Alpha-Vinylation and Fragmentations of Cyclobutanones

by

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Abstract

Cyclobutanones are an important class of compounds that are often used as intermediates for the synthesis of various natural products. Owing to their inherent ring strain, they can undergo various types of reactions including ring expansions, rearrangements, fragmentations and *alpha*-functionalization. Thus, functionalized cyclobutanones can act as junctions to access other synthetically useful compounds. The ability to functionalize cyclobutanones is highly desirable from a synthetic standpoint.

Previously our laboratory had reported palladium catalyzed *alpha*-arylation of cyclobutanones. These *alpha*-arylated cyclobutanones were then fragmented and used to prepare various natural products. Based on this precedence we sought to expand this methodology to include vinyl groups. We then sought to study various fragmentation reactions of these vinylated substrates to increase structural complexity. Additionally, reduction-rearrangement and aldol functionalization strategies were also investigated.

Keywords: Cyclobutanones; Cyclobutanols; Alpha-functionalization; Vinylation

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List of Acronyms

°C	Degree(s) Celcius
$[\alpha]_D$	Specific Rotation at the Sodium D Line (589 nm)
AcOH	Acetic Acid
BINAP	(2,2′-*bis*(diphenylphosphino)-1,1′-binaphthyl)
Bu	Butyl
Bz	Benzoyl
CAN	Ceric ammonium nitrate
d.r.	Diastereomeric ratio
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIBAL	Diisobutylaluminium hydride
DMAP	*N,N*-Dimethylpyridin-amine
DMF	Dimethylformamide
DMP	Dess-Martin eriodinane
E	*Entgegen*
E. Coli	*Escherichia coli*
e.e.	Enantriomeric excess
eq.	Equivalents
e.r.	Enantiomeric ratio
Et_2O	Diethyl ether
EtOH	Ethanol
FT-IR	Fourier-transfrom infrared spectroscopy
GABOB	*gamma*-Amino-*beta*-hydroxybutyric acid
GHz	Gigahertz
hv	Light
Hz	Hertz
KHMDS	Potassium *bis*(trimethylsilyl)amide
LC-QTO-MS	Liquid Chromatography Quadrupole Time of Flight Mass Spectrometry

LDA	Lithium diisopropylaide
LiHMDS	Lithium *bis*(trimethylsilyl)amide
m.p.	Melting point
m/z	Mass to charge ratio
mCPBA	*meta*-Chloroperoxybenzoic acid
MeCN	Acetonitrile
MeOH	Methanol
MHz	Megahertz
mL	Millilitre
mm	Millimetre
mmol	Millimole
n-BuLi	*n*-Butyllithium
NCIB	National Center for Biotechnology Information
nm	Nanometre
PhMe	Toluene
PhNO	Nitrosobenzene
pic	Picolinate
ppm	Parts per million
p-TsOH	*para*-Toluenesulfonic acid
r.t.	Room temperature
R-DTBM-SEGPHOS	(*R*)-(−)-5,5′-*Bis*[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-*bis*-1,3-benzodioxole
TBDPS	*tert*-Butyldiphenylsilyl
t-Bu	*tert*-Butyl
TD63	*Torulaspora delbueckii*
THF	Tetrahydrofuran
TMS	Tetramethyl silane
Z	*Zusammen*
α-MBA	*Alpha*-Methylbenzylamine
δ	Chemical Shift (in ppm) from tetramethylsilane
µL	Microlitre

µmol	Micromole

Chapter 1.

Introduction

1.1. Cyclobutanones as Synthetic Handles

Cyclobutanones are an important class of molecules that often posses a diverse range of reactivity such as ring expansions, *alpha*-functionalizations and ring rearrangements (Figure 1.1, A) [1]. The source of this diversity can be attributed to the ring strain of cyclobutanones, which is approximately 29 kcalmol^{-1}. This strain energy enables cyclobutanones to undergo various reactions, yet unlike their more energetic counterparts, cyclopropanones, they can be easily handled in the laboratory (Figure 1.1, B) [1,2].

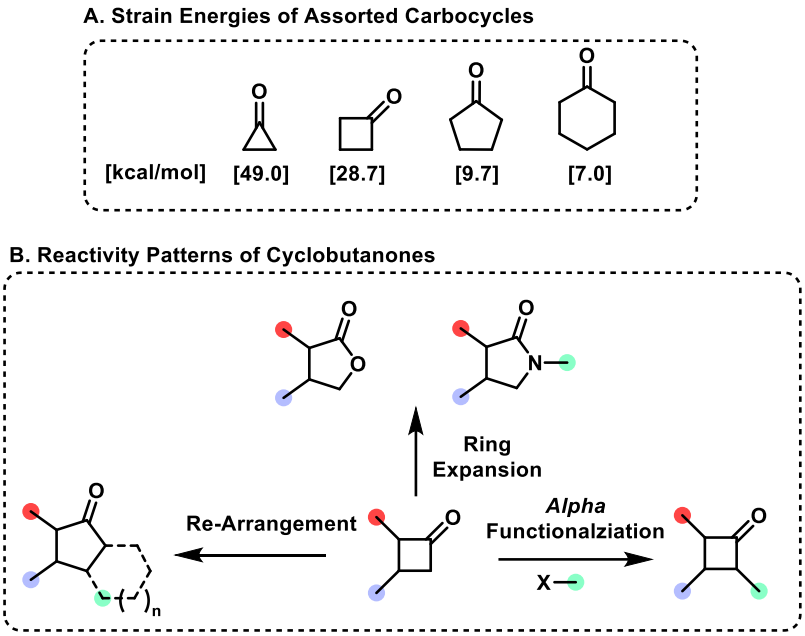


Figure 1.1 Important Cyclobutanone Reactions

Additionally, cyclobutanones have often been utilized in many total syntheses of biologically relevant molecules, including prostaglandin E_2, eleutherobin and showdamycin.[3,4,5]

Our laboratory had previously reported the *alpha*-arylation of various cyclobutanones [6], and we sought to expand this methodology to include vinyl groups. Specifically, we sought to investigate this functionalization reaction as *alpha*-vinyl cyclobutanones are underrepresented in the literature and we believed that having a methodology to access them in a reliable way would be useful to the chemical community. Additionally, our laboratory has undertaken a synthetic campaign to access eleutherobin **1** in an efficient and scalable manner. We sought access to *alpha*-vinyl cyclobutanones as we believe that they could be used to simplify the synthesis (Figure 1.2, A).

Towards the synthesis of eleutherobin, our retrosynthetic strategy involved cleaving the methylurocanic acid ester and sugar moiety to form the diol **2**. This diol could then be constructed from the macrocycle **3** *via* an epoxidation and a subsequent cyclization-elimination sequence. We believed that macrocycle **3** would be formed *via* an intramolecular Knoevenagel condensation of compound **4**. Compound **4** could then be accessed through a deprotection of the diketene-acetone adduct and fragmentation of the vinyl-cyclobutanone **5**. Compound **5** could then be accessed through various strategies such as direct *alpha*-vinylation or *via* aldol functionalization of cyclobutanone **6**.

Ultimately, the fragmentation of the vinylated cyclobutanone could be achieved through either a direct fragmentation from the ketone, or through a conversion to the corresponding cyclobutanol and then fragmention under basic or radical conditions (Figure 1.2, B). To test the validity of our fragmentation strategy, we sought to apply a method used previously to generate *alpha*-vinylated alcohols and apply them to our model cyclobutanone **6**.[7]

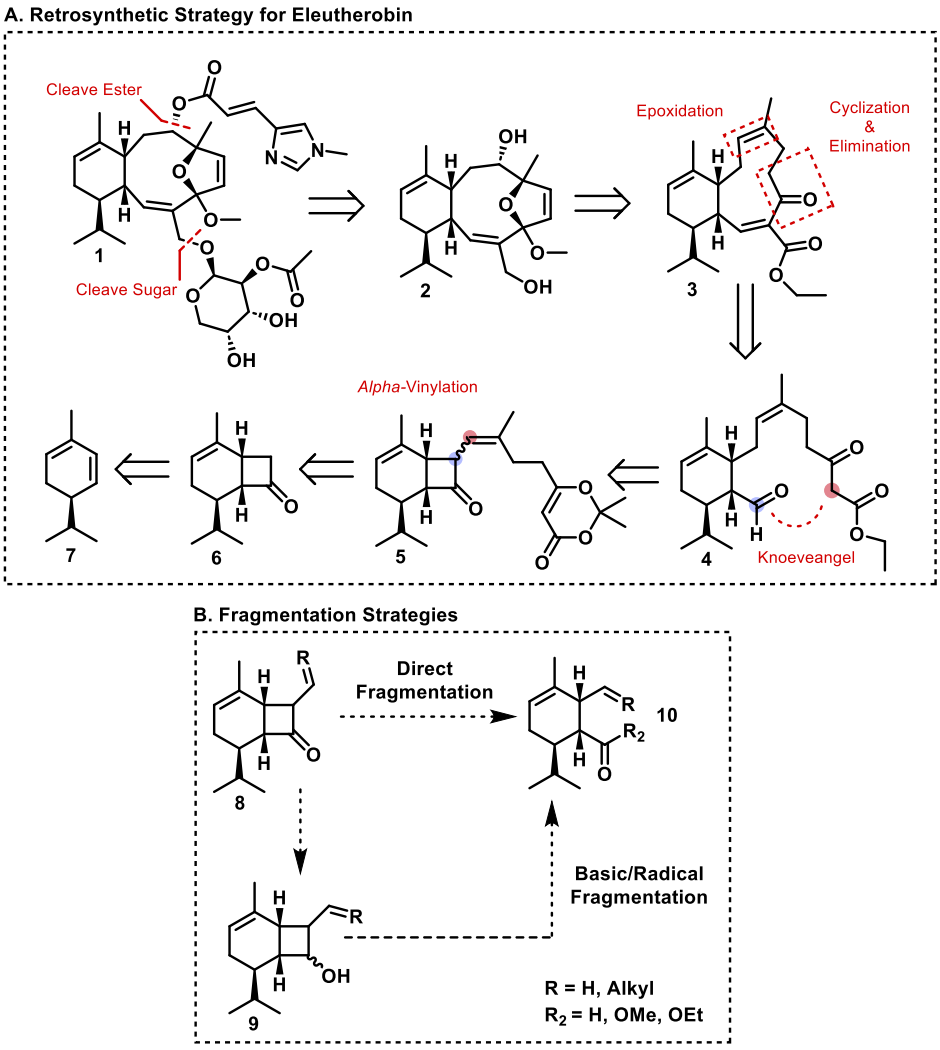


Figure 1.2 Retrosynthetic Strategy and Applications of Cyclobutanones to Eleutherobin

1.2. Ring Expansions of Cyclobutanones

1.2.1. *γ*-Lactones from Cyclobutanones

Owing to the strained nature of cyclobutanones, any reaction that expands the carbon skeleton to a 5 or 6 membered ring should be thermodynamically favourable. One of the most frequently utilized ring expansion reactions on cyclobutanones is the Baeyer-Villiger oxidation; this reaction is often conducted bio-catalytically and forms the corresponding *γ*-lactone, which are useful from a synthetic perspective and often possess

interesting biological activity.[8] One prominent example of generating *γ*-lactones from cyclobutanones was conducted by Furstoss and co-workers in 1991 (Figure 1.3, A).[9] Here, a bio-catalytic transformation using strains of the bacteria *Acinetobacter* NCIB 9871 and TD63 was conducted on a small collection of cyclobutanones and gave yields of *γ*-lactones ranging from 28 to 52 %. However, the observed enantioselectivity was excellent, with most examples exceeding 95 % e.e.. The work done by Furstoss would later be built upon by Woodley and co-workers in 2008 who demonstrated the preparation of *γ*-lactones from cyclobutanones on a process scale (Figure 1.3, B).[10] This conversion was also the first example of using whole cell bio-catalysis on a process scale. In this method the authors utilized *E. Coli* strains to oxidize racemic bicyclo[3.2.0]hept-2-en-6-one **14** and separated the resulting regioisomers **15** and **16** using column chromatography. Conducting classical Baeyer-Villiager oxidations on process scale has several disadvantages. First, massive amounts of organic solvent must be used in tandem with oxidizing agents, which could pose a significant safety risk. Biocatalytic methods can avoid this while working in aqueous solvent under mild conditions. Additionally, formation of toxic organic waste and by-products is avoided.[10]

Although useful, biocatalysis is may often prove to be quite cumbersome for regular bench use, thus *γ*-Lactones can be prepared from cyclobutanones using classical methods which involve hydrogen peroxide or metal catalysts, which are convenient to use in the laboratory (Figure 1.3, C).[11–13]

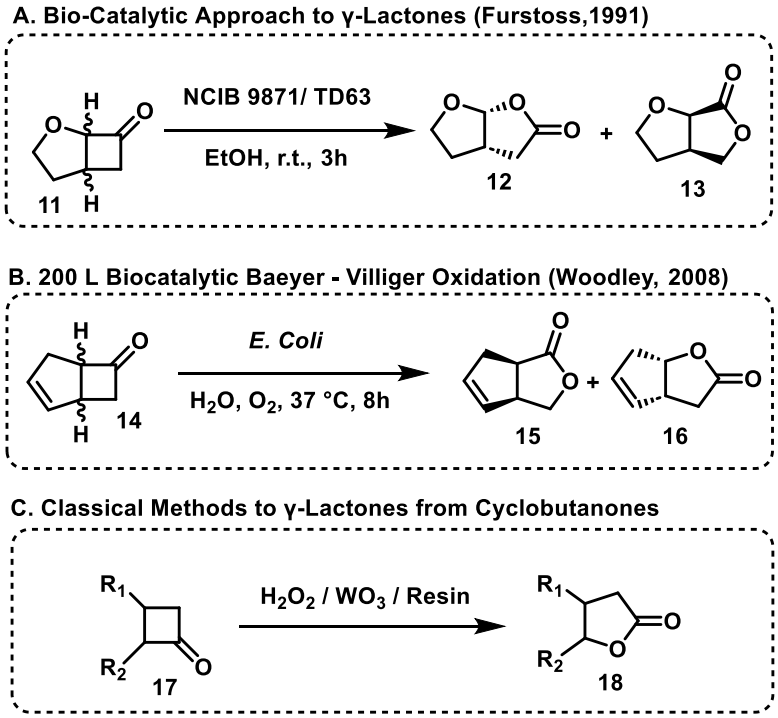
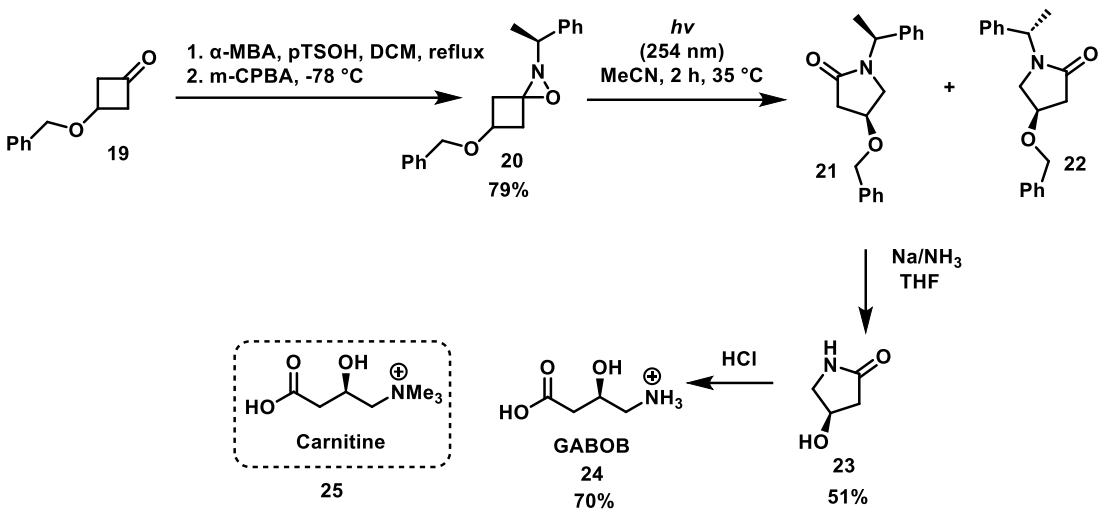


Figure 1.3 Methods Used to Generate *γ*-Lactones from Cyclobutanones.

1.2.2. *γ*-Lactams from Cyclobutanones

Although not as frequently used to prepare *γ*-lactams, in 1991, Aubé and co-workers used benzyl cyclobutanone **19** to prepare *gama*-amino-*beta*-dydroxybutyric acid (GABOB) **24** and its derivative carnitine **25** (Scheme 1.1).[14] GABOB and carnitine are both biologically-active compounds, with GABOB acting as an anti-epileptic agent while carnitine is involved with various biological functions including fatty acid transport.[15] Here, 3-benzyloxycyclobutanone **19** was condensed with (*S*)-*alpha*-methylbenzylamine and subsequently treated with *m*-CPBA to afford the oxaziridine **20** in 79% yield, as a mixture of stereoisomers. The mixture was then subjected to photolysis to afford the lactams **21** and **22** in 43% and 40% yields respectively. Lactams **21** and **22** were separated and **22** was then converted to 4-hydroxy-*γ*-lactam **23** using sodium and liquid ammonia in 51% yield. The ring was then opened under acidic conditions to yield GABOB **24** in 70% yield. Carnitine **25** could then be obtained from GABOB *via* trimethylation at the *N*-position.[15]



Scheme 1.1 Aubé's Synthesis of GABOB.

In 2012, Secci and co-workers reported their efforts directed towards the synthesis of *alpha*-aminooxylated cyclobutanone **27** (Figure 1.4, A).[16] In the key reaction, they observed no conversion to this desired product but instead isolated 3-hydroxy-*γ*-lactam **28** in 50% yield as a 7.3:1 mixture of diastereomers. This serendipitous discovery was used to develop a general method to prepare 3-hydroxy-*γ*-lactams **32** by use of nitroso benzene **30** (Figure 1.4, B). Although this method only gave the corresponding 3-hydroxy-*γ*-lactams in modest yield with limited substrate scope it was an important work in constructing functionalized *γ*-lactams.

