Metathesis routes to carbocyclic frameworks

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Metathesis routes towards carbocyclic frameworks

By

Patricia Standen, MChem

Thesis Submitted in partial fulfilment of the requirements for the award of Doctor of Philosophy at Loughborough University

Supervisor Dr. M. C. Kimber

June 2013

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Finally I would like to acknowledge the two most important people in my life, my Fiancée Sam Kilsby and our little dog Lilly. You make every day worthwhile, and I would be lost without you both.
# 1. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>[HG]-I</td>
<td>Hoveyda-Grubbs 1&lt;sup&gt;st&lt;/sup&gt; Generation catalyst</td>
</tr>
<tr>
<td>[HG]-II</td>
<td>Hoveyda-Grubbs 2&lt;sup&gt;nd&lt;/sup&gt; Generation catalyst</td>
</tr>
<tr>
<td>[Mo]-I</td>
<td>Schocks catalyst</td>
</tr>
<tr>
<td>[Ru]-I</td>
<td>Grubbs 1&lt;sup&gt;st&lt;/sup&gt; generation catalyst</td>
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<td>Grubbs 2&lt;sup&gt;nd&lt;/sup&gt; generation catalyst</td>
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<td>[Ru]-III</td>
<td>Grubbs 3&lt;sup&gt;rd&lt;/sup&gt; generation catalyst</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>ACCN</td>
<td>1,1’-Azobis(cyclohexane-1-carbonitrile)</td>
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<tr>
<td>ADDP</td>
<td>1,1’-(Azodicarbonyl)-dipiperidine</td>
</tr>
<tr>
<td>AIBN</td>
<td>Azobisisobutyronitrile</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;SnH</td>
<td>Tributyltin hydride</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyloxy</td>
</tr>
<tr>
<td>CBZ</td>
<td>Benzyloxy carbonyl</td>
</tr>
<tr>
<td>CM</td>
<td>Cross metathesis</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation spectroscopy</td>
</tr>
<tr>
<td>Cp</td>
<td>Cyclopentadiene</td>
</tr>
<tr>
<td>DCE</td>
<td>Dichloroethane</td>
</tr>
<tr>
<td>de</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
</tbody>
</table>
I. Abbreviations

DMF  Dimethylformamide
DMPU 1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone
DMS  Dimethyl sulfide
dr  Diastereomeric ratio
DSRCM Diastereoselective ring closing metathesis
Eq  Equivalents
Et₂O  Diethyl Ether
EtOAc  Ethyl Acetate
g  Gram(s)
h  Hour(s)
HMBC  Heteronuclear multiple-bond correlation spectroscopy
HMQC  Heteronuclear single-quantum correlation spectroscopy
HPLC  High performance liquid chromatography
IMES  1,3-dimesitylimidazolin-2-ylindene
iPrMgCl  Iospropylmagnesium chloride
IR  Infra Red Spectroscopy
KHDMS  Potassium bis(trimethylsilyl)amide
m/s  Mass spectrometry
Min  Minute(s)
mg  Miligrams
"Bu  n-Butyl
NCS  N-Chlorosuccinimide
NHC  N-heterocyclic carbene
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance Spectroscopy</td>
</tr>
<tr>
<td>nOe</td>
<td>Nuclear Overhauser effect</td>
</tr>
<tr>
<td>PDC</td>
<td>Pyridinium Dichromate</td>
</tr>
<tr>
<td>PE</td>
<td>Petroleum Ether</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts Per Million</td>
</tr>
<tr>
<td>p-TSA</td>
<td>p-Toluenesulfonic acid</td>
</tr>
<tr>
<td>RCM</td>
<td>Ring closing metathesis</td>
</tr>
<tr>
<td>ROM</td>
<td>Ring opening metathesis</td>
</tr>
<tr>
<td>ROMP</td>
<td>Ring opening metathesis polymerisation</td>
</tr>
<tr>
<td>RRM</td>
<td>Ring rearrangement metathesis</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>STAB</td>
<td>Sodium triacetoxyborohydride</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>Tert-butyldimethylsilyloxy</td>
</tr>
<tr>
<td>Tfa</td>
<td>Trifluoroacetamide</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TsCl</td>
<td>Tosyl Chloride</td>
</tr>
</tbody>
</table>
2. Abstract

The addition of allyl magnesium and allyl indium reagents to a key TBS protected norbornenyl building block, synthesised in 6-steps from commercially available 1,1-dimethoxy-2,3,4,5-tetrachlorocyclo-pentadiene, has been achieved providing the syn addition products with high diastereoselectivity (Scheme 1).

Scheme 1: Synthesis of Key norbornene building block

The subsequent exposure of the addition products to metathesis conditions, in the presence of ethylene, then provided cis fused [3.0.3]-carbocycles with very high regioselectivity, via a Ring Rearrangement Metathesis (RRM) transformation (Scheme 2).

Scheme 2 : cis fused [3.0.3] carbocycles via RRM

The high level of regioselectivity is due to the rearrangement of the metathesis intermediates to give the more thermodynamically stable product 9.
This work has been expanded to include [2.2.2]-bicycles, addition of allyl magnesium and indium reagents to a key bicyclo[2.2.2]oct-5-en-2-one has been achieved, giving both diastereoisomers, separable by chromatography (Scheme 3).

Scheme 3 : Synthesis of the key [2.2.2] bicycle and the magnesium and indium additions

The subsequent exposure of the addition products to optimised metathesis conditions, then provided cis fused [3.3.1] carbocycles with very high regioselectivity, via a RRM transformation (Scheme 4).

Scheme 4 : Cyclisation of the [2.22] bicyclic metathesis precursors and their outcomes

It was found that two possible cyclisation pathways occur under our reaction conditions; pathway (a) will yield a cis-fused [4.0.3]-carbicycle (22) while pathway (b) will deliver the observed [3.3.1]-carbicycle 19. Calculated energies for each regioisomer indicate that the [3.3.1]- carbicycle 19 is some 17.49 kJmol\(^{-1}\) more stable than 22, indicating that product formation is under thermodynamic control possibly via the chair conformation depicted in 24 (Scheme 5).
Scheme 5: Plausible mechanistic hypothesis and energy minimised conformations of 22, 19 and 23.
3. Introduction

3.1 What is metathesis?

Metathesis, Greek (μετάθεσις) for change of position or transposition, is a molecular process involving the exchange of bonds between two reacting species, resulting in the creation of products similar or identical in bonding. Accordingly metathesis has become a very important tool in organic chemistry, and in its various guises involves the redistribution of olefin fragments after the breaking of a carbon-carbon double bond, promoted by a metal carbene complex.

Since its first discovery almost over 50 years ago its use has become widespread in industry and research, and its popularity is in part due to its numerous advantages over other common catalytic carbon-carbon bond forming reactions. As a catalytic process the catalyst loading is low (1-5 mol %) and also gives high yields in relatively short reaction times. One notable advantage to this reaction is its tolerance of functional groups and such, minimal substrate protection is necessary. The reaction is reversible and atom efficient, with ethylene the only by-product, thus making it a good choice for industrial processes, such as the Shell Higher Olefin Production (SHOP) and Further Exploitation of Advanced Shell Technology (FEAST) process. Olefin substrates are generally easy to prepare and less expensive than those associated with other carbon-carbon bond forming reactions, such as unsaturated boranes, stannanes, halides and triflates. Olefin products are usually suitable for further structural exploration and elaboration and can undergo a variety of reactions including hydrogenation, epoxidation, halogenations and cycloaddition, making it a useful tool for natural product synthesis. It is generally accepted olefin metathesis takes place via the Chauvin mechanism which will be discussed later along with its development.

3.1.1 Definitions

Within this thesis several defined terms set out by the IUPAC commission are used to describe synthesised or literature compounds. These terms are used to eliminate ambiguity when discussing groups relating to one another, addition outcomes and stereochemistry. Here these terms will be introduced and described with examples given where necessary.
To begin with diagrams which illustrate stereochemistry will be drawn with bold wedges \(\rightarrow\) to depict atoms or groups above the plane of the drawn molecule. A dashed wedge \(\cdots\) will be used to show atoms which are below the plane of the molecule.

A bold bond is sometimes used \(-\) instead of a bold wedge, where as a broken line \(-\) will be used to depict either a partial bond, delocalisation or hydrogen bonding. If the stereo chemistry is unknown this will be indicated by the way of a wavy line \(\sim\).

In general the ortho-fused sing systems are kept in the plane of the drawing and the bridgehead substituents are shown above or below the plane (Figure 1).

![Figure 1: Structures depicting stereochemistry](image)

Double bonds will be shown (30, 31, and 32) as far as possible with the accurate angles (~120°) if stereochemistry is implied. If there is no stereochemistry present then a linear representation will be used (Figure 2).

![Figure 2: Double bond schematic with and without stereochemistry](image)

Where possible perspective drawing will be used and the edge of the ring which is considered front facing will be represented by a bold or wedged line (Figure 3).
When describing the relationship between two ligands attached to separate atoms that are connected by a double bond or contained within a ring the terms \textit{cis} and \textit{trans} will be used. The two ligands are said to be \textit{cis} to each other if they lie on the same plane, whereas \textit{trans} is used if they are on opposite sides (Figure 4).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Perspective drawings}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Relationships between ligands}
\end{figure}

As this thesis contains many examples of bicyclo[x.y.z]alkenes the terms \textit{exo}, \textit{endo}, \textit{syn} and \textit{anti} will be used to describe the relative orientations of groups attached to non-bridgehead and bridgehead atoms. If the group is oriented towards the highest number bridge (z-bridge e.g. C-7 in the example below) it is given the description \textit{exo}. If it is orientated away then it is described as \textit{endo}. If a group is attached to the highest numbered bridge and is orientated towards the lowest numbered bridge is it’s described as \textit{syn}. However, if the group is orientated away from the lowest number bridge is it’s described as being \textit{anti} (Figure 5).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Bicyclo[x.y.z]alkene ligand relationships}
\end{figure}
These descriptions also apply to addition products. Specifically, in this work *syn* and *anti* are used to describe the stereodefined Grignard reagent addition outcomes. Additions to norbornyl compounds are described as being *syn* or *anti* to the double bond and example is shown the diagram below (Figure 6).

![Norbornyl syn and anti relationships](image)

**Figure 6: Norbornyl syn and anti relationships**

The final two terms requiring definition are *de* and *dr*. The first *de* is defined as the percent diastereoisomer excess and can be calculated using the equation below.

\[
de = \frac{(D_1 - D_2)}{(D_1 + D_2)} \times 100
\]

Finally *dr* is defined as the ratio of the percentage of one diastereoisomer in a mixture to that of the other.
3. Introduction

3.1 Olefin metathesis historical overview

The first reported discovery of olefin metathesis was by Karl Ziegler in the 1950’s. It was found that by forming an *in-situ* catalyst, later known as Ziegler-Natta catalysts, from transition metal salts and main group alkylating agents, they could subsequently promote the polymerisation of alkenes. Not only this but these “Ziegler” catalysts gave an entirely different mechanistic process, a mutual alkylidene exchange reaction of alkenes and new transformation comprised of the cleavage and formation of double bonds.\(^5\)

In 1959, Montague *et al.* reported that the “polymerisation of ethylene and other olefins has also provided a means for effecting the polymerisation of norbornene, a monomer not yet polymerised by any catalytic method.” They described this new method of polymerisation as “coordination polymerisation” as it involved the coordination of group IVB or VIB organometalics (Scheme 5).

\[ \text{Scheme 5: Polymerisation of norbornene} \]

Montague demonstrated that a catalytic system derived from lithium aluminium tetraheptyl and titanium tetrachloride could ring open norbornene, allowing for its polymerisation. Scheme 6 presents what he believed to be happening mechanistically during the polymerisation of norbornene.

\[ \text{Scheme 6: Montague’s proposed mechanism using a Ti catalyst} \]
According to Montague, during the reaction the RTiX intermediate first coordinates to the double bond via a $\pi$-complex. A concerted SN1 reaction then takes place breaking the carbon-carbon double bond, forming the new alkylidene-titanium bond. This is then repeated with a second monomer of norbornene (Scheme 6).\(^6\)

In 1971, Chauvin proposed a mechanism involving a 4-membered metallacyclic intermediate, in what is now believed to be the actual mechanistic process taking place during metathesis.\(^7\) He observed in some cases where a pair-wise mechanism, such as the “quasi-cyclobutane”, predicted only the two olefin products resulting from the pair-wise exchange of the two ends of the starting olefins. However, the olefins from the cross products were also observed very early on in the reaction. Some assumptions of the pair-wise mechanism would allow for this, but instead Chauvin proposed his own idea; he proposed that the mechanism involved the fragmentation of the olefins, in a non-pairwise fashion, through what is now known as the “carbene” mechanism (Scheme 7).

\[
\begin{align*}
\text{Scheme 7: Generalised Chauvin mechanism} \\
\begin{array}{c}
\text{55} \\
R_1 \equiv M \\
R_2 \\
\end{array} & \xrightarrow{\text{R}} \\
\begin{array}{c}
\text{56} \\
R_1 \\
R_2 \\
M \\
\end{array} & \xrightarrow{\text{R}} \\
\begin{array}{c}
\text{57} \\
R_1 \\
R_2 \\
\end{array} 4 \equiv M \\
\end{align*}
\]

In 1974, Casey was the first to implement carbenes into the metathesis reaction mechanism, by using a Fischer carbene (alkylidene) in a metathesis like exchange.\(^8\) In an effort to find a less stable and therefore more reactive metal carbene complex, (diphenylcarbene) pentacarbonyl tungsten was synthesised and reacted with several alkenes (Scheme 8).
3. Introduction

Scheme 8: (Diphenylcarbene)pentacarbonyl tungsten reacted with several alkenes

The equilibrium between a metalacyclobutane and metal complex containing both an alkene and carbene ligand provided significant support for Chauvin’s olefin metathesis mechanism. In the same year, Shrock also provided support for the Chauvin mechanism by forming alkylidenes under metathesis like conditions.\(^9\)

In 1976, Grubbs provided evidence against the pair-wise mechanism and after collaboration with Casey in 1974 he devised a mechanistic study involving ring closing metathesis and deuterium labelling. This would allow distinction between the pair-wise and non-pairwise mechanisms.\(^10,11\) First he prepared 1,1,8,8-tetradeutero-1,7-octadiene 67 and then mixed it with the non-deuterated analogue and this was allowed to undergo metathesis with a catalyst (69) known at the time to give cyclohexene, which is not reactive in metathesis, and ethylene. As the unreactive cyclohexene is formed the experiment allowed for the prediction of the by-product outcome for both the pair-wise and non-pair-wise reaction mechanisms (Scheme 9).
The kinetic products formed contrary to the ratio shown for the pair-wise mechanism, and to explain this using the pair-wise mechanism would require unreasonable assumptions, and so Grubbs’ work further proved the non-pairwise Chauvin mechanism to be the more likely route.

Grubbs expanded on this and used cis,cis-1,1,1,10,10,10-hexadeutero-2,8-decadiene in place of the labelled 1,7-octadiene. In this experiment the labelled product was cyclohexene and the cis and trans 2-butene. By coupling an isotopic label and a stereochemical label they could demonstrate that the unfavoured cis isomer of the product 2-butene was completely scrambled as required in the non-pairwise mechanism. Katz went on to do a complete analysis of the Chauvin mechanism. He demonstrated that the ratios of the products obtained were inconsistent with a pair-wise mechanism; and although these experiments did not prove the Chauvin mechanism, the use of ring closing reactions to produce six-membered rings and labelled acyclic olefins finally discredited the pair-wise mechanism, and groups now considered the variations on the basic Chauvin mechanism as the most reasonable.
3.3 Catalyst Development

With the mechanistic working understood, research turned towards the catalyst and catalytic systems. The first practical metathesis system was introduced in 1978 by Tebbe, based on what later became known as the Tebbe reagent.14

Grubbs along with Evans investigated the Tebbe reagent in a “Wittig type” reaction, converting esters into vinylethers (Scheme 10).15

![Scheme 10: Conversion of esters into vinylethers using the Tebbe reagent](image)

Secondly in another mechanistic study, Grubbs made unsymmetrical Tebbe complexes to discover the structure of the metallacycle intermediate. Using the Tebbe reagent, the addition of pyridine resulted in a stable metallacyclic complex, allowing the structure of this compound to be determined (Scheme 11).16

![Scheme 11: Unsymmetrical Tebbe reagent reacting with pyridine to give a stable metallacyclic complex 79](image)

Schrock and co-workers developed tungsten and molybdenum alkylidene complexes that contained bulky imido ligands. These complexes had high activities and could be prepared easily, and importantly were stable. They provided the first controlled catalysis in metathesis and were the basis for Grubbs work on organic polymer synthesis.17
3.3.1 Developments in molybdenum catalysts

Schrock’s initial work in 1979 was based on tantalum carbenes, which he had been working on since 1974. The initial results were disappointing as the reaction of Cp(TaCH-t-bu)Cl₂ with ethylene only yielded a metallocyclopentane and no metathesis product (Scheme 12).

Scheme 12: Formation of using a tantalum carbene metallocyclopentane

However, by tweaking his original structure and replacing the chlorine groups with t-butoxide and the Cp group with an organophosphine, metathesis did take place with cis-2-pentene. Certain tungsten-oxo complexes such as W(O)(CH₃-t-bu)(Cl₂)(PEt₃) were also found to be effective. However, they are extremely sensitive to oxygen and moisture, limiting their use to Schlenk techniques only, although their super reactivity did compensate for their handling. Schrock’s alkylides for olefin metathesis (Mo(NAr)(CHMe₂)R(OC)(CH₃)(CF₃)₂) were commercialised in 1990 (Figure 8).
These catalysts allowed the formation of tri- and tetra-substituted double bonds by RCM. An important additional advantage of Schrock’s catalysts was their tolerance towards functional groups that inhibited many ruthenium based metathesis catalysts at the time (Scheme 13).

Scheme 13: Example of ruthenium inhibited reaction using a molybdenum catalyst

Adaptations were made to this successful catalyst, paving the way for different types of asymmetric metathesis.20 Schrock’s first asymmetric catalyst was reported in 1993 (Figure 9).21

Figure 9: Schrock’s asymmetric molybdenum catalysts
3. Introduction

[Mo]-II can initiate asymmetric RCM and asymmetric ring opening-ring closing (RO/RC), and contains an elaborate cyclic mimic of the OCMe$_2$(CF$_3$)$_2$ units.$^{31}$ With Schrock catalyst [Mo]-III modified with a BINOL ligand and used in a norbornadiene ring-opening polymerisation metathesis (ROMP), a highly stereoregular cis, isotactic polymer is obtained (Scheme 14).

3.3.2 Ruthenium based catalysts

In the mid 1980’s, the research that would lead to the Grubbs ruthenium catalysts was initiated. With any catalyst system, functional groups or solvents can interfere with activity. As shown in the table below, titanium and tungsten catalysts are strongly disposed to olefinate ketones and esters. However in comparison, molybdenum catalysts, which are more reactive towards olefins, also react with aldehydes in protic and aprotic solvents. Ruthenium preferentiality reacts with olefins over most other species, which makes it an excellent metathesis candidate (Table 1).$^{22}$
3. Introduction

Grubbs theorised that polymers prepared from 7-oxonorbornene might be good ionophores. After finding that none of the current catalysts based on tungsten and titanium worked during polymerisation, research began on catalysts that were prepared from late metal salts. It was found that ruthenium trichloride not only polymerised olefins, but could even generate high molecular polymers in water. It was assumed that these new catalyst systems worked in a similar way to the molybdenum and tungsten catalysts and so a metal carbene must be involved. If this was the case then it would have to be different from the alkylidene complexes known at the time.

Mechanistic studies indicated that a strained ruthenium and olefin were key to its success and these observations provided the understanding needed to form a well defined ruthenium based catalyst. Ruthenium (II) and diphenylcyclopropene were reacted together to give a stable 16e- ruthenium carbene complex. This was then used for the polymerisation of norbornene and was found to be stable in protic solvents (Scheme 15).

<table>
<thead>
<tr>
<th>Titanium</th>
<th>Tungsten</th>
<th>Molybdenum</th>
<th>Ruthenium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid</td>
<td>Acid</td>
<td>Acid</td>
<td>Olefins</td>
</tr>
<tr>
<td>Alcohol, Water</td>
<td>Alcohol, Water</td>
<td>Alcohol, Water</td>
<td>Acids</td>
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<td>Aldehydes</td>
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<td>Olefins</td>
<td>Esters, Amides</td>
<td>Esters, Amides</td>
<td>Esters, Amides</td>
</tr>
</tbody>
</table>

Table 1: Table showing the reactivity of metals towards functional groups

Grubbs theorised that polymers prepared from 7-oxonorbornene might be good ionophores. After finding that none of the current catalysts based on tungsten and titanium worked during polymerisation, research began on catalysts that were prepared from late metal salts. It was found that ruthenium trichloride not only polymerised olefins, but could even generate high molecular polymers in water. It was assumed that these new catalyst systems worked in a similar way to the molybdenum and tungsten catalysts and so a metal carbene must be involved. If this was the case then it would have to be different from the alkylidene complexes known at the time.

Mechanistic studies indicated that a strained ruthenium and olefin were key to its success and these observations provided the understanding needed to form a well defined ruthenium based catalyst. Ruthenium (II) and diphenylcyclopropene were reacted together to give a stable 16e- ruthenium carbene complex. This was then used for the polymerisation of norbornene and was found to be stable in protic solvents (Scheme 15).

![Scheme 15: Formation of the stable 16e- ruthenium carbene](image)

Compound 94 was only reactive for metathesis with electron rich and strained olefins, and so in order to increase its reactivity it was subjected to ligand exchange experiments. Schrock had previously shown that activity increased as the metal centre became more electrophilic.
When substituted with a basic cyclohexylphosphine ligand the desired reactivity was achieved, the compound would now polymerise unsaturated and acyclic olefins. These were shown to have just as much reactivity as Schrock’s catalysts and promoted many of the same reactions. What was unique was that they did not share the same instability in air as Schrock’s catalysts and could consequently be handled using standard organic techniques in air, and under a N₂ atmosphere in reaction flasks.

By 1996, an excellent route to ruthenium benzylidene complexes had been developed. These complexes showed high activity and rapid initiation, and quickly became the basis of development for the ruthenium metathesis technology (Scheme 16).

![Scheme 16: Development of [Ru]-I catalyst](image)

The mechanistic understanding was important to the catalyst development. The key discovery was that the reaction proceeded after the loss of one neutral ligands to produce the 14e⁻ species. Grubbs’ group proposed that the higher activity of the more basic phosphine is a result of the intermediate metallacycle, since progression from the carbene olefin complex to the metallacycle involves the oxidation of the metal centre, in addition to favouring the addition of a π-acidic olefin (Scheme 17). The less bulky phosphines coordinated to the metal centre too strongly and were not susceptible to dissociation or initiation.
3. Introduction

Scheme 17: Catalytic cycle of Grubbs catalyst

After this the Grubbs group went on to synthesise analogues of [Ru]-I by substitution of the phosphines with NHC’s. After testing 10 different systems, the most stable was found to be an NHC substituted with mesityl groups, with 1,3-dimesitylimidazolin-2-ylindene (IMES) the key ligand. These IMES groups gave stability with only one phosphine group substituted by an NHC and showed high activity. The NHC provided a strong electron donor to stabilise the intermediates, and the phosphine provided the labile ligand to give the 14e⁻ species (Scheme 18).²⁹

Scheme 18: Development of [Ru]-II catalyst

With this knowledge Grubbs moved on to develop a chiral NHC catalyst from the commercially available (1R,2R)-diphenylethylenediamine. Palladium coupling with mesityl bromide gave the precursor for the formation of the dihydro-2-imidazazolium salt. This was
then substituted for one of the phosphines and resulted in the reactive complex [Ru]-II, which was found to be more reactive than the [Ru]-I catalyst.\textsuperscript{30}

This increased reactivity was assumed to have come from the NHC systems and their ability to donate $\sigma$ electrons, resulting in a strong \textit{trans} effect. However, mechanistic studies found that the NHC species actually slows the 14e$^-$ formation by up to $10^2$.\textsuperscript{31} The increased reactivity was actually due to the favoured reaction of the $\pi$ acidic olefin relative to the basic $\sigma$ donor system, and this accounts for the activity in metathesis.\textsuperscript{32}
3. Introduction

3.4 Types of olefin metathesis

With an understanding of mechanistic pathways and reliable, efficient catalyst systems, it is important to understand the different types of olefin metathesis. There are four fundamental types of metathesis; Ring Closing Metathesis (RCM), Cross Metathesis (CM), Ring Opening Metathesis Polymerisation (ROMP) and Acyclic Diene Metathesis Polymerisation (ADMET) (Scheme 19). Through these reactions, olefin metathesis provides a route to unsaturated molecules that are often challenging or impossible to prepare by other means. The most impressive achievements include the use of ROMP to make functionalised polymers, the synthesis of small and large heterocyclic systems by RCM and the CM of olefins with pendant functional groups.

![Scheme 19: Main types of olefin metathesis](image)

3.4.1 Cross metathesis

CM has become an invaluable method for the preparation of olefins (Scheme 20). While CM is typically conducted under mild conditions and is tolerant of a variety of functionalities, the $E/Z$ ratios of the reaction are more difficult to control and predict.21

![Scheme 20: General example of CM](image)
However, due to the recent developments in catalyst design and reaction understanding, predictability has improved. The scheme below (Scheme 21) illustrates the pathway of cross metathesis between two symmetrically substituted olefins.

![Scheme 21: CM mechanism](image)

The initial reaction is a [2+2] cycloaddition between 113 and the metal carbene 112 to give the metallacycle 106. Substrate 106 can then undergo a subsequent collapse in a productive fashion to give the new olefin 111 and metal carbene (alkylidene) 110, that can then react with a molecule of 109 via 111 to give 112 and 107 again, these then re-enter the cycle.

### 3.4.2 Ring-closing metathesis

RCM has over the last 50 years become an important tool for the formation of carbon-carbon bonds and as a consequence it has had a profound impact on total synthesis. The first examples date back to 1980 where Villemin and Tsuji used tungsten-based catalysts for the preparation of macrocycles from dialkenyl keto-esters and dialkenyl ketones. RCM consists of an intramolecular metathesis of a diene to form an olefin (Scheme 22).
3. Introduction

Scheme 22: RCM mechanism

The reaction pathway of the diene depends on several factors including the catalyst, reaction mixture dilution, ring size and the substrate. ADMET can be avoided by applying the dilution principal. Typically ruthenium catalysts are preferred over molybdenum catalysts from a synthetic standpoint as they are easier to handle and have high functional group tolerance. As discussed earlier, Grubbs and co-workers reported the first examples of carbocyclisation using a functional-group tolerant molybdenum-based carbene catalyst (silyl ethers, esters, alcohols, and benzyl ethers were all tolerated). Numerous research groups have since used RCM to synthesise highly complex and naturally occurring molecules.

3.4.3 Ring-opening metathesis polymerisation

ROMP is catalysed through the formation of a metal-carbene complex and requires a strained cyclic structure, as the driving force of the reaction is the relief of the ring strain within that structure. After the formation of the metal-carbene species attacks the carbon-carbon double bond in the ring structure forming a highly strained metallacyclobutane intermediate. This ring then opens, giving the beginning in the polymer chain, consisting of a linear chain double bonded to the metal with a terminal double bond. A new carbene then reacts with the terminal double bond on the next monomer, therefore propagating the reaction (Scheme 23).
Since its discovery, ROMP has become an important reaction for the formation of well defined polymers. Since Ziegler and Natta's early studies on ethylene and polypropylene polymerisation, extensive research efforts have been made into the transition metal catalysed polymerisation and its mechanism, which have ultimately lead to the development of ROMP. When Grubbs developed the first well defined ruthenium alkylidene, it paved the way for a new generation of functional group tolerant ROMP catalysts. These advances made ROMP the method of choice for the synthesis of complex polymeric structures. The [2.2.1] norbornenes strained bicyclic structure make an ideal monomer for ROMP and polymerisation, and using Grubbs catalysts leads to higher reaction control. Also, norbornene can be readily functionalised, which has been exploited by many research groups to synthesise polynorbornene side chain functionalities, such as catalysts, biological reagents, hydrogen bonding units and trapping molecules. The living character of this polymerisation also allows for the introduction of two monomers, resulting in the formation of alternative co-polymers. These co-polymers can impart a wide range of properties to the bulk polymer.
3. Introduction

3.5 Ring rearrangement metathesis in natural product synthesis

The aim of this chapter is to emphasise the impact metathesis has had on the synthesis of natural products and biologically active compounds, with a focus on metathesis cascades involving norbornenes. These routes have provided new and elegant solutions to many complicated synthetic puzzles. Combinations of cleverly designed cascades have led to some impressive synthesis of structurally complex natural products.\(^{37}\)

Many metathesis transformations can be promoted by the same carbene catalysts, and as such can be combined sequentially into one pot metathesis cascades. A tandem or domino process is a process in which two or more bond forming transformations take place under the same reaction conditions with no additional reagents or catalysts, and where the subsequent reaction results from the consequence of the functionality formed in the previous step.\(^{38}\) These reactions are highly desirable as they can tremendously increase molecular complexity with the use of one catalyst, and are both ecologically and economically favourable.

At the heart of metathesis’ advancement has been the development of the catalysts mentioned previously and their unique carbon-carbon bond formation. This advancement, for example, has given over 20 commercially available ruthenium based catalysts alone over the last 20 years. Ruthenium has been heavily favoured over molybdenum catalysts in this process due to their functional group tolerance and the drive towards the thermodynamically stable products and has been discussed previously (Figure 10).

![Common commercially available ruthenium catalysts used in cascade metathesis](image)

There are many possible combinations for tandem metathesis reactions, increasing the process complexity with the number of transformations needed. Much effort has been
invested into developing new methodologies and applying these to biologically active and naturally occurring compounds. This review of the area will briefly show the many possibilities and give examples of these applications towards natural product synthesis.39,40

3.5.1 RCM-ROM- ring rearrangement metathesis (RRM)

When RCM and ROM are combined together in a tandem process it is commonly referred to as Ring Rearrangement Metathesis (RRM). This process possesses an extraordinary synthetic potential when it comes to constructing carbocycles and heterocycles. It has become a key synthetic step in many natural product syntheses ever since the first application of RRM towards the synthesis of (−)-halosilane, using a ruthenium catalyst, by Blechert in 1999 (Scheme 24). 41

![Scheme 24: Blechert's use of RRM in the synthesis of (−)-halosilane](image)

By definition, in these domino reactions strained carbocyclic alkenes are transformed into a new carbocycle by an intramolecular ROM-RCM, with an endocyclic double bond. Probably the most important feature of RRM is the capacity to transfer any stereochemical information from the starting material to the product, as stereocenters remain unchanged during the metathesis process. The RRM transformation allows the stereocenter to be transferred to the side chain or *vice versa*, avoiding complicated multistep synthesis of chiral structures which are otherwise difficult to access (Scheme 25).
RRM can also be applied to mono- and polycyclic structures of varying sizes. The strategic selection of protecting groups, reaction conditions and electronic properties of the reacting parts is crucial due to the reversibility of the metathesis cascade, and it is important to shift the equilibrium towards the desired product. Bicyclic structures deserve a special mention among the different types of substrates suitable for the metathesis reactions. The highly strained ring system present in bicycles makes them highly reactive and the driving force for the reaction can be directly attributed to the release of this energy. The introduction of an external olefin, usually ethylene, is almost always necessary to avoid oligomerisation, a common and unwanted side reaction of RRM.

Blechert has also applied rearrangement metathesis to the synthesis of tetrapanerine T7. \(^{42}\) Tetraponerines are isolated from the New Guinean ant Teraonera and were synthesised using a flexible approach that permitted the construction of five and six membered heterocycles by varying the length of the \(N\)-alkenyl substituent on the cyclopentene. Blechert subjected the metathesis precursor 134a,b to ruthenium catalyst [Ru]-I (5 mol%) resulting in 135a and a 71% conversion after two days under an ethylene atmosphere. Changing the protecting group to benzyloxycarbonyl (Cbz) allowed the transformation to take place in 12 h at room temperature and 135b was isolated in 97% yield. They believed the difference in reaction time may have been a result of complexation of the ruthenium carbene during the reaction (Scheme 26).
3. Introduction

Scheme 26: Synthesis of Tetraponerine T7 using a RRM transformation

3.5.2 RRM of norbornene substrates

Norbornene derivatives have become a common substrate for ring-rearrangement domino metathesis. This is due to their highly strained ring systems, which means the equilibrium is strongly shifted towards the formation of the product (Scheme 27). As the synthesis of highly stereocontrolled norbornenes is relatively problem free this approach has granted easy access to new architectures which would otherwise be hard to achieve.

Scheme 27: General scheme for RRM of a norbornene
Several different mechanistic pathways account for the domino reactions of norbornene, for example the proposed mechanism in **scheme 28**. Initial attack at the terminal exocyclic double bond yields a metallacycle which could form a very strained intermediate \(142\). More interestingly, ring opening may also occur, leading to two intermediates \(144\) and \(148\). This has been found to depend upon the ring size of the final product, as well as the presence of ethylene in the atmosphere. By using ethylene it is possible to convert \(144\) to \(146\) and shift the equilibrium to the most stable compound \(149\). Importantly, dimeric or oligomeric material that is formed during this kind of cascade can revert back to the monomeric ruthenium-alkylidene, and thereby avoiding the formation of major by-products.

Attack at the less hindered and kinetically favoured olefin cannot be excluded, although it is more likely that the cascade starts with ROM, with the loss of ring strain being the main driving force (**Scheme 28**).\(^{43}\)
The first example of using norbornene as a ring opening precursor was conducted by Grubbs and Gillom in 1986. They found that upon heating the metallacycles 150 or 151 in the presence of excess norbornene that an amorphous polymer was afforded in a 92% yield. This system was reported to be the only example of living polymerisation involving ring opening of cyclic olefins, and opened up a new avenue of polymer synthesis (Scheme 29).
3. Introduction

Scheme 29: The first example of norbornene ring opening using an excess of norbornene

Interesting synthetic applications of RRM have been widely reported; Aubé et al. following on from pioneering work on the synthesis of bicyclic systems using RRM from norborene derivatives, applied this strategy towards the synthesis of indolizidine 251F. Enone 155 was obtained from the RRM of norbornene 154. Initial attempts gave the desired product in poor yields (30%) mainly due to olefin oligomerisation. However, when an atmosphere of ethylene was introduced it was possible to optimise the metathesis cascade and gave 155 in 93% yield using [Ru]-I (5 mol%) (Scheme 30).

