Studies towards the total synthesis of pyxidatol C; New insights into the Cope rearrangement

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Abstract

Studies towards the total synthesis of pyxidatol C I, isolated from the medicinal mushroom *Clavicorona pyxidata*, are described herein. Pyxidatol C I is a member of the africanane family of sesquiterpenes, which share a decahydro-1H-cyclopropa[e]azulene core structure. The synthetic strategy is shown below.

Chapter 1 provides an introduction while Chapter 2 outlines work on a desmethyl model system. A Cope rearrangement was used to prepare synthetic cycloheptadiene IX. Unfortunately, the analogous rearrangement using the gem-dimethyl substituted divinylcyclopropane X was unsuccessful. As such, the reactivity of a range of substituted divinylcyclopropanes towards the thermal Cope rearrangement was investigated (Chapter 3).

The effects of gem-dimethyl substitution on the alkene geometry, the relative stereochemistry of the cyclopropane and the steric and electronic effects of a range of functional groups were all examined, and the methods developed were used to synthesise a range of functionalised 1,4-cycloheptadienes in high yields.

Chapters 4 and 5 describe studies towards the total synthesis of pyxidatol C. Advanced intermediates were prepared including ester XII and lactone XIII containing the requisite gem-dimethyl substituted 7-membered ring, the cyclopropane moiety and the methyl ketone side chain in place.
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Author’s Declaration

The research presented in this Thesis was carried out at the University of York between October 2010 and December 2013. This work is, to the best of my knowledge, original except where due reference has been made to other workers. This work has not been presented for an award at this university, or any other university.

Part of the work disclosed herein has been published, during the project, in the below article:
Chapter 1

Introduction

1.1 Pyxidatol C and the Africananes

*Clavicorona pyxidata* is a wild mushroom used widely in traditional Chinese medicine for the treatment of gastric pain, dyspepsia, gout, and heat toxicity. In 2008, Zheng *et al.* reported the isolation of three novel sesquiterpene compounds from this medicinal mushroom, two belonging to the protoilludane family, pyxidatol A 1 and pyxidatol B 2, and one belonging to the africanane family, pyxidatol C 3 (Figure 1).

![Figure 1](image1.png)

*Figure 1* Structures of pyxidatol A 1, pyxidatol B 2 and pyxidatol C 3.

The structure of pyxidatol C 3 is closely related to that of omphadiol 4 (Figure 2), first isolated by McMorris *et al.* in 2000 from cultures of *Omphalutus illudens* and also isolated from *Clavicorona pyxidata* by Zheng *et al.* Pyxidatol C belongs to the africanane family of sesquiterpenes, first found in africanol 5 and later in africanene 6. The africananes are defined by their decahydro-1H-cyclopropa[e]azulene core structure (highlighted in red: Figure 2).

![Figure 2](image2.png)

*Figure 2* Structures of pyxidatol C 3, omphadiol 4, africanol 5 and africanene 6 with the common decahydro-1H-cyclopropa[e]azulene core structure highlighted in red.
1.2 Structural Elucidation of Pyxidatol C

Pyxidatol C was isolated as a colourless oil. The molecular formula was determined as C_{15}H_{26}O_{2} using HRMS. The $^{13}$C NMR spectrum with DEPT revealed the presence of 15 signals: three CH$_3$, six CH$_2$ (one oxygenated), three CH, and three quaternary C-atoms (one oxygenated). An IR absorption at 3281 cm$^{-1}$ suggested the presence of an OH group, which was supported by the $^1$H NMR and HSQC spectra which showed signals corresponding to two OH groups.$^1$

A comparison of the $^1$H NMR and $^{13}$C NMR data of pyxidatol C, with the previously reported compound omphadiol 4, revealed that the compounds share the same core structure. However the Me group (12) and CH-OH (5) in 4 were replaced by a HOCH$_2$ (12) substituent and CH$_2$ (5) in 3 (Figure 3).$^1$

![Figure 3 Structures of pyxidatol C 3, omphadiol 4 and an acetylated derivative of omphadiol 7 (Arbitrary atom numbering).](image)

The absolute configuration of omphadiol 4 was determined from the X-ray crystal structure of a 3,5-dinitrobenzoate derivative.$^2$ Zheng et al.$^1$ also obtained a crystal structure of an acetylated derivative of omphadiol, 7. The relative configuration of pyxidatol C was determined by comparison with 7. Further evidence was provided by the observation of a ROESY correlation between H-C (8) and H-C (4), and H-C (12) and H-C (15), supporting their assigned syn-relationship (Figure 3).$^1$
1.3 Biological Activity of Pyxidatol C

To date (other than the isolation paper) there have been no publications relating to pyxidatol C 3 (See Chapter 6: Addendum). However, the pharmacological activity of africanene 6 has been examined by Reddy et al.\textsuperscript{5} It was found to show mild CNS depressant activity, dose-dependant hypotensive activity, and anti-inflammatory activity. Furthermore, africanene was found to exhibit cytotoxic activity against the Ehrlich ascites carcinoma and Dalton’s lymphoma ascites tumour.\textsuperscript{5}

Pyxidatol C 3 shares a common tetrasubstituted cyclopentane ring (highlighted in blue: Figure 4) with a large family of sesquiterpenes and diterpenes, many of which display potent biological activities.\textsuperscript{6} Rossinone B 8, for example shows anti-inflammatory, antiviral, and antiproliferative activities\textsuperscript{7,8} and tomeone F 9 displays significant cytotoxicity against KB cells.\textsuperscript{9}

![Figure 4](image-url)  
Figure 4 Structures of pyxidatol C 3, rossinone B 8 and tomeone F 9 with the common tetrasubstituted cyclopentane ring highlighted in blue.

1.4 Proposed Biosynthesis of the Africananes

α-Humulene 10 is an important biogenetic precursor of a large number of sesquiterpenes, particularly in fungi.\textsuperscript{10} Although the biosynthesis of the africananes has not been established conclusively, biosynthetic pathways from α-humulene have been proposed.\textsuperscript{11,12} Braeckman et al.,\textsuperscript{11} for example, proposed a biogenesis of africanol in their original isolation paper (Scheme 1).
Bohllmann and Zderol\textsuperscript{12} reported the isolation and structural elucidation of the africanane sesquiterpene \textsuperscript{12} (Scheme 2) and proposed a biogenetic derivation from \( \alpha \)-humulene derived epoxide \textsuperscript{11}.

\textbf{Scheme 2} Proposed biosynthesis of sesquiterpene \textsuperscript{12} from \( \alpha \)-humulene \textsuperscript{10}.\textsuperscript{12}

\textit{1.5 The First Synthesis of a Natural Africanane: Shirahama's Synthesis of (\( \pm \))-Africanol}

In 1980 Shirahama \textit{et al.}\textsuperscript{13} used the \( \alpha \)-humulene-derived epoxide \textsuperscript{13} in their synthesis of (\( \pm \))-africanol \textsuperscript{5}. This was the first example of a chemical synthesis of a natural africanane (Scheme 3). They began with a transannular cyclisation of epoxide \textsuperscript{13} by treating with trimethylsilyl trifluoromethanesulfonylate followed by desilylation with KI in MeOH, obtaining a mixture of alcohols \textsuperscript{14} and \textsuperscript{15} in a 2:1 ratio. Following the
isolation of the desired isomer 15, it was treated with PBr₃ to give bromide 16 (retention is shown in the publication), which was then reduced using sodium in liquid ammonia furnishing olefin 17. Epoxidation using m-CPBA delivered epoxide 18 and treatment with LDA afforded allylic alcohol 20. Hydrogenation with Adam’s catalyst concluded the synthesis of (±)-africanol 5.

Scheme 3 Synthesis of (±)-africanol 5 by Shirahama et al.¹³

1.6 White’s Synthesis of (±)-Africanol Using the Oxy-Cope rearrangement

Africanol 5 has since been synthesised by many groups.¹⁴–¹⁸ The next racemic total synthesis was reported by Paquette et al. in 1986¹⁶ and the first asymmetric synthesis was reported by Tai et al.¹⁷ in 1990. A six-step synthesis of (±)-africanol was developed by White and Fan in 1993,¹⁸ which used a key anionic oxy-Cope rearrangement step (Scheme 4).

Conjugate addition of Bu₃SnLi into 2,5,5-trimethylcyclohex-2-enone 21 (prepared in 3 steps from commercially available dimedone),¹⁹ followed by in situ trapping of the intermediate enolate with the vinyl cation equivalent (phenylseleno)acetaldehyde started White’s synthesis of (±)-africanol.¹⁸ This afforded a 1:1 mixture of
diastereomers 22 and 23. The desired isomer 23 was isolable by chromatography. Elimination followed by Grignard addition into the ketone then furnished a single diastereomer of divinylcyclohexanol 25. An anionic oxy-Cope rearrangement then led to the generation of compound 26, which was unstable and was used without further purification. Na/naphthalene in THF promoted the cyclisation to the fused ring system 28 in 56% yield with only 6% of the unwanted diastereomer 27. Finally Simmons–Smith cyclopropanation completed the synthesis affording (±)-africanol with exclusive addition on the less hindered endo-face.

![Scheme 4](image.png)

**Scheme 4** Synthesis of (±) africanol 5 by White and Fan.\(^\text{18}\)

### 1.7 Recent Syntheses of Africananes: Romo’s Synthesis of Omphadiol

More recent synthetic routes towards members of the africanane family include Nakata’s synthesis of epoxyafricanane\(^\text{20}\) and Romo’s synthesis of omphadiol,\(^\text{6}\) both of which were published in 2011.

Romo *et al.*,\(^\text{6}\) prepared (+)-omphadiol 4 in 10 steps and in 18% overall yield (Scheme 5). Their elegant synthesis started with a [Mn\(^{\text{III}}\)(dpm)\(_3\)]-catalysed hydration of the
enone moiety of \((R)\)-carvone to afford hydroxy ketone 29. Oxidative cleavage by periodic acid delivered keto-acid 30. Upon activation of the carboxylic acid with tosyl chloride and the addition of 4-PPY as a nucleophilic catalyst, keto-acid 30 underwent an aldol lactonisation to give the unusual bicyclic lactone 31. DIBAL reduction gave the corresponding diol that was then converted into the C7 bromide. A tosylation/bromination sequence, and subsequent acylation provided ester 32. Alkylation using KHMDS, followed by quenching with excess MeI furnished the bicyclic \(\delta\)-lactone 33 bearing the requisite C6 \(\text{gem}\)-dimethyl moiety. The addition of allylithium, which was derived from allyltriphenyltin, into lactone 33 gave the \(\beta,\gamma\)-unsaturated enone 34. A tandem isomerisation/ring-closing metathesis (RCM) process using second generation Grubbs catalyst next gave cycloheptenone 35. Finally, DIBAL reduction furnished allylic alcohol 36, which underwent Simmons–Smith cyclopropanation to give synthetic (+)-omphadiol.6

Scheme 5 Synthesis of (+)-omphadiol 4 by Romo et al.6
1.8 Pyxidatol C: Retrosynthetic Analysis

Our aim was to apply established Taylor group methodologies in the total synthesis of pyxidatol C. A modified Corey–Chaykovsky protocol, developed within the Taylor group,\textsuperscript{20–23} has been used previously to synthesise cyclopropane \( \text{41} \) where \( R = \text{Et} \)\textsuperscript{23} which, it was hoped, could be readily converted into diester \( \text{40} \) via reduction followed by the group’s tandem oxidation procedure (TOP, tandem MnO\(_2\)-Wittig reaction).\textsuperscript{23,24}

It was then anticipated that the Cope rearrangement of \( \text{40} \), would generate the 7-membered ring \( \text{meso-compound 39} \) which, upon partial reduction and alkene isomerisation (thermodynamically driven by moving the alkene into conjugation) may undergo a second Corey–Chaykovsky reaction to install the cyclopropane moiety of \( \text{38} \). It was envisioned that a Wittig reaction followed by selective reduction would install the methyl ketone side chain, and a key SmI\(_2\)-mediated ring closing reaction would complete the synthesis.

\[
\begin{array}{c}
\text{Scheme 6 Retrosynthetic strategy towards pyxidatol C.}
\end{array}
\]

1.9 Asymmetric Synthesis

It was planned that the synthesis could be rendered asymmetric by the desymmetrisation of either \( \text{meso-compound 39} \) or \( \text{meso-compound 40} \). There is good precedent for related reactions, for example, the selective hydrolysis of bisacetate \( \text{43} \) using porcine pancreatic lipase (PPL) to generate enantio-enriched alcohol \( \text{44} \), which was first described by Von Langen and Tolman (Scheme 7).\textsuperscript{25}
Scheme 7 The desymmetrisation of 43 using PPL.\textsuperscript{25}

We envisioned that a similar desymmetrisation could be applied to bisacetate 46, which should be easily prepared from cycloheptadiene 39 in 2 steps (Scheme 8).

Scheme 8 The planned desymmetrisation of 46 using PPL.

The monohydrolysis of 40 using pig liver esterase enzyme (PLE) is an alternative strategy. The monohydrolysis of cyclopropyl meso-diesters has previously been reported in the literature (e.g. 48\textrightarrow 49, Scheme 9).\textsuperscript{26} Note that the monohydrolysis of the olefinic diester 40 is preferable to the monohydrolysis of diester 41 (cf. 48), as this desymmetrisation comes at a later stage in the synthetic strategy.

Scheme 9 The desymmetrisation of 48 using PLE and the proposed desymmetrisation of 40 using PLE.\textsuperscript{26}
1.10 Taylor Group Methodologies

In 2007, the Taylor group reported a gem-dimethylcyclopropanation procedure using triisopropyl-sulfoxonium tetrafluoroborate. The cyclopropanation of diethyl fumarate (Scheme 10) has since been carried out to give 53, an intermediate in our retrosynthetic analysis of pyxidatol C.

![Scheme 10](image)

Scheme 10 Taylor Group modified Corey–Chaykovsky protocol.

The Taylor group’s tandem MnO₂ oxidation then Wittig trapping process (TOP methodology) has been used previously to prepare 55. It was expected that this procedure could also be used to prepare the gem-dimethyl analogue, 57 (Scheme 11).

![Scheme 11](image)

Scheme 11 Taylor Group Tandem Oxidation Procedure (TOP).
1.11 Preliminary Work on a Model System

Preliminary work in the group carried out by Unsworth\textsuperscript{27} (Scheme 12), using a simplified desmethyl analogue, offered significant promise. Upon heating at 130 °C in xylene, the Cope rearrangement of 55 proceeded smoothly to give 58. Reduction, followed by mono-oxidation then yielded lactone 60, which was then isomerised to 61 under basic conditions. Finally a Corey-Chaykovsky reaction afforded 62 as a single diastereomer, which was believed to possess the relative stereochemistry required for pyxidatol C based on n.O.e experiments (an n.O.e enhancement between the cyclopropane CH\textsubscript{2} and the CHCH\textsubscript{2}O protons is observed, whereas no n.O.e enhancement is seen for the lactone CH\textsubscript{2} protons with the cyclopropane CH\textsubscript{2} protons).

\begin{center}
\begin{tikzpicture}
\node at (0,0) (a) {$\text{EtO}_2\text{C}\equiv\text{C}\equiv\text{CO}_2\text{Et}$};
\node at (2.5,0) (b) {$\rightarrow$};
\node at (3.5,0) (c) {xylene};
\node at (5,0) (d) {$\rightarrow$};
\node at (6,0) (e) {Lithium aluminium hydride, \text{THF}};
\node at (7.5,0) (f) {$\rightarrow$};
\node at (8.5,0) (g) {HO\textsubscript{2}C\text{CH}\text{Cl}};
\node at (0,-1.5) (h) {LiAlH\textsubscript{4}, \text{THF}};
\node at (2.5,-1.5) (i) {$\rightarrow$};
\node at (3.5,-1.5) (j) {DBU, \text{THF}};
\node at (5,-1.5) (k) {$\rightarrow$};
\node at (6,-1.5) (l) {HO\textsubscript{2}C\text{CH}\text{Cl}};
\node at (7.5,-1.5) (m) {\text{Me}_3\text{Si}^+\text{I}^-};
\node at (9,-1.5) (n) {\text{NaH, DMF}};
\node at (10.5,-1.5) (o) {$\rightarrow$};
\node at (12,-1.5) (p) {HO\textsubscript{2}C\text{CH}\text{Cl}};
\node at (10.5,0) (q) {55, 130 °C, 16 h};
\node at (12,0) (r) {58, 80%};
\node at (10.5,-1.5) (s) {60, 40-60%};
\node at (12,-1.5) (t) {61, 59%};
\node at (11,-2.5) (u) {62, 21%};
\end{tikzpicture}
\end{center}

\textbf{Scheme 12} Preliminary work on a desmethyl model system.\textsuperscript{27}

1.12 Aims and objectives

As outlined, a range of different approaches have been used to synthesise africanane natural products. We aimed to use established Taylor group methodologies in a total synthesis of the africanane, pyxidatol C.

Initial work would involve optimising Unsworth’s preliminary work on the simplified desmethyl model system (Scheme 12) before applying this chemistry to the analogous \textit{gem}-dimethyl pyxidatol C system.
Chapter 2
From the Desmethyl Model System to the Gem-Dimethyl System

2.1 Optimisation of Preliminary Work & Methyl Ketone Side-Chain Studies

Initial work towards the synthesis of pyxidatol C involved repeating Unsworth’s preliminary studies (Scheme 12) with a view to optimising the low yielding steps. The route to lactone 60 was easily reproducible and thus attention focused on improving its isomerisation. This preliminary work showed that the unwanted lactone 63 was obtained upon heating compound 60 for 1 h at 70 °C. Unsworth had also established that by lowering the temperature to RT and decreasing the reaction time to 40 min, a 59% yield of lactone 61 along with a 30% yield of lactone 63 were isolated.27 Lowering the temperature further to 0 °C was therefore considered a good starting point for further optimization and, pleasingly, after stirring lactone 60 for 2.5 h at 0 °C, the desired lactone 61 was isolated in a yield of 74%, an improvement of 15%. A small amount of the unwanted α,β-γ,δ-unsaturated lactone 63 and the trans-epimer, lactone 64, were also obtained in low yields (11% and 6% respectively).

![Scheme 13 Optimised isomerisation conditions for the synthesis of lactone 61.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Reaction Time (min)</th>
<th>Ratio of Productsa</th>
<th>61</th>
<th>63</th>
<th>64</th>
</tr>
</thead>
<tbody>
<tr>
<td>127</td>
<td>70</td>
<td>60</td>
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<td>1</td>
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</tr>
<tr>
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<td>RT</td>
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<td>1.75</td>
<td>1</td>
<td>0</td>
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</tr>
<tr>
<td>3</td>
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<td>40</td>
<td>1.75</td>
<td>0</td>
<td>1</td>
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<td>4</td>
<td>0</td>
<td>30</td>
<td>1</td>
<td>0</td>
<td>1</td>
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</tr>
<tr>
<td>5b</td>
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<td>150</td>
<td>8</td>
<td>1.5</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

aRatio determined by analysis of the 1H NMR spectra of the unpurified reaction mixtures.
bThe compounds 61, 63 and 64 were separated by flash column chromatography and the isolated yields are shown in Scheme 13.

Table 1 Optimisation of the isomerisation of lactone 60 to lactone 61.
Unfortunately, the cyclopropanation of 61 was harder to optimise. Using the Taylor group modified Corey-Chaykovsky cyclopropanation conditions\textsuperscript{23} (61 was reacted with NaH and trimethylsulfoxonium iodide in DMF at RT), furnished 62 in only 21\% yield during preliminary work.\textsuperscript{27} The same conditions were re-tested, but a similarly poor yield was obtained, with only 26\% of cyclopropane 62 isolated. An alternative procedure\textsuperscript{28} was tested using MTBD in acetonitrile at 60 °C but unfortunately this protocol furnished cyclopropane 62 in only 19\% yield. However on a more positive note both the NaH/DMF and MTBD/MeCN reaction conditions, yielded only one diastereomer; its relative stereochemistry determined as that required for pyridatol C via n.O.e (Scheme 14).\textsuperscript{27} We were surprised by the low yields as the $^1$H NMR spectra of the unpurified reaction mixtures showed very little evidence of decomposition. We considered that the sulfoxonium ylide was also adding into the enone from the other face but, rather than closing to form the other diastereomer, material was being lost as the salt. However by taking the $^1$H NMR spectrum (D$_2$O) of the aqueous extract no identifiable products were observed.

\begin{center}
\textbf{Scheme 14} Corey-Chaykovsky cyclopropanation reactions.
\end{center}

Given the difficulties associated with the cyclopropanation of lactone 61 we planned instead to install the methyl ketone side-chain first with a view to testing the Corey-Chaykovsky cyclopropanation on ester 65 (Scheme 15).

\begin{center}
\textbf{Scheme 15} Cyclopropanation of ester 65.
\end{center}
The initial strategy for installation of the side chain was via Wittig olefination, followed by selective reduction of the resulting α,β-unsaturated ketone. This strategy was tested using lactol 67, itself formed via the IBX oxidation of diol 59. However, clean material could not be recovered from the reaction, even after flash column chromatography. Based on analysis of the $^1$H NMR spectrum of the unpurified reaction mixture, we speculated that isomerisation of the C1, C2 double bond into conjugation with the newly formed α,β-unsaturated ketone was an unwanted side reaction (Scheme 16). We tentatively assigned the major component of the reaction mixture as 68 based on peaks at 7.12 (1H, d, $J$ 16.0 Hz, H-4), 6.48 (1H, t, $J$ 6.5 Hz, H-2), 6.15 (1H, d, $J$ 16.0 Hz, H-5) in the $^1$H NMR spectrum of the unpurified reaction mixture.

Scheme 16 Installation of side-chain Wittig-reduction route.

An alternative strategy to introduce the side-chain was therefore tested on a model system. A cyclohexyl model system was chosen to test this alternative route. Iodination of cyclohexylmethanol using triphenylphosphine, imidazole and iodine in CH$_2$Cl$_2$ provided iodide 69 in 62% yield. Then β-ketoester 70 was prepared in 72% yield by refluxing iodide 69, NaH and tert-butyl 3-oxobutanoate in THF. Decarboxylation of β-ketoester 70 at reflux in benzene with p-TSA furnished ketone 71 in 85% yield and completed the installation of the desired side-chain into the cyclohexyl model system. This sequence was not tested on our desmethyl analogue of pyxidatol C but this chemistry would later be trialled on the gem-dimethyl, pyxidatol C system (Chapter 4).
2.2 Further Studies on the Model System: A Simmons-Smith strategy

Given that difficulties were encountered using the Corey-Chaykovsky cyclopropanation, it was decided that an alternative method of cyclopropanation should be examined. It is well known\textsuperscript{29} that in the Simmons-Smith reaction, the rate of cyclopropanation is faster for an allylic alcohol compared with an unfunctionalised alkene and we hoped to exploit this fact to achieve a regioselective cyclopropanation in our synthesis. DIBAL reduction of lactone 60 furnished diol 72 in 82\% yield, providing a suitable test substrate for this Simmons-Smith reaction. However, treatment of diol 72 with diiodomethane and diethylzinc led only to a mixture of cyclopropanes 73, 74 and bis cyclopropane 75 in poor yield. The trace presence of cyclopropane 75 is supported by HRMS. (Scheme 18).

Scheme 18 Simmons-Smith reaction on diol 72.
The stereochemistry of cyclopropanes 73 and 74 in the Simmons-Smith reaction of diol 72 was confirmed by a comparison with the product of LiAlH₄ reduction of lactone 62 (Scheme 19), where stereochemistry had already been confirmed by n.O.e (see Chapter 1.11, Scheme 12).

![Scheme 19 LiAlH₄ reduction of lactone 62.](image)

Despite the poor yield and poor stereocontro in the Simmons-Smith reaction of diol 72, we could see sufficient scope for optimisation to believe that the reaction could be improved. For example zinc can coordinate to either alcohol of the diol 72 and we believed that protecting the non-allylic alcohol might improve the reaction.

The efficient mono-silylation of symmetric diols was established in 1986 by McDougal et al. and was employed in the mono-TBS protection of diol 59 furnishing 76 in 89% yield. As outlined in Scheme 20, Dess–Martin oxidation provided the corresponding aldehyde 77 in 97% yield, which was isomerised to α,β-unsaturated aldehyde 78 under basic conditions. Pleasingly, no unwanted side products were obtained and after 20 min at 0 °C and the desired aldehyde 78 was obtained in 77% yield. DIBAL reduction then afforded alcohol 79, the required substrate for the Simmons-Smith reaction, in 64% yield.

![Scheme 20 Mono-protection route to Simmons-Smith precursor 79.](image)
The Simmons-Smith cyclopropanation of alcohol 79 was, unfortunately, less straightforward. As outlined in Scheme 21, initial conditions trialled used four equivalents of diiodomethane and two equivalents of diethylzinc in CH₂Cl₂ at RT. After 4 h, a ratio of 7:1 bis-cyclopropane 81 to cyclopropane 80 was observed by tentative analysis of the ¹H NMR spectrum of the unpurified reaction mixture. Consumption of the peaks corresponding to the double bonds of diene 79 at 5.95 (1H, t, J 6.5 Hz), 5.78–5.72 (1H, m) and 5.47 (1H, ddt, J 12.0, 6.5, 1.5 Hz) was observed alongside the appearance of cyclopropyl peaks at 0.98–0.84 (2H, m) and 0.74–0.60 (2H, m).

Scheme 21 Simmons-Smith reaction on TBS protected alcohol 79.

Unfortunately cyclopropanes 80 and 81 are indistinguishable by thin layer chromatography (tlc) and so the reaction progress could not be followed using this method. The reaction time was decreased to 30 min, after which time a ratio of 3:1 81 to 80 was observed (Entry 2, Table 2). Between 10 and 20 min predominantly starting material was recovered (Entry 3 and 4, Table 2). The reaction temperature was lowered to 0 °C as we thought it would be easier to control the reaction and after 4 h at this temperature a ratio of 2.5:1 81 to 80 was observed (Entry 5, Table 2), a promising result. However, reducing the reaction time had very little effect on the chemo-selectivity (Entry 6, Table 2). The reaction was attempted at −10 °C but even after 4 h there was no reaction (Entry 7, Table 2). Halving the number of equivalents of diiodomethane and diethylzinc, to two and one equivalents respectively, also resulted in no reaction after 4 h at RT (Entry 8, Table 2).
Given that we were unable to achieve good chemo-selectivity using standard Simmons-Smith conditions, a Charette modification (which is also known to react faster with allylic alcohols than unfunctionalised alkenes) was trialled. The first step of the Simmons-Smith reaction using allylic alcohols is the generation of an iodomethylzinc alkoxide and computational studies by Nakamura et al. suggest that the reactive species is likely to be a multimetallic aggregate, either a dimer or a tetramer (Figure 5). A dioxaborolane additive is used in the Charette reaction and computational studies by Wang et al. suggest that the reactive species is a complex formed from dioxaboralane, Zn(CH$_2$I)$_2$ and the alcohol (Figure 5).

![Figure 5 The proposed reactive species in the Simmons-Smith cyclopropanation of allylic alcohols.](#)

It was hoped that this alternative reaction mechanism would improve the chemo-selectivity of our reaction but unfortunately this procedure only led to decomposition of substrate 79 (Scheme 22).
A TBDPS variant of the route shown in Scheme 20 was attempted. It was anticipated that the extra bulk may provide some additional steric hindrance to the unwanted cyclopropanation on the unfunctionalised alkene. Pleasingly the synthesis of TBDPS-containing 85 proved as facile as its TBS analogue (Scheme 23), but unfortunately, the protecting group switch did not improve the chemo-selectivity for the cyclopropanation of 85, which was found to be similarly poor to that of TBS variant 79; the best result was a 2:1 ratio of bis-cyclopropane 87 to cyclopropane 86 (Scheme 23). The ratio of 87 to 86 was again determined by analysis of the $^1$H NMR spectra of the unpurified reaction mixtures. Consumption of the peaks corresponding to the double bonds of diene 85 at 5.97 (1H, dd, $J$ 7.5, 5.5 Hz), 5.74–5.69 (1H, m) and 5.51–5.45 (1H, m) was observed alongside the appearance of cyclopropyl peaks at 1.01–0.91 (2H, m) and 0.77–0.62 (2H, m).
Scheme 23 TBDPS Mono-protection route to Simmons-Smith precursor 85 and subsequent Simmons-Smith cyclopropanation.

As shown, we were unable to achieve good chemo-selectivity when using Simmons-Smith cyclopropanation on the desmethyl model system. However, we believed that the gem-dimethyl group on the analogous pyxidatol C system could influence this cyclopropanation. We thought it possible that the steric bulk of the cycloheptadiene dimethyl group might hinder the unwanted cyclopropanation on the unfunctionalised alkene (Figure 6) giving greater control over the regioselectivity of the cyclopropanation. Therefore, attention turned from the model system to preparation of the gem-dimethyl equivalent of alcohol 85.

Figure 6 Potential destabilising steric interaction of gem dimethyl group toward cyclopropanation of the unfunctionalised alkene.
2.3 From the Desmethyl Model System to the Gem-Dimethyl System

The requisite gem-dimethyl cyclopropane was made using a non-commercial sulfoxonium salt, necessitating the preparation of triisopropylsulfoxonium tetrafluoroborate 52, which was prepared in two steps from commercially available diisopropyl sulfide. Badet and Julia\(^\text{34}\) reported the synthesis of sulfonium salt 51 using IPA and MSA as a source of isopropyl cation to alkylate diisopropyl sulfide, which was followed by subsequent anion exchange with tetrafluoroboric acid. A protocol for the oxidation of this salt was developed within the Taylor group by Pugh,\(^\text{23}\) based on work by Ciba-Geigy.\(^\text{35}\) A sulfonoperoxic acid is formed \textit{in situ} when ortho-nitrobenzenesulfonyl chloride, hydrogen peroxide and barium hydroxide are mixed, which oxidizes sulfonium salt 51 to sulfoxonium salt 52 (Scheme 24). With the sulfoxonium salt 52 in hand, Corey-Chaykovsky type cyclopropanation of diethyl fumarate was then performed, which gave gem-dimethyl cyclopropane 53 in 73% yield, although yields of 90% have been obtained for this reaction under these conditions, within the Taylor group.\(^\text{23}\) LiAlH\(_4\) reduction followed in 86% yield and finally a TOP reaction, furnished \(E,E\)-diester 57\textit{a} in 69% yield and \(E,Z\)-diester 57\textit{b} in 4% yield.

\[\text{Scheme 24} \text{ The synthesis of gem-dimethyl diester 57\textit{a} using Taylor group methodologies.}\]
With diester 57a in hand, we could now test the key step in our retrosynthesis, the Cope rearrangement, which we hoped would introduce the 7 membered ring found in pyxidatol C. We were very disappointed to find that, after following the same procedure as that for its desmethyl analogue 55a, heating 57a in xylene at 130 °C, only starting material was observed along with significant decomposition products in the 1H NMR spectrum of the unpurified reaction mixture (Scheme 25).

**Scheme 25** The unsuccessful thermal Cope rearrangement of 57a.

### 2.4 The Ethoxide-Promoted Cope Rearrangement

Disappointingly, gem-dimethyldivinylcyclopropane 57a did not undergo the Cope rearrangement upon heating in xylene. We therefore considered an alternative strategy in which to encourage the Cope rearrangement. The Cope rearrangements of trans-divinylcyclopropanes are understood to proceed by first epimerising to the cis-cyclopropane before undergoing a rapid [3,3]-sigmatropic shift. With this in mind, it was thought that a base-catalysed epimerisation could facilitate the Cope rearrangement. DBU (pK<sub>a</sub>H in water ~12) in THF at 70 °C was attempted but there was no reaction. The stronger base, sodium ethoxide (pK<sub>a</sub>H in water ~16) in ethanol at 90 °C, was tested and pleasingly the Cope rearrangement was successful. Unfortunately, subsequent isomerisation of the double bonds into conjugation with the ester groups also occurred in situ, providing cycloheptadiene 89 in 80% yield (Scheme 26).
Scheme 26 Ethoxide catalysed Cope rearrangement and isomerisation to give 89.

In order to confirm that the ethoxide base was indeed catalyzing the Cope rearrangement, and that the change in solvent from xylene to ethanol was not responsible for the observed Cope rearrangement, the reaction was attempted in the absence of base, using EtOH as the solvent. Thus, diester 57a was heated in ethanol at 90 °C and as expected there was no reaction, confirming that the base was responsible for the Cope rearrangement. Under otherwise identical conditions to the reaction with sodium ethoxide, but at 50 °C and 70 °C, incomplete conversion into cycloheptadiene 89 was observed and so the initial conditions, using sodium ethoxide at 90 °C, were considered optimal for the synthesis of cycloheptadiene 89.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Solvent</th>
<th>Base</th>
<th>Ratio of Products*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>130</td>
<td>xylene</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>THF</td>
<td>DBU</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>EtOH</td>
<td>NaOEt</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>EtOH</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>EtOH</td>
<td>NaOEt</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>EtOH</td>
<td>NaOEt</td>
<td>10</td>
</tr>
</tbody>
</table>

*aRatio determined by analysis of the 1H NMR spectra of unpurified reaction mixtures.

bSome decomposition was also observed.

Table 3 The base-catalysed Cope rearrangement of 57a.
While the Cope rearrangement of 57a was achieved using NaOEt as an additive, the \textit{in situ} isomerisation of the double bonds into conjugation with the ester groups was an unwanted side reaction. However, the isomerisation of one of the double bonds was necessary in the retrosynthetic plan. We therefore planned to exploit this isomerisation by preparing an unsymmetrical divinylcyclopropane 90 that could be subjected to the optimized conditions for the base-catalysed Cope rearrangement in the expectation of obtaining unsymmetrical cycloheptadiene 91 (Scheme 27). It was then hoped to synthesise alcohol 90 by monohydrolysis of diester 57a, followed by borane reduction of the resulting acid 92.

Scheme 27 The synthetic strategy towards cycloheptadiene 91.

Unfortunately, monohydrolysis proved troublesome; unsuccessful attempts using lithium hydroxide in ethanol\textsuperscript{36} and sodium hydroxide in water/THF\textsuperscript{37} led only to di-acid formation and an alternative strategy targeting protected hydroxyester 100 (Scheme 28) was planned instead, and this proved straightforward. Mono-TBS protection of diol 56a furnished alcohol 93 in 65% yield which, following Dess–Martin oxidation, gave aldehyde 94 in 60% yield. Wittig olefination followed by DIBAL reduction afforded alcohol 96 in 79% yield. Benzyl protection with benzyl bromide gave 97 which was taken on crude to the next step. TBS cleavage with TBAF, then gave 98 in 44% over two steps. Dess–Martin oxidation (68% yield) followed by Wittig olefination (96% yield) furnished the required substrate 100 for testing the key mixed Cope reaction. We trialled the reaction using the established ethoxide conditions (Entry 3, Table 3) but, disappointingly, divinylcyclopropane 100 was unreactive under these conditions and starting material 100 was recovered from the reaction unchanged.
Scheme 28 The synthesis of cyclopropane 100.

In summary the Cope rearrangement of divinylcyclopropane 55 was successful (Scheme 25). However, under identical conditions, on the analogous gem-dimethyl pyxidatol C system it was unsuccessful (Scheme 25). The Cope rearrangement of a gem-dimethyl divinylcyclopropane was fundamental to the synthetic strategy for the synthesis of pyxidatol C and presented a significant challenge. Pleasingly, the Cope rearrangement was possible, using base-catalysed trans/cis-isomerisation, and despite leading to the unwanted cyclopheptadiene 89 (Scheme 26), this result provided reason to be optimistic that this challenge could be overcome (Chapter 3).
Chapter 3
The Cope Rearrangement of \textit{Gem}-Dimethyl Substituted Divinylcyclopropanes

3.1 Introduction

3.1.1 The Cope rearrangement of divinylcyclopropanes

The thermal Cope rearrangement of divinylcyclopropanes was first described by Vogel in 1960, who reported the rearrangement of divinylcyclopropane \textit{102a} to 1,4-cycloheptadiene \textit{103} (Scheme 29).\textsuperscript{38-40}

\begin{center}
\begin{tikzpicture}
\node (start) at (0,0) {$102a$}; \node (end) at (2,0) {$103$}; \node (reaction) at (1,0) {$\xrightarrow{-50^\circ C}$};
\draw [->] (start) -- (reaction);
\draw [->] (reaction) -- (end);
\end{tikzpicture}
\end{center}

\textbf{Scheme 29} The Cope rearrangement of \textit{cis}-divinylcyclopropane \textit{102a}.

The rearrangement of \textit{cis}-divinylcyclopropane \textit{102a} to cycloheptadiene \textit{103} is facile, even at $-50^\circ C$. However, the rearrangement of its \textit{trans}-analogue \textit{102b} required temperatures of 190 $^\circ C$ (Scheme 30). The Cope rearrangements of \textit{trans}-divinylcyclopropanes are understood to proceed \textit{via} epimerisation to the \textit{cis}-cyclopropane (at temperatures in the region of 120–200 $^\circ C$) before undergoing a rapid [3,3]-sigmatropic shift.\textsuperscript{41}

\begin{center}
\begin{tikzpicture}
\node (start) at (0,0) {$102b$}; \node (end) at (2,0) {$103$}; \node (reaction) at (1,0) {$\xrightarrow{190^\circ C}$};
\node (temp) at (1,0) {$\left[\xrightarrow{190^\circ C}102a\right]$};
\draw [->] (start) -- (temp);
\draw [->] (temp) -- (reaction);
\draw [->] (reaction) -- (end);
\end{tikzpicture}
\end{center}

\textbf{Scheme 30} The Cope rearrangement of \textit{trans}-divinylcyclopropane \textit{102b} first reported by Vogel \emph{et al.}

The Cope rearrangement of divinylcyclopropanes is symmetry allowed when it is suprafacial for all three components \([\sigma_2 + \sigma_2 + \sigma_2]\). There are two possible transition state structures for an all-suprafacial reaction, one being chair-like and the other boat-like. The Cope rearrangement of divinylcyclopropanes proceeds \textit{via} a boat-
like transition state (Figure 7) because the chair-like transition state would lead to the formation of a highly strained ring containing two trans-double bonds.

**Figure 7** The symmetry-allowed chair and boat-like transition state for the Cope rearrangement of divinylcyclopropanes.

### 3.1.2 Steric Effects in the Cope Rearrangement of Divinylcyclopropanes

Literature precedent shows that the stability of this boat-like transition state is highly sensitive to steric interactions. Ohloff and Pickenhagen were the first to report this phenomenon (Scheme 31). They found that diene 104a underwent the Cope rearrangement at 15 °C whereas diene 104b required the higher temperature of 75 °C in order to react. This was attributed to a destabilising steric interaction between the cyclopropyl moiety and the butyl group in the boat-like transition state of 104b. Even higher temperatures (175 °C) were required before dienes 104c and 104d rearranged to generate cycloheptadiene 105, because in their cases epimerisation to the cis-cyclopropane was also required.

**Scheme 31** Work by Ohloff and Pickenhagen on the thermal Cope rearrangement. Reactions were performed without solvent and yields and reaction times were not reported.
Baldwin et al.\textsuperscript{43,44} tested the Cope rearrangements of compounds 106a–106c (Scheme 32). They found that the \textit{E,E}-diene 106a, underwent the thermal Cope rearrangement at 178 °C giving cycloheptadiene 107a. The Cope rearrangement of the \textit{E,Z}-diene 106b was also successful, this time at 179 °C, affording cycloheptadiene 107b. Crucially, \textit{Z,Z}-diene 106c, did not undergo a Cope rearrangement; Baldwin proposed that the boat-like transition state for this rearrangement is higher in energy than that of the analogous \textit{E,E}/\textit{E,Z} variants because of two destabilising steric interactions between the methyl substituents and the cyclopropyl moiety. As such, the rearrangement does not take place even though \textit{cis}/\textit{trans}-isomerisation of the cyclopropane takes place.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {$106a$};
\node (b) at (2,0) {$107a$, 99\%};
\node (c) at (0,-2) {$106b$};
\node (d) at (2,-2) {$107b$, 95\%};
\node (e) at (0,-4) {$106c$};
\node (f) at (2,-4) {$106d$};
\draw [->] (a) -- node [above] {178 °C} node [below] {4.2 h} (b);
\draw [->] (c) -- node [above] {179 °C} node [below] {4.2 h} (d);
\draw [->] (e) -- node [above] {179 °C} node [below] {4.2 h} (f);
\end{tikzpicture}
\end{center}

\textbf{Scheme 32} Work by Baldwin \textit{et al.} on the thermal Cope rearrangement.\textsuperscript{43–44} Reactions were performed without solvent.

Work by Schneider and Rau,\textsuperscript{45} showed that the Cope rearrangement of diene 102a to cycloheptadiene 103 occurs at a rate 5800 times faster than the conversion of diene 108 into cycloheptadiene 109 (Scheme 33). Again, a destabilising steric interaction between the methyl group in diene 108 and the cyclopropyl ring moiety in the transition state was used to explain this large difference in rate.
Scheme 33 Work by Schneider and Rau on the thermal Cope rearrangement.\textsuperscript{45} The solvent and the yields for the reactions were not reported.

Sasaki \textit{et al.}\textsuperscript{46,47} observed the profound effect a cyclopropyl \textit{gem}-dimethyl group can have on the rearrangements of aza-divinylcyclopropanes. They found that the ‘aza-divinylcyclopropane’ rearrangement (which is still a [3,3]-sigmatropic rearrangement but not strictly a Cope rearrangement) of isocyanate 110 was extremely facile; in fact, they could not isolate vinylcyclopropyl isocyanate 110, even when it was prepared at -45 °C, and instead rearranged product 111 was isolated. However, they found that the ‘aza-divinylcyclopropane’ rearrangement of the \textit{gem}-dimethyl analogue 112 required the far greater temperature of 144 °C before rearranged product 113 was observed even though the substituents are \textit{cis}-orientated (Scheme 34).

Scheme 34 Work by Sasaki \textit{et al.} on the ‘aza-divinylcyclopropane’ rearrangement.\textsuperscript{46}

Müller \textit{et al.}\textsuperscript{48} report similar findings, in which a \textit{gem}-dimethyl group had a similar effect on related ‘aza-divinylcyclopropane’ rearrangements; isocyanate 114 underwent rearrangement to product 115 at 80 °C, whereas the \textit{gem}-dimethyl analogue 116 did not rearrange, even upon heating to 144 °C.
Further work by Sasaki et al.\textsuperscript{46} showed that the cis-divinylcyclopropanes 118a and 119a, bearing a gem-dimethyl group, did not undergo the Cope rearrangement when heated to 144 °C and instead underwent cis/trans-isomerisation at the cyclopropane.

An interesting Cope rearrangement of enone 120 was reported by Piers et al.,\textsuperscript{49–51} in which after 4 h at 69 °C diene 120 was converted into cycloheptadiene 121 in 97% yield. The analogue 122a, bearing a methyl substituent on the enone, was found to be far more stable, however; on heating diene 122a to a far greater temperature (144 °C) isomerisation to the trans-isomer 122b was found to compete with the Cope rearrangement and the ratio of the two products cycloheptadiene 123 and trans-diene 122b was found to vary between 1.1:1 to 2.7:1.
The examples described above all demonstrate that the energy of the boat-like transition state in the Cope rearrangement of divinylcyclopropanes is highly sensitive to steric interactions. This may explain why in the vast majority of literature examples, the cyclopropane is substituted only with the two alkene groups involved in the rearrangement. Limited examples of the Cope rearrangement of trisubstituted cyclopropanes have also been reported, but these are far less common (e.g. 123→124, Scheme 38).
To the best of our knowledge, the only examples of tetrasubstituted cyclopropanes undergoing the Cope rearrangement, apart from the example described by Piers et al. (Scheme 37),\textsuperscript{49–51} are of fused bicyclic systems (e.g. 125→126, Scheme 39).\textsuperscript{53} In these systems the compound is much more rigid and the conformation of the starting material allows the Cope rearrangement to occur more readily. The relief of ring strain is likely to be an additional driving force in these cases.

\begin{center}
\begin{tikzpicture}
  \node [draw] (start) at (0,0) {125};
  \node [draw] (end) at (2,0) {126, 68\%};
  \draw [->] (start) -- (end) node [midway, above] {80 °C, toluene \(44\) h};
\end{tikzpicture}
\end{center}

\textbf{Scheme 39} Work by Kim \textit{et al.} on the thermal Cope rearrangement on a fused bicyclic system.\textsuperscript{53}

### 3.2 The Cope Rearrangement of Diester 57a

As outlined in Chapter two, we were able to prepare cycloheptadiene 58a by heating diester 55a in xylene for 16 h but the analogous reaction of diene 57a was unsuccessful (Scheme 40).

\begin{center}
\begin{tikzpicture}
  \node [draw] (start1) at (0,0) {EtO\textsubscript{2}C\textsubscript{2}C\textsubscript{2}Et};
  \node [draw] (end1) at (2,0) {EtO\textsubscript{2}C\textsubscript{2}CO\textsubscript{2Et}};
  \draw [->] (start1) -- (end1) node [midway, above] {xylene \(130\) °C, 16 h};
\end{tikzpicture}
\end{center}

\begin{center}
\begin{tikzpicture}
  \node [draw] (start2) at (0,0) {EtO\textsubscript{2}C\textsubscript{2}C\textsubscript{2}Et};
  \node [draw] (end2) at (2,0) {EtO\textsubscript{2}C\textsubscript{2}CO\textsubscript{2Et}};
  \draw [->] (start2) -- (end2) node [midway, above] {xylene \(130\) °C, 16 h};
\end{tikzpicture}
\end{center}

\textbf{Scheme 40} The Cope rearrangement of 55a to give 58a and the unsuccessful Cope rearrangement of 57a.

Based on the literature precedent described in section 3.1, this result is not altogether unexpected as it is known that bulky substituents typically inhibit the Cope rearrangements of divinylcyclopropanes\textsuperscript{41–51} by destabilising the boat-like transition state. A destabilising steric interaction between a \textit{geminal} methyl group and the
double bond moiety in the transition state of diene 57a (A, Figure 8) rearranging to cycloheptadiene 88a is most likely the major obstacle to rearrangement explaining why the thermal Cope rearrangement is facile with the desmethyl substrate 55a (B, Figure 8), but not with its gem-dimethyl equivalent 57a (Scheme 40).

![Figure 8](image_url) A diagram showing the potential destabilizing steric interactions when 57a adopts the required boat-like transition state (A).

### 3.3 A Systematic Study into the Cope Rearrangement

We were surprised to discover that a study comparing the Cope rearrangements of a gem-dimethyl divinylcyclopropane with its non-methylated analogue has, to the best of our knowledge, not been reported in the literature. Thus, in order to better understand how steric effects influence our system, we planned a systematic study into the Cope rearrangement of the gem-dimethyl substrate 57 and desmethyl substrate 55. We planned to prepare all of the possible cis/trans and E/Z isomers of 57 and 55 (Figure 9) and determine how readily they undergo the Cope rearrangement.

