Studies on Ring Forming Reactions: Geminal Acylation, Nazarov Cyclization and Cyclohexyne Reactions

by

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Abstract

Geminal acylation is a powerful tool for converting ketones into 1,3-diketones. An ambitious synthesis of a propellane was envisaged by three geminal acylation reactions. Geminal acylations were done on the ethylene glycol ketal of ethyl levulinate with four- and five-membered acyloins, generating, following a ring-opening process, a series of ketodiesters. A methyl substituent appeared to sterically inhibit the subsequent geminal acylation under many different reaction conditions and with different ester moieties. Thus, an unmethylated analog was prepared, but, unfortunately, the geminal acylation of that substrate was also unsuccessful.

Nazarov reactions of allenyl vinyl ketones (AVKs) can be interrupted by the addition of a nucleophile to the reaction mixture. The oxyallyl cations of AVKs were intercepted with a wide variety of oxygen-substituted dienes by (4+3) cycloaddition with a high degree of regioselectivity and with very high facial selectivity. Dienes with a substituent on the terminus of the oxygenated double bond formed (4+3) products in greater than 95% yield, but with modest diastereoselectivities, whereas dienes with a substituent on the terminus of the other double bond formed (4+3) products in modest yield but with high diastereoselectivity. The results were most consistent with a mechanism for the cycloaddition that is concerted but asynchronous.

Cyclohexyne is so strained that it cannot be isolated, but it can be generated and reacted in situ with nucleophiles. Cyclohexyne has been studied very little and not much is known about its ability to undergo Diels-Alder reactions. Diels-Alder products were produced from the reactions of cyclohexyne with furan, an oxygenated acyclic diene, and a carbocyclic diene. 3-Methylcyclohexyne was prepared, and it reacted with furan forming diastereomeric adducts in a 2:1 ratio. Attempts were made to generate 3,3-dimethylcyclohexyne, but difficulties in methylation prevented its formation. The Diels-Alder reactions were generally low yielding. Tetramerization of cyclohexyne was a dominant reaction pathway, and the tetramer was obtained as a single diastereomer in 80% yield by a novel method.
List of Abbreviations and Symbols Used

Δ heat
ΔG‡ Gibbs energy of activation
δ chemical shift
ν wavenumber(s)
Å angstrom
Ac acetyl
APCI atmospheric-pressure chemical ionization
aq aqueous
AVK allenyl vinyl ketone
Boc tert-butyloxy carbonyl
Bn benzyl
bp boiling point
br broad
nBu n-butyl
rtBu tert-butyl
calcd. calculated
COD 1,5-cyclooctadiene
conc. concentrated
COSY  correlation spectroscopy
Cy   cyclohexyl
d   doublet
dd   doublet of doublets
DBU   1,8-diazabicyclo[5.4.0]undec-7-ene
DCM   dichloromethane
dcpe   bis(dicyclohexylphosphino)ethane
Diphos   bis(diphenylphosphino)ethane
DMAD   dimethyl acetylenedicarboxylate
DMAP   4-(dimethylamino)pyridine
DME   1,2-dimethoxyethane
DMF   dimethylformamide
DMP   Dess-Martin periodinane
DMS   dimethylsulfide
dppe   see Diphos
dr   diastereomeric ratio
equiv.   equivalent(s)
ESI   electrospray ionization
Et   ethyl
g  gram(s)

h  hour(s)

HMBC  heteronuclear multiple bond correlation (spectroscopy)

HOMO  highest occupied molecular orbital

HRMS  high-resolution mass spectrometry

HSQC  heteronuclear single quantum correlation (spectroscopy)

hv  light energy

Hz  hertz

IR  infrared

J  coupling constant

kcal  kilocalorie(s)

KHMDS  potassium hexamethyldisilazide

K-Selectride  potassium tri-sec-butylborohydride

LDA  lithium diisopropylamide

LiICA  lithium cyclohexylisopropylamide

L-Selectride  lithium tri-sec-butylborohydride

LS-Selectride  lithium trisiamylborohydride

LUMO  lowest unoccupied molecular orbital

M  molar

m  multiplet
Me  methyl
mg  milligram(s)
MHz  megahertz
min  minute(s)
 mL  mililitre(s)
mmol  milimole(s)
mol  mole(s)
MOM  methoxymethyl
mp  melting point
Ms  methanesulfonyl
nm  nanometer(s)
NMR  nuclear magnetic resonance
NOE  nuclear Overhauser effect
N-Selectride  sodium tri-sec-butylborohydride
Nu  nucleophile
ORTEP  Oak Ridge thermal ellipsoid plot
iPr  isopropyl
Ph  phenyl
ppm  parts per million
pTSA  para-toluenesulfonic acid
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<td>q</td>
<td>quartet</td>
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<tr>
<td>rt</td>
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</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBATB</td>
<td>tetrabutylammonium tribromide</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBSOTf</td>
<td>tert-butyldimethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<td>TLC</td>
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<td>TMEDA</td>
<td>$N,N',N'',N''$-tetramethylethylenediamine</td>
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<tr>
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<td>ultraviolet</td>
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Chapter 1 – Introduction

Organic chemistry began as the study of the chemistry of life, then the study of carbon compounds, especially those related to coal, but now it encompasses both, including all that is carbon-based, along with other elements that are found in living organisms. From methane to enzymes, from Earth to outer space, and from living organisms to materials that improve our daily lives, organic chemicals are all around us. Organic chemists have been synthesizing and characterizing chemicals produced in nature since Wöhler’s synthesis of urea in 1828. Organic chemists around the globe have spent years dedicated to studying biologically active compounds (e.g. drugs, pesticides, natural products), materials of commercial importance (e.g. dyes, clothing fabric, oils), and other carbon-containing molecules. Some of these important chemicals are produced in abundance naturally and may not require synthesis, although you’ll likely find chemists who have prepared them synthetically, usually to confirm the molecular geometry or to highlight useful chemical transformations.

Organic synthesis is split into two subcategories. The first is total synthesis, which is the preparation of a target molecule, whether biologically interesting, materials sciences interesting, or theoretically interesting. The second is methodology, which is the investigation of chemical transformations to develop reagents, catalysts, or synthetic strategies, but ultimately methodology helps us to understand how chemical reactions work.
The following three chapters will highlight three research projects that I have undertaken during the course of my PhD studies. These three studies are diverse and do not have many similarities, other than the fact they involve the formation of cyclic products, though by very different mechanisms.

The first project explores cyclic reactions in the hope of creating an interesting molecular scaffold, a propellane, from geminal acylation reactions (see Chapter 2). The term propellane refers to a tricyclic system conjoined by a carbon-carbon single bond, creating a molecule that resembles a propeller (Figure 1). Propellanes were first synthesized in the 1930s by Diels-Alder cycloadditions, but the term propellane was only introduced in the literature in 1966.

![Figure 1. Example of a [4.4.4]propellane.](image)

The second project pertained to mechanistic insights on regio- and diastereoselectivities of a (4+3) cycloadditions of allenyl vinyl ketones and oxygen-substituted dienes in interrupted Nazarov reactions, a tandem process involving electrocyclization and cycloaddition (see Chapter 3). Electrocyclizations are appealing in synthesis because they generate rings from acyclic molecules, creating two new sp\(^3\) hybridized centers along with a new \(\sigma\) bond while losing a \(\pi\) bond. The interrupted Nazarov reaction can then introduce new carbon-carbon bonds to the product of electrocyclization, which, if done with a high degree of stereocontrol, would be a powerful method of generating complex ring systems.
The third and final project involved the study of cyclohexyne, a strained cycloalkyne, and the desire of improving its synthetic utility, as well as better understanding its limitations as an electrophilic dienophile in Diels-Alder reactions (see Chapter 4). Although arynes, particularly benzyne, have evolved as powerful tools in organic synthesis, cyclohexyne has not been used in synthesis until recently.\(^7\) Cyclohexyne has been used in a very limited number of examples undergoing (2+2), (3+2) and (4+2)-cycloadditions, although the stereoselectivity of the latter had not been studied. This study also covered a new methodology under development that was aimed at generating substituted cyclohexynes, both for the purpose of examining their stereoselectivity with unsymmetrical dienes in Diels-Alder reactions, and also to substitute the cyclohexyne in an effort to extend its synthetic utility.
Chapter 2 – Exploring the Synthesis of a Propellane via Geminal Acylation

2.1 Introduction to Geminal Acylation

Geminal acylation is the net replacement of a carbonyl group (or equivalent) by two geminal acyl groups. Up until the mid-70’s, there were no efficient processes for carrying out this transformation, but in 1977 Eiichi Nakamura and Isao Kuwajima reported a two-step process they termed geminal acylation. They prepared geminally acylated products from benzaldehyde, acetals and ketals by first forming a pinacol intermediate (1) via an acid catalyzed Mukaiyama aldol-type addition of a bis-silylated succinoin (2). This was achieved using TiCl₄, tetrabutylammonium fluoride (TBAF) for benzaldehyde derivatives, or BF₃•OEt₂ for acetal and ketal derivatives (Scheme 1). 1,3-Cyclopentanediones (3) were then obtained by way of a trifluoroacetic acid (TFA) mediated pinacol rearrangement, which was a concerted process presumably aided by the release of ring strain of the cyclobutanone. This method of forming geminally disubstituted 1,3-cyclopentanediones in two steps made these molecules, and derivatives thereof, much easier to access, and this provided an improved method for syntheses of natural products that contain these core structures.
Scheme 1 - The geminal acylation reaction.

They observed that acetals and ketals reacted more efficiently with 2 compared to their carbonyl counterparts, as indicated by higher yields of 1 and comparable yields for the second step. The synthetic utility of this process was highlighted by the formation of 2,2-disubstituted cyclopentanodiones, including spiro[4.n]alkanes such as 4, which could then be fragmented and reduced to form a lactone 5. Functionalization prior to the pinacol rearrangement was possible, as in the formation of 6 (Scheme 2).8

Scheme 2. The synthetic utility of 1,3-diketones.

Kuwajima and coworkers reported the “reductive succinoylation” via the intermediate cyclobutanone, forming silyl enol ethers of γ-keto esters (7), adding
another facet to this methodology. The preparation of such products was achieved as a result of screening various Lewis acids. SnCl₄ proved to be effective for both the initial aldol step and the subsequent ring-opening step (Scheme 3). The silyl enol ether moiety of 7 could then be used as a nucleophile for a Mukaiyama aldol-type addition or may be hydrolyzed to form a γ-keto ester.

\[ RO \quad OR \quad \xrightarrow{\text{SnCl₄, CH₂Cl₂, -78 °C}} \quad \xrightarrow{TMSO} \quad 2 \quad \xrightarrow{\text{(93%)}} \quad \text{TMSO} \quad \xrightarrow{\text{OR}} \quad 7 \]

**Scheme 3. The “reductive succinoylation” reaction.**

This geminal acylation process was improved upon in 1988 when Wu and Burnell showed that both the aldol reaction and the pinacol rearrangement could be mediated by the use of excess BF₃•OEt₂ in a one-pot synthesis. This new protocol generally worked better for ketals and benzylic acetals as it gave higher yields than the previous two-step method, it gave cleaner products, and it eliminated the need to work-up the intermediate pinacol. Ketones appeared to be unreactive toward silyl enol ethers however, careful experimentation showed that the initial aldol-like reaction did take place, but the pinacol intermediate underwent a retro-aldol reversion to starting material. This problem was overcome using a one-pot procedure, facilitated by the addition of a small amount of water after forming the pinacol. The geminal acylation of aldehydes and acetals was also improved by Martinez *et al.* by adding Nafion-H as an acidic co-catalyst to help in the pinacol rearrangement step.
Further studies have shown this methodology can be applied to various substrates using different acyloins. These modifications have been performed to examine the stereoselectivities involved in both the aldol reaction and pinacol rearrangement, as well as the functionalizability of the geminal acylation products, so as to better understand the scope and limitations of this methodology going forward in natural product synthesis.

2.2 The Scope and Limitations of the Geminal Acylation

2.2.1 Modification of the Acyloin

The initial Mukaiyama-aldol addition is not only viable with the succinoin 2, but with other acyloins as well. These can be prepared according to Bloomfield by the condensation of diesters in refluxing toluene with finely dispersed sodium metal, then trapping the dianion with chlorotrimethylsilane.\textsuperscript{15,16} Wu and Burnell have shown that a five-membered ring acyloin (8), a homolog of 2, will yield 2,2-disubstituted-1,3-cyclohexanediones following the one-pot procedure with excess BF\textsubscript{3}•OEt\textsubscript{2} (Scheme 4A).\textsuperscript{17} Relief of ring strain cannot be a necessary condition for the pinacol rearrangement step to occur because high yields (75%-95%) were obtained for unhindered ketals. In an earlier publication, Pattenden and Teague had reported that pinacol intermediate 9 underwent an alternative rearrangement (Scheme 4B) when pTSA was used to form the desired diketone.\textsuperscript{18}
Scheme 4. A) Geminal acylation with a five-membered acyloin. B) The formation of a 1,2-diketone.

Modifications were also done on four-membered acyloins to examine the effects of substitution with alkyl groups. The reactions of 10, a monomethylated analog of 2, had similar yields to the reactions of 2. Modest diastereoselectivity was observed with substituted ketone substrates, such as 4-tert-butylcyclohexanone, and its ketal. It was interesting to note that the ketone and ketal had complementary preferences for the two diastereomers produced. Whereas the ketone generated 11a predominantly (3.1:1) over 11b, and the dibenzyl ketal provided 11b predominantly (7.5:1) over 11a (Scheme 5). Because the isomeric ratios of the pinacol intermediates were similar to the ratios of the cyclopentanedione products, it is likely that the stereoselectivity was introduced during the aldol step. The reason why ketones gave largely the opposite diastereomer was thought to be due to an equilibration of the pinacol in the protic medium. A geminal dimethyl-substituted acyloin 12 was also prepared and reacted with benzylic ketones and ketals (along with acyloins 2 and 10), providing cyclohexanedione products, but also producing some furanone 13 and 1,2-diketone byproducts 14 (Scheme 6).
Scheme 5. The stereoselectivity of 10.

The dimethyl-substituted acyloin 12 gave lower yields than the less substituted acyloins, which was not surprising given the steric implications, but the diastereoselectivity was often higher for 12 than with 10.\textsuperscript{19-21} Along with modest yields, geminal acylation reactions using 12 were plagued with unwanted byproducts (Scheme 6A). To circumvent this problem, Crane and Burnell used BCl\textsubscript{3} in lieu of BF\textsubscript{3}•OEt\textsubscript{2} to initiate the reaction.\textsuperscript{21} The result of this was a boron complex, which prevented equilibration from occurring and prevented the formation of furanones and 1,2-diketones. This boron complex was then hydrolyzed with HF, and TFA was used to initiate the pinacol rearrangement. This was all in a three-step, but one-pot, reaction (Scheme 6B). Reactions were also attempted with a tetramethyl acyloin, but furanone products were obtained exclusively.\textsuperscript{19}

Several aliphatic acetals were also subjected to a cyclohexyl-fused succinoin 15 (Figure 2). Yields were comparable to those of reactions with 2, aside from the diethyl acetal of benzaldehyde, which gave a 20% increase in the yield of the 1,3-diketone. The yields of 1,3-diketones from 15 and from 2 are compared in Table 1.
2.2.2 Modification of the Substrate

This simple method of generating 1,3-diketones from carbonyl-containing molecules (or acetal/ketal derivatives) works well in general, providing high yields with the ability to control chemo- and stereoselectivity; however, there are some drawbacks to this process. Simple enones, such as 2-cyclohexen-1-one give very poor yields, unless there was substitution on the β-carbon (Entries 1 and 2, Table 2).\textsuperscript{13} α-Alkyl substituents on a ketone also lower the yield by about 30% due to steric hindrance, although α-heterosubstituted cyclohexanones can provide useful yields of products when the pinacol step was mediated by an acidic Amberlyst-15 resin (Entry 5, Table 2).\textsuperscript{13,23}
Table 2. Geminal acylation of substituted ketones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td><img src="image2.png" alt="Product" /></td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Ketone" /></td>
<td><img src="image4.png" alt="Product" /></td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Ketone" /></td>
<td><img src="image6.png" alt="Product" /></td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Ketone" /></td>
<td><img src="image8.png" alt="Product" /></td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Ketone" /></td>
<td><img src="image10.png" alt="Product" /></td>
<td>73(^a)</td>
</tr>
</tbody>
</table>

\(^a\) Pinacol rearrangement was achieved using Amberlyst-15.

Bach and Klix\(^{24-26}\) showed that dithioketals undergo the same Mukaiyama-aldol reaction as ketones and ketals, when the pinacol rearrangement step was initiated by an almost neutral mercuric chloride salt instead of under acidic conditions. Orthoesters can undergo geminal acylation, but the yields are low due to acid-catalyzed ring opening of the 1,3-diketone products to form γ-ketodiesters.\(^{27}\) The cyclobutanone intermediates, however, can be isolated in moderate to high yield.\(^{28}\) Primary and secondary amides do not afford 1,3-diketones because the acyloin reacts with the nitrogen, rather than with the carbonyl, forming
aminocyclobutanones.\textsuperscript{29} This method of making $N$-substituted cyclobutanones is still useful as it has been used to make natural products and potential drug molecules.\textsuperscript{30-32}

Geminal acylation can be carried out with 2-methoxyoxazolidines (16) to form 1,4-oxazines (18a,b).\textsuperscript{33} The initial aldol reaction displaces the methoxy group to form a cyclobutanone intermediate. Depending on the presence or absence of water, the ring expansion step either takes place by cleavage of the C-N bond, or the C-O bond, respectively (Scheme 7) to give 17a or 17b. These compounds can further cyclize to form cyclopenta[b][1,4]oxazinones (18a,b).

Scheme 7. The geminal acylation of a 2-methoxyoxazolidine.

2.2.3 Post Geminal Acylation Modifications

Aside from forming 1,3-diketones and $\gamma$-ketoesters, the products of geminal acylation contain functional groups that can be further derivatized into molecules of synthetic interest. Anderson and Lee used this method to derivatize a 1,3-diketone 19 made from the ketal of a mesylated 2’-hydroxy-5’-methoxyacetophenone. They
transformed 19 into a benzo[b]furan derivative 20 by opening the cyclic ketone using sodium hydroxide and methanol. After a few more operations, this intermediate has become a trichothecane analog 21, a class of fungal metabolites that possess biological activity (Scheme 8).34,35

![Scheme 8. The synthesis of a trichothecane analog.](image)

Further cyclizations onto the 1,3-cyclopentanedione can be achieved if the substrate contains an alkyne. The treatment of ketal 22 with the acyloin 2 following the improved methodology (15 equiv. of BF₃•OEt₂) provided the geminal acylation product 23, which was converted to the ring expanded product 24 when left in the acidic solution for 48 h (Scheme 9).36 Follow-up studies have shown that reacting molecules like 23 with different Lewis acids, in the presence or absence of water, formed many structural isomers of 24.37,38 A geminal acylation product containing an ester functionality 26 can undergo intramolecular coupling with the cyclic diketone in the presence of low-valent titanium to form a [3,3.0]bicyclic product 27 in modest yield, but in very few steps (Scheme 9).39

These post-geminal acylation modifications are especially useful when planning a synthetic route. It is easy to imagine synthetic targets that contain 1,3-cyclopentanedione moieties as prime candidates for geminal acylation, but the functionalizability of these compounds has shown many different ring systems can be achieved after geminal acylation. For example, as was previously mentioned, the derivatization of diketone 19 to form benzo[b]furans proved key in the synthesis of trichothecane analogs.

2.3 Natural Product Synthesis Using Geminal Acylation

The tricothecanes belong to the sesquiterpene family of natural products, of which many have been synthesized using a geminal acylation as a key step. Most notably, they include β-bulnesene (28),40 (±)-isokhusimone (29),12,41 (±)-pentalenene (30),42 and (±)-β-herbertenol (31)43 (Figure 3).
Considerable effort by many research groups has been directed toward the synthesis of (±)-fredericamycin A 32, a spirodiketone polycyclic molecule with potent antitumour properties. Since geminal acylation has been shown to produce spirodiketones in very few steps, the process has been used to construct the C and D rings of the natural product. Parker et al. were the first to use this geminal acylation methodology to make synthons for 32 (Scheme 10 A). They first established the A-B-C ring system by preparing 33, beginning with a geminal acylation of the methyl ketal of acetone followed by the addition of the A-B ring system in two more steps. They later published a method to prepare the D-E-F ring system by producing 34 with the idea of carrying out a geminal acylation on the ketone (or ketal derivatives) of the D ring. Bach and coworkers were also exploring various synthons during the same time period, looking to make the core structure of 32. They first synthesized the B-C-D-E ring system 35 via geminal acylation onto a thioketal, then added the A ring (unsubstituted) 36 to the same molecular framework. They later managed to substitute the A ring with three methoxy groups and the B ring with two phenolic groups to form 37. They would finally complete the total synthesis of (±)-32 in 1994 using the same thioketal approach (Scheme 10 B). The total synthesis of (±)-32 was also completed the year before...
by Saint-Jalmes et al., who also used a geminal acylation step, employing it on an already functionalized ketal 40 further on during the synthesis, forming spirocycle 41 (Scheme 10 B). In 2009, Morrison et al. reported an improved synthetic route to core synthons of 32. The geminally acylated product 43 was transformed into the A-B-C-D-E core containing molecule 44 in an overall yield of 31% (Scheme 10 D).

The fungitoxic metabolite (–)-chokol G 45 has also been synthesized using geminal acylation as a key step.⁵⁰ The synthesis began with the formation of the acyloin 46 and its reaction with 1,1-dimethoxyethane, followed by treatment with dimethylsulfate and sodium hydride to form the methyl enol ether of a geminally acylated product 47 (Scheme 11). Following a reduction and an asymmetric hydrogen transfer, intermediate (–)-48 was produced in high enantiomeric excess (87-98% ee). Compound 49 was then converted to a cuprate to form the exo product 50 from its reaction with 48. The α-methyl of ketone 50 was epimerized to the thermodynamically favoured trans product after refluxing in diphenyl ether, which also produced a cyclopentenone product from the elimination of cyclopentadiene by a retro-Diels-Alder reaction. After three more minor operations, the total synthesis of the natural product (–)-45 was accomplished. The stereoselectivity in this synthesis was largely controlled by the acyloin and the geminal acylation adduct it formed.
Scheme 11. The total synthesis of (–)-chokol G 45.

Other natural products, and analogs thereof, were synthesized with geminal acylation as a key step. These include aquariolide diterpenes, indolizidine analogs, a cephalotaxus alkaloid, and a steroidal diene. These natural products are structurally very different, but all of them were accessible through geminal acylation.

2.4 My Research Project

2.4.1 Synthesis of a Propellane Using Geminal Acylation

This geminal acylation methodology has been shown to be useful for making otherwise synthetically difficult molecules, which include cyclobutanones and spirocycles. It was hypothesized that a propellane might also be prepared using this methodology in three successive steps, although it was recognized that this was a high-risk endeavour and we anticipated some difficulties. The term “propellane” is used to describe a tricyclic system conjoined by a single carbon-carbon bond. It
is not a coincidence that these molecules are similar in appearance to a propeller. A number of natural products contain a propellane skeleton, including modhephene 51 (Figure 4), a [3.3.3]-propellane that was first isolated in 1978 from *Isocoma wrightii*.56

![Figure 4. Modhephene.](image)

Modhephene has been synthesized 18 times, via anionic cyclizations, by radical reactions, and by acid-catalyzed, thermal, and photochemical rearrangements.4 The greatest difficulty encountered in these syntheses has been the stereoselective installation of the C-8 methyl group. Incorporating this methyl group into the geminal acylation methodology was anticipated to present a challenge because a geminal acylation would have to occur onto a site with an α-substituent. Nevertheless, there was some precedent that this was achievable (Table 2, Entry 4).13,23 Other anticipated difficulties included the formation of an acyloin in the presence of other oxygen functions (where the acyloin would be made in a highly reducing medium), and a transannular geminal acylation (which would take place on the congested ketal). Transannular geminal acylation was unprecedented, but an intramolecular geminal acylation had been achieved.57
2.4.2 Retrosynthesis

Transannular ring closure had been achieved by other methods to form propellane carbon frameworks by Reingold\textsuperscript{58} and by Yamago.\textsuperscript{59,60} It was proposed that a [4.n.3]-propellane 52 might be synthesized by the intramolecular spiroannulation of 53 (Scheme 12). The tetracyclic structure of 53 could be made from the acyloin condensation of 54. Not surprisingly, the 1,3-diketone of 54 would arise from the geminal acylation of ketone 55 or its ketal. The ketodiester 55 could itself come from another geminal acylation of ethyl levulinate 56 followed by ring opening reductive succinoylation of the 1,3-diketone formed. Using either succinoin 2 or the five-membered acyloin 8, we considered that the length of the carbon chain might be varied to ultimately form [4.3.3]- or [4.4.3]propellanes.

Scheme 12. Retrosynthesis of a [4.n.3]-propellane.
If successful, this functionalizable analog of 51 would be synthesized in eight steps or less via three consecutive geminal acylation reactions, beginning with a readily available starting material.

### 2.5 Results and Discussion

Both four- and five-membered acyloins 2 and 8 were synthesized based on a literature procedure\(^\text{16}\) (Scheme 13), using diethyl succinate to make 2 and dimethyl glutarate to make 8. Yields were also noticeably better when fresh chlorotrimethylsilane from an unopened bottle was used.

![Scheme 13. Acyloin condensation using TMSCl as the trapping agent.](image)

These acyloins were surprisingly stable as long as they were kept away from moisture. Both reagents were stored at rt under a N\(_2\) atmosphere, and they did not decompose to any noticeable extent over many months.

As discussed earlier in this chapter, there are different procedures to pick from when it comes to geminal acylation. Because using ketals often leads to higher yields than from ketones, and since the one-pot procedure was previously developed in this lab, it was the methodology employed throughout this project.
The first step toward modhephene was to make a ketodiester such as 55 from the ketal of ethyl levulinate 56. Kuwajima reported that ketodiesters could be formed from ketals using SnCl₄ as a Lewis acid.⁶¹,⁶² The ethylene glycol ketal of ethyl levulinate 57 was prepared following a standard procedure.⁶³ Unfortunately, Kuwajima’s method did not produce any of the expected ketodiester 58, and the starting ketone was recovered in 70% yield (Scheme 14). The same reaction was attempted using 8, but, once again, the only material recovered was the starting ketone 56.


When 57 and 2 were reacted with excess BF₃•OEt₂, the 1,3-diketone was formed in yields near 80%, accompanied by traces of ketodiester. It was speculated that the ketodiesters were formed from an acid-catalyzed ring opening reaction involving ethylene glycol, once it has been cleaved from the ketal.⁶⁴ With this in mind, excess ethylene glycol was added to the reaction mixture of 57 and 2 after TLC analysis showed the ketal was completely consumed. The result was a mixture of 30% ketodiester 58 and 15% 1,3-diketone 59 (Scheme 15).
Scheme 15. Acid-catalyzed ring-opening of a 1,3-diketone.

However when 58 was converted to its ethylene glycol ketal, it did not undergo a second geminal acylation. It was thought this reaction might be inhibited due to the ethylene glycol ester, as previous studies have shown that ketals containing a hydroxyl substituent did not yield any geminal acylation product.\(^{27}\) Thus a tert-butyldimethylsilyl (TBS) group was used to protect the alcohol.\(^{64}\) Unfortunately, this TBS-protected derivative did not produce any 1,3-diketone, either.

When 57 was reacted with 8 in the presence of BF\(_3\)•OEt\(_2\), the reaction mixture mostly contained the ring-opened product, which was then transesterified with methanol to avoid the problems observed with the ethylene glycol ester. This polar intermediate was then converted to the ethylene glycol ketal 61 in 80% yield. Unfortunately, the standard one-pot geminal acylation procedure with 2 gave none of the desired 1,3-diketone 62; instead, only 60 was recovered (Scheme 16).
Scheme 16. Initial attempts at the geminal acylation of \(61\).

Kawata et al. had reported that a 1,3-cyclohexanedione could undergo a ring-opening reaction with an alcohol in the presence of indium(III) trifluoromethanesulfonate in catalytic amount.\(^{65}\) Unfortunately, when the same conditions were employed with the 1,3-diketone \(59\), only the transesterified product \(57\) was produced in 73% yield. Conversely, the ketodiesters could be generated by the base-induced ring-opening of \(59\), followed by esterification of the resulting carboxylic acid to produce a dimethylated ketodiester. This method gave \(63\) in 35% yield, but although the yield was low, it was still a much more attractive method than those previously mentioned (Scheme 17). Its ethylene glycol ketal \(64\) was then subjected to geminal acylation conditions with \(2\), but the diketone product \(65\) was not observed.
Scheme 17. A new method for the generation of a ketodiesther then its protection.

Because these products were very polar and difficult to purify by column chromatography on silica gel, \( n \)-hexanol was used for the transesterification of 58 to add hydrophobicity. A 43% yield was obtained when using pTSA, but indium(III) trifluoromethanesulfonate yielded 60% of the dihexyl ketodiester 66. Geminal acylation was attempted following the transformation of 66 to its ethylene glycol ketal 67, but, once again, only 66 was recovered this time in 33% yield. (Scheme 18).
Scheme 18. Attempted geminal acylation of a transesterified ketodiester.

Many attempts were made at converting 63 and its ethylene glycol ketal 64 into a geminally acylated product. Despite testing several temperatures and trying TiCl₄ as the Lewis acid, no geminal acylation product was ever observed by NMR spectroscopy. The formation of the cyclobutanone intermediate had not been observed either, so it seemed that the α-methyl substituent was simply too sterically encumbering for the initial Mukaiyama aldol-type step to occur.

The next approach to propellane synthesis involved the use of ketodiesters without the methyl substituent. It was unfortunate that the methyl could not be carried through, as it is the stereoselective installation of this methyl group that has made modhephene tricky to synthesize. It also existed as an element of non-symmetry, which could have imparted diastereoselectivity during the transannular geminal acylation step. Regardless, synthesizing a propellane via geminal acylation would still be the first of its kind, with or without a methyl group.
Thus, a methyl-free analog of 59 was made, beginning with the Michael addition of 1,3-cyclohexanedione and ethyl acrylate, generating 69, which existed largely as the enol 70. This was then followed by an acid-catalyzed ring opening of 70 to yield a diethyl ketodiester 71 (Scheme 19). After converting 71 to its ethylene glycol ketal 72, a geminal acylation was attempted using 2. This reaction was performed only once on small-scale, but the $^1$H NMR spectrum of the crude reaction mixture did not show any signals for 73, but did show reversion to 71.

Scheme 19. Synthesis of the unmethylated ketodiester.

The project was suspended at this juncture.
2.6 Conclusions & Future Work

A series of ketodiesters was synthesized with the goal of converting their ethylene glycol ketals into geminally acylated products. The presence of a methyl substituent α to the electrophilic center was hypothesized to be preventing the formation of cyclobutanone intermediates when no geminally acylated products were observed.