Scheme 30: Synthesis of Indolizine 251F involving the RRM of a functionalised norbornene

Chandler and Phillips used a similar approach in the synthesis of (+)-trans-lumausyne, a compound isolated from red algae Laurencia in Japan. They subjected oxa-norbornene derivative 159 to [Ru]-I (5 mol%) in CH2Cl2 under an ethylene atmosphere, and isolated the desired ROM-RCM tetrahydrofuran product 160 in 83% yield (Scheme 31).
A more recent approach published by the same group, used a RRM cascade to synthesise aburatubolactam A. This macrolactam is isolated from bacteria of a marine mollusc, also located in Japan. It is a member of a growing class of mixed polyketide amino acid metabolites that has been found to display a diverse range of biological activities, including cytotoxicity, antimicrobial activity and importantly the inhibition of superoxide generation, a compound released by the immune system to combat microorganisms. Their approach included a Stille coupling, a Lacey-Dieckmann cyclisation and a ROM-RCM as key features. When treated with [Ru]-I under an ethylene atmosphere, enone 163 was rearranged to 164 in 90% yield. In the absence of ethylene atmosphere the yield decreased significantly, giving 164 in only 41% yield (Scheme 32).
Another recent publication including the use of domino metathesis was reported by Barbe and Charette. Their target compound was (+)-ent-lepadine B, which is isolated from the tunicate of Claveline lepadiformis, and has been shown to exhibit significant *in vitro* cytotoxicity against several types of human cancer cells. Lepadine B has also been identified as a blocker of neuronal nicotinic acetylcholine receptors which have been implicated in many neurological conditions, ranging from nicotine addition to Parkinson and Alzheimers diseases. Compound 167 was subjected to [Ru]-II catalysis (2 mol%, toluene, 80 °C) affording the rearranged product 170 in 79% yield, after just two minutes (Scheme 33).
Scheme 33: Synthesis Lepadin B using a RRM transformation starting from pyridine
3.6 Diastereoselective Ring Closing Metathesis reactions (DSRCM)

As previously stated, the discovery of ruthenium carbene complexes and their applications as efficient catalysts for metathesis reactions had led to a plethora of different synthetic methods. One interesting avenue has been the use of chiral (racemic or non-racemic) precursors. These precursors, if they contain diastereotopic vinyl or allyl groups, can turn ring closing metathesis into a diastereoselective process (Scheme 34).

Scheme 34: Diastereoselective ring closing metathesis cis/trans outcome

The first example of this interesting process was described by Blechert and co workers in 1996. They were interested in using a RCM reaction which contained existing chiral centres that would control the cyclisation with a prochiral diene. It was hoped that this could then be used to access natural products and biologically active compounds, such as pheromones and glycosidase inhibitors, that contain α,α’-disubstituted pyrrolidine or piperidine subunits.

It was important that during the diastereoselective metathesis, the olefins at the prochiral centre did not react together, and that the primary carbene attack took place at the olefin of the chiral centre. In the case of the [Ru] and [Mo] catalysts the rate of metathesis can be significantly reduced by steric effects, and thus, they attached an additional methyl group to the prochiral olefins to prevent the formation of the metallacycle at these olefins and precluded the ring closure between these two double bonds by using a 1,4-diene.

The trienes employed by Blechert were synthesised from the racemic Cbz-protected amino acid 175 or the enantiometric pure 176 (Scheme 35). The prochiral diallyl group was prepared by the addition of propynylborane or borate to the tetrolimine, followed by a Birch reduction. RCM cannot take place in the presence of basic amines so this group was converted to its trifluoroacetamide (181 and 183) and the oxazolidinone (186).
With the metathesis precursors in-hand, the group went on to attempt the cyclisation, using either ruthenium or molybdenum catalysts (Scheme 36).

As can be seen from table 2 the cyclisation took place in good yields and the choice of catalyst made a significant difference to the cis/trans ratio obtained. When using the ruthenium catalyst to induce cyclisation to the six membered rings 187 and 188, no diastereomeric excess was observed. In contrast, the best cis/trans ratio selectivity was obtained using the molybdenum catalyst, giving a ratio of 26:74 (Entry 2). The group attempted to improve upon this selectivity by raising the temperature, but this was found to only give a moderate improvement (Table 2, Entry 7).
3. Introduction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product</th>
<th>Cat (mol%)</th>
<th>Conditions</th>
<th>cis/trans</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>Rac-181</td>
<td>Rac-187</td>
<td>[Mo] (10)</td>
<td>Rt 20h</td>
<td>34:66</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>Rac-181</td>
<td>Rac-187</td>
<td>[Mo] (10)</td>
<td>80 °C 1h</td>
<td>26:74</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>Rac-186</td>
<td>Rac-188</td>
<td>[Ru] (5)</td>
<td>Rt 20h</td>
<td>50:50</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>Rac-183</td>
<td>Rac-188</td>
<td>[Ru] (10)</td>
<td>Rt 20h</td>
<td>4:96</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>Rac-183</td>
<td>Rac-187</td>
<td>[Ru] (10)</td>
<td>80 °C 1h</td>
<td>8:92</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>Rac-183</td>
<td>Rac-187</td>
<td>[Mo] (5)</td>
<td>Rt 20h</td>
<td>84:16</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>Rac-183</td>
<td>Rac-187</td>
<td>[Mo] (10)</td>
<td>80 °C 1h</td>
<td>86:14</td>
<td>97</td>
</tr>
</tbody>
</table>

Table 2: Table of results for the cyclisation of trienes 181 – 186

The cyclisation to give the five membered rings was found to be sluggish, and required significantly longer reaction times. Interestingly, slower reaction times gave better selectivity, in this case it was the ruthenium catalyst which performed best. It provided the trans-product 191 with a de of 92%, where as the best results obtained using the molybdenum based catalyst was 72% de for the cis product 190 (Scheme 37).

Scheme 37: Cyclisation of five membered rings followed by lithium aluminium hydride reduction
Lautens and Hughes\(^5\) further utilised this new approach by applying the diastereoselective ring closing metathesis (DSRCM) to the synthesis of novel bicyclic diallylic alcohols and ethers with \(\sigma\) plane of symmetry, that are not readily accessible by conventional techniques. Their studies were conducted using tetraenes of the general structure 194 (Scheme 38).

![Scheme 38: Possible RCM pathways and products in the formation of (+)-mevinolin skeleton](image)

They understood that the initial carbene attack would take place at the olefin \(a\), and that a substituent \(\alpha\) to that olefin would hinder its participation in the RCM reaction. Using the compound 194 they anticipated that it could cyclise in two ways, to give either the cyclised product 195 or 193. Only compound 195 would further cyclise to give the desired bicyclo[4.4.0]decadiene, and even though 193 is formed initially, it would eventually yield 196 by reacting with the catalyst and ring opening to the original tetraene. They assumed that 197 would be the thermodynamically preferred system and this would be obtained in a mixture of \(cis\) and \(trans\) isomers. This would give an efficient entry into the tetrathydrophthalene skeleton found in HMG CoA reductase inhibitor (+)-mevinolin.

Using ruthenium and molybdenum catalysts the group then attempted the DSRCM and initial examination gave surprising results (Table 3).
3. Introduction

Table 3: DSRCM results if tetraenes 199 - 201

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp °C</th>
<th>cis/trans</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>199</td>
<td>202</td>
<td>[Ru]-I</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>8:1</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>199</td>
<td>202</td>
<td>[Mo]-I</td>
<td>C₆H₆</td>
<td>rt</td>
<td>8:1</td>
<td>82</td>
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<tr>
<td>3</td>
<td>200</td>
<td>203</td>
<td>[Ru]-I</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>1:2.8</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>201</td>
<td>204</td>
<td>[Ru]-I</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>cis</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>201</td>
<td>204</td>
<td>[Mo]-I</td>
<td>C₆H₆</td>
<td>rt</td>
<td>cis</td>
<td>66</td>
</tr>
</tbody>
</table>

When compound 199 was treated with conditions A, cycloheptene 202 was the major product. This allowed them to conclude that the substituents α to olefin b (Scheme 38) are more influential to the type of cyclisation occurring rather than the ring size formed.

Treatment of compounds 199 or 205 with [Ru]-I under an atmosphere of ethylene gave the desired bicycle 202 in good yield and as a mixture of diastereoisomers with a ratio of 8:1, and with the cis isomer as the major product (Scheme 39). It was found treatment using the molybdenenum catalyst gave essentially the same results.

Scheme 39: Intermediates and by-products of tetraene metathesis
When the unprotected alcohol was cyclised a 2.8:1 mixture of diastereomers was isolated in good yield, with the *trans* isomer now being the dominant product. The ethylene atmosphere presumably helps the formation of the more reactive catalyst (Table 3, Entry 3).

With these promising results the group also looked into the preparation of [3.3.0] bicyclic compounds. Tetraene 201 was treated with 4 mol% of catalyst [Ru]-I, and after 20 h the *cis* isomer was formed in 81% yield, with 12% of the monocyclic compound 206. They also prepared the trienes 157-160 to gain a better insight into the diastereoselectivity of the initial cyclisation (Table 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>R*,S*:S*,S*</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>208 R=H, n=1</td>
<td>212</td>
<td>[Ru]-I</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>1:2.8</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>209 R=PMB, n=1</td>
<td>213</td>
<td>[Ru]-I</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>6.1:1</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>209 R=H, n=0</td>
<td>213</td>
<td>[Mo]-I</td>
<td>C₆H₆</td>
<td>rt</td>
<td>7.8:1</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>210 R=H, n=1</td>
<td>214</td>
<td>[Ru]-I</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>1:1</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>211 R=H, n=0</td>
<td>215</td>
<td>[Ru]-I</td>
<td>CH₂Cl₂</td>
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<td>8.0:1</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>211 R=H, n=0</td>
<td>215</td>
<td>[Mo]-I</td>
<td>C₆H₆</td>
<td>rt</td>
<td>1.7:1</td>
<td>94</td>
</tr>
</tbody>
</table>

Table 4: Results to show diastereoselectivity of the ring closing metathesis of trienes 208 – 211

Exposing compound 208 to metathesis conditions obtained a 2.8:1 mixture of 16 with the *trans* isomer favoured (Entry 1). Again treatment of the unprotected alcohol gave the opposite result with the *cis* isomer being favoured by a ratio of 6:1. A repeat of the same reaction using the molybdenum catalyst gave a slightly better ratio of 7.8:1 (Entry 3).

Finally, treatment of trienes that would lead to vinylcyclopentene derivatives were investigated. Compounds 210 and 211 were treated with ruthenium catalyst [Ru]-I and gave
very different selectivities. Whereas 210 cyclised to 214 and gave a 1:1 mixture of isomers, the benzyl ether gave an excellent yield of 99% with a ratio of 8:1 (Entry 4). When the same benzyl ether was exposed to the molybdenum catalyst, rather than seeing an increase in diastereoselectivity the selectivity decreased to 1.7:1 (Entry 6).

One of the main uses for DSRCM since its first utilisation by Blechert has been in the synthesis of spirocyclic compounds. In 2000, Wallace and co-workers developed a synthetic route to NK-1 receptor agonists when they saw the potential to use the DSRCM as a possible route to forming spirocyclic rings in a single step. A range of N-tosyl protected key intermediates were prepared in a three step synthesis from commercially available starting materials (Scheme 40).

![Scheme 40: Synthesis of N-tosyl intermediates](image)

These were then cyclised using the optimised metathesis conditions (0.05M chloroform solution of the tetraene with 5-6% of ruthenium, at room temperature) and this led to the complete conversion of the starting material in 2 h, giving separable spirocyclic diastereomers in good to excellent yields.

Following this work, Wallace also published work detailing the possible mechanistic pathways for these reactions. They found replacing the R group with a phenyl group and using the same metathesis conditions as previous studies yielded significantly lower diastereoselectivities (70% de instead of the previously achieved >90%). To understand this change molecular modelling was carried out. In the case of 201a and 201b and their epimers, there was found to be very little energetic difference between the two diastereoisomers.
suggesting that they are not under thermodynamic control. However, upon comparing 229 with epi-230 there was found to be a large energy difference. This would suggest, based on thermodynamic considerations that you would expect to see higher selectivity, which was not what Wallace observed. To establish what exactly was going on the group resubmitted 229 and epi-230 to metathesis conditions. They observed that the two isomers did not equilibrate and so the important step must be the order of ring formation. Scheme 41 shows the suggested mechanism.

![Scheme 41: Mechanistic reasoning for the formation of five-membered rings](image)

They hypothesised that the RCM mechanism can go via a five membered or six membered intermediate (a or b). Upon taking compound 222 and cyclising using only 1 mol% of the catalyst for 30 min, several reaction intermediates were observed; 20% of the mixture was the spirodienes (70% dr) 20% was starting material; and four other compounds which were isolated by HPLC. Dihydrofurans 223 and 224 were the found in larger amounts of 226 and 227, indicating that pathway a is predominant.

Compounds 223 and 226 then underwent metathesis again, and as expected yielded product 229. Interestingly, when 224 was allowed to cyclise it formed a 65:35 mixture of 230 and 229. This enabled the group to conclude that the selectivity of the reaction is based on the first cyclisation.
Through this work, and an expansion using a stereoselective reductive Heck reaction, the group was able to form a new seven step synthesis of a key NK-1 receptor agonist (Scheme 42).

![Scheme 42: Synthesis of NK-1 receptor agonist from the spirocyclic DSRCM product](image)

Another expansion of this work by Wallace was the replacement of the vinyl groups with allyl groups which would allow access to larger ring sizes. Ethyl lactate and ethyl 2-hydroxyhexanoate were reacted with allyl magnesium bromide to give the tertiary alcohols, which were then converted in a single step to 235a and 235b. These ring closed in excellent yields, but the stereoisomers were in a 1:1 ratio. This result was not surprising given the larger flexibility of the ether rings. The 8,5 ring side product was not observed. However, during the synthesis of 7, 6 system 237, compound 238 was the major by product (Scheme 43).

![Scheme 43 : Expansion of DSRCM to larger ring sizes](image)

The group then investigated the outcome of replacing the oxygen with a CH₂ group, with the hope to access larger ring systems, using their novel methodology. Compound 240 was synthesised via the allylation of methyl 6-heptenoate with KHMDS and benzyl bromide. The
3. Introduction

benzyl ester was then converted into the tetraene in two steps. The following DSRCM reaction gave the diastereoisomers in a 2:1 ratio. Other ring sizes could be generated using this method by choosing suitable starting materials and this method gives a new rapid access to bicyclic systems with two olefins, ready for further modification (Scheme 44).

![Scheme 44: DSRCM of tetraene 239 to give seven membered spirocycles](image)

Schmidt and Wildemann first entered this field when they started a project into the utilisation of RCM to synthesise C-glycosides. It was during this that the dihydropyrans 245a and 245b were formed in a mixture of diastereomers 4:1, and 5:1 cis/trans respectively (Scheme 45).

![Scheme 45: The use of DSRCM in the synthesis glycosides](image)

Using this result, Schmidt investigated the influential factors during the RCM stage which could lead to significant diastereoselectivity during the synthesis of dihydropyran using remote stereocentres (Scheme 46).
They prepared trienes 251a-c and subjected them to DSRCM. However, only very poor diastereoselectivities were observed. In the case of 251a a mixture of 2:3 cis and trans-254a was observed, whereas, for the protecting groups benzyl and TBDMS the cis isomer was the major isomer isolated. These results and the ones presented earlier by Lautens suggest that for DSRCM to be selective there needs to be a substituent at the neighbouring position to the newly formed stereocentre (Scheme 47).

Undeterred, tetraene 257 with an allyl side chain was also subjected to the metathesis conditions. This did in fact give a better diastereomeric ratio of 7:1. This was a surprising result as the ally group is less sterically demanding than the benzyl or silyl group, and therefore it should not dictate any selectivity (Scheme 48).

After the initial DSRCM results, Schmidt then added an allyl group to the cis-254 compound and 202 precursor. These were then ring closed to give the spirocyclic furan 258a-258b. They
believed the key to the selectivity lay with which ring formed first, the five or the six membered rings. To evaluate this they conducted a NMR-tube deuteration experiment and were able to track the course of the reaction. After 1 h it was found that the starting material had been completely consumed and the compounds $251\text{a}$ and $251\text{b}$ have been formed in a 1:1 \text{dr}. The second metathesis step proceeded rapidly to $258\text{a}$ and sluggishly to $258\text{b}$ to give a \text{dr} of 7:1. During this step $251\text{b}$ can be converted into $251\text{a}$ via ring opening/ring closing tandem sequence. The final six membered ring formation step being irreversible (Scheme 49).55

Scheme 49: Proposed mechanism for the formation of $258\text{a,b}$.

Spirocyclic groups often play a key role in synthetic scaffolds such as the spirocyclic $\gamma$-butarolactone group that is contained within the natural product stemotinine, and the antitumour and antibiotic aranososin (Figure 11). Furthermore, there are a variety of the methods for the conversion of $\gamma$-butarolactone into $\alpha$-methylene-$\gamma$-butyrolactones, and the spirocyclic, steroidal derivatives of these compounds have been found to have impressive biological activity.
Schmidt expanded his previous work to an interesting approach towards the synthesis of di- or tetrahydropyran derivatives that are linked to lactones in a spirocyclic fashion, with a further intent to functionalise the lactone via cleavage, to give pyran derivatives with functionalised side chains. After preparing the monocyclic precursors, the group used their previously devised synthesis for pyran derivatives with an exo-vinyl group. RCM of divinyl carbinol 206a and 262b gave dihydropyrans 268a and 268b in a diastereomeric mixture of 3:1 and 4:1 respectively. The RCM of triene 267 yielded the dihydropyrans (3R,6S)-271 and (3S,6S)-271 as a separable mixture of diastereoisomers (Scheme 50).

![Scheme 50: DSRCM products](image-url)
The resulting hydroformylation of the dihydropyran is highly chemo- and regioselective, with only the external vinyl group being attacked under the reactions conditions used. The hemiacetals 270 and 271 were obtained as inseparable mixture of isomers which were oxidised to their corresponding lactones. These results enabled Schmidt and coworkers to use the ring closing metathesis reaction and hydroformylation-acetalation sequence to synthesise bicyclic spiro compounds with lactone groups linked to six membered oxacycles.

The final example presented by Schmidt described the stereoselectivity of RCM reactions and their applications towards the synthesis of dihydropyran with functionalisable substituents. Divinyl carbinols, the key intermediates required were synthesised from commercially available α-hydroxy carboxylic acid esters (S)-ethyl lactate and DL-methyl mandelate.57

After the synthesis of the requisite precursors Substrates 273a-274a and 273b-274b were exposed to selected metathesis conditions and 3 mol% of [Ru]-I at 20 °C was used to cyclise the trienes to their corresponding ring closed products (Table 5)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>R</th>
<th>R'-X</th>
<th>Product</th>
<th>(2S,3S)/(2S,3R)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>273a</td>
<td>Me</td>
<td>Bn-Br</td>
<td>(2S)-275a</td>
<td>3:1</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>273a</td>
<td>Me</td>
<td>All-Br</td>
<td>(2S)-276a</td>
<td>1:2</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>273b</td>
<td>Ph</td>
<td>All-Br</td>
<td>rac-276b</td>
<td>1:6</td>
<td>87</td>
</tr>
</tbody>
</table>

Table 5: Results of RCM on divinyl carbonyls

Their findings are summarised in the table 5, a 1,2 stereoinduction was found to be more efficient for the phenyl derivatives, possibly due to the steric demand of the phenyl group compared to the methyl substituents. Conversion of the products was quantitative. The unprotected alcohol preferably formed the (2S, 3S) isomer whereas the benzyl and TBDMS
protected compounds favoured the formation of (2S, 3R) isomers. Subsequent deprotection of the TBDMS ethers 276a and 276b gave the alcohols 275a and 275b.

Next, they prepared the allyl ethers 277a and 277b as suitable substrates for a double ring closing metathesis reaction, leading to the formation of spirocyclic systems 278 and 279. The reaction proceeds slowly with only moderate yields. However, in both cases only one isomer was isolated, with no trace of the other diastereoisomer detectable (Scheme 51).

\[
\begin{align*}
277a & \quad R = \text{Me} \\
277b & \quad R = \text{Ph}
\end{align*}
\]

\[
\text{[Ru]I (3 mol\%)} \\
\text{CH}_2\text{Cl}_2, 20^\circ\text{C}
\]

\[
(5R, 6S)-178 \\
(5R^*, 6S^*)-279
\]

Scheme 51: Allyl ether DSRCM substrates and products

The double ring closing metathesis reaction was extended to the formation of spirocyclic compound 243. Starting from 280, an allylation reaction, used previously in the formation of earlier products, gave dihydropyran 281. The metathesis reaction proceeded smoothly using the same metathesis conditions as before, and a mixture of diastereoisomers (5S,6S)-283 and (5R,6S)-284b were isolated in a ratio of 3:1 respectively (Scheme 52).

\[
\begin{align*}
280 & \quad \text{NaH, allyl bromide} \\
& \quad \text{THF, 65°C, (76%)}
\end{align*}
\]

\[
\begin{align*}
281 & \quad \text{Cl}(\text{Cy}_7\text{P})_2\text{Ru=CHPh (3 mol%)} \\
& \quad \text{CH}_2\text{Cl}_2, 20^\circ\text{C}
\end{align*}
\]

\[
\begin{align*}
\text{then column chromatography on silica} \\
(5S, 6S)-282a (14\%) \\
(5R, 6S)-282b (19\%)
\end{align*}
\]

\[
\begin{align*}
(5S, 6S)-283 & \quad \text{+} \\
(5R, 6S)-284
\end{align*}
\]

Scheme 52: Double ring closing metathesis to give dihydropyran

Another novel spirocycle assembly using double ring closing metathesis reaction on tetralkenes has been presented by Harrity (Scheme 53).\textsuperscript{58} Outlined below are the two possible metathesis pathways they believed would take place during cyclisation of their key tetralkene.
They were confident that the formation of a five membered ring would be the dominant process although they still expected to see trace amounts of the undesired seven membered ring, as this pathway had been proven to take place under relatively mild conditions. To test how selective this process would be they prepared a simple model substrate to examine the reaction (Scheme 54).

Pleasingly, when the cyclisation was carried out using 4% [Ru]-I catalyst in CH$_2$Cl$_2$, only the five membered dihydrofuran was formed. With this result in hand, the scope of the reaction was expanded in the hope of developing a novel selective metathesis process to the general assembly of functionalised spirocyclic systems. To do this they exposed a range of tetraolefinic precursors to their metathesis conditions (Table 6).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Cat (mol %)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="291" alt="Substrate" /></td>
<td><img src="292" alt="Product" /></td>
<td>[Ru]-I 4</td>
<td>CH$_2$Cl$_2$</td>
<td>rt</td>
<td>90</td>
</tr>
</tbody>
</table>
Table 6: Table of tetraolefinic precursors and their metathesis products

<table>
<thead>
<tr>
<th>Entry</th>
<th>Structure 1</th>
<th>Structure 2</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td><img src="image1" alt="Structure 1" /></td>
<td><img src="image2" alt="Structure 2" /></td>
<td>[Ru]-I 15</td>
<td>CH₂Cl₂</td>
<td>40°C</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Structure 1" /></td>
<td><img src="image4" alt="Structure 2" /></td>
<td>[Ru]-I 4</td>
<td>CH₂Cl₂</td>
<td>40°C</td>
<td>62%</td>
</tr>
</tbody>
</table>

Their initial focus was the preparation of the spirocycle acetal 292. There was found to be a high selectivity for the five membered ring formation, and 292 was readily assembled from 291.

Seven membered rings can also be ring opened and cyclised to give the desired spirocycles, (Entry 2, Table 6) the cyclic acetal 293 provided 294, this time in only moderate yields and after the addition of 15 mol % of catalyst, the reaction time was also sluggish compared to before and required a further 48 h to go to completion.

Moving away from spirocyclic chemistry, there have been several other interesting applications of DSRCM sequence.

In 2002, Fukuda and his group in Japan presented a new methodology for the diastereoselective construction of a quaternary carbon stereogenic centre, which contains all four carbon substituents, on the cyclohexene 299 via the RCM of triene 298 (Scheme 55).59

![Scheme 55: Diastereoselective construction of quaternary stereogenic centres](image5)

As they expected, the products could be useful as chiral building blocks for the synthesis of natural products with a quaternary stereogenic centre. They chose three basic trienes 300, 301, and 302, and converted them using conventional methods into the benzyl, TMS, MOM ethers, and benzoate derivatives. They then examined the ruthenium carbene catalysed RCM
using these synthesised derivatives. The table below presents a selection of their findings. Each substrate was treated with 10 mol% of [Ru]-I catalyst in CH$_2$Cl$_2$ at room temperature (Scheme 56).

Scheme 56: DSRCM and subsequent hydrolysis of the products to give compounds 300–302

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R1</th>
<th>R2</th>
<th>Yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>300b</td>
<td>Bn</td>
<td>Me</td>
<td>78</td>
<td>71:29</td>
</tr>
<tr>
<td>2</td>
<td>300e</td>
<td>Bz</td>
<td>Me</td>
<td>90</td>
<td>64:36</td>
</tr>
<tr>
<td>4</td>
<td>301b</td>
<td>Bn</td>
<td>Et</td>
<td>80</td>
<td>85:15</td>
</tr>
<tr>
<td>5</td>
<td>301c</td>
<td>TMS</td>
<td>Et</td>
<td>84</td>
<td>86:14</td>
</tr>
<tr>
<td>6</td>
<td>301e</td>
<td>Bz</td>
<td>Et</td>
<td>85</td>
<td>71:29</td>
</tr>
<tr>
<td>7</td>
<td>302b</td>
<td>Bn</td>
<td>Ph</td>
<td>87</td>
<td>56:44</td>
</tr>
</tbody>
</table>

Table 7: Results of RCM, and hydrolysis yields

All the expected cyclised products were obtained after hydrolysis, except for the benzyl ethers, in moderate to good diastereoselectivity. The best result obtained was with 301c, which afforded the cyclohexanol 304 in 84% yield with a de of 72% (Entry 5). It was found that when the prochiral carbon R group is a phenyl group the diastereomeric excess is lower for all entries. The unprotected triols did not cyclise when using [Ru]-I catalyst but did when this was replaced with [Ru]-II catalyst (4 mol%). All the reactions proceeded rapidly and in high yields, disappointingly, no diastereoselectivity was observed.

Another group headed by Hirama, saw the potential of this type of reaction to gain rapid access to AB ring fragment found within ciguatoxin. Previous work published by the group had included the total synthesis of ciguatoxin, however it had been linear and required 20 plus steps from D-glucose. They believed using this new method of highly stereoselective
ring closing metathesis followed by a cross metathesis reaction they would be able to manufacture the AB ring system in a rapid and convergent manner.\textsuperscript{60}

After the synthesis of the key substrate 307, the group then exposed the metathesis precursor to the key diastereoselective RCM to see if it would give the desired AB ring fragment in one step. This was accomplished by treating 307 with 10 mol% of [Ru]-I catalyst in CH\textsubscript{2}Cl\textsubscript{2} for 30 min, this yielded 309 exclusively; they believed the initial carbene attack took place at the free allyl olefin giving the intermediate 308, which would then undergo equilibration to give the most stable isomer 309.

To finish the synthesis, diene 309 underwent a cross metathesis with carbene complex 310, giving the AB ring fragment 311 of ciguatoxin in only 8 steps (Scheme 57).

Scheme 57: Final formation of AB ring fragments

Phosphorus-containing compounds have gained considerable attention as a result of their diverse biological and chemical profiles. They have been used as novel pharmaceutical, and agricultural compounds. They have also found roles as valuable chiral auxiliaries, lewis bases, organocatalysts or as ligands used in conjunction with various transition metals. In particular, there is a growing interest in cyclic compounds containing an asymmetric phosphorus atom (P-chiral heterocycles).\textsuperscript{61}
Hanson and Stoianova, have recently shown that the RCM reaction catalyzed by the Grubbs ruthenium catalyst is an effective method for the construction of phosphonate and phosphonamide P-heterocycles. Part of their program of work was aimed at developing transition metal catalysed approaches to diverse phosphorus containing compounds. They reported an important example utilising the RCM reaction in the diastereotopic differentiation of pseudo-C2-symmetric using phosphorus templates 312-314, and converted them using ruthenium catalysts, to give P-chiral phosphonamides 314 and 315, and phosphonates 317 (Scheme 58, Table 8).

Scheme 58: Construction of P-heterocycles

The phosphonamide and ester RCM precursors were prepared by the treatment of vinyl and allylphosphoric dichloride with the corresponding optically pure allylic amine or alcohol. The optically pure allylic amine was prepared using a modified Julia coupling of trityl-protected α-aminoaldehyde and 1-phenyl-1-H-tertazol-5-yl sulfone. The initial RCM reactions were carried out on the (Z)-configured iPr-substituted substrates 312a and 312b (Table 8).
Table 8: Phosponamide and ester DSRCM results and their yields

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>$ds$</th>
<th>Isolated yield/major product [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$312a$ ($R_2 = Me$)</td>
<td>2.6:1</td>
<td>$315a = 64$</td>
</tr>
<tr>
<td>2</td>
<td>$312b$ ($R_2 = iPr$)</td>
<td>5.0:1</td>
<td>$315b = 80$</td>
</tr>
<tr>
<td>3</td>
<td>$313$ ($R_2 = Me$)</td>
<td>1.3:1</td>
<td>$316 = 50$</td>
</tr>
<tr>
<td>4</td>
<td>$314$</td>
<td>3.5:1</td>
<td>$317 = 75$</td>
</tr>
</tbody>
</table>

Treatment of the vinylphosphonamides $312a$ with catalyst [Ru]-I gave the five membered cyclic product $315$ in a high yield with low diastereoselectivity of 2.6:1(Entry 1). It was found that an increase in the size of the substituent using $312b$ increased the selectivity (5.0:1) (Entry 2). They were surprised to find that the substitution on the double bond plays a much more prominent role in the selectivity of the transformation. Thus, changing the double bond substituent resulted in a slower reaction with a considerable increase in selectivity.

Formation of six-membered products from the allylphosphonamide $313$ resulted in an almost complete loss of selectivity (Table 8) although the yield was high. With their findings being in agreement with the results that Blechert and co-workers reported. The RCM of compound $314$ gave the desired six-membered product $317$ in near quantitative yield with modest selectivity ranging from 3.5:1 to 2.8:1 depending on the reaction conditions. Despite the modest selectivity, they obtained the P-chiral cyclic phosphonate $317$ in the good isolated yield of 75% (Entry 4).
Gouverneur and co-workers prepared phosphorus containing trienes featuring two diastereotopic vinyl groups derived from homoallylic alcohols and prochiral phosphinic acids (Scheme 59).

![Scheme 59: Phosphorus containing trienes](image)

The trienes 320a-j were prepared specifically so that the olefins at the prochiral centres could not react with each other and the primary attack of the catalyst would occur at the double bond positioned close to the stereogenic carbon centre, which ensured diastereoselective control (Scheme 60).

![Scheme 60: Metathesis precursors 320a-320j](image)

After the preparation of the key precursors, the diastereoselective ring closing metathesis reaction was studied using 2-5 mol % of ruthenium based catalysts [Ru]-I, [Ru]-II and [HG]-I, in CH₂Cl₂ at room temperature or reflux. All the reactions gave full conversions of the starting triene 321a into the expected P-stereogenic ring closed product 322a. The reaction times were found to reduce if the reaction mixtures were heated to elevated temperatures and gave a diastereomeric excess of approximately 60% (Scheme 61).
Following this initial study, the rest of the trienes were exposed to 2 mol % of catalyst [HG]-I in CH₂Cl₂ under reflux. Under these conditions the conversion of the trienes into the cyclised products were found to be quantitative. The level of the diastereomeric control for the trienes derived from the allylic carbon was moderate with \(de\) ranging from 13-50%. The ring closing metathesis of trienes 321i, 321j and 321e, which contain a substituent on the terminal carbon of the two double bonds conjugated to the phosphine, reflected better diastereomeric excesses. They believed this to be the result of a more favoured primary attack of the Ru-catalyst on the unsubstituted terminal double bond. The triene 321d, derived from pent-4-en-2-ol, showed much more selectivity, with a reported diastereomeric ratio of 93:7 (\(de\) 86%) (Table 9, Entry 6).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Major Product</th>
<th>Yield (%)</th>
<th>(de) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(E,E)-320i</td>
<td>(E,E)-322i</td>
<td>56</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>(E,E)-320j</td>
<td>(E,E)-322j</td>
<td>61</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>(E,E)-320e</td>
<td>(E,E)-322e</td>
<td>92</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>320a</td>
<td>322a</td>
<td>100</td>
<td>60</td>
</tr>
</tbody>
</table>
They also studied the effect on reactivity that having two isopropyl groups has on triene **320c**. It was found to have the lowest yield (33%) yet have a comparable diastereomeric excess of 76% (Entry 5). Triene **320a**, that contains two vinyl groups, was found to have a decreased \( de \) of 60% (Entry 4). These results led the group to conclude the trienes featuring two \( E \) double bonds are the best substrates for these kinds of cyclisations. Compound **320h**, derived from an unsaturated alcohol substituted with a benzyl group on the homoallylic position, cyclised to give **322h** in excellent yields and a diastereomeric excess of 82%. The results of this study allowed the group to conclude that both the substituent and the geometry of the double bonds play an important role in the selectivity for these cyclisations.

This work illustrated that a series of novel P-stereogenic hetereocycles featuring two stereogenic centres could be synthetised using a diastereoselective ring closing metathesis, of the corresponding structurally diverse P-containing trienes. The exo- and endocyclic double bonds of the cyclised products offer a variety for further functionalisation.

Most of the examples discussed so far have involved \( sp^2 \) hybridised olefins, an interesting example using \( sp \) centres has been illustrated by Gouverneur. Applying previous results they were particularly interested in developing a diastereoselective enyne ring closing metathesis as a strategically viable route to P-stereogenic compounds, with an alkynyl group (**Scheme 62**).\(^64\)
They synthesised a range of P-containing ene-dienes, specifically designed to yield a single isomer during DSRCM. The initial metathesis studies were carried out using ene-diene 325 and 2 mol% of [Ru]-II catalyst in CH₂Cl₂ under reflux. The cyclisation took place as they expected, however, with a low conversion and with only a modest diastereoselectivity. Attempts were made to increase the yield by using an atmosphere of ethylene, which did indeed lead to an improvement. The optimised conditions were found to be [HG]-I catalyst in 10 mol%, in toluene (Scheme 63).

These conditions were extended to the ene-dienes (Table 10). A range of six- and seven-membered P-stereogenic heterocycles were accessed upon DSRCM. Ethynyl-substituted substrates gave the desired products in excellent conversions, with no trace of the oligomer or homodiene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ene-diyne</th>
<th>product</th>
<th>Convn/yield (%)</th>
<th>d.r</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>325</td>
<td>326</td>
<td>&gt;98/86</td>
<td>18:1</td>
</tr>
</tbody>
</table>
Table 10: Results of ene-diyene metathesis

The yields were found to consistently high independent of the substituent on the stereogenic carbon or the ring size of the product. However, decreasing the steric bulk on the stereogenic centre led to an increase in selectivity.

With the DSRCM products in hand, the group went on to test the viability of postmetathesis transformations. The diene would be amenable for Diels–Alder chemistry and the alkyne group could possibly be used for click chemistry (Scheme 64).
This work paved the way for the development of an enantioselective ene-diene ring closing metathesis process from prochiral templates.

Diastereoselective ring closing metathesis has also been used to solve the significant limitations of long range asymmetric induction. Evans et al. described a new approach to solve this problem using a diastereoselective temporary silicon tethered ring closing metathesis (TST-RCM) reaction of mixed bisalkoxy silanes (Scheme 65).  

They believed that the TST-RCM would transpire through the favoured transition state, shown below, due to non-bonding interactions with the pseudoaxial propenyl group in the
disfavoured transition state, and the reaction would therefore only form the 1,4-cis isomer (Scheme 66).

![Scheme 66: Favoured and disfavored transition states for the TST-RCM](image)

They hypothesised that one potential advantage to their approach would be that the reaction would proceed irrespective of the ring size. The construction of mixed bisalkoxy silane 347 was achieved from the allylic alcohol 344 (Scheme 67).

![Scheme 67: Preparation of bisalkoxy silane and metathesis outcomes](image)

Initial results determined that the steric nature of the substituents on the silicon tether were indeed crucial in terms of the skeletal construction, overall efficiency, and the level of diastereoselectivity. Table 11 shows that the diisopropylsilane proved to be optimal functional group, when using optimised conditions (Entry 1). Additional studies explored the effect of different catalysts on the transformation. However, replacing [Ru]-I with [Ru]-II or Schrocks molybdenum catalyst gave no improved results (Table 11, Entry 2, 3).
Table 11: Results of the TST-RCM on the compound 347

The TST-RCM was found to be tolerant to a range of aryl, linear, and branched alkyl substituents. The unreacted starting material was recovered and resubmitted to the reaction conditions to give the desired products. The reaction was also tolerant of both benzyloxymethyl and carboalkoxy substituents.

