Reductive cyclisation cascades of lactones using SmI$_2$-H$_2$O

A dissertation submitted to the University of Manchester for the degree of Master of Science by Research in the Faculty of Engineering and Physical Sciences

2010

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School of Chemistry
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Abbreviations

Ac    acetyl
Ar    aryl
Bn    Benzyl
Bu    Butyl
d    doublet
DCM  dichloromethane
DIBAL diisobutylaluminium hydride
DMF   dimethylformamide
DMPU  1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone
DMSO  dimethyl sulfoxide
dr    diastereoisomeric ratio
Et    ethyl
Et₂O  diethylether
eq    equivalents
g     gram
gem   geminal
h     hour
HMPA  hexamethylphosphoramide
Hz    hertz
IR    infrared
J     coupling constant
LDA   lithium diisopropylamide
LiOH  lithium hydroxide
M     molar
m     multiplet
m     meta
mCPBA meta-Chloroperbenzoic acid
Me    methyl
<table>
<thead>
<tr>
<th>Abbr</th>
<th>Full Form</th>
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</thead>
<tbody>
<tr>
<td>Mel</td>
<td>methyl iodide</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
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<tr>
<td>min</td>
<td>minute</td>
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<td>mL</td>
<td>millilitre</td>
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<td>mmol</td>
<td>millimole</td>
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<tr>
<td>mp.</td>
<td>melting point</td>
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<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
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<tr>
<td>NP</td>
<td>neopentyl</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PMB</td>
<td>p-methoxybenzyl ether</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>t</td>
<td>triplet</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>Xantphos</td>
<td>4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene</td>
</tr>
</tbody>
</table>
Abstract

It was over 30 years ago when Kagan[1] and co-workers turned their attention to the field of divalent lanthanide reducing agents. Of the reductants initially chosen for investigation, samarium diiodide (SmI₂) emerged as one of the most promising and has since become one of the most important reducing agents available to the synthetic organic chemist. Samarium diiodide demonstrates great versatility, promoting a multitude of synthetic organic transformations, with its inclusion in over 100 publications per year being a testament to its synthetic importance. Until recently, the reduction of unfunctionalised esters with the reagent SmI₂ was thought to be impossible. I have employed the unusual radical-anion intermediates in cyclisations to form cycloheptandiols and in cascade reactions in which 7- and 5-membered rings are formed, with good diastereocontrol in a single step, using a single reagent.

In the Procter group, it was found that 6-membered lactones can be reduced using SmI₂-H₂O. These are the first examples of the reduction of simple, aliphatic ester carbonyl groups with SmI₂. Furthermore, the radical-anions generated have been used for the first time in cyclisations with alkenes. My work has attempted to exploit the previously unexplored reaction space by accessing unique radical-anion species. It was proposed that new reaction pathways and selectivity would result from our studies.
Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Acknowledgements

Undertaking an MSc by Research at Manchester has been both a challenging and highly rewarding experience. I have spent the last 12 months working within a fantastic group of dedicated and professional individuals, from which I feel I have benefited greatly.

I would like to express my upmost gratitude to David Procter, firstly for the opportunity and privilege to work within his group, and also for his tireless enthusiasm and encouragement throughout my Masters, which at times, was exactly what was needed.

I would also like to thank the entire Procter group, it has been a pleasure to have worked alongside you all during my time here in Manchester: Thanks to Dixit, Andrew, Neal, Matt H, Karl, Hassan, Brice, Trung, Laura, Matt L, Seidjolo, Susannah and all visiting students and undergraduates over the last year.

I would like to give special thanks to Dixit Parmar, who throughout the year was always of the upmost help with his expertise and encouragement, to Dr Matthew Helm for his encyclopaedic knowledge, and finally to Andrew Eberhart; for his words of encouragement, sense of humour, and his ability to wind me up on a daily basis.

Thanks to all departmental staff, especially Gareth Smith, for all their assistance, particularly in recent months.

Finally, thanks go to my parents, for their continued support and encouragement.
Chapter 1: Introduction

While numerous reactions and procedures have been developed over the last three decades involving SmI$_2$, the reagent’s scope is far from exhausted. It has been shown that the use of cosolvents or additives can alter the reactivity, or reducing range of SmI$_2$, opening up new paths that were previously thought closed. New work within the Procter group$^{[2]}$ has shown that SmI$_2$-H$_2$O can not only reduce lactones once thought to lie outside the range of SmI$_2$, but that the reagent system shows complete selectivity towards 6-membered lactones over other classes of lactones and esters. In addition, the exploitation of these novel reductions has led to new pathways to cyclic products.

1.1. Samarium diiodide, the reagent and the effect of additives

Like all lanthanide elements, samarium favours a +3 oxidation state. The loss of the three outermost electrons (4f$^6$, 6s$^2$) allows samarium to exist in its most thermodynamically stable state, giving itself a Xe-like electronic configuration. In SmI$_2$, samarium exists in the +2 oxidation state, readily donating its outermost electron in a thermodynamically driven process, therefore making it a powerful single-electron transfer reagent.

Samarium iodide is commercially available, but can also be easily prepared. The various methods include Kagan’s original approach$^{[1]}$ involving samarium metal and diiodoethane, and the more atom-efficient method using samarium and iodine in THF developed by Imamoto.$^{[3]}$ Imamoto’s method proceeds via the initial formation of samarium triiodide, the thermodynamically most stable state, before further reduction to SmI$_2$ through a disproportionation process aided by heat (Scheme 1.1). More recently, formation of the reagent has been facilitated by the sonication of samarium metal and iodine at room temperature.$^{[4]}$
Electrochemical techniques can be used to determine the reducing power of divalent lanthanides, and provide a convenient way for probing the energetics of single electron transfers from these reagents. Kagan first became interested in samarium when noting that a fellow divalent lanthanide salt, europium chloride, was known to reduce isonicotinic acid to the corresponding aldehyde. Realising the chemistry of this reagent did not extend to other classes of compounds, he considered a shortlist of lanthanide elements thought to be capable of a wider range of transformations. The reduction potentials of these lanthanide II reagents were reported and listed below (Table 1.1, Scheme 1.2):

### Scheme 1.1

<table>
<thead>
<tr>
<th>Lanthanide</th>
<th>$\text{Ln}^{3+}/\text{Ln}^{2+}$ ($E^0$ values in water)</th>
</tr>
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<tbody>
<tr>
<td>Eu</td>
<td>-0.43 V</td>
</tr>
<tr>
<td>Yb</td>
<td>-1.15 V</td>
</tr>
<tr>
<td>Sm</td>
<td>-1.55 V</td>
</tr>
<tr>
<td>Tm</td>
<td>-2.30 V</td>
</tr>
</tbody>
</table>

Table 1.1
Because of the prohibitive cost of thulium metal they set about preparing THF solutions of SmI$_2$, inspired by the classical Grignard procedure of preparing diethyl ether solutions of MgX$_2$ from 1,2-dichloroethane and magnesium.$^{[6]}$

Recent electrochemical studies by Flowers show the reduction potential of SmI$_2$ in THF to be $-1.33 \pm 0.01$ eV.$^{[7]}$ A key feature of SmI$_2$ chemistry is that the reagent’s reactivity can be fine-tuned through the use of various additives or cosolvents. Usually, manipulation of the reduction potential of SmI$_2$ is achieved through the addition of coordinating molecules containing neutral or Lewis basic oxygen functionalities.$^{[8]}$ The most common example is HMPA (hexamethylphosphoramid), which was introduced to SmI$_2$ chemistry by Inanega.$^{[9]}$

It has been shown that the reduction potential for Sm$^{3+}$/Sm$^{2+}$ can reach a maximum value of $-2.05$ eV through the addition of 4 equivalents of HMPA in THF.$^{[7]}$ The complex SmI$_2$-(HMPA)$_4$ was first successfully isolated and characterised by Hou in 1994.$^{[10]}$ The addition of H$_2$O as an additive is also known to increase the reduction potential of SmI$_2$ from $-1.33$ eV to $-1.9$ eV upon the addition of up to 500 equivalents of H$_2$O.$^{[7]}$ This increase in reduction potential thereby increases the potency of SmI$_2$ as a single-electron transfer reagent. Through these discoveries, it is becoming apparent that through the use of additives, we can gain access to extended transformations mediated by SmI$_2$, allowing access to new chemical space through the reduction of new carbonyl substrates (Figure 1.1).
Additives employed fall into two broad categories:

1. Electron donating ligands – HMPA, DMPU, TMU.
2. Proton donors – H$_2$O or alcohols.

In some cases, the role electron donating ligands play in SmI$_2$-mediated reactions has been explored. Without the use of kinetic studies however, it is difficult to predict exactly how ligands such as HMPA will affect the mechanism of some reactions. HMPA is known to both accelerate and hinder rates of reaction and is capable of effecting initial and/or post-electron transfer steps. Given the complex nature of SmI$_2$-additive chemistry, each class of SmI$_2$ mediated reaction should be studied separately.

It was once thought that proton sources such as H$_2$O served only to protonate anionic intermediates, preventing further reaction. However, in 1993 Curran noted that proton sources could also accelerate certain classes of SmI$_2$-mediated reductions. Unfortunately, the exact role of water in SmI$_2$ reductions is still not known, with the mechanistic understanding of SmI$_2$ reductions having lagged behind the synthetic advances made. However, studies by Dahlen, Hilmersson and Flowers have given us an insight at least into the inner mechanics of proton-donor coordination. For example, it is now known that:
• Rates of SmI$_2$ ketone reductions are proportional to the pK$_a$ of the proton source.$^{[12]}$

• Rates of carbonyl reductions are accelerated further with the use of glycols, and that rates of reduction are shown to be proportional to the number of ethereal oxygens, most likely due to the proximity of the proton donor to the carbonyl during reduction.$^{[4]}$

• Initial coordination of a proton donor liberates THF or iodine from SmI$_2$

• Saturation of SmI$_2$ with additives decreases its reactivity.

When SmI$_2$ is formed as a solution in THF it forms a characteristic deep blue colour. The reagent is air-sensitive, but is stable under nitrogen or argon and is tolerant of water. The addition of water changes the colour of the solution from a deep blue to dark red/purple, a clear visual indicator that water serves not only to donate protons in later steps, but also influences the coordination chemistry of the reagent itself. A similar colour change occurs upon coordination of HMPA to SmI$_2$.

Pleasingly, not only can additives alter the reducing range or rates of reaction, they have been shown to have an influence on the regio- and stereochemical outcomes of numerous SmI$_2$-mediated reactions.$^{[13-15]}$ Such outcomes will be discussed in further detail later.

The ability to selectively modify the reducing potential of SmI$_2$ by the simple addition of cosolvents or additives has significant consequences when considering the synthesis of complex molecules containing numerous reducible functionalities. In short, the ability to ‘fine tune’ the reagent through careful optimisation, making SmI$_2$ potent yet selective, has helped to establish SmI$_2$ as one of the most important reducing agents.
1.2. SmI₂ in organic synthesis

Samarium diiodide is a versatile and powerful reagent, mediating numerous important organic reactions. These include the reduction of a variety of functional groups, carbon-carbon bond forming reactions, reductive couplings and sequential reactions. Examples of reactions with high levels of chemoselectivity and stereoselectivity will be given to exemplify why SmI₂ is frequently the reagent of choice in natural product synthesis. This discussion will also set the scene for the subsequent description of my research. Alongside this, a short introduction to the current mechanistic understanding of SmI₂-mediated reactions, highlighting research relevant to the outcomes of my project, will be presented.

Samarium diiodide acts as a one electron donor (Sm²⁺→Sm³⁻). The basic principles of reduction using SmI₂ are exemplified using an alkylhalide (RX) in Scheme 1.3. We can assume that all transformations proceed either by a one-electron transfer, or two successive one-electron transfers depending upon the substrate in question. In a simplification, therefore, we can view the broad range of SmI₂ chemistry divided into radical and anionic subsections. For example, in the reduction of a species RX, a radical or an anion can be obtained.

![Scheme 1.3](image.png)

We describe single electron transfers from one substrate to another as inner- or outer-sphere processes. An outer-sphere process involves little or no interaction of the respective ‘coordination spheres’ of the two substrates in question (e.g. SmI₂ and organic species RX) during the transition state of the electron transfer. Conversely, in an inner-sphere electron transfer, a strong interaction occurs between the donor (SmI₂) and acceptor prior to and during the electron transfer process in the transition state.
Steric effects and the affinity of the substrate towards SmI2/ the SmI2-additive reagent system play a large part in how we believe electron transfer to occur. Sterically demanding ligands such as HMPA, often promote outer-sphere processes over inner-sphere processes through the saturation of SmII centres.

A classic method for the generation of radicals using SmI2 involves the reduction of alkyl halides. This reduction is of great synthetic value given the range of subsequent reactions that can occur. Early mechanistic studies carried out by Kagan suggested that this was indeed radical chemistry, and did not involve the formation of an organosamarium species. It has since been known that organosamarium species are often formed by further reduction of intermediate radicals. (Scheme 1.4).^[16]

![Scheme 1.4](image)

As shown in the above scheme, the initial radical can either take part in coupling reactions, gain a hydrogen by hydrogen atom abstraction or be reduced by a second electron transfer to give an alkyl samarium species. This is a key class of reactive intermediate used in one of the most important reactions mediated by SmI2, the Barbier addition.
1.3. Carbon–Carbon Bond-Forming Processes mediated by SmI$_2$

1.3.1. The Barbier Addition

The Barbier reaction is the reductive addition of an alkyl halide to a carbonyl substrate. Although the reaction mechanism for the SmI$_2$-mediated Barbier reaction is not fully understood, a well accepted view involves the nucleophilic addition of an organosamarium, or carbanion, to the carbonyl group. The first detailed study of the intermolecular SmI$_2$-mediated Barbier was reported in 1980 by Kagan.$^{[1]}$

The reaction was once thought to proceed through the coupling of an alkyl radical and ketyl radical,$^{[16]}$ however, it is now believed that two successive one-electron transfers$^{[17]}$ to the alkyl halide occur before nucleophilic attack of the resultant organosamarium on the carbonyl substrate. The ‘Barbier’ label is used to indicate that both the reactive halide and the carbonyl are present in the same pot when the reagent is added (Scheme 1.5). The Barbier addition is therefore differentiated from the ‘Grignard’ addition, whereby the alkyl halide is treated with SmI$_2$ prior to the addition of the carbonyl compound. An extensive review of the SmI$_2$-mediated Barbier reaction was published by Krief and Laval.$^{[18]}$

![Scheme 1.5](image_url)

In 1987, Molander reported the first example of an intramolecular Barbier addition promoted by SmI$_2$ (Scheme 1.6)$^{[19]}$. Molander found these reactions proceeded with high diastereocontrol due to coordination of Sm$^{III}$ to the two carbonyl groups in the substrates. Scheme 1.7 further illustrates the capabilities of the Barbier reaction, firstly for the formation of strained ring systems such as 1, in which significant steric congestion must be overcome, and secondly the two-directional synthesis of tetracyclic polyquinines 2, proceeding with syn diastereoselectivity.
Other variants of the Barbier reaction exist, most commonly utilising metals such as magnesium, zinc or tin. However, unlike SmI$_2$, none of these exist in a homogeneous solution and often give inferior results in terms of chemoselectivity. The Barbier reaction is now one of the most commonly utilised transformations mediated by SmI$_2$. It is particularly valuable when used in an intramolecular fashion, efficiently forming 5-8 membered carbocycles. Barbier additions to lactones and esters are also possible. In these cases catalytic amounts of salts such as NiI$_2$ have been shown to improve both the rate and the yield; however, it is still unclear as to how these salts effect SmI$_2$-mediated reactions. In a concise synthesis of a phorbol-like system, Carrol and Little used SmI$_2$ and NiI$_2$ to mediate an intramolecular Barbier addition involving a lactone and an alkyl halide (Scheme 1.8).}
Since Sm$^{II}$ is oxophilic in nature, it has a high affinity for functional groups such as carbonyls. Many examples of Barbier additions are therefore considered to occur through an inner-sphere pathway due to strong interactions between the reagent and the substrate. However, Flowers has shown that the presence of SmI$_2$ complexed with HMPA gave Barbier products via an outer-sphere process.$^{[21]}$ Clearly, changing the steric bulk around a reductant can alter the mode by which electron transfer occurs, and this can have telling consequences on the stereoselectivity of reactions.

1.3.2. SmI$_2$-mediated intramolecular carbonyl-alkene/alkyne couplings

Cyclisation reactions play a major role in SmI$_2$ chemistry. These reactions often proceed with excellent chemo-, regio- and stereoselectivity. A comprehensive review of SmI$_2$ cyclisations in natural product synthesis was published in 2004 by Procter.$^{[13]}$ This review underlines the extent to which the reagent has met numerous challenges in terms of selectivity and versatility in reactions involving natural product precursors.

Some of the most important carbon-carbon bond forming reactions mediated by the reagent are intramolecular carbonyl-alkene couplings.$^{[8]}$ These transformations are valuable because a wide range of carbo and heterocyclic systems of varying ring sizes
can be prepared. As expected, intramolecular carbonyl-alkene cyclisations are far more tolerant with regard to the nature of the alkene than intermolecular variants. Intermolecular reactions require activated, electron-deficient alkenes, whereas intramolecular reactions can also occur with neutral alkenes.

Intramolecular SmI$_2$-mediated ketone-olefin coupling reactions were pioneered by Molander et al.,$^{[22]}$ who presented the synthesis of a large number of products from a range of substrates, often with high diasterecontrol. For example, Scheme 1.9 shows the diastereoselective generation of spirocyclic system 3 in 87% yield using SmI$_2$.

![Scheme 1.9]

The mechanism of the cyclisation involves reduction of the ketone carbonyl group to generate a ketyl radical, which then adds to the alkene or alkyne multiple bonds. As discussed previously, coordination of Sm$^{III}$ to the β-carbonyl group controls the stereochemical course of the reaction, resulting in the formation of products in high diastereoisomeric excess (Scheme 1.10).$^{[23]}

![Scheme 1.10]
Recent work by Procter\cite{2} exploits coordination of a $\beta$-carbonyl group to Sm$^{\text{III}}$ to stabilise a ketal intermediate thus avoiding over-reduction and will be discussed in detail later.

Reissig\cite{24} discovered that SmI$_2$, with HMPA and $t$-BuOH in THF was even capable of promoting more demanding cyclisations such as the formation of 8-membered rings through an 8-endo-dig pathway (Scheme 1.11).

![Scheme 1.11]

**1.3.3. Pinacol couplings**

Since the discovery of the pinacol coupling reaction 150 years ago, it has become an important synthetic tool for the construction of carbon-carbon bonds.\cite{25,26} SmI$_2$ is routinely used to mediate the pinacol coupling reactions of aldehydes and ketones (Scheme 1.12).\cite{13} With regards to intermolecular pinacol couplings, stereochemical control is usually poor. Only in the case of sterically hindered substrates such as 4, can high levels of stereoselectivity be obtained in favour of the syn isomer (Scheme 1.13).\cite{27} The stereoselectivity of intramolecular SmI$_2$-mediated pinacol couplings is highly dependent on the substrates used. High levels of diastereoselectivity can be attained using a variety of 1,5- and 1,6-dicarbonyl substrates, yielding $cis$-vicinal diols in many cases (Scheme 1.14).

![Scheme 1.12]


Scheme 1.13

Scheme 1.14

1.3.4. Reformatsky reactions

In 1980, Kagan reported the first example of a SmI$_2$-mediated Reformatsky reaction (Scheme 1.15).$^{[1]}$ These reactions provide a useful alternative to the traditional versions of the reaction, proceeding under mild and homogeneous conditions, often with higher levels of chemo- and diastereoselectivity. These reactions are most commonly carried out by the addition of SmI$_2$ to a 1:1 mixture of the α-halocarbonyl compound and its coupling partner. The reactions proceeded by reduction of the α-halo carbonyl compound to give a samarium enolate that then adds to the carbonyl substrate.

Scheme 1.15

SmI$_2$ has also been used extensively to facilitate intramolecular Reformatsky reactions. This reaction has been frequently used to access medium and large carbocycles and lactones (Scheme 1.16).$^{[28]}$ In 1999, Mukaiyama investigated the
SmI$_2$-mediated Reformatsky cyclisation reaction, which culminated in the total synthesis of Taxol (Scheme 1.17). [29]

![Scheme 1.16](image)

**Scheme 1.16**

![Scheme 1.17](image)

**Scheme 1.17**

1.3.5. Sequential reactions

SmI$_2$ has been used to great effect to construct complex polycyclic systems in a single synthetic operation. Such cascade or sequential reactions may be described as the Holy Grail of the organic chemist in that molecular complexity is built up quickly with little synthetic effort and resource.