An unmethylated ketodiester was also prepared, but its initial reaction with 2 was also unsuccessful, therefore the presence of a diester moiety might be the reason why the reaction would not go to completion. Further attempts need to be made at synthesizing the geminally acylated product 73, possibly by employing the two-step procedure if the cyclobutanone intermediate can be isolated. Once 73 has been prepared, attempts will be made to transform its ketal 74 (with multiple variations to try) into acyloin 75 and to induce geminal acylation in situ to form propellane 76 (Scheme 20).
Scheme 20. Future attempt toward the synthesis of 76.

If successful, this would constitute the first transannular geminal acylation reaction, as well as the first propellane synthesized with geminal acylations as key steps.

2.7 Experimental

2.7.1 General Considerations

All non-aqueous reactions were conducted in oven-dried glassware under an N₂ atmosphere. Reagents were obtained from Sigma-Aldrich or Alfa/Aesar and were used as received. Dichloromethane and toluene were freshly distilled from calcium hydride. Ethyl acetate and hexanes for column chromatography were distilled. All other solvents were used without further purification.
TLC was conducted using pre-coated aluminum-backed silica plates (SiliCycle, silica gel 60 F254), using UV light (254 nm) as a visualizing agent and o-vanillin in ethanol/H2SO4 and heat as developing agents. Flash chromatography was carried out on silica gel purchased from SiliCycle (40-63 µm particle size, 230-240 mesh).

Melting points (uncorrected) were acquired using a Fisher-Johns apparatus. 1H NMR spectra were recorded at 500 MHz on a Bruker Avance spectrometer with CDCl3 as solvent (δ 7.26 ppm) with tetramethylsilane as the internal reference (δ 0.00 ppm). 13C NMR spectra were recorded at 126 MHz on the Bruker Avance spectrometer with CDCl3 as solvent and as internal reference (δ 77.16 ppm). High-resolution mass spectra were acquired by Mr. Xiao Feng on a Bruker microTOF Focus orthogonal ESI-TOF mass spectrometer.

All structures were determined using 1H and 13C NMR spectra, along with two-dimensional NMR experiments (COSY, HSQC and HMBC).

2.7.2 Preparation and Characterization Data

1,2-Bis(trimethylsilyloxy)cyclobutene (2)

A solution of diethyl succinate (16.6 mL, 100 mmol) and chlorotrimethylsilane (50.8 mL, 400 mmol) in toluene (125 mL) was added
dropwise over a period of 4 h to a refluxing dispersion of molten sodium (420 mmol, 9.71 g) in toluene (250 mL). A dark purple precipitate appeared within 20 min of addition, but then it quickly turned dark brown. The mixture was heated under reflux overnight, then cooled to rt and filtered through a sintered-glass funnel. The filtrate was concentrated in vacuo and distilled under reduced pressure (bp 53-54 °C / 5 mmHg) to yield 2 (13.1 g, 57%) as a colorless liquid: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.14 (s, 4H), 0.20 (s, 18 H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 120.2, 26.2, 0.5. These data match those in the literature.$^{66,67}$

1,2-Bis(trimethylsilyloxy)cyclopentene (8)

A solution of dimethyl glutarate (14.8 mL, 100 mmol) and chlorotrimethylsilane (50.8 mL, 400 mmol) in toluene (125 mL) was added dropwise over a period of 4 h to a refluxing dispersion of molten sodium (420 mmol, 9.71 g) in toluene (250 mL). The solution turned green within 15 min of addition, then gradually became yellow over 2 to 3 h, and eventually turned a dark brown. The mixture was heated under reflux overnight, then cooled to rt and filtered through a sintered-glass funnel. The filtrate was then concentrated in vacuo and distilled under reduced pressure (bp 90-92 °C / 4 mmHg) to yield 8 (16.0 g, 62%) as a colorless liquid: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.23 (t, $J = 7.3$ Hz, 4H),
1.76 (quintet, $J = 7.4$ Hz, 2H), 0.18 (s, 18 H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 130.7, 30.3, 17.1, 0.9. These data match those in the literature.$^{66,68,69}$

**Ethyl 4-(1,3-dioxolan-2-yl)pentanoate (57)**

![Image of compound 57]

`para-Toluenesulfonic acid (0.12 g, 6.0 mmol) was added to a solution of ethyl levulinate (28.4 mL, 200 mmol) and ethylene glycol (12.3 mL, 220 mmol) in benzene (100 mL). The solution was heated under reflux over 6 h with azeotropic removal of water using a Dean-Stark apparatus filled with 4 Å Molecular Sieves. The solution was cooled to rt, and the acid was quenched with triethylamine (2 mL). The organic solution was washed with water ($2 \times 100$ mL) and brine (100 mL), dried over MgSO$_4$, and concentrated in vacuo. The residue was purified by flash chromatography (25% ethyl acetate in hexanes) to provide 57 (33.7 g, 90%) as a colourless liquid: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.07 (q, $J = 7.1$ Hz, 2H), 3.88 (m, 4H), 2.32 (t, $J = 7.7$ Hz, 2H), 1.96 (t, $J = 7.7$ Hz, 2H), 1.26 (s, 3H), 1.19 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 173.6, 109.2, 64.8, 60.3, 34.0, 29.1, 24.0, 14.3. These data match those in the literature.$^{70}$`
1-Ethyl 8-(2-hydroxyethyl) 4-methyl-5-oxooctanedioate (58) and ethyl 3-(1-methyl-2,5-dioxocyclopentyl)propanoate (59)

A stirred solution of ketal 57 (0.25 mL, 1.3 mmol) in CH₂Cl₂ (7 mL) was cooled to –78 °C. BF₃•OEt₂ (0.25 mL, 1.95 mmol) was added, followed by the dropwise addition of a solution of acyloin 2 (0.50 mL, 1.95 mmol) in CH₂Cl₂ (3 mL). The mixture was stirred at –78 °C for 3 h, then warmed to rt over 2.5 h. An excess of ethylene glycol (0.50 mL, 8.9 mmol) was added to the mixture, followed by BF₃•OEt₂ (2.4 mL, 19.5 mmol) then stirred overnight (~ 14 h). The solution was washed with water (2 × 10 mL), and the aqueous layer was re-extracted with CH₂Cl₂ (2 × 10 mL). The combined organic solutions was washed with brine (25 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography (50% ethyl acetate in hexanes) to provide 58 (0.14 g, 30%) and 59* (42 mg, 15%), both as colourless oils: For 58: ¹H NMR (500 MHz, CDCl₃): δ 4.23-4.21 (m, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.82-3.80 (m, 2H), 2.88-2.67 (m, 3H), 2.67-2.61 (m, 3H), 2.32-2.28 (m, J = 3.9 Hz, 2H), 2.05-1.98 (m, 1H), 1.72-1.64 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.13 (d, J = 7.0 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 212.4, 173.3, 173.1, 66.3, 61.0, 60.5, 45.2, 35.8, 31.7, 27.9, 27.7, 16.4,

* 59 was made in 83% yield following the one pot procedure.⁵
14.2; HRMS (ESI) calcd for \([C_{13}H_{22}O_6Na]^+\): 297.1309, found: 297.1304. For 59: \(^1\)H NMR (500 MHz, CDCl\(_3\)) : \(\delta\) 4.10 (q, \(J = 7.1 \text{ Hz}, 2\text{H}\)), 2.88-2.81 (m, 4H), 2.32 (t, \(J = 7.5 \text{ Hz}, 2\text{H}\)), 2.00 (t, \(J = 7.5 \text{ Hz}, 2\text{H}\)), 1.27 (t, \(J = 7.1 \text{ Hz}, 3\text{H}\)), 1.17 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) : \(\delta\) 215.7, 172.8, 60.7, 55.3, 34.8, 28.8, 20.0, 14.1. These data match those in the literature.\(^27\)

**Dimethyl 4-methyl-5-oxononanedioate (60)**

![Image of chemical structure](image)

A stirred solution of ketal 57 (2.9 mL, 16 mmol) in CH\(_2\)Cl\(_2\) (20 mL) was cooled to –78 °C. BF\(_3\)•OEt\(_2\) (3.0 mL, 24 mmol) was added, followed by the dropwise addition of a solution of acyloin 8 (7.2 mL, 24 mmol) in CH\(_2\)Cl\(_2\) (10 mL). The mixture was stirred at –78 °C for 3 h, then warmed to rt over 2 h. BF\(_3\)•OEt\(_2\) (30.5 mL, 240 mmol) was added, then, the reaction mixture was stirred overnight (~ 14 h). The solution was washed with water (2 × 50 mL), and the aqueous layer was re-extracted with CH\(_2\)Cl\(_2\) (2 × 50 mL). The solvent was then removed \textit{in vacuo}. The resulting residue was dissolved in a solution of pTSA (0.15 g, 0.80 mmol) in methanol (50 mL), and the mixture was heated under reflux for 7 h. The solvent was then removed \textit{in vacuo}, and the residue was diluted with ethyl acetate (50 mL).
and washed with saturated aqueous sodium bicarbonate (2 × 50 mL). The aqueous solution was re-extracted with ethyl acetate (50 mL), and the combined organic solutions was washed with brine (75 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography (50% ethyl acetate in hexanes) to provide 60 (1.09 g, 28%) as a colourless oil: \(^1\)H NMR (500 MHz, CDCl₃): δ 3.68 (s, 3H), 3.67 (s, 3H), 2.60-2.46 (m, 3H), 2.34 (t, \(J = 7.2\) Hz, 2H), 2.31-2.24 (m, 2H), 2.02-1.95 (m, 1H), 1.89 (quintet, \(J = 7.2\) Hz, 2H), 1.69-1.62 (m, 1H), 1.09 (d, \(J = 7.0\) Hz, 3H). \(^{13}\)C NMR (126 MHz, CDCl₃): δ 213.0, 173.8, 173.7, 51.75, 51.69, 45.3, 40.1, 33.1, 31.6, 27.7, 18.9, 16.5; HRMS (ESI) calcd for [C₁₂H₂₀O₅Na]⁺: 267.1203, found: 267.1201.

Dimethyl 5-(1,3-dioxolan-2-yl)-4-methylnonanedioate (61)

According to the procedure for 57: ketodiester 60 (0.58 g, 2.0 mmol) was reacted with ethylene glycol (0.12 mL, 2.2 mmol) and \(para\)-toluenesulfonic acid (0.11 g, 0.6 mmol) in benzene (20 mL) to yield, after purification by flash chromatography (66% ethyl acetate in hexanes), 61 (0.53 g, 80%) as a colourless oil: \(^1\)H NMR (500 MHz, CDCl₃): δ 3.96-3.91 (m, 4H), 3.67 (s, 3H), 3.66 (s, 3H),
2.44-2.38 (m, J = 5.7 Hz, 1H), 2.34-2.25 (m, 3H), 1.97-1.89 (m, 1H), 1.74-1.63 (m, 5H), 1.44-1.36 (m, 1H), 0.93 (d, J = 6.9 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 174.4, 174.1, 113.3, 65.4, 65.3, 51.7, 51.6, 39.2, 34.3, 33.1, 32.6, 26.7, 18.8, 14.2; HRMS (ESI) calcd for [C$_{14}$H$_{24}$O$_6$Na]$^+$: 311.1466, found: 311.1460.

**Dimethyl 4-methyl-5-oxooctanedioate (63)**

An aqueous solution of NaOH (1 M, 4.0 mL) was added to diketone 59 (0.42 g, 2.0 mmol) and the resulting emulsion was stirred at rt for 1 h. The mixture was washed with diethyl ether (5 mL), and the aqueous layer was acidified with HCl (1 M, 5 mL). The mixture was extracted with diethyl ether (2 × 10 mL), and the combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was dissolved in a solution of sulfuric acid (0.1 M, 0.8 mL) in methanol (8.0 mL, 0.20 mol). The mixture was heated under reflux for 4 h. Distilled water (10 mL) was added and stirring was continued for 10 min. The mixture was extracted with CH$_2$Cl$_2$ (30 mL), washed with saturated aqueous sodium bicarbonate (2 × 30 mL), and brine (30 mL). The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flash chromatography (50% ethyl acetate in hexanes) to afford 63 (0.16 g, 35%) as a
colourless oil: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.67 (s, 3H), 3.67 (s, 3H), 2.85-2.57 (m, 5H), 2.31 (td, $J$ = 7.5, 2.1 Hz, 2H), 2.08-1.96 (m, 1H), 1.75-1.63 (m, 1H), 1.13 (d, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 211.8, 173.7, 173.3, 51.9, 51.7, 45.4, 35.8, 31.6, 27.8, 16.5. These data match those in the literature.$^7$1

**Dimethyl 4-(1,3-dioxolan-2-yl)-5-methyloctanedioate (64)**

![Chemical Structure](Image)

According to the procedure for 57: ketodiester 63 (0.16 g, 0.69 mmol) was reacted with ethylene glycol (0.5 mL, 0.89 mmol) and *para*-toluenesulfonic acid (0.019 g, 0.10 mmol) in benzene (10 mL) to yield, after flash chromatography (66% ethyl acetate in hexanes), 68 (0.15 g, 80%) as a colourless oil: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.93-3.89 (m, 4H), 3.65 (br s, 6H), 2.87-2.66 (m, 2H), 2.65-2.53 (m, 2H), 2.24-2.22 (m, 2H), 2.06-2.04 (m, 1H), 1.73-1.71 (m, 1H), 0.91 (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 174.0, 173.9, 113.0, 65.3, 65.1, 60.6, 60.4, 35.4, 34.2, 30.1, 27.4, 24.2, 15.6; HRMS (ESI) calcd for [C$_{13}$H$_{22}$O$_6$Na]$^+$: 297.1309, found: 297.1306.
Di-\textit{n}-hexyl 4-methyl-5-oxooctanedioate (66)

Indium(III) trifluoromethanesulfonate (45 mg, 0.080 mmol) was added to a solution of ketodiester 58 (0.11 g, 0.40 mmol) in 1-hexanol (6.0 mL). The solution was heated to 80 °C for 24 h. After being cooled to rt, the solution was diluted with ethyl acetate (20 mL) washed with H2O (20 mL). The aqueous layer was re-extracted with ethyl acetate (20 mL), washed with brine (20 mL), dried over MgSO4 and concentrated \textit{in vacuo}. The residue was purified by flash chromatography (toluene) to yield 66 (89 mg, 60%) as a colourless oil: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.06 (t, $J = 6.8$ Hz, 4H), 2.84-2.78 (m, 1H), 2.75-2.69 (m, 1H), 2.66-2.61 (m, 1H), 2.60-2.57 (m, 2H), 2.32-2.27 (m, 2H), 2.04-2.00 (m, 1H), 1.70-1.66 (m, 1H), 1.64-1.58 (m, 4H), 1.37-1.26 (m, 12H), 1.13 (d, $J = 7.0$ Hz, 3H), 0.90-0.88 (m, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 212.0, 173.4, 173.0, 65.0, 64.8, 45.4, 35.8, 31.9, 31.5 (2C), 28.7, 28.6, 28.0, 27.8, 25.7, 25.6, 22.6 (2C), 16.5, 14.1 (2C); HRMS (ESI) calcd for [C$_{21}$H$_{38}$O$_5$Na]$^+$: 393.2611, found: 393.2608.
Di-\textit{n}-hexyl 4-(1,3-dioxolan-2-yl)-5-methyloctanedioate (67)

According to the procedure for 57: ketodiester 66 (89 mg, 0.25 mmol) was reacted with ethylene glycol (0.02 mL, 0.30 mmol) and \textit{para}-toluenesulfonic acid (14 mg, 0.070 mmol) in benzene (5 mL) to yield, after flash chromatography (toluene), 67 (52 mg, 50\%) as a pale yellow oil: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.06-4.04 (m, 4H), 3.93-3.90 (m, 4H), 2.85-2.79 (m, 1H), 2.76-2.70 (m, 1H), 2.68-2.62 (m, 1H), 2.59-2.56 (m, 2H), 2.33-2.28 (m, 2H), 2.02-1.97 (m, 1H), 1.70-1.66 (m, 1H), 1.65-1.57 (m, 4H), 1.37-1.22 (m, 12H), 0.94 (d, $J = 6.9$ Hz, 3H), 0.91-0.86 (m, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 174.1, 173.2, 110.3, 66.3, 65.3, 65.0, 64.8, 60.8, 42.3, 39.3, 35.7, 32.8 (2C), 28.8, 28.5, 27.8, 26.9, 25.7, 22.7 (2C), 17.5, 14.3 (2C); HRMS (ESI) calcd for [C$_{23}$H$_{42}$O$_6$Na]$^+$: 437.2874, found: 437.2857.
Ethyl 3-(3-hydroxy-1-oxocyclohex-2-en-2-yl)propanoate (70)

A solution of 1,3-cyclohexanedione (0.28 g, 2.5 mmol) in DMF (25 mL) was added to a suspension of sodium hydride (60% dispersion in mineral oil) (100 mg, 2.5 mmol) in DMF (25 mL). Ethyl acrylate (0.30 mL, 2.8 mmol) was then added to the mixture, and the stirred solution was heated to 80 °C under an N₂ atmosphere for 4 h. The solution was diluted with ethyl acetate (100 mL) and washed with H₂O (2 × 100 mL), which was re-extracted with ethyl acetate (50 mL). The combined organic layers was washed with aqueous 5% LiCl (100 mL) and with 0.5 M HCl (100 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography (30% ethyl acetate in hexanes) to afford 70 (0.28 g, 53%) as a colourless solid: mp 129-131 °C; ¹H NMR (500 MHz, CDCl₃): δ 9.56 (s, 1H), 4.18 (q, J = 7.2 Hz, 2H), 2.57-2.55 (m, 2H), 2.52-2.49 (m, 2H), 2.46 (t, J = 6.3 Hz, 2H), 2.32 (dd, J = 9.1, 4.2 Hz, 2H), 1.91 (quintet, J = 6.5 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 198.9, 178.6, 173.6, 114.8, 62.0, 36.8, 33.3, 29.4, 20.6, 16.7, 14.2. These data match those in the literature.⁷²
Diethyl 5-oxononanedioate (71)

To a solution of keto-enol 70 (0.28 g, 1.3 mmol) in ethanol (10 mL) was added conc. HCl (1 mL). The stirred solution was heated under reflux for 7 h. The solution was diluted with ethyl acetate (25 mL) then washed with water (2 × 10 mL), with brine (10 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography (25% ethyl acetate in hexanes) to afford 71 (0.10 g, 30%) as a colourless oil: ¹H NMR (500 MHz, CDCl₃): δ 4.10 (q, J = 7.1 Hz, 4H), 2.54-2.52 (m, 4H), 2.32-2.30 (m, 4H), 1.89-1.86 (m, 4H), 1.22 (t, J = 7.1 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃): δ 209.4, 173.1, 60.5, 41.6, 35.2, 29.2, 14.3. These data match those in the literature.⁷³,⁷⁴
Diethyl 5-(1,3-dioxolan-2-yl)nonanedioate (72)

According to the procedure for 57: ketodiester 71 (0.10 g, 0.40 mmol) was reacted with ethylene glycol (0.03 mL, 0.44 mmol) and para-toluenesulfonic acid (23 mg, 0.12 mmol) in benzene (4 mL) to yield, after flash chromatography (50% ethyl acetate in hexanes), 72 (97 mg, 80%) as a colourless oil: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.14-4.10 (m, 4H), 3.93-3.91 (m, 4H), 2.56-2.54 (m, 4H), 2.37-2.35 (m, 4H), 1.93-1.90 (m, 4H), 1.23 (m, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 173.1 (2C), 113.2, 65.3 (2C), 60.5 (2C), 41.6 (2C), 35.2 (2C), 29.2 (2C), 14.3 (2C); HRMS pending.
Chapter 3 – Nazarov Reactions Intercepted by (4+3) Cycloadditions with Oxygen-Substituted Dienes

3.1 Introduction

The Nazarov reaction, named after Ivan Nikolaevich Nazarov who first reported the reaction in 1941,\textsuperscript{75} is a $4\pi$ electrocyclic reaction that converts divinyl ketones into cyclopentenones.\textsuperscript{6,76-78} The reaction is mediated by a Brønsted or Lewis acid, which generates a pentadienyl cation $77$, and ring-closure follows to form an oxyallyl carbocation $78$. A proton is eliminated from this intermediate to form an $\alpha,\beta$-unsaturated cyclopentenone after tautomerization (Scheme 21).

\begin{center}
\begin{tikzpicture}
\node[draw,shape=rectangle] (A) at (0,0) {\includegraphics[width=0.8\textwidth]{nazarovreaction}};
\node[below=0.5cm of A] {Scheme 21. The Nazarov reaction.};
\end{tikzpicture}
\end{center}

The $4\pi$ electrocyclization is a diastereospecific process that is governed by the Woodward-Hoffmann rules. The rules state that under thermal conditions, $4\pi$ electrocyclization will undergo conrotatory ring closure through the highest occupied molecular orbital (HOMO), while photochemical conditions dictate a disrotatory ring closure through the promotion of an electron to the lowest unoccupied molecular orbital (LUMO) (Scheme 22). The stereochemical outcome...
of a Nazarov reaction is therefore predictable, which makes the reaction useful for making five-membered rings.

![Scheme 22. Diastereospecificity of 4π electrocyclization.](image)

There are many natural products that contain five-membered rings, and the Nazarov reaction could be applied to make carbocycles en route to the total synthesis of a natural product. One of the major drawbacks of the Nazarov reaction is that it usually requires harsh acidic conditions, which could be undesirable if other functional groups were present in the molecule. Milder conditions can induce cyclization if the divinyl ketone has α substituents. In order for cyclization to occur, the divinyl ketone must be in the s-trans/s-trans conformation (Scheme 23). Divinyl ketones with α substituents will favour an s-trans/s-trans conformation over s-cis/s-cis or s-cis/s-trans conformations.
Scheme 23. The major conformations of divinyl ketones.

This phenomenon is due to the alleviation of a steric interaction that is presented in the $s$-cis/$s$-cis conformation. An $\alpha$-substituent that also complexes with Lewis acids can also increase the $s$-trans/$s$-trans population.\textsuperscript{79-82} This increase in the $s$-trans/$s$-trans population facilitates cyclization, and thus milder Lewis acids and lower temperatures can be used.

3.2 The Interrupted Nazarov Reaction

The interrupted Nazarov reaction takes advantage of the highly reactive oxyallyl cation intermediate by the introduction of a nucleophile to “interrupt” the proton elimination step, and instead form a new sigma bond. The term was coined by Dr. Fred West and coworkers,\textsuperscript{83} who have contributed significantly to the scope of this type of reaction. Oxyallyl cations were trapped by alkenes either by forming one new carbon-carbon bond, or by forming two new carbon-carbon bonds via (3+2) cycloaddition (Scheme 24).\textsuperscript{84-87} (4+3) Cycloadditions were also observed with dienes. Oxyallyl cations were trapped by arenes by means of a Friedel-Crafts
alkylation,\(^{88,89}\) halides after dissociating from the Lewis acid,\(^{90}\) and hydride, in a process known as the reductive Nazarov reaction.\(^{91}\)

![Scheme 24. An interrupted Nazarov reaction with an alkene.\(^{84}\)](image)

### 3.3 Nazarov Reactions with Allenyl Vinyl Ketones

Allenyl vinyl ketones (AVKs) are more reactive than divinyl ketones. Hashmi et al.\(^{92}\) were the first to report Nazarov cyclizations with AVKs in 1998. They showed AVKs to be more reactive than divinyl ketones, as cyclization of AVKs occurred spontaneously on silica gel during column chromatography (Scheme 25). This enhancement in reactivity was likely due to a number of factors, which included the release of allenic strain on the sp-hybridized central carbon during cyclization, and the reduced steric repulsion on the vinylic hydrogen when in the \(s\)-trans/\(s\)-trans conformation.
Scheme 25. The silica gel-mediated Nazarov cyclization of an AVK.

Nazarov cyclizations of AVKs are facilitated by a lower energy oxyallyl cation intermediate compared to that from a divinyl ketone. The cationic intermediate from an AVK 79 has the added stability of an additional resonance contributor arising from an exocyclic double bond, which is not present in oxyallyl cations of divinyl ketones 78 (Scheme 26).

Scheme 26. The resonance contributors of oxyallyl cation intermediates.
3.4 Interrupted Nazarov Reactions of AVKs

3.4.1 Mono-Additions to Oxyallyl π-Systems

AVKs seem better suited for interrupted Nazarov reactions as the oxyallyl cation should be longer lived. Nucleophilic addition could potentially occur on one of three carbons of the delocalized carbocation (Figure 5). Computational studies have shown position \(a\) to be the most nucleophilic site,\(^{93}\) however there have been instances of trapping at position \(c\) and, very much less often, at position \(b\).

![Figure 5. Potential trapping sites of an oxyallyl cation.](image)

Trifluoroacetic acid (TFA) has been shown to both promote cyclization and to provide a nucleophile.\(^{94}\) The results of Nazarov reactions in the presence of TFA showed only trapping at position \(a\) along with isomerization of the exocyclic double bond to form the more stable conjugated cyclopent-2-enone (Scheme 27).
Scheme 27. An interrupted Nazarov reaction with TFA.

The oxyallyl cations from AVKs were also reacted with halides as nucleophiles.\(^9^5\) Trapping was observed primarily at position \(a\) but also sometimes at \(c\), depending on the Lewis acid used. When AuCl\(_3\) was used with AVK 80, the cyclopentenone product 81 was observed, trapping the oxyallyl cation at position \(a\). When titanium tetrachloride was used, AVK 80 was rapidly consumed, but only intractable material was obtained. Titanium tetrabromide gave mixed results with different AVKs, but with AVK 80 it exclusively formed a product 82 that had trapped at position \(a\). Titanium tetraiodide, however, formed cyclopentenone 83, which was not only a product of Nazarov cyclization but also a reduction. It is likely this was a result of deiodination of an \(\alpha\)-iodocyclopentenone.\(^9^0\) Indium(III) halides consistently provided cyclopent-2-enones with nucleophilic addition exclusively at position \(c\), producing 84, 85, and 86, albeit in low yield (Scheme 28).
Nitrogen-based heterocycles intercepted Nazarov reactions of AVKs to give cyclopent-2-enones trapped at positions $a$ and $c$.\textsuperscript{96} $N$-Alkyl-, $N$-aryl- and $N$-silyl-substituted pyrroles were trapped highly regioselectively and gave products trapped only at position $a$, but only modest selectivity was observed when electron-withdrawing acyl or sulfonyl groups were bonded to the nitrogen of pyrrole (Scheme 29). Indoles were capable of trapping much more efficiently than pyrroles, and regioselectivity depended on the substitution near the reacting carbons. The results are in accord with the computational results that suggest position $a$ is the electronically preferred trapping site,\textsuperscript{93} and position $c$ must be the sterically preferred trapping site.
Scheme 29. Interrupted Nazarov reactions with $N$-substituted pyroles.

These results corroborate a previous study that used other cyclic dienes.\textsuperscript{97} Using the same AVK 80, furan trapped primarily at position $a$, with a minor product trapped at position $c$. 1,3-Cyclohexadiene trapped only at position $a$ forming 87, and the bulkier 1,2,3,4,5-pentamethycyclopentadiene trapped primarily at position $c$ to form 88 (Scheme 30).

Scheme 30. Interrupted Nazarov reactions with cyclic dienes.
Trapping at position $b$ has only been observed when an ambiphilic molecule was used, acting as both a Lewis acid and nucleophile. When AVK 80 was reacted with (Me$_2$AlCH$_2$PMe$_2$)$_2$ at rt for 40 min, a 3:7 mixture of 89 and 90 was observed by NMR spectroscopy. However, after 20 h, complete conversion to 90 was observed (Scheme 31).

Scheme 31. Nazarov cyclization with an ambiphilic molecule.

3.4.2 Bis-Additions to Oxyallyl $\pi$-Systems

Acyclic dienes when reacted with 80 did not produce products trapped at positions $a$ or $c$, but rather formed two carbon-carbon bonds across positions $a$ and $b$. These products were either (4+3) cycloadducts, where the four sp$^2$ carbons of the diene participated in a cycloaddition with the three sp$^2$ carbons of the oxyallyl cation, or (3+2) cycloadducts, where only one double bond of the diene participated in the cycloaddition reaction. When different AVKs were used, only (4+3) cycloadducts were observed (Scheme 32). This tandem Nazarov cyclization / cycloaddition strategy would be useful in the synthesis of natural products that contain [4.2.1] or [2.2.1] bicyclic ring systems.
Scheme 32. Interrupted Nazarov reactions with acyclic dienes.

Although with some dienes AVK 80 showed modest (4+3) versus (3+2) selectivity, the regioselectivity of the trapping reactions was usually high. The electron-rich terminus of the diene formed a carbon-carbon bond with the most nucleophilic terminus of the delocalized oxyallyl cation. Diastereoselectivity was high in some instances, but the interrupted Nazarov reactions of 80, 93, and 95 with trans-piperylene gave 91, 92, 94, and 96 as single diastereomers.

Divinyl ketones are also capable of trapping nucleophiles by (4+3) cycloadditions. 87 2,3-Dimethylbutadiene was used to trap the oxyallyl cation of divinyl ketone 97 to produce a (4+3) adduct 98 in 50% yield after 3 h at –78 °C.
When the same diene was used with AVK 80, the (4+3) cycloadduct 99 was produced in nearly quantitative yield in only five min at –78 °C (Scheme 33).97

Scheme 33. (4+3) Cycloadditions with 2,3-dimethylbutadiene.

3.4.3 Interrupted Nazarov Reactions with Oxygen-Substituted Dienes

It was hypothesized that a strong π-donor like a silyl enol ether would have a great effect on the regioselectivity of the cycloaddition, but what was unknown was how this functionality would affect the (3+2) versus the (4+3) selectivity as well as the diastereoselectivity. When the Nazarov reaction was carried out with 80 in the presence of trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene, commonly known as Danishefsky’s diene, intractable material was produced, with no trace of cycloadducts or alkylated minor products.97 Therefore many butadiene analogs, but limited to only one oxygen function, were prepared and tested for cycloaddition onto the oxyallyl cation of AVK 80.99
3.5 Results and Discussions

3.5.1 Synthesis of the AVKs

The AVKs can be classified into three different types (Figure 6). Type 1 AVKs have an \( \alpha \)-alkyl substituent on the allene moiety with \( \beta \)-vinylic substituents being phenyl, methyl, isopropyl, \textit{para}-methoxyphenyl, \textit{para-}\((\text{trifluoromethyl})\)phenyl, furan-2-yl, and hydrogen. Only two Type 2 AVKs have been synthesized. One of which has an \( \alpha \)-methyl substituent on the vinyl moiety with a vinylic phenyl group; the other has two substituents fused as a cyclohexene ring. The only Type 3 AVK synthesized to date has a phenyl substituent.

