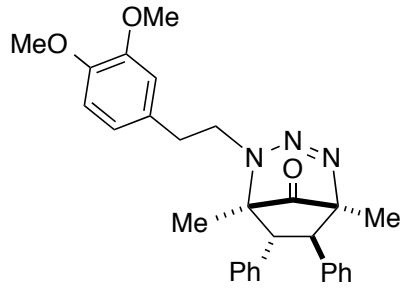
Cycloadduct 27h and **29h**. The standard procedure was used to yield **27h** and **29h** (61%) in a ratio of 1:2.1 of **27h:29h** after purification by flash chromatography (silica gel, hexanes:EtOAc 8:1).



Cycloadduct 27h. White solid, R_f 0.16 (hexanes:EtOAc 8:1); mp (dec) 118-121 °C; IR (solid cast) 3062, 3004, 2961, 2934, 2098, 1750, 1602, 1496, 1454 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 7.24-7.16 (m, 6H), 6.89-6.96 (m, 4H), 3.95 (d, *J*=6.4 Hz, 1H), 3.22 (d, *J*=6.5 Hz, 1H), 3.16 (ddd, *J*=13.6, 9.3, 5.4 Hz, 1H), 2.72 (m, 2H), 2.61 (ddd, *J*=13.5, 9.0, 7.0 Hz, 1H), 1.74 (m, 1H), 1.57 (ddd, *J*=14.3, 12.0, 4.5 Hz, 1H), 1.38 (ddd, *J*=14.2, 11.9, 4.4 Hz, 1H), 1.28 (m, 1H), 1.24 (s, 3H), 0.75 (app t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 141.8, 138.6, 136.7, 129.5, 129.2, 129.0, 128.9, 128.7, 128.5, 128.3, 127.6, 126.8, 75.2, 72.5, 64.4, 55.9, 51.9, 37.2, 31.1, 15.9, 15.0, 13.9; HRMS (ESI, M^+) Calcd for $C_{29}H_{31}N_3O$ 438.2467; Found m/z 438.2539.

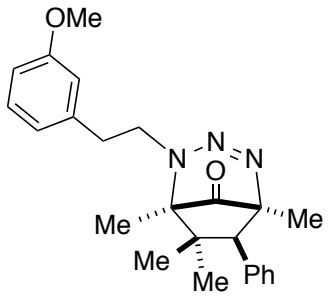


Cycloadduct 29h. White solid, R_f 0.12 (hexanes:EtOAc 8:1); mp (dec) 116-119 °C; IR (solid cast) 3086, 3062, 3028, 2964, 2933, 2873, 2098, 1749, 1602, 1496, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.31 (m, 5H), 7.30-7.19 (m, 6H), 7.01-6.91 (m, 4H), 3.99 (d, *J*=6.3 Hz, 1H), 3.70 (d, *J*=6.4 Hz, 1H), 3.13-3.06 (m, 1H), 2.81-2.68 (m, 3H), 1.66-1.50 (m, 4H), 1.14 (s, 3H), 1.05 (dd, *J*=6.8, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9, 142.1, 138.7, 137.0, 129.4, 129.2, 129.1, 129.0, 128.8, 128.5, 128.2, 127.6, 126.7, 76.4, 74.3, 59.2, 56.0, 51.6, 37.3, 29.2, 18.1, 15.0, 14.8; HRMS (ESI, M^+) Calcd for $C_{29}H_{31}N_3O$ 438.2467; Found m/z 438.2540.

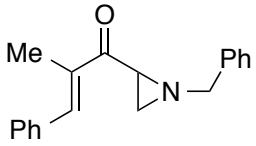


Cycloadduct 27l. yellow oil (45%). R_f 0.26 (4:1 hexanes:EtOAc); IR (cast film) 3028, 2993, 1753, 1516 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.32 (m, 4H), 7.24-7.16 (m, 4H), 6.92 (m, 2H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.51 (dd, *J* = 8.0, 2.0 Hz,) 6.45 (d, *J* = 2.1 Hz), 3.98 (d, *J* = 6.8 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.32 (d, *J* = 6.8Hz, 1H), 3.20 (ddd, *J* = 13.8, 9.0, 4.9 Hz, 1H), 2.72-2.64 (m, 2H), 2.57 (ddd, *J* = 13.5, 8.4, 7.1 Hz, 1H), 1.24 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.3, 148.9, 147.7, 141.2, 136.3, 130.9, 129.3, 128.9, 128.8, 128.3, 128.0, 127.4, 120.6, 112.0, 111.3, 73.1, 72.4, 63.8,

56.2, 55.9, 55.8, 52.0, 36.5, 14.6, 13.7; HRMS (ESI, M+H$^+$) Calcd for $C_{29}H_{32}N_3O_3$ 470.2438; Found m/z 470.2438.

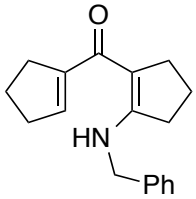


Cycloadduct 27m. yellow oil (54%). R_f 0.40 (5:1 hexanes:EtOAc); IR (cast film) 3029, 2974, 1750, 1601 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.22 (m, 5H), 6.94-6.90 (m, 2H), 6.82-6.78 (m, 2H), 6.74 (dd, *J* = 2.2, 1.8 Hz, 1H), 3.95 (ddd, *J* = 13.9, 10.3, 5.6 Hz, 1H), 3.81 (s, 3H), 3.48-3.42 (m, 2H), 3.14 (ddd, *J* = 13.4, 9.5, 5.5 Hz, 1H), 3.01 (ddd, *J* = 13.3, 10.0, 6.4 Hz, 1H), 1.29 (s, 3H), 1.20 (s, 3H), 1.12 (s, 3H), 0.43 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 213.0, 159.9, 140.0, 136.4, 130.9, 129.7, 127.8, 127.2, 121.2, 114.6, 112.2, 74.0, 70.6, 63.9, 55.2, 52.5, 50.6, 37.5, 25.0, 23.8, 15.2, 10.9; HRMS (ESI, M+H$^+$) Calcd for $C_{24}H_{30}N_3O_2$ 392.2333; Found m/z 392.2329.



Compound 30. Dienone **17f** (40 mg, 0.23 mmol) and **18a** (61 mg, 0.46 mmol, 2.0 equiv) were dissolved in DCM (6 mL, 0.04M), the solution flushed with argon and cooled to 0 °C. Trifluoromethanesulfonic acid (45 μL, 0.51 mmol, 2.2 equiv) was added dropwise, resulting in a bright yellow solution. The reaction mixture was stirred for 30 min. The reaction was quenched with sat'd $NaHCO_3$ (10 mL) and warmed to room temperature. The aqueous layer was extracted with DCM (2 x 15

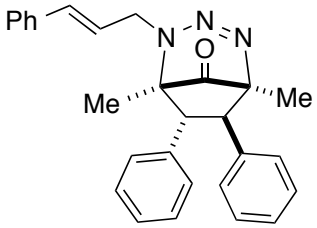
mL), the combined organic layers were washed with brine solution (1 x 15 mL) and dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation providing a semi-solid that was purified by flash column chromatography (silica gel, hexanes:EtOAc 5:1) to provide **30** (52%) as a yellow oil: R_f 0.12 (hexanes:EtOAc 5:1); IR (neat) 3061, 3028, 2979, 2923, 2839, 1651, 1623, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.46-7.27 (m, 10H), 3.88 (d, *J*=13.4 Hz, 1H), 3.50 (d, *J*=13.6 Hz, 1H), 2.89 (dd, *J*=6.4, 3.3 Hz, 1H), 2.43 (dd, *J*=3.2, 1.4 Hz, 1H), 2.09 (d, *J*=1.4 Hz, 3H), 1.88 (dd, *J*= 6.4, 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 140.1, 138.4, 137.8, 135.9, 130.0, 128.9, 128.7, 128.6, 128.4, 127.6, 64.8, 40.4, 36.5, 13.7; HRMS (ESI, M^+) Calcd for $C_{19}H_{19}NO$ 278.1467; Found m/z 278.2.



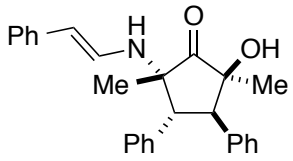
Compound 31. Dienone **17g** (40 mg, 0.25 mmol) and **18a** (66 mg, 0.50 mmol, 2.0 equiv) were dissolved in DCM (6 mL, 0.04M), and the solution flushed with argon. Trifluoromethanesulfonic acid (49 μL, 0.55 mmol, 2.2 equiv) was added dropwise, resulting in a bright yellow solution. The reaction mixture was stirred for 5 min. The reaction was quenched with sat'd $NaHCO_3$ (10mL) and warmed to room temperature. The aqueous layer was extracted with DCM (2 x 15 mL), the combined organic layers were washed with brine solution (1 x 15 mL) and dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation providing a semi-solid that was purified by flash column chromatography (silica gel, hexanes:EtOAc 9:1) to provide **31** (57%) as a yellow oil: R_f 0.34 (hexanes:EtOAc 5:1); IR (neat)

3344, 3062, 3028, 2951, 2850, 1601, 1529, 1496, 1467 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.61, (br s, 1H), 7.39-7.22 (m, 5H), 6.32-6.30 (m, 1H), 4.48 (d, *J*=6.4 Hz, 2H), 2.78 (t, *J*=7.0 Hz, 2H), 2.70-2.65 (m, 2H), 2.58 (t, *J*=7.7 Hz, 2H), 2.55-2.50 (m, 2H), 1.90-1.84 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.6, 169.4, 147.0, 138.6, 136.5, 129.0, 127.6, 127.2, 105.5, 48.8, 34.4, 33.2, 31.8, 31.7, 22.7, 22.4; HRMS (ESI, M^+) Calcd for $C_{18}H_{21}NO$ 268.1623; Found m/z 268.1693.

Cycloadduct 27k and 5-(*N*-cinammyl)amino-2-hydroxy-2,5-dimethyl-3,4-diphenylcyclopentanone 32. The standard procedure was used to yield **27k** (11%) and a 1:3 ratio of **27k** and **32** (45%) after flash chromatography (silica gel, hexanes:EtOAc 8:1). The mixture of **27k** and **32** was then triturated with hexanes and re-crystallized with ethyl acetate and hexanes to yield **32**.

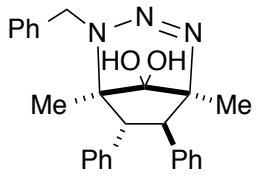


Cycloadduct 27k. Yellow oil: R_f 0.31 (hexanes:EtOAc 4:1); IR (Film) 3084, 3061, 3028, 2976, 2931, 2102, 1753, 1451 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.20 (m, 13H), 6.89 (m, 2H), 6.23 (app dt, *J*=15.9, 1.5 Hz, 1H), 5.90 (ddd, *J*=15.9, 6.3, 5.5 Hz, 1H), 4.10 (ddd, *J*=16.6, 5.4, 1.8 Hz, 1H), 4.02 (d, *J*=6.9 Hz, 1H), 3.37 (d, *J*=6.8 Hz, 1H), 3.27 (ddd, 16.7, 6.4, 1.5 Hz, 1H), 1.42 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 141.4, 136.5, 136.4, 132.1, 129.6, 129.2, 129.0, 128.7, 128.5, 128.4, 128.0, 127.7, 126.7, 125.9, 73.6, 72.7, 64.1, 56.5, 53.1, 14.8, 14.0; HRMS (ESI, M^+) Calcd for $C_{28}H_{27}N_3O$ 422.2154; Found m/z 422.2225.



5-(*N*-Cinammyl)amino-2-hydroxy-2,5-dimethyl-3,4-diphenylcyclopentanone

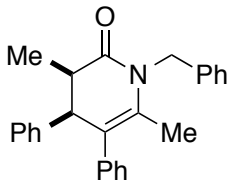
32. White solid: R_f 0.19 (hexanes:EtOAc 5:1); mp 158-160 °C; IR (solid cast) 3433, 3377, 3035, 3023, 2975, 2923, 1732, 1599, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.18 (m, 15H), 6.42 (app dt, J=17.0, 1.1 Hz, 1H), 6.15 (ddd, J_{trans}=15.9 Hz, J_{AX}=7.1 Hz, J_{BX}=4.9 Hz, 1H), 4.22 (d, J=13.0 Hz, 1H), 3.86 (d, J=13.1 Hz, 1H), 3.23 (ddd, J_{AB}=14.2 Hz, J_{AX}=7.1 Hz, J_4=1.3 Hz, 1H), 3.21 (ddd, J_{AB}=14.2 Hz, J_{BX}=4.9 Hz, J_4=1.3 Hz, 1H), 1.53 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.0, 137.4, 136.0, 135.3, 130.8, 130.1, 129.8, 129.0, 128.8, 128.8, 128.5, 127.6, 127.6, 127.4, 126.5, 76.2, 63.6, 54.8, 52.1, 44.7, 24.3, 18.7; HRMS (ESI, M^+) Calcd for $C_{28}H_{29}NO_2$ 412.2198; Found m/z 412.2226.



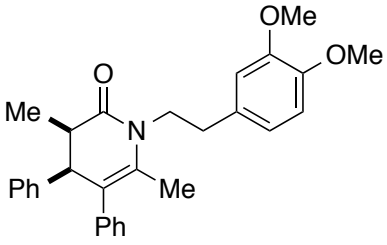
Hydrate 36. Dienone **17b** (500 mg, 1.91 mmol) and azide **18a** (507 mg, 3.82 mmol, 2 equiv) were dissolved in CH_2Cl_2, flushed with argon, and cooled to –78 °C. TfOH (371 μL, 4.19 mmol, 2.2 equiv) was added dropwise. The reaction was stirred for 5 minutes and then quenched with saturated $NaHCO_3$ solution (10 mL). The mixture was warmed to room temperate, extracted with CH_2Cl_2 (10 mL), washed with water (10 mL), and brine (10 mL). Upon washing with brine, a white precipitate formed,

which was filtered and dried. This solid was characterized as hydrate **36** (50 mg, 7% yield).

mp (dec) 148-150 °C; IR (cast film) 3350, 3063, 2929, 1601 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.29 (m, 7H), 7.22-7.14 (m, 8H), 4.93 (d, *J* = 16.9 Hz, 1H), 3.82 (d, *J* = 8.6 Hz, 1H), 3.74 (d, *J* = 8.6 Hz, 1H), 3.38 (d, *J* = 16.5 Hz, 1H), 2.76 (bs, 2H), 1.17 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 139.7, 136.7, 129.7, 129.3, 128.6, 128.5, 128.2, 127.7, 127.2, 127.0, 126.8, 96.5, 72.0, 68.8, 65.5, 57.3, 55.4, 14.7, 11.9. HRMS (ESI, $M+H^+$) Calcd for $C_{26}H_{28}N_3O_2$ 414.2176; Found m/z 414.2168.



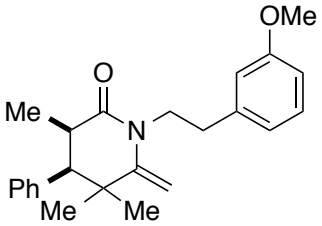
Dihydropyridone 19c. Cycloadduct **27a** (80 mg, 0.20 mmol) was dissolved in toluene, flushed with argon and heated to reflux for 48 hours. The mixture was concentrated, dissolved in DCM (2 mL), and passed through a plug of silica to produce **19c** as a yellow oil (74 mg, quantitative). The ^{1}H and ^{13}C spectra were found to be in agreement with those provided by Song, Rostami, and West.[31]



Dihydropyridone 19d. Cycloadduct **27l** (80 mg, 0.17 mmol) was dissolved in toluene (2 mL), flushed with argon, and heated to reflux for 48 h. The solution was

then concentrated and purified by flash chromatography (silica gel, hexanes:EtOAc 3:1) to yield **19d** as a yellow oil (52 mg, 70 %).

R_f 0.16 (4:1 hexanes:EtOAc); IR (cast film) 3026, 2929, 1668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.22 (m, 5H), 7.17-7.08 (m, 5H), 6.80-6.75 (m, 3H), 4.17 (ddd, *J* = 13.8, 10.1, 6.7 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.62 (ddd, *J* = 14.1, 10.4, 6.1 Hz, 1H), 3.47 (bs, 1H), 2.86 (qd, *J* = 7.4, 2.0 Hz, 1H), 2.81 (m, 2H), 1.97 (s, 3H), 1.46 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 149.0, 147.7, 141.2, 141.0, 131.5, 129.7, 129.5, 129.3, 128.7, 128.3, 127.3, 126.8, 120.7, 118.6, 112.1, 111.3, 56.0, 55.9, 51.2, 44.1, 35.2, 29.7, 17.6, 16.6; HRMS (ESI, M^+) Calcd for $C_{29}H_{31}O_3N$ 441.2304; Found m/z 441.2301.



6-Methylenepiperidone 19e. Cycloadduct **27m** (100 mg, 0.26 mmol) was dissolved in toluene (2 mL) and heated to reflux for 48 h. The solution was concentrated and purified by flash chromatography (silica gel, hexanes:EtOAc 4:1) to yield **19e** as a yellow oil (70 mg, 74%) in a 2.3:1 (*cis:trans*) ratio of inseparable diastereomers .

R_f 0.27 (4:1 hexanes:EtOAc); IR (cast film) 3059, 2973, 1672 cm^{-1}; ^1H (500 MHz, $CDCl_3$) major diastereomer: δ 7.31-7.20 (m, 5H), 6.88-6.78 (m, 4H), 4.63 (d, *J* = 1.9 Hz, 1H), 4.31 (d, *J* = 2.0 Hz, 1H), 4.14-4.04 (m, 2H), 3.85 (s, 3H), 3.18 (app p, *J* = 6.8 Hz, 1H), 3.06 (ddd, *J* = 14.1, 11.3, 6.1 Hz, 1H), 2.95 (m, 1H), 2.75 (d, *J* = 6.4 Hz, 1H),

1.37 (s, 3H), 0.98 (d, *J* = 7.2 Hz, 3H), 0.95 (s, 3H); characteristic peaks of minor diastereomer: δ 4.53 (m, 2H), 3.96 (m, 1H), 3.73 (s, 3H), 2.84 (ddd, *J* = 16.5, 12.8, 5.7 Hz, 1H), 2.59 (d, *J* = 11.3 Hz, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.06 (s, 3H), 0.94 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) major diastereomer: δ 171.6, 159.8, 151.0, 140.6, 139.1, 129.6, 128.1, 126.8, 121.1, 114.3, 112.0, 92.1, 55.9, 55.2, 45.6, 38.4, 36.9, 32.7, 30.3, 27.7, 15.2; minor diastereomer: δ 171.6, 159.8, 151.0, 140.6, 129.6, 129.5, 128.3, 127.1, 121.2, 114.4, 111.9, 90.7, 55.0, 46.2, 43.5, 39.6, 38.5, 33.2, 26.6, 21.5, 17.6; HRMS (EI, $M+H^+$) Calcd for $C_{24}H_{30}NO_2$ 364.2271; Found m/z 364.2269.

2.7 References

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Chapter 3

Domino Nazarov Cyclization/Baeyer-Villiger Oxidation

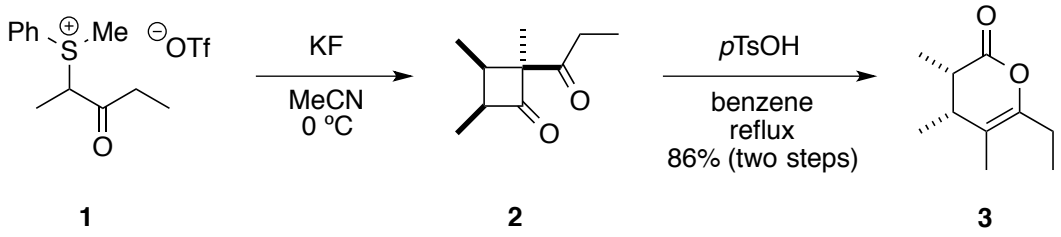
3.1 3,4-Dihydropyran-2-ones

3,4-Dihydropyran-2-ones and their derivatives are notable structures in a variety of biologically active compounds. They have been found in compounds displaying activity as HIV-1 protease inhibitors,[1] as inhibitors against acetylcholinesterase,[2] and as intermediates in the biosynthesis of secologanin.[3] 3,4-Dihydropyran-2-ones are also useful as synthetic building blocks as they can be easily converted into 2-pyranones,[4,5] butyrolactones,[6] and cyclic enamines.[7] Furthermore, the electron-rich alkene in this ring system can be used as a synthetic handle as seen in the synthesis of (+)-englerin A by the Christmann group.[8]

3.1.1 Synthesis of 3,4-Dihydropyran-2-ones

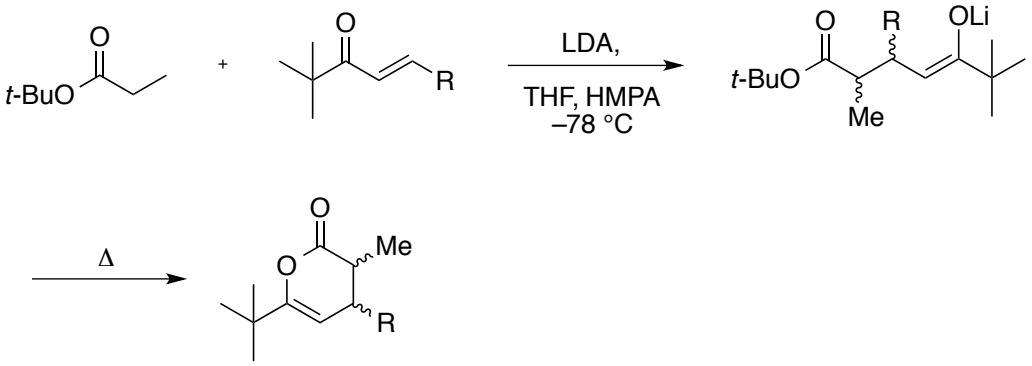
There are a variety of ways to synthesize 3,4-dihydropyran-2-ones. Early examples include the acid-catalyzed intramolecular cyclization of δ-oxoalkanoic acids[9] and dimerization of α,β-unsaturated acyl cyanides.[10] In 1987, the Ito group showcased α-(sulfonio)ketone triflate salts as precursors to 3,4-dihydropyran-2-ones (Scheme 3.1).[11] When potassium fluoride was added to a solution of triflate **1**, dimerization occurred to form cyclobutanone **2**. Subsequent exposure of the

cyclobutanone to *p*-TsOH resulted in ring expansion to form 3,4-dihydropyran-2-one **3**.

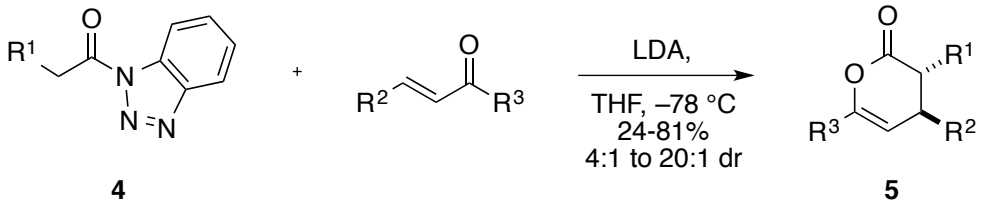


Scheme 3.1 Dimerization of α-(Sulfonio)ketone Triflates.

In 1990, Oare and Heathcock published their findings on the addition of litihium enoates into α,β-unsaturated ketones in a 1,4-addition pathway with cyclization to form the lactone (Scheme 3.2).[12] This result was produced upon warming the reaction mixture to room temperature and was viewed by the authors as an unwanted byproduct during the production of acyclic 1,5-diketones. Later, Katritzky built on Heathcock's findings, using lithiated acylbenzotriazoles **4** in the place of esters to add into α,β-unsaturated ketones, followed by cyclization to form 3,4-dihydropyran-2-one **5** (Scheme 3.3).[13]



Scheme 3.2 Domino Michael Addition/Cyclization Reaction to Form 3,4-Dihydropyran-2-ones.

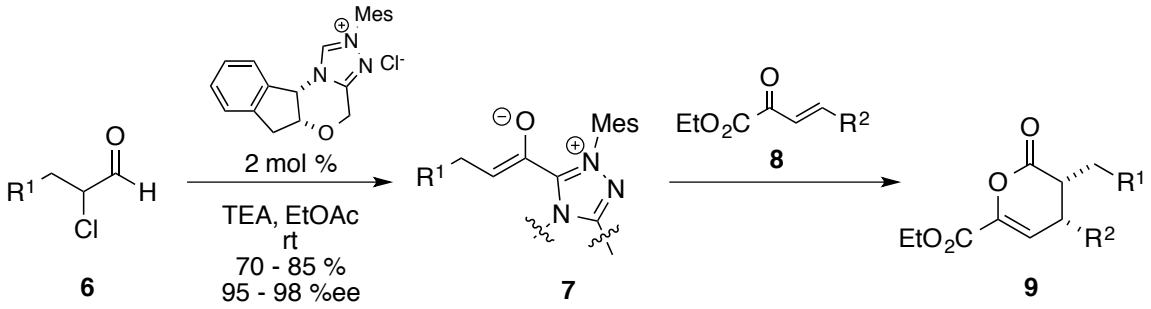


4 **5**

Scheme 3.3 Acylbenzotriazoles as Reagents in Domino Michael Addition/Cyclization Reactions

3.1.2 Asymmetric Synthesis of 3,4-Dihydropyran-2-ones

Recently, attention has focused on the enantioselective synthesis of 3,4-dihydropyran-2-ones. The Bode group has showcased the elegant use of N-heterocyclic carbenes as enantioselective catalysts for oxodiene Diels-Alder reactions to form 3,4-dihydropyran-2-ones.[14,15] The initial study[14] used α-chloroaldehyde **6**, that upon reaction with the N-heterocyclic carbene formed enolate **7.** A hetero-Diels-Alder reaction with enone **8**, and loss of the organocatalyst formed the dihydropyanone **9** (Scheme 3.4).

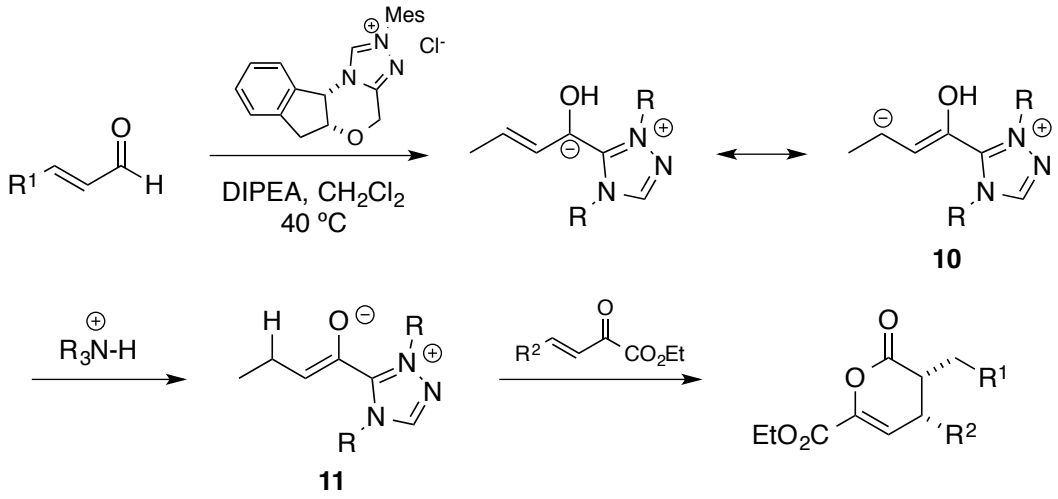


6 **7** **8** **9**

Scheme 3.4 N-Heterocylic Carbene Catalyzed Asymmetric Formation of 3,4-Dihydropyran-2-ones.

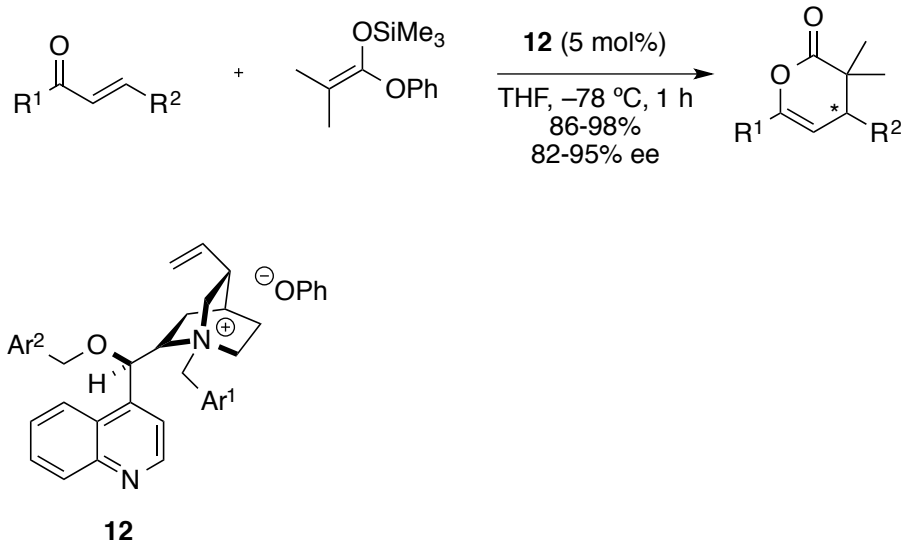
In 2011, the Bode group improved on this methodology by replacing the chloroaldehydes, which have a short shelf life, with unsaturated aldehydes (Scheme 3.5).[15] The enals reacted with the same N-heterocyclic carbene organocatalyst and

underwent the desired oxodiene Diels-Alder reaction. The authors found that the choice of base was important in the reaction. The use of DBU favored homoenolate **10** and the formation of cylcopentenes, while weaker bases like DMAP and Hünig's base favored the generation of enolate **11** and 3,4-dihydropyran-2-ones.

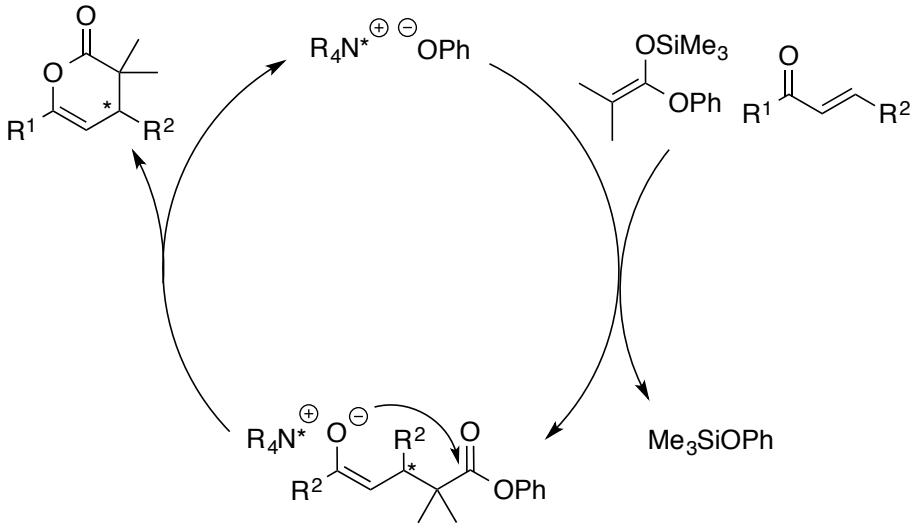


Scheme 3.5 N-Heterocyclic Carbene-Catalyzed Oxodiene Diels-Alder Reactions.

The Mukaiyama group published a series of papers on the use of chiral tertiary ammonium salts as organocatalysts for the production of chiral 3,4-dihydropyran-2-ones (Scheme 3.6).[16-18] Silyl ketene acetals and α,β-unsaturated ketones were combined with the organocatalyst **12** leading to a stepwise Michael addition/cyclization pathway and the formation of 3,4-dihydropyran-2-ones. The mechanism is postulated to begin with exchange of the silyl group from the silyl ketene acetal to the phenoxide and formation of an ionic pair between the chiral ammonium salt and the enolate (Scheme 3.7). Michael addition onto the enone sets the stereochemistry of intermediate **13**, and cyclization forms the 3,4-dihydropyran-2-one, regenerating the catalyst in the process.



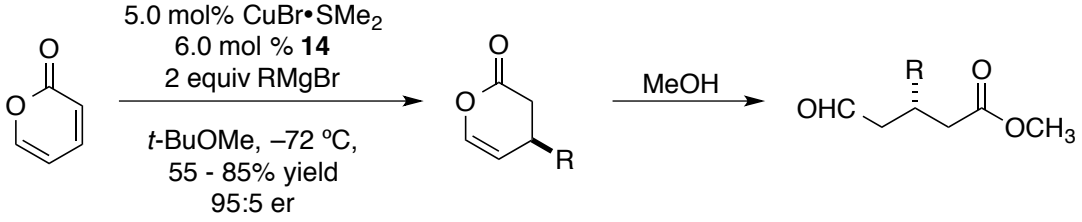
Scheme 3.6 Chiral Ammonium Salt Catalyzed Reaction of α,β-Unsaturated Ketones and Silyl Ketene Acetals.

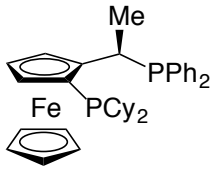


Scheme 3.7 Mechanism for Organocatalytic Reaction of α,β-Unsaturated Ketones and Silyl Ketene Acetals.

The Feringa group recently published their findings on the synthesis of chiral 3,4-dihydropyran-2-ones via enantioselective Michael additions (Scheme 3.8).[19] In the presence of the chiral diphosphine ligand (*R,S*)-Rev-Josiphos, and catalytic

quantities of CuBr•SMe_2, Grignard reagents are incorporated into 2H-pyran-2-one in good yields and enantioselectivity. These chiral 3,4-dihydropyran-2-ones could be further transformed, by cleavage of the lactone in methanol, to furnish the methyl ester and aliphatic aldehyde.



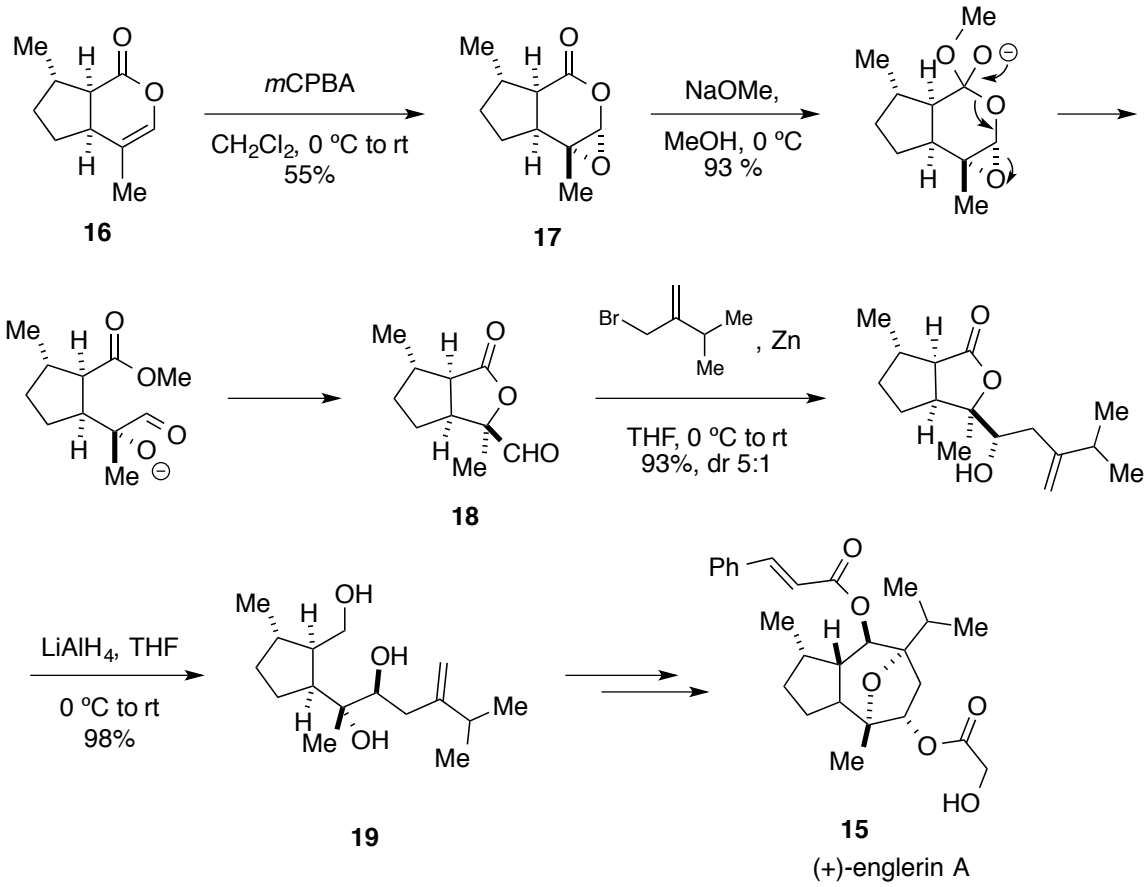


14

(*R,S*)-Rev-Josiphos

Scheme 3.8 Enantioselective Michael Additions of 2H-Pyran-2-one.

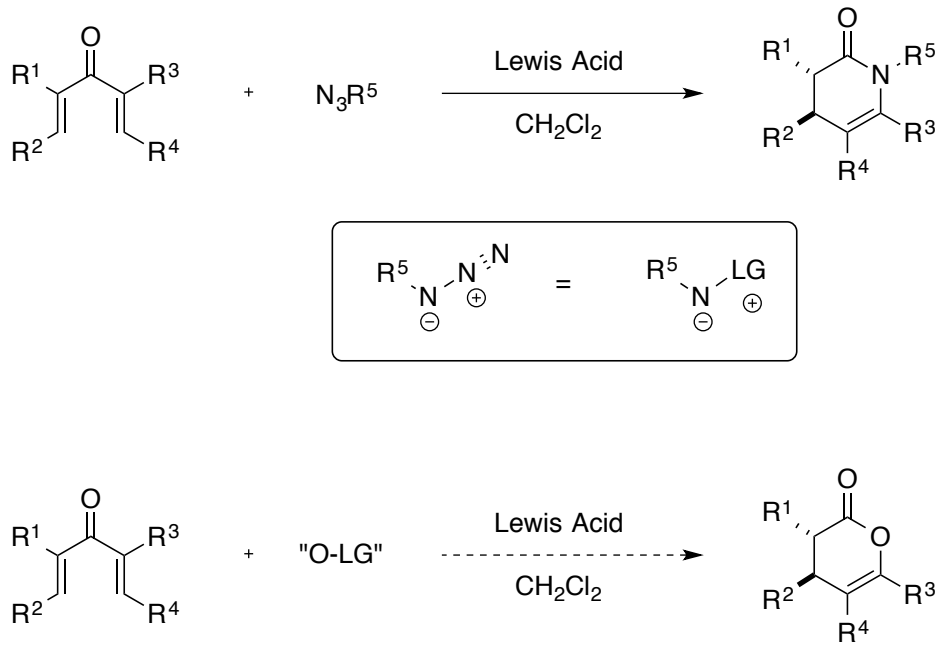
The synthetic utility of 3,4-dihydropyran-2-ones was on display in the Christmann group's total synthesis of sesquiterpene (+)-englerin A **15** (Scheme 3.9).[8] 3,4-Dihydropyran-2-one **16** was oxidized with *m*CPBA to install the epoxide **17**, which upon exposure to sodium methoxide rearranged to the 5-membered lactone **18** with an appended aldehyde. A Barbier reaction, followed by reduction of the lactone with $LiAlH_4$ produced key triol **19**. Further steps elaborated on the framework to produce (+)-englerin A in 15 steps, the first total synthesis of this enantiomer.



Scheme 3.9 Synthesis of (+)-Englerin A

3.2 Domino Nazarov Cyclization/Baeyer-Villiger Oxidation

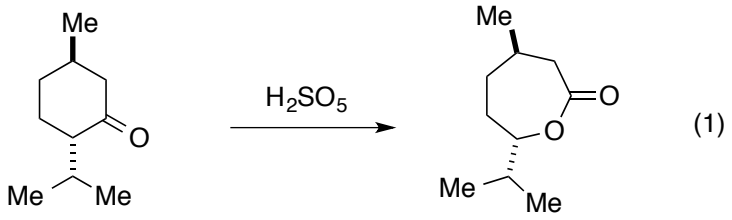
As discussed in Chapter 2, azides trap the Nazarov intermediate and produce dihydropyridones when Lewis acid conditions are used.[20,21] The azide moiety can be viewed as containing a nucleophilic group directly attached to a leaving group. We hypothesized that by finding the necessary combination of oxygen nucleophile and leaving group, an analogous procedure for the production of 3,4-dihydropyran-2-ones could be found: a domino Nazarov cyclization/Baeyer-Villiger reaction (Scheme 3.10).



Scheme 3.10 Domino Nazarov Cyclization/Baeyer-Villiger Reaction.

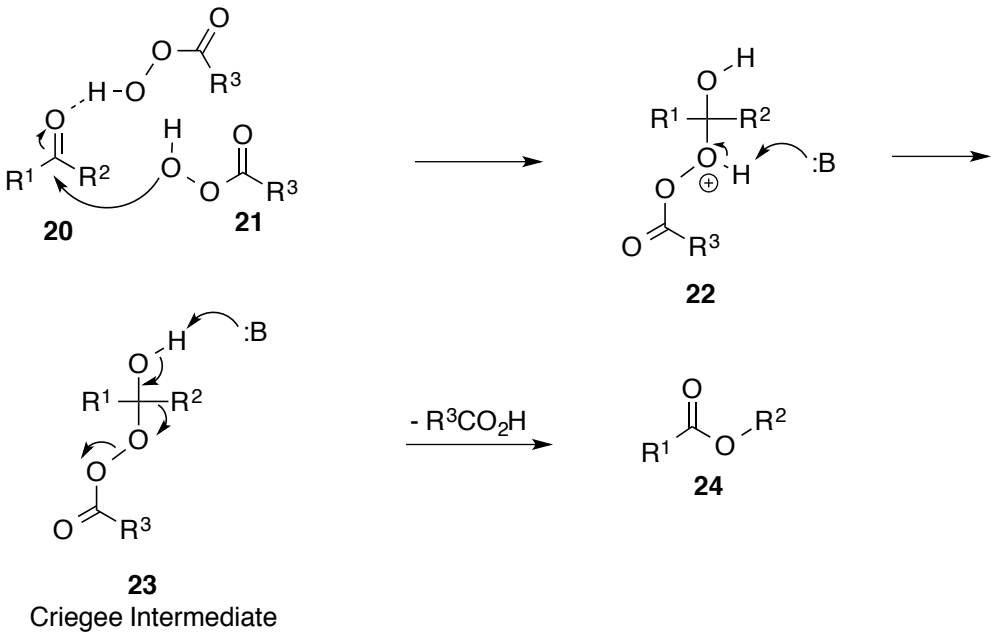
3.3 The Baeyer-Villiger Oxidation

The oxidation of ketones to esters was first discovered by Baeyer and Villiger in 1899 when the authors oxidized menthone with Caro's acid (equation 1), a mixture of sodium persulfate and concentrated sulfuric acid.[22] Today, the reaction commonly uses peroxyacids or hydrogen peroxide as the oxidizing agent, and has been shown to be compatible with a large variety of functional groups. Furthermore, the regioselectivity of the migration is often predictable, following the trend of tertiary alkyl > secondary alkyl > aryl > primary alkyl > methyl.[23] When the ketone is within a rigid cyclic system, stereoelectronic effects dominate the migration.[23b]



(1)

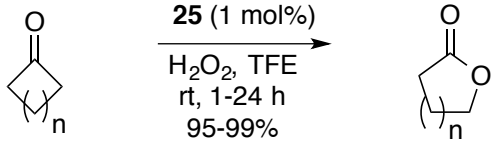
The accepted mechanism for the Baeyer-Villiger oxidation begins with activation of the ketone **20** by the peroxyacid **21** (Scheme 3.11). The peroxyacid then attacks the activated carbonyl, forming intermediate **23**, known as the Criegee intermediate. Finally, oxygen assisted alkyl migration with loss of carboxylic acid produces the desired ester **24**.

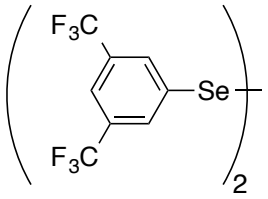


Scheme 3.11 Mechanism for the Baeyer-Villiger Oxidation.

Due to the common use of potentially explosive peroxyacids as the oxidizing agent for the Baeyer-Villiger reaction and the inherent waste production of carboxylic acid in the reaction, attention has been directed towards developing

green methods for the Baeyer-Villiger reaction.[24] These methods commonly employ hydrogen peroxide or molecular oxygen in combination with a catalyst or enzyme. The Sheldon group showcased di-selenium catalysts as effective Baeyer-Villiger catalysts with aqueous hydrogen peroxide (Scheme 3.12).[25] In their study, cyclic ketones were converted to the corresponding lactones in good yields in a solution of 60% hydrogen peroxide and trifluoroethanol.



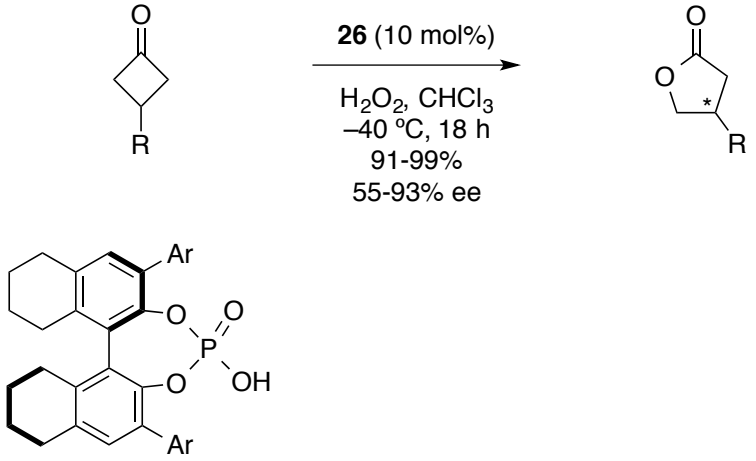


25

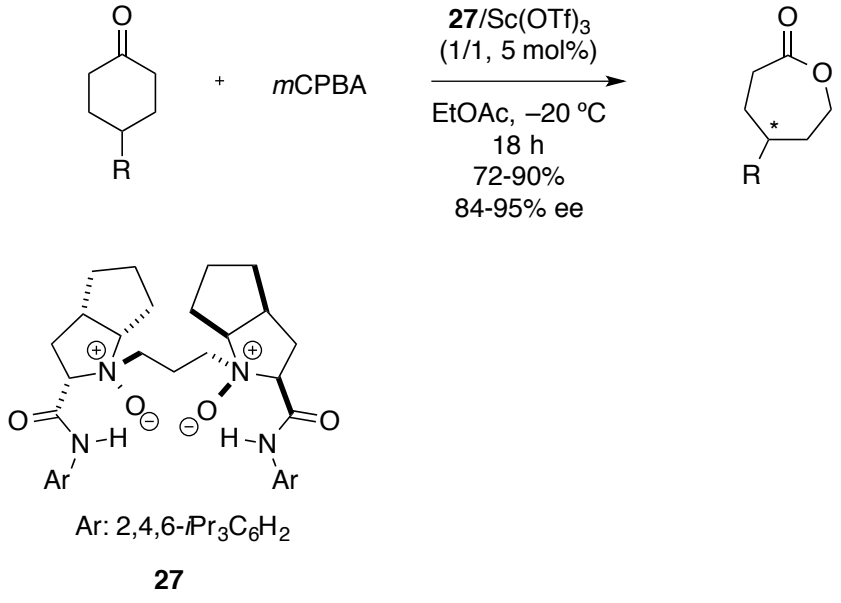
Scheme 3.12 Diselenium Catalyzed Baeyer-Villiger Oxidation.

Improvements have also been made to induce enantioselectivity in the Baeyer-Villiger reaction. While early attempts by Murahashi and coworkers[26] and the Uemura group[27] failed to produce appreciable enantioselectivities, the Ding group found that chiral Brønsted acids were effective for inducing enantioselectivity in the Baeyer-Villiger reaction of various 3-substituted cyclobutanones (Scheme 3.13).[28,29] The Ding group proposed that the phosphoric acid first acts to activate the carbonyl for attack from the hydrogen peroxide and then activates the peroxide in the Criegee intermediate for ejection. The Feng group was also able to produce

appreciable enantiomeric excesses in a Baeyer-Villiger reaction using *m*CPBA and a chiral scandium complex (Scheme 3.14).[30]



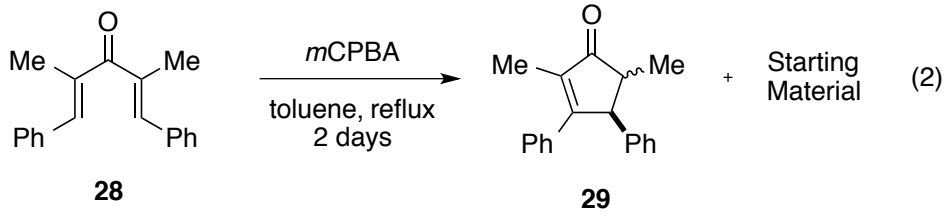
Scheme 3.13 Chiral Phosphoric Acid Catalyzed Enantioselective Baeyer-Villiger Oxidation.



Scheme 3.14 Chiral Scandium Complex Catalyzed Baeyer-Villiger Oxidation.