Working towards the synthesis of (±)-hypnophilin and (±)-coriolin (5 and 6), Curran developed a SmI$_2$-mediated cascade process as a key step in the preparation of the natural products. [30] The reactions proceeded with complete diastereocontrol (Scheme 1.18).
The mechanism of the cascade involves the formation of ketyl-radical anion 7, which undergoes a 5-exo trig cyclisation to give the tertiary cyclopentyl radical 8. A 5-exo-dig cyclisation of radical 8 creates the final 5-membered ring. Through D$_2$O experiments it was determined that the final radical species underwent hydrogen atom abstraction from THF, the only source of protons, rather than reduction to create an organosamarium species and subsequent protonation (Scheme 1.19).[30]

In his synthesis of paeonilactone B, Kilburn utilised the SmI$_2$-HMPA reagent system to mediate a sequential radical cyclisation of methylenecyclopropyl ketone 9 (Scheme 1.20).[31]
This SmI$_2$-mediated sequence involves a 5-exo-trig cyclisation from the ketyl radical formed 10 onto the methylenecyclopropane moiety, followed by a ring opening of the intermediate 11, giving rise to radical 12. Secondary radical 12 then cyclises in a 5-exo-dig manner to form the second ring (Scheme 1.21).\cite{31}

As previously mentioned, the choice of additives can have a profound influence on the course of SmI$_2$-mediated reactions. The choice of additive proved to be vital in the synthesis of paeonilactone B. When HMPA was replaced with DMPU, both the yield and diastereoselectivity of the reaction decreased. It was also noted that in the absence of an activating ligand, a reversal of selectivity was observed. Kilburn and co-workers rationalised the results through consideration of the transition structures by which the 5-exo-trig cyclisation occurs (Scheme 1.22).\cite{31}
They believed that in the presence of a strongly coordinating solvent such as HMPA, the increased steric bulk of the samarium alkoxide resulted in a preference for transition structure 13, in which the alkoxide adopts a pseudoequatorial position in order to minimise unfavourable 1,3-diaxial interactions. With DMPU, the effective steric bulk of the samarium alkoxide is reduced, and the transition structure 14 in which the alkoxide adopts a pseudoaxial orientation, must be considered.

### 1.4. The reduction and reductive cyclisations of esters

The reduction of esters to alcohols is typically achieved through the use of hydride reagents such as LiAlH₄. The Bouveault-Blanc reduction is a relatively inexpensive and scalable alternative to such reagents, and is achieved through a succession of electron and proton transfers using ethanol and sodium metal. Four equivalents of sodium metal are required for this reduction (Scheme 1.23).

A widely applied variant of the Bouveault-Blanc reduction is the acyloin condensation. In the acyloin condensation, the radical anion intermediate formed from the reduction of a diester can be used to assemble carbocyclic ring systems (Scheme 1.24).
One of the few examples of the reductive cyclisation of an ester onto an unsaturated carbon-carbon bond was reported by Cossy et al.\textsuperscript{[33]} They demonstrated that acyclic \(\delta,\varepsilon\)-unsaturated esters could be effectively transformed into cyclopentanols 15 in good to excellent yields by treatment with Na/NH\(\text{}_3\) (Scheme 1.25).

Upon treatment of an ester with Na/NH\(\text{}_3\), an electron transfer can take place to generate a ketyl radical 16, which can undergo cyclisation (Path A). Alternatively, further electron and proton transfers can generate an intermediate aldehyde 17, which can then be reduced to form a ketyl radical 18 which undergoes cyclisation (Path B) (Scheme 1.26).
Both pathways can lead to the same product, but Cossy suggests that it is the 2nd radical 18 that is involved in cyclisation, although pathway A cannot be excluded.

The scope of the reaction was fairly limited as the cyclisation was found to be highly susceptible to steric effects. For example, elaboration of the alkene by addition of a methyl group, slowed the rate of cyclisation to the point where the Bouveault-Blanc straight reduction product was the only product observed (Scheme 1.27).[33]

As previously discussed, the reduction of unfunctionalised esters was thought to be beyond the reach of SmI₂. However, through the use of additives, recent work has shown that the reduction of some of these substrates is possible. During the early 1990’s, Kamochi and Kudo showed that the SmI₂-H₂O reagent system could be utilised for the reduction of carboxylic acids and aryl esters (Scheme 1.28).[34,35]
Scheme 1.28

More recently, Marko used an aryl ester reduction in his work on a new protecting group for alcohols.[36] Marko demonstrated that benzoate ester 19 could be deprotected using SmI2-HMPA to yield the starting alcohol 20 (Scheme 1.29).[36]

Scheme 1.29

The unprecedented reduction of an unfunctionalised cyclic ester was published in 2008 by Procter et al., who used the SmI2-H2O reagent system to reduce 6-membered lactones 21 to the corresponding diols 22 (Scheme 1.30).[37] Lactone reduction will be discussed in more detail later.

Scheme 1.30

In 2009, Procter also reported the reduction of cyclic 1,3-diesters in the presence of acyclic esters using the SmI2-H2O reagent system.[38] For example, the reduction of
substrate 23 gave the product arising from the mono reduction of only the cyclic diester (Scheme 1.31).

Scheme 1.31

The mechanism involves a series of single electron transfers and protonations. The group believe that the origin of selectivity lies in the initial electron transfer to the cyclic ester, with the radical generated experiencing anomeric stabilisation in the cyclic 6-membered ester that cannot be achieved for a radical derived from an acyclic ester. It has now been shown that the ketyl radical anions generated by one electron transfer can be exploited in additions to alkene radical traps, giving cyclic products (Scheme 1.32).[39]

Scheme 1.32

It is now clear that the activation of SmI₂ using additives such as H₂O allows substrates such as unfunctionalised esters to be reduced in some cases. With this knowledge in hand, we now have access to a wealth of new unexplored chemical space and unprecedented selectivity.
Chapter 2: Results and Discussion

2.1. Previous work within the Procter group

As previously discussed, the Procter group have shown that the SmI$_2$-H$_2$O reagent system not only distinguishes between the carbonyl groups of esters and lactones, but also shows ring-size selectivity for 6-membered lactones.$^{[37]}$ Exploitation of the radical anions formed by lactone reduction with SmI$_2$-H$_2$O has yielded cyclic ketone products with high diastereoselectivity (Scheme 2.12).

During studies on SmI$_2$-mediated spirocyclisations utilising compounds such as 24, an interesting result was obtained. In addition to the expected spirolactone products, triols formed by the reduction of the spirocyclic products were also observed. As previously discussed, the only previous example of the reduction of carboxylic acid derivatives using SmI$_2$-H$_2$O was from Kamochi and Kudo in 1990.$^{[34,35]}$ There was no literature precedent for the reduction of unactivated, aliphatic esters or lactones using SmI$_2$ (Scheme 2.1).

Investigating the reduction of spirocyclic lactones further, a number of six-membered lactones were successfully reduced. However, there was no evidence of reduction of 5-membered lactones using the SmI$_2$-H$_2$O system. The use of the additives HMPA and DMPU in separate experiments also yielded no 5-membered lactone reduction, with only starting material being recovered.

A series of competition experiments were carried out. For example, treating a 1:1 mixture of closely related spirocyclic lactones 25 and 26 with SmI$_2$-H$_2$O, gave triol 27
and the recovered 5-membered lactone 28, with no trace of reduced product (Scheme 2.2).

Scheme 2.2

This is a remarkable example of the selectivity of the SmI₂-H₂O reagent system. Further competition experiments exemplifying the selectivity for 6-membered lactones over 7- and 8-membered lactones were also carried out (Scheme 2.3).

Scheme 2.3

The reduction of lactones in the presence of acyclic esters was also possible.² Finally, to underline the ring-size selectivity of SmI₂-H₂O, treatment of bis-lactone 29 allowed selective manipulation of the 6-membered lactone, leaving the 5-membered lactone intact (Scheme 2.4).

Scheme 2.4
A study of the mechanism of the reduction was undertaken in an attempt to discover the origin of the selectivity observed.

### 2.1.1. Possible origins of ring-size selectivity

SmI$_2$-D$_2$O experiments were conducted on spirolactones, with complete deuterium incorporation in the triol products being observed. This suggests that anions are generated and protonated by H$_2$O during the series of electron transfers. It was believed that the reaction proceeded via 4 single electron transfers. Initial electron transfer to the lactone generated radical anion $30$, which after a further electron transfer and subsequent protonation led to the resultant lactol. Lactol $31$ exists in equilibrium with the hydroxy-aldehyde $32$, which through two successive electron transfers, generates a second ketyl radical-anion $33$, and then an organosamarium, which is protonated by water to produce the diol product (Scheme 2.5).

![Scheme 2.5](image)

The ring-size selectivity is believed to originate in the initial electron transfer to the lactone carbonyl. In an important study, lactols prepared from both 5- and 6-membered lactones were then reduced rapidly using SmI$_2$-H$_2$O in high yields. This gave a clear indication that the ring size selectivity originated in the initial stage of the process (Scheme 2.6).
It appeared that the selectivity arose from the varying stabilities of the radical anion intermediates formed after the first reduction. It was proposed that 6-membered radical-anion intermediates benefit from optimal anomeric stabilisation of the radical, through favourable interactions with the endocyclic oxygen atom. Such beneficial interactions are best achieved in a 6-membered chair conformation.

In collaboration with Prof H. Matsubara, theoretical calculations were carried out that supported this hypothesis. The calculated relative reaction energies associated with the initial electron transfer step for selected ring sizes of lactone are shown in Scheme 2.7.\(^2\)

Calculations suggest that the first electron transfer is endothermic in all cases. However, the relative energy associated with the initial electron transfer to the 6-membered lactone is about 25-26 kJ mol\(^{-1}\) lower than that associated with the 5- and 7-membered rings. Although not shown, the second electron transfer was found to be
much lower in energy for all ring systems, suggesting that the first electron transfer is rate- determining.

2.1.2. Intercepting the radical intermediates formed in the reduction of lactones

In 2009, Procter and co-workers published the first examples of cyclisations of the lactone carbonyl group through the tethering of an alkene onto the lactone scaffold, that acts as a radical trap. \[^2\]

It was proposed that the intermediates generated during the reduction of 6-membered lactones could be intercepted and exploited in reductive stereoselective cyclisations. This was a reasonable hypothesis given that the exploitation of radicals formed from the reduction of aldehydes and ketones is well preceded.\[^{8,13,23}\]

Research would focus on 5-exo cyclisations, given their prevalence in radical reactions. Alkene radical traps were to be attached alpha to the lactone carbonyl group, giving what would be termed ‘class 1’ lactones (Figure 2.1).

![Figure 2.1](image)

Initial attempts within the Procter group to trap a radical intermediate formed using the SmI\(_2\)-H\(_2\)O reagent system gave mixtures of cyclic and acyclic products (Scheme 2.8).
Scheme 2.8

A SmI$_2$-H$_2$O cyclisation was initially attempted using lactone 34 bearing the simplest, unactivated terminal alkene tethered in the α-position (Scheme 2.8). It was found that the major product upon treatment with SmI$_2$-H$_2$O was the diol 35, the direct product of reduction of the lactone. From this initial result, it appeared that the rate of reduction of both radical intermediates during the course of the reaction pathway were sufficiently fast to compete with cyclisation. However, cyclised products 36 and 37 were also obtained, giving the first indication that such a transformation was possible.

In order to promote the cyclisation pathway over lactone reduction, the issue of over-reduction needed to be addressed. It was suggested that interception of the radical-anions with a more reactive alkene radical acceptor could be used to bring about cyclisation at a faster rate. Pleasingly, it was found that when lactone 38 (with an alkene tether activated by an aryl group) was treated with SmI$_2$-H$_2$O, cyclisation products 39 and 40 were the only products (Scheme 2.8).

As shown previously in Scheme 2.5, two radical intermediates are formed during the SmI$_2$-H$_2$O reduction of lactones; initial electron-transfer to the lactone carbonyl, and the reduction of the lactol/hydroxy-aldehyde intermediate both generate radical-anions. In considering the formation of cyclopentanol product 41, Procter and co-workers sought to clarify whether it was the trapping of first or second radical that resulted in the cyclic products (Scheme 2.9).
Trapping of the first radical would afford bicyclic hemi-ketal product \(42\), the collapse of which would yield cyclopentanone \(43\), which in the presence of excess \(\text{SmI}_2\) would be rapidly reduced in a potentially non-diastereoselective manner to give a mixture of cyclopentanols. Trapping of the second radical, an intramolecular addition of a samarium ketyl-radical anion onto the alkene, would lead directly to the product \(41\) through a more conventional cyclisation pathway (Scheme 2.10).

Product \(41\) was obtained with no diastereocontrol. This suggested that cyclisation products were formed through trapping of the first radical, followed by unselective ketone reduction.

A strategy was developed to prevent over-reduction of the cyclopentanone products. With the knowledge that \(\text{Sm}^{\text{III}}\) has a high affinity towards oxygen donors, an \(\alpha\)-ethoxycarbonyl group (previously used in the synthetic route to class 1 cyclisation substrates to facilitate alkylation) was left in place. It was believed that this ester group would chelate to \(\text{Sm}^{\text{III}}\) and therefore stabilise the hemi-ketal intermediate \(44\) and prevent collapse to reveal the ketone (Scheme 2.11).
A library of lactones containing a range of substituted alkenes with the ester functionality in place, were prepared using standard synthetic procedures. Treatment of these lactones with SmI$_2$-H$_2$O gave in most cases the corresponding cyclopentanone/hemi-ketal products, all in good to excellent yield (Scheme 2.12).
It was also believed that the $\alpha$-ethoxycarbonyl group plays a role accelerating the reduction and controlling the stereochemical course of the cyclisations by coordination to SmI$_2$ and to the radical-anion intermediates respectively.

2.2. Project Aims

In 2009, an extensive report was published by the Procter group on the radical cyclisation of ‘Class 1’ substrates (where an alkene was tethered at the $\alpha$-position).[2] The work described here seeks to further exploit the unique radical-anion intermediates formed during lactone reductions using SmI$_2$-H$_2$O. It is proposed that the attachment of alkene functionality at alternative positions on the lactone could open up new routes to substituted carbocyclic ring systems (Scheme 2.13). We decided to consider two further positions for attachment of an alkene tether, namely the $\beta$ and $\delta$-positions. We hoped to generate radical-anion intermediates capable of yielding new cyclic products through similar cyclisation processes.

![Scheme 2.13](image)

Scheme 2.13

It was proposed that positioning the alkene tether at the $\delta$-position (class 2 lactones), could open up the formation of complex 7-membered ring products, a difficult synthetic challenge by other means. In conjunction with this, we planned to extend the cyclisation methodology by consideration of ‘Class 3’ lactones as precursors to cyclopentanol products (Scheme 2.14).
Finally, once the cyclisation chemistry of these classes of lactones had been explored and was understood, it was proposed we could achieve multiple transformations through cascade cyclisations, creating complex products from simple starting materials in just one pot, using one reagent.

Using the SmI$_2$-H$_2$O reagent system, we predicted that, through the appropriate placement of alkene tethers onto a 6-membered lactone ring, we could instigate a lactone cyclisation cascade forming an azulene-like core in one pot. As shown below, the azulene core maps onto numerous biologically active natural products that have attracted widespread interest from both chemical and biological communities (*Figure 2.2*).

**Figure 2.2**
Molecules such as phorbol have proved useful in the study of carcinogenesis and the development of methods for its prevention. In addition, compounds related to phorbol such as prostratin have been identified as being active against latent HIV. Unfortunately, the levels of natural products such as prostratin found in the source plants is very low, and limited access to the natural products have slowed their development as therapeutic agents. Natural products related to phorbol are very difficult to prepare using current synthetic tools. In fact, the only attempts to prepare prostratin has been through a ‘top-down’ synthetic approach from the scarce natural product phorbol. We hope to develop a methodology that can be applied to selective cascade reactions that could one day grant us access to these targets.

For example, using our chemistry, the carbonyl group of a 6-membered lactone is synthetically equivalent to a diradical that can add to two alkenes to form azulene ring systems (*Scheme 2.15*).
2.3. Proposed synthesis of ‘class 3’ cyclisation substrates

My work began with the synthesis of Class 3 cyclisation substrates. Through a retrosynthetic analysis, it was proposed that these substrates could be obtained in two steps from commercially available 5,6-Dihydro-2H-pyran-2-one 45 (Scheme 2.16).

Scheme 2.16

Our proposed route involved the conjugate addition of an allyl group, followed by functionalisation of the alkene using olefin cross metathesis. The conjugate addition of the alkene tether onto commercially available 5,6-dihydro-2H-pyran-2-one was carried out using the procedure published by Waldmann and co-workers, in the primary step of their work towards protein phosphatase inhibitors. This was the only example of conjugate addition of an allyl metal to this particular substrate. The reaction involves initial transmetallation of allylmagnesium chloride using zinc bromide. The resultant organozinc reagent then undergoes 1,4-conjugate addition to furnish an enolate, subsequently trapped by TMS-chloride. An acidic workup yields the lactone 46 (Scheme 2.17).

Scheme 2.17

Although Waldmann reported a yield of 51 %, my initial attempts gave very poor yields (< 25% yield). TLC analysis suggested the formation of numerous by-products. NMR analysis suggested that 1,2-addition was the major problem. We next attempted the allylation through reaction of an organocuprate with substrate 45. Unfortunately...
cuprate addition resulted in no product formation. NMR analysis again showed that the product appeared to be the result of a 1,2-addition to 45.

We revisited the original conditions reported by Waldmann, and after further optimisation, we were able to obtain a significant improvement in yield. Attempting the reaction on a larger scale (33 mmol of 45) we obtained a 50 % yield of 46.

Functionalisation of allyl lactone 46 was achieved using olefin cross metathesis. Lactone 46 was treated with catalytic amounts of the Grubbs 2nd generation catalyst 47 in DCM together with two styrene derivatives. Substituted alkene-lactones were isolated in modest yields (48 and 49) (Scheme 2.18).

![Scheme 2.18](image)

Attempts to improve the yield of 48 and 49 were unsuccessful. The products of cross metathesis were strongly coloured, suggesting by-products from the catalyst were still present. Reports in the literature suggested that removal of such by-products could be effected through stirring the lactones in Et₂O with approximately 50 mol% activated charcoal. This was carried out on both 48 and 49 to obtain the compounds as colourless oils.
2.4. SmI$_2$-H$_2$O cyclisations of class 3 substrates

With 48 in hand, we next investigated our key cyclisation step using SmI$_2$ and H$_2$O. In the first attempt, lactone 48 was treated with 2 equivalents of SmI$_2$, the theoretical amount required for cyclisation to the corresponding cyclopentanone product 50. This resulted in the decolourisation of the SmI$_2$-H$_2$O reagent system after just 30 minutes. Crude NMR analysis showed only starting material, with no other species evident. However new spots by TLC analysis were faintly visible. Upon increasing the amount of SmI$_2$-H$_2$O to 4 equivalents the reaction lasted over an hour before decolourisation occurred, but unfortunately little conversion was observed. This was a surprising result considering previous work within the group (Scheme 2.15). However it was envisaged that class 3 substrates cyclise through a more strained bicyclic intermediate, and it would be predicted that the rate of cyclisation would be slower. Pleasingly, through the use of 8 equivalents of SmI$_2$, after 7 hours, approximately 50% conversion of starting material, gave cyclopentanol 51 and diol 52 in 26% and 24% yield respectively (Scheme 2.19).

Scheme 2.19

Diol 52 arises from ‘straight’ reduction of the lactone, suggesting that the radical-anion intermediate is reluctant to undergo cyclisations. Cyclopentanol 51 arises from cyclisation, then reduction of the cyclopentanone under the reaction conditions. Due to the promising results obtained with class 2 type substrates, focus was turned to these lactones.
2.5. Proposed synthesis of ‘simple’ Class 2 cyclisation substrates

Class 2 cyclisation substrates feature an alkene attached to the lactone scaffold at the \( \delta \)-position. A retrosynthetic analysis of what we term ‘simple’ class 2 substrates (‘H’ at the \( \delta \)-position) is shown below (Scheme 2.20):

![Scheme 2.20](image)

It was proposed that cyclisation substrate 53 could be synthesised via the Baeyer-Villiger oxidation of 54, which in-turn could be accessed by allylation of cyclopentanone 55. Additional functionality could be introduced to 53 through olefin cross metathesis using a range of styrenes.

The synthesis of substrate 54 commenced from commercially available cyclopentanone 55. A method published in 1979 by Posner and Lentz\(^{42}\) described the alkylation of a variety of cyclopentanones, and was employed used in an attempt to synthesise 54 (Scheme 2.21).

![Scheme 2.21](image)
The use of HMPA during the preparation of LDA aided the formation of a more reactive species, and a catalytic quantity of copper cyanide was added prior to the addition of the electrophile to form a copper enolate, which was believed to be better suited to alkylation that the analogous lithium enolate.