![Figure 9](image_url) The target substrates for a systematic study into the Cope rearrangement.
3.4 Synthesis of Substrates (Divinylcyclopropanes 57a–57f and 55a–55f)

3.4.1 Synthesis of Gem-Dimethyl Divinylcyclopropanes (57a–57f)

Commercially available ethyl chrysanthemate was used to prepare diols 56a and 56b (which were separable by flash column chromatography) via ozonolysis followed by LiAlH₄ reduction (Scheme 41).

\[
\text{EtO}_2\text{C} \quad \text{EtO}_2\text{C} \quad \text{O}_3, \text{CH}_2\text{Cl}_2
\]

-78 °C

\[
\text{EtO}_2\text{C} \quad \text{EtO}_2\text{C}
\]

127, 97%
cis:trans 2:3

LiAlH₄, THF

0 °C → RT, 10 min

HO\ldots\text{OH} +

56a, 49%

HO\ldots\text{OH}

56b, 31%

**Scheme 41** The synthesis of diols 56a and 56b.

*Trans*-dil 56a was then subjected to Taylor group TOP chemistry (Section 1.10),²⁴ resulting in the preparation of two of the required substrates, *E,E*-diene 57a and *E,Z*-diene 57b, in 69% and 4% yield respectively (Scheme 42). The double bond geometry of both compounds (and indeed throughout) was confirmed by analysis of their *J*₃ H-H alkene coupling constants. Note that an alternative preparation of dil 56a was also described earlier (see Scheme 24).

\[
\text{HO} \ldots \text{OH}
\]

**Scheme 42** The synthesis of 57a and 57b. Previously described in Section 2.3.
The Still–Gennari modification of the HWE reaction was used to prepare 57c, following manganese dioxide oxidation of diol 56a to generate dialdehyde 128 (Scheme 43).

Scheme 43 The synthesis of 57c (> 20 : 1 Z : E).

A stepwise strategy was necessary for the synthesis of the cis-variants, because the oxidation of cis-diols, for example 56b, results in lactone formation via lactol 129 (Scheme 44).

Scheme 44 MnO2 oxidation of cis-cyclopropyl diols leads to lactone formation.

Using the ethyl chrysanthemate-derived diol 56a, lactol 129 was prepared by IBX oxidation. Subsequent Wittig reaction furnished the desired compound 131.

Scheme 45 The synthesis of 131 via lactol 129 (> 20 : 1 E : Z).

However, poor yields and difficulties repeating the route shown above, led us to test an alternative synthesis of compound 131 (Scheme 46). Thus, the mono-TBS protection of 56b, followed by a TOP reaction was straightforward, affording 133 in good yield. Unfortunately, TBS cleavage using TBAF led to oxy-Michael addition.
giving rise to the unwanted tetrahydrofuran 134. Pleasingly, this unwanted side-reaction was avoided by using an acidic source of fluoride (aqueous HF) furnishing the desired alcohol 131. A TOP reaction was then performed, completing the synthesis of two of the required substrates; E,E-diene 57d was obtained in 68% yield along with E,Z-diene 57e in 16% yield. (Scheme 46).

The oxidation of alcohol 132 using MnO₂ followed by a Still–Gennari reaction, silyl deprotection using HF (again, this was necessary to avoid oxy-Michael addition) and another MnO₂ oxidation/Still–Gennari sequence afforded the final gem-dimethyl substrate, Z,Z-diene 57f (Scheme 47).
3.4.2 Synthesis of Desmethyl Divinylcyclopropanes (55a–55f)

The trans-desmethyl divinylcyclopropanes were prepared from commercially available diethyl trans-1,2-cyclopropanedicarboxylate; LiAlH₄ reduction afforded diol 54a, and the Taylor group’s TOP chemistry was then used to prepare E,E-diene 55a (Scheme 48).

Scheme 47 The synthesis of 57f.

Scheme 48 The synthesis of 55a. Previously described in Section 1.10.
The synthesis of $E,Z$-diene $55b$ began with mono-TBS protection of $54a$, followed by a TOP reaction furnishing ester $141$. TBS cleavage using TBAF furnished $142$ (oxy-Michael addition cannot take place on the trans-cyclopropane system) and subsequent MnO$_2$ oxidation to form aldehyde $143$ and a Still–Gennari reaction completed the synthesis of $E,Z$-diene $55b$ (Scheme 49).

Scheme 49 The synthesis of $55b$.

A double Still–Gennari modified HWE reaction was used to prepare $55c$ after the MnO$_2$ oxidation of $54a$ was used to generate dialdehyde $144$ (Scheme 50).

Scheme 50 The synthesis of $55c$.

The cis-desmethyl substrates were prepared from diol $54b$, which was synthesised via the LiAlH$_4$ reduction of commercially available 3-oxabicyclo[3.1.0]hexane-2,4-dione. Mono-TBS protection of diol $54b$, followed by MnO$_2$ oxidation and a Wittig reaction
furnished ester 146. TBS cleavage using aqueous HF provided alcohol 147 in good yield. MnO2 oxidation then afforded aldehyde 148. A Wittig reaction was then performed in an attempt to generate diester 55d; however, while the intermediate presumably formed, it could not be isolated and instead underwent Cope rearrangement spontaneously in situ, furnishing cycloheptadiene 58a in good yield (Scheme 51).

Scheme 51 The synthesis of 58a via 55d.

A similar result was obtained during the attempted synthesis of E,Z-diene 55e; the Still–Gennari reaction of compound 148 also afforded the Cope rearranged product 58b at RT, presumably via divinylcyclopropane 55e (Scheme 52).
Scheme 52 The synthesis of 58b via 55e.

A Still–Gennari reaction using aldehyde 145, HF mediated silyl deprotection and another MnO₂ oxidation and Still–Gennari reaction again led to the Cope rearrangement product 58a at RT, presumably via the divinylcyclopropane 55f which could not be isolated (Scheme 53).

Scheme 53 The synthesis of 58a via 55f.
By considering the symmetry of the two diastereomeric cycloheptadienes 58a and 58b, their stereochemistry could be inferred remarkably straightforwardly by analysis of their $^1$H NMR spectra. The spectrum of the cis-compound 58a has two distinct peaks for the characteristic diastereotopic protons ($J = 20$ Hz) shown in Figure 10.

![Figure 10](image10.png)

**Figure 10** The $^1$H NMR spectrum of 58a with the peaks corresponding to the characteristic diastereotopic protons highlighted.

Conversely, the corresponding protons in the trans-compound are homotopic and thus appear as a single two proton resonance (Figure 11).

![Figure 11](image11.png)

**Figure 11** The $^1$H NMR spectrum of 58b with the characteristic homotopic protons highlighted.
3.5 A Study into the Effect of Gem-Dimethyl Substitution on the Cope Rearrangement of Divinylcyclopropanes

We next tested the Cope rearrangements of all of the cis/trans and E/Z-isomers of 55 and 57 as 0.19 mol dm\(^{-3}\) solutions in xylene at 5 different temperatures: RT, 40 °C, 70 °C, 100 °C and 130 °C. Each substrate was stirred at these temperatures for 17 h before the percentage conversion was measured as a ratio of product to starting material, via analysis of the \(^1\)H NMR spectra of the unpurified reaction mixtures. The results are summarised in Table 4 and are discussed in more detail in the following section.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Product</th>
<th>% Conversion (17 h)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Temperature</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT</td>
</tr>
<tr>
<td>1</td>
<td>E=E</td>
<td>E=E</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>E=E</td>
<td>E=E</td>
<td>0</td>
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<td>3</td>
<td>E=E</td>
<td>E=E</td>
<td>0</td>
</tr>
<tr>
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<td>E=E</td>
<td>E=E</td>
<td>100(^c)</td>
</tr>
<tr>
<td>5</td>
<td>E=E</td>
<td>E=E</td>
<td>100(^c)</td>
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<tr>
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<td>E=E</td>
<td>100(^c)</td>
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<td>11</td>
<td>E=E</td>
<td>E=E</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>E=E</td>
<td>E=E</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^{a}\)E = CO\(_2\)Et. All reactions were carried out as 0.19 mol dm\(^{-3}\) solutions in xylene. All reactions were carried out for 17 h. % Conversion was determined \(via\) \(^1\)H NMR analysis of the unpurified reaction mixtures as a ratio of product to starting material.

\(^{b}\)Some decomposition was also evident.

\(^{c}\)The divinylcyclopropane could not be isolated at RT; the cycloheptadiene shown was instead isolated during the attempted preparation of the diene.

\(^{d}\)Compound 88a was isolated in 78% yield after flash column chromatography.

**Table 4** The Cope rearrangement on test substrates 55 and 57.
The $^1$H NMR spectra for the key rearrangement of 57d into 88a at the 5 different temperatures are displayed in Figure 12. The spectra show that the reaction was complete after 17 h at 100 °C and show the decomposition that was evident after 17 h at 130 °C.

**Figure 12** Following the conversion of 57a into 88a by $^1$H NMR spectroscopy at RT, 40 °C, 70 °C, 100°C and 130°C, showing complete conversion at 100 °C and signs of decomposition at 130 °C.
The key findings of the study into the Cope rearrangement are: i) cis-divinylcyclopropanes undergo the Cope rearrangement more readily than trans-divinylcyclopropanes, ii) desmethyl divinylcyclopropanes undergo the Cope rearrangement more readily than their gem-dimethyl analogues, iii) divinylcyclopropanes with E-double bonds undergo the Cope rearrangement more readily than those with Z-double bonds, and iv) there is an increased barrier to epimerisation between trans and cis-divinylcyclopropanes in the gem-dimethyl series. These observations are illustrated below:

i) cis-Divinylcyclopropanes undergo the Cope rearrangement more readily than trans-divinylcyclopropanes

The desmethyl cis-divinylcyclopropanes 55d, 55e and 55f could not be isolated at RT, and instead they underwent spontaneous Cope rearrangement under the conditions used for their formation (a TOP reaction at RT or a Still–Gennari reaction at RT, Table 4, Entries 4, 5, 6 & Scheme 54). In contrast, the desmethyl trans-divinylcyclopropanes 55a, 55b and 55c were stable at RT and required temperatures of 100–130 °C before they underwent the Cope rearrangement (Table 4, Entries 1, 2, 3 & Scheme 54).

Scheme 54 The contrasting Cope rearrangements of divinylcyclopropane 55.
A single stereoisomer of product was observed in each case, with the stereochemical outcomes being consistent with a simple concerted thermal [3,3]-sigmatropic rearrangement in the cis-series of compounds (Table 4, entries 4–6) and trans to cis-isomerisation, followed by a concerted thermal [3,3]-sigmatropic rearrangement, in the trans-series (Table 4, entries 1–3). Thus, the high temperatures necessary to induce rearrangement in the trans-series appear to be associated with overcoming the energy barrier for trans to cis-epimerisation of the cyclopropane and not with the energy of the transition state of the Cope rearrangement itself.

A similar trend was seen in the analogous gem-dimethyl series: cis-divinylcyclopropane 57d was fully converted into Cope product 88a after 17 h at 100 °C (Table 4, Entry 10 & Scheme 55). In contrast, after 17 h at 130 °C trans-divinylcyclopropane 57a did not undergo the Cope rearrangement (Table 4, Entry 7 & Scheme 55).

**Scheme 55** The contrasting Cope rearrangements of 57a and 57d.

ii) Desmethyl divinylcyclopropanes undergo the Cope rearrangement more readily than their gem-dimethyl analogues

These results support the findings described in Chapter 2, in which the reactions of desmethyl diene 55a and gem-dimethyl diene 57a were compared. The desmethyl divinylcyclopropanes 55d, 55e and 55f all underwent the Cope rearrangement readily at RT. In contrast the corresponding gem-dimethyl variants 57e and 57f did not undergo the Cope rearrangement, even at 130 °C and while 57d was converted into 88a, it required 17 h at 100 °C in order for the reaction to reach completion (Table 4, Entries 4, 5, 6, 10, 11, 12 & Scheme 56).
iii) Divinyclopropanes with $E$-double bonds undergo the Cope rearrangement more readily than those with $Z$-double bonds.

The gem-dimethyl cis-divinylcyclopropane 57d was fully converted into Cope product after 17 h at 100 °C. However, the Z-isomers 57e and 57f did not undergo the Cope rearrangement, even after 17 h at 130 °C (Table 4, Entries 10, 11, 12 & Scheme 57).

The same trend (albeit less pronounced) was also observed in the desmethyl series. The Cope rearrangements of 55a and 55b were complete after 17 h at 130 °C. By
contrast, only 80% conversion into Cope product 58a was observed under the same conditions for 55c (Table 4, Entries 1, 2, 3 & Scheme 58).

Scheme 58 The contrasting Cope rearrangements of 55a, 55b and 55c.

iv) There is an increased barrier to epimerisation between trans and cis-divinylcyclopropanes in the gem-dimethyl series.

This is without question the most surprising conclusion to be drawn from these studies. The trans-dimethyl substrates 57a, 57b or 57c did not rearrange, even at 130 °C (Table 4, entries 7–9, Scheme 59) and, importantly, epimerisation to the corresponding cis-diesters was also not observed. The cis-E,Z and cis-Z,Z-substrates 57e and 57f also failed to react at 130 °C, with each remaining unchanged, again with no evidence of cyclopropane epimerisation (Table 4, entries 11–12). This suggests that the required transition state (Figure 8) is too high in energy for the Cope rearrangement to occur under the conditions screened, probably due to steric clashes, but also indicates that the cis/trans-epimerisation occurs less readily than in the non-methylated series of compounds. The cis-E,E-diester 57d was significantly more reactive than either of compounds 57e or 57f; this substrate began to rearrange at temperatures as low as 40 °C and the rearrangement was complete after 17 h at 100 °C (Table 4, entry 10).
Scheme 59 The contrasting Cope rearrangements of 57a, 57b, 57c, 57d, 57e and 57f.

This result sheds light on the reason why our original dimethyl trans-E,E-diester 57a (Table 4, entry 7) failed to react; given that the Cope rearrangement of cis-E,E-diester 57d (Table 4, entry 10) proceeded at temperatures as low as 40 °C, and that there was no evidence of any cis/trans-epimerisation in any of the diesters 57a–57f, this suggests that the reaction of trans-E,E 57a failed at the cyclopropane epimerisation stage, and not because of the high energy of the Cope rearrangement transition state as originally thought (Figure 8). In addition, the complete lack of cis to trans-epimerisation in any of the dimethyl substituted diesters 57a–57f is in contrast to the unsubstituted diesters 55a–55c (which must have epimerised otherwise their Cope rearrangements would not have taken place). Thus, we have shown that as well raising the energy of the Cope rearrangement transition state, gem-dimethyl substitution also retards the rate of cyclopropane epimerisation of the trans-cyclopropane substrates screened.
3.6 Examining substituent effects on the Cope Rearrangement of Cis-Gem-Dimethyl Divinylcyclopropanes

It is clear that gem-dimethyl substitution significantly retards the Cope rearrangements of divinylcyclopropanes. However, it appears that its effect on the trans to cis-isomerisation of the cyclopropane, and not its effect on the [3,3]-sigmatropic rearrangement itself, is the most significant barrier to reactivity. Pleasingly, from a synthetic viewpoint, the isomerisation problem is easily negated by starting from a cis-oriented divinylcyclopropane. To demonstrate this, we went on to synthesise a range of other gem-dimethyl-cis-\(E,E\)-functionalised cyclopropanes. Cyclopropane 154 was prepared using a tandem oxidation/Wittig reaction, followed by silyl cleavage using HF. Another tandem oxidation/Wittig reaction at RT afforded the cis-\(E,E\)-functionalised cyclopropane 154.

![Scheme 60: The synthesis of 154.]

The reduction of 154 using 2 equivalents of DIBAL gave a mixture of monoester 155 and diol 156, which were easily separated by flash column chromatography.

![Scheme 61: The synthesis of 155 and 156.]

50
TBS protection of diol 156 using 1.5 equivalent of TBSCI generated a mixture of TBS compounds 157 and 158, which were easily separated by flash column chromatography.

Scheme 62 The synthesis of 157 and 158.

Finally, the hydrolysis of diester 154 using NaOH in aq. THF (1:1) afforded cyclopropane 159.

Scheme 63 The synthesis of 159.

We were pleased to find that all of these substrates 154–159 undergo the Cope rearrangement upon heating, generating 1,4-cycloheptadienes in high yields (78–97%, Table 5), with ester, alcohol, silyl ether and carboxylic acid substituents all being well tolerated. The rearrangements do not appear to be significantly affected by electronic effects, a point exemplified by the near-identical reactivity of the electron-deficient ester-substituted divinylcyclopropane 154 and the more electron-rich alcohol-substituted divinylcyclopropane 156 (entries 1 and 3, Table 5). Note that the product isolated from the Cope rearrangement of substrate 155 (entry 2, Table 5) was a lactone, presumably, formed via an intramolecular transesterification following the Cope rearrangement. The size of the substituents appears to be more significant; the addition of one 157 and then two 158 tert-butylidimethyl silyl groups to diol 156 led to a decrease in reactivity in each case (entries 4 and 5, Table 5). Diacid-substituted divinylcyclopropane 159 reacts more slowly still (entry 6, Table 5), but this reaction should not be compared directly to the other entries, as it was only sparingly soluble in the reaction solvent.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Product</th>
<th>% Conversion</th>
<th>Isolated Yield^a</th>
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<td>Temperature (°C)</td>
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<td></td>
<td></td>
<td></td>
<td>40</td>
<td>70</td>
</tr>
<tr>
<td>1</td>
<td>MeO₂C=</td>
<td>154</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>C=</td>
<td>156</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MeO₂C=</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>MeO₂C=</td>
<td>155</td>
<td>0</td>
<td>100</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>HO=C=</td>
<td>156</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>C=</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>4</td>
<td>HO=C=</td>
<td>157</td>
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<td>70</td>
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<tr>
<td></td>
<td>C=</td>
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<tr>
<td>5</td>
<td>TBSO=C=</td>
<td>158</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>C=</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>6</td>
<td>HO₂C=</td>
<td>159</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
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<td>C=</td>
<td></td>
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</tbody>
</table>

^a All reactions were carried out as 0.19 mol dm⁻³ solutions in xylene. All reactions were carried out for 17 h. % Conversion was determined via analysis of the unpurified reaction mixtures. The isolated yields were obtained from the 100 °C experiments and include purification by column chromatography in each example except for diacid 165.

Table 5 The Cope rearrangement on test substrates 154–159.

In conclusion, the rate-retarding effect of gem-dimethyl substitution on the Cope rearrangements of divinylcyclopropanes has been demonstrated directly for the first time. An examination of the effects of alkene geometry and the relative stereochemistry of the cyclopropane have revealed that gem-dimethyl substitution significantly inhibits the trans to cis-isomerisation about the cyclopropyl ring, necessary for rearrangement to occur, relative to unsubstituted desmethyl analogues. Using the information accrued, a series of ideal substrates (cis-oriented on the cyclopropane with two E-alkenes) were synthesised and all underwent the desired
Cope rearrangement smoothly, affording a range of dimethylated substituted 1,4-cycloheptadienes in high yields. The findings of this study were recently published in Organic and Biomolecular Chemistry.\textsuperscript{55} (See Appendix for full paper).

Significantly, with respect to the synthesis of pyxidatol C, we showed that by preparing the \textit{cis}-divinylcyclopropane \textbf{57d} we could access cycloheptadiene \textbf{88a}, the \textit{gem}-dimethyl-pyxidatol C analogue of cycoheptadiene \textbf{58a} and therefore attention turned to completing its total synthesis (Chapter 4).
Chapter 4
Towards the Total Synthesis of Pyxidatol C

4.1 Corey–Chaykovsky Strategy

A detailed study into the Cope rearrangements of gem-dimethyl divinylcyclopropanes revealed the importance of preparing a cis-divinylcyclopropane in the synthesis of gem-dimethyl substituted cycloheptadienes (Chapter 3). This led to the optimized synthesis of 88a, an intermediate in the synthetic route towards pyxidatol C; the TOP reaction of 131 afforded 57d in 68% yield, which was then converted into 88a in 80% yield (Scheme 64). Toluene was used as the solvent in the Cope rearrangement of 57d, in place of xylene, because it is easier to remove under vacuo. With the 7-membered ring component of the decahydro-1H-cyclopropane core structure of pyxidatol C in place attention turned to the installation of the cyclopropane moiety.

Scheme 64 Optimised synthesis of 88a.

The general strategy devised for cyclopropanation was first to perform a partial reduction of diester 88a, followed by alkene isomerisation and cyclopropanation (Scheme 65).

Scheme 65 General cyclopropanation strategy.
The Corey–Chaykovsky strategy trialled previously on the desmethyl model system was the first route to be tested on the \textit{gem}-dimethyl system. \ce{LiAlH_4} reduction of \textbf{88a} was straightforward and was followed by TEMPO oxidation, affording lactone \textbf{161} (Scheme 66). The 69\% yield for this step was reproducible, which was pleasing because on the desmethyl model system yields were inconsistent, ranging from 40–60\% (Section 1.11).

![Scheme 66](https://example.com/scheme66.png)

**Scheme 66** Synthesis of lactone \textbf{161}.

Unfortunately, base-promoted isomerisation of lactone \textbf{161} was harder to optimise than on the desmethyl model system. The initial conditions trialled (1 equivalent of DBU in THF at 0 °C for 1.5 h) resulted in the formation of a mixture of the desired lactone \textbf{168} and \(\alpha,\beta,\gamma,\delta\)-unsaturated lactone \textbf{169} in 71\% overall yield in a ratio of 1:2.1 (Scheme 67).

![Scheme 67](https://example.com/scheme67.png)

**Scheme 67** Initial conditions trialled for the isomerisation of lactone \textbf{168}.

In order to avoid isomerisation into \(\alpha,\beta,\gamma,\delta\)-unsaturated lactone \textbf{169}, the reaction time was reduced to 30 min affording \(\alpha,\beta\)-unsaturated lactone \textbf{168} in 30\% yield, epimer \textbf{170} in 52\% yield and starting material \textbf{161} in 7\% yield. Epimer \textbf{170} could in turn be converted into the desired lactone \textbf{168} in 39\% yield, thus allowing reproducible quantities of the target compound \textbf{168} to be obtained (Scheme 68).
Scheme 68 Optimised conditions for the synthesis of lactone 168.

The Corey–Chaykovsky cyclopropanation of 168 was next attempted using trimethylsulfoxonium iodide (Corey’s salt) and sodium hydride in DMF. Pleasingly the desired cyclopropane 171 was formed as a single diastereomer (Scheme 69) with the relative stereochemistry shown to be that required for pyxidatol C by an n.O.e experiment (an n.O.e enhancement between the cyclopropane CH2 and the CHCH2O protons was observed, whereas no n.O.e enhancement was observed for the lactone CH2 protons with the cyclopropane CH3). Unfortunately the yield was low, ranging from 5–20% using sodium hydride as the base in DMF. The solvent was changed to DMSO and cyclopropane 171 was formed in 11% yield. Using MTBD as the base in acetonitrile, cyclopropane 171 was formed in only 8% yield. The low yields were particularly disappointing given that the 1H NMR spectra of the unpurified reaction mixtures were clean and contained no evidence of either starting materials or side products. The fate of the rest of the material remains unclear; efforts were made to examine the contents of the aqueous extracts but no tractable material was found. This is the same problem that we observed using the analogous desmethyl lactone 61 (See Chapter 2.1).

Scheme 69 Synthesis of cyclopropane 171
4.2 Installing the Side-Chain

Despite the disappointing yields for the cyclopropanation leading to compound 171, we were able to continue the synthesis, with the aim of installing the methyl ketone side chain. We planned to install the side chain via reduction of lactone 171 to diol 172, conversion of the less hindered alcohol into a leaving group, followed by alkylation (Scheme 70). This alkylation strategy had previously been tested on a cyclohexyl model system (Section 2.1).

![Scheme 70 Installing the side chain to lactone 171.](image)

The reduction of lactone 171 with DIBAL was straightforward, affording diol 172. Unfortunately, the attempted iodination of 172 was unsuccessful affording a complex mixture of products (Scheme 71). The major component of this mixture was tentatively assigned as cyclic ether 176 based on peaks at 5.22–5.20 (2H, m, H-4 & H-5), 4.03 (1H, dd, J 11.5, 1.5 Hz, H-1a), 3.76 (2H, d, J 7.0 Hz, H-2), 2.96 (1H, dd, J 11.5, 1.0 Hz, H-1b) and 2.41 (1H, t, J 7.0 Hz, H-3) in the $^1$H NMR spectrum of the unpurified reaction mixture, which are similar to those in a related compound 209 (see later, Section 4.4). Attempts to tosylate and mesylate diol 172 were also unsuccessful with clean starting material recovered in both cases. Cyclic ether formation may well have followed had the mesylation and tosylation been successful; therefore an alternative approach was sought.
Scheme 71 Synthesis of diol 172 and attempts to install a leaving group. The numbering of 176 is for characterisation purposes only and does not conform to IUPAC rules.

A lactone ring-opening strategy was tested as an alternative way of installing the leaving group, based on work by Olah et al. who reported the use of sodium iodide and methyltrichlorosilane to cleave a range of esters and lactones in good yield (Scheme 72).56

Scheme 72 Studies by Olah et al.56 into the dealkylative cleavage of esters and lactones using trichloromethylsilane and sodium iodide.

This strategy had the advantage of affording a carboxylic acid (rather than an alcohol) containing iodide, thus negating the undesired THF formation. Unfortunately attempts to cleave lactone 161, α,β-unsaturated lactone 168 and cyclopropyl lactone 171 using trichloromethylsilane and sodium iodide were all unsuccessful (Scheme 73) and clean starting material was recovered in each case. A related ring-opening strategy using thionyl bromide was also examined,57 but again clean starting material was recovered when tested on lactones 168 and 171. The reaction with lactone 161 formed the trans-epimer 170, although there was evidence of trace formation of product 185 by mass
spectrometry \([m/z \text{ (ESI)}]: [\text{MH}^+] \text{ C}_{12}\text{H}_{18}^{79}\text{BrO}_2, 273.0503\) and \(\text{C}_{12}\text{H}_{18}^{81}\text{BrO}_2, 275.0482\). Efforts were made to promote the ring-opening of lactone 161 by increasing the reaction time from 1 to 3 days and by heating to reflux instead of stirring at RT, but in each case only trace product formation was observed.

Scheme 73 A ring-opening strategy to introduce a leaving group.

### 4.3 Simmons–Smith Strategy

As an alternative to the Corey–Chaykovsky cyclopropanation, a Simmons–Smith strategy, previously tested on the desmethyl model system, was examined. The required substrate was formed easily via the mono-TBS protection of diol 162, oxidation to generate aldehyde 188 using DMP, DBU-promoted isomerisation to \(\alpha,\beta\)-unsaturated aldehyde 189 and sodium borohydride reduction, furnishing alcohol 190 in a 62% yield over the four steps (Scheme 74).
As anticipated, the regioselectivity of the Simmons–Smith cyclopropanation was greater for the gem-dimethyl system relative to that of the desmethyl model system alcohol 79 (it was reasoned that the steric bulk of the cycloheptadiene dimethyl groups would hinder cyclopropanation on the unfunctionalised alkene, Section 2.2). Optimal conditions were found to be 4 equivalents of diidomethane and 2 equivalents of diethylzinc in CH$_2$Cl$_2$ at 0 °C for 40 min. This resulted in the synthesis of cyclopropane 191 in 32% yield and cyclopropane 192 in 27% yield, although trace impurities were evident in the $^1$H NMR spectrum of 191 and were attributed to the bis-cyclopropane 193 (supported by mass spectrometry [m/z (ESI): [MNa$^+$] C$_{19}$H$_{36}$NaO$_2$Si, 347.2362]). The relative stereochemistry of cyclopropanes 191 and 192 was determined by TBS cleavage of cyclopropane 192 using TBAF to give diol 194. The stereochemistry of diol 194 was confirmed by comparison with data for compound 172, which was prepared via the Corey–Chaykovsky route (Scheme 69).

**Scheme 74** Synthesis of alcohol 190.

**Scheme 75** Simmons–Smith cyclopropanation of alcohol 190.
4.4 Installing the Side-Chain; The Cyclic Ether Phenomenon

Before installing the side chain, it was decided to protect the alcohol of 191 with a protecting group orthogonal to the TBS ether. It was hoped that this would allow cleavage of the TBS group followed by iodination without resulting in the unwanted formation of cyclic ether 176. Unfortunately efforts to protect the alcohol as its benzyl ether were unsuccessful (Scheme 76); starting material 191 was recovered when benzyl bromide and NaH were used and decomposition was observed using the Dudley reagent. Attempts to prepare the PMB ether 196, TIPS ether 197 and methyl ether 198 were also all unsuccessful, with starting material 191 recovered in each case.

![Scheme 76 Attempts to protect alcohol 191.](image)

It was concluded that the alcohol must be extremely sterically hindered (it is neo-pentyl). A new strategy of installing the side chain before carrying out the cyclopropanation was thus planned, so that protecting group manipulations could be carried out before the bulky cyclopropane was in place. Following protecting group
manipulations, we hoped to install the methyl ketone side chain to generate intermediate 201 (Scheme 77).

Scheme 77 Synthetic strategy to install the side chain before attempting the cyclopropanation.

TIPS protection of TBS alcohol 190 was facile and TIPS containing compound 202 was obtained in 66% yield, corroborating our theory that the cyclopropane in 191 was a steric encumbrance to the alcohol protection on that system. However, we were unable to selectively cleave the TBS ether of 202, and always observed the formation of a mixture of products (starting material was observed in the $^1$H NMR spectra of the unpurified reaction mixture and although clean material could not be isolated, HRMS indicated the presence of the corresponding diol in the unpurified reaction mixture).

Scheme 78 Attempt to selectively mono-deprotect TBS compound 202.

We were also able to acetylate alcohol 190, forming acetate 204 in quantitative yield. Unfortunately, during cleavage of the TBS group of 204 with TBAF, acetate migration between the two alcohol groups was observed, resulting in the formation of an inseparable mixture of mono-acetate compounds 205 and 206 in a 1:0.8 ratio, based on HRMS data [m/z (ESI): [MNa$^+$] C$_{13}$H$_{20}$NaO$_3$, 247.1310] and the presence of two acetate methyl groups at 2.23 ppm and 2.38 ppm in the unpurified reaction mixture.
Scheme 79 Attempt to selectively mono-deprotect TBS compound 204.

In view of the various problems encountered during efforts to install orthogonal protecting groups, another change in the order of steps was planned. This involved the iodination of the alcohol of 163, and the installation of the methyl ketone side chain before isomerisation of the alkene and cyclopropanation.

Unfortunately the iodination of alcohol 163 did not go to plan. Surprisingly, the formation of the bis-TBS compound 164 and cyclic ether 209 were observed when alcohol 163 was treated with iodine, triphenylphosphine and imidazole (Scheme 81). The most likely explanation for this reactivity is that following iodination of the free alcohol, intramolecular nucleophilic attack from the oxygen of the TBS ether takes place generating an oxycation reactive intermediate, which can react with another molecule of alcohol 163 to form both the cyclic ether 209 and bis-TBS compound 164 (Scheme 81).
Scheme 81 Attempted iodination of alcohol 163.

The mono-protection of diol 162 with the bulkier, more stable silyl protecting group TBDPS was therefore considered. Mono-TBDPS protection of diol 162 furnished 210 in 95% yield, but under the same iodination conditions cyclic ether 209 and the bis-TBDPS compound 211 were again formed (Cyclic ether 209 was seen in the $^1$H NMR spectrum of the unpurified reaction mixture and the formation of 211 was inferred by HRMS).

Scheme 82 Mono-TBDPS protection of diol 162 and attempted iodination of alcohol 210.
The mesylation of alcohol 210 was considered as an alternative to iodination. Pleasingly, mesylation was achieved in 83% yield using standard conditions but the subsequent alkylation with t-butyl acetoacetate and NaH in THF was unsuccessful and only starting material was recovered from the reaction after 16 h at reflux (Scheme 83).

Scheme 83 Mesylation and triflation approach to installing the sidechain.

A Finkelstein reaction\(^{59}\) was therefore performed on mesylate 212 in an attempt to introduce the more reactive iodo-leaving group to facilitate the difficult alkylation. The desired iodide 214 is likely to have formed smoothly but unfortunately, only cyclic ether 209 was seen in the unpurified reaction mixture. Triflation of alcohol 210 was also attempted and once again the cyclic ether 209 was the only product seen in the unpurified reaction mixture.

Scheme 84 A Finkelstein and triflation approach to installing the sidechain.
In an effort to avoid cyclic ether formation during iodination, a PMB protecting group was considered. It was hoped that the PMB group would be more stable under the iodination reaction conditions than the TBS and TBDPS groups previously tested. Mono-protection of diol 162 as its PMB ether via the reduction of 215 was planned. Surprisingly under the acidic conditions necessary to prepare acetal 215, cyclic ether 209 was formed again, presumably via an intramolecular $S_N$2 reaction with loss of water. This result is particularly surprising given that $H_2O$ rarely acts as a leaving group in $S_N$2 type processes. Mono-PMB ether 216 was therefore prepared using PMBCl and NaH in THF. Disappointingly (as judged by the analysis of the $^1H$ NMR spectrum of the unpurified reaction mixture) the attempted iodination of alcohol 162 led yet again to the predominant formation of cyclic ether 209.

Scheme 85 Mono-PMB protection of diol 162 and attempted iodination of alcohol 216.

Given the previously described unwanted cyclic ether formations, this approach was abandoned. It was concluded that the alcohol groups are too prone to undergo THF formation for this strategy to succeed. It was surprising that the cyclic ether forms so readily such that the protecting groups, even PMB, are displaced. Given these setbacks the Wittig reaction, previously tested on the desmethyl system (Section 2.1) was re-examined.

During previous studies on the desmethyl model system, a Wittig reaction on lactol 67 was unsuccessful (Section 2.1, Scheme 16). However, we planned to investigate
the Wittig reaction using the *gem*-dimethyl aldehyde 217 (Scheme 86). Aldehyde 217 was prepared from alcohol 210 using DMP, in an 80% yield. Unfortunately, the Wittig reaction using 1-(triphenylphosphoranylidene)acetone in CH$_2$Cl$_2$ at RT led to decomposition.

![Scheme 86 A Wittig approach to installing the side chain using aldehyde 217.](image)

4.5 Installing the Side-Chain Before the Cope Rearrangement

As outlined in Section 4.4, many difficulties were encountered when attempting to install the methyl ketone side chain on the cycloheptadiene system. This led to another re-ordering of the synthetic strategy and the installation of the methyl ketone side chain before the Cope rearrangement was considered. By carrying out the Cope rearrangement of 219, cycloheptadiene 220 could be prepared with the side chain already in place (Scheme 87).

![Scheme 87 The Cope rearrangement of 219.](image)

The alkylation strategy tested on the cyclohexyl model system (Section 2.1) was trialled on divinylcyclopropyl alcohol 221. DIBAL reduction of ester 133 furnished the requisite alcohol 221, necessary to apply this halogenation, alkylation strategy (Scheme 88). Unfortunately attempts to iodinate, using iodine, triphenylphosphine and imidazole were unsuccessful, leading to decomposition. Bromination using carbon tetrabromide and triphenylphosphine also led to decomposition. Therefore an alternative approach towards the installation of the side chain was tested using alcohol 221.
Scheme 88 The attempted halogenation of alcohol 221.

An alternative strategy for the introduction of the methyl ketone side chain was tested using Tsuji–Trost\textsuperscript{60,61} chemistry (Scheme 89). Carbonate 223 was prepared from alcohol 221 using ethyl chloroformate, DMAP and pyridine. Carbonate 223 was then used without purification in the key Tsuji-Trost step. The reaction of carbonate 223 with tetrakis(triphenylphosphine)palladium(0) and tert-butyl 3-oxobutanoate afforded \(\text{-ketoester 224} \) in an excellent 92\% yield over the two steps. Silyl cleavage was straightforward and furnished alcohol 225, a potential substrate for a Taylor group TOP reaction. Disappointingly, this TOP reaction was unsuccessful and clean starting material was recovered from the reaction.

Scheme 89 The Tsuji–Trost reaction of carbonate 223 and the attempted TOP reaction of alcohol 225.
The oxidation, Wittig sequence was therefore completed in a step-wise manner. The MnO₂ oxidation of 225 was unsuccessful and once again clean starting material was recovered from the reaction (Scheme 90). Pleasingly, Dess–Martin oxidation generated aldehyde 227 (Scheme 91) which was used without purification in the Wittig reaction with (carbethoxymethylene)triphenylphosphorane affording divinylcyclopropane 226 in 72% yield over two steps.

![Scheme 91](image)

Scheme 91 The unsuccessful MnO₂ oxidation of alcohol 225.

The decarboxylation of t-butyl ester 226 to furnish the desired divinylcyclopropane 219, a substrate for the Cope rearrangement, was next planned (Scheme 92). However, attempts to promote decarboxylation of β-ketoester 226 using PTSA in benzene were unsuccessful, leading to decomposition of the material and when 226 was stirred in TFA, only traces of ketone 219 were evident by HRMS. The Cope rearrangement of β-ketoester 226 was therefore tested. This substrate was not considered ideal for the Cope rearrangement given its relatively high steric bulk but pleasingly the rearrangement was successful affording cycloheptadiene 228. From here, decarboxylation of the β-ketoester using TFA was straightforward thus affording the key advanced cycloheptadiene intermediate 220 with the methyl ketone side chain already in place.
Scheme 92 The Cope rearrangement of 226.

With cycloheptadiene 220 in hand and the methyl ketone side chain in place, cyclopropanation and a ketone-olefin coupling reaction would complete the synthesis of the decahydro-1H-cyclopropa[e]azulene core structure common to the africananes.

The cyclopropane moiety has been successfully installed on related systems using both Corey–Chaykovsky chemistry and Simmons-Smith chemistry (Section 4.1 and Section 4.3). These established cyclopropanation conditions were next trialled on the more advanced cycloheptadiene intermediate 220. Base-promoted isomerisation of the alkene of 220 into conjugation with the ethyl ester afforded the α,β-unsaturated ester 229, substrate for the Corey–Chaykovsky cyclopropanation (Scheme 93). Unfortunately cyclopropanation was unsuccessful using both the NaH/DMF conditions and MTBD/MeCN conditions; a complex mixture of decomposition products was observed in each case.

Scheme 93 The DBU promoted isomerisation of 220, and the failed Corey–Chaykovsky cyclopropanation of 229.

It was considered possible that the free ketone in ester 229 was interfering with the reaction and as such, protection of the ketone as ketal 231 was attempted. Ketone 229...
was heated at reflux in toluene/ethylene glycol/PTSA under Dean–Stark conditions for 16 h, (Scheme 94) but unfortunately unreacted starting material was recovered from the reaction. As such, attention turned towards Simmons–Smith cyclopropanation chemistry.

Scheme 94 The unsuccessful ketal protection of ketone 229.

DIBAL reduction of α,β-unsaturated ester 229 afforded diol 232, substrate for the Simmons-Smith cyclopropanation. However clean starting material was recovered from the reaction of allylic alcohol 232 with diethylzinc and diiodomethane.

Scheme 95 DIBAL reduction of 229 afforded diol 232 as predominantly a single diastereomer 10:1. The major diastereomer was isolated by flash column chromatography.

There is literature precedent for the high yielding and steroeselective Simmons-Smith cyclopropanation in the final step of the synthesis of other africananes. Therefore, given the difficulties with cyclopropanation on this system, it was decided that preparing the 5 membered ring before cyclopropanation would be tested. The synthetic strategy for installation of the 5 membered ring was via a samarium diiodide ketone-olefin ring closing reaction.
4.6 Samarium Diiodide Ketone-Olefin Ring Closing Reaction

4.6.1 Background

The samarium diiodide mediated ketone-olefin coupling reaction of 220 into 234 was planned (Scheme 96). This type of coupling reaction has been shown to proceed via single electron reduction of the ketone to give a ketyl anionic radical followed by addition into the olefin, subsequent single electron reduction and protonation (Scheme 96).\textsuperscript{[62]}

![Scheme 96](image)

Scheme 96 Mechanism for the SmI$_2$ mediated ketone-olefin coupling reaction.

As such, 4 diastereomers of alcohol 234 are possible and it was expected, based on precedent for similar transformations, that the required \textit{trans}-5/7 ring system with a \textit{trans}-relationship between the relatively bulky methyl group (\textit{cf}. the OH) and the 7 membered ring would predominate.\textsuperscript{[62]} The four possible diastereomers are shown in Scheme 97 with the desired diastereomer 234a boxed.

![Scheme 97](image)

Scheme 97 The 4 possible diastereomers from the ketone-olefin ring closing reaction with the desired diastereomer boxed.
4.6.2 Preparing Samarium Diiodide

A solution of SmI$_2$ in THF was required to test this chemistry. Samarium diiodide is notoriously difficult to prepare and this proved to be the case in our hands. Fortunately, after several failed attempts at its preparation, a 2012 paper by Proctor et al. provided an answer. It describes how the major factor preventing the successful formation of SmI$_2$ is an oxide layer on the samarium metal. By dry-stirring the samarium metal overnight under inert atmosphere the samarium is activated and the preparation of SmI$_2$ becomes straightforward using standard conditions.

4.6.3 Results

Clean starting material was recovered from the reaction of 220 with SmI$_2$ and t-BuOH in THF. This result was not entirely unexpected as the vast majority of literature SmI$_2$ ketone-olefin coupling reactions use HMPA as an additive. Addition of HMPA to a solution of SmI$_2$ in THF enhances the reduction potential of SmI$_2$ by coordinating to the samarium metal center, producing the more powerful reductant [Sm(HMPA)$_6$]$^{2+}$2I$^-$. 

![Scheme 98 The SmI$_2$ ketone-olefin cyclisation of 220 without HMPA.](image)

The reaction of 220 with SmI$_2$, HMPA and t-BuOH was attempted, but this led to the formation of unknown compound 235. Mass spectrometry suggests this compound is based on two molecules of the starting material (an unsymmetrical dimer) [m/z (ESI): [MNa$^+$] C$_{32}$H$_{50}$NaO$_6$, 553.3455], the IR shows a broad OH signal at 3400cm$^{-1}$ and the $^1$H NMR and $^{13}$C NMR spectra show that there are 4 alkene C-H environments and two ester C=O environments. Efforts were made to grow a crystal of the unknown compound but these were unsuccessful. In an attempt to avoid this dimerisation, the reaction was carried out at high dilution (3.7×10$^{-4}$ mol dm$^{-3}$) but unfortunately the same product was recovered from this reaction.
A much simpler, cyclohexyl model ketone-olefin compound 239 was prepared in the hope that it would shed light on the reaction of 220 with SmI₂. Treatment of cyclohexene 236 with Schlosser’s base⁶⁹ furnished alcohol 236 in 75% yield. The iodination/alkylation/decarboxylation strategy, which was previously optimized on cyclohexanol (Section 2.1), was straightforward furnishing ketone-olefin 239 in good yield.

The reaction of ketone-olefin 239 with SmI₂ furnished an unidentifiable complex mixture of products. It had been hoped that this reaction would help in the elucidation of the unidentified dimer 235 but unfortunately, as there was no evidence of dimerisation by MS in the reaction of ketone-olefin 239 with SmI₂ this was unhelpful.

However, the ring closing reaction of ketone-olefin 238, bearing the t-butyl ester group, furnished compound 241 as two isolable diastereomers in a yield of 43%. This
result is surprising as the steric bulk of the t-butyl ester moiety had been expected to hamper the reaction. The reaction was subsequently tested on the pyridatol C analogue, t-butyl ester 228, but again dimerisation was evident in the MS and the NMR spectra suggested formation of a t-butyl ester substituted analogue of the unidentified compound 235.

Scheme 102 The SmI₂ ketone-olefin cyclisation of t-butyl compound 238.
4.7 Conclusion

Having successfully overcome the challenges associated with preparing the gem-dimethyl cycloheptadiene (Chapter 3), there have been some frustrating setbacks in our efforts to synthesise pyxidatol C. We were unable to avoid cyclic ether formation when attempting to install the methyl ketone side chain to the cycloheptadiene (Scheme 103).

![Scheme 103: A review of the formation of unwanted cyclic ether 209.](image)

More positively, Tsuji–Trost chemistry was used to prepare methyl ketone 220 (Scheme 104), but the samarium diiodide promoted ketone-olefin cyclisation was unsuccessful.
Scheme 104 A review of the synthetic route to the advanced intermediate 220.

In light of these setbacks, a 2001 paper by Kerr et al.\textsuperscript{71} which uses Pauson–Khand chemistry in the synthesis of (+)-taylorione has led to the design of another alternative strategy for the installation of the 5 membered ring moiety, which is described in Chapter 5.
Chapter 5
Future Approach and Preliminary Studies

Studies into the Cope rearrangement enabled the synthesis of the gem-dimethyl containing 7-membered ring moiety present in the decahydro-1H-cyclopropa[e]azulene core structure of pyxidatol C (Chapter 3). The cyclopropane of this core structure has been installed using both Corey-Chaykovsky cyclopropanation and Simons-Smith cyclopropanation (Sections 4.1 & 4.3). The methyl ketone side chain was installed using Tsuji–Trost chemistry but unfortunately, the planned SmI₂ ketone-olefin cyclisation reaction to form the 5-membered ring moiety present in pyxidatol C was unsuccessful (Scheme 104). Future work will focus on the development of a route to install this 5 membered ring moiety at an earlier stage in the synthesis. Preliminary scoping work and future plans are described below.

5.1 A Pauson-Khand Strategy

Kerr et al. used Pauson-Khand chemistry in their synthesis of the cyclopentenone-containing compound (+)-taylorione (Scheme 105). Coordination of hexacarbonyldicobalt to the alkyne of 243 is followed by a [2+2+1]-cycloaddition which furnished cyclopentenone 245, an intermediate in the synthesis of (+)-taylorione. In one set of conditions, ethylene and carbon monoxide were used as reagents at 25 atm. In a second set of conditions, vinyl benzoate was used as an ethylene equivalent.

![Scheme 105](image_url)

Scheme 105 Pauson-Khand chemistry used in the synthesis of (+)-taylorione

It is expected that this methodology will be suitable for the preparation of the 5 membered ring present in pyxidatol C (Scheme 106). The Cope rearrangement of
cyclopropane 248 bearing a cyclopentenone moiety would furnish cycloheptadiene 249. Then, a selective reduction of the electron-deficient alkene of 249, followed by the addition of a methyl nucleophile into the ketone would furnish alcohol 234a. Alkene isomerisation/cyclopropanation would then complete the total synthesis of pyxidatol C 3.

Scheme 106 The proposed Pauson-Khand approach towards pyxidatol C 3.

The Pauson-Khand reaction was tested on ethynylbenzene 250 by Kerr et al. This chemistry was retested in order to confirm that it was reproducible in our hands (Scheme 107), and pleasingly it was easily repeated (using the vinyl benzoate, NMO.H2O conditions) both in terms of yield and purity. Alkynehexacarbonyldicobalt complex 251 was prepared in 95% yield, compared to 99% in the literature and cyclopentenone 252 was obtained in 75% yield compared to 80%. Attention therefore turned to the preparation of alkyne 246.