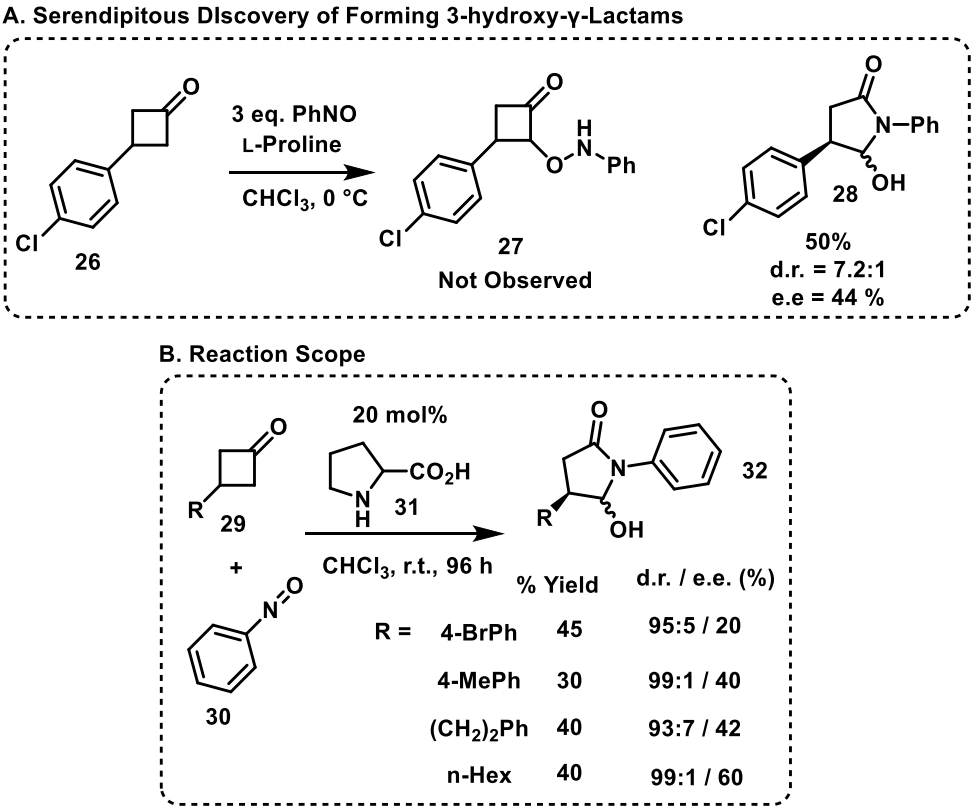


Figure 1.4 Secci's Method for Preparing 5-hydroxy-*γ*-Lactams from Cyclobutanones.

In 2022, Wahl and co-workers reported an aza-Baeyer-Villiger rearrangement of cyclobutanones **33** (Figure 1.5, A).[17] This method utilizes various commercially available (aminooxy)diphenylphosphine oxides **34** to form an initial Criegee-type intermediate **35**, which subsequently expands to form the corresponding *γ*-lactam **36**. This method allows for the convenient preparation of *γ*-lactams from various substituted cyclobutanones in good yields under mild conditions (Figure 1.5, B). Additionally, this methodology has a wide substrate scope with various substitutions being tolerated at the *alpha* and *beta* positions of the cyclobutanone with various bicyclic cyclobutanone derivatives were also tolerated. In addition to the modularity of the cyclobutanone, the amine reagent **34** can be modified to install various groups on the *N*-position of the lactam.

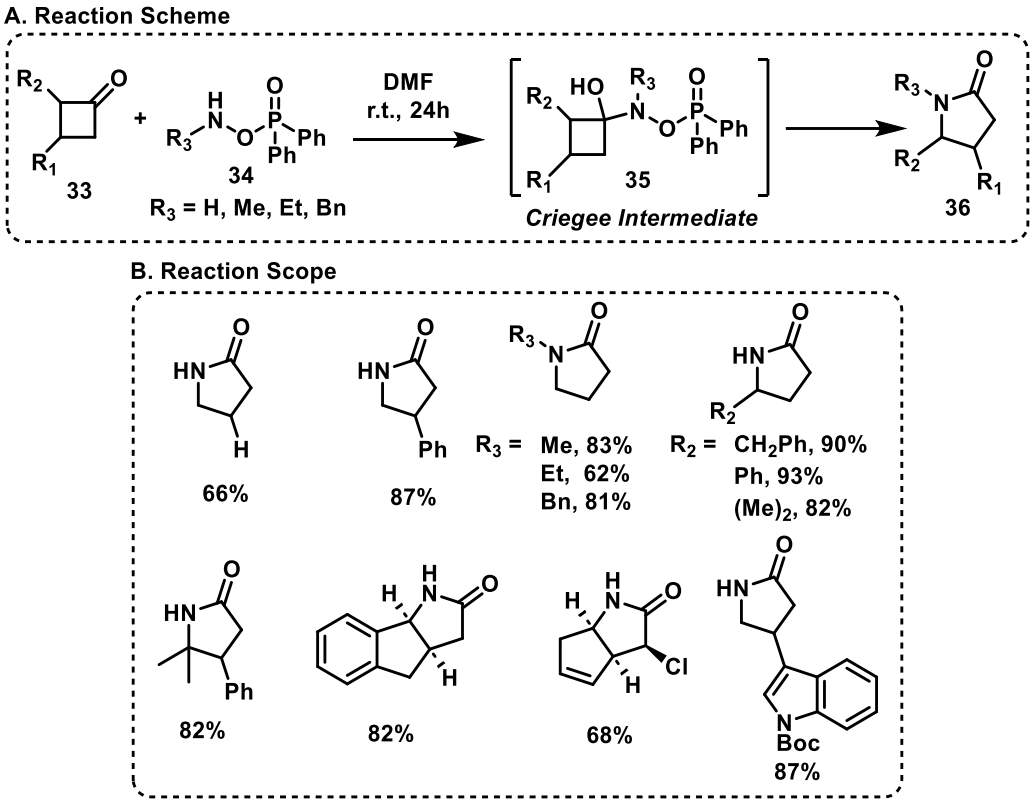


Figure 1.5 Wahl's Methodology for Preparing *γ*-Lactams.

1.3. Re-Arrangements of Cyclobutanones

Due to their ring strain and distorted σC-C orbitals, cyclobutanones are liable to undergo various rearrangement reactions. One method of initiating this type of reactivity is through the insertion of a transition metal into the C-C bond of the cyclobutanone. The first report of metal insertion into a cyclobutanone was from 1994 by Ito and coworkers (Figure 1.6).[18] When cyclobutanone **37** was treated with equimolar amounts of $RhCl(PPh_3)_3$ in refluxing toluene, the decarbonylated product **40** was observed in quantitative yield. The reaction mechanism is believed to proceed through the formation of the acylrhodium species **38**. The acylrhodium complex then undergoes a migration, in which the rhodium centre inserts itself into the carbonyl to form compound **39**. This intermediate then decarbonylates to yield the cyclopropane **40** in quantitative yield. This method for decarbonylation reaction was also successfully demonstrated on various other cyclic ketones such as **41** and **43**.

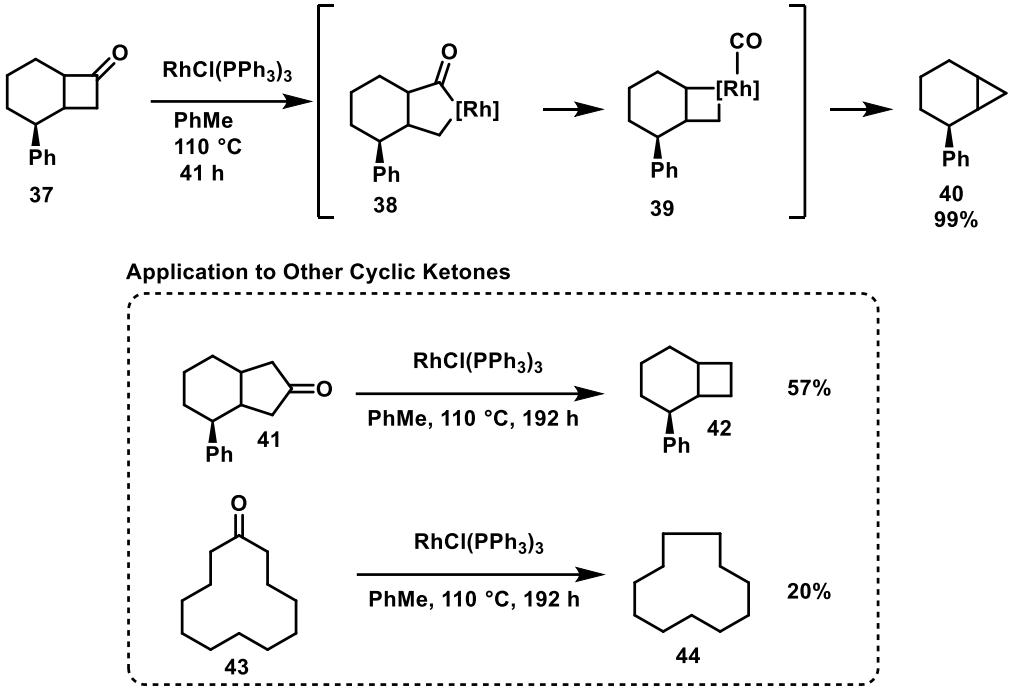
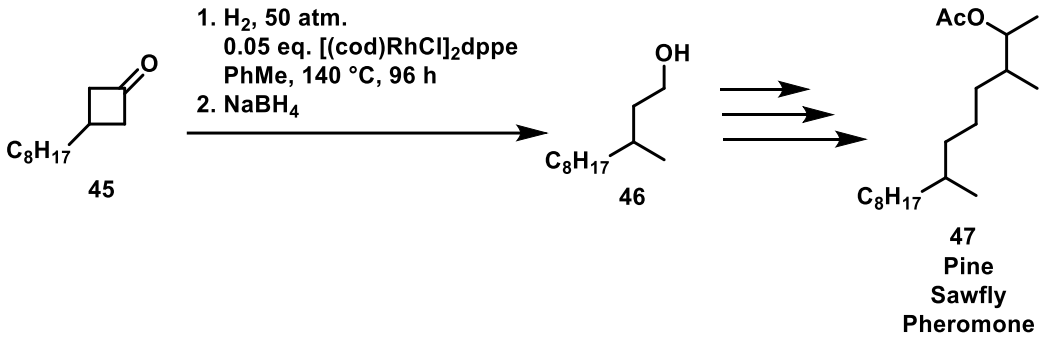


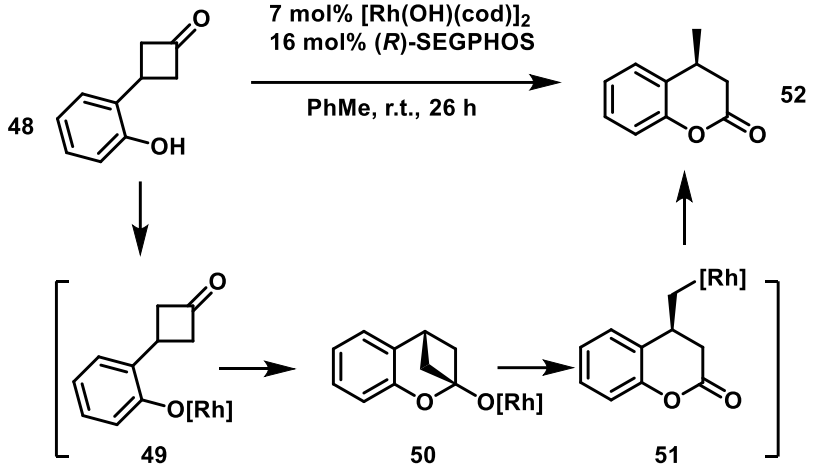
Figure 1.6 Ito's Rhodium Decabonylation of Cyclic Ketones.

Seeking to apply this newly discovered reaction, Ito combined the rhodium insertion with a hydrogenation reaction to prepare 3-methylundecanol **46** (Scheme 1.2).[19] This compound serves as an intermediate in the synthesis of a pheromone **47** belonging to the pine sawfly, an invasive species in North America that can disrupt natural ecosystems.[20] Starting from cyclobutanone **45** and treating it with $[(cod)RhCl]_2$dppe under hydrogen atmosphere and subsequent reduction yielded the alcohol **46** in 80% yield over two steps.



Scheme 1.2 Ito's Preparation of 3-methylundecanol.

Coumarins are naturally occurring compounds that are often found in many plants and are often used to deter animals from consuming the plant.[21] However, they are often responsible for desirable flavor profiles of cherry blossom and cinnamon,[21] and they have been investigated for their medicinal properties as well.[22,23] In 2007, Murakami and co-workers reported the preparation of 3,4-dihydrocoumarins from functionalized cyclobutanones (Scheme 1.3).[23] When 3-(2-hydroxyphenyl)cyclobutanone **48** was treated with 7 mol% of $[Rh(OH)(cod)]_2$ and 16 mol % of (*R*)–SEGPHOS, the coumarin **52** was formed in 77% yield. This reaction is believed to occur through the formation of rhodium aryloxide **49**. The aryloxide subsequently inserts into the carbonyl of the cyclobutanone to form the bicyclic intermediate **50**, which undergoes *beta* carbon elimination to form **51** and upon protonolysis yields the coumarin **52**.



Scheme 1.3 Murakami's Preparation of 3,4-Dihydrocoumarins.

In 2014 Cramer and co-workers demonstrated that rhodium catalysis could be utilized to prepare and lactones and bi-cyclic ketones **54** from functionalized cyclobutanones **53** (Figure 1.7, A).[24,25] The formation of these two products is believed to proceed *via* intramolecular rhodium coordination complex **55** with the carbonyl of the cyclobutanone and the alkene or aldehyde respectively (Figure 1.7, B). The rhodium center is then believed to insert into the *alpha* carbon of the cyclobutanone to form the acylrhodium complex **56**. This is followed by the addition of the alkene or aldehyde to yield **57**, which subsequently reductively eliminates to form **54** as either the bicyclic ketone or lactone.

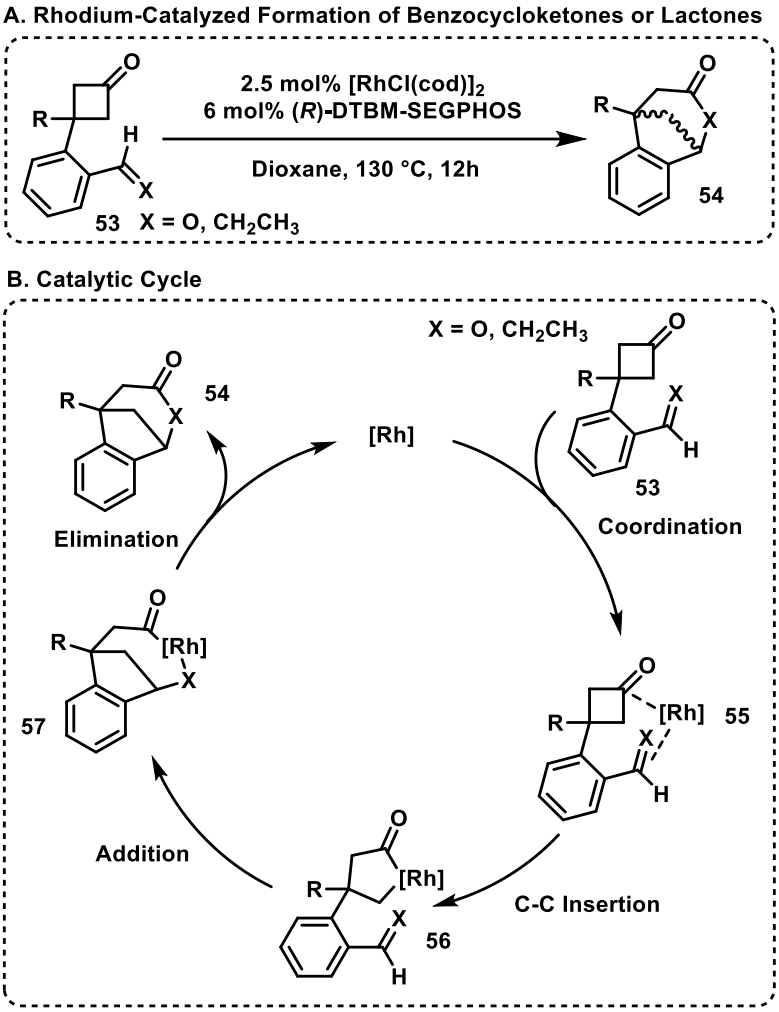


Figure 1.7 Formation of Benzocycloketones and Lactones from Cyclobutanones.

Recently, in 2022, Dong and co-workers managed to construct several complex carbon scaffolds using functionalized cyclobutanones **58** (Figure 1.8, A).[26] Using rhodium catalysis, in a single step, molecules containing four new ring systems with four new stereocentres were prepared. These scaffolds could then be functionalized in various ways including forming the corresponding oxime **61**, 1,2 addition of Grignard reagents to form the corresponding tertiary alcohol **62**, forming the corresponding enol triflate **63** as well as undergoing olefination to afford compound **64**. (Figure 1.8, B) This method demonstrates the synthetic utility of cyclobutanones to build complex scaffolds rapidly, which can then be further derivatized. Rapid access to such structurally complex molecules is of growing interest in medicinal chemistry where it has been demonstrated that sp^3-rich compounds often posses improved drug-like properties.[27,28]

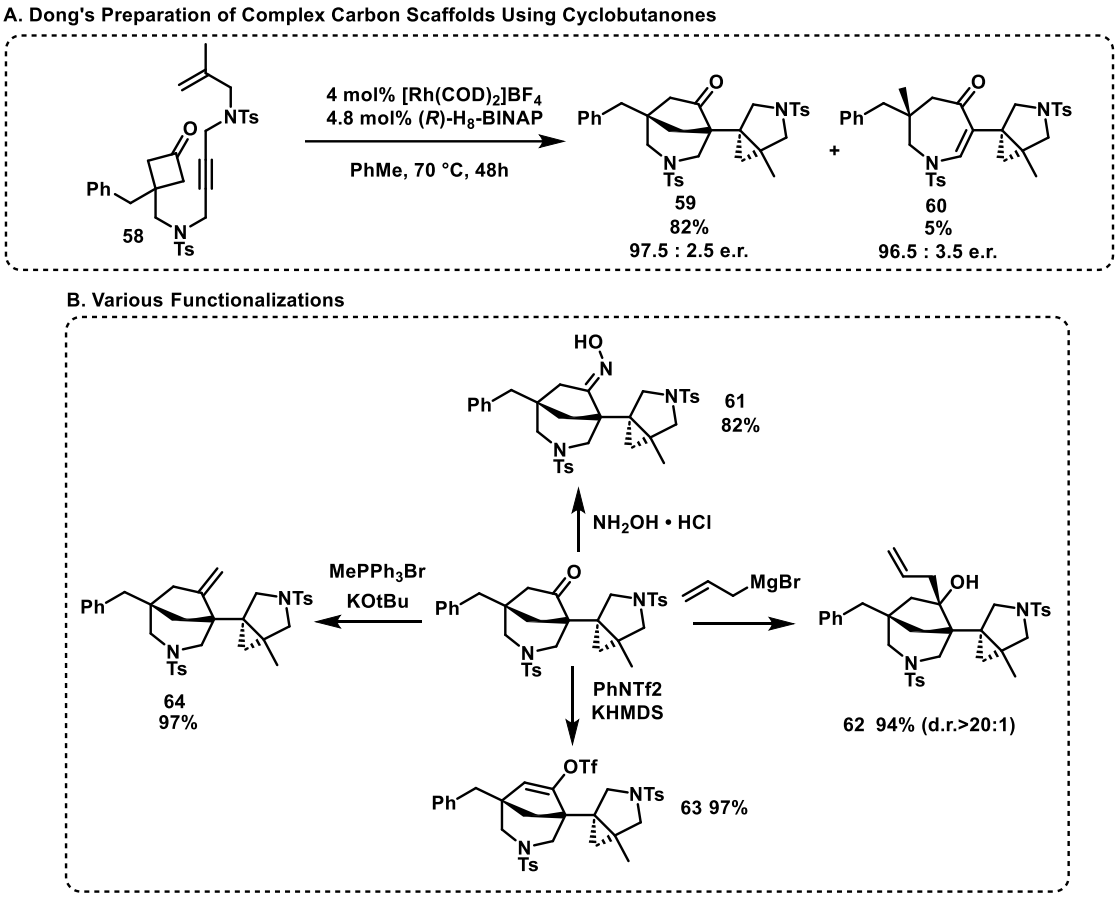


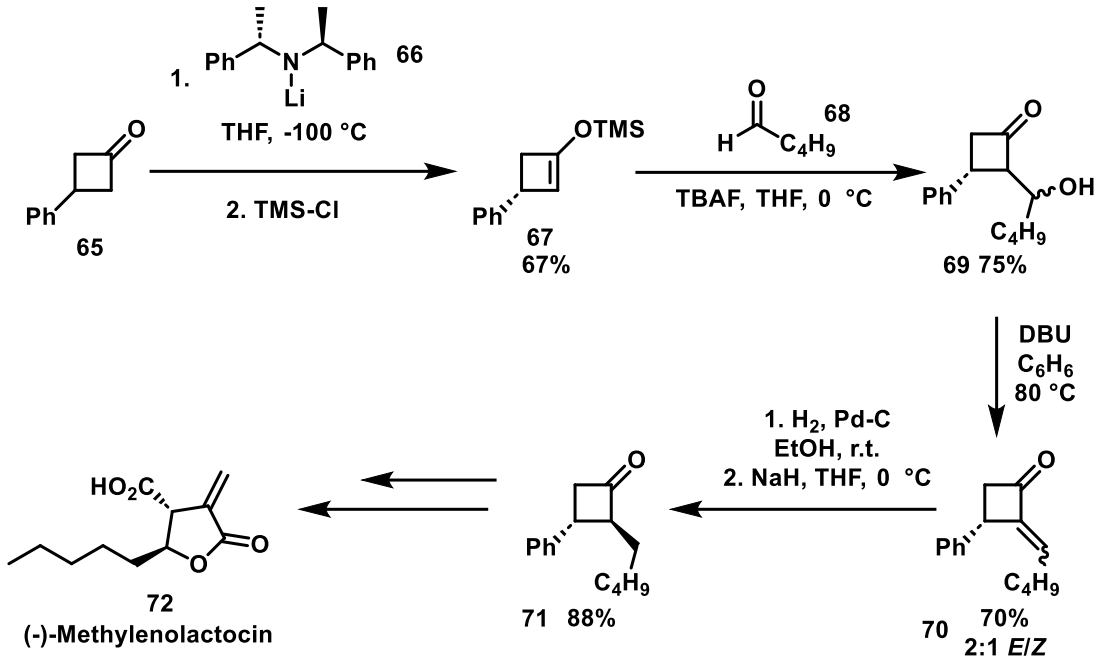
Figure 1.8 Dong's Preparation of Complex Scaffolds from Cyclobutanones.