3.4 Domino Nazarov Cyclization/Baeyer-Villiger Oxidation

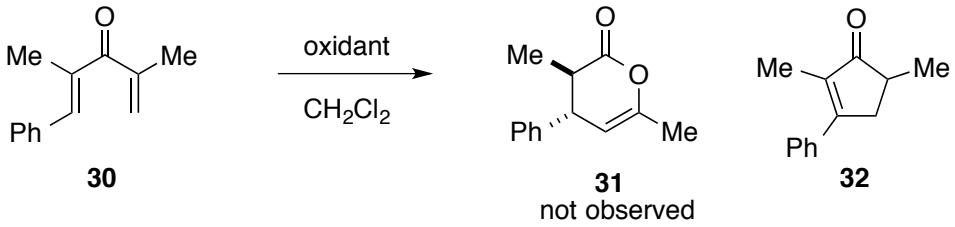
Peroxy acids are common reagents for Baeyer-Villiger oxidations and do not require a second reagent for activation of the ketone. This led us to test *m*CPBA as the potential oxidizing agent in a domino Nazarov cyclization/Baeyer-Villiger reaction (equation 2). In order for starting dienone **28** to be consumed, it was found that the reaction mixture needed to be heated at reflux in toluene. After two days and partial conversion of the starting material, the crude material was analyzed and found to be a mixture of normal Nazarov cyclization product **29** and residual starting material; no Baeyer-Villiger transformation had occurred.



Next, we tested dienone **30** with a series of potential Baeyer-Villiger oxidants and BF_3•OEt_2 (Table 3-1). Dienone **30** was chosen to replace **28** as upon successful Nazarov cyclization/Baeyer Villiger oxidation, a unique olefin proton would be identifiable in the crude ^{1}H NMR spectrum. Dienone **30** was also compatible with the Nazarov cyclization/Schmidt rearrangement methodology, producing a single diastereomer of the dihydropyridone in all reactions in which it was tested.[21] *tert*-Butyl hydrogen peroxide was tested first but found to produce an intractable mixture at –78 °C, as did cumene hydroperoxide under the same reaction conditions. Non-traditional Baeyer-Villiger reagents that could be seen as having a

nucleophilic oxygen adjacent to a suitable leaving group were examined next. Dimethylsulfoxide was tested with BF_3•OEt_2, but failed to consume any of the starting material, even after warming to 0 °C for four hours. 4-Methylmorpholine *N*-oxide acted similarly with BF_3•OEt_2, failing to consume any of the starting material. This was likely caused by the reagents forming a complex with BF_3•OEt_2, preventing it from being a strong enough Lewis acid to cyclize the dienone. Finally, nitrous oxide was examined by bubbling the gas through the solution for 15 minutes. Unfortunately, upon addition of BF_3•OEt_2, only cyclopentenone **32** was observed without any domino Baeyer-Villiger product 3,4-dihydropyan-2-one **31** seen.

Table 3-1 Attempted Domino Nazarov Cyclization/Baeyer-Villiger Reaction of 30.[a]



30 **31** not observed **32**

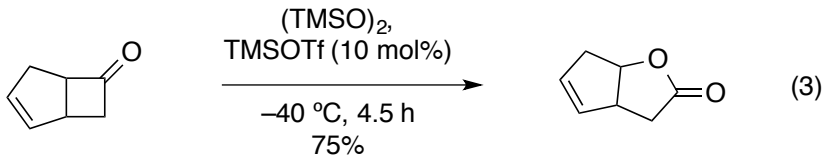
Entry	Oxidant	Conditions	Yield
1	*tert*-Butyl hydrogen peroxide	BF_3•OEt_2, CH_2Cl_2, –78 °C, 1h	Intractable mixture
2	Cumene hydroperoxide	BF_3•OEt_2, CH_2Cl_2, –78 °C, 1h	Intractable mixture
3	Dimethyl sulfoxide	BF_3•OEt_2, CH_2Cl_2, –78°C, 1h; 0 °C, 4h	No reaction
4	4-Methylmorpholine *N*-oxide	BF_3•OEt_2, CH_2Cl_2, –78°C, 1h; 0 °C, 4h	No reaction
5	Nitrous oxide	BF_3•OEt_2, CH_2Cl_2, –78°C, 1h; 0 °C, 4h	**32** (73%)

[a]Standard Procedure: Dienone **30** (0.27 mmol) and oxidant (0.32 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (5 mL) and cooled to –78 °C. BF_3•OEt_2 (0.32 mmol, 1.2 equiv) was added dropwise and the reaction stirred for 1 h before warming to 0 °C. The reaction was then quenched with NH_4Cl solution and extracted with CH_2Cl_2 and followed by aqueous workup.

3.4.1 Bis(trimethylsilyl)peroxide

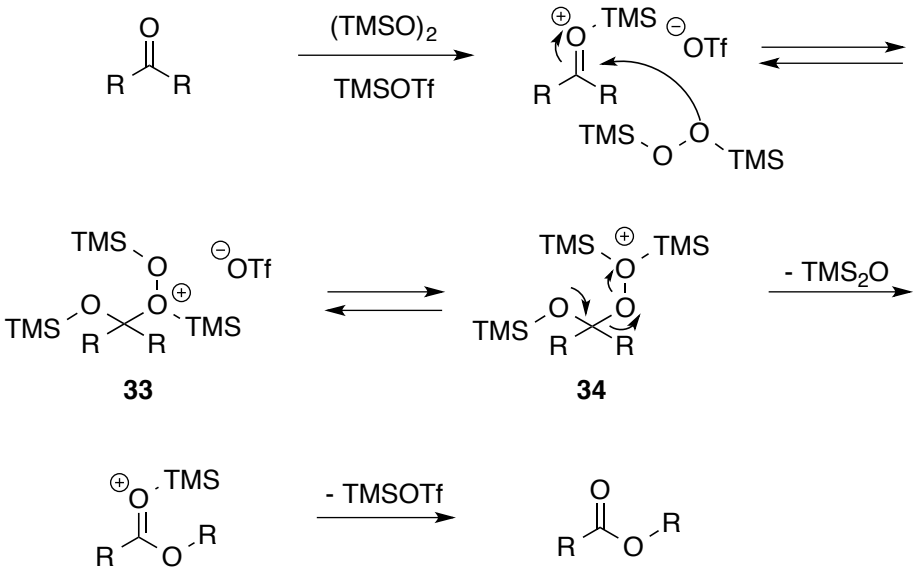
In 1982, the Noyori group identified the bissilyl ether of hydrogen peroxide as an effective Baeyer-Villiger oxidant.[31] Bis(trimethylsilyl)peroxide is advantageous as an oxidant because it does not epoxidize alkenes and it is stable to Lewis acids. In

their initial studies, the Noyori group found that a variety of ketones could be converted to their corresponding esters with a slight excess of bis(trimethylsilyl)peroxide and a catalytic quantity of trimethylsilyl triflate (equation 3). Later, the Takai group showcased that the transformation could also be accomplished with stoichiometric quantities of $BF_3 \bullet OEt_2$ or $SnCl_4$.[32]



(3)

The mechanism is believed to occur via initial activation of the ketone with the Lewis acid (Scheme 3.15). Nucleophilic attack by the bis(trimethylsilyl)peroxide then occurs, providing intermediate **33**. This intermediate then undergoes a silyl shift to produce intermediate **34,** which upon alkyl migration loses bis(trimethylsilyl)ether and forms the ester.



Scheme 3.15 Bis(trimethylsilyl)peroxide Baeyer-Villiger Oxidation.

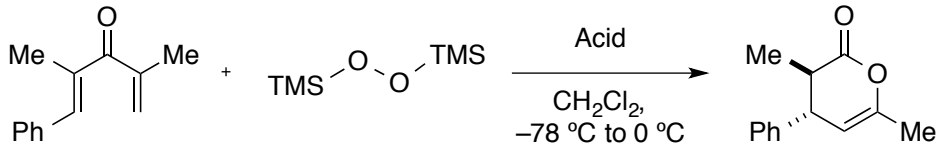
3.4.2 Bis(trimethylsilyl)peroxide and the Nazarov Reaction

Encouraged by the Lewis acid compatibility of bis(trimethylsilyl)peroxide, we investigated the reagent as an oxidant in the desired Nazarov/Baeyer-Villiger domino reaction.

Investigations began by treating **30** with two equivalents of bis(trimethylsilylperoxide) and BF_3•OEt_2 at –78 °C with gradual warming to 0 °C. Dienone **30** was thus converted in a very low yield of 10% to 3,4-dihydropyran-2-one **31**. The relative stereochemistry of **31** was determined by comparison of the coupling constant of the benzylic proton (app t, J = 6.6 Hz) to that of similar compounds published by Katrinzky and Denisko (J = 6.6 Hz for *trans*, J = 4.6 Hz for *cis*).[13] Altering the equivalents of the oxidant, temperatures, or reaction set-up (order of addition and/or rate of addition) failed to improve the yield of the reaction. Other acids were then tested, including TMSOTf, $SnCl_4$, $TiCl_4$, $Sc(OTf)_3$, and

$HNTf_2$. None of these acids led to an appreciable amount of **31**, producing a complex mixture that we were unable to characterize. Bis(trimethylsilyl)peroxide was also used to produce *in situ* bis(trimethylsilyl)peroxymonosulfate, a known reagent for Baeyer-Villiger oxidations;[33] however, this led to decomposition of the starting dienone **30**.

Table 3-2 Domino Nazarov Cyclization/Baeyer-Villiger Reaction with Bis(trimethylsilyl)peroxide.[a]



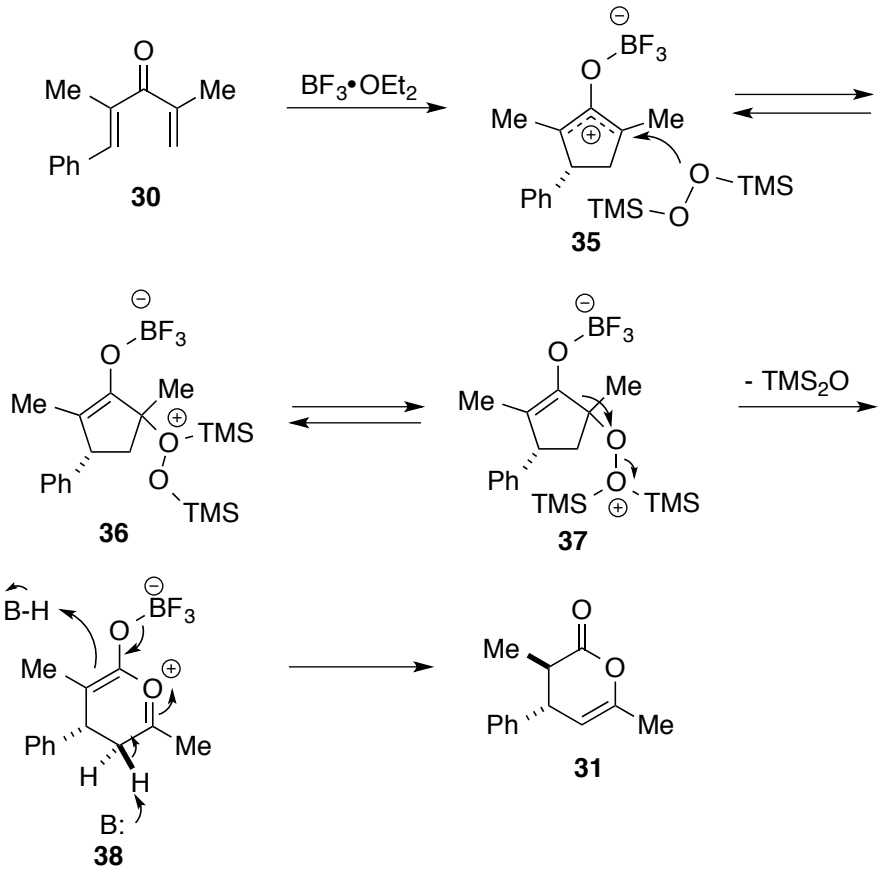
30 **31**

Entry	Peroxide Equivalents	Acid	Yield
1	2 equiv	BF_3•OEt_2	10 %
2	1 equiv	BF_3•OEt_2	Trace
3	5 equiv	BF_3•OEt_2	Trace
4	10 equiv	BF_3•OEt_2	Trace
5	2 equiv	TMSOTf	Trace
6	2 equiv	$SnCl_4$	Intractable Mixture
7	2 equiv	$TiCl_4$	Intractable Mixture
8	2 equiv	$Sc(OTf)_3$	Trace
9	2 equiv	$HNTf_2$	Intractable Mixture
10[b]	2 equiv	SO_3	Decomposition

[a]Standard Procedure: Dienone **30** (0.27 mmol) and bis(trimethylsilyl)peroxide were dissolved in CH_2Cl_2 (5 mL) and cooled to –78 °C. Lewis acid (0.32 mmol, 1.2 equiv) was added dropwise and the reaction was stirred for 15 min before warming to 0 °C. The reaction was quenched with NH_4Cl solution, and extracted with CH_2Cl_2 before undergoing aqueous workup.

The mechanism for the formation of **31** is hypothesized to occur via initial Nazarov cyclization of **30** to yield the cyclopentenyl cation **35** (Scheme 3.16). The

bis(trimethylsilyl)peroxide then attacks the oxyallyl cation to form **36**. The silyl group migrates, forming intermediate **37**, which then undergoes ring expansion and ejects bis(trimethylsilyl)ether. The zwitterion **38** then undergoes either proton exchange or a [1,5]-hydride shift to produce the 3,4-dihydropyran-2-one **31**.

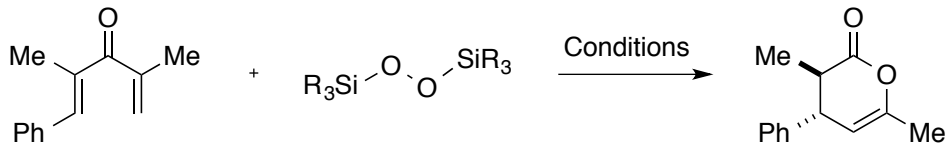


Scheme 3.16 Mechanism for the Domino Nazarov Cyclization/Baeyer-Villiger Reaction.

Our lack of success with optimization of the Lewis acid led to investigations of other oxidants. While various bis(trialkylsilyl)peroxides[34] have been reported in the literature, bis(trimethylsilyl)peroxide is the only one that has been published as a Baeyer-Villiger oxidant. A series of bis(trialkylsilyl)peroxides were synthesized and tested as oxidants. Unfortunately, altering the silyl group to triethylsilyl,

triphenylsilyl, or triethoxysilyl failed to improve the yield of the reaction, forming **31** only in trace quantities.

Table 3-3 Domino Nazarov Cyclization/Baeyer-Villiger Reaction with Bis(trialkylsilyl)peroxides.[a]



30 **31**

Entry	Silyl Group	Conditions	Yield (%)
1	$SiEt_3$	BF_3•OEt_2, DCM, –78 °C to 0 °C	Trace
2	$SiPh_3$	BF_3•OEt_2, DCM, –78 °C to 0 °C	Trace
3	$Si(OEt)_3$	BF_3•OEt_2, DCM, –78 °C to 0 °C	Trace

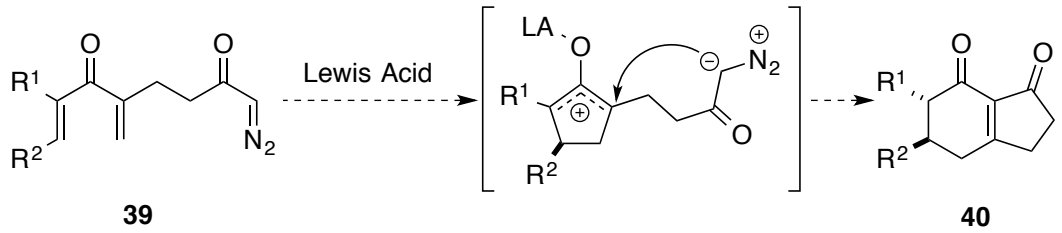
[a]Standard Procedure: Dienone **30** (0.27 mmol) and bis(trimethylsilyl)peroxide (0.54 mmol, 2.0 equiv) were dissolved in CH_2Cl_2 (5 mL) and cooled to –78 °C. BF_3•OEt_2 (0.32 mmol, 1.2 equiv) was added dropwise and the reaction was stirred for 15 min before warming to 0 °C. The reaction was quenched with NH_4Cl solution, and extracted with CH_2Cl_2 before undergoing aqueous workup.

3.5 Conclusion

A method for the production of 3,4-dihydropyran-2-ones via a domino Nazarov cyclization/Baeyer-Villiger process was investigated. The reaction of dienone **31** with bis(trimethylsilyl)peroxide and BF_3•OEt_2 produced the desired 3,4-dihydropyran-2-one in a poor yield of 10%. Attempts to improve upon this result by altering the Lewis acid and oxidant were unsuccessful, failing to lead to a synthetically useful reaction method.

3.6 Future Plans

While the use of oxidants in conjunction with the Nazarov cyclization failed to produce a viable method for a domino Nazarov cyclization/Baeyer-Villiger reaction, it is possible that other reagents could lead to analogous ring-expanded products. Appending a diazoketone to the dienone framework could potentially lead to a Nazarov cyclization/Tiffeneau-Demjanov reaction sequence. This would lead to ring-expanded products with 1,3-diketones, a useful functionality in synthesis.



39 40

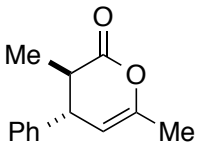
Scheme 3.17 Domino Nazarov Cyclization/Tiffeneau Demjanov Reaction.

3.7 Experimental

3.7.1 General Information

Reactions were carried out in flame-dried glassware under a positive pressure of argon unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannulae. Solvents were distilled before use: dichloromethane from calcium hydride, and tetrahydrofuran from sodium/benzophenone ketyl. Thin layer chromatography was performed on glass plates precoated with 0.25 mm Kieselgel 60 F254 (Merck). Flash chromatography column were packed with 230-400 mesh silica gel (Silicycle). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 500 MHz and coupling constants (*J*) are reported in Hertz (Hz). Standard notation was used to describe the multiplicity of signals observed in ^{1}H NMR spectra: broad (br), apparent (app), multiplet (m), singlet (s), doublet (d), triplet (t), etc. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 MHz and are reported (ppm) relative to the center line of the triplet from chloroform-*d* (77.26 ppm). Infrared (IR) spectra were measured with a Mattson Galaxy Series FT-IR 3000 spectrophotometer. Mass spectra (EI technique) were determined on a Kratos MS50 instrument.

3.7.2 Experimental Procedure and Characterization



Dienone **30** (20 mg, 0.11 mmol) and bis(trimethylsilyl)peroxide[34] (38 mg, 0.22 mmol) were dissolved in DCM (1.5 mL), flushed with argon and cooled to –78 °C. BF_3•OEt_2 (17 μL, 0.13 mmol) was added and the reaction was left to stir for 10 minutes. The solution was then warmed to 0 °C over 30 minutes at which point the starting material was consumed as indicated by TLC. The reaction was then quenched with saturated NH_4Cl solution (2 mL), extracted with DCM (2 x 5 mL), washed with H_2O (5 mL), brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. The crude oil was then purified by flash chromatography (silica gel, 12:1→10:1→8:1 hexanes:EtOAc) to yield **31** as a yellow oil (2 mg, 10 %).

R_f (0.25, 8:1 hexanes:EtOAc); IR (cast film) 3084, 2960, 1763 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 7.31-7.24 (m, 3H), 7.10-7.06 (m, 2H), 5.25 (d, *J* = 6.1Hz, 1H), 3.49 (app t, *J* = 6.6 Hz, 1H), 3.01 (dq, *J* = 6.7, 6.9 Hz, 1H), 1.99 (s, 3H), 0.99 (d, *J* = 6.9 Hz, 3H); ^{13}C (125 Hz, $CDCl_3$) δ 171.9, 150.1, 138.7, 129.1, 128.5, 127.9, 105.2, 43.4, 39.2, 19.1, 12.8; HRMS (EI, M^+) Calcd for $C_{13}H_{14}O_2$ 202.0994; Found m/z 202.0994.

3.8 References

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Chapter 4

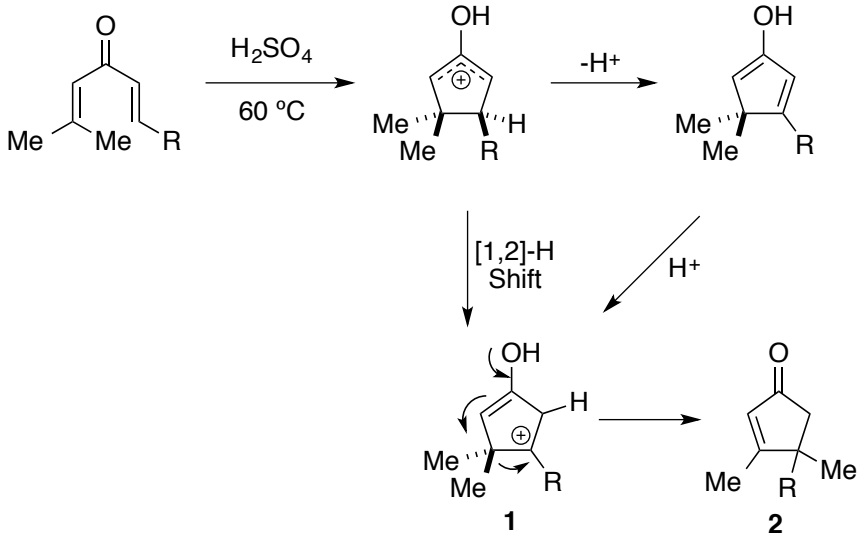
Access to Alkylidene Cyclopentenones via a Nazarov Cyclization/Dehydration Sequence

4.1 Wagner-Meerwein Rearrangements and the Nazarov Cyclization

The Nazarov cyclization is a relatively predictable reaction to produce cyclopentenones from simple cross-conjugated dienones. The reaction is traditionally terminated by removal of a proton at one of the β-positions. Multiple ways to control the regioselectivity of the Nazarov cyclization termination examples have been published. In order to control which proton is eliminated, the dienone can be polarized by either electron-rich substituents,[1] or electron-withdrawing groups.[2,3] Alternatively, stannyl[4] or silyl[5-7] groups can be utilized to control the regiochemistry of the alkene via β-elimination of the metalloid preferentially over deprotonation.

Occasionally, the product of a Nazarov cyclization is remarkably different from that of the predicted cyclopentenone. In some cases, substituents have been rearranged, via sequential [1,2]-Wagner-Meerwein shifts.[8] In 1991, Motoyoshiya published his group's findings with trisubstitued dienones producing unexpected cyclopentenones when heated in concentrated H_2SO_4.[9] In this example, the authors proposed that the dienones first undergo Nazarov cyclization, complete with deprotonation of the intermediate cyclopentenyl cation, forming a cyclopentadienol (Scheme 4.1). They then proposed that the enone is protonated to form tertiary

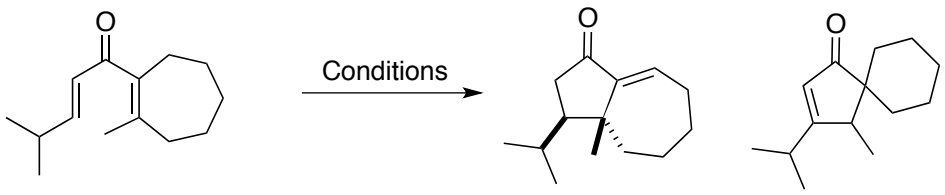
cation **1.** Alternatively, tertiary cation **1** could arise from the cyclopentenyl cation undergoing a [1,2]-hydride shift. This intermediate undergoes a [1,2]-Wagner-Meerwein rearrangement to form **2**, now with the unsaturation on the opposite side from what was expected.



Scheme 4.1 Early Example of a Nazarov Cyclization/Wagner-Meerwein Sequence.

Chiu and Li published their findings on the reactivity difference among acid initiators for a sample of dienones.[10] When attempting to find optimal conditions for the Nazarov cyclization of **3,** the authors noted that if very weak bases such as MeOH and even Et_2O were present in solution alkylidene cyclopentanone **4** was favored. However, if acids such as TfOH or BCl_3 were used with chlorinated solvents, the ring-contracted product **5** was favored.

Table 4-1 Dependence of Elimination vs Wagner-Meerwein Shift Based on Reagent.



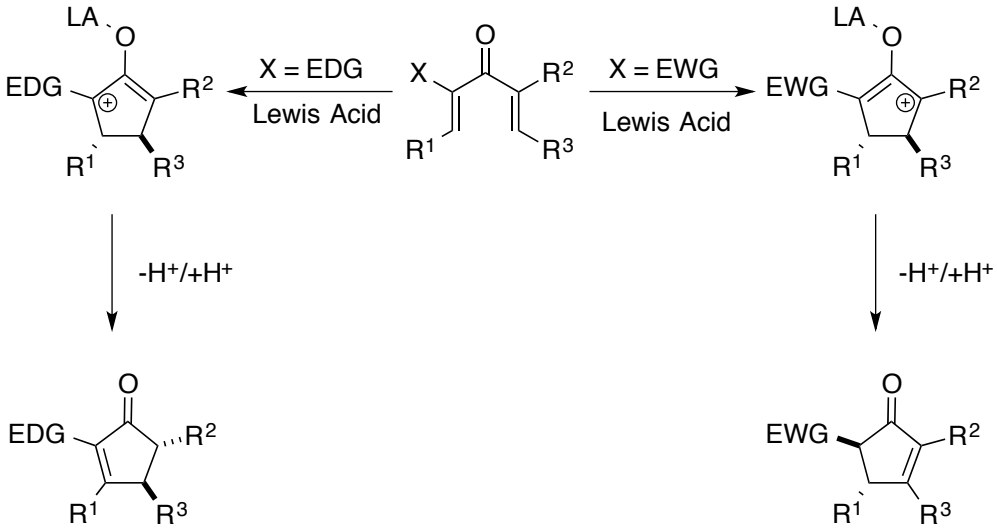
3 **4** **5**

Entry	Acid	Solvent	Temperature/ Time	Ratio **4**:**5**	Yield
1	H_2SO_4	MeOH	0 °C/1 h	>95:5	91%
2	CF_3SO_3H	CH_2Cl_2	0 °C/1 h	7:93	96%
3	BF_3•Et_2O	CH_2Cl_2	0 °C/1 h	>95:5	98%
4	BCl_3	CH_2Cl_2	0 °C/1 h	5:95	92%

4.1.1 Polarized Dienones and Wagner-Meerwein Rearrangements

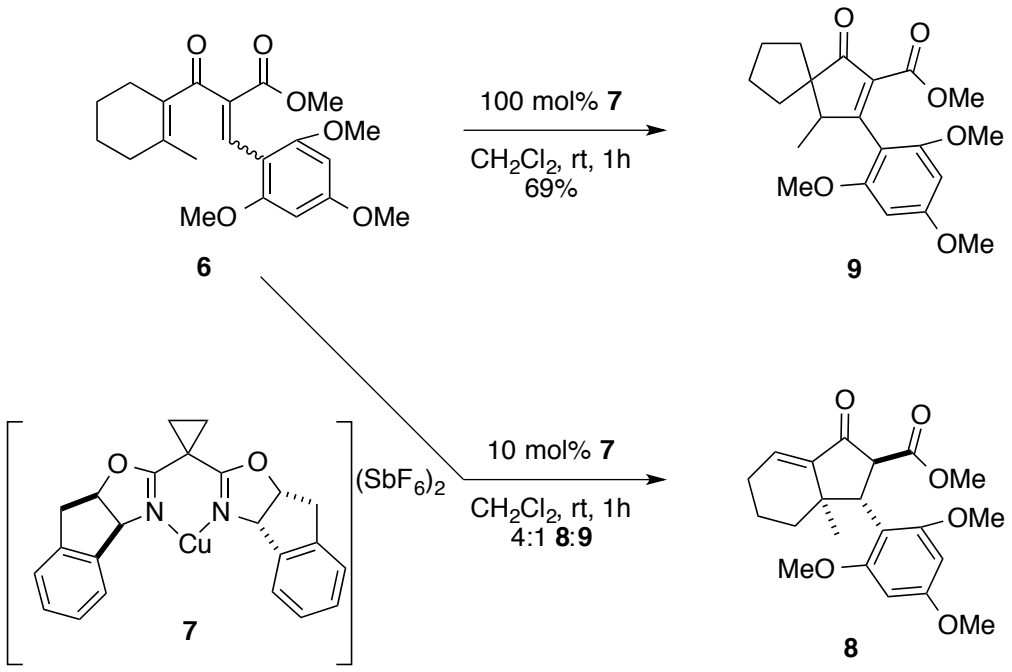
Polarized dienones are defined as dienones substituted with electron-withdrawing or -donating groups at the 2- or 4-position of the dienone, or containing both an electron-withdrawing and electron-donating group at the 2- and 4-position respectively. These specialized dienones receive attention for a variety of reasons; notably, the polarized dienone is able to undergo Nazarov cyclization under remarkably mild and often catalytic conditions, a stark contrast to traditional Nazarov cyclizations requiring superstoichiometric amounts of strong Lewis or Brønsted acids.[11,12] Furthermore, the nature of the polarizing group has a direct effect on the oxyallyl cation intermediate and the regioselectivity of the elimination

event. Electron-donating groups stabilize the oxyallyl cation and lead to elimination occurring at C-1, while electron-withdrawing groups have the opposite effect, destabilizing the oxyallyl cation, leading to elimination on the distal side (Scheme 4.2).



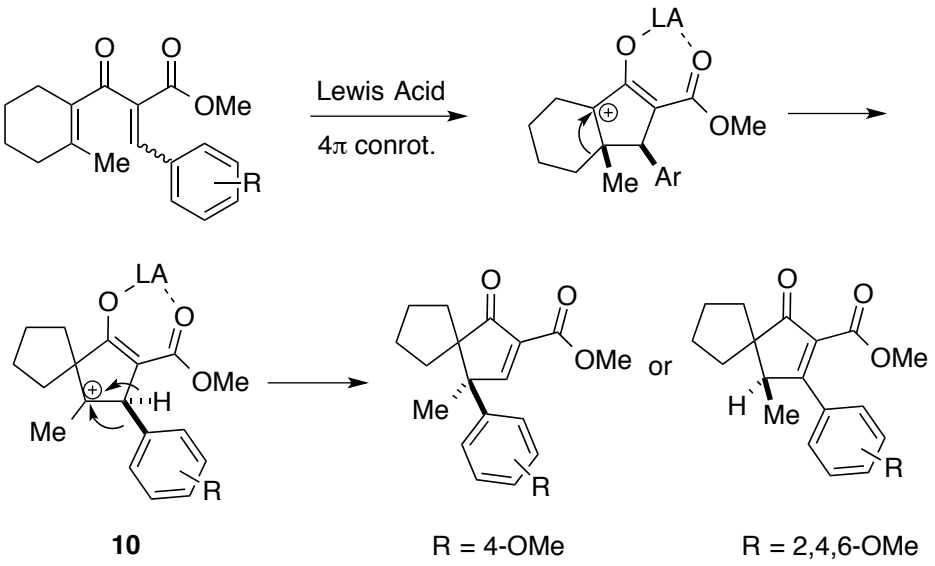
Scheme 4.2 Effect of Electron-Donating and Electron-Withdrawing Substituents on Nazarov Cyclization Product.

In 2007 the Frontier group found a surprising result when polarized dienone **6** was subjected to a stoichiometric amount of copper catalyst **7.** Instead of the expected alkylidene cyclopentanone **8**, spirocycle **9** was formed (Scheme 4.3).[13] Interestingly, lowering the catalyst loading to 10% favored the formation of **8** over **9** in a 4:1 ratio.



Scheme 4.3 Unexpected Nazarov Cyclization/Wagner-Meerwein Shift.

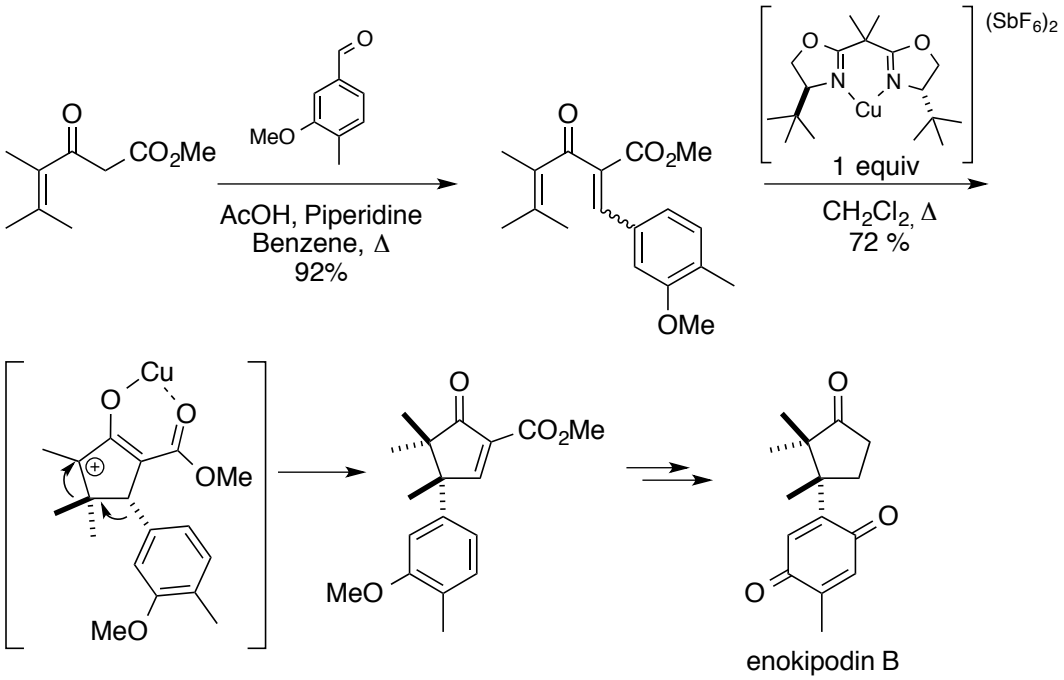
The product ratios are likely attributed to a base being available for the deprotonation event. When a substoichiometric quantity of Lewis acid is used, the carbonyl of the remaining starting material could act as the base for the deprotonation, while in the stoichiometric loading example the carbonyls encumber the Lewis acid in solution, preventing deprotonation from occurring. Instead, the oxyallyl cation intermediate undergoes a 1,2-Wagner-Meerwein rearrangement, contracting the cyclohexyl cation to form cyclopentylcarbinyl cation **10**.[14,15] A second 1,2-shift then occurs to form one of the cyclopentenone products, dependent on the steric bulk of the aryl substituent. This is especially evident in the comparison between the 2,4,6-trimethoxyphenyl example, where exclusive migration of the hydride is observed, and the 4-methoxyphenyl example, where exclusive aryl migration is seen (Scheme 4.4).



Scheme 4.4 Mechanism for Frontier's Nazarov/Wagner-Meerwein Process.

The Frontier group later found that the methodology could be expanded past the ring contraction of six membered rings to encompass aryl and aliphatic substitutions.[16] The authors were also able to utilize catalytic quantities of copper, with $Na[BAr^f_4]$ as an additive. It is believed the Na^+ ion displaces the copper ion allowing the catalyst to turn over.

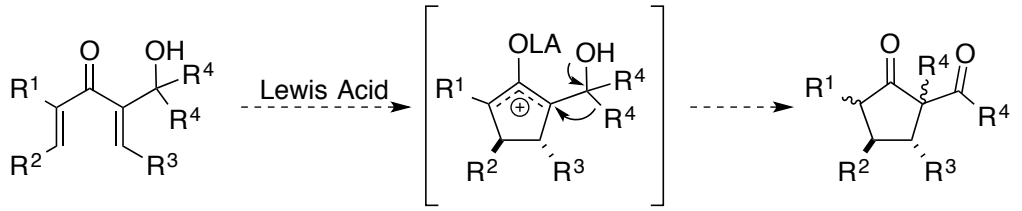
The methodology developed by the Frontier group was then applied toward the total synthesis of the natural product enokipodin B (Scheme 4.5).[17] The domino Nazarov cyclization/Wagner-Meerwein rearrangement strategy was seen as an expedient approach for the installation of the neighboring quaternary centers of enokipodin B. A series of simple steps including removal of the ester functionality, deprotection, and oxidation finished the natural product.



Scheme 4.5 Synthesis of Enokipodin B.

4.2 Semipinacol Interrupted Nazarov Reaction

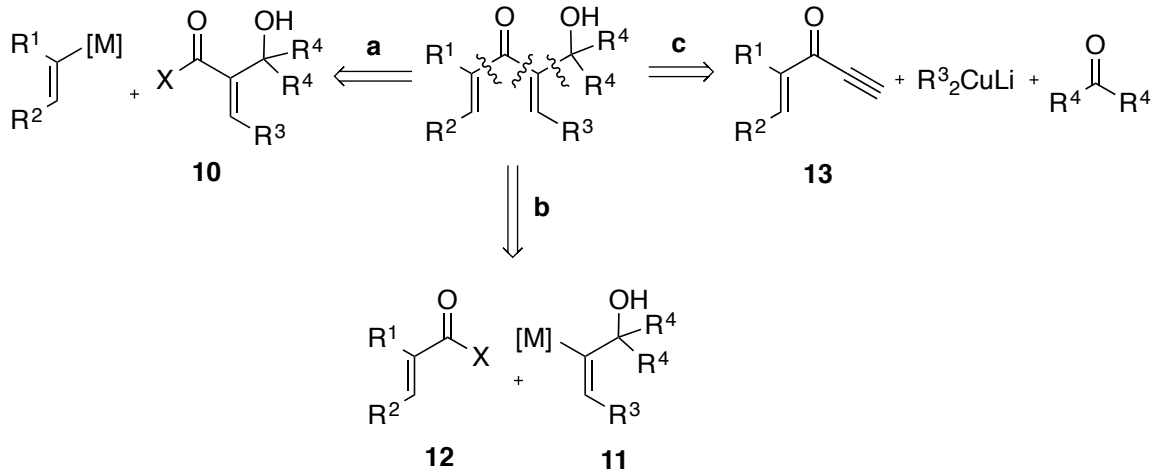
Application of the semipinacol rearrangment step in synthesis has been fruitful.[18] With the success of the Frontier's group Wagner-Meerwein interrupted Nazarov reaction in mind, we proposed that 2-hydroxyalkyl substituted 1,4-dien-3-ones would be appropriate substrates for a related [1,2]-carbon shift interruption pathway, semipinacol/Nazarov cyclization domino process (Scheme 4.6).[19] If successful, the process would produce 1,3-diketones with quaternary centers between the carbonyls. This carbon would be adjacent to three contiguous stereocenters, two of which would arise from stereospecific electrocyclization.. Additionally, if the R^4 groups are part of a ring, spirocyclic structures could easily be produced.



Scheme 4.6 Domino Nazarov Cyclization/Semipinacol Rearrangement.

4.2.1 Synthesis of 2-Hydroxyalkyl-1,4-dien-3-ones

There are three appropriate disconnections that allow for ready access to a variety of 2-hydroxyalkyl substituted dienones (Scheme 4.7). Disconnection **a**, between C-3 and C-4, could result from vinyl nucleophile addition to Morita-Baylis-Hillman adduct **10**. Similarily, a disconnection between C-3 and C-2, path **b**, would result from nucleophilic addition of a vinyl nucleophile **11** with allylic oxygenation into an α,β-unsaturated carbonyl derivative **12**. Finally there is disconnection **c**, which would result from a multi-component reaction between enynone **13**, a Gilman reagent, and a ketone.

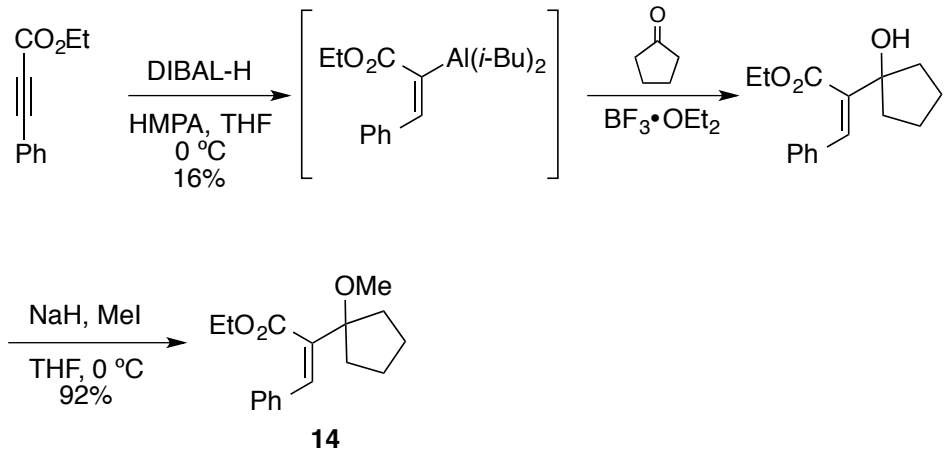


Scheme 4.7 Disconnections for the Synthesis of 2-hydroxyalkyl-1,4-dien-3-ones.

While a Morita-Baylis-Hillman reaction is an appropriate means to synthesize the desired 2-hydroxyalkyl enoates, this well-known reaction suffers from a variety of setbacks making it a less than desirable protocol.[20,21] It is well known that when the starting enoate is substituted at the β-position the reaction is unacceptably sluggish (requiring weeks to reach completion) and produces a mixture of *E*- and *Z*- isomers. Furthermore, unactivated ketones are poor coupling partners, also leading to slower reactions. Given the limitations of the Morita-Baylis-Hillman step, we turned our focus to other reactions that could furnish the desired substitutions.

2-Hydroxyalkylenoates containing β-substituents can be obtained from 1,4-reduction of substituted propiolates and trapping of the intermediate vinyl anion with the appropriate aldehyde or ketone.[22] This method is requires less time than the Morita-Baylis-Hillmann reaction, utilizes common reagents, and with the addtion of BF_3•OEt_2, allows for unactivated ketones to be used as the electrophilic trap.

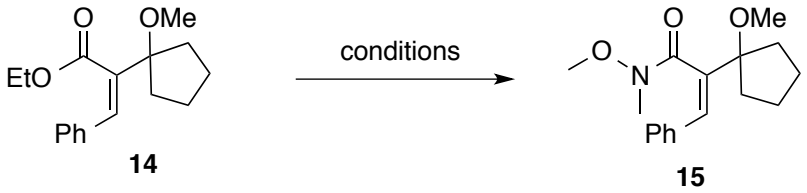
2-Hydroxyalkylenoate **14** was chosen for initial investigations. Ethyl phenylpropiolate and cyclopentanone in the presence of DIBAL-H, HMPA, and BF_3•OEt_2 cleanly produced the *E*-acrylate in 16% yield. The alcohol was then protected as the methyl ether in 92% yield via treatment with NaH and MeI (Scheme 4.8).



Scheme 4.8 Synthesis of 2-Hydroxyalkylenoate 14.

In order to build the necessary dienone framework, a suitable acyl donor for alkenyl addition was required. Weinreb amides omit the need for oxidation steps, and are easily accessible from esters by a number of methods. Conversion of ester **14** to the desired Weinreb amide **15** was attempted under a variety of standard conditions (Table 4-2). Direct methods for converting esters to Weinreb amides were tried first. Subjecting esters to excess N,O-dimethylhydroxylamine hydrochloride in the presence of isopropylmagnesium chloride has been shown to be an effective means of conversion;[23,24] however in this case, **15** was never observed. Similar direct conversion methods utilizing aluminum reagents Et_2AlCl[25] or $AlMe_3$[26] to obtain the Weinreb amide failed. After analyzing the ^1H NMR spectra of the reaction mixtures, we concluded that the dimethylhydroxylamine underwent a conjugate addition to the enoate, with concomitant elimination of the methoxy group. Formation of the Weinreb amide by a two-step route was also unsuccessful, with the production of intractable mixtures during attempted generation of the acid chloride intermediate.

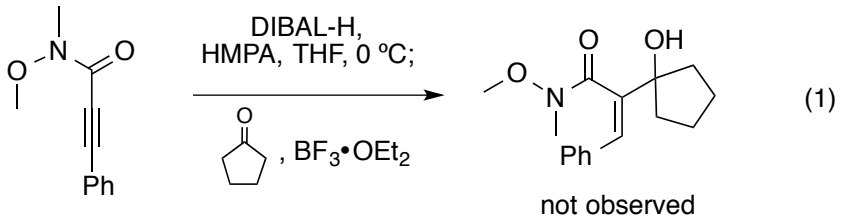
Table 4-2 Attempted Conversion of 14 to 15.



14 **15**

Entry	Conditions	Yield (%)
1	*i*PrMgCl (5.0 equiv), MeNH(OMe)•HCl (2.0 equiv), THF, 0 °C	--
2	Et_2AlCl (2.0 equiv), MeNH(OMe)•HCl (1.5 equiv), DCM, 0 °C to rt	--
3	$AlMe_3$ (2.0 equiv), MeNH(OMe)•HCl (1.5 equiv), DCM, 0 °C to rt	--
4	LiOH, MeOH, THF, H_2O; then $(COCl)_2$ (1.2 equiv), DMF, DCM; MeNH(OMe)•HCl (1.5 equiv), TEA (5 equiv)	--

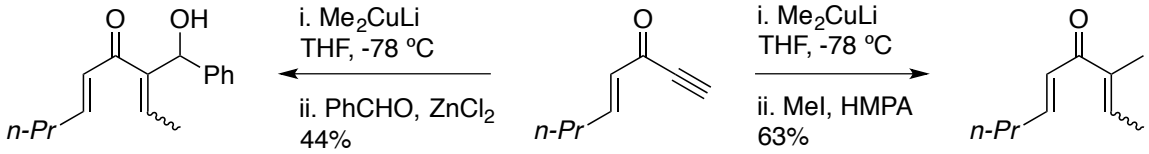
Given the difficulties converting ester **14** to amide **15**, we next examined the possibility of incorporating the Weinreb amide into the propiolic starting material used for the conjugate addition/ketone trapping process. We were disappointed to find that the propiolamide substrate was unreactive to these conditions, failing to afford any products derived from either the desired 1,4-hydride addition pathway or the undesired 1,2-reduction.



(1)

Disconnection b, between C-2 and C-3, appears at first glance to be a desirable method to produce the desired dienones. Combination of vinyl anions with different Weinreb amides would produce a diverse set of dienones. Unfortunately, the step count required to synthesize the necessary precursors of the vinyl anion synthon **11** was considered too high to pursue this method.

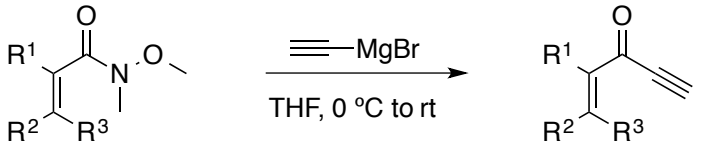
Finally, method c, where C-2 and the hydroxyalkyl substituent are disconnected, was attempted. Lee and co-workers published findings on the selectivity of alkyl- and aryl-cuprates towards alkynes over alkenes in cross-conjugated enynones to form unsymmetrical dienones from simple starting materials.[27] Additionally, carbonyl and alkyl electrophiles could quench the conjugate addition copper enolate to produce 2-hydroxyalkyl or 2-alkyl substituted dienones (Scheme 4.9).



Scheme 4.9 Lee Method for Synthesis of Unsymmetrical 1,4-Dien-3-ones.

Cross-conjugated enynones **13a-d** were prepared from addition of ethynylmagnesium bromide into the corresponding Weinreb amides in moderate to excellent yields.

Table 4-3 Synthesis of Enynones 13a-d.[a]



16a-d **13a-d**

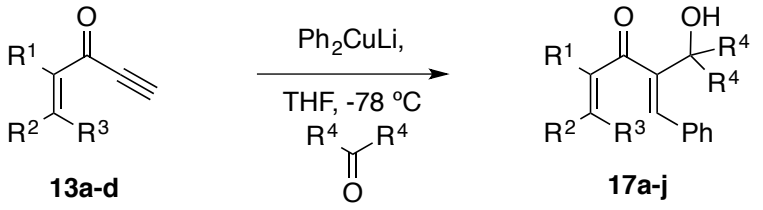
Entry	Weinreb Amide	R^1	R^2	R^3	Enynone	Yield (%)[b]
1	**16a**	Me	Ph	H	**13a**	63
2	**16b**	Me	Me	H	**13b**	55
3	**16c**	$(CH_2)_4$		H	**13c**	55
4	**16d**	H	Ph	Me	**13d**	97

[a]Standard procedure: Weinreb amide (25 mmol) was dissolved in THF (60 mL), flushed with argon, and cooled to 0 °C. A solution of ethynylmagnesium bromide (0.50 M in THF, 60 mL, 30 mmol, 1.2 equiv) was added slowly over 2 min. The solution was warmed to room temperature and stirred until complete by TLC, followed by 1N HCl quench, Et_2O extraction, aqueous workup, and chromatographic purification. [b]All provided yields are for pure product after isolation.

The desired 2-hydroxyalkyl-1,4-dien-3-ones were then prepared utilizing Lee's method. Enynones **13a-d**, in the presence of acetone, cyclopentanone, and cyclohexanone, were subjected to *in situ* generated Ph_2CuLi at low temperature (–78 °C), producing the hydroxyalkyl-dienones in moderate to good yields. Contrary to Lee's studies with Me_2CuLi and *n*-Bu_2CuLi, in which a ~1:1 (*E*)/(*Z*) ratio was found,

only the *E*-isomers were isolated. Similarly to Lee's study, only additions to the β-alkynyl position was observed.