Scheme 107 The ethynylbenzene model system.
5.2 Preliminary Results Towards Alkyne 246

Ohira-Bestmann chemistry\textsuperscript{72} was considered to be the simplest way to prepare alkyne 246. Aldehyde 253 was prepared via the MnO\textsubscript{2} oxidation of alcohol 131 but unfortunately the reaction with Ohira-Bestmann phosphonate 254 led only to a complex mixture of decomposition products (Scheme 108).

![Scheme 108 Ohira-Bestmann reaction using aldehyde 253.](image)

The Ohira-Bestmann reaction was therefore trialled on aldehyde 136 with a view to building in the unsaturated ester of 246 once the alkyne was in place. However, once again a complex mixture of decomposition products was obtained (Scheme 109). Rather than test a multitude of Ohira-Bestmann conditions, Corey-Fuchs chemistry\textsuperscript{73} was trialled in its place.

![Scheme 109 Ohira-Bestmann reaction using aldehyde 136.](image)

Dibromoalkene 256 was prepared from the reaction of aldehyde 253 with carbon tetrabromide and triphenylphosphine, in a moderate 48% yield (Scheme 110).

![Scheme 110 Corey-Fuchs reaction using aldehyde 253.](image)
It was hoped that the reaction of dibromoalkene 256 with \( n\)-BuLi would afford the desired alkyne 246. However, a complex mixture of products, inseparable by flash column chromatography was obtained. A singlet at 1.95 ppm in the \(^1\)H NMR spectrum of the unpurified reaction mixture indicated that an alkyne was present but analysis of the HRMS indicated that the desired alkyne 246 was not present in the reaction mixture. It is postulated that addition of the \( n\)Bu\(^-\) nucleophile into the ester group instead afforded alkyne 257 which is supported by mass spectrometry \([m/z \text{(ESI)}]: [M\text{Na}^+] \ C_{18}H_{30}\text{NaO}, 285.2917]\).

![Scheme 111 Formation of alkyne 257.](image)

Preparation of dibromoalkene 258 from TBS aldehyde 136 was trialled with a view to preparing the alkyne before the ester was in place, thus avoiding addition of the \( n\)Bu\(^-\) nucleophile into the ethyl ester. Unfortunately, this reaction led to a complex mixture of decomposition products (Scheme 112) and so alternative strategies to avoid this addition were tested.

![Scheme 112 Corey-Fuchs reaction using aldehyde 136.](image)

It was hoped that reduction of the electrophilic ester moiety in 256 to give alcohol 259 would stop the side-reactions during alkyne formation. DIBAL reduction of ester 256 was straightforward but treatment with \( n\)BuLi again led to decomposition and no evidence of the formation of the desired product 260 (Scheme 113).

![Scheme 113 DIBAL reduction of 256.](image)
Alcohol 259 was to be protected as a silyl ether in order to avoid deprotonation of the free alcohol group by nBuLi because the resulting alkoxide could be a reactive intermediate in decomposition pathways. Unfortunately, the DIBAL reduction of ester 256 did not work well on scale up and only trace amounts of alcohol 259 were synthesized. With time limited, an alternative route towards silyl ether 265 was tested in place of optimizing the reduction of ester 256. This strategy relied on the use of orthogonal protecting groups in the synthesis of silyl ether 265 (Scheme 114).

![Scheme 114 Using TIPS as an orthogonal protecting group.]

TIPS protection of alcohol 221 proved to be straightforward. It was expected that TBAF would cleave the TBS ether of cyclopropane 261 selectively because the TIPS ether is more stable than TBS. However, desilylation using TBAF selectively cleaved the TIPS ether, in place of the desired TBS ether and TBS compound 221 was recovered from the reaction (Scheme 115).

![Scheme 115 TIPS protection of alcohol 221 followed by unsuccessful TBS cleavage.]

The relative stability of the TBS ether of cyclopropane 261 suggests that the silicon atom is more sterically hindered on the TBS than on the TIPS ether, probably due to
its proximity to the cyclopropane. With this in mind, it was hoped that the reaction of diol 267 with only 1 equivalent of TBSCl would give selectively mono-TBS protected compound 268, but unfortunately a mixture of diol and bis-TBS compound was recovered from this reaction. This suggests that the mono-TBS protected compound 268 must silylate faster than diol 267. Speculatively, this could be due to differences in the solubility of the mono-TBS protected compound 268 and the starting material diol 267 (Scheme 116).

Scheme 116 The unsuccessful mono-TBS protection of diol 267.

Given the difficulties working with TIPS as an orthogonal protecting group, the use of a benzyl protecting group was planned. Pleasingly, benzyl protection of alcohol 221 was straightforward, as was silyl cleavage furnishing alcohol 270 in 64% yield over the two steps. Unfortunately oxidation with MnO$_2$ or DMP was unsuccessful (Scheme 117).

Scheme 117 Benzyl protection followed by silyl deprotection of alcohol 221.
The focus of future work will be to build on these preliminary studies to find an efficient synthesis of alkyne 246, thus enabling us to test the proposed Pauson-Khand strategy towards pyxidatol C (Scheme 118).

Scheme 118 The proposed Pauson-Khand approach towards pyxidatol C 3.
Chapter 6
Addendum

Total Synthesis of Pyxidatol C by G. Liang et al.74

Having completed all of the experimental and written work contained in this thesis, the total synthesis of pyxidatol C 3 was reported by G. Liang et al.74 For completeness, details are given below.

Commercially available ketone 272 was converted to trans-decalin 273 in 45% yield using the aldol–Henry reaction cascade and subsequent Parikh–Doering oxidation.75 The stereochemistry of 273 was unambiguously confirmed by single-crystal X-ray crystallographic analysis. The carbonyl group in 273 was protected as its acetal allowing palladium-catalyzed hydrogenation of the nitro group to afford the corresponding amine 275 in nearly-quantitative yield. The Tiffeneau–Demjanov rearrangement generated the desired cis-fused 5,7-carbocycle 276 in 62% yield with complete diastereocontrol.76 A Corey–Chaykovsky epoxidation77 and epoxide isomerization sequence yielded alcohol 278 as the single regioisomer shown.78 Acetal hydrolysis with 1 N HCl in THF revealed ketone 279. Addition of methyllithium then afforded the diol 280 in 59% yield; this reaction furnished a pair of separable diastereomers, with the minor diasteromer, which is not depicted in scheme 119 isolated in 15% yield. A Simmons–Smith cyclopropanation29 of 280 completed the synthesis of pyxidatol C in 68% yield with excellent stereo-chemical control (d.r. > 19:1).74
Scheme 119 The total synthesis of pyxidatol C 3 by G.Liang et al.
Chapter 7
Experimental

7.1 General Experimental

All reagents were purchased from commercial sources and were used without further purification.

Unless otherwise stated, all procedures were carried out under an atmosphere of argon. Where necessary, solvents were dried on an MBraun SPS solvent purification system. Anhydrous THF was obtained by distillation over sodium benzophenone. Hexane refers to n-hexane and pet. ether refers to light petroleum ether, bp 40–60 °C. Ethanol was dried according to the method of Lund and Bjerrum. DMP was prepared using the procedure described by Boeckmann.

Flash column chromatography was performed using Fluka silica gel 60 under positive pressure. Analytical thin layer chromatography was performed on aluminium sheets pre-coated with Merck silica gel 60 F₂₅₄ and visualised with ultraviolet light (254 nm), aqueous potassium permanganate or anisaldehyde solutions where appropriate.

¹H NMR spectra were recorded on a JEOL ECX 400 (400 MHz) instrument. The chemical shift data is reported in parts per million (ppm) on the delta (δ) scale relative to tetramethylsilane (TMS) where δ_TMS = 0.00 ppm. The number of protons (n) for a given resonance is indicated by nH. The multiplicity of each signal is indicated by: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). The coupling constants (J) are quoted to the nearest 0.5 Hz. The residual protic solvent (CHCl₃) (δ_H=7.26 ppm) was used as an internal reference. ¹³C NMR spectra were recorded on a JEOL ECX 400 instrument at 100 MHz. The central signal of CDCl₃ (δ_C=77.0 ppm) was used as an internal reference. ¹³C spectra were verified using DEPT experiments and COSY and HSQC experiments were used for assignment purposes where necessary. Chemical shifts are reported to the nearest 0.01 ppm for ¹H NMR and to the nearest 0.1 ppm for ¹³C NMR.
Infrared spectra were carried out on a ThermoNicolet IR100 spectrometer and are recorded as a thin film between NaCl discs. Absorption maxima are reported in wavenumbers (cm$^{-1}$) and only selected absorbances are reported. Mass spectra and accurate mass measurements were obtained through the University of York mass spectrometry service and were recorded on a Bruker Daltonics, Micro-tof spectrometer. All melting points were taken on a Gallenkamp instrument.

All numbering of structures is for characterisation purposes only and does not conform to IUPAC rules.

7.2 Procedures & Compound Characterisation (Chapter 1 & Chapter 2)

$(\pm)$-(1S,2S)-Cyclopropane-1,2-diyldimethanol (54a)$^{24}$

![Chemical Structure](image)

To a stirred suspension of LiAlH$_4$ (4.17 g, 110 mmol) in THF (100 mL) at 0 °C was added a solution of diethyl trans-1,2-cyclopropanedicarboxylate (13.6 g, 73.1 mmol) in THF (25 mL), over a period of 1 h via a syringe pump. The reaction mixture was then heated at reflux at 70 °C for 2 h, before being cooled to RT and stirred for 18 h. After cooling to 0 °C the mixture was diluted with EtOAc (30 mL) and washed cautiously with sat. NH$_4$Cl (aq.) (30 mL). The resulting suspension was filtered, and the insoluble salts were washed with further portions of EtOAc (2 × 50 mL). The filtrate was concentrated under reduced pressure, and the residue taken up in EtOAc (50 mL). The solution was then dried (MgSO$_4$), filtered and concentrated under reduced pressure to afford to afford the title compound 54a as a colourless oil. (5.30 g, 71%); R$_f$ (1:1 pet. ether:EtOAc) 0.34; $^1$H NMR (400 MHz; CDCl$_3$) δ 3.73–3.60 (2 H, m, H-1a), 3.35–3.21 (2 H, m, H-1b), 0.99–1.07 (2 H, m, H-2), 0.46 (2 H, dt, J 7.0, 2.5 H-3). Data in agreement with those reported in the literature.$^{24}$
(±)-(2E,2’E)-Diethyl 3,3’-cyclopropane-1R,2R-diyl)diprop-2-enoate (55a)\textsuperscript{24}

![DIAGRAM](image)

To a stirred solution of 54a (8.67 g, 85.0 mmol) in CHCl\textsubscript{3} (510 mL) was added manganese oxide (148 g, 1.7 mol) and (carbethoxymethylene) triphenyl phosphorane (71.1 g, 204 mmol). The resulting suspension was stirred vigorously with heating to maintain gentle reflux for 18 h. After cooling to room temperature, the suspension was filtered through Celite, and washed with CHCl\textsubscript{3} (50 mL). The filtrate was concentrated under reduced pressure and diethyl ether (100 mL) was added to the yellow solid residue. This suspension was stirred at room temperature for 30 mins, and the resulting white precipitate (triphenylphosphine oxide) was removed by filtration and washed with pet. ether (75 mL). The filtrate was concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether:Et\textsubscript{2}O (4:1 → 2:1) to afford the title compound 55a as a white solid (15.2 g, 75%); R\textsubscript{f} (4:1 pet. ether:Et\textsubscript{2}O) 0.41; \textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}) δ 6.45 (2 H, dd, J = 9.0, 15.5, H-2), 5.90 (2 H, d, J = 15.5 H-1), 4.17 (4 H, q, J = 7.0 CH\textsubscript{3}CH\textsubscript{2}O), 1.79 – 1.82 (2 H, m, H-3), 1.23 – 1.31 (8 H, m, CH\textsubscript{3}CH\textsubscript{2}O & H-4). Data in agreement with those reported in the literature.\textsuperscript{24}

(±)-(1R,2S,3Z,6Z)-Diethyl cyclohepta-3,6-diene-1,2-dicarboxylate (58a)

![DIAGRAM](image)

A stirred solution of 55 (5.01 g, 21.0 mmol) in xylene (50 mL) was heated at reflux at 130 °C for 16 h. After being cooled to RT the solution was concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether:Et\textsubscript{2}O (10:1 → 2:1) to afford the title compound 58a, as a colourless oil (3.96 g, 80%); R\textsubscript{f} (20:1 pet. ether:EtOAc) 0.19; ν\textsubscript{max} (thin film)/cm\textsuperscript{-1} 2981, 2937, 1735; \textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}) δ 6.08–6.02 (2H, m, H-2), 5.82–5.76 (2H, m, H-3), 4.20–4.11 (4H, m, CH\textsubscript{3}CH\textsubscript{2}O), 3.86–3.84 (2H, m, H-1), 3.06–2.97 (1H, m, H-4a), 2.68 (1H, dt, J = 20.0, 7.0 Hz H-4b), 1.25 (3H, t, J = 7.0, CH\textsubscript{3}CH\textsubscript{2}O); \textsuperscript{13}C NMR (101 MHz; CDCl\textsubscript{3}) δ 172.1 (CH\textsubscript{3}CH\textsubscript{2}OC=O), 129.4 (C-
3), 127.5 (C-2), 61.1 (OCH₂CH₃), 45.1 (C-1), 28.3 (C-4), 14.2 (OCH₂CH₃); m/z (ESI) 239 [MH⁺]; HRMS: calcd. for C₁₃H₁₉O₄, 239.1278. Found: [MH⁺], 239.1271 (2.4 ppm error).

(±)-(1R,2S,3Z,6Z)-Cyclohepta-3,6-diene-1,2-diylidimethanol (59)

To a stirred suspension of LiAlH₄ (1.26 g, 33.2 mmol) in THF (75 mL) at RT was added 58 (3.96 g, 16.6 mmol) in THF (75 mL) via cannula. After 2 h the reaction was cooled to 0 °C and Na₂SO₄.10H₂O was cautiously added until on further addition fizzing could no longer be observed. The aluminium salts were removed by filtration and washed with EtOAc (200 mL). The filtrate was concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (4:1 & 1:1) to afford the title compound 59 as a colourless oil (1.94 g, 76%); Rf (EtOAc) 0.44; νmax (thin film)/cm⁻¹ 3315, 3013, 2926, 2876, 1655; ¹H NMR (400 MHz; CDCl₃) δ 5.79–5.57 (4H, m, H-3 & H-4), 3.77–3.58 (4H, m, H-1), 3.10–2.99 (1H, m, H-5a), 2.91–2.83 (2H, m, H-2), 2.73–2.64 (1H, m, H-5b); ¹³C NMR (101 MHz; CDCl₃) δ 130.3 (C-3 or C-4), 129.1 (C-3 or C-4), 64.0 (C-1), 44.1 (C-2), 29.8 (C-5); m/z (ESI): 177 [MNa⁺]; HRMS (ESI): calcd. for C₉H₁₄NaO₂, 177.0886. Found: [MNa⁺], 177.0886 (0.0 ppm error).

(±)-(3aR,4Z,7Z,8aS)-3,3a,6,8a-Tetrahydro-1H-cyclohepta[c]furan-1-one (60)

To a stirred solution of 59 (500 mg, 3.25 mmol) in CH₂Cl₂ (18 mL) at RT was added PhI(OAc)₂ (2.62 g, 8.13 mmol) and TEMPO (508 mg, 0.325 mmol). After 2 h the reaction mixture was concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (4:1 → 1:1) to afford the title compound 60 as a colourless oil (240 mg, 49%); Rf (1:1 pet. ether:Et₂O) 0.42; νmax (thin film)/cm⁻¹ 3025, 2970, 2910, 1769; ¹H NMR (400 MHz;
To a stirred solution of 60 (120 mg, 0.799 mmol) in degassed THF (24 mL) at 0 °C was added DBU (0.12 mL, 0.799 mmol). After 2h the reaction was quenched with NH₄Cl (aq.) (30 mL), the organic layer was separated and the aqueous layer extracted with portions of EtOAc (2 × 50 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et₂O (4:1) to afford the title compound 61 as a white solid (89 mg, 74%), 63 as a colourless oil (13 mg, 11%) and 64 (7 mg, 6%) as a colourless oil (assigned tentatively by ¹H NMR spectroscopy); 61 Rᵣ (1:2 pet. ether:Et₂O) 0.54; mp 55-58 °C; νₓ (thin film)/cm⁻¹ 3026, 2949, 2906, 2854, 1754, 1678; ¹H NMR (400 MHz; CDCl₃) δ 6.96 (1H, dd, J 4.5, 9.5 Hz, H-2), 5.60 (1H, ddd, J 10.5, 2.5, 2.5 Hz, H-5), 5.98–5.90 (1H, m, H-6), 4.58 (1H, dd, J 9.0 Hz, H-8a), 4.24–4.13 (1H, m, H-7), 3.96 (1H, dd, J 9.0 Hz, H-8b), 2.60–2.47 (2H, m, H-3), 2.39–2.28 (1H, m, H-4a), 2.25–2.16 (1H, m, H-4b); ¹³C NMR (101 MHz; CDCl₃) δ 171.0 (C-9), 140.9 (C-2), 132.3 (C-5 or C-6), 130.0 (C-5 or C-6), 128.7 (C-1), 70.6 (C-8), 37.3 (C-7), 26.3 (C-3 or C-4), 25.0 (C-3 or C-4); m/z (ESI): 173 [MNa⁺]; HRMS (ESI): calcd. for C₉H₁₀NaO₂, 173.0573. Found: [MNa⁺], 173.0571
(1.5 ppm error). 63 R_f (1: 2 pet. ether: Et_2O) 0.51; \( \nu_{\text{max}} \) (thin film)/cm\(^{-1} \) 3020, 2928, 2850, 1752; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 6.34 (1H, dt, \( J \) 11.5, 5.5 Hz, H-5), 5.86 (1H, dt, \( J \) 11.5, 1.5 Hz, H-6), 4.66 (2H, t, \( J \) 2.5 Hz, H-8), 2.56–2.48 (4H, m, H-2 & H-4), 1.90–1.84 (2H, m, H-3); \(^1^3\)C NMR (101 MHz; CDCl\(_3\)) \( \delta \) 175.1 (C-9), 153.3 (C-1 or C-7), 143.9 (C-5), 127.4 (C-1 or C-7), 119.0 (C-6), 70.9 (C-8), 32.0 (C-2 or C-4), 26.8 (C-2 or C-4), 22.4 (C-3). m/z (ESI): 173 [MNa\(^+\)]; HRMS (ESI): calcd. for C\(_9\)H\(_{10}\)NaO\(_2\), 173.0573. Found: [MNa\(^+\)], 173.0575 (1.5 ppm error).

64 R_f (1: 2 pet. ether: Et_2O) 0.49; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 6.43–5.22 (2H, m, H-3 & H-5), 5.97–5.76 (1H, m, H-6), 5.60–5.51 (1H, m, H-2), 4.43 (1H, dd, \( J \) 9.5, 5.0 Hz, H-8a), 4.24 (1H, dd, \( J \) 9.5, 3.5 Hz, H-8b), 3.75–3.65 (1H, m, H-1), 3.50–3.47 (1H, m, H-7), 3.01–2.84 (2H, m H-4).

\((\pm)\)-(3\(^1\)S,4\(^a\)S,8\(^a\)R,Z)-4,4\(^a\),5,6-Tetrahydro-1\(^H\)-isochromen-3(8\(^a\)H)-one (62)

\begin{center}
\begin{tikzpicture}
\node (node1) at (0,0) {\includegraphics[width=1in]{compound.png}};
\end{tikzpicture}
\end{center}

Procedure 1: To a suspension of NaH (27.0 mg, 0.675 mmol, 60% dispersion in mineral oil) in DMF (5 mL) at 0 °C was added trimethylsulfoxonium iodide (148 mg, 0.675 mmol). The reaction mixture was stirred for 5 min the dropwise addition of 61 (85 mg, 0.567 mmol) in DMF (5 mL). The solution was stirred at 0 °C for 5 mins before warming to RT and stirring for 16 h. Sat. NH\(_4\)Cl (aq.) (10 mL) was then added followed by H\(_2\)O (50 mL). The organic layer was separated and the aqueous layer extracted with portions of Et\(_2\)O (2 × 60 mL). The combined organic extracts were dried (MgSO\(_4\)), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et\(_2\)O (4:1) to afford the title compound 62 as a colourless oil (24 mg, 26%);

Procedure 2: To a stirred solution of MTBD (104 mg, 0.68 mmol) and trimethylsulfoxonium iodide (90 mg, 0.408 mmol) in MeCN (1 mL) was added 61 (51 mg, 0.340 mmol) in MeCN (1 mL). The reaction mixture was stirred at RT overnight. It was then concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et\(_2\)O (4:1) to afford the title compound 62 as a colourless oil (11 mg, 19%); R_f (1:1 pet.
ether:Et₂O 0.46; \( \nu_{\text{max}} \) (thin film)/cm\(^{-1} \) 3002, 2919, 1767; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 5.71–5.66 (1H, m, H-5), 5.37 (1H, dd, \( J \) 11.5, 4.0 Hz, H-6), 4.50 (1H, dd, \( J \) 9.0, 7.0 Hz, H-8a), 4.28 (1H, dd, \( J \) 9.0, 1.0 Hz, H-8b), 3.14–3.10 (1H, m, H-7), 2.38–2.23 (3H, m, H-2 & H-4), 1.77–1.69 (1H, m, H-3a), 1.34–1.25 (2H, m, H-3b & H-1a), 0.99 (1H, dd, \( J \) 6.0, 4.0 Hz, H-1b); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)) \( \delta \) 179.7 (C-9), 133.3 (C-13), 129.9 (C-6), 119.6 (C-7), 74.1 (C-8), 39.9 (C-2), 30.2 (C-10), 29.4 (C-3 or C-4), 29.3 (C-3 or C-4), 24.3 (C-1), 22.9 (C-7); m/z (ESI): 187 [MNa\(^{+}\)]; HRMS (ESI): calcd. for C\(_{10}\)H\(_{12}\)NaO\(_2\), 187.0730. Found: [MNa\(^{+}\)], 187.0725 (2.7 ppm error).  

(±)-(3aR,4Z,7Z,8aS)-3,3a,6,8a-Tetrahydro-1H-cyclohepta[c]furan-1-ol (67)

To a stirred solution of 59 (100 mg, 0.650 mmol) in anhydrous DMSO (2 mL) was added IBX (218 mg, 0.780 mmol) at RT. This was stirred for 2h before the addition of H\(_2\)O (5 mL). The resulting mixture was filtered through celite, washed with CH\(_2\)Cl\(_2\) (10 mL) and water (2 mL). The filtrate was dried (MgSO\(_4\)), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et\(_2\)O (2:1) to afford the title compound 67 as a colourless oil and mixture of diastereomers in a ratio of major (A): minor (B), 2:1 (60 mg, 60%); R\(_f\) (EtOAc) 0.63; \( \nu_{\text{max}} \) (thin film)/cm\(^{-1} \) 3397, 3017, 2941, 2885; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 5.99–5.91 (1H, m, H-2 or H-3 or H-5 or H-6, A), 5.89–5.82 (1H, m, H-2 or H-3 or H-5 or H-6, A), 5.81–5.74 (1H, m, H-2 or H-3 or H-5 or H-6, A), 5.73–5.68 (1H, m, H-2 or H-3 or H-5 or H-6, B), 5.63–5.67 (1H, m, H-2 or H-3 or H-5 or H-6, B), 5.55–5.49 (1H, m, H-2 or H-3 or H-5 or H-6, A), 5.48–5.43, (2H, m, H-2 or H-3 or H-5 or H-6, B), 5.33 (1H, d, \( J \) 2.0 Hz, H-9, A), 5.29 (1H, dd, \( J \) 8.5, 5.0 Hz, H-9, B), 4.13 (1H, dd, \( J \) 8.0, 7.0 Hz, H-8a, A), 4.08 (1H, dd, \( J \) 8.5, 1.5 Hz, H-8a, B), 3.90 (1H, dd, \( J \) 8.5, 5.5 Hz, H-8b, B), 3.69 (1H, dd, \( J \) 8.0, 8.0 Hz, H-8b, A), 3.44 (1H, br s, OH, A), 3.36 (1H, br s, OH, B), 3.10–2.87 (4H, m, H-1 & H-7, A & B) 2.63 (2H, dd, \( J \) 7.0, 7.0 Hz, H-4, A), 2.58 (2H, dd, \( J \) 7.0, 7.0 Hz, H-4, B); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)) \( \delta \) 134.2 (C-2 or C-3 or C-5 or C-6, B), 133.8 (C-2 or C-3 or C-5 or C-6, A), 131.7 (C-2 or C-3 or C-5 or C-6, A), 130.7 (C-2 or C-3 or C-5 or C-6, B), 130.2, (C-2 or C-3 or C-5 or C-6, A) 127.8 (C-2 or C-3 or C-5 or C-6, A) 127.8 (C-2 or C-3 or C-5 or C-6, A).
A), 127.6 (C-2 or C-3 or C-5 or C-6, B), 124.6 (C-2 or C-3 or C-5 or C-6, B), 103.8 (C-9, A), 99.2 (C-9, B), 75.1 (C-8, B), 72.6 (C-8, A), 48.5 (C-1, A), 47.8 (C-1, B), 40.1 (C-7, A), 38.8 (C-7, B), 27.7 (C-4, A), 27.4 (C-4, B); m/z (ESI): 175 [MNa⁺]; HRMS (ESI): calcd. for C₉H₁₂NaO₂, 175.0730. Found: [MNa⁺], 175.0726 (2.6 ppm error).

Iodomethyl(cyclohexane) (69)

To a stirred solution of cyclohexylmethanol (500 mg, 4.38 mmol) in CH₂Cl₂ (25 mL) at RT was added triphenylphosphine (1.72 g, 6.57 mmol), imidazole (447 mg, 6.57 mmol) and iodine (667 mg, 5.26 mmol). After stirring for 50 mins Na₂S₂O₃ (aq.) (25 mL) was added, the organic layer was separated and the aqueous layer extracted with further EtOAc (2 × 30 mL). The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (30:1) to afford the title compound 69 as a colourless oil (608 mg, 62%); Rf (1:1 pet. ether:EtOAc) 0.78; ¹H NMR (400 MHz; CDCl₃) δ 3.10 (2H, d, J 6.5 Hz, CH₂I), 1.88–1.84 (2H, m, CH-cyclohexyl), 1.72 (2H, m, CH-cyclohexyl), 1.65–1.58 (1H, m, CH-cyclohexyl), 1.48–1.37 (1H, m, CH-cyclohexyl), 1.31–1.07 (3H, m, CH-cyclohexyl), 0.94 (2H, m, CH-cyclohexyl) Data in agreement with those reported in the literature.

tert-Butyl 2-(cyclohexylmethyl)-3-oxobutanoate (70)

To a stirring suspension of NaH (5 mg, 0.134 mmol) in THF (0.75 mL) at 0 °C was added t-butyl 3-oxobutanoate (18 µL, 0.112 mmol). 69 (25 mg, 0.112 mmol) in THF (0.75 mL) was added to the reaction mixture dropwise over 1 minute before warming to RT over 1 h and heating for 16 h in a sealed tube wrapped in tin foil at 70 °C. The reaction was diluted with Et₂O (5 mL), quenched with sat. NH₄Cl (aq.) (3 mL) and the organic layer separated. The aqueous layer was extracted with further portions of Et₂O (2 × 5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column
chromatography on silica gel, eluting with pet. ether:EtOAc (40:1) to afford the title compound 70 as a colourless oil (19 mg, 72%); Rf (20:1 pet. ether:EtOAc) 0.30; \( \nu_{\text{max}} \) (thin film)/cm\(^{-1} \) 2977, 2924, 2852, 1736, 1715; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 3.41 (1H, dd, \( J \) 8.0, 7.0 Hz, H-3), 2.19 (3H, s, H-1), 1.76–1.60 (7H, m, 3 \( \times \) CH\(_2\) & CH), 1.44 (9H, s, C(CH\(_3\))\(_3\)), 1.24–1.12 (4H, m, 2 \( \times \) CH\(_2\)), 0.90–0.84 (2H, m, CH\(_2\)); 13C NMR (101 MHz; CDCl\(_3\)) \( \delta \) 204.0 (t-BuOC=O), 169.5 (C-2), 81.8 (C(CH\(_3\))\(_3\)), 58.7 (C-3), 35.7 (C-5), 35.6 (C-4), 33.3 (CH\(_2\)), 33.0 (CH\(_2\)), 28.6 (C-1), 28.0 (C(CH\(_3\))\(_3\)), 26.5 (CH\(_2\)), 26.3 (CH\(_2\)), 26.3 (CH\(_2\)); m/z (ESI): 277 [MNa\(^+\)]; HRMS (ESI): calcd. for C\(_{15}\)H\(_{26}\)NaO\(_3\), 277.1774. Found: [MNa\(^+\)], 277.1772 (1.3 ppm error).

4-Cyclohexylbutan-2-one (71)\(^{82}\)

To a stirred solution of (32) (44 mg, 0.173 mmol) in benzene (1.5 mL) was added p-TSA (7 mg, 0.035 mmol). This was heated at reflux for 2.5h before the addition of sat. NaHCO\(_3\) (aq.) (2 mL) and Et\(_2\)O (2 mL). The organic layer was separated and the aqueous layer extracted with further portions of Et\(_2\)O (2 \( \times \) 5 mL). The combined organic extracts were dried (MgSO\(_4\)), filtered and concentrated under reduced pressure to afford the title compound 71 as a colourless oil (22 mg, 85%); Rf (10:1 pet. ether:EtOAc) 0.22; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 2.42 (2H, t, \( J \) 8.0 Hz, H-3), 2.13 (3H, s, H-1), 1.70–1.64 (5H, m, CH\(_2\)), 1.48–1.42 (2H, m, CH\(_2\)), 1.21–1.15 (4H, m, CH\(_3\)), 0.91–0.82 (2H, m, CH\(_3\)); Data in agreement with those reported in the literature.\(^{82}\)

(\(\pm\)-(R,2E,6Z)-Cyclohepta-2,6-diene-1,2-diyldimethanol (72)

To a stirred solution of 60 (99 mg, 0.666 mmol) in CH\(_2\)Cl\(_2\) (3 mL) at −78 °C was added DIBAL (3.33 mL, 3.33 mmol, 1M in hexanes). After 10 mins the reaction was warmed to RT. After 4 h the reaction mixture was diluted with CH\(_2\)Cl\(_2\) (5 mL) followed by the addition of sat. aq. Rochelle’s salt (5 mL). The mixture was stirred overnight after which time, the organic layer was separated and the aqueous layer extracted with
further portions of CH$_2$Cl$_2$ (2 × 10 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure to afford the title compound 72 as a colourless oil (84 mg, 82%); R$_f$ (1:2 pet. ether:Et$_2$O) 0.21; $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3306, 3010, 2925, 2877, 1660; $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 5.95 (1H, t, J 6.5 Hz, H-2), 5.78–5.72 (1H, m, H-5), 5.47 (1H, ddt, J 12.0, 6.5, 1.5 Hz, H-6), 4.14–3.81 (2H, br s, OH), 3.97–3.96 (2H, m, H-9), 3.77 (1H, dd, J 10.5, 8.5, H-8a), 3.70 (1H, dd, J 10.5, 5.0, H-8b), 3.03–2.97 (1H, m, H-7), 2.54–2.43 (1H, m H-3a), 2.16–2.08 (3H, m, H-3b, H-4); $^{13}$C NMR (101 MHz; CDCl$_3$) $\delta$ 142.4 (C-1), 132.4 (C-5), 130.7 (C-2), 126.7 (C-6), 68.8 (C-9), 65.1 (C-8), 45.6 (C-7), 26.2 (C-3 or C-4), 25.5 (C-3 or C-4); m/z (ESI): 177 [MNa$^+$]; HRMS (ESI): calcd. for C$_9$H$_{14}$NaO$_2$, 177.0886. Found: [MNa$^+$], 177.0885 (0.1 ppm error).

(±)-(1S,2R,7S,Z)-Bicyclo[5.1.0]oct-3-ene-1,2-diyldimethanol (73) &
(±)-(1R,2R,7R,Z)-Bicyclo[5.1.0]oct-3-ene-1,2-diyldimethanol (74)

To a stirred solution of Et$_2$Zn (0.65 mL, 1 mol in hexanes, 0.650 mmol) in CH$_2$Cl$_2$ (0.2 mL) at 0 °C was added diiodomethane (100 µL, 1.30 mmol). This was stirred for 10 mins before the addition of 72 (45 mg, 0.292 mmol) in CH$_2$Cl$_2$ (0.2 mL) via cannula. The reaction was stirred at 0 °C for 10 mins, before warming to RT. After 2h the reaction was quenched by the addition of sat. NH$_4$Cl (aq.) (2mL). The organic layer was separated and the aqueous layer extracted with further portions of CH$_2$Cl$_2$ (2 × 5 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure to afford the title compound 73 as a colourless oil (6 mg, 13%) and 74 as a colourless oil (5 mg, 10%); 73 R$_f$ (1:2 pet. ether:Et$_2$O) 0.19; $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3301, 3012, 2928, 2880, 1640; $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 5.54–5.49 (1H, m, H-5), 5.41–5.36 (1H, ddt, J 11.5, 4.0, 2.0 Hz, H-6), 3.97 (1H, dd, J 11.5, 1.0 Hz, H-9a), 3.79–3.73 (2H, m, H-8), 3.22 (2H, br s, OH), 3.01 (1H, d, J 11.5 Hz, H-9b), 2.58–2.49 (1H, m, H-7), 2.39–2.20 (2H, m, H-4), 2.05–1.98 (1H, m, H-3a), 1.65–1.53 (1H, m, H-3b), 0.78 (1H, dd, J 8.5, 4.5 Hz, H-10a), 0.73–0.65 (1H, m, H-10b), 0.48 (1H, td, J 4.5, 1.0 Hz, H-2). $^{13}$C
NMR (101 MHz; CDCl₃) δ 134.4 (C-5), 129.7 (C-6), 65.8 (C-9), 63.1 (C-8), 41.1 (C-7), 30.2 (C-3 or C-4), 29.5 (C-3 or C-4), 22.1 (C-1), 21.4 (C-2), 20.0 (C-10); 191 [MNa⁺]; HRMS (ESI): calcd. for C₁₀H₁₆NaO₂, 191.1048. Found: [MNa⁺], 191.1050 (0.3 ppm error); 74 Rf (1:2 pet. ether:Et₂O) 0.17; ¹H NMR (400 MHz; CDCl₃) δ 5.66–5.50 (1H, m, H-5), 5.46 (1H, dddd, J 12.0, 6.5, 2.5, 1.5 Hz, H-6), 3.69–3.65 (1H, m, H-8a), 3.59 (1H, dd, J 11.0, 1.5 Hz, H-9a), 3.50–3.44 (1H, m, H-8b), 3.10 (1H, d, J 11.0 Hz, H-9b), 3.01–2.96 (1H, m, H-7), 2.4 (2H, br s, OH), 2.30–2.17 (2H, m, H-4), 1.96–1.86 (1H, m, H-3a), 1.50–1.39 (1H, m, H-3b), 0.87–0.82 (1H, m, H-10a), 0.67 (1H, td, J 5.0, 1.5 Hz, H-2), 0.60 (1H, dd, J 9.0, 5.0 Hz, H-10b). ¹³C NMR (101 MHz; CDCl₃) δ 135.2 (C-5), 130.3 (C-6), 69.5 (C-9), 65.1 (C-8), 38.1 (C-7), 30.0 (C-3 or C-4), 29.2 (C-3 or C-4), 23.3 (C-1), 20.9 (C-2), 20.3 (C-10); 191 [MNa⁺]; HRMS (ESI): calcd. for C₁₀H₁₆NaO₂, 191.1048. Found: [MNa⁺], 191.1055 (1.4 ppm error)

(±)-(1R,2R,7R,Z)-Bicyclo[5.1.0]oct-3-ene-1,2-diyldimethanol (73)

To a stirred solution of LiAlH₄ (16 mg, 0.426 mmol) in THF (2 mL) at 0 °C was added a solution of 62 (35 mg, 0.213 mmol) in THF (2 mL), via cannula. The reaction mixture was warmed to RT and stirred for 45 mins. After being cooled to 0 °C, Na₂SO₄·10H₂O was cautiously added until on further addition fizzing could no longer be observed. The aluminium salts were removed by filtration and washed with EtOAc (15 mL). The filtrate was concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether:Et₂O (4:1 → 1:1) to afford the title compound 73 as a colourless oil (16 mg, 44%); For data see page 96.

(±)-((1S,2Z,5Z,7R)-7-((tert-Butyldimethylsilyloxy)methyl)cyclohepta-2,5-dienyl)methanol (76)

To a stirred solution of 59 (500 mg, 3.25 mmol) in THF (6 mL) was added NaH (156 mg, 3.90 mmol, 60% dispersion in
mineral oil) at RT and the reaction mixture stirred for 45 mins before the addition of TBSCl (588 mg, 3.90 mmol). After 2h the reaction was quenched with sat. K₂CO₃ (aq.) (5 mL) followed by Et₂O (5 mL). The organic layer was separated and the aqueous layer extracted with further portions of Et₂O (2 × 5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (40:1 → 5:1) to afford the title compound 76 as a colourless oil (775 mg, 89%); Rᵣ (1:1 pet. ether:EtOAc) 0.72; ν max (thin film)/cm⁻¹ 3430, 3014, 2955, 2929, 2884, 2858; ¹H NMR (400 MHz; CDCl₃) δ 5.77–5.69 (2H, m, H-2 or H-3 or H-5 or H-6), 5.66–5.64 (2H, m, H-2 or H-3 or H-5 or H-6), 3.84–3.80 (1H, m, H-8a or H-9a), 3.74 (1H, dd, J 10.5, 8.0 Hz, H-8a or H-9a), 3.68–3.64 (1H, m, H-8b or H-9b), 3.56 (1H, dd, J 10.5, 3.0 Hz, H-8b or H-9b), 3.07–3.00 (1H, m, H-4a), 2.89–2.85 (1H, m, H-1 or H-7), 2.80–2.76 (1H, m, H-1 or H-7), 2.71–2.62 (1H, m, H-4b), 0.91 (9H, s, C(CH₃)₃), 0.10 (6H, s, SiCH₃); ¹³C NMR (101 MHz; CDCl₃) δ 130.8 (C-2 or C-3 or C-5 or C-6), 130.2 (C-2 or C-3 or C-5 or C-6), 129.1 (C-2 or C-3 or C-5 or C-6), 128.8 (C-2 or C-3 or C-5 or C-6), 64.5 (C-8 or C-9), 64.4 (C-8 or C-9), 44.4 (C-1 or C-7), 44.2 (C-1 or C-7), 29.8 (C-4), 26.0 (C(CH₃)₃), 18.4 (C(CH₃)₃), −5.4 (SiCH₃), −5.4 (SiCH₃); m/z (ESI): 291 [MNa⁺]; HRMS (ESI): calcd. for C₁₅H₂₈NaO₂Si, 291.1751. Found: [MNa⁺], 291.1745 (2.2 ppm error).

(±)-(1S,2Z,5Z,7R)-7-((tert-Butyldimethylsilyloxy)methyl)cyclohepta-2,5-
dienecarbaldehyde (77)

To a stirred solution of 76 (725 mg, 2.70 mmol) in CH₂Cl₂ (27 mL), at 0 °C was added Dess-Martin Periodinane (1.72 g, 4.05 mmol). The reaction mixture was warmed to RT and allowed to stir for 1 h. It was then diluted with CH₂Cl₂ (20 mL), and quenched with a 1:1 solution of sat. Na₂CO₃ (aq.) and sat. Na₂S₂O₃ (aq.) (40 mL). After vigorous stirring for 30 mins, the organic layer was separated and the aqueous layer extracted with further portions of CH₂Cl₂ (2 × 50 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to
afford the title compound 77 as a colourless oil (699 mg, 97%); \( R_f \) (5:1 pet. ether:EtOAc) 0.63; \( v_{\text{max}} \) (thin film)/cm\(^{-1}\) 2954, 2930, 2885, 2858, 1725, 1692; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 9.62 (1H, br s, H-9) 6.00 (1H, ddd, \( J \) 11.0, 5.5, 2.5, Hz, H-3 or H-5), 5.89–5.84 (1H, m, H-3 or H-5), 5.72–5.63 (2H, m, H-2 & H-6), 3.57 (2H, m, H-8), 3.41–3.38 (1H, m, H-1 or H-7), 3.18–3.14 (1H, m, H-1 or H-7), 3.10–3.02 (1H, m, H-4a), 2.78 (1H, dt, \( J \) 21.0, 5.5 Hz, H-4b). 0.91 (9H, s, C(CH\(_3\))\(_3\)), 0.10 (6H, s, SiCH\(_3\)); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)) \( \delta \) 201.1 (C-9), 130.2 (C-2 or C-3 or C-5 or C-6), 129.2 (C-2 or C-3 or C-5 or C-6), 128.8 (C-2 or C-3 or C-5 or C-6), 125.1 (C-2 or C-3 or C-5 or C-6), 63.9 (C-8), 53.25 (C-1), 42.7 (C-7), 30.1 (C-4), 26.0 (C(CH\(_3\))\(_3\)), 18.4 (C(CH\(_3\))\(_3\)), −5.5 (SiCH\(_3\)), −5.5 (SiCH\(_3\)).

\((\pm)\-(R,1E,5Z)-7-\{(\text{tert-Butyldimethylsilyloxy})\text{methyl}\}\text{cyclohepta-1,5-dienecarbaldehyde} \ (78)\)

To a solution of 77 (685 mg, 2.57 mmol) in THF (24 mL) at 0 °C was added DBU (0.38 mL, 2.57 mmol). After 20 mins the reaction was quenched with NH\(_4\)Cl (aq.) (30 mL), the organic layer was separated and the aqueous layer extracted with portions of EtOAc (2 × 50 mL). The combined organic extracts were dried (MgSO\(_4\)), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (20:1) to afford the title compound 78 as a colourless oil (525 mg, 77%); \( R_f \) (5:1 pet. ether:EtOAc) 0.59; \( v_{\text{max}} \) (thin film)/cm\(^{-1}\) 2954, 2929, 2887, 2857, 1689, 1649; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 9.32 (1H, s, H-9), 6.95 (1H dd, \( J \) 7.5, 5.5 Hz, H-2), 5.87–5.82 (1H, m, H-5), 5.66–5.60 (1H, m, H-6), 3.69–3.65 (2H, m, H-8), 3.64–3.61 (1H, m, H-7), 2.91–2.82 (1H, m, H-4a), 2.46–2.33 (2H, m, H-4b & H-3a), 2.22–2.14 (1H, m, H-3b), 0.86 (9H, s, C(CH\(_3\))\(_3\)), 0.02 (3H, s, SiCH\(_3\)), 0.01 (3H, s, SiCH\(_3\)); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)) \( \delta \) 194.4 (C-9), 156.8 (C-2), 144.7 (C-1), 130.8 (C-5 or C-6), 128.6 (C-5 or C-6), 66.0 (C-8), 40.0 (C-7), 27.7 (C-3 or C-4), 26.1 (C(CH\(_3\))\(_3\)), 25.5 (C-3 or C-4), 18.4 (C(CH\(_3\))\(_3\)), −5.4 (SiCH\(_3\)), −5.4 (SiCH\(_3\)); m/z (ESI): 289 [MNa\(^+\)]; HRMS (ESI): calcd. for C\(_{15}\)H\(_{26}\)NaO\(_2\)Si, 289.1594. Found: [MNa\(^+\)], 289.1583 (3.7 ppm error).
(±)-((R,1E,5Z)-7-((tert-Butyldimethylsilyloxy)methyl)cyclohepta-1,5-dienyl)methanol (79)

To a stirred solution of 78 (14 mg, 0.053 mmol) in CH₂Cl₂ (2 mL) at 0 °C was added DIBAL (0.208 mL, 1M in hexanes). After 30 mins the reaction mixture was diluted with CH₂Cl₂ (5 mL) and washed with Rochelle’s salt (5 mL). The organic layer was separated and the aqueous layer extracted with portions of EtOAc (2 × 10 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et₂O (1:2) to afford the title compound 79 as a colourless oil (9 mg, 64%); R_f (1:1 pet. ether:EtOAc) 0.75; ν_max (thin film)/cm⁻¹ 3337, 3010, 2927, 2856; ¹H NMR (400 MHz; CDCl₃) δ 5.96–5.92 (1H, m, H-2), 5.79–5.73 (1H, m, H-6), 5.52–5.45 (1H, m, H-5), 4.01 (1H, dd, J 11.5, 4.0 Hz, H-9a), 3.94 (1H, dd, J 11.5, 6.0 Hz, H-9b), 3.83 (1H, dd, J 9.5, 9.5 Hz, H-8a), 3.72 (1H, dd, J 9.5, 5.0 Hz, H-8b), 3.21–3.16 (1H, m, H-7), 3.07–3.02 (1H, m, H-3 or H-4), 2.56–2.47 (1H, m, H-3 or H-4), 2.17–2.05 (3H, m, OCH₃ + H-3 or H-4), 0.91 (s, 9H, C(CH₃)₃), 0.09 (3H, s, SiCH₃), 0.09 (3H, s, SiCH₃); ¹³C NMR (101 MHz; CDCl₃) δ 143.6 (C-1), 132.4 (C-6), 128.5 (C-5), 124.6 (C-2), 68.3 (C-8), 64.8 (C-9), 42.9 (C-7), 26.4 (C-3 or C-4), 26.1 (C(CH₃)₃), 25.0 (C-3 or C-4), 18.4 (C(CH₃)₃), −5.5 (SiCH₃), −5.5 (SiCH₃) m/z (ESI): 291 [MNa⁺]; HRMS (ESI): calcd. for C₁₅H₂₈NaO₂Si, 291.1751 Found: [MNa⁺], 291.1746 (1.1 ppm error).