![Figure 6. Type 1, Type 2, and Type 3 AVKs.](image)

AVK 80 was chosen for the investigation of the trapping of an oxyallyl cation with a range of oxygen-substituted dienes. AVK 80 had been used in studies with other dienes, alkenes and heterocycles.\textsuperscript{93-98} It is more stable than the majority of other AVKs, so it can be prepared on a relatively large scale and stored at \(-20^\circ\text{C}\) over many months. AVK 80 has a methyl substituent on the allene moiety that provides some steric protection for the allene central carbon and probably helps to
mitigate unwanted Michael reactions. Two more AVKs were also prepared to see if the observed stereochemical trends held true for other substrates. They were both Type 2 AVKs, 93 and 95.

The AVKs were synthesized in three or four steps. The first step was to brominate commercially available propargyl alcohol with PBr₃. The second step was to couple this bromide with an α,β-unsaturated aldehyde. Using zinc provided the allene, whereas indium provided a mixture of the allene and the alkyne, albeit in better total yield. The third and fourth steps were to oxidize the resulting allylic alcohol and to isomerize the alkyne to the allene when necessary. This method produced 80 in 35% overall yield from the propargyl alcohol. AVKs 93 and 95 were not at all as stable as 80, thus their alcohol precursors were prepared and stored, and only oxidized/isomerized immediately before the initiation of the Nazarov cyclization.

![Scheme 34. Synthesis of AVKs.](image)
3.5.2 Synthesis of Dienes

Two types of oxygen-substituted dienes were prepared for this study. The first type were trimethylsilyl- (TMS) trapped enolates of \(\alpha,\beta\)-unsaturated ketones. The second type were \(\text{tert-}\)-butyldimethylsilyl- (TBS) trapped enolates of \(\alpha,\beta\)-unsaturated ketones.

TMS-trapped enolates were synthesized following a procedure by Jung and McCombs,\textsuperscript{100} but with some modifications. Triethylamine was used to form the enolate and chlorotrimethylsilane (TMSCl) was used to trap the anion. Four dienes \(100a-d\) were prepared by this method (Table 3).

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<th>Entry</th>
<th>(R_1)</th>
<th>(R_2)</th>
<th>(R_3)</th>
<th>(R_4)</th>
<th>(R_5)</th>
<th>Product</th>
<th>% Yield</th>
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<td>(\text{CH}_3)</td>
<td>(\text{H})</td>
<td>(\text{H})</td>
<td>OTMS</td>
<td>(\text{H})</td>
<td>(100a)</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>(\text{CH}_3)</td>
<td>(\text{CH}_3)</td>
<td>(\text{H})</td>
<td>OTMS</td>
<td>(\text{CH}_3)</td>
<td>(100b)</td>
<td>42</td>
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<tr>
<td>3</td>
<td>(\text{CH}_2\text{CH}_3)</td>
<td>(\text{H})</td>
<td>(\text{CH}_3)</td>
<td>OTMS</td>
<td>(\text{H})</td>
<td>(100c)</td>
<td>21</td>
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<td>4</td>
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<td>(\text{H})</td>
<td>(100d)</td>
<td>15\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Mixture of \(E,E\) and \(E,Z\) diene.
Attempts at making TBS-trapped enolates following the same procedure, but with TBSCI, failed. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) was instead used to trap the enolate using triethylamine or potassium hexamethyldisilazide (KHMDS) as the base.\textsuperscript{101,102} Nine dienes 101a-i were prepared by this method (Table 4).

**Table 4. Preparation of TBSO-substituted dienes 101a-i.**

<table>
<thead>
<tr>
<th>Entry</th>
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<td>H</td>
<td>101i</td>
<td>50&lt;sup&gt;a&lt;/sup&gt;</td>
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<sup>a</sup> Yield obtained using KHMDS and TBSOTf in THF at -78 °C. <sup>b</sup> Product was a 1:1 mixture of E and Z isomers.

Attempts at making a 1,1-dimethyl-2-silyloxy-substituted butadiene were unsuccessful. Fortunately, a methoxy analog could be prepared in three steps
(Scheme 35). This method began with the formation of an acetal of acrolein, followed by an Arbuzov reaction to make a stabilized phosphonate. The phosphonate then coupled with acetone via a Horner-Wadsworth-Emmons-type reaction to produce diene 101j.

![Scheme 35. Preparation of 101j.](image)

### 3.5.3 Interrupted Nazarov Reactions

Following the same procedure used for the cycloaddition of acyclic dienes to oxyallyl cations from an interrupted Nazarov reaction of an AVK, a series of (4+3) cycloadducts was synthesized using oxygen-substituted dienes.

Dienes 100a-c formed (4+3) cycloadducts regioselectively and with high facial selectivity (adding to the face of the oxyallyl cation opposite the phenyl) when reacted with AVK 80 (Scheme 36). Dienes 100d produced a complex mixture of intractable products. The products of dienes 100a-c were largely desilylated during the reaction and so mixtures of products were observed. Unsubstituted diene 100a gave a 1:1 mixture of silylated 102 and desilylated 103 products in a 51% combined yield favouring the (4+3) over the (3+2) or mono-addition pathways. A methyl substituent γ to the oxygen of the diene 100b led to (4+3) products with...
high diastereoselectivity, favouring products where the methyl substituent was \textit{anti} (or “down” as shown in Scheme 36) with respect to the bridging carbonyl \textbf{104} and \textbf{105}, but the yields were lower. Some mono-addition product \textbf{106} was also obtained. A methyl substituent \(\beta\) to the oxygen (on the opposite end of the diene) as in diene \textbf{100c} provided (4+3) products exclusively and in a combined 95\% yield, however, the diastereoselectivity in this example was lower than with \textbf{100b} forming a 5:1 mixture of silylated products \textbf{107a,b} and 1.2:1 mixture of desilylated products \textbf{108a,b}. The major diastereomer of \textbf{107} had the methyl \textit{syn} (or “up” as shown in Scheme 36) with respect to the bridging carbonyl, while the major diastereomer of \textbf{108} had the methyl \textit{anti} (“down”) with respect to the bridging carbonyl.
Scheme 36. Formation of (4+3) cycloadducts using 100a-c.

The relative stereochemistry of these diastereomers was determined by NOE experiments. Irradiation of the more deshielded hydrogen of the exocyclic double bond in 104 and 105 showed enhancements for the methyl doublet signal, while irradiation of the benzylic hydrogen in 107a,b and 108a,b showed enhancements for the substituent that is anti to the carbonyl (Figure 7).
Figure 7. Stereochemical assignments of Nazarov products using NOE.

Desilylation of these products posed a problem with analysis. It was not obvious whether the discrepancy in the diastereomeric ratios of 107a,b and 108a,b was due to an epimerization of the methyl group since it was α to a carbonyl, or if 107b simply desilylated faster than 107a. It was hoped that TBSO-substituted dienes would be more robust than their TMSO-counterparts and that desilylation would not occur. This was true for most cases except diene 101a, which still produced 108a,b along with 109a,b. The results with this diene were similar to those of 100c as the reactions were both high yielding and the diastereomer that was formed preferentially was the one with a methyl in the “up” position, but preferentially “down” in the desilylated product (Scheme 37).
Three other dienes with substituents on the same carbon of the diene as 101a were also investigated. The ethyl-substituted diene 101b reacted regioselectively forming 110a,b, where 110a was the major diastereomer bearing an ethyl group that was “up” as shown in Scheme 37. The slightly bulkier isopropyl-substituted diene 101c reacted with the same regioselectivity as the
previous two dienes but had the opposite diastereoselectivity. The only product isolated, 111, had the isopropyl group “down”. The structure of 111 was verified by X-ray crystallography (Figure 8). Diene 101d was obtained as an inseparable 1:1 mixture of $E$ and $Z$ isomers, but the $^1$H NMR spectrum of the crude reaction mixture with AVK 80 showed that only the $Z$ isomer had reacted. It appeared that the cation-stabilizing ability of the phenyl group competed with the electron-donating ability of the silyloxy group and the (4+3) products 112a,b were accompanied by a lesser amount of 113 with the regiochemistry reversed. Diene 101j contained geminal methyl substituents on the more nucleophilic carbon of the diene, which prevented the formation of a (4+3) cycloadduct, presumably due to steric hindrance, and formed a 9:1 mixture of (3+2) products instead. The relative stereochemistry for all compounds was determined by NOE experiments.

* X-ray crystal structures were provided by Dr. T. S. Cameron.
Dienes 101e-h had substituents on the other carbon-carbon double bond of the diene. These four dienes formed (4+3) products with a high degree of regioselectivity and diastereoselectivity (Scheme 38). Consistent with the result of the Nazarov product trapped with 100b, products 116 and 118 bore alkyl substituents that had an anti relationship with the bridging carbonyl. This high degree of stereoselectivity was in contrast with examples of modest stereoselectivity in the (4+3) cycloadditions onto oxyallyl cations.86,104-107 The yield of 116 was modest, but it was accompanied by a larger amount of 106. The structure of 116 was also confirmed by X-ray crystallography (Figure 9).
Figure 9. ORTEP of 116.

Diene 101g bore two geminal methyl groups on the carbon that was γ to the oxygen and reacted with the oxyallyl cation of 80 to form 117. This was especially noteworthy because similar dienes without an oxygen functional group gave (3+2) products exclusively.97,108
Scheme 38. Nazarov reactions of AVK 80 in the presence of dienes 101e-i.

Two equivalents (each) of dienes 101a and 101f were added to one equivalent of AVK 80, to see if the oxyallyl cation was consumed faster by one diene or the other. The $^1\text{H}$ NMR spectrum of the crude reaction mixture indicated trapped Nazarov products $116$:$106$:$109\text{a}$:$109\text{b}$ were formed in a ratio of 1:3.5:8:2,
respectively. Therefore, although diene 101a gave a higher yield of tandem product compared to diene 101f, diene 101a reacted with the oxyallyl cation only slightly faster than did diene 101f. This would imply that diene 101i, with substituents on both termini of the diene, would be subject roughly equally to the phenomena at either end of the diene that controlled the stereochemical outcome. When AVK 80 was cyclized and its oxyallyl cation was trapped with 101i, a mixture of diastereomers was produced in nearly equal quantities (Scheme 38). Cycloadduct 120 had both methyl groups in the “up” orientation, while 121 had them both “down”; no trans product was observed.

To check whether or not the observed selectivities would also be evident with other oxyallyl cations, two more AVKs were prepared for this study. Because these molecules are quite reactive, they needed to be prepared immediately before use and used without purification. The yields of the (4+3) products are thus calculated over three steps (oxidation, isomerization and cyclization) from the corresponding alcohol precursors of the AVK. The Nazarov reactions of AVK 93 were carried out in the presence of dienes 101a and 101g, forming (4+3) trapped products exclusively (Scheme 39). In the case of 101a, the opposite regioselectivity was observed with respect to the oxyallyl cation of 80, and the product favoured the diastereomer that bore the methyl group “up”. Diene 101g, however, produced an adduct with the expected regioselectivity, and it was obtained as a single diastereomer. AVK 95 was reacted with 101a to form a desilylated product in extremely low yield; however, it was interesting to note that the diene added the
same way as it did with 93 to form an analogous regioisomer, but the stereoselectivity for the opposite diastereomer of 93.

Scheme 39. Nazarov reactions with AVKs 93 and 95.

There is some debate over whether or not (4+3) cycloadditions of oxyallyl cations are concerted or stepwise. The formation of 106 and 119 could arise from a stepwise mechanism, where the second bond was not formed, possibly due to steric hindrance between the methyl and alkyl groups (Scheme 40). It is also possible that the (4+3) products could arise from an equilibration process as was demonstrated when (3+2) products were resubjected to acidic conditions. Some of the products from this study were treated again with BF$_3$•OEt$_2$ to see if they would equilibrate to form single diastereomers or new constitutional isomers.
When 116 was resubjected to acidic conditions, complete conversion to 106 was observed (Scheme 41). Therefore, a few more (4+3) products were resubjected to the same conditions. A 7:1 diastereomeric mixture of 109a,b was simply desilylated to 108a,b when resubjected to BF$_3$•OEt$_2$, but it was important that the diastereomeric ratio was unchanged during desilylation. Therefore, the diastereoselectivity of the trapping reaction was very likely to have not been altered by epimerization following desilylation. The isopropyl-substituted (4+3) cycloadduct 111 was also resubjected to these conditions as it had its substituent in the “down” orientation. The product was desilylated without fragmentation, and the relative stereochemistry of the isopropyl-substituted center had not changed.
Scheme 41. Acid treatment of 116, 109a,b and 111.

Cycloadducts 120 and 121 were also allowed to equilibrate (Scheme 42). The results of this were two desilylated products 126 and 129, two ring opened products 127 and 130, and two bicyclo[5.2.1]decenedione products 128 and 131. It is important to note that the ring opening and desilylation products did not show any epimerization, and ring closure onto the exocyclic double bond of the cationic intermediate occurred diastereoselectively.
Scheme 42. Acid treatment of 120 and 121.

The results of these reactions suggest that the alkyl substituents that end up \(\alpha\) to the carbonyl do not epimerize, and therefore the diastereoselectivity must come from the initial carbon-carbon bond formation of the \((4+3)\) process. Substituents that end up \(\beta\) to the carbonyl have a carbon-carbon bond to quaternary center, which is sufficiently labile to break under acidic conditions. There is no significant reclosure onto this quaternary center, so it would be very likely that the initial bond was formed in a concerted \((4+3)\) process.
The observed diastereoselectivity can be rationalized by an asynchronous but concerted transition state in which the shorter incipient bond is the one formed between the electron-rich terminus of the diene and the most electrophilic carbon of the oxyallyl cation (Scheme 43). Dienes that were substituted on the carbon that is \( \beta \) to the oxygen, i.e., \( \text{101a-d} \), preferred to react through a compact transition state \( \text{132C} \) forming \( \text{134a} \) predominantly, except for the diene that bore a larger isopropyl group \( \text{101c} \), which formed \( \text{134b} \) exclusively via an extended transition state \( \text{132E} \). The reason why \( \text{132C} \) appeared to be the more favourable transition state could be due to the steric influence of the benzylic hydrogen in \( \text{132E} \). In the case of \( \text{101c} \), the isopropyl group might have an unfavourable interaction with the hydrogen of the carbocation in \( \text{132C} \) that is minimized in \( \text{132E} \).

![Scheme 43](image)

Scheme 43. Compact and extended transition states of the (4+3) cycloaddition.

The same phenomena would hold true for reactions taking place with dienes substituted on the carbon \( \gamma \) to the oxygen, i.e., \( \text{101f-h} \). The compact transition state \( \text{133C} \) would be disfavoured due to the steric influence of the methyl group on the
oxyallyl cation. Instead, the dienes would react through an extended transition state 133E forming 135b exclusively. Both dienes 101g and 101j have two geminal methyl substituents on the γ carbon and the β carbon of the diene, respectively. Diene 101g gave a product of type 135, while diene 101j produced a (3+2) cycloadduct. The difference between the two was that the methyl substituents on 101j would have a larger steric influence due to their proximity to the oxyallyl cation, as they are located on the carbon that has the shorter incipient bond, whereas the incipient bond to the dimethyl substituted carbon of 101g is longer. Diene 101i also bears two methyl substituents, but they are on opposite termini of the diene. The result of its cycloaddition to the oxyallyl cation of 80 was a nearly equal amount of products arising from each transition state.

The steric influence of the methyl group of the oxyallyl cation was further exemplified during the interrupted Nazarov reaction of AVK 93 and 95 (Scheme 44). The alkyl substituents on the most electrophilic carbon of the oxyallyl cation made transition states 136 and 137 too high in energy, and thus the regioselectivity was reversed. Diene 101a reacted predominantly with the oxyallyl cation of 93 via the compact transition state 138C (for the same reasons it did with the oxyallyl cation of 80). However, 101a reacted with the oxyallyl cation of 95 exclusively via the extended transition state 140E. This could be due to the enhanced steric effects of the cyclohexyl moiety. Diene 101g reacted with the oxyallyl cation of 93 by the expected regioselectivity forming 143.
Scheme 44. The transition states of (4+3) cycloadditions with the oxyallyl cations from AVKs 93 and 95.
3.6 Conclusions and Future Work

The oxyallyl cations of AVKs have been shown to trap oxygen-substituted dienes exclusively by a (4+3) cycloaddition with the exception of one diene that trapped in a (3+2) process. These reactions occurred with high facial selectivity, high regioselectivity and high diastereoselectivity when the carbon γ to the oxygen on the diene was substituted; diastereoselectivity was modest when the carbon β to the oxygen of the diene was substituted. The (4+3) cycloaddition is concerted, with the compact transition state having a somewhat lower energy barrier than the extended one, although steric interactions from the diene and the oxyallyl cation can influence this selectivity. These results will be tested with computational studies that are currently underway.

Future work for this project would be to examine the trapping ability of sulfur containing dienes, mainly thiophenes. Pyrroles and furans have been shown to trap the oxyallyl cation of AVK 80 via a Friedel-Crafts reaction forming products that had trapped at position a and c depending on the electronic and steric influences of substituents on these aromatic molecules.
Preliminary studies had shown that thiophene was not a suitable nucleophile to trap the oxyallyl cation, but it is hypothesized that thiophenes bearing electron-donating groups would increase its nucleophilicity and possibly trap the oxyallyl cation. The thiophenes, as well as a thiazole, chosen to begin this study are shown in Figure 10.

3.7 Experimental

3.7.1 General Information

Reactions were carried out using oven-dried Teflon-coated magnetic stir bars in oven-dried glassware (150 °C), sealed with rubber septa under a positive nitrogen atmosphere. Elevated temperatures were maintained using a silicone oil bath controlled with a thermostat device. Temperatures of 0 and –78 °C were achieved using ice/water and ethyl acetate/liquid nitrogen, respectively. Concentration in vacuo was achieved using a rotary evaporator (22 mmHg) with residual solvent being removed under high vacuum (5 mmHg).
All reagents were purchased from Sigma-Aldrich, Strem Chemicals, or Alfa Aesar and were used without further purification. Tetrahydrofuran (THF) was distilled over sodium/benzophenone under a dry nitrogen atmosphere. CH$_2$Cl$_2$ was distilled over calcium hydride under a dry nitrogen atmosphere. Thin layer chromatography (TLC) was performed using 250 µm aluminum-backed F$_{254}$ silica gel plates from SiliCycle. The plates were visualized by ultraviolet light (254 nm) and treated with o-vanillin or potassium permanganate stains followed by heating on a hot plate. Flash chromatography was carried out on 230–400 mesh (40–63 µm) silica gel from SiliCycle.

Melting points (uncorrected) were acquired using a Fisher-Johns apparatus. $^1$H and $^{13}$C NMR spectra were recorded from CDCl$_3$ solutions on a Bruker Avance 500 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane but are referenced to the solvent peak (for CDCl$_3$, $^1$H NMR: 7.26 ppm; $^{13}$C NMR: 77.16 ppm). High-resolution mass spectra (HRMS) were obtained on a Bruker microTOF Focus orthogonal ESI-TOF mass spectrometer. Infrared (IR) spectra were recorded on an FT instrument. Samples were prepared as thin films on a NaCl plate. The X-ray crystal structures were provided by Dr. T. Stanley Cameron.

Structures were determined using $^1$H and $^{13}$C NMR spectra, including two-dimensional NMR experiments (COSY, HSQC and HMBC). Relative stereochemistry was assigned using one-dimensional NOE experiments.$^{109,110}$
3.7.2 Preparation and Characterization Data

**General procedure 1:** A solution of α,β-unsaturated ketone (50 mmol) in anhydrous dimethylformamide (DMF) (3.5 mL) and a solution of chlorotrimethylsilane (62 mmol) in DMF (3.5 mL) were both added dropwise over a period of 30 min to a heated (84 °C) solution of triethylamine (62 mmol) in DMF (30 mL). Heating was continued overnight (14 h). The solution was then allowed to attain rt before work-up. The solution was diluted with pentane (50 mL) and washed with cold 5% aqueous NaHCO₃ (150 mL). The aqueous layer was re-extracted with pentane (2 x 50 mL), and the combined organic extracts was washed with distilled water (50 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was then distilled under reduced pressure.

2-(Trimethylsilyloxy)-1,3-butadiene (100a)

Following General procedure 1, 3-buten-2-one (4.1 mL, 50 mmol), chlorotrimethylsilane (7.9 mL, 62 mmol), and triethylamine (8.6 mL, 62 mmol) gave 100a (2.6 g, 37%) as a colourless liquid. bp 33–35 °C (22 mmHg); ¹H NMR (500 MHz, CDCl₃): δ 6.19 (dd, J = 16.9, 10.5 Hz, 1H), 5.47 (dd, J = 16.9, 1.5 Hz, 1H), 5.08 (br d, J = 10.5 Hz, 1H), 4.35 (s, 1H), 4.34 (s, 1H), 0.23 (s, 9H); ¹³C NMR
(126 MHz, CDCl₃): δ 154.9, 134.6, 114.6, 96.5, 0.7 (3C). These data match those in the literature.

(E)-2-(Trimethylsilyloxy)-1,3-pentadiene (100b)

Following General procedure 1, 3-penten-2-one (4.9 mL, 50 mmol), chlorotrimethylsilane (7.9 mL, 62 mmol), and triethylamine (8.6 mL, 62 mmol) gave 100b (3.3 g, 42%) as a colourless liquid. bp 36–37 °C (22 mmHg); ¹H NMR (500 MHz, CDCl₃): δ 5.96 (dq, J = 15.1, 6.4 Hz, 1H), 5.90 (d, J = 15.3 Hz, 1H), 4.20 (s, 2H), 1.76 (d, J = 6.4 Hz, 3H), 0.22 (s, 9H); ¹³C NMR (126 MHz, CDCl₃): δ 155.0, 129.1 126.7, 93.8, 17.7, 0.2 (3C). These data match those in the literature.

(Z)-3-(Trimethylsilyloxy)-1,3-pentadiene (100c)

Following General procedure 1, 1-penten-3-one (4.9 mL, 50 mmol), chlorotrimethylsilane (7.9 mL, 62 mmol), and triethylamine (8.6 mL, 62 mmol) gave 100c (1.7 g, 21%) as a colourless liquid. bp 41–42 °C (22 mmHg); ¹H NMR
These data match those in the literature.112

**General Procedure 2:** A solution of α,β-unsaturated ketone (10 mmol) in THF (40 mL) was cooled to 0 °C. Triethylamine (25 mmol) was added, followed by the slow addition of tert-butyldimethylsilyl trifluoromethanesulfonate (11 mmol). The solution was stirred at 0 °C until reaction was complete, as evidenced by TLC. The solution was then diluted with pentane (80 mL), washed with saturated aqueous NaHCO$_3$ (25 mL), with water (2 × 25 mL), and with brine (25 mL). The organic layer was dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (2% triethylamine in pentane).

(Z)-3-(tert-Butyldimethylsilyloxy)-1,3-pentadiene (101a)

Following General procedure 2, 1-penten-3-one (1.0 mL, 10 mmol), tert-butyldimethylsilyl trifluoromethanesulfonate (2.5 mL, 11 mmol), and triethylamine (3.5 mL, 25 mmol) were stirred for 1 h at 0 °C to give **101a** (1.16 g, 59%) as a
colourless liquid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.16 (dd, $J = 17.1$, 10.8 Hz, 1H), 5.27 (d, $J = 17.1$ Hz, 1H), 4.94 (d, $J = 10.8$ Hz, 1H), 4.87 (q, $J = 7.1$ Hz, 1H), 1.64 (d, $J = 7.1$ Hz, 3H), 1.01 (s, 9H), 0.12 (s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 149.5, 135.7, 111.8, 110.3, 25.9 (3C), 18.3, 12.0, -2.8, -3.5. These data match those in the literature.$^{102}$

**General Procedure 3:**$^{102}$ A solution of $\alpha,\beta$-unsaturated ketone (10 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (11 mmol) in THF (80 mL) was cooled to –78 °C. A 1 M solution of potassium bis(trimethylsilyl)amide in THF (10 mmol) was slowly added. The solution was stirred at –78 °C for 30 min, then allowed to warm to rt with stirring for 1 h. The mixture was hydrolyzed using saturated aqueous NaHCO$_3$ (80 mL) and extracted with Et$_2$O (80 mL). The organic residue was washed with brine (80 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (2% triethylamine in pentane).
(Z)-3-(tert-Butyldimethylsilyloxy)-1,3-hexadiene (101b)

Following General procedure 3, 1-hexen-3-one (1.2 mL, 10 mmol), tert-butyldimethylsilyl trifluoromethanesulfonate (2.5 mL, 11 mmol), and potassium bis(trimethylsilyl)amide (10 mL, 10 mmol) gave 101b (1.59 g, 75%) as a colourless liquid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.14 (dd, $J = 17.2$, 10.8 Hz, 1H), 5.28 (dd, $J = 17.1$, 1.0 Hz, 1H), 4.94 (dd, $J = 10.8$, 0.8 Hz, 1H), 4.76 (t, $J = 7.2$ Hz, 1H), 2.12 (quintet, $J = 7.4$ Hz, 2H), 1.00 (s, 9H), 0.96 (t, $J = 7.5$ Hz, 3H), 0.11 (s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 148.0, 135.9, 118.0, 112.0, 26.2 (3C), 19.5, 18.6, 14.2, -3.5 (2C); IR (thin film): ν 1255, 1050, 839, 780 cm$^{-1}$; HRMS (APCI) calcd for [C$_{12}$H$_{25}$OSi]$^+$: 213.1669, found: 213.1663.

(Z)-3-(tert-Butyldimethylsilyloxy)-5-methyl-1,3-hexadiene (101c)

Following General procedure 3, 5-methylhex-1-en-3-one (1.12 g, 10 mmol), tert-butyldimethylsilyl trifluoromethanesulfonate (2.5 mL, 11 mmol), and potassium bis(trimethylsilyl)amide (10 mL, 10 mmol) gave 101c (2.08 g, 92%) as a colourless liquid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.10 (dd, $J = 17.1$, 10.8 Hz, 1H),
5.26 (d, J = 17.1 Hz, 1H), 4.93 (d, J = 10.8 Hz, 1H), 4.60 (d, J = 9.7 Hz, 1H), 2.75-2.65 (m, 1H), 0.98 (s, 9H), 0.94 (d, J = 7.3 Hz, 6H), 0.11 (s, 6H); 13C NMR (126 MHz, CDCl3): δ 146.6, 136.1, 123.5, 112.2, 26.2 (3C), 25.1, 23.1 (2C), 18.6, -3.6 (2C); IR (thin film): ν 1253, 1053, 844 cm⁻¹; HRMS (ESI) calcd for [C₁₃H₂₆OSiNa]+: 249.1645, found: 249.1653.

2-(tert-Butyldimethylsilyloxy)-1-phenyl-1,3-butadiene (101d)

Following General procedure 3, 1-phenylbut-3-en-2-one (1.46 g, 10 mmol), tert-butyldimethylsilyl trifluoromethanesulfonate (2.5 mL, 11 mmol), and potassium bis(trimethylsilyl)amide (10 mL, 10 mmol) gave a 1:1 mixture of E:Z isomers of 101d* (1.30 g, 50%) as a colourless liquid. For Z-isomer: ¹H NMR (500 MHz, CDCl₃): δ 7.50 (d, J = 7.8 Hz, 2H), 7.26 (t, J = 7.5 Hz, 2H), 7.14 (t, J = 7.4 Hz, 1H), 6.31 (dd, J = 17.1, 10.7 Hz, 1H), 5.78 (s, 1H), 5.48 (d, J = 17.1 Hz, 1H), 5.13 (d, J = 10.7 Hz, 1H), 0.99 (s, 9H), -0.12 (s, 6H); ¹³C NMR (126 MHz, CDCl₃): δ 149.8, 136.5, 136.3, 129.3 (2C), 128.0 (2C), 126.4, 114.6, 114.5, 26.1 (3C), 18.5, -3.6 (2C). For E-isomer: ¹H NMR (500 MHz, CDCl₃): δ 7.30-7.17 (m, 5H), 6.68 (dd, J = 16.9, 10.7 Hz, 1H), 6.01 (s, 1H), 5.67 (d, J = 16.9 Hz, 1H), 5.18 (d, J = 10.7 Hz, 1H), 1.01 (s, 9H), 0.23 (s, 6H); ¹³C NMR (126 MHz, CDCl₃): δ 150.1,

* Following General procedure 2 provides Z-101d only, but in 5% yield.
136.6, 131.2, 129.4 (2C), 128.3 (2C), 126.3, 116.5, 113.8, 26.1 (3C), 18.6, – 4.2 (2C). For mixture of isomers: IR (thin film): ν 1630, 1472, 1362, 1254, 1085, 839, 781 cm⁻¹; HRMS (ESI) calcd for [C_{16}H_{25}OSi]⁺: 261.1669, found: 261.1680.