Table 4-4 Synthesis of 2-hydroxyalkyl-1,4-dien-3-ones 17a-j.[a]



Entry	Enynone	R^1	R^2	R^3	R^4	Dienone	Yield (%)[b]
1	**13a**	Me	Ph	H	$(CH_2)_4$	**17a**	68
2	**13a**	Me	Ph	H	Me	**17b**	50
3	**13a**	Me	Ph	H	$(CH_2)_5$	**17c**	91
4	**13b**	Me	Me	H	$(CH_2)_4$	**17d**	35
5	**13b**	Me	Me	H	Me	**17e**	47
6	**13b**	Me	Me	H	$(CH_2)_5$	**17f**	35
7	**13c**	$(CH_2)_4$		H	$(CH_2)_4$	**17g**	55
8	**13c**	$(CH_2)_4$		H	Me	**17h**	63
9	**13d**	H	Ph	Me	$(CH_2)_4$	**17i**	61
10	**13d**	H	Ph	Me	$(CH_2)_3$	**17j**	76

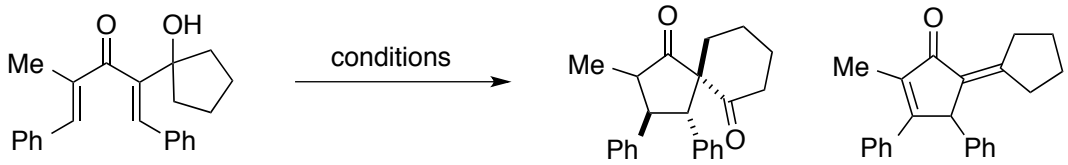
[a]Standard procedure: A solution of Ph_2CuLi (1.05 equiv, 0.24M) in THF is cooled to -78 °C. The ketone (1.1 equiv) was added, followed by slow addition of the enynone **13** (1 equiv) dissolved in THF (0.75M) over 5 min. After 30 min, the reaction was quenched with 1N HCl, extracted with Et_2O, and underwent aqueous workup before chromatographic purification. [b]All yields are of isolated products after flash chromatography.

4.2.2 Lewis Acid Screening for Nazarov/Semipinacol Process

Dienone **17a** was chosen as a test substrate to evaluate possible reaction conditions to affect the desired Nazarov/semipinacol process and produce spirocyclic product **18a**. Treatment of **17a** with BF_3•OEt_2 at low temperature with slow warming to room temperature produced an intractable mixture, as did Me_3SiOTf under similar conditions. We considered the hypothesis that competition for the Lewis acid by the alcohol side-chain might be complicating the reaction. To address this possibility, we added an equivalent of amine base (i-Pr_2NEt) with excess Me_3SiOTf to promote *in situ* silylation of the hydoxyl group. These conditions failed to convert the starting material in an appreciable amount, even after warming to room temperature.

We hypothesized that simultaneous complexation of the ketone and alcohol could promote the desired reaction. With this in mind, we examined bidentate Lewis acids. $Ti(O\textit{i}Pr)_4$ failed to convert any of the starting dienone, even after prolonged reaction time. After two hours with warming to room temperature, $TiCl_4$ had completely consumed the starting material and produced not the semipinacol rearranged product **18a,** but instead alkylidene cyclopentenone **19a** in modest yield. The use of 2.2 equivalents of Me_2AlCl increased the yield of **19a** to 51%**.** The semipinacol rearranged product was never observed. Although the desired process could not be effected, the alternative products were desirable in light of their status as double Michael acceptors, which are found in several classes of potential anticancer compounds.[28,29]

Table 4-5 Optimization of Nazarov Cyclization/Semipinacol Process.[a]



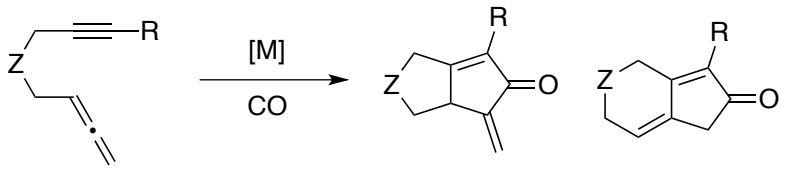
17a **18a** **19a**

Entry	Conditions	Product	Yield (%)[a]
1	BF_3•OEt_2 (1.1 equiv) CH_2Cl_2, -78 °C to rt, 4h	Intractable mixture	--
2	Me_3SiOTf (1.1 equiv), CH_2Cl_2, -78 °C to rt, 4h	Intractable mixture	--
3	Me_3SiOTf (2.1 equiv), i-Pr_2NEt (1.0 equiv), CH_2Cl_2, -78 °C to rt, 48h	Minimal conversion	--
4	$Ti(Oi\text{-}Pr)_4$ (1.1 equiv), CH_2Cl_2, 0 °C to rt, 48h	No conversion	--
5	$TiCl_4$ (1.1 equiv), CH_2Cl_2, -78 to 0 °C, 2h	**19a**	23
6	Me_2AlCl (2.2 equiv), CH_2Cl_2, 0 °C to rt, 16h	**19a**	51

[a]All yields are of isolated products after chromatographic purification

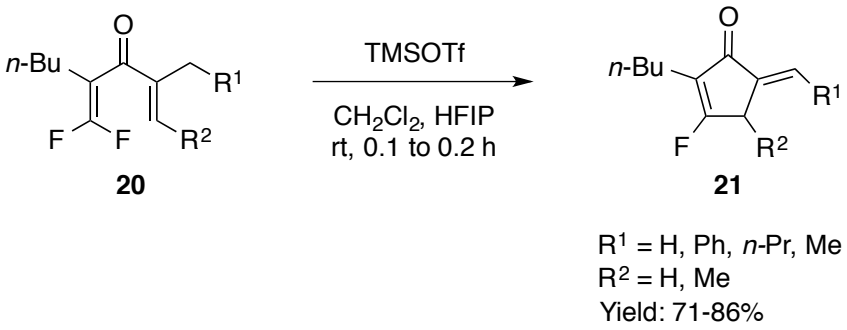
4.3 Synthesis of Alkylidene Cyclopentenones

Recently, there have been a number of methods reported to synthesize alkylidene cyclopentenones via Pauson-Khand type cyclocarbonylation of allenynes.[30-35] These methods utilize various metal species (Ir(I)[31], Rh(I)[32], Mo(0)[30,35]), but the products are often produced in mixtures of regio- and constitutional isomers (Scheme 4.10).



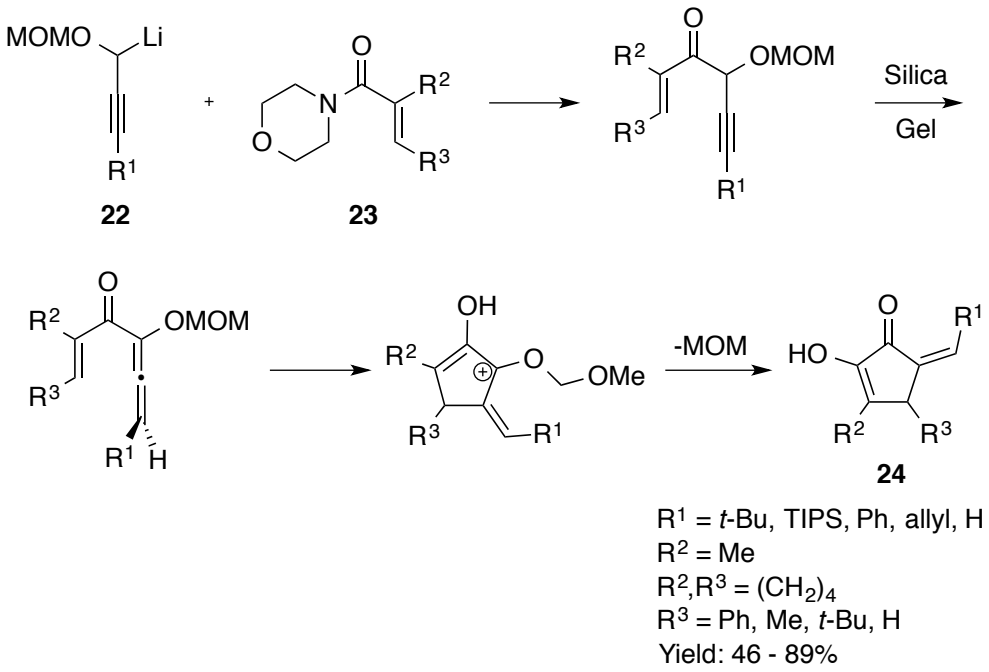
Scheme 4.10 Metal Mediated Carbonylation of Allenynes.

The Nazarov cyclization has also been utilized in the past to form alkylidene cyclopentenones. In 1995, Ichikawa and co-workers published their findings of a fluorine-directed Nazarov process that resulted in alkylidene cyclopentanones.[36] β,β-disubstituted dienones **20** underwent electrocyclization with trimethylsilyl triflate as the Lewis acid. The fluorine substituents had a β-destabilization effect on the oxyallyl cation, resulting in preferential deprotonation of the α'-carbon. This was then followed by elimination of one of the fluorides, giving **21** (Scheme 4.11).



Scheme 4.11 Fluorine Directed Nazarov Cyclization.

Tius and co-workers have also reported synthesis of alkylidene cyclopentenones via Nazarov cyclizations.[37] The addition of 1-lithio-1-methoxymethoxy-2-ynes **22** into morpholino enamides **23** produce propargyl vinyl ketones **24**. Under mild acid conditions (silica gel), the alkyne isomerizes to an allene, allowing for a Nazarov cyclization to occur. Loss of the MOM protecting group reveals the 2-hydroxy-5-alkylidene-cyclopent-2-enones (Scheme 4.12).

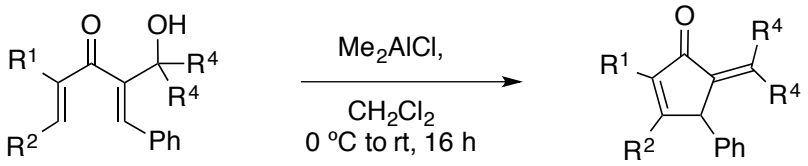


Scheme 4.12 Nazarov Cyclization to Form Alkylidene Cyclopentenones.

4.3.1 Double Eliminative Nazarov Cyclization

With the utility of alkylidene cyclopentenones evident and no semipinacol product observed, the remaining 2-hydroxyalkyl-1,4-dien-3-ones were subjected to the Me_2AlCl reaction conditions. Acetone adduct **17b** produced **19b** in a low yield of 36%, but the cyclohexanone substrate **17c** saw an improved yield of 62% (entries 2 and 3, Table 4.6). Altering of R^2 from phenyl to methyl provided similar results, with the cyclopentanone, acetone, and cyclohexanone adducts all producing the respective alkylidene cyclopentenones **19d-f** in moderate yield. Replacing R^1 and R^2 with a cyclohexene, as seen in **17g** and **17h**, produced hydrindenone ring-fused **19g** and **19h** in 34% and 58% yield respectively. Notably, in all cases, the initial deprotonation occurs within the ring at C-1; bis(alkylidene)cyclopentanones were never observed.

Table 4-6 Double Eliminative Nazarov Cyclization.[a]



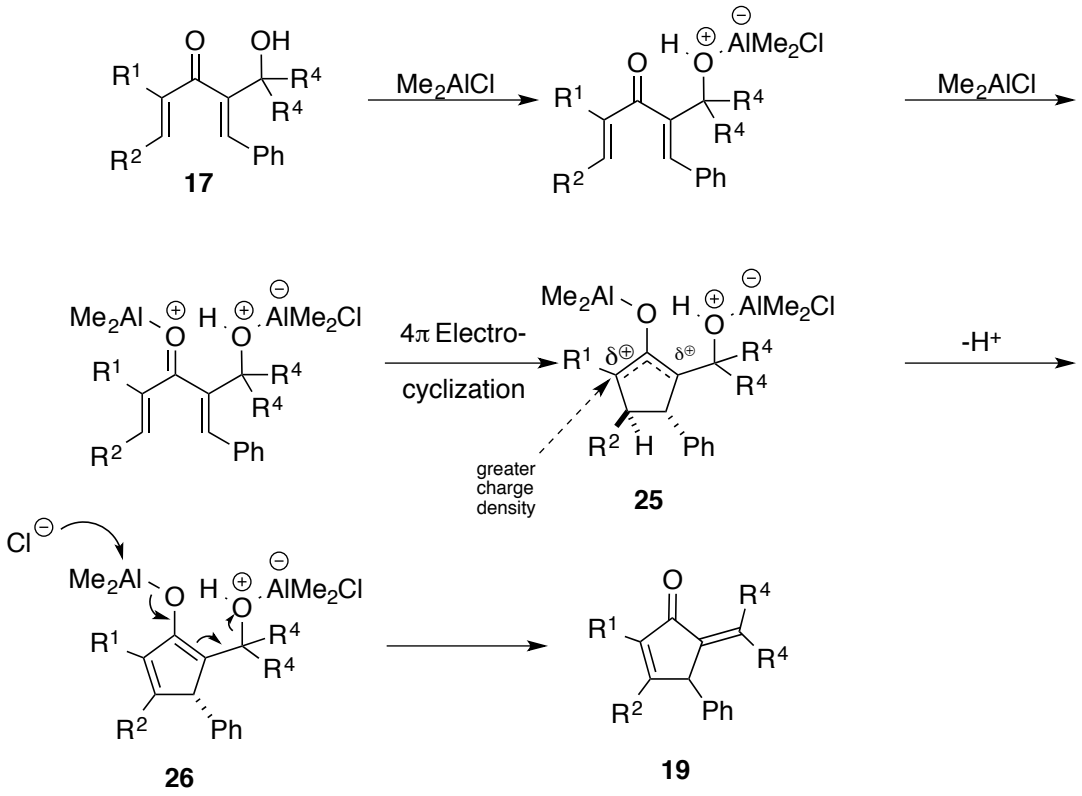
17a-h **19a-h**

Entry	Dienone	R^1	R^2	R^4	Product	Yield[b]
1	**17a**	Me	Ph	$(CH_2)_4$	**19a**	51
2	**17b**	Me	Ph	CH_3	**19b**	36
3	**17c**	Me	Ph	$(CH_2)_5$	**19c**	62
4	**17d**	Me	Me	$(CH_2)_4$	**19d**	46
5	**17e**	Me	Me	CH_3	**19e**	43
6	**17f**	Me	Me	$(CH_2)_5$	**19f**	61
7	**17g**	$(CH_2)_4$		$(CH_2)_4$	**19g**	34
8	**17h**	$(CH_2)_4$		CH_3	**19h**	58

[a]Standard procedure: Dienone **17** was dissolved in CH_2Cl_2 (0.05M) and cooled to 0 °C. A solution of Me_2AlCl (1.0 M in hexanes, 2.2 equiv) was added dropwise. The reaction was stirred at 0 °C for 30 min and then warmed to rt and stirred for 15.5 h at this temperature. The reaction was quenched with 1 N HCl, followed by aqueous work-up and chromatographic purification. [b]All yields refer to isolated products after flash chromatography.

In all instances, the initial deprotonation occurred on the side distal to the hydroxyalkyl substituent, producing the endocyclic alkene. This suggests that the hydroxyalkyl moiety leads to a greater positive charge density on C-4 versus C-2. The mechanism of the transformation is believed to begin with initial complexation of the Lewis acid with the hydroxyl group, leaving the second equivalent of Lewis acid to complex with the ketone. Electrocyclization occurs, forming cyclopentenyl

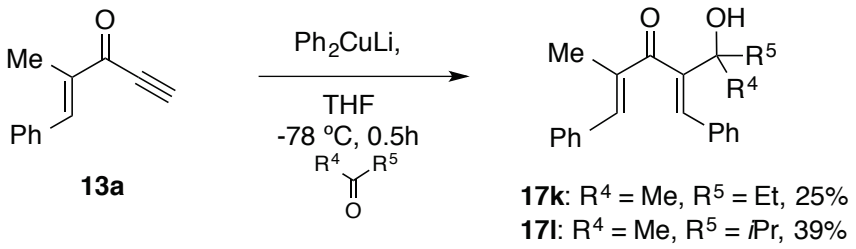
cation **25**, with greater charge density on C-4. Deprotonation of intermediate **25** furnishes aluminium dienolate **26**, which is primed to eliminate the activated hydroxyl group, providing alkylidene cyclopentenone **19** (Scheme 4.13).



Scheme 4.13 Mechanism for Double Eliminative Nazarov.

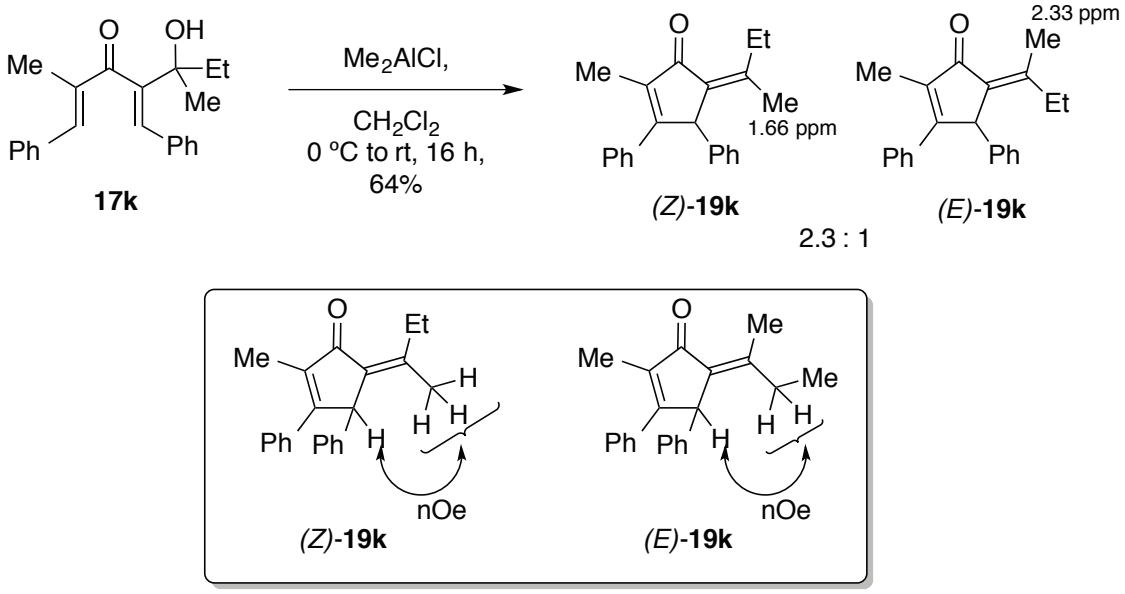
4.3.2 Unsymmetrical Ketone Adducts

Dienones **17a-h** all contained identical R^4 substituents on the tertiary alcohol. In order to test the selectivity of the hydroxyl elimination, dienones **17k** and **17l** were synthesized by the same method mentioned above. Dienone **17k** was produced in a modest yield of 25% via the addition of Ph_2CuLi to enynone **13a** in the presence of 2-butanone. Similarly, **17l** was formed in 39% in the presence of 3-methyl-2-butanone (Scheme 4.14).



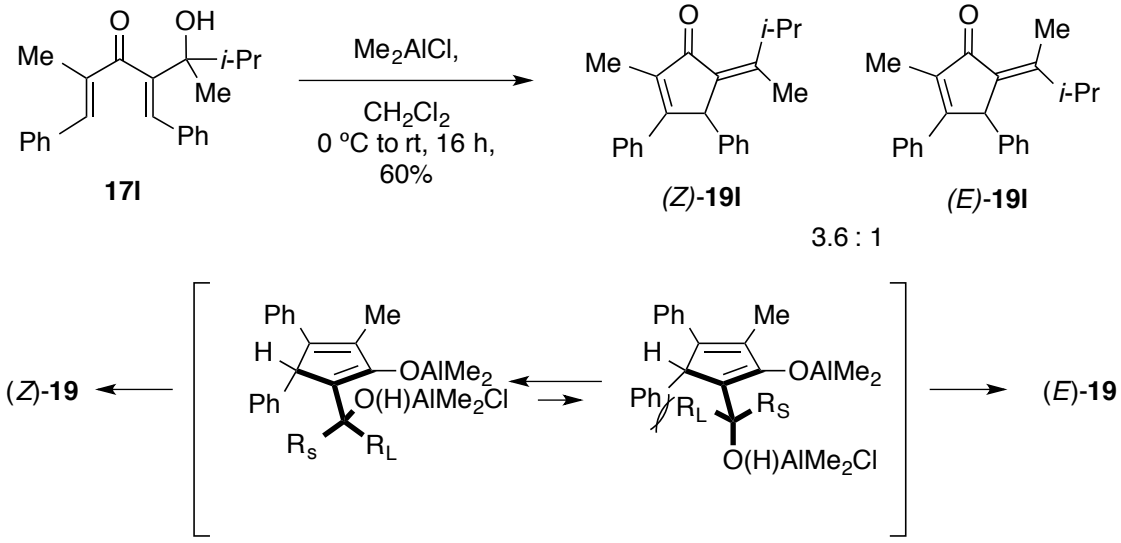
Scheme 4.14 Synthesis of Dienones 17k and 17l.

Under the standard Me_2AlCl conditions, dienone **17k** was converted to a 2.3:1 mixture of (*Z*)-**19k** and (*E*)-**19k** in 64% yield. The stereochemistry of (*Z*)-**19k** and (*E*)-**19k** was determined by NOE experiments (Scheme 4.15). Irradiation of the benzylic methine at C-4 showed a correlation with the protons in a *cis* relationship, while no correlation was observed for the protons in a *trans* relationship. Furthermore, a clear downfield shift (0.7 ppm for the methyl) was observed in the allylic protons *cis* to the carbonyl.



Scheme 4.15 Synthesis and Assignment of (*Z*)-19k and (*E*)-19k.

Dienone **17l** was also subjected to the standard reaction conditions and similarly produced a mixture of alkylidene cyclopentenone isomers. In this case, the diastereomeric ratio was 3.6:1, showing a slightly greater preference for (*Z*)-**19l** over (*E*)-**19l** than that seen with **17k** (Scheme 4.16). The allylic protons of the two diastereomers had significant chemical shift differences, allowing for stereochemical assignment based on analogy to the isomers of **19k**. The stereoselectivity observed is believed to arise from steric clash between the aryl group and the larger tertiary alcohol alkyl substituent in the transition state.

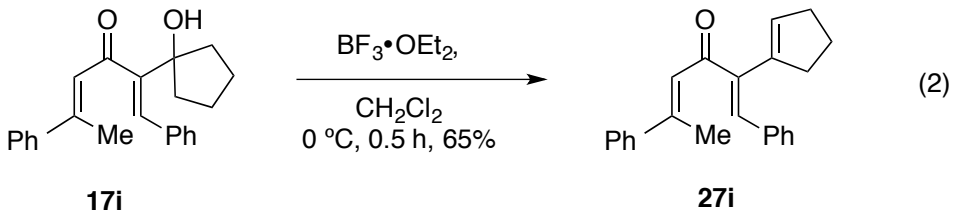


Scheme 4.16 Synthesis of (*Z*)-19l and (*E*)-19l.

4.4 2-Hydroxyalkyl-1,4-dien-3-ones Lacking C-4 Substitution

Despite the lack of success achieving a semipinacol interrupted Nazarov reaction with dienones **17a-h**, we hypothesized that dienones unable to undergo the initial deprotonation leading to **19** would undergo a semipinacol rearrangement. Dienones **17i** and **17j** were synthesized lacking substitution at C-4, preventing potential exocyclic deprotonation and decreasing cationic character at C-4 of the oxyallyl cation.

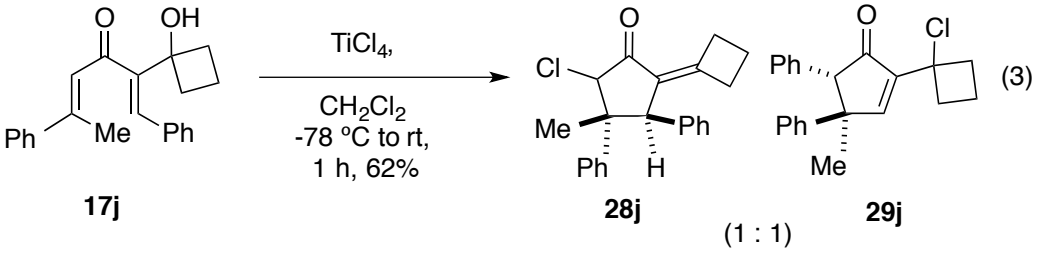
Dienone **17i** was subjected to the standard Me_2AlCl conditions, but was not consumed, even after prolonged reaction time (48 hours) and addition of more Me_2AlCl (5 equivalents). Addition of $BF_3{\bullet}OEt_2$, however, quickly consumed the starting material in 30 minutes. Isolation and characterization of the lone discernable product revealed trienone **27i**, produced by elimination of the hydroxyl group without Nazarov cyclization occurring (Equation 2).



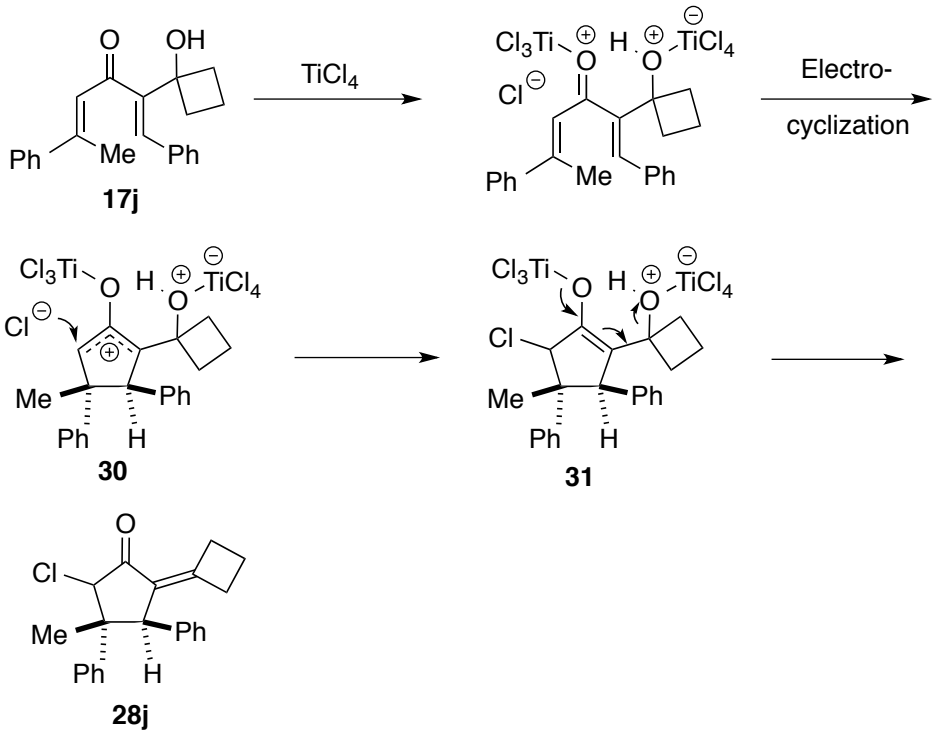
17i **27i** (2)

Dienone **17j**, similarly failed to react under the Me_2AlCl conditions. A short screen of Lewis acids found that $TiCl_4$ consumed the starting material upon warming to room temperature. Two new products were isolated, neither of which contained the desired 1,3-diketone moiety, but instead both had incorporated a single chlorine

atom. Careful structure elucidation revealed chloroenones **28j** (stereochemistry of C-2 unknown) and **29j** to have been formed in a 1:1 ratio (Equation 3).

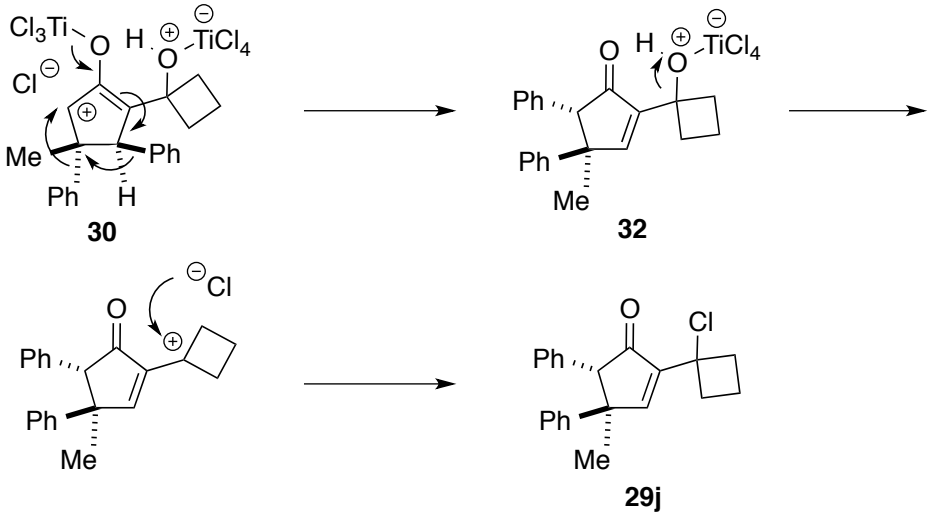


Alkylidene cyclopentanone **28j** was likely formed via initial complexation of the hydroxyl group and ketone to the Lewis acid (Scheme 4.17). Electrocyclization produces the cyclopentenyl cation **30**, which is captured by a chloride anion,[38] forming titanium enolate **31**. The hydroxyl group is then eliminated to form **28j**.



Scheme 4.17 Mechanism for formation of 28j.

Cyclopentenone **29j** is formed from common intermediate **30**. Instead of capture of the oxyallyl cation by chloride, two sequential Wagner-Meerwein shifts of the two β-phenyl substituents occur producing intermediate **32**. The hydroxyl group is eliminated to form an allylic cation, which is again captured by a chloride anion furnishing **29j** (Scheme 4.18).

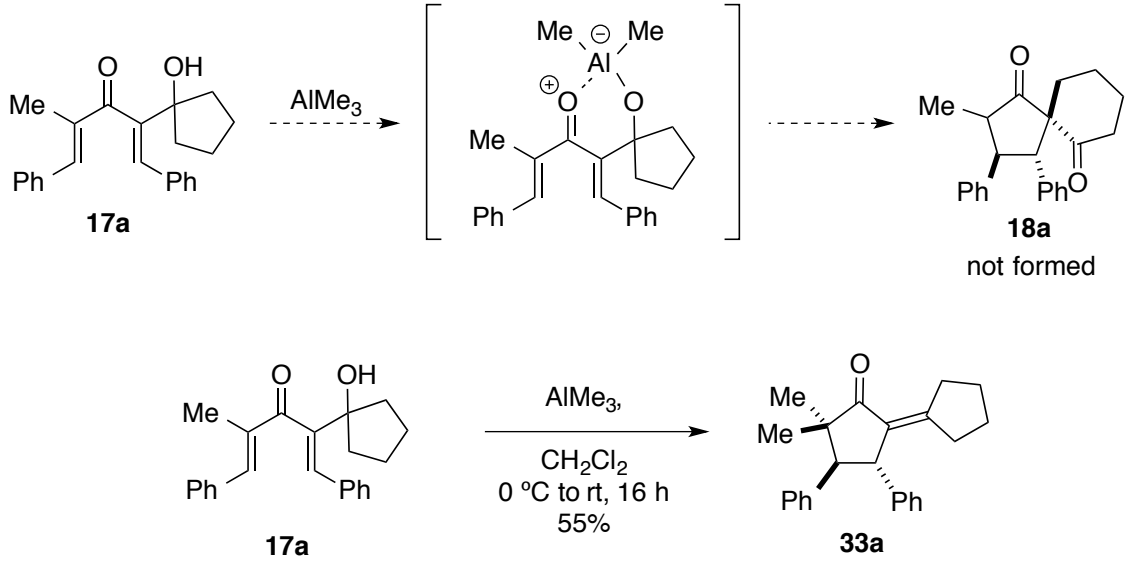


Scheme 4.18 Mechanism for Formation of 29j.

4.5 Trimethylaluminum Mediated Trapping and Hydroxyl Elimination

During the original screening of Lewis acids with dienone **17a**, trimethyaluminum was screened. It was hypothesized that trimethylaluminum would first complex with the hydroxyl group, losing a molecule of methane gas in the process. The ketone could then complex with the aluminum intramolecularly, and hopefully this complex would encourage the semipinacol rearrangement. Experimentally, trimethylaluminum was found to be required in excess (3.2 equivalents) in order to fully consume the starting material, and the semipinacol

product was not formed. Instead, the trimethylaluminum had trapped the oxyallyl cation via methyl delivery[39] to the α-carbon distal to the hydroxyl group, and the resulting aluminum enolate had ejected the hydroxyl group forming alkylidene cyclopentanone **33a** (Scheme 4.19).



Scheme 4.19 Domino Trimethylaluminum Trapped Nazarov/Hydroxyl Elimination.

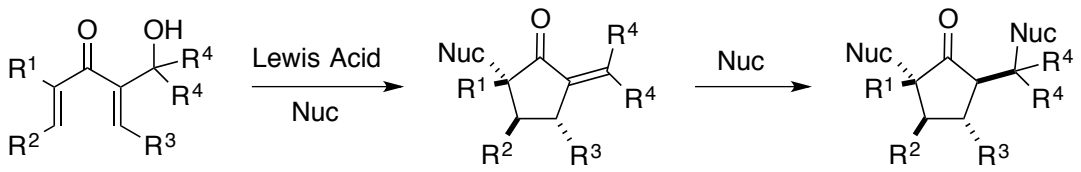
4.6 Conclusions

A series of 2-hydroxyalkyl-1,4-dien-3-ones were synthesized for the purpose of investigating a semipinacol interrupted Nazarov reaction. Instead, these dienones were found to readily undergo Nazarov cyclization followed by hydroxyl elimination to form alkylidene cyclopentenones. The initial deprotonation occurs on the side distal to the hydroxyalkyl substituent due to destabilization of the oxyallyl cation by the hydroxyl moiety. When dienones were synthesized that could not undergo the

initial deprotonation event, the oxyallyl cation was trapped by chloride and underwent a series of [1,2]-migrations.

4.7 Future Directions

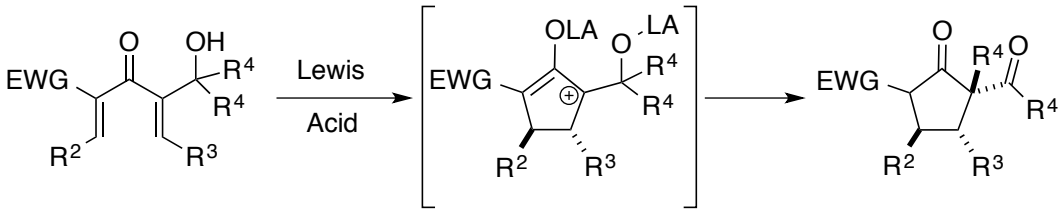
Trapping the oxyallyl cation by $AlMe_3$ provides a starting point for various other trapping reagents to be used. It is conceivable that a variety of traps could alkylate at the α-position and have the resulting metalo-enolate eliminate the hydroxyl substituent. This generates three contiguous stereocenters while preserving the useful enone structural motif common to classical Nazarov cyclizations. Furthermore, an excess of nucleophile could be used to both trap the oxyallyl cation and subsequently add into the enone in a 1,4-conjugate addition pathway to quickly build molecular complexity (Scheme 4.20).



Scheme 4.20 Dual Nucleophilic Trapping of the Double Eliminative Nazarov Cyclization.

With the evidence suggesting the hydroxyl group leads to greater positive charge density on the distal α-position, it is conceivable that a strong electron withdrawing substituent could alter the reactivity. By having a strong electron-

withdrawing group on the distal α-position the positive charge density may redistribute, encouraging the semipinacol rearrangement to occur (Scheme 4.21).



Scheme 4.21 Electron-Withdrawing Effect on Nazarov/Semipinacol Process.

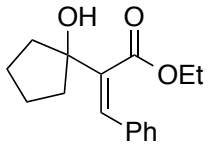
These advancements would nicely compliment the interrupted Nazarov literature, providing access to cyclopentanones with multiple contiguous stereocenters. The products would also provide functional groups for further manipulations in synthesis.

4.8 Experimental

4.8.1 General Information

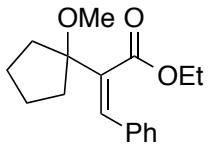
Reactions were carried out in flame-dried glassware under a positive argon atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannulae. Solvents were distilled before use: dichloromethane from calcium hydride, and tetrahydrofuran from sodium/benzophenone ketyl. Thin layer chromatography was performed on glass plates precoated with 0.25 mm Kieselgel 60 F254 (Merck). Flash chromatography column were packed with 230-400 mesh silica gel (Silicycle). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 500 MHz and coupling constants (*J*) are reported in Hertz (Hz). Standard notation was used to describe the multiplicity of signals observed in ^{1}H NMR spectra: broad (br), apparent (app), multiplet (m), singlet (s), doublet (d), triplet (t), etc. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 MHz and are reported (ppm) relative to the center line of the triplet from chloroform-*d* (77.26 ppm). Infrared (IR) spectra were measured with a Mattson Galaxy Series FT-IR 3000 spectrophotometer. Mass spectra (EI technique) were determined on a Kratos MS50 instrument.

4.8.2 Experimental Procedures and Characterization



DIBAL-H (1.5 equiv, 1.0M in hexanes) was added to a solution of HMPA (1.8 equiv) in THF (0.2 M) at 0 °C. The solution was stirred for 30 minutes at this temperature at which point ethyl phenyl propiolate (1.0 equiv) is added and stirred for 4 hours. Cyclopentanone (1.2 equiv) and BF_3•OEt_2 (1.2 equiv) are added sequently and the mixture is warmed to room temperature overnight. The reaction is then quenched with 1N HCl, extracted with Et_2O (2x), washed with brine, dried over $MgSO_4$, and concentrated. It is then purified by flash chromatography (silica gel, 5:1 hexanes:EtOAc) to yield 16% of a yellow oil.

R_f (0.25, 5:1 hexanes:EtOAc); IR (cast film) 3474, 3058, 2961, 1718, 1637 cm^{-1}; 1H (500 MHz, $CDCl_3$) δ 7.34-7.28 (m, 5H), 6.93 (s, 1H), 4.16 (q, *J* = 7.3 Hz, 2H), 2.46 (bs, 1H), 2.02-1.88 (m, 6H), 1.80 – 1.76 (m, 2H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 170.2, 139.6, 135.8, 129.7, 128.2, 128.1, 127.9, 82.8, 61.0, 39.0, 23.3, 13.7; HRMS (EI, M^+) Calcd for $C_{16}H_{20}O_3$ 260.1412; Found m/z 260.1416.



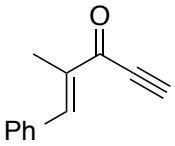
The corresponding alcohol was dissolved in THF (0.1M) and cooled to 0 °C. NaH (1.5 equiv, 60% wt dispersion in oil) was added and stirred for 15 minutes. MeI (1.5 equiv) was added to the mixture and stirred overnight with warming to room

temperature. NH_4Cl was added to quench the reaction, and it was then extracted with Et_2O, washed with water, brine, dried over $MgSO_4$, and concentrated to yield a yellow oil (92%). The concentrate was deemed pure enough by ^1H NMR to not require chromatographic purification.

R_f (0.30, 8:1 hexanes:EtOAc); IR (cast film) 3058, 2956, 1723, 1638 cm^{-1}; 1H (500 MHz, $CDCl_3$) δ 7.31 – 7.28 (m, 5H), 6.66 (s, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 3.20 (s, 3H), 2.06 – 2.00 (m, 2H), 1.88 – 1.70 (m, 6H), 1.15 (t, *J* = 7.0 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 169.6, 137.8, 135.5, 129.6, 128.4, 128.1, 128.0, 88.1, 60.8, 50.7, 35.4, 22.8, 13.9; HRMS (EI, M^+) Calcd for $C_{17}H_{22}O_3$ 274.1569; Found m/z 274.1571.

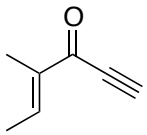
Standard Procedure for Synthesis of Enynones 13:

The Weinreb amide[40-43] (derived from the corresponding unsaturated carboxylic acid; 25 mmol) was dissolved in THF (60 mL), flushed with argon and cooled to 0 °C. A solution of ethynylmagnesium bromide (0.5 M in THF, 60 mL, 30 mmol, 1.2 equiv) was added slowly over 2 minutes. The solution was then stirred at this temperature until the starting material was consumed (as determined by TLC analysis). The reaction was then quenched with 1N HCl solution (50 mL) and extracted with Et_2O (2 x 50 mL). The organic layers were combined, washed with H_2O (50 mL), brine (50 mL) and dried over $MgSO_4$. After filtration, the solution was concentrated by rotary evaporation and the product was purified by flash chromatography (silica gel) to provide the desired enynone.



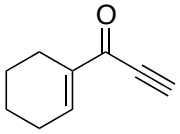
The standard procedure was used to yield **13a** (63%) as a yellow solid after purification by flash chromatography (silica gel, hexanes:EtOac 20:1):

R_f 0.43 (hexanes:EtOAc, 8:1); mp 58-60 °C; IR (cast film) 3259, 3049, 2965, 2092, 1629 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.52-7.49 (m, 2H), 7.47-7.42 (m, 2H), 7.41-7.37 (m, 1H), 3.32 (s, 1H), 2.13 (d, *J* = 1.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1, 146.7, 137.8, 135.3, 130.2, 129.5, 128.6, 79.9, 79.8, 12.1; HRMS (EI, M^+) Calcd for $C_{12}H_{10}O$ 170.0732; Found m/z 170.0729.



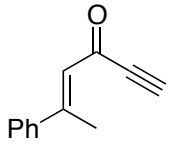
The standard procedure was used to yield **13b** (55%) as a brown oil after purification by flash chromatography (silica gel, hexanes:EtOAc 20:1):

R_f 0.38 (hexanes:EtOAc 8:1); IR (neat) 3251, 3049, 2929, 2094, 1635 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (qq, *J* = 7.2, 1.4 Hz, 1H), 3.19 (s, 1H), 1.95 (dq, *J* = 7.1, 1.1 Hz, 3H), 1.80 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.5, 146.6, 139.2, 79.7, 78.9, 15.2, 10.0; HRMS (EI, M^+) Calcd for C_7H_8O 108.0575; Found m/z 108.0575.



The standard procedure was used to yield **13c** (55%) as a dark orange oil after purification by flash chromatography (silica gel, hexanes:EtOAc 20:1):

R_f 0.43 (hexanes:EtOAc 8:1); IR (cast film) 3230, 3053, 2940, 2092, 1629 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (tt, *J* = 4.0, 1.7 Hz, 1H), 3.20 (s, 1H), 2.40-2.35 (m, 2H), 2.31-2.27 (m, 2H), 1.68 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 148.8, 140.4, 79.7, 78.6, 26.6, 22.2, 21.6, 21.5 ; HRMS (EI, M^+) Calcd for $C_9H_{10}O$ 134.0732; Found m/z 134.0731.

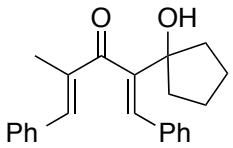


The standard procedure was used to yield **13d** (97%) as an orange oil after purfication by flash chromatography (hexanes:EtOAc 20:1):

R_f 0.35 (hexanes:EtOAc 8:1); IR (cast film) 3726, 3061, 2954, 2092, 1651 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.44 (m, 3H), 6.68 (q, *J* = 1.2 Hz, 1H), 3.24 (s, 1H), 2.67 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 157.7, 141.6, 129.9, 128.7, 126.6, 125.3, 84.1, 77.3, 19.1; HRMS (EI, M^+) Calcd for $C_{12}H_{10}O$ 170.0732; Found m/z 170.0726.

Standard Procedure for Synthesis of Dienones 17a-j:

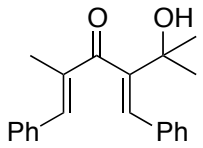
A suspension of $CuBr•SMe_2$ (322mg, 1.57 mmol, 1.05 equiv) in THF (5 mL) was flushed with argon and cooled to 0 °C. To this was added a solution of phenyllithium (1.9 M in dibutyl ether, 1.65 mL, 3.15 mmol, 2.1 equiv) dropwise. The mixture was stirred for 45 min, during which the solid slowly dissolved and the solution became a dark brown color. The solution was then cooled to –78 °C. The necessary ketone was added (1.65 mmol, 1.1 equiv), immediately followed by dropwise addition of the enynone **13** (1.5 mmol) in a solution of THF (2 mL). The solution was stirred at this temperature for 30 min, and was then quenched with 5 mL 1N aq HCl solution. The mixture was extracted with Et_2O (2 x 10 mL). The organic layers were combined, washed with H_2O (15 mL), brine (10 mL), and dried over $MgSO_4$. After filtration the solution was concentrated by rotary evaporation, and the resulting oil was purified by flash chromatography (silica) to yield the desired dienone **17**.



The standard procedure was used to yield **17a** (68%) as a white solid after purification by flash chromatography (silica gel, hexanes:EtOAc 5:1):

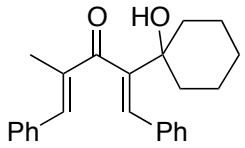
R_f 0.51 (hexanes: EtOAc 2:1); mp 107-108 °C; IR (cast film) 3445, 3025, 2961, 1637 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (br s, 1H), 7.30-7.27 (m, 2H), 7.25-7.21 (m, 3H), 7.18-7.16 (m, 1H), 7.15-7.12 (m, 2H), 7.08 (br s, 1H), 7.07-7.04 (m, 2H), 2.85 (s, 1H), 2.02-1.96 (m, 2H), 1.95 (d, *J* = 1.3 Hz, 3H), 1.94-1.86 (m, 4H), 1.78-1.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 144.8, 143.3, 137.4, 136.4, 135.8, 129.4 (2x),

128.6 (2x), 128.4, 128.3, 127.8, 83.5, 39.1, 23.1, 12.5; HRMS (ESI, $M+H^+$) Calcd for $C_{23}H_{25}O_2$ 333.1849; Found m/z 333.1852.



The standard procedure was used to yield **17b** (50%) as a viscous yellow oil after purification by flash chromatography (silica gel, hexanes:EtOAc 4:1):

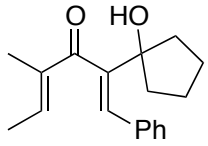
R_f 0.43 (hexanes:EtOAc 2:1); IR 3460, 3056, 2974, 1642, 1619 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (br s, 1H), 7.34-7.24 (m, 5H), 7.22-7.16 (m, 3H), 7.11 (s, 1H), 7.10-7.08 (m, 2H), 3.07 (br s, 1H), 1.98 (d, *J* = 1.3 Hz, 3H), 1.60 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 146.7, 143.3, 137.7, 136.4, 135.8, 129.4, 128.8, 128.6, 128.5, 128.4, 128.3, 127.8, 72.8, 29.7, 12.5; HRMS (EI, M^+) Calcd for $C_{21}H_{22}O_2$ 306.1620; Found m/z 306.1620.



The standard procedure was used to yield **17c** (91%) as a yellow oil after purification by flash chromatography (silica gel, hexanes:EtOAc 5:1):

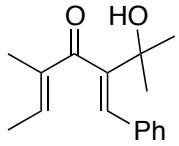
R_f 0.58 (hexanes:EtOAc 2:1); IR 3466, 3056, 2932, 1640, 1617 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (br s, 1H), 7.30-7.20 (m, 5H), 7.18-7.12 (m, 3H), 7.08-7.05 (m, 3H), 2.92 (br s, 1H), 1.94 (d, *J* = 1.3 Hz, 3H), 1.87 (m, 2H), 1.78-1.60 (m, 7H), 1.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 147.5, 143.5, 137.8, 136.6, 135.8, 129.4,

128.9, 128.5 (2x), 128.3, 128.2, 127.7, 73.6, 37.0, 25.5, 21.9, 12.5; HRMS (EI, M^+) Calcd for $C_{24}H_{26}O_2$ 346.1933; Found m/z 346.1932.



The standard procedure was used to yield **17d** (35%) as a white solid after flash chromatography (silica gel, hexanes:EtOAc 5:1):

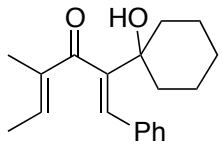
R_f 0.60 (hexanes:EtOAc 2:1); mp 106-108 °C; IR (cast film) 3467, 3042, 2953, 1636 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24-7.16 (m, 3H), 7.09-7.06 (m, 2H), 6.95 (s, 1H), 6.61 (qq, *J* = 7.0, 1.4 Hz, 1H), 2.80 (s, 1H), 1.94–1.86 (m, 4H), 1.84-1.78 (m, 2H), 1.76-1.72 (m, 2H), 1.71 (app pent, *J* = 1.2 Hz, 3H), 1.58 (dq, *J* = 7.0, 1.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 144.9, 142.9, 138.2, 136.3, 128.7, 128.5, 128.2, 127.6, 83.4, 39.0, 23.0, 14.9, 10.5; HRMS (EI, M^+) Calcd for $C_{18}H_{22}O_2$ 270.1620; Found m/z 270.1619.



The standard procedure was used to yield **17e** (47%) as a white solid after flash chromatography (silica gel, hexanes:EtOAc 4:1):

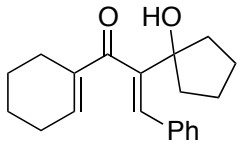
R_f 0.51 (hexanes:EtOAc 2:1); mp 128-130 °C; IR (cast film) 3459, 3025, 2975, 1637 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24-7.16 (m, 3H), 7.08-7.05 (m, 2H), 6.93 (s, 1H), 6.59 (qq, *J* = 7.0, 1.3 Hz, 1H), 2.99 (br s, 1H), 1.70 (app pent, *J* = 1.1 Hz, 3H), 1.58 (dq,

J = 7.0, 1.0 Hz, 3H), 1.48 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 146.7, 142.9, 138.5, 136.4, 128.5, 128.2, 128.1, 127.6, 72.7, 29.6, 14.9, 10.5; HRMS (EI, M^+) Calcd for $C_{16}H_{20}O_2$ 244.1463; Found m/z 244.1463.