In addition to rhodium, other metals such as palladium and zinc have been utilized to rapidly build complex scaffolds from cyclobutanones.[29,30] Overall, rearrangement reactions of cyclobutanones are probably the most diverse, and thus offer access to a variety of complex structures from often simple starting materials.

1.4. *Alpha*-Functionalization of Cyclobutanones

Due to the many ways in which cyclobutanones react, it is important to be able to functionalize cyclobutanones in as few synthetic steps as possible. One of the most versatile reactions in organic chemistry is the aldol reaction. When applied to cyclobutanones it can be used to rapidly build molecular complexity. Honda and co-workers were able to employ a chiral base **66** to form the silyl enol ether **67** and upon deprotection and reaction with valeraldehyde **68** produced the aldol product **69** in 75% yield with a d.r. of 94:6 (Scheme 1.4).[31] With a subsequent elimination reaction to form the

enones **70** in a 70% yield in a 2:1 *E*/*Z* ratio. These compounds were then reduced with palladium on carbon and the *cis* isomer was isomerized to the *trans* with sodium hydride to form **71** in 88% yield. Cyclobutanone **71** was then carried forward in the synthesis of (-)-methylenolacocin **72**, a compound initially isolated from a *penicillium* that possesses anti-microbial properties. Honda's work was the first demonstration of an asymmetric aldol reaction conducted on cyclobutanones.



Scheme 1.4 Honda's Asymmetric Aldol Reaction on Cyclobutanones.

Building on the asymmetric aldol reaction of cyclobutanones, in 2012 Froniga and Piras reported the first organocatalyzed aldol reaction on cyclobutanones (Figure 1.9).[32] Their methodology involved the use of the organocatalyst **75** and led to the successful preparation of a variety of aldol products **76** in excellent yields and e.e. .

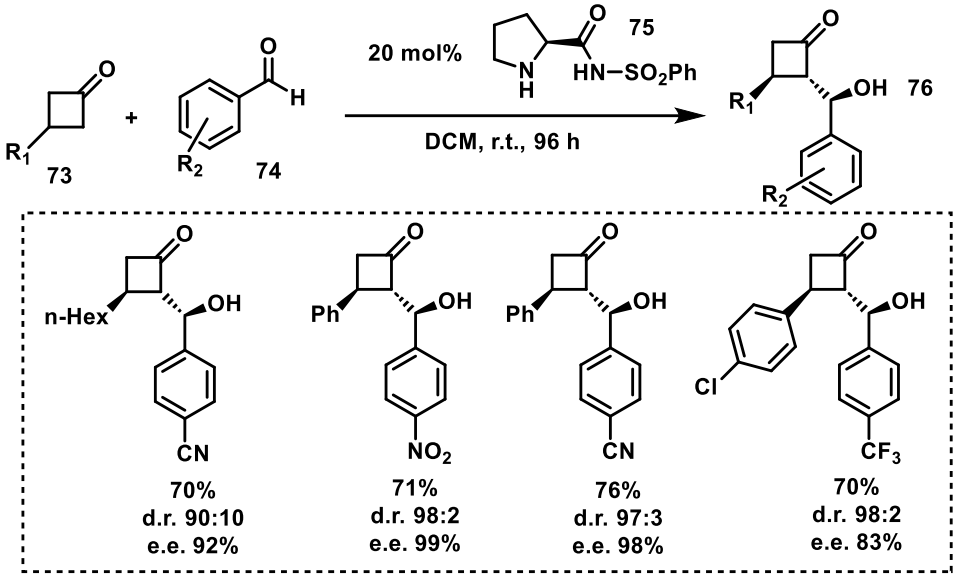
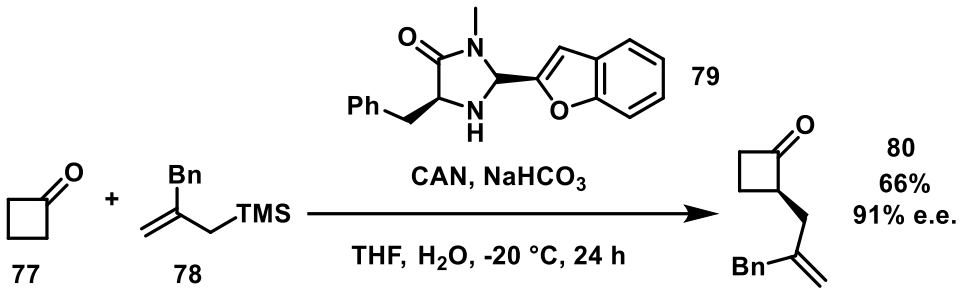


Figure 1.9 Froniga's and Piras' Preparation Organocatalayzed Aldol Reaction of Cyclobutanones.

MacMillan and co-workers published an example of *alpha*-alkylation of a cyclobutanone ring using Singly Occupied Molecular Orbital (SOMO) catalysis (Scheme 1.5).[33] In this process cyclobutanone **77** was *alpha*-alkylated using the silane **78** along with imidazolidinone catalyst **79** and cerium ammonium nitrate. This afforded the *alpha*-alkylated cyclobutanone **80** in 66% with a 91% e.e..



Scheme 1.5 MacMillan's *Alpha*-Alkylation of Cyclobutanone.

Another method that has been used in the *alpha*-functionalization of cyclobutanones has been palladium mediated catalysis. Previously applied to linear and cyclic ketones,[34] the first *alpha*-arylation of cyclobutanones was reported by Britton and co-workers in 2017 (Figure 1.10).[6] This method has a broad substrate scope, with various cyclobutanones and substituted arenes being tolerated. Heterocyclic substrates such as

bromothiophenes and pyrans were also tolerated. Diastereoselectivity of the reaction was excellent, with most cases exceeding 20:1 and yields ranging from 50 to 75%.

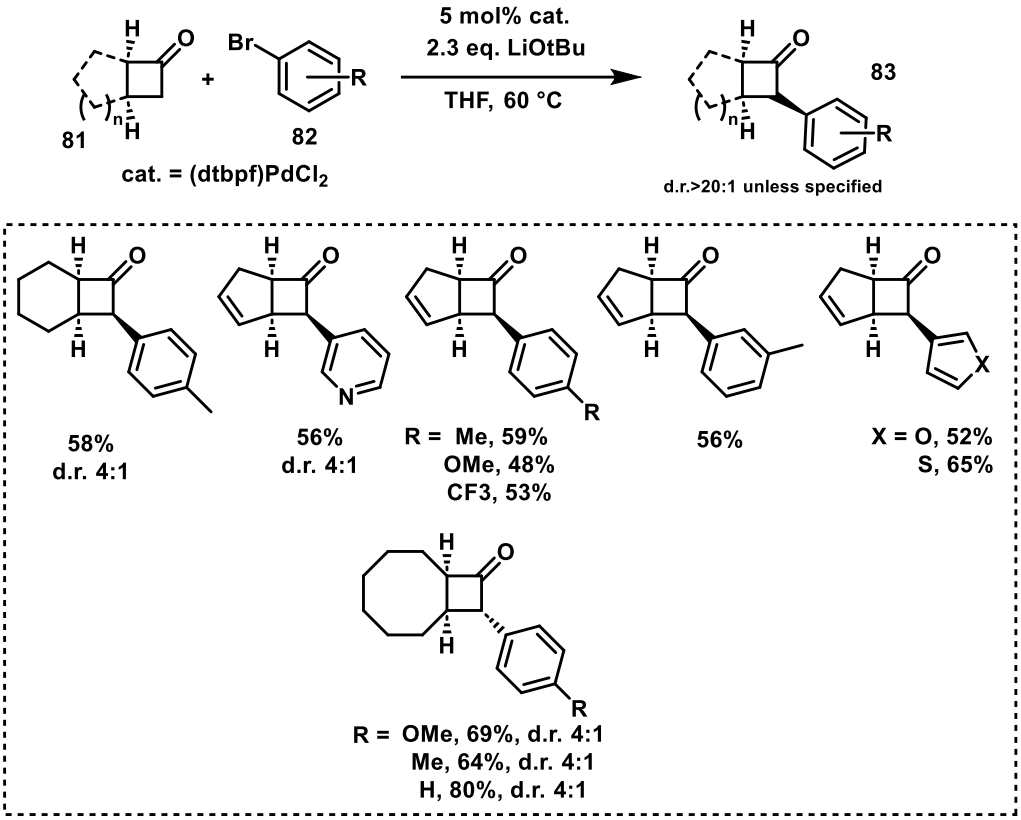
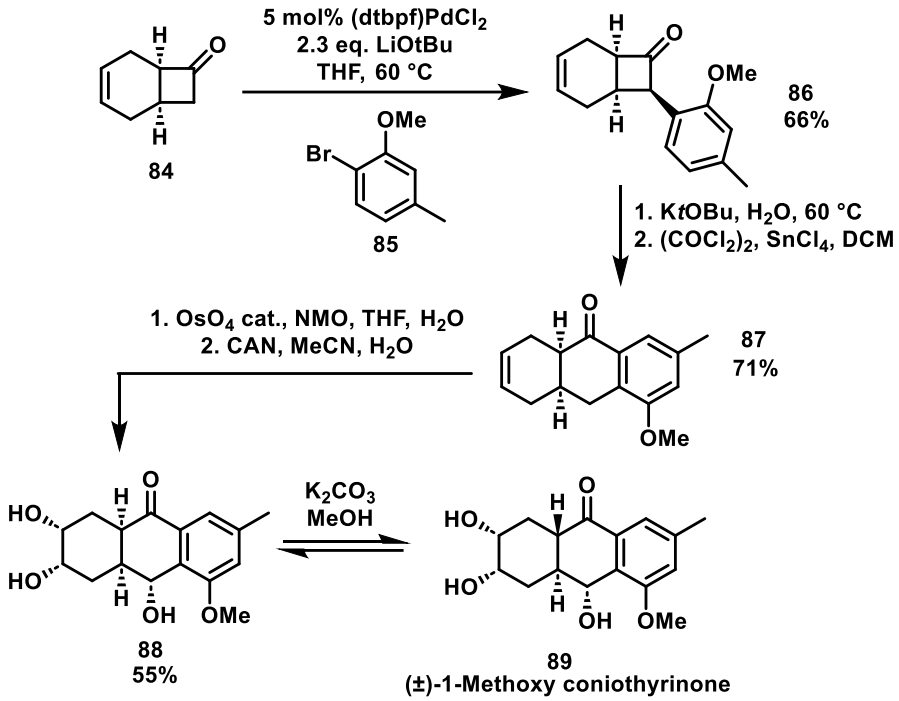


Figure 1.10 Britton's *Alpha*-Arylation of Cyclobutanones.



Scheme 1.6 Britton's Synthesis of (±)-1-Methoxy Coniothyrinone.

As an application of their *alpha*-arylation method, Britton and co-workers undertook the synthesis of (±)-1-methoxy coniothyrinone **89** (Scheme 1.6).[6] Here, a*lpha*-arylation was conducted on the cyclobutanone **84** to yield the *alpha*-aryl-cyclobutanone **86** in 66% yield as a single diastereomer. The arylated cyclobutanone was then fragmented and then subjected to a Friedel-Crafts acylation to yield the tetralone scaffold **87** in 71% yield. Upon installation of the diol across the double bond and oxidation on the A ring, the triol **88** was generated in 55% yield over two steps. This compound was then epimerized with potassium carbonate to yield (±)-1-methoxy coniothyrinone **89**.

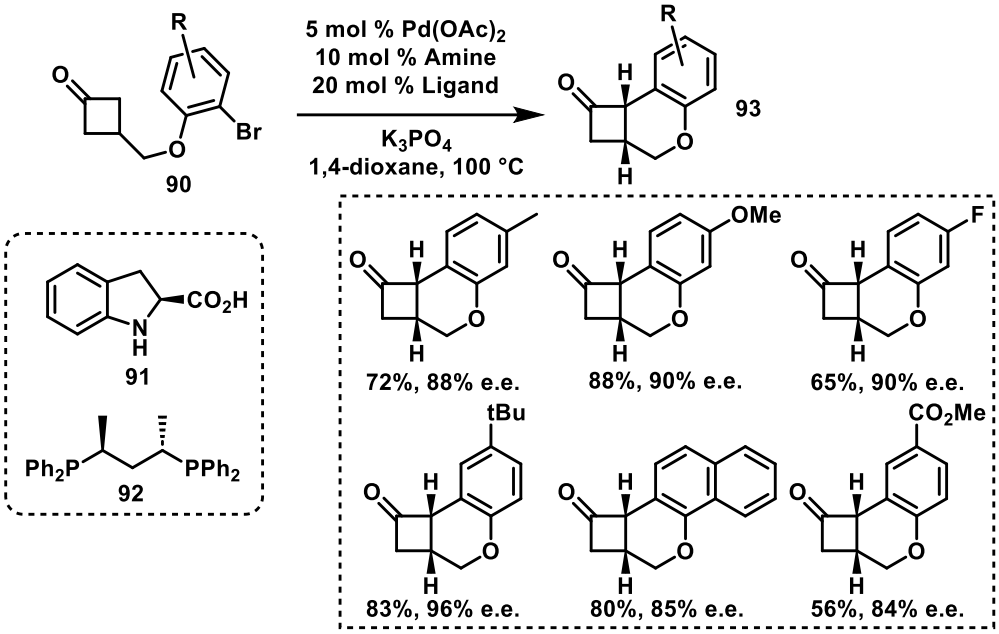


Figure 1.11 Lu's Intramolecular *Alpha*-Arylation.

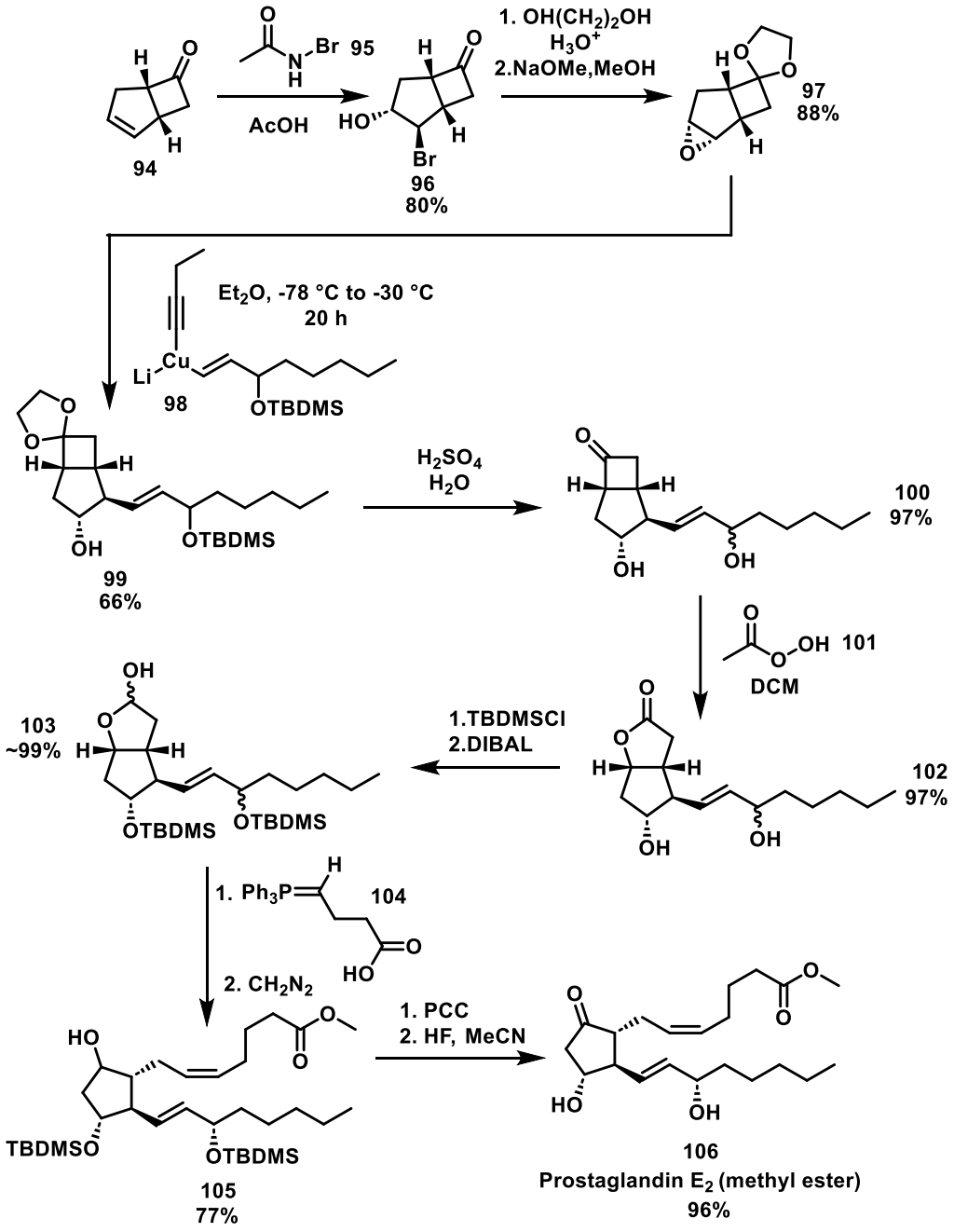
Lu and co-workers would later build upon *alpha*-arylation and conduct intramolecular *alpha*-arylation of cyclobutanones to form tricyclic systems **93** (Figure 1.11).[35] Lu's methodology allows for access to complex cyclic scaffolds in only a single step, tolerates a wide variety of aryl groups and gives excellent yields and enantioselectivity.