Unfortunately in our hands, Posner’s conditions led to numerous by-products and poor yields. An alternative strategy, and one which was used for our research was a procedure reported by Breit et al. which was used to form products such as 56 (Scheme 2.22).\(^{43}\)

![Scheme 2.22](image)

A premixed solution of cyclopentanone containing catalytic amounts of \([(\eta^3\text{-allyl})\text{PdCl}_2]\), Xantphos and (DL)-proline was formed before the addition of an allyl alcohol, which gave mono-allylated products in good yields. We applied conditions proposed by Breit to substrate 55, furnishing allyl cyclopentanone 54 in a 73 % yield (Scheme 2.23).

![Scheme 2.23](image)

Breit proposed the reaction proceeded by the \textit{in situ} condensation of (DL)-proline with cyclopentanone to form an enamine, alongside the generation of a palladium \(\pi\)-allyl intermediate from allylic alcohol. Nucleophilic attack of the enamine on the
palladium π-allyl led to the allylated product after hydrolysis during work up (Scheme 2.24).

![Scheme 2.24](image)

**Scheme 2.24**

With allyl-cyclopentanone 54 in hand, we sought to oxidise the ketone using a Baeyer-Villiger procedure to form the 6-membered lactone 53. Treatment of 54 with m-CPBA and NaHCO₃ in DCM at 0 °C furnished lactone 53 in moderate yield (Scheme 2.25). Addition of the peracid to the carbonyl group forms a tetrahedral intermediate known as the Criegee intermediate (such as 57). Migration of one of the adjacent carbon substituents results in lactone 53 after loss of carboxylic acid. In our case, we only saw migration of the carbon bearing the CHCH₂=CH₂ group.

![Scheme 2.25](image)

**Scheme 2.25**

It was thought that the volatility of the substrate accounted for moderate isolated yield. Possible by-products such as products of alkene epoxidation were not isolated.

Functionalisation of allyl-lactone 53 was achieved using olefin cross metathesis to form three substrates for cyclisation. Lactone 53 was treated with catalytic amounts of the Grubbs 2nd generation catalyst in dichloromethane together with an appropriate styrene derivative, forming substituted lactones 58-60 in modest yields (Scheme 2.26).
At this point in time, a colleague within the group had carried out several SmI$_2$-H$_2$O cyclisations and had thus established the feasibility of the cyclisation of such substrates. He had found that the treatment of unsubstituted lactone 53 with SmI$_2$-H$_2$O unfortunately led to no cyclised product. Instead, straight reduction to diol 61, and some recovery of starting material was observed (Scheme 2.27).

However, cyclisation attempts on functionalised lactones 58-60 carried out by Dixit Parmar resulted in the isolation of the desired cyclisation products 62-64 in modest yield. The highest yield of 55% was obtained for cycloheptadiol 64. Products 62-64 result from cyclisation to the cycloheptanone followed by the reduction of the ketone carbonyl by SmI$_2$-H$_2$O (Scheme 2.28).
As predicted, the presence of radical stabilising functional groups allows the rate of cyclisation to compete with the reduction of the radical-anion and formation of acyclic reduction products. These results provided us with our first examples of 7-membered ring formation. Interestingly, NMR analysis of the product mixture showed complete consumption of starting material. In spite of this, purification by column chromatography afforded both cyclised products and unreacted starting material.

2.6.1 Investigation of an ‘unproductive shunt’ in the mechanism

It was proposed that cyclisations of ‘simple’ class 2 substrates were hindered by the formation of a hydroxy-acid, through the attack of H$_2$O at the lactone carbonyl, possibly mediated by Lewis acidic Sm$^{III}$/Sm$^{II}$ present in the reaction flask (Scheme 2.29).

It was shown by Dixit Parmar that the hydroxy-acids could not be reduced by SmI$_2$-H$_2$O. In one experiment, the hydroxy-acid formed from the starting lactone was isolated and was found to lactonise in quantitative yield overnight in CDCl$_3$. Formation of this hydroxy-acid was believed to have occurred during the reaction,
shutting down reactivity. Lactonisation upon purification by column chromatography then explains the recovery of starting material after the reaction was thought to be complete.

2.6.2 Prevention of lactone hydrolysis

The manipulation of hydroxy acid formation was explored. Firstly, by reducing the number of equivalents of H$_2$O we felt that we could alter the rate of lactone hydrolysis. However, little correlation between yield and the number of H$_2$O equivalents was observed, although the presence of H$_2$O was again shown to be crucial for reactivity. The second idea was to insert a quaternary centre adjacent to the lactone carbonyl. It was suggested that gem-dimethyl substitution at the α-carbon could disfavour the formation of the hydroxy-acid over the lactone (Scheme 2.30).

![Scheme 2.30](image)

It was proposed that the gem-dimethyl group would effect a two-pronged attack; firstly, the cyclisation of the hydroxy-acid would now be promoted by a Thorpe-Ingold effect,[46] and secondly, the inserted gem-dimethyl groups would act as a steric block to the attack of water onto the carbonyl carbon.

To form such substrates, deprotonation of lactone 53 using LDA at -78°C, and quenching of the enolate with methyl iodide gave the mono-alkylated product. Without purification, the same procedure was carried out again to give the required dimethylated lactone 65 in 76% yield (Scheme 2.31).
Further functionalisation of 65 was carried out using olefin cross metathesis, producing cyclisation substrates 66-68 in modest yields (Scheme 2.32).

Scheme 2.32

2.7. SmI\textsubscript{2}-H\textsubscript{2}O cyclisations of di-substituted lactones

Treatment of the α-dimethylated lactones 66-68 with SmI\textsubscript{2}-H\textsubscript{2}O pleasingly resulted in efficient cyclisation to give products 69-71 in good to excellent yield (Scheme 2.33).

Scheme 2.33
As proposed, the insertion of this gem-dimethyl group clearly had a marked effect on the reaction outcome. To further investigate this effect, we decided to exchange the methyl groups for bulkier ethyl ester groups. This would also give products bearing more functionality.

Synthesis of the proposed di-ester substrates proved challenging. Introduction of the first ester group was achieved by deprotonation of 53 using LDA, and Claisen condensation. The addition of a second ester group using the same conditions proved unsuccessful. The second addition was therefore attempted using sodium hydride in place of LDA and the desired product was obtained in 22% yield over two steps. Unfortunately, a mixture of mono- and di-substituted compounds was formed. With the exception of the formation of di-ester cyclisation substrate 72, these compounds proved impossible to separate (Scheme 2.34).

![Scheme 2.34]

With cyclisation substrate 72 in hand, we attempted a SmI$_2$-H$_2$O cyclisation under standard conditions. Although not conclusive, it appeared that cyclisation gave cycloheptandiol 73 in a 30% conversion (Scheme 2.35).

![Scheme 2.35]
2.8. Synthesis of ‘Substituted’ class 2 cyclisation substrates

The proposed synthesis of ‘substituted’ class 2 cyclisation substrates was more direct. Retrosynthetic analysis of lactone 74 brought us back to commercially available starting material 75 after two disconnections. It was thought an intermolecular Barbier addition of an allyl organometallic species to ketoester 75 would yield 74. Further functionalisation of the alkene through olefin cross metathesis as previously discussed would be employed to build up a library of cyclisation substrates 76 (Scheme 2.36).

![Scheme 2.36](image)

We commenced the preparation of ‘substituted’ class 2 cyclisation substrates using methodology developed by Molander et al.\(^{[47]}\) This comprised of the Barbier addition of an in situ generated organo-samarium to various ketoesters. They observed selective addition into the more reactive ketone carbonyl with rapid lactonisation yielding 77 thereafter (Scheme 2.37).

![Scheme 2.37](image)
Applying Molander’s procedure, treatment of keto-ester 75 with SmI$_2$ in the presence of catalytic NiI$_2$, followed by the dropwise addition of allyl bromide afforded lactone 74 in consistently excellent yields (Scheme 2.38).

![Scheme 2.38](image)

Olefin cross metathesis was then employed for the further functionalisation of lactone 74. A similar procedure was employed as previously described, and cyclisation substrates 78-82 were obtained in 32-54 % yield after purification (Scheme 2.39).

![Scheme 2.39](image)
2.9. SmI₂-H₂O cyclisation of ‘substituted’ class 2 cyclisation substrates

As previously mentioned, the unproductive mechanistic shunt that we proposed with our ‘simple’ cyclisation substrates resulted in modest cyclisation yields. We also showed that the introduction of a gem-dimethyl group shifted the equilibrium away from the hydroxy-acid to favour the lactone. With ‘substituted’ cyclisation substrates \(78-82\), we envisaged that the presence of a quaternary carbon \(\delta\) to the carbonyl carbon would also disfavour the formation of the hydroxy-acid, thus promoting cyclisation.

I initially studied the behaviour of the unfunctionalised lactone towards cyclisation. Treatment of lactone \(74\) with the same number of equivalents of SmI₂ and H₂O as in previous attempts gave cycloheptandiol \(83\) in 68% yield as a 1:1 mixture of diastereoisomers (Scheme 2.40).

![Scheme 2.40](image)

This was a very satisfying result as attempted cyclisation of analogous substrate \(53\) (bearing a ‘H’ substituent at the \(\delta\)-position) gave acyclic diol \(61\) in 60% yield.

As cycloheptandiol products were obtained via reduction of cycloheptanone intermediates, mixtures of diastereoisomers resulted. However, we were aware that due to the presence of the quaternary centre \(\delta\) to the carbonyl, we could oxidise the secondary alcohol using the Dess-Martin periodiane reagent. Once oxidised to the hemi-ketal product, it allowed us to easily determine the diastereoselectivity of the cyclisation. The yields for formation of the ‘substituted’ cyclisation products \(83-88\) after DMP oxidation of the cycloheptandiols are reported in Table 2.1, with their respective diastereomeric ratios.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Lactone</th>
<th>Product</th>
<th>Yield (%)$^a$</th>
<th>dr$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = H</td>
<td><img src="https://example.com/image1.png" alt="Image" /></td>
<td>68</td>
<td>1:1</td>
</tr>
<tr>
<td>2</td>
<td>R = Ph</td>
<td><img src="https://example.com/image2.png" alt="Image" /></td>
<td>85</td>
<td>4:1</td>
</tr>
<tr>
<td>3</td>
<td>R = p-C₆H₄OMe</td>
<td><img src="https://example.com/image3.png" alt="Image" /></td>
<td>81</td>
<td>4:1</td>
</tr>
<tr>
<td>4</td>
<td>R = p-C₆H₄Br</td>
<td><img src="https://example.com/image4.png" alt="Image" /></td>
<td>82</td>
<td>4:1</td>
</tr>
<tr>
<td>5</td>
<td>R = m-C₆H₄CH₃</td>
<td><img src="https://example.com/image5.png" alt="Image" /></td>
<td>72</td>
<td>3:1</td>
</tr>
<tr>
<td>6</td>
<td>R = 2,6-C₆H₃(CH₃)₂</td>
<td><img src="https://example.com/image6.png" alt="Image" /></td>
<td>77</td>
<td>3:1</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield over 2 steps. $^b$ Determined by analysis of crude $^1$H NMR.

**Table 2.1**
Pleasingly, excellent overall yields for the two steps were obtained in all cases. As proposed, the presence of the quaternary centre provided a more straightforward cyclisation. It is likely that the ‘Me’ substituent helps to favour conformation \textbf{89b} over \textbf{89a}, in which the alkene tether is axial and predisposed to radical cyclisation (Fig 2.3).

The diastereomeric ratios for each reaction were all taken directly from the $^1$H NMR of the crude product mixtures. All functionalised cyclisation substrates yielded products with modest diastereoselectivity ($3:1$ dr $\rightarrow 4:1$ dr). In the case of the unfunctionalised lactone \textbf{74}, interestingly no selectivity was observed.

\begin{figure}[h]
\centering
\includegraphics[width=0.7	extwidth]{figure2.3.png}
\caption{Figure 2.3}
\end{figure}
2.10. Product stereochemistry and the mechanism of cyclisation

X-ray crystallographic analysis of the major diastereoisomer of 86 was used to confirm the relative stereochemistry of the cyclisation products (Fig 2.4).

The X-ray crystal structure of 86 clearly shows an *anti*-relationship between the oxygen bridge and the stereocentre formed during the C-C bond forming process.

This allows us to propose a mechanism for the reductive cyclisation of substituted class 2 substrates and to consider the stereochemical course of the reaction (*Scheme 2.41*):
Single electron transfer to the lactone by the SmI$_2$-H$_2$O reagent generates axial ketyl-radical anion 90. As previously discussed, the axial radical is thought to be favoured due to the radical anomeric effect. We rationalise that diastereoselective cyclisation occurs through the axially placed alkene tether. Subsequent protonation steps and a further electron transfer gives the bicyclic hemi-ketal product 91, which exists in equilibrium with hydroxy-ketone 92. A further two equivalents of SmI$_2$-H$_2$O exert a further reduction, yielding the cycloheptan-1,4-diol product 93.

In all the examples of the reaction, hemi-ketal or hydroxy-ketone products were not isolated from the reaction. It is therefore possible to suggest an alternative mechanism for the reductive cyclisation to give cycloheptan-1,4-diols (Scheme 2.42).
Scheme 2.42

An alternative mechanism could include a similar reduction of the lactone carbonyl, generating the 1st radical anion 94. This could then be further reduced, rather than the radical being trapped by the alkene, producing the lactol intermediate 95. 95 is in equilibrium with hydroxy-aldehyde 96, which can be reduced further to give a second radical-anion intermediate 97. This can undergo conventional carbonyl-alkene cyclisation, and after protonation, would yield the same cycloheptan-1,4-diol product 98. Dixit Parmar in the Procter group devised an experiment to investigate which mechanism was operating. Lactol 99 was prepared by DIBALH reduction of lactone 74 (Scheme 2.43). Lactol 99 is a proposed intermediate in the alternative mechanism shown in Scheme 2.42. Therefore, upon treatment with SmI₂·H₂O it would be expected to cyclise to give cycloheptan-1,4-diol products 98.
In fact, treatment of 99 under identical SmI$_2$-H$_2$O conditions to those used for cyclisation yielded the reduced diol product in quantitative yield. No products of cyclisation were observed. This experiment strongly suggests that cyclisation occurs via the 1$^\text{st}$ ester derived radical-anion (see Scheme 2.41) rather than via a more conventional 2$^\text{nd}$ radical-anion arising from lactol reduction (see Scheme 2.42).

**2.11. Introduction to cascade cyclisations**

With a growing understanding of the reactivity and mechanism of both ‘simple’ and ‘substituted’ class 2 substrates, in addition to previous work on class 1 substrates and the recently investigated class 3 substrates, we felt equipped to investigate the feasibility of cascade cyclisation reactions using the lactone carbonyl as a diradical equivalent. We proposed to synthesise 6-membered lactones that were doubly-armed at the $\alpha$- and $\delta$- positions. This would allow for the 1$^\text{st}$ cyclisation forming cycloheptanones 101 and reduction to form 2$^\text{nd}$ radical anions 102, which would undergo a 2$^\text{nd}$ cyclisation to form complex bicycles 103 (Scheme 2.44).
Clearly, the main challenge in developing successful cascade cyclisations is to achieve chemoselectivity. The ‘right’ cyclisation must be faster than the ‘left’ cyclisation. A diagrammatic representation of all mechanistic pathways leading to new products is shown below (Scheme 2.45).

Scheme 2.44

We envisaged that the cascade must occur ‘right then left’, resulting in a 5-exo-trig lactone-olefin cyclisation followed by a 5-exo-trig ketyl-olefin cyclisation. In following the ‘wrong’ pathway, to achieve the desired cascade product, a 5-exo-trig lactone-olefin cyclisation must precede a 7-exo-trig ketyl-olefin cyclisation, a pathway which would be less favourable. In addition to this, the possibility of ‘straight’ ketone reduction is an issue that may need to be overcome. Finally, the successful cascade would generate three new stereocentres, in which some degree of control would need to be achieved to ensure the synthetic worth of the cascade process.

Scheme 2.45
2.12. Preparation of cascade cyclisation substrates

The first cascade cyclisation substrate was prepared from lactone 79. The synthesis of 79 was covered previously in section 2.8. Lactone 79 was deprotonated using LDA and underwent Claisen condensation with Mander’s reagent to give the α-carbo-ethoxylactone 104. The presence of the ethyl ester greatly facilitated alkylation and the introduction of the 2nd alkene tether. Deprotonation of 104 with NaH and alkylation gave 105 in 43% yield. Subsequent decarboxylation of 105 under Krapcho conditions then provided us with cascade cyclisation substrate 106 as a 1:1 mixture of diastereoisomers (Scheme 2.46).

![Scheme 2.46](image)

A second cascade substrate 107 accessible from starting lactone 82 was also considered. Although 108 was successfully prepared, the Krapcho decarboxylation of 108 failed to go to completion and after several attempts, the remaining starting material was found to decompose due to the elevated temperatures involved (Scheme 2.47).
Given time constraints, the synthesis of cyclisation substrate 107 was not revisited. Instead, we chose to explore the possibility of a cyclisation substrate with an alkyne tether installed. We hoped that such a substrate would undergo a 5-exo-trig/5-exo-dig cyclisation sequence upon treatment with SmI₂·H₂O. The synthesis of cyclisations substrate 109 (Scheme 2.49) began with lactone 78, and reached 110 in similar yields, using similar reaction conditions (Scheme 2.48). Due to the complications associated with the decarboxylation of 110 under Krapcho conditions, we used a more traditional procedure for the decarboxylation. Hydrolysis of ester in 110 with LiOH furnished the carboxylic acid which, under reflux, decarboxylated with ease to give cyclisation substrate 109 in 59% overall yield and as a 1:1 mixture of diastereoisomers (Scheme 2.49).
At this point in time, co-worker Dixit Parmar had synthesised 'simple' cascade substrate 111 as a 1:1 mixture of diastereoisomers (Scheme 2.50).

From conformational analysis, we felt that syn-relative stereochemistry was important for a successful cascade cyclisation. The conformations of the two diastereoisomers of 111 are shown in Scheme 2.50. anti-Lactone 111b is expected to prefer an equatorial-equatorial conformation due to this being its lowest energy conformation. As shown,
cis-lactone 111a is likely to favour an axial-equatorial conformation, one of which is shown above. We believe that for the cascade process to be successful, cyclisation must first occur onto the δ-tethered alkene and that only the cis-lactone 111a possesses a conformation with the δ-tethered alkene in an axial orientation where this is possible.

Separation of diastereoisomers 111a and 111b was carried out by HPLC. It was found that the syn-diastereoisomer was less polar than the anti-diastereoisomer and thus had a higher R_F value. Treatment of syn-diastereoisomer 111a, as predicted, cyclised in a ‘right then left’ manner to yield bicyclic cascade product 112. Anti-diastereoisomer 111b underwent cyclisations only to the left to yield cyclopentanol 113 (Scheme 2.51).

![Scheme 2.51](image)

X-ray crystallographic analysis was used to confirm the stereochemistry of the major diastereoisomer of 112.

These observations were used to tentatively assign the relative stereochemistry in the cascade substrates 106 and 109, and in the products of cascade cyclisations.
2.13. Cascade cyclisation reactions

With the cascade substrates prepared and the syn-diastereoisomers isolated, we began our investigation into the cascade cyclisation reactions with substrate 106. Pleasingly, treatment of single diastereoisomer 106a under our standard SmI$_2$-H$_2$O conditions initiated a 4-electron cascade cyclisation sequence to yield cyclisation product 114 in a 4:1 mixture of diastereoisomers in a 70 % yield. No other products were observed (Scheme 2.52). The relative stereochemistry of the major diastereoisomer of 114 is based on the X-ray crystal structure of 112.

Scheme 2.52

In addition, unaware as to how the alkyne functionality in 109 would behave in the cyclisation cascade, we were delighted to isolate cyclisation product 115 as a 4:1 mixture of diastereoisomers, albeit in modest yield (Scheme 2.53). Cycloheptandiol 116 was also recovered.

Scheme 2.53
Again, the relative stereochemistry of major diastereoisomer 115 was assigned based on X-ray Crystallographic analysis of 112. We propose the following mechanism for the cascade process involved (Scheme 2.54).

Scheme 2.54

Electron transfer into the lactone carbonyl generates radical anion 117, which undergoes cyclisation onto the pendant alkene. Subsequent proton and electron transfers give cycloheptanone 118 after hemi-ketal collapse. A further electron transfer generates a 2\textsuperscript{nd} radical anion 119, which undergoes a 5-exo-trig cyclisation onto the equatorial positioned \( \alpha \)-tethered alkene. Further proton and electron transfers yielded product 114.
Chapter 3: Conclusion and Future Work

The discovery that SmI$_2$-H$_2$O can reduce 6-membered lactones, and finding that the radical-anions formed can be utilised in unprecedented cyclisations paved the way for my studies on the formation of 7-membered carbocyclics using SmI$_2$-H$_2$O. We have studied the reactivity of the lactone scaffold bearing δ-tethered alkenes and have shown they can be used to access cyclohepta-1,4-diols. Finally, this has allowed us to investigate SmI$_2$-H$_2$O cascade sequences that allow us to build up molecular complexity in a single reaction using a single reagent. These cascade reactions may find future application in natural product synthesis.