The standard procedure was used to yield **17f** (35%) as a white solid after flash chromatography (silica gel, hexanes:EtOAc 5:1):

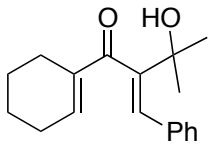
R_f 0.58 (hexanes, EtOAc 2:1); mp 130-132 °C; IR (cast film) 3462, 3024, 2932, 1635 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.18 (m, 3H), 7.08-7.05 (m, 2H), 6.90 (s, 1H), 6.61 (qq, *J* = 7.0, 1.3 Hz, 1H), 2.79 (br s, 1H), 1.82-1.76 (m, 2H), 1.74–1.64 (m, 9H), 1.60-1.56 (m, 4H), 1.28-1.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.5, 164.6, 147.6, 143.0, 138.7, 136.5, 128.5, 128.2, 127.5, 73.5, 37.0, 25.5, 21.9, 14.9, 10.5; HRMS (EI, M^+) Calcd for $C_{19}H_{24}O_2$ 284.1776; Found m/z 284.1776.



The standard procedure was used to yield **17g** (55%) as a white solid after flash chromatography (silica gel, hexanes:EtOAc 4:1):

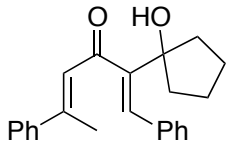
R_f 0.48 (hexanes:EtOAc 3:1); mp 84-87 °C; IR 3455, 3025, 2936, 1630 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.18 (m, 3H), 7.08 (m, 2H), 6.99 (s, 1H), 6.66 (tt, *J* = 4.1, 1.5 Hz, 1H), 2.95 (s, 1H), 2.16 (m, 2H), 1.95-1.87 (m, 6H), 1.86-1.78 (m, 2H), 1.76-1.68

(m, 2H), 1.46-1.41 (m, 2H), 1.38-1.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 145.1, 144.7, 139.2, 136.6, 129.2, 128.5, 128.2, 127.6, 83.4, 38.9, 26.2, 23.1, 22.9, 21.7, 21.4; HRMS (EI, M^+) Calcd for $C_{20}H_{24}O_2$ 296.1776; Found m/z 296.1772.



The standard procedure was used to yield **17h** (63%) as a yellow semi-solid after flash chromatography (silica gel, hexanes:EtOAc 3:1):

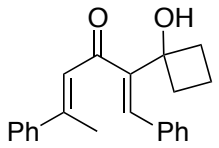
R_f 0.20 (hexanes:EtOAc 3:1); IR 3457, 3024, 2932, 1632 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.18 (m, 3H), 7.08-7.06 (m, 2H), 6.98 (s, 1H), 6.64 (tt, *J* = 4.0, 1.7 Hz, 1H), 3.14 (s, 1H), 2.17 – 2.12 (m, 2H), 1.92–1.88 (m, 2H), 1.49 (s, 6H), 1.44–1.39 (m, 2H), 1.37–1.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 146.6, 145.2, 139.5, 136.7, 128.6, 128.4, 128.2, 127.6, 72.6, 29.5, 26.2, 22.9, 21.7, 21.3; HRMS (EI, M^+) Calcd $C_{18}H_{22}O_2$ 270.1620; Found m/z 270.1618.



The standard procedure was used to yield **17i** (61%) as a yellow oil after flash chromatography (silica gel, hexanes:EtOAc 4:1):

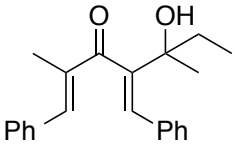
R_f 0.45 (hexanes:EtOAc 3:1); IR (cast film) 3439, 3057, 2958, 1658 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.26 (m, 5H), 7.24–7.17 (m, 3H), 7.02 (br s, 1H), 6.95-6.92 (m, 2H), 6.14 (br s, 1H), 3.45 (s, 1H), 2.52 (d, *J* = 1.1 Hz, 3H), 1.94-1.86 (m, 6H), 1.75-

1.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 154.6, 148.1, 142.5, 136.1, 129.2, 129.1, 129.0, 128.4, 128.3, 128.3, 128.2, 126.5, 83.7, 38.6, 23.1, 18.6; HRMS (EI, M^+) Calcd for $C_{23}H_{24}O_2$ 332.1776; Found m/z 332.1774.



The standard procedure was used to yield **17j** (76%) as a yellow oil after flash chromatography (silica gel, hexanes:EtOAc 5:1):

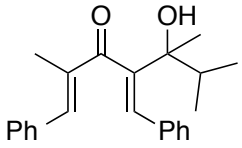
R_f 0.22(hexanes:EtOAc 8:1); IR (cast film) 3426, 3024, 2947, 1660 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 5H), 7.29 – 7.24 (m, 1H), 7.22 – 7.18 (m, 2H), 7.06 (s, 1H), 6.94 – 6.90 (m, 2H), 6.16 (q, *J* = 1.2 Hz, 1H), 4.16 (br s, 1H), 2.53 (d, *J* = 1.1 Hz, 3H), 2.44 – 2.36 (m, 2H), 2.27 – 2.20 (m, 2H), 2.06 – 1.98 (m, 1H), 1.72 – 1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 154.7, 146.2, 142.4, 135.9, 130.4, 129.4, 129.1, 128.7, 128.4, 128.3, 126.4, 126.3, 77.9, 34.4, 18.6, 13.6; HRMS (EI, M^+) Calcd for $C_{22}H_{22}O_2$ 318.1620; Found m/z 318.1621



The standard procedure (see above) was used to yield **17k** (25%) as a yellow oil after flash chromatography (silica gel, pentane:EtOAc 8:1):

R_f 0.21 (hexanes:EtOAc 8:1); IR (neat) 3484, 3081, 2970, 1640 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (bs, 1H), 7.33-7.24 (m, 5H), 7.22-7.16 (m, 3H), 7.10-7.07 (m, 2H),

7.04 (s, 1H), 2.62 (s, 1H), 1.98-1.92 (m, 4H), 1.84 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.54 (s, 3H), 1.07 (app t, *J* = 7.7 Hz, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.5, 146.2, 143.2, 137.7, 136.5, 135.9, 129.4, 129.3, 128.5 (2x), 128.4, 128.2, 127.7, 75.4, 34.8, 27.2, 12.5, 8.3; HRMS (EI, M^+) Calcd for $C_{22}H_{24}O_2$ 320.1776; Found m/z 320.1776.

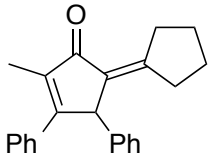


The standard procedure (see above) was used to yield **17l** (39%) as a yellow oil after flash chromatography (silica gel, pentane:EtOAc 8:1):

R_f 0.39 (hexanes:EtOAc 8:1); IR (neat) 3479, 3081, 2972, 1640 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (bs, 1H), 7.30-7.24 (m, 5H), 7.20-7.14 (m, 3H), 7.07-7.04 (m, 2H), 7.00 (s, 1H), 2.56 (bs, 1H), 2.21 (app sept, *J* = 7.0 Hz, 1H), 1.92 (d, *J* = 1.4 Hz, 3H), 1.47 (s, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 146.3, 143.2, 137.8, 136.7, 135.9, 130.0, 129.7, 129.3, 128.5, 128.4, 128.2, 127.7, 77.7, 36.2, 23.7, 17.6, 17.2, 12.6 ; HMRS (EI, M^+) Calcd for $C_{23}H_{26}O_2$ 334.1933; Found m/z 334.1929.

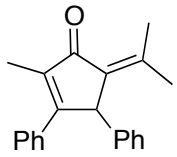
Standard Procedure for Conversion of Dienones 17a-g to Alkylidene Cyclopentenones 19a-g:

A solution of the appropriate dienone (50 mg, 0.15–0.185 mmol) in DCM (3 mL) was flushed with argon and cooled to 0 °C. A solution of $AlMe_2Cl$ (1.0 M in hexanes, 2.2 equiv) was added dropwise, causing the color of the solution to turn a dark orange. After 30 min, the cooling bath was removed and the reaction was left to stir for 16 h. Upon consumption of starting material (according to TLC analysis), 1 N HCl (1 mL) was added slowly to quench the reaction. The mixture was then extracted with DCM (5 mL) and washed sequentially with water (5 mL) and brine (5 mL) before being dried over $MgSO_4$. The mixture was then filtered, concentrated by rotary evaporation, and purified by flash chromatography (silica gel) to yield the desired alkylidene cyclopentenone.



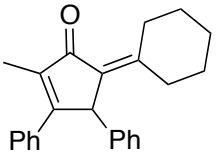
The standard procedure was used to yield **19a** (51%) as a yellow semisolid after purification by flash chromatography (silica gel, hexanes:EtOAc, 10:1):

R_f 0.38 (hexanes:EtOAc 8:1); IR 3060, 2929, 1682, 1648 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.25-7.21 (m, 3H), 7.17-7.13 (m, 2H), 7.10-7.0.5 (m, 3H), 4.69 (br s, 1H), 3.02-2.92 (m, 2H), 2.32-2.26 (m, 2H), 2.00 (d, *J* = 1.9 Hz, 3H), 1.83-1.72 (m, 2H), 1.62-1.57 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.1, 162.3, 158.7, 140.2, 139.4, 135.3, 131.4, 128.5, 128.4 (2x), 128.2 (2x), 126.5, 52.5, 33.3, 32.8, 26.5, 25.3, 10.0; HRMS (EI, M^+) Calcd for $C_{23}H_{22}O$ 314.1671; Found m/z 314.1670.



The standard procedure was used to yield **19b** (36%) as a white solid after purification by flash chromatography (silica gel, hexanes:EtOAc 10:1):

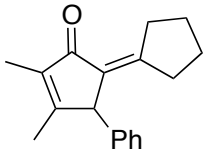
R_f 0.34 (hexanes:EtOAc 8:1); mp 129-132 °C; IR (cast film) 3026, 2921, 1678, 1649 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 3H), 7.19 – 7.12 (m, 4H), 7.09 – 7.02 (m, 3H), 4.76 (s, 1H), 2.37 (s, 3H), 1.96 (d, *J* = 1.8 Hz, 3H), 1.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 162.4, 147.3, 140.8, 139.4, 135.2, 134.4, 128.5, 128.4, 128.2, 128.2, 128.1, 126.4, 52.5, 24.0, 20.6, 9.9; HRMS (EI, M^+) Calcd for $C_{21}H_{20}O$ 288.1514; Found m/z 288.1508.



The standard procedure was used to yield **19c** (62%) as a yellow oil after purification by flash chromatography (silica gel, hexanes:EtOAc 8:1):

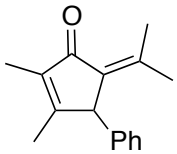
R_f 0.34 (hexanes:EtOAc 8:1); IR (neat) 3025, 2927, 1672, 1644 cm^{-1}; ^1H NMR; (500 MHz, $CDCl_3$) δ 7.34-7.28 (m, 3H), 7.23–7.21 (m, 2H), 7.19–7.25 (m, 2H), 7.11–7.08 (m, 3H), 4.85 (q, *J* = 2.1 Hz, 1H), 3.27 (ddd, *J* = 12.9, 7.6, 4.2 Hz, 1H), 3.09 (ddd, *J* = 12.7, 8.1, 4.1 Hz, 1H), 2.15 (ddd, *J* = 13.3, 8.3, 4.2 Hz, 1H), 2.09–2.03 (m, 1H), 1.99 (d, *J* = 2.0 Hz, 3H), 1.74–1.67 (m, 1H), 1.65–1.60 (m, 1H), 1.58–1.44 (m, 3H), 1.21-1.13

(m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 162.4, 155.0, 144.5, 139.7, 135.3, 131.5, 128.5, 128.3, 128.2 (2x), 128.1, 126.3, 52.0, 33.8, 29.1, 28.3, 27.4, 26.3, 9.9; HRMS (EI, M^+) Calcd for $C_{24}H_{24}O$ 328.1827; Found m/z 328.1821.



The standard procedure was used to yield **19d** (46%) as a white solid after purification by flash chromatography (silica gel, hexanes:EtOAc 10:1):

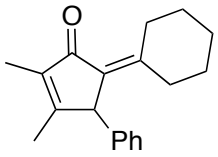
R_f 0.32 (hexanes:EtOAc 8:1); mp 148-150 °C; IR (cast film) 3025, 2923, 1688, 1637 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H), 7.22-7.18 (m, 1H), 7.08-7.06 (m, 2H), 4.06 (s, 1H), 2.98-2.84 (m, 2H), 2.17 (app dtd, *J* = 18.3, 7.0, 2.3 Hz, 1H), 1.81 (dq, *J* = 1.9, 0.9 Hz, 3H), 1.76 (app pent, *J* = 0.9 Hz, 3H), 1.72-1.67 (m, 1H), 1.62-1.54 (m, 2H), 1.54-1.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 163.2, 157.0, 140.5, 138.4, 131.0, 128.6, 128.2, 126.7, 54.1, 33.2, 32.4, 26.5, 25.3, 14.4, 8.4; HRMS (EI, M^+) Calcd for $C_{18}H_{20}O$ 252.1514; Found m/z 252.13.



The standard procedure was used to yield **19e** (43%) as a white solid after purification by flash chromatography (silica gel, hexanes:EtOAc 10:1):

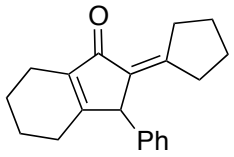
R_f 0.32 (hexanes:EtOAc 8:1); mp 164-168 °C; IR (cast film) 3023, 2921, 1672, 1622 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.25-7.21 (m, 1H), 7.12-7.10 (m,

2H), 4.17 (s, 1H), 2.34 (s, 3H), 1.82 (dq, *J* = 1.8, 0.9 Hz, 3H) 1.78 (app pent, *J* = 0.9 Hz, 3H), 1.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 162.9, 145.7, 141.3, 138.5, 134.1, 128.6, 128.0, 126.6, 54.0, 23.9, 20.3, 14.4, 8.4; HRMS (EI, M^+) Calcd for $C_{16}H_{18}O$ 226.1258; Found m/z 226.1358.



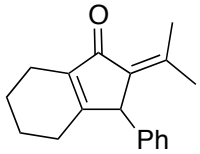
The standard procedure was used to yield **19f** (61%) as a white solid after purification by flash chromatography (silica gel, hexanes:EtOAc 10:1):

R_f 0.62 (hexanes:EtOAc 8:1); mp 116-118 °C; IR (cast film) 3018, 2924, 1669, 1623 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H), 7.21-7.17 (m, 1H), 7.11-7.08 (m, 2H), 4.19 (br s, 1H), 3.16 (ddd, *J* = 13.1, 7.9, 4.2 Hz, 1H), 3.02 (ddd, *J* = 12.5, 8.1, 4.6 Hz, 1H), 2.01 (ddd, *J* = 13.2, 8.7, 4.4 Hz, 1H), 1.92 (ddd, *J* = 13.3, 7.7, 4.4 Hz, 1H), 1.78 (dq, *J* = 1.8, 0.9 Hz, 3H) 1.75 (app pent, *J* = 0.9 Hz, 3H), 1.65-1.55 (m, 2H), 1.50-1.42 (m, 2H), 1.42-1.34 (m, 1H), 1.14 (app qd, *J* = 8.1, 3.9 Hz, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 162.9, 153.5, 141.8, 138.8, 131.1, 128.5, 128.0, 126.5, 53.5, 33.7, 28.8, 28.3, 27.4, 26.3, 14.5, 8.4; HRMS (EI, M^+) Calcd for $C_{19}H_{22}O$ 266.1670; Found m/z 266.1672.



The standard procedure was used to yield **19g** (34%) as a yellow semi-solid after purification by flash chromatography (silica gel, hexanes:EtOAc 12:1):

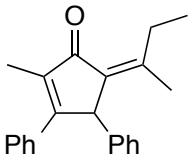
R_f 0.41 (hexanes:EtOAc 8:1); 3060, 2935, 1714, 1629; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.26 (m, 1H), 7.23-7.19 (m, 2H), 7.09-7.05 (m, 2H), 4.10 (bs, 1H), 2.33-2.28 (m, 2H), 2.22-2.12 (m, 2H), 1.98-1.92 (m, 2H), 1.82-1.78 (m, 2H), 1.74-1.62 (m, 6H), 1.56-1.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 167.0, 157.0, 140.7, 140.5, 131.4, 128.6, 128.1, 126.6, 53.0, 33.2, 32.4, 26.6, 25.4, 25.3, 22.4, 21.8, 20.3; HRMS (EI, M^+) Calcd for $C_{20}H_{22}O$ 278.1671; Found m/z 178.1671.



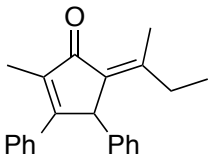
The standard procedure was used to yield **19h** (58%) as a white solid after purification by flash chromatography (silica gel, hexanes:EtOAc 12:1):

R_f 0.39 (hexanes:EtOAc 8:1); mp 136-137 °C; IR (cast film) 3025, 2922, 1674, 1627 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.26 (m, 2H), 7.22–7.18 (m, 1H), 7.09–7.06 (m, 2H), 4.18 (s, 1H), 2.32 (s, 3H), 2.28-2.20 (m, 2H), 2.16–2.09 (m, 1H), 1.92–1.84 (m, 1H), 1.68–1.62 (m, 2H), 1.60–1.57 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.0, 166.6, 145.8, 141.2, 140.7, 134.4, 128.7, 127.8, 126.6, 52.9, 25.4, 24.0, 22.3, 21.8, 20.2, 20.2; HRMS (EI, M^+) Calcd for $C_{18}H_{20}O$ 252.1514; Found m/z 252.1517.

The standard procedure was used to yield a mixture of **(*Z*)-19k** and **(*E*)-19k** (2.3:1, 64%) as a yellow oil after flash chromatography (silica gel, pentane:EtOAc 30:1). (***Z*)-19k** and (***E*)-19k** were then separated by preparatory TLC (silica gel; two successive elutions in 30:1 hexanes:EtOAc and then 15:1 hexanes:EtOAc) for analytical purposes.



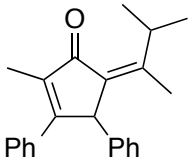
(*Z*)-19k: R_f 0.48 (hexanes:EtOAc 20:1); IR (cast film) 3026, 2962, 1677, 1621 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.31-7.24 (m, 3H), 7.18-7.12 (m, 4H), 7.09-7.02 (m, 3H), 4.73 (q, *J* = 2.0 Hz, 1H), 2.91 (dq, *J* = 12.0, 7.5 Hz, 1H), 2.87 (dq, *J* = 12.0, 7.5 Hz, 1H), 1.95 (d, *J* = 1.9 Hz, 3H), 1.66 (s, 3H), 1.07 (app t, *J* = 7.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.0, 162.5, 153.3, 140.9, 139.3, 135.3, 133.9, 128.5, 128.4, 128.2 (2x), 128.1, 126.4, 52.5, 26.7, 21.4, 12.6, 9.8; HRMS (EI, M^+) Calcd for $C_{22}H_{22}O$ 302.1671; Found m/z 302.1670.



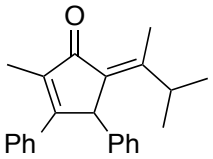
(*E*)-19k: R_f 0.46 (hexanes:EtOAc 20:1); IR (cast film) 3026, 2972, 1677, 1621 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.24 (m, 3H), 7.20-7.17 (m, 2H), 7.16-7.12 (m, 2H), 7.09-7.04 (m, 2H), 4.79 (bs, 1H), 2.33 (d, *J* = 0.8 Hz, 3H), 2.06 (m, 2H), 1.97 (d, *J* = 1.9 Hz, 3H), 0.63 (app t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 162.2, 152.1,

141.3, 139.5, 135.2, 133.8, 128.5, 128.4, 128.2 (2x), 128.1, 126.4, 52.1, 30.5, 17.8, 10.7, 9.9; HRMS (EI, M^+) Calcd for $C_{22}H_{22}O$ 302.1671; Found m/z 302.1670.

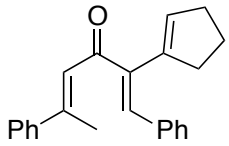
The standard procedure was used to yield a mixture of **(*Z*)-19l** and **(*E*)-19l** (3.6:1 ratio, measured by integration of the furthest upfield Me doublets of the *i*-Pr groups; 60%) as a yellow oil after flash chromatography (silica gel, pentane:EtOAc 30:1). **(*Z*)-19l** and **(*E*)-19l** were then separated by preparatory TLC (silica gel; two successive elutions in 30:1 hexanes:EtOAc and then 15:1 hexanes:EtOAc) for analytical purposes.



(*Z*)-19l: R_f 0.52 (hexanes:EtOAc 20:1); IR (cast film) 3026, 2960, 1673, 1617 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.24 (m, 3H), 7.18-7.12 (m, 4H), 7.09-7.02 (m, 3H), 4.72 (q, *J* = 1.9 Hz, 1H), 4.67 (app sept, *J* = 6.8 Hz, 1H), 1.94 (d, *J* = 2.1 Hz, 3H), 1.56 (s, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ197.1, 162.5, 157.3, 141.0, 139.4, 135.3, 133.6, 128.5, 128.4 (2x), 128.2, 128.1, 126.4, 52.7, 27.9, 20.4, 15.4, 9.8; HRMS (EI, M^+) Calcd for $C_{23}H_{24}O$ 316.1827; Found m/z 316.1829.



(*E*)-19l: R_f 0.49 (hexanes:EtOAc 20:1); IR (cast film) 3026, 2962, 1675, 1618 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.28 (m, 3H), 7.24-7.22 (m, 2H), 7.18-7.15 (m, 2H), 7.12-7.06 (m, 3H), 4.85 (bs, 1H), 2.75 (app sept, *J* = 6.7 Hz, 1H), 2.28 (d, *J* = 0.9 Hz, 3H), 2.00 (d, *J* = 1.8 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.41 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 162.2, 155.4, 141.4, 139.5, 135.2, 132.8, 128.5, 128.3, 128.2 (2x), 128.1, 126.4, 52.0, 33.5, 19.8, 18.4, 12.3, 9.9; HRMS (EI, M^+) Calcd for $C_{23}H_{24}O$ 316.1827; Found m/z 316.1829.



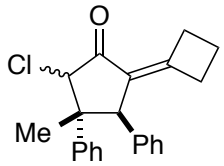
Dienone **27i** (20 mg, 0.060 mmol) was dissolved in DCM (2 mL) and cooled to 0 °C. BF_3•OEt_2 (9 μL, 0.07 mmol, 1.2 equiv) was added and the solution turned orange in color. The reaction mixture was stirred for 30 min at which point saturated NH_4Cl solution (2 mL) was added. The mixture was extracted with DCM (2 x 5 mL), the organic layers were combined and washed with brine (5 mL), dried over $MgSO_4$, and concentrated by rotary evaporation to yield a yellow oil. The product was then purified by flash chromatography (hexanes:EtOAc 20:1) to yield **6i** (12mg, 65%) as a yellow oil:

R_f 0.44 (hexanes:EtOAc 8:1); IR (cast film) 3056, 2951, 1666, 1592 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.24 (m, 9H), 7.21-7.18 (m, 1H), 6.49 (s, 1H), 6.42 (q, *J* = 1.3

Hz, 1H), 5.85 (m, 1H), 2.68-2.64 (m, 2H), 2.61 (d, *J* = 1.2 Hz, 3H), 2.56-2.52 (m, 2H), 2.04-1.97 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 154.9, 142.4, 142.3, 140.6, 136.2, 131.8, 129.1, 128.8, 128.4, 128.3, 127.7, 126.6, 126.5, 126.1, 33.8, 32.5, 22.7, 18.4; HRMS (EI, M^+) Calcd for $C_{23}H_{22}O$ 314.1671; Found m/z 314.1671.

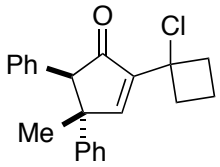
Nazarov reaction of dienone 17j—formation of alkylidenecyclobutane 28j and chlorocyclobutane 29j:

Dienone **17j** (30 mg, 0.094 mmol) was dissolved in DCM (3 mL) and cooled to -78 °C. $TiCl_4$ (200 μL, 1.0 M solution in toluene, 2.1 equiv) was added dropwise, resulting in a red-brown colour. The mixture was stirred at this temperature for 30 minutes before being warmed to room temperature where it remained for 45 minutes. The reaction mixture was then quenched with water (5 mL), extracted with DCM (2 x 5 mL), washed with water (2 x 5 mL) and brine (5 mL), dried over $MgSO_4$, and concentrated by rotarty evaporation. The products were then purified by flash chromatography (hexanes:EtOAc 15:1) to yield 10 mg **28j** (31%) and 10 mg **29j** (31%), both as yellow oils.

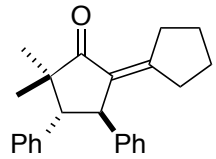


28j: R_f 0.73 (hexanes:EtOAc 8:1); IR (cast film) 3060, 2959, 1728, 1661 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.28 (m, 4H), 7.22-7.18 (m, 5H), 6.82 (br s, 1H), 5.07 (s, 1H), 4.22 (app quintet, *J* = 3.0 Hz, 1H), 3.41-3.32 (m, 1H), 3.26-3.18 (m, 1H), 2.42-

2.34 (m, 1H), 2.14-2.00 (m, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.9, 164.9, 141.9, 135.8, 130.0, 128.4, 127.6, 127.2, 127.0, 126.4, 125.4, 72.1, 56.3, 51.1, 35.0, 33.4, 18.5, 16.6; HRMS (EI, M^+) Calcd for $C_{22}H_{21}{}^{35}ClO$ 336.1281; Found 336.1281.



29j: R_f 0.82 (hexanes:EtOAc 8:1); IR (cast film) 3059, 2955, 1713, 1600 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.41-7.36 (m, 2H), 7.33-7.28 (m, 4H), 7.24-7.21 (m, 2H), 6.96-6.92 (m, 2H), 3.86 (s, 1H), 3.02-2.95 (m, 2H), 2.75-2.68 (m, 2H), 2.37 (dddd, *J* = 18.0, 9.2, 9.2, 6.7, 6.7 Hz, 1H), 1.97 (ddddd, *J* = 17.3, 8.7, 8.7, 6.1, 6.1 Hz, 1H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 163.5, 145.8, 145.5, 136.2, 130.1, 128.9, 128.4, 127.3, 127.0, 125.9 67.8, 64.9, 49.4, 38.0, 23.5, 16.6; HRMS (EI, M^+) Calcd for $C_{22}H_{21}{}^{35}ClO$ 336.1281; Found m/z 336.1280.



Dienone **17a** (50 mg, 0.15 mmol) was dissolved in DCM (5 mL) and cooled to 0 °C. $AlMe_3$ (2.0M in toluene, 3.2 equiv, 0.48 mmol, 240 μL) is added dropwise. The mixture is stirred at this temperature for 30 minutes and the cooling bath is removed and the reaction is left to stir for a further 16 hours. The reaction was then quenched with NH_4Cl solution (5 mL), extracted with DCM (2 x 10 mL), washed with H_2O (10 mL), brine (10 mL), dried over $MgSO_4$, and concentrated by rotary

evaporation. The crude oil was then purified by flash chromatography (silica gel, hexanes:EtOAc 15:1) to yield **33a** (55%).

R_f 0.43 (hexanes:EtOAc 9:1); IR (cast film) 3028, 2961, 1704, 1630 cm^{-1}; 1H (400 MHz, $CDCl_3$) δ 7.10-7.27 (m, 6H), 6.89-6.86 (m, 2H), 6.66-6.62 (m, 2H), 4.48 (d, *J* = 8.6 Hz, 1H), 3.40 (d, *J* = 8.8 Hz, 1H), 3.18 – 3.08 (m, 1H), 3.04 – 2.94 (m, 2H), 2.06 – 1.98 (m, 1H), 1.92-1.70 (m, 3H), 1.68 – 1.50 (m, 2H), 1.21 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.6, 164.6, 140.4, 138.4, 130.6, 129.7, 128.9, 127.5, 127.3, 126.3, 126.0, 58.5, 50.2, 50.1, 34.9, 33.7, 26.5, 26.4, 25.4, 22.0; HRMS (EI, M^+) Calcd for $C_{24}H_{26}O$ 330.1984; Found m/z 330.1983.

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Chapter 1: The Nazarov Reaction

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Chapter 3: Domino Nazarov Cyclization/Baeyer-Villiger Oxidation

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Chapter 4: Access to Alkylidene Cyclopentenones via a Nazarov Cyclization/Dehydration Sequence

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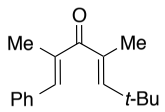
Appendix I: Selected NMR Spectra

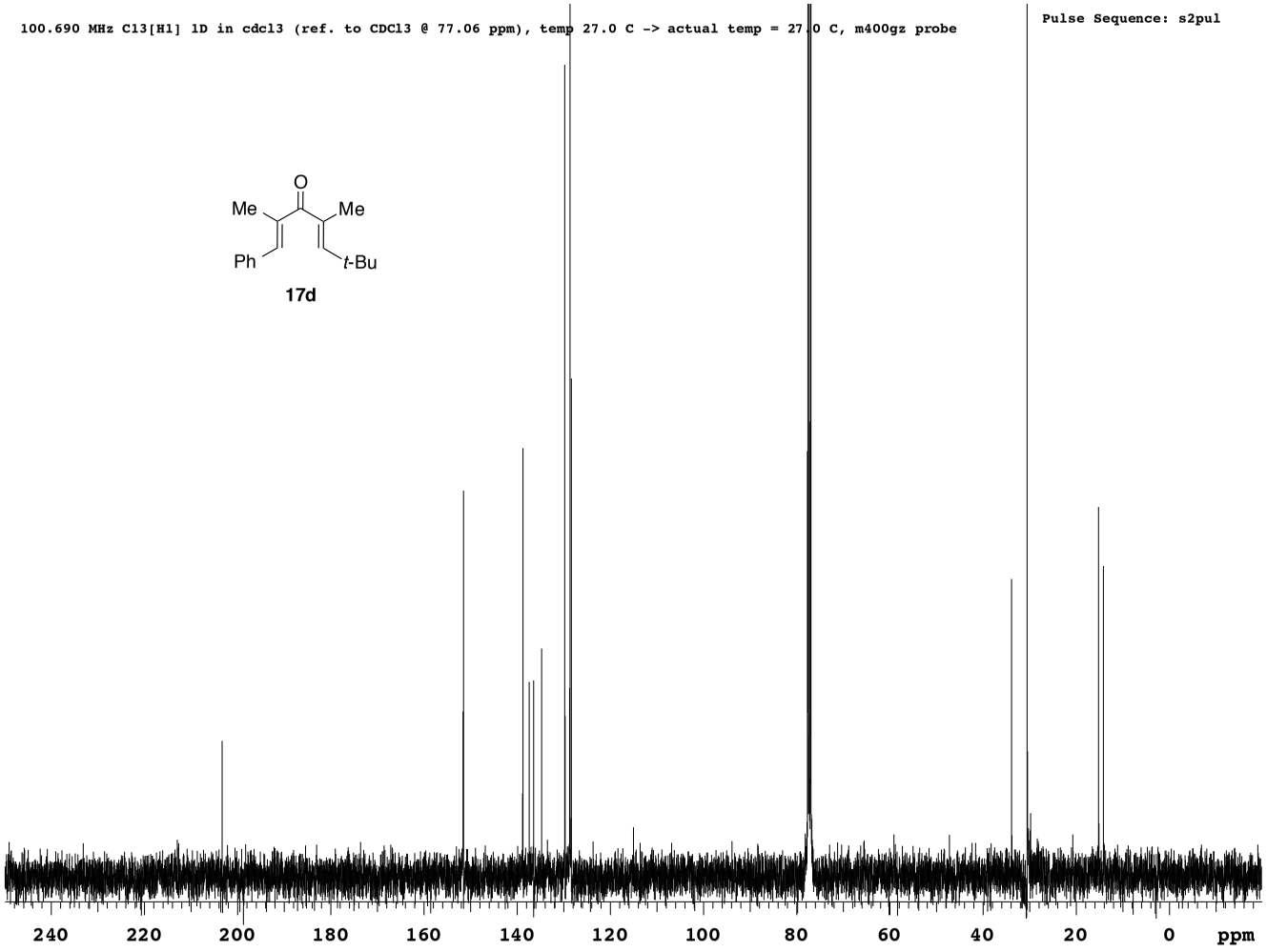
(Chapter 2)

400.393 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

Pulse Sequence: s2pul



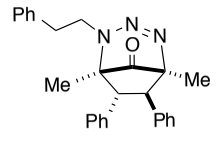
17d


100.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Pulse Sequence: s2pul
O
Me
Me
Ph
t-Bu
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

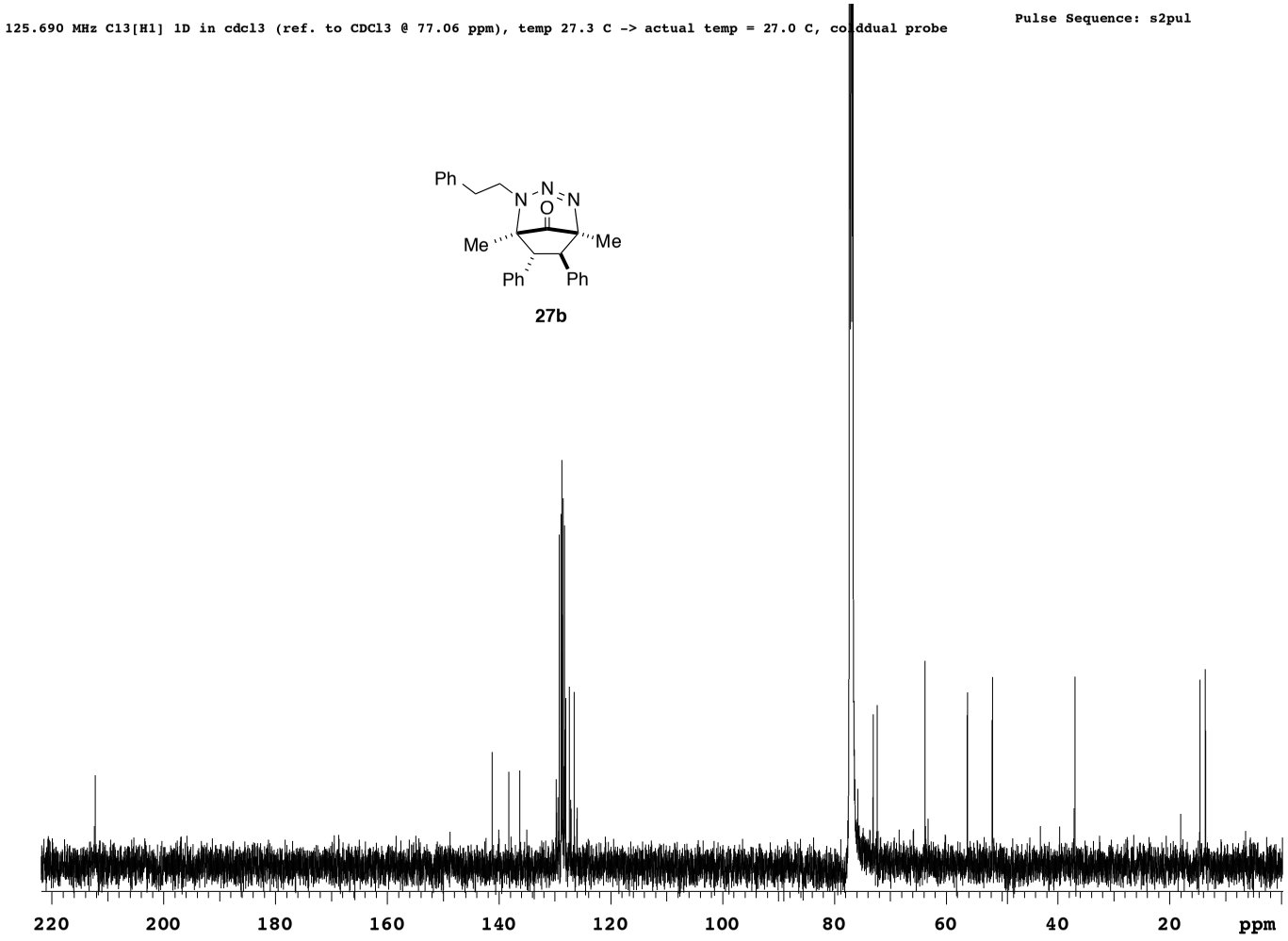
17d

499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.3 C -> actual temp = 27.0 C, colddual probe

Pulse Sequence: s2pul

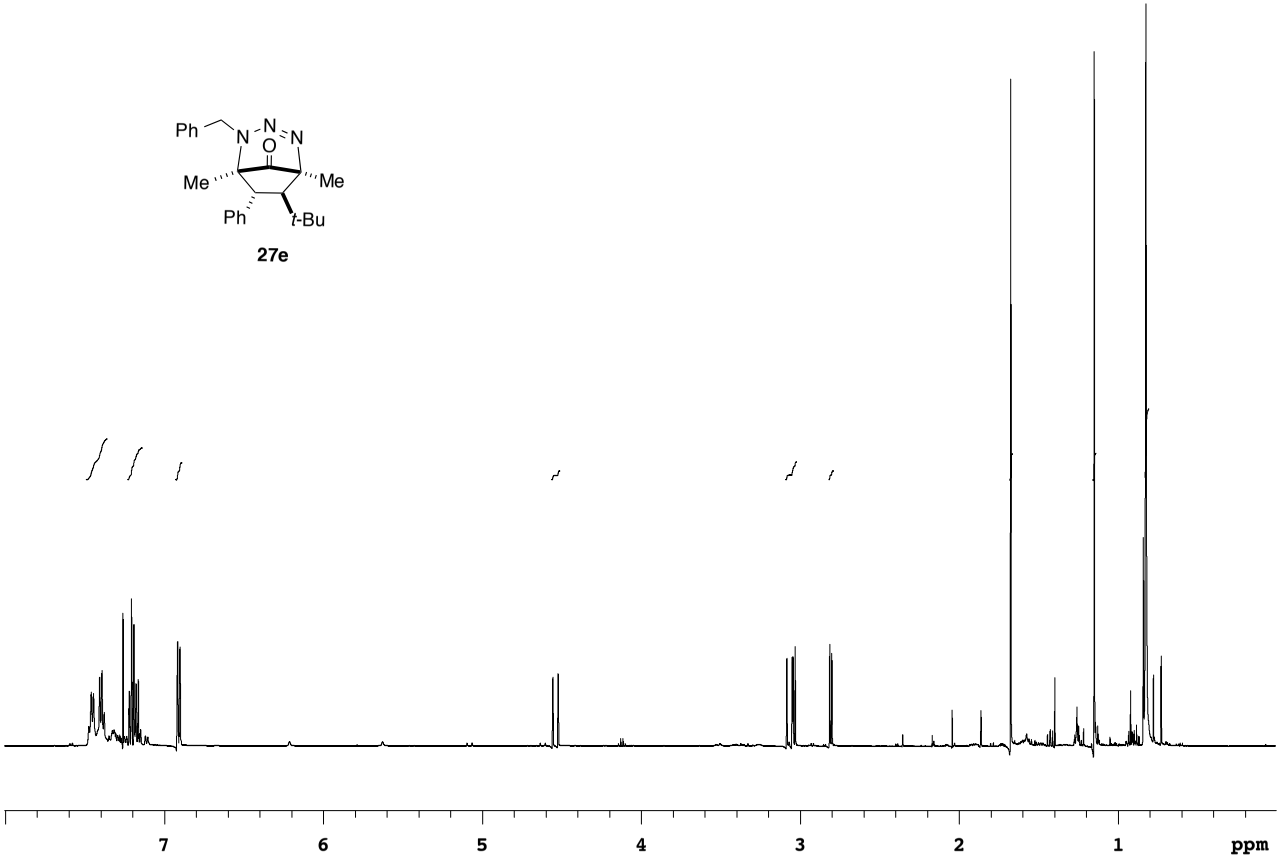


27b

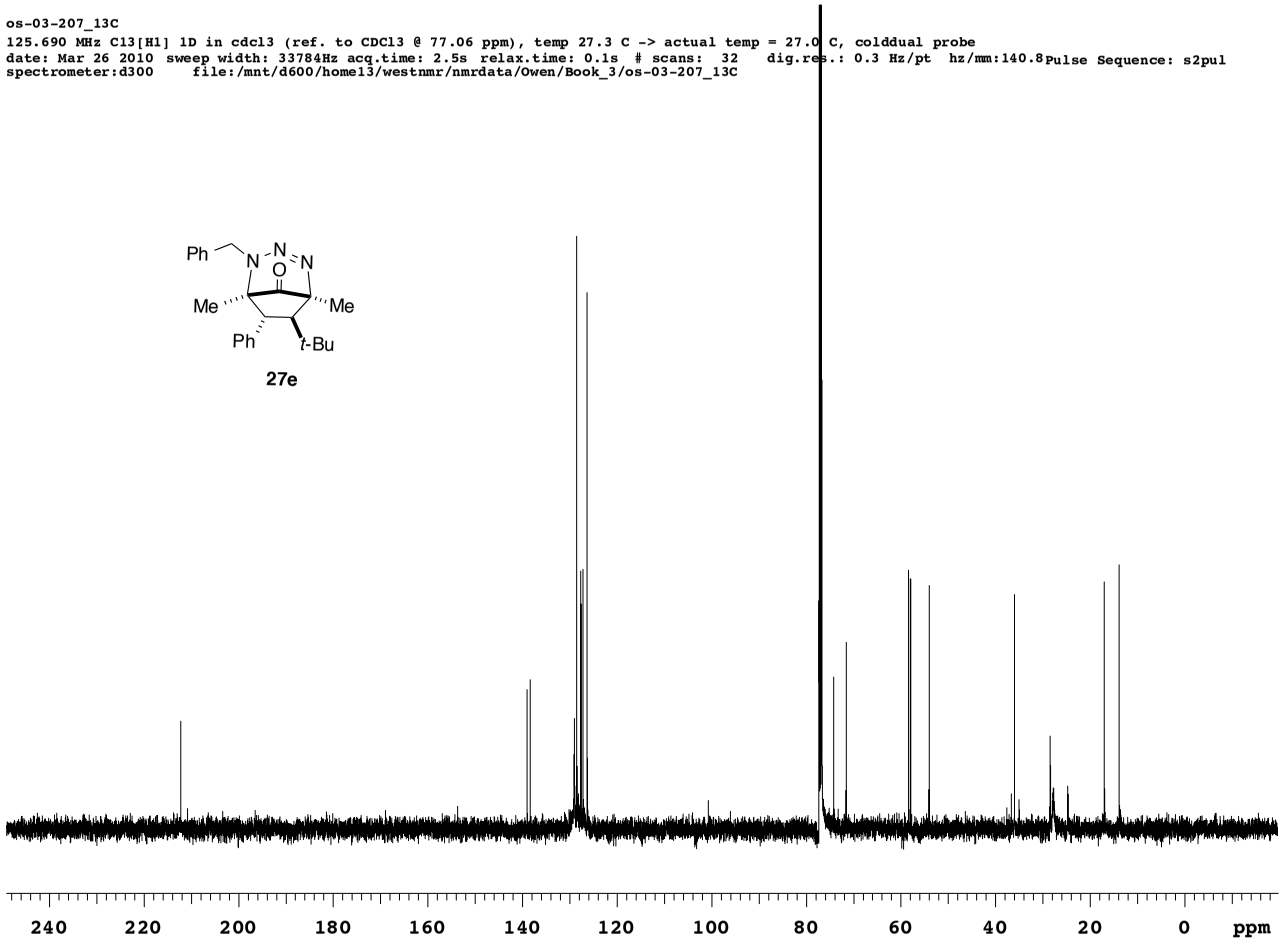

125.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.3 C -> actual temp = 27.0 C, co.ddual probe
Pulse Sequence: s2pul
Ph
N
N
N
O
Me
Me
Ph
Ph
220
200
180
160
140
120
100
80
60
40
20
ppm

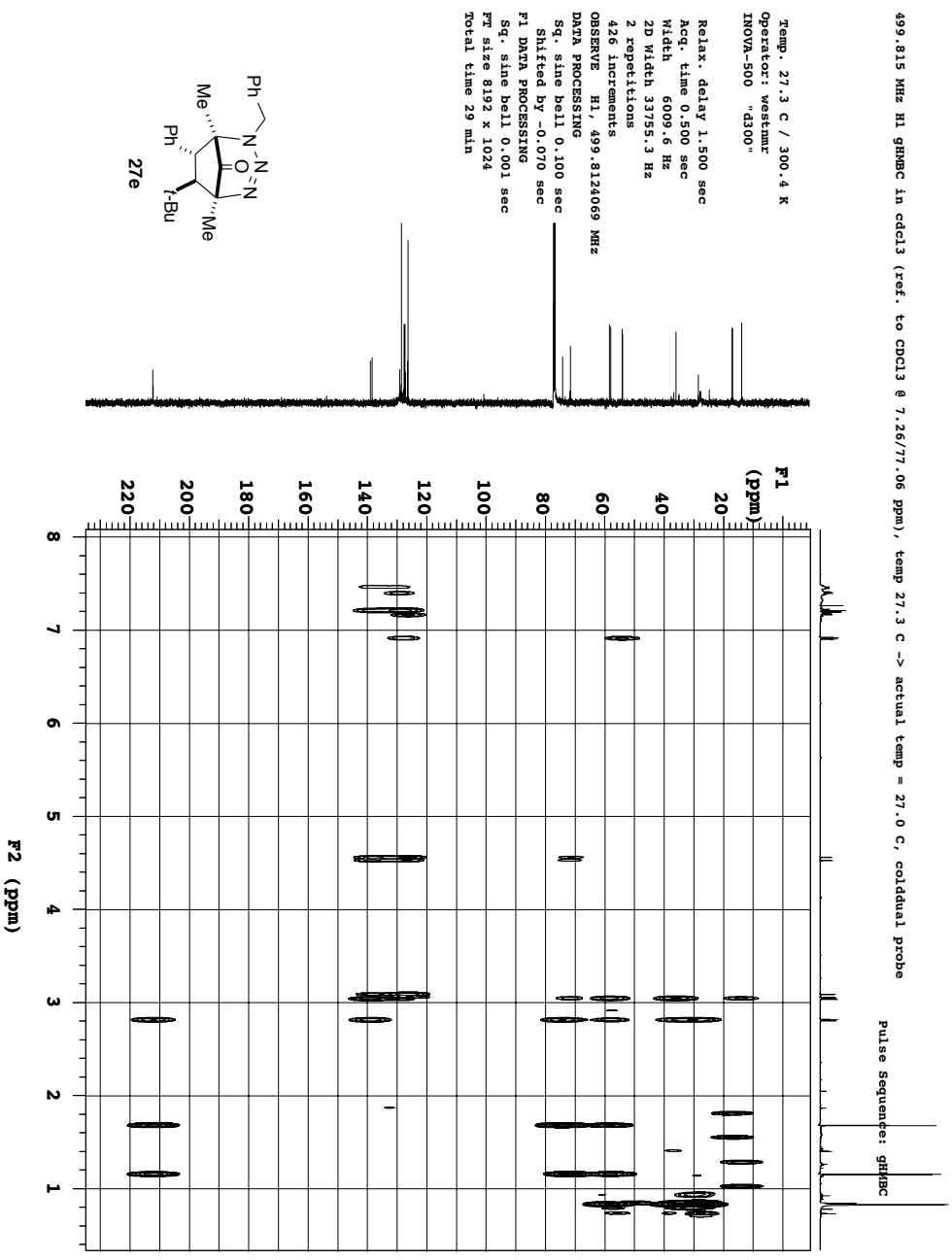
27b

os-03-207
499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.3 C -> actual temp = 27.0 C, colddual probe
date: Mar 26 2010 sweep width: 6010Hz acq.time: 5.0s relax.time: 0.1s # scans: 12 dig.res.: 0.1 Hz/pt hz/mm:16.7 Pulse Sequence: s2pul
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_3/os-03-207



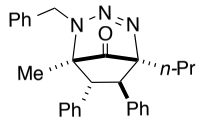
27e


os-03-207_13C
125.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.3 C -> actual temp = 27.0 C, colddual probe
date: Mar 26 2010 sweep width: 33784Hz acq.time: 2.5s relax.time: 0.1s # scans: 32 dig.res.: 0.3 Hz/pt hz/mm:140.8 Pulse Sequence: s2pul
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_3/os-03-207_13C
Ph
N
N
O
N
Me
Me
Ph
t-Bu
27e
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


499.815 MHz H1 gHMBC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm), temp 27.3 C -> actual temp = 27.0 C, coldDual probe
Pulse Sequence: gHMBC
Temp. 27.3 C / 300.4 K
Operator: westmnr
INOVA-500 "d300"
Relax. delay 1.500 sec
Acq. time 0.500 sec
Width 6009.6 Hz
2D Width 33755.3 Hz
2 repetitions
426 increments
OBSERVE H1, 499.8124069 MHz
DATA PROCESSING
Sq. sine bell 0.100 sec
Shifted by -0.070 sec
F1 DATA PROCESSING
Sq. sine bell 0.001 sec
FT size 8192 x 1024
Total time 29 min
F1 (ppm)
F2 (ppm)
Ph
Me
Ph
t-Bu
Me
27e