1.5. Cyclobutanones as Intermediates in Natural Product Synthesis

1.5.1. Newton and Robert's Prostaglandin Synthesis

Prostaglandins are an important class of molecules with a wide variety of biological functions that include effects on inflammation, blood pressure, sleep, and reproduction.[36,37] As pharmaceuticals, they have been applied to a variety of therapeutic areas and in some instances serve as veterinary aids. Overall, there are about 20 prostaglandin derived drugs on the market today.[37] Since the pioneering work by E.J Corey and co-workers,[38] there was great interest in the synthesis of prostaglandin derivatives, especially during the late 1970s and early 1980s. In 1980, Newton and Roberts, working out of Glaxo Research labs, were seeking to access prostaglandin derivatives[39–42], and employed cyclobutanones as an

easily prepared intermediate. Their synthesis of prostaglandin begins from the cyclobutanone **94** (Scheme 1.7).[42] The authors note that the reliability of preparing various cyclobutanones made them useful as intermediates as they could be produced efficiently on large scale. Compound **94** was converted into the bromohydrin **96** by use of *N*-bromoacetamine **95** and acetic acid in 80% yield. The bromohydrin **96** was subsequently protected using ethylene glycol and epoxidized to yield **97** in 82% yield over two steps. Epoxide **97** was then treated with the Gilman reagent **98** to yield the corresponding alcohol **99** in 66% yield. The acetonide and OTBDMS were removed in a single step under acidic conditions to yield the diol **100** in 97% yield. The cyclobutanone diol **100** was then converted into the corresponding *γ*-lactone **102** using peracetic acid **101** in 97% yield. The hydroxy groups were then re-protected using TBDMSCl to give the *di*-protected diol **103** in quantitative yield. The ketone was then reduced to the corresponding alcohol using DIBAL in quantitative yield. The appended methyl ester moiety was installed using a Wittig reaction with subsequent methylation reaction using diazomethane to yield compound **105** in 77% yield after two steps. This intermediate was then oxidized using PCC and subsequently deprotected to yield the prostaglandin E_2 methyl ester **106** in 96% yield over two steps. Newton and Roberts would also use cyclobutanones to synthesize various other prostaglandin derivatives.

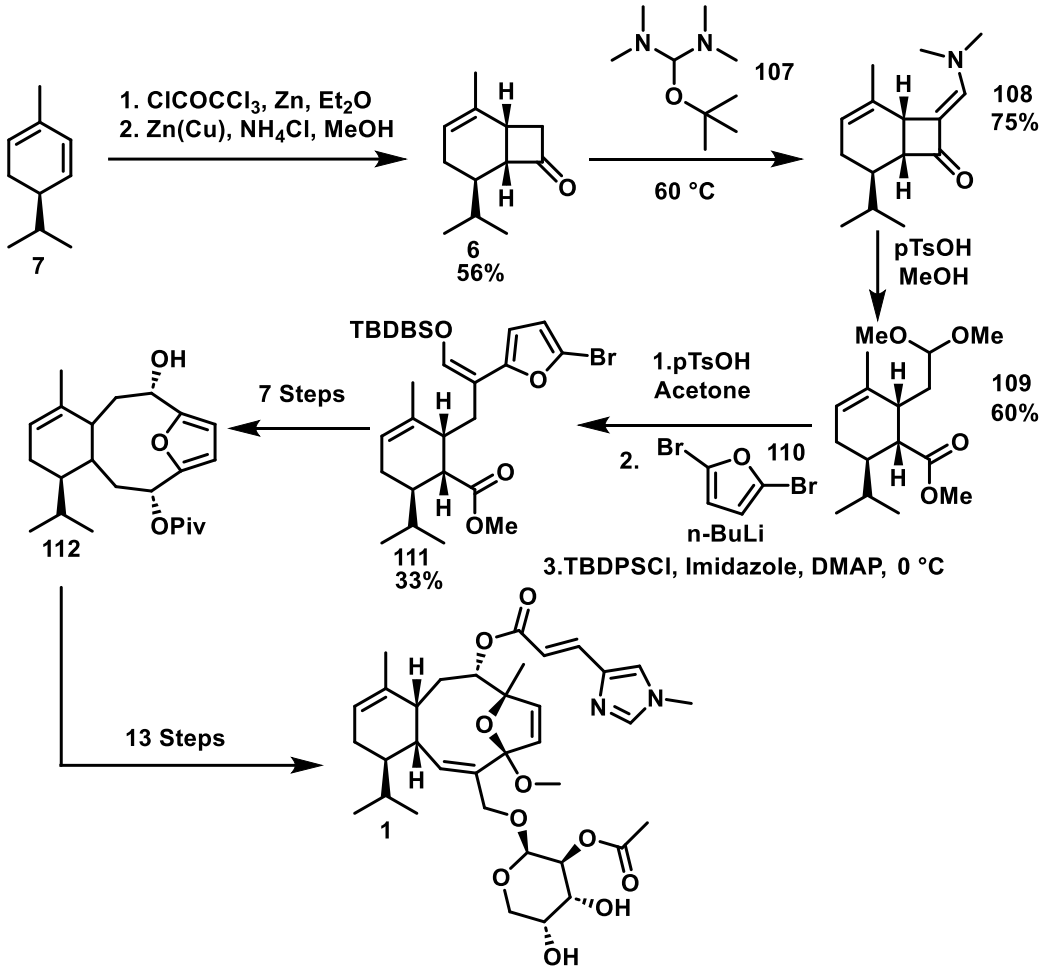


Scheme 1.7 Newton and Robert's Synthesis of Prostaglandin E_2 Methyl Ester.

1.5.2. Danishefsky's Total Synthesis of Eleutherobin

Mitotic inhibitors are an important class of chemotherapeutics with some prominent examples including taxol and vinblastine,[43] with both compounds being listed on the WHO list of essential medicines and play an important role in the fight against cancer.[44] Structurally, eleutherobin can be described as a diterpene glycoside with an appended methyl urocanic acid ester. It was first isolated from a species of soft coral from the genus *Eleutherobia*,[45] which are found in ecosystems around the world. Upon testing, it was found that eleutherobin possesses anti-cancer properties, being particularly effective at killing kidney, lung, and ovarian cancer cell lines.[45] This made eleutherobin and its derivatives exciting synthetic targets especially in the 1990s.

Eleutherobin **1** was first synthesized by K.C Nicolaou and co-workers in 1997,[46] with a subsequent synthesis being published by Danishefsky in 1998 (Scheme 1.8).[4] Danishefsky's route begins with *alpha* phellandrene **7**, a commercially-available terpene, and involves a [2+2] cycloaddition and subsequent de-chlorination reaction to yield the cyclobutanone **6** in 56% yield over two steps. This cyclobutanone **6** was then treated with Brederick's reagent **107** to afford the enamine **108**, which was fragmented with tosylic acid to yield the protected aldehyde **109** in 60% yield. This later material was then deprotected and treated with 2,5-dibromofuran **110** and n-BuLi, and subsequently re-protected to yield the adduct **111** in 33% yield over 3 steps. **111** would then go on to be converted into the tricyclic system **112** in 7 steps. Danishefsky would then use this intermediate **112** to complete the synthesis of Eleutherobin **1** in an additional 13 steps.

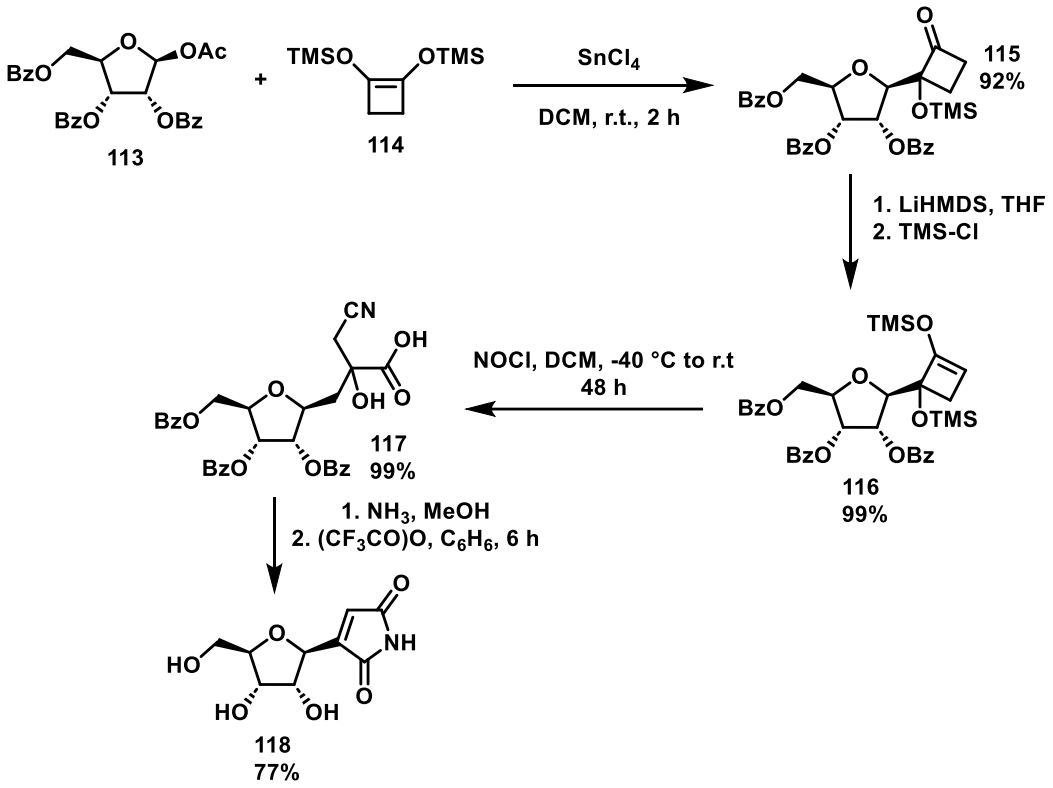


Scheme 1.8 Overview of Danishefsky's Total Synthesis of Eleutherobin.

1.5.3. Kuwajima's Preparation of Showdomycin

Nucleosides are an important class of natural products, and they are often used for their antiviral and antibacterial properties.[47] Showdomycin **118** was first isolated from the organism *Streptomyces showdoensi*s and has been found to posses exciting properties as an antibiotic.[48,49] In 1980, Kuwajima and co-workers described a concise synthesis of showdomycin starting from benzylated *beta*-D-ribose **113** and protected cyclobutene **114** (Scheme 1.9).[50] When these two staring materials were exposed to tin (IV) chloride in DCM the adduct **115** was isolated in 92% yield. Compound **115** was then converted to the silyl enol ether **116** in quantitative yield and was subsequently treated with nitrosyl chloride for a period of two days to yield the cyano carboxylic acid **117**. When treated with ammonia in methanol and then trifluoroacetic anhydride in benzene, showdomwcin **118** was produced

in 77% yield. Overall, Kuwajima reports an overall yield of 70% based on the benzylated ribose derivative **113**.

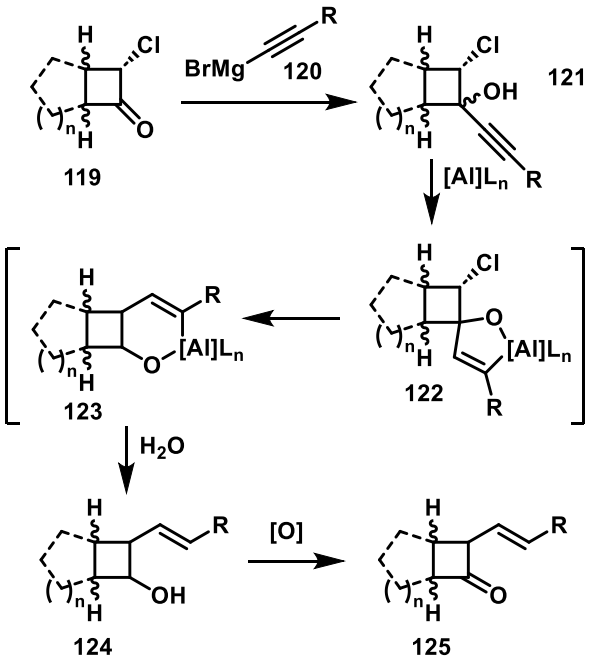


Scheme 1.9 Kuwajima's Preparation of Showdomycin.

Chapter 2. Strategies Towards *Alpha*-Vinylated Cyclobutanones and Fragmentation Studies.

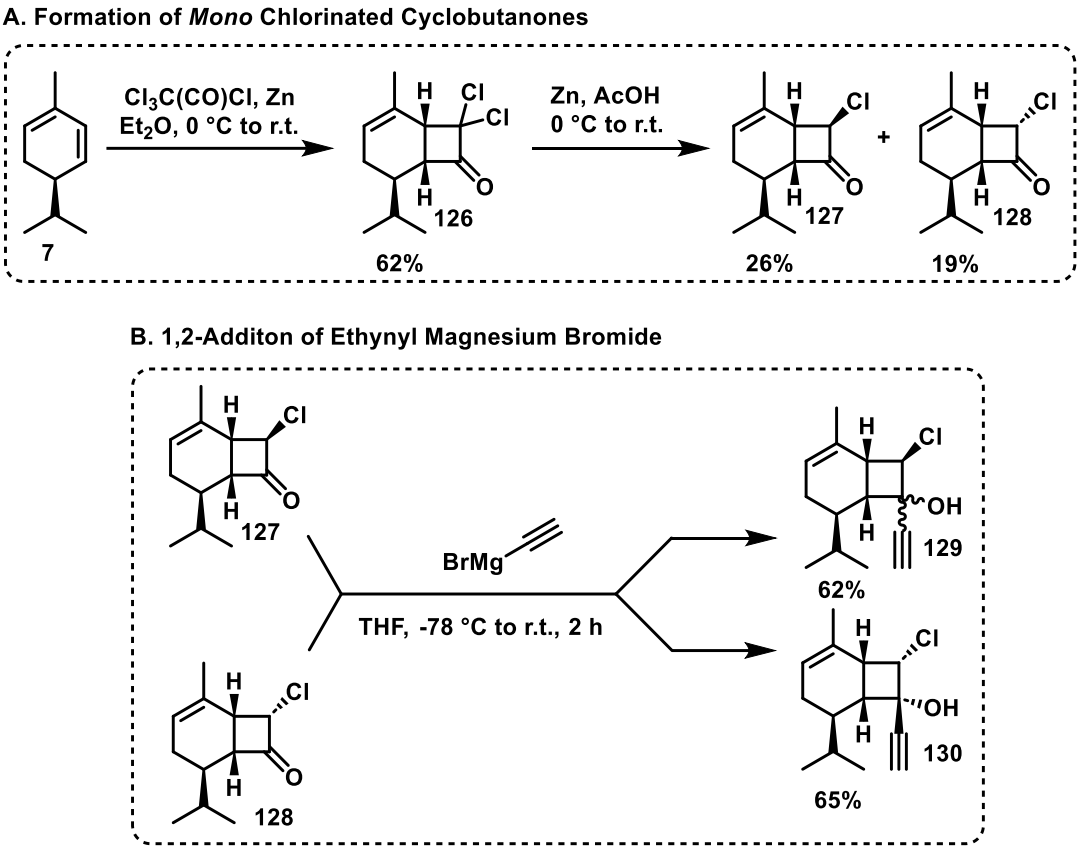
2.1. Reduction-Rearrangement Strategy

Alpha-vinylated cyclobutanones are underrepresented in the literature and are often difficult to prepare, thus finding methods to reliable prepare them would be of immense value. We initially sought to generate *alpha* vinyl cyclobutanones to study various fragmentation reactions, in order to apply this methodology to the synthesis of eleutherobin. Our initial attempt to access *alpha*-vinylated cyclobutanones was based on a procedure reported by Sieburth and co-workers (Scheme 2.1).[7] In this work, a variety of *alpha* alkenyl alcohols were accessed *via* a 1,2-addition of an alkynyl Grignard reagent **120** to an *alpha* chloro ketone **119**, forming the corresponding tertiary alcohol **121**. The alcohol is then treated with lithium aluminium hydride, or another aluminium based reducing agent such as DIBAL to form the 5 membered, spirocyclic intermediate **122**, this then re-arranges to form the six membered, bi-cyclic intermediate **123**, which upon hydrolysis yields the *alpha* vinyl cyclobutanol **124**. These can then be oxidized to form the corresponding *alpha* vinyl cyclobutanone **125**.



Scheme 2.1: Outline of Reduction-Rearrangement Strategy.

We begun our investigations by generating the corresponding *mono* chlorinated compound *via* a [2+2] cycloaddition using trichloroacetyl chloride and *alpha* phellandrene **7**, yielding the *alpha* dichloro cyclobutanone **126** in 60% yield (Scheme 2.2, A).[4] *Mono* de-chlorination was achieved using activated zinc and neat acetic acid.[51] This generated the *mono* chloro compound as a mixture of diastereomers **127** and **128** in a 4:1 ratio. A subsequent 1,2-addition reaction was conducted on both diastereomers, separately, yielding the tertiary alcohol **129** as a 1:1.6 mixture of diastereomers in 62% yield from **127**, while diastereomer **128** gave the alcohol **130** as a single diastereomer in 65% yield (Scheme 2.2, B).



Scheme 2.2*:* Formation of *mono*-Chloro Cyclobutanones 127 and 128 and 1,2-Addtion Reactions.

The formation of a single diastereomer from the 1,2-addition reaction to **128** can be rationalized through a combination of steric and electronic effects. These effects are due to the chlorine *alpha* to the carbonyl. In the case of both diastereomers **127** and **128**, the 1,2-addition reaction will favor the side opposite to the chlorine atom. In the case of diastereomer **128** the 1,2-addition will favor the top face and no competitive reaction will occur due to the concave nature of the molecule (Figure 2.1). For diastereomer **127,** addition from the face opposite the chlorine atom leads to steric repulsion, resulting in a mixture of products **129a** and **129b**.