3.1. Areas of Future research

We have explored the reactivity of lactones bearing alkene tethers at the α, β, and δ-positions. Further work would include:

- Broadening the range of alkene functionalisation. What additional functional groups can be tolerated?
- Can other ring sizes be created through the use of SmI$_2$-H$_2$O? For example, are 6- or 7-exo-trig/endo-dig cyclisations possible?
- Can alternative activators be used in place of H$_2$O?

Additional work should also include the further study of cyclisations of class 3 lactones. We have shown that cyclisations onto alkenes tethered at the β-positions were not very successful, but we have yet to explore the scope of that reaction. We also envisage the possibility of alternative cascade reactions. A proposed cascade sequence from cyclisation substrate 120, with alkene tethers at the α- and β-positions relative to the lactone carbonyl would theoretically furnish bicyclic products such as 121 (Scheme 3.1). Cyclisation substrate 122 could arise in a single step using a 1-pot conjugate addition followed by enolate interception with an appropriate alkyl halide (Scheme 3.2).
An exciting culmination of the work would be for a SmI$_2$-H$_2$O cascade cyclisation to be utilised to access the core of biologically active natural products such as prostratin (Scheme 3.3).

It is envisaged that through the functionalisation of 6-membered lactones it is possible to prepare substrates such as 123 that will react with SmI$_2$-H$_2$O to undergo cascade sequences that could yield the skeleton of prostratin in a single step (124).
Chapter 4: Experimental

4.1. General experimental

All experiments were performed under an atmosphere of nitrogen, using anhydrous solvents, unless stated otherwise. THF was distilled from sodium / benzophenone or taken directly from a solvent purification system (SPS). Dichloromethane was distilled from CaH₂. Water was distilled, before being deoxygenated by bubbling with N₂ overnight.

¹H NMR and ¹³C NMR were recorded using 300, 400 and 500 MHz spectrometers, with chemical shift values being reported in ppm relative to residual chloroform (δ_H = 7.27 or δ_C = 77.2) as internal standards. All coupling constants (J) are reported in Hertz (Hz).

Mass spectra were obtained using positive and negative electrospray (ES±) or gas chromatography (GC) methodology. Infra-red spectra were recorded as evaporated films or neat using a FT/IR spectrometer.

Column chromatography was carried out using 35 – 70 µ, 60A silica gel. Routine TLC analysis was carried out on aluminium sheets coated with silica gel 60 F254, 0.2 mm thickness. Plates were viewed using a 254 nm ultraviolet lamp and dipped in aqueous potassium permanganate, phosphomolybdic acid or p-anisaldehyde.
4.2. Preparation of Samarium Diiodide

Samarium diiodide was prepared by a modification of the procedure of Imamoto and Ono.\cite{3}

Samarium powder (2.00 g, 13.3 mmol, 1.2 eq) was added to an oven dried round-bottomed flask, the flask sealed and flushed with N\textsubscript{2} for 1 hour. THF (110 ml) was added (either taken from the SPS system and degassed for a further 30 min using N\textsubscript{2}, or taken directly from the laboratory still and deoxygenated using freeze-pump-thaw cycling under argon) and the resulting suspension bubbled with N\textsubscript{2} for a further 15 min. The flask was then covered with aluminium foil before iodine (2.80 g, 11.0 mmol, 1 eq) was added and the flask flushed again with N\textsubscript{2} for 10 min. The flask was stirred and heated at 60 °C for 18 hours. The approx 0.1 M solution was allowed to cool to room temperature and then used directly.
4.3. Experimental Procedures

2- Allylcyclopentanone 54\textsuperscript{[42]}

![Chemical Structure](image)

To a stirred solution of \([(\eta^3\text{-allyl})\text{PdCl}]_2\) (157 mg, 0.43 mmol, 0.025 eq) and Xantphos (498 mg, 0.86 mmol, 0.05 eq) in DMSO (20 mL) was added allyl alcohol (1.00 g, 17 mmol, 1 eq), cyclopentanone (4.35 g, 52 mmol, 3 eq) and (D,L)-proline (594 mg, 5.16 mmol, 0.30 eq). The resultant solution was heated to 70 °C for 18 hours, after which time the reaction mixture was filtered through a pad of silica eluting with 30% EtOAc in petroleum ether (40 – 60 °C). The solvent was then removed in vacuo to yield the crude product. Purification by column chromatography on silica gel eluting with 10% EtOAc in petroleum ether (40 – 60 °C) gave 54 (1.53 g, 12.3 mmol, 73%) as a colourless oil; \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 3003, 2964, 2913, 1712 (C=O), 1432, 1364, 1222, 1094; \(\delta_H\) (500 MHz, CDCl\(_3\)) 1.54-1.63 (1H, m, \(CH_a\text{H}_b\text{CH}\)), 1.77-1.85 (1H, m, \(CH_a\text{H}_b\text{C}(O)\)), 1.99-2.04 (1H, m, \(CH_a\text{H}_b\text{CH}_2\text{C}(O)\)), 2.05-2.08 (1H, m, \(CH_a\text{H}_b\text{CH}=CH_2\)), 2.09-2.16 (2H, m, \(CH+1H\) from \(CH_a\text{H}_b\text{C}(O)\)), 2.17-2.24 (1H, m, \(CH_a\text{H}_b\text{CH}\)), 2.31-2.36 (1H, m, \(CH_a\text{H}_b\text{C}(O)\)), 2.50-2.55 (1H, m, \(CH_a\text{H}_b\text{CH}=CH_2\)), 5.06 (2H, m, \(CH=CH_2\)), 5.74-5.82 (1H, m, \(CHF=CH_2\)); \(\delta_C\) (75 MHz, CDCl\(_3\)) 20.7 (CH\(_2\)), 29.0 (CH\(_2\)), 33.9 (CH\(_2\text{CH}=CH_2\)), 38.2 (CH\(_2\text{C}(O)\)), 48.6 (CH), 116.4 (CH=CH\(_2\)), 135.9 (CH=CH\(_2\)), 220.6 (C(O)); \(m/z\) (GC-MS) 124 (M, 40), 67 (100), 39 (57), 96 (49), 55 (37), 81 (26); (Found: (M), 124.0882. C\(_8\)H\(_{12}\)O requires M, 124.0883).
To a stirred solution of 2-allylcyclopentanone (883 mg, 7.12 mmol, 1 eq) in CH$_2$Cl$_2$ (22 mL) was added anhydrous NaHCO$_3$ (1.20 g, 14.2 mmol, 2 eq) followed by the dropwise addition of 77 % m-CPBA (1.76 g, 7.83 mmol, 2.2 M solution in CH$_2$Cl$_2$, 1.1 eq). The reaction was stirred at room temperature for 18 hours. The reaction was then quenched with saturated aqueous NaHCO$_3$ solution (20 mL), before being extracted with Et$_2$O (3 × 20 mL). The organic layers were combined and washed with H$_2$O (10 mL), then saturated NaHCO$_3$ (10 mL) before being dried (Na$_2$SO$_4$) and concentrated in vacuo to yield the crude product. Purification by column chromatography on silica gel eluting with 30% EtOAc in petroleum ether (40 – 60 °C) gave 53 (647 mg, 4.62 mmol, 65%) as a colourless oil; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2936, 1734 (C=O), 1243, 1046, 920; $\delta_H$ (400 MHz, CDCl$_3$) 1.50-1.59 (2H, m, CH$_2$H$_2$), 1.79-1.87 (1H, m, CH$_2$H$_2$C(O)), 1.88-1.96 (1H, m, CH$_2$H$_2$C(O)), 2.34-2.43 (1H, m, CH$_2$H$_2$CH=CH$_2$), 2.44-2.52 (2H, m, CH$_2$H$_2$C(O) + 1H from CH$_2$H$_2$CH=CH$_2$), 2.55-2.63 (1H, m, CH$_2$H$_2$C(O)), 4.31-4.38 (1H, m, CH), 5.12-5.18 (2H, m, CH=CH$_2$), 5.82 (1H, ddt, $J$ 17.3, 10.2, 7.1, CH=CH$_2$); $\delta_C$ (100 MHz, CDCl$_3$) 18.4 (CH$_2$), 27.2 (CH$_2$), 29.5 (CH$_2$C(O)), 40.0 (CH$_2$CH=CH$_2$), 79.8 (CH), 118.6 (CH=CH$_2$), 132.6 (CH=CH$_2$), 171.7 (C(O)); m/z (GC mode) 158 (M + NH$_4$), 99 (100), 71 (63), 55 (29); (Found: (M + NH$_4$), 158.1175. C$_8$H$_{16}$O$_2$N requires M, 158.1176).
6-Allyl-6-methyltetrahydro-2H-pyran-2-one 74

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{CH}_2
\end{align*}
\]

To a flask, degassed with N₂, was added NiI₂ (48 mg, 0.15 mmol, 2 mol%) before cooling to 0 °C. SmI₂ (0.1 M in THF, 76 mL, 7.60 mmol, 4 eq) was added and the resultant solution stirred for 5 min. Once complete, Methyl 5-oxohexanoate (300 mg, 1.90 mmol, 1 eq) was added, followed immediately by the dropwise addition of allyl bromide (1.1 M in THF, 19 mL, 2.09 mmol, 1.1 eq) over 30 min. The reaction was monitored by TLC and once complete the flask was opened to air until the reaction mixture decolourised. After the addition of a saturated solution of Rochelle’s salt (20 mL), the aqueous layer was separated and extracted with Et₂O (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL), dried (Na₂SO₄) and concentrated in vacuo to yield the crude product. Purification by flash chromatography on silica gel eluting with 30% EtOAc in petroleum ether (40 – 60 °C) gave 74 (286 mg, 1.86 mmol, 98%) as a colourless oil; \( \nu_{\text{max}} \) (neat)/cm⁻¹ 3076, 2977, 2945, 1728 (C=O), 1640, 1453, 1380, 1359, 1328, 1298, 1242, 1173, 1140, 1096, 1053, 999, 927, 852; \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 1.39 (3H, s, CH₃), 1.65-1.71 (1H, m, 1H from CH₂), 1.79-1.84 (1H, m, 1H from CH₂), 1.87-1.93 (2H, m, CH₂CH₂C(O)), 2.47-2.58 (2H, m, CH₂C(O)), 5.13-5.19 (2H, m, CH=CH₂), 5.82 (1H, dddd, J 24.2 14.6 10.1 7.3, CH=CH₂); \( \delta_{\text{C}} \) (100 MHz, CDCl₃) 16.5 (CH₂), 26.3 (CH₃), 29.3 (CH₂C(O)), 31.4 (CH₂), 46.1 (CH₂CH=CH₂), 83.6 (C), 119.4 (CH=CH₂), 132.3 (CH=CH₂), 171.2 (C(O)); m/z (ES+ mode) 155 ((M + H), 100), 309 (41), 177 ((M + Na), 5); (Found: (M + Na), 177.0878. C₉H₁₄O₂Na requires M, 177.0886).
General procedure A: Cross Metathesis

6-Cinnamyl-6-methyltetrahydro-2H-pyran-2-one 78

An oven-dried one-piece flask and condenser was thoroughly flushed with N\textsubscript{2} before the addition of Grubbs 2\textsuperscript{nd} generation catalyst (22 mg, 0.024 mmol, 1 mol\%). To this was added 6-allyltetrahydro-2H-pyran-2-one 74 (384 mg, 2.49 mmol, 1 eq) dissolved in CH\textsubscript{2}Cl\textsubscript{2} (1 mL), followed by cis-stilbene (721 mg, 3.94 mmol, 3 eq). The reaction mixture was refluxed at 40 °C for 24 hours, whilst periodically maintaining a consistent solvent level. Once complete, the solvent was removed in vacuo to yield the crude product. Purification by flash chromatography on silica gel eluting with 50% Et\textsubscript{2}O in petroleum ether (40 – 60 °C) gave 78 (205 mg, 0.69 mmol, 53%) as an off-white solid. Removal of the ruthenium residues from the product was effected by treatment of the compound in Et\textsubscript{2}O with activated charcoal and stirring for 24 hours. The product was obtained following filtration through celite; \(\nu\text{max} \text{ (neat)/cm}^{-1}: 3476, 2958, 1724 \text{ (C=O)}, 1496, 1450, 1379, 1325, 1233, 1090, 1052, 979, 923; \delta \text{H (400 MHz, CDCl}_3) 1.34 \text{ (3H, s, C}_3\text{H}_3), 1.57-1.68 \text{ (2H, m, C}_2\text{H}_2), 1.75-1.86 \text{ (2H, m, C}_2\text{H}_2\text{C}(O)), 2.35-2.46 \text{ (2H, m, C}_2\text{H}_2\text{C}(O)), 2.50 \text{ (2H, d, J 7.3, C}_2\text{H}_2\text{CH=CHPh)}, 6.13 \text{ (1H, dt, J 15.8 7.3, CH=CHPh), 6.39 \text{ (1H, d, J 15.8, CH=CHPh)}, 7.09-7.30 \text{ (5H, m, Ar-H)}; \delta \text{C (100 MHz, CDCl}_3) 16.6 \text{ (CH}_2), 26.5 \text{ (CH}_3), 29.4 \text{ (CH}_2\text{C}(O)), 31.7 \text{ (CH}_2), 45.4 \text{ (CH}_2\text{CH=CHAr), 84.1 \text{ (C), 123.8 (CH=CHAr), 126.2 (Ar-C), 127.5 (Ar-CH), 128.6 (Ar-CH), 134.3 (CH=CHAr), 137.0 (Ar-C), 171.3 (C(O)); m/z (ES+ mode) 253 ((M + Na), 100), 483 (44); (Found: (M + Na), 253.1211. C\textsubscript{15}H\textsubscript{18}O\textsubscript{2}Na requires M, 253.1199).
(E)-6-Methyl-6-(3-(m-tolyl)allyl)tetrahydro-2H-pyran-2-one 82

![Chemical Structure](image)

As for general procedure A, reaction of Grubbs 2\textsuperscript{nd} generation catalyst (15 mg, 0.0175 mmol, 1 mol\%), 6-allyl-6-methyltetrahydro-2H-pyran-2-one 74 (270 mg, 1.75 mmol, 1 eq), and 3-methyl-1-vinylbenzene (414 mg, 3.51 mmol, 4 eq), after workup and purification by flash chromatography on silica gel eluting with 15\% EtOAc in petroleum ether (40 – 60 °C), gave 82 (207 mg, 0.84 mmol, 48\%) as a colourless oil; ν\textsubscript{max} (neat)/\text{cm}^{-1} 2950, 1723 (C=O), 1602, 1453, 1290, 1245, 1053; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 1.33 (3H, s, CH\textsubscript{3}), 2.26 (3H, s, Ar\text{–}CH\textsubscript{3}), 2.31-2.45 (2H, m, CH\textsubscript{2}(O)), 2.48 (2H, d, J 7.8, CH\textsubscript{2}CH=CHAr), 6.11 (1H, dt, J 15.9, 7.8 CH=CHAr), 6.35 (1H, d, J 15.9, CH=CHAr), 6.97 (1H, d, J 7.31, Ar-H), 7.10 (3H, m, 3 × Ar-H); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 16.6 (CH\textsubscript{3}), 21.4 (Ar-CH\textsubscript{3}), 26.5 (CH\textsubscript{3}), 29.4 (CH\textsubscript{2}), 31.7 (CH\textsubscript{2}), 45.4 (CH\textsubscript{2}CH=CHAr), 84.1 (C), 123.5 (CH=CHAr), 126.8 (2 × Ar-CH), 128.3 (2 × Ar-CH), 134.3 (CH=CHAr), 136.9 (Ar-C), 138.2 (Ar-C), 171.3 (C(O)); m/z (ES\textsuperscript{+} mode) 267 ((M + Na); (found: (M + Na), 267.1365. C\textsubscript{16}H\textsubscript{20}O\textsubscript{2}Na requires M, 267.1356).

(E)-6-(3-(4-Bromophenyl)allyl)-6-methyltetrahydro-2H-pyran-2-one 79

![Chemical Structure](image)

As for general procedure A, reaction of Grubbs 2\textsuperscript{nd} generation catalyst (7 mg, 0.0085 mmol, 0.5 mol\%), 6-allyl-6-methyltetrahydro-2H-pyran-2-one 74 (261 mg, 1.69 mmol, 1 eq), and 1-bromo-4-vinylbenzene (950 mg, 5.19 mmol, 3 eq), after workup and purification by flash chromatography on silica gel eluting with 5\% Et\textsubscript{2}O in
CHCl₃, gave 79 (186 mg, 0.60 mmol, 36%) as a white solid; νₘₐₓ (neat)/cm⁻¹ 2935, 1726 (C=O), 1489, 1359, 1290, 1230, 1068, 1006; δₜ (400 MHz, CDCl₃) 1.41 (3H, s, CH₃), 1.69-1.75 (1H, m, CCH₂H₆), 1.81-1.85 (1H, m, CCH₂H₆), 1.86-1.95 (2H, m, CH₂), 2.42-2.53 (2H, m, CH₂C(O)), 2.55-2.61 (2H, m, CH₂CH=CHAr), 6.21 (1H, dt, J 15.9 7.6, CH=CHAr), 6.41 (1H, d, J 15.9, CH=CHAr), 7.23 (2H, d, J 8.3, Ar-H), 7.43 (2H, d, J 8.3, Ar-H); δC (100 MHz, CDCl₃) 16.9 (CH₂), 26.8 (CH₃), 29.6 (CH₂C(O)), 32.1 (CH₂), 45.7 (CH₂CH=CHAr), 84.1 (C), 121.5 (Ar-CHBr), 125.0 (CH=CHAr), 128.0 (Ar-CH), 131.9 (Ar-CH), 133.4 (CH=CHAr), 136.2 (Ar-C), 171.4 (C(O)); m/z (ES+ mode) 331 ((MBr⁷⁹ + Na), 100), 333 ((MBr⁸¹ + Na), 100), 349 (16), 347 (13), 233 (13), 235 (9); (Found: (M + Na), 331.0302. C₁₅H₁₇O₂BrNa requires M, 331.0304).