(±)-((1S,2Z,5Z,7R)-7-((tert-Butyldiphenylsilyloxy)methyl)cyclohepta-2,5-dienyl)methanol (82)

To a solution of 59 (100 mg, 0.650 mmol) in THF (3 mL) was added NaH (31 mg, 0.280 mmol, 60% dispersion in mineral oil) at RT and the reaction mixture stirred for 45 mins before the addition of TBDPSCI (0.17 mL, 0.650 mmol). After 45 mins the reaction was quenched with K₂CO₃ (aq.) (5 mL) followed by Et₂O (5 mL). The organic layer was separated and the aqueous layer extracted with
further portions of Et₂O (2 × 5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (40:1 → 5:1) to afford the title compound 82 as a colourless oil (196 mg, 77%); Rₜ (1:1 pet. ether:EtOAc) 0.73; vₘₐₓ (thin film)/cm⁻¹ 3364, 3071, 3015, 2931, 2858, 1471, 1428; ¹H NMR (400 MHz; CDCl₃) δ 7.71 (4H, ddd, J 8.0, 1.5, 0.5 Hz, Ar-H), 7.48–7.40 (6H, m, Ar-H), 5.82–5.71 (2H, m, H-2 or H-3 or H-5 or H-6), 5.63–5.51 (2H, m, H-2 or H-3 or H-5 or H-6), 3.84–3.71 (3H, m, H-8 or H-9), 3.61 (1H, dd, J 10.5, 4.0 Hz, H-8 or H-9), 2.88–2.80 (1H, m, H-1 or H-7). ¹³C NMR (101 MHz; CDCl₃) δ 135.7 (Ar-C), 135.7 (Ar-C), 133.0 (Ar-C), 133.0 (Ar-C), 130.9 (CH), 130.3 (CH), 130.0 (CH), 129.2 (CH), 128.8 (CH), 127.9 (CH), 65.2 (C-8 or C-9), 64.8 (C-8 or C-9), 43.8 (C-1 or C-7), 43.5 (C-1 or C-7), 29.7 (C-4), 26.9 (C(CH₃)₃), 19.2 (C(CH₃)₃); m/z (ESI): 415 [MNa⁺]; HRMS (ESI): calcd. for C₃₂H₃₉NaO₃Si, 415.2069. Found: [MNa⁺], 415.2076 (2.5 ppm error).

(±)-(1S,2Z,5Z,7R)-7-((tert-Butyldiphenylsilyloxy)methyl)cyclohepta-2,5-dienecarbaldehyde (83)

To a stirred solution of 82 (510 mg, 1.30 mmol) in CH₂Cl₂ (13 mL), at 0 °C was added Dess-Martin Periodinane (827 mg, 1.95 mmol). The reaction mixture was warmed to RT and allowed to stir for 1 h. It was then diluted with CH₂Cl₂ (15 mL), and quenched with a 1:1 solution of sat. Na₂CO₃ (aq.) and sat. Na₂S₂O₃ (aq.) (30 mL). After vigorous stirring for 30 mins, the organic layer was separated and the aqueous layer extracted with further portions of CH₂Cl₂ (2 × 30 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to afford the title compound 83 as a colourless oil (511 mg, 100%) which was used in the next step without purification; Rₜ (5:1 pet. ether:EtOAc) 0.81; ¹H NMR (400 MHz; CDCl₃) δ 9.76 (1H, s, H-9), 7.63 (4H, ddd, J 8.0, 6.0, 1.5 Hz, Ar-H), 7.45–7.36 (6H, m, Ar-H), 6.06 (1H, ddd, J 11.0, 5.5, 3.0 Hz, H-2 or H-3 or H-5 or H-6), 5.88–5.83 (1H, m, H-2 or H-3 or H-5 or H-6), 5.62–5.60 (2H, m, H-2 or H-3 or H-5 or H-6).
or H-6), 3.65–3.52 (2H, m, H-8), 3.50–3.45 (1H, m, H-1), 3.24–3.20 (1H, m, H-7), 3.07–3.00 (1H, m, H-4a), 2.78–2.70 (1H, m, H-4b), 1.01 (9H, s, C(CH₃)₃); m/z (ESI): 391 [MH⁺]; HRMS (ESI): calcd. for C₂₅H₃₁O₂Si, 391.2088. Found: [MH⁺], 391.2089 (0.3 ppm error).

(±)-(R,1E,5Z)-7-((tert-Butyldiphenylsilyloxy)methyl)cyclohepta-1,5-dienecarbaldehyde (84)

To a solution of 83 (480 mg, 1.23 mmol) in THF (40 mL) at 0 °C was added DBU (0.184 mL, 1.23 mmol). After 20 mins the reaction was diluted with EtOAc (30 mL), quenched with NH₄Cl (aq.) (30 mL) and the organic layer separated. The aqueous layer was extracted with further portions of EtOAc (2 × 50 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et₂O (10:1) to afford the title compound 84 as a colourless oil (413 mg, 86%); Rf (5:1 pet. ether:EtOAc) 0.72; v_max (thin film)/cm⁻¹ 3070, 3049, 3014, 2930, 2857, 1687, 1649, 1471, 1427; ¹H NMR (400 MHz; CDCl₃) δ 9.30 (1H, s, H-9), 7.65 (4H, ddd, J 8.0, 6.0, 1.5 Hz, Ar-H), 7.43–7.35 (6H, m, Ar-H), 6.89 (1H, dd, J 7.5, 5.5 Hz, H-2), 5.86–5.81 (1H, m, H-5), 5.69–5.64 (1H, m, H-6), 3.78–3.75 (1H, m, H-7), 3.72–3.70 (2H, m, H-8), 2.81–2.73 (1H, m, H-3a), 2.38–2.26 (2H, m H-3b & H-4a), 2.18–2.14 (1H, m, H-4b), 1.02 (9H, s, C(CH₃)₃); ¹³C NMR (101 MHz; CDCl₃) δ 194.1 (C-9), 156.3 (C-2), 144.8 (C-1), 135.9 (C-5), 133.7 (Ar-C), 131.0 (Ar-CH), 129.7 (Ar-CH), 128.4 (C-6), 127.7 (Ar-CH), 66.4 (C-8), 39.3 (C-7), 27.5 (C-3 or C-4), 27.0 (C(CH₃)₃), 25.4 (C-3 or C-4), 19.4 (C(CH₃)₃); m/z (ESI): 413 [MNa⁺]; HRMS (ESI): calcd. for C₂₅H₃₀NaO₂Si, 413.1907. Found: [MNa⁺], 413.1907 (0.8 ppm error).
(±)-(R,E,5Z)-7-((tert-Butyldiphenylsilyloxy)methyl)cyclohepta-1,5-dienyl)methanol (85)

To a stirred solution of 84 (380 mg, 0.973 mmol) in CH$_2$Cl$_2$ (11 mL) at 0 °C was added DIBAL (1.46 mL, 1M in hexanes). After 30 mins the reaction mixture was diluted with CH$_2$Cl$_2$ (10 mL) and washed with Rochelle’s salt (10 mL). The organic layer was separated and the aqueous layer extracted with portions of EtOAc (2 × 10 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (10:1) to afford the title compound 85 as a colourless oil (240 mg, 63%); R$_f$ (5:1 pet. ether:EtOAc) 0.39; $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3378, 3071, 3013, 2920, 2857, 1472, 1427; $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 7.71 (4H, ddd, J 8.0, 6.0, 1.5 Hz, Ar-$\text{H}$), 7.47–7.38 (6H, m, Ar-$\text{H}$), 5.97 (1H, dd, J 7.5, 5.5 Hz, H-2), 5.74–5.69 (1H, m, H-5), 5.51–5.45 (1H, m, H-6), 4.10 (1H, d, J 12.0 Hz, H-9a), 4.00 (1H, d, J 12.0 Hz, H-9b), 3.86 (1H, dd J 9.5, 5.5 Hz, H-8a), 3.73 (1H, dd, J 9.5, 5.5 Hz, H-8b), 3.13 (1H, m, H-7), 2.78 (1H, br s, OH), 2.44–2.37 (1H, m H-3a), 2.11–2.01 (3H, m, H-3b + H-4), 1.08 (9H, s, C(C$_3$H$_7$)$_3$); $^{13}$C NMR (101 MHz; CDC$_3$) $\delta$ 143.0 (C-1), 135.8 (Ar-$\text{CH}$), 135.8 (Ar-$\text{CH}$), 133.1 (Ar-$\text{C}$), 132.4 (C-5), 129.9 (Ar-$\text{CH}$), 128.5 (C-2), 127.9 (Ar-$\text{CH}$), 126.6 (C-6), 68.8 (C-8 or C-9), 66.5 (C-8 or C-9), 44.6 (C-7), 26.9 (C(CH$_3$)$_3$), 26.4 (C-3 or C-4), 25.2 (C-3 or C-4), 19.2 (C(CH$_3$)$_3$); m/z (ESI): 415 [MNa$^+$]; HRMS (ESI): calcd. for C$_{25}$H$_{32}$NaO$_2$Si, 415.2064. Found: [MNa$^+$], 415.2058 (1.5 ppm error).

Triisopropylsulfonylum tetrafluoroborate (51)$^{23}$

To a stirring solution of diisopropyl sulfide (7.3 mL, 0.049 mol) in iso-propyl alcohol (15 mL) was added methanesulfonic acid (32 mL, 500 mmol). The reaction was heated to reflux and held at temperature for 5 days. The brown solution was cooled to RT and tetrafluoroboric acid (31.5 mL, 500 mmol) added. The mixture was stirred for 15 mins, water (150 mL) and CH$_2$Cl$_2$ (150 mL) were added and the organic layer separated. The aqueous layer was extracted with
further portions of CH₂Cl₂ (2 × 150 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to give an orange solid. This was suspended in Et₂O (100 mL) and filtered. The filtrand was washed with Et₂O (2 x 50 mL) to give a white precipitate, which was recrystallised from MeOH/Et₂O to afford the title compound 51 as a white solid (6.90 g, 56%); ¹H NMR (400 MHz; D₂O) δ 3.88 (3H, septet, J 7.0 Hz, CH), 1.54 (18H, d, J 7.0 Hz, 18H, CH₃); Data in agreement with those reported in the literature.²³

**Triisopropylsulfoxonium tetrafluoroborate (52)²³**

![Triisopropylsulfoxonium tetrafluoroborate (52)²³]

To a stirring solution of 51 (4.96 g, 20.0 mmol) in water (400 mL) at 0 °C was added 2-Nitrobenzenesulfonyl chloride (8.86 g, 40.0 mmol) followed by barium hydroxide octahydrate (18.9 g, 60.0 mmol) to give a cream suspension. Hydrogen peroxide (12.3 mL, 120.0 mmol) was added drop-wise over 1 h. The suspension was stirred for a further 1 h at 0 °C, warmed to RT and stirred for 18 h. The reaction mixture was filtered through celite, washed with water (100 mL) and concentrated under reduced pressure. CH₂Cl₂ (250 mL) and (MgSO₄) were added, the suspension filtered and the filtrate concentrated under reduced pressure to give the crude product. This was recrystallised from MeOH/Et₂O to afford the title compound 52 as a white solid (3.31 g, 63%); ¹H NMR (400 MHz; D₂O) δ 4.43 (3H, septet, J 7.0 Hz, CH), 1.61 (18H, d, J 7.0 Hz, 18H, CH₃); Data in agreement with those reported in the literature.²³

(±)-(1R,2R)-Diethyl 3,3-dimethylocyclopropane-1,2-dicarboxylate (53)

![(±)-(1R,2R)-Diethyl 3,3-dimethylocyclopropane-1,2-dicarboxylate (53)]

To a stirred solution of NaH (920 mg, 23.0 mmol, 60% dispersion in mineral oil) in DMF (150 mL) at 0 °C was added 52 (6.08 g, 23.0 mmol). This solution was allowed to stir for 5 mins before the drop-wise addition of a solution of diethyl fumarate (3.31 g, 19.2 mmol) in DMF (35 mL). The reaction mixture was allowed to stir at 0 °C for 5 mins before being warmed to RT and stirred for a further 2 h. It was diluted with Et₂O (115
mL), washed with sat. NH₄Cl (aq.) (100 mL), the organic layer separated and the aqueous layer extracted with further portions of Et₂O (2 × 150 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et₂O (7:1 → 4:1) to afford the title compound 53 as a colourless oil (3.01 g, 73%); Rf (3:1 pet. ether:EtOAc) 0.59; vmax (thin film)/cm⁻¹ 2982, 1723; ¹H NMR (400 MHz; CDCl₃) δ 4.20–4.08 (4H, m, CH₃CH₂O), 2.21 (2H, s, H-1), 1.29 (6H, s, CH₃), 1.27 (6H, t, J 7.0, CH₃CH₂O); ¹³C NMR (101 MHz; CDCl₃) δ 170.6 (C=O), 60.9 (CH₃CH₂O), 33.7 (C-1), 30.4 (C-2), 20.5 (CH₃), 14.4 (CH₃CH₂O); m/z (ESI): 215 [MH⁺]; HRMS (ESI): calcd. for C₁₁H₁₉O₄, 215.1278. Found: [MH⁺], 215.1283 (2.3 ppm error).

(±)-(1R,2R)-3,3-Dimethylcyclopropane-1,2-diyl)dimethanol (56a)

To a stirred solution of LiAlH₄ (963 mg, 25.4 mmol) in THF (25 mL) at 0 °C was added a solution of 53 (3.63 g, 16.9 mmol) in THF (9 mL), over a period of 1 h via a dropping syringe. The reaction mixture was then heated at reflux at 70 °C for 2 h, before being cooled to RT and stirred for 18 h. After being cooled to 0 °C the mixture was diluted with EtOAc (6 mL), washed cautiously with sat. NH₄Cl (aq.) (6 mL). The resulting suspension was filtered, and the insoluble salts were washed with further portions of EtOAc (2 × 10 mL). The filtrate was concentrated under reduced pressure, and the residue taken up in EtOAc (10 mL). The solution was then dried (MgSO₄), filtered and concentrated under reduced pressure to afford the title compound 56a as a colourless oil (1.89 g, 86%); Rf (EtOAc) 0.23; vmax (thin film)/cm⁻¹ 3337, 2926, 2874; ¹H NMR (400 MHz; CDCl₃) δ 3.77–3.69 (2H, m, H-1a), 3.59–3.50 (2H, m, H-1b), 2.23 (2H, broad s, OH), 1.13 (6H, s, CH₃), 0.85–0.79 (2H, m, H-2); ¹³C NMR (101 MHz; CDCl₃) δ 63.1 (C-1), 32.1 (C-2), 21.9 (CH₃), 20.8 (C-3); m/z (ESI): 153 [MNa⁺]; HRMS (ESI): calcd. for C₇H₁₄NaO₂, 153.0886. Found: [MNa⁺], 153.0888 (−1.5 ppm error).
Diethyl (±)-(2E,2′E)-3,3′-[(1R,2R)-3,3-dimethylcyclopropane-1,2-diyl]bisprop-2-enoate (57a) & Diethyl (±)-(2Z,2′E)-3,3′-[(1R,2R)-3,3-dimethylcyclopropane-1,2-diyl]bisprop-2-enoate (57b)

To a stirred solution of 56a (934 mg, 7.17 mmol) in CHCl₃ (70 mL) was added manganese (IV) dioxide (12.4 g, 143 mmol) and (carbethoxymethylene)triphenyl phosphorane (5.99 g, 17.2 mmol). The resulting suspension was stirred vigorously with heating to maintain gentle reflux for 18 h. After cooling to room temperature, the suspension was filtered through Celite, and washed with CHCl₃ (25 mL). The filtrate was concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (20:1) to afford the title compound 57a as a white solid (1.31 g, 69%), and 57b as a colourless oil (85 mg, 4%); 57a Rf (1:1 pet. ether:EtOAc) 0.38; mp 49–52 °C; νmax (thin film)/cm⁻¹ 2934, 1687, 1616; ¹H NMR (400 MHz; CDCl₃) δ: 6.73–6.63 (2H, m, H-2), 5.91 (2H, d, J 15.5, H-1), 4.17 (4H, q, J 7.0, CH₃CH₂O), 1.77–1.72 (2H, m, H-3), 1.27 (6H, t, J 7.0, CH₃CH₂O), 1.23 (6H, s, H-5 & H-6); ¹³C NMR (101 MHz; CDCl₃) δ: 166.4 (C=O), 147.5 (C-2), 121.5 (C-1), 60.3 (CH₃CH₂O), 38.5 (C-3), 30.3 (C-4), 22.4 (2 × CH₃), 14.4 (CH₃CH₂O); m/z (ESI): 267 [MH⁺]; HRMS: calcd. for C₁₅H₂₃O₄, 267.1591. Found: [MH⁺], 267.1587 (1.1 ppm error); 57b Rf (1:1 pet. ether:EtOAc) 0.39; νmax (thin film)/cm⁻¹ 2934, 1688, 1615; ¹H NMR (400 MHz; CDCl₃) δ: 6.74 (1H, dd, J 15.5, 10.0, H-6), 5.91 (1H, d, J 15.5, H-5), 5.87–5.77 (2H, m, H-2 & H-1), 4.21–4.14 (4H, m, CH₃CH₂O), 3.08 (1H, dd, J 10.0, 5.0, H-5), 1.65 (1H, dd, J 10.0, 5.0, H-3), 1.31–1.27 (6H, m, CH₃CH₂O), 1.26 (3H, s, CH₃), 1.21 (3H, s, CH₃); ¹³C NMR (101 MHz; CDCl₃) δ: 166.8 (C=O), 166.5 (C=O), 148.3 (C-6 or C-2) 148.1 (C-6 or C-2), 121.2 (C-7 or C-1), 119.9 (C-7 or C-1), 60.3 (CH₃CH₂O), 60.0 (CH₃CH₂O), 39.7 (C-5), 35.6 (C-3), 30.6 (C-4), 22.6 (CH₃), 22.3 (CH₃), 14.5 (CH₃CH₂O), 14.4 (CH₃CH₂O); m/z (ESI): 267 [MH⁺]; HRMS: calcd. for C₁₃H₂₃O₄, 267.1591. Found: [MH⁺], 267.1587 (1.1 ppm error).
(±)-1,2-Diethyl 5,5 dimethylecyclohepta-1 (7),2-diene-1,2-dicarboxylate (89)

Sodium ethoxide (1 mL, 0.563 M), prepared in situ by the addition of sodium (129 mg, 5.63 mmol) to ethanol (10 mL) and stirring under argon for ~10 mins, was added to 57a (100 mg, 0.375 mmol). The reaction mixture was heated to 90 °C and allowed to reflux for 18 h. After cooling to RT, the reaction mixture was concentrated under reduced pressure and CH₂Cl₂ (10 mL) added. This was washed with sat. NH₄Cl (aq.) (5 mL), the organic layer separated and the aqueous layer extracted with further portions of CH₂Cl₂ (2 × 10 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (9:1) to afford the title compound 89 as a colourless oil (80 mg, 80%) Rf (1:1 pet. ether:EtOAc) 0.66; vₘₐₓ (thin film)/ cm⁻¹ 2956, 1724; ¹H NMR (400 MHz; CDCl₃) δ 7.40–7.37 (2H, m, H-2), 4.18 (4H, q, J 7.0, CH₃CH₂O), 1.86 (4H, d, J 7.5, H-3), 1.26 (6H, t, J 7.0, CH₃CH₂O), 1.03 (6H, s, CH₃); ¹³C NMR (101 MHz; CDCl₃) δ 166.1 (C=O), 145.1 (C-2), 132.3 (C-1), 60.8 (CH₃CH₂O), 52.2 (C-4), 40.9 (C-3), 29.4 (CH₃), 14.3 (CH₃CH₂O); m/z (ESI) 267 [MH⁺]; HRMS: calcd. for C₁₅H₂₃O₄, 267.1591. Found: [MH⁺], 267.1586 (0.6 ppm error).

(±)-((1R,3R)-3-((tert-Butyldimethylsilyloxy)methyl)-2,2-dimethylecyclopropyl)methanol (93)

To a stirred solution of 56a (824 mg, 6.33 mmol) in THF (13 mL) at RT was added NaH (253 mg, 6.33 mmol, 60% dispersion in mineral oil). After 45 mins, by which time a large amount of white precipitate had formed, TBSCI (954 mg, 6.33 mmol) was added. The reaction mixture was allowed to stir for a further 1 h before dilution with Et₂O (15 mL). It was then washed with sat. K₂CO₃ (aq.) (10 mL) and brine (10 mL), the organic layer separated and the aqueous layer extracted with further portions of Et₂O (2 × 20 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by
flash column chromatography on silica gel, eluting with pet. ether:EtOAc (7:1 → 1:1) to afford the title compound 93 as a colourless oil (1.55 g, 65%); \( R_f \) (1:1 pet. ether:EtOAc) 0.46; \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 3392, 2954, 2858; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 3.63–3.59 (4H, m, H-1 & H-5), 1.12 (3H, d, J 11.0, H-1a), 3.60 (1H, dd, J 11.0, 6.0, H-1b), 1.93–1.88 (1H, m, H-4), 1.60–1.56 (1H, m, H-2), 1.30 (3H, s, CH\(_3\)), 1.22 (3H, s, CH\(_3\)), 0.89 (9H, s, C(CH\(_3\))\(_3\)), 0.80 (2H, s, CH\(_2\)); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)) \( \delta \) 61.9 (C-1), 41.3 (C-4), 36.6 (C-2), 26.1 (C-3) 26.0 (C(CH\(_3\))\(_3\)), 22.2 (CH\(_2\)), 21.4 (CH\(_3\)), 18.4 (C(CH\(_3\))\(_3\)), −5.0 (SiCH\(_3\)), −5.0 (SiCH\(_3\)); m/z (ESI) 267 [MNa\(^+\)]; HRMS: calcd. for C\(_{13}\)H\(_{28}\)NaO\(_2\)Si, 267.1751. Found: [MNa\(^+\)], 267.1748 (1.0 ppm error).

(±)-(1R,3R)-3-((tert-Butyldimethylsilyl)oxy)methyl)-2,2-dimethylcyclopropanecarbaldehyde (94)

To a stirred solution of 93 (980 mg, 4.00 mmol) in CH\(_2\)Cl\(_2\) (40 mL) at 0 °C was added DMP (5.09 g, 12.0 mmol). The reaction mixture was warmed to RT and allowed to stir for 2 h. It was then diluted with CH\(_2\)Cl\(_2\) (15 mL) and quenched with a 1:1 solution of sat. Na\(_2\)CO\(_3\) (aq.) and sat. Na\(_2\)S\(_2\)O\(_3\) (aq.) (15 mL). After vigorous stirring for 30 mins, the organic layer was separated and the aqueous layer extracted with further portions of CH\(_2\)Cl\(_2\) (2 × 20 mL). The combined organic extracts were dried (MgSO\(_4\)), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (5:1 → 2:1) to afford the title compound 94 as a colourless oil (580 mg, 60%); \( R_f \) (1:1 pet. ether:EtOAc) 0.58; \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 3392, 2954, 2858, 1705; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 9.35 (1H, d, J 5.5, H-5), 3.77 (1H, dd, J 11.0, 6.0, H-1a), 1.93–1.88 (1H, m, H-4), 1.60–1.56 (1H, m, H-2), 1.30 (3H, s, CH\(_3\)), 1.22 (3H, s, CH\(_3\)), 0.89 (9H, s, C(CH\(_3\))\(_3\)), 0.80 (2H, s, CH\(_2\)); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)) \( \delta \) 201.3 (C-5), 61.9 (C-1), 41.3 (C-4), 36.6 (C-2), 26.1 (C-3) 26.0 (C(CH\(_3\))\(_3\)), 22.2 (CH\(_2\)), 21.4 (CH\(_3\)), 18.4 (C(CH\(_3\))\(_3\)), −5.0 (SiCH\(_3\)), −5.1 (SiCH\(_3\)); m/z (ESI) 243 [MH\(^+\)]; HRMS: calcd. for C\(_{13}\)H\(_{27}\)O\(_2\)Si, 243.1775. Found: [MH\(^+\)], 243.1770 (1.6 ppm error).
(±)-(E)-Ethyl 3-((1R,3R)-3-((tert-butyldimethylsilyloxy)methyl)-2,2-dimethylcyclopropyl)prop-2-enoate (95)

To a stirred solution of 94 (550 mg, 2.27 mmol) in CH₂Cl₂ (25 mL) at RT was added carbethoxymethylene triphenylphosphorane (1.58 g, 4.54 mmol). After 18 h the solution was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (9:1) to afford the title compound 95 as a colourless oil (709 mg, 82%); Rₖ (5:1 pet. ether:EtOAc) 0.63; ν_max (thin film)/cm⁻¹ 2954, 2930, 2858, 1724, 1641; ¹H NMR (400 MHz; CDCl₃) δ 6.69 (1H, dd, J 15.5, 10.0 Hz, H-5), 5.84 (1H, d, J 15.5 Hz, H-6) 4.20–4.10 (2H, m, CH₃C₂H₂O), 3.76 (1H, dd, J 11.0, 6.0 Hz, H-1a), 3.57 (1H, dd, J 11.0, 7.5 Hz, H-1b), 1.30–1.25 (2H, m, H-2 & H-4) 1.27 (3H, t, J 7.0 Hz, CH₃C₂H₂O), 1.17 (3H, s, CH₃), 1.06 (3H, s, CH₃), 0.87 (9H, s, C(CH₃)₃), 0.04 (3H, s, SiCH₃), 0.03 (3H, s, SiCH₃); ¹³C NMR (101 MHz; CDCl₃) δ 166.8 (C=O), 150.6 (C-5), 120.0 (C-6), 62.8 (C-1), 60.1 (CH₂CH₂O), 37.3 (C-2 or C-4), 33.1 (C-2 or C-4), 26.5 (C-3), 26.0 (C(CH₃)₃), 23.0 (CH₃), 21.3 (CH₃), 18.4 (C(CH₃)₃), 14.5 (CH₂CH₂O), –5.0 (SiCH₃), –5.1 (SiCH₃); m/z (ESI) 313 [MH⁺]; HRMS: calcd. for C₁₇H₃₃O₃Si, 313.2193. Found: [MH⁺], 313.2185 (2.7 ppm error).

(±)-(E)-3-((1R,3R)-3-((tert-Butyldimethylsilyloxy)methyl)-2,2-dimethylcyclopropyl)prop-2-en-1-ol (96)

To a stirred solution of 95 (460 mg, 1.47 mmol) in CH₂Cl₂ (15 mL) at 0 °C was added DIBAL (5.88 mL, 5.88 mmol, 1M in hexanes). After 30 mins the reaction mixture was diluted with CH₂Cl₂ (35 mL) and washed with sat. aq. Rochelle’s salt (20 mL). The organic layer was separated and the aqueous layer extracted with further portions of CH₂Cl₂ (2 × 20 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to afford the title compound 96 as a colourless oil (360 mg, 96%); Rₖ (1:1 pet. ether:EtOAc) 0.67; ν_max (thin film)/cm⁻¹ 3368, 2929, 2859; ¹H NMR (400 MHz; CDCl₃) δ 5.73–5.67 (1H, dt, J 15.5, 6.0 Hz,
H-6), 5.44 (1H, dd, J 15.5, 9.0, H-5), 4.09 (2H, dd, J 6.0, 6.0 Hz, H-7), 3.79 (1H, dd, J 11.0, 6.0 Hz, H-1a), 3.52 (1H, dd, J 11.0, 8.5 Hz, H-1b), 1.26–1.08 (2H, m, H-2 & H-4), 1.23–1.18 (1H, t, J 6.0 Hz, OH), 1.11 (3H, s, CH₃), 0.89 (9H, s, C(CH₃)₃), 0.04 (3H, s, SiCH₃), 0.05 (3H, s, SiCH₃); ¹³C NMR (101 MHz; CDCl₃) δ 133.4 (C-6), 128.8 (C-5), 64.0 (C-1), 63.4 (C-7), 34.7 (C-2 or C-4), 32.0 (C-2 or C-4), 26.1 (C(CH₃)₃), 23.1 (C-3), 22.7 (CH₃), 21.3 (CH₃), 18.4 (C(CH₃)₃), −4.9 (SiCH₃), −5.0 (SiCH₃); m/z (ESI) 293 [MNa⁺]; HRMS: calcd. for C₁₅H₂₆NaO₂Si, 293.1907. Found: [MNa⁺], 293.1905 (0.1 ppm error).

(±)-((1R,3R)-3-((E)-3-(Benzyloxy)prop-1-enyl)-2,2-dimethylcyclopropyl)methanol (98)

To a stirred solution of 96 (440 mg, 1.72 mmol) in THF (9 mL) at 0 °C was added NaH (103 mg, 2.58 mmol, 60% dispersion in mineral oil). This was warmed to RT and allowed to stir for 45 mins. This was re-cooled to 0 °C, benzyl bromide (307 µL, 2.58 mmol) was added and the reaction mixture was allowed to stir at RT for 18 h. The reaction mixture was diluted with Et₂O (20 mL) and washed with sat. NH₄Cl (aq.) (10 mL), the organic layer separated and the aqueous layer extracted with further portions of Et₂O (2 × 20 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was dissolved in THF (17 mL) and the solution cooled to 0 °C before the addition of TBAF (3.4 mL, 1 M in THF). After 2 h the reaction mixture was diluted with Et₂O (20 mL) and washed with sat. NH₄Cl (aq.) (10 mL), the organic layer separated and the aqueous layer extracted with further portions of Et₂O (2 × 20 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (9:1 → 1:1) to afford the title compound 98 as a colourless oil (188 mg, 44%); Rf (1:1 pet. ether:EtOAc) 0.44; υmax (thin film)/cm⁻¹ 3398, 2922, 2866, 1661; ¹H NMR (400 MHz; CDCl₃) δ 7.36–7.26 (5H, m, Ar-CH), 5.68 (1H, ddd, J 15.5, 6.5, 6.5 Hz, H-6), 5.47 (1H, dd, J 15.5, 9.0 Hz, H-5), 4.50 (2H, s, C₆H₅CH₂), 3.98 (2H, d, J 6.5 Hz, H-7), 3.75 (1H, dd, J 11.5, 6.5 Hz H-1a), 3.55 (1H, dd, J 11.5, 6.5 Hz H-1b), 3.44 (1H, dd, J 15.5, 6.5 Hz, H-2), 2.00 (3H, s, CH₃), 1.12 (3H, s, CH₃), 0.90 (9H, s, C(CH₃)₃), 0.05 (3H, s, SiCH₃), 0.04 (3H, s, SiCH₃).
8.5 Hz, H-1b), 1.42 (1H, br s, OH), 1.21–0.94 (2H, m, H-2 & H-4), 1.14 (3H, s, CH₃), 1.10 (3H, s, CH₃); ¹³C NMR (101 MHz; CDCl₃) δ 138.5 (Ar-Ç), 134.2 (C-6), 128.5 (Ar-CH), 127.9 (C-5), 127.7 (Ar-CH), 126.5 (Ar-CH) 72.0 (C₆H₅CH₂), 70.9 (C-7), 63.3 (C-2 or C-4), 32.3 (C-2 or C-4), 22.6 (CH₃), 21.3 (CH₃); m/z (ESI): 269 [MNa⁺]; HRMS (ESI): calcd. for C₁₆H₂₂NaO₂, 269.1512. Found: [MNa⁺], 269.1519 (1.4 ppm error).

(±)-(1R,3R)-3-((E)-3-(Benzzyloxy)prop-1-enyl)-2,2-dimethylcyclopropanecarbaldehyde (99)

To a stirred solution of 98 (140 mg, 0.568 mmol) in CH₂Cl₂ (6 mL), at 0 °C was added DMP (721 mg, 1.7 mmol). The reaction mixture was warmed to RT and allowed to stir for 18 h. It was then diluted with CH₂Cl₂ (14 mL), and quenched with a 1:1 solution of sat Na₂CO₃ (aq.) and sat. Na₂S₂O₃ (aq.) (10 mL). After vigorous stirring for 30 mins, the organic layer was separated and the aqueous layer extracted with further portions of CH₂Cl₂ (2 × 10 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (4:1) to afford the title compound 99 (139 mg, 68%); Rᵣ (2:1 pet. ether:EtOAc) 0.63; νmax (thin film)/cm⁻¹ 2923, 2852, 1699; ¹H NMR (400 MHz; CDCl₃) δ 9.40 (1H, d, J 5.0 Hz, H-1), 7.37–7.26 (5H, m, Ar-CH), 5.80 (1H, ddd, J 15.5, 6.0, 6.0 Hz, H-6), 5.49 (1H, dd, J 15.5, 8.5 Hz, H-5), 4.51 (2H, s, C₆H₅CH₂), 3.99 (2H, d, J 6.0 Hz, H-7), 2.33 (1H, dd, J 8.5, 5.0 Hz, H-4), 1.78 (1H, dd, J 5.0, 5.0 Hz, H-2), 1.32 (3H, s, CH₃), 1.20 (3H, s, CH₃); ¹³C NMR (101 MHz; CDCl₃) δ 200.3 (C-1), 138.3 (Ar-Ç), 130.0 (C-6), 129.3 (Ar-CH), 128.5 (Ar-CH), 127.9 (C-5), 127.79 (Ar-CH), 72.3 (C₆H₅CH₂), 70.4 (C-7), 44.1 (C-4), 37.5 (C-2), 31.8 (C-3), 22.2 (CH₃), 21.6 (CH₃); m/z (ESI): 267 [MNa⁺]; HRMS (ESI): calcd. for C₁₆H₂₂NaO₂, 267.1356. Found: [MNa⁺], 267.1355 (0.9 ppm error).
(±)-(E)-Ethyl 3-((1R,3R)-3-((E)-3-(benz氧xy)prop-1-enyl)-2,2-dimethylcyclopropyl)prop-2-enoate (100)

To a stirred solution of 99 (80 mg, 0.327 mmol) in CH₂Cl₂ (25 mL) at RT was added carbethoxymethylene triphenylphosphorane (227 mg, 0.654 mmol). After stirring for 2 days the solution was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (9:1) to afford the title compound 100 as a colourless oil (99 mg, 96%); Rf (5:1 pet. ether:EtOAc) 0.41; νₚₑₑₑ (thin film)/cm⁻¹ 2926, 1712, 1638; ¹H NMR (400 MHz; CDCl₃) δ 7.38–7.26 (5H, m, Ar-CH), 6.69 (1H, dd, J 15.5, 10.5 Hz, H-2), 5.88 (1H, d, J 15.5 Hz, H-1), 5.73 (1H, ddd, J 15.5, 6.0, 6.0 Hz, H-7), 5.48 (1H, dd, J 15.5, 9.0 Hz, H-6), 4.50 (2H, s, C₆H₅CH₂), 4.21–4.11 (2H, m, CH₃CH₂O), 3.99 (2H, d, J 6.0 Hz, H-8), 1.65 (1H, dd, J 9.0, 5.0 Hz, H-5), 1.48 (1H, dd, J 10.5, 5.0, Hz, H-3), 1.27 (3H, t, J 7.0 Hz, CH₃CH₂O), 1.19 (3H, s, CH₃), 1.15 (3H, s, CH₃); ¹³C NMR (101 MHz; CDCl₃) δ 166.7 (C=O), 149.4 (C-1 or C-2 or C-6 or C-7), 138.4 (Ar-Ç), 132.1 (C-1 or C-2 or C-6 or C-7), 128.5 (Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 127.7 (C-1 or C-2 or C-6 or C-7), 120.4 (C-1 or C-2 or C-6 or C-7), 72.2 (C₆H₅CH₂), 70.7 (C-8), 60.2 (CH₃CH₂O), 38.4 (C-3 or C-5), 36.7 (C-3 or C-5), 28.3 (C-4), 22.5 (CH₃), 22.2 (CH₃), 14.5 (CH₃CH₂O); m/z (ESI): 337 [MNa⁺]; HRMS (ESI): calcd. for C₂₀H₂₆NaO₃, 337.1774. Found: [MNa⁺], 337.1772 (0.7 ppm error).

7.3 Procedures & Compound Characterisation (Chapter 3)

Ethyl (±)-(1S,3R) -3-formyl-2,2-dimethylcyclopropanecarboxylate (127cis) & Ethyl (±)-(1R,3R)-3-formyl-2,2-dimethylcyclopropanecarboxylate (127trans)

Oxygen was bubbled through a solution of ethyl chrysanthemate (10.0 g, 0.0510 mmol) in CH₂Cl₂ (500 mL) at −78 °C for 5 min. Ozone was then bubbled through the solution until a sky blue colour could be seen (55 min), after which time oxygen was
bubbled through the solution for a further 5 min. DMS (37.4 mL, 0.510 mmol) was next added to the solution, which was then allowed to stir at RT overnight. The solution was concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (10:1) to afford the title compound as a mixture of diastereomers (127cis:127trans 2:3) and as a colourless oil (8.23 g, 97%); Rf (20:1 pet. ether:EtOAc) 0.21; 1H NMR (400 MHz; CDCl₃) 127cis δ 9.70 (1H, d, J 6.5, H-1), 4.08–4.16 (2H, m, CH₃CH₂O), 2.08 (1H, d, J 8.5, H-2 or H-6), 1.79 (1H, dd, J 6.5, 6.5, H-2 or H-6), 1.56 (3H, s, H-4), 1.24 (3H t, J 7.0, CH₃CH₂O), 1.23 (3H, s, H-5); 127trans δ 9.53 (1H, d, J 3.5, H-1), 4.08–4.16 (2H, m, CH₃CH₂O), 2.35–2.45 (2H, m, H-2 & H-6), 1.30 (3H, s, H-4), 1.26 (3H, s, H-5), 1.23 (3H, t, J 7.0, CH₃CH₂O). Data in agreement with those reported in the literature. 83

[(1R,2R)-3,3-Dimethylcyclopropane-1,2-diyl]dimethanol (56a) & (±)-(1R,2S)-3,3-Dimethylcyclopropane-1,2-diyl]dimethanol (56b)

To a stirred suspension of LiAlH₄ (7.30 g, 192 mmol) in THF (500 mL) at 0 °C was added 127 (16.4 g, 96.3 mmol) in THF (500 mL) via cannula. The reaction was warmed to RT and stirred for 10 min. The reaction was cooled to 0 °C and water (7.3 mL) was added cautiously, followed by NaOH (aq. 15%) (7.3 mL) and water (21.9 mL). The aluminium salts were removed by filtration and washed with EtOAc (500 mL). The filtrate was concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with EtOAc to afford the title compound 56a as a colourless oil (6.22 g, 49%) and 56b as a colourless oil (3.93 g, 31%); 56a For data see page 105; 56b Rf (EtOAc) 0.34; υmax (thin film)/cm⁻¹ 3342, 2987, 2929, 2887; 1H NMR (400 MHz; CDCl₃) δ 3.97 (2H, dd, J 11.5, 5.5, H-1a), 3.50–3.46 (2H, m, H-1b), 2.83 (2H, broad s, OH), 1.10–1.05 (2H, m, H-2), 1.07 (3H, s, H-4), 1.05 (3H, s, H-5); 13C NMR (101 MHz; CDCl₃) δ 59.7
(C-1), 29.2 (C-4), 29.1 (C-5), 20.2 (C-3), 15.6 (C-2); m/z (ESI): 153 [MNa⁺]; HRMS (ESI): calcd. for C₇H₁₄NaO₂, 153.0886. Found: [MNa⁺], 153.0884 (1.3 ppm error).

(2Z,2'Z)-Diethyl (±)-3,3'-(1R,2R)-3,3-dimethylcyclopropane-1,2-diyl)diprop-2-enoate (57e)

To a stirred solution of 56a (1.80 g, 13.8 mmol) in CHCl₃ (150 mL) was added manganese (IV) dioxide (24.0 g, 276 mmol). The suspension was heated at reflux gently and after 16 h, the suspension was filtered through Celite, and washed with CHCl₃ (250 mL). The filtrate was concentrated under reduced pressure to give (1.25 g, 72%) of unpurified dialdehyde. (195 mg, 1.55 mmol) of the resulting dialdehyde was diluted with THF (8 mL). This was added, via cannula, to a solution of ethyl [bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (1.33 mg, 4.00 mmol), 18-crown-6 (2.34 g, 9.02 mmol) and KHMDS (5.80 mL, 0.7 M in toluene, 3.45 mmol) at −78 °C. After 2 h the reaction was quenched with sat. NH₄Cl (aq.) (15 mL), Et₂O (25 mL) added and the organic layer separated. The aqueous layer was extracted with further portions of Et₂O (2 × 25 mL) and the combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (10:1) to afford the title compound 57e as a colourless oil (144 mg, 35%); Rₚ (1:1 pet. ether:Et₂O) 0.41; νₘₚₜ (thin film)/cm⁻¹ 2934, 1688, 1604; ¹H NMR (400 MHz; CDCl₃) δ 5.98–5.90 (2H, m, H-2), 5.80 (2H, d, J 11.5, H-1), 4.17 (4H, q, J 7.0, CH₃CH₂O), 3.04–3.00 (2H, m, H-3), 1.27 (6H, t, J 7.0, CH₃CH₂O), 1.23 (6H, s, H-5 & H-6), ¹³C NMR (101 MHz; CDCl₃) δ 167.0 (C=O), 149.3 (C-2), 119.3 (C-1), 59.9 (CH₃CH₂O), 37.0 (C-3), 30.9 (C-4), 22.5 (C-5 & C-6), 14.4 (CH₃CH₂O); m/z (ESI): 267 [MH⁺]; HRMS: calcd. for C₁₅H₂₃O₄, 267.1591. Found: [MH⁺], 267.1583 (2.8 ppm error).
(±)-(1S,5R)-6,6-Dimethyl-3-oxabicyclo[3.1.0]hexan-2-one (130)$^{84}$

To a stirred solution of 56b (180 mg, 1.38 mmol) in CHCl$_3$ (10 mL) was added manganese (IV) dioxide (2.40 g, 27.6 mmol). The suspension was stirred for 16 h, filtered through Celite and washed with CHCl$_3$ (20 mL). The filtrate was concentrated under reduced pressure to afford the title compound 130 (111 mg, 64%); $R_f$ (1:1 pet. ether:EtOAc) 0.38; $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 4.36 (1H, dd, $J$ 10.0, 5.5 Hz, H-1a), 4.15 (1H, d, $J$ 10 Hz, H-1b), 2.04 (1H, dd, $J$ 6.0, 5.5 Hz, H-2), 1.95 (1H, d, $J$ 6.0 Hz, H-6), 1.18 (3H, s, H-4), 1.17 (3H, s, H-5). Data in agreement with those reported in the literature.$^{84}$

Ethyl (±)-(2E)-3-[(1S,3R)-3-(hydroxymethyl)-2,2-dimethylcyclopropyl]prop-2-enoate (131)

To a stirred solution of 56b (3.93 g, 30.2 mmol) in anhydrous DMSO (150 mL) at RT was added IBX (10.1 g, 36.1 mmol). After 2 h the reaction was quenched with water (100 mL), filtered through celite and the filtrand washed with CH$_2$Cl$_2$ (400 mL). The organic layer was separated and the aqueous layer extracted with portions of CH$_2$Cl$_2$ (2 × 250 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure to give a colourless oil. This oil was diluted with CH$_2$Cl$_2$ (200 mL) before the addition of (carbethoxymethylene)triphenylphosphorane (9.84 g, 28.2 mmol). The reaction was stirred at RT and after 16 h the solution was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (5:1) to afford the title compound 131 as a colourless oil (2.36 g, 47%); $R_f$ (5:1 pet. ether:EtOAc) 0.14; $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3372, 2938, 2910, 1683, 1613; $^1$H NMR (400 MHz; CDCl$_3$) $\delta$: 6.76 (1H, dd, $J$ 15.0, 11.0, H-7), 5.97 (1H, d, $J$ 15.0, H-8), 4.17 (2H, q, $J$ 7.0, CH$_3$CH$_2$O), 3.83 (1H, dd, $J$ 11.5, 7.5, H-1a), 3.75 (1H, dd, $J$ 11.5, 8.0, H-1b), 1.57 (1H, dd, $J$ 11.0, 8.5, H-6), 1.50 (1H, br. s, OH), 1.42 (1H, dd, $J$ 11.0, 8.0, H-2), 1.27 (3H, t, $J$ 7.0, CH$_3$CH$_2$O), 1.19 (3H, s, H-5), 1.17 (3H, s, H-...
4). $^{13}$C NMR (101 MHz; CDCl$_3$) δ 166.6 (C=O), 146.7 (C-7), 122.0 (C-8), 60.3 (CH$_3$CH$_2$O), 60.0 (C-1) 35.5 (C-2), 31.1 (C-6), 28.9 (C-5), 25.5 (C-3), 15.9 (C-4), 14.5, (CH$_3$CH$_2$O); m/z (ESI): 221 [MNa$^+$]; HRMS: calcd. for C$_{11}$H$_{18}$NaO$_3$, 221.1148. Found: [MNa$^+$], 221.1150 (−1.0 ppm error).