499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

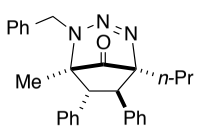
Pulse Sequence: s2pul



27g

125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

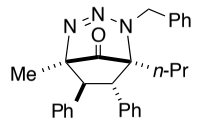
Pulse Sequence: s2pul



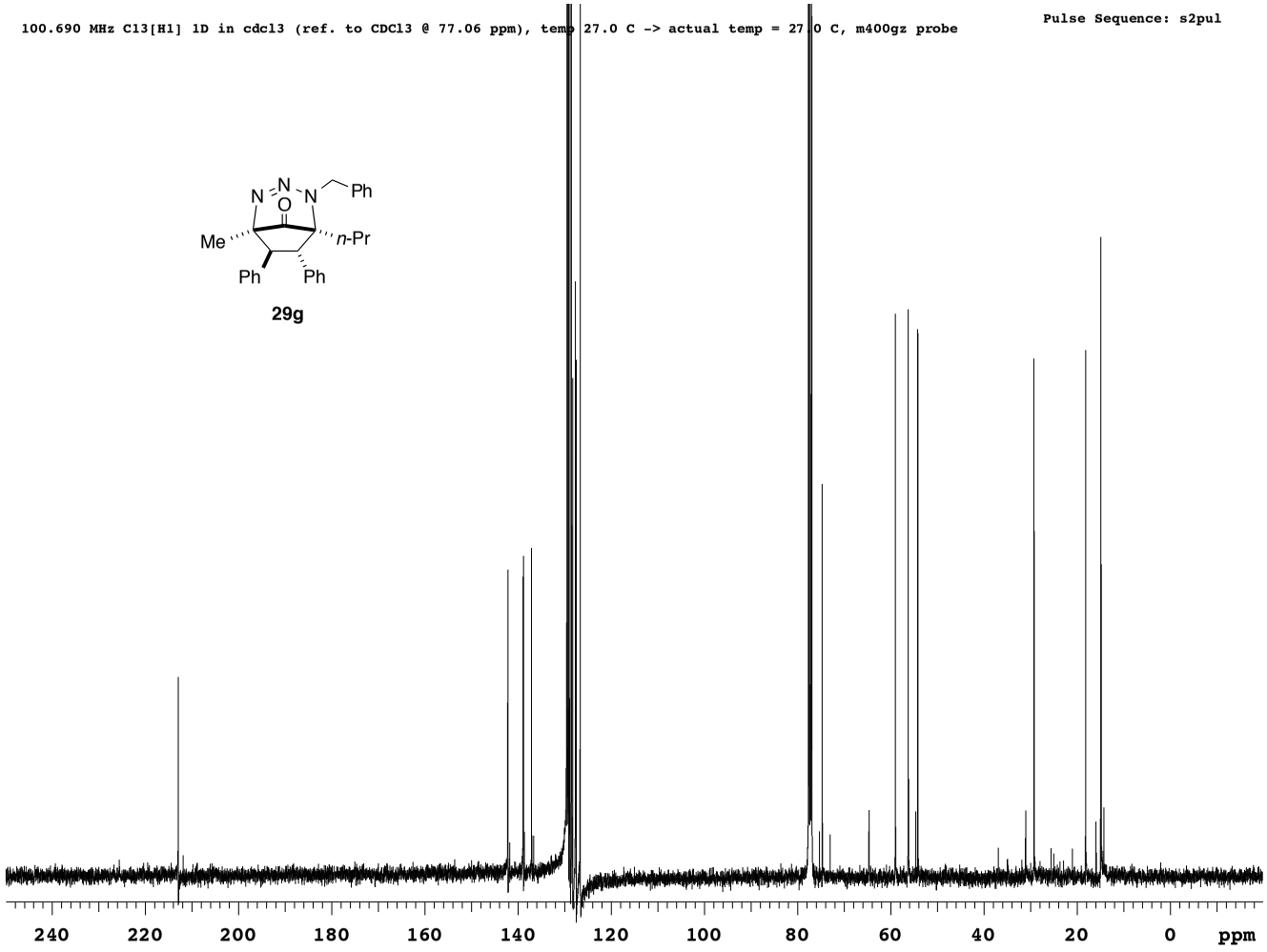
27g

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul



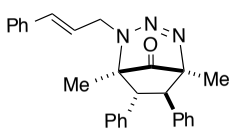
29g


100.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Pulse Sequence: s2pul
N
N
O
N
Ph
Me
n-Pr
Ph
Ph
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

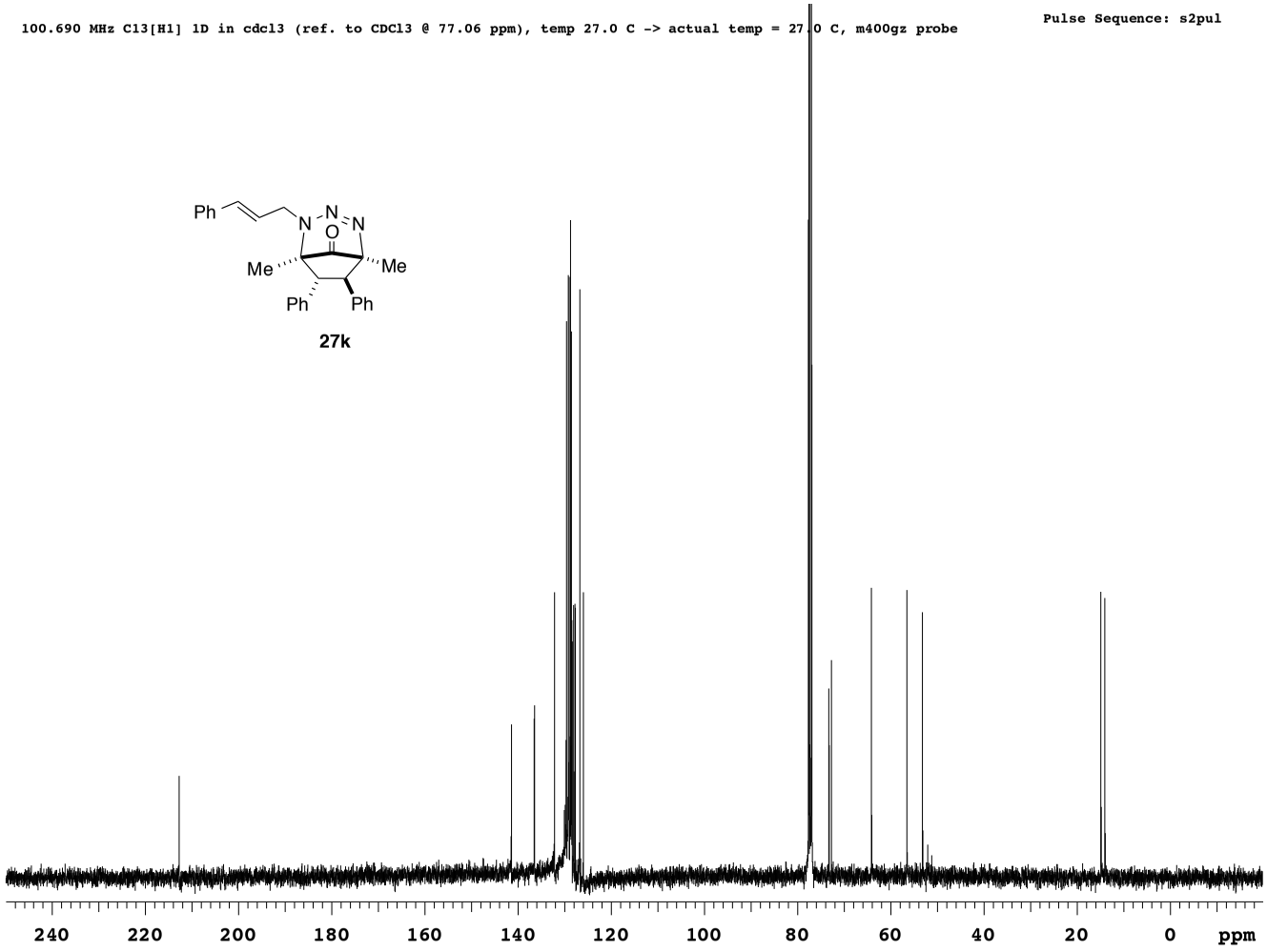
29g

400.393 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

Pulse Sequence: s2pul



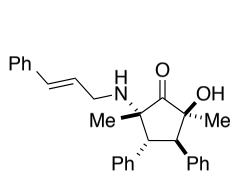
27k


100.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Pulse Sequence: s2pul
Ph
N
N
N
O
Me
Me
Ph
Ph
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

27k

400.393 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

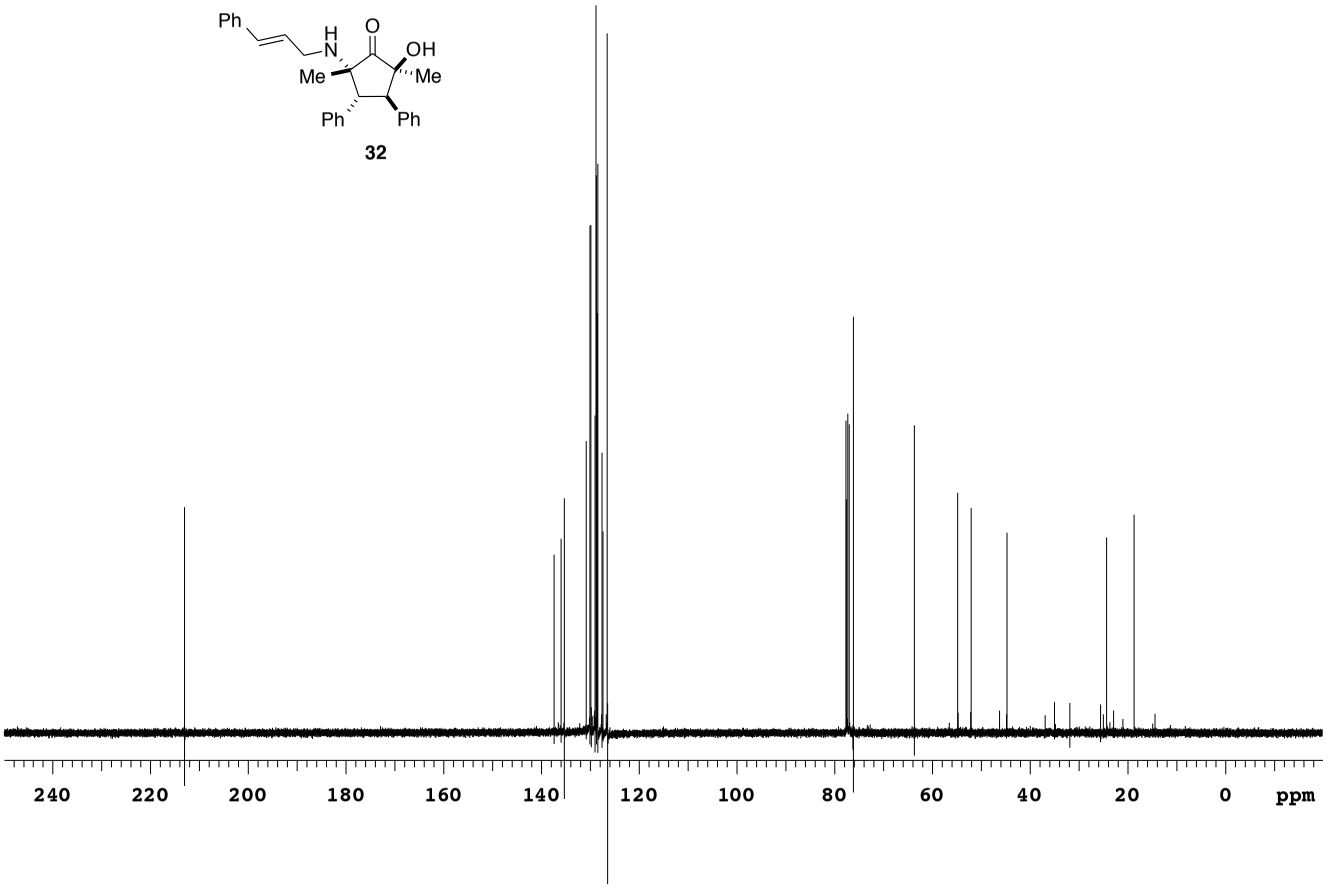
Pulse Sequence: s2pul



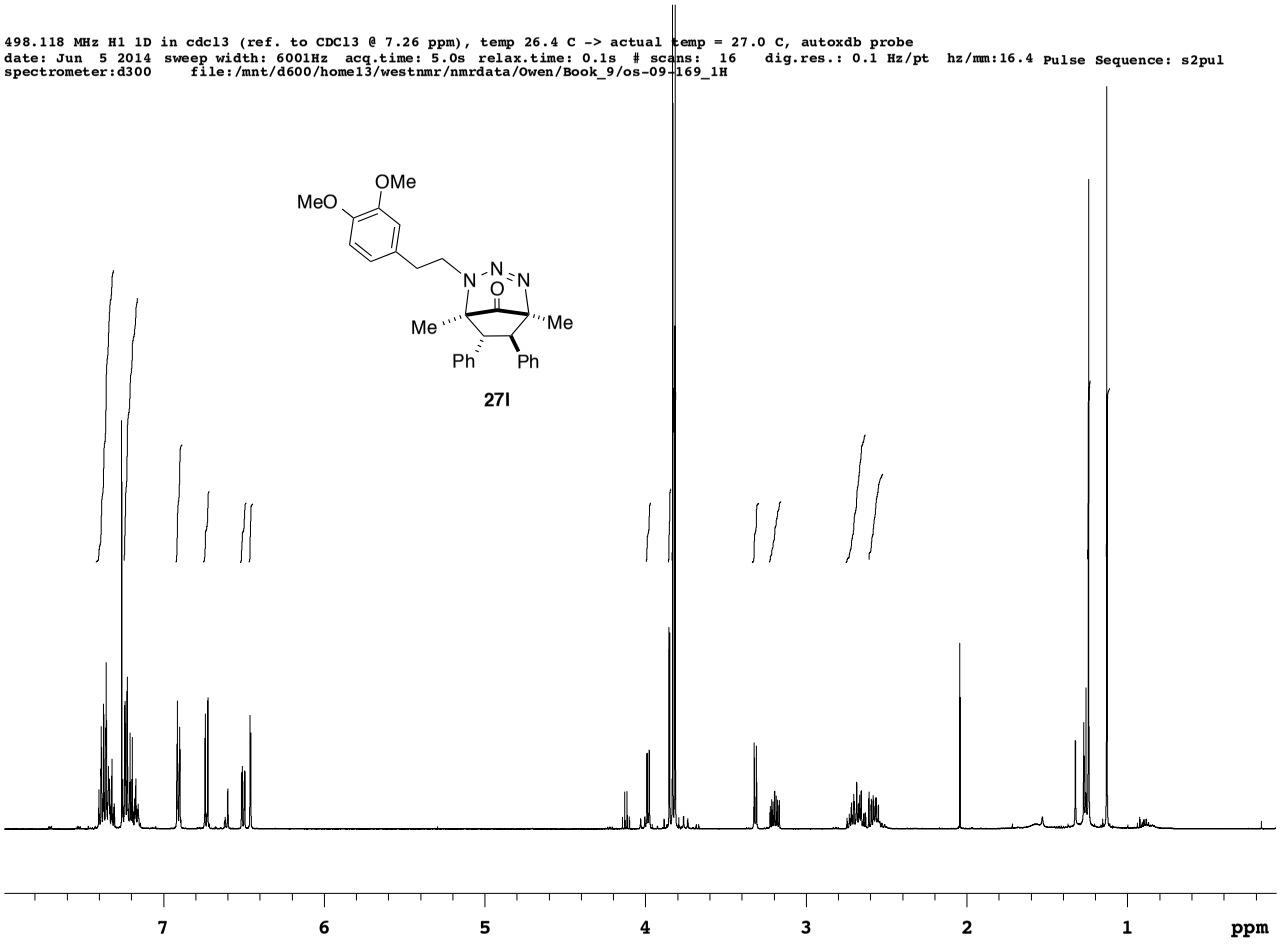
32

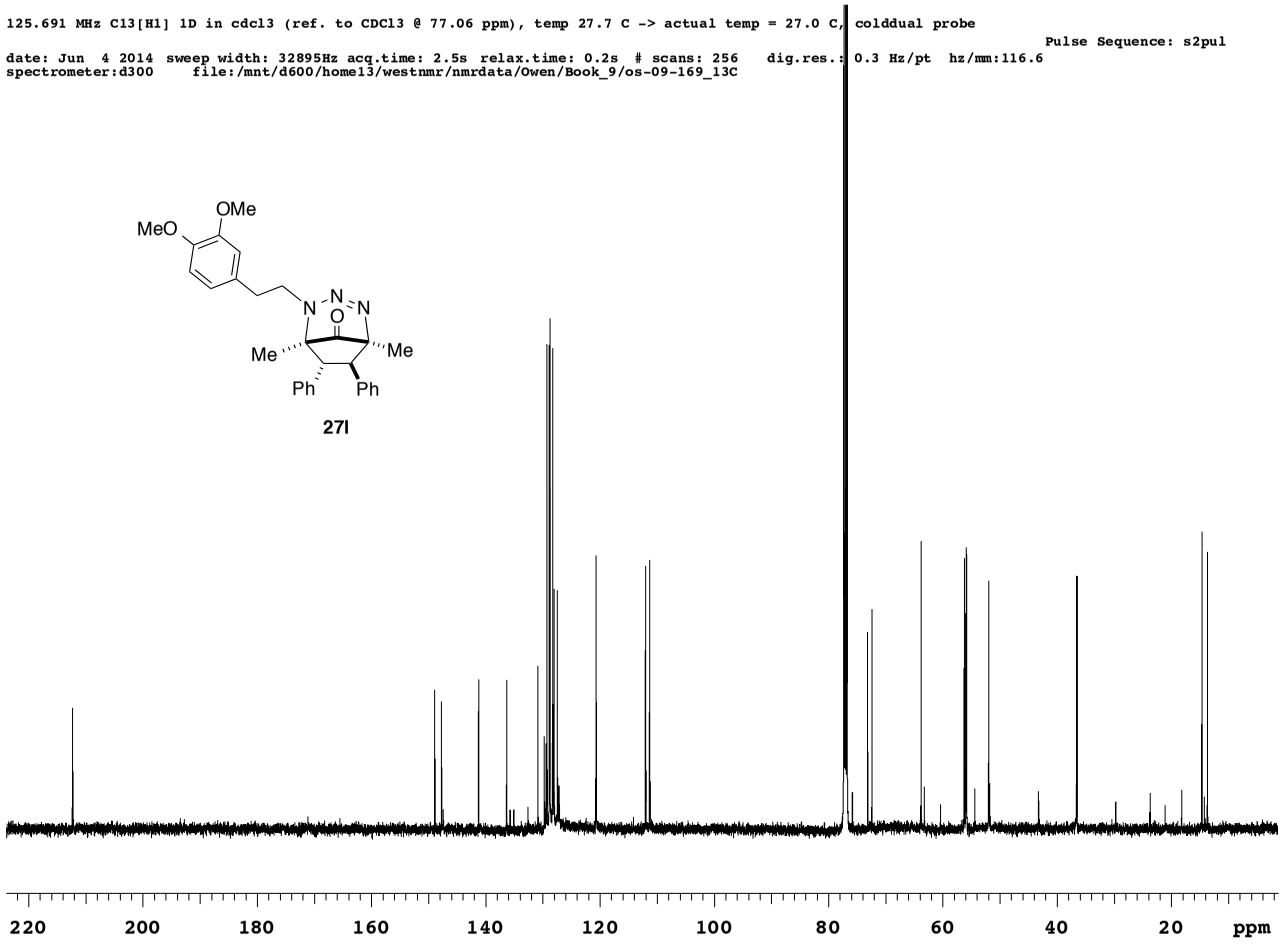
100.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

Pulse Sequence: s2pul

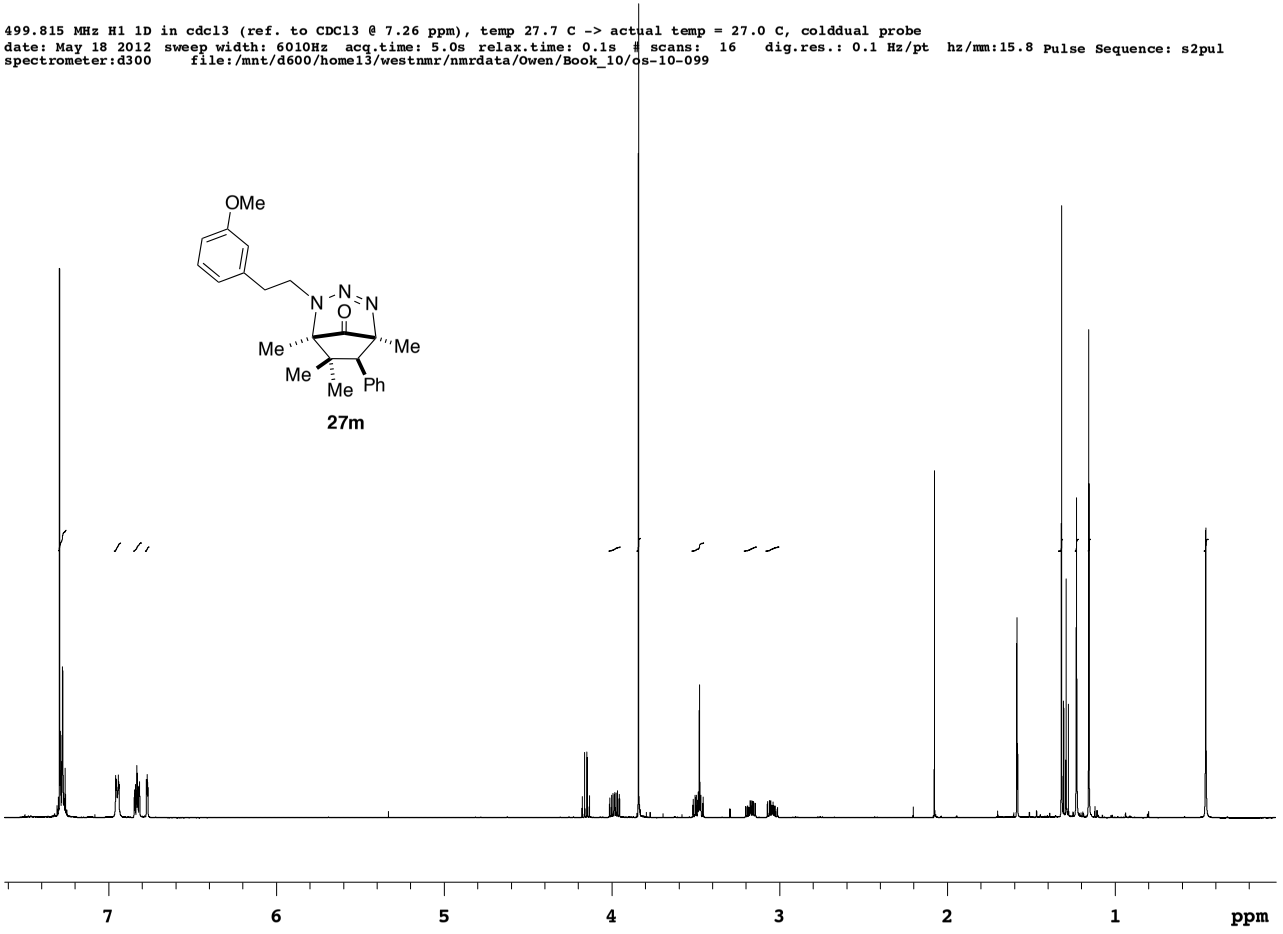


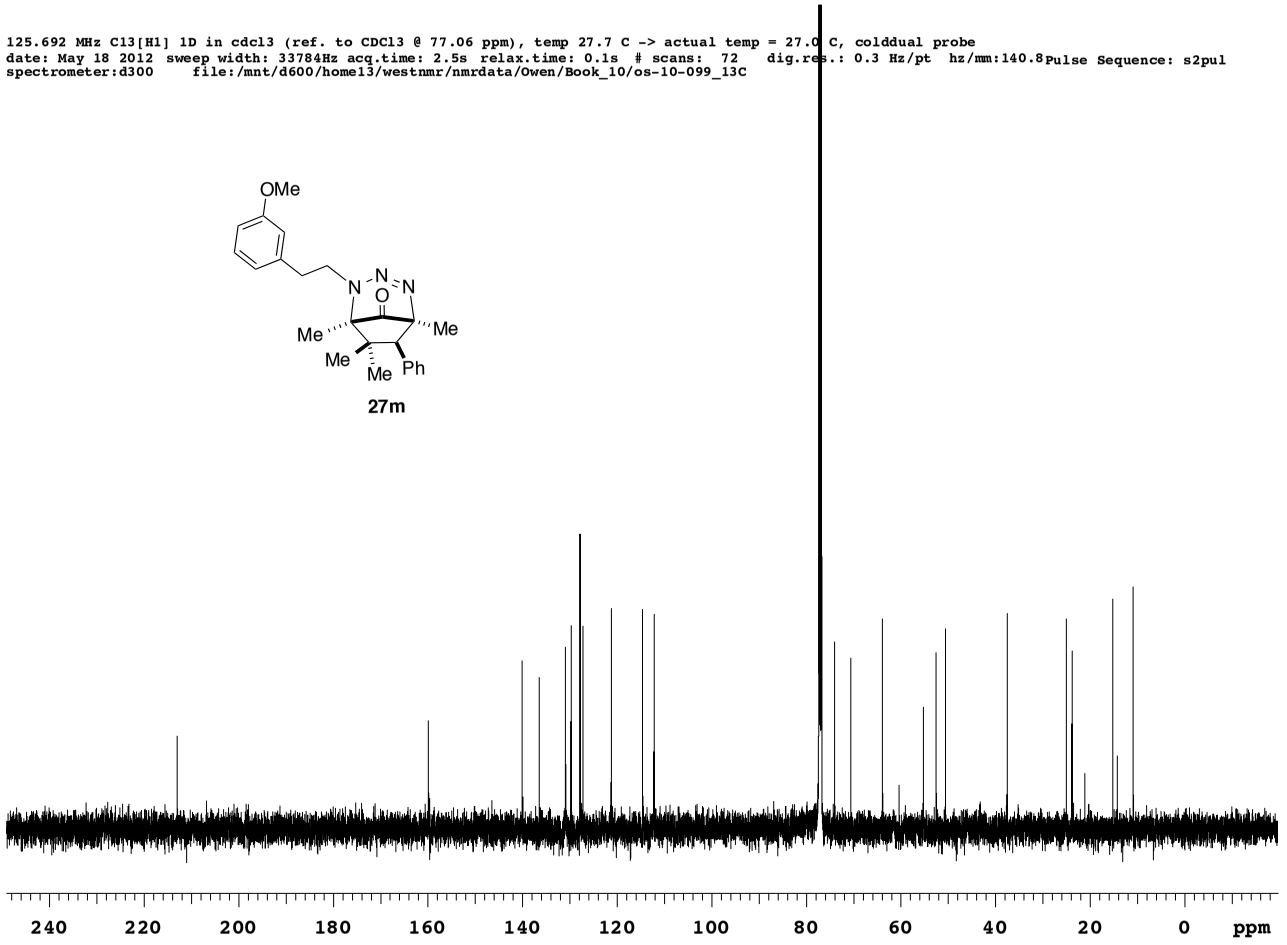
32


498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe
date: Jun 5 2014 sweep width: 6001Hz acq.time: 5.0s relax.time: 0.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:16.4 Pulse Sequence: s2pul
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_9/os-09-169_1H
OMe
MeO
N
N
N
O
Me
Me
Ph
Ph
27l
7
6
5
4
3
2
1
ppm


125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
Pulse Sequence: s2pul
date: Jun 4 2014 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 256 dig.res.: 0.3 Hz/pt hz/mm:116.6
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_9/os-09-169_13C
OMe
MeO
N
N
N
O
Me
Me
Ph
Ph
220
200
180
160
140
120
100
80
60
40
20
ppm

27l

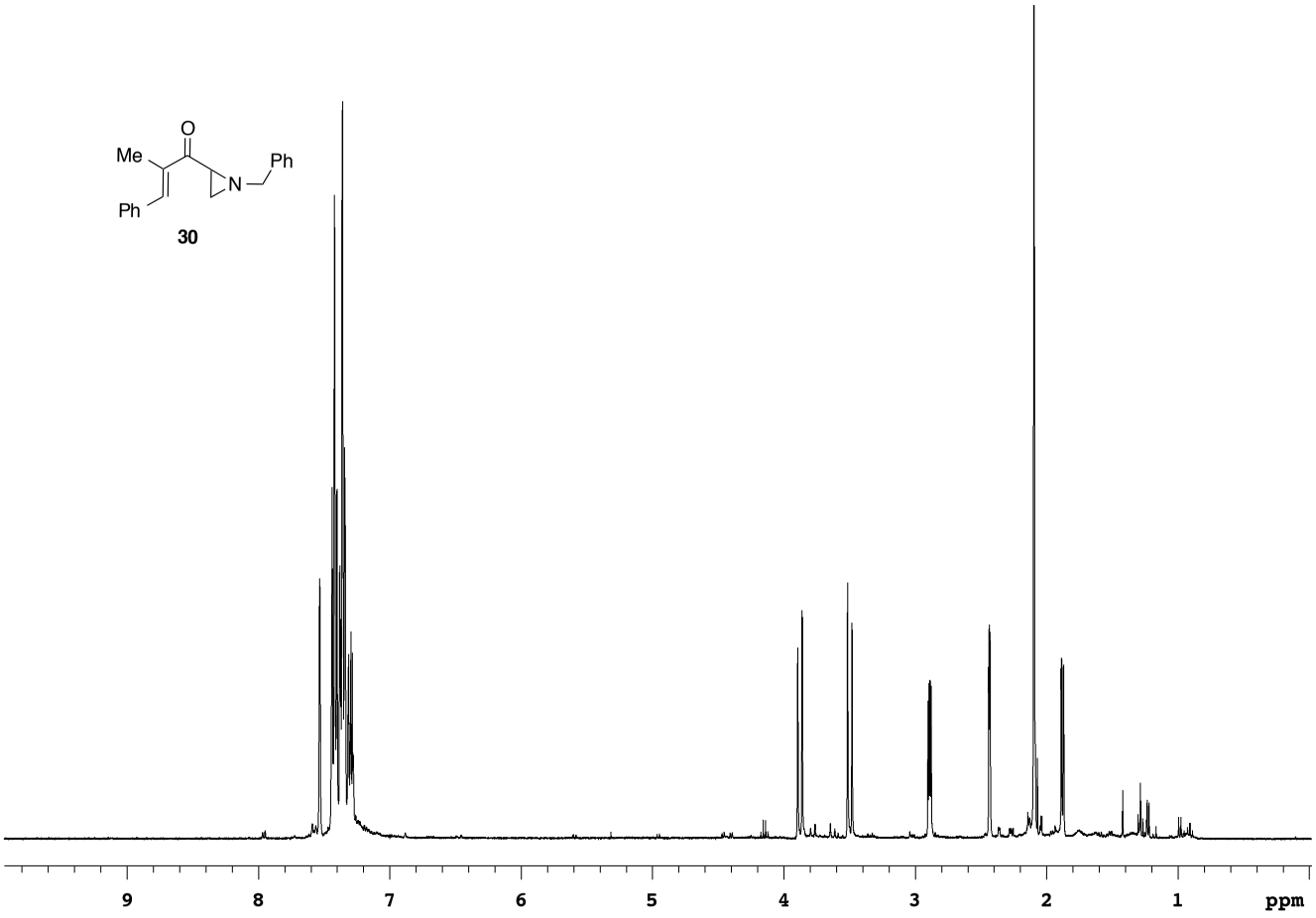

499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: May 18 2012 sweep width: 6010Hz acq.time: 5.0s relax.time: 0.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:15.8 Pulse Sequence: s2pul
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_10/os-10-099
OMe
N
N
N
O
Me
Me
Me
Me
Ph
27m
7
6
5
4
3
2
1
ppm


125.692 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: May 18 2012 sweep width: 33784Hz acq.time: 2.5s relax.time: 0.1s # scans: 72 dig.res.: 0.3 Hz/pt hz/mm:140.8Pulse Sequence: s2pul
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_10/os-10-099_13C
OMe
N
N
N
O
Me
Me
Me
Me
Ph
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

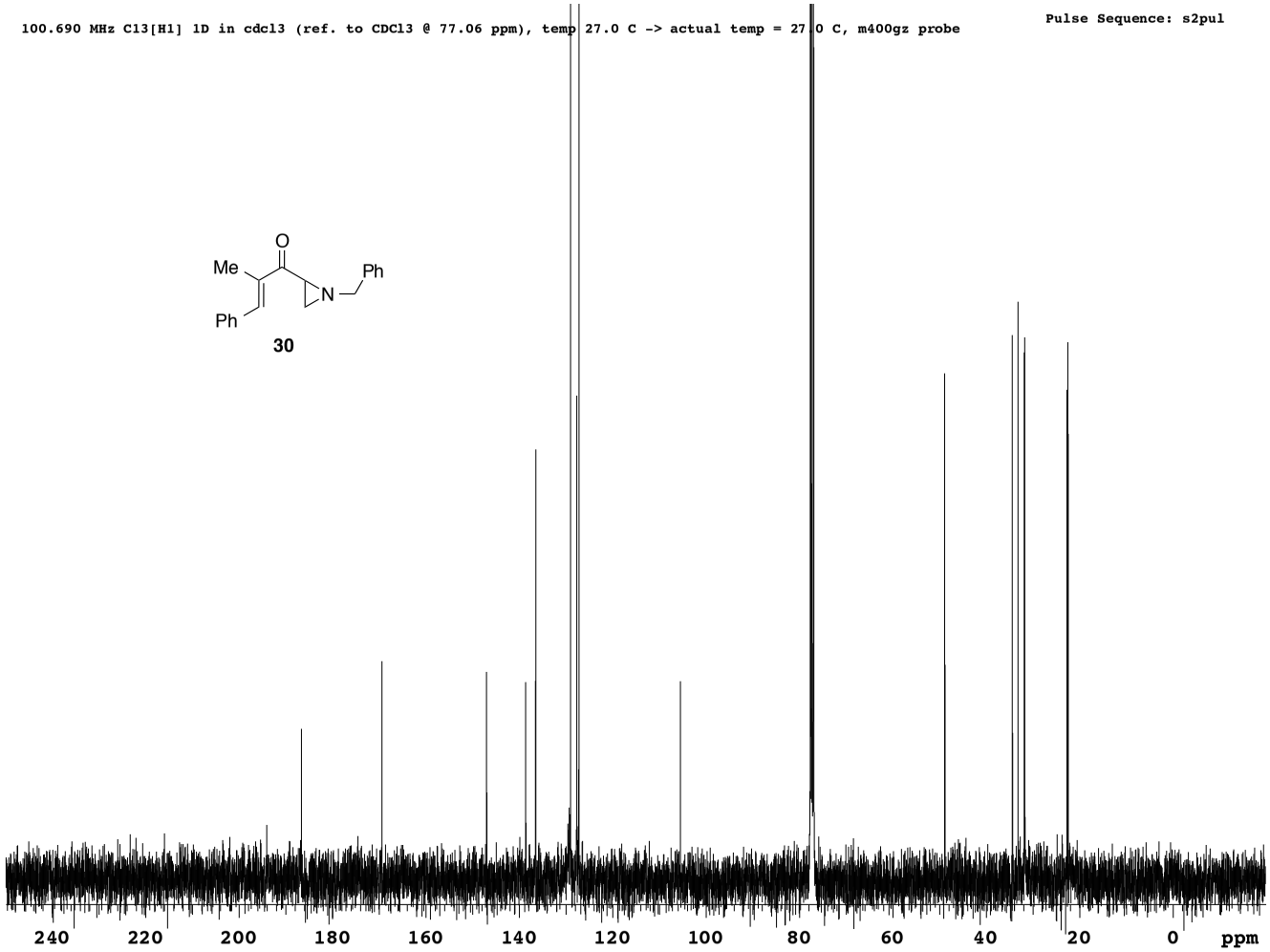
27m

400.393 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

Pulse Sequence: s2pul



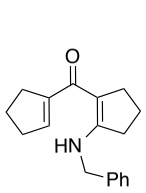
30


100.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Pulse Sequence: s2pul
O
Me
Ph
N
Ph
Ph
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

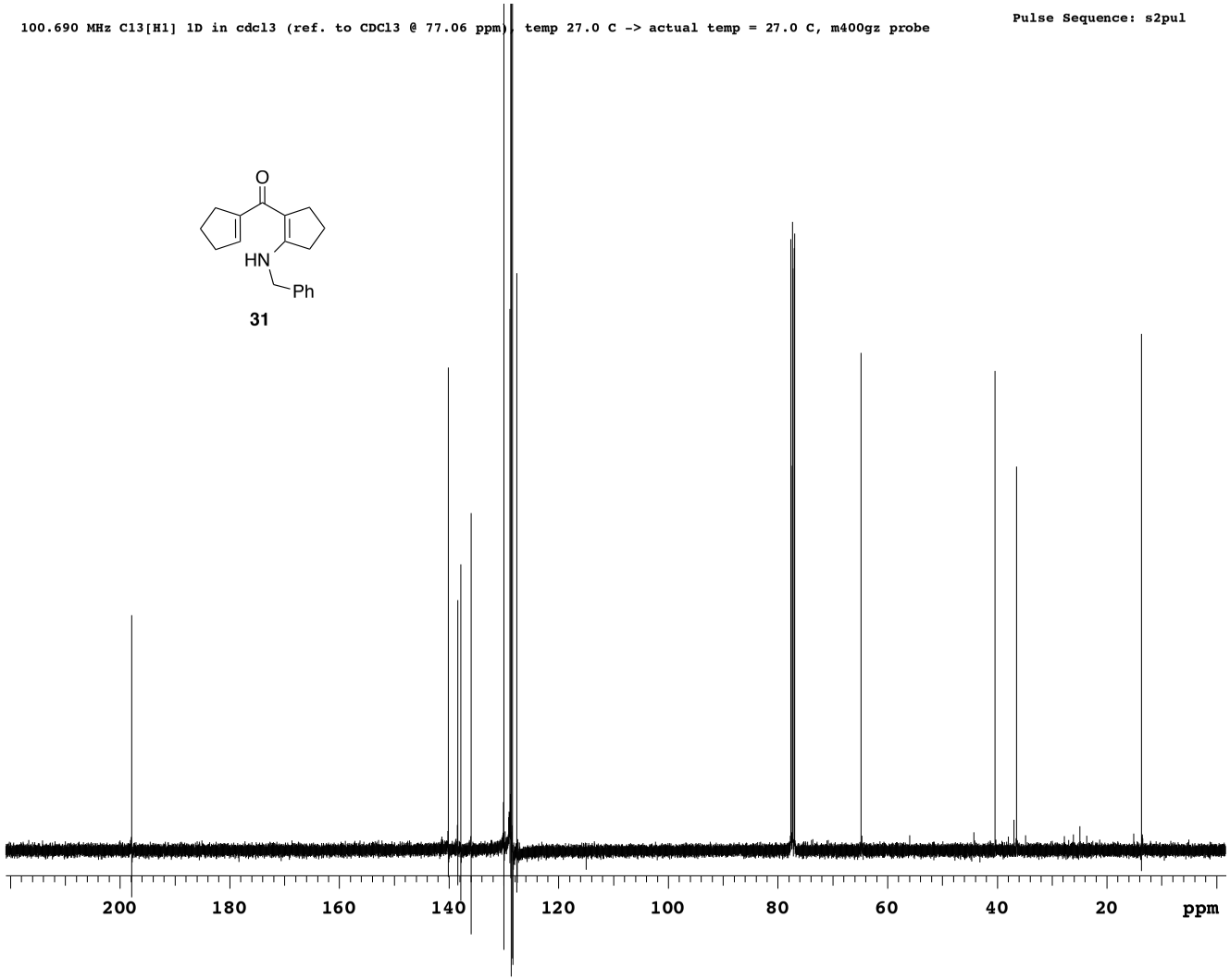
30

400.393 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

Pulse Sequence: s2pul



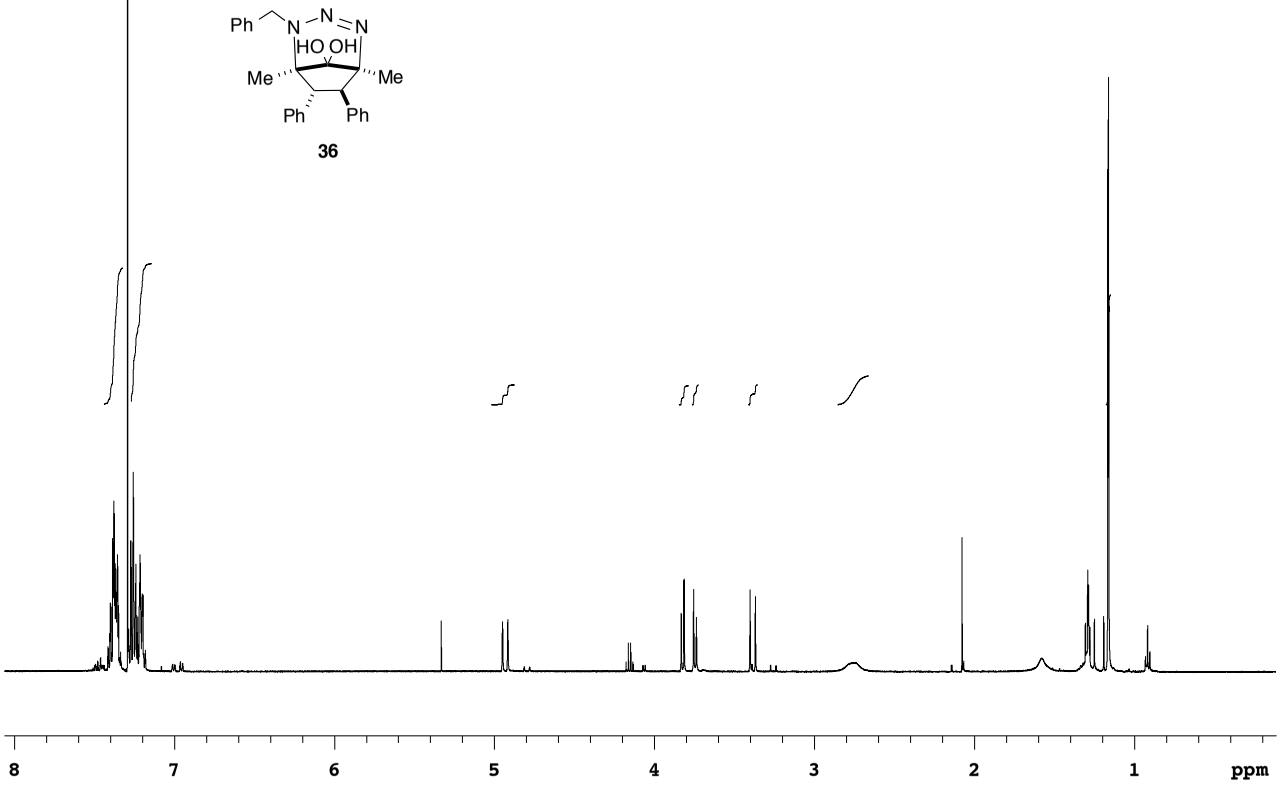
31


100.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Pulse Sequence: s2pul
O
HN
Ph
31
200
180
160
140
120
100
80
60
40
20
ppm

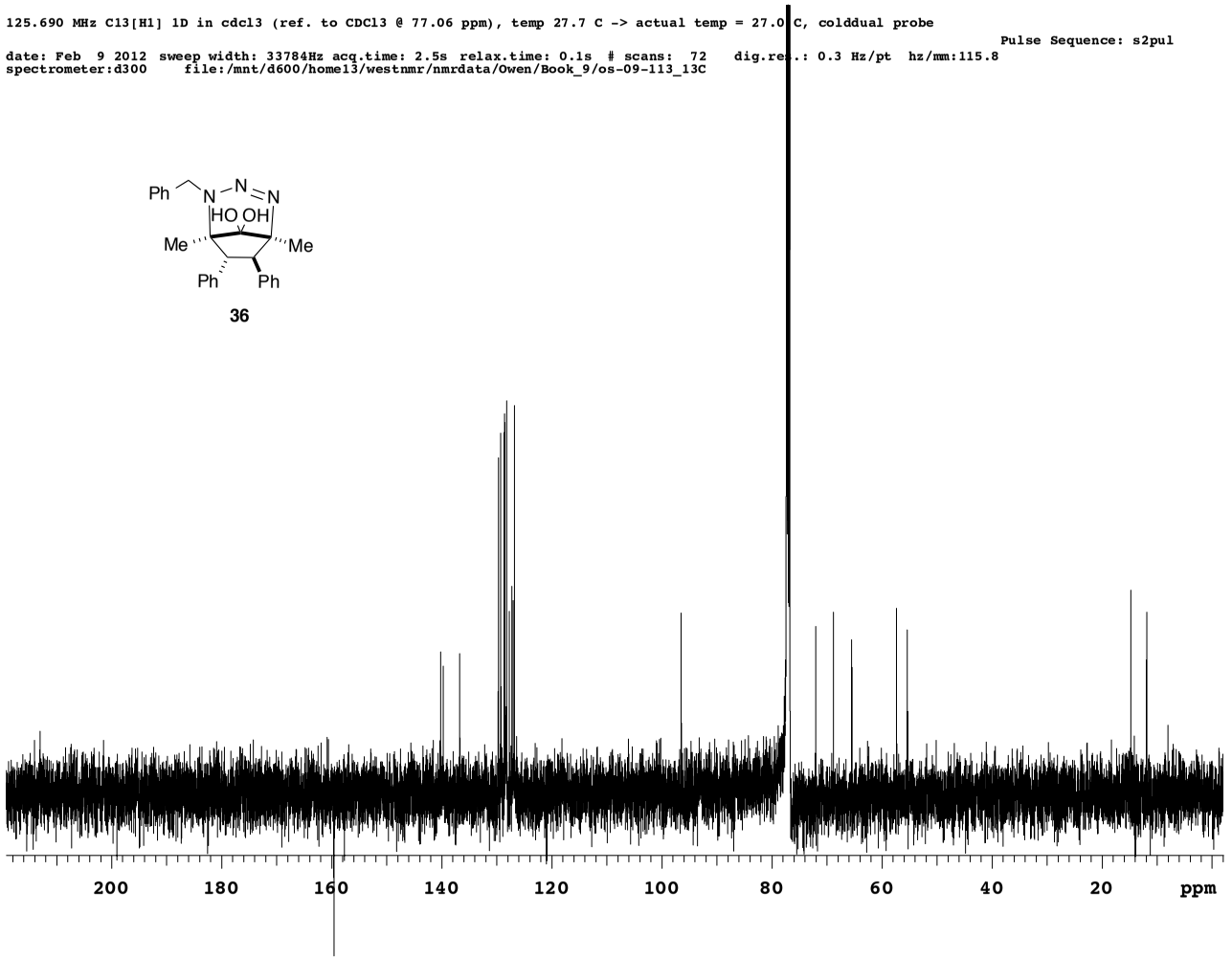
499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

Pulse Sequence: s2pul

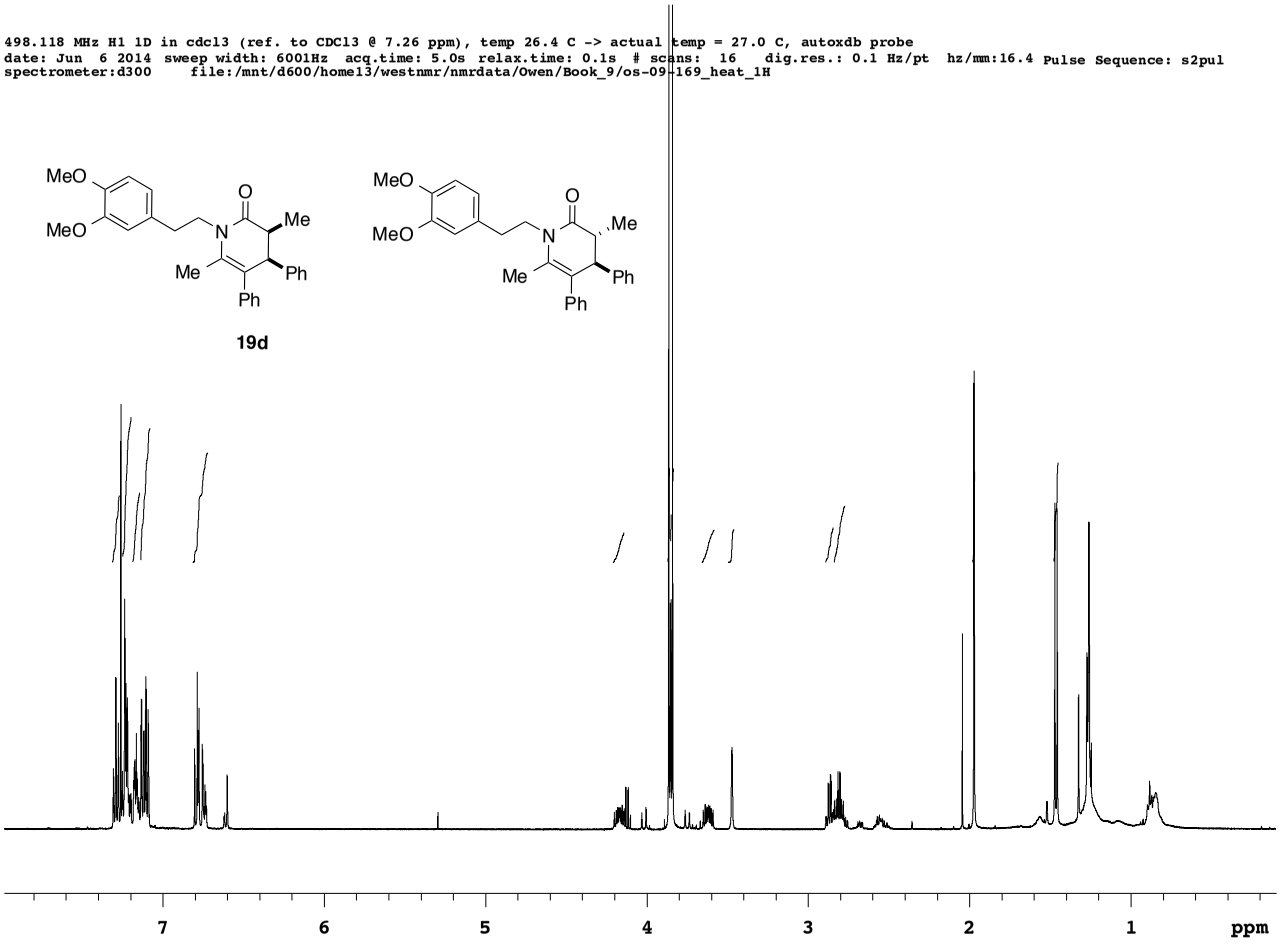
date: Feb 9 2012 sweep width: 6010Hz acq.time: 5.0s relax.time: 0.1s # scans: 4 dig.res.: 0.1 Hz/pt hz/mm:16.5
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_9/os-09-113