(⁷)-6-(3-(4-Methoxyphenyl)allyl)-6-methyltetrahydro-2H-pyran-2-one 80

As for general procedure A, reaction of Grubbs 2nd generation catalyst (5 mg, 0.0062 mmol, 1 mol%), 6-allyl-6-methyltetrahydro-2H-pyran-2-one 74 (95 mg, 0.62 mmol, 1 eq), and 1-methoxy-4-vinylbenzene (248 mg, 1.85 mmol, 3 eq), after workup and purification by flash chromatography on silica gel eluting with 30% EtOAc in petroleum ether (40 – 60 °C), gave 80 (92 mg, 0.35 mmol, 57%) as a colourless oil; νₘₐₓ (neat)/cm⁻¹ 2925, 1733 (C=O), 1605, 1504, 1243, 1173, 1088, 1049, 1028; δₜ (400 MHz, CDCl₃) 1.41 (3H, s, CH₃), 1.67-1.73 (1H, m, 1H from CH₂), 1.82-1.94 (3H, m, 3H from CH₂), 2.42-2.52 (2H, m, CH₂C(O)), 2.55-2.57 (2H, m CH₂CH=CHAr), 3.81 (3H, s, OCH₃), 6.05 (1H, dt, J 15.9 7.6, CH=CHAr), 6.41 (1H, d, J 15.9, CH=CHAr), 6.85 (2H, d, J 8.8, Ar-H), 7.30 (2H, d, J 8.8, Ar-H); δC (100 MHz, CDCl₃) 16.6 (CH₂), 26.5 (CH₃), 29.3 (CH₂C(O)), 31.6 (CH₂), 45.4 (CH₂CH=CHAr), 55.3 (OCH₃), 84.1 (C), 113.9 (Ar-CH), 121.5 (CH=CHAr), 127.3 (Ar-CH), 129.8 (Ar-C), 133.6 (CH=CHAr), 159.1 (Ar-COMe), 171.6 (C(O)); m/z (ES+ mode) 283 ((M + Na), 100), 543 (15), 299 (9); (Found: (M + Na), 283.1296. C₁₅H₂₀O₃Na requires M, 283.1305).
(E)-6-(3-(2,5-dimethylphenyl)allyl)-6-methyltetrahydro-2H-pyran-2-one 81

As for general procedure A, reaction of Grubbs 2nd generation catalyst (17 mg, 0.02 mmol, 1 mol%), 6-allyl-6-methyltetrahydro-2H-pyran-2-one 74 (310 mg, 2.01 mmol, 1 eq), and 1,4-dimethyl-2-vinylbenzene (664 mg, 5.03 mmol, 3 eq), after workup and purification by flash chromatography on silica gel eluting with 30% EtOAc in petroleum ether (40 – 60 °C), gave 81 (194 mg, 0.74 mmol, 37%) as a colourless oil; νmax (neat)/cm⁻¹ 2920, 2851, 1729 (C=O), 1455, 1378, 1239, 1132, 1089, 1052, 971, 808; δH (400 MHz, CDCl₃) 1.35 (3H, s, CH₃), 1.62-1.68 (2H, m, CH₂), 1.76-1.88 (2H, m, CH₂CH₂C(O)), 2.22 (3H, s, Ar-CH₃), 2.24 (3H, s, Ar-CH₃), 2.35-2.48 (2H, m, CH₂C(O)), 2.52 (2H, d, J 8.6, CH₂CH=CHAr), 5.98 (1H, dt, J 15.6 7.6, CH=CHAr), 6.58 (1H, d, J 15.6, CH=CHAr), 6.89 (1H, d, J 8.9, Ar-H), 6.96 (1H, d, J 7.8, Ar-H), 7.16 (1H, s, Ar-H); δC (100 MHz, CDCl₃) 16.6 (CH₂), 19.4 (CH₃), 21.0 (CH₃), 26.5 (CH₂), 29.4 (CH₂C(O)), 31.7 (CH₂), 45.7 (CH₂CH=CHAr), 84.1 (C), 124.9 (CH=CHAr), 126.2 (Ar-CH), 128.2 (Ar-CH), 130.0 (Ar-C), 130.2 (Ar-CH), 132.0 (CH=CHAr), 135.5 (Ar-C), 135.9 (Ar-C), 171.3 (CO); m/z (ES+ mode) 281 [(M + Na), 100], 313 (28), 282 (19); (Found: (M + Na), 281.1512. C₁₇H₂₂O₂Na requires M, 281.1512).
General procedure B: SmI$_2$-H$_2$O cyclisation and DMP oxidation:

*rac-(1R, 5S, 7R)-5,7-Dimethyl-8-oxabicyclo[3.2.1]octan-1-ol 83*

To a stirred solution under N$_2$ at room temperature of 6-allyl-6-methyltetrahydro-2H-pyran-2-one 74 (25 mg, 0.16 mmol, 1 eq) in THF (2 mL) was added distilled H$_2$O (2.30 mL). To this reaction mixture was then added SmI$_2$ (0.1 M in THF, 13.0 mL, 1.30 mmol, 8 eq) dropwise. The reaction was left to stir until decolourisation had occurred. The reaction was quenched by opening the flask to air and by adding aqueous saturated Rochelle’s salt (10 mL). The aqueous layer was extracted with Et$_2$O (3 × 20 mL), washed with brine and the organic extracts combined, dried (Na$_2$SO$_4$) and concentrated in *vacuo* to yield the crude product. The crude product was dissolved in dry CH$_2$Cl$_2$ (2 mL), cooled to 0 °C and the Dess-Martin periodinane (103 mg, 0.24 mmol, 1.5 eq) was added. The reaction was stirred for 12 hours whilst allowing to warm to room temperature. The reaction was then quenched by the addition of a saturated solution of Na$_2$S$_2$O$_3$ (2 mL) and NaHCO$_3$ (2 mL), whilst stirring for 30 min. The aqueous layer was extracted with Et$_2$O (3 × 20 mL), washed with brine and the organic extracts combined, dried (Na$_2$SO$_4$) and concentrated in *vacuo* to yield the crude product. Purification by column chromatography on silica gel eluting with 30% Et$_2$O in CHCl$_3$ gave 83 (19 mg, 0.12 mmol, 68%) as a colourless oil and as 1:1 mixture of diastereoisomers; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3397 (OH), 2961, 2873, 1450, 1376, 1227, 1205, 1112, 1030, 952, 922, 872, 792; For a 1:1 mixture of diastereoisomers $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 0.93 (3H, d, J 6.8, CHCH$_3$ from 1 diastereoisomer), 1.03 (3H, d, J 7.1, CHCH$_3$ from 1 diastereoisomer), 1.20-1.26 (1H, m, CH$_4$H$_6$CO(OH) from 1 diastereoisomer), 1.29 (3H, s, CH$_3$ from 1 diastereoisomer), 1.32 (3H, s, CH$_3$ from 1 diastereoisomer), 1.34-1.35 (1H, m, CHCH$_3$H$_6$ from 1 diastereoisomer), 1.35-1.43 (1H, m, CH$_4$H$_6$CO(OH) from 1 diastereoisomer), 1.40-1.45 (2H, m, CHCH$_3$H$_6$ from 1 diastereoisomer and CHCH$_3$H$_6$
from 1 diastereoisomer), 1.51-1.60 (1H, m, CH\textsubscript{CH} \textsubscript{a}H\textsubscript{b} from 1 diastereoisomer), 1.63-1.69 (2H, m, CH\textsubscript{2}COMe from 1 diastereoisomer), 1.72-1.76 (2H, m, CH\textsubscript{2} from both diastereoisomers), 1.85-1.88 (CH\textsubscript{2}COMe from 1 diastereoisomer), 1.97-2.02 (1H, m, CH from 1 diastereoisomer), 2.05-2.13 (2H, m, 1H from CH\textsubscript{a}H\textsubscript{b}CO(OH) from 1 diastereoisomer), 2.12-2.19 (1H, m, 1H from CH\textsubscript{a}H\textsubscript{b}CO(OH) from 1 diastereoisomer); \( \delta \) \textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 13.0 (CH\textsubscript{CH} \textsubscript{3} from 1 diastereoisomer), 17.4 (CH\textsubscript{CH} \textsubscript{3} from 1 diastereoisomer), 18.7 (CH\textsubscript{2} from 1 diastereoisomer), 18.8 (CH\textsubscript{2} from 1 diastereoisomer), 27.2 (CH\textsubscript{3} from both diastereoisomers), 30.3 (CH\textsubscript{CH} \textsubscript{3} from 1 diastereoisomer), 30.9 (CH\textsubscript{2}COMe from 1 diastereoisomer), 35.4 (CH\textsubscript{CH} \textsubscript{2} from 1 diastereoisomer), 35.7 (CH\textsubscript{2}COMe from 1 diastereoisomer), 38.5 (CH from 1 diastereoisomer), 41.5 (CH\textsubscript{2}CO(OH) from 1 diastereoisomer), 43.4 (CH from 1 diastereoisomer), 44.3 (CH\textsubscript{2}CO(OH) from 1 diastereoisomer), 65.8 (COMe from 1 diastereoisomer), 79.2 (COMe from 1 diastereoisomer), 104.1 (CO(OH) from 1 diastereoisomer), 105.1 (CO(OH) from 1 diastereoisomer); m/z (ES+ mode) 179 ((M + Na), 100), 195 (28); (Found: (M + Na), 179.1039. C\textsubscript{9}H\textsubscript{16}O\textsubscript{2}Na requires M, 179.1043).

**rac-(1R, 5S, 7R)-7-Benzyl-5-methyl-8-oxabicyclo[3.2.1]octan-1-ol 84**

![84](image)

As for general procedure B, reaction of 6-cinnamyl-6-methyltetrahydro-2H-pyran-2-one 78 (44 mg, 0.19 mmol, 1 eq) with SmI\textsubscript{2} (0.1 M in THF, 15.60 mL, 1.56 mmol, 8 eq) and H\textsubscript{2}O (2.80 mL) after workup gave the crude diol. Oxidation of the crude reaction mixture using the Dess-Martin periodinane (134 mg, 0.32 mmol, 1.5 eq), after workup and purification by column chromatography on silica gel eluting with 30% Et\textsubscript{2}O in CHCl\textsubscript{3}, gave 84 (37 mg, 0.16 mmol, 84%) as a colourless oil and as a 4:1 mixture of diastereoisomers; \( \nu \)\textsubscript{max} (neat)/cm\textsuperscript{-1} 3380 (OH), 2928, 1601, 1494, 1452, 1355, 1274, 1199, 1029, 974, 897, 721, 698; For a 4:1 mixture of diastereoisomers \( \delta \)\textsubscript{H}
(400 MHz, CDCl$_3$) 1.22 (3H, s, CH$_3$), 1.27-1.34 (1H, m, CH$_3$CH$_2$CO(OH)), 1.42 (1H, dd, $J$ 12.9, 7.6, CHCH$_2$H$_b$), 1.54-1.62 (1H, m, CH$_3$CH$_2$COMe), 1.64-1.67 (1H, m, 1H from CH$_2$), 1.68-1.77 (3H, m, 1H from CHCH$_2$H$_b$ and 1H from CH$_3$H$_a$CO(OH) and 1H from CH$_2$), 1.80-1.91 (1H, m, CH$_a$CH$_b$COMe), 2.24-2.31 (1H, m, C$_7$H$_2$Ar), 2.58 (1H, t, $J$ 13.4, C$_7$H$_a$H$_b$Ar from major diastereoisomer), 2.87 (1H, dd, $J$ 13.4 3.8, CH$_a$H$_b$Ar from major diastereoisomer), 3.06 (1H, dd, $J$ 12.6, 3.3, CH$_a$H$_b$Ar from minor diastereoisomer), 7.11-7.24 (5H, m, Ph-H); For the major diastereoisomer $\delta$C (100 MHz, CDCl$_3$) 18.9 (C$_7$H$_2$), 27.2 (CH$_3$), 31.4 (CH$_3$CO(OH)), 34.8 (C$_7$H$_2$Ar), 35.6 (CH$_3$COMe), 39.4 (CHCH$_2$), 50.7 (CH), 79.4 (COMe), 104.6 (CO(OH)), 126.0 (Ar-CH), 128.4 (Ar-CH), 129.1 (Ar-CH), 140.9 (Ar-C); m/z (ES+ mode) 255 ((M + Na), 100), 287 (20); (Found: (M + Na), 255.1350. C$_{15}$H$_{20}$O$_2$Na requires M, 255.1356).

(1R, 5S, 7R)-5-methyl-7-(3-methylbenzyl)-8-oxabicyclo[3.2.1]octan-1-ol 87

As for general procedure B, reaction of (E)-6-methyl-6-(3-(m-tolyl)allyl)tetrahydro-2H-pyran-2-one 82 (40 mg, 0.16 mmol, 1 eq) with SmI$_2$ (0.1 M in THF, 13.0 mL, 1.13 mmol, 8 eq) and H$_2$O (2.30 mL) after workup gave the crude diol. Following oxidation of the crude reaction mixture using the Dess-Martin periodinane (103 mg, 0.24 mmol, 1.5 eq), after workup and purification by column chromatography on silica gel eluting with 5% Et$_2$O in CHCl$_3$, gave 87 (28 mg, 0.12 mmol, 72%) as a colourless oil and as a 3:1 mixture of diastereoisomers; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3378 (OH), 2930, 1703, 1608, 1451, 1274, 1103, 940, 780, 697; For a 3:1 mixture of diastereoisomers $\delta$H (400 MHz, CDCl$_3$) 1.22 (3H, s, CH$_3$), 1.26-1.33 (2H, m, CH$_2$), 1.40-1.48 (2H, m, 1H from CH$_2$ and 1H from CH$_2$COH), 1.54-1.58 (1H, m, CH$_2$), 1.65-1.77 (3H, m, 1H from CH$_2$COH and 2H from CH$_2$), 2.23-2.28 (1H, m,
CHCH₂Ar), 2.25 (3H, s, ArCH₃), 2.50-2.57 (1H, m, CH₃CH₆Ar from major diastereoisomer), 2.85 (1H, dd, J 13.6, 4.29, CH₂H₂Ar from major diastereoisomer), 3.02 (1H, dd, J 13.1, 3.8, CH₂CH₆Ar from minor diastereoisomer), 6.93-7.12 (4H, m, Ar-H); δC (100 MHz, CDCl₃) 19.0 (CH₂), 21.4 (CH₃Ar), 27.3 (CH₃), 31.5 (CH₂), 34.7 (CH₂), 35.4 (CH₂Ar), 39.5 (CHCH₂), 50.8 (CH), 79.4 (COMe), 104.7 (CO(OH)), 125.5 (Ar-CH), 126.1 (Ar-CH), 128.3 (Ar-CH), 129.4 (Ar-CH), 138.0 (Ar-C), 140.8 (Ar-C); m/z (ES⁺ mode) 269 ((M + Na), 100); (Found: (M + Na), 269.1511. C₁₆H₂₂O₂Na requires M, 269.1512).

**rac-(1R, 5S, 7R)-7-(4-Bromobenzyl)-5-methyl-8-oxabicyclo[3.2.1]octan-1-ol 86**

[Diagram of 86]

As for general procedure B, reaction of (E)-6-(3-(4-bromophenyl)allyl)-6-methyltetrahydro-2H-pyran-2-one 79 (34 mg, 0.11 mmol, 1 eq) with SmI₂ (0.1 M in THF, 8.90 mL, 1.0 mmol, 8 eq) and H₂O (1.60 mL) after workup gave the crude diol. Oxidation of the crude reaction mixture using the Dess-Martin periodinane (95 mg, 0.22 mmol, 1.5 eq), after workup and purification by column chromatography on silica gel eluting with 50% Et₂O in CHCl₃ gave 86 (29 mg, 0.094 mmol) 84% as a white solid and as a 4:1 mixture of diastereoisomers; νmax (neat)/cm⁻¹ 3370 (OH), 2929, 1486, 1452, 1351, 1274, 1204, 1104, 1011, 796; For a 4:1 mixture of diastereoisomers δH (400 MHz, CDCl₃) 1.30 (3H, s, CH₃), 1.33-1.39 (1H, m, CH₃CH₆Ar), 1.47 (1H, dd, J 12.9, 7.6, CHCH₆Ar), 1.52-1.58 (1H, m, CH₃CH₆Ar), 1.61-1.69 (1H, m, CH₃CH₆Ar), 1.75-1.87 (3H, m, 1H from CHCH₆Ar + 2H from CH₂), 1.92-1.96 (1H, m, CH₃CH₆Ar), 2.26-2.35 (1H, m, CHCH₂Ar), 2.61 (1H, dd, J 13.6, 11.6, CH₃CH₆Ar from major diastereoisomer), 2.89 (1H, dd, J 13.6 4.0, CH₂H₂Ar from major diastereoisomer), 3.00 (1H, br s, OH), 3.07 (1H, dd, J 12.1, 2.8, CH₂H₂Ar from minor diastereoisomer), 7.09 (2H, d, J 8.3, Ar-H), 7.41 (2H, d, J 8.3, Ar-H); δC (100 MHz, CDCl₃) 18.9 (CH₂), 27.1 (CH₃), 31.5
(CH₂CO(OH)), 34.2 (CH₂Ar), 35.6 (CH₂COMe), 39.3 (CHCH₂), 50.5 (CH), 79.5 (COMe), 104.5 (CO(OH)), 119.8 (Ar-CBr), 130.2 (Ar-CH), 131.5 (Ar-CH), 139.8 (Ar-C); m/z (ES+ mode) 333 ((M\text{Br79} + Na), 100), 335 ((M\text{Br81} + Na), 100), 177 (26), 255 (24), 301 (22), 253 (15); (Found: (M\text{Br79}+ Na), 333.0461. C₁₅H₁₉O₂BrNa requires M, 333.0461).

\textit{rac-(1R, 5S, 7R)-7-(4-Methoxybenzyl)-5-methyl-8-oxabicyclo[3.2.1]octan-1-ol 85}

As for general procedure B, reaction of (\textit{E})-6-(3-(4-methoxyphenyl)allyl)-6-methyltetrahydro-2H-pyran-2-one 80 (30 mg, 0.14 mmol, 1 eq) with SmI₂ (0.1 M in THF, 11.1 mL, 0.11 mmol, 8 eq) and H₂O (1.90 mL) after workup gave the crude diol. Oxidation of the crude reaction mixture using the Dess-Martin periodinane (86 mg, 0.20 mmol, 1.5 eq), after workup and purification by column chromatography on silica gel eluting with 30% Et₂O in CHCl₃ gave 85 (27 mg, 0.10 mmol, 89%) as a colourless oil and as a 4:1 mixture of diastereoisomers; ν\text{max} (neat)/cm⁻¹ 3389 (OH), 2929, 1611, 1506, 1453, 1246, 1177, 1103, 1032, 940, 802; For a 4:1 mixture of diastereoisomers δH (400 MHz, CDCl₃) 1.20-1.26 (1H, m, CHaCHbCOMe), 1.30 (3H, s, CH₃), 1.37 (1H, dd, J 13.1 4.8, CH₄H₆CH), 1.53-1.58 (2H, m, 1H from CH₄H₆CO(OH) and 1H from CH₄CH₆COMe), 1.62-1.69 (2H, m, CH₂), 1.74 (1H, dd, J 13.1, 4.5, CH₄H₆CH), 1.83-1.89 (1H, m, CH₄H₆CO(OH)), 2.27-2.33 (1H, m, CH₄), 2.60 (1H, dd, J 13.6, 11.1, CH₄H₆Ar from major diastereoisomer), 2.89 (1H, dd, J 13.6, 4.3, CH₄H₆Ar from major diastereoisomer), 3.07 (1H, dd, J 12.9, 3.5, CH₄H₆Ar from minor diastereoisomer), 3.80 (3H, s, OCH₃), 6.84 (2H, d, J 8.6, Ar-CH₄), 7.14 (2H, d, J 8.6, Ar-CH₄); δC (100 MHz, CDCl₃) 27.2 (CH₃), 31.5 (CH₂CO(OH)), 33.9 (CH₂Ar), 35.7 (CH₂COMe), 36.5 (CH₂), 39.5 (CHCH₂), 51.0 (CH), 55.3 (ArOCH₃), 79.4 (COMe), 104.6 (CO(OH)), 113.8 (Ar-CH), 129.4 (Ar-CH), 129.9 (Ar-COMe),
133.0 (Ar-C); m/z (ES+ mode) 285 ((M + Na), 100), 286 (15); (Found: (M + Na), 285.1471. C_{16}H_{22}O_{3}Na requires M, 285.1461).