With these pleasing results the group envisioned that the method could be applied to higher homologues and would provide a general method for long range asymmetric induction, Table 12 summarises their findings.

Table 12: Results of the RCM using longer homologous chains

Treatment of trienes with [Ru]-II catalyst in refluxing CH₂Cl₂ furnished after reductive hydrogenation, the saturated intermediates with the trans isomers being favoured. Further studies showed that the RCM is a kinetic reaction giving the more thermodynamically stable product.
The final example of a DSRCM presented in this report was illustrated by Jennings in 2008.\textsuperscript{66} The group discovered routes towards the macrocycles aigialomycin D and C that involved a highly chemoselective ring closing metathesis protocol (Figure 12).

![Figure 11: Structures of aigialomycin D and C](image)

Synthesis of the first fragment was completed using a Molander procedure to give the styrene 356 (Scheme 68).\textsuperscript{67}

![Scheme 68: Synthesis of styrene 356](image)

The second fragment was synthesised as outlined in Scheme 69, and was combined with propargylic alcohol 357 to give 360 (Scheme 69).

![Scheme 69: Synthesis of fragment 360](image)

Finally upon coupling 356 with 360 using NaH, 361 and 362 were isolated. The DSRCM was then used to give the final macrocycle. Treatment of 361 and 362 with [Ru]-II catalyst in refluxing CH₂Cl₂ led to the 14-membered macrocycle, 364, and acyclic compound 363 in
13%. Treatment of the macrocycle with BBr₃ at -78 °C in CH₂Cl₂ furnished aigialomycin D (Scheme 70).

In conclusion, DSRCM has provided a fascinating and novel route to producing single diastereoisomers of cyclic compounds. This method has been expanded to heterocycles, spirocycles, and macrocycles and it can be tailored to protect functional groups though a choice in catalysts and reaction conditions. These products have found biological and pharmaceutical applications, with further examples being used to overcome synthetic difficulties. DSRCM has become a powerful tool in organic chemistry and is yet to be used to its full potential.

It is well known that alkene metathesis has revolutionised modern approaches towards the synthesis of a wide range of important organic molecules, with implications in natural
product synthesis. The examples given here are just a few to testify the importance and relevance of domino metathesis, especially how these processes permit multiple carbon-carbon bond forming and bond breaking reactions, thus allowing rapid access to impressive structures, with varying degrees of complexity, which would have otherwise proven very challenging.

The many different tandem processes have been proven to be efficient and versatile methods for the construction of carbocycles, heterocycles and polycyclic structures. One attractive feature is the transfer of stereo information in the RRM process, even if chiral starting materials are required. Given the massive advantages of metathesis cascades, and the catalytic efficiency of the catalysts involved, it can be imagined that the interest in these processes will continue to grow.

It is hoped that this project can combine aspects of the rapid and diverse nature of tandem metathesis on strained norbornenes and to use this to gain a diastereoselective outcome, giving us access to a range of interesting carboyclic scaffolds found within natural products.
4. Research Aims

The aim of this research project is to synthesise the structural skeleton found in the ottelione and hamigeran family of natural products via a metathesis process. Ottelione A and B were chosen as synthetic structural targets due to their anti-tubercular effects and high cytotoxicity. It is envisaged that the ottelione skeleton could be accessed using a 2-step sequence utilising a substituted norborneneone. To do this, first the key norborneneone building block (289) must be synthesised (Scheme 71).

![Scheme 71: Ottelione retrosynthetic route](image)

Starting from the commercially available 1,1-dimethoxy-2,3,4,5-tetrachlorocyclopentadiene, the norbornenyl could be obtained using a diastereoselective Grignard reagent addition to give the desired syn product. The subsequent exposure of this addition product to optimised metathesis conditions would provide the cis fused [3.0.3]carbocycles via an optimised RRM transformation (Scheme 72).

![Scheme 72: Possible outcomes of the RRM on compound 373](image)

At this stage it was unclear whether the RRM transformation would occur in a diastereoselective fashion, or give both possible outcomes 374 and/or 375. It was also hoped
that within this project we would be able to gain insight into the mechanism of the RRM performed on these highly substituted strained norbornenyl systems, and if any diastereoselectivity could be achieved. Further to this we hoped to expand this work to the hamigeran family using aromatic olefin tethers (Scheme 73).

Scheme 73: Retrosynthetic pathway to the hamigeran family

As a further project it was hoped that we could investigate indium mediated allylations to these interesting norbornenones, and whether any level of diastereoselectivity could be achieved during addition (Scheme 74).

Scheme 74: Possible indium mediated allylation outcomes
These allylation products would then be subjected to the metathesis conditions to hopefully synthesise new substituted bicycles (Scheme 75).

![Scheme 75: RRM on indium addition product](image)

If this work was successful we hoped to further extend it to new cyclic systems. We believed we could access a similar bicyclic scaffold starting from 1,3-cyclohexadiene (Scheme 76).

![Scheme 76: Retrosynthetic pathway to [2.2.2] systems](image)

Once the [2.2.2] ketone has been formed it would then be possible to functionalise it using the ketone through Grignard reagent additions, lithium mediated additions, and indium allylations (Scheme 77).

![Scheme 77: Metal mediated additions to bicycle 389](image)

These addition products would again be exposed to optimised RRM transformations, and as before two possible pathways may occur during the cyclisation. It was of interest to discover if either pathway was dominant (Scheme 78).
If pathway $a$ was proven to be dominant we would be able to selectively achieve the [3.1.3] metathesis product, however, if pathway $b$ is prominent then the [4.0.3] transformation product would be formed. It is unclear which pathway will be favoured, and this will likely be determined by the thermodynamic properties of the formed bicycles.
5. Results and discussion

In 2008, the Kimber group began work into the total synthesis of carbocyclic natural products derived from the sea sponge *Hamigera terangaensis*, and fresh water plant *Ottelia alismoides*.\(^{68,69}\) (Figure 13). These natural products contain a fused [4.0.3] ring system which makes them amenable to an RRM approach. Many pharmacologically significant compounds contain fused bicycle skeletons, and as such have stimulated considerable interest into their efficient construction.

![Structural similarities between Hamigeran and Ottelione](image)

**Figure 12: Structural similarities between Hamigeran and Ottelione**

Ottelione A and B were chosen as structural targets because of their anti-tubercular effects, and their cytotoxicity. *Ottelia alismoides* is isolated from a little studied freshwater plant that grows in the Nile Delta, Egypt. It was found that even the crude dried extracts showed significant growth inhibition [50% GI\(_{50} = 1\mu\text{g/mL}\)] in two cultured mouse tumour cell lines.

Ottelione A has been found to inhibit tubulin polymerisation into microtubules, the same miotic activity that is inhibited by colchicines, vincristine and vinblastine.\(^{70}\) Otteliones cytotoxicity is attributed to the presence of a unique electrophilic 4-methylenecyclohex-2-enon moiety, which engages with the sulphydryl groups of the cystine residue on the tubulin and disrupts the microtubule dynamics, *via* conjugated addition.
Additionally, along with the biological activity, ottelione A and B contain four contiguous stereogenic centres. This, combined with the cis-hydrine group with a side chain, and rare sensitive 4-methylenecyclohex-2-enone functionality all make the otteliones synthetically challenging.

In 1998, Ayyad and Hoye\textsuperscript{69} first reported the isolation and structure of the novel otteliones, and scientists working at Sanofi-Aventis determined the relative stereochemistry from a series of extensive NMR experiments. Studies on their powerful anticancer activities and the rarity of the natural material have made the otteliones very attractive to the synthetic community.

Since their discovery, several different groups have synthesised both otteliones A and B, using many synthetic pathways. Two notable examples of this synthesis have been reported independently by Mehta\textsuperscript{71} and Sha.\textsuperscript{72}

Mehta and co-workers reported the first total synthesis of the racemic otteliones in an 11-step, regio- and stereo- controlled synthesis from commercially available starting materials in 5.4\% overall yield. Key to this work was the initial Diels-Alder step to give compound 398 in which the cis hydrine framework can be seen. Following a lithium aluminium hydride reduction, Lombardo methylenation and ozonolysis, 399 and 3400 were formed in an 8:1 ratio. The major isomer 399 was then exposed to a Wittig olefination, PCC oxidation and finally the introduction of a benzylic side chain, using the lactone functionality of 401 to give ottelione A. A further reaction with DBU gave ottelione B (Scheme 79).
Clive and co-workers also reported an elegant synthesis towards Ottelione A and B, using an RCM to construct the hydride skeleton (Scheme 80).\textsuperscript{72}

More recently, in 2010, Sha and co-workers published an enantioselective total synthesis of ottelione A and B in 3.8\% and 21.8\% yields respectively. Here they used an $\alpha$-carbonyl radical cyclisation and a Suzuki-Miyaura coupling as the key steps (Scheme 81).\textsuperscript{73}
Scheme 81: Key steps in Shar’s synthesis
5. Results and discussion

5.1 Research Plan

From this work the group has devised our own synthetic work using a unique RRM transformation as our key step (Scheme 82).

Scheme 82: Ottelione retrosynthetic scheme starting from simple starting materials

It was envisaged that the ottelione skeleton could be accessed using a 2-step sequence utilising a substituted norbornenone. Norbornenone 370 could undergo a Grignard reagent addition to give alcohol 369 which in turn could then be exposed to RRM conditions to give the desired bicycle. The key building block 370, would be constructed from simple starting materials such as methyl acrylate and a substituted cyclopentadiene (Scheme 82).

The majority of examples using an RRM transformation on substituted norbornyls rely on the tethered olefin being attached to the norbornenyl skeleton via the major saturated bridge 407.74 Examples of RRM on a norbornenyl skeleton, where the tethered olefin is located on the minor saturated bridge, are relatively rare 409 (Scheme 83), with two notable examples by Korreda75 and Hoveyda.76
In 2003, Hoveyda and co-workers used a Mo catalyst in a RRM sequence on such a substituted norbronyl. They reported a tandem asymmetric RRM sequence on norbornenyls using a chiral Mo catalyst, giving rise to a [3.0.5]-bicycle which was a key intermediate in the synthesis of (+)-africanol, in a 97% yield and with 87% ee (Scheme 84).

Scheme 83: Examples of tether location

Scheme 84: Hoveyda’s construction of (+)-africanol using a RRM transformation
Koreeda and co-workers synthesised fused tricyclic enones and cyclohexa[c]indene skeletons using a tethered directed RRM sequence, starting with readily accessible norbornene derivatives bearing allyl and homoallyl groups at the bridging carbon. Using this sequence, they were able to develop an efficient route towards the construction of functionalised angular fused tricycles, cyclopenta- and cyclohexa-[c] indenes, in moderate (30%) to good yields (61%) (Scheme 85).

![Scheme 85: tricyclic enones and cyclohexa[c]indene skeletons](image)

It was envisaged that the route would present two main synthetic challenges. The first being the diastereoselective Grignard addition to the key norbornenone as during the addition two possible diastereoisomers could be formed, syn-hydroxy-417 and anti-hydroxyl-418 (Scheme 86).

![Scheme 86: Possible syn/anti addition outcomes](image)

Pioneering reports by Bly\textsuperscript{77} and Berson\textsuperscript{78} on the stereoselective addition of organometallic reagents to norbornenes indicated that Grignard reagents would provide the desired syn product via a selective syn addition.

Bly and Bly noted an interesting development while working towards the stereospecific rearrangement of spiro[bicycle[2.2.1]hept-2-en-anti-7,2'-'oxacyclopropane]. It was discovered that during the addition of methylmagnesium iodide and dimethylsulfoxonium methyldie to bicyclo[2.2.1]hept-2-en-7-one, that one stereospecific outcome was favoured. In each case the product formed was with the anti-alcohol or anti-epoxide, and were the result
5. Results and discussion

of a nucleophilic addition to the carbonyl from the side of the double bond. They considered that attack from the side of the double bond may be less hindered, and that as the negative charge on the oxygen is further removed from the region of high \( \pi \)-electron density. This charge can be delocalised by these electrons (Scheme 87).

![Scheme 87: Nucleophilic addition to ketone to give the syn product](image)

Berson found that 7-norbornene reacts with vinyl magnesium bromide to give a 4:1 mixture of \textit{syn}-7-vinyl-\textit{anti}-7-hydroxynorbornene and \textit{anti}-7-vinyl-\textit{syn}-hydroxynorbornene. The preference for the \textit{syn} addition was in accordance with the findings of Bly (Scheme 88).

![Scheme 88: Grignard addition preference](image)

More recently Paquette\(^{79}\) illustrated that the addition of organometallics to norbornenes favours alcohol products which are \textit{syn} relative to the norbornene olefin. Paquette’s group found that due to electronic effects, Grignard addition to bicycle[2.2.1]hept-2-en-7-one gave alcohol 423a in the \textit{anti} position relative to the double bond, and were able to conclude that a dominant \textit{syn} attack occurs (Scheme 89).

![Scheme 89: Grignard additions to bicycle[2.2.1]hept-2-3n-7-one to give alcohol 423a](image)
5. Results and discussion

Organolithium reagents were found to be less stereosepecific than that of the addition of Grignard reagents. Warkentin found that some cases (e.g. vinyllithium and phenyllithium) actually favoured the formation of the undesired anti addition product. Warkentin also noted that the nature of the lithium reagent plays a crucial role, and can in some cases (e.g. Et, iPr and tBu) give the anti-reduction product 425 (Figure 14).

![Figure 13: Anti-reduction product 334](image)

The second synthetic challenge is the diastereoselective nature of the RRM transformation. During this synthesis of 370, it would also be interesting to ascertain what effects, if any, an endo chelating group on the norbornene skeleton would have on product distribution when substrates such as 426 are exposed to ruthenium-catalysed metathesis. The substitution was expected to have a dramatic effect on the product distribution, potentially giving two regioisomers, 427 or 428, after the RRM step (Scheme 90).

![Scheme 90: Possible regioisomers of our ROM-RCM](image)

Having noted these synthetic challenges and literature presidents, work began on the crucial synthesis of the key norborneneone 436.
5.2 Synthesis of key intermediate

The synthesis of the key building block 436 was adapted from a known procedure reported by Thomson and Wong, and it began with a Diels-Alder reaction between methyl acrylate and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene 372. Initially a 1:1 ratio of the two reactants was used with heating at 75 °C for 48 h according to the literature; however this gave only a modest yield of 58%. Consequently, we increased the equivalents of methylacrylate two fold, and coupled with heating the reaction for 72 h, a higher yield of 85% was achieved (Scheme 91).

![Scheme 91: Diels-Alder reaction between 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and methyl acrylate](image)

With a Diels-Alder reaction we would expect to see a low ratio of exo configuration as well as the desired endo product (Figure 15).

![Figure 14: Possible endo/exo isomers from Diels Alder reaction](image)

However, only the endo product was isolated, and so it is assumed that the bulky geminal groups in the diene interfere sterically with the larger groups in the dienophile and enforce the endo stereochemistry in the product (Figure 16).
5. Results and discussion

In this case the *endo* product is favoured as electrons of the carbonyl interact with the newly forming π bond and these interactions lead to the formation of the *endo* product. The Diels-Alder diagram can be re-drawn to show this (Figure 17) (chlorine and R groups omitted for clarity).

The $^1$H NMR spectrum confirmed the presence of the desired product by the characteristic methyl singlet peaks at 3.71, 3.61, and 3.56 ppm. Thomson and Wong confirmed the endo structure using single crystal X-ray analysis, at this point the $^1$H NMR and $^{13}$C NMR data matched the literature values. Comparison of our experimentally calculated J values and those reported led us to believe that we had obtained the same structural outcome (Figure 18).
The product was subsequently saponified, to give the acid in 95% yield (Scheme 92).

**Scheme 92: Saponification of the methyl ester to the acid 432**

The literature conditions gave the desired product in near quantitative yields and the acid was confirmed by the presence of an IR stretch at 3500 cm\(^{-1}\), indicative of the OH group. The \(^1\)H NMR spectrum also showed the disappearance of the methyl peak at 3.56 ppm.

Dehalogenation was first attempted using the method described by Gassmann and Marshall,\(^82\) however, sodium metal with \(t\)-BuOH in refluxing THF afforded a complex mixture in which none of the desired product could be identified (Scheme 93).

**Scheme 93: Failed dissolving metal reduction of 432**

Consequently, a Birch reduction was trialled, a reaction that proved technically challenging. After setting up a 3-necked flask, fitted with a cold finger, addition funnel and nitrogen line, sodium metal was cut into small pieces and anhydrous liquid ammonia was condensed over it at \(-78 \, ^\circ\text{C}\). Once all the sodium had dissolved and the acid 432 was then added drop wise from the addition funnel, maintaining the temperature at \(-78 \, ^\circ\text{C}\). During the addition the reaction often stopped stirring, as the mixture became very viscous, and had to be stirred manually (Scheme 94).
5. Results and discussion

Scheme 94: Birch reduction of 432 to give compound 433

However, given these problems the reaction gave the desired product 433 in 82% yield. The product was identified using mass spectrometry which gave a m/s peak at 221.0782 (not 198.0892 due to the presence of sodium). The appearance of proton peaks at 6.25 ppm and 6.07 ppm respectively indicated the new protons on the endocyclic double bond.

The reaction was further improved by increasing the amount of solvent compound 432 was dissolved in; this allowed the addition to proceed smoothly, whilst also solving the stirring problem. With these problems overcome it was possible to scale this reaction up allowing 5g of product to be achieved at a time. With 433 in hand the next step was to reduce the acid to the primary alcohol. This was carried out under standard conditions using lithium aluminium hydride (Scheme 95).

Scheme 95: Reduction of acid 433 to the primary alcohol 434

Initially, only one equivalent of lithium aluminium hydride was used and this gave a disappointing yield of 34% of the desired alcohol. Consequently, the reaction was repeated using two equivalents and a higher yield of 84% was achieved. Additionally IR spectroscopy showed the disappearance of the carbonyl stretch at 1705 cm⁻¹.

We then focused on conditions for the protection of the primary alcohol as a TBS-ether, and the unmasking of the ketone functionality. Initially, attempts were made by protecting the primary alcohol on the dimethoxy compound 432 using a method described by Corey et al.⁸³ this was followed by the acid-mediated hydrolysis of the methoxy groups to give the ketone
functionality; however, the primary TBS group proved to be acid labile under these conditions, therefore leading to its removal (Scheme 96).

![Scheme 96: Protection and acid hydrolysis of 434](image)

Consequently, the acid mediated hydrolysis was carried out first. The method suggested by Gassman and Marshall\(^\text{16}\) of 5% sulphuric acid at 35 °C for 48 h, initially gave very disappointing yields between 15-35% of 436. These were consequently optimised by raising the temperature to 65 °C, giving 436 in 96% yield (Scheme 97).

![Scheme 97: Acid hydrolysis and TBS protection to give the key intermediate 437](image)

Finally, the protection of the alcohol gave the desired key intermediate 437 in 86% yield. Corey’s methods were optimised by raising the temperature of the reaction mixture from 25 °C to 35 °C, and by lengthening the reaction from 10 h to 48 h.

The addition of the TBS group was confirmed using \(^1\)H NMR spectroscopy, with the distinctive silyl methyl groups giving singlet peaks at 0.87 ppm (9H) and 0.03 ppm (6H). The unmasked ketone was confirmed by the disappearance of the methyl peaks on the \(^1\)H NMR and by the addition of C=O IR stretch at 1668 cm\(^{-1}\).

*Overall this gave the desired TBS-protected norbornenone key intermediate in 46% yield over 6 steps. The route allowed for the synthesis of the key norbornenone in a reproducible yield and in a large enough scale for future applications.*
5.3 Commercially Available Grignard Additions

Work now began on the addition of an allyl tether to our key building block 436. During the addition of the commercially available Grignard reagents, even with previous literature president, it was not known which addition (syn or anti) would take place, or if one would be more dominant over the other (Figure 19). We hoped that as Paquette\textsuperscript{84} illustrated the addition of organometallics to norbornenes would indeed favour addition products which are syn relative to the norbornene olefin.

![Figure 18: Possible syn/anti diastereoisomers after a Grignard reagent addition](image)

With the literature examples discussed earlier in this report in mind we began the investigation into the addition outcome with a solution of 437 in THF and added one equivalent of allyl magnesium chloride at $-78 \, ^\circ C$. This afforded 439 after chromatography in the modest yield of 50%. The stereochemistry was assigned by extensive $^1$H, $^{13}$C and selective 1D NOSEY NMR spectroscopy, which showed a large nOe enhancement for the proton at position 4 when the exocyclic olefin proton 12 was irradiated. With this result in hand it was decided to increase the equivalents of the allyl magnesium Grignard two fold. This gave the desired compound 439 in the yield of 92% (Scheme 98).

![Scheme 98: Grignard addition conditions and the formation of alcohol 439](image)
It was decided to unmask the primary alcohol group to show that this could be done without affecting the functionality of the compound and that the primary alcohol could be functionalisation further should we wish. This was achieved using TBAF in THF over 72 h. After chromatography compound 439 was isolated in 91% yield as a crystalline solid. It was then possible to obtain a single crystal X-ray analysis and determine the stereochemistry (Scheme 99).

Scheme 99: TBAF deprotection to give the diol 440

Figure 20 shows the results of the single crystal X-ray analysis. It shows clearly that the olefin tether is positioned directly over the endocyclic double bond, and therefore a syn addition to give the syn-product of 437 had taken place. It also confirmed the position of the primary alcohol to be in the endo position as we had previously identified.
Figure 20: Crystal structure of key starting material 440, thanks to Dr. M Elesegood.
With this pleasing result and the confirmed stereochemistry, we expanded the scope of this diastereoselective Grignard reagent addition reactions. Addition of two equivalents of methyl allyl Grignard reagent to 437 in THF gave the desired alcohol in 61% yield (Scheme 100).

![Chemical structure](image)

**Scheme 100: Substituted allyl tether addition to give compound 441**

Interestingly, expansion of the $^1$H NMR spectrum (Figure 21) clearly shows a very small amount of the anti-isomer present. The integrations give the minor stereoisomer present in a 10:1 mixture of the desired syn to anti diastereoisomer.
5. Results and discussion

We further expanded this work to a 1-methyl-2-propenylmagnesium chloride Grignard reagent addition (Scheme 101). Two equivalents of 1-methyl-2-propenylmagnesium chloride were added to the protected norbornene in THF to give 443 in the moderate yield of 40%.

It was not possible to determine the stereochemistry of the product via $^1$H NMR and it was carried forward as inseparable mixture of diastereoisomers, as a consequence of the methyl group, and not a result of the undesired anti-addition, (Figure 22).

Figure 19: Hydrogen NMR integrations of compound 441

Scheme 101: Substituted allyl tether addition to give compound 443
It was next decided to lengthen the chain containing the exocyclic olefin. Addition of this longer chain allyl olefin was carried out using two equivalents of homo allyl magnesium chloride in THF, this reaction gave a lower isolated yield of 50% (Scheme 102). The addition of the longer olefin tether was confirmed by both mass spectrometry, $^1$H and $^{13}$C NMR spectroscopy. The mass peak at 331.0250 is expected for the ion [M+Na]$^+$, and the addition of a multiplet at 2.66 ppm indicates the presence of the new CH$_2$ group in the olefin chain.

Finally, the addition of ethynylmagnesium chloride to a stirred solution of alcohol 437 in anhydrous THF gave the desired compound 448 in a 44% yield (Scheme 103). The $^1$H NMR spectrum indicated the presence of the alkyne group with a single peak at 3.52ppm, a peak at 2130cm$^{-1}$ in the IR spectrum also confirmed the presence of the alkyne bond.
5. Results and discussion

The selective syn addition of allyl, homo allyl and methyl substituted Grignard reagents to our key norbornene has been achieved in moderate to excellent yields. From here we can turn our attention to exposing these newly formed compounds to RRM transformation conditions.
5. Results and discussion

5. 4 Ring Rearrangement Metathesis

With these substrates in hand we then looked at the key RRM transformation step. As previously mentioned, key to this RRM transformation was the diastereoselectivity of the reaction. Both diastereoisomers could be formed during cyclisation, or the rearrangement could prove to be diastereoselective with only one isomer being favoured. To ascertain which outcome would be achieved, work began exposing our RRM precursors to a range of metathesis conditions (Scheme 104).

![Scheme 104: Possible stereo outcomes of the RRM transformation of compound 439](image)

**Entry 1 of table 13** contains our initial conditions, adapted from those used by Hoveyda. Hoveyda had demonstrated that 450 could be transformed to 451 (Scheme 105) using a Mo catalyst and a styrene additive, and as a consequence we have adapted these conditions using the ruthenium Grubbs catalyst [Ru]-II (Table 13).

![Scheme 105: Hoveyda's RRM conditions](image)

However, using these conditions only starting material was obtained (Entry 1) and an increase in catalyst loading to 10 mol % also proved inadequate, only unreacted starting material was isolated (Entry 2). In Entry 3, the reaction time was then extended to 48 h, with 10 mol% catalyst. However, after 48 h no change could be seen as indicated by TLC analysis.
5. Results and discussion

![Chemical Structure](image)

<table>
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<th>Entry</th>
<th>Alkene</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Catalyst (mol %)</th>
<th>Yield (%)</th>
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<td>24</td>
<td>rt</td>
<td>[Ru]-II 5</td>
<td>-</td>
</tr>
<tr>
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<td>Styrene</td>
<td>CH₂Cl₂</td>
<td>24</td>
<td>rt</td>
<td>[Ru]-II 10</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Styrene</td>
<td>CH₂Cl₂</td>
<td>48</td>
<td>rt</td>
<td>[Ru]-II 10</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Styrene</td>
<td>Toluene</td>
<td>24</td>
<td>rt</td>
<td>[Ru]-II 5</td>
<td>-</td>
</tr>
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<td>[Ru]-II 10</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 13: RRM conditions for the transformation of 439 into 449a and/or 449b

It was then decided to exchange the solvent; CH₂Cl₂ was exchanged for anhydrous toluene, enabling us to raise the temperature of the reactions beyond 40 °C. To set a bench mark, the reaction was first trialled at room temperature (Entry 4) to see if the solvent would have any effect on the reaction before the temperature was raised. Upon inspection via TLC only starting material was present and consequently the reaction mixture was heated to 35 °C. After 24 h a new compound was identified by TLC, and after chromatography, 449a was isolated in 20% yield (Entry 5, and Scheme 106).

![Scheme 106](image)

Scheme 106: Successful RRM conditions
In order to establish the stereo-outcome of the rearrangement compound 356a was submitted for \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectroscopy. It was expected that the proton at position 4 on isomer 356a would be represented by the splitting pattern of a doublet of doublets due to the two difference hydrogen environments either side. The same proton on the other isomer 356b would show as a doublet of triplets due to signal being split by the neighbouring proton on position 3 and the CH\(_2\) at position 5 (Figure 23). However, upon submitting a purified sample of 356a for \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectroscopy the spectrum obtained was inconclusive and so further characterisation using DEPT, COSY, HMQC, HMBC, selective TOCSY and selective 1D NOSEY NMR spectroscopy.

![Figure 21: Proton environment differences between isomers](image)

Initially HMBC was used to determine whether the carbon at position 5 (Figure 16) was a CH\(_2\) or CH, in this case it correlated to a carbon on the \(^{13}\text{C}\) spectra which when analysing the DEPT spectrum and could be seen to be a CH and furthermore to this a selective 1D TOCSY was run to confirm the assignment. By irradiating the single proton on position 4, it is possible to see peaks for the protons at 2/3, 10, 7, 5 and 6. When the protons on the cyclic double bond were irradiated (2/3) the protons either side are seen (1/4). Irradiating the protons on the tether olefin gave peaks for 9 and 7, confirming the overall structure. Finally a selective 1D NOSEY was carried out to prove the proximity of 4 to 5. When 4 was irradiated a strong enhancement was seen for 5. From this it was concluded that the CH at position 4 was located next to a CH at the position 5 not next to a CH\(_2\). Allowing us to confidently give the position of the TBS group to be off carbon 5 and not carbon 6 (Figure 24).

![Figure 22: Position of TBS group](image)
With this promising result the reaction was repeated at 60°C, but disappointing only the cross metathesis by product of stilbene was isolated as well as the starting norbornene (Figure 25).

![Figure 23: Stilbene side product](image)

We concluded from this that styrene was not the best additive to use in the transformation, and was replaced with ethylene. The use of ethylene during metathesis has been well documented, and work by Mori et al. has illustrated its potential. They discovered that when an ethylene atmosphere was used in a reaction rather than argon their experimental yields rose from 15% to a nearly quantitative 99%, however, it did elongate the reaction time (Scheme 107).

![Scheme 107: Effects of ethylene on RRM](image)

They surmised that when ethylene was used as an alkene additive the real catalyst is generated from the ruthenium carbene complex via a ruthenacyclobutane. The use of ethylene also improved the stability of the catalyst and prevented the production of dimeric material (Scheme 108).
5. Results and discussion

When ethylene was used under our new conditions the single regioisomer was isolated in 86% yield (Table 13, Entry 7 and Scheme 109).

To determine the importance of the ethylene the reaction was run in its absence, and unsurprisingly this gave only starting material. It was decided to supplement [Ru]-II for [Ru]-I. This yielded only starting material, and so we concluded that we had found our optimised conditions (Table 13, Entry 8).

In summary, our optimised RRM transformation conditions for the cyclisation 439 to 449b were found to be 5 mol% of [Ru]-II, in toluene, under an atmosphere of ethylene, at room temperature for 48 h. This selectively gave the desired cyclised product 449a in the excellent yield of 86%. With this result in hand we could now turn our attention to exposing our substituted norbornenes to these conditions.
5.4.1 Ring rearrangement metathesis reaction scope

These optimised conditions were then applied to the tethered norbornenes previously prepared and characterised in section 5.3. Firstly, we applied the optimised conditions to the longer chain olefinic tether, and this cyclised to give the compound 463 in the yield of 76\% (Scheme 110). Additionally, the formation of 463 occurs regioselectively, giving syn-463 predominantly.

![Scheme 110: Six membered RRM product 463](image)

This gave the important structural scaffold of the ottelione family in a high yield with the ability to be accessed in large quantities. The disappearance of the proton peaks associated with the endocyclic double bond in the $^1$H NMR spectrum and the presence of the new multiplets at 2.64 ppm and 2.44 ppm showed the protons were now part of the six membered ring.

Next we applied our RRM strategy to the substituted methyl olefinic tethers. When the methyl tether substituted norbornenyl 441 was exposed to our RRM conditions the desired product 464 was obtained in a 76\% yield after chromatography (Scheme 111).

![Scheme 111: Substituted RMM product 464](image)

As expected, when 443 was exposed to our RRM conditions we obtained after chromatography an inseparable mixture of diastereoisomers in a 64\% yield. A 1:1 mixture of
diastereoisomers was identified by the $^1$H NMR spectrum; however, we were unable to ascertain which isomer was which (Scheme 112).

Scheme 112: RRM products of the RRM of compound 443 to give 465

Finally, the alkyne tether was exposed to our successful RRM conditions. Unfortunately, using these conditions only starting material was isolated (Scheme 113).

Scheme 113: Failed RRM of alkyne chain

Several attempts were made to cyclise 448. Initially the catalyst loading was doubled to 10 mol%. However, TLC indicated no new product was formed and only starting material was reclaimed. Consequently it was decided to increase the temperature of the reaction mixture. This was done over a range of temperatures starting at 35°C until reflux was finally reached. Each time only starting material was recovered quantitatively (Table 14).
5. Results and discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Temp (°C)</th>
<th>Catalyst (mol %)</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethylene</td>
<td>rt</td>
<td>[Ru]-II 5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Ethylene</td>
<td>rt</td>
<td>[Ru]-II 10</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Ethylene</td>
<td>35</td>
<td>[Ru]-II 5</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Ethylene</td>
<td>50</td>
<td>[Ru]-II 5</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Ethylene</td>
<td>75</td>
<td>[Ru]-II 5</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Ethylene</td>
<td>90</td>
<td>[Ru]-II 5</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Ethylene</td>
<td>110</td>
<td>[Ru]-II 5</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 14: Table of attempted RRM conditions for the cyclisation of 448

While this final result was disappointing, the formation of the [4.0.3] bicycle showed promise, and so it was decided to switch the project focus to the addition of longer alkenyl tethers to access 7, 8 and 9 membered carbocycles.
5.5 Transmetallation reactions

We hoped with the success of forming five and six membered rings that we could extend this to form seven and eight membered bicycles. Unfortunately, the required Grignard reagents are not available to buy commercially, so work began to synthesise the required length olefin chains using transmetallation (Scheme 114). Our retrosynthetic pathway illustrates the commercially available starting alcohol that could be used. Converting this alcohol via a functional group interconversion to the chloride would give us the precursor to a transmetallation reaction, that could intern be used to create the desired Grignard reagent in situ (Scheme 114).

\[
\text{Scheme 114: Retrosynthetic pathway to the formation of 480 starting with the alcohol 468}
\]

Organometallic reagents are ubiquitous intermediates in modern organic chemistry. One method for preparing the reagents is the halogen exchange reaction. Traditionally this happens between bromine and lithium, and the reaction is fast and occurs at low temperatures. However the corresponding halogen/magnesium exchange is slower.

Work by Knochel has been at the forefront of these organometallic transformations, for example Knochel demonstrated a Br/Mg exchange between \( i\text{PrMgCl} \) and PhBr, to give Ph/PrMgCl (Scheme 115).  

\[
\text{Scheme 115: Knochel's transmetallation conditions}
\]

While this prepared the desired alcohol 483 in 18% yield after 68 h, we envisaged that a similar protocol could be applied in the synthesis of longer chain alkenyl tethers. In essence, we would utilise a similar protocol to Knochel and from this a one-pot transmetallation would take place using \( i\text{PrMgCl} \) and the desired compound 485 would be formed (Scheme 116).
5. Results and discussion

Scheme 116: Desired one pot Grignard reagents for ketone addition

Initial work towards the transmetallation precursors began using 4-penten-1-ol, \(N\)-chlorosuccinimide and dimethyl sulphide, to access the chloride 487 (Scheme 117).

Scheme 117: Initial chlorination conditions

As in an accordance with work done by Maier and Hermann,\(^{87}\) NCS and DMS were dissolved in anhydrous \(\text{CH}_2\text{Cl}_2\) at 0 °C, and after stirring for 1 h the temperature was lowered to -20 °C and a solution of the allylic alcohol in anhydrous \(\text{CH}_2\text{Cl}_2\) was added drop wise. The subsequent reaction mixture was warmed to room temperature. Unfortunately, only starting material was obtained, indicated by TLC and a prominent IR stretch of 3433 cm\(^{-1}\) showing the OH bond present in the starting alcohol.

Scheme 118: Chlorination conditions

Using the conditions illustrated by Gooch,\(^{88}\) thionyl chloride and pyridine were added to a stirring solution of \(\text{Et}_2\text{O}\), and heated to 75 °C for 1.5 h, it was hoped to isolate the corresponding chlorinated olefinic tether. However, after work up only starting material was isolated. Therefore an adaptation of the methods described by McIntosh was trialled, and the results of this are summarised in Table 15.\(^{89}\)
Table 15: Attempted chlorination conditions

The first attempt was made using anhydrous Et₂O as the solvent and the temperature kept at 0°C. However, TLC analysis revealed after 24 h no new compound, and that only starting material was present (Entry 1). The solvent was then changed to anhydrous CH₂Cl₂ and the temperature increased to 10°C, and this again only yielded starting material. The same conditions were then tried again, but at room temperature. Unfortunately, TLC again revealed no new product and only starting material was reclaimed (Table 15, Entry 3).