(±)-(1S,3R)-3-([tert-Butyl(dimethyl)silyl]oxy)methyl)-2,2-dimethyicyclopropyl)methanol (132)

To a stirred solution of 56b (276 mg, 2.12 mmol) in THF (4 mL) at 0 °C was added NaH (102 mg, 2.54 mmol, 60% dispersion in mineral oil). After 45 mins, by which time a large amount of white precipitate had formed, TBSCl (319 mg, 2.12 mmol) was added. The reaction mixture was warmed to RT and allowed to stir for a further 1 h before dilution with Et$_2$O (15 mL). It was then washed with sat. NH$_4$Cl (aq.) (10 mL) and brine (10 mL), the organic layer separated and the aqueous layer extracted with further portions of Et$_2$O (2 × 20 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (20:1 → 10:1) to afford the title compound 132 as a colourless oil (506 mg, 84%); R$_f$ (1:1 pet. ether:EtOAc) 0.48; $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3346, 2885, 2842, 22816; $^1$H NMR (400 MHz; CDCl$_3$) δ 4.07–3.98 (1H, m, H-1a or H-7a), 3.89–3.80 (1H, m, H-1a or H-7a), 3.57–3.45 (2H, m, H-1b & H-7b), 2.97 (1H, br s, OH), 1.16–1.08 (1H, m, H-2 or H-6), 1.06 (3H, s, H-4), 1.04 (3H, s, H-5), 1.03–0.93 (1H, m, H-2 or H-6), 0.90 (9H, s, SiC(CH$_3$)$_3$), 0.10 (3H, s, SiCH$_3$), 0.08 (3H, s, SiCH$_3$); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 60.6 (C-1 or C-7), 59.7 (C-1 or C-7), 29.9 (C-4), 29.2 (C-2 or C-6), 29.0 (C-2 or C-6), 26.0 (SiC(CH$_3$)$_3$), 20.3 (C-3), 18.3 (SiC(CH$_3$)$_3$), 15.7 (C-5) −5.1 (SiCH$_3$), −5.3 (SiCH$_3$); m/z (ESI) 267 [MNa$^+$]; HRMS: calcd. for C$_{13}$H$_{28}$NaO$_2$Si, 267.1751. Found: [MNa$^+$], 267.1742 (3.1 ppm error).
Ethyl (±)-(2E)-3-[(1S,3R)-3-[(1[tert-butyl(dimethyl)silyl]oxy)methyl]-2,2-dimethylcyclopropyl]prop-2-enate (133E) & Ethyl (±)-(2Z)-3-[(1S,3R)-3-[(1[tert-butyldimethyl)silyl]oxy)methyl]-2,2-dimethylcyclopropyl]prop-2-enate (133Z)

To a stirred solution of 132 (18.0 g, 73.5 mmol) in CHCl₃ (300 mL) was added manganese (IV) dioxide (63.9 g, 735 mmol) and (carbethoxymethylene) triphenyl phosphorane (30.7 g, 88.2 mmol). The resulting suspension was stirred vigorously with heating to maintain gentle reflux for 18 h. After cooling to room temperature, the suspension was filtered through Celite, and washed with CHCl₃ (500 mL). The filtrate was concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (20:1) to afford the title compound as an inseparable mixture of 133E/133Z isomers in a ratio of 5:1 and as a colourless oil (17.94 g, 78%); R₉ (20:1 pet. ether:EtOAc) 0.31; νₘₐₓ (thin film)/cm⁻¹ 2910, 2884, 2813, 1690; ¹H NMR (400 MHz; CDCl₃) 133E δ 6.75 (1H, dd, J 15.0, 11.0, H-7), 5.93 (1H, d, J 15.0, H-8), 4.19–4.13 (2H, m, OCH₃CH₂), 3.77 (1H, dd, J 11.0, 7.5, H1a), 3.72 (1H, dd, J 11.0, 7.0, H-1b), 1.51 (1H, dd, J 11.0, 9.0, H-6), 1.39–1.32 (1H, m, H-2), 1.27 (3H, t, J 7.0, OCH₃CH₂), 1.16 (3H, s, H-4), 1.15 (3H, s, H-5), 0.87 (9H, s, SiC(CH₃)₃), 0.05 (3H, s, SiCH₃), 0.04 (3H, s, SiCH₃); 133Z δ 5.98 (1H, dd, J 11.5, 11.5, H-7), 5.79 (1H, d, J 11.5, H-8), 4.19–4.13 (2H, m, OCH₃CH₂), 3.75–3.69 (1H, m, H-1a), 2.75 (1H, dd, J 11.0, 9.0, H-1b), 1.71–1.66 (1H, m, H-6 or H-2), 1.39–1.32 (1H, m, H-6 or H-2), 1.28 (3H, t, J 7.0, OCH₃CH₂), 1.16 (3H, s, H-4), 1.15 (3H, s, H-5), 0.87 (9H, s, SiC(CH₃)₃), 0.05 (3H, s, SiCH₃), 0.04 (3H, s, SiCH₃); ¹³C NMR (101 MHz; CDCl₃) 133E δ 166.6 (CH₂CH₂OC=O), 147.7 (C-7), 121.3 (C-8), 60.1 (C-1), 60.1 (CH₃CH₂O), 35.6 (C-6 or C-2), 31.2 (C-4), 28.9 (C-6 or C-2), 26.0 (SiC(CH₃)₃), 25.4 (C-3), 18.4 (SiC(CH₃)₃), 15.9 (C-5), 14.5 (CH₃CH₂O), −5.0 (SiCH₃), −5.1 (SiCH₃) 133Z δ 167.1 (CH₂CH₂OC=O), 148.1 (C-7), 119.5 (C-8), 60.0 (C-1), 59.8 (OCH₂CH₃), 35.6 (C-2), 29.0 (C-4), 28.1 (C-3), 26.0 (SiC(CH₃)₃), 25.6 (C-6), 18.4 (SiC(CH₃)₃), 15.6 (C-5), 14.5 (OCH₂CH₃), −5.0 (SiCH₃), −5.0

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(SiCH₃); m/z (ESI) 335 [MNa⁺]; HRMS: calcd. for C₁₇H₃₂NaO₃Si, 335.2013. Found: [MNa⁺], 335.2014 (−0.9 ppm error).

**Ethyl (±)-(1S,5R)-6,6-dimethyl-3-oxabicyclo[3.1.0]hex-2-yl]acetate (134)**

To a solution of 133 (102 mg, 0.327 mmol) in THF (5 mL) at 0 °C was added TBAF (0.491 mL, 1 M in THF, 0.491 mmol). After 17 h the reaction mixture was diluted with Et₂O (5 mL) and washed with sat. NH₄Cl (aq.) (5 mL), the organic layer separated and the aqueous layer extracted with further portions of Et₂O (2 x 10 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to to give the crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (5:1) to afford the title compound 88 as a colourless oil and in a diastereomeric ratio of 1:0.1

134_major: 134_minor (49 mg, 76%); Rₜ (1:1 pet. ether: Et₂O) 0.47; νₘₐₓ (thin film)/cm⁻¹ 2876, 2825, 1710;

¹H NMR (400 MHz; CDCl₃) 134_major δ 4.28 (1H, dd, J 6.5, 6.5, H-7), 4.17 (1H, q, J 7.0, OCH₂CH₂), 4.16 (1H, q, J 7.0, OCH₂CH₂), 3.93 (1H, dd, J 8.5, 4.0, H-1a), 3.75 (1H, d, J 8.5, H-1b), 2.54–2.42 (2H, m, H-8), 1.45 (1H, dd, J 7.5, 4.0, H-2), 1.32 (1H, d, J 7.5, H-6), 1.26 (3H, t, J 7.0, OCH₂CH₃), 1.05 (3H, s, H-4), 1.01 (3H, s, H-5);

134_minor δ 4.49–4.43 (1H, m, H-7), 4.21–4.11 (2H, m, OCH₂CH₂), 3.89–3.84 (2H, m, H-1), 2.67 (1H, dd, J 15.0, 7.5, H-8a), (1H, dd, J 15.0, 6.0 (H-8b), 1.42–1.35 (2H, H-6 & H-2), 1.28 (3H, t, J 7.0, OCH₂CH₃), 1.20 (3H, s, H-4), 0.99 (3H, s, H-5); ¹³C NMR (101 MHz; CDCl₃) 134_major δ 171.4 (CH₃CH₂OC=O), 75.4 (C-7) 67.2 (C-1), 60.6 (CH₃CH₂O), 41.1 (C-8), 34.3 (C-6), 29.8 (C-2), 26.2 (CH₃CH₂O), 19.5 (C-3), 14.4 (C-4), 13.0 (C-5); 134_minor δ 171.4 (CH₃CH₂OC=O), 75.4 (C-7) 68.3 (C-1), 60.6 (CH₃CH₂O), 37.7 (C-8), 32.3 (C-6), 29.5 (C-2), 26.9 (CH₃CH₂O), 19.8 (C-3), 15.3 (C-4), 13.0 (C-5); m/z (ESI): 221 [MNa⁺]; HRMS: calcd. for C₁₁H₁₈NaO₃, 221.1148. Found: [MNa⁺], 221.1154 (−2.2 ppm error).
Ethyl (±)-(2E)-3-[(1S,3R)-3-(hydroxymethyl)-2,2-dimethylcyclopropyl]prop-2-enoate (131)

To a stirred solution of 133 (5:1 E:Z) (2.06 g, 6.59 mmol) in MeCN (65 mL) in a plastic container was added HF (0.41 mL, 48 wt % in water, 9.9 mmol). This was stirred at RT for 16 h before the addition of sat. NaHCO₃ (aq.) (50 mL). The solution was diluted with CH₂Cl₂ (200 mL), the organic layer was separated and the aqueous layer extracted with further portions of CH₂Cl₂ (2 × 200 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (2:1) to afford the title compound 131 as a colourless oil (0.984 g, 75%); For data see page 115

(2E,2'E)-diethyl 3,3'-(1R,2R)-3,3-dimethylcyclopropane-1,2-diyl)diprop-2-enoate (57d) & (±)-(2E,2'Z)-diethyl 3,3'-(1R,2S)-3,3-dimethylcyclopropane-1,2-diyl)diprop-2-enoate (57e)

To a stirred solution of 131 (8.10 g, 40.9 mmol) in CHCl₃ (400 mL) was added manganese dioxide (35.6 g, 409 mmol), 4Å molecular sieves (35.6 g) and (carbethoxymethylene) triphenyl phosphorane (17.1 g, 49.1 mmol). After 16 h, the suspension was filtered through Celite, and washed with CHCl₃ (500 mL). The filtrate was concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (40:1 → 20:1) to afford the title compound 57d as a colourless oil (7.4 g, 68%) and 57e as a colourless oil (1.73 g, 16%); 57d Rₜ (1:1 pet. ether:EtOAc) 0.62; νₘₐₓ (thin film)/cm⁻¹ 2936, 2876, 1691, 1613; ¹H NMR (400 MHz; CDCl₃) δ 6.90–6.76 (2H, m, H–2), 5.95 (2H, d, J 15.0, H–1), 4.17 (4H, q, J 7.0, OCH₂CH₃), 1.91–1.85 (2H, m, H–3), 1.28 (6H, t, J 7.0, OCH₂CH₃), 1.25 (3H, s, H–5), 1.21, (3H, s, H–6); ¹³C NMR (101
MHz; CDCl$_3$ δ 166.2 (CH$_3$CH$_2$O=O), 145.4 (C-2), 123.0 (C-1), 60.3 (CH$_3$CH$_2$O), 36.6 (C-3), 29.6 (C-4), 28.6 (C-5), 16.7 (C-6), 14.4 (CH$_3$CH$_2$O); m/z (ESI) 289 [MNa$^+$]; HRMS: calcd. for C$_{13}$H$_{22}$NaO$_4$, 289.1410. Found: [MNa$^+$], 289.1406 (1.0 ppm error); 57e R$_f$ (15:1 pet. ether:EtOAc) 0.41; $v_{\text{max}}$ (thin film)/cm$^{-1}$ 2936, 2913, 2881, 1688, 1612; $^1$H NMR (400 MHz; CDCl$_3$) δ 6.82 (1H, dd, J 15.0, 11.0, H-8), 6.10 (1H, dd, J 11.5, 11.5, H-2), 5.95 (1H, d, J 15.0, H-9), 5.87 (1H, d, J 11.5, H-1), 4.17 (2H, q, J 7.0, OCH$_2$CH$_3$), 4.16 (2H, q, J 7.0, OCH$_2$CH$_3$), 3.17 (1H, dd, J 11.5, 9.0, H-3), 1.94 (1H, dd, J 11.0, 9.0, H-7), 1.28 (3H, t, J 7.0, OCH$_2$CH$_3$), 1.27 (3H, t, J 7.0, OCH$_2$CH$_3$), 1.24 (3H, s, H-5), 1.23, (3H, s, H-6); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 166.7 (CH$_3$CH$_2$O=O), 166.4 (CH$_3$CH$_2$O=O), 146.0 (C-2 or C-8), 122.6 (C-0), 121.1 (C-1), 60.3 (OCH$_2$CH$_3$), 60.0 (OCH$_2$CH$_3$), 36.7 (C-7), 33.7 (C-3), 29.9 (C-4), 28.6 (C-5), 16.5 (C-6), 14.4 (OCH$_2$CH$_3$), 14.4 (OCH$_2$CH$_3$); m/z (ESI) 289 [MNa$^+$]; HRMS: calcd. for C$_{13}$H$_{22}$NaO$_4$, 289.1410. Found: [MNa$^+$], 289.1406 (1.0 ppm error).

(±)-(1$S$,3$R$)-3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2,2-dimethylcyclopropanecarbaldehyde (136)

![Diagram](attachment:image.png)

To a stirred solution of 132 (304 mg, 1.24 mmol) in CH$_2$Cl$_2$ (10 mL) was added manganese (IV) dioxide (1.08 g, 12.4 mmol), and 4Å molecular sieves (1.08 g). After 16 h the suspension was filtered through Celite, and washed with CHCl$_3$ (50 mL). The filtrate was concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (15:1) to afford the title compound 136 as a colourless oil (166 mg, 55%); R$_f$ (15:1 pet. ether:EtOAc) 0.17; $v_{\text{max}}$ (thin film)/cm$^{-1}$ 2909, 2885, 2841, 1676; $^1$H NMR (400 MHz; CDCl$_3$) δ 9.50 (1H, d, J 5.5, H-7), 4.06 (1H, dd, J 11.5, 7.5, H-1a), 3.90 (1H, dd, J 11.5, 7.0, H-1b), 1.74–1.62 (2H, m, H-6 & H-2), 1.36 (3H, s, H-5), 1.20 (3H, s, H-4), 0.88 (9H, s, SiC(CH$_3$)$_3$), 0.05 (3H, s, SiCH$_3$), 0.05 (3H, s, SiCH$_3$); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 201.3 (C-7), 58.6 (C-1), 39.0 (C-2 or C-6), 38.8 (C-2 or C-6), 29.8 (C-3), 29.1 (C-4), 26.0 (SiC(CH$_3$)$_3$), 18.4
(SiC(CH₃)₃), 15.3 (C-5), −5.1 (SiCH₃); m/z (ESI) 265 [MNa⁺]; HRMS: calcd. for C₁₃H₂₆NaO₃Si, 265.1594. Found: [MNa⁺], 265.1593 (0.1 ppm error).

**Ethyl (±)-(2Z)-3-[(1S,3R)-3-{{[tert-butyl(dimethyl)silyl]oxy}methyl}-2,2-dimethylcyclopropyl]prop-2-enoate (137)**

To a solution of ethyl [bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (285 mg, 0.859 mmol) in THF (6 mL) was added 18-crown-6 (507 mg, 1.92 mmol). The solution was cooled to 0 °C and KHMDS (1.23 mL, 0.7 M in toluene, 0.859 mmol) was added cautiously. After 15 min the solution was cooled to −78 °C and 136 (160 mg, 0.661 mmol) in THF (3 mL) was added via cannula. After 30 min the reaction was quenched with sat. NH₄Cl (aq.) (5 mL), Et₂O (10 mL) added and the organic layer separated. The aqueous layer was extracted with further portions of Et₂O (2 × 10 mL) and the combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (40:1) to afford the title compound 137 as a colourless oil (109 mg, 53%); Rₜ (10:1 pet. ether:EtOAc) 0.57; νₘₐₓ (thin film)/cm⁻¹ 2909, 2883, 2814, 1690, 1601; ¹H NMR (400 MHz; CDCl₃) δ 5.98 (1H, dd J 11.5, 11.5, H-7), 5.79 (1H, d, J 11.5, H-8), 4.16 (2H, q, J 7.0, OCH₂CH₃), 3.74–3.71 (2H, m, H-1), 2.75 (1H, dd, J 11.5, 9.0, H-6), 1.40–1.34 (1H, m, H-2), 1.28 (3H, t, J 7.0, OCH₂CH₃), 1.18 (3H, s, H-4), 1.12 (3H, s, H-5), 0.87 (9H, s, SiC(CH₃)₃), 0.04 (6H, s, SICH₃); ¹³C NMR (101 MHz; CDCl₃) δ 167.1 (CH₂CH₂OC=O), 148.1 (C-7), 119.5 (C-8), 60.0 (C-1), 59.8 (OCH₂CH₃), 35.6 (C-2), 29.0 (C-4), 28.1 (C-3), 26.0 (SiC(CH₃)₃), 25.6 (C-6), 18.4 (SiC(CH₃)₃), 15.6 (C-5), 14.5 (OCH₂CH₃), −5.0 (SiCH₃), −5.0 (SiCH₃); m/z (ESI) 335 [MNa⁺]; HRMS: calcd. for C₁₇H₃₂NaO₃Si, 335.2013. Found: [MNa⁺], 335.2006 (1.4 ppm error).
Ethyl (±)-(2Z)-3-[(1S,3R)-3-(hydroxymethyl)-2,2-dimethylcyclopropyl]prop-2-enoate (138)

To a stirred solution of 137 (136 mg, 0.435 mmol) in MeCN (10 mL) in a plastic container was added HF (2 drops, 48 wt% in water). This was stirred at RT for 16 h before the addition of sat. NaHCO₃ (aq.) (5 mL). The solution was diluted with CH₂Cl₂ (10 mL), the organic layer was separated and the aqueous layer extracted with further portions of CH₂Cl₂ (2 × 10 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (2:1) to afford the title compound 138 as a colourless oil (73 mg, 85%); Rf (1:1 pet. ether:EtOAc) 0.38; νmax (thin film)/cm⁻¹ 3372, 2939, 2883, 2827, 1689, 1601; ¹H NMR (400 MHz; CDCl₃) δ 6.02 (1H, dd, J 11.5 10.5, H-7), 5.85 (1H, d, J 11.5, H-8), 4.17 (2H, q, J 7.0, OC₂H₂C₂H₃), 3.79 (1H, dd, J 11.5, 7.5, H-1a), 3.65 (1H, dd, J 11.5, 8.0, H-1b), 2.73–2.68 (1H, m, H-6), 1.47–1.39 (1H, m, H-2), 1.28 (3H, t, J 7.0, OCH₂CH₃), 1.19 (3H, s, H-4), 1.14 (3H, s, H-5); ¹³C NMR (101 MHz; CDCl₃) δ 167.1 (CH₃CH₂OC=O), 147.0 (C-7), 120.5 (C-8), 60.0 (C-1), 60.0 (OCH₂CH₃), 35.5 (C-2), 28.8 (C-6), 28.0 (C-5), 25.4 (C-3), 15.6 (C-4), 14.4 (OCH₂CH₃); m/z (ESI) 221 [MNa⁺]; HRMS: calcd. for C₁₁H₁₈NaO₃, 221.1148. Found: [MNa⁺], 221.1140 (3.5 ppm error).

Ethyl (±)-(2Z)-3-[(1S,3R)-3-formyl-2,2-dimethylcyclopropyl]prop-2-enoate (139)

To a stirred solution of 138 (73 mg, 0.368 mmol) in CHCl₃ (5 mL) was added manganese (IV) dioxide (320 mg, 3.68 mmol) and 4Å molecular sieves (320 mg). After 12 h the suspension was filtered through Celite, and washed with CHCl₃ (25 mL). The filtrate was concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (5:1) to afford the title compound 139 as a colourless oil (38 mg, 53%); Rf (5:1 pet. ether:EtOAc) 0.34; νmax (thin film)/cm⁻¹ 2911, 2876, 1689, 1610; ¹H NMR (400
Diethyl (2Z,2′Z)-3,3′-[(1R,2S)-3,3-diisopropyl cyclopropane-1,2-diyl]bisprop-2-enoate (57f)

To a solution of ethyl [bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (80 mg, 0.246 mmol) in THF (3 mL) was added 18-crown-6 (145 mg, 0.548 mmol). The solution was cooled to 0 °C and KHMDMS (350 µL, 0.7 M in toluene, 0.246 mmol) was added cautiously. After 15 min the solution was cooled to –78 °C and 139 (37 mg, 0.189 mmol) in THF (2 mL) was added via cannula. After 1 h the reaction was quenched with sat. NH₄Cl (aq.) (5 mL), Et₂O (10 mL) added and the organic layer separated. The aqueous layer was extracted with further portions of Et₂O (2 × 10 mL) and the combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (20:1) to afford the title compound 57f as a colourless oil (28 mg, 56%); Rₚ (1:1 pet. ether:Et₂O) 0.71; vₘₐₓ (thin film)/cm⁻¹ 2935, 2913, 2874, 1691, 1627; ¹H NMR (400 MHz; CDCl₃) δ 6.08–6.01 (2H, m, H-2), 5.85 (2H, d, J 12.0, H-1), 4.16 (4H, q, J 7.0, OCH₂CH₃), 3.17–3.11 (2H, m, H-3), 1.28 (3H, s, H-5), 1.28 (6H, t, J 7.0, OCH₂CH₃), 1.17 (3H, s, H-6); ¹³C NMR (101 MHz; CDCl₃) δ 166.7 (CH₃CH₂OC=O), 146.0 (C-2), 121.0 (C-1), 60.0 (OCH₂CH₃), 33.7 (C-3), 30.2 (C-4), 28.8 (C-5), 16.3 (C-6), 14.4 (OCH₂CH₃); m/z (ESI) 267 [MH⁺]; HRMS: calcd. for C₁₅H₂₃O₄, 267.1591. Found: [MH⁺], 267.1587 (1.1 ppm error).
(±)-(1S,2S)-2-{{[tert-Butyl(dimethyl)silyl]oxy}methyl}cyclopropyl)methanol (140)

To a stirred solution of 54a (1.00 g, 9.80 mmol) in THF (20 mL) at 0 °C was added NaH (472 mg, 11.8 mmol, 60% dispersion in mineral oil). After 45 mins, by which time a large amount of white precipitate had formed, TBSCl (1.48 g, 9.80 mmol) was added. The reaction mixture was warmed to RT and allowed to stir for a further 1 h before dilution with Et₂O (25 mL). It was then washed with sat. NH₄Cl (aq.) (20 mL) and brine (10 mL), the organic layer separated and the aqueous layer extracted with further portions of Et₂O (2 × 20 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (20:1 → 4:1) to afford the title compound 140 as a colourless oil (1.46 g, 69%); Rᵣ (EtOAc) 0.89; ν_max (thin film)/cm⁻¹ 3315, 2909, 2884, 2842; ¹H NMR (400 MHz; CDCl₃) δ 3.59 (1H, dd, J = 10.5, 6.0) and 3.51–3.42 (3H, m, H-1 & H-5), 1.06–0.90 (2H, m, H-4 & H-2), 0.89 (9H, s, SiC(CH₃)₃), 0.53–0.40 (2H, m, H-3), 0.05 (6H, s, SiCH₃); ¹³C NMR (101 MHz; CDCl₃) δ 66.6 (C-1 or C-5), 65.9 (C-1 or C-5), 26.0 (SiC(CH₃)₃), 19.5 (C-2 or C-4), 19.4 (C-2 or C-4), 18.4 (SiC(CH₃)₃), 7.9 (C-3), −5.1 (SiCH₃); m/z (ESI) 217 [MH⁺]; HRMS: calcd. for C₁₁H₂₅O₂Si, 217.1618. Found: [MH⁺], 217.1622 (−2.3 ppm error).

Ethyl (±)-(2E)-3-{{1R,2S}-2-{{[tert-butyl(dimethyl)silyl]oxy}methyl}cyclopropyl}prop-2-enoate (141)

To a stirred solution of 140 (1.46 g, 6.75 mmol) in CHCl₃ (70 mL) was added manganese (IV) dioxide (5.87 g, 67.5 mmol) and (carbethoxymethylene) triphenyl phosphorane (2.82 g, 8.10 mmol). The resulting suspension was stirred vigorously with heating to maintain gentle reflux for 18 h. After cooling to room temperature, the suspension was filtered through Celite, and washed with CHCl₃ (100 mL). The filtrate was concentrated under reduced pressure to give the crude product.
This was purified by flash column chromatography on silica gel, eluting with pet.
ether:EtOAc (40:1 → 10:1) to afford the title compound **141** as a colourless oil (1.63
g, 85%); \( R_f \) (10:1 pet. ether:EtOAc) 0.24; \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 2909, 2886, 2814,
1691, 1621; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 6.48 (1H, dd, \( J \) 15.5, 10.0, H-5), 5.85
(1H, d, \( J \) 15.5), 4.17 (2H, q, \( J \) 7.0, CH\(_2\)CH\(_2\)O), 3.65–3.54 (2H, m, H-1), 1.54–1.47
(1H, m, H-4), 1.33–1.25 (1H, m, H-2), 1.27 (3H, t, \( J \) 7.0 CH\(_2\)CH\(_2\)O), 0.96–0.90 (1H,
m, H-3a), 0.88 (9H, s, SiC(CH\(_3\))\(_3\)), 0.84–0.79 (1H, m H-3b), 0.04 (6H, s, SiCH\(_3\)); \(^{13}\)C
NMR (101 MHz; CDCl\(_3\)) \( \delta \) 166.9 (CH\(_3\)CH\(_2\)OC=O), 152.8 (C-5), 118.4 (C-6), 64.6
(C-1), 60.2 (OCH\(_2\)CH\(_3\)), 26.1 (SiC(CH\(_3\))\(_3\)), 24.8 (C-2 or C-4), 19.6 (C-2 or C-4), 18.5
(SiC(CH\(_3\))\(_3\)), 14.5 (OCH\(_2\)CH\(_3\)), 13.1 (C-3), −5.1 (SiCH\(_3\)); \( m/z \) (ESI) 285 [M\(^+\)];
HRMS: calcd. for C\(_{15}\)H\(_{28}\)O\(_3\)Si, 285.1880. Found: [M\(^+\)], 285.1877 (1.2 ppm error).

**Ethyl (±)-(2E)-3-[(1R,2S)-2-(hydroxymethyl)cyclopropyl]prop-2-enoate (142)**

![Structure of compound 142](image)

To a solution of **141** (1.60 g, 5.40 mmol) in THF (50 mL) at 0 °C was added TBAF (6.48 mL, 1 M in THF, 6.48
mmol). After 17 h the reaction mixture was diluted with Et\(_2\)O (50 mL) and washed with sat. NH\(_4\)Cl (aq.) (50 mL), the organic layer separated and the aqueous layer extracted with further portions of Et\(_2\)O (2 × 50 mL). The combined organic extracts were dried (MgSO\(_4\)), filtered and concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (2:1) to afford the title compound **142** as a colourless oil (704 mg, 77%); \( R_f \) (1:1 pet. ether:EtOAc) 0.59; \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 3374, 2938, 2893, 2830, 1687, 1670; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 6.47 (1H, dd, \( J \) 15.5, 10.0, H-5), 5.88 (1H, d, \( J \) 15.5, H-6), 4.17 (2H, q, \( J \) 7.0,
CH\(_3\)CH\(_2\)O), 3.60 (1H, dd, \( J \) 11.5, 6.5, H-1a), 3.53 (1H, dd, \( J \) 11.5, 7.0, H-1b),
1.57–1.49 (1H, m, H-2 or H-4), 1.43–1.35 (1H, m, H-2 or H-4), 1.27 (3H, t, \( J \) 7.0
CH\(_3\)CH\(_2\)O), 0.96–0.86 (2H, m, H-3); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)) \( \delta \) 166.8
(CH\(_3\)CH\(_2\)OC=O), 152.0 (C-5), 118.9 (C-6), 65.6 (C-1), 60.3 (OCH\(_2\)CH\(_3\)), 24.8 (C-2
or C-4), 20.0 (C-2 or C-4), 14.4 (OCH\(_2\)CH\(_3\)), 13.4 (C-3); \( m/z \) (ESI) 171 [M\(^+\)];
HRMS: calcd. for C\(_9\)H\(_{15}\)O\(_3\)Si, 171.1016. Found: [M\(^+\)], 171.1010 (3.8 ppm error).
**Ethyl (±)-(2E)-3-[(1R,2S)-2-formylcyclopropyl]prop-2-enoate (143)**

To a stirred solution of 142 (704 mg, 4.14 mmol) in CHCl₃ (40 mL) was added manganese (IV) dioxide (3.60 g, 41.4 mmol) and 4Å molecular sieves (3.60 g). After 20 h the suspension was filtered through Celite, and washed with CHCl₃ (100 mL). The filtrate was concentrated under reduced pressure to afford the title compound 143 as a colourless oil (468 mg, 67%); Rₐ (1:1 pet. ether:EtOAc) 0.72; v_max (thin film)/cm⁻¹ 2937, 2893, 2796, 1681, 1624; ¹H NMR (400 MHz; CDCl₃) δ 9.31 (1H, d, J 4.0, H-1), 6.42 (1H, dd, J 15.5, 9.5, H-5), 5.97 (1H, d, J 15.5, H-6), 4.17 (2H, q, J 7.0, CH₃CH₂O), 2.28 – 2.20 (1H, m, H-4), 2.17 – 2.10 (1H, m, H-2), 1.68 – 1.63 (1H, m, H-3a), 1.35 – 1.29 (1H, m, H-3b), 1.27 (3H, t, J 7.0 CH₃CH₂O), ¹³C NMR (101 MHz; CDCl₃) δ 198.7 (C-1), 166.2 (CH₃CH₂OC=O), 147.4 (C-5), 121.7 (C-6), 60.6 (OCH₂CH₃), 31.8 (C-2), 24.8 (C-4), 16.3 (C-3), 14.4 (OCH₂CH₃); m/z (ESI) 169 [MH⁺]; HRMS: calcd. for C₉H₁₃O₃, 169.0859. Found: [MH⁺], 169.0861 (–0.9 ppm error).

**Diethyl (±)-(2E,2'Z)-3,3'-(1R,2R)-cyclopropane-1,2-diylbisprop-2-enoate (55b)**

To a solution of ethyl [bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (257 mg, 0.774 mmol) in THF (6 mL) was added 18-Crown-6 (457 mg, 1.73 mmol). The solution was cooled to 0 °C and KHMD (1.10 mL, 0.7 M in toluene, 0.774 mmol) was added cautiously. After 15 min the solution was cooled to –78 °C and 143 (100 mg, 0.595 mmol) in THF (3 mL) was added via cannula. After 2 h the reaction was quenched with sat. NH₄Cl (aq.) (10 mL), Et₂O (20 mL) added and the organic layer separated. The aqueous layer was extracted with further portions of Et₂O (2 × 20 mL) and the combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (20:1) to afford the title compound 55b as a colourless oil (65 mg, 46%); Rₐ (1:1 pet. ether:Et₂O) 0.56; v_max (thin film)/cm⁻¹ 2938, 2893, 2862, 1688, 1618; ¹H NMR (400
MHz; CDCl$_3$ $\delta$ 6.50 (1H, dd, $J$ 15.5, 10.0, H-6), 5.88 (1H, d, $J$ 15.5, H-7), 5.73 (1H, d, $J$ 11.0, H-1), 5.50 (1H, dd, $J$ 11.0, 11.0, H-2), 4.17 (2H, q, $J$ 7.0, CH$_3$CH$_2$O), 4.15 (2H, q, $J$ 7.0, CH$_3$CH$_2$O) 3.24–3.13 (1H, m, H-3), 1.78–1.68 (1H, m, H-5), 1.31–1.26 (1H, m, H-4a), 1.28 (3H, t, $J$ 7.0 C$\text{H}_3$CH$_2$O), 1.26 (3H, t, $J$ 7.0 C$\text{H}_3$CH$_2$O), 1.18–1.09 (1H, m, H-4b); $^{13}$C NMR (101 MHz; CDCl$_3$) $\delta$ 166.8 (CH$_3$CH$_2$O$\text{C}$=O), 150.7 (C-2), 150.0 (C-6), 119.8 (C-7), 118.8 (C-1), 60.3 (OCH$_3$CH$_3$), 60.1 (OCH$_3$CH$_3$), 25.5 (C-5), 23.0 (C-3), 18.0 (C-4), 14.4 (OCH$_2$CH$_3$); m/z (ESI) 239 [MH$^+$]; HRMS: calcd. for C$_{13}$H$_{19}$O$_4$, 239.1278. Found: [MH$^+$], 239.1276 (0.5 ppm error).

(±)-(1S,2S)-Cyclopropane-1,2-dicarbaldehyde (144)$^{85}$

To a stirred solution of 54a (2.00 g, 19.6 mmol) in CHCl$_3$ (150 mL) was added manganese (IV) dioxide (34.1 g, 392 mmol). The suspension was heated at reflux gently and after 16 h, the suspension was filtered through Celite, and washed with CHCl$_3$ (250 mL). The filtrate was concentrated under reduced pressure to afford the title compound 144 as a colourless oil (205 mg, 11%), which was used in the next step without further purification; $R_f$ (1:1 pet. ether:EtOAc) 0.54; $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 9.34–9.32 (2H, m, H-1), 2.57–2.49 (2H, m, H-2), 1.71–1.65 (2H, m, H-3). Data in agreement with those reported in the literature.$^{85}$

Diethyl (±)-(2′Z)-3,3′-(1R,2R)-cyclopropane-1,2-diylbisprop-2-enoate (55c)

To a solution of ethyl [bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (1.32 mg, 3.98 mmol) in THF (15 mL) was added 18-crown-6 (2.30 g, 8.87 mmol). The solution was cooled to 0 °C and KHMDS (5.70 mL, 0.7 M in toluene, 3.98 mmol) was added cautiously. After 15 min the solution was cooled to −78 °C and 144 (150 mg, 1.53 mmol) in THF (8 mL) was added via cannula. After 2 h the reaction was quenched with sat. NH$_4$Cl (aq.) (15 mL), Et$_2$O (25 mL) added and the organic layer separated. The aqueous layer was extracted with further portions of
Et₂O (2 × 25 mL) and the combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (10:1) to afford the title compound 55c as a colourless oil (192 mg, 63%); Rₜ (10:1 pet. ether:EtOAc) 0.37; ν_max (thin film)/cm⁻¹ 2935, 2885, 1691, 1612; ¹H NMR (400 MHz; CDCl₃) δ 5.73 (2H, d, J 11.5, H-1), 5.60–5.53 (2H, m, H-2), 4.17 (4H, q, J 7.0, CH₃CH₂O), 3.18–3.10 (2H, m, H-3), 1.28 (6H, t, J 7.0, CH₃CH₂O), 1.20 (2H, t, J 7.0, H-4); ¹³C NMR (101 MHz; CDCl₃) δ 167.0 (CH₃CH₂O=O), 151.4 (C-2), 118.4 (C-1), 60.0 (OCH₂CH₃), 23.4 (C-3), 18.3 (C-4), 14.4 (OCH₂CH₃); m/z (ESI) 239 [MH⁺]; HRMS: calcd. for C₁₃H₁₉O₄, 239.1278. Found: [MH⁺], 239.1285 (−3.2 ppm error).

(1R,2S)-Cyclopropane-1,2-diyldimethanol (54b)⁸⁶

To a stirred suspension of LiAlH₄ (510 mg, 13.4 mmol) in THF (25 mL) at 0 °C was added 3-oxabicyclo[3.1.0]hexane-2,4-dione (1.00 g, 8.92 mmol) in THF (20 mL) via cannula. The reaction was heated to reflux and stirred for 16 h. The reaction was cooled to 0 °C and Na₂SO₄.10H₂O was cautiously added until on further addition fizzing was no longer observed. The aluminium salts were removed by filtration and washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with EtOAc to afford the title compound 54b as a colourless oil. (723 mg, 79%); Rₜ (EtOAc) 0.23; ¹H NMR (400 MHz; CDCl₃) δ 4.15–4.08 (2H, m, H-1a), 3.31–3.21 (2H, m, H-1b), 2.20 (2H, br s, OH), 1.39–1.28 (2H, m, H-2), 0.81 (1H, dt, J 8.0, 5.0, H-3a), 0.22 (1H, dt, J 5.0, 5.0, H-3b). Data in agreement with those reported in the literature.⁸⁶
(±)-(1R,2S)-2-[[tert-Butyl(dimethyl)silyl]oxy)methyl]cyclopropylmethanol (144)\textsuperscript{87}

To a stirred solution of 54b (720 mg, 7.06 mmol) in THF (14 mL) at 0 °C was added NaH (339 mg, 8.47 mmol, 60% dispersion in mineral oil). After 45 mins, by which time a large amount of white precipitate had formed, TBSCl (1.06 g, 7.06 mmol) was added. The reaction mixture was warmed to RT and allowed to stir for a further 1 h before dilution with Et\textsubscript{2}O (25 mL). It was then washed with sat. NH\textsubscript{4}Cl (aq.) (20 mL) and brine (10 mL), the organic layer separated and the aqueous layer extracted with further portions of Et\textsubscript{2}O (2 × 20 mL). The combined organic extracts were dried (MgSO\textsubscript{4}), filtered and concentrated under reduced pressure to afford the title compound 144 as a colourless oil (1.53 g, 100%), which was used in the next step without further purification; R\textsubscript{f} (EtOAc) 0.81; \textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}) δ 4.15 (1H, dd, J 11.5, 5.5, H-1a or H-5a), 3.97 (1H, dd, J 12.0, 5.5, H-1a or H-5a), 3.26–3.20 (2H, m, H-1 & H-5) 1.43-1.30 (1H, m, H-4 or H-2), 1.30-1.18 (1H, m, H-4 or H-2), 0.92 (9H, s, SiC(CH\textsubscript{3})\textsubscript{3}), 0.80–0.71 (1H, m, H-3a), 0.23–0.16 (1H, m, H-3b), 0.12 (3H, s, SiCH\textsubscript{3}), 0.10 (3H, s, SiCH\textsubscript{3}). Data in agreement with those reported in the literature.\textsuperscript{87}

(±)-(1R,2S)-2-[[tert-Butyl(dimethyl)silyl]oxy]methyl)cyclopropanecarbaldehyde (145)\textsuperscript{87}

To a stirred solution of 144 (1.61 g, 7.44 mmol) in CHCl\textsubscript{3} (75 mL) was added manganese (IV) dioxide (6.47 g, 74.4 mmol) and 4Å molecular sieves (6.47 g). After 16 h the suspension was filtered through Celite, and washed with CHCl\textsubscript{3} (150 mL). The filtrate was concentrated under reduced pressure to afford the title compound 145 as a colourless oil (1.20 g, 75%), which was used in the next step without further purification; R\textsubscript{f} (1:1 pet. ether:EtOAc) 0.86; \textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}) δ 9.41 (1H, d, J 5.0, H-5), 3.97 (1H, dd, J 11.0, 5.5, H-1a), 3.62 (1H, dd, J 11.0, 7.5, H-1b), 2.02–1.91 (1H, m, H-4 or H-2), 1.82–1.73 (1H, m, H-4 or H-2), 1.37–1.32 (1H, m, H-3a), 1.25–1.20 (1H, m, H-
3b), 0.87 (9H, s, SiC(CH$_3$)$_3$), 0.04 (3H, s, SiCH$_3$), 0.03 (3H, s, SiCH$_3$). Data in agreement with those reported in the literature.$^{87}$

**Ethyl (±)-(2E)-3-[(1S,2S)-2-({[tert-butyldimethyl)silyl]oxy}methyl)cyclopropyl]prop-2-enoate (146)$^{87}$**

![Diagram](image)

To a stirred solution of 145 (534 mg, 2.50 mmol) in CHCl$_3$ (25 mL) at RT was added (carbethoxymethylene) triphenyl phosphorane (1.04 g, 3.00 mmol). After 16 h the solution was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (40:1) to afford the title compound 146 as a colourless oil (471 mg, 63%); R$_f$ (20:1 pet. ether:EtOAc) 0.31; $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 6.72 (1H, dd, $J_{15.5, 10.5}$, H-5), 5.92 (1H, d, $J_{15.5, 10.5}$, H-6), 4.17 (2H, q, $J_{7.0}$, CH$_3$CH$_2$O), 3.82 (1H, s, SiC(CH$_3$)$_3$), 0.68 (9H, s, SiC(CH$_3$)$_3$), 0.06 (3H, s, SiC(CH$_3$)$_3$). Data in agreement with those reported in the literature.$^{87}$

**Ethyl (±)-(2E)-3-[(1S,2S)-2-(hydroxymethyl)cyclopropyl]prop-2-enoate (147)$^{86}$**

![Diagram](image)

To a stirred solution of 146 (471 mg, 1.59 mmol) in MeCN (15 mL) in a plastic container was added HF (130 $\mu$L, 48 wt % in water, 3.18 mmol). This was stirred at RT for 16 h before the addition of sat. NaHCO$_3$ (aq.) (15 mL). The solution was diluted with CH$_2$Cl$_2$ (10 mL), the organic layer was separated and the aqueous layer extracted with further portions of CH$_2$Cl$_2$ (2 x 20 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure to afford the title compound 147 as a colourless oil (254 mg, 94%), which was used in the next step without further purification; R$_f$ (1:1 pet. ether:EtOAc) 0.42; $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 6.69 (1H, dd, J 15.5, 10.0, H-5), 5.95 (1H, d, J 15.5, H-6), 4.17 (2H, q, J 7.0, CH$_3$CH$_2$O), 3.82 (1H, ddd, J 11.5, 6.0, 1.5 H-1a), 3.50 (1H, dd, J 11.5, 8.5, H-...
1b), 1.98 (1H, br s, OH), 1.81–1.70 (1H, m, H-4 or H-2), 1.63–1.52 (1H, m, H-4 or H-2), 1.25 (3H, t, J 7.0, CH₃CH₂O), 1.20–1.13 (1H, m, H-3a), 0.72–0.65 (1H, m, H-3b). Data in agreement with those reported in the literature.⁸⁶

**Ethyl (±)-(2E)-3-[(1S,2S)-2-formylcyclopropyl]prop-2-enoate (148)⁸⁶**

![Chemical structure](image)

To a stirred solution of 147 (281 mg, 1.65 mmol) in CHCl₃ (15 mL) was added manganese (IV) dioxide (1.43 g, 16.5 mmol) and 4Å molecular sieves (1.43 g). After 16 h the suspension was filtered through Celite, and washed with CHCl₃ (50 mL). The filtrate was concentrated under reduced pressure to afford the title compound 148 as a colourless oil (224 mg, 81%), which was used in the next step without further purification; Rᵣ (1:1 pet. ether: EtOAc) 0.57; ¹H NMR (400 MHz; CDCl₃) δ 9.47 (1H, d, J 4.5, H-1), 6.82 (1H, dd, J 15.5, 9.5, H-5), 6.02 (1H, d, J 15.5, H-6), 4.17 (2H, q, J 7.0, CH₃CH₂O), 2.37–2.21 (2H, m, H-4 & H-2), 1.68–1.63 (1H, m, H-3a), 1.60–1.53 (1H, m, H-3b), 1.28 (3H, t, J 7.0, CH₃CH₂O). Data in agreement with those reported in the literature.⁸⁶

**Diethyl (1R,2S)-cyclohepta-3,6-diene-1,2-dicarboxylate (58a)**

![Chemical structure](image)

To a stirred solution of 148 (132 mg, 0.786 mmol) in CHCl₃ (10 mL) was added (carbethoxymethylene)triphenylphosphorane (329 mg, 0.943 mmol) at RT. After 16 h the solution was concentrated under reduced pressure at RT and the crude product purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (20:1) to afford the title compound 58a as a colourless oil (148 mg, 79%); For data see page 89.

**Diethyl (±)-(1S,2S)-cyclohepta-3,6-diene-1,2-dicarboxylate (58b)**

![Chemical structure](image)

To a solution of ethyl [bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (236 mg, 0.712 mmol) in THF (7 mL) was added 18-crown-6 (420 mg, 1.59 mmol). The
solution was cooled to 0 °C and KHMDs (1.02 mL, 0.7 M in toluene, 0.712 mmol) was added cautiously. After 15 min the solution was cooled to −78 °C and 148 (92 mg, 0.548 mmol) in THF (7 mL) was added via cannula. After 2 h the reaction was quenched with sat. NH₄Cl (aq.) (10 mL), Et₂O (20 mL) added and the organic layer separated. The aqueous layer was extracted with further portions of Et₂O (2 × 20 mL) and the combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure at RT. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (20:1) to afford the title compound 58b as a colourless oil (98 mg, 75%); R_f (10:1 pet. ether:EtOAc) 0.27; ν_max (thin film)/cm⁻¹ 2978, 2936, 2893, 2862, 1710 \( ^1\)H NMR (400 MHz; CDCl₃) δ 5.89–5.81 (2H, m, H-3), 5.66–5.60 (2H, m, H-2), 4.17 (4H, q, \( J=7.0\), OCH₂CH₃), 3.83–3.77 (2H, m, H-1), 2.88–2.83 (2H, m, H-4), 1.26 (6H, t, \( J=7.0\), CH₃CH₂O); \( ^{13}\)C NMR (101 MHz; CDCl₃) δ 173.3 (CH₃CH₂O), 130.8 (C-3), 127.0 (C-2), 61.1 (OCH₂CH₃), 45.5 (C-1), 27.5 (C-4), 14.3 (OCH₂CH₃); m/z (ESI) 239 [MH⁺]; HRMS: calcd. for C₁₃H₁₉O₄, 239.1278. Found: [MH⁺], 239.1267 (3.8 ppm error).

Ethyl (±)-(2Z)-3-{[1S,2S]-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)cyclopropyl}prop-2-enoate (149)

To a solution of ethyl [bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (1.31 g, 4.04 mmol) in THF (40 mL) was added 18-crown-6 (2.38 g, 9.02 mmol).

The solution was cooled to 0 °C and KHMDs (5.80 mL, 0.7 M in toluene, 4.04 mmol) was added cautiously. After 15 min the solution was cooled to −78 °C and 145 (665 mg, 3.11 mmol) in THF (40 mL) was added via cannula. After 2 h the reaction was quenched with sat. NH₄Cl (aq.) (50 mL), Et₂O (50 mL) added and the organic layer separated. The aqueous layer was extracted with further portions of Et₂O (2 × 50 mL) and the combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (50:1) to afford the title compound 149 as a colourless oil (883 mg, 40%); R_f (50:1 pet. ether:EtOAc) 0.18; ν_max (thin film)/cm⁻¹ 2910, 2886, 2814, 1690, 1608; \( ^1\)H NMR (400 MHz; CDCl₃) δ 5.89–5.81 (2H, m, H-3), 5.66–5.60 (2H, m, H-2), 4.17 (4H, q, \( J=7.0\), OCH₂CH₃), 3.83–3.77 (2H, m, H-1), 2.88–2.83 (2H, m, H-4), 1.26 (6H, t, \( J=7.0\), CH₃CH₂O); \( ^{13}\)C NMR (101 MHz; CDCl₃) δ 173.3 (CH₃CH₂O), 130.8 (C-3), 127.0 (C-2), 61.1 (OCH₂CH₃), 45.5 (C-1), 27.5 (C-4), 14.3 (OCH₂CH₃); m/z (ESI) 239 [MH⁺]; HRMS: calcd. for C₁₃H₁₉O₄, 239.1278. Found: [MH⁺], 239.1267 (3.8 ppm error).
MHz; CDCl$_3$ δ 5.91 (1H, dd, J 11.5, 11.5, H-5), 5.75 (1H, d, J 11.5, H-6), 4.17 (2H, q, J 7.0, OCH$_2$CH$_3$), 3.78 (1H, dd, J 11.0, 6.0, H-1a), 3.69 (1H, dd, J 11.0, 7.0, H-1b), 3.04–2.95 (1H, m, H-4), 1.59–1.49 (1H, m, H-2), 1.29 (3H, t, J 7.0, CH$_3$CH$_2$O), 1.24–1.15 (1H, m, H-3a), 0.88 (9H, s, (Si(CH$_3$)$_3$)), 0.70–0.63 (1H, m, H-3b), 0.05 (6H, s, SiCH$_3$); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 167.2 (CH$_3$CH$_2$O=O), 151.3 (C-5), 118.7 (C-6), 62.6 (C-1), 59.8 (OCH$_2$CH$_3$), 26.1 (Si(CH$_3$)$_3$), 23.7 (C-2), 18.5 (SiC(CH$_3$)$_3$), 17.0 (C-4), 14.5 (OCH$_2$CH$_3$), 14.4 (C-3), –5.1 (SiCH$_3$), –5.1 (SiCH$_3$); m/z (ESI) 285 [MH$^+$]; HRMS: calcd. for C$_{15}$H$_{29}$O$_3$Si, 285.1880. Found: [MH$^+$], 285.1880 (0.0 ppm error).