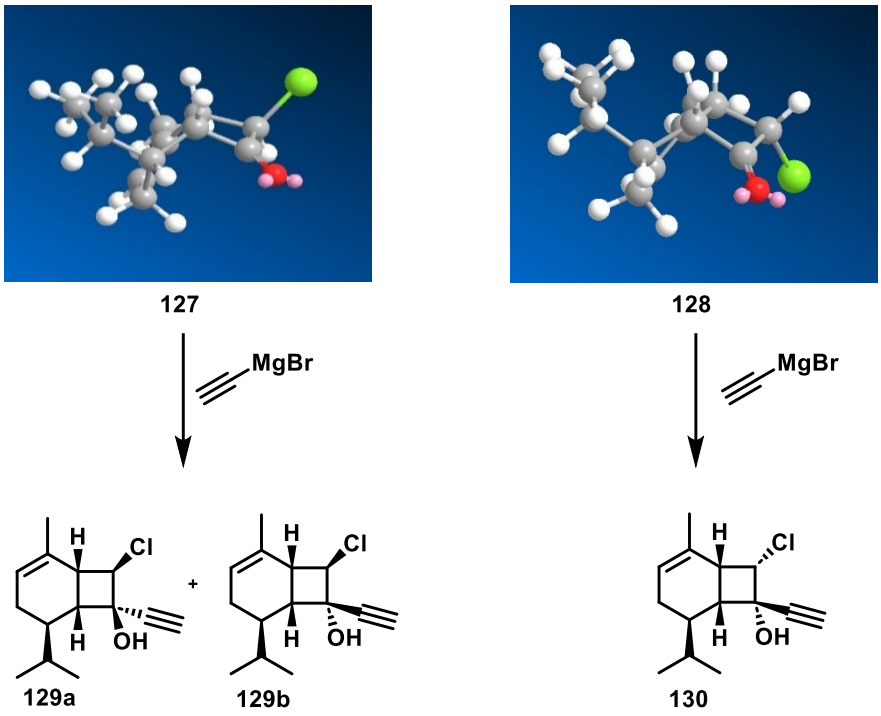
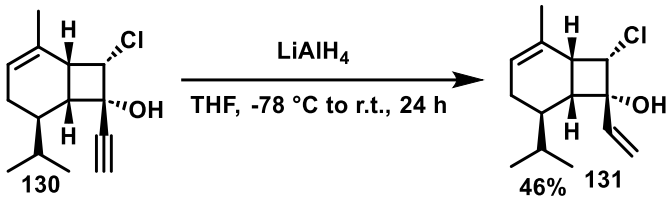


Figure 2.1: Models of the 1,2-addition to Diastereomers 127 and 128.

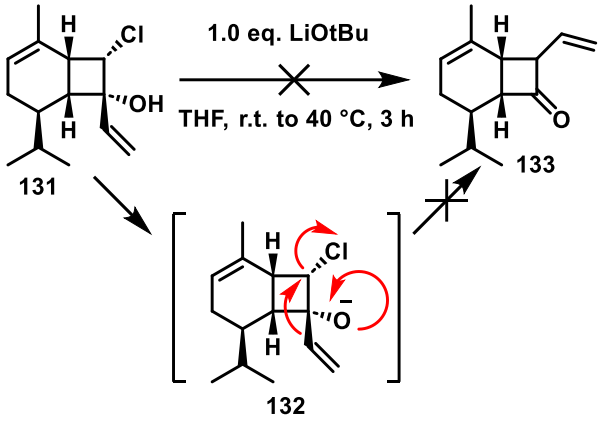
With the tertiary alcohols in hand, we began investigating the reduction and re-arrangement reactions (Scheme 2.3). When treated with lithium aluminum hydride at -78 °C and allowed to warm to room temperature, we observed reduction of the alkyne to the corresponding alkene **131** in 46% yield. Although an encouraging result, the re-arrangement reaction did not proceed as reported by Sieburth. In an effort to induce re-arrangement we experimented with time as well as temperature. When left for 24 h at room temperature, no re-arrangement product was observed. Further, increasing the reaction

temperature from room temperature to 40 °C resulted in none of the desired *alpha* alkynyl ketone **133**.



Scheme 2.3: Initial Rearrangement Attempt of 130.

In an effort to facilitate re-arrangement directly from the tertiary alcohol **130**, we proposed that deprotonation could induce a re-arrangement directly to the corresponding ketone **133** (Scheme 2.4). However, when treated with base at room temperature and slowly warmed to 40 °C no evidence of rearrangement was observed.



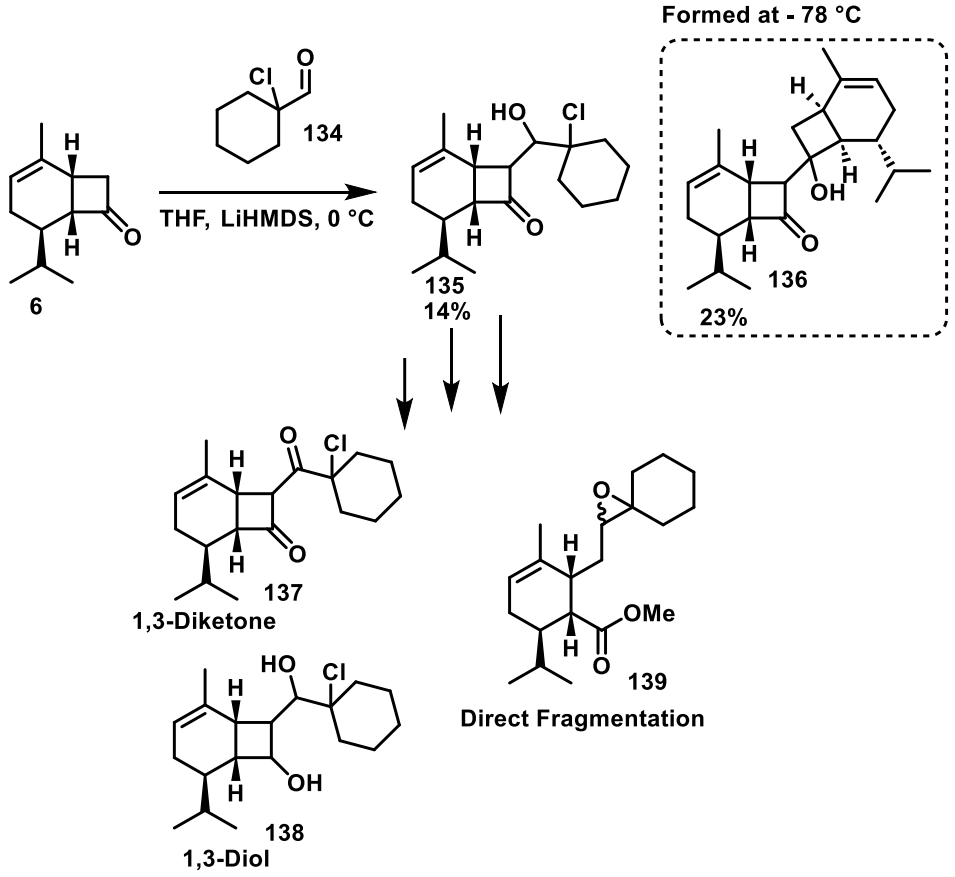
Scheme 2.4: Re-Arrangement Attempt *via Deprotonation.*

We postulate that the lack of reactivity of **131** is due to the inherent bond angles of cyclobutanols. Ideally, a 180° relationship between the chlorine and the alkene would be needed in order for rearrangement to occur. The puckered and locked conformation of compound **131** may prevent this rearrangement from occurring.

2.2. Aldol Strategy

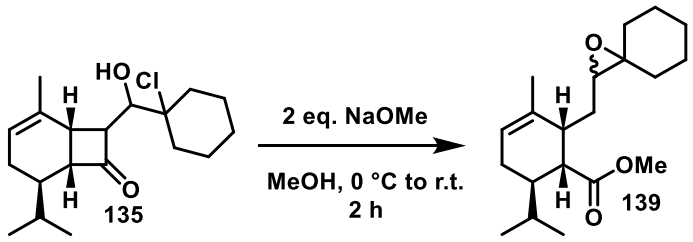
Based on the failure to induce re-arrangement *via* tertiary alcohol **131**, we next aimed to exploit aldol chemistry to functionalize the *alpha* position of cyclobutanone **6**, and then conduct a series of reactions to induce fragmentation of the 4 membered ring (Scheme 2.5). As a model substrate we chose the conveniently prepared *alpha*-chlorocyclohexanecarboxaldehyde **134** .This material was generated from the corresponding aldehyde by treatment with sulfuryl chloride.[52]

The aldol reaction between cyclobutanone **6** and **134** was conducted using LiHMDS at room temperature and gave the desired product **135** in 14% yield (Scheme 2.5). When carried out at -78 °C the reaction only yielded the dimer **136** in 23% yield. Use of other bases, such as LDA, did not improve the reaction outcome.



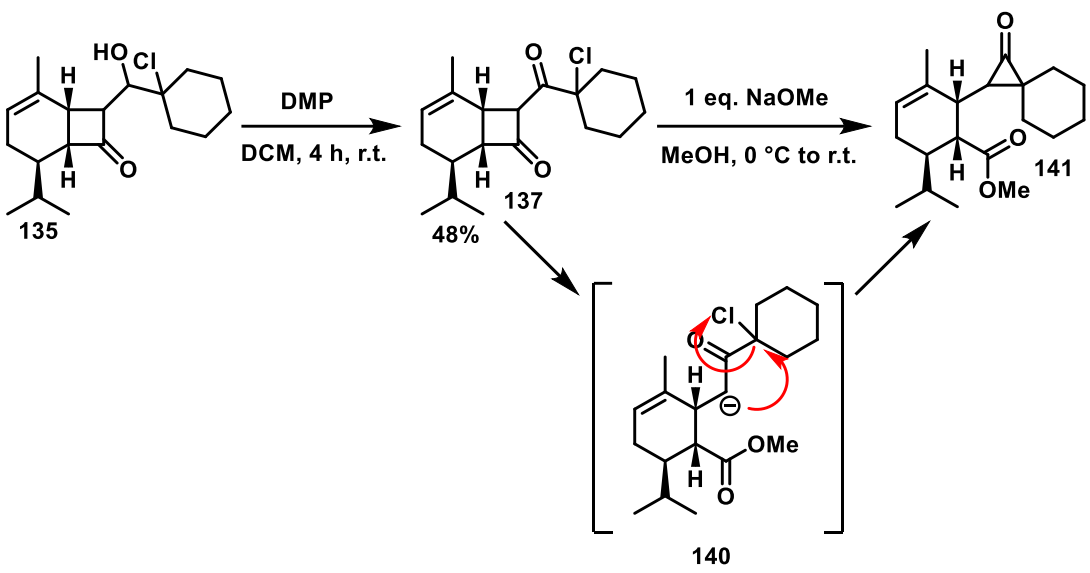
Scheme 2.5: Formation of Aldol Product 135 and Outline of the Aldol-Fragmentation Strategy.

With **135** in hand, we investigated the direct fragmentation by subjecting it to basic conditions (Scheme 2.6). When exposed to a solution of sodium methoxide in methanol, we observed the formation of the epoxide **139**, which was detected by ^{1}H NMR spectroscopic analysis of crude reaction mixtures. Here, we also observed a singlet at 3.62 ppm, which implied the formation of a methyl ester. Additionally, a doublet of doublets was observed at 2.93 ppm which suggested that the four membered ring had fragmented. A resonance corresponding to the epoxide proton could be observed at 2.86 ppm. By mass spectrometry we observed a signal at 321.2370 m/z, which corresponds to this product.



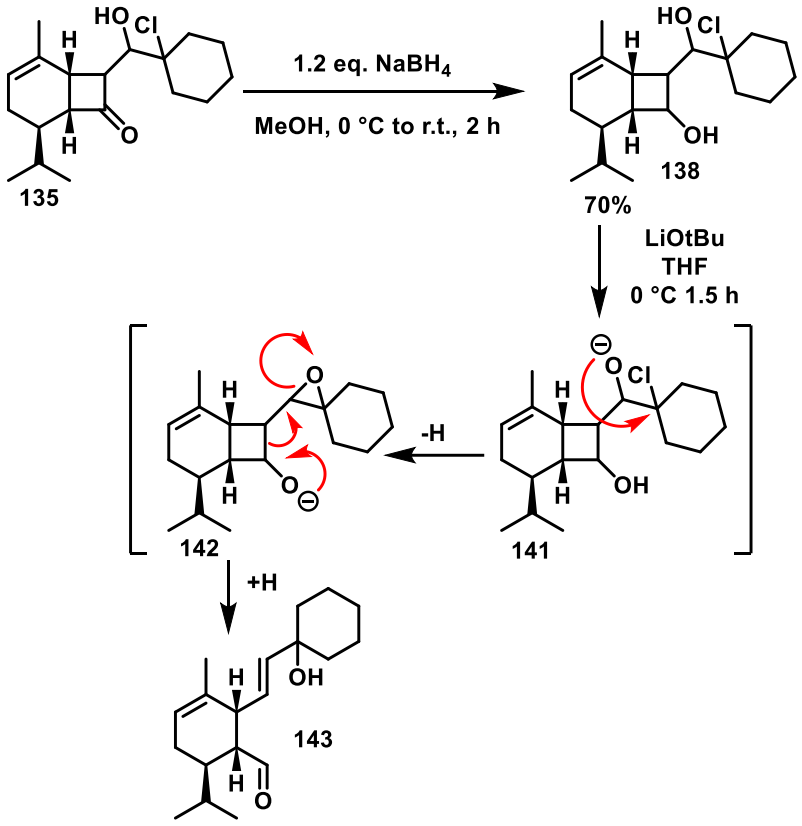
Scheme 2.6: Aldol Product Fragmentation.

The 1,3-diketone **137** was easily prepared using a DMP oxidation of the aldol product **135** (Scheme 2.7). When treated with 1 eq. of sodium methoxide we believed that the cyclopropenone **141** was being formed. We observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture a singlet at 3.58 ppm, which implied the formation of the fragmented methyl ester. A doublet of doublet could be observed at 3.03 ppm, which is indicative of the proton *alpha* to the methyl ester. Additionally, a doublet can be seen at 0.80 ppm which corresponds to the tertiary proton *alpha* to the cyclopropenone. By mass spectrometry analysis we observed a major signal at 319.2223 m/z, which implied elimination of the chlorine and corresponded to the product **141**.



Scheme 2.7: Formation of 1,3-diketone and Cyclopropanone 141.

To examine fragmentation of the 1,3-diol **138**, this material was prepared directly from the aldol product *via* reduction using sodium borohydride (Scheme 2.8), a reaction that proved to be sensitive to both temperature and equivalents of reducing agent. Attempts to induce fragmentation under basic conditions led to formation of the allylic alcohol **143** (Scheme 2.8) in low yields. We believe this product is formed *via* initial deprotonation and subsequent formation of the epoxide **142**. Subsequent deprotonation of the alcohol induces fragmentation of the four membered ring followed by epoxide opening to yield **143**. Based on the unpredictability of the previous reduction, low yield, and purity of the fragmentation product this route was abandoned.



Scheme 2.8: Preparation and Fragmentation of the 1,3-diol.

2.3. Palladium Mediated *Alpha*-Vinylation of Cyclobutanones

In an effort to access *alpha* vinylated cyclobutanones directly, we sought to exploit conditions developed for a related *alpha*-arylation previously reported by our laboratory (Figure 2.2, A).[6] Further, we believed that expanding the reaction scope to *alpha*- vinylation could prove to be a generally useful methodology.

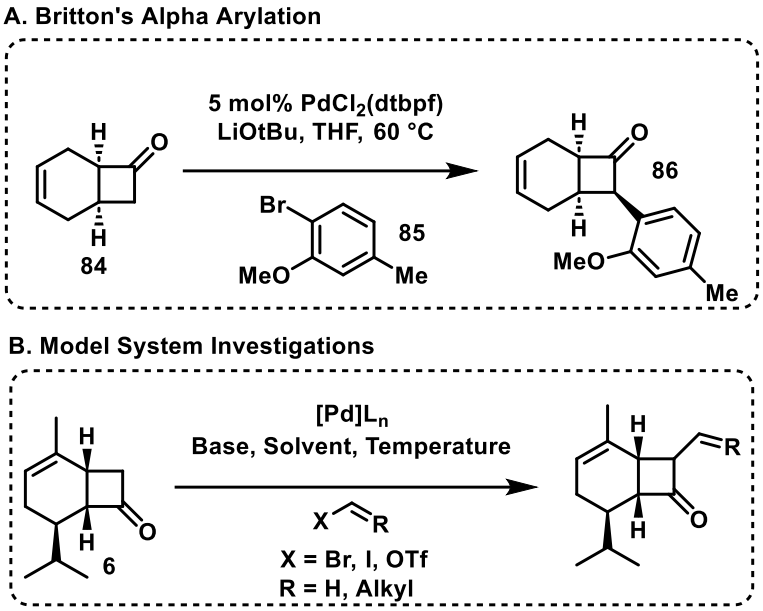
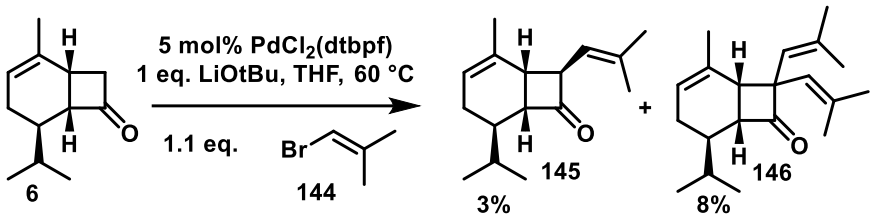


Figure 2.2: ***Alpha*-Arylations and Vinylations of Cyclobutanones.**

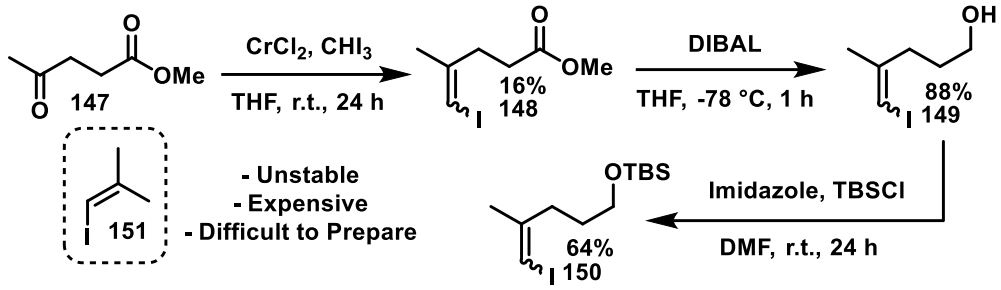
We started our efforts by using the cyclobutanone **6** and the commercially available vinyl bromide **144** (Scheme 2.9). We initially applied the reaction conditions that were reported for the *alpha*-arylation of cyclobutanones and managed to isolate the *bis* vinylated product **146** in 8% yield along with the corresponding *mono* vinylated product **145** in 3% yield. This initial result was encouraging as it had demonstrated that the reaction had succeeded and *alpha*-vinylation of cyclobutanones was feasible. To our knowledge, this is the first example of a direct *alpha*-vinylation conducted on cyclobutanones.

In an attempt to improve the yield of the mono product we first optimized the equivalent of base. Specifically, it was believed that more than one equivalent of lithium *tert*-butoxide would facilitate the formation of the *bis* vinylated product. However, with less than one equivalent of base, we observed no reaction. When potassium *tert*-butoxide was employed as the base, only decomposition of the cyclobutanone was observed.



Scheme 2.9: Initial *Alpha*-Vinylation Attempt.

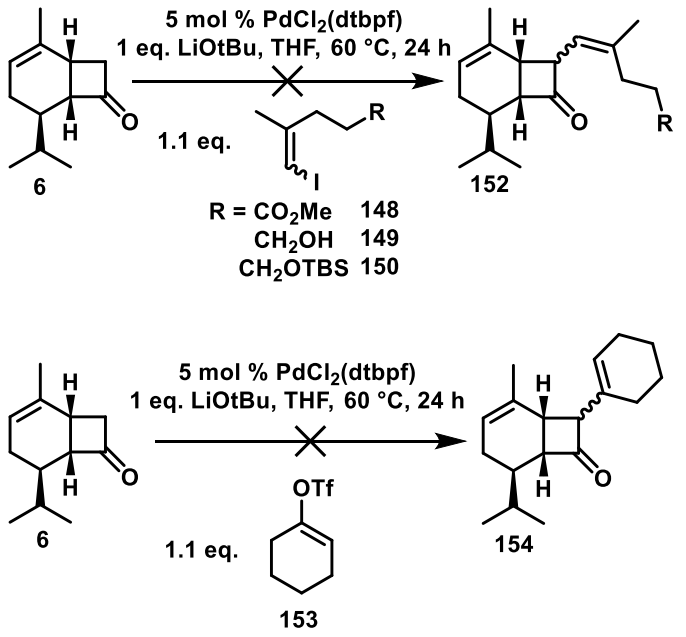
We then proceeded to screen a small selection of solvents that are typically employed in palladium catalyzed enolate coupling reactions. In particular, we found that in DMF, toluene and acetonitrile only starting materials were recovered.



Scheme 2.10: Preparation of Vinyl Iodides. [53]

It was at this point that we decided to switch the coupling partner from the vinyl bromide to a vinyl iodide. Due to the instability, cost and difficult preparation of vinyl iodide **151**, we opted to synthesize a handful of vinyl iodides that were easy to handle in the laboratory (Scheme 2.10). When the reaction was attempted using vinyl iodide **148** under standard conditions no new products were observed, with only starting material being present by NMR spectroscopic analysis of the crude reaction mixtures (Scheme 2.11). We postulated that the presence of the *alpha* carbon on the methyl ester could be problematic in this reaction. Thus, we reduced the methyl ester to the corresponding alcohol **149** as well as the TBS protected compound **150** (Scheme 2.10). We then attempted the reaction twice more under standard conditions and observed only staring materials by NMR spectroscopic analysis of the crude reaction mixtures. These results were discouraging,

given the usual reactivity trends of vinyl halides in transition mediated reactions. Analogous results were obtained when the reaction was attempted with the triflate **153**.



Scheme 2.11: Vinylation Attempts with Iodides and Triflate.

We then elected to investigate catalyst loading and temperature using vinyl bromide **144** as a substrate. We sought to examine these variables to slow down the reaction and prevent any side reactions that may occur at higher temperatures. When conducted with 5 mol% of palladium catalyst at room temperature for 3.5 h, we observed 11% yield of the *mono* product **145**. This result was encouraging, as it had demonstrated that the reaction could be conducted at lower temperature. When conducted with 1 mol% of catalyst at room temperature for 3.5 h the reaction outcome had improved to 20% yield of *mono* product with only trace amount of *bis* product forming. When 0.5 mol% was utilized, results were often inconsistent and irreproducible, with some experiments yielding only trace amounts of products while in others no reactivity was observed. Based on these results, we chose 1 mol% of catalyst at room temperature for 3.5 h as satisfactory conditions for further optimization.

Next we began investigating the effect of bromide equivalents as we believed this would have an effect on the yield and ratio between *mono* and *bis* product (Table 2.1). At the standard reaction conditions of 1.1 eq. of vinyl bromide we observed a yield of 20% of the *mono* product with a corresponding yield of 7% for the *bis* vinylated product. When increased to 1.5 eq. we observed a minor increase in yield for the *mono* vinylated product to 22%, while the bis vinylated product increased to 12%. When increased to 2 eq. we discovered that the yield of *mono* vinylated product had increased to 33%, with a of 16% yield for the *bis* vinylated product. When increased beyond 2 eq., we observed no improvement in reaction outcome. Based on these results, it appeared that 2 eq. of bromide was optimal as this gave the highest yield of *mono* vinylated product.

Equivalents of Bromide	**qNMR Yield of *Mono* 145 (%)**	**qNMR Yield of *Bis* 146 (%)**
1.1	**20**	**7**
1.5	**22**	**12**
2	**33**	**16**
3	**24**	**7**
10	**23**	**3**

Table 2.1: Effect of Bromide Equivalencies on *Alpha*-Vinylation Reaction.

We then turned our attention to base equivalencies, as we believed this was another important variable associated with reaction yield and ratio between *mono* and *bis* vinylated products (Table 2.2). At less than 1 equivalents of lithium *tert*-butoxide, we observed a lower yield for both the *mono* and *bis* vinylated products. Increasing to 2 eq. of lithium *tert*-butoxide resulted in an inflection point for yields, as more *bis* vinylated product had formed as compared to the *mono*. Increasing equivalencies past 2 eq. had an overall negative outcome, with yields being lower for both *mono* and *bis* vinylated products.

Equivalents of Lithium *tert*-Butoxide	qNMR Yield of *Mono* 145 (%)	qNMR Yield of *Bis* 146 (%)
0.9	13	3
1	33	16
2	9	13
3	9	9

Table 2.2: Effect of Base Equivalencies on *Alpha*-Vinylation Reaction.
(Entry 2 has been caried from previous experiments conducted in Table 2.1)

Additionally, we conducted a concentration screen (Table 2.3). We discovered that reaction concentrations bellow 0.1 M resulted in poor reaction outcomes, with yields of both *mono* and *bis* vinylated products being lower. When concentration was increased past 0.3 M we observed no further improvement in yield.

Concentration (Molar)	qNMR Yield of *Mono* 145 (%)	qNMR Yield of *Bis* 146 (%)
0.07	5	0
0.1	26	14
0.3	33	16
0.6	27	11

Table 2.3: Effect of Concentration on *Alpha*-Vinylation Reaction.
(Entry 3 has been caried from previous experiments conducted in Table 2.1)

Based on these sets of experiments, we concluded that 5 mol% of palladium catalyst, 2 eq. of vinyl bromide, 1 eq. of lithium *tert*-Butoxide ran at a concentration of 0.3 M at room temperature for 3.5 h were satisfactory. Using these conditions, we turned our attention to the palladium catalyst (Table 2.3). Based on literature reports on arylation and vinylation of *alpha* positions on various linear and cyclic ketones, phosphine ligated catalysts were predominant in these types of reactions.[34,54-56] Thus, we sought to investigate a variety of catalyst systems. We discovered that the only catalysts systems to yield product were $PdCl_2$(dtbpf), QPhos and XPhos yielding 33%, 11% and 2% of *mono* vinylated product respectively. Interestingly, $PdCl_2$(dtbpf), QPhos were the only catalyst systems that resulted in full consumption of starting material. In all other instances starting material was still present and comprised 28 to 41% of the crude reaction mixtures. Additionally in the cases of XPhos, PPh_3, dppf, and $PdCl_2[P(o\text{-}Tol)_3]_2$ a significant portion of starting material had dimerized.

Catalyst System	**qNMR Yield of *Mono* 145 (%)**	**qNMR Yield of *Bis* 146 (%)**	**Starting Material 6 (%) (qNMR)**	**Dimer Product 136 (%) (qNMR)**
1 mol% $PdCl_2$(dtbpf)	**33**	**16**	**0**	**0**
1 mol% $PdCl_2$ 1 mol% QPhos	**11**	**16**	**0**	**0**
1 mol% $PdCl_2$ 1mol% XantPhos	**0**	**0**	**32**	**0**
1 mol% $PdCl_2$ 1 mol% DiPhos	**0**	**0**	**30**	**0**
1 mol% $PdCl_2$(dppf)	**0**	**0**	**41**	**13**

1 mol% $PdCl_2$ 1 mol% XPhos	**2**	**0**	**32**	**14**
1 mol% $Pd(PPh_3)_4$	**0**	**0**	**28**	**19**
1 mol % $PdCl_2$ P(*o*-Tol)$_3$	**0**	**0**	**34**	**25**

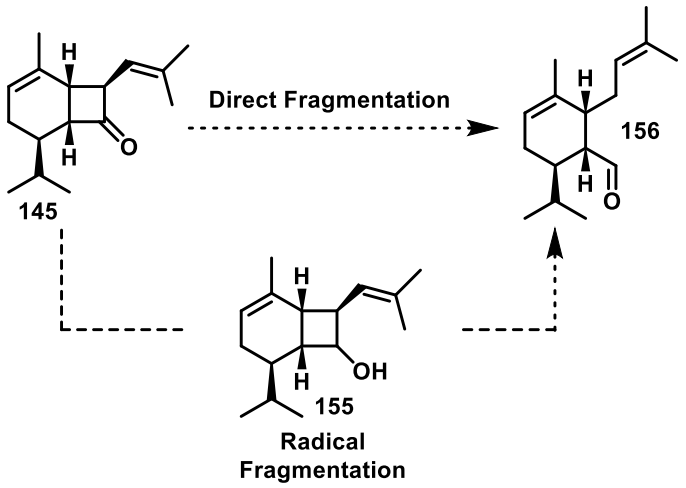
Table 2.4: Results of Catalyst System Screen.

Finally, we conducted several experiments to test the stability of both starting material and *mono* substituted product **144**. We discovered that the presence of base and catalyst, without other reagents, induced decomposition in both starting material and *mono* vinylated product. This could explain the overall low yield as both product and starting material are participating in undesirable reaction pathways. Due to the large mass imbalance, we believe that the *mono* vinylated product may also dimerize thus lowering yield. We postulate that once the initial *mono* vinylated product forms, the more acidic proton can be removed by excess base in solution and participate in unwanted side reactions. However, efforts to isolate and characterize the *mono* vinylated dimer proved futile.

In an effort to supress the formation of any decomposition or dimer products we sought to change the order and rate of addition of reagents. Our initial order of addition involved the rapid addition of a solution of the cyclobutanone and neat vinyl bromide to a suspension of base and catalyst. This method was suspected of rapidly decomposing starting material and any *mono* vinylated product that formed. To remedy this, we decided to experiment with slow addition of base over the course of the reaction. However, when we attempted to add a solution of lithium *tert*-butoxide over the course of 4 h we observed no product formation. At this point we abandoned further optimization of this reaction and turned our attention to the fragmentation of vinylated cyclobutanones now accessible *via* the optimized process.

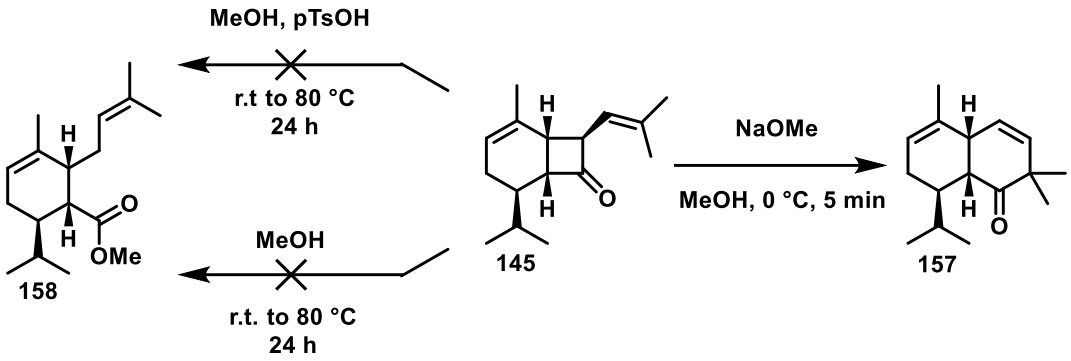
2.4. Fragmentation of Cyclobutanones and Cyclobutanols

As noted above, our goal was to affect the fragmentation of vinyl cyclobutanones or cyclobutanols in an effort to access *delta*-alkenyl ketones **156**, these types of targets would thus be useful in the synthesis of eleutherobin. Towards this goal, we investigated several methods to fragment cyclobutanones directly through a single transformation, or *via* radical methods from their corresponding cyclobutanols (Scheme 2.12).



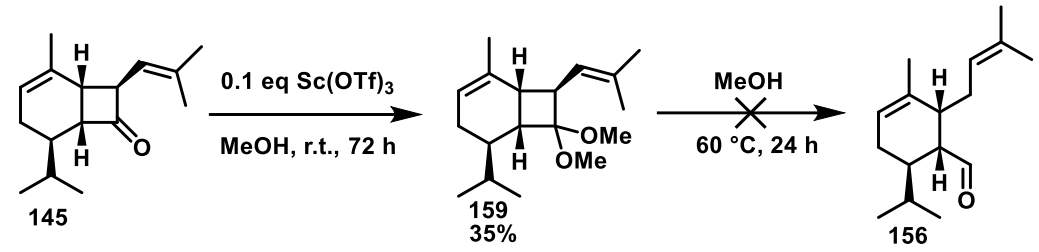
Scheme 2.12: Outline of Cyclobutanone/Cyclobutanol Fragmentation.

As indicated in Scheme 2.13, when exposed to sodium methoxide in methanol we observed what we believed to be the cyclized product **157**. Based on ^{1}H NMR spectroscopic analysis of crude reaction mixtures, we observed two new vinyl signals at 5.93 and 4.99 ppm, additionally by mass spectrometric analysis we observed a signal at 250.1880 m/z, which corresponds to the ammonium adduct of the cyclized product. Although structurally interesting, this was not a productive process and, in an attempt to avoid the basic cyclization process, we sought to induce fragmentation under neutral conditions. When **145** was heated in methanol, we did not observe evidence of fragmentation (Scheme 2.13). Using catalytic amounts of acid to activate the carbonyl also proved futile.



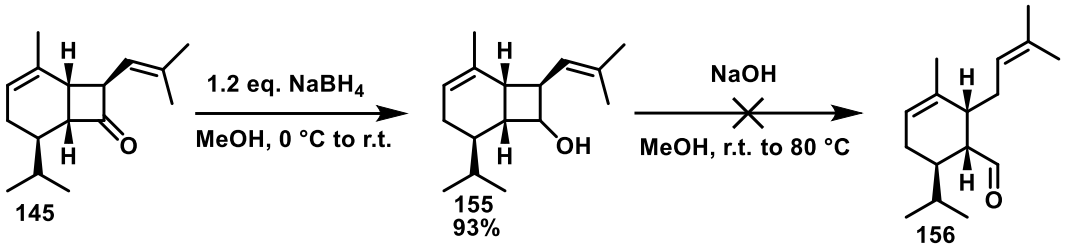
Scheme 2.13: Fragmentation Attempts with Neutral, Acidic and Basic Conditions.

Additionally, we attempted to induce fragmentation under Lewis acidic conditions (Scheme 2.14). However, when vinylated cyclobutanone **145** was exposed to $Sc(OTf)_3$ only the ketal **159** was observed in 35% yield. When heated in methanol the ketal did not fragment and only staring material was observed by ^1H NMR spectroscopic analysis.



Scheme 2.14: Lewis Acid Fragmentation Attempts.

As indicated in Scheme 2.15, we next elected to investigate the fragmentation of cyclobutanols. Towards this goal, cyclobutanol **155** was prepared *via* a sodium borohydride reduction in excellent yields. With the cyclobutanol in hand we believed that exposure to base would induce fragmentation and give the corresponding fragmented aldehyde **156**. However, when treated with sodium hydroxide and heated, only staring material was observed by ^1H NMR spectroscopic analysis of the crude reaction mixture.



Scheme 2.15: Generation of Cyclobutanol and Base Fragmentation Attempt.

After several unsuccessful attempts to fragment the cyclobutanol under basic conditions, we sought to generate an alkoxy radical from the cyclobutanol, which could be used to induce fragmentation. There have been several reports of fragmenting cyclopropanols and cyclobutanols in the literature (Figure 2.3) [57-60] and we sought to appropriate these conditions to our system to yield the corresponding *delta*-vinyl aldehyde **156**.

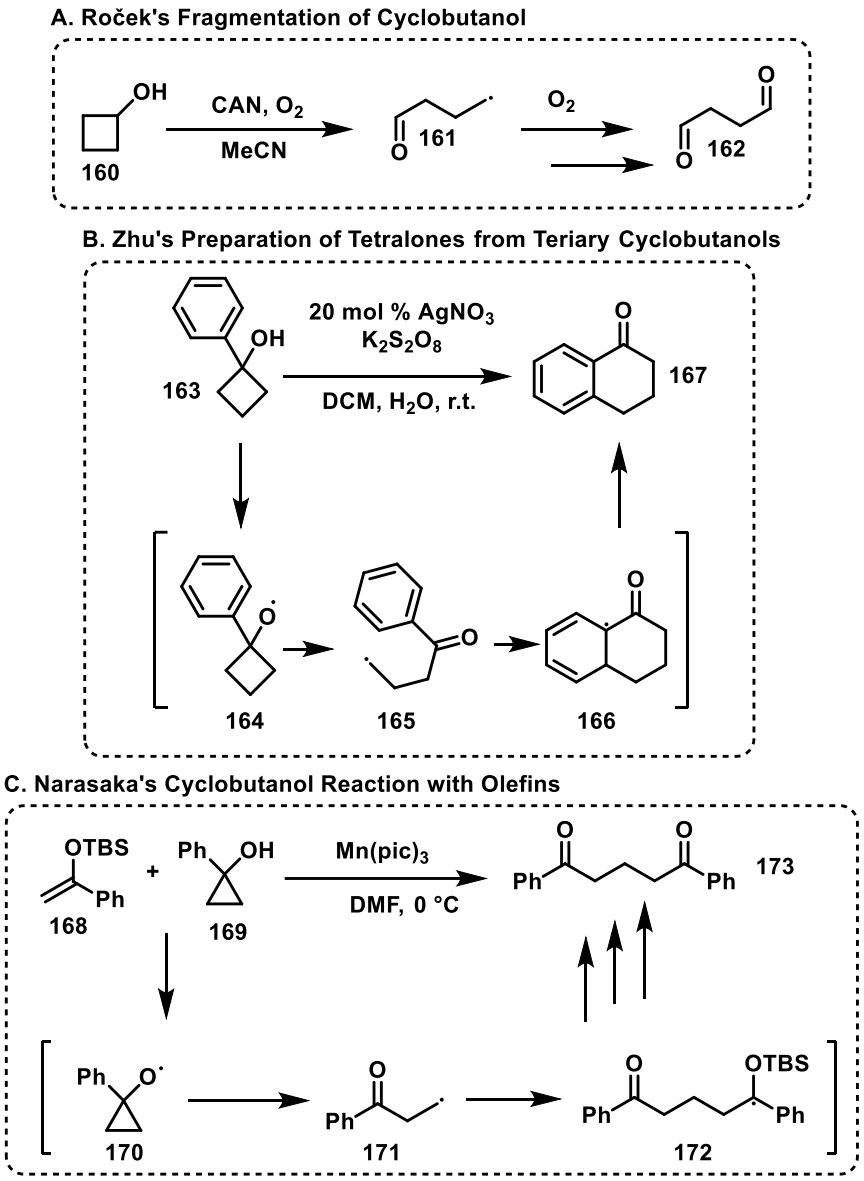
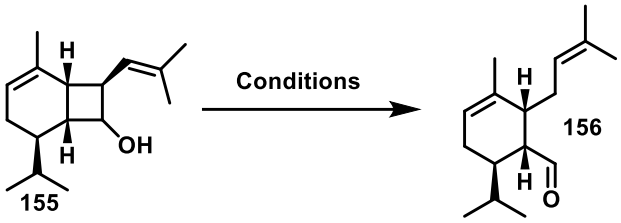


Figure 2.3: Literature Reports of Cyclobutanol and Cyclopropanol Fragmentations.