Using anhydrous CH₂Cl₂ the temperature was lowered to 0°C, and this time TLC indicated the presence of new compound after distillation attempts, the desired chloride 4 was isolated in a disappointing 8% yield.

The literature suggested the use of an anhydrous solvent as SOCl₂ reacts violently with water, but once the addition had taken place the reaction mixture was then left open to air for the excess SOCl₂ to evaporate, however, this appeared to hydrolyse the desired chloride. To prevent this happening the reaction conditions were then adapted to be anhydrous by using a nitrogen atmosphere. Using this method and after a bulb to bulb distillation the purified compound 487 was achieved in a 67% yield (Entry 5).

With this result in hand it was decided to attempt the synthesis of the longer chain olefin from 5-penten-1-ol. Using SOCl₂ under the conditions stated entry 5 of table 15, this was again successful and gave 489 in 59% yield (Scheme 119)
The desired compounds were characterised using IR, $^1$H and $^{13}$C NMR spectra. The lack of an OH stretch on the IR spectrum indicated that there was no more starting material present. The disappearance of the OH proton on the $^1$H NMR spectrum also indicated the removal and replacement of the alcohol group.

With the chlorinated olefin in hand the transmetallation was attempted. Using the methodology discussed earlier it was decided to test this new reaction using benzophenone. Benzophenone was selected as a cheap and readily available starting material, as we did not want to waste our valuable key building block 437.

To begin with the conditions involved dissolving the chlorinated olefin tether 486 in THF at -78 °C, one equivalent of $i$PrMgCl was then added and the reaction allowed to stir for 30 mins. Following this, benzophenone was then added as a solution via a cannula and the reaction mixture allowed to warm to room temperature (Table 16, Entry 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents of $i$PrMgCl</th>
<th>Solvent</th>
<th>$n =$</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>THF</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>THF</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>THF</td>
<td>1</td>
<td>73%</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>THF</td>
<td>2</td>
<td>56%</td>
</tr>
</tbody>
</table>

Table 16: Conditions used during the transmetallation of 492 and 493
After work up it these conditions were found to yield benzophenone and no addition product was observed (Entry 1). Consequently, the equivalents of \(i\)PrMgCl were increased twofold (Entry 2) and when TLC revealed no new compound had formed the equivalents of the \(i\)PrMgCl were again increased (Entry 3). This time the desired addition product 486 was isolated after chromatography in a pleasing 73% yield. These optimised conditions were then used to synthesise compound 488 in the modest yield of 56%.

The reaction was carried out at a low temperature to reduce the chance of the unwanted competing reaction between the \(i\)PrMgCl and the benzophenone. The IR spectra showed the disappearance of the ketone stretch at 1600 cm\(^{-1}\) and the presence of an alcohol group at 3434 cm\(^{-1}\). \(^1\)H NMR spectrometry provided further evidence that 486 and 488 had been isolated by the presence of the tethered olefin at 5.81 ppm and 5.14 ppm, respectively.

With these pleasing results in hand we now decided to use our key building block as the addition substrate. The optimised conditions were used and gave the addition products in the moderate isolated yields of 19% and 15% respectively (Scheme 121) providing us with enough material to carry forward with the RRM transformations.

![Scheme 121: Successful metal-halogen exchange and additions](image)

This material was then subjected to the RRM protocol, using the conditions stated in Table 17. It was hoped this would allow us to gain access to [5.0.3] and [6.0.3] ring systems.
### Table 17: Attempted RRM conditions for long chain tethers

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Catalyst (mol %)</th>
<th>Time (hr)</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethylene</td>
<td>Toluene</td>
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<td>[Ru]-II 5</td>
<td>24</td>
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</tr>
<tr>
<td>2</td>
<td>Ethylene</td>
<td>Toluene</td>
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<td>[Ru]-II 10</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Ethylene</td>
<td>Toluene</td>
<td>rt</td>
<td>[Ru]-II 20</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Ethylene</td>
<td>Toluene</td>
<td>35</td>
<td>[Ru]-II 10</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Ethylene</td>
<td>Toluene</td>
<td>50</td>
<td>[Ru]-II 10</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Ethylene</td>
<td>Toluene</td>
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<td>[Ru]-II 10</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Ethylene</td>
<td>Toluene</td>
<td>90</td>
<td>[Ru]-II 10</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Ethylene</td>
<td>Toluene</td>
<td>110</td>
<td>[Ru]-II 10</td>
<td>48</td>
<td>-</td>
</tr>
</tbody>
</table>

Naturally, we started with our previously optimised RRM cyclisation conditions ([Table 17, Entry 1](#)). However, after 24 h TLC showed no new compound, and indicated that no reaction had taken place. Accordingly, catalyst loading was doubled to 10 mol% ([Entry 2](#)). Again TLC revealed no new compound had formed. The catalyst loading was then doubled again to 20 mol%. However, only starting material was recovered upon work up ([Entry 3](#)).

With the increase in catalyst loading proving unsuccessful, it was decided to increase the temperature of the reaction ([Entry 4](#)). The reaction was attempted first at 35°C and when TLC indicated no new compound had formed the temperature was increased to 50°C ([Entry 5](#)). Again, TLC showed no reaction had taken place and so the temperature was increased steadily with TLC monitoring until reflux had been reached ([Entry 8](#)). After 48 h at reflux TLC still showed no new compound had been formed, the reaction was stopped and the starting material reclaimed ([Scheme 122](#)). The crude $^1$H NMR spectrum revealed that only starting material was present within the reaction mixture.
5. Results and discussion

**Scheme 122: Failed attempts to make seven and eight membered rings using RRM**

A possible cause for the failure of 494 and 495 to cyclise into the desired [5.0.3] and [6.0.3] bicycles is the required formation of the energetically unfavoured 7 and 8 membered rings. Potentially the Thorpe-Ingold effect could be applied to overcome this and this will be discussed later in the report (Figure 26).

**Figure 24: The required CM to give energetically unfavoured 7 and 8 membered rings**

With the moderate success of the transmetalation addition reactions to the key norbornene the addition of an alkyne was also attempted. Using the optimised conditions the reaction was tested on benzophenone (Table 16, Entry 3 and Scheme 123).

**Scheme 123: Alkyne addition test on benzophenone**

The addition of 3-chloro-1-phenyl-1-propyne to benzophenone was successful, and after chromatography was isolated in 23% yield. However, when the transmetallation was
attempted on the key building block 437, the reaction was unsuccessful, and only starting material was isolated. This unfortunately meant that the cyclisation could also not be trialled (Scheme 124).

Scheme 124: Failed alkyne addition to the key norbornene

*We were able to use a transmetallation addition to successfully synthesise the required metathesis precursors to [5.0.3] and [6.0.3] bicyclic systems. However, these did not undergo cyclisation once exposed to our optimised metathesis conditions. The project now switched focus, and the development of tricyclic systems was investigated.*
5.6 Tricyclic Systems

With our pleasing results for accessing the ottelione skeleton we decided to extend this work to make tricyclic systems similar to those found in the Hamigeran family (Figure 27).

Hamigeram B is one of eight hamigerans isolated from poecilosclerical sponge, Hamigera tarangaensis, collected from the Hen and Chicken islands east of New Zealand. It has been found to completely inhibit the herpes and polio viruses. However, its synthesis is made difficult by the cyclic quaternary centre from which two other stereocentres evolve, highlighted in red in the figure above.

Four key synthetic approaches have been reported. Firstly Nicolaou published an asymmetric synthesis utilising a [4+2] photocycloaddition, and therefore gained an enatiomerically pure epoxide obtained via the Jacobson hydrolytic kinetic resolution. Clive and co-workers described a synthesis in which the chiral quaternary centre was constructed using Meyer’s chiral auxiliary. Thirdly, Trost installed the quaternary centre by Pd catalysed asymmetric allylic alkylation of a preformed cyclopentanone. Finally, Taber reported a general route to the 6,6,5-tricyclic skeleton of (−)-Hamigeran B based on a C-H insertion of a α-arl-α-iazolketone, followed by a Friedl-Crafts cyclisation (Scheme 125).
It was envisaged from our previous work that we could apply our successful RRM cascade to provide an alternative route to forming this quaternary centre. Our retrosynthetic route is shown in **scheme 126**. For this we would have to develop aromatic olefinic tethers to add to our key building block \( \text{Scheme 126} \). 

**Scheme 125: Taber's synthesis of hamigeran skeleton**

Previous work by Mattlia *et al.* towards aromatic Grignard reagents, gave us the methodology for our first attempts at synthesising our aromatic tethers (**Scheme 127**).
5. Results and discussion

To start with, a Grignard reagent addition of vinyl magnesium bromide to 2-bromobenzyl bromide using recrystalised CuI and 2,2-bipyridyl was attempted which gave a low yield of 27% for compound 406 (Scheme 128). It also proved difficult to purify this compound as the product was often lost on silica due to product degradation to starting material. Attempts were made using a fresh bottle of vinyl magnesium bromide solution, which gave a modest yield of 38% with this yield being in line with the literature report (Scheme 128).

In hope to achieve better isolated yields it was decided to use a different method for the other tethers length. Using an adapted method from Mattlia, 2-bromobenzyl bromide and the Grignard reagent were added together in THF and stirred under reflux for 2 h (Scheme 129).

This gave the desired compounds 516a and 516 in excellent isolated yields of 81 and 87%, respectively. With such a big increase in reaction yield this method was also carried out on the allyl magnesium addition. Unfortunately, while the reaction did produced compound 516a,b it did not give it in a better yield than 38%.
The synthesis of these reagents was trouble free and the characterisation was confirmed by the presence of peaks between 6.00 – 5.93 ppm (m, 1H) and 5.13 – 5.05 ppm (m, 2H) on the \(^1\)H NMR spectra. However, while these compounds were synthesised with ease, care had to be taken due to their lachrymatory effects.

With the aryl reagents in hand it was decided to test their reactivity in the lithium/halogen exchange. Again for this we used benzophenone as we did not want to use our key intermediate (Scheme 130).

![Scheme 130: General benzophenone experiment](image)

A lithium mediated addition was attempted using compound 516a as our trial aromatic tether. In one reaction vessel benzophenone was dissolved in anhydrous THF at -78\(^\circ\)C. In another reaction vessel the aromatic olefin was also dissolved in THF at -78\(^\circ\)C, \(n\)-butyl lithium was then added drop wise. The reaction mixture containing the lithiated olefin was then added \textit{via} a cannula to the reaction mixture containing the benzophenone and the reaction allowed to warm to room temperature. After work up and chromatography, 510 was isolated in the pleasing yield of 64%.

![Scheme 131: Addition of aromatic tether 519 to benzophenone](image)

With this method proving effective we now attempted the same protocol on our key norbornenone 437 (Scheme 132).
5. Results and discussion

The lithium mediated addition worked well, giving good yields after chromatography. Characterisation of each compound was accomplished using IR, NMR spectrometry and m/s. The IR spectra gave the expected OH stretch at 3500 cm\(^{-1}\) and no ketone stretch was present. The \(^1\)H NMR spectra showed the presence of the aryl group with a multiplet between 7.25 – 7.15 ppm. Also the presence of the terminal olefin was confirmed by peaks at 6.20 ppm and 6.05 ppm, respectively. Mass spectra also showed the mass expected for the addition of the aryl tether at 393.2213.

With the precursors to the RRM in hand, work now began on trialling our RRM conditions on these substrates to generate the corresponding rearranged products (Table 18).

![Scheme 132: Addition of aromatic tethers to key norbornenone](image)

Table 18: Attempted RRM of aromatic tethers

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Catalyst (mol %)</th>
<th>Time (h)</th>
<th>Outcome</th>
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<td>1</td>
<td>Ethylene</td>
<td>Toulene</td>
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<td>48</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Ethylene</td>
<td>Toulene</td>
<td>35</td>
<td>[Ru]-II 10</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Ethylene</td>
<td>Toulene</td>
<td>50</td>
<td>[Ru]-II 10</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Ethylene</td>
<td>Toulene</td>
<td>75</td>
<td>[Ru]-II 10</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Ethylene</td>
<td>Toulene</td>
<td>90</td>
<td>[Ru]-II 10</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Ethylene</td>
<td>Toulene</td>
<td>110</td>
<td>[Ru]-II 10</td>
<td>48</td>
<td>-</td>
</tr>
</tbody>
</table>

We began with our previously successful RRM conditions (Table 18, Entry 1). After 48 h TLC indicated that no new compound had been formed (Entry 1) and consequently, the reaction temperature was increased gradually (Entry 2). Once reflux had been reached and TLC had shown no new compounds, starting material was reclaimed in quantitative yields in all cases (Scheme 133).
A possible explanation for the failure of 520, 521a and 512b to undergo metathesis may lie in its conformation. If the ruthenium alkylidene initially reacts with the exocyclic alkene then the restricted rotation around the arene- $\text{Sp}^3$ bond may preclude cyclisation. Alternatively, as the arene lies over the endocyclic olefin of the norbornene then the approach of the ruthenium complex may also be precluded due to steric congestion (Figure 28).

Figure 28 shows the energy minimised conformation calculated at 447.0922 kJ/mol. The aryl portion of the molecule is clearly positioned over the endocyclic double bond of the norbornene scaffold. This provides further evidence towards our hypothesis that the approach of the ruthenium would be blocked by the aryl ring.
5. Results and discussion

Figure 26: Schematic for the reasoning of the failed RRM of aromatic olefins, and the energy minimised conformation of 521a

With this in mind a smaller aromatic tether was synthesised from commercially available 2-bromo styrene. The same reaction conditions were used as previously stated, and this gave the desired compound 528 in 69% yield (Scheme 134).

Scheme 134: Addition of 2-bromo-styrene to the TBS protected norbornenone

Once 528 had been characterised it was subjected to our cyclisation conditions, but again TLC indicated no cyclisation had taken place, and after trialling several temperatures and catalyst loadings only starting material was reclaimed.
5. Results and discussion

Scheme 135: Failed RRM transformation of 528

For the RRM transformation to proceed, ring opening of the endocyclic double bond of the norbornene must occur. If the presence of an arene group prevents this then the metathesis cascade cannot take place. To test this hypothesis the compound 530 was synthesised via the addition of two equivalents of phenyl magnesium chloride to the key norbornenone in anhydrous THF, and gave the expected syn addition product in a modest 53% yield (Scheme 136).

Scheme 136: Addition of phenyl magnesium chloride to norbornenone 437

This was then exposed to our optimised metathesis conditions in the presence of styrene. It was hoped that once ring opening had occurred that compound 532 would be isolated as a result of the cross metathesis of styrene with the ring opened olefins (Scheme 137).
5. Results and discussion

Scheme 137: Attempted CM reaction using compound 530 and styrene, and the energy minimised conformation of 530

However, after attempting the reaction under many different metathesis conditions, either starting material or stilbene was isolated exclusively. The energy minimised calculated conformation illustrates that the lowest energy state for 530 (537.2997 kJ/mol) is with the aryl ring positioned directly above the endocyclic double bond, this and our previous results led us to conclude that the presence of an arene group prevents the initial ring opening step of the metathesis cascade and therefore making the RRM transformation unlikely (Scheme 137).

To conclude, we have found that olefin tethers with an aromatic ring attached do not undergo RRM transformations to give the desired tricyclic structures. Work on this and similar structures will continue, and the project's attention now turned to the reaction mechanism taking place during the RRM cyclisation of the [2.2.1] bicycles.
5. Results and discussion

5.7 ROM-RCM Mechanism

Such a high degree of regioselectivity for the ROM-RCM step is noteworthy and to our groups knowledge the only related study demonstrating such an effect had been conducted by Rainer.\(^{95}\)

Rainer reported a highly regioselective ROM-RCM of \textit{exo-} and \textit{endo-} substituted 7-oxa and 7-aza norbornenyl derivatives. They attributed the high regioselectivity to the directing effect of the sulfone present within the norbornene substrate, \textit{via} coordination to the ruthenium metal centre (Scheme 138).

![Scheme 138: Rainers ROM-RCM of subsituted 7-oxa and 7-aza norbornenyl derivatives](image)

From their work and our results, a plausible mechanistic rationale for the regioselectivity outcome of our ROM-RCM transformation is outlined below (Scheme 139).
5. Results and discussion

There are two possible reaction pathways, \( a \) and \( b \), by which this metathesis cascade reaction can proceed. Pathway \( a \) begins with the Ru pre-catalyst forming an alkylidene 536 via the exocyclic olefin, followed by cyclisation to give 538 through the intermediate 539 (Scheme 140).

Scheme 139: Proposed mechanism of RRM

Scheme 140: Proposed mechanism for desired RRM product
If the reaction took place through pathway \( a \) then 536 would go through a highly strained metallacyclobutane like 538 and 539. It can then be presumed that the strained intermediates would then isomerise to 545 and 546, which is required to give the observed product 544 (Scheme 140). Pathway \( b \) would involve the immediate ring opening of the strained endocyclic olefin within the norbornenyl ring system, giving either 548 or 549 (Figure 29).

![Figure 27: Proposed mechanism for minor RRM product](image)

However, only compound 549 would give the desired precursor to the desired cyclised product 550. We believe from this study that pathway \( b \) would be the more likely pathway for the reaction to precede, as it provides relief from the ring strain found in norbornenes.

We assumed, like Rainier, that the reaction regioselectivity is directed by OR alkoxy functionality, and that the formation of six-membered transition state involving the silyl ether group is responsible for the regioselectivity, explaining why at this point we had only seen one regioisomer (Figure 30).

![Figure 30: Possible six membered transition state](image)
5. Results and discussion

We then set about providing evidence to support our hypothesised mechanism. We believed we could do this once the key alcohol 552 had been synthesised (Figure 31).

![Key norbornenyl compound 552](image)

Figure 28: Key norbornenyl compound 552

With this compound in hand we would then be able to see if the side chain containing either a hydroxyl or silyl group plays any role during the RRM. If it indeed does then when 552 is exposed to our RRM conditions we would expect to see a mixture of regioisomers.

Initial attempts to synthesise 552 were made using a Barton-McCombie decarboxylation. It was imagined that after the formation of the thiol, and using the radical initiator ACCN that we would be able to remove the oxygen side arm leaving us with only the methyl group (Scheme 141).

![Mechanism of the radical reduction of 436 to give the key norbornenyl 552](image)

Scheme 141: Mechanism of the radical reduction of 436 to give the key norbornenyl 552

Diol 440 was treated with PhOC(S)Cl and DMAP in CH₂Cl₂ at room temperature for 24 h. Crude ¹H NMR spectrum indicated that the reaction had been a success due to the presence of
aromatic signals in the 7.34 ppm region. The reaction was then scaled up to allow enough compound to be purified and brought through to the second step (Scheme 142).

Scheme 142: Synthesis of thiol 559

The purified thiol was submitted to a standard radical initiation reaction involving Bu$_3$SnH and ACCN at 95$^\circ$C for 24 h in anhydrous toluene. Unfortunately, after several attempts and varying reaction times only the diol 440 was isolated (Scheme 143).

Scheme 143: Failed removal of thiol to give the methyl group

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bu$_3$SnH (Eq)</th>
<th>ACCN (Eq)</th>
<th>Temp ($^\circ$C)</th>
<th>Reaction time (h)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>2</td>
<td>95</td>
<td>24</td>
<td>-</td>
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<td>Reflux</td>
<td>24</td>
<td>-</td>
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<tr>
<td>3</td>
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<td>4</td>
<td>4</td>
<td>4</td>
<td>Reflux</td>
<td>120</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>4</td>
<td>Reflux</td>
<td>240</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 19: Table to show the conditions attempted to successfully remove the thiol group to give the alcohol 552
Increasing the equivalents of both Bu$_3$SnH and ACCN had no effect on the outcome of the reaction (Table 19, Entry 2). When the reaction was left at reflux for extended lengths of time (Entry 4 and 5) no new compound was found to be present on the crude $^1$H NMR spectrum.

A new approach was needed to access the desired compound, and so the second route investigated involved the mesylation of the primary alcohol followed by reduction. The diol was placed in a solution of pyridine and tosyl chloride, and were stirred together at room temperature for 3 h. Once again after work up the presence of the tosylate group was confirmed using the new aromatic peaks at 7.35 ppm on the $^1$H NMR spectrum and the presence of a new methyl peak at 2.45 ppm (Scheme 144).

![Scheme 144: Addition of the tosyl group to diol 440 and attempted reduction of compound 561](image)

The next step was to remove the tosyl group using LiAlH$_4$ in THF at 0°C. After quenching the reaction mixture using a saturated solution of ammonium chloride the only isolated product was again the starting diol (Scheme 144). It was decided to replace the tosylate group with the smaller mesylate group, and to determine if this would have any effect on the reduction.

To a solution of anhydrous CH$_2$Cl$_2$ was added the diol (440) and triethylamine. The reaction mixture was the cooled to -10 °C and methansulfonyl chloride was added slowly. From this reaction mixture was then isolated the desired compound 562 and a small amount of the diol. The appearance of a new methyl peak at 2.46 ppm on the $^1$H NMR spectrum confirmed that we had indeed successfully attached the mesylate group to the primary alcohol (Scheme 145).
5. Results and discussion

Scheme 145: Successful addition of the mesylate group to diol 440

Compound 462 was then treated with Superhydride® in anhydrous THF at reflux. To our delight, upon work up and purification the key norbornenyl compound with methyl group was now present in the good yield of 62%. (Scheme 146).

Scheme 146: Successful removal of the mesylate group to give the desired key alcohol 552

We confirmed the presence of the methyl by the singlet peak at 2.93 ppm, importantly the CH$_2$ peak corresponding to the CH$_2$ on the side arm of the starting material at 3.96 ppm was now absent.

With this key RRM precursor in hand, we were now able to test our hypothesis. If our RRM did indeed go through a chelated intermediate then it would be expected that this reaction, as it contains no chelating group, would yield both possible regioisomers (Scheme 147).

Scheme 147: Possible regioisomers of the RRM of compound 440
Exposure to our previously optimised rearrangement conditions (Table 13, entry 7) yielded, after column chromatography, only one of the possible regioisomers 553. The absence of the other regioisomer 554 suggests that the oxygen in the side chain does not play a role during the ring rearrangement, and that our original proposed mechanism was no longer the likely reaction pathway (Scheme 148).

Scheme 148: Regio outcome of the RRM transformation of alcohol 552

With these new results in hand we were now able to present a new credible mechanism for our RRM reaction. The transformation and the formation of the observed product 553 is explained below (Scheme 149).

Scheme 149: New mechanism for the RRM reactions

Ruthenium catalysed ring opening can give either products 555 or 558, with 558 giving rise to compound 554, and 555 giving rise to compound 553. Only 555 will give the observed
5. Results and discussion

regioisomer 554. The previously pondered chelation and therefore stabilisation through an – OR intermediate (556) is not supported by the rearrangement of 552. On the other hand, under our RRM conditions the inter-conversion of 554 and 553 via 557 is plausible, with 554 being disfavoured due to possible adverse steric interactions.

Further investigation into the RRM reaction involved the primary alcohol being converted into both an acetate and dimethoxy group. The acylation of the parent diol was achieved in a good yield of 65% to give compound 567. The IR stretch at 1741 cm\(^{-1}\) confirmed the compound now contained the C=O functionality while the proton NMR spectrum confirmed the addition of the methyl group (Scheme 150).

![Scheme 150: Addition of an acetate group to diol 552](image)

After exposure to our metathesis conditions, the analysis of the crude \(^1\)H NMR spectrum of the final ring rearranged product was found to contain a 4:1 mixture of the major isomer 568 and its minor regioisomer. Which again confirms that the oxygen atom located in the side arm does not play a role in the stabilisation of regioisomers, and does not provide a route to one isomer over the other (Scheme 151).

![Scheme 151: Results of the RRM of compound 449](image)

An interesting result came during attempts to synthesise the methyl ester side arm. First the diol was converted to the aldehyde using PDC in a DMF/H\(_2\)O solvent mix. The
disappearance of the CH$_2$ peak on the $^1$H NMR spectrum and the new IR stretch at 1715 cm$^{-1}$ confirmed that the reaction had been a success (Scheme 152).

![Scheme 152: Conversion of diol 552 to the aldehyde 570](image)

The aldehyde was then exposed to $p$-TSA in methanol and it was hoped that this would form the dimethoxy group. The reaction went to completion, with 572 being formed. Upon inspection of the $^1$H NMR spectrum, 3 new methyl peaks had appeared, and led us to believe that instead of forming the methyl ester the reaction had instead formed the trimethoxy compound 572 in an 80 % yield (Scheme 153).

![Scheme 153: Interesting result of the reaction between acid 751 and MeOH and $p$-TSA](image)

It was decided to use this compound in the RRM. After 48 h at reflux with 10 mol% [Ru-II] catalyst, TLC indicated no reaction had taken place. After work up, the crude $^1$H NMR spectrum revealed there to only be starting material present, no change in the double bond region indicated that no rearrangement had taken place, this may be due to an unfavoured interaction between the methoxy groups in the final cyclised product (Scheme 154).
5. Results and discussion

Scheme 154: Possible unfavoured steric interactions

It has been discovered that the metathesis transformation forms the most thermodynamically stable product 553, avoiding the other possible regioisomer 554 due to unfavourable steric interactions. The regioselectivity of this cascade reaction is not influenced through a chenlation intermediate between the ruthenium and the –OR side chain.

5.7.1 Reduction of the secondary alcohol

It was decided at this point to further expand previous work towards the ottelione scaffold. To get structurally closer to the ottelion skeleton the secondary alcohol would have to be reduced after the diastereoselective Grignard addition (Scheme 155).

Scheme 155: Scheme to show the removal of the alcohol group to give the ottelion skeleton

The removal of the OH group could be achieved in the presence of a strong reducing agent, such as DIBALH or sodium triacetoxyborohydride (STAB), providing the reactive
intermediate 579, this could then undergo an attack from a nucleophile to give the desired compound 580 (Scheme 156).

![Scheme 156: Mechanism for the removal and addition of a nucleophile to compound 580](image)

Scheme 156: Mechanism for the removal and addition of a nucleophile to compound 580

Taking diol 552 and exposing it to five equivalents of STAB in DCE under reflux disappointingly only yielded starting material (Scheme 157).

![Scheme 157: Treatment of diol 552 with STAB](image)

Scheme 157: Treatment of diol 552 with STAB

The equivalents of STAB were then increased twofold to 10 equivalents and this allowed for the recovery of a modest 10% yield of the desired alcohol 581, the rest of the reaction mixture was found to be starting material. Several attempts were made to improve upon this modest yield but to no avail (Table 20).

<table>
<thead>
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<th>Entry</th>
<th>Solvent</th>
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<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Outcome</th>
</tr>
</thead>
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<td>Reflux</td>
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<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>20</td>
<td>Reflux</td>
<td>72</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 20: Attempted conditions in the removal of the alcohol group
Increasing the equivalents of STAB further had no effect on the outcome of the reaction, nor did refluxing the reaction for extended lengths of time (Table 20, Entry 3). Changing the solvent to toluene allowed the reaction mixture be heated to higher temperatures; however, no desired compound was recovered and only starting material was found to be present.

In an attempt to improve upon the low yield a new approach using sodium cyanoborohydride in the presence of zinc bromide was examined. The diol was dissolved in ether and treated with three equivalents of NaBH₃CN and two equivalents of ZnBr₂. This reaction mixture was stirred at room temperature for 24 h, but TLC indicated that no change had taken place, and upon work up ¹H NMR spectrum confirmed only the presence of the starting diol (Scheme 158).

![Scheme 158: Unsuccessful attempts to use NaBH₃CN to remove the alcohol group](image)

Should more time have been allowed we would have liked to further optimise these reaction conditions and to eventually carry out the RRM on the alcohol obtained, to give the scaffold of the ottelione family.

During this interesting work it was also decided to attempt the allylation of the secondary alcohol to give a new triene that could also undergo a RRM transformation to give a cyclised product. Alcohol 439 was treated with distilled allyl bromide in the presence of NaH, and DMF at room temperature. Upon quenching the reaction and work up, the desired triene was isolated in a pleasing 71% yield (Scheme 159).

![Scheme 159: Allylation of alcohol 439 to give the triene 582](image)
The presence of the second exocyclic double bond was confirmed by appearance of peaks at 5.91 ppm on the $^1$H NMR spectrum and the disappearance of the OH stretch on the IR spectrum.

The next step was to expose the triene to our optimised RRM conditions; although we were aware that there are two possible pathways and that two different structural outcomes could arise. Pathway $a$ represents what we believe to be the most likely structural outcome, derived from the RCM of the two exocyclic double bonds. More interesting is the possibility of transformation obtained through pathway $b$ to give the spirocycle 585 (Scheme 160).

![Scheme 160: possible transformations of 582 during RRM cyclisation](image)

As expected when 582 was exposed to our previously optimised RRM conditions we did indeed obtain the ring closed product 583. The presence of the alkene peak at 5.61 and 5.68 ppm in the $^1$H NMR spectrum indicated the double bond present in the newly formed ring. The peaks associated with the endocyclic olefin bond were still present, concluding that the reaction had transpired through pathway $a$ not pathway $b$ as predicted.

![Scheme 161: Metathesis outcomes of the RRM of 582](image)

Attempts to reduce the secondary alcohol are ongoing with further work required to improve upon the modest yield of 10 %. With the work on the substituted norbornenes coming to a close our attention turned to applying what we have demonstrated to the synthesis of a new [2.2.2] bicyclic metathesis precursor.
5. Results and discussion

5. 8 Expansions to new systems: bicyclo[2.2.2]oct-5-en-2-one

It was decided to take our previously successful results using the [2.2.1] bicyclic systems and to expand them to new but similar cyclic systems. Increasing the bridge size would allow us to easily access larger bicyclic ring sizes which we had previously found troublesome. Our retrosynthetic pathway, shows the key addition precursor to be the bicyclo[2.2.2]oct-5-en-2-one. With this precursor we could then attempt similar lithium-mediated additions and Grignard additions to the carbonyl, using our previously synthesised aromatic olefin bromide compounds, and commercially available Grignard additions. Once the additions had taken place we would then be able to expose them to our optimised RRM conditions (Scheme 162).

![Scheme 162: Retrosynthetic pathway to the formation of a [2.2.2] bicycle starting from 1,3-cyclohexadiene](image)

The first step was to synthesise the key ketone. Following a simple 3-step synthesis reported by Kozikowski and co-workers\(^9\) we were able to access the important addition precursor in multi-gram amounts. The synthesis began with the preparation of 5-cyanobicyclo[2.2.2]oct-ene. A mixture of acrylonitrile, 1,3-cyclohexadiene and hydroquinone was sealed in a Pyrex tube and heated at 120 °C for 18 h. After distillation the resulting clear semi-solid material was confirmed to be the required 5-cyanobicyclo[2.2.2]oct-2-ene in a 70% yield. The IR stretch at 1454 cm\(^{-1}\) is indicative of the C≡N stretch. \(^1\)H and \(^13\)C NMR were also found to be in accordance with the values reported in the literature. Experimental concerns over using Pyrex tubes for pressure reactions caused the reaction to only be run in small batches, and therefore multiple batches were run to allow access to the multi-gram amounts required (Scheme 163).

![Scheme 163: Formation of 5-cyanobicyclo[2.2.2]oct-2-ene](image)
The next step was the $\alpha$-chlorination of the bicyclic nitrile. The nitrile was added to a refluxing mixture of pyridine, chloroform and phosphorus pentachloride. The residue obtained after 13 h was then distilled and the pure chlorinated nitrile was obtained in an excellent yield of 93%. Mass spectroscopy of the compound showed the corresponding mass for 584 and again NMR results were in line with those previously reported in the literature. Importantly, the IR spectrum still showed the stretch at 1441 cm$^{-1}$ which indicated the nitrile group had been unaffected (Scheme 164).

![Scheme 164: $\alpha$-Chlorination of 584 to give compound 585](image)

The final step of this three step synthesis was the hydrolysis of the $\alpha$-chloronitrile with potassium hydroxide. To do this the chloronitrile was placed into a stirring solution of DMSO and 85% KOH. The resulting reaction mixture was then stirred at room temperature for 24 h. Following work up and distillation the white semi-solid (389) was obtained in a 90% yield. IR spectroscopy confirmed the presence of the carbonyl group with a stretch at 1725 cm$^{-1}$, the $^1$H, $^{13}$C NMR and mass spectra were concordant with that reported in the literature (Scheme 165).

![Scheme 165: Hydrolysis of $\alpha$-chloronitrile with potassium hydroxide](image)

_Bicyclo-[2.2.2]-oct-2-en-7-one 389 has been prepared in a 3-step sequence and in gram quantities with an overall yield of 65%. With this substrate in hand, work began on the Grignard reagent additions._
5.8.1 Commercially available Grignard additions

Using our previously optimised Grignard addition conditions we began work towards adding a variety of commercially available Grignard reagents to our key bicyclo[2.2.2]oct-5-en-2-one.

The first addition was carried out using allylmagnesium chloride in anhydrous THF. The resulting alcohol was isolated as a 1:2 mixture of the cis/trans diastereoisomers, with yields of 53% and 24% respectively. The diastereoisomers were separated using graduated and exhaustive column chromatography (Scheme 166).

![Scheme 166: Addition products and their ratios](image)

To establish the identity of each isomer, extensive 1D selective NOSEY experiments were performed. As the whole molecule is structurally identical, the key protons to be investigated are located on the carbons highlighted in red, found on the bridge and side olefin tether (Figure 32).

![Figure 29: Targeted protons during 1D selective NOSEY experiments](image)

The first to be investigated was the isomer believed to be the major isomer, cis-586. When submitted to 1D selective NOSEY it became apparent that when the proton highlighted in red was irradiated it showed an interaction with the two protons highlighted in blue (Figure 33).
5. Results and discussion

**Figure 30:** The interactions noted during 1D selective NOSEY experiments.

This allowed us to conclude that for this interaction to take place the OH must be in the axial position. When the second isomer was investigated this interaction was not found and so it implied that the OH was now in the equatorial position, and that the olefin chain was pointed down in the axial position (**Figure 34**).

**Figure 31:** Interactions absent during 1D selective NOSEY.

From this we were able to identify with certainty the identity of each isomer on the \(^1\)H NMR spectra below (**Figure 35**).
5. Results and discussion

Figure 32: $^1$H NMR depicting the two isomers of the addition reactions

With this success it was decided to expand the addition to longer olefin chains and substituted olefin chains. Homoallyl magnesium chloride was added to the ketone, and after work up and a graduated column, the addition was found to give cis-586 and trans-586 in a diastereomeric ratio of 2.6:1, with a yields of 45% and 15% respectively (Scheme 167).

![Scheme 167: Addition of the homoallyl Grignard reagents to the [2.2.2] system](image)

The final addition was performed using (2-methylallyl)magnesium chloride, which gave the cis- and trans products as an inseparable mixture of isomers in a 62% yield (Scheme 168).
5. Results and discussion

Scheme 168: Addition of a substituted allyl magnesium Grignard reagent to the [2.2.2] bicycle

With the success of these three additions, it was decided to re-attempt previous work towards tricyclic systems, similar to the structural scaffold found in the hamigeran family. The retrosynthetic pathway below shows our synthetic route. Starting with the ketone, if it is possible to add our aromatic tethers via a lithium mediated addition, then we would arrive at the RRM precursor 590. If this precursor, when exposed to our optimised metathesis conditions, rearranged to give the desired tricycle 589 then this would give us a simple five step synthesis to the structural motif found in 589 (Scheme 169).