(1R, 5S, 7R)-7-(2,5-Dimethylbenzyl)-5-methyl-8-oxabicyclo[3.2.1]octan-1-ol 88

As for general procedure B, reaction of (E)-6-(3-(2,5-dimethylphenyl)allyl)-6-methyltetrahydro-2H-pyran-2-one 81 (53 mg, 0.22 mmol, 1 eq) in THF (3 ml) with SmI₂ (0.1 M in THF, 17.6 ml, 1.76 mmol, 8 eq) and distilled H₂O (3.1 mL) after workup gave the crude diol. Oxidation of the crude reaction mixture using the Dess-Martin periodinane (180 mg, 0.46 mmol, 1.5 eq), after workup and purification by column chromatography on silica gel eluting with 50% Et₂O in CHCl₃ gave 88 (39 mg, 0.68 mmol, 68%) as a colourless solid and as a 3:1 mixture of diastereoisomers; ν max (neat)/cm⁻¹: 3368 (OH), 2924, 2859, 1615, 1501, 1376, 1273, 1099, 1027, 939, 855, 734; δ_H (400 MHz, CDCl₃): 1.23 (3H, s, CH₃), 1.31 (1H, ddd, J 12.0, 8.8, 4.0 CH₃CH₆COMe), 1.46-1.56 (2H, m, 1H from CH₃CH₆COMe + 1H from CHCH₆H₆), 1.57-1.66 (3H, m, CH₃CH₆COOH and 2H from CH₂), 1.71-1.78 (1H, m, CHCH₆H₆), 1.94-1.95 (1H, dd, CH₃CH₆COOH), 2.22 (3H, s, Ar-CH₃), 2.23 (3H, s, Ar-CH₃), 2.53 (1H, dd, J 11.9, 1.8, CH₃CH₆Ar from major diastereoisomer), 2.66 (1H, br s, OH), 2.83 (1H, dd, J 11.9, 3.5, CH₃CH₆Ar from major diastereoisomer), 6.85 (1H, d, J 7.8, Ar-H), 6.89 (1H, s, Ar-H), 6.97 (1H, d, J 7.6, Ar-H); δ_C (100 MHz, CDCl₃): 19.0 (CH₂), 19.1 (Ar-CH₃), 21.0 (Ar-CH₃), 27.2 (CH₃), 31.4 (CH₂CO(OH)), 31.9 (CH₂Ar), 35.7 (CH₂COMe), 39.4 (CHCH₂), 49.3 (CH), 79.5 (COMe), 104.7 (CO(OH)), 126.8 (Ar-CH), 129.7 (Ar-CH), 130.3 (Ar-CH), 132.8 (Ar-C), 135.3 (Ar-C), 138.8 (Ar-C); m/z (ES+ mode) 283 ((M + Na), 100), 315 (20); Found: (M + Na), 283.1669. C_{17}H_{24}O_{2}Na requires M, 283.1669.
6-Allyl-3,3-dimethyltetrahydro-2H-pyran-2-one 65

A solution of LDA was prepared by adding n-butyllithium (5.9 mL, 9.44 mmol, 1.2 eq, 1.6 M solution in hexane) to diisopropylamine (955 mg, 9.44 mmol, 1.2 eq) in THF (25 mL) at -78 °C under N₂ and the solution stirred for 1 hour. To this solution was added 6-6-allyltetrahydro-2H-pyran-2-one 53 (1.10 g, 7.87 mmol, 1 eq) dissolved in THF (10 mL) over 1 hour using a syringe pump and the resulting solution stirred for a further 1 hour. At this point, MeI (1.39 g, 9.44 mmol, 1.2 eq) was added and the reaction allowed to warm to room temperature over 18 hours. The reaction was quenched by the addition of aqueous saturated NH₄Cl (40 mL) and the aqueous layer was separated and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (40 mL), dried (Na₂SO₄) and concentrated in vacuo. The crude product was subsequently dissolved in THF (10 mL) and added over 1 hour using a syringe pump to a solution of LDA (8.23 mmol, 1.2 eq). Following this MeI (1.17 g, 8.23 mmol, 1.2 eq) was added and the reaction allowed to warm to room temperature over 18 hours. The reaction was quenched by the addition of aqueous saturated NH₄Cl (40 mL) and worked up following the above procedure. Purification by column chromatography on silica gel eluting with 30% EtOAc in petroleum ether (40 – 60 °C) gave 65 (1.02 g, 6.10 mmol, 76%) as a colourless oil; ν_max (neat)/cm⁻¹ 2936, 1728 (C=O), 1472, 1385, 1287, 1138, 996, 920; δ_H (400 MHz, CDCl₃) 1.21 (3H, s, CH₃), 1.23 (3H, s, CH₃), 1.55-1.76 (4H, m, 2 × CH₂), 2.28-2.35 (1H, m, CH₉CH₉CH=CH₂), 2.37-2.44 (1H, m, CH₉CH₉CH=CH₂), 4.25-4.31 (1H, m, CH), 5.05-5.10 (2H, m, CH=CH₂), 5.75 (1H, ddt, J 17.1, 10.3, 7.0, CH=CH₂); δ_C (100 MHz, CDCl₃) 25.3 (CH₂), 27.7 (CH₃), 27.8 (CH₃), 34.4 (CH₂), 38.0 (C), 40.3 (CH₂CH=CH₂), 80.7 (CH), 118.6 (CH=CH₂), 132.6 (CH=CH₂), 177.4 (C(O)); m/z (ES+ mode) 191 ((M + Na), 100), 223 (25); (found: (M + Na), 191.1049. C₁₀H₁₆O₂Na requires M, 191.1043).
(E)-3,3-dimethyl-6-(3-(m-tolyl)allyl)tetrahydro-2H-pyran-2-one 66

As for general procedure A, reaction of Grubbs 2nd generation catalyst (18 mg, 0.02 mmol, 1 mol%), 6-allyl-3,3-dimethyltetrahydro-2H-pyran-2-one 53 (358 mg, 2.13 mmol, 1 eq), and 1-methyl-3-vinylbenzene (750 mg, 6.39 mmol, 3 eq), after workup and purification by flash chromatography on silica gel eluting with 10 % EtOAc in petroleum ether (40 – 60 °C) gave 66 (205 mg, 0.79 mmol, 37%) as a yellow oil; \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 2961, 1721 (C=O), 1602, 1471, 1385, 1286, 1154, 1017, 968, 775, 694; \( \delta \)H (400 MHz, CDCl\(_3\)) 1.29 (3H, s, C\(_3\)H), 1.31 (3H, s, C\(_3\)H), 1.73-1.89 (4H, m, 2 \times C\(_2\)H), 2.34 (3H, s, ArC\(_3\)H), 2.49-2.68 (2H, m, C\(_2\)HCH=CHAr), 4.35-4.44 (1H, m, C\(_2\)H), 6.24 (1H, dt, J 15.8, 7.2, C=CHAr), 6.46 (1H, d, J 15.8, CH=CHAr), 7.04-7.23 (4H, m, Ar-H); \( \delta \)C (100 MHz, CDCl\(_3\)) 21.4 (Ar-C\(_3\)H), 25.5 (CH\(_2\)), 27.8 (CH\(_3\)), 27.8 (CH\(_3\)), 34.4 (CH\(_2\)), 38.0 (C), 39.6 (CH\(_2\)CH=CHAr), 81.1 (CH), 123.4 (CH=CHAr), 126.9 (Ar-CH), 128.2 (Ar-CH), 128.5 (Ar-CH), 133.6 (CH=CHAr), 137.0 (Ar-C), 138.1 (2 \times Ar-C), 177.4 (C(O)); m/z (ES+ mode) 281 ((M + Na), 100); (found: (M + Na), 281.1517. C\(_{17}\)H\(_{22}\)O\(_2\)Na requires M, 281.1512).

\[
\text{(E)-6-(3-(4-Bromophenyl)allyl)-3,3-dimethyltetrahydro-2H-pyran-2-one 67}
\]

As for general procedure A, reaction of Grubbs 2nd generation catalyst (17 mg, 0.02 mmol, 1 mol%), 6-allyl-3,3-dimethyltetrahydro-2H-pyran-2-one 53 (330 mg, 1.96 mmol, 1 eq), and 1-bromo-4-vinylbenzene (720 mg, 3.93 mmol, 3 eq), after workup and purification by flash chromatography on silica gel eluting with 10 % EtOAc in...
petroleum ether (40 – 60 °C) gave 67 (184 mg, 0.57 mmol, 29%) as a yellow oil; \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 3461, 2076, 2977, 2956, 1732 (C=O), 1641, 1453, 1381, 1242, 1140, 1053, 999, 927; \( \delta_H \) (400 MHz, CDCl\(_3\)) 1.20 (3H, s, CH\(_3\)) , 1.23 (3H, s, CH\(_3\)) , 1.61-1.81 (4H, m, 2 \( \times \) CH\(_2\)) , 2.40-2.59 (2H, m, CH\(_2\)CH=CHAr), 4.31-4.37 (1H, m, CH), 6.15 (1H, dt, J 15.8, 7.2, CH=CHAr), 6.36 (1H, d, J 15.8, CH=CHAr), 7.12-7.36 (4H, m, Ar-H); \( \delta_C \) (100 MHz, CDCl\(_3\)) 25.5 (CH\(_2\)), 39.6 (CH\(_2\)CH=CHAr), 80.8 (CH), 121.4 (Ar-Br), 125.1 (Ar-CH), 127.7 (CH=CHAr), 131.7 (CH=CHAr), 132.4 (Ar-CH), 136 (Ar-C), 177.3 (C(O)); \( m/z \) (ES\(^{+}\) mode) 345 ((M + Na), 60), 281 (25), 173 (100), 137 (55), 101 (70), 85 (25). Accurate mass could not be obtained.

\( (E)\)-6-(3-(2-Chlorophenyl)allyl)-3,3-dimethyltetrahydro-2H-pyran-2-one 68

68

As for general procedure A, reaction of Grubbs 2\(^{\text{nd}}\) generation catalyst (17 mg, 0.02 mmol, 1 mol%), 6-allyl-3,3-dimethyltetrahydro-2H-pyran-2-one 53 (330 mg, 1.96 mmol, 1 eq), and 1-chloro-2-vinylbenzene (545 mg, 3.93 mmol, 3 eq), after workup and purification by flash chromatography on silica gel eluting with 10 % EtOAc in petroleum ether (40 – 60 °C) gave 68 (240 mg, 0.86 mmol, 44%) as a yellow oil; \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 2977, 1731 (C=O), 1640, 1453, 1381, 1242, 1053, 999, 927; \( \delta_H \) (400 MHz, CDCl\(_3\)) 1.22 (3H, s, CH\(_3\)), 1.24 (3H, s, CH\(_3\)), 1.64-1.85 (4H, m, 2 \( \times \) CH\(_2\)), 2.40-2.57 (2H, m, CH\(_2\)CH=CHAr), 4.32-4.38 (1H, m, CH), 6.16 (1H, dt, J 15.9, 7.2, CH=CHAr), 6.39 (1H, d, J 15.9, CH=CHAr), 7.05-7.27 (4H, m, Ar-H); \( \delta_C \) (100 MHz, CDCl\(_3\)) 25.5 (CH\(_2\)), 27.7 (CH\(_3\)), 27.8 (CH\(_3\)), 34.4 (CH\(_2\)), 38.1 (C), 39.6 (CH\(_2\)CH=CHAr), 81.1 (CH), 125.7 (CH=CHAr), 126.5 (Ar-CH), 127.2 (Ar-CH), 131.4 (Ar-CH), 132.1 (CH=CHAr), 132.9 (Ar-CH), 133.4 (Ar-Cl) 136.9 (Ar-C), 177.5 (C(O)); \( m/z \) (ES\(^{+}\) mode) 301 ((M + Na), 100), 191 (10); (found: (M + Na), 301.0970. C\(_{10}H_{19}ClO_2Na\) requires M, 301.0966).
General procedure C: SmI$_2$-cyclisation

(1S, 2R, 4S)-2-(4-bromobenzyl)-7,7-dimethylcycloheptane-1,4-diol 70

To a stirred solution of (E)-6-(3-(4-bromophenyl)allyl)-3,3-dimethyltetrahydro-2H-pyran-2-one 67 (25 mg, 0.08 mmol, 1 eq) in THF (3 mL) at room temperature under N$_2$ was added SmI$_2$ (0.1 M in THF, 6.10 mL, 0.62 mmol, 8 eq) and distilled H$_2$O (1.10 mL). The reaction was left to stir until decolourisation had occurred. The reaction was quenched by opening the flask to air and by adding aqueous saturated Rochelle’s salt (20 mL). The aqueous layer was extracted with Et$_2$O (3 × 20 mL), washed with brine (20 mL) and the organic extracts combined, dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography on silica gel eluting with 5 % Et$_2$O in CHCl$_3$ gave 70 (19.4 mg, 0.059 mmol, 78%) as a colourless oil and as a 11:7 mixture of diastereoisomers; $\nu_{\max }$ (neat)/cm$^{-1}$ 3379 (OH), 2930, 2852, 1700, 1558, 1485, 1454, 1287, 1021; $\delta$ (400 MHz, CDCl$_3$) 0.73 (3H, s, CH$_3$), 0.84 (3H, s, CH$_3$), 1.25 (2H, m, CH$_2$), 1.44 (1H, m, CHCH$_2$CH$_3$), 1.49-1.54 (1H, m, CH$_3$, CH$_2$OCH$_2$), 1.68-1.75 (1H, m, CH$_3$CH$_2$CHOH), 2.03-2.11 (1H, m, CHCH$_3$CH$_3$), 2.18-2.25 (1H, m, CH), 2.54 (2H, m, CH$_2$Ar), 3.08 (1H, s, CHCHOH), 3.92-3.98 (1H, m, CH$_3$CHOH), 6.99-7.32 (4H, m, Ar-H); $\delta$ (100 MHz, CDCl$_3$) 25.5 (CH$_3$), 28.3 (CH$_3$), 31.1 (CH$_2$), 32.2 (CH$_2$), 34.8 (CH), 36.1 (CHCH$_2$), 37.5 (C), 41.4 (CH$_2$Ar), 70.4 (CHCHOH), 79.6 (CH$_2$CHOH), 119.7 (Ar-CBr), 130.9 (Ar-CH), 131.4 (Ar-CH), 139.9 (Ar-C); Analysis by MS was uninformative.
(1S, 2R, 4S)-2-(2-chlorobenzyl)-7,7-dimethylcycloheptane-1,4-diol 71

\[
\begin{align*}
\text{HO} & \quad \text{Cl} \\
\text{HO} & \quad \text{Cl}
\end{align*}
\]

As for general procedure C, reaction of (E)-6-(3-(2-chlorophenyl)allyl)-3,3-dimethyltetrahydro-2H-pyran-2-one 68 (29 mg, 0.105 mmol, 1 eq) with SmI\(_2\) (0.1 M in THF, 8.40 mL, 0.84 mmol, 8 eq) and H\(_2\)O (1.50 mL), after purification by column chromatography on silica gel eluting with 5 % Et\(_2\)O in CHCl\(_3\) gave 71 (24 mg, 0.086 mmol, 82%) as a colourless oil and as a 5:3 mixture of diastereoisomers; \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 3393 (OH), 2928, 1474, 1388, 992, 943, 754, 680; \(\delta_\text{H}\) (400 MHz, CDCl\(_3\)) 0.71 (3H, s, CH\(_3\)), 0.85 (3H, s, CH\(_3\)), 1.14 (2H, m, CH\(_2\)CH\(_2\)CHOH), 1.29 (1H, dt, \(J\) 14.6, 4.5, CH\(_2\)CH\(_3\)CH\(_3\)CHOH), 1.45 (1H, dd, \(J\) 14.6, 12.3, CH\(_2\)CH\(_3\)CH\(_3\)CHOH), 1.50-1.56 (1H, m, CHOHC\(_3\)CH\(_3\)), 2.08 (1H, dddd, \(J\) 14.6, 10.6, 5.8, CHOHC\(_3\)CH\(_3\)), 2.32-2.39 (1H, m, CHCH\(_2\)Ar), 2.64 (1H, dd, \(J\) 13.4, 7.3, CH\(_2\)CH\(_3\)Ar), 2.75 (1H, dd, \(J\) 13.4, 7.8 CH\(_2\)CH\(_3\)Ar), 3.11 (1H, s, CHCHOH), 3.93-3.99 (1H, m, CH\(_2\)CHOH), 7.05-7.27 (4H, m, Ar-H); \(\delta_\text{C}\) (100 MHz, CDCl\(_3\)) 25.5 (CH\(_3\)), 28.9 (CH\(_3\)), 31.2 (CH\(_3\)CHOH), 32.6 (CH\(_2\)C), 33.6 (CH), 36.4 (CH\(_2\)C), 37.4 (C), 39.8 (CH\(_2\)Ar), 70.7 (CHCHOH), 80.2 (CH\(_2\)CHOH), 126.6 (Ar-CH), 127.5 (Ar-CH), 129.6 (Ar-CH), 131.5 (Ar-CH), 134.4 (Ar-CCl) 138.5 (Ar-C); \(m/z\) (ES+ mode) 305 ((M + Na), 90), 255 (40), 193 (50); (found: (M + Na), 305.1287. C\(_{10}\)H\(_{23}\)ClO\(_2\) requires M, 305.1279).
(5S, 7R)-5-hydroxy-2,2-dimethyl-7-(3-methylbenzyl)cycloheptanone 69

As for general procedure C, reaction of (E)-3,3-dimethyl-6-(3-(m-tolyl)allyl)tetrahydro-2H-pyran-2-one 66 (48 mg, 0.186 mmol, 1 eq) with SmI$_2$ (0.1 M in THF, 14.80 mL, 1.49 mmol, 8 eq) and H$_2$O (2.65 mL), purification by column chromatography on silica gel eluting with 5 % Et$_2$O in CHCl$_3$, gave 69 (33 mg, 0.129 mmol, 69%) as a colourless oil; $v_{\text{max}}$ (neat)/cm$^{-1}$ 3428 (OH), 2959, 2868, 1704 (C=O), 1468, 1446, 1384, 1083, 1049, 781, 702, 665; $\delta_H$ (400 MHz, CDCl$_3$); 0.64 (3H, s, CH$_3$), 0.96 (3H, s, CH$_3$), 1.16-1.23 (2H, m, CH$_2$CH$_2$CHOH), 1.26-1.35 (2H, m, CH$_2$CH$_2$CHOH), 1.45 (1H, apparent dt, $J$ 14.8, 3.2, CHCH$_3$CH$_2$CHOH), 1.74 (1H, d, $J$ 14.8, CHCH$_3$CH$_2$CHOH), 2.22 (Ar-CH$_3$), 2.43 (1H, dd, $J$ 13.4, 6.0, CH$_3$CH$_2$Ar), 2.94 (1H, dd, $J$ 13.4, 8.6 CH$_2$CH$_2$Ar), 3.44-3.53 (1H, m, C(O)CH), 3.98-4.01 (1H, m, CH$_2$OH), 6.87-7.07 (4H, m, Ar-H); $\delta_C$ (100 MHz, CDCl$_3$) 21.4 (Ar-CH$_3$), 22.8 (CH$_3$), 26.4 (CH$_3$), 29.6 (CH$_2$CHOH), 30.8 (CH$_2$CH$_2$CHOH), 38.0 (CH$_2$Ar), 40.9 (CHCH$_2$CHOH), 43.6 (C(O)CH), 47.3 (C(CH$_3$)$_2$), 66.9 (COH), 126.3 (Ar-CH), 126.8 (Ar-CH), 128.1 (Ar-CH), 130.1 (Ar-CH), 137.7 (Ar-C), 140.2 (Ar-C) 218.1 (C=O); $m/z$ (ES+ mode) 285 ((M + Na), 30), 283 (100); (found: M + Na), 285.1821. C$_{17}$H$_{26}$O$_2$Na requires M, 285.1826)
Diethyl 6-allyl-2-oxodihydro-2H-pyran-3,3(4H)-dicarboxylate 72

A solution of LDA was prepared by adding n-butyllithium (3.34 mL, 7.32 mmol, 1.2 eq, 2.19 M solution in hexane) to diisopropylamine (1.03 mL, 7.32 mmol, 1.2 eq) in THF (20 mL) at -78 °C under N₂ followed by stirring for 1 hour. To this solution was added 6-allyltetrahydro-2H-pyran-2-one 53 (854 mg, 6.1 mmol, 1 eq) dissolved in THF (10 mL) over 30 min using a syringe pump and the resulting solution stirred for a further 1 hour. The reaction was warmed to 0 °C for 10 min then cooled back to -78 °C before the addition of ethyl cyanoformate (0.88 mL, 9.15 mmol, 1.5 eq) and the reaction allowed to warm to room temperature over 18 hours. The reaction was quenched by the addition of aqueous saturated NH₄Cl (40 mL) and the aqueous layer was separated and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (40 mL), dried (Na₂SO₄) and concentrated in vacuo to yield the crude product. The crude product was subsequently dissolved in DMF (14 mL) and cooled down to 0 °C. To this was slowly added 60% NaH (77 mg, 1.93 mmol, 1.2 eq) and allowed to warm up to room temperature. When the initial effervescence had subsided, the reaction was heated at 60 °C for 1 hour then allowed to cool to room temperature before the addition of ethyl cyanoformate (0.19 mL, 1.93 mmol, 1.5 eq). The reaction mixture was heated to 60 °C for 18 hours then quenched with H₂O (30 mL) and extracted with Et₂O (3 × 30 mL). The organic layers were combined and washed with H₂O (3 × 30 mL) before being dried (Na₂SO₄) and the solvent removed in vacuo. Purification by flash chromatography on silica gel eluting with 40% Et₂O in petroleum ether (40 – 60 °C) gave 72 (204 mg, 0.72 mmol, 12 %) as a yellow oil;

δH (400 MHz, CDCl₃) 1.32 (6H, t, J 6.4, 2 × CH₃CH₂), 1.63-1.72 (1H, m, CH₆CH₆), 1.89-1.99 (1H, m, CH₆CH₆), 2.36-2.51 (2H, m, CH₃CH=CH), 2.52-2.60 (2H, m, CH₂), 4.33 (4H, q, J 7.1, 5.6, OCH₂), 4.35-4.41 (1H, m, CH), 5.13-5.19 (2H, m, CH=CH₂), 5.78 (1H, ddt, J 16.8, 14.1, 7.0, CH=CH₂), δC (100 MHz, CDCl₃) 13.9 (CH₃) 14.0 (CH₃), 24.6 (CH₂), 26.4 (CH₂), 39.8 (CH₂CH=CH₂) 62.1 (CH₂O), 62.9
(CH₂O), 80.0 (CH), 119.0 (CH=CH₂), 131.9 (CH=CH₂), 165.2 (C), 166.6 (C), 166.9 (C); Analysis by MS was uninformative

**General procedure D – Claisen Condensation**

**(E)-Ethyl 6-(3-(4-bromophenyl)allyl)-6-methyl-2-oxotetrahydro-2H-pyran-3-carboxylate 104**

![Image](https://via.placeholder.com/150)