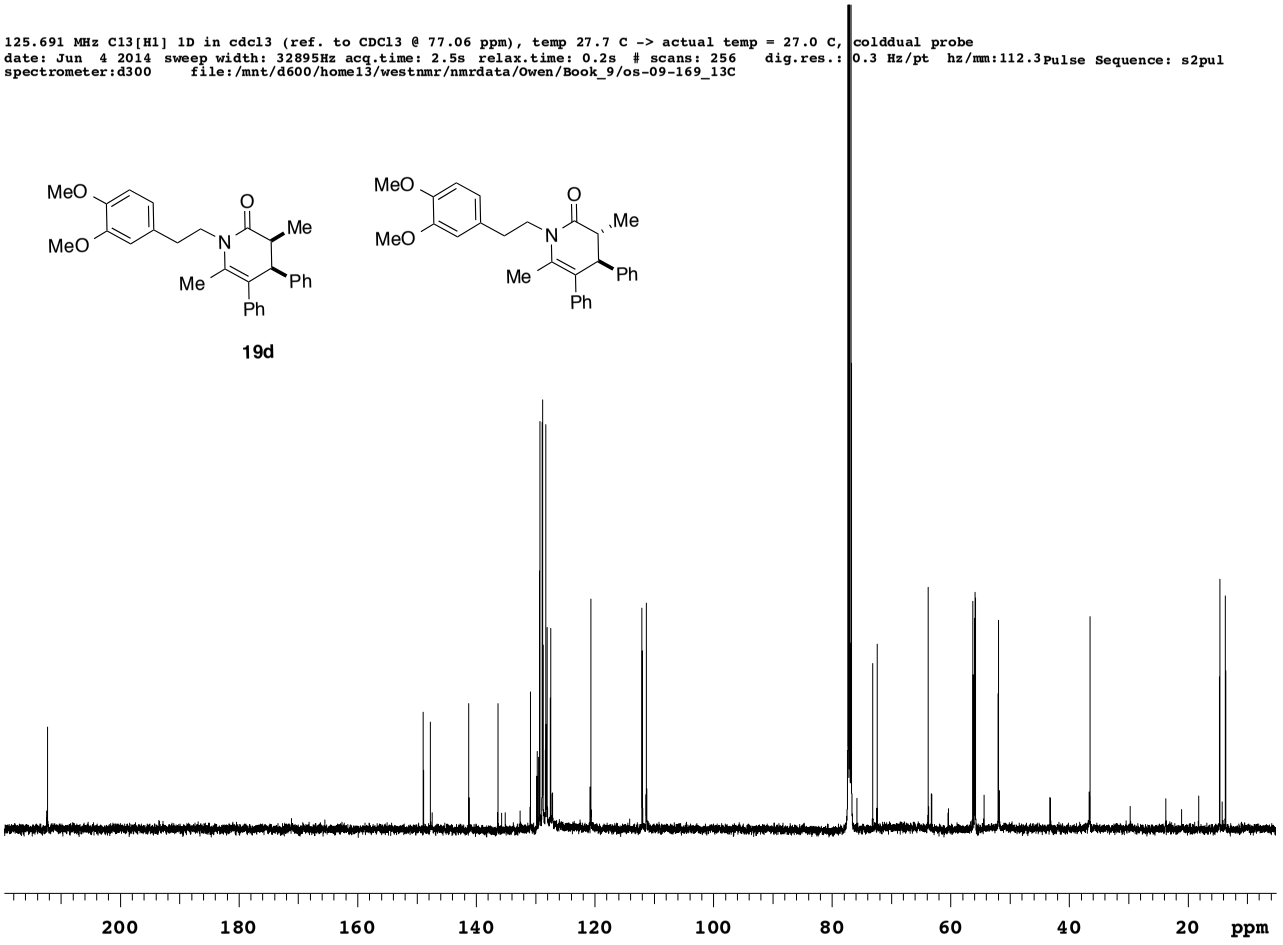


36

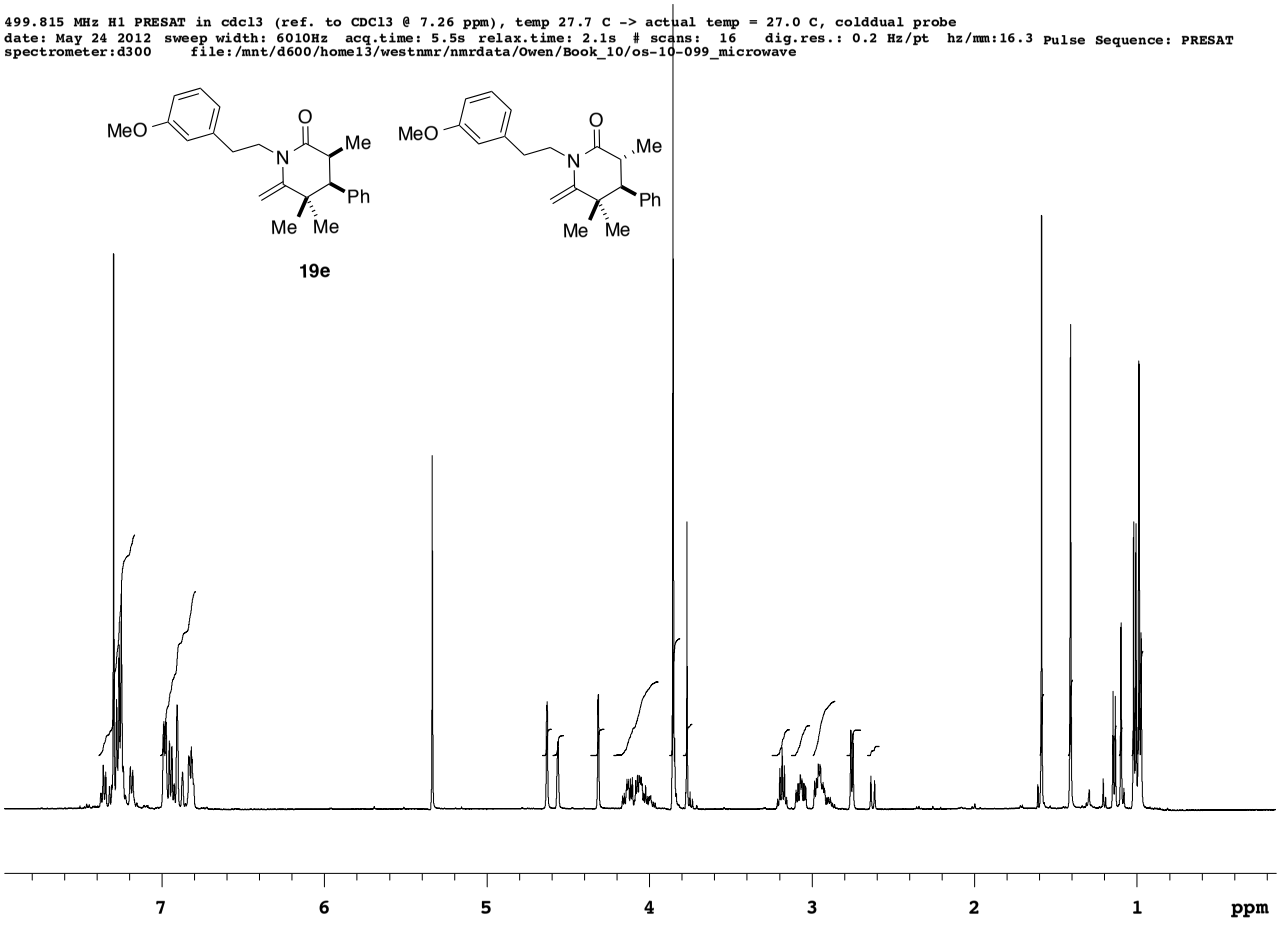

125.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
Pulse Sequence: s2pul
date: Feb 9 2012 sweep width: 33784Hz acq.time: 2.5s relax.time: 0.1s # scans: 72 dig.res.: 0.3 Hz/pt hz/mm:115.8
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_9/os-09-113_13C
Ph
N
N
N
HO OH
Me
Me
Ph
Ph
200
180
160
140
120
100
80
60
40
20
ppm

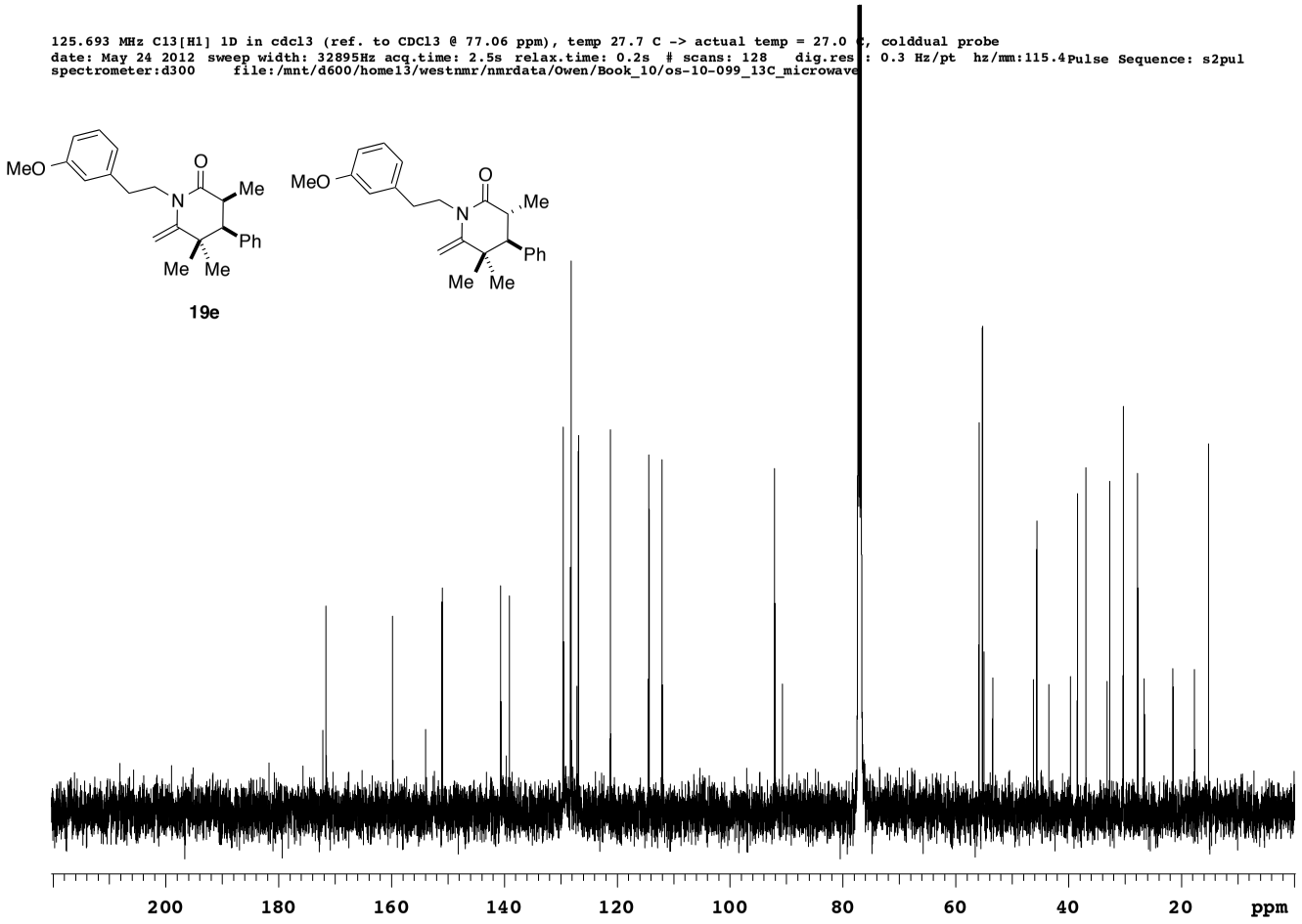
36


498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe
date: Jun 6 2014 sweep width: 6001Hz acq.time: 5.0s relax.time: 0.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:16.4 Pulse Sequence: s2pul
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_9/os-09-169_heat_1H
MeO
MeO
N
O
Me
Me
Ph
Ph
19d
7
6
5
4
3
2
1
ppm


125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Jun 4 2014 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 256 dig.res.: 0.3 Hz/pt hz/mm:112.3Pulse Sequence: s2pul
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_9/os-09-169_13C
MeO
MeO
O
N
Me
Me
Ph
Ph
MeO
MeO
O
N
Me
Me
Ph
Ph
200
180
160
140
120
100
80
60
40
20
ppm

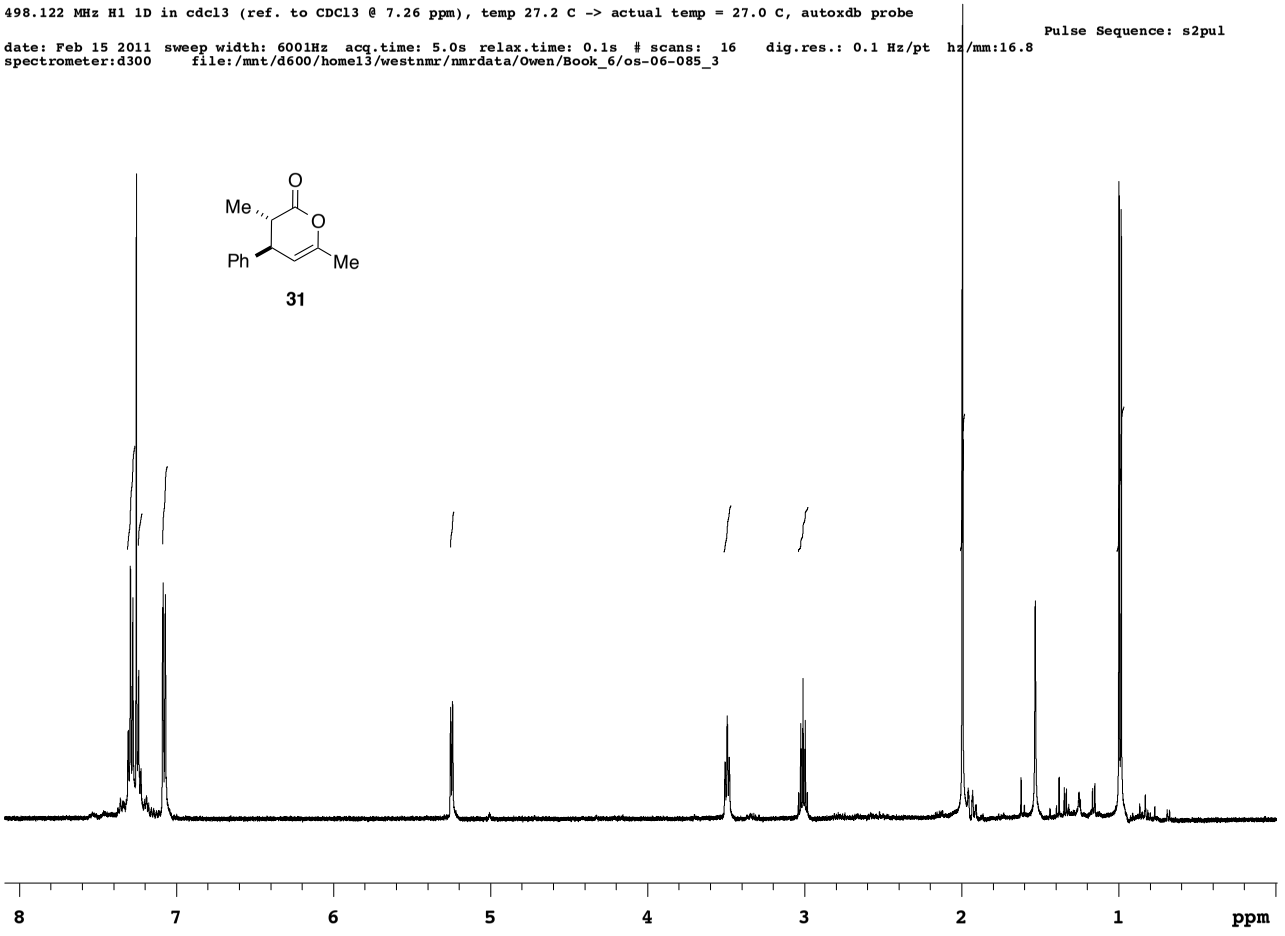
19d

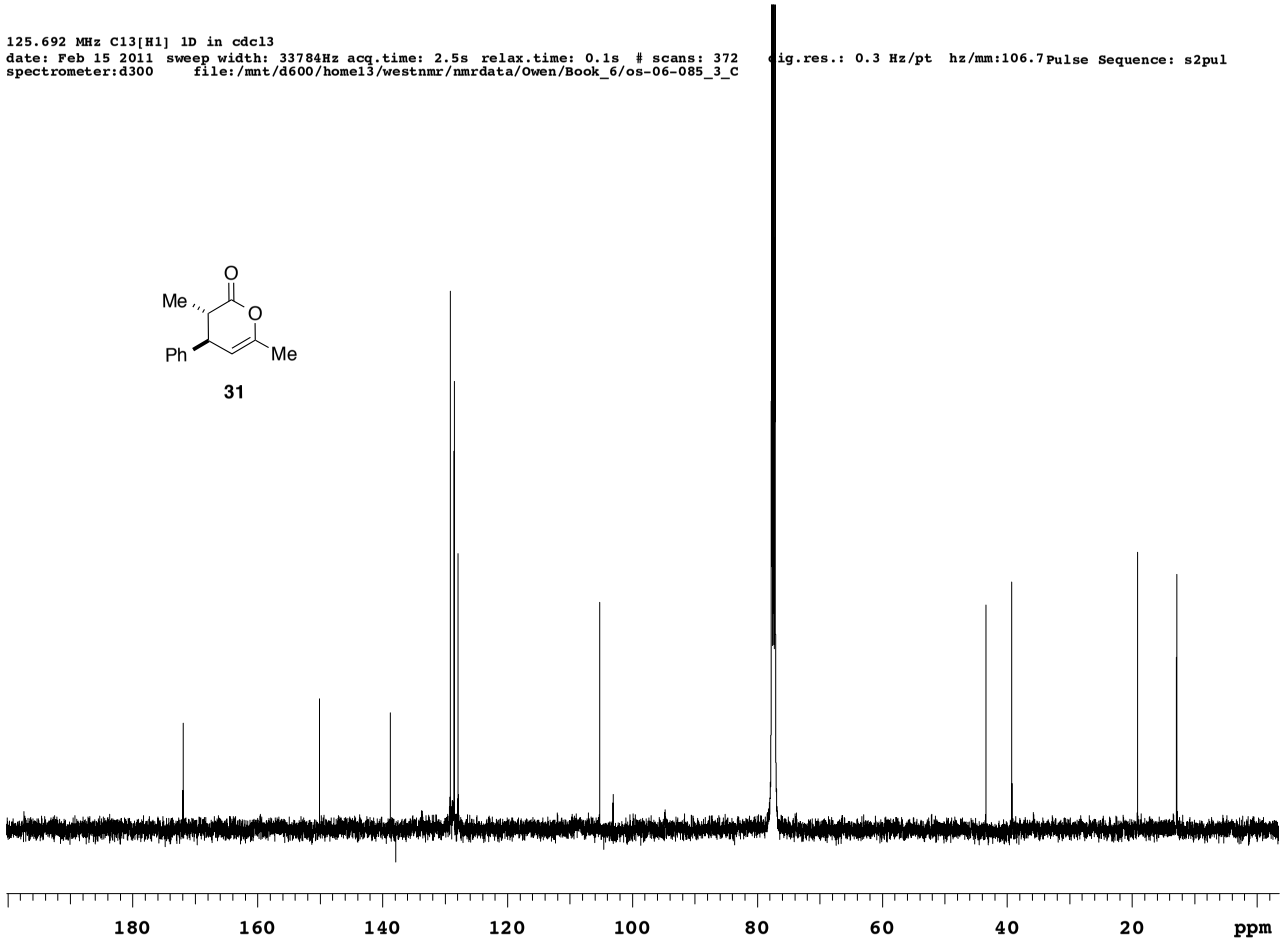

499.815 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: May 24 2012 sweep width: 6010Hz acq.time: 5.5s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:16.3 Pulse Sequence: PRESAT
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_10/os-10-099_microwave
MeO
O
N
Me
Ph
Me Me
19e
7
6
5
4
3
2
1
ppm


125.693 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: May 24 2012 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 128 dig.res : 0.3 Hz/pt hz/mm:115.4Pulse Sequence: s2pul
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_10/os-10-099_13C_microwave
MeO
O
N
Me
Ph
Me Me
MeO
O
N
Me
Ph
Me Me
19e
200
180
160
140
120
100
80
60
40
20
ppm

Appendix II: Selected NMR Spectra

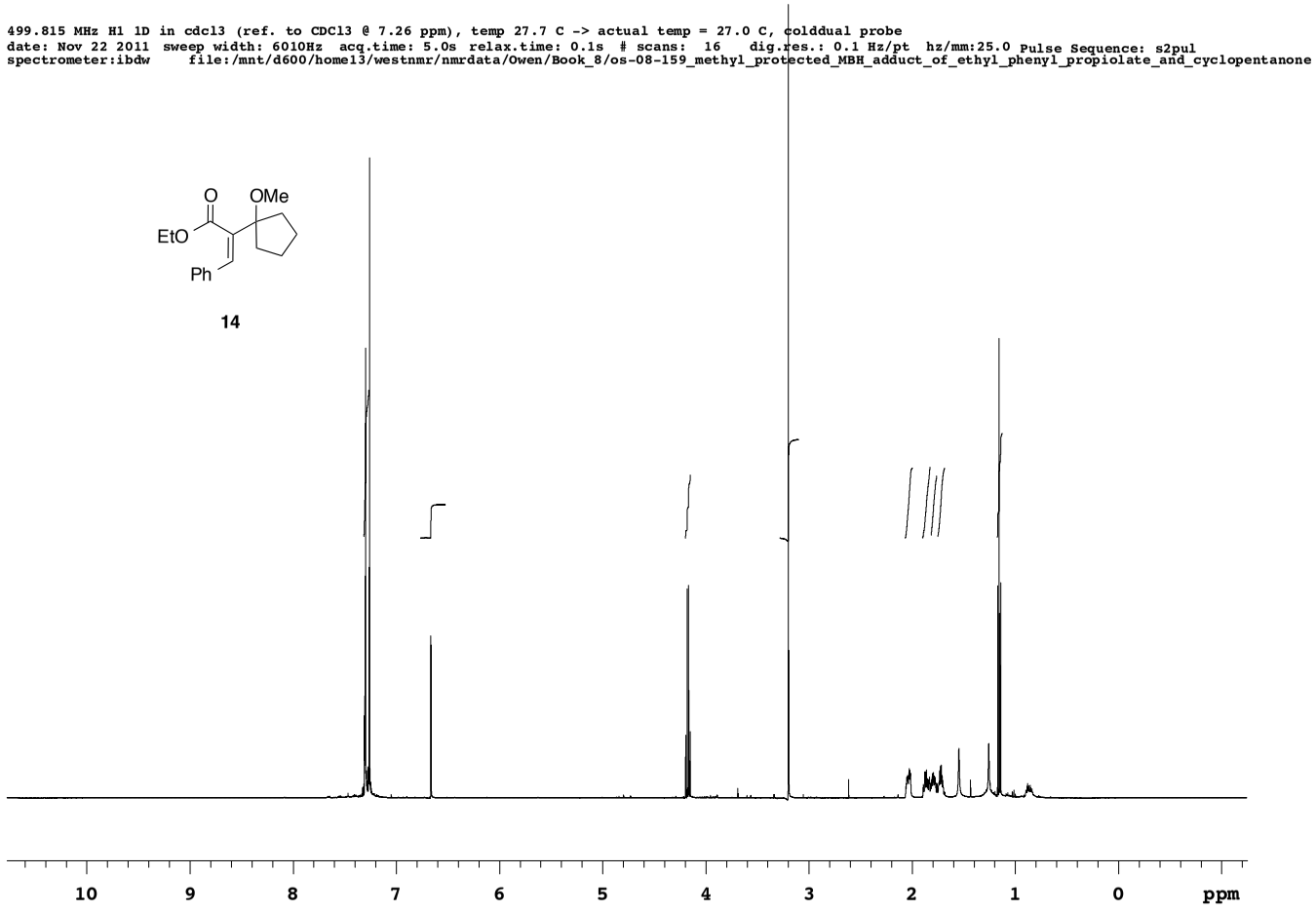
(Chapter 3)

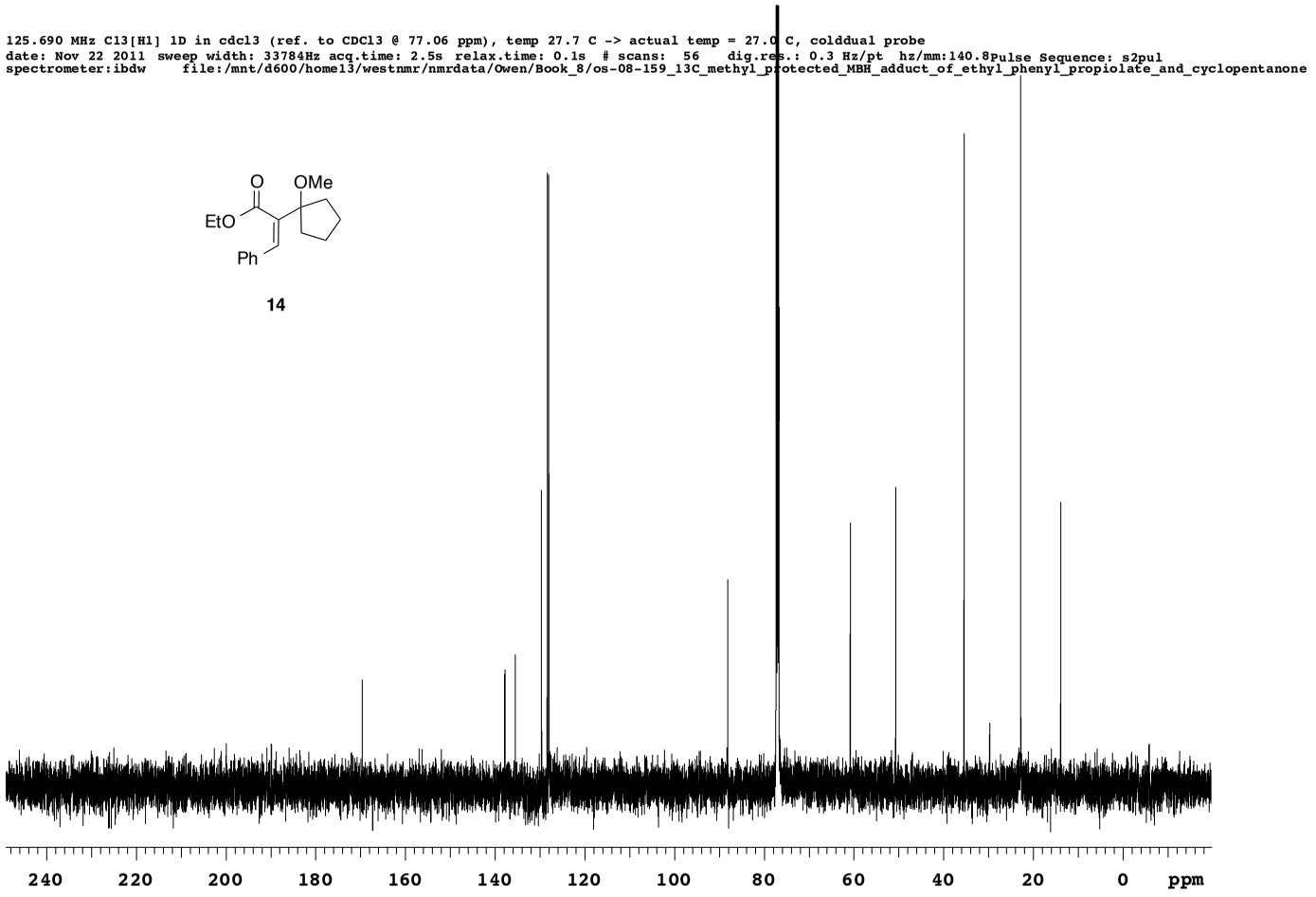

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
date: Feb 15 2011 sweep width: 6001Hz acq.time: 5.0s relax.time: 0.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:16.8
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_6/os-06-085_3
O
Me
O
Ph
Me
31
8
7
6
5
4
3
2
1
ppm

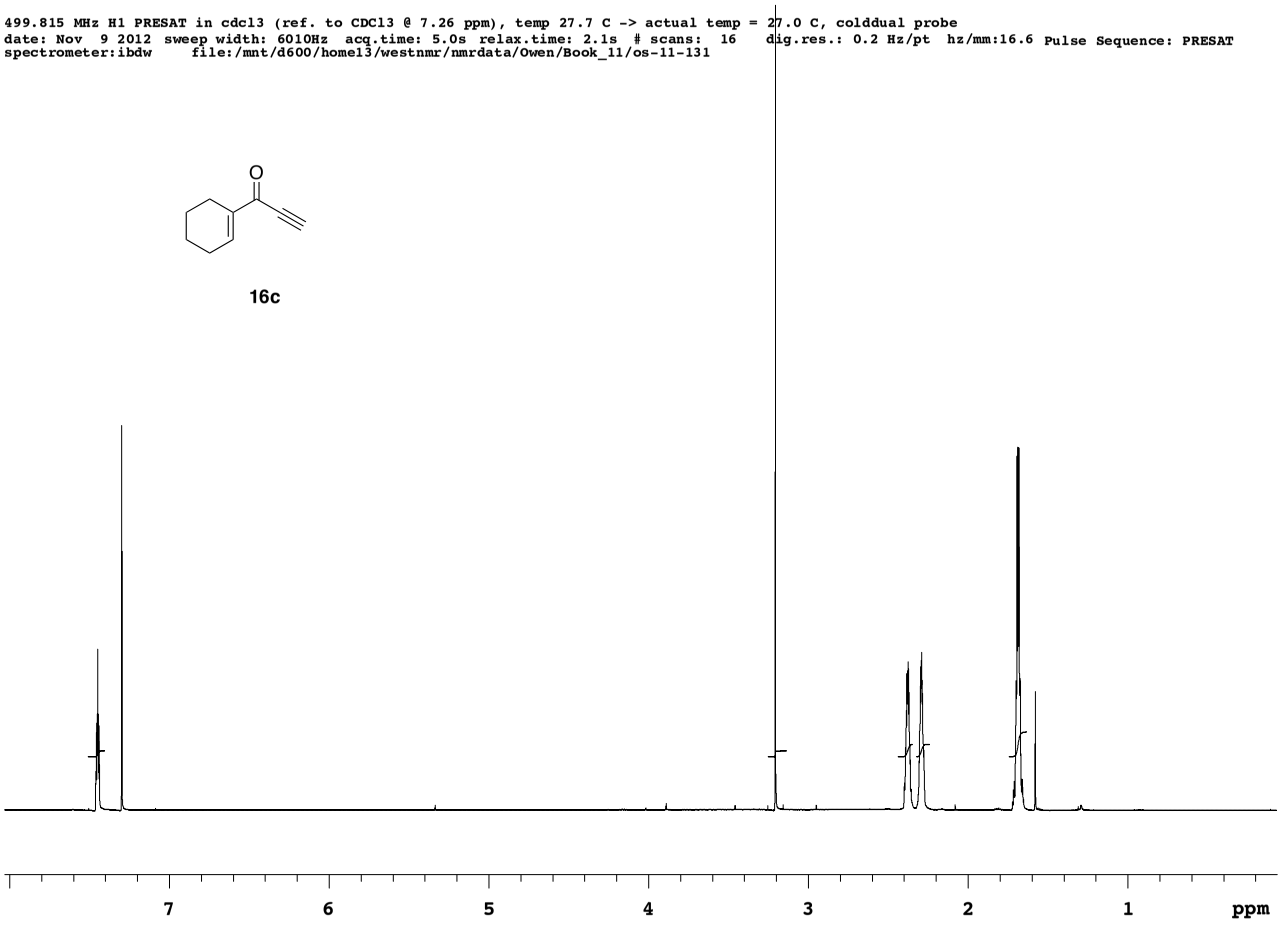

125.692 MHz C13[H1] 1D in cdcl3
date: Feb 15 2011 sweep width: 33784Hz acq.time: 2.5s relax.time: 0.1s # scans: 372 dig.res.: 0.3 Hz/pt hz/mm:106.7 Pulse Sequence: s2pul
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_6/os-06-085_3_C
O
Me
O
Ph
Me
31
180
160
140
120
100
80
60
40
20
ppm

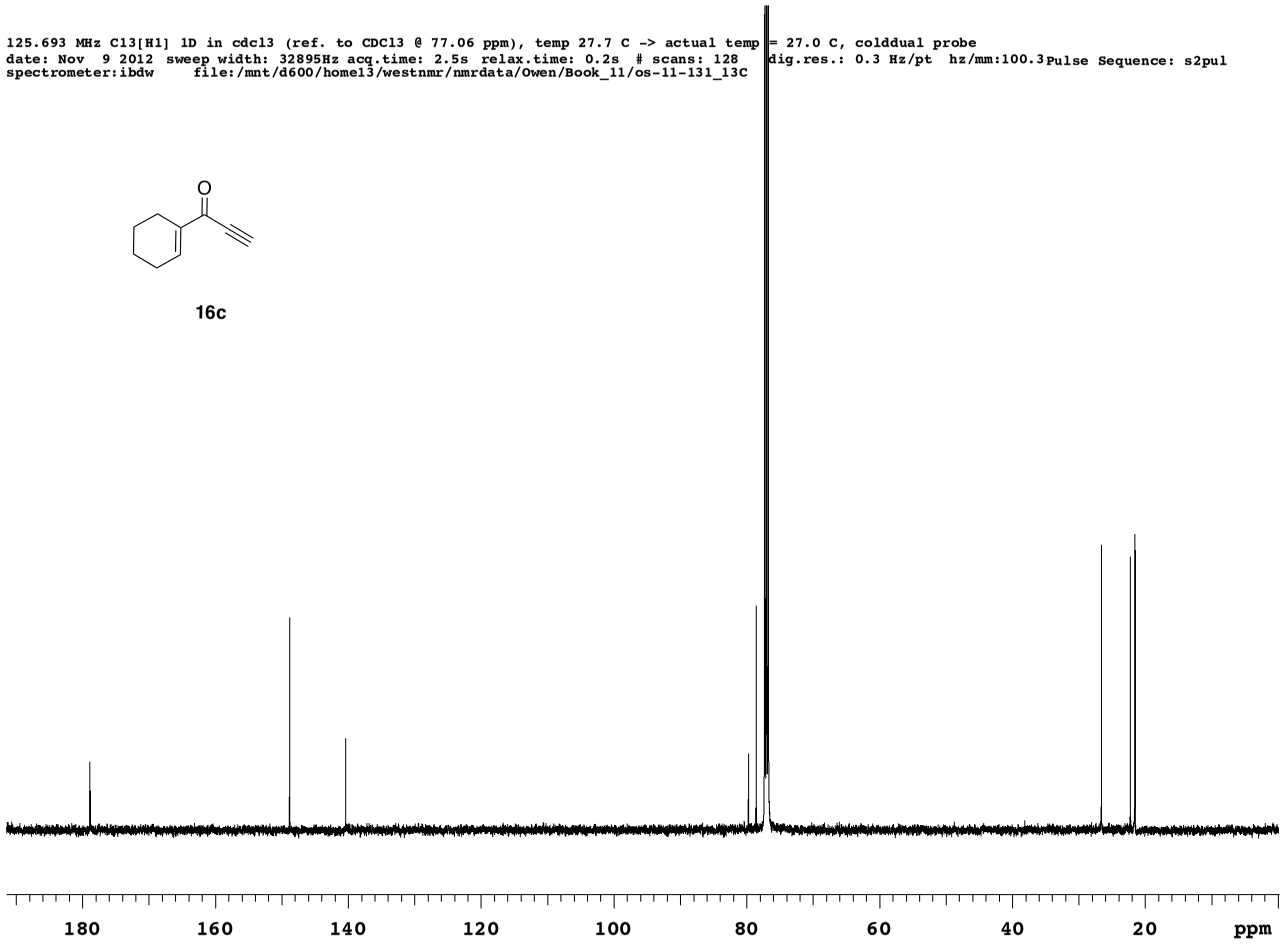
Appendix III: Selected NMR Spectra

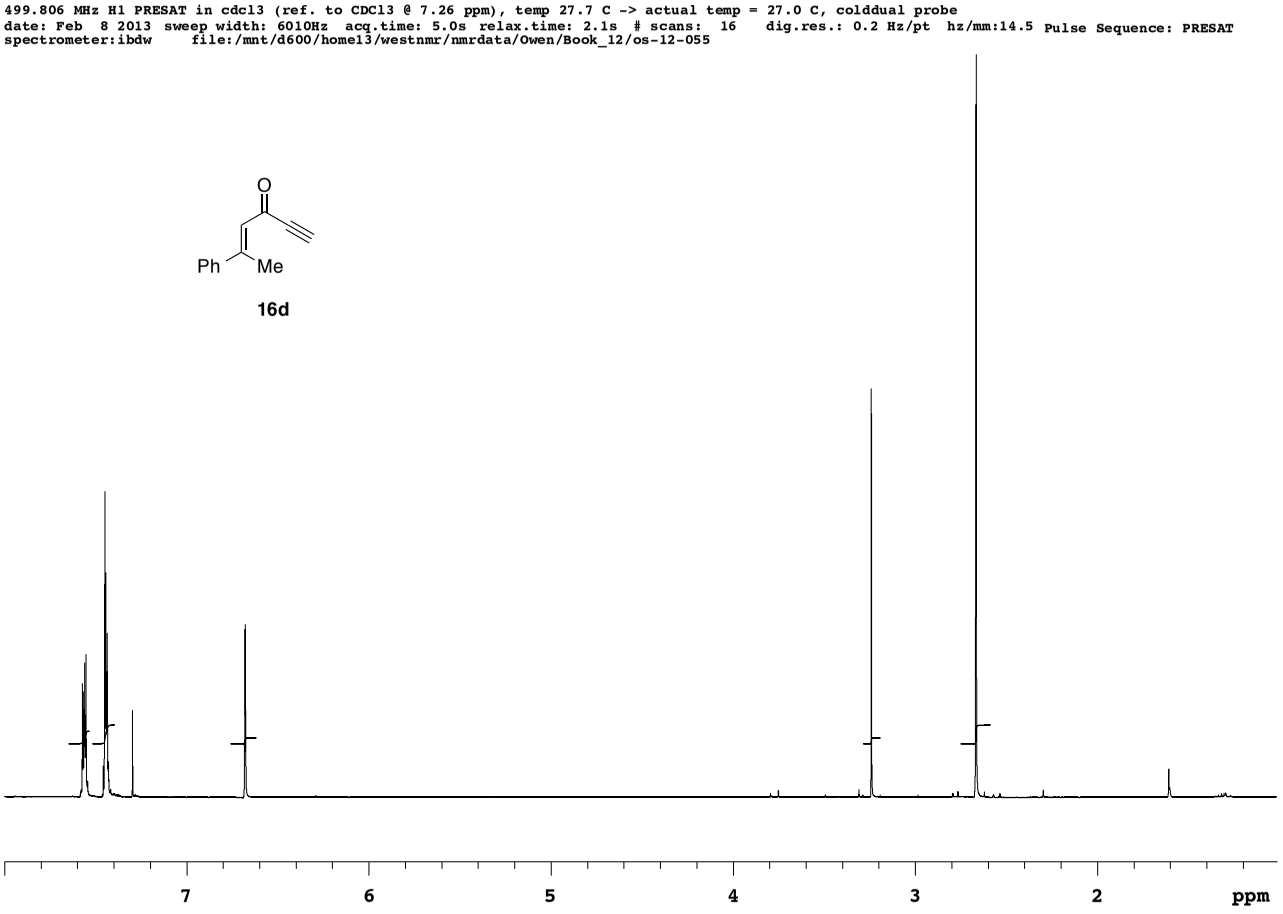
(Chapter 4)

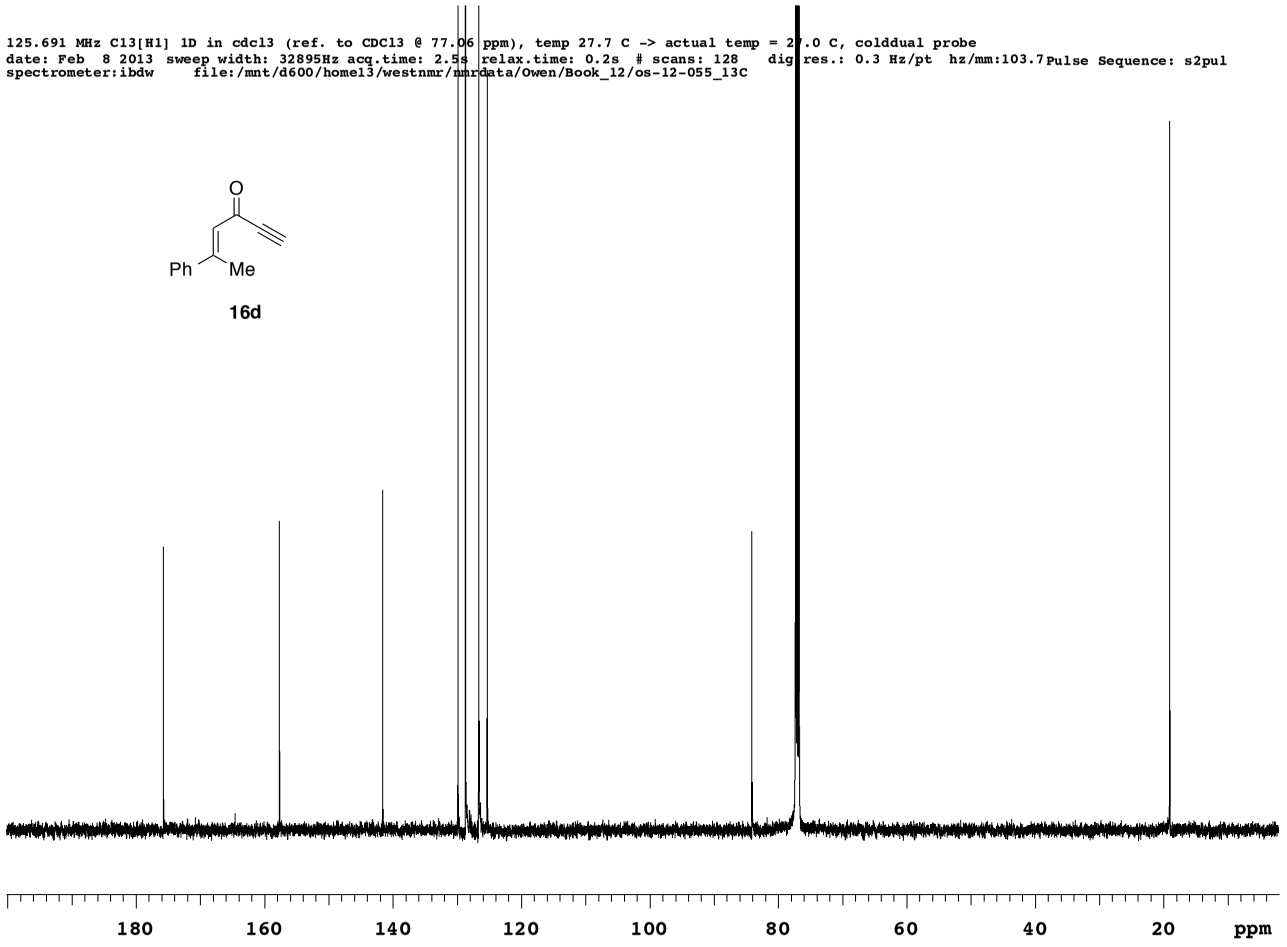

499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Nov 22 2011 sweep width: 6010Hz acq.time: 5.0s relax.time: 0.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:25.0 Pulse Sequence: s2pul
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_8/os-08-159_methyl_protected_MBH_adduct_of_ethyl_phenyl_propiolate_and_cyclopentanone
O
OMe
EtO
Ph
14
10
9
8
7
6
5
4
3
2
1
0
ppm

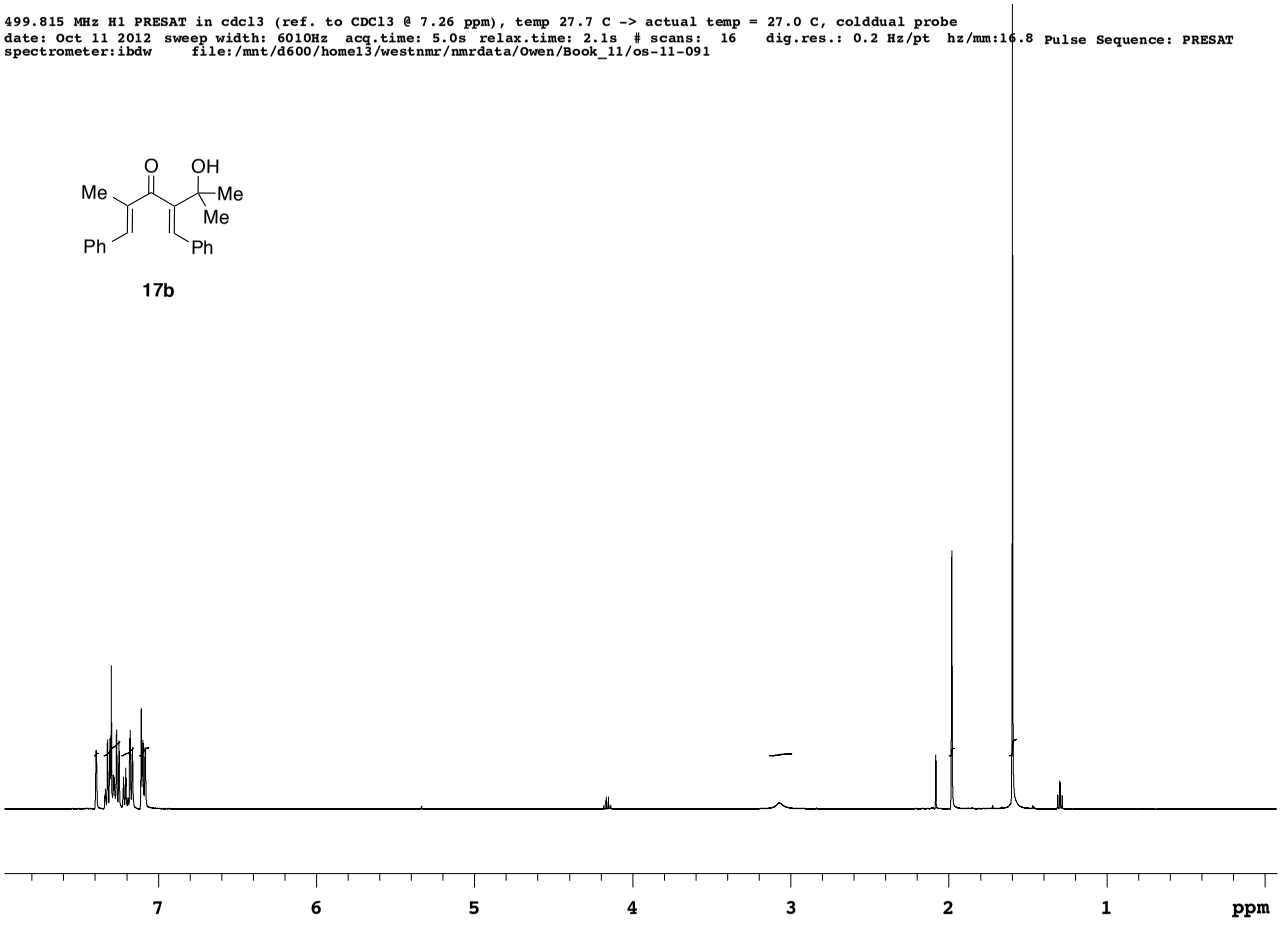

125.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Nov 22 2011 sweep width: 33784Hz acq.time: 2.5s relax.time: 0.1s # scans: 56 dig.res.: 0.3 Hz/pt hz/mm:140.8Pulse Sequence: s2pul
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_8/os-08-159_13C_methyl_protected_MBH_adduct_of_ethyl_phenyl_propiolate_and_cyclopentanone
O
OMe
EtO
Ph
14
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