**Ethyl (±)-(2Z)-3-[(1S,2S)-2-(hydroxymethyl)cyclopropyl]prop-2-enoate (150)**

To a stirred solution of 149 (339 mg, 1.14 mmol) in MeCN (10 mL) in a plastic container was added HF (90 µL, 48 wt % in water, 2.28 mmol). This was stirred at RT for 16 h before the addition of sat. NaHCO$_3$ (aq.) (15 mL). The solution was diluted with CH$_2$Cl$_2$ (15 mL), the organic layer was separated and the aqueous layer extracted with further portions of CH$_2$Cl$_2$ (2 × 20 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure to afford the title compound 150 as a colourless oil (188 mg, 97%), which was used in the next step without further purification; R$_f$ (1:1 pet. ether: EtOAc) 0.43; $v_{\text{max}}$ (thin film)/cm$^{-1}$ 3365, 2937, 2912, 2874, 1687, 1607; $^1$H NMR (400 MHz; CDCl$_3$) δ 5.89 (1H, dd, J 11.5, 10.0, H-5), 5.83 (1H, d, J 11.5, H-6), 4.19 (2H, q, J 7.0, OCH$_2$CH$_3$), 3.85 (1H, dd, J 11.5, 6.0, H-1a), 3.55 (1H, dd, J 11.5, 8.5, H-1b), 3.03–2.95 (1H, m, H-4), 1.69–1.39 (1H, m, H-2), 1.29 (3H, t, J 7.0, CH$_3$CH$_2$O), 1.28–1.23 (1H, m, H-3a), 0.67–0.62 (1H, m, H-3b); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 167.0 (CH$_3$CH$_2$O=O), 149.8 (C-5), 120.0 (C-6), 63.1 (C-1), 60.0 (OCH$_2$CH$_3$), 23.8 (C-2), 16.5 (C-4), 14.5 (C-3), 14.4 (OCH$_2$CH$_3$); m/z (ESI) 193 [MNa$^+$]; HRMS: calcd. for C$_9$H$_{14}$NaO$_3$, 193.0835. Found: [MNa$^+$], 193.0833 (0.6 ppm error).
Ethyl (±)-(2Z)-3-[(1S,2S)-2-formylcyclopropyl]prop-2-enoate (151)

To a stirred solution of 150 (185 mg, 1.09 mmol) in CHCl₃ (10 mL) was added manganese (IV) dioxide (948 mg, 10.9 mmol) and 4Å molecular sieves (948 mg). After 16 h the suspension was filtered through Celite, and washed with CHCl₃ (50 mL). The filtrate was concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (20:1) to afford the title compound 151 as a colourless oil (97 mg, 53%); Rₓ (20:1 pet. ether:EtOAc) 0.18; νₓ (thin film)/cm⁻¹ 2938, 2894, 2861, 2803, 2699, 1685, 1613; ¹H NMR (400 MHz; CDCl₃) δ 9.67 (1H, d, J 3.5, H-1), 6.09 (1H, dd, J 11.5, 10.5, H-5), 5.83 (1H, d, J 11.5, H-6), 4.18 (2H, q, J 7.0, OCH₂CH₃), 3.67–3.56 (1H, m, H-4), 2.50–2.42 (1H, m, H-2), 1.60–1.52 (2H, m, H-3), 1.29 (3H, t, J 7.0, CH₃CH₂O); ¹³C NMR (101 MHz; CDCl₃) δ 200.0 (C-1), 166.7 (CH₃CH₂OC=O), 146.0 (C-5), 121.1 (C-6), 60.2 (OCH₂CH₃), 31.1 (C-2), 23.9 (C-4), 17.3 (C-3), 14.4 (OCH₂CH₃); m/z (ESI) 191 [MNa⁺]; HRMS: calcd. for C₉H₁₂NaO₃, 191.0679. Found: [MNa⁺], 191.0676 (0.3 ppm error).

Diethyl (1R,2S)-cyclohepta-3,6-diene-1,2-dicarboxylate (58a)

To a solution of ethyl [bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (244 mg, 0.735 mmol) in THF (7 mL) was added 18-crown-6 (433 mg, 1.64 mmol). The solution was cooled to 0 °C and KHMDS (1.05 mL, 0.7 M in toluene, 0.735 mmol) was added cautiously. After 15 min the solution was cooled to −78 °C and 151 (95 mg, 0.565 mmol) in THF (7 mL) was added via cannula. After 2 h the reaction was quenched with sat. NH₄Cl (aq.) (10 mL), Et₂O (20 mL) added and the organic layer separated. The aqueous layer was extracted with further portions of Et₂O (2 × 20 mL) and the combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (20:1) to
afford the title compound 58a as a colourless oil (109 mg, 81%); For data see page 89

Methyl (±)-(E)-3-((1S,3R)-3-((tert-butyldimethylsilyloxy)methyl)-2,2-dimethylyclopropyl)prop-2-enoate (152)

To a stirred solution of 132 (200 mg, 0.818 mmol) in CHCl₃ (8 mL) was added manganese (IV) dioxide (711 mg, 8.18 mmol) and (methoxycarbonylmethylenetriphenylphosphorane (328 mg, 0.982 mmol). The resulting suspension was stirred vigorously with heating to maintain gentle reflux for 48 h. After cooling to room temperature, the suspension was filtered through Celite, and washed with CHCl₃ (20 mL). The filtrate was concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (50:1) to afford the title compound 152 as a colourless oil E:Z < 20:1 (118 mg, 48%); Rf (10:1 pet.ether:EtOAc) 0.56; vₘₐₓ (thin film)/cm⁻¹ 2908, 2814, 1696, 1242, 1066; ¹H NMR (400 MHz; CDCl₃) E δ 6.76 (1H, dd, J 15.0, 11.0, H-7), 5.93 (1H, d, J 15.0, H-8), 3.81–3.69 (2H, m, H-1), 3.71 (3H, s, OCH₃), 1.57–1.48 (1H, m, H-6), 1.39–1.32 (1H, m, H-2), 1.16 (3H, s, H-4), 1.15 (3H, s, H-5), 0.87 (9H, s, SiC(CH₃)₃), 0.05 (3H, s, SiCH₃), 0.04 (3H, s, SiCH₃) Z δ 5.99 (1H, dd, J 11.5, 11.5, H-7), 5.80 (1H, d, J 11.5, H-8), 4.00–3.86 (2H, m, H-1), 3.71 (3H, s, OCH₃), 1.50–1.44 (2H, m, H-6 & H-2), 1.20 (3H, s, H-4), 1.19 (3H, s, H-5), 0.89 (9H, s, SiC(CH₃)₃), 0.06 (6H, s, SiCH₃); ¹³C NMR (101 MHz; CDCl₃) E δ 167.0 (CH₃OC=O), 148.1 (C-7), 120.8 (C-8), 60.1 (C-1), 51.4 (CH₂O), 35.7 (C-6 or C-2), 31.2 (C-4), 28.9 (C-6 or C-2), 26.0 (SiC(CH₃)₃), 25.6 (C-3), 18.4 (SiC(CH₃)₃), 15.9 (C-5), −5.1 (SiCH₃), −5.1 (SiCH₃); m/z (ESI): 321 [MNa⁺]; HRMS: calcd. for C₁₆H₃₀NaO₃Si, 321.1856. Found: [MNa⁺], 321.1852 (1.1 ppm error).

Methyl (±)-(E)-3-((1S,3R)-3-(hydroxymethyl)-2,2-dimethylyclopropyl)prop-2-enoate (153)

To a stirred solution of 152 (100 mg, 0.335 mmol) in MeCN (4 mL) in a plastic container was added HF (23
µL, 48 wt % in water, 0.531 mmol). This was stirred at RT for 16 h before the addition of sat. NaHCO₃ (aq.) (5 mL). The solution was diluted with CH₂Cl₂ (10 mL), the organic layer was separated and the aqueous layer extracted with further portions of CH₂Cl₂ (2 × 10 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to afford the title compound 153 as a colourless oil E:Z < 20:1 (50 mg, 81%), which was used in the next step without further purification; Rₙ (1:1 pet.ether:EtOAc) 0.47; υₘₐₓ (thin film)/cm⁻¹ 3373, 2907, 1690, 1416; ¹H NMR (400 MHz; CDCl₃) δ 6.78 (1H, dd, J 15.0, 11.0, H-7), 5.98 (1H, d, J 15.0, H-8), 3.87–3.73 (2H, m, H-1), 3.71 (3H, s, OCH₃), 1.58 (1H, dd, J 11.0, 9.0, H-6), 1.43 (1H, dd, J 9.0, 7.5, H-2), 1.19 (3H, s, H-4), 1.18 (3H, s, H-5); Z δ 6.78 (1H, dd, J 11.5, 10.5, H-7), 5.87 (1H, d, J 11.5, H-8), 3.87–3.73 (2H, m, H-1), 3.72 (3H, s, OCH₃), 1.60–1.39 (2H, m, H-6 & H-2), 1.19 (3H, s, H-4), 1.18 (3H, s, H-5); ¹³C NMR (101 MHz; CDCl₃) δ 167.0 (CH₃O=O), 147.1 (C-7), 121.5 (C-8), 59.9 (C-1), 51.5 (CH₃O), 35.5 (C-6 or C-2), 31.1 (C-4), 28.9 (C-6 or C-2), 25.7 (C-3), 15.9 (C-5); m/z (ESI): 207 [MNa⁺]; HRMS: calcd. for C₁₀H₁₆NaO₃, 207.0992. Found: [MNa⁺], 207.0989 (1.0 ppm error).

Dimethyl (2E,2'E)-3,3'-((1R,2S)-3,3-diethylcyclopropane-1,2-diyl)diprop-2-enoate (154)

To a stirred solution of 153 (50 mg, 0.272 mmol) in CHCl₃ (3 mL) at RT was added (methoxycarbonylmethylene)-triphenylphosphorane (109 mg, 0.326 mmol). After 16 h the solution was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (20:1) to afford the title compound 154 as a colourless oil (32 mg, 49%); Rₙ (20:1 pet.ether:EtOAc) 0.18; υₘₐₓ (thin film)/cm⁻¹ 2908, 2873, 1689, 1610, 1413; ¹H NMR (400 MHz; CDCl₃) δ 6.89–6.78 (2H, m, H-2), 5.96 (2H, d, J 15.5, H-1), 3.72 (6H, s, OCH₃), 1.93–1.86 (2H, m, H-3), 1.26 (3H, s, H-5), 1.21, (3H, s, H-6); ¹³C NMR (101 MHz; CDCl₃) δ 166.6 (CH₃O=O), 145.7 (C-2), 122.5 (C-1), 51.6 (CH₃O), 36.7 (C-3), 29.7 (C-4),
28.5 (C-5), 16.7 (C-6); m/z (ESI): 261 [MNa⁺]; HRMS: calcd. for C₁₃H₁₈NaO₃, 261.1097. Found: [MNa⁺], 261.1096 (0.4 ppm error).

**Methyl (±)-(E)-3-((1S,3R)-3-((E)-3-hydroxyprop-1-enyl)-2,2-dimethylcyclopropyl)prop-2-en-1-olate (155) & (2E,2′E)-3,3′-((1R,2S)-3,3′-Dimethylcyclopropane-1,2-diyl)diprop-2-en-1-ol (156)**

To a stirred solution of 154 (250 mg, 1.06 mmol) in CH₂Cl₂ (10 mL) at −78 °C was added DIBAL (2.10 mL, 2.10 mmol, 1M in hexanes). After 30 mins, MeOH (1 mL) was added and the reaction was warmed to RT, sat. aq. Rochelle’s salt (5 mL) was added and the mixture was stirred overnight. The organic layer was separated and the aqueous layer extracted with further portions of CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to afford the crude compound, which was purified by flash column chromatography on silica gel, eluting with pet. ether: EtOAc (2: 1) to afford 155 as a colourless oil (21 mg, 9%) and 156 as a colourless oil (64 mg, 33%); 155 Rᵣ (2:1 pet.ether:EtOAc) 0.55; νₘₐₓ (thin film)/cm⁻¹ 3357, 2906, 2876, 1689, 1610; ¹H NMR (400 MHz; CDCl₃) δ 6.81 (1H, dd, J = 15.0, 11.0, H-2), 5.94 (1H, d, J = 15.0, H-1), 5.83 (1H, dt, J = 15.0, 6.0, H-9), 5.60 (1H, ddt, J = 15.0, 9.5, 1.5, H-8), 4.13 (2H, dd, J = 6.0, 1.5, H-10), 3.72 (3H, s, OCH₃), 1.81 (1H, dd, J = 9.5, 8.5, H-7), 1.68 (1H, dd, J = 11.0, 8.5, H-3), 1.19 (3H, s, H-5), 1.17 (3H, s, H-6); ¹³C NMR (101 MHz; CDCl₃) δ 167.0 (CH₃O), 147.7 (C-2), 132.0 (C-1), 128.2 (C-9), 121.3 (C-8), 63.8 (C-10), 51.5 (CH₂O), 36.5 (C-7), 34.4 (C-3), 28.6 (C-5), 27.6 (C-4), 16.6 (C-6); m/z (ESI): 233 [MNa⁺]; HRMS: calcd. for C₁₂H₁₈NaO₃, 233.1148. Found: [MNa⁺], 233.1143 (2.1 ppm error); 156 Rᵣ (2:1 pet.ether:EtOAc) 0.18; νₘₐₓ (thin film)/cm⁻¹ 3284, 2954, 2899, 2821, 1356; ¹H NMR (400 MHz; CDCl₃) δ 5.79 (2H, dt, J = 15.0, 6.0, H-3), 5.56–5.48 (2H, m, H-2), 4.10 (4H, dd, J = 6.0, 1.5, H-1), 1.58–1.52 (2H, m, H-4), 1.12 (3H, s, H-5), 1.09 (3H, s, H-6); ¹³C NMR (101 MHz; CDCl₃) δ 130.7 (C-3), 129.5 (C-2), 63.9 (C-1), 33.4 (C-4), 28.6 (C-7), 24.4 (C-5),
16.3 (C-6); m/z (ESI): 205 [MNa⁺]; HRMS: calcd. for C_{11}H_{18}NaO_{2}, 205.1199. Found: [M Na⁺], 205.1192 (3.0 ppm error).

(±)-(E)-3-((1S,3R)-3-((E)-3-(tert-butyldimethylsilyloxy)prop-1-enyl)-2,2-dimethylcyclopropyl)prop-2-en-1-ol (157) & (2E,2′E)-3,3′-((1R,2S)-3,3-Dimethylcyclopropane-1,2-diyl)bis(prop-2-ene-3,1-diyl)bis(oxy)bis(tert-butyldimethylsilane) (158)

To a stirred solution of diol 156 (122 mg, 0.669 mmol) in CH_{2}Cl_{2} (10 mL) was added TBSCl (150 mg, 1.00 mmol) and imidazole (68 mg, 1.00 mmol). After 2 h aq. HCl (10 mL) was added. The organic layer was separated and the aqueous layer extracted with further portions of CH_{2}Cl_{2} (2 x 20 mL). The combined organic extracts were dried (MgSO_{4}), filtered and concentrated under reduced pressure to afford the crude compound, which was purified by flash column chromatography on silica gel, eluting with pet. ether: Et_{2}O (10: 1) to afford 157 as a colourless oil (40 mg, 20%) and 158 as a colourless oil (96 mg, 35%); 157 R_{f} (10:1 pet.ether:Et_{2}O) 0.28; \nu_{\text{max}} (thin film)/cm\textsuperscript{-1} 3346, 2882, 2813, 1441; \textsuperscript{1}H NMR (400 MHz; CDCl_{3}) \delta 5.78 (1H, dt, J 15.0, 6.0, H-2 or H-10), 5.69 (1H, dt, J 15.0, 5.0, H-2 or H-10), 5.56–5.43 (2H, m, H-3 & H-9), 4.15 (2H, br d, J 5.0, H-1 or H-11), 4.09 (2H, br d, J 6.0, H-1 or H-11), 1.58–1.50 (1H, m, H-4 or H-8), 1.11 (3H, s, H-5), 1.09 (3H, s, H-6), 0.94–0.85 (1H, m H-4 or H-8), 0.905 (9H, s, SiC(C(CH_{3})_{3})), 0.06 (6H, s, SiCH_{3}); \textsuperscript{13}C NMR (101 MHz; CDCl_{3}) \delta 131.0 (C-2 or C-10), 130.5 (C-2 or C-10), 130.1 (C-3 or C-9), 127.4 (C-3 or C-9), 64.1 (C-1 or C-11), 64.1 (C-1 or C-11), 33.4 (C-4 or C-8), 33.3 (C-4 or C-8), 28.7 (C-7), 26.1 (SiC(CH_{3})_{3}), 24.3 (C-5), 18.6 (SiC(CH_{3})_{3}), 16.3 (C-6), -5.0 (SiCH_{3}) m/z (ESI): 319 [MNa⁺]; HRMS: calcd. for C_{17}H_{32}NaO_{2}Si, 319.2064. Found: [M Na⁺], 319.2047 (4.9 ppm error); 158 R_{f} (10:1 pet.ether:Et_{2}O) 0.75; \nu_{\text{max}} (thin film)/cm\textsuperscript{-1} 2909, 2885, 2813; \textsuperscript{1}H NMR (400 MHz; CDCl_{3}) \delta 5.68 (2H, dt, J 15.0, 5.5, H-3), 5.53–5.42 (2H, m, H-2), 4.18–4.08 (4H, m, H-1), 1.58–1.52 (2H, m, H-4), 1.12 (3H, s, H-5), 1.09 (3H, s,
H-6), 0.90 (18H, s, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.06 (12H, s, SIC(CH<sub>3</sub>)<sub>3</sub>); <sup>1</sup>C NMR (101 MHz; CDCl<sub>3</sub>) δ 130.8 (C-3), 127.8 (C-2), 64.2 (C-1), 33.3 (C-4), 28.7 (C-7), 26.1 (SiC(CH<sub>3</sub>)<sub>3</sub>), 24.0 (C-5), 18.6 (SiC(CH<sub>3</sub>)<sub>3</sub>), 16.4 (C-6), −5.0 (SiCH<sub>3</sub>); m/z (ESI): 433 [MNa<sup>+</sup>]; HRMS: calcd. for C<sub>23</sub>H<sub>46</sub>NaO<sub>2</sub>Si<sub>2</sub>, 433.2929. Found: [MNa<sup>+</sup>], 433.2916 (3.2 ppm error).

(2E,2′E)-3,3′-((1R,2S)-3,3-dimethylcyclopropane-1,2-diyl)diprop-2-enoic acid (159)

To a solution of 154 (71 mg, 0.298 mmol) in THF:H<sub>2</sub>O 1:1 (6 mL) was added NaOH (83 mg, 2.09 mmol). This was stirred at RT for 16 h before the addition of Et<sub>2</sub>O (10 mL). The Et<sub>2</sub>O layer was removed and the aq. layer was acidified with 10% aq. HCl (20 mL). The aqueous layer was extracted with of EtOAc (2 x 20 mL) and the combined organic extracts were dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure to afford title compound 159, without further purification as a light brown solid (62 mg, 100%); υ<sub>max</sub> (thin film)/cm<sup>−1</sup> 2879, 2600 (br), 1679, 1627, 1421; <sup>1</sup>H NMR (400 MHz; DMSO) δ 5.93–5.85 (2H, m, H-2), 5.10 (2H, d, J 15.0, H-1), 1.21–1.14 (2H, m, H-3), 0.34 (3H, s, H-5), 0.30 (3H, s, H-6) <sup>1</sup>C NMR (101 MHz; DMSO) δ 167.1 (C=O), 146.0 (C-2), 123.8 (C-1), 36.3 (C-3), 29.8 (C-5), 28.4 (C-4), 16.8 (C-6); m/z (ESI): 433 [MNa<sup>+</sup>]; HRMS: calcd. for C<sub>11</sub>H<sub>14</sub>NaO<sub>4</sub>, 233.0790. Found: [MNa<sup>+</sup>], 233.0797 (2.2 ppm error).

General Procedure for the Cope Rearrangement

A solution of divinylcyclopropane in xylene (0.19 mol dm<sup>−3</sup>) was heated to the temperature indicated and held at that temperature for 17 h. The solution was then concentrated in <i>vacuo</i>. The products in Table 5 were purified, by flash column chromatography, except for diacid 165.
Diethyl (1\textit{R},2\textit{S})-5,5-dimethylcyclohepta-3,6-diene-\(1,2\)-dicarboxylate (88a)

![Diagram of Diethyl (1\textit{R},2\textit{S})-5,5-dimethylcyclohepta-3,6-diene-\(1,2\)-dicarboxylate (88a)](image)

Synthesised from compound 57d using the general procedure at 100 °C, affording the title compound 88a as a colourless oil (78%); \(R_f\) (10:1 pet. ether: EtOAc) 0.25; \(\nu_{\text{max}}\) (thin film)/cm\(^{-1}\) 2961, 2920, 1735; \^H NMR (400 MHz; CDCl\(_3\)) \(\delta\) 5.93 (2H, dd, \(J\ 12.0, 6.0, \text{H-2}\)), 5.50 (2H, d, \(J\ 12.0, \text{H-3}\)), 4.12–4.18 (4H, m, OCH\(_2\)CH\(_3\)), 3.79 (2H, d, \(J\ 6.0, \text{H-1}\)), 1.25 (6H, t, \(J\ 7.0, \text{OCH}\(_2\)CH\(_3\)\)), 1.16 (3H, s, \text{H-5}), 1.13 (3H, s, \text{H-6}); \(^{13}\text{C}\) NMR (101 MHz; CDCl\(_3\)) \(\delta\) 172.0 (C=O), 140.0 (C-2), 123.2 (C-3), 61.1 (OCH\(_2\)CH\(_3\)), 45.1 (C-1), 39.1 (C-4), 32.4 (OCH\(_2\)CH\(_3\)), 29.3 (C-6), 14.3 (C-5); m/z (ESI): 289 [MNa\(^+\)]; HRMS: calcd. for C\(_{15}\)H\(_{22}\)NaO\(_4\), 289.1410. Found: [MNa\(^+\)], 289.1411 (0.3 ppm error).

Dimethyl (1\textit{R},2\textit{S})-5,5-dimethylcyclohepta-3,6-diene-\(1,2\)-dicarboxylate (160)

![Diagram of Dimethyl (1\textit{R},2\textit{S})-5,5-dimethylcyclohepta-3,6-diene-\(1,2\)-dicarboxylate (160)](image)

Synthesised from compound 154 using the general procedure at 100 °C, affording the title compound 160 as a colourless oil (36 mg, 83%); \(R_f\) (10:1 pet. ether: EtOAc) 0.23; \(\nu_{\text{max}}\) (thin film)/cm\(^{-1}\) 2974, 2912, 1718; \(^1\text{H}\) NMR (400 MHz; CDCl\(_3\)) \(\delta\) 5.93 (2H, dd, \(J\ 11.5, 6.5, \text{H-2}\)), 5.50 (2H, d, \(J\ 11.5, \text{H-3}\)), 3.82 (2H, d, \(J\ 6.5, \text{H-1}\)), 3.70 (6H, s, OCH\(_3\)), 1.16 (3H, s, \text{H-6}), 1.12 (3H, s, H-5); \(^{13}\text{C}\) NMR (101 MHz; CDCl\(_3\)) \(\delta\) 172.5 (C=O), 140.1 (C-2), 123.1 (C-3), 52.3 (C-1), 44.9 (OCH\(_3\)), 39.1 (C-4), 32.5 (C-6), 29.3 (C-5); m/z (ESI): 239 [MH\(^+\)]; HRMS: calcd. for C\(_{13}\)H\(_{19}\)O\(_4\), 239.1278. Found: [MH\(^+\)], 239.1269 (3.2 ppm error).

(±)-(3\textit{aR},8\textit{aS})-6,6-Dimethyl-3,3\textit{a},6,8\textit{a}-tetrahydro-1\textit{H}-cyclohepta[c]furan-1-one (161)

![Diagram of (±)-(3\textit{aR},8\textit{aS})-6,6-Dimethyl-3,3\textit{a},6,8\textit{a}-tetrahydro-1\textit{H}-cyclohepta[c]furan-1-one (161)](image)

Synthesised from compound 155 using the general procedure at 100 °C, affording the title compound 161 as a light yellow solid (32 mg, 84%); \(R_f\) (EtOAc) 0.72; mp 29–32 °C; \(\nu_{\text{max}}\) (thin film)/cm\(^{-1}\) 2917, 2880, 2824, 1744; \(^1\text{H}\) NMR (400 MHz; CDCl\(_3\)) \(\delta\) 5.67 (1H, ddd, \(J\ 12.0, 2.0, 2.0, \text{H-7 or H-3}\)), 5.61 (1H, ddd, \(J\ 12.0, 2.0, 2.0, \text{H-7 or H-3}\)), 5.61 (1H, ddd, \(J\ 12.0, 2.0, 2.0, \text{H-7 or H-3}\)), 5.61 (1H, ddd, \(J\ 12.0, 2.0, 2.0, \text{H-7 or H-3}\)), 5.61 (1H, ddd, \(J\ 12.0, 2.0, 2.0, \text{H-7 or H-3}\)), 5.61 (1H, ddd, \(J\ 12.0, 2.0, 2.0, \text{H-7 or H-3}\)), 5.61 (1H, ddd, \(J\ 12.0, 2.0, 2.0, \text{H-7 or H-3}\)), 5.61 (1H, ddd, \(J\ 12.0, 2.0, 2.0, \text{H-7 or H-3}\)), 5.61 (1H, ddd, \(J\ 12.0, 2.0, 2.0, \text{H-7 or H-3}\)), 5.61 (1H, ddd, \(J\ 12.0, 2.0, 2.0, \text{H-7 or H-3}\)), 5.61 (1H, ddd, \(J\ 12.0, 2.0, 2.0, \text{H-7 or H-3}\)), 5.61 (1H, ddd, \(J\ 12.0, 2.0, 2.0, \text{H-7 or H-3}\)), 5.61 (1H, ddd, \(J\ 12.0, 2.0, 2.0, \text{H-7 or H-3}\)).
3), 5.46 (1H, dd, J 12.0, 5.0, H-8 or H-2), 5.31 (1H, dd, J 12.0, 4.5, H-8 or H-2), 4.31 (1H, dd, J 8.5, 6.0, H-10a), 4.12 (1H, dd, J 8.5, 4.5, H-10b), 3.47–3.39 (2H, m, H-9 & H-1), 1.19 (3H, s, H-5), 1.15 (3H, s, H-6); 13C NMR (101 MHz; CDCl3) δ 176.8 (C-11), 143.4 (C-7 or C-3), 142.6 (C-7 or C-3), 123.6 (C-8 or C-2), 118.6 (C-8 or C-2), 73.2 (C-10), 44.0 (C-9 or C-1), 39.7 (C-4), 38.2 (C-9 or C-1), 32.0 (C-5), 30.1 (C-6); m/z (ESI): 179 [M+H]+; HRMS: calcd. for C11H15O2, 179.1067. Found: [M+H]+, 179.1065 (1.0 ppm error).

((1R,2S)-5,5-Dimethylcyclohepta-3,6-diene-1,2-diyldimethanol (162)

Synthesised from compound 156 using the general procedure at 100 °C, affording the title compound 162 as a colourless oil (15 mg, 83%); Rf (EtOAc) 0.43; mp 42–44 °C; *vmax (thin film)/cm⁻¹ 3304, 3008, 2958, 2923, 2871; 1H NMR (400 MHz; CDCl3) δ 5.57 (2H, dd, J 12.0, 6.5, H-2), 5.43 (2H, d, J 12.0, H-3), 3.72 (2H, dd, J 11.0, 7.0, H-7a), 3.66 (2H, br s, OH), 3.59 (2H, dd, J 11.0, 3.0, H-7b), 2.81–2.76 (2H, m, H-1), 1.13 (3H, s, H-5), 1.08 (3H, s, H-6); 13C NMR (101 MHz; CDCl3) δ 139.9 (C-3), 126.0 (C-2), 63.9 (C-7), 43.8 (C-1), 39.9 (C-4), 32.9 (C-5), 29.8 (C-6); m/z (ESI): 205 [MNa+]; HRMS: calcd. for C11H18NaO2, 205.1199. Found: [MNa+], 205.1195 (0.7 ppm error).

(±)-((1R,7S)-7-((tert-Butyldimethylsilyloxy)methyl)-4,4-dimethylcyclohepta-2,5-dienyl)methanol (163)

Synthesised from compound 157 using the general procedure at 100 °C, affording the title compound 163 as a colourless oil (10 mg, 86%); Rf (10:1 pet.ether:EtOAc) 0.52; *vmax (thin film)/cm⁻¹ 3373, 2962, 2911, 2885, 2815; 1H NMR (400 MHz; CDCl3) δ 5.58 (1H, dd, J 11.5, 6.0, H-8 or H-2), 5.50 (1H, dd, J 12.0, 6.5, H-8 or H-2), 5.45–5.37 (2H, m, H-7 & H-3), 3.74 (1H, dd, J 10.5, 8.0, H-11a or H-10a), 3.65 (1H, dd, J 11.5, 7.0, H-11a or H-10a), 3.57–3.51 (2H, m, H-11b & H-10b), 2.86–2.79 (1H, m, H-9 or H-1), 2.75–2.68 (1H, m, H-9 or H-1), 1.13 (3H,
s, H-6), 1.08 (3H, s, H-5), 0.91 (9H, s, SiC(CH$_3$)$_3$), 0.10 (6H, s, SiCH$_3$); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 140.1 (C-8 or C-2), 139.5 (C-8 or C-2), 126.5 (C-7 or C-3), 125.9 (C-7 or C-3), 64.4 (C-11 or C-10), 64.3 (C-11 or C-10), 44.0 (C-9 or C-1), 44.0 (C-9 or C-1), 39.8 (C-4), 33.0 (C-6), 29.7 (C-5), 26.0 (SiC(CH$_3$)$_3$), 18.4 (SiC(CH$_3$)$_3$), -5.4 (SiCH$_3$); m/z (ESI): 319 [MNa$^+$]; HRMS: calcd. for C$_{17}$H$_{32}$NaO$_2$Si, 319.2064. Found: [MNa$^+$], 319.2053 (2.4 ppm error).

((1R,2S)-5,5-Dimethycyclohepta-3,6-diene-1,2-diyl)bis(methylene)bis(oxy)bis(tert-butyldimethylsilane) (164)

Synthesised from compound 158 using the general procedure at 100 °C, affording the title compound 164 as a colourless oil (17 mg, 88%); R$_f$ (40:1 pet. ether: Et$_2$O) 0.76; $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 2911, 2883, 2852, 2814; $^1$H NMR (400 MHz; CDCl$_3$) δ 5.48 (2H, dd, J 11.5, 6.0, H-3), 5.35 (2H, d, J 11.5, H-4), 3.66 (2H, dd, J 10.0, 7.0, H-1a), 3.58 (2H, dd, J 10.0, 7.0, H-1b), 2.73 (2H, ddd, J 7.0, 7.0, 6.0, H-2), 1.14 (3H, s, H-6), 1.09 (3H, s, H-7), 0.88 (18H, s, SiC(CH$_3$)$_3$), 0.03 (12H, s, SiCH$_3$); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 139.1 (C-4), 128.0 (C-3), 65.5 (C-1), 42.8 (C-2), 39.8 (C-5), 32.9 (C-6), 29.9 (C-7), 26.1 (SiC(CH$_3$)$_3$), 18.5 (SiC(CH$_3$)$_3$), -5.2 (SiCH$_3$). m/z (ESI): 411 [MH$^+$]; HRMS: calcd. for C$_{23}$H$_{47}$O$_2$Si$_2$, 411.3109. Found: [MH$^+$], 411.3100 (1.1 ppm error).

((1R,2S)-5,5-Dimethycyclohepta-3,6-diene-1,2-dicarboxylic acid (165)

Synthesised from compound 159 using the general procedure at 100 °C, without chromatography, affording the title compound 165 as a light brown solid (22 mg, 97%); mp 130–132 °C; $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 2963, 2892, 2860 (br), 1693; $^1$H NMR (400 MHz; DMSO) δ 5.87–5.80 (2H, m, H-2), 5.40 (2H, d, J 12.0, H-3), 3.67 (2H, d, J 5.5, H-1), 1.12 (3H, s, H-6), 1.06 (3H, s, H-5); $^{13}$C NMR (101 MHz; DMSO) δ 172.8 (C=O), 138.4 (C-2), 124.4 (C-3), 44.1 (C-1), 38.2 (C-4), 32.1 (C-6), 28.8 (C-5); m/z (ESI): 211 [MH$^+$]; HRMS: calcd. for C$_{11}$H$_{15}$O$_4$, 211.0965. Found: [MH$^+$], 211.0971 (2.8 ppm error).
7.4 Procedures & Compound Characterisation (Chapter 4)

Diethyl (1R,2S)-5,5-dimethylcyclohepta-3,6-diene-1,2-dicarboxylate (88a)

A stirred solution of 57d (5.49 g, 20.6 mmol) in toluene (200 mL) was heated to 100 °C for 16 h. After being cooled to RT the solution was concentrated under reduced pressure to afford the title compound cis-37, as a colourless oil (4.50 g, 82%); For data see page 140

[(1R,2S)-5,5-Dimethylcyclohepta-3,6-diene-1,2-diyl]dimethanol (162)

To a stirred suspension of LiAlH₄ (86 mg, 2.26 mmol) in THF (5 mL) at 0 °C was added 88a (300 mg, 1.13 mmol) in THF (5 mL) via cannula. The reaction was warmed to RT and stirred for 16 h. The reaction was cooled to 0 °C and Na₂SO₄.10H₂O was cautiously added until on further addition fizzing could no longer be observed. The aluminium salts were removed by filtration and washed with EtOAc (20 mL). The filtrate was concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (5:1 → 1:1) to afford the title compound 162 as a white solid (127 mg, 62%); For data see page 141

(±)-(3aR,8aS)-6,6-Dimethyl-3,3a,6,8a-tetrahydro-1H-cyclohepta[c]furan-1-one (161)

To a stirred solution of 162 (100 mg, 0.549 mmol) in CH₂Cl₂ (5 mL) at RT was added Phl(OAc)₂ (441 mg, 1.37 mmol) and TEMPO (9 mg, 0.0576 mmol). After 2h the reaction mixture was concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether:Et₂O (10:1 → 2:1) to afford the title compound 161 as a light yellow solid (68 mg, 69%); For data see page 140
To a stirred solution of 161 (624 mg, 3.50 mmol) in THF (175 mL) at 0 °C was added DBU (0.52 mL, 3.50 mmol). After 30 min the reaction was quenched with NH₄Cl (aq.) (100 mL), EtOAc (100 mL) was added, the organic layer was separated and the aqueous layer extracted with portions of EtOAc (2 × 100 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et₂O (4:1) to afford the title compound 168 as a colourless oil (185 mg, 30%) and 170 as a colourless oil (322 mg, 52%); 168 Rf (1:1 pet. ether:Et₂O) 0.48; vmax (thin film)/cm⁻¹ 2915, 1731, 1663; ¹H NMR (400 MHz; CDCl₃) δ 7.00–6.95 (1H, m, H-2), 5.44 (1H, ddd, J 12.0, 3.0, 1.5, H-8 or H-7), 5.18, (1H, dd, J 12.0, 2.0, H-8 or H-7), 4.56 (1H, dd, J 9.5, 8.5, H-10a), 4.00–3.92 (1H, m, H-9), 3.85 (1H, dd, J 8.5, 8.5, H-10b), 2.57 (1H, dddd, J 14.5, 6.0, 2.5, 0.5, H-3a), 2.22 (1H, dddd, J 14.5, 7.5, 1.0, 1.0, H-3b), 1.08 (3H, s, H-6), 1.01 (3H, s, H-5); ¹³C NMR (101 MHz; CDCl₃) δ 170.3 (C-11), 141.6 (C-8 or C-7), 139.2 (C-2), 131.8 (C-1), 122.5 (C-8 or C-7), 71.1 (C-10), 39.5 (C-3), 37.5 (C-9), 35.4 (C-4), 31.4 (C-6), 29.1 (C-5); m/z (ESI): 179 [MH⁺]; HRMS: calcd. for C₁₁H₁₅O₂, 179.1067. Found: [MH⁺], 179.1066 (0.1 ppm error). 170 Rf (1:1 pet. ether:Et₂O) 0.45; vmax (thin film)/cm⁻¹ 2969, 2916, 2878, 2824, 1754; ¹H NMR (400 MHz; CDCl₃) δ 5.89 (1H, ddd, J 11.0, 3.0, 0.5, H-7 or H-3), 5.55–5.45 (3H, m, H-8, H-2 & H-7 or H-3), 4.44 (1H, dddd, J 8.5, 7.0, 0.5, H-10a), 3.92–3.85 (1H, m, H-10b), 3.26–3.13 (2H, m, H-9 & H-1), 1.17 (6H, s, H-5 & H-6); ¹³C NMR (101 MHz; CDCl₃) δ 176.7 (C-11), 141.1 (C-7 or C-3), 140.2 (C-7 or C-3), 122.3 (C-8 or C-2), 121.1 (C-8 or C-2), 70.4 (C-10), 44.3 (C-9 or C-1), 41.5 (C-9 or C-1), 41.1 (C-4), 31.6 (C-5), 31.5 (C-6); m/z (ESI): 179 [MH⁺]; HRMS: calcd. for C₁₁H₁₅O₂, 179.1067. Found: [MH⁺], 179.1068 (−1.4 ppm error).
(±)-(3aS,4aS,8aR)-6,6-Dimethyl-1,4,4a,5,6,8a-hexahydrocyclopropa[1,7]cyclohepta[1,2-c]furan-3-one (171)

Procedure 1: To a suspension of NaH (33 mg, 0.815 mmol, 60% dispersion in mineral oil) in DMF (1.5 mL) at 0 °C was added trimethylsulfoxonium iodide (179 mg, 0.815 mmol). The reaction mixture was stirred for 5 min before the dropwise addition of 168 (121 mg, 0.679 mmol) in DMF (1.5 mL). The solution was stirred at 0 °C for a further 5 min before warming to RT and stirring for 16 h. Sat. NH₄Cl (aq.) (5 mL) was then added followed by H₂O (5 mL) and Et₂O (15 mL). The organic layer was separated and the aqueous layer extracted with portions of Et₂O (2 × 15 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et₂O (4:1) to afford the title compound 171 as a colourless oil (26 mg, 20%); Procedure 2: To a suspension of NaH (29 mg, 0.734 mmol, 60% dispersion in mineral oil) in DMSO (1 mL) at 0 °C was added trimethylsulfoxonium iodide (162 mg, 0.734 mmol). The reaction mixture was stirred for 5 min before the dropwise addition of 168 (109 mg, 0.612 mmol) in DMSO (1 mL). The solution was stirred at RT for 16 h. Sat. NH₄Cl (aq.) (5 mL) was then added followed by H₂O (5 mL) and Et₂O (2 mL). The organic layer was separated and the aqueous layer extracted with portions of Et₂O (2 × 2 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et₂O (4:1) to afford the title compound 171 as a colourless oil (15 mg, 11%); Procedure 3: To a stirred solution of MTBD (208 mg, 1.36 mmol) and trimethylsulfoxonium iodide (179 mg, 0.815 mmol) in MeCN (2 mL) was added 168 (121 mg, 0.679 mmol) in MeCN (2 mL). The reaction mixture was stirred at RT overnight. It was then concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et₂O (4:1) to afford the title compound 171 as a colourless oil (10 mg, 8%); Rₛ (1:1 pet. ether:EtOAc) 0.43; νₘₐₓ (thin film)/cm⁻¹ 2956, 2915, 2871, 2825, 1740; ¹H
NMR (400 MHz; CDCl$_3$) δ 5.37 (1H, dd, J 12.0, 2.5, H-8 or H-7), 5.19 (1H, dd, J 12.0, 2.0, H-8 or H-7), 4.49 (1H, dd, J 9.0, 6.5, H-10a), 4.28 (1H, dd, J 9.0, 1.0, H-10b), 3.04–2.99 (1H, m, H-9), 2.05 (1H, ddd, J 14.0, 4.5, 2.5, H-3a), 1.82–1.73 (1H, m, H-2), 1.34 (1H, dd, J 9.0, 4.0, H-12a), 1.28 (1H, dd, J 14.0, 12.0, H-3b), 1.11 (3H, s, H-6), 1.01 – 0.98 (1H, m, H-12b), 0.99 (3H, s, H-5); 13C NMR (101 MHz; CDCl$_3$) δ 177.4 (C-11), 143.9 (C-8 or C-7), 126.5 (C-8 or C-7), 74.3 (C-10), 42.5 (C-3), 39.3 (C-9), 37.9 (C-4), 32.4 (C-2), 30.4 (C-1), 26.9 (C-6), 24.8 (C-12), 19.3 (C-5); m/z (ESI): 193 [MH$^+$]; HRMS: calcd. for C$_{12}$H$_{17}$O$_2$, 193.1223. Found: [MH$^+$], 193.1222 (0.5 ppm error).

(±)-(1S,2R,7S)-5,5-Dimethylbicyclo[5.1.0]oct-3-ene-1,2-diyl]dimethanol (172)

To a stirred solution of 171 (19 mg, 0.0990 mmol) in CH$_2$Cl$_2$ (1 mL) at -78 °C was added DIBAL (0.50 mL, 0.495 mmol, 1M in hexanes). After 10 mins the reaction was warmed to RT and after 30 min the reaction mixture was diluted with CH$_2$Cl$_2$ (2 mL) followed by the careful addition of sat. aq. Rochelle’s salt (3 mL). The mixture was stirred overnight after which time, the organic layer was separated and the aqueous layer extracted with further portions of CH$_2$Cl$_2$ (2 × 3 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure to afford the crude compound, which was purified by flash column chromatography on silica gel, eluting with pet. ether:Et$_2$O (1:1) to afford the title compound 172 as a colourless oil (15 mg, 79%); R$_f$ (1:1 pet. ether:Et$_2$O) 0.36; $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3285, 2951, 2909, 2873, 2807; $^1$H NMR (400 MHz; CDCl$_3$) δ 5.27 – 5.19 (2H, m, H-8 & H-7), 3.98 (1H, dd, J 11.5, 1.5, H-10a), 3.80 – 3.77 (2H, m, H-11), 3.04 (1H, dd, J 11.5, 1.0, H-10b), 2.46 – 2.39 (1H, m, H-9), 2.23 (2H, br s, OH$^-$), 1.78 (1H, ddd, J 14.5, 5.0, 2.0, H-3a), 1.57 (1H, dd, J 14.5, 11.5, H-3b), 1.05 (3H, s, H-6), 0.97 (3H, s, H-5), 0.94 – 0.73 (3H, m, H-12 & H-2); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 141.2 (C-8 or C-7), 125.0 (C-8 or C-7), 69.1 (C-10), 64.8 (C-11), 42.8 (C-3), 40.0 (C-9), 38.9 (C-4), 32.3 (C-2), 31.0 (C-1), 27.7 (C-6), 19.0 (C-12), 18.1 (C-5); m/z (ESI): 219 [MNa$^+$]; HRMS: calcd. for C$_{12}$H$_{26}$NaO$_2$, 219.1356. Found: [MNa$^+$], 219.1357 (–0.5 ppm error).
(±)-(1S,7R)-7-[[tert-Butyl(dimethyl)silyl]oxy]methyl]-4,4-dimethylcyclohepta-2,5-dien-1-yl]methanol (163)

To a stirred solution of 162 (370 mg, 2.03 mmol) in THF (4 mL) was added NaH (100 mg, 2.44 mmol, 60% dispersion in mineral oil) at RT and the reaction mixture was stirred for 45 min before the addition of TBSCI (306 mg, 2.03 mmol). After 2 h the reaction was quenched with sat. NH₄Cl (aq.) (5 mL) followed by Et₂O (5 mL). The organic layer was separated and the aqueous layer extracted with further portions of Et₂O (2 × 5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (40:1 → 1:1) to afford the title compound 163 as a colourless oil (495 mg, 82%); For data see page 141

(±)-(1S,7R)-7-[[tert-Butyl(dimethyl)silyl]oxy]methyl]-4,4-dimethylcyclohepta-2,5-diene-1-carbaldehyde (188)

To a stirred solution of 163 (220 mg, 0.743 mmol) in CH₂Cl₂ (10 mL), at 0 °C was added Dess–Martin Periodinane (636 mg, 1.50 mmol). The reaction mixture was warmed to RT and allowed to stir for 16 h. It was then diluted with CH₂Cl₂ (10 mL), and quenched with a 1:1 solution of sat. Na₂CO₃ (aq.) and sat. Na₂S₂O₃ (aq.) (40 mL). After vigorous stirring for 30 mins, the organic layer was separated and the aqueous layer extracted with further portions of CH₂Cl₂ (2 × 25 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to afford 200 mg of unpurified aldehyde 188, which was used in the next step without further purification; Rₜ (10:1 pet.ether:EtOAc) 0.71; ¹H NMR (400 MHz; CDCl₃) δ 9.59 (1H, s, H-11) 5.86 (1H, dd, J 11.5, 5.0, H-8 or H-2), 5.60 (1H, ddd, J 11.5, 2.0, 2.0 H-7 or H-3), 5.56 (1H, dd, J 11.5, 6.5, H-8 or H-2), 5.42 (1H, ddd, J 11.5, 2.0, 2.0 H-7 or H-3), 3.56–3.53 (2H, m, H-10), 3.33–3.51 (1H, m, H-9 or H-1), 3.12–3.05
(1H, m, H-9 or H-1), 1.14 (3H, s, H-6), 1.12 (3H, s, H-5), 0.85 (9H, s, SiC(CH₃)₃), 0.00 (3H, s, SiCH₃), −0.01 (3H, s, SiCH₃).

(±)-(7R)-7-((t-Butyl(dimethyl)silyloxy)methyl)-4,4-dimethylcyclohepta-1,5-diene-1-carbaldehyde (189)

To a solution of 188 (200 mg, 0.675 mmol) in THF (20 mL) at 0 °C was added DBU (111 µL, 0.748 mmol). After 20 mins the reaction was quenched with NH₄Cl (aq.) (20 mL). EtOAc (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with portions of EtOAc (2 × 50 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to afford 233 mg of unpurified aldehyde 189, which was used in the next step without further purification; Rf (5:1 pet. ether:Et₂O) 0.53; ¹H NMR (400 MHz; CDCl₃) δ 9.37 (1H, s, H-11) 6.87 (1H, dd, J 9.0, 5.5, H-2), 5.54 (1H, d, J 12.0, H-8 or H-7), 5.42 (1H, dd, J 12.0, 5.5, H-8 or H-7), 3.70–3.56 (3H, m, H-10 & H-9), 3.00 (1H, dd, J 13.5, 5.5 H-3a), 2.17 (1H, ddd, J 13.5, 9.0, 2.0 H-3b), 1.10 (3H, s, H-6), 1.00 (3H, s, H-5), 0.86 (9H, s, SiC(CH₃)₃), 0.02 (3H, s, SiCH₃), 0.01 (3H, s, SiCH₃).