A solution of LDA was prepared by the addition of *n*-butyllithium (0.9 mL, 1.97 mmol, 1.3 eq, 2.2 M solution in hexane) to diisopropylamine (201 mg, 1.97 mmol, 1.3 eq) in THF (8 mL) at -78 °C under N₂, followed by stirring for 1 hour. To this solution was added 6- **E**)-6-(3-(4-bromophenyl)allyl)-6-methyltetrahydro-2H-pyran-2-one 79 (475 mg, 1.52 mmol, 1 eq) dissolved in THF (7 mL) over 30 min using a syringe pump and the resulting solution was stirred for 1 hour. The reaction was warmed to -30 °C for 10 min then cooled back to -78 °C before the addition of ethyl cyanoformate (0.22 mL, 2.28 mmol, 1.6 eq) after which the resulting solution was allowed to warm to room temperature and stirred for 18 hours. The reaction was quenched by the addition of aqueous saturated NH₄Cl (30 mL) and the aqueous layer was separated and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography on silica gel eluting with 20% EtOAc in petroleum ether (40 – 60 °C) gave **104** (246 mg, 0.65 mmol, 43%) as a yellow oil and as a 1:1 mixture of diastereoisomers; ν<sub>max</sub> (neat)/cm⁻¹ 2977, 1740 (C=O), 1486, 1370, 1257, 1178, 1071, 1007; δ<sub>H</sub> (400 MHz, CDCl₃) 1.17-1.24 (3H, m, CH₃(C₆H₅O), 1.35 (3H, s, CH₃ from 1 diastereoisomer), 1.40 (3H, s, CH₃ from 1 diastereoisomer), 1.59-1.66 (1H, m, from CH₂CCH₃), 1.75-1.80 (1H, m, from CH₂CCH₃ both diastereoisomers), 2.03-2.12 (1H, m, from CHCH₂CH₂), 2.16-2.26 (1H, m, from...
CHCH₂CH₂), 2.49 (2H, d, J 7.31, CH₂CH=CH from 1 diastereoisomer), 2.51 (2H, d, J 7.31, CH₂CH=CH from 1 diastereoisomer), 3.35 (1H, dd, J 7.1, 2.5, CHCH₂CH₂ from 1 diastereoisomer), 3.43 (1H, t, J 7.1, CHCH₂CH₂ from 1 diastereoisomer), 2.10-4.18 (2H, m, CH₃C=CH), 6.11 (1H, ddt, J 15.6, 7.31, 3.0, CH₂C=CH), 6.34 (1H, d, J 15.6 CH₂CH=CH), 7.13-7.37 (4H, m, Ar-H); δC (100 MHz, CDCl₃) 14.1 (CH₃CH₂O), 20.9 (CH₂CCH₃), 25.8 (CH₃ from 1 diastereoisomer), 26.3 (CH₃ from 1 diastereoisomer), 28.1 (CHCH₂CH₂ from 1 diastereoisomer), 28.6 (CHCH₂CH₂ from 1 diastereoisomer), 44.9 (CH₂CH=CH from 1 diastereoisomer), 45.5 (CH₂CH=CH from 1 diastereoisomer), 47.4 (CHCH₂CH₂ from 1 diastereoisomer), 61.9 (CH₂CH₂O), 85.0 (CCH₃), 121.3 (ArCBr), 124.3 (CH=CHAr from 1 diastereoisomer), 124.5 (CH=CHAr from 1 diastereoisomer), 127.8 (Ar-CH), 131.7 (Ar-CH), 133.2 (CH=CHAr from 1 diastereoisomer) 133.4 (CH=CHAr from 1 diastereoisomer), 166.9 (C(O)), 167.0 (C(O)); m/z (ES+ mode) 403 ((M + Na), 95); found: (M + Na), 403.0511. C₁₈H₂₁BrO₄Na requires M, 403.0515.

**General procedure E – Alkylation**

*(E)-Ethyl 6-(3-(4-bromophenyl)allyl)-3-(but-3-en-1-yl)-6-methyl-2-oxotetrahydro-2H-pyran-3-carboxylate 105*

![Chemical structure of 105](image)

*(E)-Ethyl-6-(3-(4-bromophenyl)allyl)-6-methyl-2-oxotetrahydro-2H-pyran-3-carboxylate 104* (246 mg, 0.65 mmol, 1 eq) was dissolved in DMF (9 mL) and cooled down to 0 °C. To this solution was slowly added 60% NaH (32 mg, 1.29 mmol, 2 eq) and the reaction was allowed to warm to room temperature. When the initial effervescence had subsided, the reaction was heated to 60 °C for 1 hour then allowed to cool to room temperature before the addition of 4-bromobut-1-ene (131 mg, 0.97
mmol, 1.5 eq). The reaction mixture was then heated to 60 °C for 18 hours before being quenched with H₂O (30 mL) and extracted with Et₂O (3 × 30 mL). The organic layers were combined and washed with H₂O (3 × 30 mL) before being dried using Na₂SO₄ and the solvent removed in vacuo. Purification by flash chromatography on silica gel eluting with 40% Et₂O in petroleum ether (40 – 60 °C) gave 105 (151 mg, 0.35 mmol, 54%) as a yellow oil as a 1:1 mixture of diastereoisomers; ν_max (neat)/cm⁻¹ 2975, 1723 (C=O), 1486, 1211, 1110, 1008; δ_H (400 MHz, CDCl₃) 1.10 (3H, t, J = 7.3, OCH₂C₃H₃ from 1 diastereoisomer), 1.19 (3H, t, J = 7.3, OCH₂C₃H₃ from 1 diastereoisomer), 1.33 (3H, s, C₃H₃), 1.37 (3H, s, C₃H₃), 1.58-1.63 (1H, m, 1H from C₂H from 1 diastereoisomer), 1.68-1.74 (1H, m, 1H from CH₂ from 1 diastereoisomer), 1.82-1.93 (2H, m, CH₂), 1.82-1.96 (4H, m, 2 × CH₂), 2.08-2.20 (2H, m, CH₂CH=CH₂), 2.41-2.46 (1H, m, CH₆C₃H₆CH=CHAr from 1 diastereoisomer), 2.49-2.55 (1H, m, CH₆C₃H₆CH=CHAr from 1 diastereoisomer), 4.04 (2H, q, J = 7.3, OCH₂ from 1 diastereoisomer), 4.15 (2H, q, J = 7.3, OCH₂ from 1 diastereoisomer), 4.87-4.99 (2H, m, CH=CH₂ both diastereoisomers), 5.65-5.76 (1H, m, CH=CH₂ both diastereoisomers), 6.07-6.17 (1H, dt, J = 15.8, 7.6, CH=CHAr both diastereoisomers), 6.32 (1H, d, J = 15.8, CH=CHAr from 1 diastereoisomer), 6.33 (1H, d, J = 15.8, CH=CHAr from 1 diastereoisomer), 7.13-7.35 (4H, m, Ar-H); δ_C (100 MHz, CDCl₃) 14.0 (OCH₂C₃H₃ from 1 diastereoisomer), 14.2 (OCH₂C₃H₃ from 1 diastereoisomer), 21.0 (CH₃ both diastereoisomers), 25.9 (CH₆C₃H₆CH=CHAr from 1 diastereoisomer), 26.2 (CH₂CH=CH₂ from 1 diastereoisomer), 26.4 (CH₂ both diastereoisomers), 29.0 (CH₂ from both diastereoisomers), 29.5 (CH₂ from 1 diastereoisomer), 34.9 (CH₂ from both diastereoisomers), 44.8 (CH₆C₃H₆CH=CHAr), 46.0 (CH₆C₃H₆CH=CHAr), 53.2 (C from 1 diastereoisomer), 53.5 (C from 1 diastereoisomer), 60.4 (CH₆C₃H₆O from 1 diastereoisomer), 61.9 (CH₆C₃H₆O from 1 diastereoisomer), 84.7 (CCH₃ both diastereoisomers) 115.3 (CH=CH₂ from both diastereoisomers), 121.2 (Ar-CBr from 1 diastereoisomer), 121.3 (Ar-CBr from 1 diastereoisomer), 124.6 (CH=CHAr from 1 diastereoisomer), 124.8 (CH=CHAr from 1 diastereoisomer), 127.7 (Ar-CH from both diastereoisomers), 127.8 (Ar-CH from both diastereoisomers), 132.5 (CH=CHAr from 1 diastereoisomer), 133.1 (CH=CHAr from 1 diastereoisomer), 137.4 (CH=CH₂ from both diastereoisomers), 137.4 (Ar-C both diastereoisomers), 169.6 (C(O) from 1 diastereoisomer), 169.7 (C(O) from 1 diastereoisomer), 171.1 (C(O) from 1 diastereoisomer), 171.4 (C(O) from 1 diastereoisomer); m/z (ES+ mode) 457 ((M + Na), 100); found: (M + Na), 435.1187. C₁₉H₂₁BrO₂Na requires 435.1166.
(3R, 6R)-6-((E)-3-(4-Bromophenyl)allyl)-3-(but-3-en-1-yl)-6-methyltetrahydro-2H-pyr-2-one 106

(E)-Ethyl-6-(3-(4-bromophenyl)allyl)-3-(but-3-en-1-yl)-6-methyl-2-oxotetrahydro-2H-pyr-3-carboxylate 105 (151 mg, 0.35 mmol, 1 eq) was dissolved in DMSO (4 mL), NaCl (31 mg, 0.52 mmol, 1.5 eq) and H₂O (12 µL, 2 eq) were added to the reaction mixture, and was heated to 180 °C for 16 hours. After cooling to room temperature, saturated NaHCO₃ (5 mL) was added and the reaction diluted with H₂O (5 mL). The aqueous layer was extracted with Et₂O (3 × 20 mL) and the combined organics were washed with brine and dried (Na₂SO₄). The solvent was removed in vacuo to yield the crude product as a 1:1 mixture of diastereoisomers. Purification by column chromatography on silica gel eluting with 30% Et₂O in hexane gave 106 (42 mg, 0.16 mmol, 45%) as a yellow oil and as a single diastereoisomer; ν max (neat)/cm⁻¹ 2945, 1723 (C=O), 1486, 1450, 1380, 1251, 1113, 1007, 971; For the syn-diestereoisomer δH (400 MHz, CDCl₃); 1.31 (3H, s, CH₃), 1.54-1.64 (2H, m, CH=CHAr), 2.65-2.72 (1H, m, CH₂CH₂CH=CH₂), 2.52-2.60 (1H, m, CH₂CH=CH₂). 2.02-2.10 (2H, m, CH₂CH=CH₂), 2.22-2.32 (1H, m, CH₂CH(C)₂), 2.45-2.49 (2H, m, CH₂CH=CHAr), 4.95 (2H, m, CH=CHAr), 5.66-5.79 (1H, m, CH=CH₂), 6.14 (1H, m, CH=CHAr), 6.33 (1H, d, J 15.8, CH=CH(2), 7.13-7.37 (4H, m, Ar-H); δC (100 MHz, CDCl₃) 22.4 (CH₂), 26.3 (CH₃), 30.7 (CH₂), 30.8 (CH₂), 31.9 (CH₂), 39.4 (CH₂CHCH₂), 46.3 (CH₂CH=CHAr), 83.5 (C), 115.4 (CH=CH₂), 121.2 (Ar-CH₃), 124.9 (CH=CHAr), 127.6 (Ar-CH), 131.7 (Ar-CH) 133.1 (CH=CHAr), 136.0 (Ar-C), 137.7 (CH=CH₂), 173.8 (C(O)); m/z (ES+ mode) 385 ([M + Na], 100), 303 (10); found: (M + Na), 385.0786. C₁₅H₂₂BrO₃Na requires 385.0774.
Rac-(3S, 3aR, 4S, 6R, 8aR)-4-(4-Bromobenzyl)-3,6-dimethyldecahydroazulene-3a,6-diol 114

As for general procedure C, reaction of (3R, 6R)-6-((E)-3-(4-bromophenyl)allyl)-3-(but-3-en-1-yl)-6-methyltetrahydro-2H-pyran-2-one 106 (12 mg, 0.034 mmol, 1 eq) in THF (3 mL) with SmI$_2$ (0.1 M in THF, 2.7 mL, 0.27 mmol, 8 eq) and H$_2$O (0.5 mL) after workup and purification by column chromatography on silica gel eluting with 70% EtOAc in hexane gave 114 (9 mg, 0.024 mmol, 70%) as a white solid as a mixture of 4:1 ratio of diastereoisomers; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3458 (OH), 2927, 2347, 1487, 1372, 1072, 1010; $\delta$$_H$ (400 MHz, CDCl$_3$) taken from major diastereoisomer; 0.98 (3H, s, CH$_3$), 1.01 (3H, d, $J$ 7.8, CH$_3$), 1.03 (2H, m, 2H from CH$_2$), 1.10-1.13 (1H, dd, $J$ 14.8, 2.5, CH$_2$CH$_2$CHCH$_2$Ar), 1.18 (2H, d, $J$ 5.4, CH$_2$), 1.24-1.31 (2H, m, 2H from CH$_2$), 1.34-1.39 (2H, m, CH$_2$CH$_2$CHCH$_3$), 1.68-1.76 (1H, m, CH$_2$CHCH$_2$), 1.83 (1H, dd, $J$ 14.8, 9.4, CH$_3$CH$_2$CHCH$_2$Ar), 1.99-2.05 (1H, m, CHCH$_3$), 2.26 (1H, dd, $J$ 12.3, 1.3, CH$_3$CH$_2$Ar), 2.50-2.54 (1H, m, CHCH$_2$Ar), 2.75 (1H, d, $J$ 12.3, CH$_3$CH$_2$Ar), 7.06-7.25 (4H, m, Ar-$H$); $\delta$C (100 MHz, CDCl$_3$) 15.6 (CH$_3$CH), 29.8 (CH$_2$), 30.3 (CH$_2$), 31.4 (CH$_2$), 33.3 (CH$_3$), 35.8 (CHCH$_2$Ar), 36.7 (CHCH$_2$Ar), 39.9 (CH$_2$CHCH$_2$Ar), 43.9 (CH$_2$), 45.1 (CHCH$_3$), 53.5 (CH$_2$CHCH$_2$), 70.9 (COCH$_3$), 88.2 (COH), 119.8 (Ar-CBr), 131.1 (Ar-CH), 131.5 (Ar-CH), 140.1 (Ar-C); m/z (ES+ mode) 389 ((M + Na), 90), 309 (100), 173 (50).
(E)-Ethyl 6-methyl-2-oxo-6-(3-(m-tolyl)allyl)tetrahydro-2H-pyran-3-carboxylate

As for general procedure D, (E)-6-methyl-6-(3-(m-tolyl)allyl)tetrahydro-2H-pyran-2-one 82 (492 mg, 2.01 mmol, 1 eq) was deprotonated using LDA and reacted with Mander’s reagent (0.348 mL, 3.62 mmol, 1.8 eq). After workup, purification by column chromatography on silica gel eluting with a 20% EtOAc in petroleum ether (40 – 60 °C) gave 108 (351 mg, 1.11 mmol, 55%) as a yellow oil and as a 1:1 mixture of diastereoisomers; \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 2978, 1740 (C=O), 1452, 1370, 1319, 1248, 1032, 972, 780; \( \delta_H \) (400 MHz, CDCl\(_3\)) 1.26-1.34 (3H, s, C\(_H\)O); 45.7 (3H, s, \( CH_3 \) from 1 diastereoisomer), 1.49 (3H, s, \( CH_3 \) from 1 diastereoisomer), 1.67-1.75 (1H, m, from \( CH_2CCH_3 \)), 1.81-1.91 (1H, m, from \( CH_2CCH_3 \)), 1.99-2.08 (1H, m, from CHCH\(_2\)CH\(_2\)), 2.10-2.19 (1H, m, from CHCH\(_2\)CH\(_2\)), 2.36 (3H, s, Ar-CH\(_3\)), 2.59 (2H, d, \( J 7.5 \), \( CH_2CH=CH \) from 1 diastereoisomer), 2.64 (2H, d, \( J 7.3 \), \( CH_2CH=CH \) from 1 diastereoisomer), 3.45 (1H, dd, \( J 9.4 \), 7.0, \( CHCH_2CH_2 \) from 1 diastereoisomer) 3.51 (1H, t, \( J 7.0 \), \( CHCH_2CH_2 \) from 1 diastereoisomer), 4.10 (2H, m, \( CH_3CH_2O \)), 6.18 (1H, dt, \( J 15.6 \), 7.4, \( CH=CH \)Ar), 6.47 (1H, d, \( J 15.6 \), \( CH=CH \)Ar), 7.06-2.28 (4H, m, Ar-H); \( \delta_C \) (100 MHz, CDCl\(_3\)) 14.1 (\( CH_2CH_2O \)), 21.0 (\( CH_2CCH_3 \)), 21.4 (Ar-CH\(_3\)), 26.4 (\( CH_3 \) from 1 diastereoisomer), 26.8 (\( CH_3 \) from 1 diastereoisomer), 29.8 (CHCH\(_2\)CH\(_2\) from 1 diastereoisomer), 30.3 (CHCH\(_2\)CH\(_2\) from 1 diastereoisomer), 44.9 (CH\(_2\)CH=CH from 1 diastereoisomer), 45.7 (CH\(_2\)CH=CH from 1 diastereoisomer), 47.0 (CHCH\(_2\)CH\(_2\) from 1 diastereoisomer), 47.5 (CHCH\(_2\)CH\(_2\) from 1 diastereoisomer), 61.9 (CH\(_2\)CH\(_2\)O from 1 diastereoisomer), 62.0 (CH\(_3\)CH\(_2\)O from 1 diastereoisomer), 85.2 (CH\(_3\)), 123.1 (Ar-CH), 123.5 (CH=CHAr), 126.9 (Ar-CH), 128.3 (Ar-CH), 128.5 (Ar-CH), 134.5 (CH=CHAr), 136.9 (Ar-C), 138.2 (Ar-C), 166.9 (C(O)), 169.4 (C(O)); \( m/z \) (ES+ mode) 339 ((M + Na), 100); (found: (M + Na), 339.1569. \( C_{19}H_{24}O_4Na \) requires 339.1567).
(E)-Ethyl 6-methyl-3-(4-methylpent-3-en-1-yl)-2-oxo-6-(3-(m-tolyl)allyl)tetrahydro-2H-pyran-3-carboxylate 108(b)

As for general procedure E, (E)-ethyl 6-methyl-2-oxo-6-(3-(m-tolyl)allyl)tetrahydro-2H-pyran-3-carboxylate 108 (351 mg, 1.16 mmol, 1 eq) in DMF (11 mL) was deprotonated with NaH (56 mg, 2.21 mmol, 2 eq) and reacted with 5-bromo-2-methylpent-2-ene (271 mg, 1.66 mmol, 1.5 eq). Workup and purification by column chromatography on silica gel eluting with 40% Et₂O in petroleum ether (40 – 60 °C) gave 108(b) (154 mg, 0.35 mmol, 32%) as a yellow oil and as a 1:1 mixture of diastereoisomers; ν_max (neat)/cm⁻¹ 2973, 1740, 1602, 1448, 1380, 1292, 1213, 1108, 1024, 972; δ_H (400 MHz, CDCl₃) 1.12 (3H, t, J 7.3, CH₂CH₂O), 1.33 (3H, s, CH₃), 1.50 (3H, s, CH=CHCH₂C(CH₃)₂), 1.53 (3H, s, CH=CH(C(H₃)₂) 1.58-1.63 (2H, m, 2H from CH₂), 1.77-1.83 (2H, m, 2H from CH₂), 1.88-1.96 (3H, m, 2H from C=CHCH₂ and 1H from C=CHCH₂CH₂), 2.11-2.16 (1H, m, C=CHCH₂CH₂), 2.26 (3H, s, Ar-CH₃), 2.44-2.53 (2H, m, CH₂CH=CHAr), 3.98-4.07 (2H, m, CH₃CH₂O) 5.02 (1H, t, J 6.9, CHC(CH₃)₂), 6.09-6.15 (1H, m, CH=CHAr), 6.34 (1H, d, J 15.8, CH=CHAr), 6.96-7.19 (4H, m, Ar-H); δ_C (100 MHz, CDCl₃) 14.1 (CH₃CH₂O), 17.7 (CH=C(CH₃)₂), 21.4 (Ar-CH₃), 23.4 (C=CHCH₂CH₂), 25.7 (C=CHCH₂CH₂), 25.9 (CH=C(CH₃)₂), 26.4 (CH₃), 29.5 (CH₂), 36.0 (CH₂), 46.2 (CH₂CH=CHAr), 53.6 (CC(O)), 61.9 (CH₃CH₂O), 84.9 (CCH₃), 123.0 (CH=C(CH₃)₂), 123.5 (Ar-CH), 123.6 (CH=CHAr), 126.8 (Ar-CH), 128.3 (Ar-CH), 128.4 (Ar-CH), 132.8 (Ar-C), 134.3 (CH=CHAr), 137.0 (C), 138.1 (C), 169.9 (C(O)), 171.6 (C(O)); m/z (ES+ mode) 421 ((M + Na), 100); (found: (M + Na), 421.2353. C₂₅H₃₅O₄Na requires 421.2349).
Ethyl 6-cinnamyl-6-methyl-2-oxotetrahydro-2H-pyran-3-carboxylate