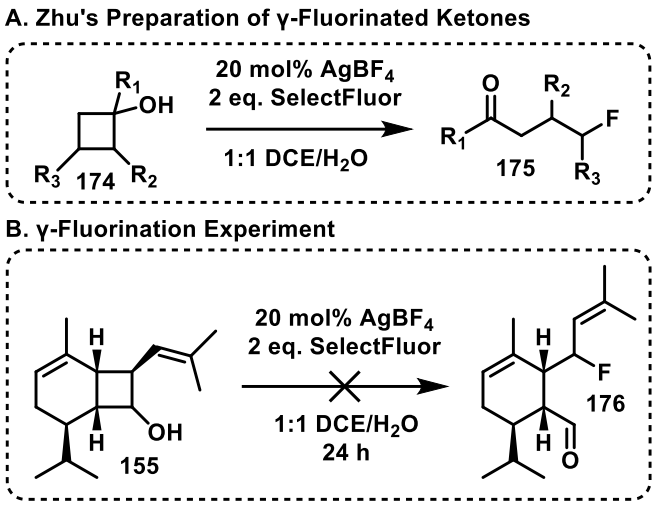
Conditions	Outcome
$AgNO_3$, $K_2S_2O_8$ 1:1 DCM:H_2O, r.t., 3 h	No product formation, only staring material present
$Mn(pic)_3$, DMF, r.t., 2 h	No product formation, only staring material present
CAN, 1:1 MeCN:H_2O, r.t., 1 h	No product formation, only staring material present

Table 2.5: Radical Fragmentation Attempts.

When silver nitrate and potassium persulfate were employed, we did not observe evidence of starting material. This was also the case with manganese picolinate and ammonium cerium nitrate.

In 2015, Zhu and co-workers reported the generation of *gamma*-fluorinated ketones **175** from the corresponding cyclobutanols **174** (Scheme 2.16, A).[61] We believed that the reaction conditions could be appropriated to generate the corresponding *gamma*-fluorinated aldehyde **176**. If successful, substituting another radical acceptor *in lieu* of

SelecFluor could generate the desired product **176**. When these conditions were assessed on cyclobutanol **155**, there was no evidence of fluorination (Scheme 2.16, B) by mass spectrometry and NMR spectroscopic analysis with all other attempts at radical fragmentation being abandoned.



Scheme 2.16: Zhu's formation of *γ*-Fluorinated Ketones and Fluorination Experiment.

2.5. Conclusion and Future Work

In summary, we have explored several reaction pathways of cyclobutanones including *alpha* vinylation, aldol reactions, 1,2-additions, skeletal re-arrangements, and fragmentation reactions. Additionally, we have explored the fragmentation of cyclobutanones directly, or *via* their cyclobutoxy radical. We have also demonstrated that the aldol product **135** can fragment directly or *via* the 1,3-diketone and 1,3-diol products. We have also shown that cyclobutanones can undergo direct *alpha* vinylation *via* enolate mediated palladium catalysis; to our knowledge this is the only known example of this reactivity.

With regards to future work, if access to the cyclopropenone **141** or the fragmentation products **139** and **143** are desired, further optimization of these reactions is needed. Additionally, the initial aldol reaction would need to be further optimized.

We believe there are several ways in which the *alpha* vinylation reaction could be improved on. Recent reports indicate that other metals besides palladium such as zinc

have been employed as catalysts for the *alpha* vinylation of various linear ketones,[55] perhaps experimenting with the metal center could result in more favorable reaction outcomes. A more rigorous screen of ligands could be conducted, ideally high throughput experimentation could be employed to gain more understanding of the reaction and more rigorous analytical techniques could be employed to isolate and characterize byproducts, as well as kinetic studies of the reactions.

2.6. Experimental

2.6.1. General

All reactions described were performed under an atmosphere of dry nitrogen using flame-dried glassware unless otherwise specified. Tetrahydrofuran was distilled over sodium and benzophenone and dichloromethane was dried by distillation from calcium hydride. All commercially obtained reagents were used as received without further purification unless otherwise specified. Reactions carried out at room temperature were conducted at approximately 22 °C. Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60). Thin layer chromatography was carried out on commercial glass backed silica gel plates (Canadian Life Sciences, MN809023, thickness 0.25 mm). Concentration and removal of trace solvents was performed using a Büchi rotary evaporating using a -30 °C ethylene glycol chiller and a Welch vacuum pump.

NMR spectra were recorded using chloroform-*d* as the solvent. Signal positions (δ) are given in parts per million from tetramethylsilane (δ = 0) and were measured relative to the signal of the solvent ($CDCl_3$: δ = 7.26, ^1H NMR; δ = 77.16, ^{13}C NMR). Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^1H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet: t, triplet; m, multiplet), coupling constants, number of protons, assignment (where possible). NMR spectra were recorded on a Bruker Avance II 600 spectrometer equipped with a QNP (600 MHz) or Burker Avance III 500 spectrometer (500 MHz), or Bruker Avance III 400 spectrometer (400 MHz). Assignments of ^1H and ^{13}C NMR spectra were assigned based on analysis of ^1H-^1H COSY, HMBC, HSQC, and 2D NOESY spectra.

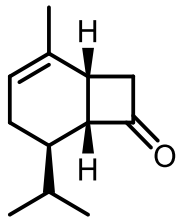
High resolution mass spectra were obtained on a Bruker maXis II Ultra-High resolution LC-QTOF mass spectrometer.

IR spectra were recorded on a PerkinElmer Spectrum Two FT-IR spectrometer. Only selected, characteristic absorption data are provided for each compound.

Optical rotation was measured on a PerkinElmer 341 polarimeter at 589 nm.

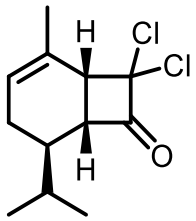
Microwave reactions were performed in a CEM Discover LabMate microwave synthesize at 2.45 GHz.

2.6.2. Preparation of (1*R*,5*R*,6*R*)-8,8-dichloro-5-isopropyl-2-methylbicyclo[4.2.0]oct-2-en-7-one (6).[4]



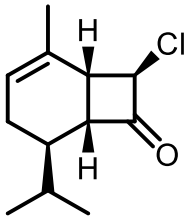
To a stirred solution of **126** (2.60 g, 11 mmol) in 30 mL of methanol at 0 °C was tipped in ammonium chloride (3.1 g, 57.6 mmol) immediately followed by zinc-copper couple (3.60 g, 55.1 mmol). The reaction mixture was allowed to stir for 24 h without re-charging the ice bath. The reaction was then filtered through a bed of ceilite and solvent removed *in vacuo*. The crude organic residue was then dissolved in a minimal amount of diethyl ether and washed with brine. The combined organic extracts were dried with magnesium sulphate, filtered, and concentrated *in vacuo*. The crude organic residue was purified using flash chromatography (1% diethyl ether in hexane) to afford **6** (1.75 g, 93 % yield) as a yellow oil with spectral data matching reported data.[4]

2.6.3. Preparation of (1*R*,5*R*,6*R*)-8,8-dichloro-5-isopropyl-2-methylbicyclo[4.2.0]oct-2-en-7-one (126).[4]

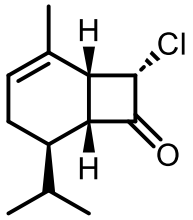


Compound **126** was obtained in 60% yield from the reported literature procedure with spectra matching reported data.[4]

2.6.4. Preparation of (1*R*,5*R*,6*R*,8*R*)-8-chloro-5-isopropyl-2-methylbicyclo[4.2.0]oct-2-en-7-one (127) and (1*R*,5*R*,6*R*,8*S*)-8-chloro-5-isopropyl-2-methylbicyclo[4.2.0]oct-2-en-7-one (128).



127



128

To a stirred solution of **126** (1.13 g, 4.6 mmol) in 20 mL of glacial acetic acid at room temperature was tipped in acid washed zinc (329 mg, 5.0 mmol). After stirring for 24 h, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate and extracted with hexanes. The combined organic extracts were washed with brine, dried with magnesium sulphate, filtered, and concentrated *in vacuo*. The crude organic residue was purified using flash chromatography (25% toluene in hexane) to afford diastereomer **127** (258 mg, 26% yield) as a white solid and diastereomer **128** (184 mg, 19 % yield) as a clear oil.

Data for compound **127**:

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (d, *J* = 6.4 Hz, 1H), 4.64 (dd, *J* = 7.3, 2.9 Hz, 1H), 3.29 (ddd, *J* = 11.3, 9.7, 2.9 Hz, 1H), 2.72 (t, *J* = 8.5 Hz, 1H), 2.08 (dt, *J* = 16.7, 5.5 Hz, 1H), 1.83 (s, 3H), 1.76 – 1.66 (m, 2H), 1.60 – 1.48 (m, 2H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 201.9, 131.8, 124.1, 67.0, 57.4, 40.6, 39.6, 31.4, 25.4, 20.6, 20.7, 19.1.

HRMS: m/z calcd. for $C_{12}H_{18}ClO$: 213.1040 (M+H); Found: 213.1045 (M+H).

FTIR (CH_2Cl_2, cast film) 2957, 2934, 1780, 1463, 1437,1369, 1063, 882, 714, 602 cm^{-1}

$[\alpha]_D^{20}$: -27 (c = 0.6, MeOH)

m.p: 65 – 67 °C

Data for compound **128**:

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67 (d, *J* = 6.4 Hz, 1H), 4.99 (dd, *J* = 9.2, 2.9 Hz, 1H), 3.61 (dq, *J* = 9.5, 3.1, 1.7 Hz, 1H), 3.13 (t, *J* = 9.3 Hz, 1H), 2.17 – 2.08 (m, 1H), 2.02 – 1.94 (m, 1H), 1.93 – 1.87 (m, 1H), 1.81 (s, 3H), 1.59 (d, *J* = 6.4 Hz, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H).

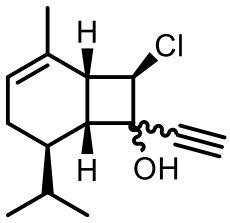
^{13}C NMR (101 MHz, $CDCl_3$) δ 204.7, 130.6, 124.4, 62.7, 57.6, 36.7, 34.9, 30.1, 24.6, 23.8, 21.0, 20.9.

HRMS: m/z calcd. for $C_{12}H_{18}ClO$: 213.1040 (M+H); Found: 213.1042 (M+H).

FTIR (CH_2Cl_2, cast film) 2957, 2934, 1785, 1462, 1386, 1297, 1166, 1061, 945, 786 cm^{-1}

$[\alpha]_D^{20}$: -56 (c = 0.3, MeOH)

2.6.5. Preparation of (1*R*,5*R*,6*R*,8*R*)-8-chloro-7-ethynyl-5-isopropyl-2-methylbicyclo[4.2.0]oct-2-en-7-ol (129).



129 (26.4 mg, 177 μmol) was prepared in the same manner as compound **130** from compound **127**, as an inseparable mixture (1.6:1) of diastereomers in 62% as an orange oil.

1H NMR (500 MHz, $CDCl_3$) δ 5.60 – 5.52 (m, 2H), 4.19 (d, *J* = 8.9 Hz, 1H), 4.01 (d, *J* = 9.2 Hz, 1H), 2.97 (t, *J* = 9.3 Hz, 1H), 2.83 – 2.75 (m, 3H), 2.62 (s, 1H), 2.58 – 2.47 (m, 2H), 2.27 (s, 1H), 2.25 – 2.13 (m, 1H), 2.04 – 1.89 (m, 3H), 1.84 – 1.50 (m, 9H), 0.99 (d, *J* = 7.0 Hz, 5H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 2H).

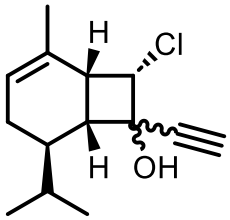
^{13}C NMR (151 MHz, $CDCl_3$) δ 133.3, 133.1, 123.6, 123.4, 84.0, 82.8, 75.8, 74.6, 73.0, 70.8, 66.0, 65.8, 45.9, 45.5, 44.9, 41.4, 39.3, 37.3, 30.2, 28.4, 22.7, 22.0, 21.7, 21.6, 20.4, 20.2, 16.4, 15.8.

HRMS: m/z calcd. for $C_{14}H_{20}ClNaO$: 261.1016 (M+Na); Found: 261.10177 (M+Na).

FTIR (CH_2Cl_2, cast film) 3296, 2957, 1446, 1464, 1384, 1367, 1260, 1233, 1074, 865 cm^{-1}

$[\alpha]_D^{20}$: +94 (c = 0.2, MeOH)

2.6.6. Preparation of (1*R*,5*R*,6*R*,8*S*)-8-chloro-7-ethynyl-5-isopropyl-2-methylbicyclo[4.2.0]oct-2-en-7-ol (130).



To a stirred solution of **128** (16.5 mg, 77 µmol) in 250 µL of THF at -78 °C was added a solution of ethynl magnesium bromide (155 µmol, 310 µL) in THF dropwise. The reaction was allowed to stir at -78 °C for 1 h. The reaction was then warmed to room temperature allowed to stir for an additional 1 h. The reaction mixture was then quenched with a saturated solution of ammonium chloride and extracted with DCM. The combined organic extracts were dried with magnesium sulphate, filtered, and concentrated *in vacuo*. The crude organic residue was purified using flash chromatography (10% diethyl ether in hexane) to afford **130** (12.1 mg, in 65% yield) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (d, *J* = 5.5 Hz, 1H), 4.77 (dd, *J* = 4.4, 2.7 Hz, 1H), 3.12 (t, *J* = 8.0 Hz, 1H), 2.88 (s, 1H), 2.77 – 2.69 (m, 1H), 2.63 (s, 1H), 2.17 – 2.09 (m, 1H), 1.90 – 1.79 (m, 2H), 1.66 (s, 3H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H).

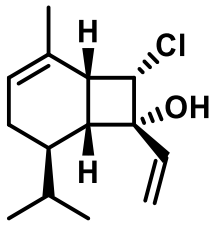
^{13}C NMR (101 MHz, $CDCl_3$) δ 129.7, 126.0, 86.1, 73.0, 67.7, 67.4, 49.0, 37.7, 37.0, 30.9, 23.5, 21.6, 21.4, 17.1.

HRMS: m/z calcd. for $C_{14}H_{20}ClO$: 239.1197 (M+H); Found: 239.1195 (M+H).

FTIR (CH_2Cl_2, cast film) 3292, 2956, 1787, 1464, 1367, 1161, 1141, 918, 777, 681 cm^{-1}

$[\alpha]_D^{20}$: +73 (c = 0.1, MeOH)

2.6.7. Preparation of (1*R*,5*R*,6*R*,7*R*,8*S*)-8-chloro-5-isopropyl-2-methyl-7-vinylbicyclo[4.2.0]oct-2-en-7-ol (131).



To a stirred solution of **130** (13.7 mg, 57.4 µmol) in 200 µL of THF in -78 °C was tipped in lithium aluminium hydride (3.3 mg, 87.0 µmol). The reaction was allowed to stir at -78 °C for 30 min and then allowed to warm to room temperature. After 3 h of stirring at room temperature, the reaction mixture was quenched with a saturated solution of Rochelle's salt and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried with magnesium sulphate, filtered, and concentrated *in vacuo*. The crude organic residue was purified using flash chromatography (50% toluene in hexane) to yield **131** (5.4 mg, 46% yield) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.11 (dd, *J* = 17.2, 10.7 Hz, 1H), 5.73 (d, *J* = 5.9 Hz, 1H), 5.47 (dd, *J* = 17.2, 1.1 Hz, 1H), 5.20 (dd, *J* = 10.7, 1.1 Hz, 1H), 4.53 (dd, *J* = 7.2, 2.9 Hz, 1H), 2.89 (d, *J* = 13.3 Hz, 2H), 2.46 (ddd, *J* = 11.1, 8.6, 2.9 Hz, 1H), 2.13 (dd, *J* = 16.2, 5.9 Hz, 1H), 1.90 – 1.74 (m, 2H), 1.67 (d, *J* = 2.6 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H).

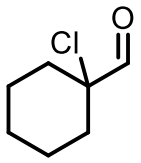
^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3, 130.2, 125.9, 113.4, 74.0, 67.6, 46.2, 37.2, 37.1, 30.8, 23.7, 21.6, 21.5, 17.0.

HRMS: m/z calcd. for $C_{14}H_{21}ClNaO$: 263.1173 (M+Na); Found: 263.1167 (M+Na)

FTIR (CH_2Cl_2, cast film): 2956, 2925, 1638, 1463, 1367, 987, 924, 780, 688 cm^{-1}

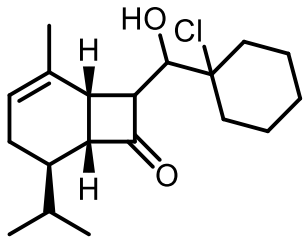
$[\alpha]_D^{20}$: +32 (c = 0.2, MeOH)

2.6.8. Preparation of 1-chlorocyclohexane-1-carbaldehyde (134).[53]



Compound **134** was obtained in 66% yield from the reported literature procedure with spectra matching reported data.[53]

2.6.9. Preparation of (1*S*,5*R*,6*R*)-8-((1-chlorocyclohexyl)(hydroxy)methyl)-5-isopropyl-2-methylbicyclo[4.2.0]oct-2-en-7-one (135).



To a stirred solution of **6** (103.6 mg, 581 µmol) in 1 mL of THF at 0 °C was added a 1 M solution of LiHMDS (588 µmol, 588 µL) in THF and the reaction mixture was allowed to stir for 30 min. A solution of **134** (94.5 mg, 645 µmol) in 1 mL of THF was then added to the reaction mixture dropwise. After 20 min the reaction was brought up to room temperature and allowed to stir for an additional 3.5 h. The reaction was then quenched with a saturated solution of ammonium chloride and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried with magnesium sulphate, filtered, and concentrated *in vacuo*. The crude organic residue was purified using flash chromatography (10% ethyl acetate in hexane) to afford compound **135** (26.5 mg, 14% yield) as a yellow oil.

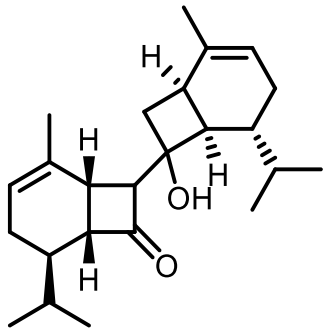
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 – 5.53 (m, 1H), 3.90 (dd, *J* = 7.0, 1.5 Hz, 1H), 3.59 (dt, *J* = 7.3, 2.0 Hz, 1H), 3.25 (td, *J* = 9.2, 2.6 Hz, 1H), 2.74 (t, *J* = 8.2 Hz, 1H), 2.51 (d, *J* = 8.1 Hz, 1H), 2.15 – 2.00 (m, 1H), 1.96 – 1.83 (m, 3H), 1.83 – 1.56 (m, 9H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 209.6, 134.0, 122.9, 80.2, 80.2, 66.0, 58.8, 38.9, 35.1, 34.5, 33.0, 31.1, 25.4, 25.2, 22.0, 21.9, 21.2, 20.9, 19.4.

HRMS: m/z calcd. for $C_{19}H_{33}ClKO_2$: 342.2194 (M+K); Found: 342.2200 (M+K).

FTIR (CH_2Cl_2, cast film) 3536, 2926, 1757, 1447, 1383, 1086, 875, 800 cm^{-1}

2.6.10. Preparation of (1*R*,1'*R*,2*R*,5'*R*,6*S*,6'*R*)-7'-hydroxy-2,5'-diisopropyl-2',5-dimethyl-[7,7'-bi(bicyclo[4.2.0]octane)]-2',4-dien-8-one (136).