2-(tert-Butyldimethylsilyloxy)-3-methyl-1,3-butadiene (101e)

Following *General procedure* 2, 3-methyl-3-buten-2-one (1.0 mL, 10 mmol), tert-butyldimethylsilyl trifluoromethanesulfonate (2.5 mL, 11 mmol), and triethylamine (3.5 mL, 25 mmol) were stirred for 1 h at 0 °C to give 101e (0.34 g, 17%) as a colourless liquid.¹¹ H NMR (500 MHz, CDCl₃): δ 5.43 (narrow m, 1H), 4.96 (narrow m, 1H), 4.47 (narrow m, 1H), 4.32 (narrow m, 1H), 1.87 (s, 3H), 0.97 (s, 9H), 0.17 (s, 6H);¹³ C NMR (126 MHz, CDCl₃): δ 156.6, 140.0, 113.8, 92.9, 26.0 (3C), 19.8, 18.4, – 4.6 (2C). These data match those in the literature.¹¹⁵
(E)-2-(tert-Butyldimethylsilyloxy)-1,3-pentadiene (101f)

Following *General procedure 2*, 3-penten-2-one (0.98 mL, 10 mmol), tert-butyldimethylsilyl trifluoromethanesulfonate (2.5 mL, 11 mmol), and triethylamine (3.5 mL, 25 mmol) were stirred for 1 h at 0 °C to give **101f** (1.50 g, 73%) as a colourless liquid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.00 (dq, $J$ = 15.1, 6.7 Hz, 1H), 5.89 (dq, $J$ = 15.1, 1.5 Hz, 1H), 4.19 (s, 1H), 4.18 (s, 1H), 1.77–1.75 (m, 3H), 0.97 (s, 9H), 0.17 (s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 155.2, 129.3, 126.5, 93.6, 26.0 (3C), 18.4, 17.8, −4.5 (2C). These data match those in the literature.$^{101}$

2-(tert-Butyldimethylsilyloxy)-4-methyl-1,3-pentadiene (101g)

Following *General procedure 2*, 4-methyl-3-penten-2-one (1.1 mL, 10 mmol), tert-butyldimethylsilyl trifluoromethanesulfonate (2.5 mL, 11 mmol), and triethylamine (3.5 mL, 25 mmol) were stirred for 1 h at 0 °C to give **101g** (1.95 g, 90%) as a colourless liquid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.56 (s, 1H), 4.30 (s, 1H), 4.16 (s, 1H), 1.89 (s, 3H), 1.77 (s, 3H), 0.94 (s, 9H), 0.16 (s, 6H); $^{13}$C NMR
(126 MHz, CDCl₃): δ 155.8, 136.8, 123.3, 95.0, 27.1, 26.0 (3C), 20.0, 18.5, – 4.3 (2C). These data match those in the literature.¹¹⁶

1-\((\text{tert-Butyldimethylsilyloxy})\)-1-(1-cyclohexenyl)ethene (101h)

Following General procedure 2, 1-acetyl-1-cyclohexene (1.3 mL, 10 mmol), tert-butyldimethylsilyl trifluoromethanesulfonate (2.5 mL, 11 mmol), and triethylamine (3.5 mL, 25 mmol) were stirred for 2 h at 0 °C to give 101h (2.15 g, 90%) as a colourless liquid. ¹H NMR (500 MHz, CDCl₃): δ 6.26–6.24 (narrow m, 1H), 4.34 (s, 1H), 4.18 (s, 1H), 2.14–2.12 (narrow m, 4H), 1.68–1.57 (m, 4H), 0.97 (s, 9H), 0.17 (s, 6H); ¹³C NMR (126 MHz, CDCl₃): δ 156.9, 133.3, 125.5, 89.6, 26.0 (3C), 25.6, 25.1, 22.9, 22.3, 18.5, – 4.5 (2C). These data match those in the literature.¹⁰¹
(2Z,4E)-3-(tert-Butyldimethylsilyloxy)-2,4-hexadiene (101i)

Following General procedure 3, 4-hexen-3-one (1.1 mL, 10 mmol), tert-butyldimethylsilyl trifluoromethanesulfonate (2.5 mL, 11 mmol), and potassium bis(trimethylsilyl)amide (10 mL, 10 mmol) gave 101i (1.06 g, 50%) as a colourless liquid. $^1$H NMR (500 MHz, CDCl₃): δ 5.85 (br d, $J = 15.4$, 1H), 5.74 (dq, $J = 15.4$, 6.6 Hz, 1H), 4.72 (q, $J = 7.0$ Hz, 1H), 1.73 (d, $J = 6.6$ Hz, 3H), 1.61 (d, $J = 7.0$ Hz, 3H), 1.00 (s, 9H), 0.10 (s, 6H); $^{13}$C NMR (126 MHz, CDCl₃): δ 149.2, 130.0, 123.5, 107.1, 26.1 (3C), 18.6, 17.8, 11.8, −3.5 (2C); IR (thin film): ν 1255, 1073, 837 cm$^{-1}$; HRMS (ESI) calcd for [C₁₂H₂₅OSi]+: 213.1669, found: 213.1667.

3-Methoxy-4-methyl-1,3-pentadiene (101j)

A solution of dimethyl 1-methoxyallylphosphonate (1.7 g, 9.6 mmol) in THF (5.0 mL) was added to a solution of lithium diisopropylamide (11.5 mmol) in THF (20 mL) at −78 °C and stirred for 30 min. A solution of acetone (0.74 mL, 9.6 mmol) in THF (5.0 mL) was added to the mixture. The mixture was allowed to warm slowly to rt over 1 h. The reaction was quenched by addition of saturated
aqueous NH₄Cl (25 mL), and the mixture was extracted with Et₂O (25 mL). The organic layer was washed with brine (25 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (10% Et₂O in pentane) to give 101j (0.30 g, 28%) as a colourless liquid. ¹H NMR (500 MHz, CDCl₃): δ 6.46 (dd, J = 17.1, 10.8 Hz, 1H), 5.33 (d, J = 17.0 Hz, 1H), 5.04 (dd, J = 10.8, 0.4 Hz, 1H), 3.52 (s, 3H), 1.77 (s, 3H), 1.74 (s, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 149.1, 127.9, 122.0, 112.3, 59.0, 18.5, 18.0. These data match those in the literature.¹⁰³

**General procedure 4:**⁹⁷ BF₃•OEt₂ (0.44 mmol) was added to a solution of the allenyl vinyl ketone⁹³ (0.40 mmol) and the diene (2.0 mmol) in CH₂Cl₂ (40 mL) at –78 °C. The solution was stirred for 5 min then saturated aqueous NaHCO₃ (40 mL) was added at –78 °C. After warming to rt, the aqueous layer was extracted with CH₂Cl₂ (3 × 40 mL). The combined organic solutions were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash chromatography (5% Et₂O in pentane).
(1R*,6S*,7S*)-1-Methyl-8-methylene-7-phenyl-4-(trimethylsilyloxy)bicyclo-[4.2.1]non-3-en-9-one (102) and (1R*,6S*,7S*)-1-methyl-8-methylene-7-phenyl-bicyclo[4.2.1]nonane-4,9-dione (103)

Following General procedure 4, 80 (70 mg, 0.40 mmol), 100a (0.28 g, 2.0 mmol), and BF₃•OEt₂ (0.050 mL, 0.44 mmol) gave 102 (35 mg, 27%) and 103 (24 mg, 24%) as colourless oils. For 102: ¹H NMR (500 MHz, CDCl₃): δ 7.28–7.26 (m, 2H), 7.19 (tt, J = 7.4, 1.5 Hz, 1H), 7.04–7.02 (m, 2H), 5.09 (d, J = 2.4 Hz, 1H), 4.96 (dt, J = 7.4, 2.5 Hz, 1H), 4.86 (d, J = 2.1 Hz, 1H), 4.38 (q, J = 2.1 Hz, 1H), 3.80 (q, J = 2.1 Hz, 1H), 2.70–2.68 (m, 1H), 2.57–2.52 (m, 1H), 2.38–2.30 (m, 2H), 2.15 (dd, J = 15.8, 7.4 Hz, 1H), 1.30 (s, 3H), 0.19 (s, 9H); ¹³C NMR (126 MHz, CDCl₃): δ 222.0, 157.7, 149.1, 146.3, 128.9 (2C), 127.5 (2C), 126.6, 110.0, 106.9, 54.7, 53.5, 52.0, 42.6, 37.3, 21.2, 0.5 (3C); IR (thin film): ν 1750 cm⁻¹; HRMS (ESI) calcd for [C₂₀H₂₆O₂SiNa]⁺: 349.1594, found: 349.1581. For 103: ¹H NMR (500 MHz, CDCl₃): δ 7.29 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.4 Hz, 1H), 7.07 (d, J = 7.4 Hz, 2H), 5.25 (d, J = 1.9 Hz, 1H), 5.12 (d, J = 1.7 Hz, 1H), 3.87 (q, J = 1.8 Hz, 1H), 2.86–2.84 (m 1H), 2.78 (dd, J = 15.1, 5.8 Hz, 1H), 2.68–2.62 (m, 1H), 2.60–2.52 (m, 2H), 1.95–1.90 (m, 1H), 1.87–1.82 (m, 1H), 1.31 (s, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 220.2, 209.4, 156.1, 145.0, 129.1 (2C), 127.1 (2C), 127.0, 113.0, 54.0, 53.0, 51.3, 45.5, 41.3, 40.0, 22.3;
IR (thin film): \( v \) 1743, 1704 cm\(^{-1} \); HRMS (ESI) calcd for \([C_{17}H_{18}O_2Na]^+\): 277.1199, found: 277.1196.

\((1R^*,2R^*,6S^*,7S^*)-1,2\text{-dimethyl-8-methylene-7-phenyl-4-(trimethylsilyloxy)-}\text{bicyclo}[4.2.1]\text{non-3-en-9-one} \ (104), \ (1R^*,2R^*,6S^*,7S^*)-1,2\text{-dimethyl-8-methylene-7-phenylbicyclo}[4.2.1]\text{nonane-4,9-dione} \ (105), \ \text{and} \ (4R^*,5R^*)-2,3\text{-dimethyl-5-((E)-2-oxopent-3-en-1-yl)-4-phenylcyclopent-2-enone} \ (106)

Following \textit{General procedure 4}, \( 80 \) (70 mg, 0.40 mmol), \( 100b \) (0.31 g, 2.0 mmol), and BF\(_3\)•OEt\(_2\) (0.050 mL, 0.44 mmol) gave \( 104 \) (11 mg, 8\%), \( 105 \) (19 mg, 18\%) and \( 106 \) (24 mg, 22\%) as colourless oils. For \( 104 \): \(^1\text{H NMR} \) (500 MHz, CDCl\(_3\)): \( \delta \) 7.30–7.27 (m, 2H), 7.23–7.20 (m, 1H), 7.08–7.06 (m, 2H), 5.00 (d, \( J = 2.9 \) Hz, 1H), 4.79–4.78 (m, 2H), 3.71 (q, \( J = 3.2 \) Hz, 1H), 2.65 (q, \( J = 4.2 \) Hz, 1H), 2.62–2.58 (m, 1H), 2.38–2.32 (m, 2H), 1.24 (s, 3H), 1.07 (d, \( J = 7.1 \) Hz, 3H), 0.19 (s, 9H); \(^{13}\text{C NMR} \) (126 MHz, CDCl\(_3\)): \( \delta \) 221.8, 154.2, 147.2, 145.6, 128.9 (2C), 128.2 (2C), 126.7, 115.5, 112.5, 58.4, 53.3, 52.2, 40.8, 37.8, 19.5, 17.7, 0.5 (3C); IR (thin film): \( v \) 1747 cm\(^{-1} \); HRMS (ESI) calcd for \([C_{21}H_{28}O_2SiNa]^+\): 363.1751, found: 363.1754. For \( 105 \): \(^1\text{H NMR} \) (500 MHz, CDCl\(_3\)): \( \delta \) 7.32–7.28 (m, 2H), 7.25–7.21 (m, 1H), 7.07–7.05 (m, 2H), 5.16 (d, \( J = 2.8 \) Hz, 1H), 5.05 (d, \( J = 2.4 \) Hz, 1H),
3.87 (q, \( J = 2.7 \) Hz, 1H), 2.85-2.78 (m, 2H), 2.61-2.51 (m, 3H), 1.26 (s, 3H), 1.04 (d, \( J = 6.8 \) Hz, 3H); \(^{13}\)C NMR (126 MHz CDCl\(_3\)): \( \delta \) 220.7, 208.5, 152.8, 146.0, 129.1 (2C), 127.7 (2C), 127.0, 115.4, 58.1, 54.0, 51.5, 50.4, 46.2, 40.7, 19.9, 16.2; IR (thin film): \( \nu \) 1744, 1712 cm\(^{-1}\); HRMS (ESI) calcd for [C\(_{18}\)H\(_{20}\)O\(_2\)Na]\(^+\): 291.1356, found: 291.1348. For \( 106 \): \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.31 (t, \( J = 7.3 \) Hz, 2H), 7.24 (t, \( J = 7.4 \) Hz, 1H), 7.06 (d, \( J = 7.6 \) Hz, 2H), 6.82 (dq, \( J = 15.5, 6.9 \) Hz, 1H), 6.08 (d, \( J = 15.8 \) Hz, 1H), 3.56 (s, 1H), 3.04 (dd, \( J = 16.9, 3.7 \) Hz, 1H), 2.80 (dd, \( J = 16.9, 7.8 \) Hz, 1H), 2.58 (t, \( J = 3.9 \) Hz, 1H), 1.86 (d, \( J = 6.8 \) Hz, 3H), 1.82 (s, 3H), 1.80 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \( \delta \) 209.3, 198.1, 169.8, 143.3, 141.6, 136.4, 131.6, 129.0 (2C), 127.9 (2C), 127.2, 56.0, 51.9, 40.3, 18.4, 15.6, 8.6; IR (thin film): \( \nu \) 1700, 1648 cm\(^{-1}\); HRMS (ESI) calcd for [C\(_{18}\)H\(_{20}\)O\(_2\)Na]\(^+\): 291.1356, found: 291.1352.
(1R*,5S*,6S*,7S*)-1,5-Dimethyl-8-methylene-7-phenyl-4-(trimethylsilyloxy)bicyclo[4.2.1]non-3-en-9-one (107a), (1R*,5R*,6S*,7S*)-1,5-dimethyl-8-methylene-7-phenyl-4-(trimethylsilyloxy)bicyclo[4.2.1]non-3-en-9-one (107b), (1R*,5S*,6S*,7S*)-1,5-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]nonane-4,9-dione (108a), and (1R*,5R*,6S*,7S*)-1,5-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]nonane-4,9-dione (108b)

Following General procedure 4, 80 (70 mg, 0.40 mmol), 100c (0.31 g, 2.0 mmol), and BF$_3$•OEt$_2$ (0.050 mL, 0.44 mmol) gave a 5:1 mixture of 107a and 107b (89 mg, 66%) and a 1:1.2 mixture of 108a and 108b (31 mg, 29%) as colourless oils. For 107a: $^1$H NMR (500 MHz, CDCl$_3$): δ 7.30 (t, $J$ = 7.5 Hz, 2H), 7.22 (t, $J$ = 7.3 Hz, 1H), 7.06 (d, $J$ = 7.8 Hz, 2H), 5.13 (d, $J$ = 2.0 Hz, 1H), 4.90 (d, $J$ = 1.2 Hz, 1H), 4.85 (dd, $J$ = 7.7, 1.9 Hz, 1H), 3.80 (s, 1H), 2.54-2.52 (m, 2H), 2.33 (d, $J$ = 16.0 Hz, 1H), 2.13 (dd, $J$ = 15.9, 7.7 Hz, 1H), 1.32 (s, 3H), 1.20 (d, $J$ = 6.4 Hz, 3H), 0.26 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 219.7, 157.5, 154.2, 146.6, 128.9 (2C), 127.4 (2C), 126.5, 109.8, 104.4, 59.7, 54.2, 53.0, 42.9, 41.6, 21.2, 17.6, 0.7 (3C).

For 107b: $^1$H NMR (500 MHz, CDCl$_3$): δ 7.30 (t, $J$ = 7.5 Hz, 2H), 7.22 (t, $J$ = 7.3 Hz, 1H), 7.08 (d, $J$ = 7.8 Hz, 2H), 5.09 (d, $J$ = 2.4 Hz, 1H), 4.98-4.97 (m, 1H), 4.76 (d, $J$ = 1.7 Hz, 1H), 3.93 (d, $J$ = 2.5 Hz, 1H), 2.72-2.71 (m, 1H), 2.64 (t, $J$ = 3.3 Hz, 1H), 2.31-2.28 (m, 1H), 2.20-2.15 (m, 1H), 1.34 (s, 3H), 1.23 (d, $J$ = 7.2 Hz, 3H),
0.23 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 221.4, 158.4, 151.6, 146.5, 128.9 (2C), 128.0 (2C), 126.4, 109.4, 106.2, 60.8, 54.9, 48.6, 42.0, 39.4, 20.1, 17.5, 0.4 (3C).

For **107a** and **107b**: IR (thin film): ν 1741 cm$^{-1}$; HRMS (ESI) calcd for [C$_{21}$H$_{28}$O$_2$SiNa]$^+$: 363.1751, found: 363.1747. For **108a**: $^1$H NMR (500 MHz, CDCl$_3$): δ 7.30-7.26 (m, 2H), 7.23-7.18 (m, 1H), 7.07-7.04 (m, 2H), 5.22 (d, $J$ = 2.2 Hz, 1H), 5.08 (d, $J$ = 2.0 Hz, 1H), 3.96 (q, $J$ = 2.1 Hz, 1H), 2.69-2.50 (m, 4H), 1.98-1.80 (m, 2H), 1.27 (s, 3H), 1.25 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 218.8, 211.6, 156.2, 145.4, 129.1 (2C), 127.1 (2C), 126.9, 112.5, 58.3, 54.4, 54.2, 50.4, 40.6, 38.8, 22.1, 16.5. For **108b**: $^1$H NMR (500 MHz, CDCl$_3$): δ 7.30-7.26 (m, 2H), 7.23-7.18 (m, 1H), 7.07-7.04 (m, 2H), 5.21 (d, $J$ = 2.2 Hz, 1H), 5.00 (d, $J$ = 1.9 Hz, 1H), 3.81 (q, $J$ = 2.1 Hz, 1H), 2.90 (qd, $J$ = 6.8, 4.6 Hz, 1H), 2.69-2.50 (m, 3H), 1.98-1.80 (m, 2H), 1.31 (s, 3H), 1.21 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 221.0, 211.2, 156.6, 145.1, 129.0 (2C), 127.3 (2C), 126.8, 112.7, 57.9, 53.2, 47.1, 46.9, 40.7, 40.5, 22.5, 13.9. For **108a** and **108b**: IR (thin film): ν 1743, 1745, 1711, 1709 cm$^{-1}$; HRMS (ESI) calcd for [C$_{18}$H$_{20}$O$_2$Na]$^+$: 291.1356, found: 291.1346.
(1\text{R}*,5\text{S}*,6\text{S}*,7\text{S}*)-4-(\text{tert-Butyldimethylsilyloxy})-1,5-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (109a), (1\text{R}*,5\text{R}*,6\text{S}*,7\text{S}*)-4-(\text{tert-butyl-dimethylsilyloxy})-1,5-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (109b), (1\text{R}*,5\text{S}*,6\text{S}*,7\text{S}*)-1,5-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]nonane-4,9-dione (108a) and (1\text{R}*,5\text{R}*,6\text{S}*,7\text{S}*)-1,5-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]nonane-4,9-dione (108b)

Following General procedure 4, 80 (70 mg, 0.40 mmol), 101a (0.40 g, 2.0 mmol), and BF₃•OEt₂ (0.050 mL, 0.44 mmol) gave a 7:1 mixture of 109a and 109b (86 mg, 56%) and a 1:1.2 mixture of 108a and 108b (46 mg, 43%) as colourless oils. For 109a: \textsuperscript{1}H NMR (500 MHz, CDCl₃): \( \delta \) 7.28–7.25 (m, 2H), 7.21–7.17 (m, 1H), 7.03–7.02 (m, 2H), 5.09 (d, \( J = 2.5 \) Hz, 1H), 4.85 (d, \( J = 2.1 \) Hz, 1H), 4.79 (dd, \( J = 7.6, 2.4 \) Hz, 1H), 3.75 (t, \( J = 2.1 \) Hz, 1H), 2.51–2.47 (m, 2H), 2.31–2.27 (m, 1H), 2.09 (dd, \( J = 16.0, 7.7 \) Hz, 1H), 1.28 (s, 3H), 1.17 (d, \( J = 6.8 \) Hz, 3H), 0.94 (s, 9H), 0.20 (s, 3H), 0.15 (s, 3H); \textsuperscript{13}C NMR (126 MHz, CDCl₃): \( \delta \) 219.9, 157.5, 154.2, 146.5, 128.9 (2C), 127.4 (2C), 126.5, 109.8, 104.2, 59.7, 54.2, 53.0, 42.9, 41.7, 25.8 (3C), 21.2, 18.1, 17.6, – 4.1, – 4.2. For 109b: \textsuperscript{1}H NMR (500 MHz, CDCl₃): \( \delta \) 7.27–7.24 (m, 2H), 7.19–7.16 (m, 1H), 7.04–7.02 (m, 2H), 5.07 (d, \( J = 2.3 \) Hz, 1H), 5.05 (dd, \( J = 7.2, 2.4 \) Hz, 1H), 4.88 (d, \( J = 2.0 \) Hz, 1H), 3.77 (d, \( J = 1.8 \) Hz, 1H), 2.64 (dd, \( J = 7.8, 3.2 \) Hz, 1H), 2.56–2.52 (m, 1H), 2.36–2.32 (m, 1H), 2.28–2.24 (m, 1H)
1.29 (s, 3H), 0.97 (d, \(J = 6.9\) Hz, 3H), 0.93 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta\) 220.3, 162.2, 159.7, 147.6, 128.9 (2C), 127.2 (2C), 126.5, 114.4, 109.7, 56.8, 53.7, 51.9, 46.4, 36.7, 25.9 (3C), 20.2, 18.2, 17.1, – 4.0, – 4.4. For 109a and 109b: IR (thin film): \(\nu\) 1737 cm\(^{-1}\); HRMS (ESI) calcd for [C\(_{24}\)H\(_{34}\)O\(_2\)SiNa]\(^+\): 405.2220, found: 405.2203.

(1\(R^*\),5\(S^*\),6\(S^*\),7\(S^*\))-4-(tert-Butyldimethylsilyloxy)-5-ethyl-1-methyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (110a) and (1\(R^*\),5\(R^*\),6\(S^*\),7\(S^*\))-4-(tert-butyldimethylsilyloxy)-5-ethyl-1-methyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (110b)

Following General procedure 4, 80 (70 mg, 0.40 mmol), 101b (0.42 g, 2.0 mmol), and BF\(_3\)•OEt\(_2\) (0.050 mL, 0.44 mmol) gave a 2:1 mixture of 110a and 110b (54 mg, 34%) as a colourless oil. For 110a: \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.27 (t, \(J = 7.4\) Hz, 2H), 7.19 (t, \(J = 7.3\) Hz, 1H), 7.03 (d, \(J = 7.3\) Hz, 2H), 5.09 (d, \(J = 2.3\) Hz, 1H), 4.86 (d, \(J = 2.0\) Hz, 1H), 4.81 (dd, \(J = 8.2, 2.3\) Hz, 1H), 3.72 (d, \(J = 1.9\) Hz, 1H), 2.69 (dd, \(J = 5.3, 1.8\) Hz, 1H), 2.29-2.25 (m, 2H), 2.06 (dd, \(J = 15.9, 8.2\) Hz, 1H), 1.64-1.62 (m, 1H), 1.48-1.35 (m, 1H), 1.27 (s, 3H), 0.99 (t, \(J = 7.4\) Hz, 3H), 0.95 (s, 9H), 0.22 (s, 3H), 0.17 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta\) 220.0,
157.5, 154.3, 146.7, 128.9 (2C), 127.4 (2C), 126.5, 109.8, 104.1, 56.2, 54.4, 52.8, 50.3, 41.3, 25.8 (3C), 24.5, 21.0, 18.1, 12.6, – 4.1, – 4.3. For 110b: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.27 (t, $J = 7.4$ Hz, 2H), 7.19 (t, $J = 7.3$ Hz, 1H), 7.07 (d, $J = 7.3$ Hz, 2H), 5.03 (d, $J = 2.7$ Hz, 1H), 4.92-4.89 (m, 1H), 4.63 (d, $J = 2.3$ Hz, 1H), 3.90 (q, $J = 3.0$ Hz, 1H), 2.81 (t, $J = 3.9$ Hz, 1H), 2.42-2.39 (m, 1H), 2.29-2.25 (m, 1H), 2.19-2.14 (m, 2H), 1.48-1.35 (m, 1H), 1.30 (s, 3H), 0.94 (s, 9H), 0.67 (t, $J = 7.4$ Hz, 3H), 0.15 (s, 3H), 0.12 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 221.4, 158.8, 151.5, 145.9, 128.8 (2C), 128.1 (2C), 126.4, 108.9, 105.9, 55.9, 55.5, 48.4, 46.8, 41.8, 26.0 (3C), 22.3, 19.9, 18.4, 11.9, – 4.1, – 4.4. For 110a and 110b: IR (thin film): $\nu$ 1743 cm$^{-1}$; HRMS (ESI) calcd for [C$_{25}$H$_{36}$O$_2$SiNa]$^+$: 419.2377, found: 419.2382.

(1$R^*$,5$R^*$,6$S^*$,7$S^*$)-4-(tert-Butyldimethylsilyloxy)-1-methyl-8-methylene-7-phenyl-5-isopropylbicyclo[4.2.1]non-3-en-9-one (111)

Following General procedure 4, 80 (70 mg, 0.40 mmol), 101c (0.45 g, 2.0 mmol), and BF$_3$$\cdot$OEt$_2$ (0.050 mL, 0.44 mmol) gave 111 (62 mg, 38%) as a colourless solid. mp: 168-169 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.25 (t, $J = 7.5$ Hz, 2H), 7.17 (t, $J = 7.4$ Hz, 1H), 6.99 (d, $J = 7.3$ Hz, 2H), 4.99-4.96 (m, 2H), 4.61 (d, $J = 2.2$ Hz, 1H), 3.74 (q, $J = 2.4$ Hz, 1H), 2.74 (br s, 1H), 2.46-2.41 (m, 1H), 2.06-2.02 (m, 1H), 2.02-1.98 (m, 1H), 1.94-1.89 (m, 1H), 1.88-1.83 (m, 1H), 1.83-1.80 (m, 1H), 1.79-1.76 (m, 1H), 1.75-1.71 (m, 1H), 1.71-1.67 (m, 1H), 1.66-1.62 (m, 1H), 1.62-1.58 (m, 1H), 1.57-1.53 (m, 1H), 1.53-1.49 (m, 1H), 1.49-1.45 (m, 1H), 1.45-1.41 (m, 1H), 1.41-1.37 (m, 1H), 1.37-1.33 (m, 1H), 1.33-1.29 (m, 1H), 1.29-1.25 (m, 1H), 1.25-1.21 (m, 1H), 1.21-1.17 (m, 1H), 1.17-1.13 (m, 1H), 1.13-1.09 (m, 1H), 1.09-1.05 (m, 1H), 1.05-1.01 (m, 1H), 1.01-0.97 (m, 1H), 0.97-0.93 (m, 1H), 0.93-0.89 (m, 1H), 0.89-0.85 (m, 1H), 0.85-0.81 (m, 1H), 0.81-0.77 (m, 1H), 0.77-0.73 (m, 1H), 0.73-0.69 (m, 1H), 0.69-0.65 (m, 1H), 0.65-0.61 (m, 1H), 0.61-0.57 (m, 1H), 0.57-0.53 (m, 1H), 0.53-0.49 (m, 1H), 0.49-0.45 (m, 1H), 0.45-0.41 (m, 1H), 0.41-0.37 (m, 1H), 0.37-0.33 (m, 1H), 0.33-0.29 (m, 1H), 0.29-0.25 (m, 1H), 0.25-0.21 (m, 1H), 0.21-0.17 (m, 1H), 0.17-0.13 (m, 1H), 0.13-0.09 (m, 1H), 0.09-0.05 (m, 1H), 0.05-0.01 (m, 1H), 0.01-–0.00 (m, 1H).
2.39 (br s, 1H), 2.15-2.05 (m, 2H), 1.26 (s, 3H), 0.95 (s, 9H), 0.89 (d, \( J = 6.8 \) Hz, 3H), 0.84 (d, \( J = 6.8 \) Hz, 3H), 0.21 (s, 3H), 0.15 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \( \delta \) 223.0, 159.1, 153.4, 146.2, 128.7 (2C), 128.2 (2C), 126.3, 109.0, 104.4, 56.1, 54.4, 51.3, 49.7, 41.2, 28.5, 26.1 (3C), 21.9, 19.9, 19.6, 18.4, –4.1, –4.4; IR (thin film): \( \nu \) 1737 cm\(^{-1}\); HRMS (ESI) calcd for \([\text{C}_{26}\text{H}_{38}\text{O}_2\text{Si}\text{Na}]^{+}\): 433.2533, found: 433.2533.

\((1R^*,5S^*,6S^*,7S^*)\)-4-(tert-Butyldimethylsilyloxy)-1-methyl-8-methylene-5,7-diphenylbicyclo[4.2.1]non-3-en-9-one (112a), \((1R^*,5R^*,6S^*,7S^*)\)-4-(tert-butyldimethylsilyloxy)-1-methyl-8-methylene-5,7-diphenylbicyclo[4.2.1]non-3-en-9-one (112b), and \((1R^*,2R^*,6S^*,7S^*)\)-3-(tert-butyldimethylsilyloxy)-1-methyl-8-methylene-2,7-diphenylbicyclo[4.2.1]non-3-en-9-one (113)

Following *General procedure 4*, 80 (70 mg, 0.40 mmol), 101d (0.52 g, 2.0 mmol), and BF\(_3\)•OEt\(_2\) (0.050 mL, 0.44 mmol) gave 112a (59 mg, 33%) and a 1.3:1 mixture of 112b and 113 (37 mg, 21%) as colourless oils. For 112a: \(^{1}\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.28-7.17 (m, 6H), 7.05 (d, \( J = 7.3 \) Hz, 4H), 5.14 (d, \( J = 2.3 \) Hz, 1H), 5.07 (dd, \( J = 7.9, 2.3 \) Hz, 1H), 4.92 (d, \( J = 2.0 \) Hz, 1H), 3.97 (d, \( J = 2.0 \) Hz, 1H), 3.74 (d, \( J = 4.7 \) Hz, 1H), 2.75 (dd, \( J = 4.8, 2.0 \) Hz, 1H), 2.51 (d, \( J = 16.1 \) Hz,
H), 2.23 (dd, J = 16.1, 7.9 Hz, 1H), 1.28 (s, 3H), 0.75 (s, 9H), 0.13 (s, 3H), -0.11 (s, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 217.8, 157.2, 151.7, 146.4, 139.3, 128.9 (2C), 128.45 (2C), 128.37 (2C), 127.39 (2C), 127.21, 126.6, 110.2, 106.5, 60.7, 54.8, 54.3, 53.2, 41.7, 25.6 (3C), 21.4, 18.0, – 4.1, – 4.7; IR (thin film): ν 1744 cm⁻¹; HRMS (ESI) calcd for [C₂₉H₃₆O₂SiNa]⁺: 467.2377, found: 467.2381. For 112b: ¹H NMR (500 MHz, CDCl₃): δ 7.29-7.02 (m, 8H), 6.52 (d, J = 6.5 Hz, 2H), 5.15 (d, J = 2.4 Hz, 1H), 5.08-5.07 (m, 1H), 4.82 (d, J = 2.0 Hz, 1H), 4.10 (d, J = 2.4 Hz, 1H), 3.92-3.91 (m, 1H), 2.78 (dd, J = 5.0, 3.1 Hz, 1H), 2.43 (dt, J = 16.5, 3.3 Hz, 1H), 2.33 (dd, J = 17.9, 5.3 Hz, 1H), 1.35 (s, 3H), 0.58 (s, 9H), 0.05 (s, 3H), -0.10 (s, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 219.8, 157.5, 148.4, 145.8, 140.0, 129.8 (2C), 128.4 (2C), 128.1 (2C), 127.0, 126.6, 126.0 (2C), 109.8, 108.6, 61.6, 54.6, 50.7, 47.5, 42.8, 25.4 (3C), 21.0, 17.8, – 4.1, – 5.1. For 113: ¹H NMR (500 MHz, CDCl₃): δ 7.29-7.02 (m, 10H), 5.02-5.01 (m, 1H), 4.54 (d, J = 2.5 Hz, 1H), 4.15 (d, J = 3.0 Hz, 1H), 3.92-3.91 (m, 1H), 3.35 (d, J = 1.8 Hz, 1H), 2.84 (q, J = 4.3 Hz, 1H), 2.71-2.66 (m, 1H), 2.52-2.48 (m, 1H), 1.19 (s, 3H), 0.51 (s, 9H), -0.02 (s, 3H), -0.03 (s, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 220.3, 153.3, 150.1, 145.1, 137.9, 128.8 (2C), 128.6 (2C), 127.5 (2C), 127.0, 126.7, 126.5 (2C), 114.6, 106.3, 57.7, 56.6, 55.8, 52.4, 32.2, 25.3 (3C), 21.4, 17.8, – 4.4, – 4.8. For 112b and 113: IR (thin film): ν 1745 cm⁻¹; HRMS (ESI) calcd for [C₂₉H₃₇O₂Si]⁺: 445.2557, found: 445.2556.
(1R*,2S*,4S*,5S*)-2-(1-Methoxy-2-methylprop-1-en-1-yl)-1-methyl-6-methylene-5-phenylbicyclo[2.2.1]heptan-7-one (114a), and (1R*,2R*,4S*,5S*)-2-(1-methoxy-2-methylprop-1-en-1-yl)-1-methyl-6-methylene-5-phenylbicyclo[2.2.1]heptan-7-one (114b)

Following *General procedure 4*, 80 (70 mg, 0.40 mmol), 101j (0.52 g, 2.0 mmol), and BF$_3$•OEt$_2$ (0.050 mL, 0.44 mmol) gave a 9:1 mixture of 114a and 114b (64 mg, 54%) as a colourless oil. For **114a**: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.25 (t, $J$ = 7.5 Hz, 2H), 7.18 (t, $J$ = 7.1 Hz, 1H), 7.11 (d, $J$ = 7.8 Hz, 2H), 5.10 (d, $J$ = 2.0 Hz, 1H), 4.81 (s, 1H), 3.78 (s, 1H), 3.55 (s, 3H), 3.04 (dd, $J$ = 10.3, 5.1 Hz, 1H), 2.30 (d, $J$ = 4.7 Hz, 1H), 2.24 (dt, $J$ = 12.4, 5.0 Hz, 1H), 1.96 (dd, $J$ = 12.2, 10.7 Hz, 1H), 1.71 (s, 3H), 1.64 (s, 3H), 1.08 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 214.0, 153.3, 150.7, 143.3, 128.6 (2C), 127.5 (2C), 126.7, 117.0, 107.9, 61.3, 52.9, 51.9, 48.1, 43.4, 28.7, 19.7, 18.7, 9.4. For **114b**: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.26 (t, $J$ = 7.4 Hz, 2H), 7.19 (t, $J$ = 7.3 Hz, 1H), 7.11 (d, $J$ = 7.8 Hz, 2H), 4.95 (d, $J$ = 2.6 Hz, 1H), 4.77 (d, $J$ = 2.1 Hz, 1H), 3.83 (s, 1H), 3.59 (s, 3H), 3.13 (dd, $J$ = 10.8, 6.5 Hz, 1H), 2.17-2.08 (m, 2H), 1.95 (d, $J$ = 10.4 Hz, 1H), 1.76 (s, 3H), 1.66 (s, 3H), 1.12 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 215.1, 150.4, 149.8, 143.9, 128.7 (2C), 127.7 (2C), 126.7, 119.1, 109.6, 61.9, 55.1, 52.9, 48.2, 41.3, 28.1, 20.1, 19.3, 11.4. For
114a and 114b: IR (thin film): ν 1777, 1767 cm\(^{-1}\); HRMS (ESI) calcd for [C\(_{20}\)H\(_{24}\)O\(_2\)Na\(^+\)]: 319.1669, found: 319.1670.

\((1R^*,6S^*,7S^*)\)-4-(tert-Butyldimethylsilyloxy)-1,3-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (115)

\[ \text{Following General procedure 4, 80 (70 mg, 0.40 mmol), 101e (0.40 g, 2.0 mmol), and BF}_3\cdot\text{OEt}_2 (0.050 mL, 0.44 mmol) gave 115 (54 mg, 35%) as a colourless oil.} \]

\( ^1\text{H NMR (500 MHz, CDCl}_3\)): δ 7.26–7.25 (m, 2H), 7.20–7.17 (m, 1H), 7.03–7.01 (m, 2H), 5.08 (d, \( J = 2.4 \text{ Hz, 1H} \)), 4.85 (d, \( J = 2.1 \text{ Hz, 1H} \)), 3.80 (q, \( J = 2.0 \text{ Hz, 1H} \)), 2.66–2.59 (m, 2H), 2.46 (dd, \( J = 16.4, 5.7 \text{ Hz, 1H} \)), 2.40 (br d, \( J = 15.6 \text{ Hz, 1H} \)), 2.04 (d, \( J = 15.6 \text{ Hz, 1H} \)), 1.64 (br s, 3H), 1.28 (s, 3H), 0.96 (s, 9H), 0.13 (s, 3H), 0.13 (s, 3H); \( ^{13}\text{C NMR (126 MHz, CDCl}_3\)): δ 222.5, 157.2, 146.3, 142.3, 128.9 (2C), 127.4 (2C), 126.5, 113.9, 109.7, 54.1, 53.8, 51.5, 38.7, 26.1 (3C), 21.0, 20.9, 18.4, – 3.4, – 3.6; IR (thin film): ν 1737 cm\(^{-1}\); HRMS (ESI) calcd for [C\(_{24}\)H\(_{34}\)O\(_2\)SiNa\(^+\)]: 405.2220, found: 405.2229.
(1R*,2R*,6S*,7S*)-4-(tert-Butyldimethylsilyloxy)-1,2-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (116) and (4R*,5R*)-2,3-dimethyl-5-((E)-2-oxopent-3-en-1-yl)-4-phenylcyclopent-2-enone (106)

Following General procedure 4, **80** (70 mg, 0.40 mmol), **101f** (0.40 g, 2.0 mmol), and BF$_3$•OEt$_2$ (0.050 mL, 0.44 mmol) were stirred for 5 min at –78 °C to give **116** (41 mg, 27%) as a colourless solid, and **106** (37 mg, 35%) as a colourless oil. For **116**: mp: 93-94 °C; $^1$H NMR (500 MHz, CDCl$_3$): δ 7.30–7.28 (m, 2H), 7.23–7.20 (m, 1H), 7.09–7.07 (m, 2H), 4.99 (d, $J$ = 2.9 Hz, 1H), 4.79 (d, $J$ = 2.5 Hz, 1H), 4.78 (t, $J$ = 2.5 Hz, 1H), 3.72 (q, $J$ = 3.2 Hz, 1H), 2.66 (q, $J$ = 4.2 Hz, 1H), 2.63–2.58 (m, 1H), 2.38–2.32 (m, 2H), 1.24 (s, 3H), 1.08 (d, $J$ = 7.1 Hz, 3H), 0.92 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 221.6, 154.2, 147.4, 145.5, 128.8 (2C), 128.2 (2C), 126.6, 115.1, 112.4, 58.4, 53.1, 52.2, 40.9, 37.7, 25.8 (3C), 19.5, 18.1, 17.7, – 4.1, – 4.3; IR (thin film): ν 1734 cm$^{-1}$; HRMS (ESI) calcd for [C$_{24}$H$_{34}$O$_2$SiNa]$^+$: 405.2220, found: 405.2204.
(1R*,6S*,7S*)-4-(tert-Butyldimethylsilyloxy)-1,2,2-trimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (117)

Following General procedure 4, 80 (70 mg, 0.40 mmol), 101g (0.42 g, 2.0 mmol), and BF₃•OEt₂ (0.050 mL, 0.44 mmol) gave 117 (63 mg, 40%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.27 (t, J = 7.5 Hz, 2H), 7.19 (t, J = 7.3 Hz, 1H), 7.06 (d, J = 7.8 Hz, 2H), 5.04 (d, J = 2.7 Hz, 1H), 4.85–4.82 (m, 2H), 3.75 (q, J = 2.6 Hz, 1H), 2.62–2.57 (m, 2H), 2.35 (dd, J = 17.8, 6.2 Hz, 1H), 1.22 (s, 3H), 1.12 (s, 3H), 1.01 (s, 3H), 0.93 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 220.9, 157.0, 146.6, 146.3, 128.8 (2C), 128.1 (2C), 126.5, 121.8, 113.3, 60.0, 53.6, 51.8, 40.6, 37.5, 26.3, 26.0, 25.9 (3C), 18.2, 17.1, −3.9, −4.3; IR (thin film): ν 1740 cm⁻¹; HRMS (ESI) calcd for [C₂₅H₃₆O₂SiNa]⁺: 419.2377, found: 419.2369.
(1\textsuperscript{R\,*},2\textsuperscript{R\,*},10\textsuperscript{S\,*},11\textsuperscript{S\,*})-8-(tert-Butyldimethylsilyloxy)-1-methyl-12-methylene-11-phenyltricyclo[8.2.1.2\textsuperscript{7}]tridec-7-en-13-one (118) and (4\textsuperscript{R\,*},5\textsuperscript{R\,*})-2,3-dimethyl-5-(1-(cyclohex-1-enyl)-1-oxoethan-2-yl)-1-oxoethan-2-yl)-4-phenylcyclopent-2-enone (119)

Following General procedure 4, 80 (70 mg, 0.40 mmol), 101h (0.48 g, 2.0 mmol), and BF\textsubscript{3}\cdot\text{OEt}_2 (0.050 mL, 0.44 mmol) gave 118 (69 mg, 41%) as a colourless oil.\textsuperscript{*} \textsuperscript{\textsuperscript{\textsuperscript{1}}}H NMR (500 MHz, CDCl\textsubscript{3}): δ 7.26–7.25 (m, 2H), 7.19–7.17 (m, 1H), 7.05–7.02 (m, 2H), 5.07 (d, \textit{J} = 2.2 Hz, 1H), 4.90 (d, \textit{J} = 2.0 Hz, 1H), 3.80 (q, \textit{J} = 2.7 Hz, 1H), 3.09–3.06 (m, 1H), 2.67–2.62 (m, 2H), 2.49–2.45 (m, 1H), 2.08–2.05 (m, 2H), 1.84 (br d, \textit{J} = 12.6 Hz, 1H), 1.73 (br d, \textit{J} = 12.6 Hz, 1H), 1.43–1.38 (m, 2H), 1.27 (s, 3H), 1.26–1.22 (m, 1H), 1.07–0.99 (m, 1H), 0.95 (s, 9H), 0.15 (s, 3H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}): δ 220.9, 159.9, 146.5, 138.1, 128.9 (2C), 127.1 (2C), 126.5, 123.6, 109.5, 58.4, 55.4, 53.5, 52.3, 38.4, 32.6, 30.8, 28.8, 27.7, 26.1 (3C), 20.8, 18.5, – 3.4, – 3.5; IR (thin film): ν 1729 cm\textsuperscript{−1}; HRMS (ESI) calcd for [C\textsubscript{27}H\textsubscript{39}O\textsubscript{2}Si]\textsuperscript{+}: 423.2714, found: 423.2699.

\textsuperscript{*} Small signals at δ 3.56 and 2.58 ppm in the \textsuperscript{1}H NMR spectrum of the crude mixture indicated a trace amount of 27.
(1R*,2S*,5S*,6S*,7S*)-4-(tert-Butyldimethylsilyloxy)-1,2,5-trimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (120) and (1R*,2R*,5R*,6S*,7S*)-4-(tert-butyldimethylsilyloxy)-1,2,5-trimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (121)

Following General procedure 4, 80 (70 mg, 0.40 mmol), 101i (0.42 g, 2.0 mmol), and BF₃•OEt₂ (0.050 mL, 0.44 mmol) gave a mixture of 120 (35 mg, 22%) and 121 (32 mg, 20%) as colourless oils. For 120: ¹H NMR (500 MHz, CDCl₃): δ 7.26 (t, J = 7.5 Hz, 2H), 7.18 (t, J = 7.3 Hz, 1H), 7.02 (d, J = 7.7 Hz, 2H), 5.06 (d, J = 1.5 Hz, 1H), 4.89 (d, J = 7.2 Hz, 1H), 4.86 (s, 1H), 3.73 (s, 1H), 2.46-2.44 (m, 2H), 2.22 (quintet, J = 7.0 Hz, 1H), 1.29 (s, 3H), 1.16 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.95 (s, 9H), 0.21 (s, 3H), 0.16 (s, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 218.5, 159.6, 152.5, 146.9, 128.9 (2C), 127.2 (2C), 126.4, 112.1, 109.5, 59.9, 56.5, 53.0, 46.1, 42.9, 25.9 (3C), 20.3, 18.4, 18.2, 17.8, – 3.9, – 4.2. For 121: ¹H NMR (500 MHz, CDCl₃): δ 7.28 (t, J = 7.5 Hz, 2H), 7.20 (t, J = 7.0 Hz, 1H), 7.10 (d, J = 7.8 Hz, 2H), 4.93 (d, J = 2.7 Hz, 1H), 4.73 (s, 1H), 4.63 (d, J = 1.8 Hz, 1H), 3.78 (t, J = 2.2 Hz, 1H), 2.76-2.74 (m, 1H), 2.64 (t, J = 4.6 Hz, 1H), 2.30-2.26 (m, 1H), 1.23 (s, 3H), 1.12 (d, J = 7.1 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.93 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 220.4, 154.8, 150.0, 145.5, 128.8 (2C), 128.7 (2C), 126.5, 113.9, 111.6, 59.7, 58.4, 49.0, 40.6, 40.2, 26.0
For 120 and 121: IR (thin film): ν 1740 cm⁻¹; HRMS (ESI) calcd for [C₂₅H₃₆O₂SiNa]⁺: 419.2377, found: 419.2362.

(1R*,5R*,6S*,8R*)-4-(tert-Butyldimethylsilyloxy)-1,5-dimethyl-7-methylene-8-phenylbicyclo[4.2.1]non-3-en-9-one (122a), and (1R*,5S*,6S*,8R*)-4-(tert-butyldimethylsilyloxy)-1,5-dimethyl-7-methylene-8-phenylbicyclo[4.2.1]non-3-en-9-one (122b)

Following General procedure 4, 93 (70 mg, 0.40 mmol), 101a (0.40 g, 2.0 mmol), and BF₃•OEt₂ (0.050 mL, 0.44 mmol) gave a 2.7:1 mixture of 122a and 122b (34 mg, 22%) as a colourless oil. For 122a: ¹H NMR (500 MHz, CDCl₃): δ 7.26-7.22 (m, 2H), 7.18-7.15 (m, 1H), 6.96-6.93 (m, 2H), 5.16 (s, 1H), 4.93 (s, 1H), 4.80 (dd, J = 5.7, 4.6 Hz, 1H), 3.78 (s, 1H), 3.05 (dd, J = 5.7, 1.0 Hz, 1H), 2.47 (quintet, J = 6.7 Hz, 1H), 2.24-2.19 (m, 2H), 1.24 (d, J = 7.1 Hz, 3H), 0.92 (s, 9H), 0.66 (s, 3H), 0.14 (s, 6H); ¹³C NMR (126 MHz, CDCl₃): δ 219.8, 155.3, 152.2, 144.5, 128.9, 128.4 (2C), 126.5 (2C), 111.6, 102.9, 57.9, 56.8, 54.4, 44.9, 41.5, 26.0 (3C), 20.4, 18.1, 16.7, – 4.1, – 4.2. For 122b: ¹H NMR (500 MHz, CDCl₃): δ 7.26-7.22 (m, 2H), 7.18-7.15 (m, 1H), 6.96-6.93 (m, 2H), 5.18 (s, 1H), 4.91-4.90 (m, 2H), 3.72 (s, 1H), 3.08 (s, 1H), 2.71-2.69 (m, 1H), 2.24-2.19 (m, 1H), 2.15-2.11 (m,
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.25 (t, $J = 7.4$ Hz, 2H), 7.20 (t, $J = 7.2$ Hz, 1H), 7.03 (d, $J = 7.3$ Hz, 2H), 5.15 (d, $J = 2.5$ Hz, 1H), 4.90 (s, 1H), 4.83 (d, $J = 1.9$ Hz, 1H), 3.95 (d, $J = 1.7$ Hz, 1H), 2.81 (s, 1H), 2.31 (dd, $J = 16.8$, 2.3 Hz, 1H), 2.17 (d, $J = 16.8$ Hz, 1H), 1.25 (s, 3H), 1.17 (s, 3H), 0.94 (s, 9H), 0.63 (s, 3H), 0.17 (s, 3H), 0.12 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 219.3, 149.5, 146.7, 143.1, 130.1, 128.2 (2C), 126.7 (2C), 118.8, 114.4, 65.9, 57.2, 51.1, 47.7, 38.9, 30.6, 29.2, 25.9 (3C), 21.0, 18.2, – 4.0, – 4.3; IR (thin film): $\nu$ 1742 cm$^{-1}$; HRMS (ESI) calcd for [C$_{25}$H$_{36}$O$_2$SiNa]$^+$: 419.2377, found: 419.2371.

Following General procedure 4, 93 (70 mg, 0.40 mmol), 101g (0.40 g, 2.0 mmol), and BF$_3$$\cdot$OEt$_2$ (0.050 mL, 0.44 mmol) gave 123 (43 mg, 27%) as a colourless oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.25 (t, $J = 7.4$ Hz, 2H), 7.20 (t, $J = 7.2$ Hz, 1H), 7.03 (d, $J = 7.3$ Hz, 2H), 5.15 (d, $J = 2.5$ Hz, 1H), 4.90 (s, 1H), 4.83 (d, $J = 1.9$ Hz, 1H), 3.95 (d, $J = 1.7$ Hz, 1H), 2.81 (s, 1H), 2.31 (dd, $J = 16.8$, 2.3 Hz, 1H), 2.17 (d, $J = 16.8$ Hz, 1H), 1.25 (s, 3H), 1.17 (s, 3H), 0.94 (s, 9H), 0.63 (s, 3H), 0.17 (s, 3H), 0.12 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 219.3, 149.5, 146.7, 143.1, 130.1, 128.2 (2C), 126.7 (2C), 118.8, 114.4, 65.9, 57.2, 51.1, 47.7, 38.9, 30.6, 29.2, 25.9 (3C), 21.0, 18.2, – 4.0, – 4.3; IR (thin film): $\nu$ 1742 cm$^{-1}$; HRMS (ESI) calcd for [C$_{25}$H$_{36}$O$_2$SiNa]$^+$: 419.2377, found: 419.2371.

Following General procedure 4, 95 (70 mg, 0.40 mmol), 101a (0.40 g, 2.0 mmol), and BF$_3$•OEt$_2$ (0.050 mL, 0.44 mmol) gave 124 (3 mg, 3%) as a colourless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ 5.21-5.20 (m, 1H), 5.14-5.13 (m, 1H), 3.00-2.98 (m, 1H), 2.88-2.82 (m, 1H), 2.76-2.71 (m, 1H), 2.55-2.51 (m, 1H), 2.32-2.27 (m, 1H), 2.21-2.17 (m, 1H), 1.92-1.88 (m, 1H), 1.75-1.70 (m, 1H), 1.65-1.57 (m, 3H), 1.33 (d, $J = 7.4$ Hz, 3H), 1.20-1.10 (m, 3H), 0.97-0.87 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 219.1, 212.3, 149.8, 110.7, 53.5, 51.3, 49.7, 47.5, 39.6, 38.9, 34.7, 30.6, 24.4, 23.0, 16.3. HRMS pending.

General procedure 5: BF$_3$•OEt$_2$ (1.1 equiv) was added to a solution of a Nazarov product in CH$_2$Cl$_2$ (0.1 M) at rt. The solution was stirred for 5 min before saturated aqueous NaHCO$_3$ (40 mL) was added. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 40 mL). The combined organic solutions were dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash chromatography (15% Et$_2$O in pentane).
Following General procedure 5, 116 (41 mg, 0.11 mmol) and BF$_3$•OEt$_2$ (0.010 mL, 0.12 mmol) gave 106 (29 mg, 90%) as a colourless oil.

Following General procedure 5, a 7:1 mixture of 109a and 109b (86 mg, 0.22 mmol) and BF$_3$•OEt$_2$ (0.030 mL, 0.25 mmol) gave a 7:1 mixture of 108a and 108b (57 mg, 95%) as a colourless oil.
Following General procedure 5, 111 (62 mg, 0.40 mmol) and BF$_3$•OEt$_2$ (0.050 mL, 0.44 mmol) gave 125 (42 mg, 94%) as a colourless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.29-7.26 (m, 2H), 7.20 (t, $J = 7.4$ Hz, 1H), 7.03 (d, $J = 7.2$ Hz, 2H), 5.16 (d, $J = 2.1$ Hz, 1H), 4.95 (d, $J = 1.8$ Hz, 1H), 3.88 (d, $J = 2.0$ Hz, 1H), 2.88 (dd, $J = 5.1$, 2.4 Hz, 1H), 2.57-2.53 (m, 1H), 2.47-2.41 (m, 2H), 2.25-2.22 (m, 1H), 1.94-1.87 (m, 2H), 1.30 (s, 3H), 0.91 (d, $J = 6.5$ Hz, 3H), 0.77 (d, $J = 6.7$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 221.7, 210.8, 157.6, 146.0, 129.1 (2C), 127.3 (2C), 126.8, 112.4, 59.8, 54.4, 53.8, 47.2, 41.3, 40.5, 26.1, 22.3, 21.9, 20.4; IR (thin film): ν 1742, 1708 cm$^{-1}$; HRMS (ESI) calcd for [C$_{20}$H$_{24}$O$_2$Na]$^+$: 319.1669, found: 319.1667.
(1R*,2S*,5S*,6S*,7S*)-1,2,5-Trimethyl-8-methylene-7-phenylbicyclo[4.2.1]-nonane-4,9-dione (126), (4R*,5R*)-2,3-dimethyl-5-((R*,E)-3-oxohex-4-en-2-yl)-4-phenylcyclopent-2-enone (127), and (1R*,2R*,5S*,10R*)-2,5,8-trimethyl-10-phenylbicyclo[5.2.1]dec-7-ene-3,9-dione (128)

Following General procedure 5, 120 (35 mg, 0.40 mmol) and BF₃•OEt₂ (0.050 mL, 0.44 mmol) gave 126 (4 mg, 15%), 127 (11 mg, 46%), and 128 (9 mg, 38%) as colourless oils. For 126: ¹H NMR (500 MHz, CDCl₃): δ 7.31 (t, J = 7.6 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 7.09 (d, J = 7.7 Hz, 2H), 5.24 (s, 1H), 5.10 (s, 1H), 4.00 (s, 1H), 3.00-2.97 (m, 1H), 2.63-2.62 (m, 2H), 2.43-2.39 (m, 1H), 2.00-1.97 (m, 1H), 1.28 (s, 3H), 1.26 (s, 3H), 0.96 (d, J = 7.0 Hz, 3H); ¹³C NMR discernable signals (126 MHz, CDCl₃): δ 146.0, 129.1 (2C), 127.1 (2C), 126.9, 112.2, 58.7, 57.3, 54.8, 50.4, 44.3, 20.4, 16.5; IR (thin film): ν 1737, 1704 cm⁻¹; HRMS (ESI) calcd for [C₁₉H₂₂O₂Na]⁺: 305.1512, found: 305.1506. For 127: ¹H NMR (500 MHz, CDCl₃): δ 7.26-7.24 (m, 2H), 7.20-7.17 (m, 1H), 6.99 (d, J = 7.8 Hz, 2H), 6.73 (dq, J = 14.9, 7.3 Hz, 1H), 6.01 (d, J = 15.6 Hz, 1H), 3.57 (s, 1H), 3.38-3.33 (m, 1H), 2.67 (s, 1H), 1.80 (s, 3H), 1.79 (s, 3H), 1.70 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 208.9, 201.4, 171.5, 142.9, 141.4, 137.2, 130.0, 128.8 (2C), 128.0 (2C), 127.0, 56.6, 51.5, 44.0, 18.2, 15.6, 10.8, 8.4; IR (thin film): ν 1702, 1649 cm⁻¹; HRMS (ESI) calcd for [C₁₉H₂₂O₂Na]⁺: 305.1512, found:
305.1513. For **128**: $^1$H NMR (500 MHz, CDCl$_3$): δ 7.30 (t, $J$ = 7.5 Hz, 2H), 7.24 (t, $J$ = 6.9 Hz, 1H), 7.14 (d, $J$ = 7.7 Hz, 2H), 4.31 (s, 1H), 3.27 (dd, $J$ = 6.6, 3.9 Hz, 1H), 3.01 (dd, $J$ = 14.0, 3.3 Hz, 1H), 2.85 (d, $J$ = 3.7 Hz, 1H), 2.74 (dt, $J$ = 7.0, 3.6 Hz, 1H), 2.64-2.60 (m, 1H), 2.52 (dd, $J$ = 12.5, 3.8 Hz, 1H), 2.17 (dd, $J$ = 14.0, 7.1 Hz, 1H), 1.68 (s, 3H), 1.28 (d, $J$ = 7.0 Hz, 3H), 1.12 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 211.1, 208.4, 173.5, 141.0, 135.2, 129.1 (2C), 127.5, 127.2 (2C), 65.4, 58.5, 53.3, 48.2, 35.3, 34.2, 22.7, 14.6, 9.4; IR (thin film): ν 1703, 1641 cm$^{-1}$; HRMS (ESI) calcd for [C$_{19}$H$_{22}$O$_2$Na]$^+$: 305.1512, found: 305.1499.

**(1R*,2R*,5R*,6S*,7S*)-1,2,5-Trimethyl-8-methylene-7-phenylbicyclo[4.2.1]-nonane-4,9-dione (129), (4R*,5R*)-2,3-dimethyl-5-((S*,E)-3-oxohex-4-en-2-yl)-4-phenylcyclopent-2-enone (130), and (1R*,2S*,5S*,10R*)-2,5,8-trimethyl-10-phenylbicyclo[5.2.1]dec-7-ene-3,9-dione (131)**

![Structures](image)

Following *General procedure 5*, **121** (32 mg, 0.40 mmol) and BF$_3$•OEt$_2$ (0.050 mL, 0.44 mmol) gave **129** (1 mg, 5%), **130** (16 mg, 70%), and **131** (3 mg, 15%) as colourless oils. For **129**: $^1$H NMR (500 MHz, CDCl$_3$): δ 7.28 (t, $J$ = 7.1 Hz, 2H), 7.20 (t, $J$ = 7.4 Hz, 1H), 7.04 (d, $J$ = 7.5 Hz, 2H), 5.10 (s, 1H), 4.93 (s, 1H), 3.71-3.70 (m, 1H), 2.95-2.93 (m, 1H), 2.65-2.59 (m, 2H), 2.39-2.36 (m, 1H), 2.04-
2.00 (m, 1H), 1.29 (s, 3H), 1.17 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 220.7, 210.7, 153.1, 146.3, 129.0 (2C), 128.0 (2C), 126.8, 115.2, 57.9, 57.6, 48.5, 48.1, 47.8, 40.3, 20.7, 16.6, 14.4; IR (thin film): ν 1740, 1708 cm$^{-1}$; HRMS (ESI) calcd for [C$_{19}$H$_{22}$O$_2$Na]$^+$: 305.1512, found: 305.1500. For 130: $^1$H NMR (500 MHz, CDCl$_3$): δ 7.30 (t, J = 7.3 Hz, 2H), 7.23 (t, J = 7.0 Hz, 1H), 7.09 (d, J = 7.6 Hz, 2H), 6.85 (dq, J = 14.8, 7.3 Hz, 1H), 6.11 (d, J = 15.5 Hz, 1H), 3.86 (s, 1H), 2.51-2.41 (m, 2H), 1.85 (d, J = 6.9 Hz, 3H), 1.75 (s, 6H), 1.17 (d, J = 7.2 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 209.3, 201.5, 170.7, 143.5, 142.4, 136.4, 130.5, 129.0 (2C), 127.9 (2C), 127.1, 58.4, 53.0, 44.5, 18.4, 15.6, 15.5, 8.4; IR (thin film): ν 1710, 1650 cm$^{-1}$; HRMS (ESI) calcd for [C$_{19}$H$_{22}$O$_2$Na]$^+$: 305.1512, found: 305.1507. For 131: $^1$H NMR (500 MHz, CDCl$_3$): δ 7.28 (d, J = 7.9 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 7.08 (d, J = 7.5 Hz, 2H), 3.96 (s, 1H), 2.87-2.83 (m, 1H), 2.68-2.59 (m, 4H), 2.42 (dd, J = 11.8, 4.4 Hz, 1H), 2.06-2.02 (m, 1H), 1.79 (s, 3H), 1.31 (d, J = 7.0 Hz, 3H), 1.23 (d, J = 6.4 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 213.1, 210.2, 175.8, 141.0, 135.7, 129.1 (2C), 127.4, 127.2 (2C), 64.6, 54.1, 53.5, 45.7, 35.9, 35.0, 23.7, 17.5, 9.4; IR (thin film): ν 1705, 1640 cm$^{-1}$; HRMS (ESI) calcd for [C$_{19}$H$_{22}$O$_2$Na]$^+$: 305.1512, found: 305.1498.
Chapter 4 – The Study of Cyclohexyne

4.1 Introduction

Angle-strained cycloalkynes have been studied for quite some time, yet their use in organic synthesis has been limited. Cyclooctyne is the smallest isolable unsubstituted cycloalkyne, whereas cycloheptyne, cyclohexyne (144) and cyclopentyne can only be prepared in situ and reacted immediately with nucleophiles. Cyclohexyne is of particular interest because its aromatic analog, benzyne, has been studied and used extensively in synthesis, whereas cyclohexyne has been used very little.

Experiments by Wittig and Harboth involving elimination-addition reactions of 1-chlorocyclohexene (145) with phenyllithium were described as proceeding via a putative cyclohexyne intermediate (Scheme 45). This hypothesis was later corroborated by experiments using $^{14}$C-labeled precursors of 145, providing strong evidence for a cyclohexyne intermediate. This method of forming cyclohexyne by the β-elimination of a halogen has since been used to form 1-aminated, and 1-propargyl cyclohexene derivatives. This method often yields multiple byproducts, presumed to be due to an isomerization of 144 to the cycloallene.
It was later shown by Caubere and coworkers that base-mediated elimination of 1-choro-substituted cyclohexene derivatives could also undergo (2+2) additions with enolates (Scheme 46). Depending on which cyclohexyne and enolate precursors were used, mixtures of the (2+2) adduct 146 and a ring expanded product 147 were formed in different proportions.

Forming (2+2) adducts like 146, or ring expanded products like 147, is more synthetically attractive than simple elimination-addition reactions because the products are more complex and give rise to rings that are more synthetically difficult to achieve, such as cyclobutene in 146.

The harsh basic conditions and low yields are drawbacks to this methodology, and thus an alternative method that was analogous to benzyne synthesis was employed. Guitián and coworkers generated 144 by the fluoride-
assisted β-elimination of a trimethylsilyl-substituted vinyl triflate 148, which was trapped using the simple α-pyrone derivative 149 to form 150 (by intermediate 151) via a (4+2) Diels-Alder reaction (Scheme 47). This was the first, and until recently, only known (4+2) reaction of cyclohexyne.