Scheme 169: Retrosynthetic pathway to show the possible tricyclic outcome of the RRM of aromatic olefin tethers on the [2.2.2] system

The additions began using commercially available 2-bromostyrene. To a solution of anhydrous THF and 2-bromostyrene at –78°C was added a solution of n-BuLi. After stirring for 10 min the cyclic ketone was added, and the reaction mixture allowed to warm to room temperature. After work-up and exhaustive column chromatography, the diastereoisomers cis-592 and trans-592 were isolated in 42% and 15% yields. The crude 1H NMR spectrum allowed the d.r of the isomers to be calculated as a ratio of 3:1 (Scheme 170).
The next addition attempted was using one of our previously synthesised aromatic tethers, 515. To a stirring solution of compound 305 in anhydrous THF at −78 °C was added n-BuLi. After 10 min this reaction mixture was transferred to a second reaction mixture of the key cyclic ketone in anhydrous THF also at −78 °C. Only cis-593 was isolated in a 48% yield (Scheme 171).

**Scheme 171: The single isomer obtained from the addition of the aromatic tether to the [2.2.2] ketone**

### 5.8.2 Ring rearrangement metathesis

With the addition products in hand we could now trial our metathesis conditions. As before two regio-chemical outcomes were possible during the rearrangement reaction; after ring opening the ring closing could take one of two pathways, pathway \( a \) and/or pathway \( b \). Only upon RRM would we find out the outcome of the RRM rearrangement and this could be determined through \(^1\text{H}, \text{COSY and HMQC NMR spectroscopy (Scheme 172).} \)
The first compound to undergo RRM was compound cis-586. When this compound was treated with [Ru-II] in toluene at room temperature, under an atmosphere of ethylene, the corresponding rearrangement compound was isolated in a 70% yield, with a small amount of starting material. The change in chemical shift of the endocyclic double bond from 6.25-6.12 ppm on the 1H NMR spectrum to 5.78-5.69 ppm indicated that the compound had correctly ring opened, and the corresponding ring closed product had been formed (Scheme 173).

It was determined by COSY NMR spectroscopy that the final rearranged product formed was that of compound 596 (Figure 36) and not of the expected bicycle 595.

Both the exo- and endocyclic double bonds would appear the same on a 1H NMR spectrum of each diastereomer. The important proton is that opposite the OH on the bridge, highlighted in red. We believed that its interactions would help determine which isomer had been formed. If
the bicycle 595 been formed we would expect to see interactions on the COSY spectra between the proton on red and those in blue (Figure 37).

Figure 34: Interactions of protons on the COSY spectra expected for compound 595

If the other isomer had been formed we would expect to see interactions between the same protons in red and blue, but also those in green (Figure 30). It is this interaction that can be clearly be seen on the COSY spectra, with the CH peak at 2.19ppm coupling with the methylene signal at 2.41ppm, which has allowed us to conclude that it was indeed the [3.3.1] system that was formed and not the [4.0.1] bicycle (Figure 38).

Figure 35: The obtained interactions on the COSY spectra for compound 596

With this result in hand, trans-596 was exposed to the same RRM conditions. However, these conditions failed to give the rearranged product, with only starting material being isolated. Fascinatingly, upon heating the reaction mixture to 60 °C for 16 h all of the starting material was consumed and the rearranged product 586 was isolated in a moderate yield of 24%. The increase in temperature to achieve the rearrangement of trans-596 is presumably due to the formation of the strained trans-fused carbocycles, 595 (Scheme 174).

Scheme 174: RRM transformation outcome for transi-595
The homoallyl addition product was then treated with the RRM conditions. Once again compound cis-587 rearranged to give the new bicycle 597 in a 55% yield (Scheme 175).

![Scheme 175: Successful RRM transformation of compound cis-587](image)

When its diastereoisomer was exposed to the same conditions, a change was noted on the TLC. Several different reaction conditions were attempted and it was found adding another 5 mol % of the catalyst and increasing the temperature had no effect on the cyclisation (Scheme 176, Table 21).

![Scheme 176: Unsuccessful RRM of compound trans-587](image)

<table>
<thead>
<tr>
<th>Catalyst (mol %)</th>
<th>Temp (°C)</th>
<th>Reaction time (h)</th>
<th>Solvent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
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<td>Toluene</td>
<td>-</td>
</tr>
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<td>[Ru-II] 10 mol %</td>
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<td>48</td>
<td>Toluene</td>
<td>-</td>
</tr>
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<td>48</td>
<td>Toluene</td>
<td>-</td>
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<tr>
<td>[Ru-II] 10 mol %</td>
<td>110</td>
<td>72</td>
<td>Toluene</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 21: Attempted reaction conditions for the RRM transformation of compound trans-587

Due to the poor yield when the RRM transformation was performed on trans-596, along with the failure of trans-587 to undergo any rearrangement, all subsequent RRM reactions were performed solely on the cis-addition products. The 2-methallyl substrate mixture 588 gave the rearranged product 599 in a moderate isolated yield of 24% (Scheme 181).
This interesting transformation has provided us with a new route to bridged bicycloalkenes via a RRM metathesis pathway, a route similar to that reported by Grubbs and Morehead in 1998.\textsuperscript{97} They reported a series of monocyclic diene substrates were synthesised and exposed to [Ru-I] to give [3.X.1], [4.X.1] and [5.X.1] bicycloalkenes in excellent yields (84-95\%) (Scheme 182).

A more elaborate example has been presented by Pattenden \textit{et al.}\textsuperscript{98} this work used a radical cascade to access the desired tricycle structure found in taxol and taxotene (Figure 39).

With the two successful results it was time to expose our aromatic tethered olefins to the rearrangement conditions. As with the previous [2.2.2] systems we were aware that two regio- outcomes were possible during the transformation (Scheme 183).
5. Results and discussion

Scheme 179: Both possible pathways for the RRM transformation of syn-475

We exposed both cis-475 and trans-475 to our metathesis conditions. After 48 h at room temperature no change was indicated on the TLC for either compounds and as with the previous unsuccessful rearrangements it was decided to alter the conditions (Scheme 184, Table 22).

Scheme 180: Unsuccessful RRM of bicycle cis-592

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Temp (°C)</th>
<th>Reaction time (h)</th>
<th>Solvent</th>
<th>Results</th>
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</tr>
<tr>
<td>6</td>
<td>[HG-II] 10 mol%</td>
<td>reflux</td>
<td>72</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>[HG-II] 10 mol%</td>
<td>reflux</td>
<td>72</td>
<td>CH₂Cl₂</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 22: The reaction conditions attempted during the unsuccessful RRM of compound 592

This time it was decided to not only increase the catalyst loading and temperature but to also change the solvent and the catalyst (Entry 6). Changing the solvent had no effect on the
reaction outcome and it was hoped that changing the catalyst from [Ru-II] catalyst to a [HG-II] catalyst that we would see some improvement (Entry 7). However, still no rearranged product was detected via TLC. This led to the reaction being worked up and the crude $^1$H NMR was inspected for any new material, however, only starting material was found to be present.

Our final attempt at the tricyclic rearranged product was to expose compound cis-593 to several metathesis conditions (Scheme 185).

Scheme 181: Unsuccessful RRM of the aromatic compound cis-593

Yet again after attempting several different reaction conditions, no cyclised product was discovered and the $^1$H NMR spectrum confirmed only the presence of starting material.

To confirm whether the ring opened intermediate could undergo cross metathesis, and to discover if the catalyst was able to form the important metallacycle, the reaction was repeated but in the presence of styrene (Scheme 186).

Scheme 182: Attempted CM reaction between cis-592 and styrene

After 48 h, no reaction had taken place under our standard metathesis conditions (Table 13, Entry 7); so it was decided to try the several different reaction conditions as before (Table 23).
5. Results and discussion

<table>
<thead>
<tr>
<th>Catalyst (mol %)</th>
<th>Temp (°C)</th>
<th>Reaction time (h)</th>
<th>Solvent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Ru-II] 5 mol %</td>
<td>rt</td>
<td>48</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>[Ru-II] 10 mol %</td>
<td>50</td>
<td>48</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>[Ru-II] 10 mol %</td>
<td>90</td>
<td>48</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>[Ru-II] 10 mol %</td>
<td>reflux</td>
<td>72</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>[HG-II] 10 mol%</td>
<td>reflux</td>
<td>72</td>
<td>CH₂Cl₂</td>
<td>-</td>
</tr>
<tr>
<td>[HG-II] 10 mol%</td>
<td>reflux</td>
<td>72</td>
<td>CH₂Cl₂</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 23: Metathesis conditions for the CM of compound syn-475 with styrene

Unfortunately, no reaction was found to have taken place, only starting material and styrene were isolated. A possible explanation is the interaction of the ruthenium alkylidene with the tertiary hydroxyl group, reminiscent to the Hoveyda-Grubbs catalysts, giving an intermediate such as 608 (Figure 40).

![Image of possible interaction between the ruthenium alkylidene and the hydroxyl group](image)

Figure 40: Possible interaction between the ruthenium alkylidene and the hydroxyl group

For cis-586 and trans-586 a mechanistic rationale for the formation of each carbocycle is shown below in scheme 183. Reminiscent of [2.2.1]-norbornenyl derivatives, the exposure of csi-469 to [Ru]-II and ethene should deliver 609. This triene has two possible cyclisation pathways to follow under our reaction conditions; pathway (a) will yield a cis fused [4.0.3]-carbocycle (595) while pathway (b) will deliver the observed [3.3.1]-carbocycle 596. Calculated energies for each regioisomer indicate that the [3.3.1]- carbocycle 596 is some 17.49 kJmol⁻¹ more stable than 595, indicating that product formation is under thermodynamic control possibly via the chair conformation depicted in 610 (Scheme 183). This is further supported by the work of Grubbs and Goldring, introduced above, who independently demonstrated that similarly substituted precursors undergo RCM to give [3.3.1]-carbocycles (Scheme 183).
In summary, we have successfully added a range of organometallic reagents to bicyclo-[2.2.2]-oct-2-en-7-one 389 and demonstrated that a moderate degree of diastereoselectivity is displayed in favour of the syn-addition products. These syn-addition products successfully undergo a ruthenium catalysed RRM transformation at room temperature to give [3.3.1]- and [4.3.1]-carbocycles, while the eanti-addition product (trans-586) gave the corresponding trans fused-[4.0.3]-carbocycle in moderate yield and crucially at elevated temperatures.
5.9 Selective Dehalogenation

As a side project it was attempted to selectively dehalogenate compound 611 using a chromium perchlorate solution in DMF, based on the work done by Kochi.\textsuperscript{99} They found that it is possible to eliminate halogens selectively in good yields. They describe the addition of a green solution of Cr\textsuperscript{III} to a solution of ethylenediamine (en) in DMF, this solution would then turn purple once the Cr\textsuperscript{II}en\textsubscript{2} reagent had been formed \textit{in situ}. As the halogen in question was the less reactive chlorine the reaction would also have to be carried out over 24 h (Scheme 184).

We hoped to utilise this methodology to give us compound 612 and therefore enable us to functionalise at the double bond at a later date. However after several attempts and careful use of anhydrous conditions no purple solution was ever created and the desired compound 612 was never isolated.

Although this work had been abandoned temporarily, a more recent literature president was discovered, and it was decided it would be worth attempting as it had been carried out on molecules very similar to our own. Kahn \textit{et al.}\textsuperscript{100} had developed a simple Bu\textsubscript{3}SnH mediated bridgehead reduction of a tetrahalonorbornene (Scheme 185).

\begin{center}
\textbf{Scheme 184: Attempted selective dehalogenation of compound 611}
\end{center}

\begin{center}
\textbf{Scheme 185: Suggested selective dehalogenation conditions}
\end{center}
This time using AIBN and Bu₃SnH, it was hoped after heating at reflux in benzene for 60 h that the dehaolgenated compound 617 could be isolated. However, after several attempts ¹H NMR spectrum showed that the reaction had not taken place, and only starting material was recovered. Consequently the alcohol and ester compounds were also exposed to these conditions. Disappointingly only starting material was isolated (Scheme 186).

Scheme 186: Attempted selective dehalogenation

Unfortunately, time has not allowed a repeat of these reactions, nor optimisation had they been successful. More interestingly is that from this work, functionalisation at the bridgehead could be possible, and is another area for further work (Scheme 187).

Scheme 187: Further selective dehalogenation conditions

This work, while unsuccessful, presents an interesting side project. It was hoped by using these literature examples we could selectively dehalogenate our norbornene and therefore functionalise the endocyclic double bond at a later date.
6. Indium mediated allylations

The Grignard additions to the key norbornenone have been found to be extremely stereoselective. With our work currently using magnesium or lithium as the metal during additions to the ketone, we decided to extend the additions to include a different metal indium. Indium-mediated allylations can take place in aqueous media, which has the obvious advantage of being non-toxic, non-flammable and cheaper to use. There is also no need for anhydrous or inert atmospheres as indium metal does not react with moisture like lithium and sodium. Protecting reactive hydroxyl groups is also not required, and finally compounds insoluble in organic solvents can react directly. With olefin metathesis now found to be possible in water and indium believed to be non-toxic, this work could be promising for bio-molecule synthesis. Grubbs recently reported a novel water soluble catalyst, which is both stable and active in water, and capable of ROMP, RCM and CM in excellent yields (Scheme 188).

![Scheme 188: Grubbs' metathesis in aqueous media](image)

Indium has many advantages over other metals used in allylation such as Zn and Sn. As discussed it is believed to be non-toxic, it also has the lowest first ionisation energy. (5.79eV) even compared to Mg (7.64 eV), making it more reactive. We started this investigation by testing indium allylation on benzophenone. Using indium powder in a 1:1 mixture of water and THF, the reaction mixture was heated to 50°C and monitored via TLC. After 24 h, TLC indicated no starting material remained and the desired product was isolated in a 91% yield (Scheme 189).
With this promising result in hand we decided to reduce the amount of THF present in the reaction mixture to see if this would have any effect, and if indeed we could carry out the allylations without the presence of an organic solvent (Table 24).

<table>
<thead>
<tr>
<th>Entry</th>
<th>THF (%)</th>
<th>Percentage yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
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<td>10</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 24: Indium mediated allylation conditions

When the THF was reduced to 40% of the solvent mixture there was a substantial drop in the percentage of product 623 recovered (Table 24, Entry 2). This decrease in isolated product continued as the amount of THF was reduced gradually. Although, regardless of low yields, it does show that the reaction can take place in the presence of only water. This trend in reactivity may be due to the solubility of the starting materials in water (Scheme 195). Further work is required here to investigate and understand the limiting factor.

Scheme 190: Allylation mechanism
5. Results and discussion

During this work it was noticed that at the end of each reaction the indium powder had formed into solid round pellets. Consequently, it was decided to test these pellets for re-usability.

Using the optimised conditions from before (Table 24, Entry 1), at the end of each reaction the indium pellet was reclaimed and reused. It was discovered that the pellet could be re-used up to four times before there was a detrimental effect on the yield.

Finally, addition to the norbornenone intermediate was attempted, it was unknown if we would see the same diastereoselective addition as we had during magnesium Grignard reagent additions or the lithium mediated additions. To a stirring solution of ketone 437 in THF:H₂O (1:1) was added indium and two equivalents of freshly distilled allyl bromide. The desired syn addition was observed and the alcohol 631 was isolated in a 68% yield (Scheme 191).

Scheme 191: Indium mediated addition to our key norbornenone

We further expanded the indium mediated allylation to include the indium mediated γ-pentadienylation of our starting carbonyl. Following previous examples by Fallis and co-workers we supposed that we could follow their methods and apply it to our own important norbornenone. Fallis104 established that the treatment of 5-bromo-1,3-pentadiene with indium metal in DMF or water in the presence of a variety of carbonyl compounds results in a γ-pentadienylation to generate the 1,4-diene-alcohol (Scheme 192).

Scheme 192: Indium mediated allylation of 632
Chan and colleagues had previously demonstrated, using allylindium, that even though both $\alpha$ and $\gamma$ addition are possible, indium react at the $\gamma$ position selectively.$^{105}$ Fallis confirmed that this was also the case for 5-bromo-1,3-pentadiene when reacted with indium metal to give non-conjugated compounds of the type 636 (Scheme 193).

\[
\text{Scheme 193: $\alpha$ and $\gamma$ addition possibilities}
\]

After expanding their work to a variety of unsaturated carbonyls, Fallis found that the $\gamma$-pentadienylation was considerably slower than the allylation, taking up to 3 days to go to completion rather than the 12 h required for the indium mediated allylation.$^{106}$

Accordingly, we believed the treatment of our key norbornenone, with the bromide 437, and a stochimetric amount of indium metal would allow us to achieve the same level of regioselectivity during a similar $\gamma$-pentadienylation. We began using the conditions we had previously optimised (Table 24, entry 1), however when a solvent mix of THF and water (1:1) was used only modest amounts of the desired addition product 638 were achieved (12%) (Scheme 194).

\[
\text{Scheme 194: Indium mediated addition of our key norborneneone using Tetrahydrofuran and water}
\]

Using the further modified conditions of Fallis, specifically using DMF instead of THF and water, over a 48 h period, gave the addition product 638 in a yield of 49% and as a single diastereoisomer. This result is significant as it now incorporates an alpha substituent on the organometallic reagent without compromising on diastereoselectivity. This would also provide a synthetic handle on the reaction product for further functionalisation (Scheme 195).
The triene was confirmed by mass spectroscopy, mass peak 343.2057 \([M+Na]^+\) was found as expected. The $^1$H NMR confirmed the presence of the new diene at 5.96, 5.18 and 5.07 ppm.

**Scheme 195: Indium-mediated addition to the key norborneneone 437 using DMF as the solvent**

Compound 638 was exposed to our standard RRM conditions (**Table 13, Entry 7**), which delivered the rearranged product 639 predominantly, but as an inseparable 4:1 mixture of diastereoisomers, as indicated by the crude $^1$H NMR spectrum, in a respectable yield of 54% (**Scheme 196**).

**Scheme 196: Product of the rearrangement metathesis, compound 639**

With this exciting result, we also extended this further to our [2.2.2] system. Using the same modified conditions from Fallis, we were able to successfully carry out the pentadienylolation on the bicyclo[2.2.2]oct-5-en-2-one (**Scheme 197**).

**Scheme 197: Indium mediated additions to the [2.2.2] bicycle 389**
The desired triene, 640, was produced in the disappointingly low yield of 28%. Further attempts to increase this yield, including, adding more indium metal and increasing the equivalents of the bromide, had no effect. As with the similar addition products to this [2.2.2] system, 1D selective NOSEY, COSY, HMQC and $^1$H NMR spectroscopy confirmed that the isolated isomer was the syn isomer 640.

The triene, cis-640, was then exposed to our optimised metathesis conditions, in the hope of forming a bicycle with two endocyclic olefins. After stirring for 48 h at room temperature, the TLC showed no change in $R_f$ value. The experimental conditions were then changed (Scheme 198, Table 25).

**Scheme 198: Unsuccessful RRM transformation of the indium addition product 640**

<table>
<thead>
<tr>
<th>Catalyst (mol %)</th>
<th>Temp (°C)</th>
<th>Reaction time (h)</th>
<th>Solvent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Ru-II] 5 mol %</td>
<td>rt</td>
<td>48</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>[Ru-II] 10 mol %</td>
<td>50</td>
<td>48</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>[Ru-II] 10 mol %</td>
<td>90</td>
<td>48</td>
<td>Toluene</td>
<td>-</td>
</tr>
<tr>
<td>[Ru-II] 10 mol %</td>
<td>110</td>
<td>72</td>
<td>Toluene</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 25: Reaction conditions used in the unsuccessful RRM cyclisation of 640**

Upon increasing the catalyst loading no change was noted, so next the temperature was elevated. However, even at reflux no reaction took place, and the only isolated product after work up was revealed to be starting material.

*The diastereoselective indium mediated additions to norbornenyl derivatives give the syn addition products have been achieved and expanded to include further additions to bicyclo[2.2.2]oct-5-2-one. These addition products have then gone on to successfully cyclise under*
our RRM transformation conditions to give compound 639. However, when the same transformation was attempted for the [2.2.2] substituted olefin no reaction took place.
7. Future work and conclusions

In conclusion, the addition of allyl magnesium and allyl indium reagents to a key TBS protected norbornenyl building block, synthesised in 6-steps from commercially available 1,1-dimethoxy-2,3,4,5-tetrachlorocyclo-pentadiene, has been achieved providing the \textit{syn} addition products with high diastereoselectivity (Scheme 199). Overall this gave the desired TBS-protected norbornenone key intermediate in 46% yield over 6 steps. The route allowed for the synthesis of the norbornenone in a reproducible and large scale.

\begin{center}
\textbf{Scheme 199: Synthesis of Key norbornene building block}
\end{center}

This procedure works on simple straight chain alkenes and has been extended to more elaborate olefin tethers (Scheme 200).

\begin{center}
\textbf{Scheme 200 : \textit{cis} fused [3.0.3] carbocycles via RRM}
\end{center}

A plausible mechanism has also been presented, concluding that there is no stabilisation effect from the oxygen containing side tether, and that the observed regioselectivity is due to a thermodynamic consideration as reflected in the product (Scheme 201).
7. Future work and conclusions

Scheme 201: Plausible mechanism for the RRM cyclisation of our functionalised norbornenones

It has also been found that an indium mediated allylation is possible on the same norbornenone, giving the same desired diastereoselectivity (Scheme 202).

Scheme 202: Successful indium allylations of the protected norbornenone

Unfortunately work on constructing tricyclic structures using the same RRM sequence has not been successful, along with the selective dehalogenation of the substituted norborne (Scheme 203).
7. Future work and conclusions

Scheme 203: Unsuccessful rearrangement of the aromatic olefin norbornenyls

Successful expansion of this work to [2.2.2] systems has also been achieved and ketone 389 has been functionalised in the same manner as before, using Grignard reagent additions and indium mediated allylations (Scheme 204).

Scheme 204: Synthesis of [2.2.2] bicyclic systems and Grignard reagent additions

The syn-addition products successfully undergo a ruthenium catalysed RRM transformations at room temperature to give [3.3.1]- and [4.3.1]-carbocycles (Scheme 205).

Scheme 205: The rearrangement reactions and products of the [2.2.2] systems

While the trans-addition product (trans-586) gave the corresponding trans fused-[4.0.3]-carbocycle in moderate yield and crucially at elevated temperatures (Scheme 206).
7. Future work and conclusions

Scheme 206: RRM transformation outcome for trans-586

Unfortunately, when this work was expanded to involve aromatic olefin tethers, no RRM transformation took place (Scheme 207).

Scheme 207: Unsuccessful RRM of the aromatic compound cis-474

However, new attempts should be made in the addition of the longer chain tethers. Work recently published by Knochel suggests that if the reaction is carried out in the presence of LiCl the yields are drastically improved (Scheme 208).

Scheme 208: Future transmetallation reaction conditions

Investigations into the addition of side chains at the bridgehead should also be carried out as this would give us further unique functionalisation options in the future (Scheme 209).
7. Future work and conclusions

Work should also continue on the longer chain tethers, especially on improving the yields, and then further attempts could be made to use the RRM conditions to cyclise to give the seven and eight membered bicycles. This may be achieved by using the brominated primary alcohol rather than the chlorinated. (Scheme 210).

As suggested in Knochels work, the addition of LiCl greatly improved their transmetallation results and our reactions may be improved when including this additive.

The success of the RRM step for the 7 and 8 membered rings can possibly be improved by adding methyl substituents to the olefin tether. Using the Thorpe-Ingold effect this should allow for the formation of the 7 and 8 membered rings (Figure 41).
Further important work is the optimisation of the removal of the OH group. The current 10% yield of the primary alcohol needs to be improved upon if the compound is going to be used for the RRM transformation (Scheme 211).

![Scheme 211: Further STAB optimisation is required](image)

With more product, this could then be exposed to our optimised metathesis conditions to give us the bicycle 577, the structural back bone of the ottelione family (Scheme 212).

![Scheme 212: Intended reaction sequence to gain entry to the ottelion skeleton](image)
8. Experimental

**General.** Commercially available reagents and solvents were used throughout without further purification, except tetrahydrofuran (benzophenone/Na) and dichloromethane (CaH) which were freshly distilled. Et₂O was purchased dry from commercial suppliers. Light petroleum refers to the fraction with bp 40-60 °C. Thin layer chromatography was carried out on Merck Kieselgel 60 GF254 aluminum foil backed plates. The plates were visualized under UV light and/or anisaldehyde stain. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrix silica 60, with the eluent specified. IR spectra were recorded using Perkin Elmer FTIR Spectrometer (Paragon 100) as solutions using CH₂Cl₂ as solvent, unless otherwise stated. ^1^H and ^13^C NMR spectra were recorded using Bruker 400 MHz NMR machine (^1^H 400 MHz, ^13^C frequencies 100 MHz respectively) and a Joel ECS-400 MHz NMR; chemical shifts are quoted in ppm and coupling constants, J, are quoted in Hz; d-Chloroform was used throughout unless otherwise stated. In the ^13^C spectra, signals corresponding to C, CH, CH₂ or CH₃ groups, as assigned from DEPT, are noted. Spectra were calibrated to residual solvent peaks. High and low resolution mass spectra were carried out on a Thermofisher exactive (orbi) resolution mass spectrometer. Optical rotation measurements were recorded on a polAAr 2001 polarimeter using chloroform as solvent. Melting points were recorded on a Stuart Scientific apparatus and are uncorrected.

**Synthetic procedures**

7,7-Dimethoxy-2-endo-carboethoxy-1,4,5,6-tetrachlorobicyclohept-5-ene 429

\[
\begin{align*}
\text{MeO} & \quad \text{OMe} \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{CO₂Me} & 
\end{align*}
\]

5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene 372 (4.54 g, 3.00 mL, 17.0 mmol) was added to methyl acrylate (2.94 g, 3.00 mL, 34 mmol) and the reaction mixture heated to 75 °C for 48 h under nitrogen. The crude residue was then distilled at 200 °C at 7 mbar (literature bp 120-125 °C at 1.0 mbar) to give the title compound as a clear oil (4.94 g, 83%); IR (CH₂Cl₂) ν max 3155 (OH), 2953, 2254, 1737 (C=O) cm⁻¹; ^1^H (400 MHz, CDCl₃) δ 3.76 (s, 3H), 3.61 (s, 3H), 3.56 (s, 3H), 3.46 (dd, J = 4.2, 9.2 Hz, 1H), 2.54 (dd, J = 4.6, 9.2 Hz, 1H).
8. Experimental

Hz, 1H), 2.29 (dd,  J = 4.2, 11.8 Hz, 1H); $^{13}$C (100 MHz, CDCl$_3$) δ 170.3, 130.6, 128.0, 111.9, 76.9, 74.1, 52.8, 52.5, 51.8, 50.4, 38.9; MS-ESI found 372.9345 C$_{11}$H$_2$Cl$_4$O$_4$, [M+Na]$^+$ requires 372.9352. Anal. Calcd for C$_{11}$H$_2$Cl$_4$O$_4$: C. 37.75; N. 0.00; H. 3.36. Found: C. 37.71; N. 0.00; H 3.34.

7,7-Dimethoxy-1,4,5,6-tetrachlorobicyclohept-5-ene-2-endo-carboxylic acid 432$^{84}$

![Chemical Structure]

KOH (1.23 g, 22 mmol) was dissolved in EtOH/H$_2$O (50 mL, 1:1) and added to 7,7-Dimethoxy-2-endo-carboethoxy-1,4,5,6-tetrachlorobicyclohept-5-ene 429 (1.50 g, 4.3 mmol) and once dissolved the reaction was heated to reflux for 45 min under nitrogen. The volume was then partially reduced under vacuum to remove the EtOH. A saturated oxalic acid solution was then added and the aqueous layer extracted with EtOAc and the organic layers then dried over magnesium sulfate. The excess volatiles were removed under reduced pressure furnishing the title compound as colourless solid (1.37 g, 95%); m.p. 161-163 °C (literature m.p 163-164 °C);$^{84}$ IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 3500 (OH), 2900 (C-H), 1713 (C=O), 1423 cm$^{-1}$; $^1$H (400 MHz, CDCl$_3$) δ 3.62 (s, 3H), 3.54 (s, 3H), 3.50 (dd,  J = 4.4, 9.6 Hz, 1H), 2.57 (dd,  J = 9.6, 11.0 Hz, 1H), 2.27 (dd,  J = 4.4, 11.6 Hz, 1H); $^{13}$C (100 MHz, CDCl$_3$) δ 175.5, 130.7, 127.8, 111.9, 77.0, 73.9, 52.8, 51.8, 50.2, 38.9; MS-ESI found 358.9193 C$_{10}$H$_9$Cl$_4$O$_4$, [M+Na]$^+$ requires 358.9196. Anal. Calcd for C$_{10}$H$_9$Cl$_4$O$_4$: C. 35.75; H. 3.00. Found: C. 34.57; H 2.82.

7,7-Dimethoxyhept-5-ene-2-endo-carboxylic acid 433$^{84}$

![Chemical Structure]

Sodium (4.00 g, 170 mmol) was chopped into 1mm by 1mm cubes and dissolved in anhydrous liquid ammonia (75-100 mL). 7,7-Dimethoxy-1,4,5,6-tetrachlorobicyclohept-5-ene-2-endo-carboxylic acid 432 (3.00 g, 8.9 mmol) was then dissolved in 1:1 mixture of EtOH/Et$_2$O (50 mL) and added drop wise for 30 min. The reaction was then quenched using
solid NH₄Cl and then left to warm to room temperature while the ammonia evaporated off. The resulting reaction mixture was then added to ice-water and acidified using 2M HCL. Aqueous work-up afforded organic layers dried over magnesium sulfate. Excess volatiles were removed under reduced pressure. This furnished the title compound as colourless solid (1.48 g, 84%); m.p. 75-78 °C (literature m.p 78-79°C);\(^8^4\) IR (CH₂Cl₂) \(\nu_{\text{max}}\) 3050 (OH), 2955, 2253, 1705 (C=O) cm\(^{-1}\); \(^1\)H (400 MHz, CDCl₃) \(\delta\) 6.27 (dd, \(J = 2.3, 6.2\) Hz, 1H), 6.07 (dd, \(J = 2.3, 6.2\) Hz, 1H), 3.22 (s, 3H), 3.16 (s, 3H), 2.88 (t, \(J = 3.7\) Hz, 1H), 2.11 – 2.05 (m, 1H), 1.43 (dd, \(J = 3.7, 11.9\) Hz, 1H), 1.28 – 1.24 (m, 2H); \(^1^3\)C (100 MHz, CDCl₃) \(\delta\) 179.7, 135.6, 130.5, 118.6, 52.0, 49.8, 47.4, 44.8, 41.2, 27.2; MS-ESI found 221.0782, C\(_{10}\)H\(_{13}\)O\(_4\) \([M+Na]^+\) requires 221.0790. Anal. Calcd for C\(_{10}\)H\(_{13}\)O\(_4\): C. 60.59; H. 7.12. Found: C. 62.58; H 6.75.

7,7-Dimethoxybicyclohept-5-en-2-yl methanol 434

![Image](image_url)

7,7-Dimethoxyhept-5-ene-2-endo-carboxylic acid 433 (1.40 g 6.90 mmol) was dissolved in anhydrous THF (30 mL). The reaction mixture was cooled to 0 °C and a solution of LiAlH₄ (2M in THF, 6.9 mL, 13.8 mmol) added drop wise over 30 min. The reaction mixture was then left to warm to room temperature and stirred for 12 h. The reaction mixture was then cooled to 0 °C, and a saturated solution of sodium potassium tartrate added to quench the excess LiAlH₄. The aqueous layer was extracted with Et₂O and the combined organic layers dried over magnesium sulfate, filtered, and excess volatiles were removed under reduced pressure. The crude mixture was then purified by column chromatography (10:1 PE:EtOAc) which furnished the title compound as a colourless oil (1.10 g, 87%); IR (CH₂Cl₂) \(\nu_{\text{max}}\) 3405 (OH), 2934, 2076, 1636 (-C-O-C-) cm\(^{-1}\); \(^1\)H (400 MHz, CDCl₃) \(\delta\) 6.19 (dd, \(J = 3.2, 6.0\) Hz, 1H), 6.06 (dd, \(J = 3.2, 6.0\) Hz, 1H), 3.37 - 3.31 (m, 2H), 3.22 (s, 3H), 3.16 (s, 3H), 2.97 – 2.95 (m, 1H), 2.80 - 2.27 (m, 1H), 2.52 – 2.48 (m, 2H), 2.04 (dd, \(J = 4.0, 8.4\) Hz, 1H); \(^1^3\)C (100 MHz, CDCl₃) \(\delta\) 134.4, 133.7, 119.3, 64.4, 51.9, 50.8, 46.3, 44.6, 39.0, 27.0; MS-ESI found 207.1001, C\(_{10}\)H\(_{15}\)O\(_3\) \([M+Na]^+\) requires 207.0997.
5-(Hydroxymethyl)-bicyclohept-2-en-7-one 436

7,7-Dimethoxybicyclohept-5-en-2-yl methanol 434 (1.10 g, 5.90 mmol) was dissolved in 5% sulfuric acid in H₂O (30 mL) and heated to 65 °C for 72 h. The aqueous layer was then extracted with Et₂O and the combined organic layers dried over magnesium sulfate, filtered, and the excess volatiles were removed under reduced pressure. This crude product was purified by column chromatography (10:1 PE:EtOAc) to give the title compound as yellow oil (0.98 g, 96%); IR (CH₂Cl₂) νₘₐₓ 3387 (OH), 2931, 1771 (C=O), 1649 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 6.60 (dd, J = 3.7, 6.7 Hz, 1H), 6.45 (dd, J = 3.0, 7.3 Hz, 1H), 3.71 – 3.42 (m, 2H), 3.36 (t, J = 9.9 Hz, 1H), 3.09 (t, J = 3.5 Hz, 1H), 2.88 (t, J = 3.8 Hz, 1H), 2.15 – 2.08 (m, 1H), 1.22 - 1.19 (t, J = 7.0 Hz, 1H), 0.76 (dd, J = 5.4, 12.2 Hz, 1H); ¹³C (100 MHz, CDCl₃) δ 204.3, 133.7, 130.1, 64.5, 48.6, 46.3, 36.2, 25.8; MS-ESI found 161.0571, C₈H₁₀O₂ [M+Na]^⁺ requires 161.0578.

5-(((tert-butyldimethylsilyl)oxy)methyl)bicyclo[2.2.1]hept-2-en-7-one 437

Imidazole (0.20 g, 3.60 mmol) and TBS (0.26 g, 7.50 mmol) were added together and. To this mixture was added 5-hydroxymethyl bicyclohept-2-en-7-one 436 (0.20 g 1.40 mmol) in anhydrous DMF (20 mL) and the resulting solution was heated to 35 °C and stirred for 48 h. Water was added and the reaction mixture extracted using EtOAc. The organic layer was then washed with brine and finally dried over magnesium sulfate, the excess volatiles were removed under reduced pressure and the crude product purified by column chromatography (10:1 PE:EtOAc) which furnished the title compound as colourless yellow oil (0.31 g, 89%); IR (CH₂Cl₂) νₘₐₓ 2930, 2856, 1778 (C=O), 1668 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 6.56 (dd, J = 3.4, 6.6Hz, 1H), 6.40 (dd, J = 3.4, 6.6 Hz, 1H), 3.39 (dd, J = 6.6, 10.4 Hz, 1H), 3.26 (t, J = 10.4 Hz, 1H), 3.05 (t, J = 3.6Hz, 1H), 2.84 (t, J = 3.6Hz, 1H), 2.51 – 2.46 (m, 1H), 2.09 –
2.02 (m, 1H), 0.87 (s, 9H), 0.69 – 0.64 (dd, J = 5.6, 12.0 Hz, 1H), 0.03 (s, 6H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 204.6, 135.0, 133.0, 130.1, 64.2, 48.5, 46.3, 36.5, 30.3, 25.6, 25.3, -3.5; MS-ESI found 275.1441, C$_{14}$H$_{24}$O$_2$Si [M+Na]$^+$ requires 275.1443.