To a stirred solution of **6** (112.7 mg, 632 µmol) in 1 mL of THF at -78 °C was added a solution of LiHMDS (695 µmol, 695 µL) in THF dropwise. After 30 min of stirring at -78 °C, a solution of **134** (109.4 mg, 746 µmol) in 1 mL of THF was added. After an additional 1 h and 15 min at -78 °C the reaction was quenched with a 1:1 solution of MeOH and saturated ammonium chloride and allowed to warm to room temperature. The reaction mixture was then extracted with DCM and the combined organic extracts were washed with brine, dried with magnesium sulphate, filtered, and concentrated *in vacuo*. The crude organic residue was purified using flash chromatography (7% ethyl acetate in hexane) to afford **136** (51.4 mg, 23% yield) as a clear oil that solidifies at room temperature.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 – 5.52 (m, 1H), 5.48 (d, *J* = 6.9 Hz, 1H), 3.40 (ddd, *J* = 9.5, 6.3, 2.8 Hz, 1H), 3.18 (ddd, *J* = 5.3, 2.8, 1.0 Hz, 1H), 2.77 (dd, *J* = 9.8, 5.3 Hz, 1H), 2.61 (ddd, *J* = 11.3, 8.7, 3.0 Hz, 1H), 2.50 (ddd, *J* = 11.6, 8.5, 3.2 Hz, 1H), 2.21 (q, *J* = 9.0 Hz, 1H), 2.12 – 2.02 (m, 1H), 1.96 (ddd, *J* = 15.6, 6.8, 3.7 Hz, 1H), 1.90 – 1.59 (m, 10H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.85 (dd, *J* = 8.2, 6.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.1, 135.8, 134.3, 122.7, 122.1, 73.6, 73.1, 60.2, 45.6, 42.4, 38.4, 37.9, 31.7, 30.6, 29.6, 25.1, 22.4, 22.2, 21.8, 21.0, 19.8, 16.0.

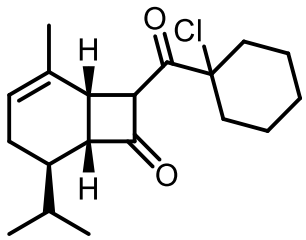
HRMS: m/z calcd. for $C_{24}H_{37}O_2$: 357.2788 (M+H); Found: 357.2787 (M+H).

FTIR (CH_2Cl_2, cast film) 3536, 2953, 1749, 1440, 1383, 1365, 1383, 1199, 1115, 912 cm^{-1}

$[\alpha]_D^{20}$: -12 (c = 0.4, MeOH)

m.p: 34 – 37 °C

2.6.11. Preparation of (1*S*,5*R*,6*R*)-8-(1-chlorocyclohexane-1-carbonyl)-5-isopropyl-2-methylbicyclo[4.2.0]oct-2-en-7-one (137).



DMP (54.3 mg, 128 µmol) was tipped into a stirred solution of **135** (20.8 mg, 64.0 µmol) in 250 µL of DCM at room temperature. After stirring at room temperature for 3 h, the reaction was diluted with ethyl acetate and quenched with saturated aqueous solutions of sodium bicarbonate and sodium thiosulphate. The organic layer was washed with brine, dried with magnesium sulphate, filtered, and concentrated *in vacuo*. The crude organic residue was purified using flash chromatography (7% ethyl acetate in hexane) to yield **137** (10 mg, 48% yield) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 – 5.55 (m, 1H), 4.75 (dd, *J* = 6.0, 2.5 Hz, 1H), 3.55 (ddd, *J* = 9.8, 7.3, 2.5 Hz, 1H), 3.19 – 3.14 (m, 1H), 2.14 – 2.07 (m, 2H), 1.97 (d, *J* = 5.0 Hz, 2H), 1.88 – 1.58 (m, 8H), 1.32 – 1.23 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H).

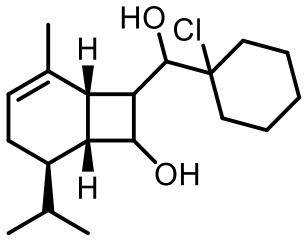
^{13}C NMR (151 MHz, $CDCl_3$) δ 133.1, 123.5, 71.6, 60.8, 38.0, 35.0, 34.7, 31.0, 30.7, 25.0, 21.2, 20.9, 19.7.

HRMS: m/z calcd. for $C_{19}H_{28}ClO_2$: 323.1772 (M+H); Found: 323.1770 (M+H).

FTIR (CH_2Cl_2, cast film) 2937, 1778, 1699, 1447, 908, 731 cm^{-1}

$[\alpha]_D^{20}$: +38 (c = 0.8, CH_2Cl_2)

2.6.12. Preparation of (1*S*,5*R*,6*R*)-8-((1-chlorocyclohexyl)(hydroxy)methyl)-5-isopropyl-2-methylbicyclo[4.2.0]oct-2-en-7-ol (138).

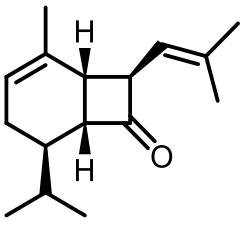


Sodium borohydride (12.2 mg, 322 µmol) was tipped into a solution of **135** (49.4 mg, 152 µmol) in 1 mL of methanol at 0 °C. Stirring was continued for 1 h and the reaction was allowed to warm to room temperature. After 1 h of additional stirring, the reaction was quenched with water and extracted with DCM. The combined organic extracts were washed with brine, dried with magnesium sulphate, filtered, and concentrated *in vacuo* to afford **138** (34.9 mg, 70% yield) as a clear oil.

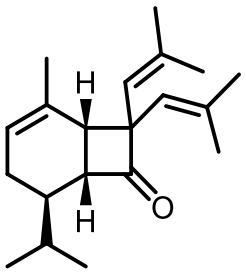
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 – 5.53 (m, 1H), 3.89 (dd, *J* = 8.1, 1.6 Hz, 1H), 3.60 (dt, *J* = 7.3, 2.1 Hz, 1H), 3.48 (q, *J* = 7.0 Hz, 1H), 3.25 (td, *J* = 9.2, 2.5 Hz, 1H), 2.74 (t, *J* = 8.2 Hz, 1H), 2.51 (d, *J* = 8.1 Hz, 1H), 2.09 – 2.02 (m, 1H), 1.95 – 1.84 (m, 3H), 1.79 – 1.59 (m, 12H), 1.21 (t, *J* = 7.0 Hz, 2H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H).

HRMS: m/z calcd. for $C_{19}H_{31}ClNaO_2$: 349.1904 (M+H); Found: 349.1905 (M+H).

2.6.13. Preparation of (1*S*,5*R*,6*R*,8*R*)-5-isopropyl-2-methyl-8-(2-methylprop-1-en-1-yl)bicyclo[4.2.0]oct-2-en-7-one (145) and (1*R*,5*R*,6*R*)-5-isopropyl-2-methyl-8,8-bis(2-methylprop-1-en-1-yl)bicyclo[4.2.0]oct-2-en-7-one (146).



145



146

A stirred solution of 1 M LiOtBu (270 µmol, 270 µL) in THF and $PdCl_2$(dtbpf) (6.4 mg, 9.8 µmol) was sparged with nitrogen for 5 min. A solution containing isocrotyl bromide (72.0 mg, 530 µmol) and **4** (46.7 mg, 262 µmol) in 1 mL of THF was sparged with nitrogen for 5 min and rapidly added to the solution of base and catalyst. The reaction mixture was allowed to stir at room temperature for 3.5 h upon which the reaction was quenched with a saturated aqueous solution of ammonium chloride and extracted with DCM. The combined organic extracts were washed with brine, dried with magnesium sulphate, filtered, and concentrated *in vacuo*. The crude organic residue was purified using flash chromatography (5% diethyl ether in hexane) to afford the *mono* vinylated cyclobutanone **150** (20 mg, 33% yield) as a yellow oil and *bis* vinylated cyclobutanone **151** (11.9 mg, 16% yield) as a clear oil.

Data for compound **144:**

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (ddt, *J* = 6.1, 2.9, 1.5 Hz, 1H), 5.19 (m, 1H), 3.88 (ddd, *J* = 9.5, 7.5, 2.6 Hz, 1H), 3.13 (ddd, *J* = 10.2, 8.7, 2.6 Hz, 1H), 2.40 (t, *J* = 8.2 Hz, 1H), 2.05 (dt, *J* = 15.9, 5.5 Hz, 1H), 1.75 (d, J 1.4 Hz, 3H), 1.75 – 1.68 (m, 1H), 1.71 – 1.58 (m, 7H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 211.3, 136.1, 134.4, 122.3, 120.2, 65.5, 58.6, 39.5, 36.5, 31.1, 25.9, 25.2, 21.0, 19.1, 18.7.

HRMS: m/z calcd. for $C_{16}H_{25}O$: 233.1894 (M+H); Found: 233.1899 (M+H).

FTIR (CH_2Cl_2, cast film) 2959, 2926, 1769, 1445,1370, 1137, 1071, 949, 911, 732 cm^{-1}

$[\alpha]_D^{20}$: + 32 (c = 0.2, MeOH)

Data for compound **146**:

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (d, *J* = 2.0 Hz, 1H), 5.47 (tt, *J* = 4.4, 1.4 Hz, 1H), 5.28 (t, *J* = 1.4 Hz, 1H), 3.20 (ddd, *J* = 8.9, 5.5, 1.0 Hz, 1H), 3.08 (d, *J* = 8.9 Hz, 1H), 2.05 – 1.97 (m, 1H), 1.88 – 1.80 (m, 1H), 1.78 (d, *J* = 1.8 Hz, 3H), 1.66 (d, *J* = 1.5 Hz, 3H), 1.58 (d, *J* = 1.3 Hz, 3H), 1.31 (s, 3H), 1.27 (s, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H).

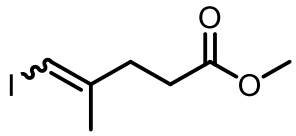
^{13}C NMR (151 MHz, $CDCl_3$) δ 200.7, 145.5, 145.0, 134.3, 133.9, 132.6, 121.8, 56.9, 38.6, 38.0, 37.9, 30.6, 30.0, 29.7, 26.8, 24.8, 22.4, 21.1, 20.1, 19.5.

HRMS: m/z calcd. for $C_{20}H_{31}O$: 287.2369 (M+H); Found: 287.2372 (M+H).

FTIR (CH_2Cl_2, cast film) 2959, 2928, 1744, 1638, 1446, 1369, 1071 cm^{-1}

$[\alpha]_D^{20}$: + 48 (c = 1.7, $CDCl_3$)

2.6.14. Preparation of methyl 5-iodo-4-methylpent-4-enoate (148).[53]



Chromium(II) chloride (1.28 g, 10.4 mmol) was weighed out rapidly into a round bottom flask and the vessel was purged with nitrogen for 5 min. The flask was subsequently wrapped in tin foil and removed from sources of light. The chromium (II) chloride was then dissolved in 3 mL of THF and allowed to stir at room temperature. A solution of methyl 4-oxopentanoate **147** (277 mg, 2.13 mmol) and iodoform (2.52 g, 6.40 mmol) in 5 mL of THF was then added to the reaction mixture. After 24 h of stirring at room temperature the reaction mixture was quenched with water and extracted with diethyl ether. The combined organic extracts were washed with brine, dried with magnesium sulphate, filtered, and concentrated *in vacuo*. The crude organic residue was purified using flash chromatography (5% diethyl ether in hexane) to afford **148** (85 mg, 16 % yield) as an off-white liquid.

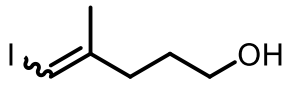
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (q, *J* = 1.2 Hz, 1H), 5.93 (q, *J* = 1.5 Hz, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 2.57 – 2.48 (m, 4H), 2.48 – 2.40 (m, 4H), 1.89 (d, *J* = 1.5 Hz, 3H), 1.85 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 173.0, 146.2, 145.8, 76.0, 75.6, 51.9, 34.5, 34.2, 32.6, 31.6, 24.0, 23.3.

HRMS: m/z calcd. for $C_7H_{12}IO_2$: 254.9875 (M+H); Found: 254.9873 (M+H).

FTIR (CH_2Cl_2, cast film): 2949,1733,1435,1364, 1165, 1053, 665 cm^{-1}

2.6.15. Preparation of 5-iodo-4-methylpent-4-en-1-ol (149).



To a stirred solution of **148** (131.1 mg, 516 µmol) in 2 mL of dry THF at -78 °C was added a solution of DIBAL (1.13 mmol, 1.25 mL) in THF dropwise. After 1 h of stirring at -78 °C the reaction was quenched with a saturated solution of Rochelle's salt and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried with magnesium sulphate, filtered, and concentrated *in vacuo*. The crude organic residue was purified using flash chromatography (5% diethyl ether in hexane) to afford **149** as an inseparable mixture (1:1) of *E*/*Z* isomers (103.2 mg, 88% yield) as a yellow oil.

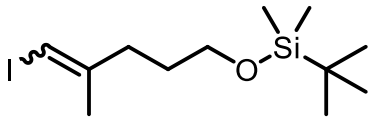
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (m, 1H), 5.88 (m, 1H), 3.71 – 3.61 (m, 4H), 2.35 – 2.27 (m, 4H), 1.91 (d, *J* = 1.5 Hz, 3H), 1.85 (d, *J* = 1.1 Hz, 3H), 1.76 – 1.66 (m, 4H), 1.40 (t, *J* = 5.6 Hz, 1H), 1.26 (t, *J* = 5.2 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 147.6, 147.2, 75.1, 74.8, 62.4, 62.2, 35.9, 35.2, 30.7, 30.0, 24.0, 23.4.

HRMS: m/z calcd. for $C_6H_{12}IO$: 226.9927 (M+H); Found: 226.9926 (M+H).

FTIR (CH_2Cl_2, cast film) 3322, 2937, 2858, 1765, 1616, 1438, 1374, 1265, 1141, 1059 cm^{-1}

2.6.16. Preparation of tert-butyl((5-iodo-4-methylpent-4-en-1-yl)oxy)dimethylsilane (150).



Imidazole (13.7 mg, 201 µmol) and TBSCl (14.3 mg, 94.9 µmol) were tipped into a stirred solution of **149** (18 mg, 79.6 mmol) in 500 µL of DMF at room temperature. After 24 h of stirring at room temperature the reaction was quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried with magnesium sulphate, filtered, and concentrated *in vacuo*. The crude organic extract was purified using

flash chromatography (40% ethyl acetate in hexane) to afford **150** (17.3 mg, 64% yield) as a clear oil.

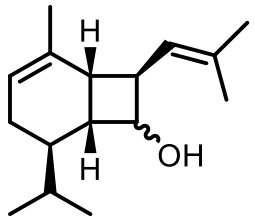
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 – 5.87 (m, 1H), 5.85 – 5.82 (m, 1H), 3.64 (t, *J* = 6.5 Hz, 2H), 3.58 (t, *J* = 6.3 Hz, 2H), 2.31 – 2.19 (m, 4H), 1.89 (d, *J* = 1.5 Hz, 3H), 1.84 (d, *J* = 1.1 Hz, 3H), 1.69 – 1.59 (m, 4H), 0.91 (s, 8H), 0.89 (s, 9H), 0.07 (s, 6H), 0.04 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 147.9, 147.6, 74.8, 74.2, 62.9, 62.3, 36.0, 35.5, 30.9, 30.4, 26.1, 26.1, 24.0, 23.5, 18.5, 18.5, -5.1, -5.2.

HRMS: m/z calcd. for $C_{12}H_{26}IOSi$: 341.0792 (M+H); Found: 341.0783 (M+H).

FTIR (CH_2Cl_2, cast film) 2950, 2855, 1470, 1253, 1100, 832, 773 cm^{-1}

2.6.17. Preparation of (1*S*,5*R*,6*R*,8*R*)-5-isopropyl-2-methyl-8-(2-methylprop-1-en-1-yl)bicyclo[4.2.0]oct-2-en-7-ol (155).



To a stirred solution of **145** (66.5 mg, 286 μmol) in 1 mL of MeOH at 0 °C was added $NaBH_4$ (15.5 mg, 410 μmol) in one portion. The reaction mixture was allowed to stir at 0 °C for 15 min, upon which the reaction was allowed to warm to room temperature. After 1 h of additional stirring, the reaction was quenched with water and extracted with DCM. The combined organic extracts were washed with brine, dried with magnesium sulphate, filtered, and concentrated *in vacuo* to afford the cyclobutanol **155** (62.2 mg, 93% yield) a white solid without need for further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (d, *J* = 6.2 Hz, 1H), 5.22 (dt, *J* = 9.6, 1.4 Hz, 1H), 4.02 (q, *J* = 7.3 Hz, 1H), 2.74 (q, *J* = 8.9, 1.1 Hz, 1H), 2.50 – 2.41 (m, 1H), 2.00 – 1.73 (m, 4H), 1.71 (d, *J* = 1.4 Hz, 3H), 1.66 (d, *J* = 1.4 Hz, 3H), 1.51 (d, *J* = 0.8 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 136.0, 132.5, 127.5, 121.5, 72.9, 52.8, 40.0, 37.4, 37.3, 30.0, 26.0, 22.5, 21.9, 20.3, 18.6, 16.3.

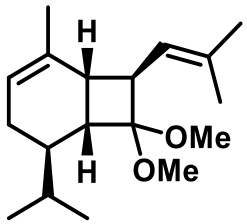
HRMS: m/z calcd. for $C_{16}H_{27}O$: 235.2056 (M+H); Found: 235.2050 (M+H).

FTIR (CH_2Cl_2, cast film) 3450, 2962, 2925, 2878, 1437, 1376, 1063, 1026, 865, 520 cm^{-1}

$[\alpha]_D^{20}$: + 172 (c = 0.3, MeOH)

m.p: 129 – 130 °C

2.6.18. Preparation of (1*S*,5*R*,6*R*,8*R*)-5-isopropyl-7,7-dimethoxy-2-methyl-8-(2-methylprop-1-en-1-yl)bicyclo[4.2.0]oct-2-ene (159).



To a solution of **145** (17.8 mg, 76.6 µmol) in 500 µL of MeOH was tipped in scandium (III) triflate (6.8 mg, 14.0 µmol) and the reaction was allowed to stir at room temperature. After 72 h the reaction mixture was quenched with water and extracted with DCM. The combined organic extracts were washed with brine, dried with magnesium sulphate, filtered and concentrated *in vacuo* to afford **159** (7.5 mg, 33% yield) as a white solid without need for further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 – 5.37 (m, 2H), 3.20 (s, 3H), 3.06 (s, 3H), 2.88 (t, *J* = 10.3 Hz, 1H), 2.43 – 2.35 (m, 1H), 2.09 (t, *J* = 9.1 Hz, 1H), 1.96 (s, 1H), 1.91 – 1.83 (m, 1H), 1.73 (d, *J* = 1.4 Hz, 3H), 1.65 (d, *J* = 1.4 Hz, 3H), 1.51 (dt, *J* = 2.5, 1.1 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.2, 131.1, 124.3, 121.7, 104.2, 50.4, 48.6, 48.4, 41.6, 38.3, 38.0, 29.1, 26.3, 21.9, 20.2, 18.4, 15.7.

HRMS: m/z calcd. for $C_{18}H_{30}NaO_2$: 301.2138 (M+Na); Found: 301.2137 (M+

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