Scheme 47. (4+2) Cycloaddition of an α-pyrone to cyclohexyne.

The formation of cyclohexyne via base-promoted elimination of a substituted cyclohexene was later improved by the use of a hypervalent iodide salt. Fujita et al. were the first to report the formation of 144 via the β-elimination of a cyclohexenyl(phenyl)iodonium tetrafluoroborate salt 152 using milder basic conditions than 1-chlorocyclohexene had required. This resulted in less isomerization to the allene and better yields of elimination-addition products, although often mixtures of regioisomers were produced (Scheme 48). The regioselectivity was hypothesized to be the result of the difference in LUMO populations between the two carbons of the cyclohexyne.
Scheme 48. The generation and trapping of cyclohexyne from iodonium salt 152.

Cyclohexyne 144 generated from iodonium salt 153 was also shown to undergo (2+2) additions with enolates.\textsuperscript{129} When KOCE\textsubscript{3} was used to generate 144, ring expanded products were predominantly observed (Table 5).
Table 5. Ring-expanded cyclic ketones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Substrate 1" /></td>
<td><img src="image2.png" alt="Product 1" /></td>
<td>67&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Substrate 2" /></td>
<td><img src="image4.png" alt="Product 2" /></td>
<td>76&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Substrate 3" /></td>
<td><img src="image6.png" alt="Product 3" /></td>
<td>64&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Substrate 4" /></td>
<td><img src="image8.png" alt="Product 4" /></td>
<td>51&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Substrate 5" /></td>
<td><img src="image10.png" alt="Product 5" /></td>
<td>74&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Combined yield with its deconjugated isomer. <sup>b</sup> Cyclobutene adduct isolated and opened in a successive step. <sup>c</sup> Product was obtained as a 2.5:1 mixture of E and Z isomers.
4.2 Metal Complexes of Cyclohexyne

The previous examples are indirect evidence for the existence of cyclohexyne as a short-lived intermediate, but cyclohexyne cannot be isolated and characterized due to its highly reactive nature. Cyclohexyne can, however, complex to transition metals, which allows its characterization by x-ray crystallography, and the complex can be used in organometallic reactions. The first transition metal complexes of cyclohexyne reported were platinum complexes (Scheme 49). Treatment of 1,2-dibromocyclohexene with sodium amalgam in the presence of Pt(PPh₃)₃ generated the η²-complex 154, which could then be treated with TFA to form the σ-cyclohexenyl complex 155. The triphenylphosphine ligands of 154 were substituted for 1,2-bis(diphenylphosphino)ethane (dppe or diphos) to generate 156, which was more susceptible to attack by weak acids, such as methanol that formed the σ-cyclohexenyl complex 157.

Scheme 49. Cyclohexyne complexes with platinum.
Similar complexes have also been made using palladium \([\text{Pd(PPh}_3)_4]^{135}\) and nickel \([\text{Ni(}\eta^2\text{-C}_2\text{H}_4)(\text{PPh}_3)_3, \text{Ni(}\eta^2\text{-C}_2\text{H}_4)(\text{PEt}_3)_3, \text{and Ni(}\eta^2\text{-C}_2\text{H}_4)(\text{dcpe})]^{136}\) all of which have been useful in derivatizing cyclohexyne into more functionalized species.\(^{137}\) Platinum complexes, for example, reacted with dimethyl acetylenedicarboxylate (DMAD), carbon dioxide and acrolein to form insertion products \(158, 159\) and \(160\), respectively (Scheme 50). Furthermore, nickel complexes undergo two insertion reactions. Nickel \(\eta^2\)-complex \(161\) was able to undergo an insertion reaction with carbon dioxide to form \(162\), which was then converted to \(163\) by the insertion of DMAD.
4.3 Applications of Cyclohexyne in Total Synthesis

One of the benefits of cyclohexyne as an electrophile is it provides a way of appending a six-membered ring. Carreira and coworkers had shown that Fujita’s method of generating cyclohexyne could be used to expand five-membered ring enolates to cyclohexene-appended seven-membered rings, which they used to produce the core of sandresolide A. They later used this methodology in the
divergent syntheses of guanacastepenes N and O. The guanacastepenes are a structurally diverse class of diterpenes that have activity against drug-resistant strains of *E. faecalis* and *S. aureus*. Guanacastepenes N and O are interesting from a synthetic point of view, in that they contain annealed five-, seven-, and six-membered rings. Guanacastepenes N 164 and O 165 are diastereomeric at C-13 (denoted by an asterisk in Scheme 51).

Scheme 51. Retrosynthesis of guanacastepenes N and O.

In their retrosynthetic analysis, the hydroxyl and acetate appendages were envisioned to be installed at a late stage into intermediate 166. Previous work by Gampe *et al.* highlighted that annealed seven-, and six-membered rings could be obtained by the (2+2) cycloaddition of cyclohexyne to the enolate of a five-membered ring, followed by a ring opening (which occurred spontaneously in some instances, but could also be induced by the addition of tBuOK). Thus, intermediate 166 was seen as the product of a cycloinsertion of cyclohexyne 144 with 167.

Because 167 contains two enolizable ketones, and therefore cycloinsertion could potentially occur onto either of the five-membered rings, the ketal protected analog 168 would have to be used instead. They managed to prepare precursor 168
in six steps (31% overall yield) from commercially available methyl 3,3-dimethylacrylate. The enolate and cyclohexyne were generated \textit{in situ} using iodonium salt 153 and KOCEt$_3$, which upon mixing formed the (2+2) adduct 169 (Scheme 52). The cyclobutene would not undergo ring-opening using the typical conditions (tBuOK, THF), thus alternative methods were pursued. They were able to open the ring using Fe$_2$(CO)$_9$ and then the resulting double bond was isomerized using DBU to form the conjugated product 170 in 51% yield.

\begin{center}
\textbf{Scheme 52. The cycloinsertion of cyclohexyne in the total synthesis of guanacastepenes N and O.}
\end{center}

The syntheses of guanacastepenes N and O were accomplished from 170 in fourteen more steps, which were largely due to the difficulty in functionalizing the six-membered ring.

\begin{center}
\textbf{Figure 11. Batrachotoxin.}
\end{center}
Devlin and Du Bois also made use of cyclohexyne in their modular synthesis of core structures of batrachotoxin (Figure 11). Their approach made use of a furan-appended intermediate that could undergo (4+2) reactions with various dieneophiles, including cyclohexyne. They initially tried the Diels-Alder reaction at a late stage using intermediate 172 and cyclohexyne precursor 148, but they obtained a low yield with low facial selectivity, forming a 3:1 mixture of diastereomers 173 (Scheme 53). They then tried the Diels-Alder reaction onto 174, a synthetic precursor to 172, and observed much greater selectivity (20:1 $dr$) producing 175 in nearly quantitative yield. They also mentioned that when the same reaction was carried out with iodonium salt 153 as a cyclohexyne precursor, no trace of 175 was observed.

Scheme 53. Synthesis of batrachotoxin core structures.

Although the use of cyclohexyne in total synthesis is limited, it could have a much higher impact if more was understood about its reactivity and selectivity. Benzyne has had considerable impact in the scientific community ("benzyne" has
been cited over 3000 times in the literature, whereas “cyclohexyne” has barely been cited 100 times), because cyclohexyne has not yet been studied thoroughly.

4.4 Results and Discussion

4.4.1 Introduction

The overall goal of this project was to examine reactions of cyclohexyne and substituted derivatives with dienes to better understand their (4+2) reactions. Aside from the work of Atanes et al. on α-pyrones (two examples)\textsuperscript{125} and the work of Devlin and Du Bois on batrachotoxin (two examples),\textsuperscript{139} there are no other examples of cyclohexyne participating in Diels-Alder reactions. The method chosen for generating cyclohexynes was via trimethylsilyl vinyltriflates, because this method avoids the strongly basic conditions that may not be compatible with other functional groups, and it is the only method known to produce (4+2) cycloadducts.

4.4.2 Diels-Alder Reactions of Cyclohexyne 144

Cyclohexyne precursor 148 was prepared starting from cyclohex-2-en-1-one in four steps. 1-Bromocylohex-2-enone (176) was made in 97% yield by the bromination and subsequent dehydrobromination of cyclohex-2-en-1-one (Scheme 54).\textsuperscript{140} The product decomposed if left at rt over 24 h, but it could be stored at –20 °C for more than a year. The ketone function of 176 was then protected as an ethylene glycol ketal, following a standard procedure, forming 177.\textsuperscript{141} This protection was necessary to prevent the formation of an enolate in the following
step. With ketal 177 in hand, a lithium-halogen exchange reaction was undertaken to generate an organolithium intermediate, which was trapped subsequently with trimethylsilyl chloride, forming 178 upon hydrolysis of the ketal during workup. 142 A Wurtz-Fittig coupling using sodium metal and trimethylsilyl chloride was also done, but the yield was slightly lower and the reaction itself was more hazardous. 143 A 1,4-reduction of 178 was effected smoothly using L-Selectride (lithium tri-sec-butylborohydride), and the resulting enolate was trapped by a triflyl-delivering agent forming 148. 144 Yields of 148 were initially quite low due to decomposition on silica gel during chromatography. This was circumvented by treating the silica gel with a small amount of triethylamine before loading the column.

Scheme 54. Preparation of cyclohexyne precursor 148.

The literature was sometimes vague and often inconsistent on the conditions used to generate cyclohexyne from trimethylsilyl vinyltriflates. Atanes et al. did not specify the solvent used, but they did specify that reactions with α-pyrone using CsF required heating between 90-100 °C and a reaction time of over 30 h (see Scheme 47, page 117). 125 Peña and coworkers reported that cyclohexyne
oligomerized when generated using CsF at rt in acetonitrile, forming its trimer 179 in 30% yield (they stated that using 10 mol% of Pd(PPh$_3$)$_4$ increased the yield of trimer to 64%) (Scheme 55 A).$^{145}$ They also mentioned that the tetramer 180 could also be formed, but only in the presence of Ni(COD)$_2$ (10 mol%) (Scheme 55 B).$^{146}$ These results were in contrast with a previous report by Wittig and Mayer that stated that tetramerization of cyclohexyne occurred when 1,2-dihalogenated cyclohexenes were reacted with magnesium or lithium amalgam.$^{147}$ Yoshida et al. performed distannylation reactions of cyclohexynes generated using KF (3 equiv.) and 18-crown-6 (3 equiv.), with hexabutylditin, Pd(OAc)$_2$ (2 mol%), and tert-octyl isocyanide (30 mol%) in THF at rt, with yields ranging from 60-90% over the course of three to four hours, forming 181 (Scheme 55 C).$^{148}$ Finally Allan et al. generated cyclohexyne using CsF in acetonitrile with methyl acetoacetate with heating to 80 °C to give acyl-alkylated cyclohexene 182, followed by condensation with ammonia to provide 3-hydroxyisoquinoline product 183 (Scheme 55 D).$^{149}$

Based on these results, it would appear that cyclohexyne could be generated at rt in acetonitrile or in tetrahydrofuran, but that increasing the temperature might be necessary in order to induce certain reactions. Therefore, reactions were carried out in both solvents, using three equiv. of CsF and 148 without any nucleophile, to see which compounds would be produced and in what sort of yield they could be obtained. This would give an approximate yield of cyclohexyne 144. CsF, even after drying under reduced pressure at 100 °C for several hours, had poor solubility in both solvents, and TLC analysis showed no sign of conversion to cyclohexyne oligomers. The reaction mixtures were then heated to 60 °C to induce reaction, but
the only reaction that appeared to work was in THF. The result of this was a 17% yield of tetramer 180 and no sign of trimer 179. These conditions were then used to trap dienes, but the yields were low and the resulting reaction mixtures were always contaminated with about 20% of the tetramer 180.

Table 6. Reactions of cyclohexyne with dienes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diene</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Furan" /></td>
<td><img src="image2" alt="Product 184" /></td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Pyrrole" /></td>
<td><img src="image4" alt="Product 185" /></td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Thiophene" /></td>
<td><img src="image6" alt="Product 186" /></td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Acetate" /></td>
<td><img src="image8" alt="Product 187" /></td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Benzene" /></td>
<td><img src="image10" alt="Product 188" /></td>
<td>20</td>
</tr>
</tbody>
</table>

Reaction conditions: 148, diene (3 equiv.), CsF (3 equiv.) in THF heated to 60 °C for 20 h.

Cyclohexyne was generated in the presence of three heteroaromatic nucleophiles; furan, pyrrole and thiophene. The reaction with furan gave the (4+2) product 184 in 31% yield, whereas pyrrole and thiophene did not yield any of the
expected products 185 and 186. The yield of 184 appeared low when compared to Devlin and Du Bois’ yield of 99% when the reaction was done on their more complex furan derivative 174 (see Scheme 53, page 125). The reason that their yield was so high was possibly because they used three equiv. of cyclohexyne precursor 148, and so their limiting reagent was the furan derivative 174. Therefore, it is possible that one equiv. of 148 would have only formed their product 175 in one-third the yield.

Cyclohexyne also reacted with acetate-substituted 1,3-butadiene 187, which was prepared from methyl vinyl ketone and acetic anhydride, providing 188 in 35% yield. 1,3-Cyclohexadiene also reacted with cyclohexyne, providing 189 in 20% yield. The lack of functional groups on 189 made it difficult to ionize it for mass spectrometry using ESI, thus a silver complex was formed by stirring 189 in a 1:1 solution of methanol and acetonitrile containing AgNO₃.

Because the yields were not as high as desired, an alternative source of fluoride was used to generate cyclohexyne. When 148 was allowed to react with tetrabutylammonium fluoride (TBAF) at rt, the reaction was conducted in less than five minutes and formed tetramer 180 in 50% yield (Scheme 56). This result suggested that cyclohexyne was generated more efficiently from TBAF because CsF only gave 180 in 17% yield. This increase in yield was likely due to the increased solubility of the fluoride anion. When the same conditions were employed using three equiv. of furan as a nucleophile to trap cyclohexyne, it was disappointing that only 20% of the trapped product 184 was obtained, accompanied by 60% of the tetramer. The yield of 184 was increased to 72% by running the
reaction with furan as the solvent, which suppressed the formation of tetramer to only 5%. This method, however, required a large excess of TBAF.

Scheme 56. Generating cyclohexyne using TBAF.

4.4.3 Diels-Alder Reactions of a Substituted Cyclohexyne

The regioselectivity of cyclohexynes in elimination-addition reactions was studied using substituted iodonium salt precursors, and the results were limited to seven examples.\textsuperscript{128} The selectivity was hypothesized to result from LUMO populations.\textsuperscript{127,128,150} The only example of regioselectivity in (2+2) reactions of a substituted cyclohexyne was reported by Fixari et al. in 1976 using a chloro-substituted cyclohexene (see Scheme 46, page 116). Since the (2+2) reaction was likely to be a two-step process, it was postulated that the first bond was made from
the enolate to the less sterically encumbered carbon of the cyclohexyne. A recent study from Medina et al. observed regioselectivity in a (3+2) reaction of benzyloxy-substituted cyclohexyne 190 with benzyl azide forming a 5:1 mixture of products favouring 191 over 192 (Scheme 57). The reaction’s preference for 191 was explained through computational studies, which showed that the transition state leading to 191 was 2.8 kcal/mol lower than the transition state leading to 192. Regio- and diastereoselectivity in (4+2) reactions of cyclohexyne have not been studied.

Scheme 57. (3+2) Reaction of 193 with benzyl azide.

The vertical plane of symmetry that cuts through the triple bond of cyclohexyne 144 makes it impossible to observe any regioselectivity in these (4+2) reactions, therefore substituted derivatives were sought for this purpose. They were 3-methylcyclohexyne (193), 3,3-dimethylcyclohexyne (194) and 3,5,5-trimethylcyclo-hexyne (195) (Figure 12).
The preparation of these substituted cyclohexynes was envisioned to proceed via the same reactions as those that were employed for the formation of 148. The monosubstituted cyclohexyne precursor 196 could be prepared from 6-methylcyclohex-2-en-1-one 197, the disubstituted cyclohexyne precursor 198 could be prepared from 6,6-dimethylcyclohex-2-en-1-one 199, and the trisubstituted cyclohexyne precursor 200 could be prepared from isophorone 201 (Scheme 58).
The methyl-substituted cyclohexenones 197 and 199 were obtained from the methylation of cyclohex-2-enone using lithium diisopropylamide (LDA) and iodomethane (Scheme 59).151 Bromination of 197 and 199 provided 202 and 204, respectively, but, protection as their ethylene glycol ketals, 203 and 205, was unsuccessful. Attempts of forming the desired ketals using Noyori’s conditions that uses the bis-TMS ethylene glycol derivative 206 were also unsuccessful. It was presumed that the ketone was simply too sterically congested for ketalization, and thus a new approach needed to be taken.

Scheme 59. Attempts at preparing methylated cyclohexynes from 2-cyclohexenones.
To avoid the issue of having a congested ketone for ketalization, methylation was to be done at a later stage. The same methylation conditions were employed using the trimethylsilyl-substituted cyclohexenone 178, forming monomethylated compound 207 and dimethylated compound 208 (Scheme 60). Attempts at trapping the enolates of 207 and 208 with PhNTf₂ did not produce any of the desired compounds 209 and 211, but instead the reduced compounds 210 and 212 were recovered. This result indicated that the reduction step had occurred, but the enolate had difficulty in accepting a triflyl substituent from PhNTf₂. Therefore, a more reactive triflyl delivering agent, Comins reagent 213, was tested, but, alas, the desired triflates were not produced.
Scheme 60. Attempts at forming methyl-substituted cyclohexyne precursors.

A new approach was undertaken to install the methyl groups at the 3-position instead of the 6-position. Attempts at the \( \alpha \)-bromination of 3-methylocyclohex-2-en-1-one using the same method of bromination and dehydrobromination provided 214 in only 7\% yield along with a mixture of phenols 215 and 216 (Scheme 61). Instead, 214 was formed in higher yield using tetrabutylammonium tribromide (TBATB) and potassium carbonate.\(^{154}\) Now that the methyl substituent was further away from the carbonyl, the ethylene glycol ketal 217 was obtained without any complications. It was then converted to compound 218 via a lithium-halogen exchange reaction followed by TMSCl, then reduced with L-Selectride followed by the addition of PhNTf₂ to give 219.
Scheme 61. The preparation of methyl-substituted cyclohexyne precursor 219.

Due to the low yield of 219, other reagents for 1,4-reduction were explored (Table 7). Reagents were first tested on the unsubstituted precursor 178 before attempting reactions on 218. N-Selectride (sodium tri-sec-butylborohydride) gave the best results, as 148 was produced in 96% yield. K-Selectride (potassium tri-sec-butylborohydride) produced a 1:1 mixture of 148 and the reduced product 220. Both LS-Selectride (lithium trisamylborohydride) and copper hydride (generated in situ by the reaction of CuI and LiAlH$_4$) gave 220 only. Since N-Selectride had given the best results with 178, it was used to generate 219 from 218, increasing the yield to 48%.
Table 7. The 1,4-reduction of 178 and the trapping of its enolate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reductant</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L-Selectride</td>
<td>148</td>
<td>61&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>N-Selectride</td>
<td>148</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>K-Selectride</td>
<td>148 + 220</td>
<td>56&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>LS-Selectride</td>
<td>220</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>CuI, LiAlH&lt;sub&gt;4&lt;/sub&gt;</td>
<td>220</td>
<td>76</td>
</tr>
</tbody>
</table>

Reaction conditions: 178, reductant (1.1 equiv.), THF, -78 °C, 1 h; then PhNTf<sub>2</sub> (1 equiv.) in THF, -78 °C → rt.  
<sup>a</sup> Addition of TMEDA resulted in a 58% yield of 148.  
<sup>b</sup> 1:1 mixture of products.

The dimethyl-substituted cyclohexyne precursor was expected to be obtained relatively simply using a Gillman reagent to methylate the β -position, while a subsequent trapping of the enolate would occur using PhNTf<sub>2</sub>. However, when 218 was reacted with Me<sub>2</sub>CuLi (generated <i>in situ</i> from CuI and MeLi),<sup>156</sup> followed by PhNTf<sub>2</sub>, no triflate product 221, nor any addition product was observed (Scheme 62). The reaction was tried again using CuBr•DMS and MeMgBr to generate the cuprate,<sup>157</sup> but again this method did not provide any triflate product 221 and only starting material was recovered. A higher order cuprate was then generated <i>in situ</i> from CuCN and MeLi,<sup>158</sup> and, although this procedure appeared to generate the addition product 222, none of the triflate product 221 was obtained, and the majority of the recovered material was the starting ketone 218. The fact that 222...
and \( \text{218} \) appeared as a single spot on TLC made it difficult to track the progress of this reaction. To see if there was any issue with reactive copper species reacting prematurely with \( \text{PhNTf}_2 \), and thus preventing the formation of the triflate, 3-methylcyclohex-2-en-1-one was reacted with \( \text{Me}_2\text{CuLi} \) followed by \( \text{PhNTf}_2 \). The result was the triflate product \( \text{223} \) in high yield. The only difference between 3-methylcyclohex-2-en-1-one and \( \text{218} \) was an \( \alpha \)-TMS substituent, and so it was likely to be inhibiting both the alkylation and \( O \)-sulfonylation steps.

**Scheme 62. Attempts at generating a dimethyl-substituted cyclohexyne precursor.**
The methyl-substituted cyclohexyne precursor 219 was reacted with furan, as furan had worked well with an unsubstituted cyclohexyne, to see if there would be any diastereoselectivity. The result was a complex mixture of tetrameric diastereomers 224 and a 2:1 $dr$ of the Diels-Alder adduct 225 (Scheme 63).

![Scheme 63. Diastereoselective Diels-Alder of a methyl-substituted cyclohexyne.](image)

Although it is difficult to deduce which diastereomer was predominantly formed, the fact that this reaction had any selectivity at all was surprising. Computational results suggested that a reactive substrate like cyclohexyne would have almost no energy barrier for reaction therefore no selectivity.\(^{159}\) This *endo-exo* selectivity was essentially controlled by the relative position of the methyl group, where one of the transition states had the methyl group pointing toward the diene moiety 226, and the other had the methyl group pointing toward the oxygen 227 (Figure 13).
Before continuing with more examples, it was desirable to assess if there was any way that the formation of the tetramer could be suppressed.

### 4.4.4 Tetramerization of Cyclohexyne

The formation of tetramer in such high yields was a little puzzling. According to Wittig and Weinlich, the tetramer 180 is formed by the Diels-Alder reaction of two molecules of the dimer 228, whereas the trimer 179 is formed by the rapid conversion of the intermediate 229, which is the result of a Diels-Alder reaction between the dimer 228 and cyclohexyne 144. (Scheme 64).\textsuperscript{160} The dimer 228 is a cyclobutadiene derivative, and it would undoubtedly be less thermodynamically stable than the product of a simple Diels-Alder of cyclohexyne 144 with an electron rich diene, such as furan.
The reaction of cyclohexyne precursor 148 with TBAF produced more tetramer at rt than CsF at 60 °C, and, as previously noted, CsF did not dissolve well in THF, therefore it was possible that the formation of the tetramer could be suppressed by controlling the rate that cyclohexyne 144 was generated. To this end, a series of halogen-substituted cyclohexene triflates 230 was prepared for lithium halogen-exchange reactions, so that cyclohexyne could be generated by the β-elimination of the triflate 231 (Scheme 65). Since this method of generating cyclohexyne would be done at colder temperatures, it was thought that cyclohexyne might be generated much more slowly. Rates of interchange have been observed to decrease from I > Br > Cl and never with F.161 Although the mechanisms by which these exchanges proceed is still under debate, the balance of evidence suggests that lithium’s exchange with iodine and bromine proceeds through an “ate-complex” whereas chlorine, although often unreactive in lithium-halogen exchanges, often initiates radical-mediated reactions.161 This process would also generate cyclohexyne in less steps than the previously used method (only three steps from 232).
Scheme 65. Generating cyclohexyne from a halogenated cyclohexene triflate.

The bromo-substituted triflate 233 was prepared from 176, then reacted with $n$-butyllithium in the presence of three equiv. of 2,3-dimethylbutadiene in the hope of generating the Diels-Alder adduct 234 (Scheme 66). Unfortunately, this reaction produced a large amount of tetramer 180, as well as a small amount of trimer 179 but none of the desired compound 234.

Scheme 66. Results of the generation of cyclohexyne from bromocyclohexene triflate 233.

The iodo-substituted analog was made from the $\alpha$-iodination of cyclohexenone to form 235 in 91% yield (Scheme 67). This was then converted to the cyclohexyne precursor 236 with L-Selectride and PhNTf$_2$ in a modest yield of 33%. The reaction with three equiv. of 2,3-dimethylbutadiene was unsuccessful in forming a Diels-Alder product, but trimer 179 was formed in 22% yield along with 55% of the tetramer 180.
Scheme 67. The generation of cyclohexyne from iodocyclohexene triflate 236.

To finish off this series of halogen-substituted vinyl triflates, a chloro-substituted derivative was also prepared (Scheme 68). Cyclohexenone was α-chlorinated, generating 237 in 47% yield.\textsuperscript{162} This was then reduced with L-Selectride and the resulting enolate was trapped with PhNTf₂, giving 238 in 52% yield. Unfortunately, 238 was not able to generate any product under the conditions.

Scheme 68. The attempted generation of cyclohexyne from chlorocyclohexene triflate 238.

Although these methods did not provide any Diels-Alder adducts, the bromo-substituted triflate 233 did provide the tetramer 180 in 80%, which is the highest yield for this molecule to date. An X-ray crystal structure of 180 was obtained to confirm the stereochemistry (Figure 14).
The oligomerization process did not proceed the same way with the halogen-substituted cyclohexyne precursors 233 and 236 as well as the trimethylsilyl-substituted cyclohexyne precursor 178. The halogen-substituted compounds produced oligomers in roughly equal amounts, although the bromo-substituted compound 233 produced the tetramer in 80% yield, whereas the iodo-substituted compound 236 produced the tetramer in 55% yield (along with 22% trimer). The trimethylsilyl-substituted precursor 178 produced the tetramer in 50% yield using TBAF, but only in 17% yield when using CsF. To better understand the tetramerization process, some computational studies using the ω B97xD/6-311G(d,p) level of theory, were undertaken by Stephen Driscoll, an MSc student in our group, who examined the energies associated with the possible transition states during the course of this reaction. The results suggested that dimerization likely
occurs from the attack of carbanion 239 onto cyclohexyne 144, forming 240 with a barrier of only 2.4 kcal/mol (Scheme 69). This would then undergo a $4\pi$-electrocyclization to generate the intermediate 241 with a transition state barrier of 32.9 kcal/mol (when calculated using formate rather than triflate). This intermediate would then eliminate the triflate to form the dimer 228, which would then undergo a Diels-Alder reaction with another dimer, which was calculated to have a $\Delta G^\ddagger$ of only 0.8 kcal/mol.

**Scheme 69. Computationally derived mechanism for the formation of tetramer 180.**

The energy barrier for the initial step of the dimerization is fairly low, and so it would seem that the best way to avoid this process would be to minimize the concentration of cyclohexyne. This could encourage cyclohexyne to react with the diene if the concentration of carbanion is very low.
4.5 Conclusions and Future Work

The library of Diels-Alder cycloadducts of cyclohexyne 144 with dienes was expanded to include a furan, an acetate-substituted 1,3-butadiene, and 1,3-cyclohexadiene, albeit that these were formed along with significant amounts of tetramer 180. A methyl-substituted cyclohexyne was also prepared and its reaction with furan provided a 2:1 mixture of diastereomers, but a complex mixture of tetramers were also obtained in relatively high yield. Many different methods were assessed in an attempt to suppress the formation of the tetramer, including the use of TBAF as a source of fluoride, increasing the amount of diene, and using halogen-substituted cyclohexene triflates in lieu of the trimethylsilyl-substituted compound 148. Although increasing the amount of diene did increase the yield of (4+2) product, a more atom-economical procedure would be best. The end goal is to be able to form complex cyclohexyne derivatives so they can better serve in synthesis, and it would be ideal if the diene to dienophile ratio could be 1:1.

To this end, future work will be to look at diluting TBAF at various concentrations and adding the mixture over a longer period of time to a solution of cyclohexyne precursor 148 and diene. If the cyclohexyne is generated slowly by this method, it should minimize any interaction it could have with another cyclohexyne molecule or with a carbanion intermediate. Once the formation of tetramer is significantly reduced, a larger library of (4+2) cycloadducts will be produced.
4.6 Experimental

4.6.1 General Information

Reactions were carried out using oven-dried Teflon-coated magnetic stir bars in oven-dried glassware (150 °C), sealed with rubber septa under a positive nitrogen atmosphere. Elevated temperatures were maintained using a silicone oil bath controlled with a thermostat device. Temperatures of 0 and –78 °C were achieved using ice/water and ethyl acetate/liquid nitrogen, respectively. Concentration in vacuo was achieved using a rotary evaporator (22 mmHg) with residual solvent being removed under high vacuum (5 mmHg).

All reagents were purchased from Sigma-Aldrich, Strem Chemicals, or Alfa Aesar and were used without further purification. Tetrahydrofuran (THF) was distilled over sodium benzophenone under a dry nitrogen atmosphere. CH$_2$Cl$_2$ was distilled over calcium hydride under a dry nitrogen atmosphere. Thin layer chromatography (TLC) was performed using 250 µm aluminum-backed F$_{254}$ silica gel plates from SiliCycle. The plates were visualized by ultraviolet light (254 nm) and treated with o-vanillin or potassium permanganate stains followed by heating on a hot plate. Flash chromatography was carried out on 230–400 mesh (40–63 µm) silica gel from SiliCycle.

Melting points (uncorrected) were acquired using a Fisher-Johns apparatus. $^1$H and $^{13}$C NMR spectra were recorded from CDCl$_3$ solutions on a Bruker Avance 500 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm).
downfield from tetramethylsilane and are referenced to the solvent peak (for CDCl₃, ¹H NMR: 7.26 ppm, ¹³C NMR: 77.16 ppm). High-resolution mass spectra (HRMS) were obtained on a Bruker microTOF Focus orthogonal ESI-TOF mass spectrometer. The X-ray crystal structure was provided by Dr. T. Stanley Cameron.

Structures were determined using ¹H and ¹³C NMR spectra, including two-dimensional NMR experiments (COSY, HSQC and HMBC).

### 4.6.2 Preparation and Characterization Data

#### 2-Bromocyclohex-2-en-1-one (176)

A solution of bromine (3.24 mL, 63.2 mmol) in CH₂Cl₂ (160 mL) was added dropwise over 1 h to a solution of cyclohex-2-en-1-one (6.0 mL, 62 mmol) in CH₂Cl₂ (160 mL) cooled to 0 °C. Triethylamine (14.4 mL, 103.5 mmol) was then added to the reaction mixture, and the mixture was stirred at rt for 1.5 h. The reaction was then quenched with aqueous 1 M HCl (100 mL) and stirred an additional 10 min. The mixture was washed with brine (100 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude solid was recrystallized from a solution of 25% ethyl acetate in hexanes to give 176 (10.5 g, 97%) as a colourless solid. mp: 74-75 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.41 (t, J = 4.5 Hz, 1H), 2.60 (t, J = 6.7 Hz, 2H), 2.43 (q, J = 5.3 Hz, 2H), 2.05 (quintet, J = 6.5 Hz, 2H); ¹³C NMR
(126 MHz, CDCl₃): δ 191.4, 151.4, 123.9, 38.4, 28.4, 22.7. These data match those in the literature.¹⁶³

6-Bromo-1,4-dioxaspiro[4.5]dec-6-ene (177)

para-Toluenesulfonic acid (0.16 g, 0.82 mmol) was added to a solution of ketone 176 (2.87 g, 16.4 mmol) and ethylene glycol (1.83 mL, 32.8 mmol) in benzene (200 mL). The solution was heated under reflux over 14 h with azeotropic removal of water using a Dean-Stark apparatus filled with 4 Å molecular sieves. The solution was cooled to rt, and the acid was neutralized by addition of triethylamine (2 mL). The organic solution was washed with water (2 × 100 mL) and brine (100 mL), dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash chromatography (33% ethyl acetate in hexanes) to provide 177 (3.08 g, 86%) as a colourless oil: ¹H NMR (500 MHz, CDCl₃): δ 6.32 (t, J = 4.1 Hz, 1H), 4.18-4.16 (m, 2H), 3.98-3.95 (m, 2H), 2.09-2.06 (m, 2H), 1.91-1.88 (m, 2H), 1.79-1.74 (m, 2H); ¹³C NMR (126 MHz, CDCl₃): δ 136.2, 124.7, 105.9, 65.9, 35.7, 27.6, 20.4. These data match those in the literature.¹⁶⁴
A solution of \( n \)-butyllithium (2.5 M in hexanes, 5.8 mL) was added dropwise over 10 min to a solution of ketal 177 (2.68 g, 12.2 mmol) in THF (40 mL) at –78 °C. A solution of chlorotrimethylsilane (2.93 mL, 23.2 mmol) in THF (10 mL) was then added to the mixture, which was stirred an additional 5 min at –78 °C before allowing the solution to attain rt. The reaction mixture was washed with water (20 mL), aqueous saturated sodium bicarbonate (20 mL), then brine (20 mL) before drying over MgSO\(_4\) and concentrating \textit{in vacuo}. The residue was purified by flash chromatography (10% ethyl acetate in hexanes) to provide 178 (1.45 g, 71%) as a colourless oil: \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.06 (t, \( J = 3.9 \) Hz, 1H), 2.29-2.27 (m, 2H), 2.25-2.22 (m, 2H), 1.87 (quintet, \( J = 6.5 \) Hz, 2H), 0.01 (s, 9H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \( \delta \) 202.7, 158.4, 142.0, 38.8, 27.4, 23.0, -1.3. These data match those in the literature.\(^{143}\)
2-(Trimethylsilyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (148)

L-Selectride (1 M in THF, 9.0 mL) was added dropwise to a solution of α-silyl ketone 178 (1.45 g, 8.60 mmol) in THF (25 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min before adding in a solution of PhNTf₂ (3.23 g, 9.0 mmol) in THF (25 mL). The reaction mixture was then allowed to attain rt and it was stirred an additional 30 min. The mixture was diluted with pentane (100 mL) and washed with water (3 × 25 mL) and the combined aqueous washes were re-extracted with pentane (20 mL). The combined organic extracts were washed with aqueous 10% NaOH (2 × 25 mL), followed by brine (25 mL), then dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography (2.5% triethylamine in pentane) to give 148 (1.58 g, 61%) as a colourless oil.* ¹H NMR (500 MHz, CDCl₃): δ 2.40-2.38 (m, 2H), 2.20-2.17 (m, 2H), 1.77-1.72 (m, 2H), 1.59-1.55 (m, 2H), 0.18 (s, 9H); ¹³C NMR (126 MHz, CDCl₃): δ 154.6, 128.1, 118.5 (q, J = 320 Hz), 28.57, 28.41, 23.2, 21.9, -1.2. These data match those in the literature.¹³⁹

* A yield of 96% was obtained when N-Selectride was used in lieu of L-Selectride.
Method A: A solution of cyclohexyne precursor 148 (0.36 g, 1.2 mmol) in THF (10 mL) was added to a stirred suspension of CsF (0.55 g, 3.6 mmol) in THF (10 mL) at rt. The solution was heated to 60 °C and stirred for 24 h. The mixture was diluted with pentane (20 mL), then washed with water (20 mL). The aqueous phase was re-extracted with pentane (2 × 15 mL), and the combined organic phases were dried over MgSO₄, then concentrated *in vacuo*. The residue was purified by flash chromatography (pentane) to give 180 (16 mg, 17%) as a colourless solid.

Method B: Tetrabutylammonium fluoride (1 M in THF, 0.9 mL) was added to cyclohexyne precursor 148 (0.14 g, 0.45 mmol) at rt. The mixture was stirred for 5 min, then diluted with pentane (10 mL), and then washed with water (10 mL). The aqueous phase was re-extracted with pentane (2 × 10 mL), and the combined organic phases was dried over MgSO₄, then concentrated *in vacuo*. The residue was purified by flash chromatography (pentane) to give 180 (18 mg, 50%) as a colourless solid. mp: 128-132 °C; ¹H NMR (500 MHz, CDCl₃): δ 2.19 (dd, *J* = 13.9, 4.7 Hz, 2H), 1.87-1.82 (m, 4H), 1.71-1.68 (m, 4H), 1.65-1.56 (m, 12H), 1.39-1.33 (m, 2H), 1.30-1.25 (m, 2H), 1.23-1.18 (m, 2H), 1.17-1.12 (m, 2H), 1.02-0.93 (m,
2H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 143.7, 137.4, 48.9, 47.7, 26.8, 24.5, 23.9, 23.5, 23.4, 23.3, 22.1, 21.3. These data match those in the literature.$^{165}$

(8aR*,8bS*,12bR*,12cS*)-1,2,3,4,5,6,7,8,9,10,11,12-Dodecahydro-8b,12b-butanobenzo[3',4']cyclobuta[1',2':3,4]cyclobuta[1,2-e]biphenylene (180), and (1R*,4S*)-1,4,5,6,7,8-hexahydro-1,4-epoxynaphthalene (184)

![Diagram](image)

Method A: A solution of cyclohexyne precursor 148 (0.20 g, 0.66 mmol) and furan (0.14 mL, 1.98 mmol) in THF (8 mL) was added to a stirred suspension of CsF (0.30 g, 1.98 mmol) in THF (7 mL) at rt. The solution was then heated to 60 °C and stirred for 24 h. The reaction mixture was diluted with ether (20 mL), then washed with water (20 mL). The aqueous phase was re-extracted with ether (2 × 15 mL), and the combined organic phases was dried over MgSO$_4$, and concentrated in vacuo. The residue was purified by flash chromatography (pentane to 10% ether in pentane) to give 180 (10 mg, 18%) as a colourless solid and 184 (30 mg, 31%) as a colourless oil.

Method B: Tetrabutylammonium fluoride (1 M in THF, 0.75 mL) was added to a solution of cyclohexyne precursor 148 (0.15 g, 0.50 mmol) and furan (0.11 mL, 1.5 mmol) in THF (10 mL) at rt. The mixture was stirred for 15 min, then
was diluted with ether (20 mL), then washed with water (20 mL). The aqueous phase was re-extracted with ether (2 × 15 mL), and the combined organic phases were dried over MgSO₄, then concentrated in vacuo. The residue was purified by flash chromatography (pentane to 10% ether in pentane) to give 180 (24 mg, 60%) as a colourless solid and 184 (15 mg, 20%) as a colourless oil.

Method C: Tetrabutylammonium fluoride (1 M in THF, 7.5 mL) was added dropwise to a solution of cyclohexyne precursor 148 (0.15 g, 0.50 mmol) and furan (10 mL) at rt. The mixture was stirred an additional 15 min before removal of the solvents in vacuo. The residue was diluted with ether (20 mL), then washed with water (20 mL), then with brine (20 mL), and dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash chromatography (pentane to 10% ether in pentane) to give 180 (2 mg, 5%) as a colourless solid and 184 (53 mg, 72%) as a colourless oil. For 184: ¹H NMR (500 MHz, CDCl₃): δ 7.07 (s, 2H), 5.13 (s, 2H), 2.38-2.33 (m, 2H), 1.86-1.81 (m, 2H), 1.69-1.63 (m, 2H), 1.49-1.42 (m, 2H); ¹³C NMR (126 MHz, CDCl₃): δ 149.0, 143.8, 84.5, 24.2, 23.0; HRMS (ESI) calcd for [C₁₀H₁₂ONa]⁺: 171.0780, found: 171.0778.
Buta-1,3-dien-2-yl acetate (187)

A solution of n-butyllithium (2.5 M in hexanes, 10 mL) was added dropwise to a solution of diisopropylamine (3.84 mL, 27.3 mmol) in THF (15 mL) at –78 °C and the resulting mixture was stirred for 5 min. A solution of methyl vinyl ketone (1.85 mL, 22.7 mmol) in THF (2.0 mL) was added dropwise to the lithium diisopropylamide (LDA) solution, and the solution was stirred for 15 min at –78 °C. Acetic anhydride (2.79 mL, 29.5 mmol) was added slowly to the solution, then the mixture was allowed to slowly attain rt, and it was stirred for 15 h. The solution was diluted with pentane (20 mL), and then washed with aqueous saturated sodium bisulfate (20 mL), and brine (20 mL). The organic solution was dried over MgSO4 and concentrated in vacuo. The residue was purified by flash chromatography (10% ether in pentane) to give 187 (0.84 g, 33%) as a colourless oil. 1H NMR (500 MHz, CDCl3): δ 6.25 (dd, J = 17.2, 10.9 Hz, 1H), 5.27 (d, J = 17.2 Hz, 1H), 5.16 (d, J = 10.9 Hz, 1H), 5.01 (s, 1H), 4.92 (s, 1H), 2.22 (s, 3H); 13C NMR (126 MHz, CDCl3): δ 168.8, 151.9, 131.0, 115.4, 106.3, 20.9. These data match those in the literature.166
1,4,5,6,7,8-Hexahydronaphthalen-2-yl acetate (188)

According to the procedure for 180 + 184, method A: cyclohexyne precursor 148 (0.20 g, 0.66 mmol) and diene 187 (0.22 g, 1.98 mmol) in THF (8 mL) was added to CsF (0.30 g, 1.98 mmol) in THF (7 mL) to give 180 (11 mg, 19%) as a colourless solid and 188 (44 mg, 35%) as a colourless oil. For 188: ¹H NMR (500 MHz, CDCl₃): δ 5.37 (br s, 1H), 2.69-2.64 (m, 4H), 2.12 (s, 3H), 1.87 (br s, 4H), 1.64-1.61 (m, 4H); ¹³C NMR (126 MHz, CDCl₃): δ 169.7, 145.9, 125.1, 124.7, 111.7, 32.9, 32.1, 29.7, 29.3, 23.1, 22.9, 21.2; HRMS (ESI) calcd for [C₁₂H₁₆O₂Na]⁺: 215.1043, found: 215.1038.

(1R*,4S*)-1,4,5,6,7,8-Hexahydro-1,4-ethanonaphthalene (189)

According to the procedure for 180 + 184, method A: cyclohexyne precursor 148 (0.20 g, 0.66 mmol) and 1,3-cyclohexadiene (0.19 mL, 1.98 mmol) in THF (8 mL) was added to CsF (0.30 g, 1.98 mmol) in THF (7 mL) to give 180 (12 mg, 21%) as a colourless solid and 189 (21 mg, 20%) as a colourless oil. For 189: ¹H NMR (500 MHz, CDCl₃): δ 6.31-6.30 (m, 2H), 3.23 (br s, 2H), 2.05 (br s,
6-Methylenehex-2-en-1-one (197)

A solution of *n*-butyllithium (2.5 M in hexanes, 4.9 mL) was added dropwise to a solution of diisopropylamine (1.70 mL, 12.2 mmol) in THF (30 mL) at –78 °C and the resulting mixture was stirred for 5 min. A solution of cyclohex-2-en-1-one (1.00 mL, 10.2 mmol) in THF (60 mL) was added dropwise to the LDA solution, and the mixture was stirred for 30 min at rt before it was cooled to –78 °C. Iodomethane (3.18 mL, 51.0 mmol) was added slowly to the solution. The mixture was allowed to slowly attain rt, and then it was stirred for 12 h. Water (100 mL) was added, and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash chromatography (25% ether in pentane) to give 197 (0.84 g, 75%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃): δ 6.93-6.90 (m, 1H), 5.98 (br d, *J* = 10.0 Hz, 1H), 2.42-2.37 (m, 3H), 2.08-2.05 (m, 1H), 1.77-1.70 (m, 1H), 1.14 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 138.5, 134.6, 41.8, 27.0, 25.8, 23.5; HRMS (ESI) calcd for [C₁₂H₁₆Ag]⁺: 267.0297, found: 267.0306. These data are consistent with, and an improvement on, of those in the literature.¹⁶⁷
CDCl₃): δ 202.4, 149.7, 129.5, 41.8, 31.0, 25.6, 15.2. These data match those in the literature.¹⁵¹

6,6-Dimethylcyclohex-2-en-1-one (199)

According to the procedure for 197: n-butyllithium (2.5 M in hexanes, 1.5 mL), and diisopropylamine (0.46 mL, 3.3 mmol) in THF (10 mL) were reacted with ketone 197 (0.30 g, 2.7 mmol) in THF (20 mL). Iodomethane (0.68 mL, 11 mmol) was added to give 199 (0.16 g, 48%) as a colourless oil.¹⁶⁰ ¹H NMR (500 MHz, CDCl₃): δ 6.83 (dt, J = 10.0, 4.0 Hz, 1H), 5.88 (dt, J = 10.0, 2.0 Hz, 1H), 2.34 (tdd, J = 6.0, 4.0, 2.0 Hz, 2H), 1.80 (t, J = 6.1 Hz, 2H), 1.08 (s, 6H); ¹³C NMR (126 MHz, CDCl₃): δ 202.4, 149.7, 129.5, 41.8, 31.0, 25.6, 15.2. These data match those in the literature.¹⁶⁸
2-Bromo-6-methylcyclohex-2-en-1-one (202)

According to the procedure for 176: bromine (0.26 mL, 5.0 mmol) in CH$_2$Cl$_2$ (15 mL) was added to a solution of ketone 197 (0.55 g, 5.0 mmol) in CH$_2$Cl$_2$ (15 mL). Triethylamine (1.2 mL, 8.5 mmol) was added to give, after flash chromatography (5% ether in pentane), 202 (0.60 g, 63%) as a colourless oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.28 (t, $J = 4.5$ Hz, 1H), 2.75-2.68 (m, 1H), 2.44-2.30 (m, 2H), 2.15-1.90 (m, 2H), 1.21 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 194.3, 145.9, 131.7, 42.6, 30.5, 26.3, 15.3. These data match those in the literature.169

2-Bromo-6,6-dimethylcyclohex-2-en-1-one (204)

According to the procedure for 176: bromine (0.26 mL, 5.0 mmol) in CH$_2$Cl$_2$ (15 mL) was added to a solution of ketone 199 (0.62 g, 5.0 mmol) in CH$_2$Cl$_2$ (15 mL). Triethylamine (1.2 mL, 8.5 mmol) was added to give, after flash chromatography (5% ether in pentane), 204 (0.68 g, 67%) as a colourless oil. $^1$H
NMR (500 MHz, CDCl₃): δ 7.30 (t, J = 4.4 Hz, 1H), 2.45-2.42 (m, 2H), 1.88 (t, J = 6.0 Hz, 2H), 1.16 (s, 6H); ¹³C NMR (126 MHz, CDCl₃): δ 196.3, 149.4, 123.1, 43.1, 36.0, 25.7, 24.5. HRMS pending.

1,2-Bis(trimethylsilyloxy)ethane (206)

![TMSO~OTMS](206)

To a solution of ethylene glycol (1.7 mL, 30 mmol) in CH₂Cl₂ (150 mL) was added triethylamine (12 mL, 90 mmol) and chlorotrimethylsilane (9.5 mL, 75 mmol). The mixture was stirred at rt for 30 min, and then the precipitate was removed by suction filtration. The solid was washed with dichloromethane (3 × 20 mL) and the filtrate was concentrated in vacuo to give 206 (4.9 g, 79%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃): δ 3.64 (s, 4H), 0.11 (s, 18H); ¹³C NMR (126 MHz, CDCl₃): δ 64.1, -0.3. These data match those in the literature.¹⁷⁰
6-Methyl-2-(trimethylsilyl)cyclohex-2-en-1-one (207)

According to the procedure for 197: n-butyllithium (2.5 M in hexanes, 4.8 mL), and diisopropylamine (1.70 mL, 12.2 mmol) in THF (30 mL) were reacted with ketone 178 (1.71 g, 10.2 mmol) in THF (60 mL). Iodomethane (3.18 mL, 51.0 mmol) was added to give 207 (1.48 g, 80%) as a colourless oil. $^1$H NMR (500 MHz, CDCl₃): δ 7.09 (td, $J = 3.9, 1.0$ Hz, 1H), 2.42-2.38 (m, 2H), 2.37-2.34 (m, 1H), 2.07-2.01 (m, 1H), 1.74-1.66 (m, 1H), 1.11 (d, $J = 6.8$ Hz, 3H), 0.12 (s, 9H); $^{13}$C NMR (126 MHz, CDCl₃): δ 205.2, 157.3, 141.5, 41.9, 31.1, 27.5, 15.2, -1.2; HRMS pending.

6,6-Dimethyl-2-(trimethylsilyl)cyclohex-2-en-1-one (208)

According to the procedure for 197: n-butyllithium (2.5 M in hexanes, 4.6 mL), and diisopropylamine (1.37 mL, 9.74 mmol) in THF (20 mL) were reacted with ketone 207 (1.48 g, 8.12 mmol) in THF (40 mL). Iodomethane (1.66 mL, 32.5 mmol) was added to give 208 (1.20 g, 75%) as a colourless oil. $^1$H NMR (500 MHz,
CDCl$_3$): $\delta$ 7.02 (t, $J = 3.7$ Hz, 1H), 2.39-2.36 (m, 2H), 1.80 (t, $J = 6.1$ Hz, 2H), 1.07 (s, 6H), 0.11 (s, 9H); HRMS pending.

2-Bromo-3-methylcyclohex-2-en-1-one (214), meta-cresol (215), and 4-bromo-3-methylphenol (216)

According to the procedure for 176: bromine (2.67 mL, 50.0 mmol) in CH$_2$Cl$_2$ (130 mL) was added to a solution of 3-methylcyclohex-2-en-1-one (5.67 mL, 50.0 mmol) in CH$_2$Cl$_2$ (130 mL). Triethylamine (11.8 mL, 85.0 mmol) was added to give, after flash chromatography (25% ether in pentane), a mixture of 214 (0.66 g, 7%), 215 (1.46 g, 27%), and 216 (1.50 g, 16%), as colourless oils. For 214: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.51 (t, $J = 6.8$ Hz, 2H), 2.47 (t, $J = 6.1$ Hz, 2H), 2.11 (s, 3H), 1.95 (quintet, $J = 6.5$ Hz, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 190.9, 160.5, 122.7, 37.6, 34.1, 25.9, 21.8. These data match those in the literature. For 215: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.16 (t, $J = 7.7$ Hz, 1H), 6.79 (d, $J = 7.5$ Hz, 1H), 6.71-6.68 (m, 2H), 5.93 (br s, 1H), 2.33 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 154.9, 140.0, 129.5, 121.8, 116.2, 112.5, 21.4. These data match those in the literature. For 216: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.37 (d, $J = 8.6$ Hz, 1H), 6.76 (d, $J = 2.9$ Hz, 1H), 6.59 (dd, $J = 8.6$, 2.9 Hz, 1H), 5.93 (br s, 1H), 2.35 (s, 3H); $^{13}$C
NMR (126 MHz, CDCl$_3$): $\delta$ 155.4, 139.2, 133.1, 118.0, 115.4, 114.7, 23.0. These data match those in the literature.$^{172}$

2-Bromo-3-methylcyclohex-2-en-1-one (214)

To a solution of 3-methylcyclohex-2-en-1-one (2.95 mL, 26.0 mmol) in CH$_2$Cl$_2$ (250 mL) was added tetrabutylammonium tribromide (25 g, 52 mmol) and potassium carbonate (21.6 g, 156 mmol) at 0 °C. The reaction mixture was allowed to warm to rt and it was stirred for 48 h. The solids were filtered from the solution and washed with CH$_2$Cl$_2$ (3 × 50 mL), and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (25% ether in pentane) to give 214 (3.67 g, 75%).
6-Bromo-7-methyl-1,4-dioxaspiro[4.5]dec-6-ene (217)

According to the procedure for 177: para-toluenesulfonic acid (0.63 g, 0.33 mmol) was added to 214 (1.26 g, 6.67 mmol) and ethylene glycol (2.23 mL, 40.0 mmol) in benzene (200 mL) to give, after flash chromatography (10% ether in pentane), 217 (3.08 g, 75%) as a colourless solid. mp: 58-60 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.23-4.17 (m, 2H), 4.00-3.94 (m, 2H), 2.14 (t, $J = 6.1$ Hz, 2H), 1.90-1.87 (m, 5H), 1.78-1.73 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 141.2, 121.9, 106.9, 65.9, 35.6, 33.3, 24.0, 20.4. These data match those in the literature.143

3-Methyl-2-(trimethylsilyl)cyclohex-2-en-1-one (218)

According to the procedure for 178: n-butyllithium (2.5 M in hexanes, 7.3 mL) was added to 217 (3.52 g, 15.1 mmol) in THF (50 mL). Chlorotrimethylsilane (3.62 mL, 28.7 mmol) in THF (10 mL) was added to give, after flash chromatography (10% ether in pentane), 218 (2.00 g, 73%) as a colourless oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.28 (t, $J = 6.6$ Hz, 4H), 2.01 (s, 3H), 1.89 (quintet, $J =$
6.5 Hz, 2H), 0.20 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 203.2, 169.5, 136.7, 38.0, 34.8, 24.9, 22.3, 1.8. These data match those in the literature.$^{143}$

3-Methyl-2-(trimethylsilyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (219)

According to the procedure for $^{148}$: L-Selectride (1 M in THF, 1.42 mL) was added to 218 (246 mg, 1.35 mmol) in THF (10 mL). PhNTf$_2$ (530 mg, 1.48 mmol) in THF (10 mL) was added to give, after flash chromatography (2.5% triethylamine in pentane), 219 (121 mg, 28%) as a colourless oil.$^*$

* 1H NMR (500 MHz, CDCl$_3$): δ 2.56-2.53 (m, $J = 1.7$ Hz, 1H), 2.42-2.36 (m, 2H), 1.88-1.84 (m, $J = 3.2$ Hz, 1H), 1.75-1.72 (m, $J = 3.4$ Hz, 1H), 1.64-1.57 (m, $J = 3.5$ Hz, 1H), 1.45-1.41 (m, 1H), 1.07 (d, $J = 7.0$ Hz, 3H), 0.22 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 155.7, 132.9, 118.5 (q, $J = 320$ Hz), 32.5, 29.2, 28.4, 21.3, 19.0, -0.4; HRMS pending.

* A yield of 48% was achieved when N-Selectride was used in lieu of L-Selectride.
To a stirred suspension of copper (I) iodide (348 mg, 1.83 mmol) in diethyl ether (2 mL) at 0 °C was added methyllithium (1.6 M, 2.29 mL) dropwise. The solution was stirred for 30 min before cooling to –78 °C. A solution of 3-methylcyclohex-2-en-1-one (0.208 mL, 1.83 mmol) in THF (4 mL) was added dropwise to the Me2CuLi solution, and the solution was stirred for 1 h at –78 °C before it was warmed to 0 °C for an additional 1 h. A solution of PhNTf2 (720 mg, 2.02 mmol) in THF (4 mL) was added to the mixture, which was stirred for 2 h at 0 °C. The mixture was diluted with pentane (10 mL) and washed with aqueous saturated ammonium chloride (15 mL). The phases were separated and the organic layer was washed with brine (15 mL), dried over MgSO4 and concentrated in vacuo. The residue was purified by flash chromatography (pentane) to give 223 as a colourless oil. 1H NMR (500 MHz, CDCl3): δ 5.50 (br s, 1H), 2.28-2.25 (m, 2H), 1.79-1.74 (m, 2H), 1.43-1.40 (m, 2H), 1.05 (s, 6H); 13C NMR (126 MHz, CDCl3): δ 148.3, 128.1, 45.8, 35.7, 32.9, 29.2, 27.4, 19.6. These data match those in the literature.
(8aR*,8bS*,12bR*,12cS*)-1,5,12,16-Tetramethyl-1,2,3,4,5,6,7,8,9,10,11,12-dodecahydro-8b,12b-butano-benzoi[3’,4’]cyclobuta[1’,2’:3,4]cyclobuta[1,2-e]biphenylene (224), and (1R*,4S*)-5-methyl-1,4,5,6,7,8-hexahydro-1,4-epoxynaphthalene (225)

According to the procedure for 180 + 184, method B: tetrabutylammonium fluoride (1 M in THF, 3.84 mL) was added to a solution of cyclohexyne precursor 219 (607 mg, 1.92 mmol) and furan (4.2 mL, 57 mmol) in THF (60 mL) to give a complex mixture of diastereomers 224 (73 mg, 40%) as a colourless oil and a 2:1 mixture of diastereomers 225 (24 mg, 8%) as a colourless oil. * For 224: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.32-0.90 (complex m); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 139.4, 138.17, 138.14, 133.46, 133.42, 126.7, 120.5, 115.2, complex mixture of signals between 33.0-18.7. HRMS (ESI) calcd for [C$_{28}$H$_{40}$Ag]$^+$: 483.2175, found: 483.2162. For major diastereomer of 225: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.07 (s, 1H), 7.06 (s, 1H), 5.25 (s, 1H), 5.13 (s, 1H), 2.60 (br s, 1H), 2.39-1.61 (m, 6H), 0.84 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 152.3, 149.3, 144.2, 143.7, 84.8, 83.9, 32.1, 28.7, 24.5, 21.4, 16.8. For minor diastereomer of 225: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.03 (s, 1H), 7.02 (s, 1H), 5.25 (s, 1H), 5.14 (s, 1H), 2.39-1.61 (m, 7H), 1.14 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 153.7,

* NMR sample was contaminated with 3-methylcyclohexan-1-one.
148.5, 144.3, 143.6, 84.6, 82.6, 31.8, 30.0, 24.3, 21.8, 19.8. HRMS (ESI) calcd for [C\textsubscript{11}H\textsubscript{14}ONa]\textsuperscript{+}: 185.0937, found: 185.0937.

2-Bromocyclohex-1-en-1-yl trifluoromethanesulfonate (233)

![Image](image.png)

According to the procedure for 148: L-Selectride (1 M in THF, 6.98 mL) was added to a solution of \(\alpha\)-bromo ketone 176 (1.16 g, 6.65 mmol) in THF (50 mL). PhNTf\textsubscript{2} (2.49 g, 6.98 mmol) in THF (50 mL) was added to give, after flash chromatography (2.5% triethylamine and 5% ether in pentane), 233 (1.59 g, 78%) as a colourless oil. \(^1\)H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 2.62-2.60 (m, 2H), 2.42-2.40 (m, 2H), 1.84-1.82 (m, 2H), 1.75-1.73 (m, 2H); \(^1\)C NMR (126 MHz, CDCl\textsubscript{3}): \(\delta\) 145.5, 122.8, 118.4 (q, \(J = 320 \text{ Hz}\)), 29.5, 28.2, 23.4, 22.4. These data match those in the literature.\(^{174}\)
1,2,3,4,5,6,7,8,9,10,11,12-Dodecahydrotriphenylene (179), and (8aR*,8bS*,12bR*,12cS*)-1,2,3,4,5,6,7,8,9,10,11,12-dodecahydro-8b,12b-butanobenzo-[3',4']cyclobuta[1',2':3,4]cyclobuta[1,2-e]biphenylene (180)

To a solution of cyclohexyne precursor 233 (0.46 g, 1.2 mmol) and 2,3-dimethylbutadiene (0.41 mL, 3.6 mmol) in THF (15 mL) was added n-butyllithium (2.5 M, 0.56 mL) at –78 °C. The mixture was allowed to attain rt over 1 h. The mixture was diluted with pentane (15 mL), then it was washed with aqueous saturated ammonium chloride (15 mL) and brine (15 mL), dried over MgSO4 and concentrated in vacuo. The residue was purified by flash chromatography (pentane) to give 179 (1 mg, 1%) and 180 (77 mg, 80%).* For 179: ¹H NMR (500 MHz, CDCl₃): δ 2.61 (br s, 12 H), 1.81 (br 2, 12 H); ¹³C NMR (126 MHz, CDCl₃): δ 132.8, 27.0, 23.2. These data match those in the literature.¹⁷⁵

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* When the reaction was done with 236 in lieu of 233, a 22% yield of 179 and 55% yield of 180 was obtained.
To a solution of cyclohex-2-en-1-one (1.93 mL, 20.0 mmol) in a 1:1 mixture of THF:H₂O (100 mL) was added potassium carbonate (3.31 g, 24.0 mmol), then iodine (7.6 g, 30.0 mmol) and DMAP (0.49 g, 4.0 mmol). The mixture was stirred at rt for 3 h, and it was diluted with ethyl acetate (100 mL), washed with aqueous saturated sodium thiosulfate (100 mL), 0.1 M HCl (100 mL), and then with brine (100 mL). The organic phase was dried over MgSO₄ and concentrated in vacuo. The residue was crystallized from 25% ethyl acetate in hexanes to give 235 (4.05 g, 91%) as a colourless solid. mp: 47-49 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.75 (t, J = 4.3 Hz, 1H), 2.83-2.54 (m, 2H), 2.44 (dt, J = 5.9, 4.5 Hz, 2H), 2.11-2.08 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 192.2, 159.4, 103.9, 37.2, 29.8, 22.8. These data match those in the literature.¹⁶³
2-Iodocyclohex-1-en-1-yl trifluoromethanesulfonate (236)

According to the procedure for 148: L-Selectride (1 M in THF, 1.20 mL) was added to a solution of α-iodo ketone 235 (245 mg, 1.1 mmol) in THF (10 mL). PhNTf₂ (394 mg, 1.1 mmol) in THF (10 mL) was added to give, after flash chromatography (2.5% triethylamine and 5% ether in pentane), 236 (128 mg, 33%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃): δ 2.72-2.69 (m, 2H), 2.48-2.45 (m, 2H), 1.88-1.83 (m, 2H), 1.71-1.66 (m, 2H); ¹³C NMR (126 MHz, CDCl₃): δ 150.2, 118.6 (q, J = 320 Hz), 90.9, 39.1, 29.3, 24.4, 22.6. HRMS pending.