7-Allyl-5-([(tert-butyldimethylsilyloxy)methyl]bicyclohept-2-en-7-ol 439

![Chemical Structure](image)

To a solution of 5-((tert-butyldimethylsilyl)oxy)methyl)bicyclo[2.2.1]hept-2-en-7-one 436 (0.20 g, 0.80 mmol) in anhydrous THF (10 mL) cooled to $-78$ °C, was added allyl magnesium chloride (2M in THF; 1.60 mL, 1.60 mmol) and the reaction mixture allowed to warm to room temperature and stirred for 12h. To the reaction mixture was then added a solution of saturated NH$_4$Cl and the resultant solution extracted with EtOAc. The combined organic extracts were then dried over magnesium sulfate, filtered, and the excess volatiles removed under reduced pressure. Product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as yellow oil (0.22 g, 95%); IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 3398 (OH), 2928, 2856, 1638 cm$^{-1}$; $^1$H (400 MHz, CDCl$_3$) $\delta$ 6.06 (ddd, J = 0.8, 3.2, 6.4 Hz, 1H), 5.93 (dd, J = 3.2, 6.0 Hz, 1H), 5.79 (ddt, J = 6.8, 10.0, 7.6 Hz, 1H), 5.13 – 5.06 (m, 2H), 3.38 (dd, J = 6.4, 10.0 Hz, 1H), 3.22 (t, J = 9.6 Hz, 1H), 2.68 – 2.63 (m, 2H), 2.59 (t, J = 3.6 Hz, 1H), 2.51 – 2.41 (m, 2H), 2.39 (t, J = 3.6 Hz, 1H), 2.12 (ddd, J = 4.0, 8.8, 11.6 Hz, 1H), 0.89 (s, 9H), 0.50 (dd, J = 4.4, 11.6 Hz, 1H), 0.28 (s, 6H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 135.6,135.4, 132.7, 118.4, 92.0, 65.3, 50.8, 48.8, 39.6, 37.7, 27.2, 25.9, 18.3, -5.2 -5.4; MS-ESI found 317.1915, C$_{17}$H$_{30}$O$_2$Si [M+Na]$^+$ requires 317.1913. Anal. Calcd for C$_{17}$H$_{30}$O$_2$Si: C, 69.33; H, 10.27. Found: C, 69.20; H, 9.71.
7-Allyl-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-ol 440

To a solution of 7-allyl-5-[(tert-butyldimethylsilyloxy)methyl]bicyclohept-2-en-7-ol 439 (0.08 g, 0.27 mmol) in anhydrous THF (10 mL) cooled to −78 °C, was added tetra-n-butylammonium fluoride (2M in THF; 0.54 mL, 0.54 mmol) and the reaction mixture stirred for 72 h. EtOAc was then added and the organic layer washed with water and brine. The organic extract was then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure. The crude product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as white solid (70 mg, 72%) m.p. 96-97 °C; IR (CH₂Cl₂) ν max 3398 (OH), 2856, 1955, 1638 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 6.12 (dd, J = 3.6, 6.4 Hz, 1H), 5.97 (dd, J = 3.2, 6.0 Hz, 1H), 5.78 (ddt, J = 7.2, 9.6, 7.6 Hz, 1H), 5.15–5.13 (m, 1H), 5.13–5.09 (m, 1H), 3.42 (dd, J = 6.4, 10.4 Hz, 1H), 3.34 (dd, J = 9.2, 10.4 Hz, 1H), 2.71–2.67 (m, 1H), 2.62–2.60 (m, 1H), 2.53–2.41 (m, 2H), 2.45–2.43 (m, 1H), 2.22–2.16 (m, 1H), 0.60 (dd, J = 4.4, 11.6 Hz, 1H); ¹³C (100 MHz, CDCl₃) δ 136.1, 135.1, 132.3, 118.6, 92.1, 65.4, 50.4, 48.8, 39.7, 37.6, 27.4; MS-ESI found 203.1040, C₁₁H₁₆O₂ [M+Na]⁺ requires 203.1043.

5-[(tert-Butyldimethylsilyloxy)methyl]-7-(2-methylallyl)bicyclohept-2-en-7-ol 441

To a solution of 5-(((tert-butyldimethylsilyl)oxy)methyl)bicyclo[2.2.1]hept-2-en-7-one 437 (0.20 g, 0.80 mmol) in anhydrous THF (10 mL) cooled to -78 °C was added 2-methylallylmagnesium magnesium chloride (0.5M in THF; 3.34 mL, 1.60 mmol) and the reaction mixture allowed to warm to room temperature and stirred for 12 h. To the reaction mixture was then added a solution of saturated NH₄Cl and the resultant solution extracted with EtOAc. The combined organic extracts were then dried over magnesium sulfate, filtered
and the excess volatiles removed under reduced pressure. The product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as a clear yellow oil (90 mg, 38%); IR (CH₂Cl₂) νmax 3434, 2928, 2856 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 6.05 (ddd, J = 6.4, 3.6, 0.8 Hz, 1H), 5.93 (dd, J = 6.4, 3.2 Hz, 1H), 4.89 – 4.88 (m, 1H), 4.76 – 4.75 (m, 1H), 3.40 (dd, J = 6.4, 10.0 Hz, 1H), 3.75 – 3.72 (m, 1H), 3.24 (t, J = 9.6 Hz, 1H), 2.72 – 2.68 (m, 1H), 2.60 – 2.58 (m, 1H), 2.16 – 2.09 (m, 2H), 1.86 – 1.83 (m, 1H), 1.76 (s, 3H), 0.88 (s, 9H), 0.52 (dd, J = 4.0, 11.6 Hz, 1H), 0.02 (s, 6H); ¹³C (100 MHz, CDCl₃) δ 144.0, 134.9, 132.7, 114.3, 91.5, 65.6, 50.5, 49.6, 39.7, 38.6, 30.9, 27.3, 25.6, 23.8, 18.3, -5.3; MS-ESI found 331.2061, C₁₈H₃₂O₂Si [M+Na]⁺ requires 331.2069. Anal. Calcd for C₁₈H₃₂O₂Si : C. 70.07; N.0.00; H. 10.45. Found : C. 69.07; N. 0.00; H 9.82.

7-(But-3-en-2-yl)-5-((tert-butyldimethylsilyloxy)methyl)bicyclo[2.2.1]hept-2-en-7-ol 443

To a solution of 5-(((tert-butyldimethylsilyl)oxy)methyl)bicyclo[2.2.1]hept-2-en-7-one 437 (0.20 g, 0.80 mmol) in anhydrous THF (10 mL) cooled to -78 °C was added but-3-en-2-yl magnesium chloride (0.5M in THF, 3.33 mL, 1.60 mmol) and the reaction mixture allowed to warm to room temperature and stirred for 12 h. To the reaction mixture was then added a solution of saturated NH₄Cl and the resultant solution extracted with EtOAc. The combined organic extracts were then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure. The product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as a clear yellow oil (100 mg, 42%); IR (CH₂Cl₂) νmax 3468 (OH), 3069, 2929, 2857 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 6.07 – 6.04 (m, 1H), 5.91 – 5.85 (m, 2H), 5.15 (t, J = 1.4 Hz, 1H), 5.12 – 5.00 (m, 1H), 3.38 – 3.35 (m, 1H), 3.25 (t, J = 4.8 Hz, 1H), 2.99 – 2.94 (m, 1H), 2.70 – 2.26 (m, 2H), 2.51 – 2.48 (m, 1H), 2.13 – 2.06 (m, 1H), 1.56 (d, J = 6.8 Hz, 1H), 0.97 (t, J = 6.8 Hz, 3H), 0.88 (s, 9H), 0.52 (dd, J = 4.0, 11.6 Hz, 1H) 0.06 (s, 6H); ¹³C (100 MHz, CDCl₃) δ 140.9, 135.7, 132.9, 115.6, 94.7, 65.4, 50.2, 47.5, 39.7, 36.6, 29.7, 25.9, 18.3, 14.1,-5.3, -5.2; MS-ESI found 331.2051, C₁₈H₃₂O₂Si [M+Na]⁺ requires 331.2069.
7-(But-3-enyl)-5-[(tert-butyldimethylsilyloxy)methyl]bicyclohept-2-en-7-ol 446

To a solution of 5-((((tert-butyldimethylsilyloxy)methyl)bicyclo[2.2.1]hept-2-en-7-one 437 (0.20 g, 0.80 mmol) in anhydrous THF (10 mL) cooled to -78 °C was added ethynylmagnesium chloride (0.5M in THF, 3.34 mL, 1.60 mmol) and the reaction mixture allowed to warm to room temperature and stirred for 12 h. To the reaction mixture was then added a solution of saturated NH₄Cl and the resultant solution extracted with EtOAc. The combined organic extracts were then dried over magnesium sulfate, filtered, and the excess volatiles removed under reduced pressure. Product was then purified by column chromatography (10:1 PE:EtOAc) to give the title compound as clear oil (0.13 g, 53%); IR (CH₂Cl₂) νmax 3414 (OH), 2927, 2855 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 6.07 (dd, J = 1.8, 4.6Hz, 1H), 5.93 – 5.82 (m, 2H), 5.12 – 4.98 (m, 2H), 3.36 (dd, J = 3.4, 5.0 Hz, 1H), 3.22 (t, J = 2.9 Hz, 1H), 2.95 – 2.92 (m, 1H), 2.66 – 2.62 (m, 2H), 2.47 – 2.43 (m, 1H), 2.08 – 2.05 (m, 1H), 0.95 (t, J = 9.5 Hz, 3H), 0.86 (s, 9H), 0.50 (dd, J = 3.8, 11.4 Hz, 1H), 0.02 (s, 6H); ¹³C (100 MHz, CDCl₃) δ 139.8, 134.7, 133.7, 114.6, 93.8, 64.3, 48.2, 47.4, 38.7, 35.6, 30.9, 28.6, 26.4, 17.3, -5.2 -5.0; ; MS-ESI found 331.2050, C₁₈H₃₂O₂Si [M+Na]^+ requires 331.2069.

1-(Hydroxymethyl)-3-vinyl-1,2,3,3a,4,6a-hexahydropentalen-3a-ol 648

7-Allyl-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-ol 439 (0.5 g, 0.16 mmol) was dissolved in anhydrous toluene (5 mL). Grubbs second generation catalyst (5 mol%, 6 mg, 0.008 mmol) was then added and the reaction mixture left to stir for 24 h. The excess volatiles removed under reduced pressure and the product purified by column chromatography (10:1 PE:EtOAc) giving the title compound as yellow oil (0.1 g, 20 %) IR (CH₂Cl₂) νmax 3884 (OH), 2253 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 5.91 – 5.86 (m, 1H), 5.72 – 5.57 (m, 2H), 5.14 – 5.07 (m, 2H), 3.59 (m, 2H), 3.04 (d, J = 2.8 Hz, 2H), 2.55 – 2.51 (m, 4H), 1.52 – 1.18 (m,
Grubbs second generation catalyst (5 mol%, 6 mg 0.169 mmol) was dissolved in anhydrous toluene (5 mL). Ethylene was then bubbled through the reaction mixture for 2-3 mins. The ethylene atmosphere was then maintained and 7-allyl-5-[(tert-butyldimethylsilyloxy)methyl]bicyclohept-2-en-7-ol 439 (50 mg 1.69 mmol) was added. The reaction mixture was then stirred at room temperature for 48 h with monitoring by TLC. The excess volatiles removed under reduced pressure. The crude product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as colourless oil (40 mg 86%). IR (CH₂Cl₂) ν max 3433 (OH), 2955, 2926, 2852, 1641, 1471 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 5.94 (ddd, J = 10.0, 10.8, 17.2 Hz, 1H), 5.68 – 5.66 (m, 1H), 5.63 – 5.61 (m, 1H), 5.11 – 5.07 (m, 2H), 3.50 (quin, J = 6.7 Hz, 1H), 3.00 (d, J = 9.6 Hz, 1H), 2.67 – 2.58 (m, 2H), 2.57 (dd, J = 2.4, 4.2 Hz, 1H), 2.48 – 2.35 (m, 1H), 2.16 (t, J = 9.0Hz, 1H), 1.80 – 1.74 (m, 2H), 0.88 (s, 9H), 0.33 (s, 6H); ¹³C (100 MHz, CDCl₃) δ 137.5, 129.6, 129.5, 116.1, 90.4, 64.2, 59.7, 54.1, 44.2, 43.4, 32.7, 25.9, 18.2, -5.3, -5.2; MS-ESI found 317.1907 C₁₇H₃₀O₂Si [M+Na]⁺ requires 317.1913. Anal. Calcd for C₁₇H₃₀O₂Si : C. 69.33; H. 10.27. Found : C. 68.57; H 9.79.
1-((tert-Butyldimethylsilyloxy)methyl)-5-methyl-3-vinyl-1,2,3,3a,4,6a-hexahydropentalen-3a-ol 464

Grubbs second generation catalyst 2 mg 0.0032 mmol) was dissolved in anhydrous toluene (5 mL). Ethylene was then bubbled through the reaction mixture for 2-3 mins. The ethylene atmosphere was then maintained and 5-((tert-butyldimethylsilyloxy)methyl)-7-(2-methylallyl)bicyclohept-2-en-7-ol 441 (20 mg 0.064 mmol) was added. The reaction mixture was then stirred at room temperature for 48 h with monitoring by TLC. The excess volatiles were removed under reduced pressure. The crude product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as colourless oil (15 mg 76 %). IR (CH$_2$Cl$_2$) \( \nu_{\text{max}} \) 3633 (OH), 3584, 3500, 2958, 2927, 2856, 1639 (C-O), 1437 cm$^{-1}$; \( ^1 \text{H} \) (400 MHz, CDCl$_3$) \( \delta \) 5.90 – 5.81 (m, 1H) 5.58 (dt, \( J = 8.4, 19.3 \) Hz, 1H), 5.18 (t, \( J = 1.4 \) Hz, 1H), 5.07 – 5.00 (m, 2H) 3.45 – 3.36 (m, 3H), 3.20 (t, \( J = 9.8 \) Hz, 1H), 2.91 (d, \( J = 8.4 \) Hz, 1H), 2.56 – 2.50 (m, 2H), 2.46 – 2.40 (m, 1H), 1.67 (s, 3H), 0.82 (s, 9H), 0.01 (s, 6H); \( ^{13} \text{C} \) (100 MHz, CDCl$_3$) \( \delta \) 139.3, 137.6, 123.1, 115.9, 91.1, 64.4, 59.9, 54.2, 48.2, 43.5, 32.8, 25.9, 18.2, 16.5, -5.2, -5.3; MS-ESI found 331.2072 C$_{18}$H$_{32}$O$_2$Si [M+Na]$^+$ requires 331.2066

1-((tert-Butyldimethylsilyloxy)methyl)-4-methyl-3-vinyl-1,2,3,3a,4,6a-hexahydropentalen-3a-ol 464

Grubbs second generation catalyst (100 mg 0.0126 mmol) was dissolved in anhydrous toluene (5 mL). Ethylene was then bubbled through the reaction mixture for 2-3 mins. The ethylene atmosphere was then maintained and 7-(but-3-en-2-yl)-5-((tert-butyldimethylsilyloxy)methyl)bicyclo[2.2.1]hept-2-en-7-ol 442 (39 mg 0.12 mmol) was added. The reaction mixture was then stirred at room temperature for 48 h with monitoring by TLC. The excess volatiles were removed under reduced pressure. The crude product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as colourless.
8. Experimental

oil (0.024 g 61 %). IR (CH₂Cl₂) ν<sub>max</sub> 3400 (OH), 3043, 2956, 2928, 2895, 1638 (C-O), 1471 cm⁻¹; <sup>1</sup>H (400 MHz, CDCl₃) δ 5.88 (dd, <i>J</i> = 7.2, 10.0, 7.2 Hz, 1H), 5.61 – 5.39 (m, 2H), 5.08 – 4.96 (m, 2H), 3.54 (dd, <i>J</i> = 6.4, 10.0 Hz, 1H), 3.44 – 3.39 (m, 1H), 2.95 – 2.89 (m, 1H), 2.70 – 2.52 (m, 2H), 2.52 – 2.42 (m, 1H), 2.17 – 2.09 (m, 1H), 1.77 - 1.71 (m, 1H), 0.95 (s, 3H), 0.85 (s, 9H), 0.03 (s, 6H); <sup>13</sup>C (100 MHz, CDCl₃) δ 137.3, 134.8, 132.6, 117.4, 92.1, 64.0, 59.3, 57.0, 45.8, 43.5, 32.0, 25.9, 18.2, 15.1-5.3, -5.1; MS-ESI found 331.2072 C₁₈H₃₂O₂Si [M+Na]<sup>+</sup> requires 331.2069.

1-((tert-butyldimethylsilyloxy)methyl)-3-vinyl-2,3,3a,4,5,7a-hexahydro-1H-inden-3a-ol

Grubbs second generation catalysts (30 mg 0.0036 mmol) was dissolved in anhydrous toluene (5 mL). Ethylene was then bubbled through the reaction mixture for 2-3 mins. The ethylene atmosphere was then maintained and 7-(but-3-enyl)-5-[(tert-butyldimethylsilyloxy)methyl]bicyclohept-2-en-7-ol 436 (20 mg 0.064 mmol) was added. The reaction mixture was then stirred at room temperature for 48 h with monitoring by TLC. The excess volatiles removed under reduced pressure. The crude product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as colourless oil (15 mg 76 %). IR (CH₂Cl₂) ν<sub>max</sub> 3399 (OH), 2956, 2928, 2857, 1638 (C-O), 1462 cm⁻¹; <sup>1</sup>H (400 MHz, CDCl₃) δ 5.89 – 5.79 (m, 1H), 5.58 – 5.51 (m, 1H), 5.49 (d, <i>J</i> = 8.0 Hz, 1H), 5.42 (dt, <i>J</i> = 2.2, 6.0 Hz, 1H), 5.09 (dt, <i>J</i> = 1.6, 4.9 Hz, 1H), 5.04 (t, <i>J</i> = 3.0 Hz, 1H), 5.01 (dd, <i>J</i> = 4.0, 6.4 Hz, 1H), 3.54 – 3.50 (m, 1H), 3.46 – 3.37 (m, 1H), 2.97 – 2.95 (m, 1H), 2.64 - 2.54 (m, 2H), 2.44 – 2.37 (m, 1H), 1.77 – 1.70 (m, 1H), 1.21 (s, 3H), 0.83 (s, 9H), 0.03 (s, 6H); <sup>13</sup>C (100 MHz, CDCl₃) δ 137.3, 136.4, 132.6, 116.2, 90.4, 64.4, 60.2, 57.0, 44.7, 43.5, 33.1, 25.9, 15.1 -5.2, -5.3; MS-ESI found 331.2073 C₁₈H₃₂O₂Si [M+Na]<sup>+</sup> requires 331.2069.
5-Chloropent-1-ene 487

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\text{Cl}
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4-Penten-1-ol (0.50 g, 5.80 mmol) was added to CH₂Cl₂ (30 mL) and cooled to 0 °C. Pyridine (0.46 mL, 5.80 mmol) was added followed by thionyl chloride (0.42 mL, 5.80 mmol), drop wise, the reaction mixture was then allowed to warm to room temperature and stirred over night. The reaction mixture was then poured over ice and washed with aqueous NaHCO₃ and brine. The organic layer was then dried over magnesium sulfate, filtered and excess volatiles removed under reduced pressure. The purified product was collected using careful distillation at 25 °C 5 mbar (literature b.p 95-103 °C)⁠¹⁰⁷ to give a viscous yellow oil (0.27 g 45 %) IR (CH₂Cl₂) \(\nu_{\text{max}}\) 3079, 2997, 2942, 2849 cm⁻¹ ; \(^1\)H (400 MHz, CDCl₃) \(\delta\) 5.85 (ddt, \(J = 5.6, 8.4, 4.4\) Hz, 1H), 5.09 – 4.99 (m, 2H), 4.08 (m, 2H), 2.20 (q, \(J = 4.3\) Hz, 2H), 1.82 (quin, \(J = 5.6\) Hz, 2H); \(^1^3\)C (100 MHz, CDCl₃) \(\delta\) 137.1, 115.6, 61.5, 29.8, 28.6; GC-Ms No parent Ion noted, C₅H₉Cl, Fragment : 69.0 (C₅H₅).

6-Chlorohex-1-ene 489

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\text{Cl}
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5-Hexene-1-ol (0.50 g, 5.80 mmol) was added to CH₂Cl₂ (30 mL) and cooled to 0 °C. Pyridine (0.46 mL, 5.80 mmol) was added followed by thionyl chloride (0.42 mL, 5.80 mmol), drop wise, liberating gas, the reaction mixture was then allowed to warm to room temperature and stirred over night. The reaction mixture was then poured over ice and washed with aqueous NaHCO₃ and brine. The organic layer was then dried over magnesium sulfate, filtered and excess volatiles removed under reduced pressure. The purified product was collected using careful distillation at 40 °C 5 mbar (literature b.p 130 -132 °C)⁠¹⁰⁸ to give a viscous orange oil (0.36 g 53 %) IR (CH₂Cl₂) \(\nu_{\text{max}}\) 2924, 2853 cm⁻¹ ; \(^1\)H (400 MHz, CDCl₃) \(\delta\) 5.87 – 5.71 (m, 1H), 5.06 – 4.97 (m, 2H), 4.09 – 3.93 (m, 2H), 2.15 (q, \(J = 4.5\) Hz, 2H), 1.76 (quin, \(J = 4.3\)Hz, 2H), 1.54 (quin, \(J = 3.0\) Hz, 2H); \(^1^3\)C (100 MHz, CDCl₃) \(\delta\) 138.1, 115.0, 62.1, 33.1, 28.9, 25.0; GC-Ms retention time 19.65 - 19.89min, parent Ion found 119.6059, C₆H₁₂Cl⁺.
5-Chloropent-1-ene (0.10 g, 0.96 mmol) was added to anhydrous THF (25 mL). The reaction mixture was then cooled to -78°C and treated with isopropyl magnesium chloride (1M in THF, 1.47 mL, 1.92 mmol), this was then left to stir for 10 mins. Benzophenone (0.1 g, 0.54 mmol) was added and the reaction mixture was allowed to warm to room temperature over 12 h, finally the reaction mixture was quenched using a saturated solution of NH₄Cl. The organic layer was extracted using Et₂O and was washed with brine and water, the organic layer was then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure to give the title compound as yellow oil (0.07 g 51%) IR (CH₂Cl₂) 3434 (OH), 3067, 2854, 2859νmax; ¹H (400 MHz, CDCl₃) δ 7.50 - 7.13 (m, 10H), 5.81 – 5.71 (m, 1H), 5.14 – 5.00 (m, 2H), 3.73 – 3.68 (m, 1H), 3.42 (t, J = 6.8 Hz, 2H), 2.93 (quin, J = 6.7 Hz, 2H), 2.08 – 1.89 (m, 2H), ¹³C (100 MHz, CDCl₃) δ 129.1, 128.8, 127.3, 127.0, 126.5, 126.2, 125.3, 124.1, 79.4, 34.0, 29.2, 23.0, 21.4, 16.1; MS-ESI found 253.1599 C₁₈H₂₀O [M+H]+ requires 253.1592.

6-Chlorohex-1-ene (0.10 g, 1 mmol) was added to anhydrous THF (25 mL). The reaction mixture was then cooled to -78°C and treated with isopropyl magnesium chloride (1M in THF, 1.47 mL, 2.00 mmol) this was then left to stir for 10 mins and then the benzophenone (0.10 g, 0.54 mmol) was added. The reaction mixture was then warmed to room temperature and stirred for 12 h and finally quenched using a saturated solution of NH₄Cl. The reaction mixture was extracted using Et₂O and was washed with brine and water. The organic layer was then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure to give the title compound as yellow oil (0.07 g 51%) IR (CH₂Cl₂) 3434 (OH), 3067, 2854, 2859νmax; ¹H (400 MHz, CDCl₃) δ 7.50 - 7.13 (m, 10H), 5.81 – 5.71 (m, 1H), 5.14 – 5.00 (m, 2H), 3.73 – 3.68 (m, 1H), 3.42 (t, J = 6.8 Hz, 2H), 2.93 (quin, J = 6.7 Hz, 2H), 2.08 – 1.89 (m, 2H), ¹³C (100 MHz, CDCl₃) δ 129.1, 128.8, 127.3, 127.0, 126.5, 126.2, 125.3, 124.1, 79.4, 34.0, 29.2, 23.0, 21.4, 16.1; MS-ESI found 253.1599 C₁₈H₂₀O [M+H]+ requires 253.1592.
8. Experimental

reduced pressure to give the title compound as yellow oil (0.08 g 61 %) IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 3434 (OH), 3067, 2854, 2859 cm$^{-1}$; $^1$H (400 MHz, CDCl$_3$) $\delta$ 7.50 – 7.13 (m, 10H), 5.81 – 5.71 (m, 1H), 5.14 – 5.00 (m, 2H), 3.73 – 3.68 (m, 1H), 3.42 (t, $J$ = 6.8 Hz, 2H), 2.93 (quin, $J$ = 6.7 Hz, 2H), 2.08 – 1.89 (m, 2H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 146.1, 142.8, 136.7, 134.1, 131.3, 129.3, 128.9, 127.4, 127.2, 126.8, 79.4, 52.3, 48.2, 45.5, 33.2, 29.1, 23.0, 16.1, 13.1; MS-ESI found 289.1158 C$_{19}$H$_{22}$O $[\text{M+Na}]^+$ requires 289.1568.

5-((tert-Butyldimethylsilyloxy)methyl)-7-(pent-4-enyl)bicyclo[2.2.1]hept-2-en-7-ol 494

5-Chloropent-1-ene (80 mg, 0.36 mmol) was added to anhydrous THF (25 mL). The reaction mixture was then cooled to -78°C and treated with isopropyl magnesium chloride (1M in THF, 0.76mL, 0.72mmol), this was then left to stir for 10 mins and then the 5-((tert-butyldimethylsilyl)oxy)methyl)bicyclo[2.2.1]hept-2-en-7-one 437 (0.10 g, 0.11 mmol) was added. The reaction mixture was then warmed to room temperature and stirred for 12 h and finally quenched using a saturated solution of NH$_4$Cl. The reaction mixture was extracted using Et$_2$O and was washed with brine and water. The organic layer was then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure to give the title compound as yellow oil (20 mg 19%) IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 3560 (OH), 2954, 2933, 2843 cm$^{-1}$; $^1$H (400 MHz, CDCl$_3$) $\delta$ 6.53 (dd, $J$ = 3.6, 6.0 Hz, 1H), 6.37 (dd, $J$ =3.2, 6.0 Hz, 1H), 5.82 – 5.70 (m, 2H), 5.13 – 4.95 (m, 2H), 4.11 (q, $J$ = 5.3 Hz, 1H), 3.72 - 3.96 (m, 1H), 3.47 (q, $J$ = 5.3 Hz, 1H), 3.01 (t, $J$ = 5.4 Hz, 1H), 2.80 (t, $J$ = 5.4 Hz, 1H), 2.16 – 2.08 (m, 2H), 2.00 (s, 2H), 1.86 – 1.81 (m, 2H), 1.23 (t, $J$ = 5.4 Hz, 2H), 0.83 (s, 9H), 0.01 (s, 6H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 139.1, 135.9, 134.4, 115.7, 96.0, 66.3, 62.5, 49.8, 38.3, 35.3, 34.5, 25.9, 21.6, 21.2, -2.3 -2.1; MS-ESI found 345.0219, C$_{19}$H$_{34}$O$_2$Si $[\text{M+Na}]^+$ requires 345.2226.
5-((tert-Butyldimethylsilyloxy)methyl)-7-(hex-5-enyl)bicyclo[2.2.1]hept-2-en-7-ol

6-Chlorohex-1-ene (90 mg, 1.5 mmol) was added to anhydrous THF (25 mL). The reaction mixture was then cooled to -78°C and treated with isopropyl magnesium chloride (1M in THF, 0.75 mL, 3 mmol), this was then left to stir for 10 mins and then the 5-((tert-butyldimethylsilyl)oxy)methyl)bicyclo[2.2.1]hept-2-en-7-one (0.10 g, 0.36 mmol) was added. The reaction mixture was then warmed to room temperature and stirred for 12 h and finally quenched using saturated solution of NH₄Cl. The organic layer was extracted using Et₂O and was washed with brine and water, this was then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure to give the title compound as a yellow oil (0.13 g, 25%) IR (CH₂Cl₂) νmax 3399 (OH), 2868, 1949 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 6.52 (dd, J = 3.2, 6.9 Hz, 1H), 6.37 (dd, J = 3.6, 6.8 Hz, 1H), 5.86 – 5.72 (m, 2H), 5.00-4.90 (m, 2H), 3.72 (t, J = 6.6 Hz, 1H), 3.61 (t, J = 6.6 Hz, 1H), 3.47 (q, J = 5.3 Hz, 2H), 3.00 (t, J = 4.4 Hz, 1H), 2.79 (t, J = 4.4 Hz, 1H), 1.83 (quin, J = 3.3 Hz, 2H), 1.58 – 1.51 (m, 1H), 1.46 – 1.39 (m, 1H), 1.24 (t, J = 7.2 Hz, 2H), 1.18 (t, J = 7.0 Hz, 2H), 0.81 (s, 9H), 0.04 (s, 6H) ¹³C (100 MHz, CDCl₃) δ 140.1, 136.2, 153.1, 116.0, 96.2, 66.3, 61.9, 49.8, 39.1, 35.2, 34.4, 30.6, 29.4, 25.4, 24.5, 21.6, 20.9, -2.1; MS-ESI found 359.2373 C₂₀H₃₆O₂Si [M+Na]⁺ requires 359.2382.

1,4-Triphenylbut-3-yn-1-ol

3-Chloro-1-phenyl-1-propyne (0.10 mL, 0.24 mmol) was added to anhydrous THF (25 mL). The reaction mixture was then cooled to -78°C and treated with isopropyl magnesium chloride (1M in THF, 0.2 mL, 0.48 mmol), this was then left to stir for 10 mins and then the benzophenone (0.30 g, 0.11 mmol) was added. The reaction mixture was then warmed to room temperature and stirred for 12 h and finally quenched using a saturated solution of NH₄Cl. The reaction mixture was extracted using Et₂O and was washed with brine and water.
The organic layer was then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure to give the title compound as yellow oil. (20 mg 74 %) IR (CH$_2$Cl$_2$) $\nu$max 3409 (OH), 3073, 2985, 2865, 2851 cm$^{-1}$; $^1$H (400 MHz, CDCl$_3$) $\delta$ 7.80 – 7.15 (m, 15H), 5.83 (s, 1H), 4.30 (s, 2H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 145.1, 129.4, 128.4, 128.3, 127.4, 126.2, 122.7, 100.6, 82.3, 32.9; MS-ESI found 321.1267 C$_{22}$H$_{18}$O [M+Na]$^+$ requires 321.1255.

1-Allyl-2-bromobenzene 515

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\begin{array}{c}
\text{Br} \\
\text{H} \\
\text{H}
\end{array}
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2-Bromobenzylbromide (3.00 g, 12 mmol), 2,2-bipyridyl (0.18 g, 1.2 mmol) and copper iodide (0.22 g, 1.2 mmol) were dissolved in anhydrous THF (40 mL) under nitrogen. The reaction mixture was then cooled to 0 °C and vinylmagnesium bromide (2M in THF, 8 mL, 24 mmol) was added drop wise, when the addition was complete the reaction mixture was allowed to warm to room temperature and monitored by TLC. To the reaction mixture was then added a saturated solution of NH$_4$Cl and the resultant solution extracted with EtOAc. The combined organic extracts were then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure to give the title compound as dark orange oil (1.07 g, 45 %) IR (CH$_2$Cl$_2$) $\nu$max 3065, 2925, 2859, 1567, 1476, 1441 cm$^{-1}$; $^1$H (400 MHz, CDCl$_3$) $\delta$ 7.54 (d, $J = 0.8$ Hz, 1H), 7.24 – 7.02 (m, 3H), 6.00 – 5.93 (m, 1H), 5.13 – 5.05 (m, 2H), 3.51 (d, $J = 1.6$ Hz, 2H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 138.3, 137.0, 132.7, 128.4, 127.9, 127.2, 124.5, 115.6, 38.0; MS-ESI found 196.9916, C$_9$H$_9$Br [MBr$^{79}$+H]$^+$ requires 196.9966.

1-Bromo-2-(but-3-enyl)benzene 516a

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\begin{array}{c}
\text{Br} \\
\text{H} \\
\text{H}
\end{array}
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2-Bromobenzyl bromide (4.20 g, 16 mmol) was added to anhydrous THF (100 mL). The reaction mixture was then cooled to 0 °C in an ice bath and allylmagnesium chloride (2M in THF, 16 mL, 32 mmol) was added drop wise. A condenser was then added to the flask and the reaction mixture refluxed under nitrogen for 2 h. To the reaction mixture was then added a saturated solution of NH$_4$Cl and the resultant solution extracted with EtOAc. The combined organic extracts were then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure to give the title compound as dark orange oil (2.73 g, 81 %).
IR (CH₂Cl₂) ν\textsubscript{max} 3065, 2931, 2860, 1640, 1567, 1470, 1439 cm\(^{-1}\); \(^1\)H (400 MHz, CDCl₃) δ 7.50 (d, \(J = 8.0\) Hz, 1H), 7.20 – 6.98 (m, 3H), 5.91 – 5.81 (m, 1H), 5.01 – 4.91 (m, 2H), 2.83 (t, \(J = 6.8\) Hz, 2H), 2.30 (q, \(J = 6.8\) Hz, 2H); \(^13\)C (100 MHz, CDCl₃) δ 141.6, 138.8, 132.8, 130.6, 127.8, 127.6, 124.4, 116.1, 33.8, 32.6; MS-ESI found 211.0150, C\(_{10}\)H\(_{11}\)Br [MBr\(^{79}\)+H]\(^+\) requires 211.0122.

1-Bromo-2-(pent-4-enyl)benzene 516b

2-Bromobenzyl bromide (3.00 g, 12 mmol) was added to anhydrous THF (100 mL). The reaction mixture was then cooled to 0°C in an ice bath and 2-butenylmagnesium chloride (0.5M in THF, 48 mL, 24 mmol) was added drop wise. A condenser was then added to the flask and the reaction mixture refluxed under nitrogen for 2 h. To the reaction mixture was then added a saturated solution of NH₄Cl and the resultant solution extracted with EtOAc. The combined organic extracts were then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure to give the \textit{title compound} as clear dark orange oil (2.24 g, 83%) IR (CH₂Cl₂) ν\textsubscript{max} 3068, 2962, 2925, 1640, 1567, 1470, 1442 cm\(^{-1}\); \(^1\)H (400 MHz, CDCl₃) δ 7.56-7.00 (m, 4H), 5.88-5.75 (m, 1H), 4.95-4.89 (m, 2H), 2.80-2.54 (m, 4H), 1.42 (s, 2H); \(^13\)C (100 MHz, CDCl₃) δ 140.1, 136.4, 132.8, 131.5, 129.4, 127.0, 124.2, 113.0, 33.3, 32.8, 30.3; MS-ESI found 225.0279, C\(_{11}\)H\(_{13}\)Br [MBr\(^{79}\)+H]\(^+\) requires 225.1011.