(±)-(7R)-7-((t-Butyl(dimethyl)silyloxy)methyl)-4,4-dimethylcyclohepta-1,5-dien-1-yl)methanol (190)

To a stirred solution of 189 (233 mg of crude material) in MeOH (10 mL) at 0 °C was added NaBH₄ (28 mg, 0.748 mmol). After 30 min the reaction mixture was diluted with CH₂Cl₂ (25 mL) and quenched with NaHCO₃ (aq.) (5 mL). The organic layer was separated and the aqueous layer extracted with portions of CH₂Cl₂ (2 × 25 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et₂O (5:1) to afford the title compound 190 as a colourless oil (165 mg, 75% over 3 steps); Rf (5:1 pet. ether:Et₂O) 0.18; νmax (thin film)/cm⁻¹ 3298, 2909, 2883, 2815; ¹H NMR (400 MHz;
CDCl$_3$ $\delta$ 5.83 (1H, ddd, $J$ 8.5, 6.0, 1.0, H-2), 5.43 (1H, ddd, $J$ 12.0, 2.0, 1.0, H-8 or H-7), 5.32 (1H, dd, $J$ 12.0, 7.0, H-8 or H-7), 4.06–3.94 (2H, m, H-10 or H-11), 3.79 (1H, dd, $J$ 9.5, 9.5, H-10a or H-11a), 3.68 (1H, dd, $J$ 9.5, 5.0, H-10a or H-11a), 3.04–2.97 (1H, m, H-6), 2.52 (1H, dd, $J$ 14.0, 6.0, H-3a), 1.90 (1H, ddd, $J$ 14.0, 8.5, 2.0, H-3b), 1.00 (3H, s, H-5), 0.98 (3H, s, H-5), 0.91 (9H, s, SiC(CH$_3$)$_3$), 0.10 (3H, s, SiCH$_3$), 0.09 (3H, s, SiCH$_3$); $^{13}$C NMR (101 MHz; CDCl$_3$) $\delta$ 142.9 (C-7), 140.4 (C-1), 127.4 (C-8), 121.6 (C-2), 68.5 (C-10), 65.0 (C-11), 44.1 (C-3), 43.1 (C-4), 33.3 (C-6), 29.8 (C-9), 28.9 (C-5), 26.1 (C(CH$_3$)$_3$), 18.5 (C(CH$_3$)$_3$), $\delta$-5.5 (SiCH$_3$), $\delta$-5.5 (SiCH$_3$); m/z (ESI): 319 [MNa$^+$]; HRMS: calcd. for C$_{17}$H$_{32}$NaO$_2$Si, 319.2064. Found: [MNa$^+$], 319.2063 (0.2 ppm error).


To a stirred solution of Et$_2$Zn (170 µL, 1 M in hexanes, 0.170 mmol) in CH$_2$Cl$_2$ (1 mL) at 0 °C was added diiodomethane (27 µL, 0.340 mmol). This was stirred for 10 min before the addition of 139 (25 mg, 0.0850 mmol) in CH$_2$Cl$_2$ (1 mL) via cannula. The reaction was stirred at 0 °C for 30 min before it was quenched by the addition of sat. NH$_4$Cl (aq.) (5 mL). The organic layer was separated and the aqueous layer extracted with further portions of CH$_2$Cl$_2$ (2 × 10 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et$_2$O (15:1) to afford the title compound 191 as a colourless oil (8 mg, 32%) and 192 as a colourless oil (7 mg, 27%); 1H NMR (400 MHz; CDCl$_3$) $\delta$ 5.25–5.15 (2H, m, H-7 & H-8), 3.82–3.73 (3H, m, H-10 & H-11), 3.04 (1H, d, J H-10b or H-11b), 2.37–2.31 (1H, m, H-9), 1.80–1.74 (1H, m, H-3a), 1.57–1.43 (1H, m, H-3b), 1.06 (3H, s, H-5), 0.98 (3H,
s, H-6), 0.92 (9H, s, Si(CH$_3$)$_3$), 0.90–0.88 (1H, m, H-12a), 0.82–0.77 (2H, m, H-12b & H2), 0.10 (3H, s, SiCH$_3$), 0.10 (3H, s, SiCH$_3$); $^{13}$C NMR (101 MHz; CDCl$_3$) $\delta$ 140.9 (C-8), 125.0 (C-7), 68.9 (C-10 or C-11), 65.3 (C-10 or C-11), 48.2 (C-9), 42.7 (C-2), 40.2 (C-3), 39.0 (C-4), 32.3 (C-6), 30.7 (C-1), 27.7 (C-5), 25.9 (C(CH$_3$)$_3$), 19.3 (C-12), 18.3 (C(CH$_3$)$_3$), –5.3 (SiCH$_3$), –5.3 (SiCH$_3$); m/z (ESI): 333 [MNa$^+$]; HRMS: calcd. for C$_{18}$H$_{34}$NaO$_2$Si, 333.2220. Found: [MNa$^+$], 333.2220 (0.0 ppm error);

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R$_f$ (4:1 pet. ether:Et$_2$O) 0.16; $\nu$$_{max}$ (thin film)/cm$^{-1}$ 3354, 2910, 2884, 2814; $^1$H NMR $\delta$ 5.38–5.28 (2H, m, H-7 & H-8), 3.54–3.50 (2H, m, H-10), 3.36 (1H, dd, J 10.0, 8.5, H-11a), 3.06 (1H, d, J 10.0, H-11b), 2.93–2.88 (1H, m, H-9), 1.84 (1H, ddd, J 14.0, 5.0, 2.0, H-3a), 1.44–1.22 (2H, m, H-3b & H-2), 1.09 (3H, s, H-5), 0.93 (3H, s, H-6), 0.89 (9H, s, Si(CH$_3$)$_3$), 0.63–0.53 (2H, m, H-12), 0.06 (6H, s, SiCH$_3$); $^{13}$C NMR (101 MHz; CDCl$_3$) $\delta$ 142.5 (C-8), 124.7 (C-7), 77.4 (C-9) 73.5 (C-11), 66.5 (C-10), 42.5 (C-2), 41.4 (C-3), 38.0 (C-4), 32.7 (C-5), 28.4 (C-1), 27.0 (C-6), 26.0 (C(CH$_3$)$_3$), 18.3 (C(CH$_3$)$_3$), 16.1 (C-12), –5.2 (SiCH$_3$); m/z (ESI): 333 [MNa$^+$]; HRMS: calcd. for C$_{18}$H$_{34}$NaO$_2$Si, 333.2220. Found: [MNa$^+$], 333.2222 (0.3 ppm error).

(±)-(1R,2R,7R)-5,5-Dimethylbicyclo[5.1.0]oct-3-ene-1,2-diyl|dimethanol (194)

To a solution of 192 (6 mg, 0.0195 mmol) in THF (0.5 mL) at 0 °C was added TBAF (23 µL, 1 M in THF, 0.0230 mmol). After 2 h the reaction mixture was diluted with Et$_2$O (5 mL) and washed with sat. NH$_4$Cl (aq.) (2 mL), the organic layer separated and the aqueous layer extracted with further portions of Et$_2$O (2 × 5 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure to afford the title compound 194 as a colourless oil (4 mg, 100%) which was assigned tentatively using $^1$H NMR spectroscopy and HRMS; R$_f$ (EtOAc) 0.47; $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 5.42–5.29 (2H, m, H-8 & H-7), 3.60–3.55 (2H, m, H-10a & H-11a), 3.30 (1H, dd, J 10.5, 9.0, H-10b or H-11b), 3.12 (1H, d, J 11.0, H-10b or H-11b), 2.99–2.90 (1H, m, H-9), 1.86 (1H, ddd, J 14.5, 6.5, 1.5, H-3a), 1.34 (1H, ddd, J 14.5, 12.0, H-3b), 1.09 (3H, s, H-6), 0.94 (3H, s, H-5), 0.93–0.84 (1H, m, H-2), 0.67 (1H, dd, J 9.0, 5.0, H-12a), 0.59 (1H, dd, J 5.0, 5.0, H-12b); m/z (ESI): 219
[MNa⁺]; HRMS: calcd. for C₁₂H₂₀NaO₂, 219.1356. Found: [MNa⁺], 219.1358 (−1.0 ppm error).

(±)-tert-Butyl[(1R,5,5-dimethyl-2-[(tripropan-2-ylsilyl)oxy]methyl)cyclohept-2,6-dien-1-yl]methoxy]dimethylsilane (202)

To a stirred solution of 190 (25 mg, 0.0850 mmol) in CH₂Cl₂ (1.5 mL) at RT was added lutidine (25 µL, 0.213 mmol) and TIPSOTf (30 µL, 0.111 mmol). After 2 h the reaction was quenched by the addition of water (2 mL). The organic layer was separated and the aqueous layer extracted with further portions of CH₂Cl₂ (2 × 5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et₂O (40:1) to afford the title compound 202 as a colourless oil (25 mg, 66%) which was assigned tentatively using ¹H NMR spectroscopy and HRMS; Rᵣ (40:1 pet. ether:Et₂O) 0.36; ¹H NMR (400 MHz; CDCl₃) δ 5.85–5.79 (1H, m, H-2), 5.43–5.38 (2H, m, H-7 & H-8), 4.18–4.06 (2H, m, H-11), 3.77 (1H, dd, J 9.5, 7.0, H-10a), 3.71 (1H, dd, J 9.5, 7.0, H-10b), 2.78–2.70 (1H, m, H-9), 2.52 (1H, dd, J 14.0, 5.5, H-3a), 1.88 (1H, dd, J 14.0, 8.5, H-3b), 1.06 (18H, s, CH(CH₃)₃), 1.05 (3H, s, CH(CH₃)₂), 0.99 (3H, s, H-5), 0.98 (3H, s, H-6), 0.89 (9H, s, Si(CH₃)₃), 0.04 (3H, s, SiCH₃), 0.04 (3H, s, SiCH₃); m/z (ESI): 475 [MNa⁺]; HRMS: calcd. for C₂₆H₅₂NaO₂Si₂, 475.3404. Found: [MNa⁺], 475.3409 (2.1 ppm error).

(±)-(7R)-7-([(tert-Butyl(dimethyl)silyl)oxy]methyl)-4,4-dimethylcyclohepta-1,5-dien-1-yl)methyl acetate (204)

To a stirred solution of 190 (25 mg, 0.0850 mmol) in CH₂Cl₂ (1 mL) at RT was added triethylamine (23 µL, 0.168 mmol), acetic anhydride (16 µL, 0.168 mmol) and DMAP (2 mg, 0.0170 mmol). After 30 min the reaction was quenched by the addition of sat. NH₄Cl (aq.) (2 mL). The organic layer was
separated and the aqueous layer extracted with further portions of CH₂Cl₂ (2 x 5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to afford the title compound 204 as a colourless oil (29 mg, 100%), which was assigned tentatively using ¹H NMR spectroscopy and HRMS; Rₜ (4:1 pet. ether:Et₂O) 0.77; ¹H NMR (400 MHz; CDCl₃) δ 5.87–5.81 (1H, m, H-2), 5.46–5.41 (1H, m, H-7), 5.38 (1H, dd, J 12.0, 6.0, H-8), 4.55–4.45 (2H, m, H-10), 3.77 (1H, dd, J 9.50, 7.5, H-11a), 3.71 (1H, dd, J 9.5, 7.0, H-11b), 3.14–3.06 (1H, m, H-9), 2.52 (1H, dd, J 14.0, 6.5, H-3a), 2.06 (3H, s, OCOC₃H₃), 1.88 (1H, ddd, J 14.0, 9.0, 1.5, H-3b), 1.00 (6H, s, H-5 & H-6), 0.88 (9H, s, SiC(CH₃)₃), 0.04 (3H, s, SiCH₃); m/z (ESI): 361 [MNa⁺]; HRMS: calcd. for C₁₉H₃₄NaO₃Si, 361.2175. Found: [MNa⁺], 361.2179 (1.3 ppm error).

(3aR,8aS)-6,6-Dimethyl-3,3a,6,8a-tetrahydro-1H-cyclohepta[c]furan (209) & {[(1R,2S)-5,5-Dimethylcyclohepta-3,6-diene-1,2-diyl|bis(methanediyloxy)|bis[tert-butyl(dimethyl)silane] (164)

To a stirred solution of 163 (100 mg, 0.340 mmol) in CH₂Cl₂ (3 mL) at RT was added triphenylphosphine (134 mg, 0.510 mmol), imidazole (35 mg, 0.510 mmol) and iodine (52 mg, 0.408 mmol). After stirring for 50 min, Na₂S₂O₃ (aq.) (5 mL) was added, the organic layer was separated and the aqueous layer extracted with portions of CH₂Cl₂ (2 x 10 mL). The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et₂O (30:1) to afford the title compound 164 as a colourless oil (31 mg, 22%) and 209 as a colourless oil (53 mg, 38%) 209 Rₜ (15:1 pet. ether:Et₂O) 0.32; ¹H NMR (400 MHz; CDCl₃) δ 5.49 (2H, d, J 12.0, H-4), 5.32 (2H, dd, J 12.0, 4.0, H-3), 3.93 (2H, dd, J 7.5, 6.5, H-1a), 3.67 (2H, dd, J 7.5, 6.0, H-1b), 3.07–2.99 (2H, m, H-2), 1.20 (3H, s, H-6), 1.12 (3H, s, H-7); ¹³C NMR (101 MHz; CDCl₃) δ 140.9 (C-4), 125.4 (C-3), 74.6 (C-1), 42.5 (C-2), 38.2 (C-5), 32.7 (C-6), 30.0 (C-7); m/z (ESI): 165 [MH⁺]; HRMS: calcd. for C₁₉H₁₉O, 165.1274. Found: [MH⁺], 165.1280 (3.5 ppm error).

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(±)-(15S,7R)-7-[[tert-Butyl(diphenyl)silyloxy]methyl]-4,4-dimethylcyclohepta-2,5-dien-1-yl]methanol (210)

To a solution of 162 (200 mg, 1.10 mmol) in THF (3 mL) was added NaH (53 mg, 1.32 mmol, 60% dispersion in mineral oil) at 0 °C and the reaction mixture stirred for 45 mins before the addition of TBDPSCl (285 µL, 1.10 mmol). After 45 mins the reaction was quenched with K$_2$CO$_3$ (aq.) (10 mL) followed by Et$_2$O (20 mL). The organic layer was separated and the aqueous layer extracted with further portions of Et$_2$O (2 × 20 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (40:1 → 1:1) to afford the title compound 210 as a colourless oil (440 mg, 95%); R$_f$ (4:1 pet. ether:EtOAc) 0.32; $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3301, 3024, 3003, 2964, 2913, 2887, 2815; $^1$H NMR (400 MHz; CDCl$_3$) δ 7.70–7.64 (4H, m, Ar-H), 7.48–7.35 (6H, m, Ar-H), 5.61 (1H, dd, J 11.5, 6.0, H-2 or H-8), 5.44 (1H, d, J 11.5, H-3 or H-7), 5.35 (1H, dd, J 12.0, 6.0, H-2 or H-8), 5.30 (1H, d, J 12.0, H-3 or H-7), 3.77 (1H, dd, J 10.5, 8.5, H-10a or H-11a), 3.74 (1H, dd, J 11.5, 6.5, H-10a or H-11a), 3.68 (1H, dd, J 11.5, 4.5, H-10b or H-11b), 3.55 (1H, dd, J 10.5, 4.0, H-10b or H-11b), 2.93–2.84 (1H, m, H-1 or H-9), 2.77–2.70 (1H, m, H-1 or H-9), 1.11 (3H, s, H-5), 1.07 (9H, s, SiC(CH$_3$)$_3$), 1.03 (3H, s, H-6); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 139.9 (C-8 or C-2), 139.9 (C-7 or C-3), 135.8 (Ar-CH), 135.7 (Ar-CH), 134.9 (C-8 or C-2), 133.0 (Ar-C), 132.9 (Ar-C), 130.0 (Ar-CH), 129.8 (C-7 or C-3), 127.9 (Ar-CH), 127.9 (Ar-CH), 66.0 (C-11 or C-10), 65.0 (C-11 or C-10), 43.1 (C-9 or C-1), 39.7 (C-4), 32.9 (C-5), 29.7 (C-6), 27.0 (SiC(CH$_3$)$_3$), 26.7 (C-9 or C-1), 19.3 (SiC(CH$_3$)$_3$). m/z (ESI): 443 [MNa$^+$]; HRMS: calcd. for C$_{27}$H$_{36}$NaO$_2$Si, 443.2377. Found: [MNa$^+$], 443.2357 (4.4 ppm error).
(±)-[(1S,7R)-7-[(tert-Butyl(diphenyl)silyl)oxy]methyl]-4,4-dimethylcyclohepta-2,5-dien-1-yl]methyl methanesulfonate (212)

To a stirred solution of 210 (50 mg, 0.119 mmol) in CH₂Cl₂ (2 mL) at RT was added triethylamine (50 µL, 0.357 mmol) and MsCl (14 µL, 0.179 mmol). After 1.5 h the reaction was quenched by the addition of sat. NH₄Cl (aq.) (5 mL). The organic layer was separated and the aqueous layer extracted with further portions of CH₂Cl₂ (2 × 10 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et₂O (4:1) to afford the title compound 212 as a colourless oil (49 mg, 83%); Rf (4:1 pet. ether:Et₂O) 0.29; *ν*max (thin film)/cm⁻¹ 2967, 2914, 2887, 2850, 2815; ¹H NMR (400 MHz; CDCl₃) δ 7.69–7.63 (4H, m, Ar-H), 7.46–7.35 (6H, m, Ar-H), 5.52 (1H, dd, J 12.0, 5.5, H-2 or H-8), 5.46 (1H, d, J 12.0, H-3 or H-7), 5.37 (1H, d, J 12.0, H-3 or H-7), 5.31 (1H, dd, J 12.0, 5.5, H-2 or H-8), 4.38–4.31 (2H, m, H-11), 3.71 (1H, dd, J 10.5, 9.0, H-10a), 3.60 (1H, dd, J 10.5, 5.5, H-10b), 3.16–3.08 (1H, m, H-1), 2.89 (3H, s, SO₂CH₃), 2.87–2.79 (1H, m, H-9), 1.13 (3H, s, H-5), 1.07 (3H, s, H-6), 1.06 (9H, s, Si(CH₃)₃); ¹³C NMR (101 MHz; CDCl₃) δ 140.8 (C-8 or C-2), 140.2 (C-7 or C-3), 135.7 (Ar-CH), 135.7 (Ar-CH), 135.3 (C-8 or C-2), 134.9 (C-7 or C-3), 133.5 (Ar-CH), 133.5 (Ar-CH), 129.9 (Ar-CH), 129.8 (Ar-CH), 127.9 (Ar-CH), 127.9 (Ar-CH), 72.6 (C-11), 65.1 (C-10), 42.3 (C-1), 40.0 (C-4), 37.3 (SO₂CH₃), 32.6 (C-5), 29.6 (C-6), 27.0 (Si(CH₃)₃), 26.7 (C-9), 19.3 (Si(CH₃)₃). m/z (ESI): 521 [MNa⁺]; HRMS: calcd. for C₂₈H₃₈NaO₄Si, 521.2152. Found: [MNa⁺], 521.2153 (0.1 ppm error).

(±)-[(1R,7S)-7-[(4-Methoxybenzyl)oxy]methyl]-4,4-dimethylcyclohepta-2,5-dien-1-yl]methanol (216)

To a stirred solution of 162 (200 mg, 1.10 mmol) in THF (10 mL) was added NaH (53 mg, 1.32 mmol, 60% dispersion in mineral oil) at 0 °C After 30 min PMBCl (149 µL, 1.10 mmol)
was added and the reaction mixture was warmed to RT. After 2h the reaction was quenched with sat. NH₄Cl (aq.) (10 mL) followed by Et₂O (20 mL). The organic layer was separated and the aqueous layer extracted with further portions of Et₂O (2 × 20 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et₂O (3:1 → 2:1) to afford the title compound 216 as a colourless oil (123 mg, 41%); Rₚ (2:1 pet. ether:Et₂O) 0.34; νmax (thin film)/cm⁻¹ 3349, 2959, 2912, 2858, 2822; ¹H NMR (400 MHz; CDCl₃) δ 7.25 (2H, d, J 9.0, Ar-H), 6.88 (2H, d, J 9.0, Ar-H), 5.88 – 5.48 (2H, m, H-2 & H-8), 5.44 – 5.35 (2H, m, H-3 & H-7), 4.46 (2H, s, C₆H₄CH₂), 3.80 (3H, s, C₆H₄OCH₃), 3.64 (1H, dd, J 11.5, 7.0, H-10a or H-11a), 3.58 (1H, dd, J 9.5, 8.0, H-10a or H-11a), 3.54 (1H, dd, J 11.5, 4.0, H-10b or H-11b), 2.87 – 2.76 (2H, m, H-1 & H-9), 1.13 (3H, s, H-5), 1.07 (3H, s, H-6); ¹³C NMR (101 MHz; CDCl₃) δ 159.5 (Ar-C), 139.9 (C-3 or C-7), 139.7 (C-3 or C-7), 129.7 (Ar-CH), 129.5 (Ar-C), 126.3 (C-2 or C-8), 126.2 (C-2 or C-8), 114.0 (Ar-CH), 73.2 (C₆H₄CH₂), 71.1 (C-10 or C-11), 64.5 (C-10 or C-11), 55.5 (C₆H₄OCH₃), 43.7 (C-1 or C-9), 41.6 (C-1 or C-9), 39.8 (C-4), 32.9 (C-5), 29.7 (C-6); m/z (ESI): 325 [MNa⁺]; HRMS: calcd. for C₁₉H₂₆Na₃O₃, 325.1774. Found: [MNa⁺], 325.1770 (1.1 ppm error).

(±)-(15,7R)-7-([(tert-Butyl(diphenyl)silyl)oxy]methyl)-4,4-dimethylcyclohepta-2,5-diene-1-carbaldehyde (217)

To a stirred solution of 210 (99 mg, 0.235 mmol) in CH₂Cl₂ (5 mL), at 0 °C was added Dess–Martin periodinane (199 mg, 0.470 mmol). The reaction mixture was warmed to RT and allowed to stir for 1 h. It was then diluted with CH₂Cl₂ (15 mL), and quenched with a 1:1 solution of sat. Na₂CO₃ (aq.) and sat. Na₂S₂O₃ (aq.) (30 mL). After vigorous stirring for 30 mins, the organic layer was separated and the aqueous layer extracted with further portions of CH₂Cl₂ (2 × 30 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to afford the title compound 217 as a colourless oil (78 mg, 80%) which was assigned
tentatively using $^1$H NMR spectroscopy; $R_f$ (2:1 pet. ether:Et$_2$O) 0.48; $^1$H NMR (400 MHz; CDCl$_3$) δ 9.76 (1H, s, H-11), 7.69–7.61 (4H, m, Ar-H), 7.47–7.35 (6H, m, Ar-H), 5.94 (1H, dd, J 11.5, 5.0, H-2 or H-8), 5.60 (1H, d, J 11.5, H-3 or H-7), 5.50 (1H, dd, J 12.0, 6.5, H-2 or H-8), 5.37 (1H, d, J 12.0, H-3 or H-7), 3.62 (1H, dd, J 9.5, 9.5, H-10a), 3.43 (1H, dd, J 4.5, 9.5, H-10b), 3.20–3.13 (1H, H-1 or H-9), 1.13 (3H, s, H-5), 1.08 (3H, s, H-6) 1.01 (9H, s, SiC(CH$_3$)$_3$).

$\text{(-)}$-$\text{(E)}$-3-((1S,3R)-3-((tert-Butyldimethylsilyloxy)methyl)-2,2-dimethylcyclopropyl)prop-2-en-1-ol (221)

To a stirred solution of 133 (1.00 g, 3.20 mmol) in CH$_2$Cl$_2$ (30 mL) at $-78$ °C was added DIBAL (12.8 mL, 12.8 mmol, 1M in hexanes). After 10 mins the reaction was warmed to RT and after 30 min the reaction mixture was diluted with CH$_2$Cl$_2$ (50 mL) followed by the careful addition of sat. aq. Rochelle’s salt (30 mL). The mixture was stirred for 2 h after which time, the organic layer was separated and the aqueous layer extracted with further portions of CH$_2$Cl$_2$ (2 × 100 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure to afford the crude compound, which was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (10:1) to afford the title compound 221 as a colourless oil (710 mg, 82%); $R_f$ (10:1 pet. ether:EtOAc) 0.24; $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3346, 2929, 2858; $^1$H NMR (400 MHz; CDCl$_3$) δ 5.83–5.74 (1H, m, H-2), 5.49–5.41 (1H, m, H-3), 4.08 (2H, d, J 6.0, H-1), 3.70–3.66 (2H, m, H-9), 1.37 (1H, t, J 9.5, H-4), 1.10 (3H, s, H-6), 1.08–1.01 (1H, m, H-8), 1.06 (3H, s, H-7), 0.88 (9H, s, SiC(CH$_3$)$_3$), 0.04 (6H, s, SiCH$_3$); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 131.5 (C-3), 130.2 (C-2), 64.1 (C-1), 60.5 (C-9), 32.3 (C-6), 30.0 (C-4 or C-8), 28.9 (C-4 or C-8), 26.1 (SiC(CH$_3$)$_3$), 21.7 (C-5), 18.4 (SiC(CH$_3$)$_3$), 15.6 (C-7), −5.0 (SiCH$_3$), −5.0 (SiCH$_3$); m/z (ESI): 293 [MNa$^+$]; HRMS: calcd. for C$_{15}$H$_{30}$NaO$_2$Si, 293.1907. Found: [MH$^+$], 293.1900 (2.6 ppm error).
(±)-(E)-3-((1S,3R)-3-((tert-Butyldimethylsilyloxy)methyl)-2,2-dimethylcyclopropyl)allyl ethyl carbonate (223)

To a solution of alcohol 221 (420 mg, 1.55 mmol) in CH₂Cl₂ (30 mL) at 0 °C was added DMAP (38 mg, 0.31 mmol) and pyridine (499 µL, 6.2 mmol). This was stirred at 0 °C for 10 min before the addition of ethyl chloroformate (505 mg, 4.65 mmol). The reaction was warmed to RT and after 30 min was quenched with a solution of sat. NH₄CL (aq.) (30 mL). The organic layer was separated and the aqueous layer extracted with further portions of CH₂Cl₂ (2 × 50 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to afford the title compound 223 as a colourless oil which was used in the next step without further purification; Rᵥ (30:1 pet. ether:EtOAc) 0.31; ʋₘₐₓ (thin film)/cm⁻¹ 2954, 2930, 2858, 1745; ¹H NMR (400 MHz; CDCl₃) δ 5.73 (1H, dt, J 15.0, 6.5, H-8), 5.56 (1H, dd, J 15.0, 10.0, H-7), 4.58 (1H, dd, J 13.5, 6.5, H-9a), 4.55 (1H, dd, J 13.5, 6.5, H-9b), 4.18 (2H, q, J 7.0, CH₃C₂H₂O), 3.68 (1H, d, J 7.5 H-1a), 3.67 (1H, d, J 7.5 H-1b), 1.30 (3H, t, J 7.0, C₃H₉CH₂O), 1.11–1.08 (2H, m, H-2 & H-6), 1.10 (3H, s, H-5), 1.07 (3H, s, H-4), 0.88 (9H, s, SiC(CH₃)₃), 0.04 (6H, s, SiCH₃); ¹³C NMR (101 MHz; CDCl₃) δ 155.2 (C=O), 134.3 (C-2), 124.3 (C-7), 68.7 (C-1), 64.0 (C-9), 60.4 (CH₂CH₂O), 32.7 (C-4), 30.1 (C-6 or C-2), 28.9 (C-6 or C-2), 26.1 (SiC(CH₃)₃), 22.1 (C-3), 18.4 (SiC(CH₃)₃), 15.7 (C-5), 14.4 (CH₂CH₂O), −5.0 (SiCH₃), −5.0 (SiCH₃); m/z (ESI): 365 [MNa⁺]; HRMS: calcd. for C₁₈H₃₄NaO₄Si, 365.2119. Found: [MNa⁺], 365.2108 (2.1 ppm error).

(±)-(E)-tert-Butyl 5-((1S,3R)-3-((tert-butyldimethylsilyloxy)methyl)-2,2-dimethylcyclopropyl)-2-ethanoylpent-4-enoate (224)

To a solution of carbonate 223 (1.55 mmol) in degassed THF at 0 °C was added tert-butyl 3-oxobutanoate (308 µL, 1.86 mmol) and
tetrakis(triphenylphosphine)palladium(0) (179 mg, 0.155 mmol). This reaction mixture was warmed to 45 °C and stirred for 1h. It was then concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (30:1) to afford the title compound **224** as a colourless oil (584 mg, 92%) as a mixture of diastereomers in a ratio of ~ 1:1; Rf (30:1 pet. ether:EtOAc) 0.19; \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 2954, 2930, 2858, 1745, 1716; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 5.50–5.40 (1H, m, H-8), 5.29–5.21 (1H, m, H-7), 3.70–3.57 (2H, m, H-1), 3.38–3.32 (1H, m, H-10), 2.53–2.47 (2H, m, H-9), 2.20 (3H, s, H-12), 1.45 (9H, s, C(CH\(_3\))\(_3\)), 1.28 (1H, dt, J 9.0, 1.5, H-2), 1.06 (3H, s, H-5), 1.02 (3H, s, H-4), 1.00–0.96 (1H, m, H-6), 0.88 (9H, s, SiC(CH\(_3\))\(_3\)), 0.04 (6H, s, Si(CH\(_3\))\(_3\)); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)) \( \delta \) 203.3, and 203.3 (C H\(_3\)C=O), 168.7, and 168.7 ((CH\(_3\))\(_3\)CO=O), 129.6, and 129.6 (C-8), 127.1, and 127.0 (C-7), 82.0, and 82.0 (C(CH\(_3\))\(_3\)), 61.2, and 61.1 (C-10), 60.6, and 60.6 (C-1), 31.9, and 31.9 (C-5), 31.8, and 31.7 (C-9), 30.1, and 30.0 (C-6 or C-2), 29.2, and 29.1 (C-6 or C-2), 28.1, and 28.1 (C(CH\(_3\))\(_3\)), 26.1, and 26.1 (SiC(CH\(_3\))\(_3\)), 21.2, and 21.2 (C-3), 18.4, and 18.4 (SiC(CH\(_3\))\(_3\)), 15.7, and 15.7 (C-4), −4.9, and −4.9 (SiCH\(_3\)), −5.0, and −5.0 (SiCH\(_3\)); m/z (ESI): 433 [MNa\(^+\)]; HRMS: calcd. for C\(_{23}\)H\(_{42}\)NaO\(_4\)Si, 433.2745. Found: [MNa\(^+\)], 433.2733 (2.9 ppm error).

(\(\pm\)-(E)-**tert**-Butyl 2-ethanoyl-5-((1S,3R)-3-(hydroxymethyl)-2,2-dimethylecyclopropyl)pent-4-enoate (225)

To a solution of **224** (167 mg, 0.421 mmol) in THF (4 mL) at 0 °C was added TBAF (505 µL, 1 M in THF, 0.505 mmol). After 2 h the reaction mixture was diluted with Et\(_2\)O (5 mL) and washed with sat. NH\(_4\)Cl (aq.) (5 mL), the organic layer separated and the aqueous layer extracted with further portions of Et\(_2\)O (2 × 10 mL). The combined organic extracts were dried (MgSO\(_4\)), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (1:1) to afford the title compound **225** as a colourless oil (86 mg, 72%) as a mixture of diastereomers and
enol/keto tautomers; \( R_f \) (1:1 pet. ether:Et\(_2\)O) 0.24; \( \nu_{\text{max}} \) (thin film)/cm\(^{-1} \) 3444, 2980, 1714; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 5.58–5.24 (2H, m, H-8 & H-7), 3.77–3.47 (2H, m, H-1), 3.41–3.35 (1H, m, H-10), 2.81–2.47 (2H, m, H-9), 2.22, 2.21, 2.20 (3H, s, H-12), 1.47, 1.44 (9H, s, C(C\(_3\)H\(_3\))\(_3\)), 1.30–1.25 (3H, m, \( \text{C} \text{H}_3\text{CH}_2\text{O} \)), 1.17–1.09 (6H, m, tBuO\(_2\)C)

\((\pm)-(4E)-\text{tert-Butyl 2-ethanoyl-5-}((1\text{S},3\text{R})-3-(3-ethoxy-3-oxoprop-1-enyl)-2,2-dimethylecyclopropyl)pent-4-enoate \( \text{(226)} \)

To a stirred solution of \( \text{225} \) (58 mg, 0.198 mmol) in CH\(_2\)Cl\(_2\) (2 mL), at 0 °C was added Dess-Martin periodinane (126 mg, 0.297 mmol). The reaction mixture was warmed to RT and allowed to stir overnight. It was then diluted with CH\(_2\)Cl\(_2\) (5 mL), and quenched with a 1:1 solution of sat. Na\(_2\)CO\(_3\) (aq.) and sat. Na\(_2\)S\(_2\)O\(_3\) (aq.) (3 mL). After vigorous stirring for 30 mins, the organic layer was separated and the aqueous layer extracted with further portions of CH\(_2\)Cl\(_2\) (2 × 10 mL). The combined organic extracts were dried (MgSO\(_4\)), filtered and concentrated under reduced pressure to afford aldehyde \( \text{227} \). This was dissolved in CHCl\(_3\) (5 mL) and (carbethoxymethylene) triphenyl phosphorane (83 mg, 0.238 mmol) was added. After 16 h the solution was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (5:1) to afford the title compound \( \text{226} \) as a colourless oil (52 mg, 72%) as a mixture of diastereomers and enol/keto tautomers; \( R_f \) (5:1 pet. ether:EtOAc) 0.29; \( \nu_{\text{max}} \) (thin film)/cm\(^{-1} \) 2980, 2954, 2930, 1714; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 6.83–6.61 (1H, m, olefinic CH), 6.04–5.77 (1H, m, olefinic CH), 5.58–5.21 (2H, m, olefinic CH), 4.25–4.12 (2H, m, CH\(_3\)CH\(_2\)O), 3.42–3.30 (1H, m, H-11), 2.94–2.43 (2H, m, H-10), 2.23–2.18 (3H, m, H-13), 1.80–1.40 (2H, m, H-3 & H-7), 1.48–1.41 (9H, m, C(CH\(_3\))\(_3\)), 1.30–1.25 (3H, m, CH\(_3\)CH\(_2\)O), 1.17–1.09 (6H, m,
H-5 & H-6); m/z (ESI): 387 [MNa⁺]; HRMS: calcd. for C₂₁H₃₂NaO₅, 387.2142. Found: [MNa⁺], 387.2413 (0.1 ppm error). Note that the compound exists as a mixture of diastereoisomers, E/Z isomers and enol/keto tautomers, therefore assignment of the ¹³C NMR spectrum was complex and could not be assigned with confidence.

(±)-(1S,2Z,5Z,7R)-Ethyl 4,4-dimethyl-7-(3-oxobutyl)cyclohepta-2,5-dienecarboxylate (220)

A stirred solution of 226 (1.00 g, 2.74 mmol) in toluene (100 mL) was heated to 100 °C for 16 h. After being cooled to RT the solution was concentrated under reduced pressure. The resulting light yellow oil was dissolved in CH₂Cl₂ (50 mL) and stirred. TFA (2.8 mL) was then added and the reaction mixture was refluxed for a further 16 h before concentrating under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (20:1) to afford the title compound 220 as a colourless oil (369 mg, 51%); Rf (20:1 pet. ether:EtOAc) 0.18; v_{max} (thin film)/cm⁻¹ 2954, 2930, 2858, 1745; ¹H NMR (400 MHz; CDCl₃) δ 5.83 (1H, dd, J 11.5, 6.0, H-2), 5.56 (1H, dd, J 12.0, 7.0, H-8), 5.50 (1H, dt, 11.5, 2.0, H-3), 5.33 (1H, d, 12.0, H-7), 4.15 (2H, q, J 7.0, CH₃CH₂O), 3.67–3.58 (1H, m, H-1), 2.76–2.65 (1H, m, H-9), 2.53–2.35 (2H, m, H-11), 2.11 (3H, s, H-13), 1.79–1.63 (2H, m, H-10), 1.26 (3H, t, J 7.0, CH₂CH₂O), 1.13 (3H, s, H-5), 1.10 (3H, s, H-6); ¹³C NMR (101 MHz; CDCl₃) δ 208.9 (C=O), 173.2 (CH₃CH₂O=), 139.9 (C-3), 139.2 (C-7), 128.7 (C-8), 123.2 (C-2), 60.9 (CH₃CH₂O), 47.4 (C-1), 41.9 (C-11), 39.4 (C-4), 39.1 (C-9), 32.5 (C-5), 29.9 (C-13), 29.5 (C-6), 27.0 (C-10), 14.4 (CH₃CH₂O); m/z (ESI): 287 [MNa⁺]; HRMS: calcd. for C₁₆H₂₄NaO₃, 287.1618. Found: [MNa⁺], 287.1610 (2.0 ppm error).
(±)-(R,1E,5Z)-Ethyl 4,4-dimethyl-7-(3-oxobutyl)cyclohepta-1,5-dienecarboxylate (229)

To a stirred solution of 220 (200 mg, 0.757 mmol) in degassed THF (8 mL) at 0 °C was added DBU (113 µL, 0.757 mmol). The reaction was heated to 60 °C and held at this temperature for 16 h. The reaction was then cooled to RT and the reaction mixture concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (10:1) to afford the title compound 229 as a colourless oil (181 mg, 91%) which was assigned tentatively using 1H NMR spectroscopy; Rf (10:1 pet. ether:EtOAc) 0.38; 1H NMR (400 MHz; CDCl3) δ 7.13 (1H, dd, J 9.5, 6.0, H-2), 5.43–5.36 (2H, m, H-8 & H-7), 4.21–4.15 (2H, m, CH3CH2O), 3.45–3.38 (1H, m, H-9), 2.56–2.38 (2H, m, H-11), 2.13 (3H, s, H-13), 1.92–1.83 (2H, m, H-3), 1.29 (3H, t, J 7.0, CH3CH2O), 1.16–1.10 (2H, m, H-10), 1.05 (3H, s, H-6), 0.98 (3H, s, H-5).

4-((R,2E,6Z)-2-(Hydroxymethyl)-5,5-dimethylcyclohepta-2,6-dienyl)butan-2-ol (232)

To a stirred solution of 229 (84 mg, 0.318 mmol) in CH2Cl2 (3 mL) at −78 °C was added DIBAL (1.27 mL, 1.27 mmol, 1M in hexanes). After 1 h the reaction mixture was diluted with CH2Cl2 (5 mL) followed by the careful addition of MeOH (5 drops). The solution was warmed to RT and sat. aq. Rochelle’s salt (5 mL) was added. It was stirred for 2 h after which time, the organic layer was separated and the aqueous layer extracted with further portions of CH2Cl2 (3 × 10 mL). The combined organic extracts were dried (MgSO4), filtered and concentrated under reduced pressure to afford the crude compound. The major diastereomer was isolated by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (1:1) to afford the title compound 232 as a colourless oil (27 mg, 38%). which was assigned tentatively using 1H NMR spectroscopy; Rf (1:1 pet.
ether:EtOAc) 0.18; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \(\delta\) 5.75 (1H, dd, \(J\) 8.5, 6.5, H-2), 5.43 (1H, ddd, \(J\) 12.0, 6.5, 2.5, H-8), 5.33 (1H, d, \(J\) 12.0, H-7), 4.02–3.98 (2H, m, H-14), 3.85–3.74 (1H, m, H-12), 2.74–2.65 (1H, m, H-9), 2.56–2.50 (1H, m, H-3a), 1.95–1.84 (1H, m, H-3b), 1.82–1.43 (4H, m, H-10 & H-11), 1.20 (3H, d, \(J\) 6.0, H-13), 1.00 (3H, s, H-5), 0.98 (3H, s, H-6).

Cyclohex-2-enylmethanol (236)

\(\text{n-BuLi (1.6 M in hexanes, 200 mL, 320 mmol) was added to a suspension of KOtBu (33.9 g, 302 mmol) in cyclohexene (270 mL, 2.7 mol). The reaction mixture was kept below 15 °C for a period of 2 h, and then allowed to warm to RT over 16 h. The resultant suspension was cooled to 0 °C and (CH}_2\text{O})^n (9.98 g, 332 mmol) was added carefully. The reaction mixture was heated to 60 °C for 3 h, then cooled to 0 °C and quenched with sat. aq. NaHCO}_3 (200 mL). The mixture was extracted with CH\(_2\text{Cl}_2\) (3 \(\times\) 200 mL). The combined organic extracts were washed sequentially with sat. aq. NaHCO}_3 (200 mL) and brine (200 mL), dried and concentrated in vacuo. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et\(_2\)O (1:1) to afford the title compound 236 as a pale yellow oil (25.5 g, 75%); R\(_f\) (1:1 pet. ether:Et\(_2\)O) 0.19; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \(\delta\) 5.77–5.70 (1H, m, olefinic CH), 5.57–5.48 (1H, m, olefinic CH), 3.40 (2H, d, \(J\) 6.5, H-7), 2.25–2.17 (1H, m, H-4), 1.92–1.86 (2H, m, CH\(_2\)), 1.75–1.63 (2H, m, CH\(_2\)), 1.53–1.47 (1H, m, CH\(_a\)), 1.33–1.25 (1H, m, CH\(_b\)). Data in agreement with those reported in the literature.\(^{88}\)

3-(Iodomethyl)cyclohex-1-ene (237)

To a stirred solution of cyclohex-2-enylmethanol 236 (20 g, 178 mmol) in CH\(_2\text{Cl}_2\) (500 mL) at RT was added triphenylphosphine (69.8 g, 267 mmol), imidazole (18.1 g, 267 mmol) and iodine (27.1 g, 214 mmol). After stirring for 50 mins Na\(_2\text{S}_2\text{O}_3\) (aq.) (250 mL) was added, the organic layer was separated and the aqueous layer extracted with further EtOAc (2 \(\times\)
300 mL). The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (30:1) to afford the title compound 237 as a colourless oil (22.9 g, 58%); Rf (1:1 pet. ether:EtOAc) 0.81; 1H NMR (400 MHz; CDCl3) δ 5.82–5.77 (1H, m, olefinic CH), 5.59–5.54 (1H, m, olefinic CH), 3.21–3.10 (2H, m, H-7), 2.40–2.29 (1H, m, H-4), 2.00–1.83 (2H, m, CH2), 1.76–1.69 (2H, m, CH2), 1.61–1.50 (1H, m, CHa), 1.44–1.33 (1H, m, CHb); Data in agreement with those reported in the literature.89

tert-Butyl 2-(cyclohex-2-enylmethyl)-3-oxobutanoate (238)  

To a stirring suspension of NaH (1.00 g, 26.9 mmol) in THF (135 mL) at 0 °C was added tert-butyl 3-oxobutanoate (3.62 mL, 22.5 mmol). 237 (5 g, 22.5 mmol) in THF (135 mL) was added to the reaction mixture over 20 minutes before warming to RT over 1 h and heating for 16 h at 70 °C. The reaction was diluted with Et2O (500 mL), quenched with sat. NH4Cl (aq.) (300 mL) and the organic layer separated. The aqueous layer was extracted with further portions of Et2O (2 x 200 mL). The combined organic extracts were dried (MgSO4), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (40:1) to afford the title compound 238 as a colourless oil and inseperable mixture of 2 diastereomers 238a & 238b in a ratio ~ 1:1 (3.86 mg, 68%); Rf (20:1 pet. ether:EtOAc) 0.30; vmax (thin film)/cm−1 2968, 2932, 2884, 1712, 1689; 1H NMR (400 MHz; CDCl3) δ 5.76–5.66 (1H, m, H-6A+B), 5.58–5.48 (1H, m, H-5A+B), 3.50–3.41 (1H, m, H-8A+B), 2.22 (3H, s, H-10A), 2.22 (3H, s, H-10B), 2.08–2.00 (1H, m, H-4A+B), 1.99–1.93 (2H, m, CH2A+B), 1.93–1.67 (4H, m, 2 x CH2A+B), 1.46 (9H, s, C(CH3)2A), 1.46 (9H, s, C(CH3)2B), 1.30–1.13 (2H, m, CH2A+B); 13C NMR (101 MHz; CDCl3) δ 203.8 (C=Oa), 203.8 (C=Ob), 169.3 (t-BuOC=Oa), 169.3 (t-BuOC=Ob), 130.7 (C-5a), 130.7 (C-5b), 128.2 (C-6a), 128.1 (C-6b), 82.0 (C(CH3)2A), 82.0 (C(CH3)2B) 58.7 (C-8a), 58.7 (C-8b), 34.4 (C-7A), 34.4 (C-7B), 33.1 (C-4A), 33.1 (C-4B), 29.0 (CH2A), 28.7 (CH2B), 28.0 (C(CH3)2A), 28.0 (C(CH3)2B), 25.4 (CH2A), 25.3 (CH2B), 21.2 (CH2A), 21.2 (CH2B);
m/z (ESI): 275 [MNa⁺]; HRMS (ESI): calcd. for C₁₅H₂₄NaO₃, 275.1618 Found: [MNa⁺], 275.1606 (3.5 ppm error).

4-(Cyclohex-2-enyl)butan-2-one (239)

To a stirred solution of 238 (1.00 g, 3.96 mmol) in benzene (1.5 mL) was added p-TSA (160 mg, 0.802 mmol). This was refluxed for 2.5h before the addition of sat. NaHCO₃ (aq.) (50 mL) and Et₂O (50 mL). The organic layer was separated and the aqueous layer extracted with further portions of Et₂O (2 × 50 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to afford the title compound 239 as a colourless oil (518 mg, 86%); Rf (20:1 pet. ether:Et₂O) 0.28; νₘₐₓ (thin film)/cm⁻¹ 2971, 2884, 2817, 1759, 1670; ¹H NMR (400 MHz; CDCl₃) δ 5.72–5.66 (1H, m, H-6), 5.52 (1H, dd, J 10.0, 2.0, H-5), 2.47 (2H, t, J 8.0, H-8) 2.15 (3H, s, H-10), 2.10–2.02 (1H, m, H-4), 2.00–1.92 (2H, m, CH₂), 1.83–1.46 (4H, m, 2 × CH₃), 1.30–1.14 (2H, m, CH₂); ¹³C NMR (101 MHz; CDCl₃) δ 208.9 (C-9), 131.1 (C-5), 127.7 (C-6), 41.2 (C-8), 34.7 (C-4), 30.1 (C-10), 30.0 (CH₂), 28.8 (CH₂), 25.4 (CH₂), 21.4 (CH₂); m/z (ESI): 175 [MNa⁺]; HRMS: calcd. for C₁₀H₁₀NaO₂, 175.1093 Found: [MNa⁺], 175.1094 (1.6 ppm error).