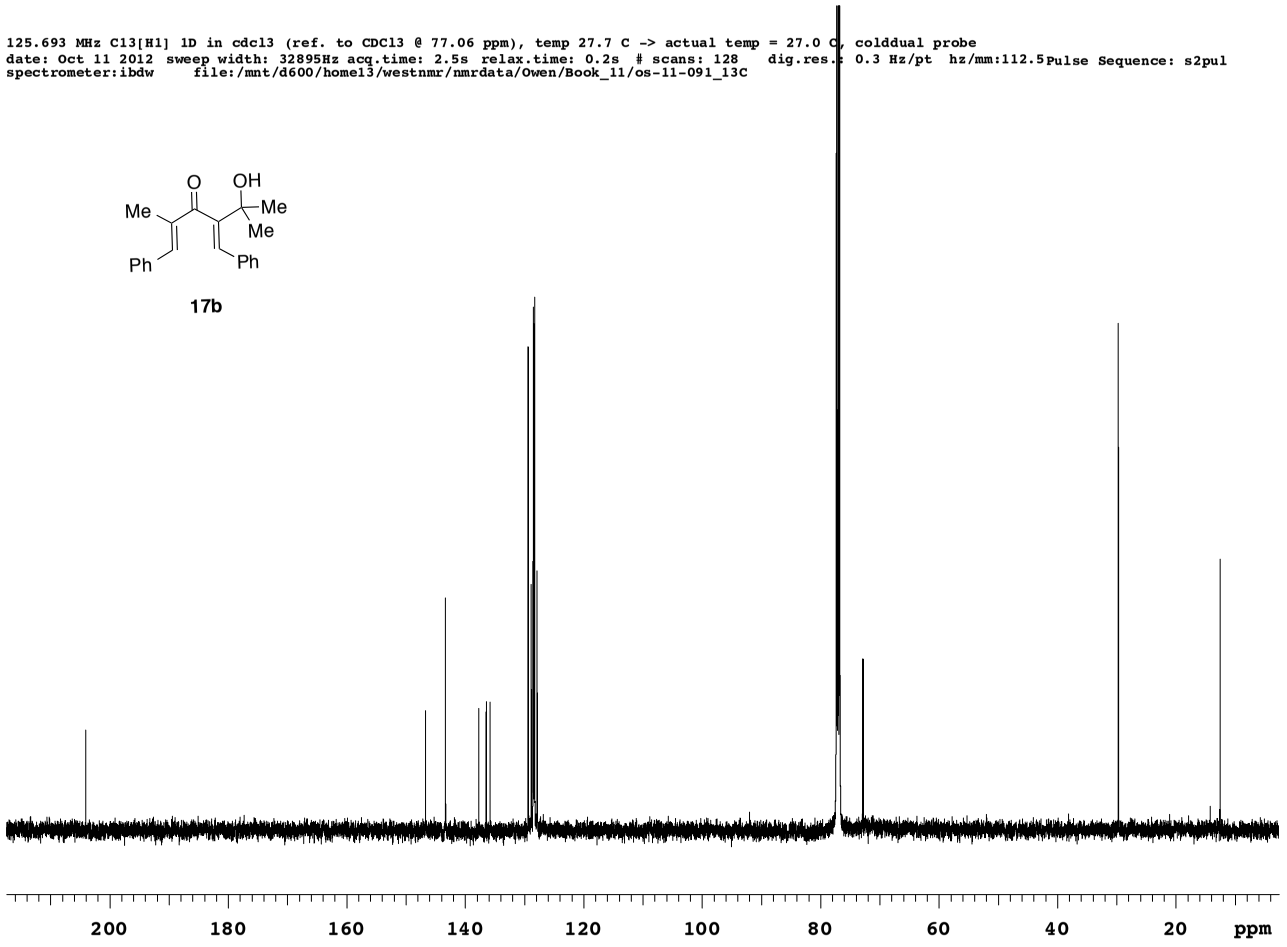

499.815 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Nov 9 2012 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:16.6 Pulse Sequence: PRESAT
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_11/os-11-131
O
16c
7
6
5
4
3
2
1
ppm


125.693 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Nov 9 2012 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 128 dig.res.: 0.3 Hz/pt hz/mm:100.3Pulse Sequence: s2pul
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_11/os-11-131_13C
O
16c
180
160
140
120
100
80
60
40
20
ppm

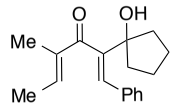

499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Feb 8 2013 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:14.5 Pulse Sequence: PRESAT
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_12/os-12-055
O
Ph
Me
16d
7
6
5
4
3
2
ppm


125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Feb 8 2013 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 128 dig res.: 0.3 Hz/pt hz/mm:103.7 Pulse Sequence: s2pul
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_12/os-12-055_13C
O
Ph
Me
16d
180
160
140
120
100
80
60
40
20
ppm

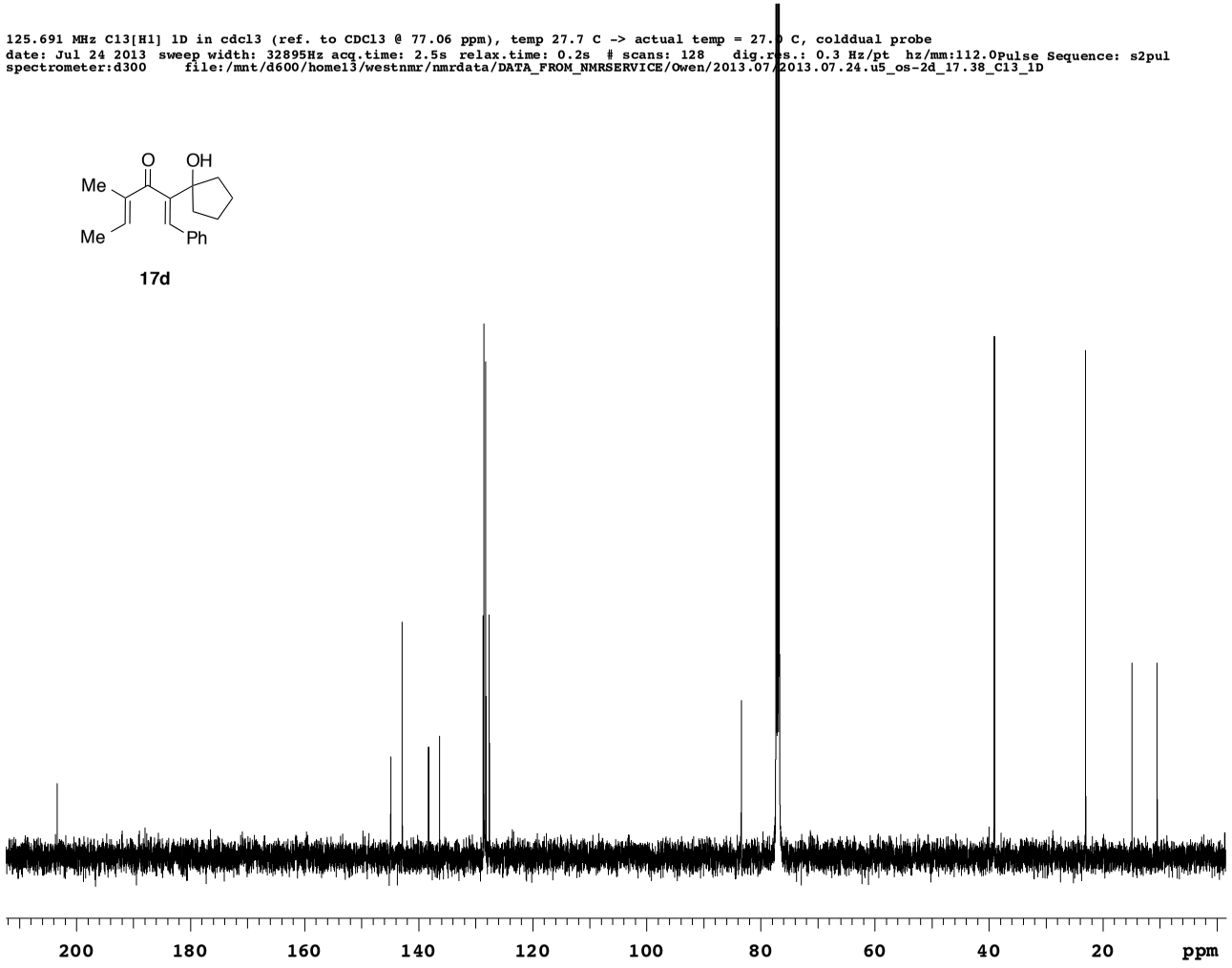

499.815 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Oct 11 2012 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:16.8 Pulse Sequence: PRESAT
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_11/os-11-091
O
OH
Me
Me
Me
Ph
Ph
17b
7
6
5
4
3
2
1
ppm

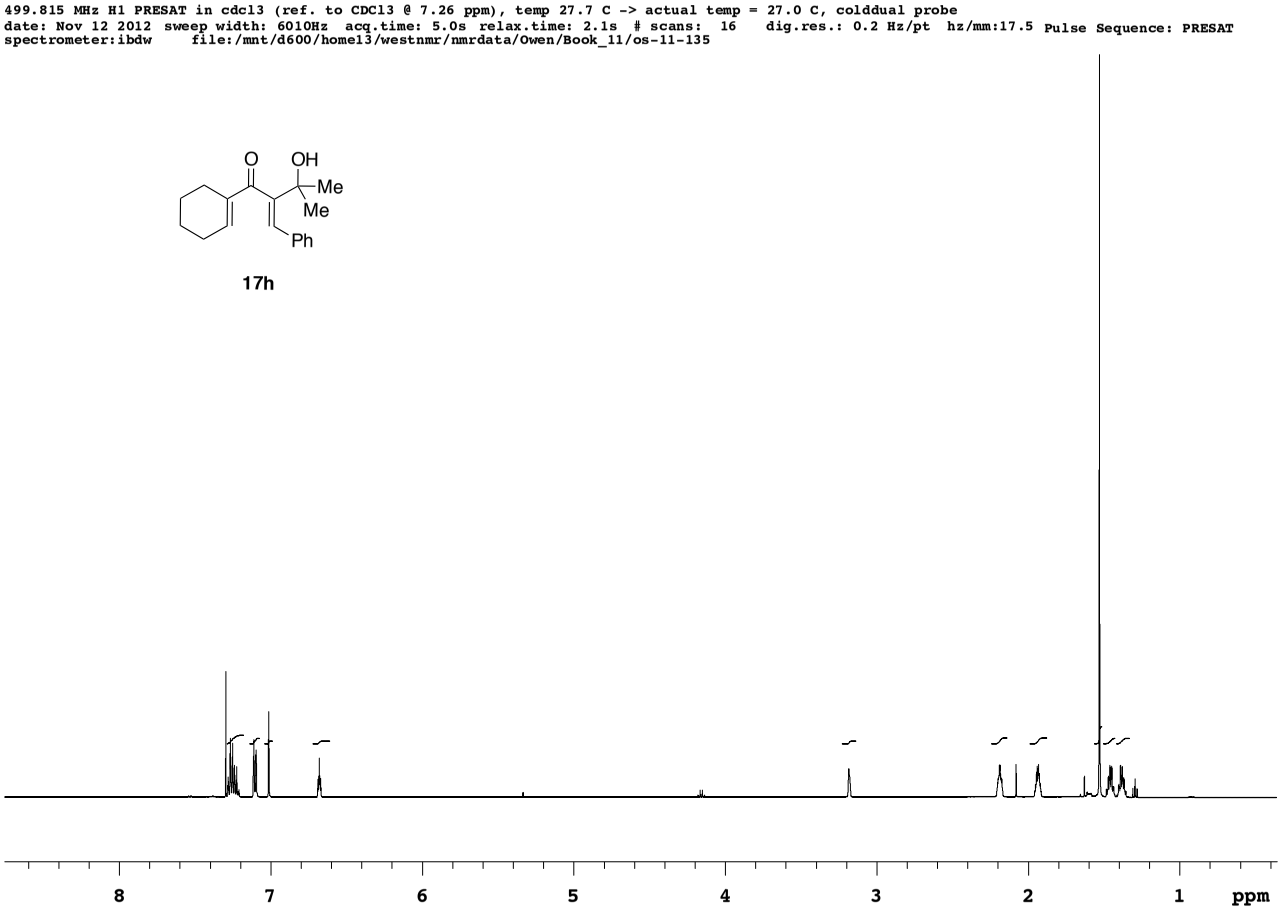

125.693 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Oct 11 2012 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 128 dig.res.: 0.3 Hz/pt hz/mm:112.5Pulse Sequence: s2pul
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_11/os-11-091_13C
O
OH
Me
Me
Me
Ph
Ph
17b
200
180
160
140
120
100
80
60
40
20
ppm

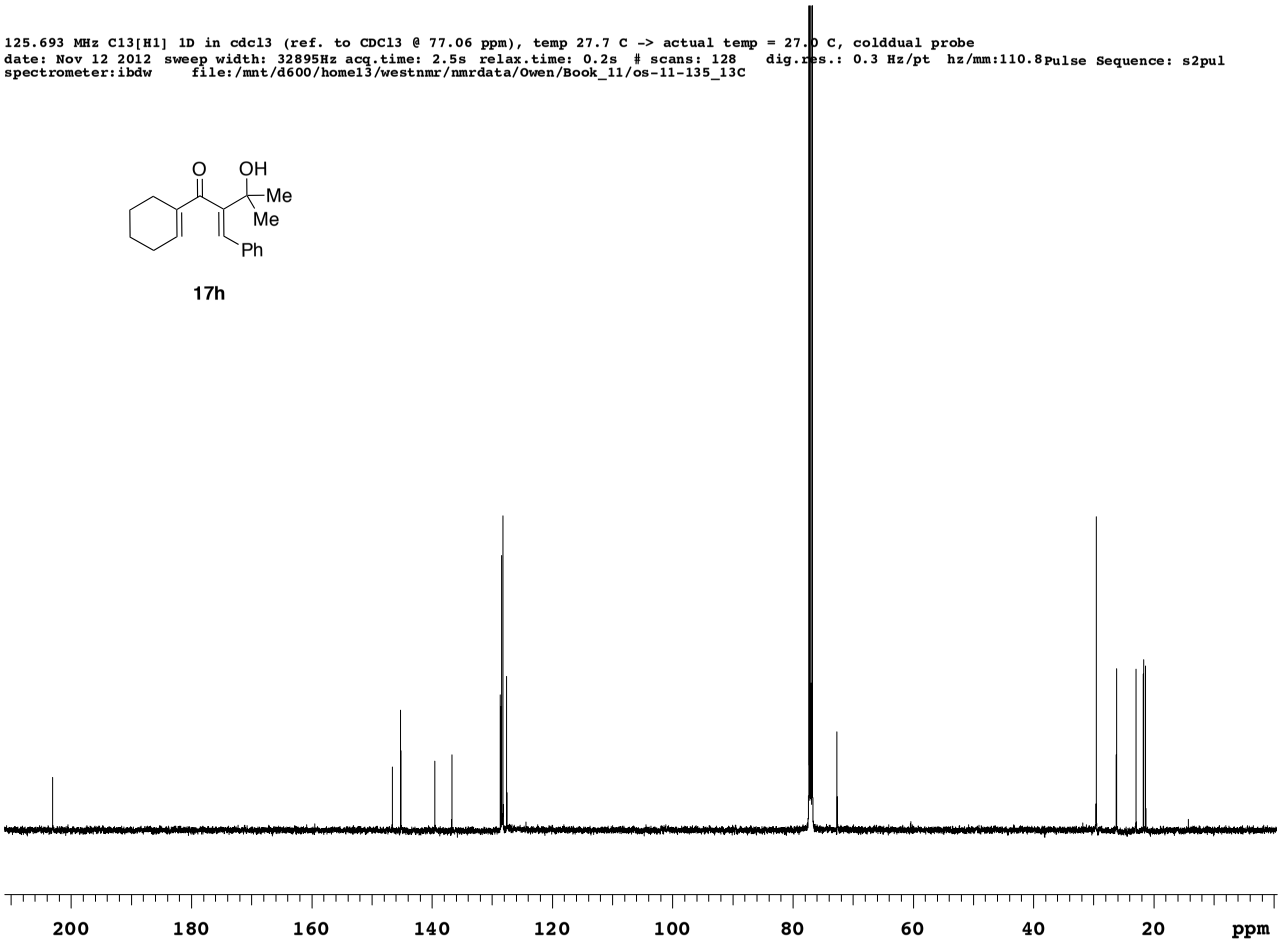
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Jul 24 2013 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:15.5 Pulse Sequence: PRESAT
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Owen/2013.07/2013.07.24.u5_os-2d_17.36_H1_1D



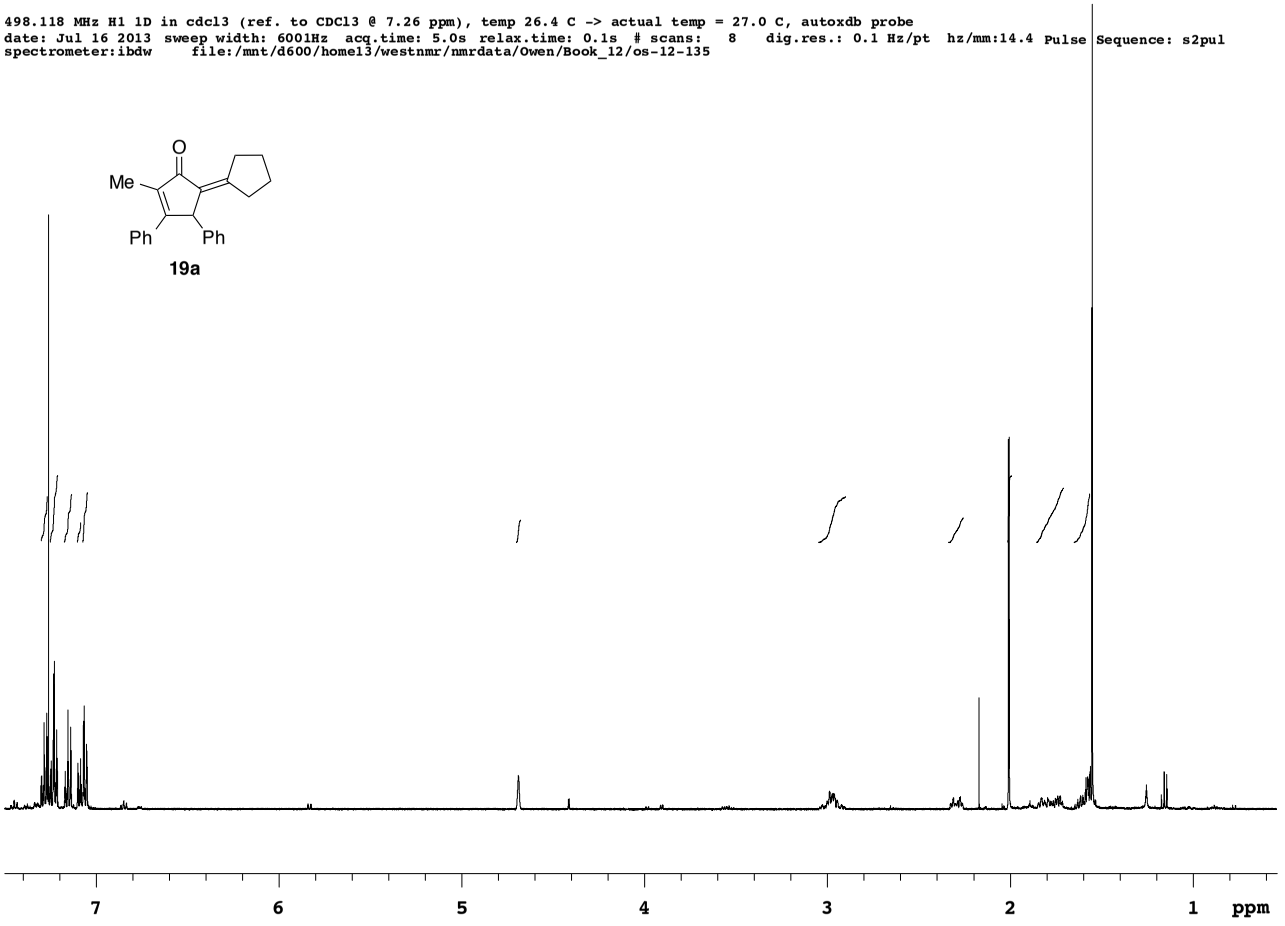
17d

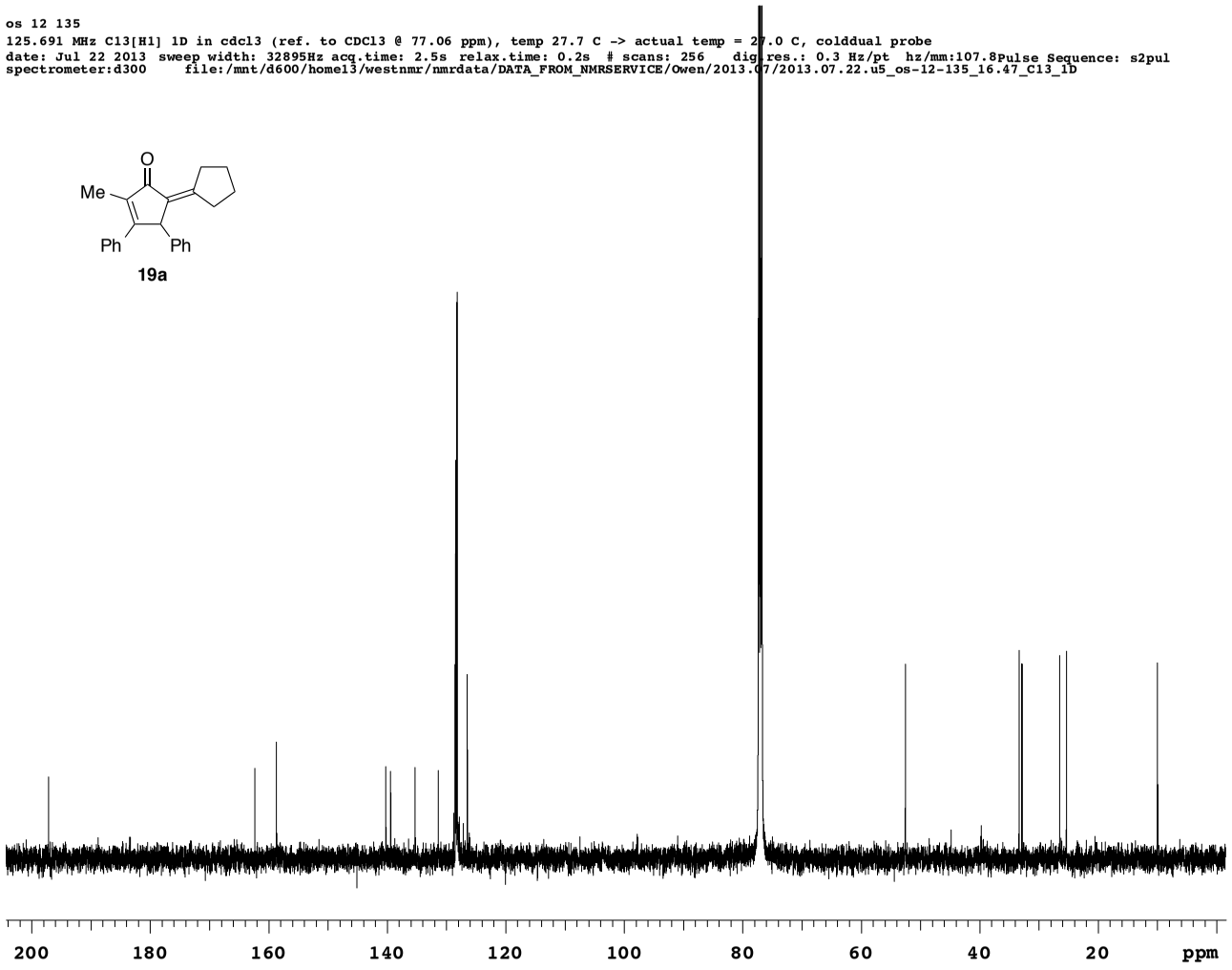

125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Jul 24 2013 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 128 dig.res.: 0.3 Hz/pt hz/mm:112.0Pulse Sequence: s2pul
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Owen/2013.07/2013.07.24.u5_os-2d_17.38_C13_1D
O
OH
Me
Me
Ph
17d
200
180
160
140
120
100
80
60
40
20
ppm


499.815 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Nov 12 2012 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:17.5 Pulse Sequence: PRESAT
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_11/os-11-135
O
OH
Me
Me
Ph
17h
8
7
6
5
4
3
2
1
ppm


125.693 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Nov 12 2012 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 128 dig.res.: 0.3 Hz/pt hz/mm:110.8 Pulse Sequence: s2pul
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_11/os-11-135_13C
O
OH
Me
Me
Ph
200
180
160
140
120
100
80
60
40
20
ppm

17h

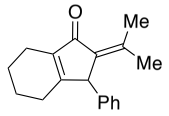

498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe
date: Jul 16 2013 sweep width: 6001Hz acq.time: 5.0s relax.time: 0.1s # scans: 8 dig.res.: 0.1 Hz/pt hz/mm:14.4 Pulse Sequence: s2pul
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_12/os-12-135
O
Me
Ph
Ph
19a
7
6
5
4
3
2
1
ppm


os 12 135
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Jul 22 2013 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 256 dig res.: 0.3 Hz/pt hz/mm:107.8Pulse Sequence: s2pul
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Owen/2013.07/2013.07.22.u5_os-12-135_16.47_C13_1D
O
Me
Ph
Ph
19a
200
180
160
140
120
100
80
60
40
20
ppm

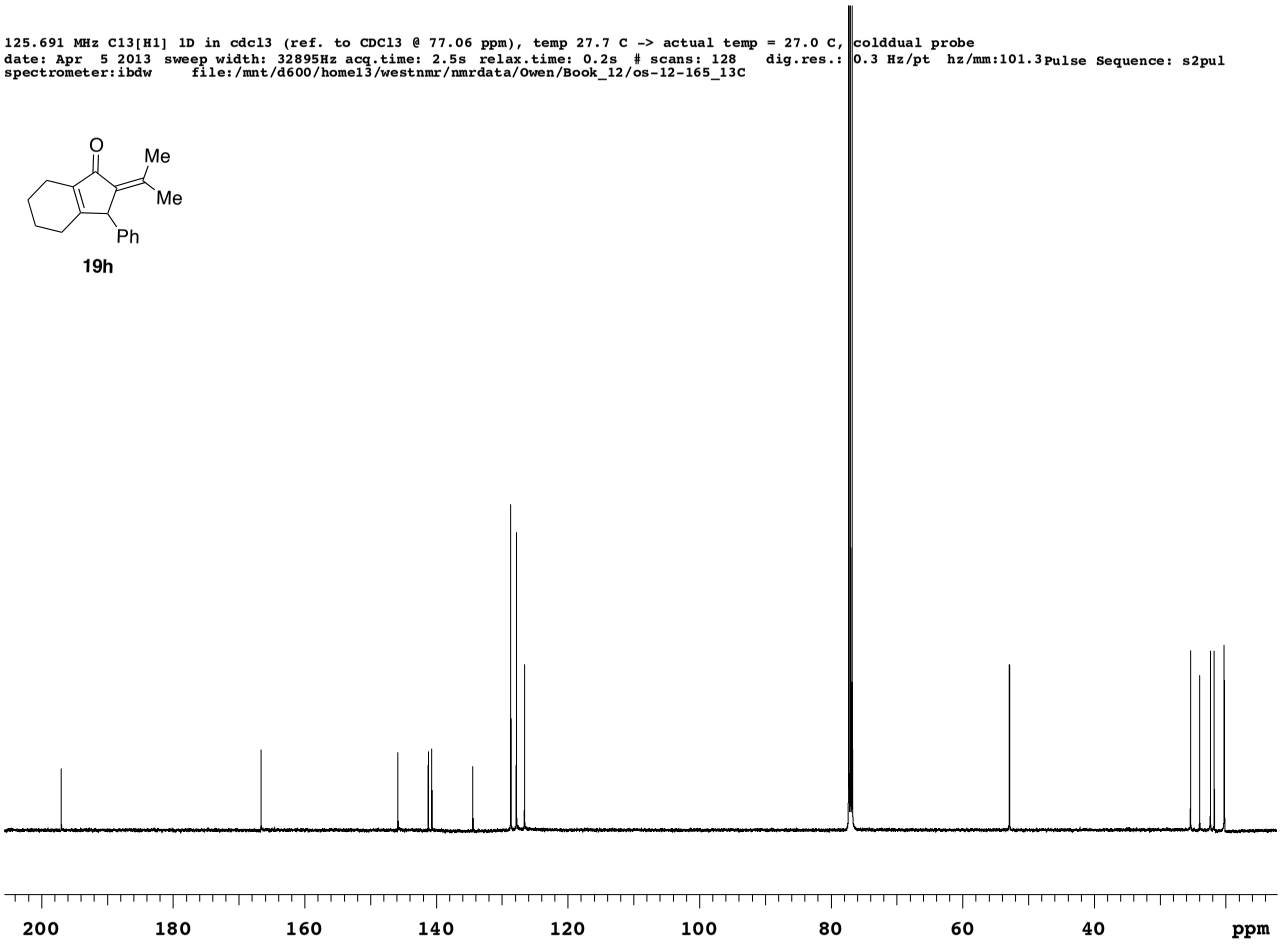
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

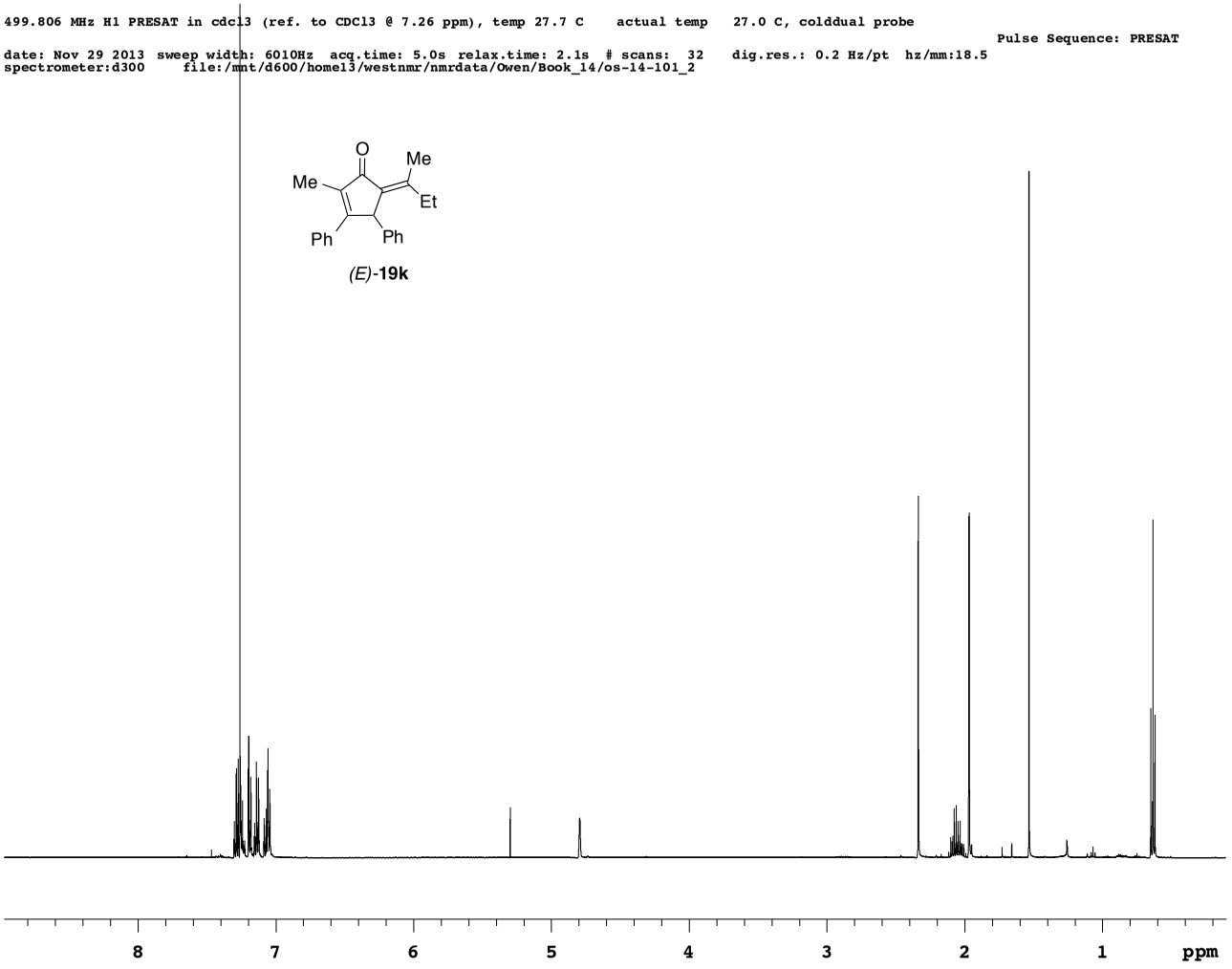
Pulse Sequence: PRESAT

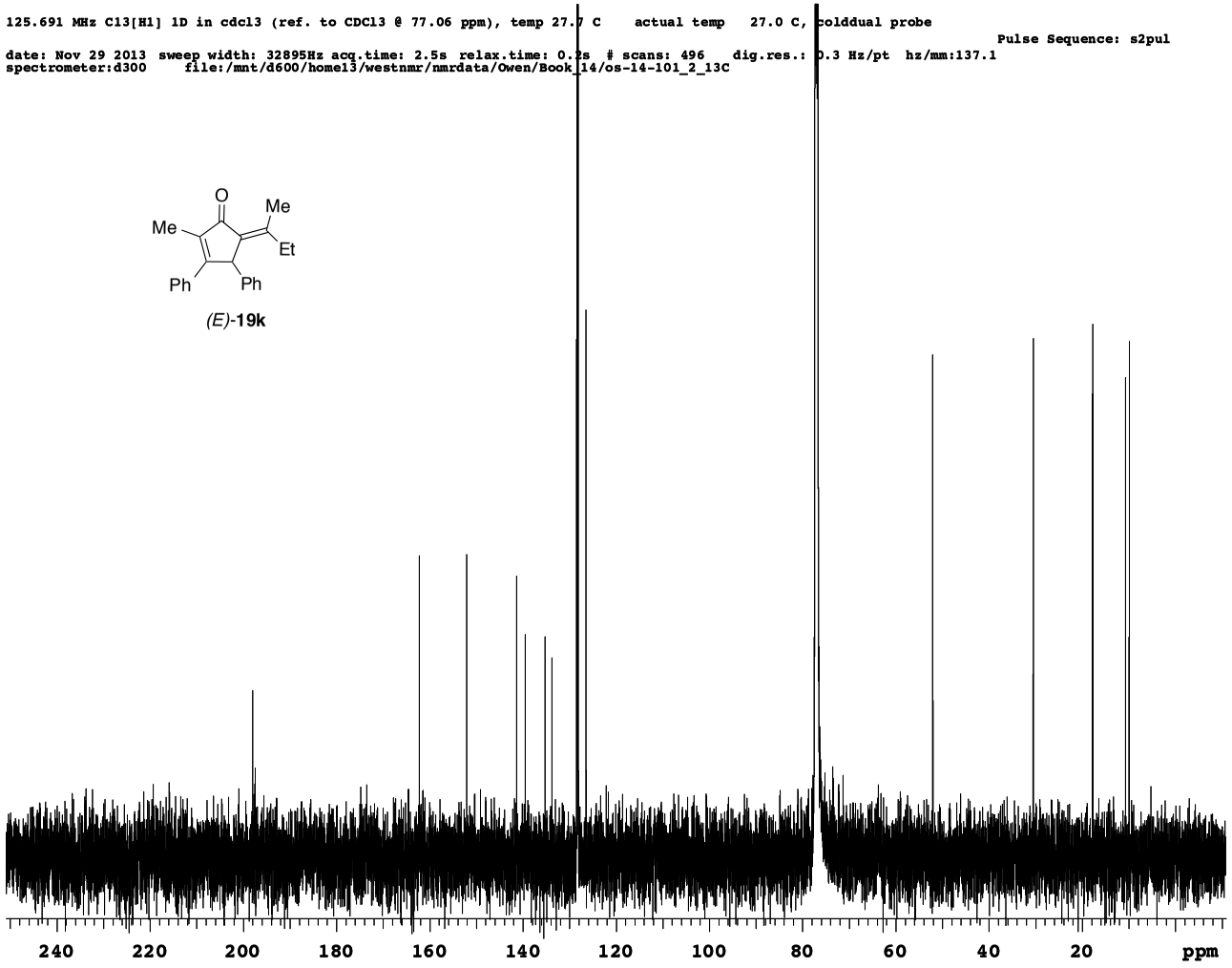
date: Apr 5 2013 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:16.6
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_12/os-12-165



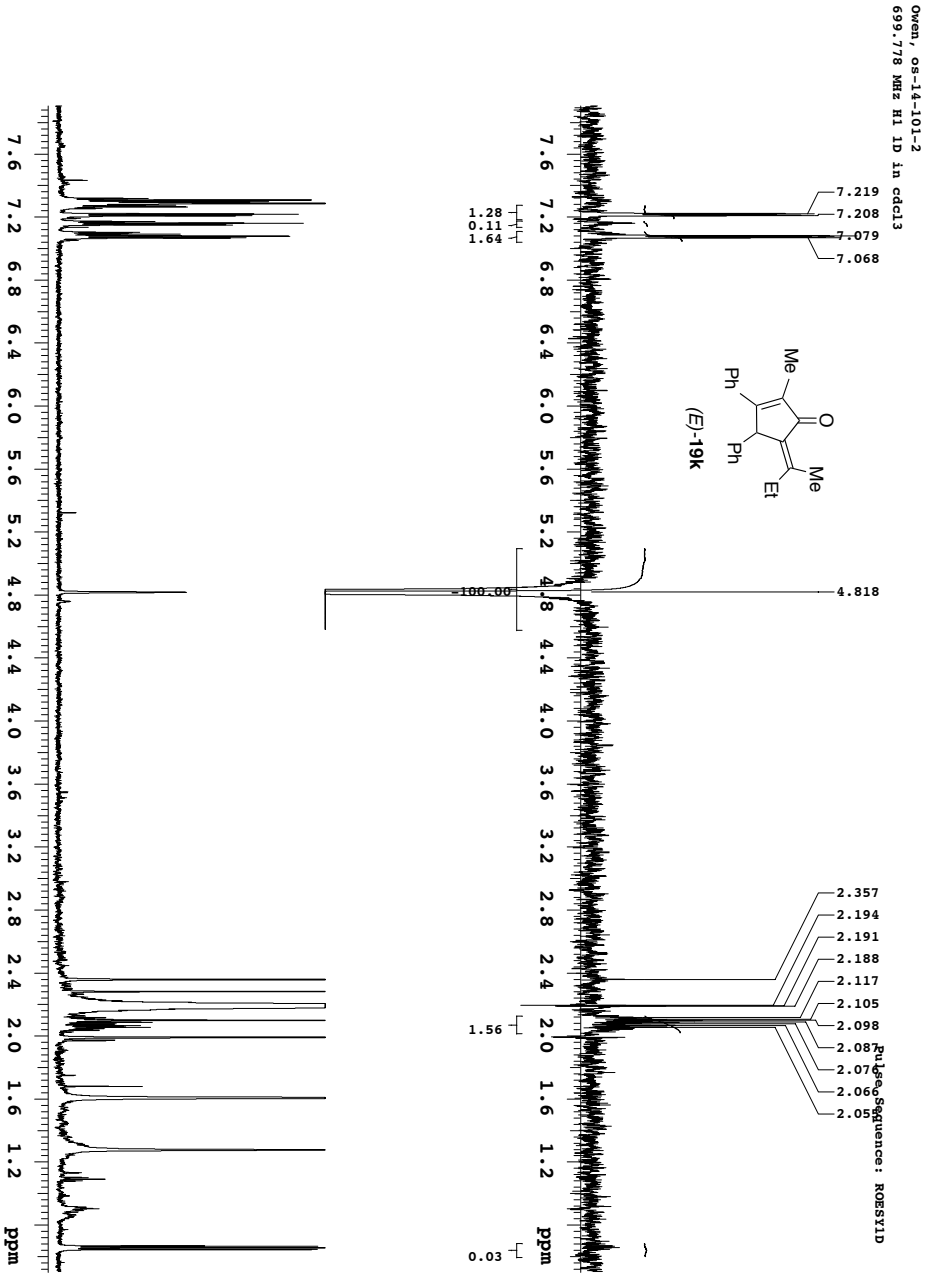
19h


125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Apr 5 2013 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 128 dig.res.: 0.3 Hz/pt hz/mm:101.3Pulse Sequence: s2pul
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_12/os-12-165_13C
O
Me
Me
Ph
19h
200
180
160
140
120
100
80
60
40
ppm


499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C actual temp 27.0 C, colddual probe
Pulse Sequence: PRESAT
date: Nov 29 2013 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 32 dig.res.: 0.2 Hz/pt hz/mm:18.5
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_14/os-14-101_2
O
Me
Me
Et
Ph
Ph
(E)-19k
8
7
6
5
4
3
2
1
ppm


125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C actual temp 27.0 C, colddual probe
Pulse Sequence: s2pul
date: Nov 29 2013 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 496 dig.res.: 0.3 Hz/pt hz/mm:137.1
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_14/os-14-101_2_13C
O
Me
Me
Et
Ph
Ph
240
220
200
180
160
140
120
100
80
60
40
20
ppm

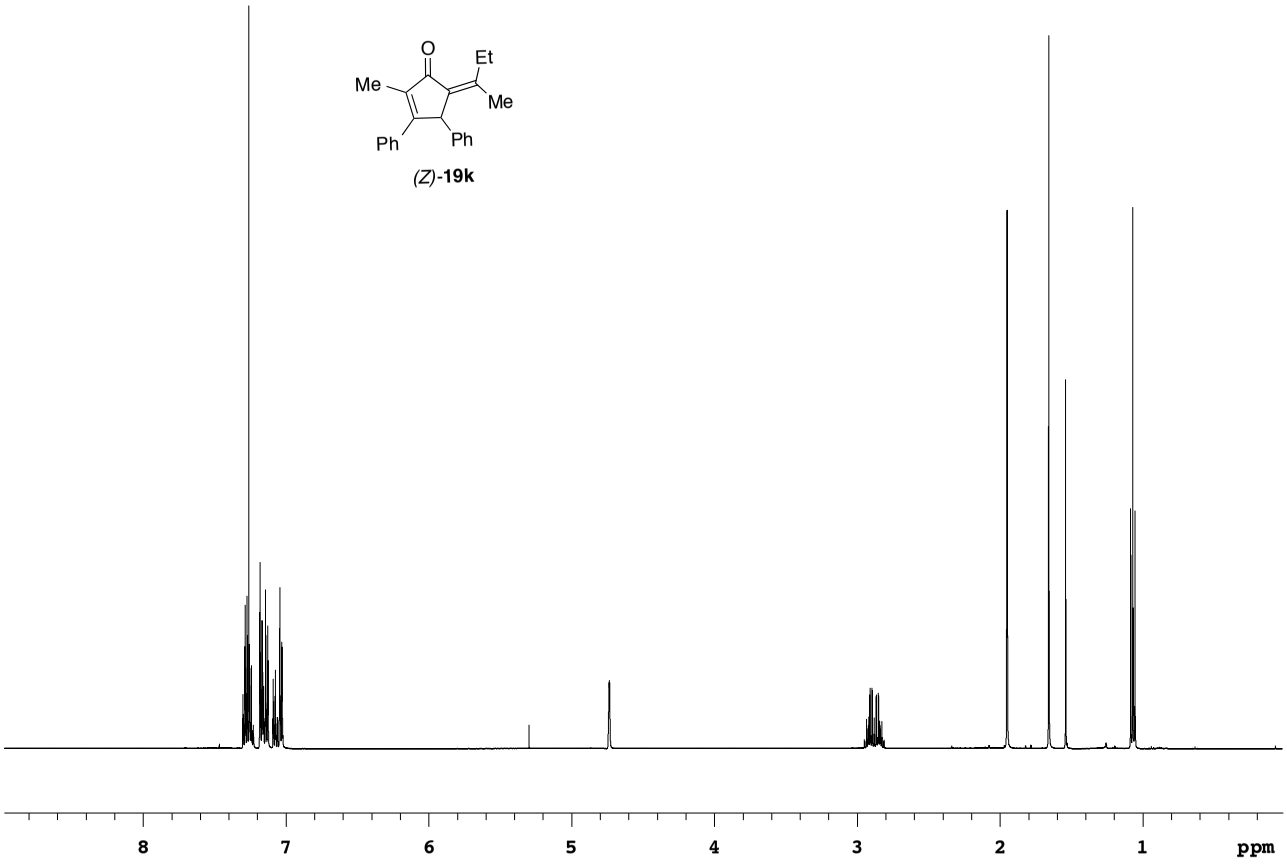
(E)-**19k**


Owen, os-14-101-2
699.778 MHz H1 1D in cdcl3
7.219
7.208
7.079
7.068
1.28
0.11
1.64
Me
Ph
O
Me
Ph
Et
(E)-19k
4.818
100.00
2.357
2.194
2.191
2.188
2.117
2.105
2.098
2.087
2.076
2.066
2.055
1.56
0.03
Pulse Sequence: ROESYID
ppm

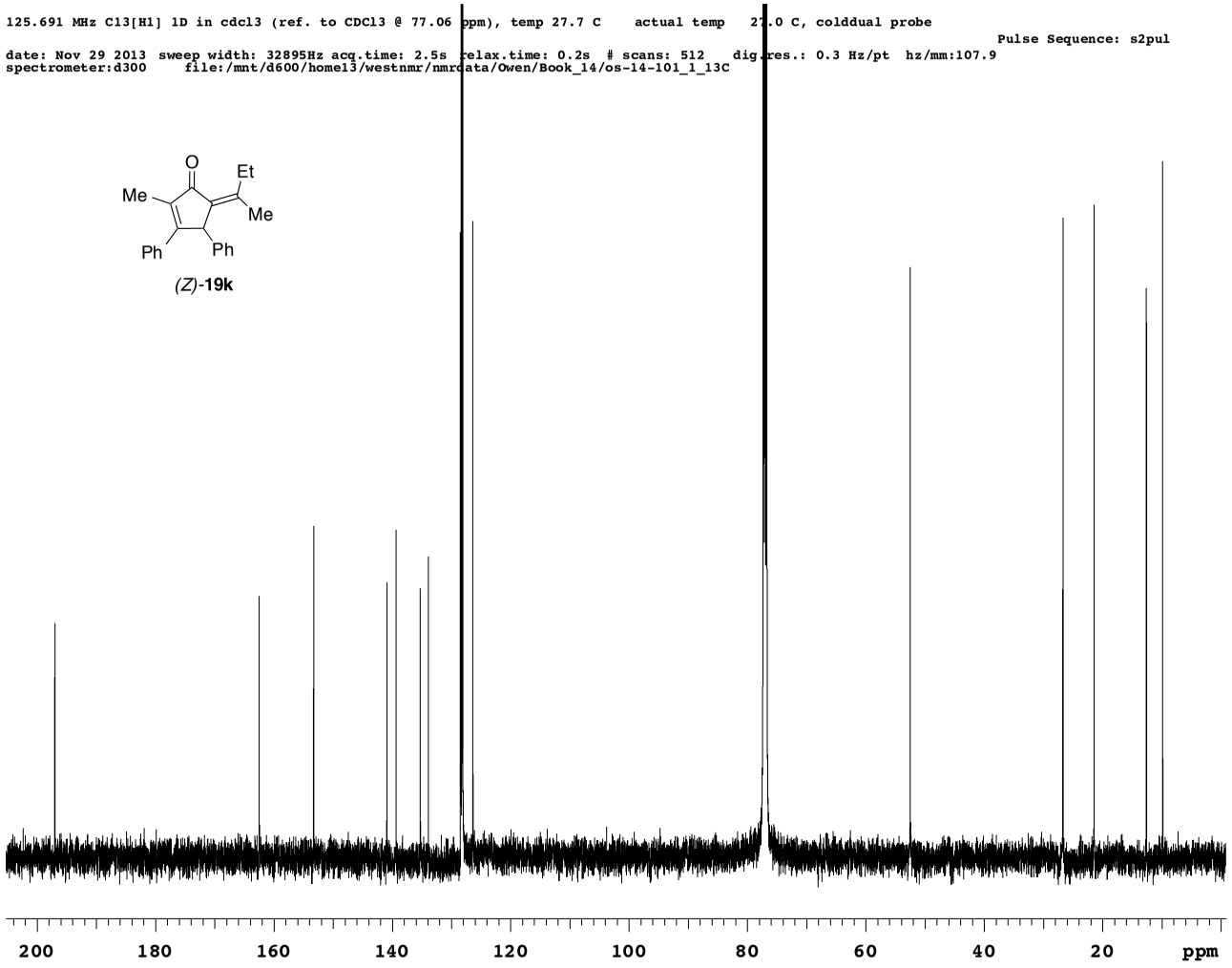
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C actual temp 27.0 C, colddual probe

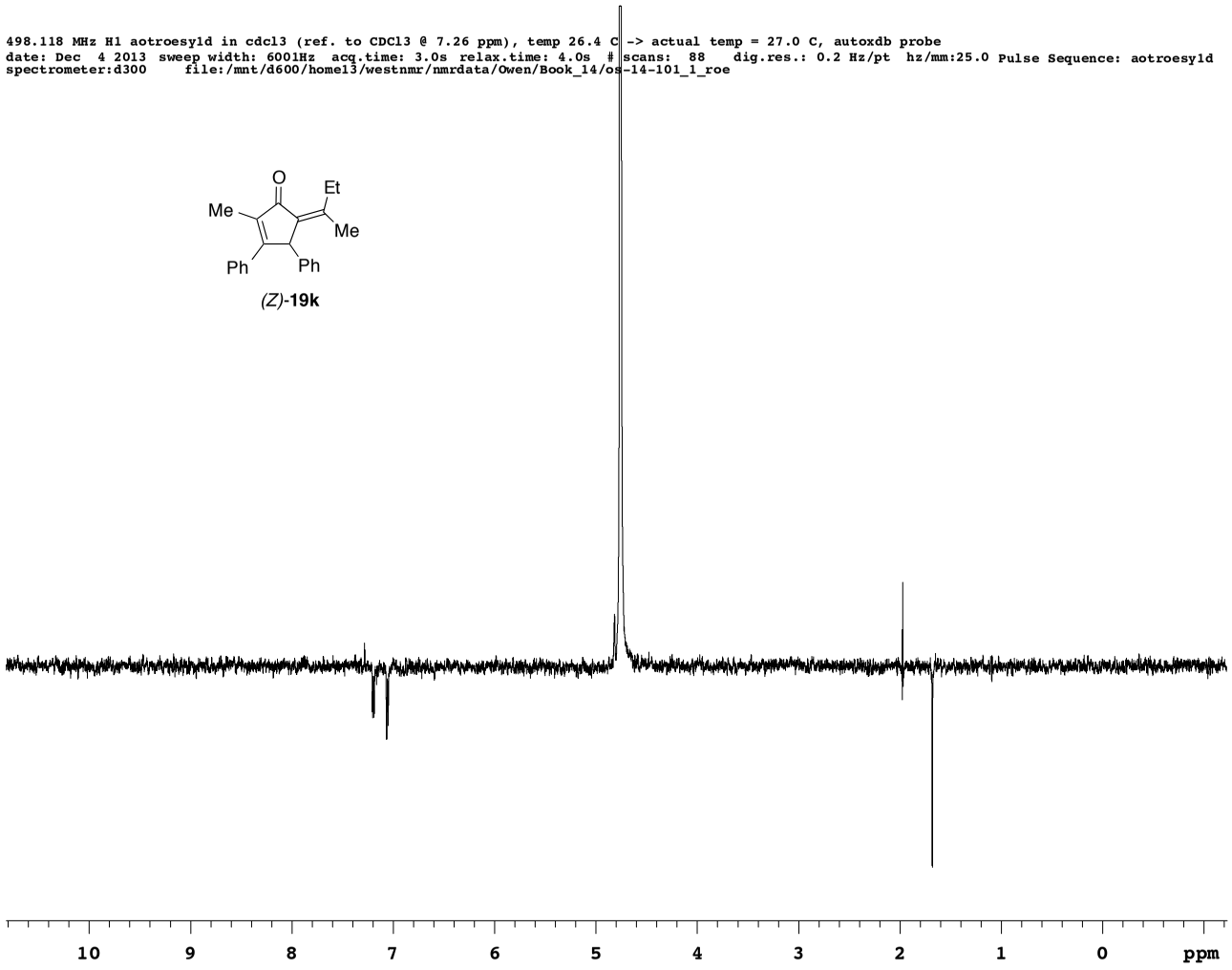
Pulse Sequence: PRESAT

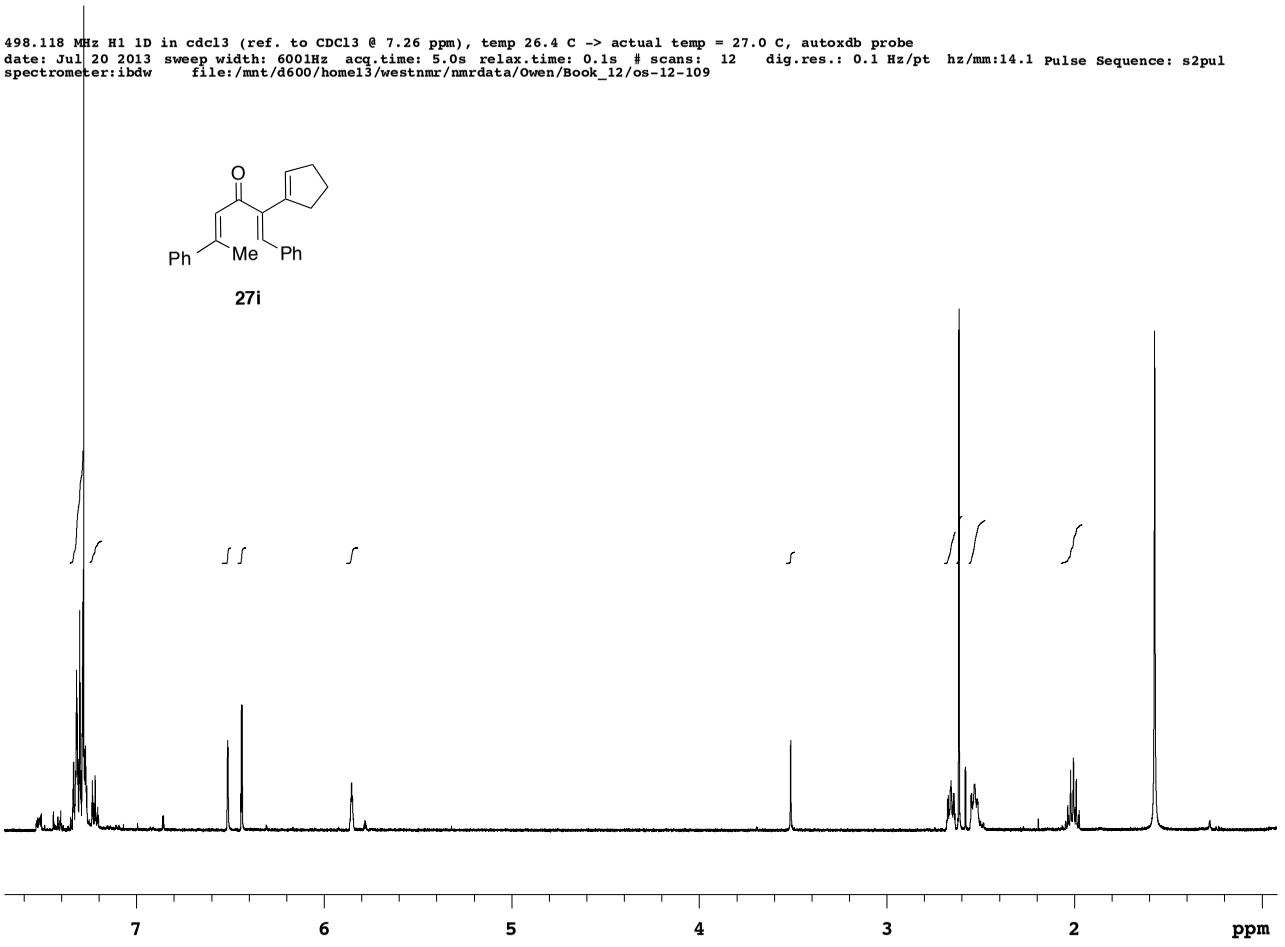
date: Nov 29 2013 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 32 dig.res.: 0.2 Hz/pt hz/mm:18.6
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_14/os-14-101_1

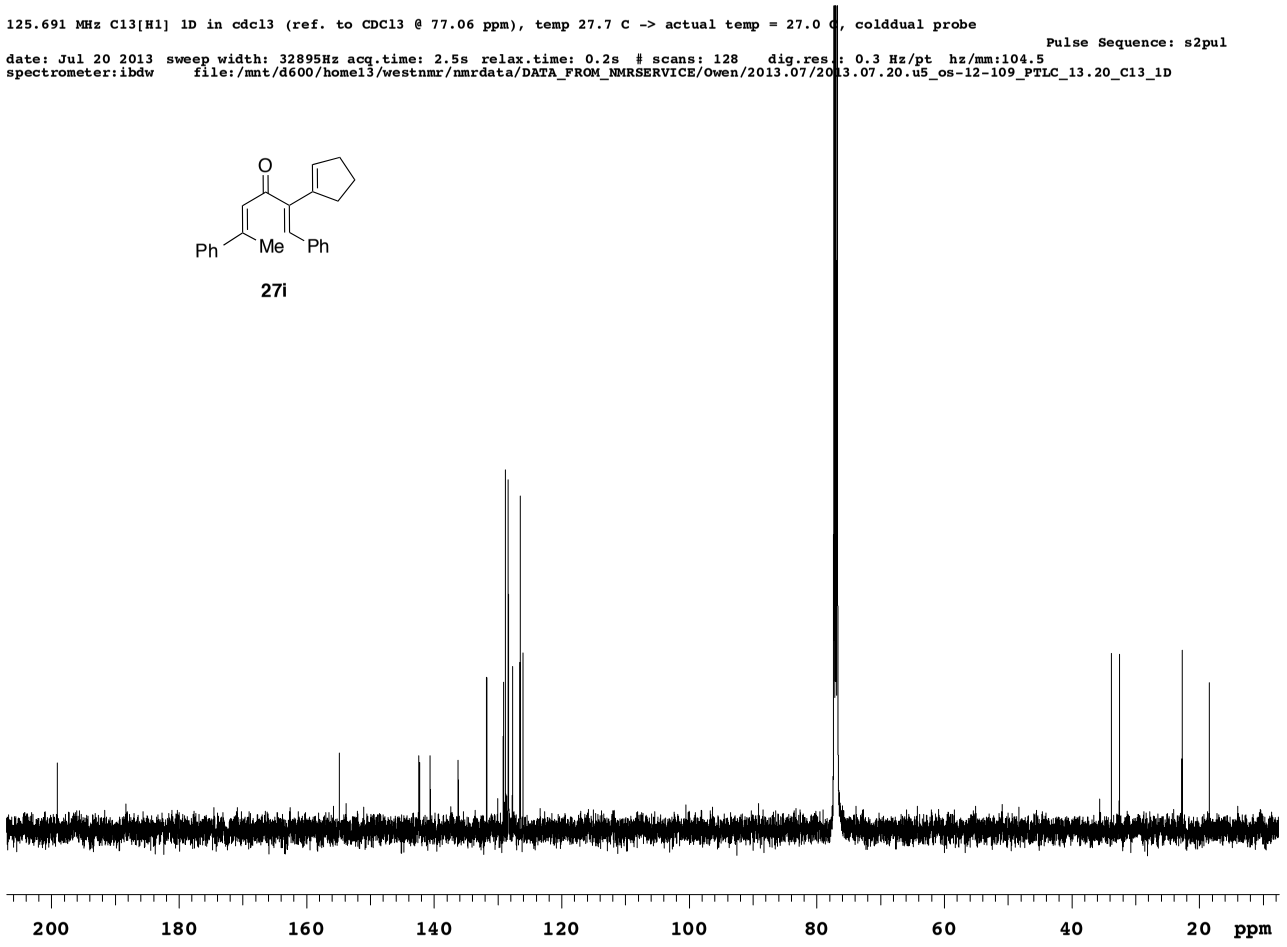


(Z)-**19k**

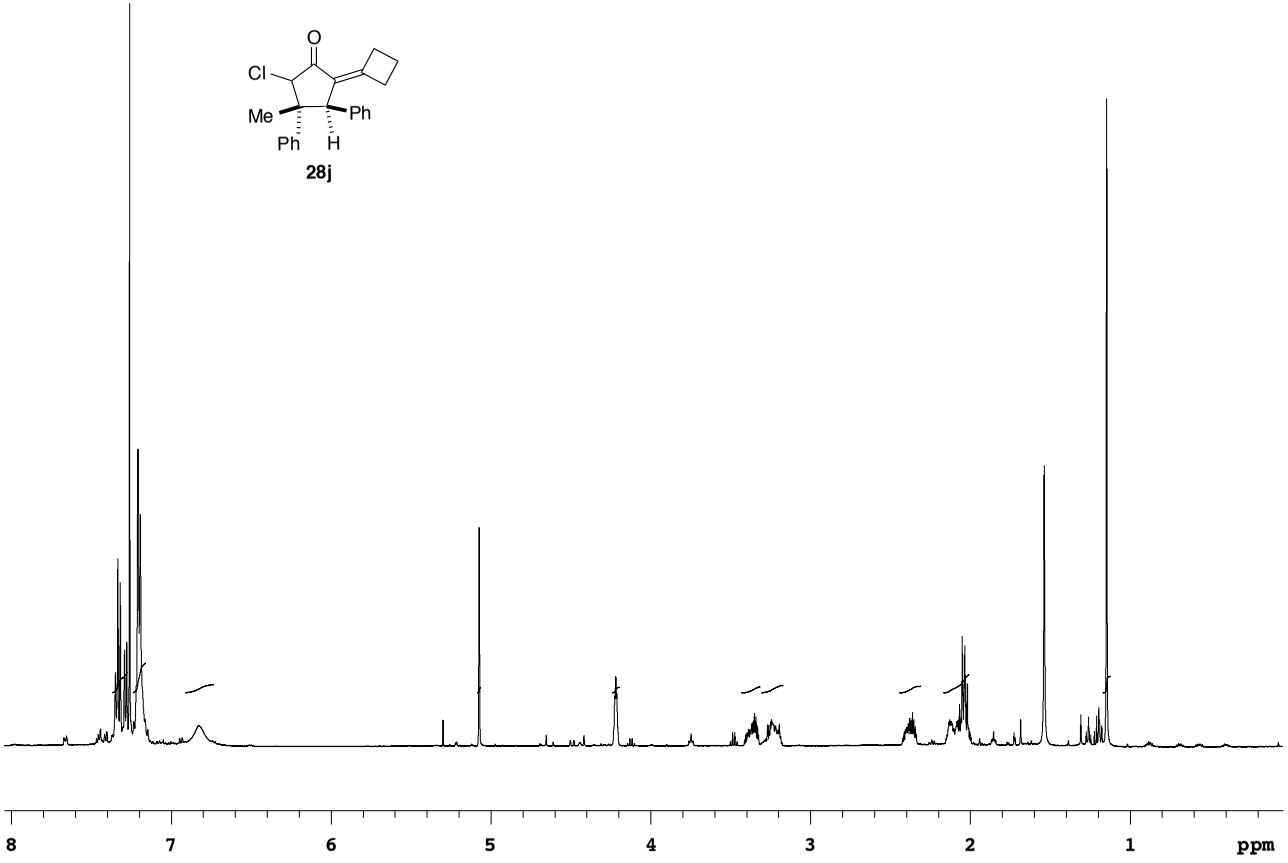

125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C actual temp 27.0 C, colddual probe
Pulse Sequence: s2pul
date: Nov 29 2013 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 512 dig.res.: 0.3 Hz/pt hz/mm:107.9
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_14/os-14-101_1_13C
O
Et
Me
Me
Ph
Ph
(Z)-19k
200
180
160
140
120
100
80
60
40
20
ppm

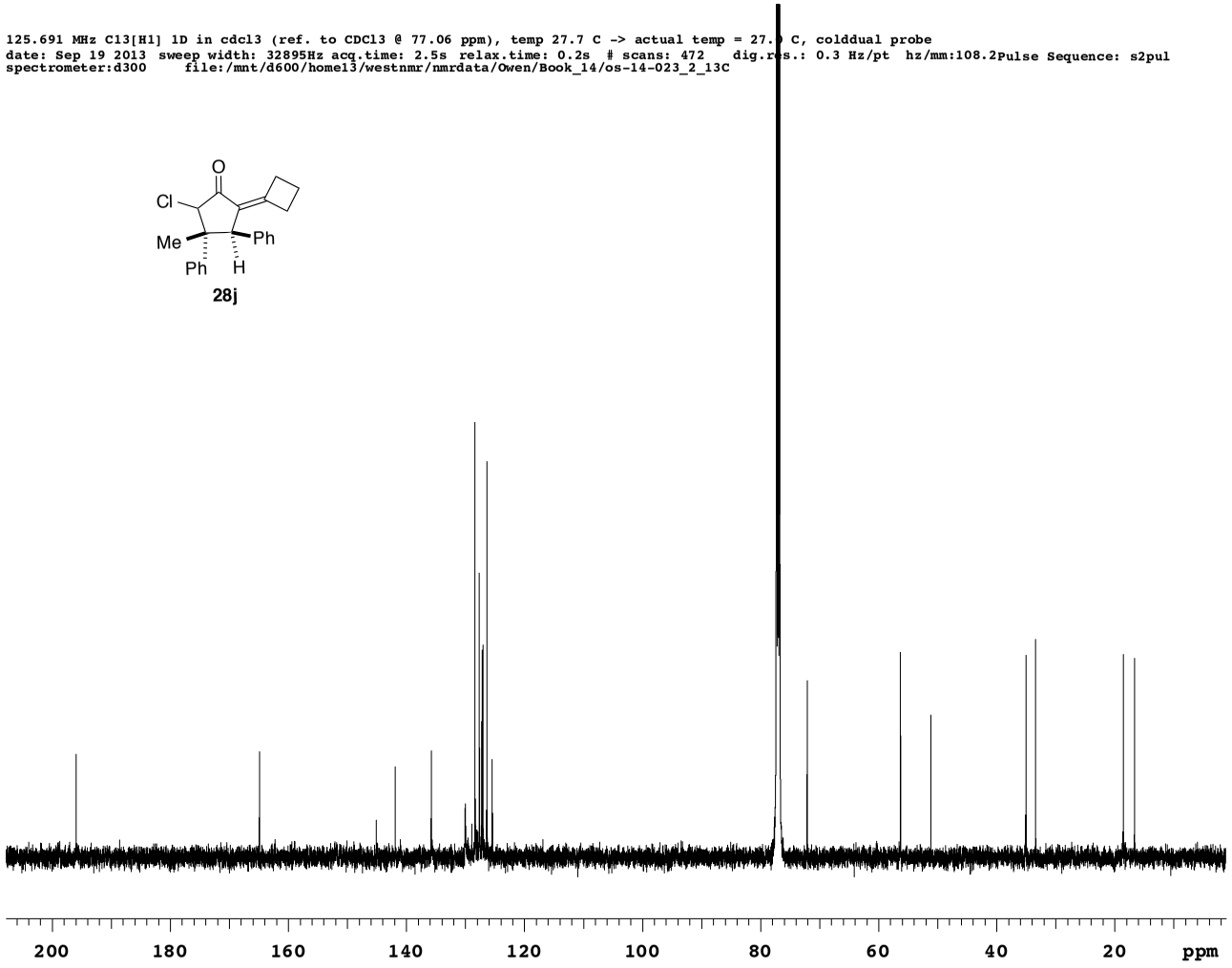

498.118 MHz H1 aotroesy1d in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe
date: Dec 4 2013 sweep width: 6001Hz acq.time: 3.0s relax.time: 4.0s # scans: 88 dig.res.: 0.2 Hz/pt hz/mm:25.0 Pulse Sequence: aotroesy1d
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_14/os-14-101_1_roe
O
Et
Me
Me
Ph
Ph
(Z)-19k
10
9
8
7
6
5
4
3
2
1
0
ppm


498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe
date: Jul 20 2013 sweep width: 6001Hz acq.time: 5.0s relax.time: 0.1s # scans: 12 dig.res.: 0.1 Hz/pt hz/mm:14.1 Pulse Sequence: s2pul
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_12/os-12-109
O
Ph
Me
Ph
27i
7
6
5
4
3
2
ppm

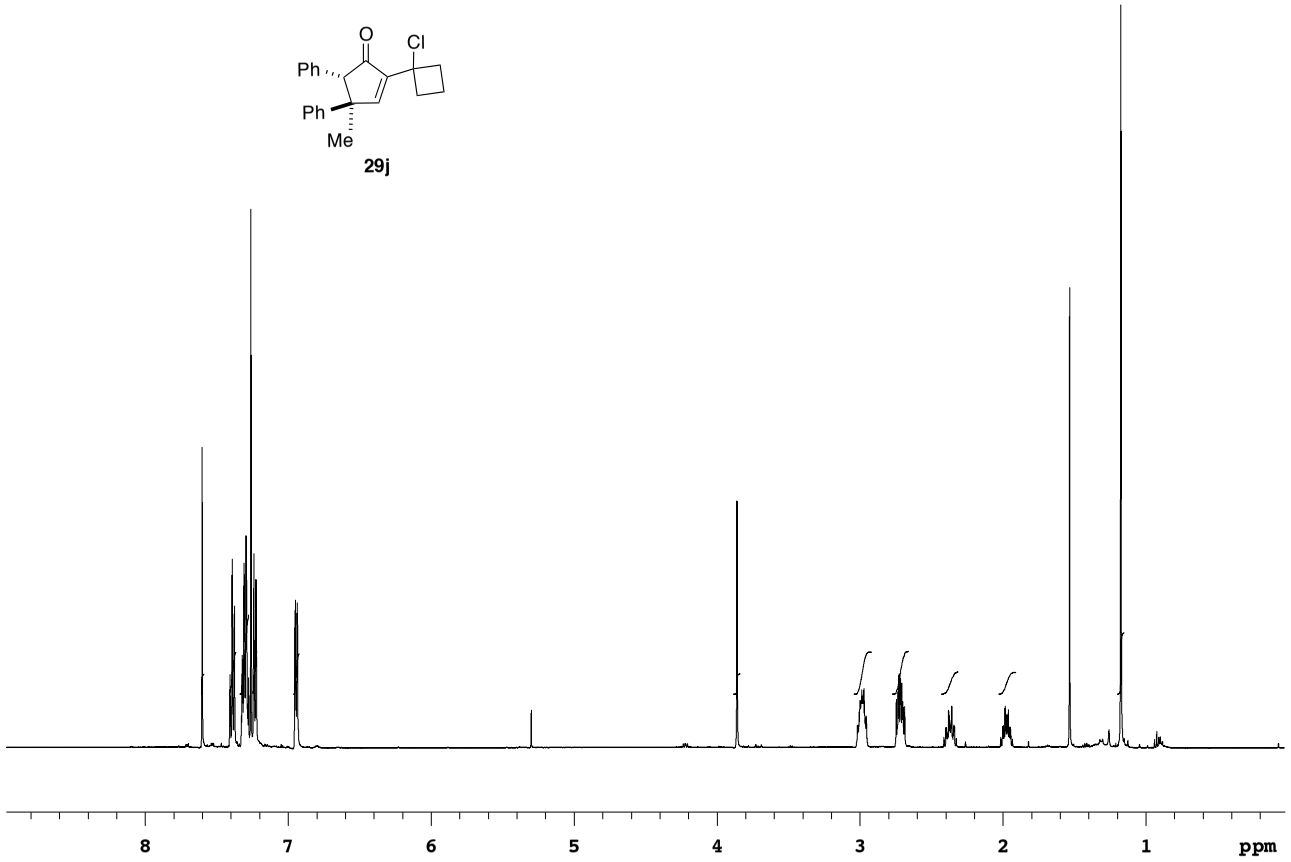

125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
Pulse Sequence: s2pul
date: Jul 20 2013 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 128 dig.res.: 0.3 Hz/pt hz/mm:104.5
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Owen/2013.07/2013.07.20.u5_os-12-109_PTLC_13.20_C13_1D
O
Ph
Me
Ph
27i
200
180
160
140
120
100
80
60
40
20
ppm

499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Sep 19 2013 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 64 dig.res.: 0.2 Hz/pt hz/mm:16.7 Pulse Sequence: PRESAT
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_14/os-14-023_2

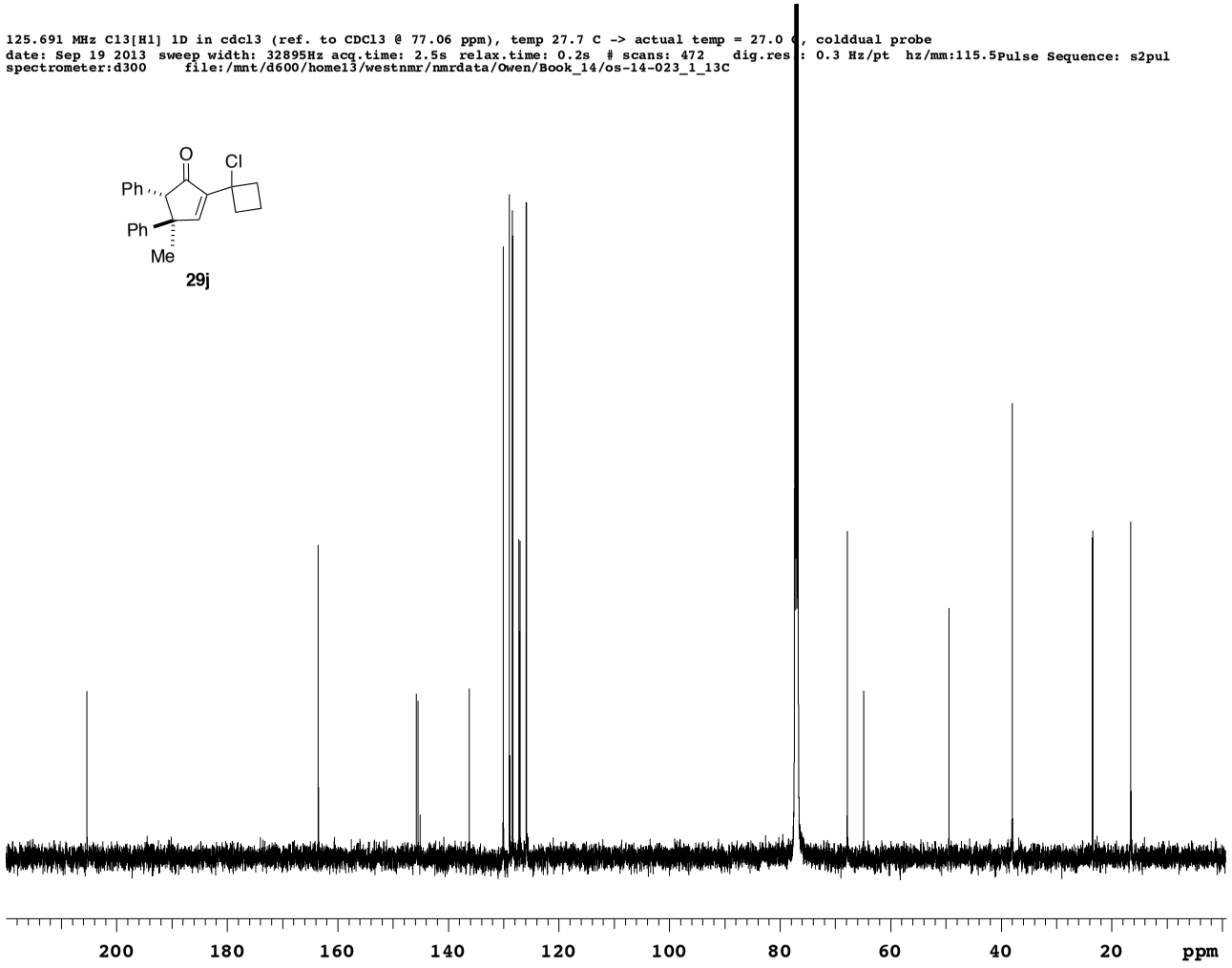


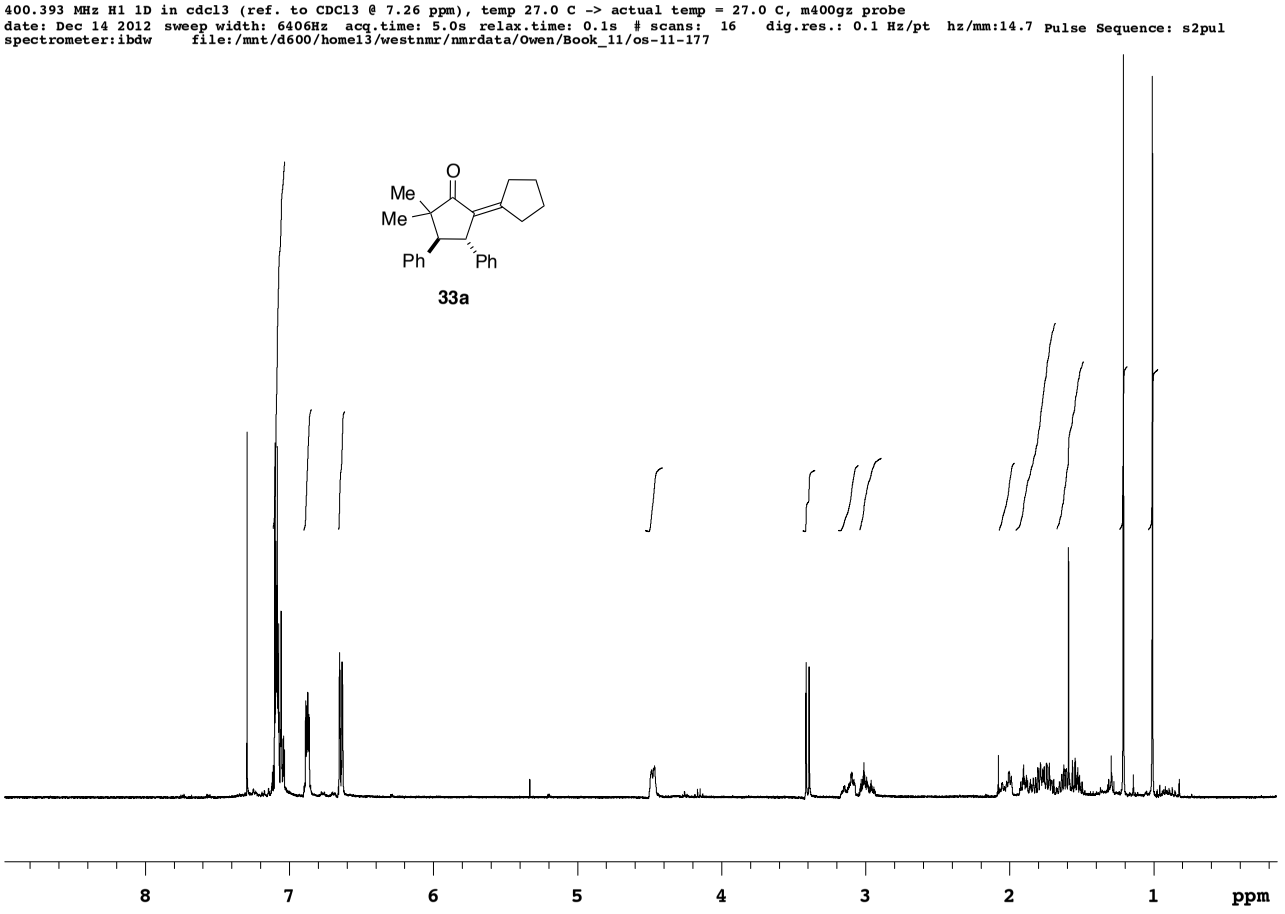

125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Sep 19 2013 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 472 dig.res.: 0.3 Hz/pt hz/mm:108.2Pulse Sequence: s2pul
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_14/os-14-023_2_13C
O
Cl
Me
Ph
Ph
H
28j
200
180
160
140
120
100
80
60
40
20
ppm

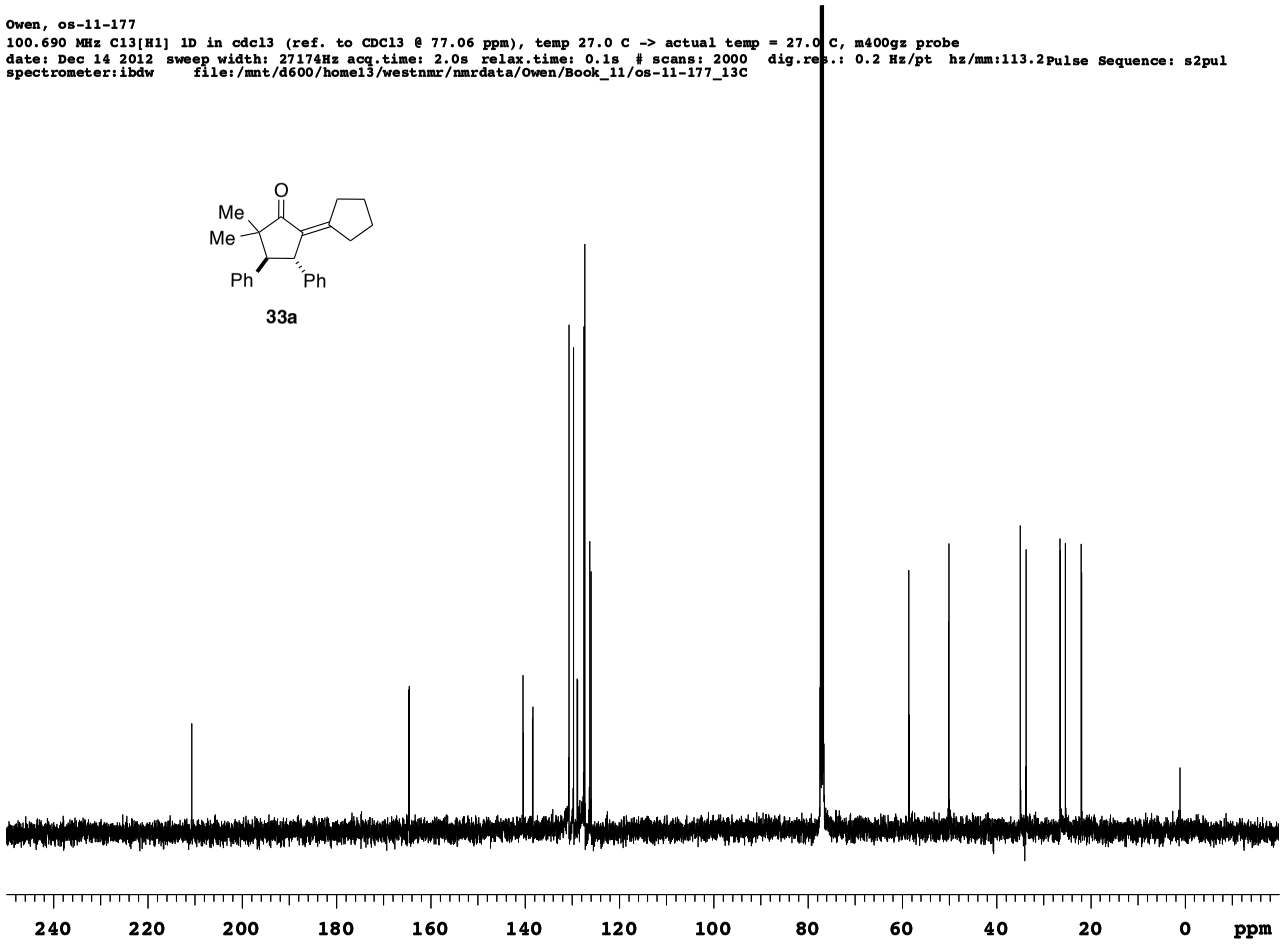
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Sep 19 2013 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 64 dig.res.: 0.2 Hz/pt hz/mm:18.6 Pulse Sequence: PRESAT
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_14/os-14-023_1



29j


125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Sep 19 2013 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 472 dig.res : 0.3 Hz/pt hz/mm:115.5Pulse Sequence: s2pul
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_14/os-14-023_1_13C
O
Cl
Ph
Ph
Me
29j
200
180
160
140
120
100
80
60
40
20
ppm


400.393 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
date: Dec 14 2012 sweep width: 6406Hz acq.time: 5.0s relax.time: 0.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:14.7 Pulse Sequence: s2pul
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_11/os-11-177
O
Me
Me
Ph
Ph
33a
8
7
6
5
4
3
2
1
ppm


Owen, os-11-177
100.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
date: Dec 14 2012 sweep width: 27174Hz acq.time: 2.0s relax.time: 0.1s # scans: 2000 dig.res.: 0.2 Hz/pt hz/mm:113.2Pulse Sequence: s2pul
spectrometer:ibdw file:/mnt/d600/home13/westnmr/nmrdata/Owen/Book_11/os-11-177_13C
O
Me
Me
Ph
Ph
33a
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Appendix IV: X-ray Crystallographic Data for Cycloadduct 27a

(Chapter 2)

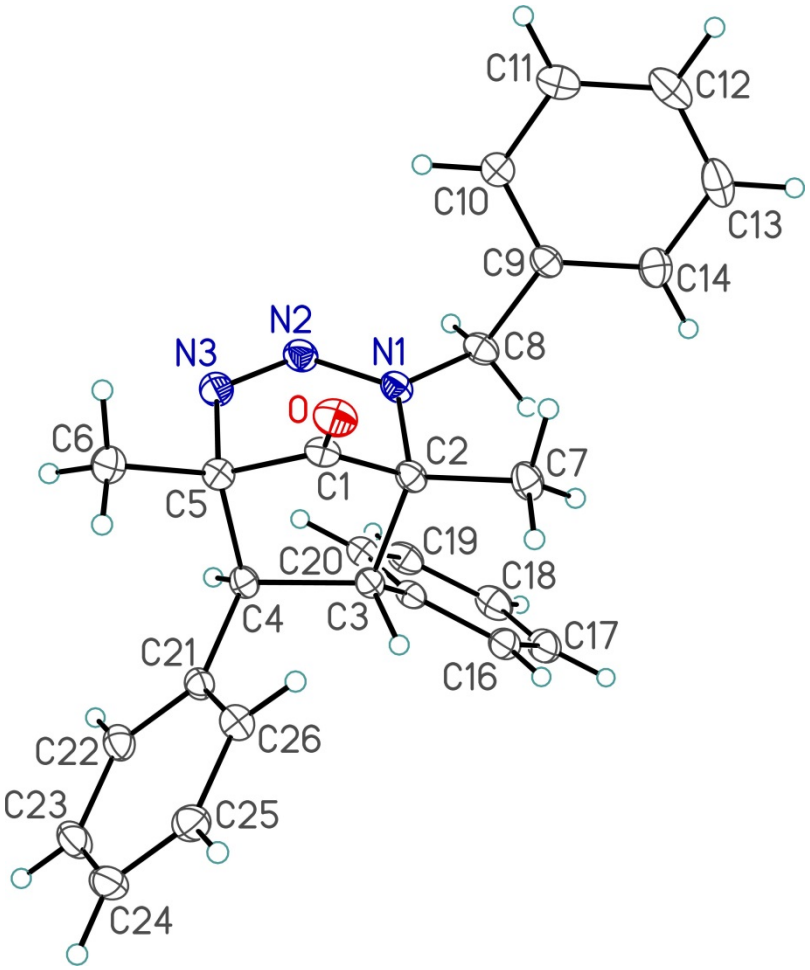
STRUCTURE REPORT

XCL Code: FGW1002 **Date:** 22 January 2010

Compound: 4-benzyl-1,5-dimethyl-6,7-diphenyl-2,3,4-triazabicyclo[3.2.1]oct-2-en-8-one

Formula: $C_{26}H_{25}N_3O$

Supervisor: F. G. West **Crystallographer:** M. J. Ferguson



Cycloadduct 27a

Figure Legends

Figure 1. Perspective view of the 4-benzyl-1,5-dimethyl-6,7-diphenyl-2,3,4-triaza-bicyclo[3.2.1]oct-2-en-8-one molecule showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{26}H_{25}N_3O$
formula weight	395.49
crystal dimensions (mm)	0.63 × 0.50 × 0.34
crystal system	triclinic
space group	*P1* (No. 2)
unit cell parameters[a]	
a (Å)	9.5322 (3)
b (Å)	10.3847 (3)
c (Å)	12.3527 (3)
α (deg)	84.4292 (3)
β (deg)	72.2128 (3)
γ (deg)	66.9269 (3)
V (Å^3)	1070.83 (5)
Z	2
ρ_{calcd} (g cm^{-3})	1.227
μ (mm^{-1})	0.076
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–100
scan type	ω scans (0.3°) (20 s exposures)
data collection 2θ limit (deg)	55.10
total data collected	9467 (-12 ≤ *h* ≤ 12, -13 ≤ *k* ≤ 13, -16 ≤ *l* ≤ 16)
independent reflections	4876 (R_{int} = 0.0096)
number of observed reflections (*NO*)	4497 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–97*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–97*[c])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9745–0.953
data/restraints/parameters	4876 / 0 / 273
goodness-of-fit (*S*)[d] [all data]	1.072
final *R* indices[e]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0386
wR_2 [all data]	0.1054
largest difference peak and hole	0.281 and –0.200 e Å^{-3}

[a]Obtained from least-squares refinement of 9950 reflections with $4.86° < 2\theta < 55.10°$.

(continued)

Table 1. Crystallographic Experimental Details (continued)

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

[c]Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

[d]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0541P)^2 + 0.2358P]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$).

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

Appendix V: X-ray Crystallographic Data for Cycloadduct 27c

(Chapter 2)

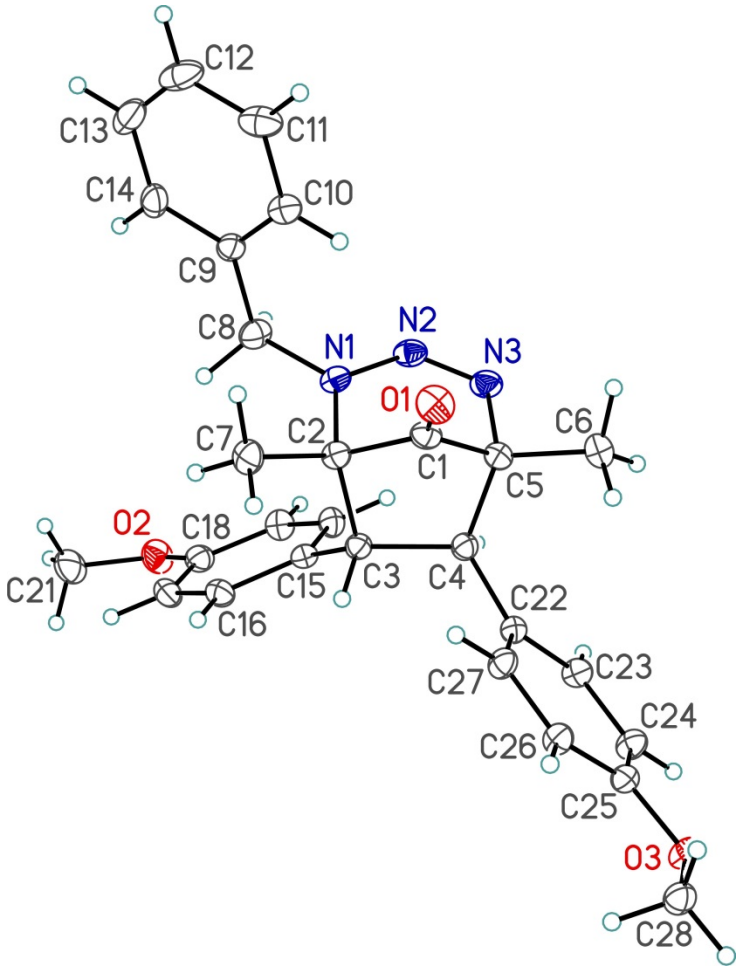
STRUCTURE REPORT

XCL Code: FGW1006 **Date:** 1 April 2010

Compound: 4-benzyl-6,7-bis(4-methoxyphenyl)-1,5-dimethyl-2,3,4-triazabicyclo[3.2.1]oct-2-en-8-one

Formula: $C_{28}H_{29}N_3O_3$

Supervisor: F. G. West **Crystallographer:** M. J. Ferguson



Cycloadduct 27c

Figure Legends

Figure 1. Perspective view of the 4-benzyl-6,7-bis(4-methoxyphenyl)-1,5-dimethyl-2,3,4-triazabicyclo[3.2.1]oct-2-en-8-one molecule showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{28}H_{29}N_3O_3$
formula weight	455.54
crystal dimensions (mm)	0.50 × 0.19 × 0.14
crystal system	monoclinic
space group	*Cc* (No. 9)
unit cell parameters[a]	
a (Å)	16.7182 (13)
b (Å)	15.0048 (12)
c (Å)	9.8096 (8)
β (deg)	102.8601 (8)
V (Å^3)	2399.0 (3)
Z	4
ρ_{calcd} (g cm^{-3})	1.261
μ (mm^{-1})	0.083
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–100
scan type	ω scans (0.3°) (20 s exposures)
data collection 2θ limit (deg)	54.96
total data collected	10405 (-21 ≤ *h* ≤ 21, -19 ≤ *k* ≤ 19, -12 ≤ *l* ≤ 12)
independent reflections	2764 (R_{int} = 0.0148)
number of observed reflections (*NO*)	2685 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (*SIR*97[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–97*[d])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9882–0.9599
data/restraints/parameters	2764 / 0 / 309
Flack absolute structure parameter[e]	0(10)
goodness-of-fit (*S*)[f] [all data]	1.046
final *R* indices[g]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0280
wR_2 [all data]	0.0765
largest difference peak and hole	0.175 and –0.153 e Å^{-3}

[a]Obtained from least-squares refinement of 9276 reflections with 5.00° < 2θ < 54.78°.

(continued)

Table 1. Crystallographic Experimental Details (continued)

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

[c]Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **1999**, *32*, 115–119.

[d]Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

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

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0469P)^2 + 0.5360P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

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

Appendix VI: X-ray Crystallographic Data for Compound 32

(Chapter 2)

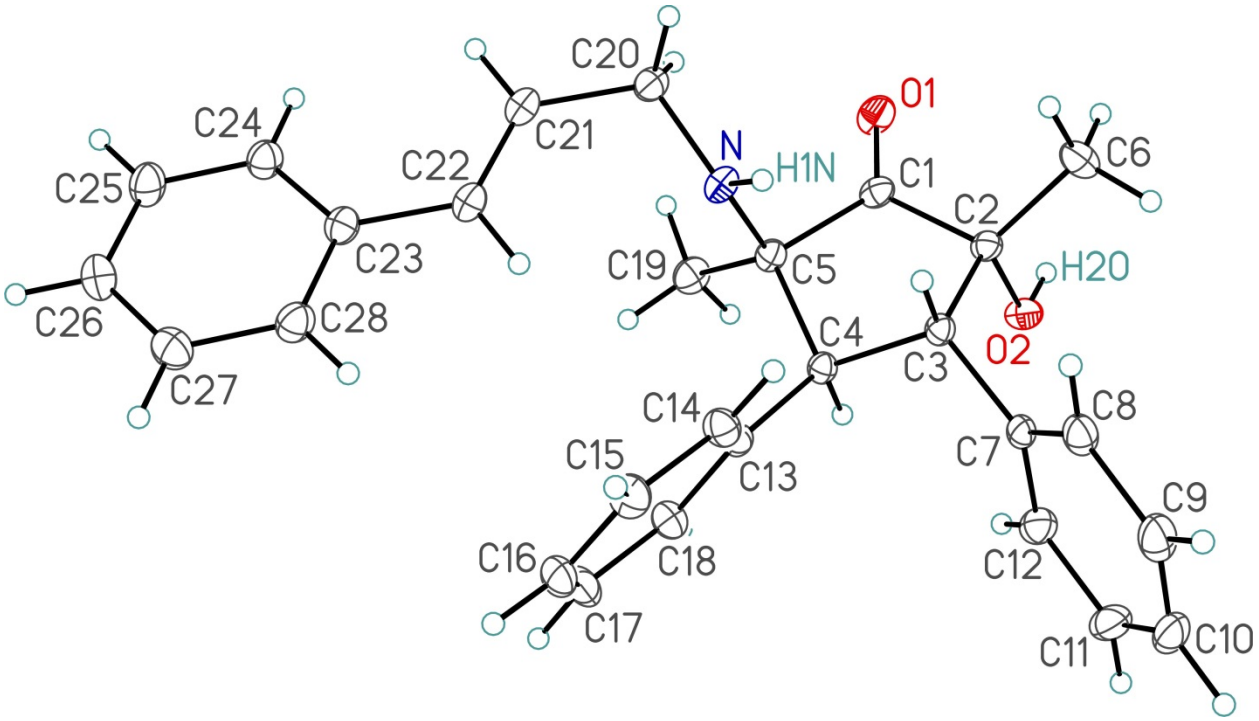
STRUCTURE REPORT

XCL Code: FGW1010 **Date:** 15 September 2010

Compound: 2-Hydroxy-2,5-dimethyl-3,4-diphenyl-5-({(2*E*)-3-phenylprop-2-en-1-yl}-amino)cyclopentanone

Formula: $C_{28}H_{29}NO_2$

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



Compound 32

Figure Legends

Figure 1. Perspective view of the 2-hydroxy-2,5-dimethyl-3,4-diphenyl-5-({(2*E*)-3-phenylprop-2-en-1-yl}amino)cyclopentanone molecule showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{28}H_{29}NO_2$
formula weight	411.52
crystal dimensions (mm)	0.51 × 0.31 × 0.08
crystal system	triclinic
space group	*P1* (No. 2)
unit cell parameters[a]	
a (Å)	8.3049 (4)
b (Å)	9.4980 (4)
c (Å)	15.5636 (7)
α (deg)	99.4404 (5)
β (deg)	99.1386 (5)
γ (deg)	107.5372 (5)
V (Å^3)	1126.09 (9)
Z	2
ρ_{calcd} (g cm^{-3})	1.214
μ (mm^{-1})	0.075
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–100
scan type	ω scans (0.4°) (10 s exposures)
data collection 2θ limit (deg)	54.28
total data collected	9595 (-10 ≤ *h* ≤ 10, -12 ≤ *k* ≤ 12, -19 ≤ *l* ≤ 19)
independent reflections	4950 (R_{int} = 0.0168)
number of observed reflections (*NO*)	4047 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXD*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–97*[d])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9938–0.9626
data/restraints/parameters	4950 / 0 / 281
goodness-of-fit (*S*)[e] [all data]	1.053
final *R* indices[f]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0400
wR_2 [all data]	0.1084
largest difference peak and hole	0.323 and –0.374 e Å^{-3}

[a]Obtained from least-squares refinement of 4848 reflections with 4.80° < 2θ < 54.24°.

(continued)

Table 1. Crystallographic Experimental Details (continued)

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

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

[d]Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

[e]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0491P)^2 + 0.2700P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

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