2-Chlorocyclohex-2-en-1-one (237)

To a suspension of oxone (18.5 g, 30.0 mmol) in CH₂Cl₂ (100 mL) was added cyclohex-2-en-1-one (2.45 mL, 25.0 mmol), followed by 2 M HCl (27.5 mL). The mixture was stirred at rt for 2 h until the yellowish green colour disappeared. Triethylamine (20 mL) was added slowly to the mixture, which was stirred an additional 12 h. The mixture was diluted with ethyl acetate (100 mL) and washed
with water (3 × 100 mL), aqueous saturated sodium bicarbonate (2 × 100 mL), and brine (100 mL) before being dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography (20% ether in pentane) to give 237 as a colourless solid. mp: 67-72 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.15 (t, J = 4.5 Hz, 1H), 2.61 (dd, J = 6.4, 5.9 Hz, 2H), 2.49 (td, J = 5.9, 4.5 Hz, 2H), 2.11-2.07 (m, 2H); ¹³C NMR (126 MHz, CDCl₃): δ 191.3, 146.5, 132.2, 38.4, 27.0, 22.5. These data match those in the literature.¹⁷⁶

2-Chlorocyclohex-1-en-1-yl trifluoromethanesulfonate (238)

According to the procedure for 148: L-Selectride (1 M in THF, 12.1 mL) was added to a solution of α-chloro ketone 237 (1.50 g, 11.5 mmol) in THF (100 mL). PhNTf₂ (4.10 g, 11.5 mmol) in THF (100 mL) was added to give, after flash chromatography (2.5% triethylamine and 5% ether in pentane), 238 (1.58 g, 52%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃): δ 2.48 (tt, J = 5.9, 2.8 Hz, 1H), 2.42 (tt, J = 5.9, 2.8 Hz, 1H), 1.83-1.73 (m, 2H); ¹³C NMR (126 MHz, CDCl₃): δ 143.6, 125.5, 118.5 (q, J = 320 Hz), 32.7, 28.6, 22.71, 22.56; HRMS pending.
Chapter 5 – Conclusions and Future Directions

Although a propellane may not have been synthesized using geminal acylation methods, the techniques and skills developed working on that project helped me along the way. A series of ketodiesters with different ester moieties and of different carbon lengths were prepared, but geminal acylation was unsuccessful when the carbonyl was sterically congested by an α-methyl group. A geminal acylation reaction was attempted using an unmethylated derivative on a small scale, but no product of geminal acylation was observed.

Future efforts in this domain would be to make further attempts at the geminal acylation using the unmethylated derivative in the hope that varying the conditions might be met with success. For instance, reverting to the two-step procedure might allow the test of different acid regimes for the pinacol rearrangement. The rearrangement in the case of substrates with α-halogen substituents would not work until Amberlyst-15 was employed. It is possible that the diester moiety also makes the reaction difficult, and thus another approach might be to change the ester functionalities to something less reactive and then to reconvert them into esters after the geminal acylation step has occurred (Scheme 70). For example, a dibromo-substituted ketone, such as 242, could undergo geminal acylation with 2 to give 243. The conversion of 243 to an ester would begin with the formation of a Grignard reagent by the addition of magnesium,
which could then react with diethyl carbonate to generate, after deprotecting the ketal, 73.

![Scheme 70](image)

**Scheme 70. Alternative method for generating 73.**

A series of bicyclic compounds were prepared from a tandem Nazarov cyclization / (4+3) cycloaddition of AVKs with oxygen-substituted dienes. With one extreme exception, the oxygen-substituted dienes intercepted the Nazarov reactions exclusively by (4+3) cycloaddition, in contrast with all-carbon dienes. The process had very high facial selectivity, high regioselectivity, and modest to high diastereoselectivity depending on the substitution of both the oxyallyl cation of the AVK and the diene. These experimental results, in conjunction with computational studies that are currently underway, will provide valuable information regarding the mechanism of such (4+3) cycloadditions. Already, we are reasonably sure that the cycloadditions are concerted, which is in contrast with a number of studies that have hypothesized that the reaction is stepwise. The yields were nevertheless disappointing because the oxygen-bearing dienes were not stable to the reaction conditions. A thorough survey of Lewis acids might be worthwhile with the aim of finding a Lewis acid that can mediate the Nazarov reaction but not destroy the dienes.
Related work on the interrupted Nazarov reaction is exploring interception by five-membered heteroatomic aromatics, particularly thiophenes and furans. The products of these reactions could arise from mono-addition (Friedel-Crafts chemistry) or bis-addition, i.e., (3+2) or (4+3) cycloadditions. Depending on the substituents and their positions on the heteroaromatics, different trapping patterns might be observed. Preliminary studies are showing that thiophenes trap exclusively by mono-addition at position α on the oxyallyl cation of 80, but thiazole is destroyed by the Lewis acid before the AVK can even cyclize. Furan has been known to intercept photochemical Nazarov reactions, so photochemical reactions with AVKs might be attempted.

Progress has been made in the study of cyclohexyne and its Diels-Alder reactivity. These reactions often formed mainly a tetramer byproduct 180 unless the diene was used in large excess. Current work was to make this process more effective in order to suppress the formation of the tetramer. Future work to this end would be to build a library of compounds with fused cyclohexene moieties and look for trends in selectivity and reactivity and to discover what steric or electronic influences could have on regioselectivity and even facial selectivity in cycloaddition reactions.

Other future work would include forming the trisubstituted cyclohexyne 195. The α-bromination of isophorone 201 using Br₂ and NEt₃ was unsuccessful in forming 243, but tetrabutylammonium tribromide should improve the yield (Scheme 71). The remaining steps to generate the cyclohexyne precursor 200 will likely mirror the reactions used to form its unsubstituted analog, firstly, by
converting 244 to its ethylene glycol ketal 245, then the installation of the trimethylsilyl group to form 246, and finally, the 1,4-reduction and trapping of the resulting enolate to generate 200. This methodology could also be extended to form the chiral cyclohexyne 247 from (S)-(−)-verbenone 248.

**Scheme 71. Proposed route to forming trisubstituted cyclohexyne precursor 200 and the retrosynthesis of a chiral cyclohexyne.**

Future work might involve studying substituted cyclohexynes with various substituents to examine how steric and electronic effects play a factor in reactivity and selectivity. Adding functionality to the cyclohexyne moiety would also help cut down steps in natural product synthesis and perhaps making cyclohexyne a more powerful tool that could rival the popularity of benzyne.
References


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Appendix A: \(^1\text{H}\) and \(^{13}\text{C}\) NMR Spectra for Chapter 2
$^1$H NMR (CDCl$_3$, 500 MHz): 1-Ethyl 8-(2-hydroxyethyl) 4-methyl-5-oxooctanedioate (58)
$^{13}$C NMR (CDCl$_3$, 126 MHz): 1-Ethyl 8-(2-hydroxyethyl) 4-methyl-5-oxooctanedioate (58)
$^1$H NMR (CDCl$_3$, 500 MHz): Dimethyl 4-methyl-5-oxononanedioate (60)
$^{13}$C NMR (CDCl$_3$, 126 MHz): Dimethyl 4-methyl-5-oxononanedioate (60)
$^1$H NMR (CDCl$_3$, 500 MHz): Dimethyl 5-(1,3-dioxolan-2-yl)-4-methylnonanedioate (61)
$^{13}$C NMR (CDCl$_3$, 126 MHz): Dimethyl 5-(1,3-dioxolan-2-yl)-4-methylnonanedioate (61)
$^1$H NMR (CDCl$_3$, 500 MHz): Dimethyl 4-methyl-5-oxooctanedioate (63)
$^{13}$C NMR (CDCl$_3$, 126 MHz); Dimethyl 4-methyl-5-oxooctanedioate (63)
$^1$H NMR (CDCl$_3$, 500 MHz): Dihexyl 4-methyl-5-oxooctanedioate (66)
$^{13}$C NMR (CDCl$_3$, 126 MHz): Dihexyl 4-methyl-5-oxooctanedioate (66)
$^1$H NMR (CDCl$_3$, 500 MHz): Ethyl 3-(3-hydroxy-1-oxocyclohex-2-en-2-yl)propanoate (70)
$^{13}$C NMR (CDCl$_3$, 126 MHz): Ethyl 3-(3-hydroxy-1-oxocyclohex-2-en-2-yl)propanoate (70)
Appendix B: $^1$H and $^{13}$C NMR Spectra for Chapter 3
$^{1}H$ NMR (CDCl$_3$, 500 MHz): (Z)-3-(tert-Butyldimethylsilyloxy)-1,3-hexadiene (101b)
\textbf{$^{13}$C NMR (CDCl$_3$, 126 MHz): (Z)-3-(tert-Butyldimethylsilyloxy)-1,3-hexadiene (101b)}

![Carbon NMR spectrum of 101b]
$^1$H NMR (CDCl$_3$, 500 MHz): (Z)-3-(tert-Butyldimethylsilyloxy)-5-methyl-1,3-hexadiene (101c)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (Z)-3-(tert-Butyldimethylsilyloxy)-5-methyl-1,3-hexadiene (101c)
$^1$H NMR (CDCl$_3$, 500 MHz): (E)-2-(tert-Butyldimethylsilyloxy)-1-phenyl-1,3-butadiene ($E$-101d)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (E)-2-(tert-Butyldimethylsilyloxy)-1-phenyl-1,3-butadiene (E-101d)
$^1$H NMR (CDCl$_3$, 500 MHz): (Z)-2-((tert-Butyldimethylsilyloxy)-1-phenyl-1,3-butadiene (Z-101d)

![NMR spectrum](image-url)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (Z)-2-(tert-Butyldimethylsilyloxy)-1-phenyl-1,3-butadiene (Z-101d)
\(^{1}\)H NMR (CDCl\(_3\), 500 MHz): (2Z,4E)-3-(tert-Butyldimethylsilyloxy)-2,4-hexadiene (101i)

TBSO

Me

Me

101i
$^{13}$C NMR (CDCl$_3$, 126 MHz): (2Z,4E)-3-(tert-Butyldimethylsilyloxy)-2,4-hexadiene (101i)
$^1$H NMR (CDCl$_3$, 500 MHz): (1$R^*$.6$S^*$.7$S^*$)-1-Methyl-8-methylene-7-phenyl-4-(trimethylsilyloxy)bicyclo[4.2.1]non-3-en-9-one (102)
\( ^{13}C \text{NMR (CDCl}_3, 126 \text{ MHz):} \ (1R^*,6S^*,7S^*)-1\)-Methyl-8-methylene-7-phenyl-4-(trimethylsilyloxy)bicyclo[4.2.1]non-3-en-9-one (102) \)
\(^1\)H NMR (CDCl\(_3\), 500 MHz): (1\(R^*,6S^*,7S^*\))-1-Methyl-8-methylene-7-phenylbicyclo[4.2.1]nonane-4,9-dione (103)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*$,6$S^*$,7$S^*$)-1-Methyl-8-methylene-7-phenylbicyclo[4.2.1]nonane-4,9-dione (103)
\(^1\)H NMR (CDCl\(_3\), 500 MHz): \((1R^*,2R^*,6S^*,7S^*)\)-1,2-Dimethyl-8-methylene-7-phenyl-4-(trimethylsilyloxy)bicyclo[4.2.1]non-3-en-9-one (104)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*$,2$R^*$,6$S^*$,7$S^*$)-1,2-Dimethyl-8-methylene-7-phenyl-4-(trimethylsilyloxy)bicyclo[4.2.1]non-3-en-9-one (104)
$^1$H NMR (CDCl$_3$, 500 MHz): (1$R^*$,2$R^*$,6$S^*$,7$S^*$)-1,2-Dimethyl-8-methylene-7-phenylbicyclo[4.2.1]nonane-4,9-dione (105)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*$,2$R^*$,6$S^*$,7$S^*$)-1,2-Dimethyl-8-methylene-7-phenylbicyclo[4.2.1]nonane-4,9-dione (105)
\[ ^1H \text{NMR (CDCl}_3, \text{500 MHz): (}4R*,5R*)-2,3-\text{Dimethyl-5-}((E)-2-\text{oxopent-3-en-1-yl})-4-\text{phenylcyclopent-2-enone (106)} \]
$^{13}$C NMR (CDCl$_3$, 126 MHz): (4$R^*$,5$R^*$)-2,3-Dimethyl-5-(\(E\))-2-oxopent-3-en-1-y-4-phenylcyclopent-2-ene (106)
$^{1}$H NMR (CDCl$_3$, 500 MHz): (1R*,5S*,6S*,7S*)-1,5-Dimethyl-8-methylene-7-phenyl-4-(trimethylsilyloxy)bicyclo[4.2.1]non-3-en-9-one (107a)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*, 5S^*, 6S^*, 7S^*$)-1,5-Dimethyl-8-methylene-7-phenyl-4-(trimethylsilyloxy)bicyclo[4.2.1]non-3-en-9-one (107a)
\[ ^1H \text{ NMR (CDCl}_3, 500 \text{ MHz):} \quad (1R^*, 5R^*, 6S^*, 7S^*)-1,5\text{-Dimethyl-8-methylene-7-phenyl-4-(trimethylsilyloxy)bicyclo[4.2.1]} 9\text{-en-3-one (107b)} \]
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*$,5$R^*$,6$S^*$,7$S^*$)-1,5-Dimethyl-8-methylene-7-phenyl-4-(trimethylsilyloxy)bicyclo[4.2.1]non-3-en-9-one (107b)
$^1$H NMR (CDCl$_3$, 500 MHz): ($1R^*,5S^*,6S^*,7S^*$)-1,5-Dimethyl-8-methylene-7-phenylbicyclo[4.2.1]nonane-4,9-dione (108a) and ($1R^*,5R^*,6S^*,7S^*$)-1,5-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]nonane-4,9-dione (108b)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*$,5$S^*$,6$S^*$,7$S^*$)-1,5-Dimethyl-8-methylene-7-phenylbicyclo[4.2.1]nonane-4,9-dione (108a) and (1$R^*$,5$R^*$,6$S^*$,7$S^*$)-1,5-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]nonane-4,9-dione (108b)
$^1$H NMR (CDCl$_3$, 500 MHz): (1$^{R*}, 5^{S*}, 6^{S*}, 7^{S*}$)-4-(tert-Butyldimethylsilyloxy)-1,5-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (109a)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$^{R^*}$,5$^S^*,6^S^*,7^S^*$)-4-(tert-Butyldimethylsilyloxy)-1,5-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (109a)
$^1$H NMR (CDCl$_3$, 500 MHz): (1$R^\#$,5$R^\#$,6$S^\#$,7$S^\#$)-4-(tert-Butyldimethylsilyloxy)-1,5-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (109b)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$^{R*}$,5$^{R*}$,6$^{S*}$,7$^{S*}$)-4-(tert-Butyldimethylsilyloxy)-1,5-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (109b)
$^1$H NMR (CDCl$_3$, 500 MHz): (1$^R$,5$^S$,6$^S$,7$^S$)-4-(tert-Butyldimethylsilyloxy)-5-ethyl-1-methyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (110a) and (1$^R$,5$^R$,6$^S$,7$^S$)-4-(tert-butylidimethylsilyloxy)-5-ethyl-1-methyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (110b)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*$,5$S^*$,6$S^*$,7$S^*$)-4-(tert-Butyldimethylsilyloxy)-5-ethyl-1-methyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (110a) and (1$R^*$,5$R^*$,6$S^*$,7$S^*$)-4-(tert-butylidimethylsilyloxy)-5-ethyl-1-methyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (110b)
$^1$H NMR (CDCl$_3$, 500 MHz): $(1R^*, 5R^*, 6S^*, 7S^*)$-4-(tert-Butyldimethylsilyloxy)-1-methyl-8-methylene-7-phenyl-5-isopropylbicyclo[4.2.1]non-3-en-9-one (111)
$^{13}$C NMR (CDCl$_3$, 126 MHz): ($1R^*, 5R^*, 6S^*, 7S^*$)-4-(tert-Butyldimethylsilyloxy)-1-methyl-8-methylene-7-phenyl-5-isopropylbicyclo-[4.2.1]non-3-en-9-one (111)
$^1$H NMR (CDCl₃, 500 MHz): ($^{1R,*},^{5S,*},^{6S,*},^{7S,*}$)-4-(tert-Butyldimethylsilyloxy)-1-methyl-8-methylene-5,7-diphenylbicyclo[4.2.1]non-3-en-9-one (112a)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*, 5S^*, 6S^*, 7S^*$)-4-(tert-Butyldimethylsilyloxy)-1-methyl-8-methylene-5,7-diphenylbicyclo[4.2.1]non-3-en-9-one (112a)
$^1$H NMR (CDCl$_3$, 500 MHz): (1$^R$*,$5^R$*,$6^S$*,$7^S$*)-4-(tert-Butyldimethylsilyloxy)-1-methyl-8-methylene-5,7-diphenylbicyclo[4.2.1]non-3-en-9-one (112b) and (1$^R$*,$2^R$*,$6^S$*,$7^S$*)-3-(tert-butyldimethylsilyloxy)-1-methyl-8-methylene-2,7-diphenylbicyclo[4.2.1]non-3-en-9-one (113)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*$,5$R^*$,6$S^*$,7$S^*$)-4-(tert-Butyldimethylsilyloxy)-1-methyl-8-methylene-5,7-diphenylbicyclo[4.2.1]non-3-en-9-one (112b) and (1$R^*$,2$R^*$,6$S^*$,7$S^*$)-3-(tert-butylidimethylsilyloxy)-1-methyl-8-methylene-2,7-diphenylbicyclo[4.2.1]non-3-en-9-one (113)
$^1$H NMR (CDCl$_3$, 500 MHz): (1R*,25*,45*,55*)-2-(1-Methoxy-2-methylprop-1-en-1-yl)-1-methyl-6-methylene-5-phenylbicyclo[2.2.1]heptan-7-one (114a)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*$,2$S^*$,4$S^*$,5$S^*$)-2-(1-Methoxy-2-methylprop-1-en-1-yl)-1-methyl-6-methylene-5-phenylbicyclo[2.2.1]heptan-7-one (114a)
$^1$H NMR (CDCl$_3$, 500 MHz): (1$R^*$,2$R^*$,4$S^*$,5$S^*$)-2-(1-Methoxy-2-methylprop-1-en-1-yl)-1-methyl-6-methylene-5-phenylbicyclo[2.2.1]heptan-7-one (114b)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*$,2$R^*$,4$S^*$,5$S^*$)-2-(1-Methoxy-2-methylprop-1-en-1-yl)-1-methyl-6-methylene-5-phenylbicyclo[2.2.1]heptan-7-one (114b)
$^{1}H$ NMR (CDCl$_3$, 500 MHz): (1R*,6S*,7S*)-4-(tert-Butyldimethylsilyloxy)-1,3-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-ene-9-one (115)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*$,6$S^*$,7$S^*$)-4-(tert-Butyldimethylsilyloxy)-1,3-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (115)
$^1$H NMR (CDCl$_3$, 500 MHz): (1$^R$,2$^R$,6$^S$,7$^S$)-4-(tert-Butyldimethylsilyloxy)-1,2-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (116)
\[ ^{13}\text{C NMR (CDCl}_3, 126 \text{ MHz): (1}^{\text{R}^*}\text{,2}^{\text{R}^*}\text{,6}^{\text{S}^*}\text{,7}^{\text{S}^*}\text{)-}4\text{-}(\text{tert-Butyldimethylsilyloxy)-1,2-dimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (116)}} \]
$^1$H NMR (CDCl$_3$, 500 MHz): (1$^R$,6$^S$,7$^S$)-4-(tert-Butyldimethylsilyloxy)-1,2,2-trimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (117)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*$,6$S^*$,7$S^*$)-4-(tert-Butyldimethylsilyloxy)-1,2,2-trimethyl-8-methylene-7-phenylbicyclo[4.2.1]non-3-en-9-one (117)
$^1$H NMR (CDCl$_3$, 500 MHz): (1$R^*, 2R^*, 10S^*, 11S^*)$-8-(tert-Butyldimethylsilyloxy)-1-methyl-12-methylene-11-phenyltricyclo[8.2.7.1]tridec-7-en-13-one (118)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1R*,2R*,10S*,11S*)-8-(tert-Butyldimethylsilyloxy)-1-methyl-12-methylene-11-phenyltricyclo[8.7.2.1]tridec-7-en-13-one (118)
$^1$H NMR (CDCl$_3$, 500 MHz): (1$^{R\#}$,2$^{S\#}$,5$^{S\#}$,6$^{S\#}$,7$^{S\#}$)-4-(tert-Butyldimethylsilyloxy)-1,2,5-trimethyl-8-methylene-7-phenylbicyclo-[4.2.1]non-3-en-9-one (120)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*, 2S^*, 5S^*, 6S^*, 7S^*$)-4-(tert-Butyldimethylsilyloxy)-1,2,5-trimethyl-8-methylene-7-phenylbicyclo-[4.2.1]non-3-en-9-one (120)
$^1$H NMR (CDCl$_3$, 500 MHz): (1$^{R*},2^{R*},5^{R*},6^{S*},7^{S*})$-4-(tert-Butyldimethylsilyloxy)-1,2,5-trimethyl-8-methylene-7-phenylbicyclo-[4.2.1]non-3-en-9-one (121)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*$.2$R^*$.5$R^*$.6$S^*$.7$S^*$)-4-(tert-Butyldimethylsilyloxy)-1,2,5-trimethyl-8-methylene-7-phenylbicyclo-[4.2.1]non-3-en-9-one (121)
$^1$H NMR (CDCl$_3$, 500 MHz): (1$^R$$^*, 5^R$$^*, 6^S$$^*, 8^R$$^*$)-4-(tert-Butyldimethylsilyloxy)-1,5-dimethyl-7-methylene-8-phenylbicyclo[4.2.1]non-3-en-9-one (122a), and (1$^R$$^*, 5^S$$^*, 6^S$$^*, 8^R$$^*$)-4-(tert-Butyldimethylsilyloxy)-1,5-dimethyl-7-methylene-8-phenylbicyclo[4.2.1]non-3-en-9-one (122b).
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*,5R^*,6S^*,8R^*$)-4-(tert-Butyldimethylsilyloxy)-1,5-dimethyl-7-methylene-8-phenylbicyclo[4.2.1]non-3-en-9-one (122a), and (1$R^*,5S^*,6S^*,8R^*$)-4-(tert-butyldimethylsilyloxy)-1,5-dimethyl-7-methylene-8-phenylbicyclo[4.2.1]non-3-en-9-one (122b)
$^1$H NMR (CDCl$_3$, 500 MHz): (1$^R$,6$^S$,8$^R$)-4-(tert-Butyldimethylsilyloxy)-1,5,5-trimethyl-7-methylene-8-phenylbicyclo[4.2.1]non-3-en-9-one (123)

\[ \text{ppm} \]
$^{13}$C NMR (CDCl$_3$, 126 MHz): ($1R^*,6S^*,8R^*$)-4-($t$-Butyldimethylsilyloxy)-1,5,5-trimethyl-7-methylene-8-phenylbicyclo[4.2.1]non-3-en-9-one (123)
$^1$H NMR (CDCl$_3$, 500 MHz): (4a$R^*$,8$R^*$,9$R^*$)-8-Methyl-10-methyleneoctahydro-1$H$-4a,9-methanobenzo[8]annulene-7,11(2$H$)-dione (124)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (4a$R^*$,8$R^*$,9$R^*$)-8-Methyl-10-methyleneoctahydro-1$H$-4a,9-methanobenzo[8]annulene-7,11(2$H$)-dione (124)
\[^1\text{H NMR (CDCl}_3, \text{500 MHz)}: (1^{R*},5^{R*},6^{S*},7^{S*})\text{-1-Methyl-8-methylene-7-phenyl-5-iso-propylbicyclo[4.2.1]nonane-4,9-dione (125)}\]
$^{13}$C NMR (CDCl$_3$, 126 MHz): ($1R^*,5S^*,6S^*,7S^*$)-1-Methyl-8-methylene-7-phenyl-5-iso-propylbicyclo[4.2.1]nonane-4,9-dione (125)
1H NMR (CDCl₃, 500 MHz): (1R*,2S*,5S*,6S*,7S*)-1,2,5-Trimethyl-8-methylene-7-phenylbicyclo[4.2.1]nonane-4,9-dione (126)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1R*,2S*,5S*,6S*,7S*)-1,2,5-Trimethyl-8-methylene-7-phenylbicyclo[4.2.1]nonane-4,9-dione (126)
$^1$H NMR (CDCl$_3$, 500 MHz): (4$^{R*}$,5$^{R*}$)-2,3-Dimethyl-5-((R*,E)-3-oxohex-4-en-2-yl)-4-phenylcyclopent-2-enone (127)
$^{13}$C NMR (CDCl$_3$, 126 MHz): $^{(4R^*,5R^*)}$-2,3-Dimethyl-5-((R*,E)-3-oxohex-4-en-2-yl)-4-phenylcyclopent-2-enone (127)
$^{1}$H NMR (CDCl$_3$, 500 MHz): (1$^{R*}$,2$^{R*}$,5$^{S*}$,10$^{R*}$)-2,5,8-Trimethyl-10-phenylbicyclo[5.2.1]dec-7-ene-3,9-dione (128)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*$,2$R^*$,5$S^*$,10$R^*$)-2,5,8-Trimethyl-10-phenylbicyclo[5.2.1]dec-7-ene-3,9-dione (128)
$^1$H NMR (CDCl$_3$, 500 MHz): (1$R^*$,2$R^*$,5$R^*$,6$S^*$,7$S^*$)-1,2,5-Trimethyl-8-methylene-7-phenylbicyclo[4.2.1]nonane-4,9-dione (129)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$R^*$,2$R^*$,5$R^*$,6$S^*$,7$S^*$)-1,2,5-Trimethyl-8-methylene-7-phenylbicyclo[4.2.1]nonane-4,9-dione (129)
1H NMR (CDCl₃, 500 MHz): (4R*,5R*)-2,3-Dimethyl-5-((S*,E)-3-oxohex-4-en-2-yl)-4-phenylcyclopent-2-enone (130)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (4$R^*$,5$R^*$)-2,3-Dimethyl-5-((S$^*$,E)-3-oxohex-4-en-2-yl)-4-phenylcyclopent-2-enone (130)
$^1$H NMR (CDCl$_3$, 500 MHz): ($1R^*, 2S^*, 5S^*, 10R^*$)-2,5,8-Trimethyl-10-phenylbicyclo[5.2.1]dec-7-ene-3,9-dione (131)
$^{13}$C NMR (CDCl$_3$, 126 MHz): (1$^{R*}$,2$^{S*}$,5$^{S*}$,10$^{R*}$)-2,5,8-Trimethyl-10-phenylbicyclo[5.2.1]dec-7-ene-3,9-dione (131)
Appendix C: $^1$H and $^{13}$C NMR Spectra for Chapter 4
$^1$H NMR (CDCl$_3$, 500 MHz): (1$R^*$,4$S^*$)-1,4,5,6,7,8-Hexahydro-1,4-epoxynaphthalene (184)
$^{13}$C NMR (CDCl$_3$, 126 MHz): ($1R^*,4S^*$)-1,4,5,6,7,8-Hexahydro-1,4-epoxynaphthalene (184)
$^1$H NMR (CDCl$_3$, 500 MHz): 1,4,5,6,7,8-Hexahydronephthalen-2-yl acetate (188)
$^{13}$C NMR (CDCl$_3$, 126 MHz): 1,4,5,6,7,8-Hexahydronaphthalen-2-yl acetate (188)
\(^1\)H NMR (CDCl\(_3\), 500 MHz): (1\(R^*,4S^*\))-1,4,5,6,7,8-Hexahydro-1,4-ethanonaphthalene (189)
$^1$C NMR (CDCl$_3$, 126 MHz): (1R,4S$^*$)-1,4,5,6,7,8-Hexahydro-1,4-ethanophthalene (189)
$^1$H NMR (CDCl$_3$, 500 MHz): 2-Bromo-6,6-dimethylcyclohex-2-en-1-one (204)
$^{13}$C NMR (CDCl$_3$, 126 MHz): 2-Bromo-6,6-dimethylcyclohex-2-en-1-one (204)
$^1$H NMR (CDCl$_3$, 500 MHz): 6-Methyl-2-(trimethylsilyl)cyclohex-2-en-1-one (207)
$^{13}$C NMR (CDCl$_3$, 126 MHz): 6-Methyl-2-(trimethylsilyl)cyclohex-2-en-1-one (207)
$^1$H NMR (CDCl$_3$, 500 MHz): 6,6-Dimethyl-2-(trimethylsilyl)cyclohex-2-en-1-one (208)
$^1$H NMR (CDCl$_3$, 500 MHz): 3-Methyl-2-(trimethylsilyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (219)
$^{13}$C NMR (CDCl$_3$, 126 MHz): 3-Methyl-2-(trimethylsilyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (219)
$^1$H NMR (CDCl$_3$, 500 MHz): (8a$^R$,8b$^S$,12b$^R$,12c$^S$)-1,5,12,16-Tetramethyl-1,2,3,4,5,6,7,8,9,10,11,12-dodecahydro-8b,12b-butanobenzo[3',4']cyclobuta[1',2':3,4]cyclobuta[1,2-e]biphenylene (224)
$^{13}$C NMR (CDCl₃, 126 MHz): (8a$^{R*}$,8b$^{S*}$,12c$^{S*}$,12c$^{S*}$)-1,5,12,16-Tetramethyl-1,2,3,4,5,6,7,8,9,10,11,12-dodecahydro-8b,12b-butanobenzol[3',4']cyclobuta[1',2':3,4]cyclobuta[1,2-e]biphenylene (224)
1H NMR (CDCl₃, 500 MHz): (1R*,4S*)-5-Methyl-1,4,5,6,7,8-hexahydro-1,4-epoxynaphthalene (225)
$^{13}$C NMR (CDCl$_3$, 126 MHz): ($1R^*,4S^*$)-5-Methyl-1,4,5,6,7,8-hexahydro-1,4-epoxynaphthalene (225)
$^1$H NMR (CDCl$_3$, 500 MHz): 2-Iodocyclohex-1-en-1-yl trifluoromethanesulfonate (236)
$^{13}$C NMR (CDCl$_3$, 126 MHz): 2-Iodocyclohex-1-en-1-yl trifluoromethanesulfonate (236)
$^1$H NMR (CDCl$_3$, 500 MHz): 2-Chlorocyclohex-1-en-1-yl trifluoromethanesulfonate (238)
$^{13}$C NMR (CDCl$_3$, 126 MHz): 2-Chlorocyclohex-1-en-1-yl trifluoromethanesulfonate (238)