1-Bromo-2-(2-methylbut-3-enyl)benzene 516c

2-Bromobenzyl bromide (3.00 g, 12 mmol) was added to anhydrous THF (100 mL). The reaction mixture was then cooled to 0°C in an ice bath and 3-(1-methyl)-2-propenylmagnesium chloride (0.5M in THF, 48 mL, 24 mmol) was added drop wise. A condenser was then added to the flask and the reaction mixture refluxed under nitrogen for 2 h. To the reaction mixture was then added a saturated solution of NH₄Cl and the resultant reaction mixture extracted with EtOAc. The combined organic extracts were then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure to give the \textit{title compound} as dark orange oil (2.61 g, 85%) IR (CH₂Cl₂) ν\textsubscript{max} 3068, 2962, 2926, 1640,
1566, 1470, 1438 cm⁻¹; \(^1\)H (400 MHz, CDCl\(_3\)) \(\delta\) 7.53 – 7.30 (m, 4H), 5.84 – 5.75 (m, 1H), 4.95 – 4.89 (m, 2H), 2.8 – 2.58 (m, 3H), 1.02 (s, 3H); \(^1\)H (100 MHz, CDCl\(_3\)) \(\delta\) 140.5, 138.2, 132.7, 131.5, 129.0, 127.8, 124.9, 113.0, 42.8, 36.4, 20.1; MS-ESI found 247.0175 C\(_{11}\)H\(_{13}\)Br \([\text{MBr}^{79+}\text{Na}]^+\) requires 247.0098.

(2-(But-3-enyl)phenyl)diphenylmethanol 518

1-Bromo-2-(but-3-enyl)benzene (0.50 g, 2.0 mmol) was dissolved in anhydrous THF (20 mL) and cooled to -78°C, \(n\)BuLi (2M in THF, 1 mL, 4.0 mmol) was then added dropwise. In another 50 mL round bottomed flask a separate solution of benzophenone (0.50 g, 2.0 mmol) in THF (20 mL) at -78°C was prepared. The first reaction mixture was then transferred into the second via cannula, and the resulting reaction mixture allowed to warm to room temperature. To the reaction mixture was then added a solution of saturated NH\(_4\)Cl and the resultant reaction mixture extracted with EtOAc. The combined organic extracts were then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure. The product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as clear yellow oil (0.42 g, 67%). IR (CH\(_2\)Cl\(_2\)) \(\nu\)max , 3063, 2855, 2857cm⁻¹; \(^1\)H (400 MHz, CDCl\(_3\)) \(\delta\) 7.81-6.73 (m, 14H), 5.63 (m, 1H), 4.78 (m, 2H), 2.64 (m, 2H), 2.07 (m, 2H); \(^1\)C (100 MHz, CDCl\(_3\)) \(\delta\) 147.1, 144.4, 142.0, 138.6, 137.6, 131.3, 130.0, 129.5, 128.2, 127.9, 127.7, 127.1, 126.5, 124.8, 114.5, 83.0, 41.7, 35.4, 33.3, 25.9, 23.0, 14.0; MS-ESI found 314.1653 C\(_{23}\)H\(_{22}\)O \([\text{M}+]^+\) requires 314.1671.
7-(2-Allylphenyl)-5-((tert-butyldimethylsilyloxy)methyl)bicyclo[2.2.1]hept-2-en-7-ol 520

1-Allyl-2-bromobenzene (0.20 g, 0.7 mmol) was dissolved in anhydrous THF (20 mL) and cooled to -78°C, nBuLi (2M in THF, 0.37 mL, 1.4 mmol) was then added dropwise. In another 50 mL round bottomed flask a separate solution of 5-(((tert-butyldimethylsilyl)oxy)methyl)bicyclo[2.2.1]hept-2-en-7-one 437 (0.3 g, 1.5 mmol) in THF (20 mL) at -78°C was prepared. The reaction mixture containing the lithiated aromatic tether was then transferred into the second via cannula, and the resulting reaction mixture allowed to warm to room temperature. To the reaction mixture was then added a solution of saturated NH₄Cl and the resultant reaction mixture extracted with EtOAc. The combined organic extracts were then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure. The product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as a yellow oil (0.15 g 58 %) IR ν\text{max} (CH₂Cl₂) 3428 (OH), 3460, 2956, 2928, 2857 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 7.25 – 7.23 (m, 2H), 7.17 – 7.15 (m, 2H), 6.20 (dd, J = 4.7, 7.8 Hz, 1Hz), 6.05 – 6.01 (m, 2H), 5.89 (dd, J = 2.2, 5.0 Hz, 2H), 3.37 (dd, J = 7.2, 9.2 Hz, 2H), 3.34 – 3.12 (m, 2H), 2.71 – 2.64 (m, 1H), 2.61 – 2.59 (m, 1H), 2.56 - 2.53 (m, 1H), 2.10 – 2.04 (m, 1H), 1.91 – 1.84 (m, 1H), 1.65 – 1.61 (dd, J = 6.8, 9.6 Hz, 1H), 0.87 (s, 9H), 0.02 (s, 6H); ¹³C (100 MHz, CDCl₃) δ 141.7, 136.5, 135.7, 132.6, 128.4, 125.9, 115.9, 93.7, 65.4, 51.5, 50.6, 48.8, 39.6, 37.9, 33.1, 27.9, 25.9, 18.3, 14.0, -5.2, -5.3 ; MS-ESI found 393.2213 C₂₃H₃₄O₂Si [M+Na]⁺ requires 393.2226.
7-(2-(But-3-enyl)phenyl)-5-((tert-butyldimethylsilyloxy)methyl)bicyclo[2.2.1]hept-2-en-7-ol 521a

1-Bromo-2-(but-3-enyl)benzene (100 mg, 0.3 mmol) was dissolved in anhydrous THF (20 mL) and cooled to -78°C, nBuLi (2.5M in THF, 0.4 mL, 0.6 mmol) was then added dropwise. In another flask a separate solution of 5-((tert-butyldimethylsilyl)oxy)methyl)bicyclo[2.2.1]hept-2-en-7-one 437 (0.14 g, 0.7 mmol) in THF (20 mL) at -78 °C was prepared. The reaction mixture containing the lithiated aromatic tether was then transferred into the second via cannula, and the resulting reaction mixture allowed to warm to room temperature. To the reaction mixture was then added a solution of saturated NH₄Cl and the resultant reaction mixture extracted with EtOAc. The combined organic extracts were then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure. The product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as yellow oil (150 mg 56 %) IR (CH₂Cl₂) ν max 3399 (OH), 3063, 2995 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 7.80 – 7.20 (m, 4H), 6.20 (dd, J = 2.8, 5.6 Hz, 1H) 5.89 (dd, J = 3.2, 6.4 Hz, 1H) 5.67 – 5.57 (m, 1H) 4.84 (d, J = 1.6 Hz, 1H), 4.78 (d, J = 4.0 Hz, 1H), 4.19 (d, J = 5.6 Hz, 1H), 2.96 (s, 1H), 2.64 - 2.60 (t, J = 8.0 Hz, 2H), 2.29 (t, J = 8.2 Hz, 2H), 2.09 – 2.3 (m, 2H), 1.53 – 1.31 (m, 1H), 1.29 – 1.23 (m, 1H), 0.88 (s, 9H), 0.50 (dd, J = 2.4, 12 Hz, 1H), 0.02 (s, 6H); ¹³C (100 MHz, CDCl₃) δ 142.1, 140.0, 138.2, 135.7, 132.2, 130.8, 128.8, 127.2, 124.7, 114.9, 93.7, 65.1, 50.6, 48.8, 39.6, 36.2, 33.1, 32.1, 25.9, 18.3, 14.1, -5.2; MS-ESI found 407.2332 C₂₄H₃₆O₂Si [M+Na]⁺ requires 407.2382.
5-((tert-butyldimethylsilyloxy)methyl)-7-(2-(pent-4-enyl)phenyl)bicyclo[2.2.1]hept-2-en-7-ol 521b

1-Bromo-2-(pent-4-enyl)benzene (0.62 g, 2.7 mmol) was dissolved in anhydrous THF (20mL) and cooled to -78°C, nBuLi (2.5M in THF, 2.2 mL, 5 mmol) was then added dropwise. In another flask a separate solution of 5-(((tert-butyldimethylsilyl)oxy)methyl)bicyclo[2.2.1]hept-2-en-7-one 437 (0.35 g 1.5 mmol) in THF (20 mL) at -78°C was prepared. The reaction mixture containing the lithiated aromatic tether was then transferred into the second via cannula, and the resulting reaction mixture allowed to warm to room temperature. To the reaction mixture was then added a saturated solution of NH₄Cl and the resultant reaction mixture was extracted with EtOAc. The combined organic extracts were then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure. Product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as yellow oil (70 mg 25%) IR (CH₂Cl₂) νₓ₅ 3379, 3027, 3063, 2995, 2928, 2857 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 7.26 – 7.15 (m, 4H), 6.20 (dd, J = 2.8, 5.6 Hz, 1H), 6.05 – 6.01 (m, 2H), 5.82 (dd, J = 3.2, 6.4 Hz, 2H), 4.98 – 4.78 (m, 2H), 3.37 – 3.33 (m, 1H), 3.27 – 3.21 (m, 1H), 2.71 – 2.65 (m, 1H), 2.63 – 2.61 (m, 1H), 2.55 – 2.50 (m, 1H), 2.37 – 2.35 (m, 1H), 2.10 (ddd, J = 4.3, 8.4, 3.6 Hz, 2H), 1.90 (ddd, J = 3.6, 8.0, 4.4 Hz, 2H), 0.87 (s, 9H), 1.65 (dd, J = 4.2, 11.6 Hz, 2H), 0.01 (s, 6H); ¹³C (100 MHz, CDCl₃) δ 141.7, 135.6, 132.7, 128.4, 128.3, 125.9, 115.8, 93.7, 65.4, 50.6, 50.6, 48.8, 39.6, 37.9, 33.1, 27.9, 27.2, 26.1, 25.9, 18.3, 14.0, -5.3, -5.2 ; MS-ESI found 399.2641 C₂₅H₃₈O₂Si [M]+ requires 399.2719.
5-((tert-butyldimethylsilyloxy)methyl)-7-(2-(2-methylbut-3-enyl)phenyl)bicyclo[2.2.1]hept-2-en-7-ol 528

2-Bromostyrene (0.14 g, 0.7 mmol) was dissolved in anhydrous THF (20 mL) and cooled to -78 °C, nBuLi (2.5M in THF, 0.3 mL, 1.4 mmol) was then added dropwise. In another flask a separate solution of 5-((tert-butyldimethylsilyl)oxy)methyl)bicyclo[2.2.1]hept-2-en-7-one 437 (0.10 g, 0.39 mmol) in THF (20 mL) at -78 °C was prepared. The reaction mixture containing the lithiated aromatic tether was then transferred into the second via cannula, and the resulting reaction mixture allowed to warm to room temperature. To the reaction mixture was then added a solution of saturated NH₄Cl and the resultant reaction mixture was extracted with EtOAc. The combined organic extracts were then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure. The product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as yellow oil (90 mg 64 %) IR (CH₂Cl₂) νmax 3399 (OH), 3062, 3027, 2955, 2928, 2857 cm⁻¹; ¹H (400 MHz, CDCl₃) δ ; 7.45 – 7.09 (m, 4H), 6.76 (d, J = 8.0 Hz, 1H), 6.03 (dd, J = 3.4, 6.2 Hz, 1H), 5.89 (dd, J = 3.2, 6.0 Hz, 1H), 5.73 (dd, J = 1.4, 17.8 Hz, 1H), 5.58 (dd, J = 1.6, 17.6 Hz, 1H), 5.24 (dd, J = 1.4, 11.0 Hz, 1H), 3.37 – 3.15 (m, 2H), 2.97 (s, 1H), 2.55 (s, 1H), 2.37 (s, 1H), 2.14 – 2.04 (m, 1H), 1.25 – 1.22 (m, 1H), 0.88 (s, 9H), 0.02 (s, 6H); ¹³C (100 MHz, CDCl₃) δ 132.7, 131.5, 128.8, 128.0, 127.3, 120.8, 115.8, 98.8, 65.4, 50.6, 48.8, 39.6, 33.9, 27.9, 23.2, 14.0, 13.9, -5.2, -5.3; MS-ESI found 379.2058 C₂₂H₃₂O₂Si [M+Na]⁺ requires 379.2069.

5-((tert-butyldimethylsilyloxy)methyl)-7-phenylbicyclo[2.2.1]hept-2-en-7-ol 530

5-Hydroxymethyl bicyclohept-2-en-7-one 437 (100 mg, 3.0 mmol), was dissolved in anhydrous tetrahydrofuran (10 mL), the reaction mixture was then cooled to -78 °C and
phenyl magnesium bromide (0.79 mL, 2M in THF, 6.0 mmol) added drop wise. The reaction mixture was the quenched using a saturated solution of NH₄Cl, and extracted using EtOAc. The organic layer was then washed with water and brine, dried over magnesium sulfate, filtered and excess volatiles were then removed under reduced pressure. The product was the purified by column chromatography (10:1 PE:EtOAc) to give the title compound as clear oil (90 mg, 53%). IR (CH₂Cl₂) ν max 3496 (OH), 3395, 3016, 2891 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 7.31 – 7.14 (m, 5H), 5.94 – 5.91 (m, 1H), 5.81 – 5.79 (m, 1H), 3.43 – 3.22 (m, 3H), 3.11 (t, J = 3.2 Hz, 1H), 2.91 (t, J = 3.2 Hz, 1H), 2.86 – 2.78, (m, 1H), 2.28 – 2.22 (m, 1H), 0.86 (s, 9H), 0.65 (dd, J = 4.4, 11.6 Hz, 1H), -0.02 (s, 6H); ¹³C (400 MHz, CDCl₃) δ 143.4, 135.6, 132.7, 128.0, 127.6, 127.1, 94.1, 65.2, 50.6, 49.0, 40.8, 27.5, 26.0, 18.3, -5.2, -5.3; MS-ESI found 353.1901, C₂₀H₃₀O₂SiNa [M+Na]^+ requires 353.1907.

7-Allyl-7-hydroxybicyclo[2.2.1]hept-5-en-2-yl)methyl) O-phenyl carbonothioate 559

Under a nitrogen atmosphere was added 7-allyl-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-ol 440 (0.10 g, 0.50 mmol) in dry CH₂Cl₂ (10 mL). DMAP (0.10 g 0.80 mmol) and phenylchlorothionoformate (0.40g, 0.80 mmol) were added and the reaction mixture was stirred at room temperature for 24 h. The organic layer was washed with water and brine and then dried over magnesium sulfate, filtered and excess volatiles were removed under reduced pressure. The product was the purified by column chromatography (2:1 PE: EtOAc) to give the title compound as clear yellow oil (0.10 g 63%); IR (CH₂Cl₂) ν max 3583, 3444, 2970 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 7.43 – 7.99 (m, 5H), 6.19 (dd, J = 0.8, 3.8 Hz, 1H), 6.02 (dd, J = 3.2, 6.4 Hz, 1H), 5.83 – 5.72 (m, 1H), 5.17 – 5.10 (m, 2H), 4.36 – 4.17 (m, 2H), 3.08 – 3.00 (m, 1H), 2.66 – 2.65 (m, 1H), 2.56 – 2.41 (m, 2H), 2.33 – 2.27 (m, 2H), 0.73 (dd, J = 4.4, 11.6 Hz, 2H); ¹³C (100 MHz, CDCl₃) δ 195.1 153.4, 136.7, 134.9, 132.2, 129.5, 126.5, 121.1, 119.1, 92.1, 50.7, 49.0, 42.2, 37.5, 35.5, 27.5; MS-ESI found 339.1003, C₁₈H₂₀O₃SiNa [M+Na]^+ requires 339.1025.
8. Experimental

7-Allyl-7-hydroxybicyclo[2.2.1]hept-5-en-2-yl)methyl benzenesulfonate 561

\[
\text{CH}_2=CH-\text{C} (\text{O}) \text{H} \quad \text{CH}_3
\]

7-Allyl-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-ol 440 (0.11 g, 0.64 mmol) and 4-toluenesulfonyl chloride (0.18 g, 0.96 mmol) were dissolved in pyridine (5 mL) and stirred at room temperature for 12 h. The reaction mixture was then acidified using 2M HCl and CH$_2$Cl$_2$ (20 mL) was added. The organic layer was then washed with water and brine and dried over magnesium sulfate, filtered and excess volatiles removed under reduced pressure. The product was the purified by column chromatography (2:1 PE:EtOAc) and the title compound obtained as clear yellow oil (0.18 g 87%); IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 3538, 3062, 2974, 2866, 1638, 1175 cm$^{-1}$, $^1$H (400 MHz, CDCl$_3$) $\delta$ 7.78 (d, $J = 8.4$ Hz, 2H), 7.35 (d, $J = 8.0$ Hz, 2H), 6.08 – 6.06 (m, 2H), 5.78 – 5.67 (m, 1H), 5.15 – 5.07 (m, 2H), 4.14 – 3.38 (m, 2H), 2.84 – 2.81 (m, 1H), 2.57 – 2.55 (m, 1H), 2.49 – 2.34 (m, 5H), 2.20 – 2.14 (m, 2H), 0.50 (dd, $J = 4.4, 11.6$ Hz, 1H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 144.6, 136.7, 134.8, 133.1, 131.9, 129.7, 127.8, 119.1, 91.9, 72.6, 60.4, 50.4, 48.8, 37.5, 36.6, 27.2, 21.6, 14.2; MS-ESI found 357.1131, C$_{18}$H$_{22}$O$_4$SNa [M+Na]$^+$ requires 357.1136.

7-Allyl-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-ene-7-ol 440

To CH$_2$Cl$_2$ (5 mL) was added 7-allyl-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-ol 440 (0.10 g, 0.55 mmol) and triethylamine (0.12 mL, 0.86 mmol). The reaction mixture was then cooled to 0 ºC and methansulfonyl chloride (0.05 mL, 0.66 mmol) was added drop wise and the reaction mixture stirred for a further 30 mins. To the reaction mixture was washed using
ice-cold water (10 mL), HCl (5 M, 10 mL), NaHCO₃ (10 mL) and saturated brine solution (10 mL). The organic layer was then dried over magnesium sulfate, filtered and excess volatiles removed under reduced pressure. The product was the purified by column chromatography (2:1 petroleum ether: EtOAc) to give the title compound as clear yellow oil (90 mg 70%); IR (CH₂Cl₂) νₘₐₓ 3531 (OH), 3061, 2973, 2940, 2867, 1638 (C-O) cm⁻¹; ¹H (400 MHz, CDCl₃) δ 6.12 (dd, J = 0.8, 3.6 Hz, 1H), 5.94 (dd, J = 3.2, 6.4 Hz, 1H), 5.74 – 5.64 (m, 1H), 5.10 – 5.02 (m, 2H), 3.96 – 3.81 (m, 2H), 2.87 – 2.82 (m, 1H), 2.58 (t, J = 3.4 Hz, 1H), 2.46 – 2.32 (m, 3H), 2.22 – 2.16 (m, 1H), 1.90 (s, 1H), 0.56 (dd, J = 4.4, 11.6 Hz, 1H); ¹³C (100 MHz, CDCl₃) δ; 135.9, 133.7, 130.7, 118.1, 91.0, 71.2, 51.0, 49.4, 36.5, 36.2, 35.9, 26.3. MS-ESI found 281.0811, C₁₂H₂₀O₄SNa [M+Na]⁺ requires 281.0818.

7-Allyl-5-methylbicyclo[2.2.1]hept-2-en-7-ol 552

To a stirring solution of 7-Allyl-7-hydroxybicyclo[2.2.1]hept-5-en-2-yl)methyl methanesulfonate 562 (0.10 g, 0.38 mmol) in THF (20 mL) was added Superhydride® (1M in THF, 3.8 mL, 0.38 mmol) and the reaction mixture brought to reflux overnight. The Superhydride® was the quenched using ice-cold water and the organoboranes were oxidised by the addition of 3M aqueous NaOH and cold 30% H₂O₂. The mixture was then heated to reflux for a further 1.5 h. The reaction mixture was then extracted using hexane. The organic layer was washed with water and brine, dried over magnesium sulfate, filtered and excess volatiles removed under reduced pressure. The product was the purified by column chromatography (2:1 PE: EtOAc) to give the title compound as clear oil (0.04 g 62%) IR (CH₂Cl₂) νₘₐₓ 3420 (OH), 2845, 1452 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 6.10 (dd, J = 0.8, 3.6 Hz, 1H), 5.92 (dd, J = 3.2, 6.4 Hz, 1H), 5.74–5.64 (m, 1H), 5.10–5.02 (m, 2H), 3.96–3.81 (m, 2H), 2.93 (s, 3H), 2.87–2.82 (m, 1H), 2.57 (t, J = 3.4 Hz, 1H), 2.46–2.32 (m, 3H), 2.22–2.16 (m, 1H), 1.90 (s, 1H), 0.54 (dd, J = 4.4, 11.6 Hz, 1H); ¹³C (100 MHz, CDCl₃) δ 135.9, 133.7, 130.7, 118.1, 91.0, 71.2, 51.0, 49.4, 36.5, 36.2, 35.9, 26.3; MS-ESI found 282.0964, C₁₂H₂₀O₄SNa [M+Na]⁺ requires 282.0975.
Grubbs’ second generation catalysts (100 mg, 0.003 mmol) was dissolved in anhydrous toluene (5 mL) in a 5 mL round bottomed flask. Ethylene was then bubbled through the reaction mixture for 2–3 min. The ethylene atmosphere was then maintained and 7-allyl-5-methylbicyclo[2.2.1]hept-2-en-7-ol 552 (0.05 g, 0.03 mmol) was added. The reaction mixture was then stirred at room temperature for 48 h with monitoring by TLC. The excess volatiles removed under reduced pressure. The crude product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as clear yellow oil (71 mg, 71%); IR (CH2Cl2) νmax 3647 (OH), 3381, 3050, 2965, 2925, 2913 cm−1; 1H NMR (400 MHz, CDCl3) δ 5.94 – 5.86 (m, 1H), 5.68 – 5.66 (m, 1H), 5.58 – 5.52 (m, 1H), 5.11 – 5.03 (m, 2H), 2.92 (d, J = 8.0 Hz, 1H), 2.65 – 2.58 (m, 2H), 2.38 – 2.25 (m, 1H), 2.18 – 2.08 (m, 1H), 1.29 – 1.20 (m, 3H), 0.91 (d, J = 12.0 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 169.4, 137.7, 129.6, 115.9, 92.2, 61.7, 51.2, 44.4, 37.2, 35.1, 16.1; MS-ESI found 163.1121, C11H15O [M − H]+ requires 163.1123.

7-Allyl-7-hydroxybicyclo[2.2.1]hept-5-en-2-yl)methyl acetate 567

7-Allyl-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-ol 552 (0.10 g, 0.10 mmol) was dissolved in CH2Cl2 (10 mL) and acetic anhydride (0.10 mL, 0.10 mmol) and triethylamine (0.15 mL, 0.10 mmol) were added and the reaction mixture stirred at room temperature for 5 days. The organic layer was washed with water and brine and then dried over magnesium sulfate, filtered and excess volatiles were removed under reduced pressure. The product was then purified by column chromatography (2:1 PE:EtOAc) to give the title compound as clear yellow oil (0.16 g 65%); IR (CH2Cl2) νmax 3464 (OH), 3060, 2967, 2865, 1741 (C=O), 1718, 1638 (C-O), 1573 cm−1; 1H (400 MHz, CDCl3) δ 6.14 (dd, J = 0.8, 3.2 Hz, 1H), 5.95 (dd, J =
8. Experimental

3.2, 6.4Hz, 1H), 5.82 – 5.72 (m, 1H), 5.15 – 5.08 (m, 2H), 3.88 – 3.72 (m, 2H), 2.84 – 2.76 (m, 1H), 2.56 (t, J = 3.4Hz, 1H), 2.47 – 2.36 (m, 3H), 2.25 (ddd, J = 4.0, 2.8, 4.0 Hz, 1H), 2.03 (s, 3H), 0.64 (dd, J = 4.0, 11.6Hz, 1H); 13C (100 MHz, CDCl 3) δ 171.1, 136.4, 135.0, 132.2, 118.8, 92.0, 66.8, 50.7, 48.9, 37.6, 35.9, 27.7, 21.0; MS-ESI found 245.1140, C13H18O3Na [M+Na]+ requires 245.1154.

3a-Hydroxy-3-vinyl-1,2,3,3a,4,6a-hexahydropentalen-1-yl)methyl acetate 568

Grubbs second generation catalysts (20 mg 0.02 mmol) was dissolved in anhydrous toluene (5 mL). Ethylene was then bubbled through the reaction mixture for 2-3 mins. The ethylene atmosphere was then maintained and 7-allyl-7-hydroxybicyclo[2.2.1]hept-5-en-2-yl)methyl acetate 567 (0.10 g 0.44 mmol) was added. The reaction mixture was then stirred at room temperature for 48 h with monitoring by TLC. The excess volatiles removed under reduced pressure. Product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as clear yellow oil was obtained (80 mg 76%); IR (CH 2Cl2) 3419 (OH), 3076, 3050, 3001, 2950, 2923, 1720 (C=O), 1639 (C-O), 1621 cm⁻¹; ¹H (400 MHz, CDCl 3) δ 5.94 – 5.85 (m, 1H), 5.73 – 5.71 (m, 1H), 5.66 – 5.54 (m, 1H), 5.14 – 5.06 (m, 2H), 4.00 – 3.89 (m, 2H), 3.03 (d, J = 9.6 Hz, 1H), 2.70 – 2.63 (m, 2H), 2.59 (t, J = 2.8 Hz, 1H), 2.18 (t, J = 2.8 Hz, 1H), 2.03 (s, 3H), 1.89 – 1.86 (m, 1H),1.29 – 1.20 (m, 1H); 13C (100 MHz, CDCl 3) δ 171.1, 136.9, 130.8, 128.5, 118.5, 90.4, 65.7, 59.4, 53.9, 44.2, 39.5, 32.5, 21.0; MS-ESI found 245.1148, C13H18O3Na [M+Na]+ requires 245.1154.

7-Allyl-7-hydroxybicyclo[2.2.1]hept-5-ene-2-carbaldehyde 570

7-Allyl-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-ol 552 (0.2 g,1.1 mmol) was added to a flask containing DMF (40 ml) and water (1.6 mL). PDC was then added and the reaction mixture stirred for 3 h. EtOAc (25 mL) was the added and washed with water and brine. The
8. Experimental

organic layer was dried over magnesium sulfate, filtered and excess volatiles were removed under reduced pressure. Product was isolated and purified using column chromatography (1:1 PE:EtOAc) giving the title compound as yellow oil (50 mg 25%); IR (CH2Cl2) \( \nu_{\text{max}} \) 3426, 3072 (OH), 2975, 2721, 1715 (C=O) cm\(^{-1}\); \(^1\)H (400 MHz, CDCl3) \( \delta \) 9.58 (s, OH), 6.18 (dd, \( J = 2.4, 3.2 \) Hz, 1H), 6.16 (dd, \( J = 2.8, 3.6 \) Hz, 1H), 5.79 -5.71 (m, 2H), 5.19 – 5.11 (m, 2H), 3.36 – 3.32 (m, 1H), 2.90 – 2.89 (m, 3H), 2.41 – 1.21 (m, 3H); \(^{13}\)C (100 MHz, CDCl3) \( \delta \) 204.7, 137.5, 134.4, 131.6, 119.4, 91.7, 51.2, 50.9, 49.3, 36.6, 25.9; MS-ESI found 201.0911, C\(_{11}\)H\(_{14}\)ONa [M+Na]\(^+\) requires 201.0891.

7-Allyl-5-(dimethoxymethyl)-7-methoxybicyclo[2.2.1]hept-2-ene 573

![7-Allyl-5-(dimethoxymethyl)-7-methoxybicyclo[2.2.1]hept-2-ene](image)

7-Allyl-7-hydroxybicyclo[2.2.1]hept-5-ene-2-carbaldehyde 571 (0.05 g, 0.28 mmol) was dissolved in dry methanol (20 mL) and \( p \)-toluenesulfonic acid (excess) added. The reaction mixture was then heated to reflux and reaction progression measured by TLC. After 48 h the reaction mixture was extracted using EtOAc (20 mL), and the organic layer washed with water and brine. The organic layer was then dried over magnesium sulfate, filtered and excess volatiles were removed under reduced pressure. Product was isolated and purified using column chromatography (1:1 PE:EtOAc) giving the title compound as yellow oil (0.054 g 80%); IR (CH2Cl2) \( \nu_{\text{max}} \) 3062, 2941, 2827, 1719, 1639 cm\(^{-1}\); \(^1\)H (400 MHz, CDCl3) \( \delta \) 6.12 (dd, \( J = 3.2, 6.0 \) Hz, 1H), 5.95 (dd, \( J = 2.4, 5.6 \) Hz, 1H), 5.79 – 5.72 (m, 1H), 5.01 – 4.96 (m, 2H), 3.90 (d, \( J = 9.2 \) Hz, 1H), 3.32 (s, 3H), 2.28 (s, 3H), 3.19 (s, 3H), 2.74 – 2.69 (m, 2H), 2.66 – 2.60 (m, 1H), 2.48 (d, \( J = 7.2 \) Hz, 2H), 2.12 – 2.06 (m, 1H), 0.83 (dd, \( J = 3.4, 11.8 \) Hz, 1H); \(^{13}\)C (100 MHz, CDCl3) \( \delta \) 135.8, 134.6, 134.0, 117.6, 116.2, 103.1, 55.8, 54.4, 50.0, 48.1, 37.6, 25.4, 18.1; MS-ESI found 261.1453, C\(_{14}\)H\(_{22}\)O\(_3\)Na [M+Na]\(^+\) requires 261.1467.
7- Allyl-7-(allyloxy)bicyclo[2.2.1]hept-5-en-2-yl)methoxy)(tert-butyl)dimethylsilane 582

Grubbs second generation catalysts (60 mg 0.07mmol) was dissolved in anhydrous toluene (5mL). Ethylene was then bubbled through the reaction mixture for 2-3 mins. The ethylene atmosphere was then maintained and 7-allyl-7-(allyloxy)bicyclo-[2.2.1]hept-5-en-2-yl)methoxy)(tert-butyl)dimethylsilane 582 (0.5g 1.4mmol) was added. The reaction mixture
was then stirred at room temperature for 48 h with monitoring by TLC. The excess volatiles removed under reduced pressure. Product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as clear yellow oil (55 mg, 91 %); IR (CH$_2$Cl$_2$) $\nu_{max}$ 3012, 2869, 1231 (-C-O-C-) cm$^{-1}$; $^1$H (400 MHz, CDCl$_3$) $\delta$ 6.05 (dd, $J$ = 3.6, 3.2 Hz, 1H), 5.91 (dd, $J$ = 3.2, 3.2 Hz, 1H), 5.69 – 5.60 (m, 2H), 4.13 – 4.02 (m, 2H), 3.36 – 3.19 (m, 2H), 2.76 (t, $J$ = 3.2 Hz, 1H), 2.62 – 2.56 (m, 1H), 2.53 (t, $J$ = 3.6 Hz, 1H), 2.11 – 2.05 (sept, $J$ = 4.0 Hz, 1H), 1.90 – 1.80 (m, 1H), 1.26 – 1.20 (m, 2H), 0.86 (s, 9H), 0.48 (dd, $J$ = 4.0, 4.4 Hz, 1H), 0.02 (s, 6H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 135.3, 132.4, 125.0, 124.7, 92.1, 65.3, 62.5, 48.6, 47.7, 39.6, 27.3, 27.1, 26.3, 18.2, -5.0; MS-ESI found 329.1916, C$_{18}$H$_{30}$O$_2$SiNa [M+Na]$^+$ requires 329.1913.

**Bicyclo[2.2.2]oct-5-ene-2-carbonitrile 584**

Acrylonitrile (1.5 mL, 24 mmol), 1,3-cyclohexadiene (1.1 mL, 12 mmol) and hydroquinone (0.01 g, 0.1 mmol) were added to a pyrex压力 reaction tube. The reaction mixture was heated to 120°C for 18 h. Upon cooling the desired nitrile was purified using bulb-to-bulb distillation 75 – 80 °C (1 mm Hg) (literature B.p 85 – 90 °C, 3mm Hg) to give a clear semi-solid (0.95 g, 70%); IR (CH$_2$Cl$_2$) $\nu_{max}$ 3500, 2945, 2571, 2235, 1453 (C≡N) cm$^{-1}$; $^1$H (400 MHz, CDCl$_3$) $\delta$ 6.48 (ddd, $J$ = 7.3, 7.3, 1.3 Hz, 2H), 2.90 – 2.42 (m, 2H), 2.06 – 1.92 (m, 1H), 1.76 – 1.26 (m, 5H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 136.3, 135.3, 132.4, 125.0, 124.7, 92.1, 65.3, 62.5, 48.6, 47.7, 39.6, 27.3, 27.1, 26.3, 18.2, -5.0; MS-ESI found 156.0785, C$_9$H$_{11}$NNa [M+Na]$^+$ requires 156.0789.

**2-Chlorobicyclo[2.2.2]oct-5-ene-2-carbonitrile 585**

Phosphorus pentachloride (7.2 g, 35 mmol) and pyridine (3.2 mL, 40 mmol) were added to cholorform (100 mL) and refluxed. To this refluxing reaction mixture was added bicyclo[2.2.2]oct-5-ene-2-carbonitrile (3.5 g, 20 mmol) and the reaction refluxed for 13h. The reaction mixture was then allowed to cool down and was the poured over ice. The organic layer was washed with water (2x50 mL) and brine (3x50 mL) and dried over magnesium sulfate, filtered and the excess volatiles were removed under reduced pressure. The product was then purified by a bulb-to-bulb distillation 95 – 100 °C (1 mm Hg) (literature B.p 95 –
100 °C, 2mm Hg\textsuperscript{99}) to give a clear semi-solid (2 g, 60%); IR (CH\textsubscript{2}Cl\textsubscript{2}) \textnu max 3056, 2949, 2872, 2239, 1441(C≡N) cm\textsuperscript{-1}; \textsuperscript{1}H (400 MHz, CDCl\textsubscript{3}) \delta 6.51 – 6.20 (m, 2H), 3.13 – 3.03 (m, 1H), 2.73 – 2.70 (m, 1H), 2.52 – 2.09 (m, 3H), 1.68 - 1.29 (m, 3H); \textsuperscript{13}C (100 MHz, CDCl\textsubscript{3}) \delta 137.0, 134.6, 131.0, 129.5, 121.1, 57.0, 44.2, 29.6, 22.3; MS-ESI found 190.0394, C\textsubscript{9}H\textsubscript{10}NClNa [M+Na]\textsuperscript{+} requires 190.0399.

**Bicyclo[2.2.2]oct-5-en-2-one 389\textsuperscript{99}**

![Bicyclo[2.2.2]oct-5-en-2-one](image)

To a stirring solution of 2-chlorobicyclo[2.2.2]oct-5-ene-2-carbonitrile (2.0 g, 10 mmol) in DMSO (10 mL) was added a slurry of 85% KOH (3 mL). The reaction mixture was stirred for 13 h at room temperature. EtOAc (20 mL) and water (20 mL) were then added and the organic layer washed with water and brine. The organic layer was then dried over magnesium sulfate and excess solvent removed under vacuum, the excess volatiles were removed under reduced pressure. Product was purified using a bulb-to-bulb distillation 75 – 80 °C (3 mm Hg) (literature B.p 95 – 100 °C, 13mm Hg\textsuperscript{99}) and a clear semi-solid isolated (1.03 g, 70%); IR (CH\textsubscript{2}Cl\textsubscript{2}) \textnu max 3052, 2947, 2911, 2873, 1725 (C=O), 1610 cm\textsuperscript{-1}; \textsuperscript{1}H (400 MHz, CDCl\textsubscript{3}) \delta 6.50 (ddd, \textit{J} = 7.3, 7.3, 1.0 Hz, 1H), 6.22 (ddd, \textit{J} = 7.3, 7.3, 1.6 Hz, 1H), 3.14 – 3.00 (m, 1H), 2.99 – 2.60 (m, 1H), 2.04 – 2.02 (m, 2H), 1.89 – 150 (m, 4H); \textsuperscript{13}C (100 MHz, CDCl\textsubscript{3}) \delta 213.3, 137.0, 128.4, 48.5, 40.5, 32.3, 24.2, 22.5; MS-ESI found 123.0805, C\textsubscript{8}H\textsubscript{10}ONa [M+H]\textsuperscript{+} requires 123.0810.

**2-Allylbicyclo[2.2.2]oct-5-en-2-ol 586**

![2-Allylbicyclo[2.2.2]oct-5-en-2-ol](image)

To a solution of bicyclo[2.2.2]oct-5-en-2-one 389 (1.0 g, 8.0 mmol) in anhydrous THF (10 mL) cooled to -78 °C was added allyl magnesium chloride (2M in THF, 8.6 mL, 16.0 mmol) and the reaction mixture allowed to warm to room temperature and stirred for 12 h. To the reaction mixture was then added a solution of saturated NH\textsubscript{4}Cl and the resultant solution extracted with EtOAc. The combined organic extracts were then dried over magnesium sulfate and the excess volatiles removed under reduced pressure. Product was then purified by graduated column chromatography (40:1,38:1, 36:1, 34:1, 32:1, 30:1, 28:1, 26:1, 24:1, 22:1, 20:1, 18:1, 16:1, 14:1, 12:1, 10:1, 8:1, 6:1, 4:1, 2:1 PE:Et\textsubscript{2}O graduated column) giving
the title compounds as separated isomers each as clear oil (0.32 g, 24%); IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 3419 (OH), 2940, 2864 cm$^{-1}$; $^1$H (400 MHz, CDCl$_3$) 6.41 (t, $J = 5.4$ Hz, 1H), 6.27 (t, $J = 7.0$ Hz, 1H), 6.02 – 5.59 (m, 1H), 5.15 – 5.11 (m, 2H), 2.60 – 2.57 (m, 2H), 2.46 – 2.28 (m, 2H), 1.71 – 1.55 (m, 2H), 1.44 – 1.35 (m, 2H), 1.26 – 1.20 (m, 2H) $\delta$; $^{13}$C (100 MHz, CDCl$_3$) 136.0, 134.5, 132.2, 117.9, 81.2, 45.0, 44.7, 40.5, 30.9, 23.7, 20.9 $\delta$; MS-ESI found 187.1093 C$_{11}$H$_{16}$ONa $[\text{M+Na}]^+$ requires 187.1099.

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\text{\begin{align*}
\text{\includegraphics[width=0.2\textwidth]{106x595.png}}
\end{align*}}
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(0.71 g, 53%); $^1$H (400 MHz, CDCl$_3$) $\delta$ 6.25 – 6.17 (m, 2H), 5.94 – 5.84 (m, 1H), 5.17 – 5.10 (m, 2H), 2.30 – 2.56 (m, 1H), 2.40 (t, $J = 3.0$ Hz, 1H), 2.22 – 2.07 (m, 2H), 1.66 – 1.61 (m, 2H), 1.47 – 1.39 (m, 2H), 1.25 – 1.03 (m, 2H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 133.8, 133.1, 132.4, 119.2, 75.1, 47.8, 41.8, 40.8, 31.6, 24.4, 19.6.

2-(But-3-en-1-yl)bicyclo[2.2.2]oct-5-en-2-ol 587

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\text{\begin{align*}
\text{\includegraphics[width=0.2\textwidth]{119x414.png}}
\end{align*}}
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To a solution of bicyclo[2.2.2]oct-5-en-2-one 389 (0.50 g, 3.7 mmol) in anhydrous THF (10 mL) cooled to -78 °C was added homoallyl magnesium chloride (0.5M in THF, 15 mL, 7.5 mmol) and the reaction mixture allowed to warm to room temperature and stirred for 12 h. To the reaction mixture was then added a solution of saturated NH$_4$Cl and the resultant solution extracted with EtOAc. The combined organic extracts were then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure. Products was then purified by graduated column chromatography (40:1, 38:1, 36:1, 34:1, 32:1, 30:1, 28:1, 26:1, 24:1, 22:1, 20:1, 18:1, 16:1, 14:1, 12:1, 10:1, 8:1, 6:1, 4:1, 2:1 PE:Et$_2$O graduated column) giving the title compound as separated isomers each as a clear oil (0.11 g, 15%); IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 3427 (OH), 2940 cm$^{-1}$; $^1$H (400 MHz, CDCl$_3$) $\delta$ 6.43 – 6.21 (m, 2H), 5.91 – 5.82 (m, 1H), 5.11 – 5.00 (m, 2H), 2.69 – 2.67 (m, 1H), 2.63 – 2.60 (m, 1H), 2.32 – 2.28 (m, 1H) 1.65 – 1.56 (m, 2H), 1.42 – 1.32 (m, 3H), 1.25 – 1.16 (m, 1H), 1.13 – 1.05 (m, 4H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 140.7, 133.8, 132.9, 115.3, 76.6, 47.4, 41.6, 39.6, 31.3, 24.3, 20.8, 12.9; MS-ESI found 201.1248 C$_{12}$H$_{18}$ONa $[\text{M+Na}]^+$ requires 201.1250.
(0.32 g, 45%); $^1$H (400 MHz, CDCl$_3$) $\delta$ 6.25 – 6.21 (m, 1H), 5.96 – 5.90 (m, 2H), 5.08 – 5.03 (m, 2H), 2.69 – 2.67 (m, 1H), 2.63 – 2.60 (m, 1H), 2.32 – 2.24 (m, 2H), 1.70 – 1.64 (m, 2H), 1.42 – 1.41 (m, 2H), 1.25 – 1.16 (m, 2H), 1.13 – 1.05 (m, 2H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 141.1, 139.9, 136.4, 132.5, 114.9, 76.7, 45.7, 39.7, 31.1, 24.1, 20.2, 15.2.

2-(2-Methylallyl)bicyclo[2.2.2]oct-5-en-2-ol 588

To a solution of bicyclo[2.2.2]oct-5-en-2-one 389 (0.50 g, 3.7 mmol) in anhydrous THF (10 mL) cooled to -78 °C was added 3-(1-methyl)-2-propenylmagnesium chloride (0.5M in THF, 48 mL, 24 mmol) and the reaction mixture allowed to warm to room temperature and stirred for 12h. To the reaction mixture was then added a solution of saturated NH$_4$Cl and the resultant solution extracted with EtOAc. The combined organic extracts were then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure. Products was then purified by graduated column chromatography (40:1, 38:1, 36:1, 34:1, 32:1, 30:1, 28:1, 26:1, 24:1, 22:1, 20:1, 18:1, 16:1, 14:1, 12:1, 10:1, 8:1, 6:1, 4:1, 2:1 PE:Et$_2$O graduated column) giving the title compound as separated isomers each as a clear oil (0.44 g, 62%); IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 3435 (OH), 3044, 2942 cm$^{-1}$; $^1$H (400 MHz, CDCl$_3$) $\delta$ 6.25 – 6.17 (m, 2H), 4.93 – 4.79 (m, 1H), 4.78 – 4.76 (m, 1H), 2.58 – 2.40 (m, 1H), 2.38 – 2.31 (m, 1H), 2.14 – 2.09 (m, 4H), 1.77 (s, 3H), 1.66 – 1.16 (m, 4H); $^{13}$C (400 MHz, CDCl$_3$) $\delta$ 143.4, 135.8, 133.6, 114.9, 75.1, 50.8, 42.1, 41.0, 31.1, 23.1, 24.4, 23.8, 14.6; MS-ESI found 201.1271 C$_{12}$H$_{18}$ONa [M+Na]$^+$ requires 201.1250

2-(2-Vinylphenyl)bicyclo[2.2.2]oct-5-en-2-ol 592

1-Bromo-2-vinylbenzene (2.0 mL, 16.0 mmol) was dissolved in anhydrous THF (10 mL) and cooled to -78°C, n-BuLi (13.0 mL, 64.0 mmol, 2.4 M) was then added dropwise. In another flask a separate solution of bicyclo[2.2.2]oct-5-en-2-one 389 (1.0 g, 8.0 mmol) in THF (10
8. Experimental

mL) at -78°C was prepared. The reaction mixture containing the lithiated aromatic tether was then transferred into the second via a cannula, and the resulting reaction mixture allowed to warm to room temperature. To the reaction mixture was then added a solution of saturated NH₄Cl, filtered and the resultant solution extracted with EtOAc (3x20 mL). The combined organic extracts were then dried over Na₂SO₄ and the excess volatiles removed under reduced pressure. Products was then purified by column chromatography (40:1,38:1, 36:1, 34:1, 32:1, 30:1, 28:1, 26:1, 24:1, 22:1, 20:1, 18:1, 16:1, 14:1, 12:1, 10:1, 8:1, 6:1, 4:1, 2:1 PE:Et₂O graduated column) giving the title compound as separated isomers each as crystalline solid (0.27 g 15%, m.p 67-70°C). IR (CH₂Cl₂) νmax 3395 (OH), 2932, 2869 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 7.60 – 7.17 (m, 4H), 6.42 (t, J = 4.0 Hz, 1H), 6.16 (t, J = 7.4 Hz, 1H), 5.54 (dd, J = 1.6, 17.6 Hz, 1H), 5.26 (dd, J = 1.6, 11.2 Hz, 1H), 3.08 – 3.06 (m, 1H), 2.64 – 2.61 (m, 1H), 2.39 – 2.32 (m, 1H), 2.07 – 1.93 (m, 2H), 1.78 – 1.71 (m, 2H), 1.42 – 1.20 (m, 3H); ¹³C (100 MHz, CDCl₃) δ 146.0, 138.2, 138.0, 133.2, 133.0, 128.1, 127.1, 126.7, 125.3, 122.1, 114.4, 78.2, 44.8, 41.1, 31.1, 24.4, 20.3; MS-ESI found 249.1246 C₁₆H₁₈ONa [M+Na]⁺ requires 249.1255.

(0.88 g, 45%); ¹H (400 MHz, CDCl₃) δ 7.56 – 7.16 (m, 4H), 6.62 (t, J = 7.2 Hz, 1H), 6.39 (t, J = 4.0 Hz, 1H), 6.27 – 6.17 (m, 2H), 5.55 (dd, J = 1.6, 17.7 Hz, 1H), 5.23 (dd, J = 1.6, 10.8 Hz, 1H), 3.38 – 3.36 (m, 1H), 2.75 – 2.74 (m, 1H), 2.62 – 2.57 (m, 1H), 2.31 (dd, J = 2, 14.4 Hz, 1H), 2.07 – 2.05 (m, 2H), 1.94 – 1.89 (m, 2H); ¹³C (100 MHz, CDCl₃) δ 141.1, 139.6, 139.2, 133.5, 131.4, 128.9, 127.5, 126.7, 125.8, 114.3, 78.3, 45.6, 40.5, 32.3, 25.9, 20.9. Anal. Calcd for C₁₆H₁₈O: C 84.92; N 0.00; H 8.02. Found : C 84.39; N 0.00; H 8.39.

2-(2-Allylphenyl)bicyclo[2.2.2]oct-5-en-2-ol 593

1-Allyl-2-bromobenzene (3.0 g, 16.0 mmol) was dissolved in anhydrous THF (10 mL) and cooled to -78°C, n-BuLi (13 mL, 32 mmol, 2.5 M) was then added dropwise. In another flask a separate solution of bicyclo[2.2.2]oct-5-en-2-one 389 (1.0 g, 8.0 mmol) in THF (10 mL) at
-78°C was prepared. The reaction mixture containing the lithiated aromatic tether was then transferred into the second via a cannula, and the resulting reaction mixture allowed to warm to room temperature. To the reaction mixture was then added a solution of saturated NH₄Cl, filtered and the resultant solution extracted with EtOAc (3x20 mL). The combined organic extracts were then dried over Na₂SO₄ and the excess volatiles removed under reduced pressure. Products was then purified by column chromatography (40:1, 38:1, 36:1, 34:1, 32:1, 30:1, 28:1, 26:1, 24:1, 22:1, 20:1, 18:1, 16:1, 14:1, 12:1, 10:1, 8:1, 6:1, 4:1, 2:1 PE:Et₂O graduated column) giving the title compound as colourless yellow oil (0.94 g 48%). IR (CH₂Cl₂) ν max 3390 (OH), 2933, 2870 cm⁻¹; ¹H (100 MHz, CDCl₃) δ 7.36 - 7.32 (m, 2H), 7.16 – 7.02 (m, 2H), 6.47 (t, J = 7.2 Hz, 1H), 6.26 (t, J = 7.2 Hz, 1H), 5.87 – 5.79 (m, 1H), 4.96 (d, J = 10.0 Hz, 1H), 4.86 (d, J = 16.8 Hz, 1H), 3.64 – 3.61 (m, 1H), 3.26 – 3.11 (m, 1H), 2.61 – 2.58 (m, 1H), 2.15 – 2.10 (m, 4H), 1.28 – 1.08 (m, 4H); ¹³C (400 MHz, CDCl₃) δ 140.8, 139.8, 137.0, 131.9, 131.6, 129.2, 127.4, 125.7, 115.3, 78.3, 46.0, 40.3, 33.2, 24.7, 20.6; MS-ESI found 263.1404 C₁₇H₂₀ONa [M+Na]⁺ requires 263.1412.

8-Vinylbicyclo[3.3.1]non-3-en-1-ol 596

Grubbs second generation catalysts (0.05g, 0.6 mmol, 10 mol%) was dissolved in anhydrous toluene (4 mL). Ethylene was then bubbled through the reaction mixture for 2–3 min. The ethylene atmosphere was then maintained and a solution of 2-allyl bicyclo[2.2.2]oct-5-en-2-ol 586 (100 mg, 0.21 mmol) in toluene (1 mL) was added. The reaction mixture was then stirred at room temperature for 48 h with monitoring by TLC. The excess volatiles removed under reduced pressure. The products was then purified by column chromatography (20 : 1 petroleum ether : EtOAc) giving the title compound as pale yellow oil (70 mg, 70%) IR (CH₂Cl₂) ν max 3455 (OH), 3018, 2975 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 5.78 – 5.69 (m, 1H), 5.67 – 5.63 (m, 1H), 5.59 – 5.56 (m, 1H), 5.00 (dt, J = 1.2, 16.8 Hz, 1H), 4.92 (dt, J = 1.4, 18.8 Hz, 1H), 2.71 – 2.68 (m, 1H), 2.48 (dq, J = 2.4, 15.2 Hz, 1H), 2.28 (dt, J = 1.4, 15.3 Hz, 1H), 2.22 – 2.15 (m, 1H), 1.81 – 1.72 (m, 3H), 1.68 – 1.49 (m, 3H); ¹³C (100 MHz, CDCl₃) δ 143.8, 135.4, 129.0, 112.2, 49.9, 48.1, 40.8, 36.1, 29.7, 27.8, 24.4; MS-ESI found 163.1116 C₁₁H₁₆O [M-H]⁻ requires 163.1117.
9-Vinylbicyclo[4.3.1]dec-4-en-1-ol 597

Grubbs second generation catalysts (0.05 g, 0.05 mmol, 10 mol%) was dissolved in anhydrous toluene (4.0 mL). Ethylene was then bubbled through the reaction mixture for 2–3 min. The ethylene atmosphere was then maintained and a solution of 2-allylbicyclo[2.2.2]oct-5-en-2-ol 587 (100 mg, 0.21 mmol) in toluene (1 mL) was added. The reaction mixture was then stirred at room temperature for 48 h with monitoring by TLC. The excess volatiles removed under reduced pressure. The products was then purified by column chromatography (20 : 1 petroleum ether : EtOAc) giving the title compound as pale yellow oil (55 mg, 55%) IR (CH2Cl2) νmax 3405 (OH), 3393, 2983, 2888 cm⁻¹; ¹H (400 MHz, CDCl3) δ 5.77 – 5.69 (m, 2H), 5.52 – 5.51 (m, 1H), 4.99 (dt, 1H, J = 1.6, 17.5 Hz), 4.95 (dt, J = 1.4, 10.4 Hz, 1H), 2.72 – 2.69 (m, 1H), 2.60 – 2.51 (m, 1H), 2.29 – 2.22 (m, 2H), 1.81 – 1.71 (m, 2H), 1.62 – 1.56 (m, 4H), 1.25 – 1.22 (m, 1H), 0.99 – 0.97 (m, 2H); ¹³C (100 MHz, CDCl3) δ 142.9, 136.1, 133.7, 112.1, 80.1, 49.6, 46.8, 41.7, 36.5, 28.0, 24.1, 12.3; MS-ESI found 177.1274 C12H17O [M-H]⁺ requires 177.1272.

6-Vinyl-3a,4,5,6,7,7a-hexahydro-1H-inden-7a-ol 595

Grubbs second generation catalysts (0.05 g, 0.6 mmol, 10 mol%) was dissolved in anhydrous toluene (4 mL). Ethylene was then bubbled through the reaction mixture for 2–3 min. The ethylene atmosphere was then maintained and a solution of 2-(2-vinylphenyl)bicyclo-[2.2.2]oct-5-en-2-ol 586 (100 mg, 0.21 mmol) in toluene (1 mL) was added. The reaction mixture was then stirred at room temperature for 48 h with monitoring by TLC. The excess volatiles removed under reduced pressure. The products was then purified by column chromatography (20 : 1 petroleum ether : EtOAc) giving the title compound as pale yellow oil (24 mg, 24%) IR (CH2Cl2) νmax 3463 (OH), 3023, 2986 cm⁻¹; ¹H (400 MHz, CDCl3) δ; 6.02 (dd, J = 5.4, 1.6 Hz, 1H), 5.71 – 5.59 (m, 1H), 5.00 – 4.98 (m, 2H), 2.75 (dd, J = 14.3, 1.9 Hz, 1H), 2.29 – 2.12 (m, 3H), 2.00 (dd, J = 9.9, 2.9 Hz, 1H), 1.70 – 1.58 (m, 3H), 1.43 -
1.27 (m, 4H); $^{13}$C (100 MHz, CDCl$_3$) δ 140.5, 133.6, 133.1, 116.4, 78.4, 50.4, 46.3, 40.0, 31.1, 25.4, 18.1 MS-ESI found 187.1097 C$_{11}$H$_{16}$ONa [M-Na]$^+$ requires 187.1099.

3-Methyl-8-vinylbicyclo[3.3.1]non-3-en-1-ol 599

Grubbs second generation catalysts (0.05g, 0.6 mmol, 10 mol%) was dissolved in anhydrous toluene (4 mL). Ethylene was then bubbled through the reaction mixture for 2–3 min. The ethylene atmosphere was then maintained and a solution of 2-(2-Methylallyl)bicyclo[2.2.2]oct-5-en-2-ol 588 (100 mg, 0.21 mmol) in toluene (1 mL) was added. The reaction mixture was then stirred at room temperature for 48 h with monitoring by TLC. The excess volatiles removed under reduced pressure. The products was then purified by column chromatography (20 : 1 petroleum ether : EtOAc) giving the title compound as pale yellow oil (70 mg, 70%) IR (CH$_2$Cl$_2$) ν$_{max}$ 3433 (OH), 2975, 2933, 2870 cm$^{-1}$; $^1$H (400 MHz, CDCl$_3$) δ 5.78 – 5.63 (m, 1H), 5.24 (d, $J$ =5.5 Hz, 1H), 4.92 (dd, $J$ = 10.6, 2.3 Hz, 1H), 4.91 (dd, $J$ = 17.2, 2.3 Hz, 1H), 2.19 – 1.94 (m, 4H), 1.81 (s, 3H), 1.56 – 1.43 (m, 6H); $^{13}$C (100 MHz, CDCl$_3$) δ 137.1, 133.7, 124.3, 117.1, 76.7, 47.8, 44.2, 42., 26.2, 24.1, 18.4, 17.9 ; MS-ESI found 201.1251 C$_{12}$H$_{18}$ONa [M+Na]$^+$ requires 201.1251.

7-Allyl-5-[(tert-butyldimethylsilyloxy)methyl]bicyclohept-2-en-7-ol 361, via Indium mediated allylation 512

7-Allyl-5-[(tert-butyldimethylsilyloxy)methyl]bicyclohept-2-en-7-ol 437 (0.02 g, 0.10 mmol) was dissolved in THF/H$_2$O (10 mL 50:50) and allyl bromide (0.03 mL, 0.28 mmol) added. Indium powder (0.02 g, 0.18 mmol) was then added to the reaction mixture, and the reaction mixture heated to 50 °C for 12 h. More water was then added (10 mL) and the reaction mixture extracted using EtOAc (3x10 mL). The combined organic extracts were washed with
brine and then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure. Product was then purified by column chromatography (10:1 PE:EtOAc) giving the title compound as yellow oil (0.22 g, 94 %); IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 3398 (OH), 2928, 2856, 1638 cm$^{-1}$; $^1$H (400 MHz, CDCl$_3$) $\delta$ 6.08 (dd, $J = 3.2$, 6.4 Hz, 1H), 5.94 (dd, $J = 3.2$, 6.4 Hz, 1H), 5.84 – 5.73 (m, 1H), 5.13 – 5.06 (m, 2H), 3.40 (dd, $J = 6.4$, 10.0 Hz, 1H), 3.21 (t, $J = 9.6$ Hz, 1H), 2.68 – 2.63 (m, 2H), 2.59 (t, $J = 3.6$ Hz, 1H), 2.51 – 2.41 (m, 2H), 2.39 (t, $J = 3.6$ Hz, 1H) 2.14 (dd, $J = 4.0$, 8.8, 11.6 Hz, 1H), 0.89 (s, 9H), 0.52 (dd, $J = 4.4$, 11.6 Hz, 1H) 0.02 (s, 6H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 135.6, 132.7, 118.4, 92.0, 65.3, 50.8, 48.8, 39.6, 37.7, 27.2, 26.4, 25.9, 18.3, -5.3, -5.2; MS-ESI found 317.1895, C$_{17}$H$_{30}$O$_2$Si [M+Na]$^+$ requires 317.1913.

5-Bromopenta-1,3-diene 367

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\text{Br}
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Penta-1,4-dien-3-ol (2 g, 23 mmol) and HBr (48% 6.16 mL, 54 mmol) was added together and the reaction mixture stirred at room temperature for 1.5 h. Water (20 mL) was then added and the reaction mixture extracted using EtOAc (3x20 mL). The organic layer was then washed with a saturated brine solution, dried over magnesium sulfate, filtered, and the excess volatiles were removed under reduced pressure, and the product was then purified by a bulb-to-bulb distillation at 25 °C, 4 mbar (Literature b.p 56-57 °C)$^{105}$ to give clear oil (3.25 g, 96%) IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 2955, 1820, 1604, 1280, 1157, 1003, 949 (C-Br), 910 cm$^{-1}$; $^1$H (400 MHz, CDCl$_3$) $\delta$ 6.28 – 6.30 (m, 2H), 5.93 – 5.89 (m, 1H), 5.28 (d, $J = 10.4$ Hz, 1H), 5.16 (d, $J = 8.8$ Hz, 1H), 4.02 (d, $J = 6.7$Hz, 2H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 135.5, 135.2, 129.1, 119.4, 32.8; MS-ESI found, 145.9701 C$_5$H$_7$Br$_79$ [M]$^+$ requires 145.9731.

5-((((tert-Butyldimethylsilyl)oxy)methyl)-7-(penta-1,4-dien-3-yl)bicyclo[2.2.1]hept-2-en-7-ol 638

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\text{OH}
\]

5-(((tert-Butyldimethylsilyl)oxy)methyl)bicyclo[2.2.1]hept-2-en-7-one 433 (0.20 g, 0.84 mmol) and 5-bromo-1,3-pentadiene (0.29 g, 1.99 mmol) were dissolved in DMF (0.30 mL).
Indium powder (0.13 g, 1.13 mmol) was added slowly to the reaction mixture and the subsequently stirred for 48 h at room temperature. The reaction mixture was then diluted with CH₂Cl₂ (5 mL) and then added to Et₂O (25 mL) and the resultant mixture filtered through a pad of silica. The silica was washed with additional Et₂O, and the filtrate concentrated under vacuum. This afforded a yellow oil which was then purified by column chromatography (10:1 PE:EtOAc) to give the title compound as colourless oil (0.13 g, 49%); IR (CH₂Cl₂) νmax 3368 (OH), 2851, 1950, 1631 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 5.90 (ddd, J = 6.4, 10.8, 17.2 Hz, 1H), 5.79–5.70 (m, 2H), 5.54 (d, J = 6.0 Hz, 1H), 5.21–4.94 (m, 4H), 3.43 (d, J = 7.2 Hz, 1H), 3.41 (d, J = 5.6 Hz, 1H), 3.31 (d, J = 7.6 Hz, 1H), 3.02 (d, J = 8.8 Hz, 1H), 2.67 (dt, J = 6.0, 13.2 Hz, 1H), 2.47–2.36 (m, 1H), 1.77 (dt, J = 5.6, 12.0 Hz, 1H), 1.03 (q, J = 12.4 Hz, 1H), 0.85 (s, 9H), −0.01 (s, 6H); ¹³C (100 MHz CDCl₃) δ 137.7, 137.5, 135.3, 132.4, 117.1, 116.9, 94.4, 65.4, 49.7, 48.0, 47.9, 39.7, 27.2, 26.0, 22.6, −5.3, −5.4; MS-ESI found 343.2057, C₁₉H₃₂O₂Si [M + Na]^+ requires 343.2069.
1-((tert-Butyldimethylsilyl)oxy)-3,4-divinyl-1,2,3,3a,4,6a-hexahydropentalen-3a-ol 639

Grubbs second generation catalysts (10 mol%) was dissolved in anhydrous toluene (5 mL). Ethylene was then bubbled through the reaction mixture for 2–3 min. The ethylene atmosphere was then maintained and a solution of 5-(((tert-butyldimethylsilyl)oxy)methyl)-7-(penta-1,4-dien-3-yl)bicyclo[2.2.1]hept-2-en-7-ol 368 (0.67 g, 0.21 mmol) in toluene (1 mL) was added. The reaction mixture was then stirred at room temperature for 48 h with monitoring by TLC. The excess volatiles removed under reduced pressure. The products was then purified by column chromatography (10 : 1 PE : EtOAc) giving the title compound as pale yellow oil (0.36 g, 54%); IR (CH₂Cl₂) νmax 3420 (OH), 2845, 1452 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.90 (ddd, J = 6.4, 10.8, 17.2 Hz, 1H), 5.79 – 5.70 (m, 2H), 5.54 (d, J = 6.0 Hz, 1H), 5.21 – 4.94 (m, 4H), 3.43 (d, J = 7.2 Hz, 1H), 3.41 (d, J = 5.6 Hz, 1H), 3.31 (d, J = 7.6 Hz, 1H), 3.02 (d, J = 8.8 Hz, 1H), 2.67 (dt, J = 6.0, 13.2 Hz, 1H), 2.47 – 2.36 (m, 1H), 1.77 (dt, J = 5.6, 12.0 Hz, 1H), 1.03 (q, J = 12.4 Hz, 1H), 0.85 (s, 9H), −0.01 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 137.2, 136.5, 132.3, 131.1, 118.2, 116.3, 90.2, 64.4, 60.1, 54.2, 53.9, 43.4, 32.4, 25.9, 18.2, −5.3, −5.4; MS- ESI found 343.3055, C₁₉H₃₂O₂Si [M + Na]⁺ requires 343.2069.

2-(Penta-1,4-dien-3-yl)bicyclo[2.2.2]oct-5-en-2-ol 340

Bicyclo[2.2.2]oct-5-en-2-one (0.50 g 3.70 mmol) 389 and 5-bromo-1,3-pentadiene (1.27 g, 8.60 mmol) were dissolved in DMF (10 mL). Indium powder (0.55 g, 4.8 mmol) was added slowly to the reaction mixture and the subsequently stirred for 48 h at room temperature. The reaction mixture was then diluted with CH₂Cl₂ (5 mL) and then added to Et₂O (25 mL) and the resultant mixture filtered through a pad of silica. The silica was washed with additional Et₂O, and the filtrate concentrated under vacuum. This afforded a yellow oil which was then
purified by column chromatography (10:1 PE:EtOAc) to give the **title compound** as colourless oil (0.20 g 28%) IR (CH₂Cl₂) ν max 3349 (OH), 2985, 2880 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 6.48 – 6.48 (m, 1H), 6.22 – 6.20 (m, 1H), 5.98 – 5.87 (m, 2H), 5.17 (dd, J = 2.0, 10.4 Hz, 2H), 5.11 – 5.02 (m, 2H), 3.14 – 3.12 (m, 1H), 3.01 – 2.96 (m, 1H), 2.69 – 2.56 (m, 2H), 2.12 – 2.03 (m, 2H), 1.69 – 1.51 (m, 2H), 1.42 – 1.21 (m, 2H); ¹³C (100 MHz, CDCl₃) δ 137.0, 134.1, 132.9, 128.4, 117.6, 116.9, 72.3, 58.5, 48.5, 41.6, 32.3, 24.4, 22.5; MS-ESI found 190.1352 C₁₃H₁₈ONa [M]⁺ requires 190.1358.
9. 7-Allyl-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-ol X-Ray Data
Table 1. Crystal data and structure refinement for 7- Allyl-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-ol.

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<tr>
<td>Formula weight</td>
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</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>synchrotron, 0.7749 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>monoclinic, P2$_1$/n</td>
</tr>
<tr>
<td>Unit cell parameters</td>
<td>$a = 11.3188(14)$ Å, $\alpha = 90^\circ$</td>
</tr>
</tbody>
</table>
9. X-Ray Data

<table>
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<tr>
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<th>Value</th>
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<td>b = 7.8255(10) Å</td>
<td>β = 107.7750(18)°</td>
</tr>
<tr>
<td>c = 11.8409(15) Å</td>
<td>γ = 90°</td>
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<td>Cell volume</td>
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<tr>
<td>Z</td>
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<tr>
<td>Calculated density</td>
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<td>F(000)</td>
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<td>Crystal colour and size</td>
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<tr>
<td>Reflections for cell refinement</td>
<td>6497 (θ range 3.46 to 33.60°)</td>
</tr>
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<td>Data collection method</td>
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<td>Independent reflections</td>
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<td>Reflections with F²&gt;2σ</td>
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<td>Absorption correction</td>
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<td>Min. and max. transmission</td>
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<td>Structure solution</td>
<td>direct methods</td>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<td>Weighting parameters a, b</td>
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<td>R indices (all data)</td>
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</tbody>
</table>
9. X-Ray Data

Goodness-of-fit on $R^2$ 1.045

Largest and mean shift/su 0.000 and 0.000

Largest diff. peak and hole 0.328 and −0.185 e Å$^{-3}$

Acknowledgement: The Advanced Light Source is supported by the Director, Office of Science, Office of Basic Energy Sciences, of the U.S. Department of Energy under Contract No. DE-AC02-05CH11231.

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å$^2$) for am1. $U_{eq}$ is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

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<th>z</th>
<th>$U_{eq}$</th>
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<td>0.04096(7)</td>
<td>0.79369(5)</td>
<td>0.02265(14)</td>
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<td>C(1)</td>
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<td>0.03635(10)</td>
<td>0.78060(7)</td>
<td>0.02147(16)</td>
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<tr>
<td>C(2)</td>
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<td>0.20243(11)</td>
<td>0.71900(7)</td>
<td>0.02679(18)</td>
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<td>C(3)</td>
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<td>C(4)</td>
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<td>0.11714(12)</td>
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<td>0.93041(7)</td>
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<td>C(7)</td>
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<td>0.80680(8)</td>
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<td>C(8)</td>
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<td>C(11)</td>
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<td>O(2)</td>
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Table 3. Bond lengths [Å] and angles [°] for am1.

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<th>Length</th>
<th>Bond</th>
<th>Length</th>
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<td>C(1)–C(5)</td>
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<td>C(2)–C(3)</td>
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<td>C(2)–C(7)</td>
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<td>C(3)–C(4)</td>
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<td>O(1)–C(1)–C(8)</td>
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<td>C(8)–C(1)–C(2)</td>
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<td>C(10)–C(9)–C(8)</td>
<td>125.08(9)</td>
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Table 4. Hydrogen coordinates and isotropic displacement parameters (Å²) for am1.

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<th>x</th>
<th>y</th>
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Table 5. Torsion angles [°] for am1.

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<td>C(8)–C(1)–C(2)–C(7)</td>
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<td>C(8)–C(1)–C(2)–C(7)</td>
<td>-176.68(7)</td>
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<td>C(1)–C(2)–C(3)–C(4)</td>
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<td>C(8)–C(1)–C(2)–C(7)</td>
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<td>C(1)–C(2)–C(3)–C(4)</td>
<td>-34.29(10)</td>
</tr>
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</table>
9. X-Ray Data

O(1)–C(1)–C(5)–C(6)  \(-54.17(8)\)
C(2)–C(1)–C(5)–C(6)  \(58.60(7)\)
C(1)–C(5)–C(6)–C(11)  \(-161.12(7)\)
C(1)–C(5)–C(6)–C(7)  \(-38.30(8)\)
C(5)–C(6)–C(7)–C(2)  \(2.03(8)\)
C(1)–C(2)–C(7)–C(6)  \(35.25(8)\)
C(2)–C(1)–C(8)–C(9)  \(-65.20(10)\)
C(1)–C(8)–C(9)–C(10)  \(-116.93(12)\)
C(5)–C(6)–C(11)–O(2)  \(-64.30(10)\)

C(8)–C(1)–C(5)–C(6)  \(-179.98(7)\)
C(4)–C(5)–C(6)–C(11)  \(-57.29(9)\)
C(4)–C(5)–C(6)–C(7)  \(65.52(8)\)
C(11)–C(6)–C(7)–C(2)  \(125.54(8)\)
C(3)–C(2)–C(7)–C(6)  \(59.95(9)\)
C(5)–C(1)–C(8)–C(9)  \(-172.31(7)\)
C(7)–C(6)–C(11)–O(2)  \(178.91(7)\)

Table 6. Hydrogen bonds for am1 [Å and °].

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<th>D–H...A</th>
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<th>d(H...A)</th>
<th>d(D...A)</th>
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</table>

Symmetry operations for equivalent atoms

\( ^{'} -x+1, -y, -z+2 \)  "  \( x+1/2, -y+1/2, z+1/2 \)
10. References

18 Schrock, R.R.; Rocklage, S.; Wengrovius, J.; Rupprecht G.; Fellmann, J. Journal of Molecular Catalysis., 1980, 8, 1, 73.

75 Holtsclaw, J.; Koreeda, M. Org. Lett., 2004, 6, 3719
11. Apendicies: Research Papers

11.1 The stereochemical outcome of allyl magnesium and indium additions to 5-substituted norbornen-7-ones and its application to cis fused carbocycles formation via ring rearrangement metathesis.

11.2 The regioselective outcome of the ring rearrangement metathesis transformations performed on bicycloc-[2.2.2]-oct-2-ene derivatives.