As for general procedure D, 6-cinnamyl-6-methyltetrahydro-2H-pyran-2-one 78 (600 mg, 2.61 mmol, 1 eq) was treated with LDA and Mander’s reagent (310 mg, 3.13 mmol, 1.2 eq). Workup and purification by column chromatography on silica gel eluting with a 20% EtOAc in petroleum ether (40 – 60 °C) gave the title compound (346 mg, 1.15 mmol, 44%) as a yellow oil and as a 1:1 mixture of diastereoisomers; ν<sub>max</sub> (neat)/cm<sup>-1</sup> 2979, 1742 (C=O), 1720 (C=O), 1450, 1370, 1320, 1259, 1176, 1098, 1032, 970, 928; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 1.27 (3H, t, J 7.3, OCH<sub>2</sub>CH<sub>3</sub> from 1 diastereoisomer), 1.31 (3H, t, J 7.3, OCH<sub>2</sub>CH<sub>3</sub> from 1 diastereoisomer), 1.44 (3H, s, CH<sub>3</sub> from 1 diastereoisomer), 1.49 (3H, s, CH<sub>3</sub> from 1 diastereoisomer), 1.67-1.75 (1H, m, CH<sub>2</sub>H<sub>b</sub>), 1.80-1.90 (1H, m, CH<sub>2</sub>H<sub>b</sub>), 2.11-2.20 (1H, m, CHCH<sub>2</sub>H<sub>b</sub>), 2.24-2.34 (1H, m, CHCH<sub>2</sub>H<sub>b</sub>), 2.59 (1H, dd, J 7.6 3.5, CH<sub>2</sub>H<sub>b</sub>CH=CHAr), 2.64 (1H, d, J 7.6, CH<sub>2</sub>H<sub>b</sub>CH=CHAr), 3.44 (1H, dd, J 9.6 7.1, CH from 1 diastereoisomer), 3.51 (1H, t, J 7.1, CH from 1 diastereoisomer), 4.20 (2H, q, J 7.3, OCH<sub>2</sub>CH<sub>3</sub> from 1 diastereoisomer), 4.26 (2H, q, J 7.3, OCH<sub>2</sub>CH<sub>3</sub> from 1 diastereoisomer), 6.20 (1H, dt, J 15.9 7.6, CH=CHAr), 6.48 (1H, d, J 15.9, CH=CHAr), 7.22-7.39 (5H, m, Ar-CH); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 14.0 (OCH<sub>2</sub>CH<sub>3</sub>), 20.9 (CHCH<sub>2</sub> from 1 diastereoisomer), 21.0 (CHCH<sub>2</sub> from 1 diastereoisomer), 26.3 (CH<sub>3</sub> from 1 diastereoisomer), 26.8 (CH<sub>3</sub> from 1 diastereoisomer), 29.7 (CH<sub>2</sub> from 1 diastereoisomer), 30.2 (CH<sub>2</sub> from 1 diastereoisomer), 44.9 (CH<sub>2</sub>CH=CHAr from 1 diastereoisomer), 45.7 (CH<sub>2</sub>CH=CHAr from 1 diastereoisomer), 46.9 (CH from 1 diastereoisomer), 47.4 (CH from 1 diastereoisomer), 61.8 (OCH<sub>2</sub>CH<sub>3</sub> from 1 diastereoisomer), 61.9 (OCH<sub>2</sub>CH<sub>3</sub> from 1 diastereoisomer), 85.1 (C), 123.3 (CH=CHAr from 1 diastereoisomer), 123.5 (CH=CHAr from 1 diastereoisomer), 126.2 (Ar-CH), 127.5 (Ar-CH from 1 diastereoisomer), 127.6 (Ar-CH from 1 diastereoisomer), 128.5 (Ar-CH from 1 diastereoisomer), 128.6 (Ar-CH from 1 diastereoisomer), 134.4 (CH=CHAr from 1 diastereoisomer), 134.6 (CH=CHAr from 1 diastereoisomer), 136.8 (Ar-C from 1 diastereoisomer).
diastereoisomer), 136.9 (Ar-C from 1 diastereoisomer), 166.9 (C(O) from 1 diastereoisomer), 167.0 (C(O) from 1 diastereoisomer), 169.3 (C(O) from 1 diastereoisomer), 169.4 (C(O) from 1 diastereoisomer); m/z (ES+ mode) 303 ((M + H), 100), 285 (23), 325 (19), 239 (19), 171 (18); (Found: (M + H), 303.1592. C_{18}H_{22}O_4 requires M, 303.1591).

**Ethyl 3-(but-3-yn-1-yl)-6-cinnamyl-6-methyl-2-oxotetrahydro-2H-pyran-3-carboxylate 110**

As for general procedure E, ethyl 6-cinnamyl-6-methyl-2-oxotetrahydro-2H-pyran-3-carboxylate (352 mg, 1.16 mmol, 1 eq) in DMF (9 mL) was treated with NaH (111 mg, 2.9 mmol, 2.5 eq) and with 4-bromobut-1-yn (0.23 mL, 2.33 mmol, 2 eq). Workup and purification by column chromatography on silica gel eluting with 40% Et2O in petroleum ether (40 – 60 °C) gave 110 (89 mg, 0.25 mmol, 21%) as a yellow oil and as a 1:1 mixture of diastereoisomers; ν_{max}(neat)/cm^{-1} 3281, 2979, 1733 (C=O), 1449, 1233, 1106, 969, 928; δ_{H} (400 MHz, CDCl3) 1.10 (3H, t, J 7.2, OCH_{2}CH_{3} from 1 diastereoisomer), 1.22 (3H, t, J 7.2, OCH_{2}CH_{3} from 1 diastereoisomer), 1.35 (CH_{3} from 1 diastereoisomer) 1.38 (CH_{3} from 1 diastereoisomer), 1.64-1.74 (2H, m, CH_{2}), 1.88-2.32 (7H, m, 4H from 2 × CH_{2}, 1H from CH_{2}(C)CH and 2H from CH_{2}(C)=CH), 2.47-2.57 (2H, m, CH_{2}CH=CHAr), 4.01-4.28 (2H, m, OCH_{2}CH_{3}), 6.04-6.18 (1H, m, CH=CHAr), 6.39 (1H, d, J 16.2, CH=CHAr from 1 diastereoisomer), 6.40 (1H, d, J 15.8, CH=CHAr from 1 diastereoisomer), 7.14-7.30 (5H, m, Ar-H); δ_{C} (100 MHz, CDCl3) 13.9 (OCH_{2}CH_{3} from 1 diastereoisomer), 14.0 (OCH_{2}CH_{3} from 1 diastereoisomer), 14.6 (CH_{2}(C)CH), 26.1 (CH_{3}), 26.6 (CH_{2} from 1 diastereoisomer), 28.7 (CH_{2} from 1 diastereoisomer), 29.3 (CH_{2} from 1 diastereoisomer), 31.6 (CH_{2} from 1 diastereoisomer), 34.5 (CH_{2} from 1 diastereoisomer), 34.8 (CH_{2} from 1 diastereoisomer), 44.6 (CH_{2}CH=CHAr from 1 diastereoisomer), 45.8 (CHCH=CHAr from 1 diastereoisomer), 53.0 (CC(O)) from 1 diastereoisomer), 53.2 (CC(O)) from 1
diastereoisomer), 62.1 (OCH₂CH₃ from 1 diastereoisomer), 63.7 (CH₂CCH), 85.1 (CCH from 1 diastereoisomer), 86.7 (CCH from 1 diastereoisomer), 122.9 (CH=CHAr from 1 diastereoisomer), 123.0 (CH=CHAr from 1 diastereoisomer), 126.2 (Ar-CH from 1 diastereoisomer), 127.5 (Ar-CH from 1 diastereoisomer), 127.6 (Ar-CH from 1 diastereoisomer), 128.6 (Ar-CH from 1 diastereoisomer), 134.4 (CH=CHAr from 1 diastereoisomer), 134.6 CH=CHAr from 1 diastereoisomer), 136.7 (Ar-C from 1 diastereoisomer), 136.8 (Ar-C from 1 diastereoisomer), 166.7 (C(O) from 1 diastereoisomer), 169.7 (C(O) from 1 diastereoisomer), 171.0 (C(O) from 1 diastereoisomer), 171.1 (C(O) from 1 diastereoisomer); m/z (ES+ mode) 377 ((M + Na), 100), 359 (22); (Found: (M + H), 355.1906. C₂₂H₂₇O₄ requires M, 355.1904).

**Ethyl-3-(but-3-yn-1-yl)-6-cinnamyl-6-methyltetrahydro-2H-pyran-3-carboxylate**

Ethyl-3-(but-3-yn-1-yl)-6-cinnamyl-6-methyl-2-oxotetrahydro-2H-pyran-3-carboxylate 110 (89 mg, 0.25 mmol, 1eq) was dissolved in THF/MeOH (1.5 mL and 1.5 mL) and the solution was heated to 50 °C. LiOH (1.5 mL, 1M solution) was then added and the reaction mixture was stirred for a further 5 hours. After cooling to room temperature, the reaction was quenched with HCl and the pH adjusted to 3. Extraction using Et₂O (3 × 30 mL) washed with brine (20 mL) and dried (Na₂SO₄) and the solvent removed *in vacuo*. The crude mixture was then dissolved in toluene and heated at reflux for 15 hours. The solvent again was then removed *in vacuo* giving the crude product as a 1:1 mixture of diastereoisomers. The product was purified by column chromatography on silica gel eluting with 10% EtOAc in hexane and gave 109 (42 mg, 0.15 mmol, 59%) as a yellow oil as a single diastereoisomer; ν<sub>max</sub> (neat)/cm⁻¹ 3291, 2935, 1721 (C=O), 1449, 1106, 970, 749, 694; For the syn-diastereoisomer δ<sub>H</sub> (400 MHz, CDCl₃) 1.33 (3H, s, CH₃), 1.57-1.71 (2H, m, CH₂),
1.88-1.91 (3H, m, CH₂(C)CH and 1H from CH₂) 2.09-2.37 (4H, m, 3H from CH₂ and 1H from CH₂(C)=CH), 2.39-2.44 (1H, m, CHC(O)), 2.49 (2H, d, J 7.5 CH₂CH=CHAr), 6.04-6.19 (1H, m, CH=CHAr), 6.40 (1H, d, J 15.8, CH=CHAr), 7.13-7.31 (5H, m, Ar-H); δC (100 MHz, CDCl₃) 16.2 (CH₂), 22.6 (CH₂), 26.4 (CH₃), 30.3 (CH₂), 31.9 (CH₂), 38.4 (CHC(O)), 46.3 (CH₂CH=CHAr), 69.3 (CCH), 83.2 (CCH), 83.8 (CCH₃), 123.8 (CH=CHAr), 126.2 (Ar-CH), 127.5 (Ar-CH), 128.6 (Ar-CH), 134.3 (CH=CHAr), 137.0 (Ar-C), 173.5 (C(O); m/z (ES+ mode) 305 ((M + Na), 100)); found: (M + Na), 305.1512.

(3aR, 4S, 6R, 8aR)-4-Benzyl-6-methyl-3-methylenedecahydroazulene-3a,6-diol

As for general procedure C, treatment of (3R, 6R)-3-(but-3-yn-1-yl)-6-cinnamyl-6-methyltetrahydro-2H-pyran-2-one 109 (13 mg, 0.046 mmol, 1 eq) with SmI₂ (0.1 M in THF, 3.7 mL, 0.368 mmol, 8 eq) and H₂O (1.0 mL), after workup and purification by column chromatography on silica gel eluting with 60% EtOAc in hexane gave 115 (7 mg, 0.024 mmol, 51%) as a colourless oil and as a 4:1 mixture of diastereoisomers; νmax (neat)/cm⁻¹ 3410, 2919, 2852, 2361, 1651, 1555, 1493, 1372, 1129, 1108, 1070, 940, 891, 742, 698; taken from major diastereoisomer δH (400 MHz, CDCl₃) 1.02 (CH₃), 1.13 - 1.21 (5H, m, 4H from 2 × CH₂ and 1H from CH₃CH₃CH₃CHAr), 1.52-1.69 (2H, m, CH₂CH₂C=CH₂), 1.75-1.83 (1H, m, CH₂CHCH₂), 2.06 (1H, m, CH₃CH₃CH₃CHAr), 2.10-2.24 (2H, m, 1H from CHCH₂Ar and 1H from CH₃CH₃CHAr), 2.39 (2H, apparent t, J 7.4, CH₂C=CH₂), 2.98 (1H, d, J 12.8, CH₂CH₂Ar), 4.97 (1H, t, J 5.05 (1H, s, C=CH₃CH₂), 5.05 (1H, s, C=CH₃CH₂), 7.10-7.23 (5H, m, Ar-H); δC (100 MHz, CDCl₃) 25.0 (CH₂CH₂C=CH₂), 26.3 (CH₂), 28.9 (CH₂C=CH₂), 32.1 (CH₃OH), 35.6 (CHCH₂Ar), 37.2 (CH₂Ar), 37.4 (CH₂) 39.9 (CH₂CHCH₂Ar), 51.2 (CH₂CHCH₂), 102.
72.1 (COH), 83.7 (COH), 107.5 (C=CH₂), 125.8 (Ar-CH), 128.3 (Ar-CH), 129.3 (Ar-CH), 141.5 (Ar-C), 157.5 (C=CH₂); m/z (ES+ mode) 309 ((M + Na), 100), 369 (90), 251 (85); found: (M + Na), 309.1823. C₁₉H₂₆O₂Na requires M, 309.1826.

(1R, 2S, 4R)-2-benzyl-4-(2-hydroxyethyl)cyclopentanol 51

As for general procedure C, reaction of 4-cinnamyltetrahydro-2H-pyran-2-one 48 (63 mg, 0.29 mmol, 1 eq) with SmI₂ (0.1 M in THF), 23 mL, 2.32 mmol, 8 eq), and H₂O (4.1 mL) after workup and purification by column chromatography on silica gel eluting with 70% EtOAc in hexane, gave 51 (16 mg, 0.074 mmol, 26%) as a white solid; ν max (neat)/cm⁻¹ 3338 (OH), 3023, 2919, 2847, 1599, 1491, 1449, 1049, 749, 698; δH (400 MHz, CDCl₃) 0.81 (2H, m, CH₂CH), 1.45-1.71 (4H, m, 2H from CH₂OHC₂H and 2H from CH₂CH₂OH), 1.97-2.03 (1H, m, ArCH₂CH), 2.05-2.14 (1H, m, CH₂CHCH₂), 2.50 (1H, dd, J 13.4, 8.3, CH₄CH₃Ar), 2.73 (1H, dd, J 13.4, 6.8 CH₂CH₃Ar), 3.54 (2H, t, 6.8 CH₂OH), 3.87-3.91 (1H, m, CHOH), 7.11-7.23 (5H, m, Ar-H); δC (100 MHz, CDCl₃) 33.3 (CH₂CH₂CH), 38.2 (CHCH₂CH), 39.3 (CHCH₂CH₂OH), 39.8 (ArCH₂), 40.3 (CH₂OHCH₂), 50.6 (ArCH₂CH), 61.9 (CH₂OH), 77.8 (CHOH), 126.0 (Ar-CH), 128.5 (Ar-CH), 128.8 (Ar-CH), 141.0 (Ar-C); m/z (ES+ mode) 243 ((M + Na), 100) 304 (45); (Found: (M + Na), 243.1349. C₁₄H₂₀O₂Na requires M, 243.1349).
4-allyltetrahydro-2H-pyran-2-one 46

![4-allyltetrahydro-2H-pyran-2-one 46](image)

To a solution of allylmagnesium chloride in THF (2M, 39.7 mL, 79.4 mmol) was added a stirred solution of ZnBr$_2$ (8.94 g, 39.7 mmol, 1.2 eq) in THF (140 mL) at 0 °C. The solution was then cooled to -78 °C and TMSCl (14.8 g, 132.4 mmol, 4 eq) was added. Finally, a solution of 5,6-dihydro-2H-pyran-2-one 45 (3.24g, 33.1 mmol, 1 eq) in THF (56 ml) was added dropwise over a period of 1 h. The mixture was stirred for 1 h at -78°C, quenched with water (40 mL) and the pH was adjusted to 2 with 1 N HCl. The solution was extracted with ether (3 × 50 ml), and the combined organic layers were washed with 1 N HCl, water and brine. The organic layers were combined, dried (Na$_2$SO$_4$) and concentrated *in vacuo* to yield the crude product. Purification by flash chromatography on silica gel eluting with 30% EtOAc in petroleum ether (40 – 60 °C) gave 46 (2.32g, 16.55 mmol, 50%) as a colourless oil; δ$_H$ (400 MHz, CDCl$_3$) 1.38-1.48 (1H, m, CH$_2$CH$_3$CH=CH$_2$), 1.82-1.87 (1H, m, CH$_2$CH$_3$CH=CH$_2$), 1.92-1.97 (1H, m, CH$_2$CH$_3$CH=CH$_2$), 1.95-1.99 (1H, m, CH$_2$CH$_3$CH=CH$_2$), 2.05-2.10 (1H, m, CH$_2$CH$_3$CH=CH$_2$), 2.53 (1H, dd, $J$ 5.6, 1.8, C(O)CH$_3$CH$_3$CH=CH$_2$), 2.58 (1H, dd, $J$ 5.6, 1.5, C(O)CH$_3$CH$_3$CH=CH$_2$), 4.24 (1H, dt, $J$ 9.1, 3.3, OCH$_3$CH$_3$CH=CH$_2$), 4.36 (1H, dt, $J$ 9.1, 3.3, OCH$_3$CH$_3$CH=CH$_2$), 5.04-5.11 (2H, m, CH=CH$_2$), 5.56-5.66 (1H, m, CH=CH$_2$); δ$_C$ (100 MHz, CDCl$_3$) 28.3 (CH$_2$CH$_3$CH=CH$_2$), 31.1 (CH$_2$CH=CH$_2$), 36.1 (C(O)CH$_3$CH=CH$_2$), 40.2 (CH$_2$CH=CH$_2$), 68.5 (OCH$_3$CH$_3$CH=CH$_2$), 117.8 (CH=CH$_2$), 134.6 (CH=CH$_2$), 171.3 (C(O))
4-Cinnamyltetrahydro-2H-pyran-2-one XX

As for general procedure A, reaction of Grubbs 2nd generation catalyst (2.4 mg, 0.0028 mmol, 0.5 mol%), 4-allyltetrahydro-2H-pyran-2-one 46 (80 mg, 0.57 mmol, 1 eq), and cis-stilbene (206 mg, 1.14 mmol, 2 eq), after workup and purification by flash chromatography on silica gel eluting with 20% EtOAc in petroleum ether (40 – 60 °C), gave 48 (52 mg, 0.24 mmol, 42%) as a colourless oil; \( \delta_H \) (400 MHz, CDCl\(_3\)) 1.58-1.68 (1H, m, \( \text{CH}_2 \)), 2.01-2.05 (1H, m, \( \text{CH}_2 \)), 2.13-1.19 (1H, m, \( \text{CH}_3 \)), 2.21-2.28 (1H, m, \( \text{CH}_2 \)), 2.37-2.32 (1H, m, \( \text{CH}_4 \)), 2.73 (1H, dd, \( J \) 5.8, 1.8, \( \text{C(O)CH}_2 \)), 2.77 (1H, dd, \( J \) 5.8, 1.5, \( \text{C(O)CH}_2 \)), 4.28 (1H, dt, \( J \) 11.4, 3.8, \( \text{OCH}_2 \)), 4.46 (1H, m, \( \text{OCH}_2 \)), 6.15 (1H, m, \( \text{CH=CHAr} \)), 6.46 (1H, d, \( J \) 15.6, \( \text{CH=CHAr} \)), 7.23-7.37 (5H, m, \( \text{Ar-H} \)); \( \delta_C \) (100 MHz, CDCl\(_3\)) 28.5 (\( \text{CH}_2 \)), 31.8 (\( \text{CH}_2 \)), 36.2 (\( \text{C(O)CH}_2 \)), 39.4 (\( \text{CH}_2 \)), 68.5 (\( \text{OCH}_2 \)), 126.1 (\( \text{Ar-CH} \)), 126.2 (\( \text{CH=CHAr} \)), 127.5 (\( \text{Ar-CH} \)), 128.6 (\( \text{Ar-CH} \)), 132.8 (\( \text{CH=CHAr} \)), 137.0 (\( \text{Ar-C} \)), 171.2 (\( \text{C(O)} \))
References

(7) Flowers, R. A. Synlett 2008, 10, 1427.