Samarium diiodide solution in THF (0.1 M)

To an oven dried RBF, equipped with a Teflon-coated magnetic stir bar, was added samarium metal (1.65 g, 11.0 mmol). This was left stirring at medium to high speed under a positive pressure of argon for 24 h. THF (45 mL) was added, followed by iodine (1.40 g, 5.5 mmol) dissolved in THF (10 mL). The reaction flask was heated at 60 °C for 18 h. The stirring was turned off and the solution of SmI₂ (0.1 M) was allowed to settle for 2 h.
**tert-Butyl 1-hydroxy-1-methyloctahydro-1H-indene-2-carboxylate (241)**

To a solution of ester 238 (42 mg, 0.166 mmol), t-BuOH (32 µL, 0.332 mmol), HMPA (1.01 mL, 5.81 mmol) in THF (37 mL) at −78 °C, was added SmI\(_2\) (4.9 mL, 0.1 M in THF, 0.498 mmol) dropwise. The reaction was stirred for 10 minutes before the addition of sat. aq. NaHCO\(_3\) (50 mL). The mixture was extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried (MgSO\(_4\)) and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (10:1) to afford the title compound 241 as two isolated diastereomers 241a and 241b in a ratio of 1:0.8 (10 mg, 24%) and (8 mg, 19%); 241a; \(^1\)H NMR (400 MHz; CDCl\(_3\)) δ 2.7 (1H, t, J 9.0, H-6), 2.52–2.37 (1H, m, H-8) 2.16–2.04 (1H, m, H-4), 2.00–1.90 (1H, br s, O\(_\text{H}\)), 1.86–1.76 (1H, m, CH\(_3\)) 1.75–1.55 (5H, m, CH\(_3\)), 1.46 (9H, s, C(CH\(_3\))\(_3\)), 1.52–1.33 (2H, m, CH\(_2\)), 1.25 (3H, s, H-10), 1.19–1.06 (2H, m, CH\(_2\)); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)) δ 173.9 (C=O), 84.1 (C(CH\(_3\))\(_3\)), 80.7 (C-7), 57.5 (C-6), 51.6 (C-8), 35.3 (C-4), 30.6 (CH\(_2\)), 28.3 (C(CH\(_3\))\(_3\)), 26.9 (CH\(_2\)), 25.1 (CH\(_2\)), 22.7 (CH\(_2\)), 22.3 (C-10), 20.9 (CH\(_2\)); m/z (ESI): 277 [MNa\(^+\)]; HRMS: calcd. for C\(_{15}\)H\(_{26}\)NaO\(_3\), 277.1774 Found: [MNa\(^+\)], 277.1772 (0.6 ppm error); 241b; \(^1\)H NMR (400 MHz; CDCl\(_3\)) δ 3.39 (1H, s, O\(_\text{H}\)), 2.77 (1H, dd, J 11.5, 6.5, H-6), 2.04–2.1.76 (4H, m, H-8 & H-4 & CH\(_3\)), 1.71–1.56 (6H, m, CH\(_3\)), 1.47 (9H, s, C(CH\(_3\))\(_3\)), 1.29 (3H, s, H-10), 1.28–0.70 (2H, m, CH\(_2\)), \(^{13}\)C NMR (101 MHz; CDCl\(_3\)) δ 175.1 (C=O), 83.1 (C(CH\(_3\))\(_3\)), 81.2 (C-7), 58.6 (C-6 or C-8), 51.1 (C-6 or C-8), 35.2 (C-4), 30.0 (CH\(_2\)), 28.3 (C(CH\(_3\))\(_3\)), 26.7 (CH\(_2\)), 25.0 (CH\(_2\)), 25.0 (CH\(_2\)), 23.3 (C-10), 20.7 (CH\(_2\)); m/z (ESI): 277 [MNa\(^+\)]; HRMS: calcd. for C\(_{15}\)H\(_{26}\)NaO\(_3\), 277.1774 Found: [MNa\(^+\)], 277.1767 (0.4 ppm error).

### 7.5 Procedures & Compound Characterisation (Chapter 5)

(±)-Ethyl (2E)-3-[(1S,3R)-3-formyl-2,2-dimethylcyclopropyl]prop-2-enolate (253)

To a stirred solution of 131 (259 mg, 1.31 mmol) in CHCl\(_3\) (13 mL) was added manganese (IV) dioxide (1.13 g, 13.1
mmol) and 4Å molecular sieves (1.13 g). After 16 h the suspension was filtered through Celite, and washed with CHCl₃ (50 mL). The filtrate was concentrated under reduced pressure to give the crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (5:1) to afford the title compound 253 as a colourless oil (183 mg, 72%). Rₛ (5:1 pet. ether:EtOAc) 0.19; νₘₐₓ (thin film)/cm⁻¹ 2935, 2915, 2888, 1688, 1617; ¹H NMR (400 MHz; CDCl₃) δ 9.62 (1H, d, J 5.0, H-1), 7.19 (1H, dd, J 15.5, 10.5, H-7), 5.99 (1H, d, J 15.5, H-8), 4.17 (2H, q, J 7.0, OCH₂CH₃), 2.14 (1H, dd, J 10.5, 8.5, H-6), 2.07 (1H, dd, J 8.5, 5.0, H-2), 1.40 (3H, s, H-4), 1.26 (3H, t, J 7.0, OCH₂CH₃), 1.25 (3H, s, H-5); ¹³C NMR (101 MHz; CDCl₃) δ 199.5 (C-1), 166.0 (CH₃CH₂O), 142.9 (C-7), 123.6 (C-8), 60.4 (CH₃CH₂O), 43.2 (C-2), 38.7 (C-6), 32.4 (C-3), 28.6 (C-5), 15.7 (C-4), 14.4 (CH₃CH₂O); m/z (ESI) 219 [MNa⁺]; HRMS: calcd. for C₁₁H₁₆NaO₃, 219.0992. Found: [MNa⁺], 219.0991 (0.5 ppm error).

(±)-(E)-ethyl 3-((1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropyl)prop-2-enoate (256)

To a stirring solution of aldehyde 253 (2.04 g, 10.4 mmol) in CH₂Cl₂ (100 mL) at 0 °C was added PPh₃ (15.0 g, 57.2 mmol) and CBr₄ (5.17 g, 15.6 mmol). After 20 min the reaction mixture was filtered through a silica pad and washed through with Et₂O (50 mL). The filtrate was concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (60:1 → 40:1) to afford the title compound 256 as a colourless oil (1.76 g, 48%). Rₛ (10:1 pet. ether:EtOAc) 0.44; νₘₐₓ (thin film)/cm⁻¹ 2934, 1712, 1638; ¹H NMR (400 MHz; CDCl₃) δ 6.67 (1H, dd, J 15.0, 10.5, H-2), 6.27 (1H, d, J 8.0, H-8), 5.96 (1H, d, J 15.0, H-1), 4.17 (2H, q, J 7.0, CH₃CH₂O), 1.89–1.77 (2H, m, H-3 & H-7), 1.27 (3H, t, J 7.0, CH₃CH₂O), 1.20 (3H, s, H-6), 1.17 (3H, s, H-5); ¹³C NMR (101 MHz; CDCl₃) δ 166.2 (C=O), 145.5 (C-2), 134.1 (C-7), 122.9 (C-1), 90.6 (C-9), 60.3 (CH₃CH₂O), 36.7 (C-3 or C-7), 34.1 (C-3 or C-7), 28.3 (C-5) 27.6 (C-4), 16.9 (C-6), 14.4
(±)-(E)-3-(((1R,3R)-3-(2,2-Dibromovinyl)-2,2-dimethylcyclopropyl)prop-2-en-1-ol (259)

To a stirred solution of 256 (50 mg, 0.142 mmol) in CH2Cl2 (2 mL) at −78 °C was added DIBAL (0.43 mL, 0.426 mmol, 1M in hexanes). After 1 h the reaction mixture was diluted with CH2Cl2 (5 mL) followed by the careful addition of MeOH (2 drops). The solution was warmed to RT and sat. aq. Rochelle’s salt (2 mL) was added. It was stirred for 2 h after which time, the organic layer was separated and the aqueous layer extracted with further portions of CH2Cl2 (3 × 5 mL). The combined organic extracts were dried (MgSO4), filtered and concentrated under reduced pressure to afford the crude compound, which was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (20:1) to afford the title compound 259 as a colourless oil (32 mg, 74%) which was assigned tentatively using 1H NMR spectroscopy and HRMS; Rf (10:1 pet. ether:EtOAc) 0.34; 1H NMR (400 MHz; CDCl3) δ 6.20 (1H, d, J 8.5, H-9), 5.83 (1H, dt, J 15.5, 6.5, H-2), 5.43 (1H, ddt, J 15.5, 9.0, 1.5 H-3), 4.14 (2H, dd, J 6.5, 1.5, H-1), 1.32–1.04 (2H, m, H-4 & H-8), 1.17 (3H, s, H-6), 1.09 (3H, s, H-7); HRMS: calcd. for C10H14Br2NaO2, 330.9309. Found: [MNa+] 330.9305 (0.3 ppm error).

(±)-tert-Butyl(((1S,3R)-2,2-dimethyl-3-((E)-3-(triisopropylsilyloxy)prop-1-enyl)cyclopropyl)methoxy)dimethylsilane (261)

To a stirring solution of alcohol 221 (594 mg, 2.01 mmol) at 0 °C in CH2Cl2 (20 mL), was added lutidine (0.698 mL, 6.03 mmol) and TIPS sulfonate (616 mg, 2.01 mmol). The reaction was warmed to RT and stirred for 10 min. The reaction mixture was diluted with CH2Cl2 (20 mL) and washed with sat. NH4Cl (aq.) (10 mL),
the organic layer separated and the aqueous layer extracted with further portions of CH$_2$Cl$_2$ (2 × 20 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (60:1) to afford the title compound 261 as a colourless oil (790 mg, 92%); R$_f$ (60:1 pet. ether:EtOAc) 0.27; $\nu$$_{\max}$ (thin film)/cm$^{-1}$ 2942, 2864; $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 5.68 (1H, dt, J 15.0, 5.0, H-2), 5.46 (1H, ddt, J 15.0, 10.0, 1.5, H-3), 4.20 (2H, dd, J 5.0, 1.5, H-1), 3.73 (1H, dd, J 11.0, 6.0, H-9a), 3.61 (1H, dd, J 11.0, 8.5, H-9b), 1.11–1.02 (2H, m, H-4 & H-8), 1.09 (3H, s, H-6), 1.07 (18H, s, SiCH(CH$_3$)$_2$), 1.06 (3H, s, H-7), 1.05 (3H, s, SiCH(CH$_3$)$_2$), 0.89 (9H, s, Si(C(H$_3$)$_3$)$_2$, 0.04 (6H, s, SiCH$_3$); $^{13}$C NMR (101 MHz; CDCl$_3$) $\delta$ 130.5 (C-3), 126.8 (C-2), 64.1 (C-9), 60.7 (C-1), 32.1 (C-4 or C-8), 30.0 (C-4 or C-8), 26.1 (SiC(CH$_3$)$_3$), 26.1 (C-6), 23.6 (SiCH(CH$_3$)$_2$), 21.3 (C-5), 18.1 (SiC(CH$_3$)$_3$), 15.6 (C-7), 12.2 (SiCH(CH$_3$)$_2$), −5.0 (SiCH$_3$), −5.0 (SiCH$_3$); m/z (ESI): 449 [MNa$^+$]; HRMS: calcd. for C$_{24}$H$_{50}$NaO$_2$Si$_2$, 449.3242. Found: [MNa$^+$], 449.3248 (1.0 ppm error).

(±)-(E)-3-((1R,3S)-3-(Hydroxymethyl)-2,2-dimethylcyclopropyl)prop-2-en-1-ol (267)

To a solution of 224 (731 mg, 2.70 mmol) in THF (30 mL) at 0 °C was added TBAF (3.24 mL, 1 M in THF, 3.24 mmol). After 2 h the reaction mixture was diluted with Et$_2$O (30 mL) and washed with sat. NH$_4$Cl (aq.) (30 mL), the organic layer separated and the aqueous layer extracted with further portions of Et$_2$O (2 × 30 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (1:1) to afford the title compound 225 as a colourless oil (354 mg, 84%) which was assigned tentatively using $^1$H NMR spectroscopy; R$_f$ (1:1 pet. ether:EtOAc) 0.18; $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 5.84 (1H, dt, J 15.5, 6.0, H-2), 5.51 (1H, ddt, J 15.5, 9.0, 1.5, H-3), 4.12 (2H, dd, J 6.0, 1.5, H-1), 3.77 (1H, dd, J 11.5, 7.5, H-9a), 3.68 (1H, dd, J 11.5, 8.0, H-9b),
1.60–1.49 (1H, m, H-4 or H-8), 1.23–1.15 (1H, m, H-4 or H-8), 1.15 (3H, s, H-6), 1.11 (3H, s, H-7).

(±)-**tert**-Butyl((E)-3-((1R,3S)-3-**((tert-**butyldimethylsilyloxy)methyl)-2,2-dimethylcyclopropyl)allyloxy)dimethylsilane (269)

![Diagram of compound 269]

To a solution of 267 (100 mg, 0.641 mmol) in CH₂Cl₂ (5 mL) was added TBS chloride (96.6 mg, 0.641 mmol) followed by imidazole (52.4 mg, 0.769 mmol). After 2 h the reaction mixture was diluted with CH₂Cl₂ (5 mL) and washed with sat. NH₄Cl (aq.) (5 mL), the organic layer separated and the aqueous layer extracted with further portions of CH₂Cl₂ (2 × 5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to afford a mixture of 267 and the title compound 269 as a yellow oil (178 mg) in a ratio of 3:2 which was assigned tentatively using ¹H NMR spectroscopy; 269; Rᵣ (40:1 pet. ether:EtOAc) 0.22; ¹H NMR (400 MHz; CDCl₃) δ 5.98 (1H, dt, J 15.5, 6.5, H-2), 5.57 (1H, ddt, J 15.5, 9.5, 1.5, H-3), 4.46 (2H, dd, J 6.5, 1.5, H-1), 3.99 (1H, dd, J 10.5, 7.0, H-9a), 3.62 (1H, dd, J 10.5, 7.5, H-9b), 1.50–1.42 (1H, m, H-4 or H-8), 1.19–1.07 (1H, m, H-4 or H-8), 1.13 (3H, s, H-6), 1.10 (3H, s, H-7), 0.98 (9H, s, SiC(CH₃)₃), 0.95 (9H, s, SiC(CH₃)₃), 0.16 (6H, s, SiCH₃), 0.03 (6H, s, SiCH₃).

(±)-**((15R,3R)-3-((Benzyloxy)prop-1-enyl)-2,2-dimethylcyclopropyl)methanol** (270)

![Diagram of compound 270]

To a stirred solution of 221 (500 mg, 1.95 mmol) in THF (20 mL) at 0 °C was added NaH (117 mg, 2.93 mmol, 60% dispersion in mineral oil). This was warmed to RT and allowed to stir for 45 mins. This was re-cooled to 0 °C, benzyl bromide (350 µL, 2.93 mmol) was added and the reaction mixture was allowed to stir at 40 °C for 18 h. The reaction mixture was diluted with Et₂O (20 mL) and washed with sat. NH₄Cl (aq.) (10 mL), the organic layer separated and the aqueous layer extracted with further portions of Et₂O (2 × 20 mL). The combined organic phases
were dried (MgSO$_4$), filtered and concentrated under reduced pressure. The resulting crude product was dissolved in THF (20 mL) and the solution cooled to 0 °C before the addition of TBAF (2.93 mL, 1 M in THF). After 2 h the reaction mixture was diluted with Et$_2$O (20 mL) and washed with sat. NH$_4$Cl (aq.) (10 mL), the organic layer separated and the aqueous layer extracted with further portions of Et$_2$O (2 × 20 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (10:1) to afford the title compound 270 as a colourless oil (307 mg, 64%) which was assigned tentatively using $^1$H NMR spectroscopy; R$_f$ (2:1 pet. ether:EtOAc) 0.57; $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 7.38–7.26 (5H, m, Ar-CH), 5.79 (1H, dt, J 15.0, 6.5, H-3), 5.51 (1H, ddt, J 15.0, 10.0, 1.5, H-4), 4.50 (2H, s, H-1), 3.98 (2H, dd, J 6.5, 1.5, H-2), 3.74 (1H, dd, J 11.5, 7.5, H-10a), 3.67 (1H, dd, J 11.5, 8.0, H-10b), 1.48–1.43 (1H, m, H-5 or H-9), 1.19–1.14 (1H, m, H-5 or H-9), 1.12 (3H, s, H-6), 1.11 (3H, s, H-8).
Appendix I

$^1$H- & $^{13}$C-NMR Spectra for cycloheptadienes 58a, 58b, 88a and 160-164

Diethyl (1R,2S)-cyclohepta-3,6-diene-1,2-dicarboxylate (58a)
Diethyl (±)-(1S,2S)-cyclohepta-3,6-diene-1,2-dicarboxylate (58b)
Diethyl (1R,2S)-5,5-dimethylcyclohepta-3,6-diene-1,2-dicarboxylate (88a)
Dimethyl (1R,2S)-5,5-dimethylcyclohepta-3,6-diene-1,2-dicarboxylate (160)
(±)-(3aR,8aS)-6,6-Dimethyl-3,3a,6,8a-tetrahydro-1H-cyclohepta[c]furan-1-one (161)
((1R,2S)-5,5-Dimethylcyclohepta-3,6-diene-1,2-diyl)dimethanol (162)
(±)-((1R,7S)-7-((tert-Butyldimethylsilyloxy)methyl)-4,4-dimethylcyclohepta-2,5-dienyl)methanol (163)
((1R,2S)-5,5-Dimethylcyclohepta-3,6-diene-1,2-diy1)bis(methylene)bis(oxy)bis(tert-butylidimethylsilane) (164)
The Cope rearrangement of gem-dimethyl substituted divinylcyclopropanes†

Jonathan D. Osler, William P. Unsworth and Richard J. K. Taylor*

The reactivity of a range of substituted divinylcyclopropanes towards the thermal Cope rearrangement has been examined. The effects of gem-dimethyl substitution on the cyclopropane, the alkene geometry, the relative stereochemistry of the cyclopropane and the steric and electronic effects of a range of functional groups were all examined, and the methods developed were used to synthesise a range of functionalised 1,4-cycloheptadienes in high yields.

Introduction

The thermal Cope rearrangement of a divinylcyclopropane was first described by Vogel in 1960 (Scheme 1).1 The rearrangement normally proceeds via a [3,3]-sigmatropic rearrangement, including ring-opening of the strained cyclopropane moiety, leading to the convenient construction of 1,4-cycloheptadiene scaffolds from relatively simple starting materials. Numerous applications of this reaction have since appeared in the literature,2 but in the majority of examples the cyclopropane moiety is substituted only with the two alkene groups involved in the rearrangement.3,4 In this study we compare the reactivity of gem-dimethyl substituted divinylcyclopropanes with their unsubstituted analogues, examining the effects of alkene geometry, the relative stereochemistry of the cyclopropane and the steric and electronic effects of a range of functional groups.

Results

Our interest in the Cope rearrangements of divinylcyclopropanes arose as an extension to our work concerning the use of tandem reaction sequences,5 particularly those involving oxidation with manganese(IV) oxide.6 As part of these studies, we reported the tandem oxidation and Wittig reaction of diol 3 that resulted in its conversion into E,E-diester 4a in a high yielding, one-pot process.6d We have since discovered that heating the resulting trans-divinylcyclopropane in xylene at 130 °C results in its smooth conversion into 1,4-cycloheptadiene 5a. The generally accepted mechanism for this process is presented (Scheme 2): a reversible epimerisation of trans-divinylcyclopropane 4a to the corresponding cis-divinylcyclopropane takes place first, which is believed to proceed via a diradical opening of the cyclopropane.6,7 The resulting cis-divinylcyclopropane then undergoes a thermal [3,3]-sigmatropic rearrangement via a boat-like transition state 6.

Our group has also reported improved conditions for the formation of gem-dimethylcyclopropanes using triisopropylsulfoxonium tetrafluoroborate and sodium hydride.8 Thus, using the reported procedure, dimethylcyclopropane 7 was synthesised in high yield and subsequent reduction with lithium aluminium hydride, followed by a tandem oxidation/Wittig reaction resulted in the formation of E,E-diester 9a, as well as a small amount E,Z-diester 9b. We then went on to attempt the Cope reaction of 9a under the same conditions used for the rearrangement of its non-methylated analogue 4a (130 °C in
xylene) but no reaction ensued and the starting material 9a was recovered cleanly upon evaporation of the solvent (Scheme 3).

This result is not altogether unexpected, as a review of the related literature revealed that bulky substituents typically inhibit the Cope rearrangements of divinyl cyclopropanes,\(^5\) by destabilising the previously invoked boat-like transition state (see 11, Scheme 3). For example, it has been observed that substitution on the vinyl groups can retard the reaction significantly,\(^6\) and that this effect is more pronounced for Z-substituents than E-substituents, as the ensuing steric clash with the cyclopropane moiety in the transition state is greater.\(^7\)

Far less is known about the effect of dimethyl substitution on the cyclopropane, however; indeed, to the best of our knowledge, there are no reports that directly compare the Cope rearrangements of divinyl dimethylcyclopropanes with their non-methylated analogues. The closest precedent was reported by Sasaki et al.\(^8\) who found that methyl substitution on the ‘aza-divinylcyclopropanes’ 12 and 13 had a significant effect on their reactivity; the non-methylated variant 12 underwent [3,3]-sigmatropic rearrangement at RT, whereas its methylated analogue 13 required the far greater temperature of 144 °C before rearrangement occurred (Scheme 4).\(^9\)

The preceding example (Scheme 4) demonstrates the profound effect that dimethyl substitution can have on the [3,3]-sigmatropic rearrangements of cyclopropane-containing systems. However, we were surprised to discover that our study is the first direct comparison of the Cope rearrangements of a divinyl dimethylcyclopropane with its non-methylated analogue. In view of this, we decided to investigate how dimethyl substitution affects such rearrangements, by synthesising all of the possible stereoisomers (cis/trans and E,E,E,Z,Z,Z) of the diesters 4 and 9 and examining their propensity to undergo Cope rearrangement.

The syntheses of two of the required diesters (9a, 9b) are described above (Scheme 3) and the Z,Z-diester 9c was readily synthesised from diol 8, via oxidation with manganese(IV) dioxide, followed by a Still–Gennari–Horner–Wadsworth–Emmons (HWE) olefination (Scheme 5).\(^10\)

The synthesis of diester 4a is described in Scheme 2. The Z,Z-diester 4c was prepared from diol 3, via oxidation with manganese(IV) dioxide, followed by a Still–Gennari–modified Horner–Wadsworth–Emmons (HWE) olefination (Scheme 6). The synthesis of E,Z-diester 4b began with mono-TBS protection of diol 3, and was followed by a tandem oxidation/Wittig reaction to install the E-alkene portion, furnishing compound 17. Silyl cleavage using TBAF, manganese(IV) dioxide oxidation and Still–Gennari olefination was then used to install the Z-alkene and complete the synthesis (Scheme 6).

Similair reaction sequences were employed in the synthesis of the dimethyl cis-cyclopropane diesters 9d, 9e, and 9f. To begin, subjecting ethyl chrysanthemate\(^11\) to ozonolysis followed by reduction with lithium aluminium hydride afforded a mixture of cis-cyclopropane diol 19 and its trans-analogue 8, which were readily separated by column chromatography. On all of the cis-cyclopropane diesters synthesised, the alkene components were installed sequentially, to avoid competing intramolecular cyclisation reactions. First, diol 19 was converted into mono-silyl ether 20 under standard conditions\(^12\) and this common intermediate was then converted into either E-alkene 21 using our standard tandem oxidation/Wittig conditions or to Z-alkene 24 via oxidation and Still–Gennari olefination. Silyl cleavage of each of 21 and 24 using HF\(^13\) and oxidation/olefination in the same way completed the syntheses of the required cyclopropane diesters 9d, 9e and 9f (Scheme 7).

The syntheses of the non-methylated cis-cyclopropane diesters 4d, 4e, and 4f were completed using the same sequence
Scheme 7 The synthesis of cis-gem-dimethyldivinylcyclopropanes. Reagents and conditions: (a) O₃, DCM, −78 °C then DMS, 97%. (b) LiAlH₄, THF, 0 °C → RT, 19, 31%, 8, 49%. (c) NaH, TBSCl, THF 0 °C → RT, 84%. (d) MnO₂, Ph₃PCH₂CO₂Et, CHCl₃, reflux, 78% (5:1 E:Z). (e) HF, MeCN, 75% (5:1 E:Z; E-isomer was isolated by chromatography). (f) MnO₂, CHCl₃, reflux, 46%. (g) Ph₃PCH₂CO₂Et, CHCl₃, RT, 47% (>20:1 E:Z; E-isomer was isolated by chromatography). (h) (F₃C)₂CH₂O₂PO(CH₂CO₂Et)₃, KHMDS, 18-crown-6, THF, toluene, 52% (>20:1 Z:Z). (i) MnO₂, CHCl₃, reflux, 55%. (j) (F₃C)₂CH₂O₂PO(CH₂CO₂Et)₃, KHMDS, 18-crown-6, THF, toluene, 53% (>20:1 Z:Z). (k) HF, MeCN, 85%. (l) MnO₂, CHCl₃, reflux, 53%. (m) (F₃C)₂CH₂O₂PO(CH₂CO₂Et)₃, KHMDS, 18-crown-6, THF, toluene, 56% (>20:1 Z:Z).

of steps described in Scheme 7, with the exception that diol 27 was accessed readily via the reduction of cyclic anhydride 26. Otherwise, the syntheses proceeded as above until the final step of the sequence; each of the target substrates 4d, 4e, or 4f spontaneously undergo the Cope rearrangement at room temperature as they are generated, hence cycloheptadiene 5a (from 4d and 4f) and cycloheptadiene 5b (from 4e) were instead obtained (Scheme 8).

Scheme 8 The synthesis of cis-divinylcyclopropanes. Reagents and conditions: (a) LiAlH₄, THF, reflux, 79%. (b) NaH, TBSCl, THF 0 °C → RT, 100%. (c) MnO₂, CHCl₃, reflux 75%. (d) Ph₃PCH₂CO₂Et, CHCl₃, 63% (>10:1 E:Z; E-isomer was isolated by chromatography). (e) HF, MeCN, 94%. (f) MnO₂, CHCl₃, 81%. (g) Ph₃PCH₂CO₂Et, CHCl₃, RT, 79%. (h) (F₃C)₂CH₂O₂PO(CH₂CO₂Et)₃, KHMDS, 18-crown-6, THF, toluene 75%. (i) (F₃C)₂CH₂O₂PO(CH₂CO₂Et)₃, KHMDS, 18-crown-6, THF, toluene 40% (>20:1 Z:Z). (j) HF, MeCN, 97%. (k) MnO₂, CHCl₃, reflux 53%. (l) (F₃C)₂CH₂O₂PO(CH₂CO₂Et)₃, KHMDS, 18-crown-6, THF, toluene 81%.

With the requisite substrates, 4a–f and 9a–f, in hand their propensity to undergo the Cope rearrangement was then examined. Each was stirred in xylene for 17 h at five different temperatures (RT, 40 °C, 70 °C, 100 °C, 130 °C) before removing the solvent in vacuo. The reaction conversion into product was then measured via analysis of the ¹H NMR spectra of the unpurified reaction mixtures as a ratio of product to starting material (Table 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Product</th>
<th>Temperature (°C)</th>
<th>% Conversion (17 h)</th>
</tr>
</thead>
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<td></td>
<td></td>
<td>RT</td>
<td>0 0 0 20 100⁶</td>
</tr>
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<td></td>
<td>40</td>
<td>0 0 0 20 100⁶</td>
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<td>3</td>
<td></td>
<td></td>
<td>70</td>
<td>0 0 0 0 80⁸</td>
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<td>170</td>
<td>0 0 0 0 0⁵</td>
</tr>
</tbody>
</table>

E = CO₂Et. All reactions were carried out as 0.19 mol dm⁻³ solutions in xylene. All reactions were carried out for 17 h. % Conversion was determined via ¹H NMR analysis of the unpurified reaction mixtures as a ratio of product to starting material. Some decomposition was also evident. The divinylcyclopropane could not be isolated at RT; the cycloheptadiene shown was instead isolated during the attempted preparation of the diene. Compound 10a was isolated in 78% yield after flash column chromatography.
A number of conclusions can be drawn from these experiments. First, each of the unsubstituted trans-divinylcyclopropanes 4a, 4b, and 4c underwent the Cope rearrangement only upon heating; a temperature of 130 °C was needed before the trans-E,E and trans-E,Z-substrates 4a and 4b rearranged (Table 1, entries 1–2) whereas only 80% conversion was observed in the more sterically encumbered trans-Z,Z-substrate 4c under identical conditions (Table 1, entry 3). These results are in stark contrast to those of their cis-analogues 4d, 4e, and 4f which rearrange spontaneously at room temperature during their generation (Table 1, entries 4–6). A single stereoisomer of product was observed in each case, with the stereochemical outcomes being consistent with a simple concerted thermal [3,3]-sigmatropic rearrangement in the cis-series of compounds (Table 1, entries 4–6) and trans to cis-isomerisation, followed by a concerted thermal [3,3]-sigmatropic rearrangement, in the trans-series (Table 1, entries 1–3). Thus, the high temperatures necessary to induce rearrangement in the trans-series appear to be associated with overcoming the energy barrier for trans to cis-epimerisation of the cyclopropane and not with the energy of the transition state of the Cope rearrangement itself.

The trans-dimethyl substrates 9a, 9b or 9c did not rearrange, even at 130 °C (Table 1, entries 7–9) and, importantly, epimerisation to the corresponding cis-diesters was also not observed. The cis-E,Z and cis-Z,Z-substrates 9e and 9f also failed to react at 130 °C, with each remaining unchanged, again with no evidence of cyclopropane epimerisation (Table 1, entries 11–12). This suggests that the required transition state (Scheme 3) is too high in energy for the Cope rearrangement to occur under the conditions screened, probably due to steric clashes, but also indicates that the cis/trans-epimerisation occurs less readily than in the non-methylated series of compounds. Interestingly, the cis-E,E-diester 9d was significantly more reactive than either of compounds 9e or 9f; this substrate began to rearrange at temperatures as low as 40 °C and the rearrangement was complete after 17 h at 100 °C (Table 1, entry 10). As before, a single stereoisomer of product was observed with the stereochemical outcome consistent with a concerted thermal [3,3]-sigmatropic rearrangement. Of course, the rearrangement occurred less readily than it did on the analogous desmethyl-cis-E,E substrate 4d (Table 1, entry 4), as was expected, but the fact that it began to rearrange at temperatures as low as 40 °C is significant, given the dearth of examples on other divinyl dimethylcyclopropanes in the literature. This result also sheds light on the reason why our original dimethyl trans-E,E-diester 9a (Table 1, entry 7) failed to react; given that the Cope rearrangement of cis-E,E-diester 9d (Table 1, entry 10) proceeded at temperatures as low as 40 °C, and that there was no evidence of any cis/trans-epimerisation in any of the diesters 9a–9f, this suggests that the reaction of trans-E,E 9a failed at the cyclopropane epimerisation stage, and not because of the high energy of the Cope rearrangement transition state as originally thought.16 In addition, the complete lack of cis to trans-epimerisation in any of the dimethyl substituted diesters 9a–9f is in contrast to the unsubstituted diesters 4a–4c (which must have epimerised otherwise their Cope rearrangements would not have taken place). Thus, we have shown that as well raising the energy of the Cope rearrangement transition state, gem-dimethyl substitution also retards the rate of cyclopropane epimerisation of the trans-cyclopropane substrates screened.

It is clear that gem-dimethyl substitution significantly retards the Cope rearrangements of divinylcyclopropanes. However, it appears that its effect on the trans to cis-isomerisation of the cyclopropane, and not its effect on the [3,3]-sigmatropic rearrangement itself, is the most significant barrier to reactivity. Pleasingly, from a synthetic viewpoint, the isomerisation problem is easily negated by starting from a cis-oriented divinylcyclopropane. To demonstrate this, we then went on to synthesise a range of other dimethyl-cis,E,E-functionalised cyclopropanes (Scheme 9). Cyclopropane 35 was prepared using a tandem oxidation/Wittig reaction, followed by silyl cleavage using HF.15 Another tandem oxidation/Wittig reaction at RT afforded the cis,E,E-functionalised cyclopropane 36. The reduction of 36 using 2 equivalents of DIBAL gave a mixture of monoester 37 and diol 38, and TBS protection of diol 38 using 1.5 equivalent of TBSCI generated a mixture of TBS compounds 39 and 40. Finally, the hydrolysis of diester 36 afforded cyclopropane 41.

We were pleased to find that all of these substrates 36–41 undergo the Cope rearrangement upon heating, generating 1,4-cycloheptadienes in high yields (83–97%, Table 2), with ester, alcohol, silyl ether and carboxylic acid substituents all being well tolerated. The rearrangements do not appear to be significantly affected by electronic effects, a point exemplified by the near-identical reactivity of the electron-deficient ester-substituted divinylcyclopropane 36 and the more electron-rich alcohol-substituted divinylcyclopropane 38 (entries 1 and 3). Note that the product isolated from the Cope rearrangement of substrate 37 (entry 2) was a lactone, presumably, formed via an intramolecular transesterification following the Cope rearrangement.
rearrangement. The size of the substituents appears to be more significant; the addition of one \(39\) and then two \(40\) tert-butyldimethyl silyl groups to diol \(38\) led to a decrease in reactivity in each case (entries 3–5). Diacid-substituted divinylcyclopropane \(41\) reacts more slowly still (entry 6), but this reaction should not be compared directly to the other entries as compound \(41\) was only sparingly soluble in the reaction solvent.

### Conclusions

The rate-retarding effect of gem-dimethyl substitution on the Cope rearrangements of divinylcyclopropanes has been demonstrated directly for the first time. An examination of the effects of alkene geometry and the relative stereochemistry of the cyclopropane have revealed that gem-dimethyl substitution significantly inhibits the trans to cis-isomerisation about the cyclopropyl ring, necessary for rearrangement to occur, relative to unsubstituted analogues. Using the information accrued, a series of ideal substrates (cis-oriented on the cyclopropane with two \(E\)-alkenes) were synthesised and all underwent the desired Cope rearrangement smoothly, affording a range of dimethylated substituted 1,4-cycloheptadienes in high yields. Future work will focus on the application of this methodology in the synthesis of natural products and pharmaceutically important targets.

### Experimental

#### General remarks

Experimental procedures and data for the characterisation of Cope rearrangement products can be found below. Experimental procedures and characterisation data of all other compounds presented in this paper can be found in the ESI.

All reagents were purchased from commercial sources and were used without further purification. Where necessary, solvents were dried on an MBraun SPS solvent purification system. Anhydrous THF was obtained by distillation over sodium/benzophenone. Xylene refers to a mixture of \(ortho\), \(meta\) and \(para\)-xylene and pet. ether refers to light petroleum ether, bp 40–60 °C.

\(^1\)H NMR spectra were recorded on a JEOL ECX 400 (400 MHz) instrument. \(^13\)C NMR spectra were recorded on a JEOL ECX 400 instrument at 100 MHz. Infrared spectra were carried out on a Perkin Elmer FT-IR spectrometer UATR 2 or on a ThermoNicolet IR100 spectrometer (recorded as a thin film between NaCl discs). Mass spectra and accurate mass measurements were recorded on a Bruker Daltonics, Micro-tof spectrometer.

### Table 2  Substrate scope in the Cope rearrangement of substituted gem-dimethyl divinylcyclopropanes

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Product</th>
<th>% Conversion</th>
<th>Isolated yield (%)</th>
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</tbody>
</table>

\(^a\) All reactions were carried out as 0.19 mol dm\(^{-3}\) solutions in xylene. All reactions were carried out for 17 h. % Conversion was determined via analysis of the unpurified reaction mixtures. The isolated yields were obtained from the 100 °C experiments and include purification by column chromatography in each example except for diacid 47.
Diethyl (1R,2S)-cyclohepta-3,6-diene-1,2-dicarboxylate (5a)

Procedure 1: from diethyl (+)-(2E,2′E)-3,3′-(1R,2R)-cyclopropane-1,2-diylbisprop-2-enolate 4a (Scheme 2). A stirred solution of 4a (5.01 g, 21.0 mmol) in xylene (50 mL) was refluxed at 130 °C for 16 h. After being cooled to RT the solution was concentrated under reduced pressure to give a crude product. This was purified by flash column chromatography on silica gel, eluting with pet. ether–EtOAc (20:1) to afford the title compound 5a as a colourless oil (3.96 g, 80%).

Procedure 2: from ethyl (+)-(2E)-3-(15,2S)-2-formylcyclopentyprop-2-enolate 31 (Scheme 8). To a stirred solution of 31 (132 mg, 0.786 mmol) in CHCl₃ (10 mL) at RT was added (carbethoxymethylene)triphenylphosphorane (329 mg, 0.943 mmol). After 16 h the solution was concentrated under reduced pressure at RT and the crude product purified by flash column chromatography on silica gel, eluting with pet. ether–EtOAc (20:1) to afford the title compound 5a as a colourless oil (148 mg, 79%).

Procedure 3: from ethyl (+)-(2Z)-3-(15,2S)-2-formylcyclopropylprop-2-enolate (Scheme 8). To a solution of ethyl [bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (244 mg, 0.735 mmol) in THF (7 mL) was added 18-crown-6 (433 mg, 1.64 mmol). The solution was cooled to 0 °C and KHMDS (1.05 mL, 0.7 M in THF (7 mL) was added 18-crown-6 (433 mg, 1.64 mmol). The solution was quenched with sat. NH₃ solution and the resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether–EtOAc (20:1) to afford the title compound 5a as a colourless oil (3.96 g, 80%).

General procedure for the Cope rearrangement

A solution of divinylcyclopropane in xylene (0.19 mol dm⁻³) was heated to the temperature indicated and held at that temperature for 17 h. The solution was then concentrated in vacuo. The products in Table 2 were purified by flash column chromatography, except for diacid 47.

Diethyl (1R,2S)-5,5-dimethylcyclohepta-3,6-diene-1,2-dicarboxylate (10a)

Synthesised from compound 9d using the general procedure at 100 °C, affording the title compound 10a as a colourless oil (78%); Rₐ (10:1 pet. ether–EtOAc) 0.25; νmax (thin film)/cm⁻¹ 2961, 2920, 1735, 1H NMR (400 MHz; CDCl₃) δ 5.93 (2H, dd, J 12.0, 6.0), 5.30 (2H, d, J 12.0), 4.12–4.14 (4H, m), 3.70 (2H, d, J 6.0), 1.25 (6H, t, J 7.0), 1.16 (3H, s), 1.13 (3H, s); 13C NMR (101 MHz; CDCl₃) δ 172.0, 146.0, 123.2, 61.1, 45.1, 39.1, 32.4, 29.3, 14.3; m/z (ESI): 239 [MNa⁺]; HRMS: calcd for C₁₄H₂₀NaO₄, 289.1410. Found: [MNa⁺], 289.1411 (0.3 ppm error).

Diethyl (1R,2S)-5,5-dimethylcyclohepta-3,6-diene-1,2-dicarboxylate (42)

Synthesised from compound 36 using the general procedure at 100 °C, affording the title compound 42 as a colourless oil (36 mg, 83%); Rₐ (10:1 pet. ether–EtOAc) 0.23; νmax (thin film)/cm⁻¹ 2974, 2924, 1718; 1H NMR (400 MHz; CDCl₃) δ 5.93 (2H, dd, J 11.5, 6.5), 5.50 (2H, d, J 11.5), 3.82 (2H, d, J 6.5), 3.70 (6H, s), 1.16 (3H, s), 1.12 (3H, s); 13C NMR (101 MHz; CDCl₃) δ 172.5, 140.1, 123.1, 52.3, 44.9, 39.1, 32.5, 29.3; m/z (ESI): 239 [MNa⁺]; HRMS: calcd for C₁₄H₂₅NaO₄, 289.1278. Found: [M⁺], 239.1271 (2.4 ppm error).

Diethyl (±)-(15,2S)-cyclohepta-3,6-diene-1,2-dicarboxylate (5b)

From ethyl (+)-(2E)-3-(15,2S)-2-formylcyclopentyprop-2-enolate 31 (Scheme 8). To a solution of ethyl [bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (236 mg, 0.712 mmol) in THF (7 mL) was added 18-crown-6 (420 mg, 1.59 mmol). The solution was cooled to 0 °C and KHMDMS (1.02 mL, 0.7 M in toluene, 0.712 mmol) was added cautiously. After 15 min the solution cooled to ~78 °C and ethyl (+)-(2Z)-3-(15,2S)-2-formylcyclopropylprop-2-enolate was added via cannula. After 2 h the reaction was quenched with sat. NH₃Cl (aq) (10 mL), Et₂O (20 mL) added and the organic layer separated. The aqueous layer was extracted with further portions of Et₂O (2 × 20 mL) and the combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure at RT. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether–EtOAc (20:1) to afford the title compound 5b as a colourless oil (98 mg, 75%). Rₐ (10:1 pet. ether–EtOAc) 0.27; νmax (thin film)/cm⁻¹ 2978, 2926, 2893, 2862, 1710 1H NMR (400 MHz; CDCl₃) δ 5.89–5.81 (2H, m), 5.66–5.60 (2H, m), 4.17 (2H, q, J 7.0), 4.16 (2H, q, J 7.0), 3.83–3.77 (2H, m), 2.91–2.84 (2H, m), 1.26 (6H, t, J 7.0); 13C NMR (101 MHz; CDCl₃) δ 173.3, 130.8, 127.0, 61.1, 45.1, 27.5, 14.3; m/z (ESI) 239 [M⁺]; HRMS: calcd for C₁₃H₁₀O₄, 239.1278. Found: [M⁺], 239.1267 (3.8 ppm error).

Diethyl (±)(3aR,8aS)-6,6-Dimethyl-3,3a,6,8a-tetrahydro-1H-cyclohepta[c]-furan-1-one (43)

Synthesised from compound 37 using the general procedure at 100 °C, affording the title compound 43 as a colourless oil (32 mg, 84%); Rₐ (10:1 pet. ether–EtOAc) 0.25; νmax (thin film)/cm⁻¹ 3528, 2961, 1770; 1H NMR (400 MHz; CDCl₃) δ 5.69–5.59 (2H, m), 5.46 (2H, dd, J 12.0, 4.0), 4.30 (1H, dd, J 8.5, 6.5), 4.12 (1H, dd, J 8.5, 4.5), 3.47–3.39 (2H, m), 1.19 (3H, s), 1.15 (3H, s); 13C NMR (101 MHz; CDCl₃) δ 176.9, 143.5, 142.6, 123.6, 118.6, 73.2, 44.0, 39.7, 38.3, 32.0, 30.2; m/z (ESI): 233 [M⁺Na⁺]; HRMS: calcd for C₁₃H₁₄NaO₄, 201.0891. Found: [M⁺Na⁺], 201.0888 (1.2 ppm error).
Synthesised from compound 38 using the general procedure at 100 °C, affording the title compound 44 as a colourless oil (15 mg, 83%); Rf (EtOAc) 0.43; mp 42–44 °C; \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 3304, 3008, 2952, 2823, 2871; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 5.57 (2H, dd, J 12.0, 6.5), 5.43 (2H, d, J 12.0), 3.72 (2H, dd, J 11.0, 7.0), 3.66 (2H, br s), 3.59 (2H, dd, J 11.0, 3.0), 2.81–2.76 (2H, m), 1.13 (3H, s), 1.08 (3H, s); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)) \( \delta \) 139.9, 126.0, 63.9, 43.8, 39.9, 32.9, 29.8; m/z (ESI): 205 [MNa\(^+\)]; HRMS: calc'd for C\(_{11}\)H\(_{18}\)NaO\(_2\): 205.1195 (0.7 ppm error).

((1R,2S)-5,5-Dimethylcyclohepta-3,6-diene-1,2-diyldimethanol (44)

Notes and references


13 Ethyl chrysanthemate was purchased as a mixture (2:3) of cis and trans-diastereomers.


15 Silyl cleavage of 21, 24, 29, 32 and 34 using TBAF rather than HF led to competing oxy-Michael addition.

16 Otherwise the Cope rearrangement would have taken place, as observed when cis-E,E-9d was heated at this, and indeed lower, temperature (Table 1, entry 10).
**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Ac</td>
<td>acetate</td>
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<tr>
<td>aq</td>
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<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
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<tr>
<td>br</td>
<td>broad (NMR)</td>
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<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>d</td>
<td>doublet (NMR)</td>
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<tr>
<td>δ</td>
<td>chemical shift</td>
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<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
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<tr>
<td>DCM</td>
<td>dichloromethane</td>
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<tr>
<td>DEPT</td>
<td>distortionless enhancement by polarization transfer</td>
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<tr>
<td>DIBAL</td>
<td>di-iso-butylaluminium hydride</td>
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<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
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<tr>
<td>DMP</td>
<td>Dess–Martin periodinane</td>
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<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
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<td>eq.</td>
<td>equivalent</td>
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<td>ESI</td>
<td>electrospray ionization</td>
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<td>Et</td>
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<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
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<tr>
<td>h</td>
<td>hour(s)</td>
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<tr>
<td>HRMS</td>
<td>high-resolution mass spectrometry</td>
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<tr>
<td>HSQC</td>
<td>heteronuclear single quantum coherence</td>
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<td>HWE</td>
<td>Horner–Wadsworth–Emmons</td>
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<tr>
<td>IBX</td>
<td>2-iodoxybenzoic acid</td>
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<tr>
<td>IPA</td>
<td>iso-propyl alcohol</td>
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195
IR  infrared
K  Kelvin
KHMDS  potassium hexamethyldisilazide
LDA  lithium diisopropylamide
m  meta
m  multiplet
M  molarity
mCPBA  meta-chloroperoxybenzoic acid
Me  methyl
mg  milligram(s)
min  minutes
mL  milliliter
mmol  millimoles
mp  melting point
Ms  methanesulfonyl
MS  mass spectrometry
MSA  methanesulfonic acid
MTBD  7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
m/z  mass to charge ratio
n  normal
NMR  nuclear magnetic resonance
n.O.e  nuclear Overhauser effect
Nu  nucleophile
p  para
pet. ether  petroleum ether (light petroleum ether, bp 40–60°C)
Ph  phenyl
PIDA  (diacetoxyiodo)benzene
PMB  p-methoxybenzyl
ppm  parts per million
4-PPY  4-pyrrolidinopyridine
Py  Pyridine
p-TSA  p-toluenesulfonic acid
q  quartet (NMR)
RCM  ring-closing metathesis
Rf  retention factor
ROESY  rotating-frame Overhauser effect spectroscopy
RT  room temperature
s  second(s); singlet (NMR)
sat.  saturated
SN1  unimolecular nucleophilic substitution
SN2  bimolecular nucleophilic substitution
t  triplet (NMR)
t  tert
TBAF  tetra-n-butylammonium fluoride
TBS  tert-butylidemethylsilyl
TBDPS  tert-butyldiphenylsilyl
TEMPO  2,2,6,6-tetramethylpiperidinyloxy
Tf  trifluoromethanesulfonyl
TFA  trifluoroacetic acid
THF  tetrahydrofuran
TIPS  triisopropylsilyl
tlc  thin layer chromatography
TOP  tandem oxidation procedure
UV  ultraviolet
References


52. For examples of the Cope rearrangement of trisubstituted cyclopropanes see: