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Investigations Into The Stereochemical Outcome Of Intramolecular Diels-Alder Reactions

Presented in partial fulfillment of the requirements for the degree of

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Massey University

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BSc, MSc(Hons), DipTchg

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Investigations
Into
The Stereochemical Outcome
Of
Intramolecular
Diels-Alder Reactions
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Abstract

The Diels-Alder (DA) reaction is an important tool in synthetic organic chemistry, since it allows the simultaneous formation of two carbon-carbon (or carbon-heteroatom) bonds. The stereoselectivity of intramolecular versions of this reaction is, however, difficult to predict. A systematic study of the intramolecular Diels-Alder (IMDA) reaction has been carried out which provides new insights into factors affecting stereocontrol. Ester tethered substrates were chosen for this investigation because there are relatively few literature examples of this type and esterification provides a versatile way of attaching the diene to the dienophile.

Two chiral dienols were prepared and these were used to synthesize a range of precursors for investigating asymmetric induction in ester tethered DA (ETDA) reactions. When a stereogenic centre was incorporated into precursors at the allylic position to the diene terminus, high levels of \( \pi \)-facial stereoselectivity were observed. The amount of stereocontrol was dependent on the size of the stereocontrolling element that was used, but diastereoisomer ratios of up to 96:4:0:0 were achieved. This method of stereocontrol represents a powerful new method for achieving asymmetric induction in IMDA reactions. Conversely, no diastereofacial selectivity was observed when the ETDA precursor lacked a stereocentre at the allylic position.

The \textit{endo:exo} and \( \pi \)-facial stereoselectivity of maleate and fumarate derivatives of the chiral dienols (and achiral examples prepared from \((2E,4E)-2,4\text{-hexadien}-1\text{-ol}) were compared and an explanation of the observed stereoselectivity is proposed. For maleates there was a clear preference for \textit{trans}-fused \textit{exo} adducts, whether the dienophile was terminated with a carboxylic acid or a methyl ester group. In contrast to this, \textit{cis}-fused \textit{endo} adducts were favoured for chiral fumarate precursors, regardless of the type of functional group that the dienophile was terminated with. In each case the \( \pi \)-facial stereoselectivity was slightly greater for the ester than the corresponding carboxylic acid. These observations undermine previous literature reports which claim that the geometry of the dienophile is not a dominant factor in the \textit{endo:exo} stereoselectivity of ETDA reactions. It is also counter to the view that carboxylic acids promote the formation of \textit{endo} adducts, and esters promote \textit{exo} adducts respectively.

Determination of the stereochemistry of the ETDA adducts was accomplished by taking into account the absolute stereochemistry of existing stereogenic centres in the precursors, COSY and NOESY spectra of the adducts, the coupling constants arising at the ring junction, and conformational analysis using molecular models. A tricyclic derivative was prepared from one of the ETDA adducts and nOe difference experiments were carried out on it, which confirmed the stereochemical assignments that were made. Preparation of this derivative serves as a model system for the syntheses of himbacine.
(which is a lead compound in the treatment of Alzheimer’s disease) and velutinal (a powerful antifeedant for the opossum), both of which possess a similar carbocyclic backbone to the tricycle that was formed.

The assertion that carboxylic acids form endo adducts in ETDA reactions has gone unchallenged for over twenty years. The most frequently cited evidence for this behaviour involves DA reactions of citraconate derivatives of (2E,4E)-2,4-hexadien-1-ol. Since the results obtained for a range of maleate half esters conflicted with the published results for citraconate half esters, a thorough reinvestigation of the literature examples was carried out. Each of the possible exo and endo DA adducts for the two regioisomeric (2E,4E)-2,4-hexadien-1-yl hydrogen citraconate precursors was prepared and characterized independently, to enable the products formed in the DA reactions to be identified by proton NMR analysis. It was demonstrated that (2E,4E)-2,4-hexadien-1-yl citraconate half esters are thermally labile and break down when heated in refluxing solvent to form citraconic anhydride and (2E,4E)-2,4-hexadien-1-ol. This impacts upon the commonly held belief that (2E,4E)-2,4-hexadien-1-yl citraconate half esters undergo ETDA reactions to form predominantly endo adducts. In fact, the experiments described herein demonstrate that the endo adducts form by way of bimolecular DA reactions between citraconate anhydride and (2E,4E)-2,4-hexadien-1-ol, which occur subsequent to cleavage of the ester tether. In reactions of other citraconate half esters (involving alcohols which are less volatile than (2E,4E)-2,4-hexadien-1-ol) it was possible to isolate the respective alcohols in yields of 54-63%.

Steroids are attractive synthetic targets, since rare examples of steroidal natural products with potent biological activity are regularly discovered. Practical synthesis of steroids via transannular Diels-Alder (TDA) reactions is an attractive strategy, since it should be accomplished by simply heating the starting material in an appropriate solvent (which can be subsequently recycled). A more ambitious approach involves the stereocontrolled tandem TDA reaction of a macrocycle containing a bis-diene (in the form of a conjugated tetræne) and a bis-dienophile. Such a reaction would involve the simultaneous formation of four carbon-carbon bonds and eight new stereogenic centres in a single step. A chiral tetraenol and a monoprotected dienedioic acid containing a bis-dienophile moiety have been prepared. Esterification of these materials and selective manipulation of the protecting groups was carried out, but macrocyclisation has yet to be achieved. Progress in this area has set the scene for tandem TDA reactions to be attempted.
Adele,

Mum and Jim,

Dad,

Philip and Greg,

Nanna Morris, Nanna Lilly and Grandy.
It gives me great pleasure to thank the following people for their help!

**Mick Sherburn** for offering me support of every kind throughout this project and for the unshakable conviction that the transformations eventually would work.

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**All of the Sherburnites (past and present)** who made this process much more fun than it otherwise might have been.

Cheers,

Mike.
“What have you lost Mulla?”
“My key,” said Nasrudin.
“Where did you drop it?”
“At home.”
“Then why, for heaven’s sake, are you looking for it here?”
“There is more light here.”

*A Sufi Parable.*
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Abbreviations

%  percentage yield
Δ  heat
Ac -O₂CCH₃
AIBN  2,2’-azo-bis-isobutyronitrile
APT attached proton test
BDA bimolecular Diels-Alder
BHT 2,6-di-tert-butyl-4-methylphenol
BMS borane methyl sulphide complex
Bn benzyl
°C degree Celsius
α circa (approximately)
CA citraconic anhydride
CI chemical ionization
COSY correlated spectroscopy
d day/s or duplicate/s
DA Diels-Alder
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DCC dicyclohexylcarbodiimde
DEPT distortionless enhancement by polarization transfer
DMAP N,N-diethylaminopyridine
DMES dimethylethylsilyl
dmf dimethylformamide
DMP dimethoxypropane
DIBALH diisobutylaluminium hydride
DMSO dimethylsulphoxide
EDG electron donating group
EI electron impact
endo tether carbonyl distant from diene in the transition state
eq molar equivalents
Et ethyl
ETDA ester tethered Diels-Alder
EWG electron withdrawing group
eV electron Volts
exo tether carbonyl close to diene in transition state
h hour/s
HEΤCΟR heteronuclear COSY
<table>
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<th>Description</th>
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<tr>
<td>HMQC</td>
<td>heteronuclear multiple quantum correlation</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>HSQC</td>
<td>heteronuclear single quantum correlation</td>
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<tr>
<td>IMDA</td>
<td>intramolecular Diels-Alder</td>
</tr>
<tr>
<td>imid.</td>
<td>imidazole</td>
</tr>
<tr>
<td>internal</td>
<td>carbon atom/bond close to tether</td>
</tr>
<tr>
<td>iPr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>MA</td>
<td>maleic anhydride</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
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<tr>
<td>MOM</td>
<td>methoxymethyl</td>
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<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
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<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear Overhauser and exchange spectroscopy</td>
</tr>
<tr>
<td>peripheral</td>
<td>carbon atom/bond distant from tether</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PhCH₃</td>
<td>toluene</td>
</tr>
<tr>
<td>PhH</td>
<td>benzene</td>
</tr>
<tr>
<td>Pip</td>
<td>piperonyl</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
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<tr>
<td>pyr.</td>
<td>pyridine</td>
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<tr>
<td>q</td>
<td>quartet</td>
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<tr>
<td>ROESY</td>
<td>rotating frame Overhauser enhancement spectroscopy</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singulet</td>
</tr>
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<td>t</td>
<td>time or triplet</td>
</tr>
<tr>
<td>T</td>
<td>temperature</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyldiphenylsilyl</td>
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<tr>
<td>TDA</td>
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<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>TIMDA</td>
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TLC  thin layer chromatography
TMS  trimethylsilyl
xyl  xylene
χρ  chiral group
1 Background

1.1 Introduction

Since its inception in 1928\(^1\) the Diels-Alder (DA) reaction has become one of the mainstays of synthetic organic chemistry. The significance of this reaction was recognized in 1950 when Otto Diels (1876-1954) and Kurt Alder (1902-1958) were awarded the Nobel Prize for Chemistry for its discovery (although there is some controversy concerning the first time that this most ubiquitous of chemical transformations was actually observed.\(^2\))

The DA reaction is a thermally allowed pericyclic process in which a conjugated diene and a dienophile add together to form a cyclohexene (Figure 1.1). There are several aspects of this [4+2] cycloaddition reaction which render it a powerful synthetic tool. The most important of these is that two carbon-carbon bonds can be formed in a single step, rapidly advancing any stepwise synthesis. It is also an important method of forming six membered carbocycles, often involving no more than the judicious application of heat to the starting materials in an appropriate solvent. When the diene or dienophile has appropriate functionality up to four new stereogenic centres can be produced simultaneously, allowing structurally complex molecules to be built up very quickly. In addition, aromatic, acetylenic and heteroatomic moieties may be incorporated into the diene or dienophile greatly augmenting the structural diversity which can be achieved.\(^3\)-\(^6\)

![Figure 1.1](image)

The DA reaction is very flexible but there are some criteria which must be considered in order to ensure that the reaction is successful. The diene must be conjugated and it must be able to adopt an \(s\)-\(cis\) conformation in order for the two ends of the molecule to be close enough together to react with the dienophile. Electron withdrawing groups (EWG) are normally attached to the dienophile and electron donating groups (EDG) to the diene. This lowers the energy of the lowest unoccupied molecular orbital (LUMO) of the dienophile and raises the energy of the highest occupied molecular orbital (HOMO) of the diene, which increases the overlap between these orbitals and reduces the amount of thermal energy required.\(^7\) Inverse electron demand DA reactions
(in which EDG are attached to the dienophile or EWG to the diene) have also been reported.\textsuperscript{8}

The first intramolecular Diels-Alder (IMDA) reactions (\textbf{Section 1.2}) were reported in 1963,\textsuperscript{9-11} although the idea was proffered by Alder ten years earlier.\textsuperscript{12} Despite the entropic, regiochemical and stereochemical advantages that these reactions have over their bimolecular Diels-Alder (BDA) counterparts, they have not achieved the synthetic prominence that might have been expected. IMDA reactions are often employed late in a synthetic regime and the precursors often incorporate complex functionality which poses a very real risk to the completion of a synthesis, because reactivity and stereoselectivity can be difficult to predict. Despite these problems several reviews on IMDA reactions are available\textsuperscript{13-20} and there are many recent asymmetric total syntheses which demonstrate that it is a versatile synthetic tool.\textsuperscript{21-27} Due to this versatility one reviewer\textsuperscript{15} has quipped that “if it’s worth synthesizing, an IMDA reaction is worth considering”.

The first transannular Diels-Alder (TDA) reaction (\textbf{Section 1.3}) was reported in 1962.\textsuperscript{28} The potential pitfalls and rewards associated with IMDA reactions are even further accentuated with TDA reactions, with the result that literature accounts of them are rare. However, one review in the area has been published\textsuperscript{29} and several natural product directed syntheses incorporating TDA reactions have been reported.\textsuperscript{30-35} The stereochemical characteristics of these reactions are now becoming better understood.

\section{1.2 The intramolecular Diels-Alder (IMDA) reaction}

The most frequently reported IMDA reactions are those in which the tether connecting the diene and dienophile is made up entirely of carbon atoms. This includes examples which have unsaturated carbons in the tether arising from olefinic, aromatic or carbonyl groups. (Carbonyl groups are often used to activate the starting material in carbocyclic systems by placing them in conjugation with the dienophile.) IMDA reactions where the tether contains one or more heteroatoms (particularly nitrogen or oxygen) have also been investigated. A range of functional groups have been used to connect the diene to the dienophile, including amines, amides, ethers and esters. In addition the tether can be substituted with further branching groups, which often have a marked effect on the stereochemical outcome of the reaction.
Figure 1.2 shows six different arrangements which can lead to IMDA reactions. Arrangements 1-4, in which the tether is attached to the first carbon of the diene, are referred to as Type 1 reactions, whereas 5 and 6 are referred to as Type 2 reactions.

The number of atoms in the diene-dienophile tether has a dramatic effect on the regioselectivity and stereoselectivity of the IMDA reaction which ensues. For E-dienes, arrangements 1 and 2 are both possible, leading to fused and bridged products respectively (Figure 1.3). No reaction occurs if the chain contains less than three atoms because the transition states which lead to either product are highly strained. With three to five atoms arrangement 1 is highly preferred and fused adducts are produced exclusively. There are few Type 1 examples in the literature in which six to nine atoms have been incorporated in the tether, highlighting the entropic problems associated with forming eight to eleven membered rings.

\[ E- \text{or } Z \text{-dien}\]

\[ E- \text{or } Z \text{-dien}\]

---

\[ E- \text{or } Z \text{-dien}\]

---

---

---
In rare cases where Type 1 reactions have been carried out on substrates with ten to twelve atom tethers the regiochemical and stereochemical outcome is similar to the BDA case. Two ester tethered examples involving substrates with ten atom tethers (9a and b) are shown in Figure 1.4. It is evident from the product distribution that there is little regiochemical or stereochemical preference in the ETDA reaction of diester 9a, although triester 9b exhibits some regioselectivity for bridged adducts 12b and 13b.

The situation for arrangements 3-6 (Figure 1.2) is quite different. For Z-dienes with arrangements 3 and 4, shorter tethers can be accommodated than for E-dienes and arrangement 4 is more frequently encountered. Arrangements 5 and 6 both produce bridged adducts (Figure 1.5). Meta-bridged adducts (14) are favoured with tethers of up to five atoms but small amounts of para-bridged regioisomers (15) may be produced when six or more atoms are used.
For each of the six arrangements depicted in Figure 1.2 four modes of cycloaddition are possible: two of these are syn and two are anti. Cycloaddition is classified as syn or anti depending on the way in which the tether carbon of the dienophile is orientated with respect to the diene, as illustrated for arrangement 1 in Figure 1.6. For arrangement 1, anti addition leads to the formation of trans adducts 16 and 17, whereas syn addition leads to cis fused adducts 18 and 19. If the dienophile approaches from below the plane of the diene then anti addition leads to adduct 16, whereas approach from above leads to adduct 17. Conversely, syn addition leads to adducts 18 and 19 when the dienophile approaches from below or above the plane of the diene respectively.
The preference for transition states which determine the stereoselectivity of the cycloaddition are difficult to predict. However, with the exception of furan dienes, IMDA reactions are normally irreversible and therefore kinetically controlled, so a knowledge of the relative energy of each transition state is useful in terms of explaining the final product distribution. Some examples which highlight the syn:anti stereoselectivity of IMDA reactions are discussed below.

For 1,3,9-decatrienes (Figure 1.7) a strong preference for the cis adduct is observed if the dienophile is conjugated to a carbonyl in the tether as in the case of trienone 20f. However, the exo:endo ratio tends towards unity when the system is unactivated (20a) or activation is provided by a terminal ester group in conjugation with the dienophile (20b-e).

![Image of Reaction Scheme]

<table>
<thead>
<tr>
<th>20</th>
<th>W</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Solvent</th>
<th>T/°C</th>
<th>t/°C</th>
<th>21:22</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CH₂ cyclohexane</td>
<td>250</td>
<td>1.5</td>
<td>48:52</td>
<td>95</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>H</td>
<td>CO₂Me</td>
<td>H</td>
<td>CH₂ toluene</td>
<td>155</td>
<td>45</td>
<td>51:49</td>
<td>90</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>CO₂Me</td>
<td>H</td>
<td>CH₂ toluene</td>
<td>155</td>
<td>45</td>
<td>51:49</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>iPr</td>
<td>H</td>
<td>CO₂Me</td>
<td>H</td>
<td>CH₂ toluene</td>
<td>180</td>
<td>3</td>
<td>55:45</td>
<td>71</td>
</tr>
<tr>
<td>e</td>
<td>iPr</td>
<td>CO₂Me</td>
<td>H</td>
<td>CH₂ toluene</td>
<td>160</td>
<td>48</td>
<td>50:50</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CO</td>
<td>CH₂ chloroform</td>
<td>22</td>
<td>4</td>
<td>5:95</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 1.7

For 1,3,8-nonatrienes (Figure 1.8) cis fused adducts are favoured when the starting material is unactivated (23a) or has a tether carbonyl in conjugation with the dienophile (23f). However, when the dienophile is in conjugation with a terminal ester functionality there is a marked preference for the trans adduct, particularly when the terminus of the diene is also substituted (23b-e).
For BDA reactions the \textit{anti:syn} stereoselectivity can often be explained by invoking the Alder \textit{endo} rule.\cite{51} This explanation relies on the effect of secondary orbital overlap\cite{52} between the $\pi$-system of the diene and unsaturated substituents on the dienophile. The dienophile approaches the diene so that there is maximum overlap of the $\pi$-orbitals in the transition state and this affects the \textit{anti:syn} product ratio.

The preceding discussion shows that for IMDA reactions the Alder \textit{endo} rule is generally not observed (Figure 1.7 and 1.8). This is further illustrated in Figure 1.9 for compounds 23b and 23c. Compound 23b may cyclise via an \textit{anti} or a \textit{syn} transition state to form \textit{trans} adduct 24b or \textit{cis} adduct 25b respectively. (Only one of the possible \textit{anti} and \textit{syn} transition states are shown.) Compound 25b is termed the \textit{endo} adduct because the carbonyl of the ester group in 23b is proximal to the diene in transition state 27, whereas compound 24b is called the \textit{exo} adduct. The situation is quite different for compound 23c, because it has an \textit{E}-dienophile instead of a \textit{Z}-dienophile. Here the \textit{trans} adduct is formed via an \textit{endo} transition state and the \textit{cis} adduct via an \textit{exo} transition state. If secondary orbital overlap were the dominant factor affecting \textit{syn:anti} stereoselectivity then \textit{endo} compounds 25b and 24c would be favoured in the IMDA reactions, however, a modest stereoselectivity for \textit{exo} adduct 24b is observed for \textit{Z}-dienophile compound 23b (Figure 1.8) and with the \textit{E}-dienophile substrate 23c, the selectivity for the \textit{exo} product is very modest.
Instead, the observed stereoselectivity in IMDA reactions can be explained by invoking concerted but asynchronous transition states. This explanation assumes that the two new $\sigma$-bonds begin to form (and finish forming) simultaneously, but the progress in the formation of one of the bonds is greater. The extent of the asynchronicity depends on the coefficients of the HOMO of the diene and the LUMO of the dienophile and the geometrical constraints imposed on the transition state by the tether. These factors play a much greater role in the cycloaddition of 1,3,8-nonatrienes than 1,3,9-decatrienes, hence the stereoselectivity of the former are affected to a greater extent by the position of the substituents.

Figure 1.9
Consider compounds 23a, 23b and 23f (Figure 1.10). In 23a the LUMO coefficients for the two carbon atoms of the dienophile are approximately the same. However, in 23b the LUMO coefficient of the internal carbon atom of the dienophile\(^7\) is larger than the peripheral one, whereas in 23f the peripheral carbon atom has the largest LUMO coefficient.\(^7\) This implies that activation by an internal carbonyl, such as the ketone in compound 23f, will cause the peripheral \(\sigma\)-bond (Figure 1.11) to form more rapidly than the internal one. In this case nine membered ring character is displayed in the transition state, which favours the formation of \(cis\) fused products.\(^{56, 57, 17}\)

Conversely, peripheral dienophile activating groups, such as the carbonyl in methyl ester 23b, cause the internal \(\sigma\)-bond to form more rapidly. The steric demands of substituents near the newly forming internal \(\sigma\)-bond are the dominant stereocontrolling factors in this case. Two different types of asynchronicity have been identified (Figure 1.12):\(^{58}\) asymmetric stretch asynchronicity and twist asynchronicity. Asymmetric stretch asynchronicity causes the internal carbon atoms of the diene and dienophile to move together with a concomitant lengthening of the distance between the peripheral carbon atoms. Consequently the transition state has more of the character of the incipient five membered ring. For steric reasons \(trans\) fused rings are favoured in this case. Twist asynchronicity occurs about the bond which is more fully formed in the transition state. For compounds such as 23b twisting occurs about the internal \(\sigma\)-bond due to conformational pressure exerted by the incipient five membered ring. This forces the

\(^7\) The internal carbon atoms of the diene or dienophile are the ones nearest the tether. The peripheral carbon atoms are the ones nearest the diene or dienophile terminus.
dienophile to twist in an *exo* direction (away from the diene, or to the right in Figure 1.12). This increases the non-bonded interactions in the *endo* transition state and destabilizes it relative to the *exo* transition state, hence *trans* adduct 24b becomes more favoured. It is important to stress that whilst these models give insight into the stereoselectivity of IMDA reactions, other factors may come into play which can markedly affect the product distributions which are observed.\textsuperscript{17}

These arguments are difficult to apply when the precursor for the IMDA reaction has both an internal and a peripheral dienophile activating group (Figure 1.13).\textsuperscript{59} In this case it is not possible to say which of the two $\sigma$-bonds will be more fully developed, therefore the stereoselectivity cannot be accurately predicted because it isn’t certain whether the transition state will resemble the incipient five or nine membered ring. (This is also the case for the ester tethered IMDA (ETDA) reactions discussed in Section 1.2.1.) Experimentally, no stereoselectivity is observed for compounds 30a and 33b, but there is a reasonable preference for the *trans* adducts in the IMDA reaction of 30b and 33a.

A second problem encountered for precursors with both internal and peripheral activating groups is the use of the terms *exo* and *endo* to describe the transition states and the geometry of the resulting adducts. Precursors 33a and b have an $E$-dienophile so a transition state which is *exo* with respect to the peripheral carbonyl is *endo* with respect to the internal carbonyl. To avoid this confusion, the terms *exo* and *endo* will refer to the position of the tether carbonyl from this point on, by definition. (In all cases addition occurs suprafacially with respect to both the diene and the dienophile and the stereochemistry of the starting material is conserved.\textsuperscript{7})
Esterification provides a very versatile way of connecting the diene to the dienophile and the ester group can be orientated in several different ways as shown in Figure 1.14. Formally, structure 36 arises from a reaction between a dienol and an alkenoic acid, whereas structure 37 is formed from condensation of a dienoic acid with an alkenol. In general, ester tethered substrates have low reactivity and ETDA reactions are favoured only if the tether carbonyl is conjugated to the dienophile (Section 1.2.1.2).
A general summary of the functional groups present in the substrates which have been prepared in this Thesis for subsequent ETDA reactions is shown in Figure 1.15. (ETDA reactions were also carried out on an acrylate and a propiolate derivative (Section 3.3.4). (One hundred and ninety two different precursors could be prepared using the functional groups indicated in Figure 1.15 but ETDA reactions were actually carried out on a specific subset of these.) The main features of each of the ETDA precursors that were prepared are: they were all Type 1 (Figure 1.2); the tether between the diene and the dienophile contained three atoms; the diene and dienophile were acyclic; maleate, fumarate and citraconate diesters and half esters were used; and the tether carbonyl was in conjugation with the dienophile.

Because of the number of literature examples available and the requirement that the discussion of these examples is relevant to the current work, it is necessary to limit the scope of the review that follows. ETDA reactions of precursors with three atom tethers are discussed in detail, excluding examples with: furan dienes;62-66 other cyclic dienes;67-72 semicyclic dienes;73-88 cyclic dienophiles;89, 90 tether carbonyls which are not conjugated to the dienophile;91-93 and those which are ambiguous (for example the stereochemistry has not been rigorously demonstrated, the synthetic methodology is unclear or the yields are low).94-96, 24 However, examples of this type have occasionally been included to illustrate specific points.
1.2.1.1 Doubly activated dienophiles

The first series of examples (Figure 1.16) illustrate the endo:exo diastereoselectivity of citraconic acid derivatives obtained by White et al.\textsuperscript{97, 98} Methyl ester 38a was heated to reflux in xylene yielding the highly strained trans fused product 39a, which arises through an exo cycloaddition mode. Likewise, 38b produced 39b exclusively. It was reported that cis fused lactones 40a and 40b were not formed.

![Figure 1.16](image)

| 38 R X Y Z t/h 39:40 % |
|-----------------------|-----------------|-----------------|------------------|
| a Me Me Me H 24h 100:0 40 |
| b Me H Me H 24h 100:0 55 |
| c H Me Me H 15h 0:100 32 |
| d H Me H Me 15h - - |
| e H H Me H 15h 0:100 50 |
| f H H H Me 15h - - |

An unexpected result was obtained for analogous carboxylic acids 38c and 38d. These regioisomeric acids were formed in a 1:1 ratio from the reaction of sorbyl alcohol with citraconic anhydride and they were found to be inseparable. A portion of this mixture was heated in refluxing xylene and on cooling 40c crystallized from the mixture in 32\% yield (based on 38c). No evidence for the formation of the three other adducts (39c, 40c or 40d) was obtained from the reaction mixture although a substantial amount of polymer had been formed. It was assumed that 38c had cyclised via the endo mode and that 38d had suffered ‘autocatalytic polymerization’. A similar result was obtained on heating pentadienol derived acids 38e and 38f, with 40e being produced exclusively in 50\% yield.\textsuperscript{99}
It appeared from these examples that the group terminating the dienophile was affecting the outcome of the ETDA reaction, causing it to be kinetically controlled for the methyl esters and thermodynamically controlled when the carboxylic acids were used. This phenomenon had not been observed previously. The authors\textsuperscript{98} admitted that this effect could not be explained satisfactorily in terms of steric or electronic effects and suggested that protonation of the lactone carbonyl by the carboxylic acid group could catalyze the reverse DA reaction, which would enable the cis fused thermodynamic adduct to form. However, they warned that this proposition was tentative since the yield of the reaction was low and most of the material was unaccounted for.

Similar trends in \textit{exo:endo} diastereoselectivity were observed by Mellor \textit{et al.}\textsuperscript{100, 101} in systems where the dienophile was substituted with chlorine or bromine (\textbf{Figure 1.17}). Esters 41a-e cyclised primarily \textit{via} the \textit{exo} mode to produce \textit{trans} fused adducts 42a-e in variable yield. On the other hand, carboxylic acid 41f produced the \textit{endo} adduct 43f exclusively, albeit in low yield. Polymeric products were produced when acid 41g was heated.

\begin{table}[h]
\begin{center}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
41 & R & X & Y & t/h & 42:43 \\
\hline
a & Me & Cl & Cl & 48 & 100:0 & 68 \\
b & Bn & Cl & Cl & 24 & 89:11 & 57 \\
c & Pip & Cl & Cl & 18 & 100:0 & 33 \\
d & DMES & Cl & Cl & 36 & 72:28 & 53 \\
e & Me & Br & H & 18 & 83:17 & 80 \\
f & H & Cl & Cl & 18 & 0:100 & 20 \\
g & H & H & Br & - & - & - \\
\hline
\end{tabular}
\end{center}
\caption{Figure 1.17}
\end{table}
Mellor did not accept White’s view that thermodynamic control was responsible for the formation of cis fused adducts when carboxylic acids were cyclised and put forward the hypothesis that acid catalysis might lead to kinetic control. In this scenario the endo adducts arise from a syn transition state resulting from protonation of the ester carbonyl group in the starting material. In order to test which of these theories was correct, Mellor attempted to prepare 42f which he then planned to heat in xylene (under the same conditions as used for 41a-g) to investigate isomerisation to 43f. However, this compound could not be isolated even though a number of derivatives (42a-d) were available.

In a study by Becher et al., a series of substituted pentadienols 44a-d were themolysed in chloroform in the presence of maleic anhydride (45) (Figure 1.18). In each case, cis fused lactones 48a-d crystallised from the reaction mixture when it was cooled. These results seemed to be in keeping with results obtained by White and Mellor. It was assumed that initial esterification produced half esters 46a-d with subsequent cycloaddition.

![Diagram of chemical reaction]

<table>
<thead>
<tr>
<th>44</th>
<th>X</th>
<th>Y</th>
<th>t/h</th>
<th>47:48</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>H</td>
<td>4</td>
<td>0:100</td>
<td>72</td>
</tr>
<tr>
<td>b</td>
<td>PhCHCH</td>
<td>H</td>
<td>12</td>
<td>0:100</td>
<td>80</td>
</tr>
<tr>
<td>c</td>
<td>Ph</td>
<td>Me</td>
<td>10</td>
<td>0:100</td>
<td>76</td>
</tr>
<tr>
<td>d</td>
<td>EtO</td>
<td>H</td>
<td>12</td>
<td>0:100</td>
<td>77</td>
</tr>
</tbody>
</table>

Figure 1.18
The evidence provided for the initial esterification was that the analogous BDA reaction between protected alcohol 49 and maleic anhydride (45) (Figure 1.19) only produced cis fused adduct 50 when they were heated together in toluene at higher temperatures than those employed for unprotected alcohols 44a-d. However, since half esters 46a-d were not isolated, there was no direct evidence for the initial esterification. This has lead to speculation that BDA reactions may have occurred initially with subsequent intramolecular lactonisation, since the endo products obtained (48a-d) are those expected for the BDA case.51

\[
\begin{align*}
\text{C}_4\text{H}_5\text{CO}_2^- + \text{HOAc} &\rightarrow \text{C}_4\text{H}_5\text{CO}_2^- \text{OAc} \\
\Delta \text{toluene} &\rightarrow \text{C}_4\text{H}_5\text{CO}_2^- \text{OAc} \\
110^\circ\text{C}, 4\text{h} &\rightarrow \text{C}_4\text{H}_5\text{CO}_2^- \text{OAc} \\
60\% &\rightarrow \text{C}_4\text{H}_5\text{CO}_2^- \text{OAc} \\
50 (\text{endo}) &\rightarrow \text{C}_4\text{H}_5\text{CO}_2^- \text{OAc}
\end{align*}
\]

Figure 1.19

\[
\begin{align*}
\text{X}\text{C} &\rightarrow \text{X}\text{C} \\
\Delta \text{chloroform, 63°C, 8h} &\rightarrow \text{X}\text{C} \\
\text{52} &\rightarrow \text{52} \\
\text{HO} &\rightarrow \text{HO} \\
\text{X} &\rightarrow \text{X} \\
\text{51} &\rightarrow \text{51} \\
\text{45} &\rightarrow \text{45} \\
\end{align*}
\]

\[
\begin{align*}
\text{X} &\rightarrow \text{X} \\
\text{51} &\rightarrow \text{51} \\
\text{45} &\rightarrow \text{45} \\
\end{align*}
\]

\[
\begin{align*}
\text{51 X} &\rightarrow \text{51 X} \\
55:56 &\rightarrow 55:56 \\
\% &\rightarrow \%
\end{align*}
\]

<table>
<thead>
<tr>
<th>51 X</th>
<th>55:56</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Me</td>
<td>50:50</td>
<td>72</td>
</tr>
<tr>
<td>b CH3OTBDPS</td>
<td>70:30</td>
<td>80</td>
</tr>
</tbody>
</table>

* To facilitate separation of the ETDA adducts the crude mixture of carboxylic acids (53 and 54) was treated with diazomethane prior to chromatography. Structures 53-56 indicate relative stereochemistry only, since the compounds they represent are racemic.

Figure 1.20
Similar results were obtained by Gree et al.\textsuperscript{105} when alcohols 51a and b (Figure 1.20) were heated with maleic anhydride (45) in chloroform and then the cycloadduct mixture was treated with diazomethane. Endo adducts 55 and 56 were the only products observed in each case. Again the intermediate half acids (52a and b) were not isolated and adducts 53 and 54 were assumed to form via IMDA reactions. In the case of alcohol 51b there was evidence of diastereofacial selectivity between the two endo modes of cycloaddition, leading to an excess of adduct 55b. This will be discussed more fully in Section 1.2.3.

There are three examples in the literature in which maleate half esters have been isolated prior to carrying out ETDA reactions, with variable results.\textsuperscript{106-109} In the first example\textsuperscript{108} (Figure 1.21) the authors compared the assumed BDA reaction of alcohol 57 and maleic anhydride (45) with the ETDA reaction of triene 58. Both of these reactions gave rise to the same adduct, however, no spectroscopic data was provided for compound 59 and there was no rigorous explanation of the way in which the stereochemistry was determined. It will be shown (Section 3.1) that this result is counter to the stereoselectivity obtained for the analogous ETDA reaction of sorbyl maleate, in which the exo adduct is favoured under similar conditions. It is possible that the stereochemistry of 59 has been misassinged and the exo adduct was produced in both cases. The reaction of 57 and 45 may occur via intermolecular esterification with subsequent ETDA reaction, although the authors used the apparent production of the endo adduct as evidence for an initial BDA reaction followed by intramolecular esterification (in spite of the fact that their own results do not exclude the possibility that the esterification may have occurred first, since the same product was observed in both cases.)

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure121.png}
\caption{Figure 1.21}
\end{figure}
Furan derivatives 60a and 60b\textsuperscript{106, 107} (Figure 1.22) were extremely labile and cycloaddition occurred in a few days at 25°C in diethyl ether to give exo adducts 61a and 61b respectively. Compound 60c polymerized under these conditions, preventing the isolation of ETDA adducts. (Another example bearing a furan diene has been published,\textsuperscript{110} but in this case the ETDA precursor was not isolated prior to cycloaddition.) IMDA reactions involving furan dienes are reversible and therefore thermodynamically controlled,\textsuperscript{44} whereas IMDA reactions involving simple dienes are irreversible and therefore kinetically controlled.\textsuperscript{11} Hence it is not possible to compare the stereoselectivities of the furan derivatives in Figure 1.22 with those given earlier (Figures 1.16-1.18 and 1.20).

![Figure 1.22]
In the ETDA reaction of maleate esters 62a and 62b\textsuperscript{109} (Scheme 1.23) containing semicyclic dienes, \textit{exo} adducts (63a and 63b) were favoured over \textit{endo} adducts (64a and 64b) regardless of whether the dienophile was terminated with a methyl ester (Entry 1) or a carboxylic acid group (Entry 2). A small amount of epimerized material was also produced which brings into question the suitability of this system as a vehicle for investigating stereochemical control in IMDA reactions of this type. (Microwave radiation was also used to effect the IMDA reactions of 62a (2 x 9min) and 62c (5 x 9min). It was found that the reaction time was considerably shorter, but the product ratios and yields obtained were nearly identical to those obtained with prolonged heating in xylene.) In these examples the conformational rigidity of the semicyclic diene might override the subtle factors responsible for causing methyl esters and carboxylic acids to give different \textit{exo}:\textit{endo} stereoselectivity in open chain systems (Figure 1.16 and 1.17). The last example (62c, Entry 3) is a fumarate diester and this also predominantly gave rise to an \textit{exo} adduct (63c). The corresponding fumarate half ester was not reported.

![Scheme 1.23](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>62</th>
<th>X</th>
<th>Y</th>
<th>%</th>
<th>63:64:65</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>H</td>
<td>CO₂Et</td>
<td>63</td>
<td>91:8:1</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>H</td>
<td>CO₂H</td>
<td>51</td>
<td>82:6:12</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>CO₂Et</td>
<td>H</td>
<td>76</td>
<td>87:13:0</td>
</tr>
</tbody>
</table>

Figure 1.23
Other triene esters incorporating $E$-dienophiles have also been investigated (Figure 1.24). Reactions of citraconate esters 66a and b\textsuperscript{97, 98} were very slow but a clear preference for $trans$ fused products was observed and good yields were obtained (84\% of 67a and 68a based on 60\% conversion, and 85\% of 67b and 68b based on 50\% conversion). A similar observation was made for fumarate example 66c.\textsuperscript{101} When the diene was activated with an EDG (66d-f) $trans$ fused isomers (67d-f) were obtained exclusively as white solids when the reaction mixtures were cooled,\textsuperscript{102, 103} although the yield of 67e was very low. Unfortunately there have been no literature reports of EIDA reactions on precursors with $E$-dienophiles terminated with carboxylic acids. A study of this type would clearly shed new light on the $endo:exo$ preference of ETD reactions.

![Diagram](image)

<table>
<thead>
<tr>
<th>66</th>
<th>R</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>t</th>
<th>67:68</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>6d</td>
<td>81:19</td>
<td>84</td>
</tr>
<tr>
<td>b</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>11d</td>
<td>83:17</td>
<td>85</td>
</tr>
<tr>
<td>c</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>18h</td>
<td>67:33</td>
<td>48</td>
</tr>
<tr>
<td>d</td>
<td>Et</td>
<td>PhCO\textsubscript{2}</td>
<td>H</td>
<td>H</td>
<td>18h</td>
<td>100:0</td>
<td>74</td>
</tr>
<tr>
<td>e</td>
<td>Et</td>
<td>PhCHCHCO\textsubscript{2}</td>
<td>H</td>
<td>H</td>
<td>24h</td>
<td>100:0</td>
<td>13</td>
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<tr>
<td>f</td>
<td>Me</td>
<td>PhCO\textsubscript{2}</td>
<td>H</td>
<td>H</td>
<td>20h</td>
<td>100:0</td>
<td>88</td>
</tr>
</tbody>
</table>

**Figure 1.24**

When examples 38a and b (Figure 1.16) and 41a-e (Figure 1.17) are taken in conjunction with 62a and 62c (Figure 1.23) and 66a-f (Figure 1.24) it is clear that the geometry of the dienophile does not have a significant impact on the $exo:endo$ diastereoselectivity of ETD reactions where the dienophile is terminated with a terminal ester group. Because $trans$ fused adducts are produced from starting materials with $Z$-dienophiles it is clear that secondary orbital effects\textsuperscript{52} are not the dominant factors involved in the $exo:endo$ diastereoselectivity in this case, since neither the terminal EWG or the tether carbonyl are proximal to the diene in the transition state.\textsuperscript{47} Instead, the stereoselectivity of ETD reactions is best explained in terms of concerted but asynchronous transition states (Section 1.2).
1.2.1.2 The rate retarding effect of the ester tether

Compound 69a (Figure 1.25) required strong heating in toluene at 295°C for 4h in a sealed tube in order for a reaction to occur. The analogous BDA reaction between 73 and 74 proceeded at 110°C to give 75 and 76 after ring closure, which highlights the rate retarding effect of the ester tether in ETDA reactions.

\[
\begin{align*}
\text{69} & \xrightarrow{\Delta \text{toluene}} \text{70} \\
295°C, 4h & \\
\end{align*}
\]

\[
\begin{array}{|c|c|c|c|}
\hline
\text{X} & \text{Y} & \text{71:72} & \% \\
\hline
\text{a} & \text{H} & \text{CO}_2\text{Me} & 37:63 & 15 \\
\text{b} & \text{CO}_2\text{Et} & \text{H} & 89:11 & 40 \\
\hline
\end{array}
\]

* After heating in toluene the acetate group was removed by treatment with sodium methoxide in methanol at RT. Lactonisation was effected with hydrochloric acid in methanol at RT.

Figure 1.25

In addition to the low reactivity, the ETDA adducts obtained from 69a were not the expected δ-lactones 75 and 76, but γ-lactones 71a and 72a. This indicates that rearrangement of 69a to 70a (by an undisclosed mechanism) occurs prior to cycloaddition. Compound 70a was prepared and heated independently, resulting in a similar yield and ratio of 71a and 72a to that obtained for 69a. Similar results were obtained when 69b and 70b were heated under the same conditions. Trans fused adducts were favoured in each case, as expected for γ-lactone systems (Section 1.2.2.1).
In order to demonstrate that the ester tether itself was the cause of the lack of reactivity, a second series of reactions was carried out (Figure 1.26). Ether 77a underwent cycloaddition under comparatively mild conditions to give 78a and 79a. Ether 77b and ketone 77c also reacted under similar conditions. No rearranged products were observed in any of these examples.

![Figure 1.26](image)

<table>
<thead>
<tr>
<th>77</th>
<th>W</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>78:79</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>CO₂Me</td>
<td>CH₂</td>
<td>O</td>
<td>30:70</td>
<td>50</td>
</tr>
<tr>
<td>b</td>
<td>CO₂Et</td>
<td>H</td>
<td>CH₂</td>
<td>O</td>
<td>60:40</td>
<td>86</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>CO₂Me</td>
<td>CO</td>
<td>CH₂</td>
<td>25:75</td>
<td>50</td>
</tr>
</tbody>
</table>

Figure 1.26

The reason for the low reactivity of IMDA precursors bearing ester tethers can be explained in terms of the transoid effect (Figure 1.27). The unfavourable dipole-dipole interactions in the s-cis conformation (80) cause esters to adopt the s-trans conformation (81), which does not dispose the molecule towards intramolecular cycloaddition. It has been proposed that the barrier to rotation is not high enough to account for the low reactivity which is observed, however, recent investigations into solvent effects which arise for ETDA reactions (vide infra) are counter to this view.

![Figure 1.27](image)
The polarity of $\textbf{81}$ (in which the dipoles are additive) is greater than $\textbf{80}$ and this has been used to explain why the rate of formation of $\textbf{84}$ (Figure 1.28) increases as a function of the dielectric constant of the solvent used.$^{112, 113, 64}$ Polar solvents favour conformer $\textbf{82}$ which promotes the formation of transition state $\textbf{83}$, causing the rate constant $k_1$ to increase. These results give weight to the theory that the conformational rigidity illustrated in Figure 1.27 is largely responsible for the lack of reactivity conferred on ETDA precursors by the ester tether. A computational study which augments this experimental investigation has also been reported.$^{114}$

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Dielectric constant (relative)</th>
<th>$k_1$ (relative)</th>
<th>$k_{-1}$ (relative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO-$d_6$</td>
<td>48.9</td>
<td>220</td>
<td>4.8</td>
</tr>
<tr>
<td>CD$_3$CN</td>
<td>37.9</td>
<td>37</td>
<td>1.3</td>
</tr>
<tr>
<td>acetone-$d_6$</td>
<td>20.5</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>CD$_2$Cl$_2$</td>
<td>8.9</td>
<td>10</td>
<td>1.7</td>
</tr>
<tr>
<td>CDCl$_3$</td>
<td>4.7</td>
<td>14</td>
<td>2.6</td>
</tr>
<tr>
<td>toluene-$d_8$</td>
<td>2.38</td>
<td>1</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Compounds $\textbf{82}$ and $\textbf{84}$ were racemic. Structure $\textbf{84}$ indicates relative stereochemistry only.

Figure 1.28

Unfortunately the yield and selectivity of ETDA reactions do not seem to be improved by the addition of Lewis acid catalysts (Figure 1.29).$^{115}$ In examples where the dienophile was activated only by the carbonyl of the ester group in the tether ($\textbf{85a-d}$) no real advantage was gained by the addition of diethylaluminium chloride and the catalyst had an adverse effect where the dienophile was doubly activated ($\textbf{85e}$ and $\textbf{8f}$). In addition, the catalyst caused epimerisation of $\textbf{86c}$ to $\textbf{88c}$ and $\textbf{86f}$ to $\textbf{88f}$ respectively, since the geometry of the diene in $\textbf{85c}$ and $\textbf{85f}$ preclude the formation of these compounds in a normal ETDA reaction.$^7$
A: Yield from uncatalysed reactions (toluene, 160°C).
B: Yield from catalyzed reactions (toluene, 160°C, Et₂AlCl (0.2eq)).

Figure 1.29

In a similar reaction catalyzed by diethyl aluminium ethoxide (Figure 1.30) a
cationic rearrangement of ETDA adducts 90a or 90b (mediated by the Lewis acid)
results in the formation of d-lactones 91a and 91b respectively in modest yield.116
1.2.1.3 Singly activated dienophiles

The rate of ETDA reactions is often lower than expected (Section 1.2.1.2) and this is highlighted by the unsuccessful examples compiled in Figure 1.31.\textsuperscript{103} Even though the diene is activated by an EDG in 92a-g the dienophile is only activated by a single carbonyl, which forms part of the ester tether. No reaction was observed for any of these cases, even when strong heating was applied. Other unsuccessful examples of this type have also been reported.\textsuperscript{117-119}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure131.png}
\caption{Figure 1.31}
\end{figure}

In contrast to cinnamate ester 92a, phenylpropiolate ester 93 (Figure 1.32) cyclised readily in xylene over 20h.\textsuperscript{103} Instead of expected product 94, aromatic compound 95 was produced due to in situ loss of benzoic acid. Adduct 94 could be produced by heating 93 in chloroform for 12 days and this could be converted into 95 by further heating in refluxing xylene.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure132.png}
\caption{Figure 1.32}
\end{figure}
Additional examples which highlight the difference in reactivity between acrylate and propiolate derivatives are shown on Figure 1.33. Acrylate 96a\textsuperscript{11} was recovered in near quantitative yield after heating in refluxing in xylene, whereas 96b was found to be prone to polymerization\textsuperscript{120} to the extent that an ETDA reaction was not even attempted. In contrast, 97a reacted readily in toluene\textsuperscript{120} yielding predominantly 98a in which the hydrogen on the ring junction is cis to the alkyl group in the lactone ring. A similar observation was made for 97b. (The influence of tether groups on the diastereofacial selectivity of ETDA reactions will be discussed in Section 1.2.2.1) Achiral starting material 97c gave racemates 98c and 99c in high yield.\textsuperscript{98}

![Chemical structure of 96](image1)

<table>
<thead>
<tr>
<th>96</th>
<th>X</th>
<th>Solvent</th>
<th>T/°C</th>
<th>t/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Me</td>
<td>xylene</td>
<td>140</td>
<td>18</td>
</tr>
<tr>
<td>b</td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Chemical structure of 97](image2)

<table>
<thead>
<tr>
<th>97</th>
<th>W</th>
<th>X</th>
<th>Y</th>
<th>Solvent</th>
<th>T/°C</th>
<th>t/h</th>
<th>98:99</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>toluene</td>
<td>110</td>
<td>15</td>
<td>86:14</td>
<td>97</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>iPr</td>
<td>H</td>
<td>toluene</td>
<td>80</td>
<td>18</td>
<td>97:3</td>
<td>97</td>
</tr>
<tr>
<td>c</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>xylene</td>
<td>140</td>
<td>24</td>
<td>50:50</td>
<td>96</td>
</tr>
</tbody>
</table>

All of the compounds represented in this Figure are racemic. Structures 98 and 99 indicate relative stereochemistry only.

Figure 1.33
Two examples of attempted ETDA reactions in which the carbonyl of the ester was conjugated to the diene are shown in Figure 1.34. The lack of reactivity of triene 100 is unsurprising (vide supra), but the inertia of 101 demonstrates that even the more reactive acetylenic dienophile requires the additional activation of the tether carbonyl in order for an ETDA reaction to occur. 121

![Figure 1.34](image)

In direct conflict with these results, precursor 102 122 (Figure 1.35) has been shown to undergo cycloaddition at 250°C over 5 days with a modest selectivity for exo adduct 103. This brings into question the results illustrated in Figure 1.34.

![Figure 1.35](image)

1.2.2 Diastereofacial control of IMDA reactions

The examples in Section 1.2.1 deal mainly with differentiation between the exo and endo modes of cycloaddition, which is sometimes termed simple diastereoselection. What follows is an account of the way in which facial diastereoselection can be superimposed onto these two modes. This has been achieved by placing substituents in the tether between the diene and the dienophile (Section 1.2.2.1), incorporation of chiral auxiliaries (Section 1.2.3.2) and enantioselective catalysis (Section 1.2.3.3). (In examples where the starting materials and reagents are achiral, the relative stereochemistry of the racemic products is represented by a single enantiomer only.)
**1.2.2.1 Tether control of facial diastereoselectivity**

The examples in Figure 1.36 each have a tether group allylic to the diene. In each case *trans* fused adducts 106 and 107 were favoured over *cis* adducts 108 and 109, as expected for 1,3,8-nonatrienes with terminally activated dienophiles (Section 1.2). In the case of alcohol 105a there was a modest diastereofacial selectivity for adduct 107a over 106a. This increased to a 2:1 preference for silyl derivative 105b. However, no increase in diastereoselectivity was observed when the benzyl derivative 105c was heated. Greater diastereofacial selectivity was also observed for silyl derivative 105e compared to alcohol 105d, although adduct 106f was favoured when benzyl derivative 105f was heated.

![Chemical structures](image)

| 105 X Y Z T°C t/h 106:107:108:109 % |
|---|---|---|---|---|---|
| a H CO₂Me OH 150 36h 32:45:23:0 60 |
| b H CO₂Me OTMS 150 36h 25:50:25:0 73 |
| c H CO₂Me OBn 115 44h 29:37:34:0 92 |
| d CO₂Me H OH 150 36h 37:33:26:4 71 |
| e CO₂Me H OTMS 150 36h 31:48:17:4 83 |
| f CO₂Me H OBn 115 110h 53:30:13:4 78 |

All of the compounds represented in this Figure are racemic. Structures 106-109 indicate relative stereochemistry only. Figure 1.36
Diastereofacial selectivity in IMDA reactions is demonstrated further by the ester tethered examples in Figure 1.37. In the first two examples only enantiomeric \( \textit{exo} \) adducts with structures 111 and 112 are observed. (In precursors 110a and 110b there are no stereogenic centres (because \( Y \) is a hydrogen atom), hence the two \( \textit{exo} \) transition states which lead to structures 111 and 112 are equal in energy and racemic mixtures of these adducts are produced.) The third example has a stereogenic centre in the tether which causes the \( \textit{exo} \) transition states to be unequal in energy, hence adduct 112c is favoured over 111c. However, starting material 110c is racemic, hence 111c, 112c and 113c are also racemic. (The structures illustrated indicate the relative stereochemistry of the products only.)

\[
\begin{align*}
\text{X} & \quad \text{Me}_2\text{O} & \quad \text{O} & \quad \text{O} \\
\text{Y} & \quad \Delta & \quad o\text{-dichlorobenzene}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>110</th>
<th>X</th>
<th>Y</th>
<th>T/°C</th>
<th>t/h</th>
<th>%</th>
<th>111:112:113:114</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>PhCO₂</td>
<td>H</td>
<td>110</td>
<td>3</td>
<td>50</td>
<td>50:50:0:0</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>CH₃CH₂CH₂CO₂</td>
<td>H</td>
<td>130</td>
<td>3</td>
<td>85</td>
<td>50:50:0:0</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>CH₃CH₂CH₂CO₂</td>
<td>Me</td>
<td>130</td>
<td>5</td>
<td>83</td>
<td>19:76:5:0*</td>
</tr>
</tbody>
</table>

* The relative stereochemistry of the \( \textit{endo} \) adduct was not determined and so the product formed in this case could be either 113c or 114c. All of the compounds represented in this Figure are racemic. Structures 111-114 indicate relative stereochemistry only.

Figure 1.37
A similar investigation was carried out on precursor 115\textsuperscript{125, 126} (Figure 1.38). Exo adducts were produced in excess with a significant stereoselectivity for compound 118 (having the same relative stereochemistry as adduct 112c, illustrated in Figure 1.37).

\[ \text{EtO}_2\text{C} \quad \rightarrow \quad \text{toluene, 24h} \]

\[ \begin{align*}
\text{EtO}_2\text{C} \quad & \quad \text{116} \quad + \quad \text{EtO}_2\text{C} \\
\text{118} \quad & \quad + \quad \text{EtO}_2\text{C} \\
\text{119} \quad & \quad + \quad \text{EtO}_2\text{C}
\end{align*} \]

\[116:117:118:119 \quad (8:83:7:2) \quad 92\% \quad (at \quad 92\% \quad \text{conversion})\]

All of the compounds represented in this Figure are racemic. Structures 116-119 indicate relative stereochemistry only.

**Figure 1.38**

As a synthetic organic chemist it is rewarding to work with enantiopure compounds since these are by far the most commonly encountered targets in natural product synthesis. An example of such a reaction is given in Figure 1.39.\textsuperscript{127} Adduct 121 was obtained in good yield with high enantiopurity. This compound was later elaborated to compound 122 (the ionophore antibiotic indanomycin).\textsuperscript{128} The diastereofacial selectivity was greater for the ethyl moiety than any of the alcohol derivatives in Figure 1.36, highlighting the increased steric demand of the alkyl group.
A successful ETDA reaction on a conjugated dienoic acid derivative is shown in Figure 1.40. Good diastereoselectivity was obtained for compound 125 which arises from epimerization of trans fused exo ETDA adduct 124, under the reaction conditions used.

As part of a recent synthetic study towards the superstolides an IMDA reaction was carried out on chiral aldehyde 126 (Figure 1.41). In this case the two tether groups responsible for the relative diastereoselection work synergistically with each other to produce the major isomer (130) with a reasonable yield and diastereofacial selectivity.
The chair-like transition state (131) which leads to adduct 130 (Figure 1.42) is representative for precursors with saturated four carbon tethers. For IMDA reactions of precursors with four carbon tethers containing a carbonyl in conjugation with the dienophile it was found that the position and character of the tether substituents had a profound effect on the diastereofacial selectivity of the cycloaddition. Compound 132a (Figure 1.43) cyclised to give trans fused ring system 135 predominantly, whereas 132b (in which the protecting groups at C5 and C6 were replaced with the rigid dioxolane ring) produced cis fused variant 136 exclusively. In contrast to 132a, cycloaddition of 133a (in which the stereochemistry at C5 and C6 was inverted) favoured cis fused ring system 137, whereas the rigid dioxolane moiety in 133b instigated a slight preference for trans fused structure 135.
The cycloadducts in Figure 1.43 arise from the intervention of boat-like transition states. These are generally favoured for precursors with four carbon tethers containing one or more sp² centres. A specific example (transition state 138 arising from starting material 132b leading to cis fused ring system 136b) is given in Figure 1.44.
1.2.2.2 Chiral auxiliaries at the dienophile terminus

In the first report in which chiral auxiliaries attached to the dienophile terminus were used to control the facial diastereoselectivity of IMDA reactions, (+)-phenylmenthyl esters (Figure 1.45) were cyclised in the presence of a range of Lewis acid catalysts at various temperatures (Entries 1-6). Only trans fused structures 140 and 141 were obtained in each case. The results for Entries 1-4 show that the choice of catalyst has a dramatic effect on the diastereofacial selectivity and yield of the reaction. The best results (which combined good yields and diastereoselectivities) were obtained when low temperatures and long reaction times were used (Entries 5 and 6). However, even then the highest d.e. obtained was only 72% (Entry 6). The results were not as good as those obtained in the BDA case, where it was possible to carry out the cycloadditions at much lower temperatures.\textsuperscript{133,134}

![Figure 1.45](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Catalyst</th>
<th>T/°C</th>
<th>t</th>
<th>140:141</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>iPr</td>
<td>TiCl\textsubscript{4}</td>
<td>23</td>
<td>6h</td>
<td>14:86</td>
</tr>
<tr>
<td>2</td>
<td>a</td>
<td>iPr</td>
<td>EtAlCl\textsubscript{2}</td>
<td>23</td>
<td>18h</td>
<td>42:58</td>
</tr>
<tr>
<td>3</td>
<td>a</td>
<td>iPr</td>
<td>menthylomegaAlCl\textsubscript{2}</td>
<td>23</td>
<td>84h</td>
<td>33:67</td>
</tr>
<tr>
<td>4</td>
<td>a</td>
<td>iPr</td>
<td>(\textit{l})-bornyloxyAlCl\textsubscript{2}</td>
<td>23</td>
<td>92h</td>
<td>33:67</td>
</tr>
<tr>
<td>5</td>
<td>a</td>
<td>iPr</td>
<td>menthylomegaAlCl\textsubscript{2}</td>
<td>8</td>
<td>10d</td>
<td>32:68</td>
</tr>
<tr>
<td>6</td>
<td>b</td>
<td>H</td>
<td>(\textit{l})-bornyloxyAlCl\textsubscript{2}</td>
<td>8</td>
<td>14d</td>
<td>14:86</td>
</tr>
</tbody>
</table>

**Figure 1.45**
Much better yields and diastereofacial selectivities were obtained for [4.2.0] and [4.3.0] bicyclic adducts with chiral $\alpha,\beta$-unsaturated N-acyloxazolidinone auxiliaries (Entries 1-4 and 5-8 respectively, Figure 1.46). In each series, auxiliaries A and B produced ring system 144 in excess, whereas C and D produced 143. The \textit{exo:endo} diastereoselectivity was excellent in each case, particularly for Entries 1-4.

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>142</th>
<th>$\chi_\rho$</th>
<th>n</th>
<th>143:144</th>
<th>trans:cis</th>
<th>% (maj)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>A</td>
<td>1</td>
<td>17:83</td>
<td>99:1</td>
<td>60</td>
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<td>b</td>
<td>B</td>
<td>1</td>
<td>5:95</td>
<td>99:1</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>C</td>
<td>1</td>
<td>85:15</td>
<td>99:1</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>D</td>
<td>1</td>
<td>97:3</td>
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<td>B</td>
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<td>D</td>
<td>2</td>
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<td>30:1</td>
<td>70</td>
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</table>

Figure 1.46
The diastereofacial selectivity induced by chiral N-acyl-camphor-sultams has also been investigated\textsuperscript{138} and this methodology has been utilized in the synthesis of enantiomerically pure natural product \textbf{147} \textit{(\textsuperscript{(-)}-pulo'upone)}.\textsuperscript{139} These results are summarized in Figure 1.47. Compound \textbf{146} was produced with a yield of 71\% and 93\% d.e., which was increased to 100\% d.e. by crystallization. This provided a highly efficient pathway to the target as well as direct confirmation of the absolute stereochemistry. Comparison to the BDA case\textsuperscript{140} indicates that chelation of the catalyst not only increases the rate of the reaction but it also enhances the \textit{\pi}-facial selectivity observed.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1_47.png}
\caption{Figure 1.47}
\end{figure}

In addition to the diastereofacial selectivity conferred upon the IMDA reaction by the sultam (Figure 1.47) it is also easy to remove and recycle. There have also been reports in which the dienophile has been terminated with more permanent chiral moieties responsible for diastereofacial induction.\textsuperscript{94, 95}
1.2.2.3 Enantioselective catalysis

Boron catalysts $^{148}_{141}$, $^{142}$ and $^{149}_{143}$ (Figure 1.48) have been used successfully to control the enantiofacial selectivity of the IMDA reactions of 2,7,9-decatrienals. Chiral (acyloxy) borane (CAB) complex $^{148}$ is formed from borane:THF and the (+)-tartaric acid derivative shown. Although the exact nature of the catalyst is not yet known, it produced an excellent yield and enantiofacial selectivity of trans fused adduct $^{152a}$ over $^{151a}$ (Entry 1). This was not matched in the case of $^{152b}$ (Entry 2) which was produced with an e.e. of 46%. $^{144}$ It was possible to increase the yield and enantioselectivity of $^{150b}$ by using chiral Bronsted Lewis acid (BLA) $^{149}$, however, the opposite enantiomer $^{151b}$ was produced (Entry 3).$^{143}$

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>$^{150}$</th>
<th>X</th>
<th>Catalyst</th>
<th>$^{151}:^{152}$</th>
<th>trans:cis</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>Me</td>
<td>$^{148}$</td>
<td>4:96</td>
<td>1:99</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>H</td>
<td>$^{148}$</td>
<td>27:73</td>
<td>1:99</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>b</td>
<td>H</td>
<td>$^{149}$</td>
<td>90:10</td>
<td>100:0</td>
<td>95</td>
</tr>
</tbody>
</table>

Figure 1.48
Good results have also been obtained with titanium catalysts 153 and 154 (Figure 1.49) derived from (+)- and (-)-tartaric acid respectively. Catalyst 153 produced good yields and enantiofacial selectivity in IMDA reactions of triene starting materials with three or four carbon tethers (Entries 1-3). In each case, trans fused ring system 156 was favoured. The enantioselectivity of the third reaction was increased by carrying out the reaction with catalyst 154 in toluene/petroleum ether instead of mesitylene (Entry 4). As expected, the opposite enantiomer (157c) was produced in excess.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>156:157</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>153 (0.1eq)</td>
<td>mesitylene</td>
<td>98:2</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>153 (0.1eq)</td>
<td>mesitylene</td>
<td>93:7</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>153 (0.1eq)</td>
<td>mesitylene</td>
<td>94:6</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>154 (0.3eq)</td>
<td>toluene/pet. ether</td>
<td>2:98</td>
<td>70</td>
</tr>
</tbody>
</table>

Figure 1.49
In a similar study, starting materials **159a-d** were treated with chiral copper catalyst **158** (Figure 1.50). Treatment of three of the starting materials (**159a,b and d**) with the catalyst provided high levels of asymmetric induction and excellent yields, but the fourth (**159c**) failed to cyclise even after extended periods of time. This anomalous behaviour has not yet been rationalized. The high level of enantiofacial control possible for the cycloaddition of **159a and b** provided the authors with the methodology for total synthesis of (-)-isopulo'upone.

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>159</th>
<th>X</th>
<th>n</th>
<th>Catalyst</th>
<th>t/h</th>
<th>160:161</th>
<th>trans:cis</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>1</td>
<td>158 (1.0eq)</td>
<td>24</td>
<td>93:7</td>
<td>99:1</td>
<td>89</td>
</tr>
<tr>
<td>b</td>
<td>Ph</td>
<td>1</td>
<td>158 (0.5eq)</td>
<td>5</td>
<td>96:4</td>
<td>95:5</td>
<td>86</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>2</td>
<td>158 (1.0eq)</td>
<td>24</td>
<td>99:1</td>
<td>-</td>
<td>&lt;20</td>
</tr>
<tr>
<td>d</td>
<td>Ph</td>
<td>2</td>
<td>158 (1.0eq)</td>
<td>14</td>
<td>98:2</td>
<td>84:16</td>
<td>97</td>
</tr>
</tbody>
</table>

**Figure 1.50**
1.3 The transannular Diels-Alder (TDA) reaction

The TDA reaction is a special subset of IMDA reactions in which the diene and dienophile are connected by two tethers to form a macrocycle. Cycloaddition produces a tricyclic structure which has four new stereogenic centres and an alkene functional group, which provides a convenient access point for elaboration of the product (Figure 1.51). Structure 163 (which arises from the TDA reaction of fourteen membered macrocycle 162) and 165 (from thirteen membered macrocycle 164) provide potential access to the ABC and BCD rings of the cyclopentano perhydrophthalene nucleus of steroids (166) respectively. From a synthetic viewpoint, consideration of the TDA strategy is eminently worthwhile in the synthesis of rare and biologically active steroids.

Figure 1.51

In an even more elaborate scenario (Figure 1.52) it may be possible that macrocycle 167, containing a bis-diene (in the form of a conjugated tetraene) and a bis-dienophile, could undergo a tandem TDA reaction to produce the ABCD ring system of a steroid (168) in a single step. A suitable stereocontrolling element (R) could be included to influence the relative stereochemistry of the eight incipient stereogenic centres. The elegance of this strategy cannot be overemphasized. It may be possible that four carbon-carbon bonds could be formed simultaneously in a stereocontrolled manner, simply by heating the starting material in an appropriate solvent. Recycling of the solvent, the only other substance required, would result in a synthesis that was both economically and environmentally sound. The operational simplicity of this reaction being matched only by the remarkable stereochemical complexity of the adduct produced.
1.3.1 TDA of carbocyclic systems

Deslongchamps has been pre-eminent in unlocking the stereochemical factors affecting TDA reactions of thirteen, fourteen and fifteen membered macrocycles.\textsuperscript{29} An example of a TDA reaction of a fourteen membered macrocycle is given in Figure 1.40. Each of the alkenes in the starting material can be either \textit{cis} or \textit{trans}, giving rise to eight stereoisomers of macrocycle 170. These in turn can give rise to eight diastereomeric TDA adducts.
Each of the eight triene precursors were prepared, macrocyclised and subjected to conditions intended to promote TDA reactions. Macrocycle 170 was formed under mildly basic conditions from acyclic starting material 169 at 80°C. This Z,Z,E-cyclooctadecatriene proved to be very reactive and cyclised to give racemic adduct 171 exclusively under the conditions used for macrocyclisation, albeit with an unimpressive yield. Adduct 172 was not detected.

The reactivity of the starting materials and stereoselectivity of each reaction could be predicted by invoking chair-boat-chair transition states. Two of these transition states are possible for each of the macrocycles and they are illustrated for starting material 170 in Figure 1.54. In this case there are unfavourable steric interactions in syn transition state 174 which are not found in anti transition state 173, hence adduct 171 was formed exclusively.

In five out of the eight examples this transition state model accurately predicted the adducts which formed. The study also showed that six out of the eight possible diastereomeric products could be produced with remarkable levels of stereocontrol. For the three macrocycles which gave rise to unexpected products it was found that transannular ene reactions, 1,5-sigmatropic hydrogen migrations and thermal isomerisation of the diene or dienophile had occurred. Semiempirical calculations on some of these competing processes have been undertaken and good correlation between the experimental results and theoretical studies were observed.
This methodology has been utilized in a study directed towards the enantioselective synthesis of quassine (178), from the quassinoid family of steroids (Figure 1.55). Adducts 176 and 177 both arise from anti chair-boat-chair transition states, however, severe steric interactions in the latter result in a high level of diastereofacial selectivity and impressive yield of the major tricycle. Products arising from syn transition states were not reported.

![Figure 1.55](image)

### 1.3.2 TDA of macrocyclic lactones

Three examples of TDA reactions on macrolactones have been reported. In the first example, the intramolecular Horner-Emmons reaction of aldehyde 179 resulted in the formation of endo adduct 181 directly, as a single racemic product in 63% yield. The intermediate macrocycle 180 was not detected.

![Figure 1.56](image)
Production of *endo* adduct 181 (Figure 1.56) via TDA reaction of 179 is in sharp contrast to the ETDA reaction of 140 (Figure 1.57), which required heating in toluene for 44h at 170°C to cause cycloaddition and produced *exo* adduct 183 in excess (*exo:endo* (4:1)).

![Reaction Scheme](image)

Figure 1.57

The enantioselective synthesis of (-)-oblongolide (186) is shown in Figure 1.58.32 This reaction has the same *exo:endo* selectivity as the example shown in Figure 1.56 although a higher temperature was required for the cycloaddition to occur. The presence of the methyl group in the carbon tether between the diene and dienophile of starting material 185 was sufficient to provide excellent diastereofacial selectivity for the desired natural product.

![Reaction Scheme](image)

Figure 1.58
The starting material in the final example (compound 187, Figure 1.59), investigated as an approach to Nargenicin A1, has many more stereochemical features than the previous two. The cis fused product (188) was obtained in high yield and no other adducts were detected.

![Chemical structure of 187 and 188](image)

**Figure 1.59**

The IMDA reaction in Figure 1.60 is much less stereoselective than the TDA reaction in Figure 1.59. Also, the main product which resulted was trans fused adduct 189. This gives weight to the hypothesis that the exo:endo diastereoselectivity in the former reaction is due to conformational preferences of macrocycle 187. The minor product from the IMDA reaction (190) has the same absolute stereochemistry as the compound obtained from the TDA reaction (188) and the configuration of the carbon atom in the ring junction closest to the acetonide group is the same for all three adducts (188, 189 and 190). This indicates that the diastereofacial selectivity arises from the same stereocontrolling element in each case. The origin of this selectivity is the 1,3-allylic strain between the bulky bromine atom and the acetonide moiety, which raises the energy of the transition state leading to one of the two facial isomers.
Figure 1.60

\[
\Delta \text{toluene, } 110^\circ C, \ 24h
\]

190:191 (67:33), 83%

Figure 1.60
2 Remote stereocontrol of ETDA reactions

2.1 Introduction

The absolute stereoselectivity of IMDA reactions can be controlled by incorporating stereogenic centres into the tether connecting the diene and the dienophile; by attaching a chiral auxiliary to the dienophile terminus; or by enantioselective catalysis of an achiral triene (Section 1.2.2). However, the effect of placing a stereogenic centre allylic to the diene but remote from the tether (Figure 2.1) is an unexplored method of controlling the π-facial selectivity of IMDA reactions. Four examples in which the IMDA precursor has a stereogenic centre in this position are discussed below.

![Figure 2.1](image)

![Figure 2.2](image)
The diastereoselective IMDA reaction of 201 (Figure 2.2) occupied a central position in the strategy developed for the synthesis of 203 (the aglycone of (+)-lepicidin). The IMDA precursor has a number of stereogenic centres which could affect the overall stereoselectivity: in the tether; in the dienophile auxiliary; and in the macrolide. The observed diastereoselectivity (91:9) could also have been influenced by chelation of the Lewis acid catalyst. It is therefore not possible to gauge the contribution of the chiral lactone to the overall stereoselectivity which was observed, or even to determine whether it had any effect at all. In fact, the outcome of this reaction is comparable to the outcome of the IMDA reaction of 142b (Entry 2, Figure 1.46, Section 1.2.2.2) in which neither the tether group nor the chiral lactone were present in the starting material.

An IMDA reaction also played a central role in a recent synthesis of (+)-himbacine (206) (Figure 2.3). The diene in starting material 204 had a remote chiral allylic substituent, which engendered a useful diastereoselectivity for adduct 205. However, in this example the diene is semicyclic and the stereogenic centre is located within the lactone ring. Prediction of the π-facial selectivity is more straightforward in this case since bond rotation at the stereogenic centre cannot occur (i.e. the dienophile is expected to approach the diene from above, as drawn in Figure 2.3). A number of similar syntheses of himbacine (or derivatives) involving this strategy have been reported.157-159

![Figure 2.3](image-url)
A semicyclic diene was also utilized in the ETDA reaction depicted in Figure 2.4. Under the reaction conditions employed, the major product from the reaction (209) arises from double bond migration of ETDA adduct 208. Although the combined yield of compounds 208 and 209 was low, no other cycloaddition products (or compounds derived from them) were isolated with yields of greater than 1%, which could indicate that the dioxolane ring conferred a high level of diastereoselectivity in the initial ETDA reaction.

Figure 2.4

An ETDA reaction involving an acyclic precursor is shown in Figure 2.5. In this case the starting material (210) has a stereogenic centre allylic to the diene, but the tether connecting the diene and dienophile was also asymmetric. In addition, the starting material consisted of mixture of diastereomers, epimeric at the remote allylic position. The authors commented that the tether substituent provided good stereochemical transcription at the adjacent ring junction site for major isomers 212 and 214, however, there was little endo:exo discrimination. Because the starting material contains a mixture of epimers at the remote allylic site it is possible for double stereodifferentiation to occur. For this reason, each of the products isolated (212-214) need not contain equimolar amounts of their component diastereomeric epimers, however, no information about this was provided. Consequently, it is not possible to extract any useful information about the effect of the remote allylic substituent from this very complicated example.
Figure 2.5

Placing substituents allylic to the diene but remote from the tether could potentially provide a new and versatile way of controlling the stereochemical outcome of IMDA reactions. With the exception of the stereochemically biased semicyclic dienes, very little information can be gained about the stereocontrolling effect of the remote allylic substituent in the examples shown above, so it was decided to undertake a systematic study of reactions on simple ETDA precursors, unburdened by extra stereocontrolling elements, of the type shown in Figure 2.6.

Figure 2.6
Ester tethered substrates were chosen for a number of reasons. There are very few examples of asymmetric ETDA reactions and stereocontrol cannot normally be augmented by the addition of Lewis acid catalysts (Section 1.2.1.1), so it is desirable to find alternative methods. The ester tether itself provides a convenient means of attaching the diene to the dienophile, allowing a range of IMDA precursors to be constructed from simple chiral dienols. By activating the dienophile with a second (terminal) EWG the rate retarding effect of the ester tether is largely compensated for. The inherent flexibility of this system means that the effect of the dienophile geometry can also be readily investigated (by preparing maleate and fumarate derivatives), as can the nature of the dienophile which can be terminated with either a carboxylic acid or a derivative thereof (Chapter 3).

In order to ascertain whether or not it is possible to control the stereochemical outcome of ETDA reactions using a remote chiral allylic substituent, an initial investigation involving maleate esters of the type shown in Figure 2.7 was undertaken. It was anticipated that exo adducts 217 and 218 would be favoured since the dienophile portion was terminated with a methyl ester group (Section 1.2.1.1). It was also hoped that the asymmetric moiety would provide a high level of \( \pi \)-facial stereoselectivity, such that one of the exo adducts (217 or 218) would be produced in good yield with a high diastereomeric excess.

![Figur 2.7]
2.2 Synthesis of dienols

The synthesis of the two chiral dienols, which were used to prepare precursors for subsequent ETDA reactions, are discussed in Sections 2.2.1 and 2.2.2.

2.2.1 Synthesis of TBS dienol

L-ascorbic acid (221) was treated with acetone (Scheme 2.1) according to the method of Jung and Shaw\textsuperscript{163} to give acetonide 222 as a white crystalline solid. Oxidative cleavage of 222 was accomplished with potassium carbonate and hydrogen peroxide in water and the resulting potassium salt (potassium (2R,3S)-3,4-O-isopropylidene-2,3,4-trihydroxybutanoate) was treated with ethyl iodide to give $\alpha$-hydroxy ester 223 according to the method of Abushanab et al.\textsuperscript{164} (This paper provides a detailed experimental procedure for preparing an epimer of 223 from D-isoascorbic acid. An earlier reference by the same author\textsuperscript{165} outlines the synthesis of the corresponding methyl ester of 223. Although both of these papers refer to the preparation of compound 223, neither of them report the physical properties of this material.)

Treatment of $\alpha$-hydroxy ester 223 with tert-butyldimethylsilyl chloride\textsuperscript{166} produced silyl ether 224, which could be purified conveniently by distillation. Reduction of 224 with DIBALH (1.1eq) at -78°C produced a mixture of alcohol 225, aldehyde 226 and unreacted starting material. Addition of further DIBALH (1.1eq) produced alcohol 225 cleanly and this material could then be oxidized to aldehyde 226 by the addition of the Dess-Martin periodinane\textsuperscript{167} (Section 6.6.1). It was subsequently found that ester 224 could be reduced directly to aldehyde 226 provided that the temperature was maintained at -100°C, rapid stirring was applied and the DIBALH was added slowly using a syringe pump. The yield of aldehyde 226 achieved using this method was 86% after distillation.
Conditions: (i) acetone, CH$_3$COCl, RT, 8h, 76%; (ii) K$_2$CO$_3$, H$_2$O$_2$, H$_2$O, RT, 24h then CH$_3$CH$_2$I, CH$_3$CN, reflux, 44h, 83%; (iii) TBSCl, imid., DMF, RT, 30min, 68%; (iv) DibalH, CH$_3$Cl, -78°C, 10min then RT, 1h; (v) Dess-Martin periodinane, CH$_3$Cl$_2$, RT, 1h, 58% (2 steps); (vi) DibalH, CH$_3$Cl$_2$, -100°C, 86%; (vii) Ph$_3$PCHCHCHCO$_2$Et, CH$_3$Cl$_2$, reflux, 1.5h then thiophenol, AIBN, PhH, reflux, 3h; (viii) DibalH, CH$_3$Cl$_2$, -78°C, 58% (3 steps).

Scheme 2.1
Treatment of aldehyde 226 with the stabilized ylid ethyl 4-(triphenylphosphoranylidene)-(2E)-2-butenoate\textsuperscript{168, 169} (Section 6.6.2) in refluxing dichloromethane produced homologated ester 227 as a mixture of Z- and E-stereoisomers\textsuperscript{7} (79:21) with a yield of 78% after chromatography. Radical isomerisation of the Z-stereoisomer was accomplished by treating the mixture with catalytic thiophenol and AIBN in the presence of ultraviolet light.\textsuperscript{170} It was found that complete isomerisation could only be achieved by recharging the reaction mixture with fresh thiophenol and AIBN at 1h intervals, with a total reaction time of 3h. The crude product from the isomerisation was used in the subsequent steps without additional purification. Reduction of homologated ester 227 with DIBALH produced TBS dienol 228 as a colourless oil in 58% yield from aldehyde 226 after chromatography.

2.2.2 Synthesis of deoxy dienol

Diethyl L-malate (230) was prepared from L-malic acid (229) by refluxing in ethanol (Scheme 2.2) in the presence of catalytic sulphuric acid. Regioselective reduction of 230 with borane-dimethyl sulphide complex, followed by treatment of the resulting diol (ethyl (3S)-3,4-O-isopropylidene-3,4-dihydroxybutanoate) with 2,2-dimethoxypropane according to the method of Saito \textit{et al.}\textsuperscript{171} produced acetonide 231 in 70% yield after distillation.

Attempted preparation of aldehyde 233 directly from acetonide 231 with DIBALH at -100°C (using the method devised for aldehyde 226, Section 2.2.1) inexplicably resulted in yields ranging from 4-10%. For this reason it was more practical to prepare aldehyde 233 using a two step procedure. Acetonide 231 was cleanly reduced with lithium aluminium hydride in refluxing THF, producing a 92% yield of alcohol 232 after Kugelrohr distillation. (Reduction of the corresponding methyl ester with lithium aluminium hydride can be accomplished at room temperature.\textsuperscript{171}) Oxidation of alcohol 232 with the Dess-Martin periodinane\textsuperscript{167} (Section 6.6.1) furnished aldehyde 233 in 78% yield after chromatography.

\textsuperscript{1} E- and Z- refer to the geometry of the newly formed double bond.
Homologation of aldehyde 233 with ethyl 4-(triphenylphosphoranylidene)-(2E)-2-butenooate\textsuperscript{168, 169} (Section 6.6.2) produced diene ester 234 as a mixture of Z- and E- stereoisomers (50:50) in a 35% yield after chromatography. (An attempt to increase the yield of this reaction using triethyl (2E)-4-phosphono-2-butenooate and sodium hydride in THF\textsuperscript{172} did not produce any of the desired product by TLC, but resulted in complete destruction of the starting material.) Isomerisation of the Z-stereoisomer was accomplished by treating the mixture with thiophenol and AIBN\textsuperscript{170} using the method developed for homologated ester 227 (Section 2.2.1), although it was only necessary to recharge the reaction mixture once with fresh reagents and shorter reaction times were used. The yield of pure diene ester 234 was 78% after chromatography. Reduction of 234 with Dibal-H at -78°C gave deoxy dienol 235 in 40% yield as a colourless oil. It is not clear why the reactions in this sequence produced low yields compared to those in Section 2.2.1, but since a quantity of deoxy dienol was available it was decided to postpone optimization of these procedures in favour of carrying out the subsequent ETDA reactions.

\[ \text{Conditions: (i) EtOH, H}_2\text{SO}_4, \text{reflux, 16h, 76%; (ii) BMS, NaBH}_4, \text{THF, RT, 30min then DMP, p-} \]
\[ \text{TsOH.H}_2\text{O, acetone, RT, 30min, 70% (2 steps); (iii) LiAlH}_4, \text{THF, reflux, 14h, 92%; (iv) Dess-Martin periodinane, CH}_2\text{Cl}_2, \text{16h, 78%; (v) Ph}_3\text{PCHCHCHCO}_2\text{Et, CH}_2\text{Cl}_2, \text{reflux, 1.5h 35% then thiophenol, AIBN, PhH, reflux, 1h, 78%; (vi) Dibal-H, CH}_2\text{Cl}_2, -78^\circ\text{C, 40%}.} \]

Scheme 2.2
2.3 Synthesis of ETDA precursors

The preparation of a range of ETDA precursors from the two chiral dienols (Section 2.2) and maleic anhydride, followed by treatment with diazomethane\textsuperscript{173} (Section 6.6.3) are given in Sections 2.3.1 and 2.3.2.

2.3.1 Synthesis of hydroxy and silyloxy precursors

Dienol 228 (Section 2.2.1) was reacted with maleic anhydride\textsuperscript{174} (Scheme 2.3) to form carboxylic acid 236 in near quantitative yield after chromatography. Deprotection of the silyl group\textsuperscript{166} gave alcohol 237 which was converted to methyl ester 238a using an ethereal solution of diazomethane\textsuperscript{173} (Section 6.6.3). Compound 238a was used to prepare trimethylsilyl derivative 238b and triisopropylsilyl derivative 238d using the appropriate trialkylsilyl triflate.\textsuperscript{175} The poor reactivity of the 2° alcohol was highlighted by the long reaction times which were required and the modest yields which were obtained, in spite of the highly reactive reagents used. (No reaction was observed between alcohol 238a and triisopropylsilyl chloride in the presence of imidazole and DMAP.\textsuperscript{176}) Treatment of carboxylic acid 236 with diazomethane\textsuperscript{173} (Section 6.6.3) gave tert-butyldimethylsilyl derivative 238c.

Outwardly, a more economical strategy can be devised in which silyl ether 238c is deprotected to form alcohol 238a, thereby eliminating one step (formation of compound 237) from the overall scheme. In practice this approach was rendered undesirable because treatment of tert-butyldimethylsilyl ether 238c with tetrabutylammonium fluoride gave rise to an unacceptably low yield of secondary alcohol 238a (26%).
Conditions: (i) TEA, MA, DMAP, CH$_2$Cl$_2$, RT, 10 min, 99%; (ii) TBAF, THF, RT, 16 h, 85%; (iii) CH$_3$N$_2$, diethyl ether, 0°C, 74%; (iv) TMSOTf, TEA, DMAP, CH$_2$Cl$_2$, RT, 2.5 h, 51%; (v) CH$_3$N$_2$, diethyl ether, RT, 80%; (vi) TIPSOTf, TEA, CH$_2$Cl$_2$, RT, 20 h, 58%.

Scheme 2.3
2.3.2 Synthesis of deoxy precursors

Treatment of alcohol 235 with maleic anhydride\(^1\) (Scheme 2.4) produced carboxylic acid 239 in quantitative yield after chromatography. The yield of methyl ester 240 obtained from acid 239 by treatment with diazomethane\(^3\) (Section 6.6.3) was discouraging and unexpected. From this point on it was decided to carry out small scale diazomethane reactions at low temperatures (< 0°C) and to follow the reactions by TLC, rather than follow the standard procedure which is to add the reagent until a yellow colour persists and evolution of nitrogen subsides. In this way it was hoped to minimize side reactions (such as addition to activated alkenes to form 4,5-dihydro-3,4-pyrazoles\(^,\) which could cause low yields in the highly functionalised olefins reported here.

![Diagram](image)

Conditions:  
(i) TEA, MA, DMAP, CH\(_2\)Cl\(_2\), RT, 30 min, 100%;  
(ii) CH\(_2\)N\(_2\), diethyl ether, RT, 18%.

Scheme 2.4

2.4 ETDA reactions

Each of the ETDA precursors prepared in Section 2.3 was heated in refluxing toluene under an argon atmosphere. Dilute solutions of the starting material (5mmol/L) were used in order to minimize BDA reactions and a small amount of 2,6-di-tert-butyl-4-methylphenol (0.20eq) was added to prevent oxidation of the conjugated diene moiety of the starting material. The same conditions were employed in each case to allow direct comparisons with other ETDA reactions to be made. Product ratios were determined from proton NMR spectra of crude reaction mixtures and yields were calculated from the amount of material isolated after chromatography.
2.4.1 ETDA reactions of the *hydroxy* and *silyloxy* precursors

The ETDA reactions of precursors *238a-d* each produced a mixture of isomers *241* and *242* (Scheme 2.5). In all of the isomers (*241a-d* and *242a-c*) the coupling constant between the two hydrogen atoms at the ring junction was found to be 13.6-13.8Hz, which indicates that the two rings are *trans* fused in each case. It can be deduced from this that the ETDA adducts originated from *exo* transition states (Section 1.2). (Unfortunately it was not possible to characterize compound *242d* since the amount of it produced was very small and it could not be isolated in pure form.) Trace amounts of other compounds could be detected in the proton NMR spectra of the crude reaction mixtures which may have been due to *endo* adducts, however, it was not possible to isolate sufficient quantities of these very minor components to allow full characterization.

![Diagram of ETDA reactions](image)

<table>
<thead>
<tr>
<th>238 P</th>
<th>t/h</th>
<th>241:242 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>a H</td>
<td>5</td>
<td>66:34</td>
</tr>
<tr>
<td>b TMS</td>
<td>12</td>
<td>82:12</td>
</tr>
<tr>
<td>c TBS</td>
<td>15</td>
<td>91:9</td>
</tr>
<tr>
<td>d TIPS</td>
<td>18</td>
<td>96:4</td>
</tr>
</tbody>
</table>

*Conditions:* BHT, toluene, reflux.

*Scheme 2.5*
Diastereofacial selectivity was observed in all of the ETDA reactions and in each case the major isomer produced had general structure 241 (Section 2.4.1.1). As expected the lowest level of stereocontrol was observed for alcohol 238a and this increased according to the size of the silyl protecting group. The triisopropylsilyl derivative 238d exhibited the largest ratio between structures 241 and 242 (96:4) corresponding to a diastereomeric excess of 92%. This remarkable level of diastereococontrol (coupled with the favourable yield of the major isomer and the ease with which it could be isolated) signals the power of remote allylic substituents to control the \( \pi \)-facial selectivity of IMDA reactions.

It was not possible to separate dienols 241a and 242a, however, it was possible to unambiguously show that the major diastereomer from the ETDA reactions of precursors 238a and 238b had identical stereochemistry. A mixture of alcohols 241a and 242a (66:34) was treated with trimethylsilyl chloride to produce ether derivatives 241b and 242b (66:34) in 61\% yield (Scheme 2.6). The major and minor isomers in this reaction were identical in every respect to those produced in the ETDA reaction of precursor 238b (Scheme 2.5). This could indicate that the transition states responsible for stereocontrol of the ETDA reactions of silyl precursors 238b-d might be similar to those involved in the formation of 241a and 242a (Section 2.4.1.2).

![Scheme 2.6](image)

Conditions: TMSCl, imid., DMF, RT, 74\%.
Several attempts were made to prepare the tert-butyldimethylsilyl and triisopropylsilyl derivatives (reactions (i)a-e and (ii)a-d respectively) from a mixture of alcohols 241a and 242a (66:44) (Scheme 2.7). These reactions were not successful and generally resulted in complex mixtures or recovery of the starting material. Two unsuccessful attempts ((iii)a, b) were also made to deprotect the tert-butyldimethylsilyl derivative 241c. The first resulted in degradation of the starting material, whereas no reaction was observed in the second. These unsuccessful reactions all highlight the steric inaccessibility of the secondary alcohol or ether group adjacent to the bicyclic framework in compounds 241a-d and 242a-c.

(i)a-e

241a + 242a (1.9:1) \( \xrightarrow{\text{imid., DMAP, DMF, RT, 24h; (i)b TBSCl, pyr., DMAP, CH}_2\text{Cl}_2, 80^\circ\text{C, 5h, (i)c TBSCl, imid, DMF, 80^\circ\text{C, 18h;}}\) 241c + 242c

(ii)a-d

241a + 242a (1.9:1) \( \xrightarrow{\text{imid., DMAP, DMF, RT, 24h; (i)b TBSCl, pyr., DMAP, CH}_2\text{Cl}_2, 80^\circ\text{C, 18h;}}\) 241d + 242d

(iii)a, b

241c \( \xrightarrow{\text{imid., DMAP, DMF, 80^\circ\text{C, 18h;}}\) 241a

Conditions: (i)a TBSCl, imid., DMAP, DMF, RT, 24h; (ii)b TIPSCI, pyr., DMAP, CH2Cl2, 80°C, 5h, (i)c TBSCl, imid, DMF, 80°C, 18h; (ii)d TBSCI, DMAP, DMF, 80°C, 18h; (iii)e TBSOTf, TEA, DMAP, CH2Cl2, RT, 18h; (iiia) TIPSCI, imid., DMAP, DMF, RT, 24h; (iiib) TIPSCI, pyr., DMAP, CH2Cl2, 80°C, 18h; (iiic) TIPSCI, 2,6-lutidene, DMAP, DMF, 80°C; (iiid) TIPSOTf, TEA, CH2Cl2, DMAP, RT, 18h; (iiie)a TBAF, THF, RT, 15min; (iiie)b KF, 18-Crown-6, THF, RT, 48h.

Scheme 2.7

2.4.1.1 Determination of the stereochemistry of the hydroxy and silyloxy ETDA adducts

COSY spectra (Appendices 1.2C and 1.3C) were used to confirm the connectivity of the major and minor adducts produced in the ETDA reaction of 238b (Section 2.4.1), then NOESY spectra (Appendices 1.2N and 1.3N) were used to determine the relative stereochemistry. The absolute stereochemistry of the starting material was known and proton NMR spectra indicated that both of the ETDA adducts possessed trans fused ring systems. This limited the structures of the two products to 241b and 242b, but it was still necessary to determine which isomer was which. Fortunately the nOe’s observed for hydrogen atoms in the side chain were strikingly different for the two adducts (Figure 2.8). These facts, combined with conformational analysis using molecular models, enabled a confident assignment of the absolute stereochemistry of each isomer to be made.
Selected data from the NOESY spectrum observed for the major adduct is given in Figure 2.8 along with the two trans fused bicyclic structures which are possible for this compound.

<table>
<thead>
<tr>
<th>major adduct</th>
<th>H</th>
<th>nOe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>8, 10</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>4, 5</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

The numbering system used to identify the hydrogen atoms in structures 241b and 242b has been customized to simplify the explanation of the observed nOe's. This numbering system has also been used to identify the carbon and oxygen atoms to which the respective hydrogen atoms are attached.

Figure 2.8

Rotation of C5-C8 bond in structures 241b or 242b gives rise to three staggered conformations, each of which corresponds to an energy minimum. The three conformations for structure 241b (243, 244 and 255) are illustrated in Figure 2.9.

Figure 2.9
A molecular model (MM2 force field,\textsuperscript{181, 182} local minimum) for conformation 243 of structure 241b is shown Figure 2.10. (In order to see the pertinent atoms more clearly, the hydrogen atoms attached to the methyl groups in the molecule have been removed.) In this conformation, the dihedral angle between hydrogen atom H5 and the oxygen atom on C8 bearing the trimethylsilyl group is approximately 180°. Rotation about the C8-C9 bond places the molecule in a conformation that simultaneously situates hydrogen atom H8 proximate to H4 and H5; H9 to H6; and H10 to H5. This corresponds to the nOe's observed for the major adduct of the ETDA reaction (Figure 2.8). No other reasonable conformation can simultaneously give rise to these four nOe's.

![A molecular model (MM2 forcefield, local minimum) of compound 241b (with 24 hydrogen atoms removed) in conformation 243 (Figure 2.9). The arrows indicate hydrogen atoms which are in close proximity.](Figure 2.10)
Selected data from the NOESY spectrum observed for the minor adduct is given in Figure 2.8 along with the two possible trans fused bicyclic structures.

The numbering system used to identify the hydrogen atoms in structures 241b and 242b has been customized to simplify the explanation of the observed nOe's. This numbering system has also been used to identify the carbon and oxygen atoms to which the respective hydrogen atoms are attached.

Figure 2.11

A similar conformational analysis to the one carried out for structure 241b was carried out for structure 242b. Figure 2.12 shows structure 242b in a staggered conformation, where the dihedral angle between hydrogen atom H5 and the oxygen atom on C8 bearing the trimethylsilyl group is approximately 180° (analogous to conformation 243 of structure 241b in Figures 2.9 and 2.10). Rotation about the C8-C9 bond places the molecule in a conformation that simultaneously brings hydrogen atom H8 close to H5 and H6; H9 to H4; and H10 to H5. This corresponds to the nOe's observed for the minor adduct of the ETDA reaction (Figure 2.11). No other reasonable conformation brings these atoms into close proximity at the same time.
A molecular model (MM2 forcefield, local minimum) of compound 242b (with 24 hydrogen atoms removed). The arrows indicate hydrogen atoms which are in close proximity.

Figure 2.12

The previous discussion demonstrates that structure 241b has access to a staggered conformation which is expected to simultaneously give rise to all of the nOe's observed in the NOESY spectrum of the major adduct of the ETDA reaction of 238b. Likewise, one of the staggered conformations available to structure 242b is expected to generate the nOe's observed for the minor adduct concurrently. Even more importantly than this, there is no single conformation for structure 241b (staggered or eclipsed) which can simultaneously account for the nOe's observed for the minor adduct. In addition, structure 242b cannot be placed in any conformation which would simultaneously give rise to the nOe's observed for major adduct. These observations provide convincing evidence that the major adduct from the ETDA reaction of 238b has structure 241b and the minor adduct has structure 242b. Although this analysis does not constitute unequivocal proof of the absolute stereochemistry of these compounds, it does allow a confident stereochemical assignment of each adduct to be made.
It is important to stress that this argument rests on the fact that there is constant rotation about the C5-C8 bond, but in certain conformations the molecule experiences energy minima. Statistically, it is likely that at any given point in time the number of molecules with this conformation would be disproportionately high and that nOe’s would be observed for the hydrogen atoms which are placed in close proximity because of it. It follows that the number of molecules in less favourable conformations, at the same point in time, would be lower and that the nOe’s arising from them would be weaker. For conformations corresponding to energy maxima, the nOe’s might even fall below detectable levels. The fact that strong nOe’s were observed for some of the protons in each of the NOESY spectra (but not for the others) is evidence of this effect; the fact that the NOESY spectra are different for each of the adducts is a consequence of their dissimilar structure; and the fact that only one of the structures can adequately explain the origin of the nOe’s in each NOESY spectrum, permits the stereochemical assignment of each ETDA adduct to be made. (The configuration of the C1-C14 side chain of maitotoxin has been determined using a similar approach.\textsuperscript{183})

The NOESY spectra elicited for 241c and 241d were similar to that obtained for 241b (Appendix 1.2C), hence the major isomer has the same relative stereochemistry throughout the series. This is also substantiated by the fact that the ratio of the major adduct to the minor adduct increased as the size of the silyl protecting group was increased from trimethylsilyl to triisopropylsilyl (Section 2.4.1). (Unfortunately it wasn’t possible to obtain reliable NOESY spectra for minor adduct 242c because the amount of material isolated was too small. Even when FID’s were collected for a period of 64h the nOe’s were not large enough to be detected.)

Further evidence for these stereochemical assignments was sought from X-Ray crystallographic studies which necessitated the derivation of alcohols 241a and 242a into separable, crystalline products. Esterification of the alcohol mixture (241a:242a (66:34)) with acetic anhydride (using triethylamine and DMAP in dichloromethane) or 4-nitrobenzoyl chloride (with pyridine and DMAP in dichloromethane) gave mixtures of the corresponding esters (66:34) in yields of 62% and 100% respectively, but in each case the adducts were found to be chromatographically inseparable. No reaction was observed with 3,5-dinitrobenzoyl chloride or 4-biphenylcarbonyl chloride (using the same conditions as those used for 4-nitrobenzoyl chloride), further highlighting the low reactivity of the secondary alcohol group.
A mixture of alcohols 241a and 242a (66:34) was treated with sulfonic acid resin in acetone, resulting in transesterification of the starting materials to derivatives 246 and 247 (66:34) respectively (Scheme 2.8). Transesterification to the more highly substituted acetonide is possible where the two secondary alcohols bear a trans relationship to each other in the incipient five membered ring.\(^\text{132}\) Whereas 241a could not be separated from 242a, 246 was separable from 247 using standard chromatographic techniques.

**Conditions:** Amberlist IR-118 resin, acetone, RT, 21h, 96%.

**Scheme 2.8**

Treatment of 247 with 4-nitrobenzoyl chloride produced ester derivative 248 (Scheme 2.9). This material was found to be unsuitable for X-Ray crystallographic analysis since it was not crystalline. Preparation of a range of derivatives in the hope that one of them might produce crystals suitable for X-Ray analysis could have proven to be a futile exercise, hence it was decided to abandon this strategy in favour of preparing adducts suitable for carrying out further nOe difference experiments, which do not rely on the physical state of the material.
In order to ensure that the nOe difference experiments were successful it was decided to form a tricyclic derivative of alcohol 246, thereby restricting the conformational mobility of the side chain. Iodination\(^\text{184}\) of alcohol 246 (Scheme 2.10) gave compound 249 in good yield, however, radical cyclisation of the primary iodide to the alkene using *tris*(trimethylsilyl)silane\(^\text{185}\) did not occur. This was presumably due to the conformational restrictions imposed on the side chain by the isopropylidene group. These restrictions were alleviated by removing the isopropylidene group using sulfonic acid resin in a protic solvent to form diol 251. This was treated with *tris*(trimethylsilyl)silane\(^\text{185}\) to form tricycle 252 in 64\% yield. The two hydrogen atoms at the newly formed ring junction are *cis* to each other because conformational restraints inherent in the three carbon chain between the bicyclic portion of the molecule and the primary alkyl radical mean that radical addition must occur to the bottom face of the alkene.\(^\text{186, 187}\)

**Scheme 2.9**

**Scheme 2.10**

**Conditions:** (i) imid., triphenylphosphine, I\(_2\), CH\(_2\)Cl\(_2\), RT, 20h, 67\%; (ii) *tris*(trimethylsilyl)silane, AIBN, benzene, reflux, 4h; (iii) Amberlite IR-118 resin, MeOH:H\(_2\)O (5:1), reflux, 18h, 82\%; (iv) *tris*(trimethylsilyl)silane, AIBN, benzene, reflux, 45min, 64\%.
The nOe difference experiments carried out on tricycle 252 (Figure 2.13) corroborate the stereochemical assignments for the major ETDA adduct proposed earlier. If alcohol 247 were to be treated in an analogous manner to 246 (Scheme 2.10) then tricycle 253 would be produced. However, tricycle 253 cannot produce the large nOe differences observed for tricycle 252, since the hydrogen atoms at the newly formed ring junction are on the opposite side of the molecule to the requisite hydrogen atom in the cyclopentane ring.

![Figure 2.13](image)

**Figure 2.13**

### 2.4.1.2 The origin of the diastereofacial selectivity

*Exo:endo* stereocontrol of IMDA reactions was discussed in Section 1.2, however, it still remains to discuss the origin of the π-facial selectivity observed for the hydroxy and silyloxy precursors in Section 2.4.1. In open chain molecules containing an existing stereogenic centre there are two criteria which must be satisfied in order for asymmetric induction to occur. First, the number of conformations available to the molecule in the transition state must be severely restricted, preferably to one. Second, the preferred conformation must allow differentiation between the diastereotopic faces or groups present in the molecule by the incoming reagent. This differentiation can be due to a bulky group on the existing stereogenic centre which shields one of the diastereotopic faces of the molecule, or one of the groups can coordinate to the incoming reagent and deliver it to one face at the expense of the other.155
Since the present study is the first one in which the π-facial stereoselectivity of an IMDA reaction has been controlled by the presence of a remote allylic stereogenic centre on an acyclic diene, the conformational preferences of such molecules have not been investigated. However, there have been a number of studies carried out on the analogous BDA case.\textsuperscript{188-190} The examples most closely related to ours\textsuperscript{188} are shown in Figure 2.14. Racemic dienols 254a-c reacted with maleic anhydride (45) to form mixtures of racemic endo adducts with structures 255 and 256. (The corresponding exo adducts were not reported.) The π-facial selectivity of 254a was increased by protecting the alcohol with a trimethylsilyl or tert-butyldimethylsilyl group, although the level of stereocontrol was still low.

\vspace{4pt}

\begin{center}
\begin{tabular}{|c|c|c|c|c|}
\hline
254 P & t/d & 255:256 & \% \\
\hline
a & H & 3 & 27:73 & 83 \\
b & TMS & 5 & 20:80 & 69 \\
c & TBS & 7 & 15:85 & 65 \\
\hline
\end{tabular}
\end{center}

All of the compounds represented in this Figure are racemic. Structures 255 and 256 indicate relative stereochemistry only.

\textbf{Figure 2.14}

The investigators\textsuperscript{188} attempted to rationalize their results based on a consideration of conformers 257-262 (Figure 2.15). Each conformer has the diene in the \textit{s-cis} conformation required for the DA reaction, but differs from the others due to rotation about the C1-C2 bond. (It is apparent that there are three pairs of conformers which would be expected to provide almost the same level of π-facial stereoselectivity, but in the opposite sense: 257 and 260; 258 and 261; and 259 and 262.) The major product in each reaction (56a-c, Figure 2.13) arises from approach of the dienophile to the upper
face of the diene and it was proposed that conformers 257 and 258 might be actively involved in the transition state responsible for the π-facial selectivity that was observed.

![Diagram of conformers 254, 257, 258, 259, 260, 261, 262](image)

Six conformations which can be adopted by compound 254 are shown inside the box. Compound 254 is racemic, but for simplicity only the conformations for one of the enantiomers are shown.

**Figure 2.15**

In substrates where the hydrogen atom H’ is replaced by a larger group, conformations 257 and 258 are favoured because they are significantly lower in energy (3-4 kcal/mol in both the ground and excited states) than 259-262, due to 1,3-allylic strain. In this case conformations 257 and 258 both strongly influence the dienophile to approach from above the plane of the diene, due to steric and electronic effects respectively and this usually results in high levels of stereocontrol. An example of the enhanced stereoselectivity made possible by the incorporation of a bulky group to provide 1,3-allylic strain is illustrated in **Figure 2.16**. The methoxymethyl ether in compound 263b provided a dramatic improvement in stereocontrol compared to compound 263a which had a hydrogen atom in this position.
In the absence of significant 1,3-allylic strain, the difference in energy between the six conformers in Figure 2.15 is low. This means that the transition state conformation of the molecule may be affected by subtle stereoelectronic effects, due to a conformational preference for a particular alignment of the C1-OP bond with the \( \pi \) system of the diene or the type of dienophile used. In addition, computational studies have shown that a number of transition states may be available and there is no simple parameter which can accurately predict the stereochemical outcome of a particular reaction. As a consequence of this, the stereochemical outcomes of these reactions are difficult to explain and the stereoselectivities obtained are often characteristically low.

The major product from the ETDA reaction of 238c (Section 2.4.1) and the BDA reaction of 254c are illustrated in Figure 2.17. The endo:exo stereoselectivity is opposite in the two reactions and so is the \( \pi \)-facial stereocontrol. Endo adduct 256c, in which the dienophile approaches the diene from above, is favoured in the BDA reaction, whereas exo adduct 241c, in which the dienophile approaches the diene from below, is favoured in the ETDA reaction. Conformations 257 and 258 are thought to direct the dienophile to the top face of the diene in the transition state leading to the BDA reaction, leaving conformations 259-262 to account for the results observed in the ETDA case.
Gung et al.\textsuperscript{196-198} have shown that conjugated chiral alkenes having the general structure 267 (Figure 2.18) generally prefer to adopt conformation 259 in which the C1-OP oxygen atom is eclipsed with C3. Precursor 238c (Figure 2.19) may also prefer this conformation in the transition state. Conformation 259 can be imagined to lead to major product 241c since the lower face of the diene is only shielded by the hydrogen atom on C1, whereas the a dienophile approaching the upper face encounters the more sterically demanding R and OP (dioxolane and tert-butyldimethylsilyl) groups.

<table>
<thead>
<tr>
<th>Conformation</th>
<th>R</th>
<th>Me</th>
<th>Et</th>
<th>iPr</th>
<th>tBu</th>
</tr>
</thead>
<tbody>
<tr>
<td>267</td>
<td>H</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>TMS</td>
<td>*</td>
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<td>*</td>
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<tr>
<td></td>
<td>TIPS</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Favoured conformations for 259 for each of the combinations of P and R. The compounds used in this study were racemic, but for simplicity only one of the enantiomers is shown for structure 267 and conformation 259.
Conformation 259 may be involved in the transition states which lead to major adduct 241c, however, the precise conformational nature of the transition state remains to be experimentally determined. Many factors could affect this conformation including: the steric constraints imposed on the molecule by the ester tether; the effect of the twist and stretch asynchronicity (Section 2.1); dominant HOMO-LUMO interactions; or stereoelectronic effects arising due to the dioxolane ring, the dienophile terminus and the nature of the protecting group. These factors contribute to the propensity of IMDA reactions to give exo adducts (instead endo adducts as in the BDA case) and they are also likely to affect the π-facial selectivity.

![Figure 2.19](image)

It is clear that the situation is complicated, but when the factors responsible for the π-facial selectivity are eventually uncovered valuable information may be gained about the conformational preferences involved in the transition states of IMDA reactions. This discussion is continued in Section 3.3.3.
2.4.2 ETDA reaction of the deoxy precursor

In order to be sure that the diastereofacial stereoselectivities observed for the ETDA reactions in Section 2.4.1 were due to the stereogenic centre in the position allylic to the diene, an analogous reaction was carried out on precursor 240 (Scheme 2.11). This precursor does not have a stereogenic centre allylic to the diene but it still has a chiral dioxolane moiety in the same position as compounds 238a-d. (The stereogenic centre in precursor 240 has the opposite absolute configuration to the one in the analogous position in precursors 238a-d, however, this is not important because the present study is designed to gauge the ability of remote stereogenic centres to control the stereochemical outcome of IMDA reactions, which does not depend on the absolute stereochemistry of the starting materials.)

\[ \text{Conditions: BHT, toluene, reflux, 18h, 89\%, 270:271 (50:50).} \]

Scheme 2.11

The ETDA reaction of 240 led to a mixture of 270 and 271 in excellent yield, although it was not possible to separate the adducts chromatographically. The proton NMR spectrum of the purified mixture contained a pair of overlapping doublet of doublets at 2.34 and 2.39ppm (Figure 2.20). Each doublet of doublets is due to the hydrogen atom at the ring junction adjacent to the lactone carbonyl in one of the ETDA adducts. Analysis of the splitting pattern for each doublet of doublets reveals that the coupling constant between the two hydrogen atoms on the ring junction for each adduct is 13.6Hz, indicating that both isomers possess trans fused rings.98 Traces of other compounds could be detected in the proton NMR spectrum of the crude reaction mixture, which may have been due to small amounts of endo products. However, the amount of these was negligible, indicating that the ETDA reaction had again proceeded with a high degree of exo:endo stereocontrol. Integration of the signals shown in Figure 2.20 (and others in the spectrum) showed that the ratio of the two major isomers was 50:50, indicating that the homoallylic stereogenic centre in the dioxolane ring did not produce any detectable facial diastereoselectivity. (Even though this stereogenic centre did not control the facial stereoselectivity in the ETDA reaction of compound 240, this does not mean that it is unimportant in the corresponding reactions of precursors 238a-d. Further
experiments are necessary to establish whether the second chiral entity contributes to the overall stereoselectivity in those cases."

**Figure 2.20**

This result is commensurate with the IMDA reaction of 272 (Figure 2.21),

which contains a chiral homoallylic tert-butyldimethylsilyl group. This reaction proceeded without endo:exo or diastereofacial control to produce equal amounts of each of the four possible IMDA adducts 273-276. (Compound 272 consisted of a mixture of E- and Z-stereoisomers of which only the latter underwent cycloaddition. Sigmatropic rearrangement of the E-stereoisomer occurred and the product of the rearrangement was recovered in 20% yield, along with a further 10% of unreacted starting material.)

**Figure 2.21**
2.5 Conclusion

In this Chapter two chiral dienols were prepared and these were used to synthesize a range of precursors for investigation of asymmetric induction in ETDA reactions. The results (Sections 2.4.1 and 2.4.2) demonstrate that it is possible to achieve a high level of diastereofacial control in ETDA reactions in which the starting material has a stereocontrolling element remote from the tether and allylic to the diene (Figure 2.22). Diastereofacial selectivity was shown to depend on the size of the stereocontrolling element that was attached to the diene terminus and no \( \pi \)-facial stereocontrol was observed when a stereocontrolling element was placed in the homoallylic position (Section 2.4.2). If this method of stereocontrol proves to be applicable to other related systems then it represents a powerful new method for achieving asymmetric induction in IMDA reactions.

The attachment of a bulky chiral group to the diene provides a novel method for providing stereochemical control in IMDA reactions.\(^{156}\)

**Figure 2.22**

Determination of the stereochemistry of the adducts which were generated in these stereochemical studies was accomplished by taking into account the absolute stereochemistry of the existing stereogenic centres, coupling constants between protons in the bicyclic five-six ring system that formed, COSY and NOESY spectra obtained for the ETDA adducts and molecular models. Further evidence for these stereochemical assignments was obtained from nOe difference experiments carried out on a tricyclic derivative (52) (Figure 2.23) prepared from one of the ETDA adducts. A tentative proposal for the origin of the observed stereochemistry has also been provided.

**Figure 2.23**
Radical cyclisation of 251 serves as a model study for the synthesis of himbacine (206) and velutinal (277) (Figure 2.24), both of which possess a similar carbocyclic backbone to tricycle 252 (Figure 2.23). Himbacine, which is found in the bark of *Galbulimima baccata*, is a lead compound in the treatment of Alzheimer's disease. Velutinal is a marasmane sesquiterpene found in the tissue of several genera of *Basidiomycetes*. Damage to the surface of the fungi causes conversion of velutinal into isovaleral (278) by an unknown mechanism. This compound is a potent antifungal and antibacterial agent as well as a powerful antifeedant for the opossum.
3 The effect of the dienophile

3.1 Introduction

In Chapter 2 it was demonstrated that the diastereofacial stereoselectivity of ETDA reactions can be controlled by placing a stereogenic centre allylic to the diene and remote from the ester tether. It was also observed that ETDA reactions carried out on maleate esters of this type occur with high levels of exo stereocontrol. In this Chapter the effect of dienophile geometry and functionality is investigated, since these have been reported to significantly affect the stereochemical outcome and rate of ETDA reactions (Section 1.2.1).

3.2 Preparation of ETDA precursors

3.2.1 Maleate precursors

ETDA reactions were carried out on methyl esters 238c and 240 (Figure 3.1) in Sections 2.4.1 and 2.4.2. ETDA reactions on the corresponding carboxylic acids 36 and 39 (Sections 2.3.1 and 2.3.2) are reported in Section 3.3.1.

![Figure 3.1](image)

In order to compare the endo:exo stereoselectivity of the precursors in Figure 3.1 with less complicated systems, the sterically unencumbered achiral precursors in Scheme 3.1 were also prepared. Sorbyl alcohol (301) was treated with maleic anhydride to produce carboxylic acid 302,\textsuperscript{174} which was then reacted with diazomethane\textsuperscript{173} (Section 6.6.3) to produce methyl ester 303. The yield of compound 303 was moderate, reinforcing the observation that trienes such as 302 are sensitive to addition of diazomethane (Section 2.3.2).
Conditions: (i) TEA, MA, DMAP, CH₂Cl₂, RT, 15 min, 88%; (ii) CH₃N₃, diethyl ether, 0°C, 58%.

Scheme 3.1

3.2.2 Fumarate precursors

Carboxylic acid 304 (Scheme 3.2) was prepared by isomerisation of maleate precursor 236 (Section 2.3.1) with thiophenol and 2,2'-azo-bis-isobutyronitrile. It was fortunate that this isomerisation was possible, since the transformation requires the starting material to be irradiated with ultraviolet light in refluxing benzene. The rate of the competing ETDA reactions (of 236 and 304) were sufficiently slow to allow a good yield of the isomerised product to be obtained. Methyl ester 305 was obtained via a straightforward esterification of dienol 228 (Section 2.2.1) and methyl hydrogen fumarate.

Conditions: (i) thiophenol, AIBN, benzene, reflux, 2h 65%; (ii) methyl hydrogen fumarate, DCC, DMAP, diethyl ether, 22h, 96%.

Scheme 3.2
3.2.3 Propiolate and acrylate precursors

Propiolate precursor 306 and acrylate precursor 307 (Scheme 3.3) were both prepared by esterification of TBS dienol 228 (Section 2.2.1).

Conditions: (i) propionic acid, DCC, DMAP, diethyl ether, 0°C for 30min then 30°C for 1h, 65%; (ii) acrylic acid, DCC, DMAP, diethyl ether/CH₂Cl₂, 9d, 47%.

Scheme 3.3

3.3 ETDA reactions

Each of the carboxylic acid precursors prepared in Section 3.2 was heated in refluxing toluene (5mmol/L) under an argon atmosphere in the presence of 2,6-di-tert-butyl-4-methylphenol (0.20eq). The reaction mixture was then cooled and diazomethane (Section 6.6.3) was added dropwise to the stirred solution. Product ratios were determined from proton NMR spectra of crude reaction mixtures (before and after the addition of diazomethane) and yields were calculated from the amount of material isolated after chromatography. The other precursors prepared in Section 3.2 were treated in an identical fashion, except that the diazomethane was not added.

3.3.1 Maleates

After precursor 236 had been heated in refluxing toluene for 17h (Scheme 3.4) proton NMR analysis indicated that there were two major products present in the crude reaction mixture. In order to simplify the purification procedure the reaction mixture was cooled and treated with diazomethane (Section 6.6.3) to convert the carboxylic acid adducts to the corresponding methyl esters. Proton NMR analysis of the crude mixture of esters confirmed the presence of two products and it was clear that the ratio of these two compounds (89:11) was not affected by the addition of the diazomethane.
The diazomethane treatment also facilitated direct comparison of the products formed in the ETDA reaction of carboxylic acid 236 and methyl ester 238c (Section 2.4.1). Astonishingly, it was determined that the products had identical stereochemistry regardless of whether the dienophile was terminated with a carboxylic acid or a methyl ester group. In both of the ETDA reactions exo-adducts were produced with a high level of stereocontrol. In addition, the major product was the same in each reaction, indicating that the transition states providing π-facial stereoselectivity of the methyl ester and the carboxylic acid may also be similar. The level of π-facial stereocontrol was only slightly greater in the case of the methyl ester (91:9) than the carboxylic acid (89:11). This is surprising since the steric bulk of the methyl group is significantly greater than the hydrogen atom. However, the position of the methyl group in the transition state may cause it to play a minor role in the stereoselectivity of the reaction (Section 3.3.3).

![Scheme 3.4](image)

**Conditions:** (i) BHT, toluene, reflux, 17h; (ii) 0°C, CH$_2$N$_2$, 62% (2 steps), 241c:242c (89:11).

**Scheme 3.4**

Formation of exo-adducts from ETDA reactions of carboxylic acids is counter to previous literature reports (Section 1.2.1.1). However, none of the previously reported examples had a bulky group at the diene terminus. It was envisioned that the bulky terminal substituent might be responsible for the formation of exo-adducts during the ETDA reaction of carboxylic acid 236. For example, the acid could adopt an exo conformation in the transition state to place the carboxylic acid moiety as far away from the terminal substituent as possible, in order to minimize unfavourable steric interactions between the two groups. This might override the factors which normally influence carboxylic acids to cyclise via endo transition states.
For the reasons outlined above it was decided to investigate the ETDA reaction of deoxy precursor 239 (Scheme 3.5). After the crude reaction mixture had been refluxed in toluene for 6h it was treated with diazomethane\(^{173}\) (Section 6.6.3) whereupon proton NMR analysis revealed that the products (270 and 271) were identical to those formed in the ETDA reaction of the methyl ester derivative of 239 (compound 240, Section 2.4.2). The carboxylic acid again exclusively gave rise to exo adducts. (In congruity with the ETDA reaction of 240, there was no diastereofacial selectivity and equimolar amounts of each exo adduct were observed.)

![Scheme 3.5](image)

Conditions: (i) BHT, toluene, reflux, 6h; (ii) 0°C; CH\(_2\)N\(_2\), 66% (2 steps), 270:271 (50:50).

Scheme 3.5

The generality of these results was investigated by comparing the ETDA reactions of carboxylic acid 302 and methyl ester 303 (Scheme 3.6). These sterically unencumbered, achiral starting materials clearly illustrate the underlying exo:endo preference for ETDA reactions of precursors with three atom tethers. The ETDA reactions of compounds 302 and 303 were both rapid but they proceeded with only modest levels of exo:endo stereocontrol. These observations may indicate that both of the starting materials possess elevated levels of conformational freedom compared to the chiral trienes described above, although electronic factors cannot be excluded at this stage. In each case trans fused adduct 308 (identified from the coupling constant of 13.5Hz between the two hydrogen atoms at the ring junction\(^{98}\) was the major isomer, accounting for nearly 70% of the material isolated in the ETDA reaction of carboxylic acid 303.
In agreement with the previous examples, there was little difference in the endo:exo stereoselectivity of carboxylic acid 302 and methyl ester 303. With hindsight there is scant evidence that carboxylic acids and esters should behave differently in ETDA reactions, yet this assertion \(^98, 103, 101\) has gone unchallenged for nearly twenty years. The reasons for this apparent anomaly will be discussed in Chapter 4.

### 3.3.1.1 Comparison of reactions of maleate derivatives with those involving maleic anhydride

For completeness, two DA reactions involving TBS dienol 228 (Section 2.2.1) and sorbyl alcohol (301) with maleic anhydride (45) were also investigated (Schemes 3.7 and 3.8). These reactions were carried out by heating a mixture of the alcohol and maleic anhydride (1:1) in refluxing toluene with 2,6-di-tert-butyl-4-methylphenol (0.20eq). Concentrated solutions of the starting materials (0.1mol/L) were used in order to ameliorate the BDA reactions. Once the starting materials were consumed (TLC) the reaction mixtures were cooled and diazomethane \(^{173}\) (Section 6.6.3) was added dropwise.

**Scheme 3.6**

Conditions: (i) BHT, toluene, 2h; (ii) 0°C, CH\(_2\)N\(_2\), 83% (2 steps), 308:309 (69:31); (iii) BHT, toluene, reflux, 2h, 79%, 308:309 (79:21).
TBS dienol 228 reacted slowly with the maleic anhydride to produce a mixture of adducts 241c, 242c, 310 and 311 (42:4:27:27) in modest yield. In BDA reactions, endo adducts are favoured, but in this case a significant amount of the exo adducts were produced as well. It is likely that these products formed subsequent to esterification of the reactive primary alcohol with maleic anhydride, since the BDA reaction is hindered by the bulky groups allylic to the diene. Evidence for this is twofold: compound 236 (Section 3.4) was observed in proton NMR spectra of the crude reaction mixture in the early stages of the reaction; and the same ratio was observed between 241c and 242c (90:10) as in the ETDA reaction of 236 described in Section 3.3.1. There did not appear to be any π-facial discrimination between endo adducts 310 and 311. Only one of the adducts 310 and 311 could be isolated and characterized. The coupling constant between the two hydrogen atoms at the ring junction was 11 Hz for the isolated compound (310) indicating that the two rings were cis fused, but it was not possible to determine the relative stereochemistry of this adduct. The structure of the unisolated compound (311) is speculative and based on limited proton NMR analysis of mixtures only.

It is interesting to compare these results with the BDA reaction of sorbyl alcohol (301) and maleic anhydride (45) (Scheme 3.8). In this case the BDA reaction was not hampered by steric factors and proceeded rapidly to produce endo adduct 313 with a high level of stereoselectively and in excellent yield.
Conditions: (i) BHT, toluene, reflux, 70min; (ii) -65°C, CH₂N₂, 90% (2 steps), 312:313 (4:96).

Scheme 3.8

3.3.2 Fumarates

Fumarate half ester 304 and diester 305 were treated in an analogous fashion to the maleate examples reported in Section 3.3.1 (Scheme 3.9). As in the previous examples, each of the ETDA reactions gave rise to two major products which were identical regardless of whether the dienophile in the starting material was terminated with either a carboxylic acid or methyl ester group. It was also noted that adduct 314 was the major product in each case, although the ratio of the two adducts was greater for the methyl ester (86:14) than the carboxylic acid (71:29).

Closer inspection revealed a significant difference between the ETDA reactions of the fumarates and the maleates. The coupling constant between the two hydrogen atoms at the ring junction for minor cycloadduct 315 was 13.4Hz indicating that the two rings were trans fused, but no such coupling constant could be distinguished for major product 314. Each of the hydrogen atoms at the ring junction in this compound gave rise to complicated multiplets which were only partially resolved at 500MHz. However, it was apparent that neither of these multiplets contained a coupling constant in the range 13-14Hz, indicating that the compound was cis fused and had been formed by an endo transition state.

Details of the way in which the stereochemistry of each of these adducts was determined are presented in Section 3.3.2.1 and an attempt to explain the stereoselectivity of these results appears in Section 3.3.3. It is noteworthy that the hydrogen atoms allylic to the alkene have the same absolute configuration in adducts 314 and 315 which means that the dienophile has approached the lower face of the diene in both cases.

Proton NMR recorded on a Varian Unity Series 500MHz instrument.
Conditions: (i) BHT, toluene, 142h; (ii) 0°C, CH₂N₂, 42% (2 steps), 314:315 (71:29); (iii) BHT, toluene, reflux, 167h, 76% (69% conversion), 314:315 (86:14).

Scheme 3.9

A literature example of an ETDA reaction carried out on a fumarate diester¹²⁵ is illustrated in Figure 3.2. In this case a high proportion of endo adduct 318 was produced but the major adduct still contained a trans fused ring system. There are two structural differences between substrates 305 and 316: the diene terminus; and the dienophile terminus. Which of these two structural features plays the dominant role in determining the endo:exo stereoselectivity is unclear at this stage. These ideas are discussed further in Section 3.3.3.

Figure 3.2
3.3.2.1 Determination of the stereochemistry of the fumarate cycloadducts

COSY spectra (Appendices 1.4C and 1.5C) were used to confirm the connectivity of the major and minor adducts produced in the ETDA reaction of 304 and 305 (Section 3.3.2), then NOESY spectra (Appendices 1.4N and 1.5N) were used to determine the relative stereochemistry. The absolute stereochemistry of adducts 314 and 315 (Section 3.3.2) were determined by considering the stereochemistry of the starting material, the coupling constants for the protons at the ring junction, NOESY spectra for each adduct and molecular models. (This method was used earlier to determine the absolute stereochemistry of adducts 241b and 242b (Section 2.4.1.1)).

Selected data from the NOESY spectrum of major adduct 314 is given in Figure 3.3. The signals for hydrogen atoms H3a and H4 overlap. (The complete NOESY spectrum is provided in Appendix 1.4N) Because it has a cis fused ring system, the absolute stereochemistry of adduct 80 is limited to either structure 314a or 314b. The cis fused ring system is also confirmed by the nOe between H5 and H3a.

![Diagram of major adducts 314a and 314b]

The purpose of the numbering system illustrated here is to simplify the discussion of the nOe’s, vide infra. (The side chain would not normally be numbered this way.)
Molecular models indicate that there is one C5-C9 staggered conformation for structure 314a which can simultaneously generate all of the nOe's observed for major adduct 314. A molecular model (MM2 force field,\textsuperscript{181,182} localized minimum) of this conformation is given in Figure 3.4 and the proximal hydrogen atoms are indicated by double headed arrows. (In this conformation, the dihedral angle between hydrogen atom H5 and the oxygen atom on C8 bearing the tert-butylidemethylsilyl group, is approximately 180°.) Conversely, there is no conformation (staggered or eclipsed) for structure 314b which can simultaneously give rise to the nOe's observed for the major adduct. These observations suggest that the major product of the ETDA reaction has the absolute stereochemistry associated with structure 314a.

![Diagram](image-url)

A molecular model (MM2 forcefield, local minimum) of structure 314a (with 24 hydrogen atoms removed). The arrows indicate hydrogen atoms which are in close proximity.

Figure 3.4
Selected data from the NOESY spectrum of minor adduct 315 is given in Figure 3.5. (The complete NOESY spectrum is provided in Appendix 1.5N) The absolute stereochemistry of adduct 315 is limited to either structure 315a or 315b, since this compound has been shown to contain a trans fused ring system.

The purpose of the numbering system illustrated here is to simplify the discussion of the nOe's, *vide infra*. (The side chain would not normally be numbered this way.)

Figure 3.5

Molecular models indicate that there is one staggered conformation for structure 315a which simultaneously generates all of the nOe's observed for major adduct 315. A molecular model (MM2 force field,\textsuperscript{181,182} localized minimum) of this conformation is given in Figure 3.6 and the proximal hydrogen atoms are indicated by double headed arrows. (In this conformation, the dihedral angle between hydrogen atom H5 and the oxygen atom on C8 bearing the tert-butyldimethylsilyl group is again approximately 180°.) As in the previous case, there is no conformation (staggered or eclipsed) for the alternate structure (315b) which can simultaneously give rise to the observed nOe's. These observations suggest that the minor product of the ETDA reaction has the absolute stereochemistry associated with structure 315a.
A molecular model (MM2 forcefield, local minimum) of structure 315a (with 24 hydrogen atoms removed). The arrows indicate hydrogen atoms which are in close proximity.

Figure 3.6

These stereochemical assignments would be reinforced if data for both of the possible exo and endo compounds were available and comparison of the NOESY spectra of all four adducts could be made. However, if the structure of adduct 314 is compared with the major adducts generated by precursors 238a-d (Section 2.4.1.1) it is apparent that the π-facial selectivity is consistent throughout the series. In each case the dienophile approaches from below the plane of the diene. In addition, each of the conformations which account for the observed nOe’s (Figures 2.10, 2.11, 3.4 and 3.6) have approximately the same dihedral angle between hydrogen atom H5 and the oxygen atom on C8. If all of the possible structures and the myriad of conformations available to each one are considered, logic precludes this from being coincidental.

3.3.3 A discussion of the stereoselectivity arising in ETDA reactions of maleates and fumarates

Simple endo:exo stereocontrol was discussed in Section 1.2 and in Section 2.4.1.2, transition state 268 (Figure 3.7) was proposed to explain the preferential formation of major adduct 241c from the ETDA reaction of 238c. It is likely that the π-facial stereoselectivity arises because of steric interactions between the dienophile and the chiral allylic moiety which cause the dienophile to approach from below the plane of the diene. However, each of these effects is likely to influence the other. Based on a simple steric argument these transition states can also be used to account for the observation that
a slightly lower π-facial selectivity is observed for carboxylic acid 36 than methyl ester 38c (Sections 3.3.1), since the hydrogen atom is considerably smaller than the methyl group. However, the difference in selectivity between the carboxylic acid and the methyl ester is minor suggesting that it may be the terminal hydrogen of the dienophile which is involved in stereocontrol. Other factors may also be involved, since the electronic demands of ester groups and carboxylic acids are quite different.

In the case of carboxylic acid 236, the major ETDA adduct is converted to methyl ester 241c with diazomethane after cycloaddition.

\[ \text{Figure 3.7} \]

As is the case with maleate precursors 238c and 236 (Section 2.4.1) the π-facial stereoselectivity of fumarate precursors 304 and 305 (Section 3.3.2) arises mainly from approach of the dienophile to the lower face of the diene. The fundamental difference between these ETDA reactions is that the former mainly proceed via exo transition states and the latter via endo transition states. Before a discussion of the π-facial selectivity of fumarates 304 and 305 is undertaken, it is pertinent to consider the endo:exo selectivity of achiral esters 303 (Section 3.3.1) and 316 shown in Figure 3.8.
<table>
<thead>
<tr>
<th>Entry</th>
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<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>238c</td>
<td>100:0</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>303</td>
<td>79:21</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>316</td>
<td>60:40</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>305</td>
<td>9:91</td>
<td>76</td>
</tr>
</tbody>
</table>

Overall exo:endo selectivities are given in the table above. Two adducts were produced in the ETDA reaction of 238c, but they were both exo adducts.

**Figure 3.8**

A gradual change in exo:endo stereoselectivity is observed for cycloaddition of precursors 238c-305. Exo products are favoured for maleate precursor 238c, which has a bulky group attached to the diene terminus, whereas compound 303 produces a significant amount of the endo adduct. The exo adduct is not favoured to such an extent for fumarate precursor 316 and addition of the bulky group to the diene terminus results in a high level of endo stereoselectivity for compound 305. (The difference in the endo:exo stereoselectivity observed for compounds 316 and 305 may be due in part to the dienophile terminating group, but the size of the groups attached to the dienophile do not normally have a significant impact on stereocontrol.208)

The trend illustrated in **Figure 3.8** can be explained by considering the transition states postulated in **Figure 3.9**. For the maleates, the endo transition state has more unfavourable intramolecular steric interactions than the exo transition state which leads to a preference for the exo adducts. This steric effect (specifically the steric effect between the \(-\text{CO}_2\text{Me}\) group and the \(\text{R}\) group) is increased if the size of \(\text{R}\) is increased. For the fumarates, the situation is not so clear-cut. The exo transition state has two significant steric interactions, both of which are located at the peripheral \(\sigma\)-bond. The endo transition state also has two significant steric interactions, one of which is near the tether and the other at a distance from it. If the size of the \(\text{R}\) group is increased it is conceivable that there might be a greater amount of steric compression generated in the exo transition
state, leading to increased stereoselectivity for *endo* adducts, such as that observed for compound 305.

**Maleate series.**

![Maleate series diagram](image)

**Fumarate series.**

![Fumarate series diagram](image)

**Figure 3.9**

The π-facial stereoselectivity of fumarates 304 and 305 is the final aspect to be considered. The products of these reactions arise because the dienophile approaches from below the plane of the diene. In this case the major product arises from an *endo* transition state, but the conformational preferences of the chiral allylic substituent may well be similar to those for maleate precursors 238c (Section 2.4.1.2). Consequently the transition state which is involved in the formation of the major adduct in the fumarate series may resemble 319 (Figure 3.10). Although the major product arises from an *endo* transition state, the top face of the diene might be shielded in a similar to the way it is shielded in the *exo* transition state of the maleate series (Figure 3.7). Greater *endo:exo* stereocontrol was observed for methyl ester 305 than carboxylic acid 304, which can also be explained in terms of simple steric effects.
In the case of carboxylic acid 304, the major ETDA adduct is converted to methyl ester 305 with diazomethane.

**Figure 3.10**

It is necessary to stress that the preceding discussion is speculative and based on the results of a limited number of experiments. It is clear that a complex situation exists and there may be a number of crucial factors, significantly affecting the stereochemical outcome of ETDA reactions, which have yet to be determined. What is presented here is a simple 'working model' which explains the observed stereoselectivities in a consistent manner and paves the way for further investigation to be made.

### 3.3.4 Propiolates and acrylates

The successful reactions of the fumarate and maleate derivatives described above provided the impetus to investigate the \( \pi \)-facial selectivity involved in the ETDA reactions of the chiral propiolates and acrylates shown below.

Propionate ester 306 reacted readily in refluxing toluene to produce adducts 320 and 321 in good yield with modest \( \pi \)-facial stereoselectivity (Scheme 3.10). In this case only two products are possible since the exo and endo transition states which arise at each face of the diene yield identical products. Unfortunately the NOESY spectra for these two compounds were identical so it was not possible to distinguish the two adducts. (This is presumably because rotation of the side chain is less hindered than in the maleate or fumarate adducts (Sections 2.4.1.2 and 3.3.1.1) so the conformational preferences of the molecules are less well defined and nOe’s unique to each molecule do not arise.) The absolute stereochemistry of the two adducts has been tentatively assigned.
based on previous experience with the maleate and fumarate derivatives, where the major product of the reaction arose from approach from the lower face of the diene in each case.

\[
\text{Conditions: } \text{BHT, toluene, 29h, 85\% (72\% conversion), 320:321 (65:35).}
\]

\textbf{Scheme 3.10}

As expected (Section 1.2.1.3), the reactivity of acrylate ester 57 was much lower than propiolate ester 56 (Scheme 3.11). No reaction was observed in refluxing toluene after a period of 43h, or in refluxing xylene after a period of 23h. A separate sample was heated to 210°C in toluene in a sealed tube for 30h. Some starting material (39\%) was recovered, but the reaction was not clean and produced a complex mixture of products without any apparent stereocontrol. These products were chromatographically inseparable and so it was not possible to identify them.

\[
\text{Conditions: } (i) \text{BHT, toluene, 43h; (ii) BHT, xylene, 23h; (ii) BHT, toluene, 210°C, 30h.}
\]

\textbf{Scheme 3.11}

\textbf{3.4 Conclusion}

The examples presented in Chapter 3 challenge the current understanding of stereocontrol of IMDA reactions. The \(\pi\)-facial stereoselectivity of IMDA reactions of maleates, fumarates and propiolates can be controlled by placing a sterically demanding chiral substituent allylic to the diene and remote from the tether, although the stereoselectivity observed in the last case was modest. For maleates there is a clear preference for \textit{exo} adducts regardless of whether the dienophile is terminated with a carboxylic acid or an ester group. (This was observed with both complicated chiral starting materials and simpler achiral examples.) The reasons why apparent anomalies can be found in previous literature reports concerning carboxylic acids (Section 1.2.2.1) will be investigated further in Chapter 4. Placement of a bulky substituent
allylic to the diene in fumarates can alter the expected *endo:exo* stereoselectivity causing methyl esters, as well as carboxylic acids, gave rise to *endo* adducts as the major products. These results can be rationalized by consideration of developing steric effects in the triene during the intramolecular cycloaddition.
# ETDA reactions of citraconate esters

## 4.1 Introduction

The effect of the dienophile terminating group on the stereochemical outcome of ETDA reactions of maleate and fumarate precursors was investigated in Sections 3.3.1 and 3.3.2. Sorbyl maleates gave rise to mixtures of exo and endo adducts, but when a larger group was incorporated at the diene terminus, exo adducts were favoured. This was observed regardless of whether the Z-dienophile was terminated with a carboxylic acid or a methyl ester group. The nature of the functional group at the dienophile terminus also had little effect on the exo:endo stereoselectivity of fumarate precursors. When a bulky group was incorporated at the terminus of the diene, endo adducts were produced with a high level of stereocontrol regardless of whether fumarate diesters or half esters were employed. The results for the precursors prepared from TBS dienol 228 (Section 2.2.1) are illustrated in Figure 4.1.

*The cycloaddition products prepared from carboxylic acids 236 and 304 were converted to methyl esters using diazomethane.*

**Figure 4.1**

These results were unexpected since ETDA reactions of carboxylic acids have been reported to give endo adducts exclusively (Section 1.2.2.1). The assertion that citraconate diesters form exo adducts and half esters form endo adducts 97, 98 has been reinvestigated and this Chapter describes the surprising results that were obtained.
4.2 Preparation of citraconate precursors

Citraconate half esters were prepared from dienols 228 (Section 2.2.1), 235 (Section 2.2.2) and 301 by treating the starting material with citraconic anhydride in the presence of triethylamine and N,N-dimethylaminopyridine (Scheme 4.1). In addition, the esterification of sorbyl alcohol (301) was carried out at 50°C with pyridine in benzene according to the method of White et al. Although this paper reported that half esters 38d and 38c were inseparable, it was found that separation could be achieved by repeated chromatography, using polar solvents spiked with methanol:acetic acid (1:1, 0.5%) to reduce the effect of tailing. (Since these compounds were not separated in the original paper their physical properties were not reported.)

**Scheme 4.1**

Conditions: (i) TEA, citraconic anhydride, DMAP, CH₂Cl₂, RT, 1h, 62%, 401:402 (77:23); (ii) TEA, citraconic anhydride, DMAP, CH₂Cl₂, RT, 21h, 77%, 403:404 (67:33); (iii)a TEA, citraconic anhydride, DMAP, CH₂Cl₂, RT, 3h, 100%, 38d:38c (86:14); (iii)b pyr., citraconic anhydride, benzene, 50°C, 8h, 89%, 38d:38c (50:50).
Sorbyl citraconate precursors $38d$ and $38c$ were treated with diazomethane\textsuperscript{173} (Section 6.6.3) to form the corresponding methyl esters in good yield (Scheme 4.2).

![Scheme 4.2](image)

**Conditions:** (i) $\text{CH}_2\text{N}_2$, $\text{CH}_2\text{Cl}_2$, RT, 81%; (ii) $\text{CH}_2\text{N}_2$, $\text{CH}_2\text{Cl}_2$, RT, 85%.

Scheme 4.2

Initially, it was not possible to unequivocally assign the regiochemistry of any of the compounds illustrated in Schemes 4.1 or 4.2 spectroscopically (using NMR or IR) or spectrometrically (using mass spectrometry) since the spectra of the two compounds in each regioisomeric pair did not allow bond connectivity to be established. However, it was possible to unequivocally distinguish the regiochemistry of compound $38a$ since the structure of one of the ETDA adducts generated from it (compound $39a$, Section 4.4.2) was determined by X-Ray crystallographic analysis. Once compound $38a$ had been identified it was possible to deduce the structures of compounds $38d$, $38c$ and $405$.

![Figure 4.2](image)
The regiochemistry of compounds 401-404 could not be determined using the same method as that used for compound 38a, since they did not produce crystalline ETDA adducts (Section 4.3). In spite of this there were a number of observations which enabled confident structural assignments of each of these citraconate half esters to be made (by analogy with the assignment of 38d-38a). Nucleophilic addition to citraconic anhydride (406) (Figure 4.2) normally occurs at the more sterically demanding α-carbonyl (since it has the larger LUMO coefficient of the two carbonyl carbons) which leads to major regioisomers 401, 403 and 38d. The relative polarity of the major and minor regioisomers was similar for each regioisomeric pair. (The Rf of the major isomer was always significantly higher than the minor isomer by TLC analysis on silica plates.) The chemical shift of the dienophile hydrogen atom and methyl group in each compound (Figure 4.3) also provided data which enabled the regiochemistry to be determined. The chemical shifts of the dienophile substituents of the major isomers produced in each reaction are very similar, as are those of the minor isomers, yet the chemical shifts obtained for the major and minor isomers are quite different from each other. Since the structure of compounds 38d and 38c were known, it was possible to determine the regiochemistry of citraconate half esters 401-404 on this basis. (This was confirmed by spectral data obtained on the adducts produced in subsequent ETDA reactions.)

![major regioisomer](image1)

![minor regioisomer](image2)

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</table>

![Figure 4.3](image3)
4.3 Attempted ETDA reactions on citraconate half esters

When compound 401 (Scheme 4.3) was heated under standard conditions (Section 2.4) in refluxing toluene for 12h in the presence of BHT there was no evidence for the formation of the expected ETDA adducts. Instead, the material isolated from the reaction mixture once the solvent had been evaporated was TBS dienol 228. Initially it was suspected that this outcome was the result of contamination of the solvent with trace amounts of moisture, leading to acid-catalyzed hydrolysis of the ester linkage of the starting material. For this reason the toluene was redistilled from sodium benzophenone ketyl and a second ETDA reaction was attempted, but this gave the same result as the previous reaction. Although these ETDA reactions were carried out under an argon atmosphere using oven dried glassware, it was conceivable that adventitious moisture might still be affecting the reaction. For this reason an ETDA reaction was carried out in toluene in the presence of 4Å molecular sieves, but this still resulted in formation of TBS dienol 228. In a fourth reaction the starting material was heated in refluxing toluene in the presence of 4Å molecular sieves and anhydrous potassium carbonate (equimolar with the starting material) in order to neutralize the citraconate half ester and prevent any acid catalyzed processes from occurring. This too resulted in hydrolysis of the ester linkage of the starting material. In a final attempt to cyclise this starting material it was heated in refluxing xylene, but TBS dienol 228 was still produced.

It soon became clear that the formation of TBS dienol 228 was not due to inadequacies in the experimental methods employed, but resulted from unexpected thermal lability of the ester tether. For this reason it was decided to investigate the behaviour of regioisomeric acid 402 (Scheme 4.3) under the standard ETDA reaction conditions. Not unexpectedly, this also resulted in the exclusive formation of TBS dienol 228.
It was proposed that the bulky substituent at the diene terminus in precursors 401 and 402 might be responsible for the anomalous results of these citraconate half esters (cf. the maleate half ester series (Section 3.3.1)). Hence it was decided to attempt ETDA reactions on deoxy dienol derivatives derivatives 403 and 404 (Scheme 4.4). In each case the expected ETDA reaction did not occur and deoxy dienol 235 was produced instead.

Conditions: (i) BHT, toluene, reflux, 12h, 61%; (ii) BHT, toluene, reflux, 24h, 57%.

**Scheme 4.3**

Conditions: (i) BHT, toluene, reflux, 3h, 63%; (ii) BHT, toluene, reflux, 5h, 54%.

**Scheme 4.4**
Formation of dienols 228 and 235 when half esters 401-404 were heated was completely unexpected and totally different from the results reported for citraconate derivatives of sorbyl alcohol,97, 98 therefore it was decided to carefully reinvestigate these published results. It was reported97, 98 that a mixture of the two regioisomeric acids 38d and 38c (50:50) was heated in xylene under a nitrogen atmosphere for 15h (Figure 4.4). The solvent was then removed yielding a thick brown oil which partially crystallized on standing. Trituration of this material with chloroform:cyclohexane followed by recrystallisation gave a 32% yield of adduct 40c (based on the mass of compound 38c). It was reported that a substantial amount of polymeric material was formed, but there was no evidence for the formation of any other adducts. From these observations it was concluded that compound 38c reacted exclusively via the endo mode of cycloaddition and compound 38d was apparently destroyed through “autocatalytic polymerization”.98

![Figure 4.4](image)

In general, for IMDA reactions in which the tether contains three atoms, exo adducts are formed (Section 1.2). This is the case for ETDA reactions in which the dienophile of the precursor is terminated with an ester group, however, when the dienophile is terminated with a carboxylic acid, formation of endo adducts has come to be expected. The reaction illustrated in Figure 4.4 is one of the most frequently cited examples14, 15, 17, 19 of the apparently anomalous behaviour of carboxylic acids, however, no satisfactory explanation of this phenomenon has yet been provided.

It was decided to repeat the reaction shown in Figure 4.4 using the same solvent (xylene), reaction time (15h) and concentration (115mmol/L) that was used by the original investigators.98 Proton NMR analysis of the crude reaction mixture after removal of the xylene (Figure 4.5) revealed that a very complicated mixture containing several distinct products was produced.
Figure 4.5
Assuming a standard IMDA reaction pathway it is possible for four products to be formed in this reaction (Figure 4.6) and at least four products were present in the reaction mixture. It was determined that separation of these adducts was not practical and that independent syntheses of each of the individual compounds would be more expedient. These syntheses are discussed in Section 4.4.

The structures represent relative stereochemistry only. Each of these cycloadducts is produced as a racemate. Only adduct 40c was isolated by White et al.\textsuperscript{98}

Figure 4.6

4.4 Synthesis of ETDA adducts of sorbyl citraconates

Synthesis of the four adducts shown in Figure 4.6 (Section 4.3) are discussed in this Section as well as the formation of methyl ester derivatives of each one.

4.4.1 Endo adducts

The endo adducts of citraconate half esters 38d and 38c (i.e. compounds 40c and 40d) were prepared by using a BDA reaction (Scheme 4.5). Sorbyl alcohol (301) was treated with tert-butyldimethylsilyl chloride\textsuperscript{176} to form silyl ether 407 which was then reacted with citraconic anhydride in refluxing toluene to form a mixture of endo adducts 408 and 409. (Equimolar amounts of the two starting materials were used and the concentration of each was 0.50mol/L.) The regioisomeric cycloadducts were easily separated, then treated with trifluoroacetic acid to cleave the tert-butyldimethylsilyl groups and form γ-lactones 40c and 40d in a single step. Treatment of each of these lactones with diazomethane\textsuperscript{173} (Section 6.6.3) formed methyl esters 40a and 410 respectively in high yield. It is likely that the regioselectivity observed in this reaction is due to unfavourable steric interactions between the bulky tert-butyldimethylsilyl group on the diene and the methyl group on the dienophile.
Conditions:  
(i) TBSCl, imid., CH₂Cl₂, RT, 30 min, 97%;  
(ii) citraconic anhydride, BHT, toluene, 
reflux, 36 h, 93% (at 80% conversion), 408:409 (76:24);  
(iii) TFA, CH₂Cl₂, RT, 2 h, 94%;  
(iv) TFA, 
CH₂Cl₂, RT, 2 h, 76%;  
(v) CH₃N₂, diethyl ether, -65°C, 95%;  
(vi) CH₃N₂, diethyl ether, -65°C, 95%.

Scheme 4.5

Methyl ester 40a had identical physical properties to those reported in the 
previously published paper by White et al.⁹⁸ for which the investigators obtained X-Ray 
 crystallographic data. The regiochemistry of adduct 410 was obtained from a COSY 
spectrum. Unfortunately it was not possible to determine the ring junction 
esterchemistry of this compound using coupling constants, since it has a methyl group 
in this position. However, the NOESY spectrum of 410 showed strong interactions 
between the two hydrogen atoms and the methyl group which are pointing up in Figure 
4.7, establishing that this compound has a cis fused ring system.

Figure 4.7
4.4.2 Exo adducts

Exo cycloadducts adducts can be readily prepared from ETDA reactions (Section 1.2.1.1), however, in the case of the citraconate half esters it was first of all necessary to protect the carboxylic acid groups as labile esters. Citraconate half ester 38c (Scheme 4.6) was treated with chloromethyl methyl ether to form diester 411, which was then refluxed in toluene to give cycloadducts 412 and 413. Major compound 412 had a coupling constant of 13.6Hz between the hydrogen atoms at the ring junction indicating that they are trans fused, whereas the coupling constant between the same protons in minor compound 413 was only 9.2Hz corresponding to a cis fused ring system.98 Treatment of cyclic methoxymethyl ester 412 with trifluoroacetic acid exposed carboxylic acid 39c which was then treated with diazomethane173 (Section 6.6.3) to furnish methyl ester 39a. This adduct had identical physical properties to the previously published compound.98

![Scheme 4.6](image)

**Conditions:**  
(i) MOMCl, TEA, CH₂Cl₂, RT, 10min, 59%; (ii) BHT, toluene, reflux, 22h, 96%  
412:413 (88:12); (iii) TFA, CH₂Cl₂, RT, 18h, 96%; (iv) CH₃N₂, diethyl ether, -65°C, 66%.

Scheme 4.6
Methyl ester 39a was highly crystalline and a sample suitable for single crystal X-Ray diffraction was obtained after recrystallisation from tert-butyl methyl ether. The crystal structure of this compound is shown in Figure 4.8. (Other parameters are summarized in Appendix 2) It is clear from the structure that the two rings are trans fused and therefore the compound was formed via an exo transition state. The structure also unequivocally proves the regiochemistry of the molecule, establishing that the methyl group of the dienophile in compound 38c is distal to the ester tether. (From this it was possible to deduce the regiochemistry of each of the citraconate precursors prepared in Section 4.2.)

X-Ray crystallographic structure of adduct 39a, recrystallised from tert-butyl methyl ether.

Figure 4.8
The protocol which was used to prepare adducts 39c and 39a from carboxylic acid 38c was repeated on regioisomeric acid 38d (Scheme 4.7). The highly stereoselective ETDA reaction of 82 produced a mixture of two adducts (415 and 416), which were assumed to be the *exo* and *endo* products respectively. (It is likely that the *exo*:endo stereoselectivity is greater the ETDA reaction of 38d than 38c due to the position of the vinylic methyl group of the dienophile. The steric compression around the developing internal σ-bond will be more acute in compound 38d, resulting in higher *exo* stereoselectivity.) Major adduct 415 was treated with trifluoroacetic acid to form carboxylic acid 39d and this was subsequently treated with diazomethane\textsuperscript{173} (Section 6.6.3) to form methyl ester 417.

\[
\text{Conditions: } \begin{align*}
(i) & \text{ MOMCl, TEA, CH}_2\text{Cl}_2, \text{ RT, 5min, 86\%; } \\
(ii) & \text{ BHT, toluene, reflux, 22h, 99\%; } \\
(iii) & \text{ TFA, CH}_2\text{Cl}_2, \text{ RT, 6h, 89\%; } \\
(iv) & \text{ CH}_2\text{N}_2, \text{ diethyl ether, -65\°C, 100\%}. \\
\end{align*}
\]

Scheme 4.7

The regiochemistry of compound 417 was established using a COSY spectrum. It was not possible to use coupling constants to determine the stereochemistry at the ring junction in 417 since there is a methyl group in that position. However, the NOESY spectrum of this compound indicated strong through-space coupling between the hydrogen atom and the two methyl groups pointing down in structure 417 (Figure...
4.9). The nOe between the two methyl groups is indicative that the cycloadduct formed *via* an *exo* transition state. (Because of the high stereoselectivity of the ETDA reaction of 414 (415:416, 93:7) and difficulties encountered during chromatography, it was not possible to isolate a pure sample of compound 416. However, based on the result of the ETDA reaction of 411 (Scheme 4.6) it seems likely that it should have structure shown.)

![Figure 4.9](image-url)
4.5 Reinvestigation of DA reactions on sorbyl citraconate precursors

With the four possible regioisomeric and stereoisomeric adducts 40c, 39c, 40d, and 39d in hand (Section 4.4) it was possible to analyze the proton NMR spectrum of the ETDA reaction of the 50:50 mixture of citraconate half esters 38d and 38c (Figure 4.5). Similar reactions were carried out on pure samples of precursors 38d and 38c, and the reaction of sorbyl alcohol (301) with citraconic anhydride (406) was also investigated. These results are discussed in Section 4.5.1.

4.5.1 Comparison of the reactions of the sorbyl hydrogen citraconates and the reaction of sorbyl alcohol with citraconic anhydride

The DA reactions carried out on the citraconate half esters (38d and 38c) and sorbyl alcohol (301) with citraconic anhydride (406) are illustrated in Scheme 4.8. For ease of interpretation each of the starting materials is illustrated, as are the four possible products. The reactions which were carried out are tabulated directly below this. In each case the starting materials were heated to reflux in xylene under an argon atmosphere for 15h using exactly the same conditions as White et al. After this, the solvent was removed in vacuo, the residue was dissolved in deuterated chloroform and a proton NMR spectrum was recorded. These samples were then dissolved in dichloromethane and treated with trifluoroacetic acid to ensure that any unlactonised BDA endo adducts underwent intramolecular esterification to form the required γ-lactones. The trifluoroacetic acid and dichloromethane were then evaporated and proton NMR spectra were again obtained in deuterated chloroform. (The trifluoroacetic acid treatment was found to simplify the proton NMR spectra of the crude materials, but it did not appear to have a significant effect on the product ratios observed.)

When a mixture of the two regioisomeric citraconate half esters 38d and 38c (50:50) was heated (Entry 1), all of the four possible adducts (40c, 39c, 40d, and 39d) were produced. This is in direct contrast to the published results, which specify that only adduct 40c was formed under these conditions. When reactions were carried out separately on pure samples of regioisomeric acids 38d and 38c (Entries 2 and 3
respectively), each of the four adducts was again produced. In a fourth experiment (Entry 4), sorbyl alcohol (301) was heated with citraconic anhydride (406) to produce the same four products. In each case (Entries 1-4) the product ratio was almost identical. Endo adducts were favoured over exo adducts (ca. endo:exo (60:40)) and adduct 40c represented approximately 50% of the material produced in each case.

\[
\begin{align*}
&\text{HO:C} \\
&38d \\
&\text{HO:C} \\
&38c \\
&\text{HO:C} \\
&301 \\
&\text{HO:C} \\
&406
\end{align*}
\]

Conditions: (i) xylene (115mmol/L), reflux, 15h; (ii) TFA, dichloromethane, RT, 24h.

Scheme 4.8
These results have a significant impact upon the mechanism of product formation. There is no mechanism by which citraconate 38d can form adduct 40c via a normal ETDA reaction, since it would require migration of the methyl group of the dienophile from the ring junction to the adjacent carbon atom in the product. The only way in which adduct 40c can form under the reaction conditions used is if the ester tether between the diene and the dienophile is cleaved prior to the DA reaction, resulting in the reformation of sorbyl alcohol (301) and citraconic anhydride (406). Once this has occurred, a BDA reaction can follow between the diene and the dienophile, or re-esterification can ensue followed by a subsequent ETDA reaction. Formation of endo adducts is favoured in BDA reactions and so it seems likely that this is what occurs. These ideas are illustrated in Figure 4.10.

Figure 4.10
4.5.2 Proton NMR experiments

In order to reinforce this postulated mechanism, it was decided to heat precursors 38d and 38c separately in refluxing $d_6$-toluene in an NMR tube, at the same concentration (115mmol/L) as that used for the reactions in Section 4.5.1. The results of these experiments are illustrated in time-lapse NMR spectra in Figures 4.11 to 4.14. (The quintet at 2.3ppm is due to toluene. Toluene also has three broad multiplets at 7.15-7.35ppm but these are not shown in Figures 4.11-4.14.)

The time-lapse NMR spectra in Figure 4.11 and 4.12 show the results obtained when precursor 38d was heated. Figure 4.11 includes chemical shifts form 0.0-7.0ppm, whereas the range has been reduced to 0.7-2.0ppm in Figure 4.12 to allow some of the extra detail to be observed.
Figure 4.12

After fifteen minutes in refluxing toluene, approximately 50% of precursor 38d has been cleaved into sorbyl alcohol (301) and citraconic anhydride (406). After one hour there is only a small amount of compound 64 left in the reaction mixture. DA adducts begin to form subsequent to this.
Similar spectra were also observed when precursor $38c$ was heated in $d_8$-toluene. The time-lapse NMR spectra for this precursor are illustrated in Figures 4.13 and 4.14. The results for precursor $38c$ were almost identical to those obtained for precursor $38d$, with approximately 50% of the starting material cleaved within the first fifteen minutes and the remainder cleaved after one hour.
Thermal lability of citraconate half esters has no precedent in the literature and it is difficult to explain why the ester bond in these compounds should be so much more labile than those of maleate and fumarate half esters. However, all of the solvents and glassware used in these experiments were carefully dried and the reactions were carried out under an argon atmosphere, therefore it is not reasonable to propose that hydrolysis is responsible for the rapid cleavage of the ester tether. An alternative mechanism (illustrated in Figure 4.15) entails protonation of the carbonyl group of the tether, then proton exchange, intramolecular addition of the weakly nucleophilic carboxylate ion and subsequent cleavage of the ester bond. The citraconate half esters are clearly more susceptible to this process than the maleate or fumarate derivatives. This could be due to steric compression of bond angles by the dienophile methyl group, facilitating the protonation and nucleophilic addition steps. Reformation of citraconic anhydride may be

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† An STN REACS search was conducted in February, 1998. Sincere thanks is extended to Associate Professor Damon Ridley for helping with this search.
more favoured than maleic anhydride because the alkene in the product is more highly substituted and therefore it has greater stability. (In the case of the fumarate derivatives it is not possible for an anhydride to form, unless isomerisation of the double bond occurs.)

**Figure 4.15**

### 4.5.3 ETDA reactions of methyl sorbyl citraconates

For completeness, the ETDA reactions of methyl ester derivatives 66 and 67 are reported in Scheme 4.9. In this case (as with the MOM esters in Section 4.4.2) the reformation of sorbyl alcohol and citraconic anhydride is prevented by the presence of a terminal methyl ester on the dienophile. In each case the *exo* adduct is favoured, as is usual for ETDA reactions of esters (Chapters 1, 2 and 3). In an analogous fashion to the MOM esters in Section 4.4.2 the *exo* stereoselectivity was greater in the ETDA reaction of 405 than 38a, due to the position of the vinylic methyl group of the dienophile. Previously, the ETDA reaction of compound 67 was carried out in refluxing xylene, resulting in a 40% yield of 81 after 24h, however, the authors did not mention the presence of adduct 76.
Conditions: (i) BHT, toluene, reflux, 24h, 71% (95% conversion), 417:410 (93:7); (ii) BHT, toluene, reflux, 24h, 65% 39a:40a (84:16).

Scheme 4.9

4.6 Conclusion

The assertion that citraconate half esters form endo adducts via ETDA reactions has gone unchallenged for over twenty years. In this Chapter it has been demonstrated that citraconate half esters are thermally labile and break down when heated in refluxing solvent to form citraconic anhydride and an alcohol. This has a big impact upon the commonly held belief that citraconate half esters formed from dienols undergo ETDA reactions to form predominantly endo adducts. In fact, the reaction proceeds via initial cleavage of the ester tether, followed by a BDA reaction and then an intramolecular esterification, leading to the formation of cis fused bicyclic lactone acids. The isolation of chiral dienols 228 and 235 (Figures 4.3 and 4.4) from heating dilute solutions of precursors 401 or 402 and 403 or 404 respectively, is consistent with these new mechanistic insights. Clearly, if exo cycloadducts are required then citraconate diesters, such as methoxymethyl esters 411 and 414 (Schemes 4.6 and 4.7) or methyl esters 405 and 38a (Scheme 4.9) must be employed.

There are two further examples in which ester tethered precursors were preformed, isolated and then subjected to conditions which would normally lead to ETDA reactions. These derivatives are shown in Figure 4.16. Dichloromaleate 41f and bromomaleate 41g have one structural feature in common with the citraconate half esters already discussed, which is the presence of substituents (other than hydrogen atoms) on the dienophile. It is proposed that dichloromaleate 41f generates endo adduct 43f via the same mechanism as the citraconate half esters 38d and 38c form 40c and
The reaction of bromomaleate 41g is not reported to produce ETDA adducts, but instead results in extensive polymerization. Based on the results described for the citraconate half esters in this Chapter, it is likely that this process begins with cleavage of the ester tether.

\begin{equation}
\begin{array}{c}
\text{H}_2\text{C} \quad \text{CH}_2 \quad \text{CH} \quad \text{CH}_3 \\
\text{Cl} \quad \text{Cl} \quad \text{O} \\
\text{HO}_2\text{C} \\
41f \\
\end{array}
\xrightarrow{\Delta \text{xylene} 140^\circ\text{C}, 15\text{h}}
\begin{array}{c}
\text{H} \\
\text{Cl} \quad \text{Cl} \\
\text{HO}_2\text{C} \\
43f \\
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{H}_2\text{C} \quad \text{CH}_2 \quad \text{CH} \quad \text{CH}_3 \\
\text{HO}_2\text{C} \quad \text{BR} \\
\text{Cl} \quad \text{O} \\
41g \\
\end{array}
\xrightarrow{\Delta \text{xylene} 140^\circ\text{C}, 15\text{h}}
\text{polymer}
\end{equation}

Figure 4.16
5 Attempted transannular Diels-Alder (TDA) and tandem IMDA (TIMDA) reactions

5.1 Introduction

Steroids feature prominently in the regulation of metabolism in every organ of the human body. They are also responsible for initiating all of the major physiological changes an individual goes through during the course of their life and for controlling the reproductive cycle. As a consequence of this they are used extensively in the treatment of a wide variety of diseases and they are the major active ingredients of the contraceptive pill. Steroids therefore represent attractive targets for synthetic organic chemists and a number of strategies involving DA reactions have been reported.

Steroids have featured in the development of some recent therapeutic agents with diverse delivery systems (Figure 5.1). These include: oestradiol (1) which has been incorporated into patches for transdermal hormonal replacement in menopausal women; hydrocortisone derivatives such as betamethasone valerate (2) which is the active ingredient in creams for the treatment of inflammatory skin conditions such as psoriasis; and beclomethasone dipropionate (3) which is inhaled directly into the lungs for the control of asthma. Plant natural extracts containing steroids have been known for much longer. Digoxin (4) is a steroid glycoside found in foxgloves (Digitalis purpurea or Digitalis lanata) which can be administered intravenously in the emergency treatment of cardiac arrest. The efficacy of foxglove extracts in the treatment of heart ailments was reported as early as 1250 and the active agents contained in these extracts have not been improved upon.

New steroids are constantly being isolated from diverse sources and some of these are unsurpassed in their biological activity. However, in their natural setting, many of these compounds occur in only trace amounts and synthesis is the only way that they can become readily available.
Any synthetic approach to a specific molecule, which is ultimately intended for pharmacological use, must meet a set of strict criteria in order for commercial manufacture to be considered economically viable. The synthesis must be short, the starting materials and reagents must be inexpensive, the reactions must be easily and safely carried out on large scale and the products must be obtained in enantiomerically pure form.\textsuperscript{222}

Synthesis of steroids \textit{via} a tandem transannular Diels-Alder (TTDA) reaction of a macrocyclic precursor, containing a \textit{bis}-diene (in the form of a conjugated tetraene) and a \textit{bis}-dienophile, should satisfy all of the criteria listed above. This novel approach is illustrated retrosynthetically (from the cyclopentano perhydrophenanthrene nucleus (X) of steroids) in \textbf{Figure 5.2}. Esterification is a convenient way of attaching the \textit{bis}-diene to the \textit{bis}-dienophile and the inclusion of a stereogenic centre in lactone 7 provides a potential method for controlling the stereochemical outcome of the TTDA reaction. A high level of stereochemical control is essential in this setting because the TTDA reaction generates eight new stereogenic centres in a single step. It was anticipated that the low reactivity of the singly activated \textit{E}-dienophiles in structure 7 (Sections 1.2.1.3, 3.3.2 and 3.3.4) and the rate retarding effect of the two ester tethers (Section 1.2.1.2) might be compensated for by the entropic advantage inherent in the TTDA reaction.
catalytic hydrogenation TF ➞
convert one lactone into a cyclopentane;
remove the other lactone

TDA reaction TF

macrocyclisation TF

esterification TF ➞

Figure 5.2
5.2 Attempts to synthesize single TDA reaction precursors

Because of the complexity of precursors such as 508 (Figure 5.2) it was decided to carry out a model study involving the TDA reaction of a macrocycle containing a single diene and dienophile, as illustrated in Scheme 5.1.

Carboxylic acid 236 was treated with tetrabutylammonium fluoride to expose the secondary alcohol, then a modified Yamaguchi macrocyclisation protocol was attempted on compound 237 with 2,4,6-trichlorobenzoyl chloride, but the latter reaction was not successful. The reason for this was revealed by inspecting Dreiding models of compound 237, which indicated that a very high level of strain would need to be overcome in order for lactonisation to occur.

![Scheme 5.1](image-url)

**Conditions:**
- (i) TBAF, THF, RT, 16h, 85%.
- (ii) TEA, 2,4,6-trichlorobenzoyl chloride, toluene, RT, 2h, then DMAP, 10h.
- (iii) TFA, CH₂Cl₂, RT, 20min, 59%.
- (iv) a) TEA, 2,4,6-trichlorobenzoyl chloride, toluene, RT, 18h, then DMAP, 3h.
- (iv) b) DCC, DMAP, TfOH, chloroform, (slow addition of 53 via syringe pump), RT, 8h.
Due to the difficulties encountered in the macrocyclisation of compound 237, it was decided to attempt to form a larger macrocycle with significantly more inherent conformational mobility. This strategy has the advantage that the bulky tert-butyldimethylsilyl group (which is intended to control the stereoselectivity in the ensuing TDA reaction) is retained. Carboxylic acid 236 was treated with trifluoroacetic acid\textsuperscript{224} to form diol 515 in modest yield. Macrocyclisation of 515 using the modified Yamaguchi protocol\textsuperscript{223} was then attempted. Unfortunately this reaction did not occur although a variety of solvents (benzene, toluene and xylene), starting material concentrations (1-10 mmol/L) and reagent equivalents were tested. Mass spectral data (EI, 70 eV) of the crude reaction mixture produced in reaction (iv)a disclosed fragments which had masses in excess of 700 amu, indicating that intermolecular esterification may have been more rapid than macrolactonisation, in spite of the high dilution (up to 1 mmol/L) that was used. A modified Steglich esterification protocol\textsuperscript{225} using dicyclohexylcarbodiimide was also attempted, however, this too was unsuccessful.

5.3: Attempts to synthesize TTDA reaction precursors

In spite of the lack of success with the model system (Section 5.2), synthesis of macrocyclic precursors for a TTDA reactions was still attempted. This involved three stages: synthesis of a bis-diene in the form of a conjugated tetraene (Section 5.3.1); synthesis of a bis-dienophile (Section 5.3.2) with an appropriate protecting group; and formation of the macrocycle (Section 5.3.3).

5.3.1 Synthesis of a chiral tetraenol

Dienol 228 (Section 2.2.1) was treated with Dess-Martin periodinane\textsuperscript{167} (Section 6.6.1) to form aldehyde 518 in high yield (Scheme 5.2). This was then homologated with methyl 4-triphenylyphosphoranylidene)-(2E)-2-butenoate\textsuperscript{168} \textsuperscript{169} (Section 6.6.2) to give tetraene ester 519 as a mixture of E- and Z-stereoisomers in modest yield. It was found that isomerisation with thiophenol and AIBN\textsuperscript{170} was ineffective. Treatment of ester 519 with catalytic iodine in dichloromethane\textsuperscript{226} afford the E-stereoisomer although nearly 40% of the material was unaccounted for. (This may have been due to loss of the isopropylidene group,\textsuperscript{227} since isomerisation required the addition of extra iodine (0.2 equivalents) in this case.) It was found that the addition of 2,6-di-tert-butyl-4-methylphenol (0.2 equivalents) in the esterification step increased the yield of compound 519 to 78%, however, the presence of minute traces of the
antioxidant was detrimental to the subsequent isomerisation. Reduction of ester 519 with diisobutyl aluminium hydride afforded conjugated tetraenol 520 in excellent yield.

![Scheme](image)

**Conditions:** (i) Dess-Martin Periodinane, CH₂Cl₂, RT, 30min, 83%; (ii) Ph₃P=CHCHCH₂Me, CH₂Cl₂, reflux, 3h, 46% then 1, CH₂Cl₂, 5h, 59%; (iii) DIBALH, CH₂Cl₂, -110°C to -80°C, 88%.

**Scheme 5.2**

### 5.3.2 Synthesis of a *bis*-dienophile

A monoprotected *bis*-dienophile was prepared (Scheme 5.3) from 2,5-dimethoxytetrahydrofuran (521) via succinaldehyde¹¹ (522, Section 6.6.4). The dialdehyde was homologated with ethyl (triphenylphosphoranylidene)ethanoate to form diene 524 in excellent yield. Unlike previous reactions involving the related ylid (Sections 2.2.1, 2.2.2 and 5.3.1), the E-stereoisomer was produced exclusively and no isomerisation was necessary after the Wittig reaction. Hydrolysis of the diester 524 with aqueous potassium hydroxide in tetrahydrofuran (followed by solvent extraction of the aqueous phase with diethyl ether, adjustment to pH 1 and filtration) produced diacid 525 in 68% yield. One equivalent of triisopropylsilyl chloride was slowly added to the diacid and triethylamine in dichloromethane producing monoprotected *bis*-dienophile 525 with an overall yield of 46% (along with disubstituted adduct 526 (22%) and recovered diacid 524 (20%))
Scheme 5.3

5.3.3 Attempts to synthesize TTDA precursors

Esterification\textsuperscript{206} of tetraenol \textit{520} and monoprotected dienedioic acid \textit{525} (Scheme 5.4) proved to be difficult to accomplish and yields were generally lower than 40\%. However, compound \textit{527} was isolated cleanly and exhibited infrared, NMR, UV and mass spectra commensurate with the structure shown.\textsuperscript{228-231} An attempt was made to simultaneously remove the isopropylidene group\textsuperscript{224} and triisopropyl group in compound \textit{527} using trifluoroacetic acid, but the product (\textit{529}) could not be identified in the crude reaction mixture, so it was decided to attempt these deprotections separately. Triisopropylsilyl esters are conveniently removed using potassium carbonate in methanol\textsuperscript{232} and a quantitative yield was realized in the conversion of compound \textit{527} to carboxylic acid \textit{528}. Attempted removal of the isopropylidene group from \textit{528} with trifluoroacetic acid caused decomposition of the starting material and so the deprotection was attempted using milder conditions. Aqueous acetic acid in THF has been successfully used to deprotect isopropylidene groups\textsuperscript{224} and to deprotect primary TBS ethers in the presence of secondary ones.\textsuperscript{233-235} In one example the starting material also incorporated an ester functionality.\textsuperscript{236} This protocol was investigated in an attempt to deprotect compound \textit{528} and proton NMR analysis indicated that some level of success may have been achieved. However, optimal conditions need to be found for this difficult deprotection. (Catalytic iodine in methanol is another gentle method which can be used to remove isopropylidene groups.\textsuperscript{227})
Scheme 5.4

Because it was not possible to form compound 529, the macrocyclisation step could not be attempted. However, if conditions cannot be found which facilitate access to compound 529, other strategies are available (Figure 5.3). Removal of the tert-butylidemethylsilyl group in compound 528 reveals a secondary alcohol group which has the potential to lactonise with the carboxylic acid group, but Dreiding models suggest that dilactone 532 would be highly strained. This strain could provide the impetus for a TTDA reaction to occur, but it also renders the dilactone difficult to form. One way of relieving some of this strain could be to isomerise acid 531 into 533 with sulphonic acid resin in acetone\textsuperscript{132} (Section 2.4.1.1) and then attempt the macrocyclisation reaction.
The advantage which compound 533 has over 529 is that there is only one hydroxyl group which can participate in the macrocyclisation (although the secondary alcohol in compound 529 would be appreciably less reactive than the primary one). Compound 533 does not have the bulky tert-butyldimethylsilyl group to direct the stereochemical outcome of the TDA reaction, but it does have an isopropylidene group which would increase the conformational rigidity of the dilactone, which might lead to a measure of stereoselectivity.

![Figure 5.3](image-url)
5.3.4 Attempted TIMDA reactions

Since the substrates were available, it was decided to attempt TIMDA reactions on compounds 527 and 528 (Scheme 5.5). It was anticipated that the singly activated $E$-dienophile in compound 527 (Sections 1.2.1.3, 3.3.2 and 3.3.4) and the rate retarding effect of the ester tether (Section 1.2.1.2) would cause the molecule to be resistant to cycloaddition, therefore it was decided to carry out an ETDA reaction in $d_6$-DMSO to allow the reaction to be monitored easily by proton NMR analysis and to permit high temperatures to be used. The reaction was carried out for 11h at 110°C in an NMR tube, but unfortunately the starting material was completely destroyed under these conditions.

A TIMDA reaction was carried out on compound 528 in water with ten equivalents of sodium bicarbonate. (The sodium bicarbonate was added to solubilise the starting material, which proved to be successful at elevated temperatures.) It was thought that the water might force the hydrophobic molecule to coil in upon itself bringing the alkene moieties together to provide the impetus for a TIMDA reaction to occur. However, refluxing for five days did not cause any change in the starting material.

It is apparent from these reactions that more forcing conditions are required to secure a TIMDA reaction. A number of options are available, including the application of high pressure. These studies await future investigation.

Conditions: (i) $d_6$-DMSO, 110°C, 11h; (ii) NaHCO$_3$, H$_2$O, reflux, 5d.

Scheme 5.5
5.5 Conclusion

Whist the reactions in this Section were not all successful, the elegance of the strategy to form steroid skeletons via TTDA reactions is still compelling. A chiral conjugated tetraenol (520) has been prepared, as has a monoprotected dienedioic acid containing a suitable bis-dienophile moiety (525). Esterification of these materials produced a TIMDA precursor (527), albeit in modest yield. Selective deprotection of this TIMDA precursor was also achieved, but some of the other deprotections were troublesome. Preliminary investigations carried out on TIMDA precursors (527 and 528) confirm the fact that forcing conditions will be necessary to cause cycloaddition to occur. Formation of macrocyclic dilactones was difficult and, due to time constraints, this prevented any TTDA reactions from being attempted. However, a number of strategies are still available which may eventually enable stereocontrolled TTDA reactions to be carried out on these systems.
6 Experimental

6.1 Introduction

All moisture sensitive reactions were done under an argon atmosphere using oven dried (150°C) glassware. Benzene, toluene, xylene, THF and diethyl ether were purified and dried by distillation from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Other commercial reagents were used as supplied (except in specific cases as indicated in the appropriate text).

Reactions were normally monitored by thin layer chromatography (TLC) on aluminium backed 60 F254 silica gel plates (Merck). Unless otherwise specified, compounds were detected by visualization under an ultraviolet lamp followed by treatment with alkaline potassium permanganate dip and strong heating. In some cases reactions were followed by proton NMR analysis, vide infra.

Slow addition of solutions to reaction mixtures was accomplished using a Cole Parmer 74900 series syringe pump. Organic solvents partitioned against water as part of an aqueous work up were dried with anhydrous magnesium sulphate:sodium sulphate (3:1) prior to filtration and evaporation of the solvent in vacuo. Celite (Serva 545, 0.020-0.044mm) was occasionally used as a filtration aid. Kugelrohr distillation was carried out on a Buchi GKR-51.

Flash column chromatography and rapid vacuum filtration were carried out using oven dried (150°C) 60 silica gel (40-63μm, Merck). Radial chromatography was carried out with a Harrison Research 7924T chromatotron using 230mm diameter glass plates, precoated with a slurry of silica gel 60 HF254 (63-200μm, Merck):calcium sulphate hemihydrate (BDH) (17.5:1) and oven dried overnight (150°C). Hexane and ethyl acetate (distilled from laboratory grade solvents) were the principal eluents, although diethyl ether, dichloromethane, methanol and acetic acid (analytical grades) were also used when required. Product ratios were determined by integration of proton NMR spectra of crude reaction mixtures prior to chromatography. Unless indicated otherwise yields were determined from actual masses of material isolated in analytically pure form. Where diastereomeric mixtures were produced the overall yield given includes the contribution made from mixed fractions in which the individual stereoisomers could be identified by NMR spectra and were shown to be free of other impurities.
Melting points of crystalline materials were measured on a Reichert hot stage apparatus and are uncorrected. Optical rotation ([α]D) was measured on an Optical Activity Limited AA-100 polarimeter. The path length for neat samples was 0.05dm and 1.0dm was used for solutions. Infrared measurements were carried out on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. (Only the major peaks have been reported.) Proton and carbon nuclear magnetic resonance (NMR) spectra were recorded on a Jeol JNM-GX270W instrument. The following abbreviations were used: s, singulet; d, doublet; t, triplet, q, quartet; m, multiplet; b, broad; and obs, obscured (where the multiplicity could not be determined due to the position of a much larger peak). Unless otherwise specified chemical shifts (δ) are reported in parts per million values (ppm) relative to chloroform as the internal standard (7.27ppm for 1H NMR and 77.0ppm for 13C NMR respectively) and coupling constants (J) are given in hertz (Hz). Where necessary DEPT, APT, HETCOR, HSQC, HMQC, ROESY, phase sensitive COSY, NOESY and nOe difference experiments were performed. (A summary of the two dimensional NMR experiments carried out is contained in Appendix 2.) Ultraviolet-visible spectra were recorded on a Shimadzu UV-3101PC scanning spectrophotometer. (Spectroscopic grade methanol was used throughout.) Mass spectral measurements were made on a VG Instruments VG70-250S double focusing magnetic sector mass spectrometer. Electron Impact (EI) was carried out at 40, 70 or 80eV and Chemical Ionization (CI) was accomplished at 40eV and 70eV with ammonia gas. The source temperature was 180-200°C, the trap current was 200μA and for high resolution experiments a resolving power of 5000-6000 was used. Crystallographic analysis was performed on an Enraf Nonius Delft Diffractus 586 diffractometer.

6.1.1 General procedure for ETDA reactions

To a stirred solution of the starting material (5mmol/L) in benzene, toluene or xylene was added 2,6-di-tert-butyl-4-methylphenol (0.2eq) under argon. The solution was heated to reflux and heating continued until the starting material was consumed (as judged by proton NMR analysis or TLC of crude reaction mixtures), whereupon the solvent was evaporated and the products were separated chromatographically. (Proton NMR analysis of the crude reaction mixtures was used to determine the product ratios.)
6.1.2 General procedure for ETDA reactions of carboxylic acids

To a stirred solution of the starting material (5mmol/L) in benzene, toluene or xylene was added 2,6-di-tert-butyl-4-methylphenol (0.2eq) under argon. The solution was heated to reflux and heating continued until the starting material was consumed (as judged by proton NMR analysis or TLC of crude reaction mixtures), whereupon the reaction mixture was cooled to RT, 0°C or -60°C and diazomethane\textsuperscript{173} (Section 6.6.3) was added. The solvent was then evaporated and the products were separated chromatographically. (Proton NMR analysis of the crude reaction mixtures (before and after the addition of diazomethane) was used to determine the product ratios.)

6.2 Experimental for Chapter Two

6.2.1 Preparation of chiral dienols

5,6-\textit{O}-isopropylidene-L-ascorbic acid (222)

Protection of L-ascorbic acid (221) was based on the method of Jung and Shaw.\textsuperscript{163} To a stirred solution of L-ascorbic acid (221) (100g, 0.568mol) in acetone (400mL, 5.68mol, 10eq) at RT under a calcium chloride drying-tube was added acetyl chloride (10.0mL, 1.50mol, 2.64eq). Further acetone (200mL) was subsequently added to aid stirring, which was continued for 8h. The mixture was refrigerated overnight and the resulting precipitate rinsed with cold acetone (3 x 100mL) then dried under vacuum yielding the title compound (222) (93.6g, 0.433mol, 76%) as a white crystalline solid: mp 217-219°C dec. [lit.\textsuperscript{240}] 214-218°C dec.]; [\alpha]_D^{22} = +25.7° (c = 1.00, water) [lit.\textsuperscript{240} [\alpha]_D^{19} = +25.3° (c = 1.00, water)]; (Found: M+, 216.0632. C\textsubscript{9}H\textsubscript{12}O\textsubscript{6} requires M, 216.0633); \nu_{max} (KBr disc) 3243, 3074, 2992, 1754 and 1664cm\textsuperscript{-1}; \delta_{H} (270MHz, d\textsubscript{6}-DMSO/internal reference 2.50ppm) 1.25 (6H, s, -CH\textsubscript{3}CH\textsubscript{3}), 3.17-3.64 (2H, m, -COH=COH-), 3.88 (1H, dd, J 6.4, 8.3Hz, C6-H ), 4.09 (1H, dd, J 7.2, 8.3Hz, C6-H’), 4.26 (1H, m, C5-H) and 4.70 (1H, d, J 2.9Hz, C4-H); \delta_{C} (68.1MHz,
Oxidative cleavage of 5,6-0-isopropylidene-L-ascorbic acid (222) and esterification of the resulting potassium salt was based on the method of Abushanab et al.165, 164. To a stirred solution of 5,6-0-isopropylidene-L-ascorbic acid (222) (93.6 g, 0.433 mol) in water (457 mL) containing potassium carbonate (119 g, 0.866 mol, 2 eq), chilled in an ice bath and maintained below 20°C, was added 30% hydrogen peroxide (95.0 mL, 0.866 mol, 2 eq). On completion of the addition the solution was warmed to RT and stirring was continued for 24 h. The solvent was evaporated and the moist solid was extracted with boiling absolute ethanol (6 x 200 mL). After filtration and evaporation the material was dried under vacuum to give crude potassium (2R,3S)-3,4-O-isopropylidene-2,3,4-trihydroxybutanoate salt (107 g) as a white powder. To a stirred solution of the crude salt in acetonitrile (500 mL) at RT under argon was added ethyl iodide (55 mL, 1.5 mol, ca 3.5 eq) and the solution was warmed to reflux. Stirring was continued for 44 h and then the solvent was evaporated. The residue was partitioned between water (100 mL) and dichloromethane (3 x 100 mL). The combined organic layers were then washed with water (100 mL), brine (2 x 100 mL), dried, filtered and evaporated to produce the crude product (73.2 g) as an orange oil. Distillation gave the title compound (223) (69.0 g, 0.338 mol, 78%) as a yellow oil: bp 84-88°C/0.5 mmHg; [α]_D^21 = +4.2° (c = 1.50, methanol); Rf = 0.20 (hexane:ethyl acetate (5:1)); (Found: M^+ -CH₃ 189.0762. C₈H₁₃O₅ requires M, 189.0763); ν_max (film) 3489, 2986, 2937, 2906 1743 and 1208 cm⁻¹; δ_H (270 MHz, CDCl₃/D₂O shake) 1.29 (3H, t, J = 7.3 Hz, -OCH₂CH₃), 1.34 and 1.41 (6H, 2 x s, -C(CH₃)₂⁻), 3.99 (1H, dd, J = 7.0, 8.3 Hz, C₄-H'), 4.08 (1H, dd, J = 6.6, 8.3 Hz, C₄-H'), 4.09 (1H, d, J = 3.1 Hz, C₂-H), 4.26 and 4.27 (2H, 2 x q, J = 7.3 Hz, -OCH₂CH₃) and 4.35 (1H, ddd, J = 3.1, 6.6, 7.0 Hz, C₃-H); δ_C (68.1 MHz, CDCl₃) 14.2, 25.4, 26.1, 61.9, 65.6, 70.4, 76.4, 109.8 and 171.8; m/z (EI, 40 eV) 189 (73%), 131 (28), 101 (100), 60 (54) and 42 (84).
ethyl (2R,3S)-3,4-O-isopropylidene-2-(1-tert-butyl-1,1-dimethylsilyl)oxy-3,4-dihydroxybutanoate (224)

![Chemical structure](image)

To a stirred solution of ethyl (2R,3S)-3,4-O-isopropylidene-2,3,4-trihydroxybutanoate (223) (10.2g, 0.0500mol) in DMF (10mL) at 0°C under argon was added imidazole (4.08g, 0.0600mol, 1.2eq) and tert-butyldimethylsilyl chloride (7.90g, 0.0525mol, 1.05eq). On completion of the addition the resulting solution was allowed to warm to RT and stirred for 30min. The reaction mixture was partitioned between water (50mL) and ethyl acetate (3 x 50mL) and the combined extracts were dried, filtered and evaporated to give the crude product (15.9g) as a yellow oil. Distillation gave the title compound (224) (10.8g, 0.0340mol, 68%) as a colourless oil: bp 148-150°C/14mmHg; [α]_D^20 = +28.0° (c = 4.65, dichloromethane); R_f = 0.63 (hexane:ethyl acetate (5:1)); (Found: M^-CH₃, 303.1628. C_{14}H₂₉O₅Si requires M, 303.1614); ν_max (film) 2985, 2955, 2932, 2896, 2858, 1735, 1473, 1464, 1380, 1370 and 1156cm⁻¹; δ_H (270MHz, CDCl₃) 0.08 and 0.11 (6H, 2 x s, -Si(CH₃)₂), 0.92 (9H, s, -C(CH₃)₃), 1.30 (3H, t, J 7.1Hz, -OCH₂CH₃), 1.35 and 1.41 (6H, 2 x s, -C(CH₃)₂), 3.97 (1H, dd, J 6.4, 8.5Hz, C4-H), 4.05 (1H, dd, J 6.4, 8.5Hz, C4-H'), 4.20 (1H, d, J 5.3Hz, C2-H), 4.21 and 4.22 (2H, 2 x q, J 7.1Hz, -OCH₂CH₃) and 4.33 (1H, td, J 6.4, 5.3Hz, C3-H); δ_C (68.1MHz, CDCl₃) -5.17, -4.92, 14.2, 18.4, 25.3, 25.7, 26.3, 60.9, 65.5, 73.3, 77.1, 109.5 and 170.8; m/z (EI, 70eV) 303 (22%), 261 (52), 203 (35), 101 (54) and 75 (100).

(2S,3S)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2,4-butanetriol (225)

![Chemical structure](image)
To a stirred solution of ethyl (2R,3S)-3,4-O-isopropylidene-2-(1-tert-butyl-1,1-dimethylsilyl)oxy-3,4-dihydroxybutanoate (224) (4.44g, 0.0157mol) in dichloromethane (200mL) at -78°C under argon was added dropwise diisobutylaluminium hydride (1.0mol/L in toluene, 34.5mL, 0.0345mol, 2.2eq). On completion of the addition stirring was continued for 10min at -78°C then the mixture was allowed to warm to RT and stirred for a further 1h. The excess diisobutylaluminium hydride was quenched at RT with 2% aqueous sodium hydroxide solution (20mL). The material was filtered through celite and the filtrate was rinsed with dichloromethane (3 x 50mL). The combined extracts were washed with water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (3.15g) as a colourless oil. A small portion of the crude material (174mg) was purified on silica (10g) with hexane:ethyl acetate (10:1 then 5:1) to give an analytically pure sample of the title compound (225) (147mg) as a colourless oil: \([\alpha]_D^{18.5} = -11.0^o\) (c = 6.80, dichloromethane); \(R_f = 0.20\) (hexane:ethyl acetate (5:1)); (Found: \(M^+\)-CH$_3$, 261.1522. C$_{12}$H$_{25}$O$_4$Si requires \(M\), 261.1522); \(\nu_{\text{max}}\) (film) 3462, 2985, 2954, 2930, 2887, 2858, 1472, 1463, 1380 and 1370cm$^{-1}$; \(\delta_H\) (270MHz, CDCl$_3$/D$_2$O shake) 0.12 (6H, s, -Si(CH$_3$)$_2$-), 0.91 (9H, s, -C(CH$_3$)$_3$), 1.36 and 1.43 (6H, 2 x s, -C(CH$_3$)$_2$-), 3.53 (1H, dd, J 4.7, 11.4Hz, C1-H), 3.67 (1H, dd, J 4.8, 11.4Hz, C1-H'), 3.78-3.89 (2H, m, C2-H and C3-H), 4.00 (1H, dd, J 6.6, 8.3Hz, C4-H) and 4.20 (1H, dd, J 6.6, 12.6Hz, C4-H'); \(\delta_C\) (68.1MHz, CDCl$_3$) -4.71, -4.59, 18.1, 25.1, 25.8, 26.3, 63.6, 65.3, 72.8, 77.1 and 109.1; \(m/z\) (EI, 40eV) 261 (10%), 161 (59), 131 (66), 117 (100) and 75 (91).

(2R,3S)-3,4-O-isopropylidene-2-(1-tert-butyl-1,1-dimethylsilyl)oxy-3,4-dihydroxybutanal (226)

Method A

To a stirred solution of crude (2S,3S)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2,4-butanetriol (225) (2.98g, ca 0.0108mol) in dichloromethane (30mL) was added Dess-Martin periodinane$^{167}$ (Section 6.6.1) (5.02g, 0.0119mol, \(\alpha\) 1.1eq) at RT under argon. After 1h the reaction mixture was filtered and the filtrate was
rinsed with dichloromethane (3 x 15mL). The combined extracts were washed with saturated aqueous sodium bicarbonate (50mL) containing sodium thiosulphate pentahydrate (10g), saturated aqueous sodium bicarbonate (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (3.30g) as a yellow oil. The crude material was adsorbed onto silica (9g) then loaded onto a silica column (36g) and eluted with hexane:ethyl acetate (5:1) to give the title compound (226) (2.20g, 8.02mmol, 58% (2 steps)) as a colourless oil, *vide infra.*

**Method B**

To a stirred solution of ethyl (2R,3S)-3,4-O-isopropylidene-2-(1-tert-butyl-1,1-dimethylsilyl)oxy-3,4-dihydroxybutanoate (224) (10.8g, 0.0338mol) in dichloromethane (100mL) at -100°C under argon was added diisobutylaluminium hydride (1.5mol/L in toluene, 33.8mL, 0.0570mol, 1.5eq) using a syringe pump over 1h. The excess diisobutylaluminium hydride was quenched at -100°C with 2% aqueous sodium hydroxide (30mL) then the mixture was allowed to warm to RT. Water (50mL) and dichloromethane (50mL) were added resulting in an emulsion, which was eliminated by the stepwise addition of saturated aqueous potassium sodium (+)-tartrate. The aqueous layer was extracted with dichloromethane (3 x 50mL) and the combined extracts were washed with 50% aqueous potassium sodium (+)-tartrate (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (11.0g) as a yellow oil. Distillation gave the title compound (226) (7.97g, 0.0290mol, 86%) as a colourless oil: bp 96°C/0.01mmHg; [α]_D^{21} = +2.0° (c = 4.79, dichloromethane); R_t = 0.46 (hexane:ethyl acetate (5:1)); (Found: M^+H, 275.1671. C_{13}H_{27}O_4Si requires M, 275.1679); ν_max (film) 2986, 2954, 2931, 2888, 2858, 1737, 1472, 1463, 1380 and 1371cm⁻¹; δ_H (270MHz, CDCl₃) 0.09 and 0.11 (6H, 2 x s, -Si(CH₃)₂-), 0.94 (9H, s, -C(CH₃)₃), 1.35 and 1.42 (6H, 2 x s, -C(CH₃)₂-), 3.95 (1H, dd, J 6.2, 8.7Hz, C4-H ), 4.04 (1H, dd, J 1.4, 4.7Hz, C2-H), 4.07 (1H, dd, J 6.4, 8.7Hz, C4'-H'), 4.32 (1H, ddd, J 4.7, 6.2, 6.4Hz, C3-H) and 9.70 (1H, d, J 1.4Hz, -CHO); δ_C (68.1MHz, CDCl₃) -5.00, -4.68, 18.3, 25.1, 25.7, 26.1, 65.1, 76.4, 77.7, 109.6 and 202.0; m/z (EI, 70eV) 275 (3%), 131 (25), 117 (31), 101 (100) and 75 (69).
ethyl (2E,4E,6S,7S)-7,8-O-isopropylidene-6-(1-tert-butyl-1,1-dimethylsilyl)oxy-7,8-dihydroxy-2,4-octadienoate (227)

To a stirred solution of (2R,3S)-3,4-O-isopropylidene-2-(1-tert-butyl-1,1-dimethylsilyl)oxy-3,4-dihydroxybutanal (226) (5.00g, 0.0182mol) in dichloromethane (50mL) at RT under argon was added ethyl 4-(triphenylphosphoranylidene)-(2E)-2-butenoate \(^{168, 169}\) (Section 6.6.2) (9.55g, 0.0255mol, 1.4eq) and the resulting mixture warmed to reflux and heating continued for 1.5h. (Consumption of the starting material was monitored by proton NMR analysis.) Evaporation gave the crude product (14.5g) as a yellow oil. This material was adsorbed onto silica (15g) then loaded onto a silica column (15g) and eluted with hexane:ethyl acetate (10:1) to give a mixture of Z- and E-stereoisomers (79:21) of compound 227 (5.24g, 0.0141mol, 78%).

Isomerisation.

To a stirred solution of the Z- and E-stereoisomers of compound 227 (5.24g, 0.0141mol) in benzene (50mL) at RT under argon was added thiophenol (0.435mL, 4.23mmol, 0.3eq) and 2,2’-azo-bis-isobutyronitrile (0.345g, 0.213mmol, 0.15eq) in three potions at one hour intervals, during which time the reaction mixture was irradiated with ultraviolet light at reflux for a total of 3h. (Isomerisation was monitored by proton NMR analysis.) The solvent was evaporated to give the crude product (5.65g) as a yellow oil, which was used without further purification. A small portion of the crude material (103mg) was purified on silica (10g) with hexane:ethyl acetate (20:1 then 10:1) to give an analytically pure sample of the title compound (227) (77.0mg) as a pale yellow oil: \([\alpha]_D^{20} = -29.7^\circ\) (c = 1.84, dichloromethane); \(R_e = 0.26\) (hexane:ethyl acetate (10:1)); (Found: \(M^+\), 370.2174 \(C_{19}H_{34}O_{11}Si\) requires \(M\), 370.2176); \(\nu_{max}\) (film) 2985, 2956, 2931, 2887, 2858, 1714, 1646, 1620, 1472, 1463, 1380, and 1370 cm\(^{-1}\); \(\delta_H\) (270MHz, CDCl\(_3\)) 0.048 and 0.071 (6H, 2 x s, -Si(CH\(_3\))\(_2\)-), 0.894 (9H, s, -C(CH\(_3\))\(_3\)), 1.29 (3H, t, \(J\) 7.2Hz, -OCH\(_2\)CH\(_2\)\(_3\)), 1.33 and 1.39 (6H, 2 x s, -C(CH\(_3\))\(_3\)), 3.77 (1H, dd, \(J\) 6.0, 8.6Hz, C8-H\(_2\)), 3.95 (1H, dd, \(J\) 6.7, 8.6Hz, C8-H\(_3\)), 4.07-4.15 (1H, m, C7-H), 4.20 (2H, q, \(J\) 7.2Hz, -OCH\(_2\)CH\(_3\)), 4.38 (1H, td, \(J\) 5.3, 0.8Hz, C6-H), 5.88 (1H, d, \(J\) 15.4Hz, C2-H), 6.13 (1H, dd, \(J\) 5.3, 15.3Hz, C5-H), 6.41 (1H, ddd, \(J\) 0.8, 11.0,
15.3 Hz, C4-H) and 7.28 (1H, dd, J 11.0, 15.4 Hz, C3-H); δ_C (68.1 MHz, CDCl_3) -4.76, -4.61, 14.4, 18.3, 25.1, 25.8, 26.4, 60.3, 65.1, 72.8, 78.2, 109.5, 121.5, 129.1, 140.4, 143.4 and 166.7; m/z (EI, 70 eV) 370 (0.3%), 313 (25), 270 (67), 101 (100) and 73 (62).

(2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)-oxy-4,6-octadien-1,2,8-triol (228)

To a stirred solution of the crude ethyl (2E,4E,6S,7S)-7,8-O-isopropylidene-6-(1-tert-butyl-1,1-dimethylsilyl)oxy-7,8-dihydroxy-2,4-octadienoate (227) (5.55 g, α 0.0150 mol) in dichloromethane (75 mL) at -78°C under argon was added dropwise diisobutylaluminium hydride (1.5 mol/L in toluene, 22.0 mL, 0.0330 mol, ca 2.2 eq). The starting material was consumed immediately and the excess diisobutylaluminium hydride was quenched at -60°C with 2% aqueous sodium hydroxide (20 mL). Saturated aqueous potassium sodium (+)-tartrate (50 mL) was added to disperse the emulsion which formed and the aqueous layer was extracted with further dichloromethane (3 x 50 mL). The combined extracts were washed with brine (50 mL) then dried, filtered and evaporated to give the crude product (6.07 g) as a yellow oil. The crude product was adsorbed onto silica (10 g) then loaded onto a silica column (100 g) and eluted with hexane:ethyl acetate (3:1) to give the title compound (228) (3.50 g, 0.0107 mol, 58% (3 steps)) as a pale yellow oil: [α]_D^24 = -26.0° (c = 1.33, dichloromethane); R_f = 0.14 (hexane:ethyl acetate (3:1)); (Found: M^+, 328.2066. C_{17}H_{32}O_4Si requires M, 328.2070); ν_{max} (film) 3418, 2954, 2929, 2886, 2857, 1661, 1626, 1472, 1462, 1380, and 1371 cm^{-1}; δ_H (270 MHz, CDCl_3) 0.02 and 0.43 (6H, 2 x s, -Si(CH_3)_2-), 0.87 (9H, s, -C(CH_3)_3), 1.30 and 1.36 (6H, 2 x s, -C(CH_3)_2-), 2.37 (1H, s, -OH), 3.75 (1H, dd, J 6.2, 8.4 Hz, C1-H'), 4.05 (1H, m, C2-H), 4.14 (2H, d, J 5.3 Hz, C8-H), 4.24 (1H, t, J 5.7 Hz, C3-H), 5.59-5.70 (1H, m, C4-H), 5.73-5.88 (1H, m, C7-H) and 6.15-6.32 (2H, m, C5-H and C6-H); δ_C (68.1 MHz, CDCl_3) -4.75, -4.52, 18.3, 25.2, 25.8, 26.4, 63.0, 65.2, 73.4, 78.6, 109.3, 130.3, 130.9, 131.6 and 132.2; m/z (EI, 70 eV) 328 (2%), 227 (44), 210 (32), 101 (100) and 73 (77).
diethyl L-malate (230)

\[
\text{HO-} \quad \text{CO}_2\text{Et} \\
\text{CO}_2\text{Et}
\]

To a stirred solution of L-malic acid (229) (13.4 g, 0.100 mol) in ethanol (200 mL) was added concentrated sulphuric acid (17.8 mol/L, 13.4 mL, 0.240 mol, 2.4 eq) at RT. On completion of the addition the solution was warmed to reflux and stirring was continued for 16 h. The ethanol was partially evaporated then the residue was partitioned between dichloromethane (200 mL) and saturated aqueous sodium bicarbonate (50 mL). Solid sodium bicarbonate was added until effervescence subsided. The extract was washed with water (2 x 50 mL) and brine (50 mL) then dried, filtered and evaporated to give the crude product (21.0 g) as a colourless oil. Distillation gave the title compound (230) (14.4 g, 0.0757 mol, 76%) as a colourless oil: bp 134-136°C/11 mmHg [lit.241 85-86°C/0.5 mmHg]; [\alpha]_D^{19} = -10.2° (neat) [lit.241 [\alpha]_D^{22} = -10.4° (neat)]; R_f = 0.48 (hexane:ethyl acetate (2:1)); (Found: \text{M}^+\text{H}, 191.0923. \text{C}_8\text{H}_{15}\text{O}_5 \text{ requires M, 191.0919}; \nu_{\text{max}} \text{(film)} 3490, 2984, 2940, 2908, 1736, 1374, and 1271 cm\textsuperscript{-1}; \delta_H (270 MHz, CDCl_3) 1.26 (3H, t, J 7.3 Hz, -CH\textsubscript{2}CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 1.30 (3H, t, J 7.3 Hz, -CHOHCO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 2.77 (1H, dd, J 5.9, 16.5 Hz, C3-H), 2.82 (1H, dd, J 4.6, 16.5 Hz, C3-H'), 3.27 (1H, d J 5.3 Hz, -OH), 4.18 (2H, q, J 7.3 Hz, -CH\textsubscript{2}CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 4.27 (2H, dq, J 1.1, 7.3 Hz, -CHOHCO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}) and 4.43-4.52 (1H, m, C2-H); \delta_C (68.1 MHz, CDCl_3) 14.2 (2 x C), 38.7, 61.0, 62.0, 67.3, 170.3 and 173.2; m/z (El, 70 eV) 191 (1%), 149 (6), 117 (100), 89 (36), 71 (94) and 43 (36).

ethyl (3S)-3,4-O-isopropylidene-3,4-dihydroxybutanoate (231)

\[
\text{CO}_2\text{Et}
\]

Regiochemical reduction of diethyl L-malate (230) and protection of the resulting diol was based on the method of Saito et al.\textsuperscript{171} To a stirred solution of diethyl L-malate (230) (9.00 g, 0.0473 mol) in THF (85 mL) at RT under argon in a 500 mL flask fitted with a short reflux condenser was added dropwise borane-dimethyl sulphide complex (2.0 mol/L in THF, 24.8 mL, 0.0496 mol, 1.05 eq). On completion of the addition stirring
was continued for 30 min then the solution was cooled to 10°C and sodium borohydride (0.0882 g, 2.33 mmol, 0.05 eq) was added. After effervescence had ceased the solution was warmed to RT and stirring was continued for 30 min. Ethanol (16.2 mL, 0.276 mol, 5.84 eq) and para-toluenesulphonic acid monohydrate (0.450 g, 2.33 mmol, 0.05 eq) were added and the resulting cloudy solution was stirred for 30 min. Benzenecethanol (1:1, 220 mL) was added and evaporated in two equal portions, followed by benzene (80 mL) to give the crude diol (7.82 g) as a colourless gum. Chromatography of this material on silica (32 g) with ethyl acetate gave ethyl (3S)-3,4-dihydroxybutanoate (6.16 g, 0.0416 mol, 88%) as a colourless oil: $R_f = 0.39$ (ethyl acetate). To a stirred solution of ethyl (3S)-3,4-dihydroxybutanoate (6.16 g, 0.0416 mol) in acetone (25 mL) at RT under argon was added 2,2-dimethoxypropane (6.2 mL, 0.050 mol, 1.2 eq) and para-toluenesulphonic acid monohydrate (0.399 g, 2.10 mmol, 0.05 eq). On completion of the addition the solution was stirred for 30 min then triethylamine (0.291 mL, 2.09 mmol, 0.05 eq) and diethyl ether (70 mL) were added. The reaction mixture was filtered through a silica plug (50 g) which was rinsed with diethyl ether (250 mL) and the combined extracts were evaporated to give the crude product (7.58 g) as an opaque oil. Distillation of this material gave the title compound (231) (6.16 g, 0.0327 mol, 69%) as a colourless oil: bp 98°C/11 mmHg [lit.171 bp 110°C/23 mmHg]; $[\alpha]^D_{20} = +18.5^\circ$ (c = 1.17, chloroform) [lit.171 $[\alpha]^D_{20} = +27.0^\circ$ (c = 1.17, chloroform)]; $[\alpha]^D_{20} = +6.4^\circ$ (c = 1.38, ethanol) [lit.171 $[\alpha]^D_{20} = +15.4^\circ$ (c = 1.38, ethanol)]; $R_f = 0.70$ (hexane:ethyl acetate (2:1)); (Found: $M^+ - CH_3$, 173.0812. $C_8H_{12}O_4$ requires $M$, 173.0814); $\nu_{\text{max}}$ (film) 2986, 2936, 1736, 1371, 1380 and 1066 cm$^{-1}$; $\delta_H$ (270 MHz, CDCl$_3$) 1.27 (3H, t, $J$ 7.3 Hz, -OCH$_2$CH$_3$), 1.36 and 1.42 (6H, 2 x s, -C(CH$_3$)$_2$-), 2.52 (1H, dd, $J$ 7.3, 15.8 Hz, C2-H), 2.72 (1H, dd, $J$ 6.2, 15.8 Hz, C2-H$'$), 3.66 (1H, dd, $J$ 6.4, 8.3 Hz, C4-H), 4.16 (2H, q, $J$ 7.3 Hz, -OCH$_2$CH$_3$), 4.17 (1H, dd, $J$ 5.1, 8.3 Hz, C4-H$'$) and 4.41-4.53 (1H, m, C3-H); $\delta_C$ (68.1 MHz, CDCl$_3$) 14.2, 25.5, 26.9, 39.0, 60.6, 69.1, 72.0, 109.0 and 170.3; $m/z$ (El, 40 eV) 173 (47%), 113 (55), 101 (32), 85 (100) and 42 (81).

(2S)-1,2-O-isopropylidene-1,2,4-butanetriol (232)

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\begin{center}
\text{O} \quad \text{O} \\
\text{1} \quad \text{2} \quad \text{3} \quad \text{4} \\
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To a stirred solution of ethyl (3S)-3,4-O-isopropylidene-3,4-dihydroxybutanoate (231) (2.16 g, 0.0115 mol) in THF (30 mL) at 0°C under argon was added lithium
aluminium hydride (1.09g, 0.0287mol, 2.5 eq). On completion of the addition the solution was warmed to reflux and stirring was continued for 14h. The reaction mixture was diluted with dichloromethane (25mL) and the excess lithium aluminium hydride was quenched with THF:water (1:1, 7.5mL). The reaction mixture was filtered through celite (20g) which was rinsed with dichloromethane (3 x 100mL), then the combined extracts were dried, filtered and evaporated to give the crude product (1.70g) as a colourless oil. Kugelrohr distillation (87.5°C/0.05mmHg) gave the title compound (232) (1.54g, 0.0105mol, 91%) as a colourless oil: \[ [\alpha]_D^{195} = -2.29^\circ \text{ (c = 9.80, methanol)} \], [Lit.\textsuperscript{242} \[ [\alpha]_D = -2.23^\circ \text{ (c = 9.80, methanol)} \]; \( R_f = 0.31 \) (hexane:ethyl acetate (1:1)); (Found: \( M^+ + CH_3 \), 131.0709. \( C_6H_{11}O_3 \) requires \( M \), 131.0708); \( \nu_{\text{max}} \) (film) 3423, 2985, 2937, 2878, 1421, 1380, 1370, and 1059cm\(^{-1}\); \( \delta_H \) (270MHz, CDCl\(_3\)) 1.37 and 1.44 (6H, 2 x d, 0.7Hz, -C(CH\(_3\)\(_2\))\(_2\)), 1.79-1.87 (2H, m, C3-H), 2.20-2.26 (1H, m, -OH), 3.61 (1H, dd, \( J \) 7.5, 8.1Hz, C1-H\(_2\)), 3.76-3.86 (2H, m, C4-H), 4.10 (1H, dd, \( J \) 6.2, 8.1Hz, C1-H\(_3\)) and 4.23-4.24 (1H, m, C2-H); \( \delta_C \) (68.1MHz, CDCl\(_3\)) 25.6, 26.8, 35.7, 60.1, 69.3, 74.6 and 108.8; \( m/z \) (EI, 40eV) 131\% (57%), 71 (78), 60 (36), 42 (100) and 31 (21).

(3S)-3,4-O-isopropylidene-3,4-dihydroxybutanal (233)

To a stirred solution of (2S)-1,2-O-isopropylidene-1,2,4-butanetriol (232) (1.29g, 8.83mmol) in dichloromethane (20mL) at RT under argon was added Dess-Martin periodinane\textsuperscript{167} (Section 6.6.1) (6.73g, 15.9mmol, 1.8eq). Stirring was continued for 16h then the reaction mixture was filtered through celite (10g) and evaporated to give the crude product (1.54g) as a colourless oil. Chromatography of this material on silica (60g) with hexane:ethyl acetate (2:1) gave the title compound (233) (0.989g, 6.86mmol, 78%) as a colourless oil: \( [\alpha]_D^{20} = +15.4^\circ \) (neat) [Lit.\textsuperscript{242} \( [\alpha]_D^{20} = +16.5^\circ \) (neat)]; \( R_f = 0.64 \) (hexane:ethyl acetate (2:1)); (Found: \( M^+ + H \), 145.0865. \( C_7H_{13}O_3 \) requires \( M \), 145.0865); \( \nu_{\text{max}} \) (film) 2987, 2937, 2877, 1725, 1372 and 1382cm\(^{-1}\); \( \delta_H \) (270MHz, CDCl\(_3\)) 1.31 and 1.36 (6H, 2 x d, 0.7Hz, -C(CH\(_3\)\(_2\))\(_2\)), 2.60 (1H, ddd, \( J \) 1.3, 6.0, 17.4Hz, C2-H\(_2\)), 2.80 (1H, ddd, J 1.9, 6.6, 17.4Hz, C2-H\(_3\)), 3.54 (1H, dd, J 6.6, 8.3Hz, C4-H), 4.14 (1H, dd, J 5.9, 8.3Hz, C4-H\(_2\)), 4.43-4.53 (1H, m C3-H) and 9.73-9.76 (1H, m, -CHO); \( \delta_C \) (68.1MHz, CDCl\(_3\)) 25.4, 26.8, 47.7, 69.0, 70.5, 109.0 and 199.6; \( m/z \) (EI, 40eV) 145 (1%), 129 (15), 69 (100) 59 (18) and 43 (51).
ethyl (2E,4E,7S)-7,8-O-isopropylidene-7,8-dihydroxy-2,4-octadienoate (234)

To a stirred solution of (3S)-3,4-O-isopropylidene-3,4-dihydroxybutanal (233) (1.02g, 7.06mmol) in dichloromethane (10mL) at RT under argon was added ethyl 4-(triphenylphosphoranylidene)-(2E)-2-butenoate\(^{169}\) (Section 6.6.2) (3.70g, 9.89mmol, 1.4eq). On completion of the addition stirring was continued at RT for 1h. Silica gel (7.5g) was added and the solvent was evaporated. This material was loaded onto a silica column (75g) which was eluted with hexane:ethyl acetate (10:1 then 5:1) to give a mixture of Z- and E-stereoisomers (50:50) of compound 234 (0.598g, 2.49mmol, 35%).

Isomerisation.

To a stirred solution of the Z- and E-stereoisomers of compound 234 (0.598g, 2.49mmol) in benzene (5mL) at RT under argon was added thiophenol (0.11mL, 0.98mmol, 0.2eq) and 2,2'-azo-bis-isobutyronitrile (40.8mg, 0.250mmol, 0.1eq) in two potions at one hour intervals, during which time the reaction mixture was irradiated with ultraviolet light at reflux for a total of 2h. (Isomerisation was monitored by proton NMR analysis.) The solvent was evaporated to give the crude product (0.740g) as a yellow oil. Chromatography of this material on silica (20g) with hexane:ethyl acetate (10:1 then 5:1) gave the title compound (234) (0.464g, 1.93mmol, 78%) as a colourless oil: \([\alpha]_D^{21} = -4.1^\circ\) (c = 0.40, dichloromethane); R\(_f\) = 0.41 (hexane:ethyl acetate (5:1)); (Found: \(M^+\)-CH\(_3\), 225.1116. \(C_{12}H_{17}O_4\) requires \(M^+\), 225.1127); \(\nu_{\text{max}}\) (film) 2984, 2936, 2904, 2875, 1714, 1644, 1618, 1379, 1369 and 1262cm\(^{-1}\); \(\delta_H\) (270MHz, CDCl\(_3\)) 1.30 (6H, 2 x s, -C(CH\(_3\))\(_2\)-), 2.34-2.71 (2H, m, C6-H), 3.58 (1H, dd, J 6.8, 8.0Hz, C8-H), 4.04 (1H, dd, J 6.2, 8.0Hz, C8-H'), 4.20 (2H, q, J 7.3Hz, -OCH\(_2\)CH\(_3\)), 4.14-4.26 (1H, m, C7-H), 5.83 (1H, d, J 15.6Hz, C2-H), 6.03-6.16 (1H, m, C5-H), 6.26 (1H, dd, J 10.8, 15.1Hz, C4-H) and 7.26 (1H, dd, J 10.8, 15.6Hz, C3-H); \(\delta_C\) (68.1MHz, CDCl\(_3\)) 14.4, 25.6, 26.9, 37.2, 60.3, 68.8, 74.8, 109.1, 120.4, 130.8, 138.1, 144.1 and 166.8; m/z (Cl/\(\text{NH}_3\), 40eV) 225 (10%), 101 (100), 83 (8), 73 (13) and 43 (28).
(2S,4E,6E)-1,2-O-isopropylidene-4,6-octadiene-1,2,8-triol (235)

To a stirred solution of ethyl (2E,4E,7S)-7,8-O-isopropylidene-7,8-dihydroxy-2,4-octadienoate (234) (472mg, 1.96mmol) in dichloromethane (20mL) at -80°C under argon was added diisobutylaluminium hydride (1.5mol/L, 2.88mL, 4.32mmol, 2.2eq). On completion of the addition the excess diisobutylaluminium hydride was quenched by the addition of ethyl acetate (1.0mL) and the reaction mixture was diluted with hexane (50mL) and filtered through silica gel (10g) which was eluted with hexane, hexane:ethyl acetate (5:1 then 2:1) and ethyl acetate. Evaporation of the combined extracts gave the crude product (313mg) as a colourless oil. Chromatography of this material on silica (10g) with hexane:ethyl acetate (2:1) gave the title compound (235) (155mg, 0.782mmol, 40%) as a colourless oil: $[\alpha]_D^{21} = +13.2^\circ$ (c = 0.650, dichloromethane); Rf = 0.32 (hexane:ethyl acetate (2:1)); (Found: $M^+$, 198.1253. C11H18O3 requires $M^+$, 198.1255); $\nu_{\text{max}}$ (film) 3418, 2986, 2934, 2873, 1659, 1455, 1371, 1381 and 1216cm⁻¹; $\delta_h$ (270MHz, CDCl₃) 1.36 and 1.42 (6H, 2 x s, -C(CH₃)₂), 1.70 (1H, s, -OH), 2.23-2.61 (2H, m, C₃-H), 3.57 (1H, dd, $J$ 7.0, 7.9Hz, C₁-H), 4.02 (1H, dd, $J$ 5.9, 7.9Hz, C₁-H'), 4.09-4.24 (3H, m, C₂-H and C₈-H), 5.67 (1H, dt, $J$ 14.5, 7.1Hz, C₄-H) 5.77 (1H, dt, $J$ 14.5, 5.9Hz, C₇-H) and 6.06-6.29 (2H, m, C₅-H and C₆-H); $\delta_c$ (68.1MHz, CDCl₃) 25.7, 26.9, 36.9, 63.3, 68.8, 75.3, 109.0, 129.2, 130.7, 131.1 and 132.1; m/z (EI, 70eV) 198 (2%), 183 (47), 101 (100), 80 (81) and 59 (49).

6.2.2 Preparation of ETDA precursors

(2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (236)
To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)-oxy-4,6-octadien-1,2,8-triol (228) (0.492g, 1.50mmol) in dichloromethane (25mL) at RT under argon was added triethylamine (0.334mL, 2.40mmol, 1.6eq), maleic anhydride (0.330g, 3.37mmol, 2.25eq) and N,N-dimethylaminopyridine (0.0180g, 0.150mmol, 0.1eq). Stirring was continued for 10min and the reaction mixture was diluted with dichloromethane (100mL) and partitioned against 10% aqueous hydrochloric acid (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (0.735g) as a yellow oil. Chromatography of this material on silica (20g) with ethyl acetate:hexane:acetic acid (200:50:1) gave the title compound (236) (0.631g, 1.48mmol, 99%) as a pale yellow oil: [α]D18 = -39.4° (c = 0.62, dichloromethane); Rf = 0.46 (ethyl acetate:hexane:acetic acid (200:50:1)); (Found: M+, 426.2043, C21 H34O7Si requires M, 426.2074); νmax (film) 3175, 2986, 2955, 2930, 2889, 2857, 1732, 1714, 1642, 1472, 1462, 1413, 1382, 1372 and 1256cm⁻¹; δH (270MHz, CDCl₃) 0.057 and 0.077 (6H, 2 x s, -Si(CH₃)₂⁻), 0.902 (9H, s, -C(CH₃)₃), 1.34 and 1.40 (6H, 2 x s, -C(CH₃)₂⁻), 3.79 (1H, dd, J 6.0, 8.6Hz, C1-H), 3.95 (1H, dd, J 6.6, 8.6Hz, C1'-H'), 4.05-4.16 (1H, m, C2-H), 4.32 (1H, t, J 5.6Hz, C3-H), 4.80 (2H, d, J 7.0Hz, C8-H), 5.71-5.86 (2H, m, C4-H and C7-H) 6.20-6.52 (2H, m, C5-H and C6-H) and 6.39 and 6.46 (2H, 2 x d, B and A of AB, JAB 12.5Hz, -CH=CHCO₂H); δC (65.1MHz, CDCl₃) -4.73, -4.51, 18.3, 25.1, 25.9, 26.4, 65.1, 67.0, 72.9, 78.4, 109.4, 124.1, 129.0, 129.8, 134.4, 135.6, 136.1, 164.1 and 167.2; m/z (EI, 70eV) 426 (0.1%), 227 (24), 210 (44), 101 (100), 75 (69) and 43 (27).

(2S,3S,4E,6E)-1,2-O-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl hydrogen maleate (237)

To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (236) (1.20g, 2.81mmol) in THF (15mL) at RT under argon was added tetrabutylammonium fluoride (1.0mol/L in THF, 5.62mL, 5.62mmol, 2eq). On completion of the addition stirring was continued for 16h then the reaction mixture was diluted with dichloromethane (300mL) and partitioned against saturated aqueous ammonium chloride solution (150mL). The
ammonium chloride solution was further extracted with chloroform (2 x 150mL) and the combined extracts were washed with brine (150mL), dried (anhydrous sodium sulphate only), filtered and evaporated to give the crude product (3.35g) as a yellow oil. The crude product was adsorbed onto silica (7.5g) then loaded onto a silica column (55g) and eluted with ethyl acetate:acetic acid (40:1) gave the title compound (237) (0.751g, 2.41mmol, 85%) as a colourless oil: $[\alpha]_D^{195} = -16.4^\circ$ (c = 1.28, dichloromethane); R$_f$ = 0.50 (ethyl acetate:acetic acid (40:1)); (Found: $M^+$, 311.1130). $C_{15}H_{19}O_7$ requires $M$, 311.1131; $\nu_{\text{max}}$ (film) 3433, 2989, 2937, 2944, 1730, 1713, 1644, 1415, 1383, 1372 and 1215 cm$^{-1}$; $\delta$ (70MHz, CDCl$_3$) 1.37 and 1.46 (6H, 2 x s, -C(CH$_3$)$_2$), 3.78 (1H, dd, J 5.0, 7.8Hz, C1-H), 3.96-4.16 (3H, m, C1-H', C2-H and C3-H), 4.78 (2H, d, J 6.4Hz, C8-H), 5.62-5.93 (2H, m, C4-H and C7-H), 6.16-6.47 (2H, m, C5-H and C6-H) and 6.36 and 6.43 (2H, 2 x d, B and A of AB, $J_{AB}$ 12.5Hz, -CH=CHCO$_2$H); $\delta$ (68.1MHz, CDCl$_3$) 25.3, 26.8, 65.8, 66.6, 73.1, 78.6, 109.9, 125.6, 129.1, 131.1, 133.1, 134.7, 135.2, 164.9 and 166.8; m/z (EI, 70eV) 311 (2%), 113 (17), 101 (100), 59 (14) and 43 (25).

(2S,3S,4E,6E)-1,2-O-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl methyl maleate (238a)

![238a]

To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl hydrogen maleate (237) (7.51g, 2.41mmol) in diethyl ether (30mL) at 0°C was added dropwise an ethereal solution of diazomethane$^{173}$ (Section 6.6.3). On completion of the addition the solvent was evaporated to give the crude product (0.800g) as a yellow oil. Chromatography of this material on silica (25g) with hexane:ethyl acetate (1:1) gave the title compound (238a) (0.582g, 1.78mol, 74%) as a pale yellow oil: $[\alpha]_D^{20} = -14.3^\circ$ (c = 1.47, dichloromethane); R$_f$ = 0.34 (hexane:ethyl acetate (1:1)); (Found: $M^+$, 325.1282. $C_{16}H_{21}O_7$ requires M, 325.1287); $\nu_{\text{max}}$ (film) 3467, 2987, 2953, 2887, 1731, 1647, 1438, 1372, 1383 and 1215 cm$^{-1}$; $\delta$ (70MHz, CDCl$_3$) 1.31 and 1.40 (6H, 2 x s, -C(CH$_3$)$_2$), 2.77 (1H, s, -OH), 3.70 (1H, dd, J 5.1, 7.7Hz, C1-H), 3.72 (3H, s, -CO$_2$CH$_3$), 3.87-4.11 (3H, m, C1-H', C2-H and C3-H), 4.67 (2H, d, J 6.4Hz, C8-H), 5.64 (1H, dd, J 6.4, 14.3Hz, C4-H), 5.77 (1H, dt, J 14.3, 6.4Hz, C7-H), 6.22 (2H, d, J 0.4Hz, -CH=CHCO$_2$CH$_3$) and 6.15-6.38 (2H, m, C5-H and...
C6-H); δc (68.1MHz, CDCl3) 25.2, 26.6, 52.1, 65.1, 65.6, 73.1, 78.5, 109.6, 126.7, 129.3, 129.7, 131.2, 132.3, 133.4, 164.5 and 165.3; m/z (EI, 70eV) 325 (0.06%), 121 (6), 101 (100), 59 (13) and 43 (45).

\((2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1,1,1-trimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (238b)\)

To a stirred solution of \((2S,3S,4E,6E)-1,2-O-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl methyl maleate (238a)\) (101mg, 0.311mmol) in dichloromethane (5mL) at 0°C under argon was added triethylamine (94.7μL, 0.684mmol, 2.2eq), trimethylsilyl trifluoromethanesulphonate (108μL, 0.559mmol, 1.8eq) and N,N-dimethylaminopyridine (crystal). On completion of the addition the solution was warmed to RT and stirring was continued for 2.5h. The reaction mixture was diluted with diethyl ether (20mL) and partitioned against saturated aqueous sodium bicarbonate (20mL). The aqueous layer was extracted with diethyl ether (2 x 10mL) and the combined extracts were washed with brine (10mL) then dried, filtered and evaporated to give the crude product (0.162g) as a yellow oil. Chromatography of this material on silica (8g) with hexane:ethyl acetate (10:1 then 5:1) gave the title compound (238b) (63.0mg, 0.159mmol, 51%) as a colourless oil: \(\left[\alpha\right]_D^{20} = -16.2^\circ\) (c = 0.680, dichloromethane); Rf = 0.28 (hexane:ethyl acetate (5:1)); (Found: \(M^+\), 398.1755. \(C_{19}H_{30}O_{7}Si\) requires \(M\), 398.1761); \(\nu_{max}\) (film) 2986, 2955, 2898, 1732, 1645, 1438, 1380, 1371 and 1213cm⁻¹; δH (270MHz, CDCl3) 0.127 (9H, s, -Si(CH3)3), 1.34 and 1.40 (6H, 2 x s, -C(CH3)2-), 3.75 (1H, dd, J 6.1, 8.4Hz, C1-H'), 3.79 (3H, s, -CO2CH3), 3.95 (1H, dd, J 6.5, 8.4Hz, C1-H'), 4.02-4.10 (1H, m, C2-H) 4.19-4.26 (1H, m, C3-H), 4.73 (2H, d, J 7.0Hz, C8-H), 5.66-5.89 (2H, m, C4-H and C7-H), 6.20-6.40 (2H, m, C5-H and C6-H) and 6.27 (2H, s, -CH=CHCO2CH3); δc (68.1MHz, CDCl3) 0.252, 25.2, 26.4, 52.1, 65.3 (2 x C), 73.5, 78.6, 109.3, 125.9, 129.4, 129.7, 130.4, 133.2, 133.9, 164.6 and 165.3; m/z (EI, 40eV) 398 (0.1%), 168 (64), 113 (35), 101 (100) and 73 (31).
(2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (238c)

To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (236) (0.503 g, 1.18 mmol) in diethyl ether (10 mL) at RT was added dropwise an ethereal solution of diazomethane173 (Section 6.6.3). On completion of the addition the solvent was evaporated to give the crude product (0.535 g) as a yellow oil. Chromatography of this material on silica (20 g) with hexane:ethyl acetate (5:1) gave the title compound (238c) (0.417 g, 0.946 mmol, 80%) as a pale yellow oil: $\left[\alpha\right]_{D}^{20} = -27.6^\circ$ (c = 1.89, dichloromethane); $R_f = 0.32$ (hexane:ethyl acetate (5:1)); (Found: $M^+\text{-CH}_3$, 425.2022. C$_{21}$H$_{33}$O$_7$Si requires $M^+$, 425.1996); $\nu_{\text{max}}$ (film) 2985, 2954, 2931, 2887, 2857, 1735, 1472, 1462, 1438, 1380, 1371 and 1253 cm$^{-1}$; $\delta_{\text{H}}$ (270 MHz, CDCl$_3$) 0.047 and 0.068 (6H, 2 x s, -Si(CH$_3$)$_2$-), 0.893 (9H, s, -C(CH$_3$)$_3$), 1.33 and 1.39 (6H, 2 x s, -C(CH$_3$)$_2$-), 3.77 (1H, dd, J 6.3, 8.4 Hz, C1-H), 3.78 (3H, s, -CO$_2$CH$_3$), 3.93 (1H, dd, J 6.6, 8.4 Hz, C1-H'), 4.04-4.12 (1H, m, C2-H), 4.29 (1H, t, J 5.5 Hz, C3-H), 4.72 (2H, d, J 6.6 Hz, C8-H), 5.67-5.88 (2H, m, C4-H and C7-H), 6.21-6.39 (2H, m, C5-H and C6-H) and 6.27 (2H, s, -CH=CHCOCH$_3$); $\delta_{\text{C}}$ (68.1 MHz, CDCl$_3$) -4.84, -4.64, 18.2, 25.1, 25.7, 26.3, 52.0, 65.1, 65.2, 73.2, 78.5, 109.2, 125.7, 129.4, 129.6, 130.1, 133.3, 133.9, 164.5 and 165.2; $m/z$ (EI, 40 eV) 425 (1%), 210 (56), 187 (36), 113 (56) and 101 (100).

(2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1,1,1-triisopropylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (238d)
To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl methyl maleate (238a) (51.5mg, 0.158mmol) in dichloromethane (5mL) at 0°C under argon was added triethylamine (49.1μL, 0.347mmol, 2.2eq), triisopropylsilyl trifluoromethanesulphonate (60.8μL, 0.284mmol, 1.8eq) and N,N-dimethylaminopyridine (crystal). On completion of the addition the solution was warmed to RT and stirring was continued for 20h. Additional triethylamine (49.1μL, 0.347mmol, 2.2eq), triisopropylsilyl trifluoromethanesulphonate (60.8μL, 0.284mmol, 1.8eq) and N,N-dimethylaminopyridine (crystal) were added and stirring continued for a further 20h. The reaction mixture was diluted with diethyl ether (20mL) and partitioned against saturated aqueous sodium bicarbonate (20mL). The aqueous layer was extracted with diethyl ether (2 x 10mL) and the combined extracts were washed with brine (10mL) then dried, filtered and evaporated to give the crude product (0.129g) as a yellow oil. Chromatography of this material on silica (6g) with hexane:ethyl acetate (10:1 then 5:1) gave the title compound (238d) (43.9mg, 0.091mol, 58%) as a colourless oil: [α]_D^{20} = -13.8° (c = 0.26, dichloromethane); R_f = 0.26 (hexane:ethyl acetate (5:1)); (Found: M⁺, 482.2720. C_{25}H_{42}O_{7}Si requires M⁺, 482.2700); v_{max} (film) 2944, 2891, 2867, 1731, 1645, 1462, 1381, 1370 and 1213cm⁻¹; δ_H (270MHz, CDCl₃) 0.96-1.13 (21H, m, -Si(CH(CH₃)₂)₃), 1.33 and 1.37 (6H, 2 x s, -C(CH₃)₂-), 3.78 (3H, s, -CO₂CH₃), 3.82 (1H, dd, J 6.1, 8.6Hz, C1-H), 3.95 (1H, dd, J 6.8, 8.6Hz, C1'-H'), 4.14-4.24 (1H, m, C2-H), 4.46 (1H, t, J 5.4Hz, C3-H), 4.73 (2H, d, J 6.6Hz, C8-H), 5.68-5.89 (2H, m, C4-H and C7-H), 6.18-6.40 (2H, m, C5-H and C6-H) and 6.27 (2H, s, -CH=CHCOCH₃); δ_C (68.1MHz, CDCl₃) 12.4, 18.1, 25.1, 26.3, 52.2, 65.1, 65.5, 73.3, 78.5, 109.3, 125.7, 129.5, 129.7, 130.5, 133.5, 134.0, 164.6 and 165.4; m/z (EI, 40eV) 482 (0.7%), 252 (33), 243 (83), 113 (100) and 101 (73).

(2S,4E,6E)-1,2-O-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (239)

To a stirred solution of (2S,4E,6E)-1,2-O-isopropylidene-4,6-octadiene-1,2,8-triol (235) (38.2mg, 0.190mmol) in dichloromethane (10mL) at 0°C under argon was added triethylamine (42.9μL, 0.310mmol, 1.6eq), maleic anhydride (42.5mg, 0.430mmol, 2.25eq) and N,N-dimethylaminopyridine (2.4mg, 0.019mmol, 0.1eq). On completion
of the addition the solution was allowed to warm to RT and stirring was continued for 30 min. The solvent was evaporated to give the crude product (0.414g) as a yellow oil. Chromatography of this material on silica (5g) with ethyl acetate:acetic acid:methanol (98:1:1) gave the title compound (239) (56.3mg, 0.190mmol, 100%) as a colourless oil: \([\alpha]_D^{21} = +7.3^\circ\) (c = 0.510, dichloromethane); \(R_f = 0.40\) (ethyl acetate:acetic acid:methanol (98:1:1); (Found: \(M^+, 296.1256\). \(C_{15}H_{20}O_6\) requires \(M, 296.1260\); \(\nu_{\text{max}}\) (film) 3470, 2986, 2936, 1731, 1714, 1643, 1416, 1382, 1372, and 1214cm\(^{-1}\); \(\delta_H\) (270MHz, CDCl\(_3\)) 1.36 and 1.42 (6H, 2 x s, -C(CH\(_3\))\(_2\)-), 2.27-2.56 (2H, m, C3-H), 3.58 (1H, dd, J \(= 6.8, 7.9\)Hz, C1-H), 4.04 (1H, dd, J \(= 6.0, 7.9\)Hz, C1-H'), 4.11-4.23 (1H, m, C2-H), 4.77 (2H, d, J 6.8Hz, C8-H), 6.63-6.87 (2H, m, C4-H and C7-H), 6.07-6.50 (2H, m, C5-H and C6-H) and 6.35 and 6.46 (2H, B and A of AB, J\(_{AB}\) 12.6Hz, \(-CH=CHCO_2H\)); \(\delta_C\) (68.1MHz, CDCl\(_3\)) 25.7, 26.9, 37.0, 67.1, 68.8, 75.1, 109.1, 123.0, 128.9, 131.3, 131.9, 136.1 (2 x C), 164.6 and 167.1; \(m/z\) (EI, 70eV) 296 (0.3%), 281 (59), 131 (37), 101 (100) and 72 (43).

\((2S,4E,6E)-1,2-O\)-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (240)

![Diagram of the molecule](https://example.com/diagram.png)

To a stirred solution of \((2S,4E,6E)-1,2-O\)-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (239) (56.3mg, 0.190mmol) in diethyl ether (5mL) at RT was added dropwise an ethereal solution of diazomethane\(^{173}\) (Section 6.6.3). On completion of the addition the solvent was evaporated to give the crude product (65.0mg) as a yellow oil. Chromatography of this material on silica (2g) with hexanecetyl acetate (5:1 then 2:1) gave the title compound (240) (10.6mg, 0.0342mmol, 18%) as a pale yellow oil: \([\alpha]_D^{21} = +5.6^\circ\) (c = 0.290, dichloromethane); \(R_f = 0.56\) (hexanecetyl acetate (2:1)); (Found: \(M^+, 310.1416\). \(C_{16}H_{22}O_8\) requires \(M, 310.1416\); \(\nu_{\text{max}}\) (film) 2986, 2921, 2851, 1731, 1644, 1437, 1380, 1370 and 1212cm\(^{-1}\); \(\delta_H\) (270MHz, CDCl\(_3\)) 1.36 and 1.43 (6H, 2 x s, -C(CH\(_3\))\(_2\)-), 2.27-2.57 (2H, m, C3-H), 3.58 (1H, dd, J \(= 6.8, 7.9\)Hz, C1-H), 3.79 (3H, s, \(-CO_2CH_3\)), 4.03 (1H, dd, J 5.9, 7.9 Hz, C1-H'), 4.11-4.21 (1H, m, C2-H), 4.71 (2H, d, J 6.6Hz, C8-H), 5.66-5.80 (2H, m, C4-H and C7-H), 6.07-6.36 (2H, m, C5-H and C6-H) and 6.27 (2H, s, \(-CH=CHCO_2CH_3\)); \(\delta_C\) (68.1MHz, CDCl\(_3\)) 25.7, 27.0, 37.0, 52.2, 65.6, 68.9, 75.2, 109.0, 124.5, 129.6,
129.7, 130.9, 131.6, 134.8, 164.7 and 165.5; \( m/z \) (CI/\( \text{NH}_3 \), 40eV) 310 (3%), 295 (55), 113 (100), 101 (94) and 73 (47).

### 6.2.3 ETDA reactions

**ETDA reaction of (2S,3S,4E,6E)-1,2-O-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl methyl maleate (238a)**

To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl methyl maleate (238a) (0.522g, 1.60mmol) in toluene (320mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (71.0mg, 0.320mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 5h. Evaporation of the solvent gave the crude product (0.640g) as a yellow oil. Chromatography of this material on silica (30g) with hexane:ethyl acetate (1:1) gave the **ETDA adducts (241a and 242a)** as an inseparable mixture (448mg, 1.37mmol, 86%, 241a:242a (66:34)): \( R_f \) (241a and 242a) = 0.24 (hexane:ethyl acetate (1:1)). (Derivatives of these adducts which are separable are described in Section 6.2.4).

**ETDA reaction of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1,1,1-trimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (238b)**

To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1,1,1-trimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (238b) (45.3mg, 0.114mmol) in toluene (27.8mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (6.1mg, 0.0283mmol, 0.2eq). The solution was warmed to reflux and
heating was continued for 12h. Evaporation of the solvent gave the crude product (65.7mg) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (4:1) gave the ETDA adducts (241b and 242b) (30.3g, 0.0760mmol, 67%, 241b:242b (82:18)), vide infra.

methyl (3aR, 4S, 5R, 7aS)-5-((2S,3S)-1,2-0-isopropylidene-3-(1,1,1-trimethylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofuran carboxylate (241b)

![Chemical Structure](image)

Colourless oil; [α]_D^{20} = -46.3° (c = 0.990, dichloromethane); R_f = 0.22 (hexane:ethyl acetate (4:1)); (Found: M'-CH₃, 383.1524. C_{18}H_{27}O_{7}Si requires M, 383.1526); ν_{max} (film) 2985, 2954, 2897, 1789, 1731, 1436, 1379 and 1370 cm⁻¹; δ_H (270MHz, CDCl₃) 0.144 (9H, s, -Si(CH₃)₃), 1.33 and 1.41 (6H, 2 x s, -C(CH₃)₂-), 2.77-2.88 (1H, m, C5-H), 2.84 (1H, dd, J 3.9, 13.7Hz, C3a-H), 3.03-3.21 (1H, m, C7a-H), 3.39 (1H, d, J 3.9Hz, C4-H), 3.57-3.83 (1H, obs, -CHOTMS), 3.71 (3H, s, -CO₂CH₃), 3.78 (1H, dd, J 3.9, 5.5Hz, -CHH'OC(CH₃)₂OCH-), 3.85 (1H, dd, J 8.0, 11.3Hz, C1-H), 4.02 (1H, dd, J 6.2, 7.8Hz, -CHH'OC(CH₃)₂OCH-), 4.03-4.15 (1H, m, -CHH'OC(CH₃)₂OCH-), 4.52 (1H, dd, J 7.0, 8.0Hz, C1'-H'), 5.63 (1H, dt, J 10.2, 3.1Hz, C6-H) and 6.02 (1H, dt, J 10.2, 2.0Hz, C7-H); δ_C (68.1MHz, CDCl₃) 13.4, 18.4, 25.5, 26.5, 36.5, 39.1, 42.8, 43.6, 52.2, 66.3, 70.2, 109.4, 126.8, 128.7, 172.8 and 173.9; (HETCOR demonstrated that δ_C for -CHOTMS was completely obscured by the 77.0ppm peak of the CDCl₃ triplet.); m/z (EI, 40eV) 383 (10%), 297 (21), 268 (99), 237 (72) and 73 (100).
methyl (3aS, 4R, 5S, 7aR)-5-((2S,3S)-1,2-O-isopropylidene-3-(-1,1,1-trimethylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofuran carboxylate (242b)

![Chemical Structure](image)

**242b**

Colourless oil; \([\alpha]_D^{19.5} = +54.5^\circ \) (c = 0.110, dichloromethane); \(R_f = 0.26\) (hexane:ethyl acetate (4:1)); (Found: \(M^+ - CH_3 = 383.1526\)). \(\nu_{\text{max}}\) (film) 2986, 2955, 2927, 2855, 1786, 1736, 1437, 1381 and 1371 cm\(^{-1}\); \(\delta_H\) (270MHz, CDCl\(_3\)) 0.101 (9H, s, -Si(CH\(_3\))\(_3\)), 1.38 and 1.44 (6H, 2 x s, -C(CH\(_3\))\(_2\)-), 2.51-2.57 (1H, m, C5-H), 2.71 (1H, dd, \(J = 4.2\), 13.8Hz, C3a-H), 3.12-3.30 (1H, m, C7a-H), 3.45 (1H, d, \(J = 4.2\), C4-H), 3.59 (1H, t, \(J = 4.2\)Hz, C4-H), 3.60 (1H, dd, \(J = 8.1\), 11.5Hz, Cl-H), 4.13 (1H, dd, \(J = 6.4\), 8.1Hz, -CHH’OC(CH\(_3\))\(_2\)OCH-), 4.15 (1H, m, -CHH’OC(CH\(_3\))\(_2\)OCH-), 4.53 (1H, dd, \(J = 7.2\), 8.1Hz, C1-H’), 5.16 (1H, dt, \(J = 10.0\), 3.2Hz, C6-H) and 6.01 (1H, dt, \(J = 10.0\), 2.0Hz, C7-H); \(\delta_C\) (68.1MHz, CDCl\(_3\)) 0.699, 25.5, 26.8, 35.7, 36.3, 42.2, 42.7, 52.4, 66.2, 70.5, 77.8, 78.0, 109.4, 126.3, 131.9, 172.5 and 174.5; \(m/z\) (EI, 40eV) 383 (13%), 297 (23), 268 (99), 237 (73), 145 (45), 101 (52) and 73 (100).

**ETDA reaction of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (238c)**

![Chemical Structure](image)

**238c**

241c  242c

To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (238c) (0.115g, 0.261mmol) in toluene (52.0mL) at RT under argon was added 2,6-di-tert-butyl-4-
methylphenol (0.0116g, 0.0522mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 15h. Evaporation of the solvent gave the crude product (0.128g) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (4:1) gave the ETDA adducts (241c and 242c) (0.0922g, 0.209mmol, 80%, 241c:242c (91:9)), *vide infra.*

**methyl (3aR, 4S, 5R, 7aS)-5-((2S,3S)-1,2-O-isopropylidene-3-(-1,1-dimethyl-1-tert-butylidimethylsilyloxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (241c)**

![Chemical Structure](image)

Yellow oil; [α]_D^{21} = -34.3° (c = 2.98, dichloromethane); R_f = 0.29 (hexane:ethyl acetate (4:1)); (Found: M^+-CH_3, 425.1972. C_{21}H_{33}O_7Si requires M, 425.1972); ν_max (film) and 2985, 2953, 2892, 2857, 1789, 1731, 1472, 1462, 1436, 1472, 1462 1380and 1370cm^{-1}; δ_H (270MHz, CDCl_3) 0.114 (6H, s, -Si(CH_3)_2), 0.903 (9H, s, -C(CH_3)_3), 1.31 and 1.42 (6H, 2 x s, -C(CH_3)_2), 2.78 (1H, dd, J 4.2, 13.8Hz, C3a-H), 2.91-2.97 (1H, m, C5-H), 3.05-3.23 (1H, m, C7a-H), 3.58 (1H, d, J 4.2Hz, C4-H), 3.70 (3H, s, -CO_2CH_3), 3.70-3.82 (2H, m, -CHH'OOC(CH_3)_2OCH- and -CHOTBS), 3.84 (1H, dd, J 7.9, 11.4Hz, C1-H), 3.96 (1H, dd, J 6.4, 7.9Hz, -CHH'OOC(CH_3)_2OCH-), 4.05-4.16 (1H, m, -CHH'OOC(CH_3)_2OCH-), 4.48-4.70 (1H, m, C1'-H'), 5.66 (1H, dt, J 10.1, 3.1Hz, C6-H) and 6.00 (1H, dt, J 10.1, 2.2Hz, C7-H); δ_C (68.1MHz, CDCl_3) -4.43, -4.32, 18.2, 25.6, 25.9, 26.4, 36.4, 38.0, 42.6, 43.6, 52.0, 66.1, 70.2, 74.6, 76.6, 109.4, 126.7, 128.7, 172.9 and 174.1; m/z (EI, 40eV) 425 (7%), 279 (28), 265 (100), 117 (25) and 73 (57).
methyl (3aS, 4R, 5S, 7aR)-5-\((2S,3S)-1,2-O-isopropylidene-3-\((1,1\text{-dimethyl-1-}tert\text{-butyl}dime}thylsilyl)oxy-1,2-dihydroxy-3-propanyl\)-3-\(\text{oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofuran}c\text{arboxylate (242c)}\)

![Diagram](image)

Colourless oil; $[\alpha]_D^{20} = +18.0^\circ$ (c = 0.100, dichloromethane); $R_f = 0.29$ (hexane:ethyl acetate (4:1)); (Found: $M^\ast$-CH$_3$, 425.1994. C$_{21}$H$_{33}$O$_7$Si requires $M^\ast$, 425.1996); $\nu_{\text{max}}$ (film) and 2925, 2853, 1789, 1737, 1463, 1378, 1368 and 1255 cm$^{-1}$; $\delta_H$ (270 MHz, CDCl$_3$) 0.048 and 0.127 (6H, 2 x s, -Si(CH$_3$)$_3$), 0.853 (9H, s, -C(CH$_3$)$_3$), 1.38 and 1.44 (6H, 2 x s, -C(CH$_3$)$_3$), 2.52-2.58 (1H, m, C5-H), 2.80 (1H, dd, J 4.2, 13.5 Hz, C3a-H), 3.10-3.32 (1H, m, C7a-H), 3.46 (1H, d, J 4.2 Hz, C4-H), 3.57 (1H, t, J 8.1 Hz, -CHH'OC(CH$_3$)$_2$OCH-), 3.72 (3H, s, -CO$_2$CH$_3$), 3.81 (1H, t, J 8.1 Hz, -CHH'OC(CH$_3$)$_2$OCH-), 3.82 (1H, dd, J 8.0, 13.7 Hz, C1-H), 4.13 (1H, dd, J 6.2, 8.1 Hz, -CHH'OC(CH$_3$)$_2$OCH-), 4.20-4.30 (1H, m, -CHH'OC(CH$_3$)$_2$OCH-), 4.54 (1H, dd, J 7.2, 8.0 Hz, C1-H'), 5.60 (1H, dt, J 10.0, 3.1 Hz, C6-H) and 6.01 (1H, dt, J 10.0, 2.2 Hz, C7-H); $\delta_C$ (68.1 MHz, CDCl$_3$) -4.14, -3.97, 18.5, 25.5, 26.2, 26.8, 30.4, 35.7, 36.3, 42.3, 42.9, 52.4, 66.2, 70.4, 77.8, 78.3, 109.4, 126.3, 132.3 and 172.5; $m/z$ (El, 70 eV) 425 (4%), 279 (17), 265 (100), 101 (100) and 73 (57).

**ETDA reaction of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1,1,1-triisopropylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (238d)**

![Reagents](image)

To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1,1,1-triisopropylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (238d) (37.0 mg, 0.0767 mmol) in toluene (15.3 mL) at RT under argon was added 2,6-di-tert-butyl-4-
methylphenol (3.4mg, 0.015mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 18h. Evaporation of the solvent gave the crude product (40.3mg) as a yellow oil. Chromatography on silica (4g) with hexane:ethyl acetate (4:1) gave the ETDA adducts (241d and 242d) (25.1mg, 0.0520mmol, 68%, 241d:242d (96:4), vide infra. (Adduct 242d was unable to be isolated and characterised. The structure of this compound is speculative and based on limited proton NMR analysis of mixtures only.)

methyl (3aR, 4S, 5R, 7aS)-5-((2S,3S)-1,2-O-isopropylidene-3-((1,1,1-triisopropylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (241d)

![Image of structure 241d]

Colourless oil; \([\alpha]_D^{21} = -50.0^\circ\) (c = 1.04, dichloromethane); \(R_f = 0.17\) (hexane:ethyl acetate (4:1)); (Found: \(M^+-CH_3\), 467.2466. \(\text{C}_{24}\text{H}_{39}\text{O}_7\text{Si}\) requires \(M\), 467.2465); \(v_{\text{max}}\) (film) 2945, 2866, 1789, 1731, 1462, 1380, 1370, 1327, 1317 and1215cm\(^{-1}\); \(\delta_H\) (270MHz, CDCl\(_3\)) 0.959-1.20 (21H, m, -Si(CH(CH\(_3\))\(_2\))\(_3\)), 1.32 and 1.41 (6H, 2 x s, -C(CH\(_3\))\(_3\)), 2.77 (1H, dd, \(J\) 4.1, 13.7Hz, C3a-H), 2.85-2.92 (1H, m, , C5-H), 3.00-3.17 (1H, m, C7a-H), 3.52 (1H, d, \(J\) 4.1Hz, C4-H), 3.68 (1H, t, \(J\) 8.0Hz, -CHH'OC(CH\(_3\))\(_2\)OCH-), 3.70 (3H, s, -CO\(_2\)CH\(_3\)), 3.84 (1H, dd, \(J\) 8.0, 11.4Hz, C1-H), 3.99 (1H, dd, \(J\) 6.1, 8.0Hz, -CHH'OC(CH\(_3\))\(_2\)OCH-), 4.03 (1H, dd, \(J\) 3.7, 6.1Hz, -CHOTBS), 4.54-4.18 (1H, m, -CHH'OC(CH\(_3\))\(_2\)OCH-), 4.53 (1H, dd, \(J\) 7.2, 8.0Hz, C1'-H'), 5.69 (1H, dt, \(J\) 10.1, 3.0Hz, C6-H), 6.01 (1H, dt, \(J\) 10.1, 2.1Hz, C7-H); \(\delta_C\) (68.1MHz, CDCl\(_3\)) 13.4, 18.4, 25.5, 26.5, 36.5, 39.1, 42.8, 43.6, 52.2, 66.3, 70.2, 109.4, 126.8, 128.7, 172.8 and 173.9; (HETCOR demonstrated that \(\delta_C\) for -CHOTIPS and -CHH'OC(CH\(_3\))\(_2\)OCH- were obscured by the 76.5 and 77.5ppm peaks of the CDCl\(_3\) triplet respectively); \(m/z\) (EI, 40eV) 467 (4%), 439 (20), 381 (25), 321 (100) and 173 (31).
ETDA reaction of (2S,4E,6E)-1,2-O-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (240)

To a stirred solution of (2S,4E,6E)-1,2-O-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (240) (0.9mg, 2.9mmol) in toluene (0.6mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (0.1mg, 0.6mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 18h. Evaporation of the solvent gave the crude product (1.0mg) as a yellow oil. Chromatography of this material on silica (1g) with hexane:ethyl acetate (2:1) gave the ETDA adducts (270 and 271) (0.8mg, 2.6mmol, 89%, 270:271 (50:50)) as an inseparable mixture, vide infra.

methyl (3aR, 4S, 5R, 7aS)-5-[(2S)-1,2-O-isopropylidene-1,2-dihydroxy-3-propanyl]-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (270) and methyl (3aS, 4R, 5S, 7aR)-5-[(2S)-1,2-O-isopropylidene-1,2-dihydroxy-3-propanyl]-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (271) (270:271 (50:50))

Colourless oil; Rf = 0.24 (hexane:ethyl acetate (2:1)); (Found: M+, 310.1418. C16H22O6 requires M, 310.1416; νmax (film) 2985, 2933, 1788, 1731, 1436, 1380, 1371 and 1217 cm⁻¹; δH (270MHz, CDCl3) 1.35, 1.37, 1.42 and 1.43 (12H, 4 x s, 2 x -C(CH3)2-), 1.57-1.86 (4H, m, 2 x -C5-CH2-), 2.34 and 2.39 (2H, 2 x dd, J 3.5, 13.6Hz and J 3.9, 13.6Hz, 2 x C3a-H), 2.92-3.08 (2H, 2 x dd, J 12H, 4 x s, 2 x -C(CH3)2-), 3.72 (6H, s, 2 x -CO2CH3), 3.87 (2H, dd, J 8.1, 11.4Hz, 2 x C1-H), 4.04-4.14 (2H, m, 2 x -CHH'OC(CH3)2OCH-), 4.15-4.30 (2H, m, 2 x
-CHH‘OC(CH3)2OCH-, 4.53 and 4.56 (2H, 2 x dd, J 1.5, 6.8Hz and J 1.8, 6.6Hz, 2 x C1-H’), 5.71 and 5.75 (2H, 2 x dt, J 9.9, 3.1Hz and J 10.3, 3.3Hz, 2 x C6-H) and 5.86 and 5.88 (2H, 2 x dt, J 10.3, 1.8Hz and J 9.9, 2.0Hz, 2 x C7-H); δC (68.1MHz, CDCl3) 25.8 (2 x C), 27.0, 27.1, 29.7, 36.3, 36.6, 36.7, 37.0, 39.4, 39.8, 40.7, 40.9, 41.7, 41.9, 52.3, 69.4, 69.7, 70.6 (2 x C), 73.5, 74.3, 109.2, 109.3, 124.2, 124.3, 132.6, 133.0, 172.0, 172.2, 174.4 and 174.5; (A Pure Inverse Gated Decoupling NMR experiment was used to confirm that δC at 25.8ppm and 70.6ppm each contained two overlapping peaks.); m/z (EI, 40eV) 310 (1%), 295 (100), 252 (23), 221 (28), 175 (45), 131 (50), 91 (64), 72 (32), 59 (26) and 43 (71).

6.2.4 Miscellaneous reactions of ETDA adducts

Methyl (3aR, 4S, 5R, 7aS)-5-((2S,3S)-1,2-O-isopropylidene-3-(1,1,1-trimethylsilyloxy)-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (241b) and methyl (3aS, 4R, 5S, 7aR)-5-((2S,3S)-1,2-O-isopropylidene-3-(1,1,1-trimethylsilyloxy)-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (242b) (241b:242b (66:34))

To a stirred solution of methyl (3aR, 4S, 5R, 7aS)-5-((2S,3S)-1,2-O-isopropylidene-1,2,3-trihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (241a) and methyl (3aS, 4R, 5S, 7aR)-5-((2S,3S)-1,2-O-isopropylidene-1,2,3-trihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexa-hydro-4-isobenzofurancarboxylate (242a) (241a:242a (66:34)) (15.0mg, 0.0460mmol) in dimethylformamide (50μL) at RT under argon was added imidazole (18.8mg, 0.276mmol, 6eq) and trimethylsilyl chloride (29.2μL, 0.230mmol, 5eq). Stirring was continued for 20min then the reaction mixture was diluted with dichloromethane (30mL) and partitioned against water (30mL). The aqueous layer was extracted with dichloromethane (2 x 30mL) and the combined extracts were washed with brine (30mL) then dried, filtered and evaporated to give the crude product (25.1mg) as a yellow oil. Chromatography of this material on silica (0.5g) with hexane:ethyl acetate (4:1) gave the title compounds (241b and 242b) (11.2mg, 0.0343mmol, 74%, 241b:242b
Methyl (3aR, 4S, 5R, 7aS)-5-(((1S,2S)-1,2-O-isopropylidene-1,2,3-tri hydroxy-1-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (246) and methyl (3aS, 4R, 5S, 7aR)-5-((1S,2S)-1,2-O-isopropylidene-1,2,3-trihydroxy-1-propanyl)-3-oxo-1,3,3a,4,5,7a-hexa-hydro-4-isobenzofurancarboxylate (247) (246:247 (66:34))

To a stirred solution of methyl (3aR, 4S, 5R, 7aS)-5-((2S,3S)-1,2-O-isopropylidene-1,2,3-trihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (241a) and methyl (3aS, 4R, 5S, 7aR)-5-((2S,3S)-1,2-O-isopropylidene-1,2,3-trihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexa-hydro-4-isobenzofurancarboxylate (242a) (241a:242a (66:34)) (36.0mg, 0.110mmol) in acetone (2mL) at RT under argon was added Amberlist IR-118 resin (36mg). Stirring was continued for 21h then the reaction mixture was filtered and evaporated to give the crude product (36.0mg) as a yellow oil. Chromatography of this material on silica (5g) with ethyl acetate:hexane (1.5:1) gave the title compounds (246 and 247) (34.5mg, 0.106mmol, 96%, 246:247 (66:34)), vide infra.

methyl (3aR, 4S, 5R, 7aS)-5-(((1S,2S)-1,2-O-isopropylidene-1,2,3-trihydroxy-1-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (246)
Colourless oil; $[\alpha]_D^{21} = -96.8^\circ$ (c = 0.440, dichloromethane); $R_t = 0.33$ (ethyl acetate:hexane (1:5:1)); (Found: $M^*-\text{CH}_3$, 311.1139. C$_{15}$H$_{19}$O$_7$ requires $M$, 311.1131); 
$\nu_{\text{max}}$ (film) 3468, 2986, 2932, 1783, 1732, 1437, 1381, 1371 and 1218cm$^{-1}$; $\delta_\text{H}$ (270MHz, CDCl$_3$) 1.39 and 1.41 (6H, 2 x s, -C(CH$_3$)$_2$-), 2.06 (1H, t, $J$ 6.0Hz, -OH), 2.66 (1H, dd, $J$ 3.8, 13.5Hz, C3a-H), 2.98-3.05 (1H, m, C5-H), 3.11-3.28 (1H, m, C7a-H), 3.26 (1H, d, $J$ 3.8Hz, C4-H), 3.64-3.77 (1H, m, -CHH'OH), 3.73 (3H, s, -CO$_2$CH$_3$), 3.78-3.95 (1H, m, -CHH'OH), 3.88 (1H, dd, $J$ 7.9, 11.4Hz, C1-H), 3.98-4.06 (2H, m, -CHO(CH$_3$)$_2$OCH-), 4.53 (1H, dd, $J$ 7.3, 7.9Hz, C1'-H'), 5.82 (1H, dt, $J$ 10.1, 3.3Hz, C6-H) and 6.03 (1H, dt, $J$ 10.1, 2.2Hz, C7-H); $\delta_\text{C}$ (68.1MHz, CDCl$_3$) 27.3, 27.4, 36.6, 40.1, 40.5, 42.3, 52.5, 62.5, 70.4, 78.7, 80.6, 109.4, 126.7, 127.8, 171.9 and 174.2; $m/z$ (El, 70eV) 311 (12%), 196 (19), 131 (76), 91 (19), 59 (100) and 43 (29).

methyl (3aS, 4R, 5S, 7aR)-5-((1S,2S)-1,2-O-isopropylidene-1,2,3-trihydroxy-1-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (247)  

\[
\begin{align*}
&\text{HO} \\
&\text{O} \\
&\text{CO}_3\text{Me} \\
\end{align*}
\]

Colourless oil; $[\alpha]_D^{21} = +20.0^\circ$ (c = 0.460, dichloromethane); $R_t = 0.25$ (ethyl acetate:hexane (1:5:1)); (Found: $M^*-\text{CH}_3$, 311.1138. C$_{15}$H$_{19}$O$_7$ requires $M$, 311.1131); 
$\nu_{\text{max}}$ (film) 3458, 2984, 2923, 1782, 1731, 1437, 1380, 1370 and 1215cm$^{-1}$; $\delta_\text{H}$ (270MHz, CDCl$_3$) 1.42 and 1.44 (6H, 2 x s, -C(CH$_3$)$_2$-), 2.57 (1H, dd, $J$ 3.7, 13.6Hz, C3a-H), 2.89-2.96 (1H, m, C5-H), 3.11-3.30 (1H, m, C7a-H), 3.45 (1H, m, C4-H), 3.49-3.89 (1H, m, -CHH'OH), 3.73 (3H, s, -CO$_2$CH$_3$), 3.81-3.93 (1H, m, -CHH'OH), 3.91 (1H, dd, $J$ 8.1, 11.4Hz, C1-H), 4.00-4.06 (2H, m, -CHO(CH$_3$)$_2$OCH-), 4.49-4.59 (1H, m, C1'-H'), 5.67 (1H, dt, $J$ 9.9, 3.1Hz, C6-H), 6.03 (1H, dt, $J$ 9.9, 2.0Hz, C7-H); $\delta_\text{C}$ (68.1MHz, CDCl$_3$) 27.2, 27.3, 36.2, 37.0, 41.2, 42.5, 52.5, 62.1, 70.3, 78.9, 79.1, 109.5, 126.8, 130.0, 172.2 and 174.1; $m/z$ (El, 70eV) 311 (%), 196 (19), 131 (75), 59 (100) and 43 (29).
methyl (3aS, 4R, 5S, 7aR)-5-((1S,2R)-1,2-O-isopropylidene-3-(4-nitrobenzoyl)oxy-1,2-dihydroxy-1-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (248)

To a stirred solution of methyl (3aS, 4R, 5S, 7aR)-5-((1S,2S)-1,2-O-isopropylidene-1,2,3-trihydroxy-1-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (247) (8.9mg, 0.028mmol) in dichloromethane (1mL) at RT under argon was added pyridine (22μl, 0.27mmol, 10eq), 4-nitrobenzoyl chloride (12.7mg, 0.0684mmol, 2.5eq) and N,N-dimethylaminopyridine (crystal). Stirring was continued for 2h then the reaction mixture was diluted with diethyl ether (60mL) and partitioned against 10% aqueous hydrochloric acid (30mL), water (30mL) and brine (30mL) then dried, filtered and evaporated to give the crude product (22.4mg) as a yellow oil. Chromatography of this material on silica (0.5g) with hexane:ethyl acetate (2:1) gave the title compound (248) (9.2mg, 0.019mmol, 70%) as a colourless oil: [α] D 19.5 = +27.0° (c = 0.300, dichloromethane); Rf = 0.25 (hexane:ethyl acetate (2:1)); (Found: M'·CH3, 460.1234. C22H22NO10 requires M, 460.1244); ν max (film) 2987, 2955, 2926, 2854, 1787, 1731, 1607, 1529, 1381 and 1371 cm⁻¹; δ H (270MHz, CDCl3) 1.43 and 1.47 (6H, 2 x s, -C(CH3)2), 2.60 (1H, dd, J 4.0, 13.6Hz, C3a-H), 2.83-3.23 (1H, m, C5-H), 3.14-3.30 (1H, m, C7a-H), 3.46 (1H, d, J 4.0Hz, C4-H), 3.73 (3H, s, -CO2CH3), 3.92 (1H, dd, J 8.2, 11.6Hz, -CHH'CHOC(CH3)2OCH-), 4.01 (1H, dd, J 4.2, 7.7Hz, C1-H), 4.29-4.37 (1H, m, -CHH'CHOC(CH3)2OCH-), 4.44-4.64 (1H, m, (1H, dd, C1-H', -CHH'CHOC(CH3)2OCH-), 5.71 (1H, dt, J 9.9, 3.2Hz, C6-H), 6.06 (1H, dt, J 9.9, 2.0Hz, C7-H) and 8.26 and 8.33 (4H, B and A of AB, JAB 8.9Hz, aromatic-H); δ C (68.1MHz, CDCl3) 27.1, 27.2, 36.2, 37.0, 41.3, 42.5, 52.5, 65.8, 70.2, 76.6, 80.2, 109.8, 110.3, 123.6 (2 x C), 127.3, 129.7, 130.8 (2 x C), 164.3, 172.0 and 173.9; m/z (EI, 70eV) 450 (5%), 280 (6), 222 (100), 149 (16) and 57 (19).
methyl (3aR, 4S, 5R, 7aS)-5-((2R,3S)-1-iodo-2,3-O-isopropylidene-2,3-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (249)

To methyl (3aR, 4S, 5R, 7aS)-5-((1S,2S)-1,2-O-isopropylidene-1,2,3-trihydroxy-1-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (246) (18.0 mg, 0.0552 mmol) at RT under argon was added chloroform (1 mL) containing imidazole (7.1 mg, 0.11 mmol, 1.9 eq), triphenylphosphine (23.2 mg, 0.0880 mmol, 1.6 eq) and iodine (21.0 mg, 0.0827 mmol, 1.5 eq) and the solution was stirred for 8 h. An additional volume of the chloroform solution (1 mL) was added and stirring was continued for 12 h. The reaction mixture was diluted with hexane:ethyl acetate (20:1, 5 mL), silica (0.1 g) was added and then rapid vacuum filtration through a silica plug (0.5 g) was carried out with hexane:ethyl acetate (20:1 then 5:1) to give the title compound (249) (15.9 mg, 0.0364 mmol, 67%) as a yellow oil: $[\alpha]_D^{21} = -76.3^\circ$ (c = 0.79, dichloromethane); R$_f$ = 0.09 (hexane:ethyl acetate (5:1)). (Found: M$^+$-CH$_3$ 421.0149. C$_{15}$H$_{18}$O$_4$I requires M, 421.0148; v$_{max}$ (film) 2987, 2932, 1789, 1731, 1435, 1381, 1371 and 1218 cm$^{-1}$; $\delta_{\rm H}$ (270 MHz, CDCl$_3$) 1.38 and 1.45 (6 H, 2 x s, -C(CH$_3$)$_2$-), 2.46 (1 H, dd, J = 4.0, 13.4 Hz, C$_{3a}$-H), 3.09-3.15 (1 H, m, C$_5$-H), 3.16-3.29 (1 H, m, C$_{7a}$-H), 3.27 (1 H, d, J = 4.0 Hz, C$_4$-H), 3.29-3.35 (2 H, m, -CH$_2$I), 3.74 (3 H, s, -CO$_2$CH$_3$), 3.89 (1 H, dd, J = 8.1, 11.4 Hz, C$_1$-H), 3.95 (1 H, dd, J = 4.6, 6.4 Hz, -CHO(C(CH$_3$)$_2$OCHCH$_2$I), 4.01-4.10 (1 H, m, -CHOOC(CH$_3$)$_2$OCHCH$_2$I), 4.55 (1 H, dd, J = 7.0, 8.1 Hz, C$_1$-H'), 5.82 (1 H, dt, J = 10.1, 3.1 Hz, C$_6$-H) and 6.06 (1 H, dt, J = 10.1, 2.0 Hz, C$_7$-H); $\delta_C$ (68.1 MHz, CDCl$_3$) 62.6, 27.8, 27.9, 36.5, 40.4, 41.0, 42.2, 52.5, 70.4, 77.6, 85.0, 110.1, 127.1, 127.3, 171.8 and 174.0; m/z (EI, 70 eV) 421 (10%), 241 (100), 183 (49), 91 (35) and 43 (44).
methyl (3aR, 4S, 5R, 7aS)-5-((2R,3S)-2,3-dihydroxy-1-iodo-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (251)

To a stirred solution of methyl (3aR, 4S, 5R, 7aS)-5-((2R,3S)-1-iodo-2,3-O-isopropylidene-2,3-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (249) (13.8mg, 0.0316mmol) in methanol:water (5:1, 1mL) at RT under argon was added Amberlite IR 118 ion exchange resin (16.0mg). On completion of the addition the solution was warmed to 50°C and stirred for 30min. The solution was then warmed to reflux and stirring was continued for 18h. The solution was filtered through cotton wool and evaporated to give the crude product (13.8mg) as a yellow oil. Chromatography of this material on silica (0.5g) with benzene then hexane:ethyl acetate (1:1 then 1:2) gave recovered starting material (249) (5.8mg, 0.0133mmol, 42%) followed by the title compound (251) (5.8mg, 0.015mmol, 82% based on 58% conversion) as a yellow oil: [α]D21 = -28.0° (c = 0.054, dichloromethane); Rf = 0.36 (hexane:ethyl acetate (1:2)); (Found: M+H, 397.0138. C13H18O6I requires M, 397.0148); νmax (film) 3444, 2919, 2850, 1777, 1731, 1435 and 1378cm⁻¹; δH (270MHz, CDCl3) 2.60-2.76 (1H, m, -CHH'I), 2.71 (1H, dd, J 4.2, 13.6Hz, C3a-H), 2.95-3.05 (1H, m, C5-H), 3.12-3.22 (1H, m, C7a-H), 3.32-3.45 (2H, m, C4-H and -CHH'I), 3.74 (3H, s, -CO₂CH₃), 3.79-3.90 (2H, m, -CHOH-CHOH-), 3.92 (1H, dd, J 8.1, 11.4Hz, C1-H), 4.56 (1H, dd, J 7.3, 8.1Hz, C1-H'), 5.81 (1H, dt, J 10.1, 3.1Hz, C6-H) and 6.08 (1H, dt, J 10.1, 2.2Hz, C7-H); δC (68.1MHz, CDCl3) 10.5, 36.4, 39.2, 42.5, 42.8, 52.5, 70.4, 71.6, 75.5, 127.4, 127.7, 172.3 and 174.4; m/z (EI, 70eV) 397 (2%), 196 (46), 136 (44), 91 (100) and 77 (34).
methyl 2-oxa-3-oxo-[4R,5S,6R,7S,8S,10S,12S]-7,8-dihydroxytricyclo[7.3.0.0^6,10]-5-dodecanecarboxylate (252)

To a stirred solution of methyl (3aR, 4S, 5R, 7aS)-5-((2R,3S)-2,3-dihydroxy-1-iodo-3-propanyl)-3-oxo-1,3,4,5,7a-hexahydro-4-isobenzofurancarboxylate (251) (5.8mg, 0.015mmol) in benzene (0.6mL) at RT under argon was added tris(trimethylsilylsilane (5.2μL, 0.016mmol, 1.1eq) and 2,2'-azo-bis-isobutyronitrile (crystal). On completion of the addition the solution was warmed to reflux and stirring was continued for 45min. The solvent was evaporated to give the crude product (9.7mg) as a yellow oil. Chromatography of this material on silica (0.5g) with ethyl acetate gave the title compound (252) (2.6mg, 0.0096mmol, 64%) as a colourless oil: [α]_D^21 = -6.0° (c = 0.100, dichloromethane); Rr = 0.40 (ethyl acetate); (Found: M^+H, 271.1196. C_{13}H_{19}O_6 requires M, 271.1181); ν_max (film) 3440, 2920, 2851, 1731 and 1426cm\(^{-1}\); δ_H (270MHz, CDCl_3) 1.21-1.41 (1H, m, C11-H), 1.84 (1H, ddd, J 4.0, 8.2, 14.3Hz, C9-H), 1.95 (1H, ddd, J 2.4, 6.3, 12.0Hz, C11-H'), 2.03 (1H, ddd, J 2.4, 6.8, 14.3Hz, C9-H'), 2.18-2.37 (1H, m, C10-H), 2.67 (1H, dd, J 5.8, 7.6Hz, C6-H), 2.72-2.89 (2H, m, C4-H and C12-H), 3.40 (1H, d, J 4.2Hz, C5-H), 3.72 (3H, s, -CO_2CH_3), 3.81 (1H, dd, J 8.3, 11.1Hz, C1-H), 4.13-4.25 (2H, m, C7-H and C8-H) and 4.42 (1H, dd, J 6.4, 8.3Hz, C1-H'); δ_C (68.1MHz, CDCl_3) 29.8, 34.6, 35.4, 37.5, 37.9, 42.4, 44.2, 52.2, 72.1, 79.4, 83.0, 173.4 and 176.4; m/z (EI, 70eV) 271 (3%), 192 (48), 91 (100), 105 (46) and 77 (70).
6.3 Experimental for Chapter Three

6.3.1 Preparation of ETDA Precursors

\[(2E,4E)-2,4-hexadien-1-yl hydrogen maleate (302)\]

\[
\text{To a stirred solution of } (2E,4E)-2,4-hexadien-1-ol (301) (0.500g, 5.10mmol) in \text{ dichloromethane (25mL) at 0°C under argon was added triethylamine (1.14mL, 8.20mmol, 1.6eq), maleic anhydride (1.12g, 11.5mmol, 2.25eq) and N,N-dimethylaminopyridine (0.0620g, 0.508mmol, 0.1eq). Stirring was continued for 15min and the reaction mixture was diluted with diethyl ether (100mL) and partitioned against 10% aqueous hydrochloric acid (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (1.25g) as a yellow oil. Chromatography of this material on silica (30g) with hexane:ethyl acetate:acetic acid:methanol (20:20:1:1) gave the title compound (302) (0.880g, 4.49mmol, 88%) as a pale yellow oil: Rf = 0.49 (hexane:ethyl acetate:acetic acid:methanol (20:20:1:1)); (Found: M+, 196.0738. C_{10}H_{12}O_{4} requires M, 196.0736); \nu_{\text{max}} \text{ (film) 3153, 3025, 2963, 2691, 1735, 1636, 1413 and 1210cm}^{-1}; \delta_{\text{H}} \text{ (270MHz, CDCl}_{3}\text{) 1.75 (3H, d, J 6.6Hz, C6-H), 4.71 (2H, d, J 6.8Hz, C1-H), 5.21-5.86 (2H, m, C2-H and C5-H), 5.98-6.10 (1H, m, C4-H), 6.21-6.34 (1H, m, C3-H) and 6.35 (2H, d, J 0.4Hz, -CH=CHCO}_{2}H); \delta_{\text{C}} \text{ (68.1MHz, CDCl}_{3}\text{) 18.1, 66.9, 121.7, 129.9, 130.0, 132.0, 133.0, 136.3, 166.3, and 166.5; m/z (EI, 70eV) 196 (7%), 107 (79), 97 (100), 91 (67) and 79 (65).}\]

\[(2E,4E)-2,4-hexadien-1-yl methyl maleate (303)\]
To a stirred solution (2E,4E)-2,4-hexadien-1-yl hydrogen maleate (302) (0.463g, 2.36mmol) in diethyl ether (20mL) at 0°C was added dropwise an ethereal solution of diazomethane\textsuperscript{173} (Section 6.6.3). On completion of the addition the solvent was evaporated to give the crude product (0.480g) as a yellow oil. Chromatography of this material on silica (20g) with hexanecetyl acetate (10:1 then 5:1) gave the title compound (303) (0.287g, 1.37mmol, 58%) as a colourless oil: $R_f = 0.33$ (hexane:ethyl acetate (10:1)); (Found: $M^+$, 210.0891. $C_{11}H_{14}O_4$ requires $M^+$, 210.0892); $\nu_{\text{max}}$ (film) 3023, 2953, 2881, 2853, 1730, 1647, 1438, 1397, 1378, 1367 and 1214 cm$^{-1}$; $\delta_H$ (270MHz, CDCl$_3$) 1.73 (3H, d, $J$ 6.8Hz, C6-H), 3.74 (3H, s, -CO$_2$CH$_3$), 4.65 (2H, d, $J$ 6.8Hz, C1-H), 5.61 (1H, dt, $J$ 15.2, 6.8Hz, C2-H), 5.75 (1H, dq, $J$ 14.9, 6.8Hz, C5-H), 5.94-6.09 (1H, m, C3-H), 6.22 (2H, s, -CH=CHCO$_2$CH$_3$) and 6.25 (1H, dd, $J$ 10.1, 14.9Hz, C4-H); $\delta_C$ (68.1MHz, CDCl$_3$) 18.1, 52.0, 65.6, 122.7, 129.4, 129.5, 130.1, 131.4, 135.3, 164.6 and 165.3; $m/z$ (El, 70eV) 210 (2%), 113 (64), 97 (100), 85 (12) and 79 (23).

(2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen fumarate (304)

To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (236) (0.682g, 1.68mmol) in benzene (20mL) at RT under argon was added thiophenol (34.4μL, 0.336mmol, 0.2eq) and 2,2'-azo-bis-isobutyronitrile (27.6mg, 0.168mmol, 0.1eq) in two potions at one hour intervals, during which time the reaction mixture was irradiated with ultraviolet light at reflux for a total of 2h. (Isomerisation was monitored by proton NMR analysis.) The solvent was evaporated to give the crude product (0.710g) as a yellow oil. Chromatography of this material on silica (10g) with hexanecetyl acetate:acetic acid (150:150:1) gave the title compound (304) (0.442g, 1.09mmol, 65%) as a yellow oil: $[\alpha]_D^{21} = -21.3^\circ$ (c = 0.360, diethyl ether); $R_f = 0.24$ (hexane:ethyl acetate:acetic acid (150:150:1)); (Found: $M^+$-CH$_3$, 411.1841. $C_{20}H_{31}O_7$Si requires $M^+$, 411.1839); $\nu_{\text{max}}$ (film) 3153, 2929, 2856, 1727, 1714, 1644, 1472, 1462, 1380, 1370 and 1258 cm$^{-1}$; $\delta_H$ (270MHz, CDCl$_3$) 0.061 and 0.080 (6H, 2 x s, -Si(CH$_3$)$_2$), 0.905 (9H, s, -C(CH$_3$)$_3$), 1.34 and 1.41 (6H, 2 x s, -C(CH$_3$)$_2$), 3.79 (1H, dd, $J$ 6.2, 8.6Hz, 170
C1-H), 3.95 (1H, dd, J 6.7, 8.6Hz, C1-H’), 4.05-4.14 (1H, m, C2-H), 4.31 (1H, t, J 5.6Hz, C3-H), 4.75 (2H, d, J 6.6Hz, C8-H), 5.69-5.89 (2H, m, C4-H and C7-H) 6.20-6.41 (2H, m, C5-H and C6-H) and 6.87 and 6.96 (2H, 2 x d, B and A of AB, JAB 15.7Hz, -CH=CHCO2H); δc (68.1MHz, CDCl3) -4.74, -4.52, 18.3, 25.7, 25.8, 26.4, 65.2, 65.6, 73.1, 78.5, 109.5, 125.5, 130.2, 132.9, 133.5, 134.2, 135.0, 164.2 and 168.9; m/z (El, 40eV) 411 (2%), 369 (12), 210 (18), 173 (37), 143 (27), 101 (100) and 73 (35).

(2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl fumarate (305)

To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)-oxy-4,6-octadien-1,2,8-triol (228) (297mg, 0.903mmol) in diethyl ether (15mL) at RT under argon was added methyl hydrogen fumarate207 (141mg, 1.08mmol, 1.2eq), dicyclocohexylcarbodiimide (242mg, 1.17mmol, 1.3eq) and N,N-dimethylaminopyridine (11.0mg, 0.090mmol, 0.1eq). Stirring was continued for 19h then further methyl fumarate (71mg, 0.59mmol, 0.60eq), dicyclohexylcarbodiimide (0.121mg, 0.585mmol, 0.65eq) and N,N-dimethylaminopyridine (5.0mg, 0.045mmol, 0.05eq) was added and the solution was stirred for a further 3h. The reaction mixture was filtered and the solvent evaporated to give the crude product (0.621g) as a yellow oil. Chromatography of this material on silica (4g) with hexane:ethyl acetate (5:1) gave the title compound (305) (0.383g, 0.869mmol, 96%) as a colourless oil: [α]D 21 = -25.6° (c = 8.60, dichloromethane); [α]D = 0.20 (hexaneeethyl acetate (8:1)); (Found: M*, 440.2240. C22H36O7Si requires M, 440.2230); νmax (film) 2986, 2953, 2931, 2857, 1727, 1645, 1472, 1462, 1437, 1380 and 1370cm-1; δh (270MHz, CDCl3) 0.035 and 0.055 (6H, 2 x s, -Si(CH3)2s), 0.879 (9H, s, -C(CH3)3), 1.31 and 1.37 (6H, 2 x s, -C(CH3)s), 3.75 (1H, dd, J 6.2, 8.5Hz, C1-H), 3.79 (3H, s, -CO2CH3), 3.92 (1H, dd, J 6.6, 8.5Hz, C1-H’), 4.02-4.11 (1H, m, C2-H), 4.28 (1H, t, J 5.6Hz, C3-H), 4.71 (2H, d, J 6.4Hz, C8-H), 5.67-5.86 (2H, m, C4-H and C7-H), 6.19-6.38 (2H, m, C5-H and C6-H) and 6.86 (2H, s, -CH=CHCO2H); δc (68.1MHz, CDCl3) -4.77, -4.55, 18.3, 25.2, 25.8, 26.4, 52.3, 65.2, 65.4, 73.1, 78.5, 109.3, 125.6, 130.1, 133.3,
133.4, 133.5, 134.0, 164.4 and 165.1; m/z (EI, 40eV) 440 (0.1%), 383 (13), 210 (28), 187 (33), 101 (100) and 73 (30).

(2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl propiolate (306)

To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-4,6-octadien-1,2,8-triol (228) (0.515g, 1.57mmol) in diethyl ether (20mL) at 0°C under argon was added propiolic acid (0.174mL, 2.82mmol, 1.8eq), dicyclohexylcarbodiimide (0.647g, 3.13mmol, 2eq) and N,N-dimethylaminopyridine (0.0290g, 0.235mmol, 0.15eq). Stirring was continued for 30min then a further amount of propiolic acid (0.087mL, 1.4mmol, 0.9eq) and dicyclohexylcarbodiimide (0.323g, 1.57mmol, 1eq) were added. After 30min the reaction mixture was warmed to 30°C and stirring continued for 1h. The reaction mixture was filtered and the filtrate was rinsed with diethyl ether (20mL), then the supernatant was partitioned against saturated aqueous sodium bicarbonate (20mL), water (20mL) and brine (20mL) then dried, filtered and evaporated to give the crude product (1.237g) as a yellow oil. Chromatography of this material on silica (30g) with hexane:ethyl acetate (10 :1, then 5:1, then 2:1) gave the title compound (306) (0.388g, 1.02mmol, 65%) as a colourless oil: [α]D 19° = -26.9° (c = 5.4, dichloromethane); Rf = 0.62 (hexane:ethyl acetate (2:1); (Found: M*, 380.2039. C20H32O5Si requires M, 380.2019); νmax (film) 3256, 2987, 2955, 2931, 2887, 2858, 2120, 1716, 1472, 1462, 1381, 1371 and 1222cm⁻¹; δH (270MHz, CDCl3) 0.057 and 0.077 (6H, 2 x s, -Si(CH3)2-), 0.90 (9H, s, -C(CH3)3), 1.34 and 1.40 (6H, 2 x s, -C(CH3)2-), 2.91 (1H, s, -CCH), 3.78 (1H, dd, J 6.2, 8.6Hz, C1-H), 3.94 (1H, dd, J 6.6, 8.6Hz, C1'-H'), 4.05-4.13 (1H, m, C2-H), 4.30 (1H, t, J 5.6Hz, C3-H), 4.73 (2H, d, J 6.8Hz, C8-H), 5.69-5.89 (2H, m, C4-H and C7-H) and 6.22-6.41 (2H, m, C5-H and C6-H); δc (68.1MHz, CDCl3) -4.70, -4.49, 18.3, 25.2, 25.8, 25.9, 26.4, 65.3, 66.3, 73.3, 74.6, 74.8, 109.4, 125.0, 130.1, 133.9, 134.7 and 152.1; m/z (EI, 40eV) 380 (0.1%), 323 (11), 210 (34), 101 (100) and 73 (34).
To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl acrylate (228) (98.3mg, 0.299mmol) in diethyl ether (2.5mL) at RT under argon was added acrylic acid (36.9μL, 0.539mmol, 1.8eq), dicyclohexylcarbodiimide (123mg, 0.598mmol, 2eq) and N,N-dimethylaminopyridine (5.5mg, 0.045mmol, 0.15eq). The reaction mixture was stirred for 2d then the solvent was evaporated and replaced with dichloromethane (2.5mL) and stirring was continued for a further 7d. The reaction mixture was filtered through celite and evaporated to give the crude product (0.176mg) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (10:1 then 3:1) gave the title compound (307) (54.0mg, 0.141mmol, 47%) as a colourless oil: [α]D20 = -27.4° (c = 1.51, dichloromethane); Rf = 0.32 (hexane:ethyl acetate (10:1)); (Found: M+-CH3, 367.19 49. C19H310SSi requires M, 367.19 41) ; v max (film) 2985, 2954, 2930, 2886, 2857, 1728, 1472, 1462, 1407, 1380, and 1370cm⁻¹; δH (270MHz, CDCl3) 0.45 and 0.065 (6H, 2 x s, -Si(CH3)2-), 0.889 (9H, s, -C(CH3)3), 1.32 and 1.38 (6H, 2 x s, -C(CH3)2-), 3.76 (1H, dd, J 6.3, 8.5Hz, C1-H), 3.92 (1H, dd, J 6.7, 8.5Hz, C1-H'), 4.03-4.12 (1H, m, C2-H), 4.30 (1H, t, J 5.5Hz, C3-H), 4.69 (2H, d, J 6.4Hz, C8-H), 5.68-5.84 (2H, m, C4-H and C7-H), 5.84 (1H, dd, A of ABX, JAB 1.5Hz and JAX 10.4Hz, -CH=CHH'), 6.17 (1H, dd, X of ABX, JAX 10.4Hz and JBX 17.4Hz, -CH=CHH'), 6.20-6.37 (2H, m, C5-H and C6-H) and 6.43 (1H, dd, B of ABX, JAB 1.5Hz and JBX 17.4Hz, -CH=CHH'); δC (68.1MHz, CDCl3) -4.73, -4.51, 18.3, 25.2, 25.9, 26.4, 64.7, 65.2, 73.3, 78.6, 109.3, 126.4, 128.2, 130.3, 130.8, 133.1, 133.5 and 165.7; m/z (El, 70eV) 367 (0.4%), 325 (7), 281 (11), 210 (28), 195 (18), 129 (42), 101 (100), 73 (44), 55 (52) and 43 (19).
6.3.2 ETDA reactions

ETDA reaction of \((2S,3S,4E,6E)-1,2-O\text{-isopropylidene-3-(1-} \text{-tert-buty}1,1\text{-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (236)}\)

\[
\begin{align*}
\text{236} & \xrightarrow{\Delta} \text{241c} + \text{242c} \\
\text{CH}_2\text{N}_2 & \text{H} \\
\end{align*}
\]

To a stirred solution of \((2S,3S,4E,6E)-1,2-O\text{-isopropylidene-3-(1-} \text{-tert-buty}1,1\text{-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (236)}\) (137mg, 0.322mmol) in toluene (64.4mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (14.2mg, 0.0646mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 17h. The solution was cooled to 0°C, then an ethereal solution of diazomethane\(^{173}\) (Section 6.6.3) was added. On completion of the addition the solvent was evaporated to give the crude product (148.1mg) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (4:1) gave the ETDA adducts (241c and 242c) (86.3mg, 0.196mmol, 62%, 241c:242c (89:11)), vide supra.

ETDA reaction of \((2S,4E,6E)-1,2-O\text{-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (239)}\)

\[
\begin{align*}
\text{239} & \xrightarrow{\Delta} \text{270} + \text{271} \\
\text{CH}_2\text{N}_2 & \text{H} \\
\end{align*}
\]

To a stirred solution of \((2S,4E,6E)-1,2-O\text{-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (239)}\) (8.7mg, 0.029mmol) in toluene (5.9mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (1.3mg, 0.0059mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 6h. The solution was cooled to 0°C, then an ethereal solution of diazomethane\(^{173}\) (Section 6.6.3) was
added. On completion of the addition the solvent was evaporated to give the crude product (10.0mg) as a yellow oil. Chromatography of this material on silica (1g) with hexane:ethyl acetate (2:1) gave the ETDA adducts (270 and 271) (5.9mg, 0.019mmol, 66%, 270:271 (50:50)), *vide supra.*

**ETDA reaction of (2E,4E)-2,4-hexadien-1-yl hydrogen maleate (302)**

To a stirred solution of (2E,4E)-2,4-hexadien-1-yl hydrogen maleate (302) (36.0mg, 0.180mmol) in toluene (36.6mL) at RT under argon was added 2,6-di-tert-buty1-4-methylphenol (8.1mg, 0.037mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 2h. The solution was cooled to 0°C, then an ethereal solution of diazomethane\(^\text{173}\) (*Section 6.6.3*) was added. On completion of the addition the solvent was evaporated to give the crude product (45.0mg) as a yellow oil. Chromatography of this material on silica (4g) with hexane:ethyl acetate (5:1 then 2:1) gave the ETDA adducts (308 and 309) (31.6mg, 0.150mmol, 83%, 308:309 (69:31)), *vide infra.*

**rel-methyl (3aR, 4S, 5R, 7aS)-5-methyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (308)**

Colourless oil; R\(_t=0.23\) (hexane:ethyl acetate (5:1)); (Found: \(M^+\), 210.0891. \(C_{11}H_{14}O_4\) requires \(M, 210.0892\); \(\nu_{max}\) (film) 3026, 2959, 2901, 1782, 1732, 1437, 1326, 1312 and 1216cm\(^{-1}\); \(\delta_H\) (270MHz, CDCl\(_3\)) 1.18 (3H, d, \(J 7.3\)Hz, C5-\(CH_3\)), 2.35 (1H, dd, \(J 3.6\), 13.5Hz, C3a-\(H\)), 2.87-2.99 (1H, m, C5-\(H\)), 2.96 (1H, d, \(J 3.6\)Hz, C4-\(H\)), 3.11-3.27 (1H, m, C7a-\(H\)), 3.69 (3H, s, -CO\(_2\)CH\(_3\)), 3.87 (1H, dd, \(J 7.9\), 11.4Hz, C1-\(H\)),
4.51 (1H, dd, $J$ 7.3, 7.9Hz, C1-$H'$), 5.65 (1H, dt, $J$ 10.0, 3.3Hz, C6-$H$) and 5.72 (1H, dt, $J$ 10.0, 1.9Hz, C7-$H$); $\delta_c$ (68.1MHz, CDCl$_3$) 22.0, 34.1, 36.4, 41.5, 42.7, 52.1, 70.6, 123.0, 134.5, 172.1 and 174.6; $m/z$ (EI, 70eV) 210 (0.5%), 179 (13), 105 (100), 91 (61) and 77 (20).

**rel-methyl (3aS, 4R, 5R, 7aS)-5-methyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (309)**

![Molecule Diagram]

Colourless oil; $R_f = 0.13$ (hexane:ethyl acetate (2:1)); (Found: $M^+$, 210.0893. C$_{11}$H$_{14}$O$_4$ requires $M$, 210.0892); $\nu_{max}$ (film) 3022, 2953, 2913, 1770, 1732 1435 and 1212cm$^{-1}$; $\delta_h$ (270MHz, CDCl$_3$) 1.16 (3H, d, $J$ 7.5Hz, C5-CH$_3$), 2.62-2.77 (1H, m, C5-$H$), 3.09 (1H, t, $J$ 5.3Hz, C4-$H$), 3.14-3.26 (1H, m, C7a-$H$), 3.33 (1H, dd, $J$ 5.3, 9.7Hz, C3a-$H$), 3.75 (3H, s, -CO$_2$CH$_3$), 4.17 (1H, dd, $J$ 4.4, 8.6Hz, C1-$H$), 4.44 (1H, dd, $J$ 7.8, 8.6Hz, C1-$H'$), 5.60 (1H, dt, $J$ 10.1, 2.4Hz, C7-$H$) and 5.82 (1H, ddd, $J$ 2.4, 4.0, 10.1Hz, C6-$H$); $\delta_c$ (68.1MHz, CDCl$_3$) 17.8, 30.3, 35.3, 38.6, 42.1, 51.8, 71.4, 124.3, 133.9, 171.7 and 177.0; $m/z$ (EI, 70eV) 210 (19%), 178 (59), 150 (55), 105 (56) and 93 (100).

**ETDA reaction of (2E,4E)-2,4-hexadien-1-yl methyl maleate (303)**

![Reaction Diagram]

To a stirred solution of (2E,4E)-2,4-hexadien-1-yl methyl maleate (303) (37.0mg, 0.176mmol) in toluene (35.2mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (7.8mg, 0.035mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 2h. Evaporation of the solvent gave the crude product (45.0mg) as a yellow oil. Chromatography of this material on silica (4g) with
hexane:ethyl acetate (5:1 then 2:1) gave the ETDA adducts (308 and 309) (29.2mg, 0.139mmol, 79%, 308:309 (79:21), vide supra.

ETDA reaction of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen fumarate (304)

To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen fumarate (304) (97.0mg, 0.239mmol) in toluene (47.8mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (10.5mg, 0.0477mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 142h. The solution was cooled to 0°C, then an ethereal solution of diazomethane\textsuperscript{173} (Section 6.6.3) was added. On completion of the addition the solvent was evaporated to give the crude product (117mg) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (5:1 then 2:1) then ethyl acetate gave the ETDA adducts (314 and 315) (44.6mg, 0.101mmol, 42%, 314:315 (71:29), vide infra.

methyl (3aS, 4S, 5R, 7aS)-5-((2S,3S)-1,2-O-isopropylidene-3-((1,1-dimethyl-1-tert-butyldimethylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofuran-6-carboxylate (314)

Colourless oil; [α]_D\textsuperscript{21} = -66.1° (c = 1.20, dichloromethane); Rf = 0.50 (hexane:ethyl acetate (2:1)); (Found: M\textsuperscript{+}-CH\textsubscript{3}, 425.1996. C\textsubscript{21}H\textsubscript{33}O\textsubscript{7}Si requires M, 425.1996); ν\textsubscript{max} (film) 2984, 2953, 2930, 2897, 2856, 1787, 1738, 1472, 1462, 1435, 1380, 1370 and
1208 cm⁻¹; δₜ (270 MHz, CDCl₃) 0.46 and 0.88 (6H, 2 x s, -Si(CH₃)₂⁻), 0.863 (9H, s, -C(CH₃)₃), 1.35 and 1.40 (6H, 2 x s, -C(CH₃)₂⁻), 2.40-2.50 (1H, m, C5-H), 2.91-3.06 (2H, m, C3a-H and C4-H), 3.07-3.25 (1H, m, C7a-H), 3.57 (1H, t, J 8.2 Hz, -CHH'OC(CH₃)₂OCH-), 3.62 (1H, dd, J 2.8, 7.3 Hz, -CHOTBS), 3.77 (3H, s, -CO₂CH₃), 3.91 (1H, t, J 8.8 Hz, C1-H), 3.97 (1H, dd, J 6.2, 8.2 Hz, -CHH'OC(CH₃)₂OCH-), 4.17-4.27 (1H, m, -CHH'OC(CH₃)₂OCH-), 4.49 (1H, dd, J 8.0, 8.8 Hz, C1-H'), 5.70 (1H, dt, J 10.4, 3.3 Hz, C7-H) and 5.94 (1H, dt, J 10.4, 2.2 Hz, C6-H); δC (68.1 MHz, CDCl₃) -5.18, -3.86, 18.5, 25.5, 26.1, 26.6, 35.0, 40.4, 40.5, 40.7, 52.2, 66.0, 71.6, 73.9, 78.0, 109.3, 123.8, 129.2, 173.6 and 176.3; m/z (EI, 40 eV) 425 (12%), 383 (28), 339 (66), 325 (85), 293 (89), 265 (64), 89 (42) and 73 (100).

**methyl (3αR, 4R, 5R, 7aS)-5-((2S,3S)-1,1-dimethyl-1-tert-butyldimethylsilyloxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (315)**

![Chemical Structure](image)

Colourless oil; [α]D⁰ = -137° (c = 0.190, dichloromethane); Rf = 0.42 (hexane:ethyl acetate (2:1)); (Found: M+·CH₃, 425.1999 C₂₁H₃₃O₇Si requires M, 425.1996); vₘₐₓ (film) 2984, 2952, 2928, 2855, 1789, 1738, 1471, 1462, 1435, 1380 and 1370 cm⁻¹; δH (270 MHz, CDCl₃) 0.118 (6H, s, -Si(CH₃)₂⁻), 0.878 (9H, s, -C(CH₃)₃), 1.35 and 1.41 (6H, 2 x s, -C(CH₃)₂⁻), 2.54-2.62 (1H, m, C5-H), 2.70-2.86 (1H, m, C7a-H), 2.96 (1H, dd, J 7.2, 11.6 Hz, C4-H), 3.16 (1H, dd, J 11.6, 13.4 Hz, C3a-H), 3.56 (1H, t, J 8.1 Hz, -CHH'OC(CH₃)₂OCH-), 3.79 (1H, dd, J 2.0, 7.5 Hz, -CHOTBS), 3.80 (3H, s, -CO₂CH₃), 3.90 (1H, dd, J 8.0, 11.4 Hz, C1-H), 3.99 (1H, dd, J 6.4, 8.1 Hz, -CHH'OC(CH₃)₂OCH-), 4.08-4.19 (1H, m, -CHH'OC(CH₃)₂OCH-), 4.45 (1H, dd, J 6.6, 8.0 Hz, C1-H'), 5.74 (1H, dt, J 9.9, 3.5 Hz, C6-H) and 5.96 (1H, dt, J 9.9, 2.0 Hz, C7-H); δC (68.1 MHz, CDCl₃) -4.53, -3.64, 18.6, 25.5, 26.3, 26.6, 40.7, 41.1, 41.4, 44.1, 51.9, 66.2, 70.1, 74.9, 78.3, 109.6, 124.7, 129.1, 170.7 and 173.7; m/z (EI, 70 eV) 425 (9%), 383 (19), 339 (65), 325 (61), 293 (55), 265 (49), 89 (36) and 73 (100).
ETDA reaction of \((2S,3S,4E,6E)-1,2-O\text{-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl fumarate (305)}\)

To a stirred solution of \((2S,3S,4E,6E)-1,2-O\text{-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl fumarate (305)}\) (92.5mg, 0.210mmol) in toluene (42mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (9.3mg, 0.042mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 167h. Evaporation of the solvent gave the crude product (98.9mg) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (5:1 then 3:1) gave recovered starting material (305) (29.4mg, 0.067mmol, 31%) followed by the ETDA adducts (314 and 315) (48.3mg, 0.110mmol, 76% (at 69% conversion), \(314:315\) (86:14), vide supra.

ETDA reaction of \((2S,3S,4E,6E)-1,2-O\text{-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl propiolate (306)}\)

To a stirred solution of \((2S,3S,4E,6E)-1,2-O\text{-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl propiolate (306)}\) (97.1mg, 0.255mmol) in toluene (51.0mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (5.6mg, 0.026mmol, 0.1eq). The solution was warmed to reflux and heating was continued for 29h. Evaporation of the solvent gave the crude product (0.101g) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (3:1) gave recovered starting material (56) (27.2mg,
0.0715 mmol, 28%) followed by the ETDA adducts (320 and 321) (59.6 mg, 0.157 mmol, 85% (at 72% conversion), 320:321 (65:35), *vide infra.*

***(5R, 7aS)**-5-((2S,3S)-1,2-0-isopropylidene-3-(1,1-dimethyl-1-tert-butylidimethylsilyloxy)-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,5,7a-tetrahydroisobenzofuran (320)

![Chemical Structure](image)

Colourless oil; [α]_D^20 = -13.5° (c = 1.12, dichloromethane); R_f = 0.30 (hexanecetyl acetate (3:1)); (Found: M^+, 380.2030. C_{20}H_{32}O_{5}Si requires M, 380.2019); ν_{max} (film) 2984, 2954, 2929, 2897, 2856, 1769, 1482, 1471, 1380 and 1370 cm⁻¹; δ_{H} (270 MHz, CDCl_3) 0.080 and 0.112 (6H, 2 x s, -Si(CH$_3$)$_2$-), 0.871 (9H, s, -C(CH$_3$)$_3$), 1.33 and 1.41 (6H, 2 x s, -C(CH$_3$)$_2$-), 3.05-3.16 (1H, m, C5-H), 3.46-3.59 (1H, m, C7a-H), 3.58 (1H, t, J 8.1 Hz, -CHH'OC(CH$_3$)$_2$OCH-), 3.82 (1H, t, J 8.6 Hz, C1-H), 3.85 (1H, dd, J 4.4, 8.1 Hz, -CHH'OC(CH$_3$)$_2$OCH-), 3.92 (1H, dd, J 3.7, 6.6 Hz, -CHOTBS), 4.00-4.10 (1H, m, CHH'OC(CH$_3$)$_2$OCH-), 4.64 (1H, dd, J 8.2, 8.6 Hz, C1'-H'), 5.76-5.93 (2H, m, C6-H and C7-H) and 6.96-7.01 (1H, m, C4-H'); δ_{C} (68.1 MHz, CDCl$_3$) -4.74, -4.18, 18.3, 25.7, 25.9, 26.6, 37.8, 42.8, 65.9, 70.4, 75.2, 77.9, 108.9, 123.8, 127.5, 128.0, 135.1 and 168.9; m/z (EI, 40 eV) 380 (0.3%), 187 (35), 131 (59), 101 (39), 91 (42) and 73 (100).

**(5S, 7aR)**-5-((2S,3S)-1,2-0-isopropylidene-3-(1,1-dimethyl-1-tert-butylidimethylsilyloxy)-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,5,7a-tetrahydroisobenzofuran (321)

![Chemical Structure](image)
Colourless oil; $[\alpha]_D^{20} = +51.8^\circ$ (c = 0.36, dichloromethane); $R_1 = 0.39$ (hexane:ethyl acetate (3:1)); (Found: $M^+$, 380.1999 C$_{20}$H$_{32}$O$_8$Si requires $M$, 380.2019); $\nu_{\text{max}}$ (film) 2984, 2953, 2929, 2897, 2856, 1770, 1697, 1471, 1462, 1380, 1370 and 1206 cm$^{-1}$; $\delta_H$ (270MHz, CDCl$_3$) 0.052 and 0.098 (6H, 2 x s, -Si(CH$_3$)$_2$-), 0.841 (9H, s, -C(CH$_3$)$_3$), 1.35 and 1.41 (6H, 2 x s, -C(CH$_3$)$_3$-), 2.95-3.05 (1H, m, C5-H), 3.46-3.63 (1H, m, C7a-H), 3.61 (1H, t, $J = 8.1$Hz, -CHH’OC(CH$_3$)$_2$OCH-), 3.82 (1H, dd, $J = 8.3$, 10.4Hz, C1-H), 3.87-3.95 (2H, m, -CHH’OC(CH$_3$)$_2$OCH-), 4.13-4.22 (1H, m, -CHOTBS), 4.65 (1H, t, $J = 8.3$Hz, C1-H'), 5.82-5.99 (2H, m, C6-H and C7-H) and 6.86-6.90 (1H, m, C4-H); $\delta_C$ (68.1MHz, CDCl$_3$) -4.74, -4.10, 18.3, 25.6, 25.9, 26.6, 37.8, 42.0, 65.8, 70.4, 75.7, 78.1, 109.2, 123.2, 128.8, 130.4, 133.3 and 168.9; $m/z$ (El, 40eV) 380 (0.1%), 265 (25), 187 (36), 131 (69), 91 (50) and 73 (100).

Attempted ETDA reactions of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl acrylate (307)

Method A

To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl acrylate (307) (17.5mg, 0.0457mmol) in toluene (9.2mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (2.0mg, 0.0091mmol, 0.2eq). The solution was warmed to reflux and heating continued for 43h, but no reaction was detected by TLC. The solvent was evaporated and replaced with xylene (9.2mL), then the solution was warmed to reflux and heating was continued for 23h. No change was detected by TLC.

Method B

To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl acrylate (307) (30.2mg, 0.0789mmol) in toluene (9.2mL) was added 2,6-di-tert-butyl-4-methylphenol (3.5mg, 0.016mmol, 0.2eq) under argon. The solution was heated to 210°C in a sealed tube.
(without refluxing) for 30h. TLC indicated that a portion of the starting material was consumed, so the solvent was evaporated to give the crude product (29.6mg) as a yellow oil. Chromatography of this material on silica (1g) with dichloromethane:hexane:ethyl acetate gave recovered starting material (307) (6.1mg, 0.016mmol, 39%) followed by a mixture of compounds which were found to be chromatographically inseparable in a range of solvent systems. (Proton NMR analysis indicated that a complex mixture of compounds was produced.)

### 6.3.3 Miscellaneous DA reactions

DA reaction between (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-4,6-octadien-1,2,8-triol (22S) and maleic anhydride (45).

To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-4,6-octadien-1,2,8-triol (228) (100mg, 0.304mmol) in toluene (3.0mL) at RT under argon was added maleic anhydride (45) (29.8mg, 0.304mmol, 1eq) and 2,6-di-tert-butyl-4-methylphenol (13.4mg, 0.0608mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 67h. The solution was cooled to -65°C then an ethereal solution of diazomethane \(^\text{173}\) (Section 6.6.3) was added dropwise. On completion of the addition the solvent was evaporated to give the crude product (126.9mg) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (3:1) then ethyl acetate gave the DA adducts (241c, 242c, 310 and 311) (60.3mg, 0.137mmol, 45%, 241c:242c:310:311 (42:4:27:27)), vide supra/infra. (Only one of the adducts 310 and 311 was able to be isolated and characterised. Coupling constants for the isolated compound (310) indicated that the two
rings were cis fused, but it was not possible to determine the relative stereochemistry of this adduct. The structure of the unisolated compound (311) is speculative and based on limited proton NMR analysis of mixtures only.

**methyl (3aS, 4R, 5R, 7aS)-5-((2S,3S)-1,2-O-isopropylidene-3-(1,1-dimethyl-1-tert-butylidimethylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (310)**

![Structure diagram](image)

Colourless oil; [α]_D^21 = +4.3° (c = 0.31, dichloromethane); Rf = 0.45 (hexane:ethyl acetate (3:1)); (Found: M+CH_3, 425.1990. C_{21}H_{33}O_7Si requires M, 425.1996); v_max (film) 2953, 2928, 2856, 1769, 1738, 1473, 1436, 1380 and 1370 cm⁻¹; δ_Η (270MHz, CDCl_3) 0.073 and 0.115 (6H, 2 x s, -Si(CH_3)_2-), 0.870 (9H, s, -C(CH_3)_3), 1.35 and 1.42 (6H, 2 x s, -C(CH_3)_2-), 2.40-2.49 (1H, m, C5-H), 2.97 (1H, dd, J 6.2, 11.0Hz, C3a-H), 3.13-3.29 (1H, m, C7a-H), 3.42 (1H, dd, J 4.2, 6.2Hz, C4-H), 3.65 (3H, s, -CO_2CH_3), 3.77 (1H, dd, J 7.3, 8.3Hz, -CHH'OC(CH_3)_2OCH-), 4.01 (1H, dd, J 4.6, 8.3Hz, -CHH'OC(CH_3)_2OCH-), 4.04 (1H, t, J 8.3Hz, C1-H), 4.20 (1H, dd, J 6.2, 7.3Hz, -CHOTBS), 4.39-4.47 (1H, m, -CHH'OC(CH_3)_2OCH-), 4.51 (1H, dd, J 8.3, 9.6Hz, C1-H'), 5.65 (1H, dt, J 10.1, 2.9Hz, C7-H) and 5.91 (1H, dt, J 10.1, 2.2Hz, C6-H); δ_C (68.1MHz, CDCl_3) -4.80, -4.03, 18.6, 24.9, 26.2, 26.4, 34.3, 39.6, 40.9, 41.6, 51.7, 65.3, 71.6, 73.6, 77.9, 109.3, 124.2, 129.5, 171.6 and 177.1; m/z (EI, 70eV) 425 (7%), 383 (19), 339 (77), 325 (100), 265 (34) and 73 (77).

**DA reaction between (2E,4E)-2,4-hexadien-1-ol (228) and maleic anhydride (45)**
To a stirred solution of (2E,4E)-2,4-hexadien-1-ol (228) (103mg, 1.05mmol) in toluene (2.00mL) at RT under argon was added maleic anhydride (45) (103mg, 1.05mmol, 1eq) and 2,6-di-tert-butyl-4-methylphenol (44.1mg, 0.200mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 70min. Toluene (10mL) was added and the solution was cooled to -65°C then an ethereal solution of diazomethane \(^{173}\) (Section 6.6.3) was added dropwise. On completion of the addition the solvent was evaporated to give the crude product (250mg) as a yellow oil. Chromatography of this material on silica (10g) with hexane:ethyl acetate (5:1 then 2:1) gave the DA adducts (312 and 313) (198mg, 0.942mmol, 90%, 312:313 (4:96)), vide supra.

6.4 Experimental for Chapter four

6.4.1 Preparation of citraconate precursors

1-((2S,3S,4E,6E)-1,2-0-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2Z)-2-methyl-2-butenedioate (401) and 1-((2S,3S,4E,6E)-1,2-0-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (402)

To a stirred solution of (2S,3S,4E,6E)-1,2-0-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)-oxy-4,6-octadien-1,2,8-triol (228) (102mg, 0.310mmol) in dichloromethane (10mL) at RT under argon was added triethylamine (69.2μL, 0.497mmol, 1.6eq), citraconic anhydride (62.6μL, 0.699mmol, 2.25eq) and N,N-dimethylaminopyridine (crystal). Stirring was continued for 1h then the reaction mixture was diluted with diethyl ether (50mL) and partitioned against 10% aqueous hydrochloric acid (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (152mg) as a yellow oil. Chromatography of this material on silica (5g) with ethyl acetate:hexane (2:1) then ethyl acetate:acetic acid (100:1) gave the title compounds (401 and 402) (84.7mg, 0.192mmol, 62%, 401:402 (77:23)), vide infra.
1-((2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2Z)-2-methyl-2-butenedioate (401)

![Chemical Structure](image)

Colourless oil; $[\alpha]_D^{21} = -27.4^\circ$ (c = 1.29, dichloromethane); $R_t = 0.70$ (ethyl acetate:acetic acid (100:1)); (Found: $M^+$, 440.2220. $C_{22}H_{36}O_7Si$ requires $M$, 440.2230); $\nu_{\text{max}}$ (film) 3437, 3157, 2950, 2930, 2857, 1732, 1714, 1651, 1471, 1462, 1382 and 1372 cm$^{-1}$; $\delta_H$ (270MHz, $CDCl_3$) 0.047 and 0.67 (6H, 2 x s, -Si(CH$_3$)$_2$), 0.891 (9H, s, -C(CH$_3$)$_3$), 1.33 and 1.39 (6H, 2 x s, -C(CH$_3$)$_3$), 2.09 (3H, d, $J$ 1.5Hz, -CH=CCCH$_3$), 3.78 (1H, dd, $J$ 6.2, 8.6Hz, C1-H), 3.93 (1H, dd, $J$ 6.7, 8.6Hz, C1-H'), 4.04-4.12 (1H, m, C2-H), 4.29 (1H, $t$, $J$ 5.5Hz, C3-H), 4.73 (2H, d, $J$ 6.6Hz, C8-H), 5.69-5.83 (2H, m, C4-H and C7-H), 5.88 (1H, q, $J$ 1.5Hz, -CH=CCCH$_3$ and 6.21-6.39 (2H, m, C5-H and C6-H); $\delta_C$ (68.1MHz, $CDCl_3$) -4.75, -4.50, 18.3, 20.9, 25.2, 25.9, 26.4, 65.2, 65.9, 73.2, 78.5, 109.4, 120.7, 125.5, 130.2, 133.3, 134.3, 147.3, 168.4 and 168.6; $m/z$ (CI/NH$_3$, 40eV) 440 (0.03%), 271 (13), 227 (33), 210 (24), 101 (100), 75 (76) and 39 (30).

1-((2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (402)

![Chemical Structure](image)

Colourless oil; $[\alpha]_D^{21} = -26.1^\circ$ (c = 0.88, dichloromethane); $R_t = 0.33$ (ethyl acetate:acetic acid (100:1)); (Found: $M^+$, 440.2212 $C_{22}H_{36}O_7Si$ requires $M$, 440.2230); $\nu_{\text{max}}$ (film) 3468, 3155, 2985, 2954, 2930, 2893, 2857, 1730, 1714, 1472, 1462, 1447, 1380, 1370 and 1255 cm$^{-1}$; $\delta_H$ (270MHz, $CDCl_3$) 0.055 and 0.075 (6H, 2 x s, -Si(CH$_3$)$_2$),
0.900 (9H, s, -C(CH₃)₃), 1.34 and 1.40 (6H, 2 x s, -C(CH₃)₂-), 2.15 (3H, d, J 1.5Hz, -CH=CH₂), 3.79 (1H, dd, J 6.0, 8.6Hz, C₁-H), 3.95 (1H, dd, J 6.6, 8.6Hz, C₁-H’), 4.05-4.14 (1H, m, C₂-H), 4.27-4.34 (1H, m, C₃-H), 4.72 (2H, d, J 6.6Hz, C₈-H), 5.69-5.83 (2H, m, C₄-H and C₇-H), 6.16 (1H, q, J 1.5Hz, -CH=CH₂-) and 6.20-6.42 (2H, m, C₅-H and C₆-H); δₗ (68.1MHz, CDCl₃) -4.71, -4.50, 18.3, 22.2, 25.2, 25.9, 26.4, 65.1, 66.1, 73.0, 78.5, 109.5, 122.6 (2 x C), 125.0, 130.0, 133.8, 134.7 and 166.4 (2 x C); m/z (El, 70eV) 440 (0.05%), 271 (15), 227 (36), 210 (33), 101 (100), 75 (81) and 39 (37).

1-(((2S,4E,6E)-1,2-0-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2Z)-2-methyl-2-butenedioate (403) and 1-(((2S,4E,6E)-1,2-O-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (404)

![Chemical Structures](image)

To a stirred solution of (2S,4E,6E)-1,2-O-isopropylidene-4,6-octadiene-1,2,8-triol (235) (45.5mg, 0.230mmol) in dichloromethane (5mL) at 0°C under argon was added triethylamine (48.0µL, 0.345mmol, 1.5eq), citraconic anhydride (25.7µL, 0.290mmol, 1.25eq) and N,N-dimethylaminopyridine (crystal). Stirring was continued for 3h then a further amount of triethylamine (48.0µL, 0.345mmol, 1.5eq) and citraconic anhydride (25.7µL, 0.290mmol, 1.25eq) was added and the solution was warmed to RT and stirred for 18h. The reaction mixture was diluted with diethyl ether (50mL) and partitioned against 10% aqueous hydrochloric acid (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (140mg) as a yellow oil. Chromatography of this material on silica (10g) with ethyl acetate:acetic acid:methanol (200:1:1 then 20:1:1) gave the title compounds (403 and 404) (55.0mg, 0.177mmol, 77%, 403:404 (67:33)), vide infra.
1-((2S,4E,6E)-1,2-O-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2Z)-2-methyl-2-butenedioate (403)

![Chemical Structure]

**403**

Colourless oil; [α]_D^21 = +8.5° (c = 0.41, dichloromethane); R_t = 0.69 (ethyl acetate:acetic acid: methanol (20:1:1)); (Found: M*, 310.1418. C_{16}H_{22}O_6 requires M, 310.1416); v_{max} (film) 3435, 3151, 3028, 2986, 2934, 2883, 1731, 1654, 1448, 1379, 1369 and 1340 cm⁻¹; δ_H (270MHz, CDCl₃) 1.35 and 1.42 (6H, 2 x s, -C(CH₃)₂-), 2.08 (3H, d, J 1.5Hz, -CH=CH₂), 2.24-2.55 (2H, m, C3-H), 3.57 (1H, dd, J 6.8, 8.0Hz, C1-H), 4.02 (1H, dd, J 6.0, 8.0Hz, C1'-H'), 4.16 (1H, m, C2-H), 4.72 (2H, d, J 6.7Hz, C8-H), 5.83-5.62 (2H, m, C4-H and C7-H), 5.89 (1H, q, J 1.5Hz, -CH=CH₂), 6.13 and 6.29 (2H, 2 x dd, J 10.4, 15.1Hz and J 10.4, 15.1Hz, C5-H and C6-H); δ_C (68.1MHz, CDCl₃) 21.0, 25.7, 26.9, 37.0, 66.1, 68.8, 75.2, 109.0, 121.7, 124.2, 130.9, 131.7, 135.1, 146.5, 168.0 and 168.4; m/z (Cl/NH₃, 40eV) 310 (0.02%), 183 (13), 101 (100), 80 (27), 68 (35) and 43 (24).

1-((2S,4E,6E)-1,2-O-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (404)

![Chemical Structure]

**404**

Colourless oil; [α]_D^21 = +6.3° (c = 0.58, dichloromethane); R_t = 0.44 (ethyl acetate:acetic acid: methanol (2:1:1)); (Found: M*, 310.1400. C_{16}H_{22}O_6 requires M, 310.1416); v_{max} (film) 3435, 3153, 2984, 2935, 2877, 1729, 1653, 1447, 1380 and 1370 cm⁻¹; δ_H (270MHz, CDCl₃) 1.36 and 2.17 (6H, 2 x d, 0.5Hz, -C(CH₃)₂-), 2.17 (3H, d, J 1.5Hz, -CH=CH₂), 2.28-2.53 (2H, m, C3-H), 3.58 (1H, dd, J 6.8, 8.0Hz, C1-H), 4.04 (1H, dd, J 6.8, 8.0Hz, C1'-H'), 4.17 (1H, m, C2-H), 4.74 (2H, d, J 6.8Hz, C8-H), 5.62-5.85 (2H, m, C4-H and C7-H), 6.08-6.39 (2H, m, C5-H and C6-H) and 6.25
(1H, q, J 1.5Hz, -CH=CHCH3); δc (68.1MHz, CDCl3) 22.9, 25.7, 27.0, 37.0, 66.7, 68.8, 75.1, 109.1, 123.2, 123.4, 131.4, 131.7, 135.7, 147.7, 166.4 and 167.2; m/z (Cl/NIH3, 40eV) 310 (0.2%), 295 (6), 183 (39), 101 (100), 80 (74), 68 (86) and 43 (81).

1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-2-methyl-2-butenedioate (38d) and 1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (38c)

Method A

To a stirred solution of (2E,4E)-2,4-hexadien-1-ol (301) (2.00g, 20.4mmol) in dichloromethane (100mL) at 0°C under argon was added triethylamine (3.00mL, 21.5mmol, 1.05eq), citraconic anhydride (2.74mL, 30.6mmol, 1.5eq) and N,N-dimethylaminopyridine (0.124g, 1.01mmol, 0.05eq). On completion of the addition the solution was warmed to RT and stirring was continued for 30min. An extra amount of triethylamine (1.56mL, 11.2mmol, 0.55eq), citraconic anhydride (1.60mL, 14.3mmol, 0.7eq) and N,N-dimethylaminopyridine (0.124g, 0.510mmol, 0.025eq) was added and stirring was continued for 3h. The reaction mixture was partitioned against 10% aqueous hydrochloric acid (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (6.021g) as a yellow oil. The crude product was adsorbed onto silica (9g) then loaded onto a silica column (90g) and eluted with hexane:ethyl acetate (2:1), ethyl acetate, ethyl acetate:acetic acid (165:1) then ethyl acetate:acetic acid:methanol (38:1:1) to give the title compounds (38d and 38c) (4.30g, 20.4mmol, 100%, 38d:38c (86:14)), vide infra.

Method B

Compounds 38d and 38c were also prepared using the method of White et al.98

To a stirred solution of (2E,4E)-2,4-hexadien-1-ol (301) (1.96g, 20.0mmol) in benzene (4mL) at RT under argon was added pyridine (1.60mL, 48.3mmol, 2.42eq) and citraconic anhydride (1.80mL, 20.0mmol, 1eq). On completion of the addition the
solution was warmed to 50°C and stirring was continued for 8 h. The solvent was evaporated then dichloromethane (50 mL) was added and this was partitioned against 10% aqueous hydrochloric acid (2 x 50 mL), water (50 mL) and brine (50 mL) then dried, filtered and evaporated to give the crude product (3.87 g) as a yellow oil. Half of the crude product (1.91 g) was columned in two portions on silica (50 g) with hexane:ethyl acetate:acetic acid:methanol (260:130:1:1) to give the title compounds (38d and 38c) (1.847 g, 8.79 mmol, 44% (corresponding to an overall yield of 89%), 38d:38c (50:50), vide infra.

1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-2-methyl-2-butenedioate (38d)

1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (38c)
Wax; \( R_t = 0.05 \) (hexane:ethyl acetate:acetic acid:methanol (260:130:1:1); (Found: \( M^+ \), 210.0898. \( \text{C}_{11}\text{H}_{14}\text{O}_4 \) requires \( M \), 210.0892); \( \nu_{\text{max}} \) (film) 3412, 3026, 2936, 1713, 1650, 1446, 1431, 1484, 1474 and 1345 cm\(^{-1}\); \( \delta_{\text{H}} \) (270MHz, CDCl\(_3\)) 1.78 (3H, d, \( J 6.6\text{Hz}, \text{C6-H} \)), 2.14 (3H, d, \( J 1.5\text{Hz}, -\text{CH}=\text{CHH}_3 \)), 4.70 (2H, d, \( J 7.0\text{Hz}, \text{C1-H} \)), 5.56-5.87 (2H, m, C2-H and C5-H), 5.99-6.13 (1H, m, C4-H), 6.16 (1H, q, \( J 1.5\text{Hz}, -\text{CH}=\text{CHH}_3 \)) and 6.29 (1H, dd, \( J 10.3, 14.9\text{Hz}, \text{C3-H} \)); \( \delta_{\text{C}} \) (68.1MHz, CDCl\(_3\)) 18.2, 22.2, 66.6, 122.1, 122.9, 130.1, 132.0, 136.1, 146.5, 166.6 and 168.6; \( m/z \) (EI, 70eV) 210 (2%), 113 (23), 97 (87), 79 (43), 68 (51) and 39 (100).

1-((2E,4E)-2,4-hexadien-1-yl) 4-methyl (2Z)-2-methyl-2-butenedioate (405)

To a stirred solution of 1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-2-methyl-2-butenedioate (38d) (30.0mg, 0.143mmol) in dichloromethane (10mL) at RT was added dropwise an ethereal solution of diazomethane\(^1\) (Section 6.6.3). On completion of the addition the solvent was evaporated to give the crude product (32.0mg) as a yellow oil. Chromatography of this material on silica (2g) with hexane:ethyl acetate (8:1) gave the title compound (405) (25.7mg, 0.115mmol, 81%) as a colourless oil: \( R_t = 0.40 \) (hexane:ethyl acetate (8:1)); (Found: \( M^+ \), 224.1044. \( \text{C}_{12}\text{H}_{16}\text{O}_4 \) requires \( M \), 224.1049); \( \nu_{\text{max}} \) (film) 3024, 2952, 2853, 1731, 1656, 1446, 1352 and 1268 cm\(^{-1}\); \( \delta_{\text{H}} \) (270MHz, CDCl\(_3\)) 1.77 (3H, d, \( J 6.8\text{Hz}, \text{C6-H} \)), 2.06 (3H, d, \( J 1.5\text{Hz}, -\text{CH}=\text{CHH}_3 \)), 3.71 (3H, s, -\text{CO}_2\text{CH}_3), 4.72 (2H, d, \( J 6.8\text{Hz}, \text{C1-H} \)), 5.67 (1H, dt, \( J 15.2, 6.8\text{Hz}, \text{C2-H} \)), 5.77 (1H, dq, \( J 15.2, 6.8\text{Hz}, \text{C5-H} \)), 5.85 (1H, q, \( J 1.5\text{Hz}, -\text{CH}=\text{CHH}_3 \)), 6.00-6.13 (1H, m, C4-H) and 6.29 (1H, dd, \( J 10.5, 15.2\text{Hz}, \text{C3-H} \)); \( \delta_{\text{C}} \) (68.1MHz, CDCl\(_3\)) 18.2, 20.5, 51.8, 66.0, 120.6, 122.9, 130.2, 131.4, 135.3, 145.2, 165.1 and 168.3; \( m/z \) (Cl/NH\(_3\), 40eV) 224 (2%), 128 (100), 113 (18), 97 (37) and 81 (35).
1-((2E,4E)-2,4-hexadien-1-yl) 4-methyl (2Z)-3-methyl-2-butenedioate (38a)

To a stirred solution of 1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (38c) (85.0mg, 0.400mmol) in dichloromethane (10mL) at RT was added dropwise an ethereal solution of diazomethane\(^{173}\) (Section 6.6.3). On completion of the addition the solvent was evaporated to give the crude product (88.1mg) as a yellow oil. Chromatography of this material on silica (4g) with hexane:ethyl acetate (10:1 then 5:1) gave the title compound (38a) (76.4mg, 0.341mmol, 85%) as a colourless oil: \(R_f = 0.21\) (hexane:ethyl acetate (10:1)); (Found: \(M^+\), 224.1042. \(C_{12}H_{16}O_4\) requires \(M^+\), 224.1049); \(\nu_{\text{max}}\) (film) 3023, 2952, 2879, 2853, 1735, 1724, 1654, 1446, 1354 and 1269cm\(^{-1}\); \(\delta_6\) (270MHz, CDCl\(_3\)) 1.74 (3H, d, \(J = 6.8\)Hz, C\(_6\)-lf), 3.78 (3H, s, \(-C_02CH_3\)), 4.59 (2H, d, \(J = 6.8\)Hz, Cl-lf), 5.59 OH, dt, \(J = 15.2, 6.8\)Hz, C2-lf), 5.73 (1H, dq, \(J = 14.9, 6.8\)Hz, C5-H), 5.84 (1H, q, \(J = 1.5\)Hz, -CH=CCH\(_3\)-), 5.96-6.09 (1H, m, C4-H) and 6.23 (1H, dd, \(J = 10.8, 15.2\)Hz, C3-H); \(\delta_c\) (68.1MHz, CDCl\(_3\)) 18.1, 20.5, 52.3, 65.2, 120.7, 123.0, 130.2, 131.2, 135.0, 145.2, 164.3 and 169.0; \(m/z\) (EI, 70eV) 224 (3%), 128 (100), 113 (16), 97 (37), 79 (19) and 38 (16).

6.4.2 Preparation of endo adducts

\((2E,4E)-1-(1-tert-butyl-1,1-dimethylsilyloxy-2,4-hexadiene \ (407)\)

To a stirred solution of \((2E,4E)-2,4-hexadien-1-ol\) (301) (0.512g, 5.22mmol) in dichloromethane (5mL) at RT under argon was added imidazole (0.710g, 10.4mmol, 2.0eq), tert-butylidimethylsilyl chloride (1.38g, 7.80mmol, 1.5eq) and N,N-dimethylaminopyridine (0.128g, 1.04mmol, 0.2eq).\(^{176}\) Stirring was continued for 30min then the reaction mixture was diluted with hexane (30mL) and filtered through a
silica plug (2cm diameter x 4cm deep) which was eluted with hexane:ethyl acetate (20:1 then 10:1 then 5:1) and evaporated to give the title compound (407) (1.07g, 5.04mmol, 97%) as a colourless oil: $R_f = 0.95$ (hexane:ethyl acetate (5:1)); (Found: $M^+$-H, 211.1516 C_{12}H_{23}OSi requires $M^+$, 211.1518); $v_{\text{max}}$ (film) 3345, 2956, 2930, 2884, 2857, 1654, 1472, 1462, 1379, 1362 and 1255cm$^{-1}$; $\delta$ (270MHz, CDCl$_3$) 0.080 (6H, s, -Si(CH$_3$)$_3$), 0.919 (9H, s, -C(CH$_3$)$_3$), 1.76 (3H, d, $J$ 6.6Hz, C6-H), 4.20 (2H, d, $J$ 5.5Hz, Cl-H), 5.57-5.77 (2H, m, C2-H and C5-H) and 6.00-6.25 (2H, m, C3-H and C4-H); $\delta$ (68.1MHz, CDCl$_3$) -5.01, 18.2, 18.5, 26.1, 63.7, 128.8, 129.7, 130.1 and 130.9; $m/z$ (El, 40eV) 211 (12%), 169 (12), 89 (10), 75 (100) and 41 (10).

rel-(1S,2S,5R,6R)-2-(1-tert-butyl-1,1-dimethylsilyl)oxymethyl-5,6-dimethyl-1,2,5,6-tetrahydropthalic anhydride (408) and rel-(1S,2S,5R,6R)-2-(1-tert-butyl-1,1-dimethylsilyl)oxymethyl-1,5-dimethyl-1,2,5,6-tetrahydropthalic anhydride (409)

To a stirred solution of (2E,4E)-1-(1-tert-butyl-1,1-dimethylsilyl)oxy-2,4-hexadiene (407) (0.429g, 2.02mmol) in toluene (4.0mL) was added citraconic anhydride (181µL, 2.02mmol, 1eq) and 2,6-di-tert-butyl-4-methylphenol (89.0mg, 0.40mmol, 0.2eq) at RT under argon. The solution was warmed to reflux and heating continued for 36h. Evaporation of the solvent gave the crude product (700mg) as a yellow oil. Chromatography of this material on silica (35g) with hexane:diethyl ether (20:1 then 10:1), hexane:ethyl acetate (20:1 then 10:1) then ethyl acetate gave recovered starting material (407) (86.4mg, 0.406mmol, 20%) followed by the title compounds (408 and 409) (0.485g, 1.49mmol, 93% (at 80% conversion), 408:409 (76:24)), vide infra.
**rel-** (1S,2S,5R,6R)-2-(1-tert-butyl-1,1-dimethylsilyl)oxymethyl-5,6-dimethyl-1,2,5,6-tetrahydrophthalic anhydride (408)

![Structure of 408](image)

Crystalline solid; mp 79-80°C (from tert-butyl methyl ether); R_t = 0.50 (hexane:ethyl acetate (10:1)); (Found: M^+-CH_3, 309.1532. C_{16}H_{25}O_4Si requires M, 309.1522); v_{max} (KBr disc) 3039, 2982, 2956, 2933, 2881, 2857, 1839, 1777, 1474, 1463 and 1103 cm^{-1}; δ_{H} (270MHz, CDCl_3) 0.102 (6H, s, -Si(CH_3)_2), 0.907 (9H, s, -C(CH_3)_3), 1.29 (3H, d, J 7.5Hz, C5-CH_3), 1.48 (3H, s, C6-CH_3), 2.05-2.19 (1H, m, C5-H), 2.42-2.56 (1H, m, C2-H), 3.14 (1H, d, J 4.8Hz, C1-H), 3.99 (1H, dd, J 7.3, 9.9Hz, -CHH'-OTBS), 4.17 (1H, dd, J 9.0, 9.9Hz, -CHH'-OTBS), 5.74 (1H, dt, J 9.2, 2.9Hz, C4-H) and 5.85 (1H, dt, J 9.2, 3.1Hz, C3-H); δ_{C} (68.1MHz, CDCl_3) -5.27, -5.25, 15.4, 18.3, 22.1, 25.9, 38.2, 38.7, 49.9, 50.6, 62.2, 131.0, 134.4, 170.7 and 174.0; m/z (EI, 40eV) 309 (6%), 267 (100), 209 (45), 195 (32), 89 (92) and 75 (53).

**rel-** (1S,2S,5R,6R)-2-(1-tert-butyl-1,1-dimethylsilyl)oxymethyl-1,5-dimethyl-1,2,5,6-tetrahydrophthalic anhydride (409)

![Structure of 409](image)

Colourless oil; R_t = 0.36 (hexane:ethyl acetate (10:1)); (Found: M^+-CH_3, 309.1511. C_{16}H_{25}O_4Si requires M, 309.1522); v_{max} (film) 2955, 2950, 2883, 2857, 1850, 1780, 1472, 1462 and 1104 cm^{-1}; δ_{H} (270MHz, CDCl_3) 0.071 (6H, s, -Si(CH_3)_2), 0.885 (9H, s, -C(CH_3)_3), 1.49 (3H, d, J 7.3Hz, C5-CH_3), 1.52 (3H, s, C1-CH_3), 2.08-2.17 (1H, m, C5-H), 2.38-2.51 (1H, m, C2-H), 2.86 (1H, d, J 5.3Hz, C1-H), 3.77 (1H, dd, J 7.3, 10.1Hz, -CHH'-OTBS), 3.98 (1H, dd, J 4.6, 10.1Hz, -CHH'-OTBS) and 5.81-5.92 (2H, m, C3-H and C4-H); δ_{C} (68.1MHz, CDCl_3) -5.42, 16.9, 18.3, 23.0, 25.9,
To a stirred solution of rel-(1S,2S,5R,6R)-2-(1-tert-butyl-1,1-dimethylsilyloxy)methyl-5,6-dimethyl-1,2,5,6-tetrahydrophthalic anhydride (408) (218mg, 0.672mmol) in dichloromethane (2.5mL) at 0°C under argon was added trifluoroacetic acid (514µL, 6.72mmol, 10eq). On completion of the addition the solution was warmed to RT and stirring was continued for 2h. Evaporation of the solvent gave the crude product (168mg) as a yellow oil. Chromatography of this material on silica (10g) with hexane:ethyl acetate:methanol:acetic acid (50:10:0.3:0.3, 60:30:0.45:0.45 then 50:50:0:0.5:0.5) gave the title compound (40c) (132mg, 0.628mmol, 94%) as a crystalline solid: mp 171-174°C (from tert-butyl methyl ether) [lit.98 168-170°C]; Rf = 0.25 (hexane:ethyl acetate:methanol:acetic acid (60:30:0.45:0.45)); (Found: M+, 210.0896. C11H14O4 requires M, 210.0892); v_max (KBr disc) 3393, 3018, 2979, 2935, 2891, 1766, 1758, 1707, 1694 and 1452 cm⁻¹; δ_H (270MHz, CDCl₃/CD₃OD) 1.15 (3H, d, J 7.3Hz, C5-CH₃), 1.44 (3H, s, C4-CH₃), 2.23-2.37 (1H, m, C5-H), 2.97 (1H, d, J 9.4Hz, C3a-H), 3.07-3.20 (1H, m, C7a-H), 4.10 (1H, dd, J 4.2, 8.6Hz, C1-H), 4.36 (1H, dd, J 7.7, 8.6Hz, C1-H'), 5.48 (1H, dt, J 10.1, 2.3Hz, C7-H) and 5.72 (1H, ddd, J 2.4, 4.2, 10.1Hz, C6-H); δ_C (68.1MHz, CDCl₃/CD₃OD) 17.4, 26.4, 35.2, 37.6, 44.3, 45.6, 71.0, 123.1, 134.1, 176.6 and 179.2; m/z (EI, 40eV) 210 (20%), 192 (26), 164 (48), 121 (51), 107 (100), 97 (64), 91 (68) and 80 (72).
rel-(3aS, 4R, 5R, 7aS)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylic acid (40d)

To a stirred solution of rel-(1S,2S,5R,6R)-2-(1-tert-butyl-1,1-dimethylsilyloxymethyl)-1,5-dimethyl-1,2,5,6-tetrahydrophthalic anhydride (409) (21.6mg, 0.0666mmol) in dichloromethane (2.5mL) at 0°C under argon was added trifluoroacetic acid (51.0µL, 0.666mmol, 10eq). On completion of the addition the solution was warmed to RT and stirring was continued for 2h. Evaporation of the solvent gave the crude product (16.7mg) as a yellow oil. Chromatography of this material on silica (3g) with hexane:ethyl acetate:methanol:acetic acid (50:10:0.3:0.3, 60:30:0.45:0.45 then 50:50:0.5:0.5) gave the title compound (40d) (10.6mg, 0.0504mmol, 76%) as a crystalline solid: mp 112-114°C (from tert-butyl methyl ether); \( R_f = 0.54 \) (hexane:ethyl acetate:methanol:acetic acid (60:30:0.45:0.45)); Found: \( M^+ \), 210.0892. \( C_{11}H_{14}O_4 \) requires \( M \), 210.0892; \( \nu_{\text{max}} \) (KBr disc) 3361, 3024, 2972, 2884, 1764 and 1707cm\(^{-1}\); \( \delta_H \) (270MHz, CDCl\(_3\)) 1.16 (3H, d, J7.5Hz, C3a-CH\(_3\)), 1.50 (3H, s, C3a-CH\(_3\)), 2.70-2.84 (2H, m, C5-H and C7a-H), 2.98 (1H, d, J 6.2Hz, C4-H), 4.20 (1H, dd, J 4.6, 8.8Hz, C1-H), 4.56 (1H, dd, J 7.9, 8.8Hz, C1-H'), 5.59 (1H, dt, J 10.1, 2.4Hz, C6-H) and 5.74-5.88 (1H, m, C7-H); \( \delta_C \) (68.1MHz, CDCl\(_3\)) 17.5, 24.2, 30.4, 42.6, 43.0, 51.7, 71.7, 123.9, 133.0, 173.6 and 183.5; \( m/z \) (EI, 40eV) 210 (14%), 192 (12), 164 (25), 121 (67), 107 (100), 98 (35) and 91 (59).

rel-methyl (3aS, 4R, 5R, 7aS)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (40a)
To a stirred solution of rel-(3aS, 4R, 5R, 7aS)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylic acid (40c) (57.0 mg, 0.271 mmol) in diethyl ether (10 mL) at -65° was added dropwise an ethereal solution of diazomethane\textsuperscript{173} (Section \textbf{6.6.3}). On completion of the addition the solvent was evaporated to give the crude product (62.0 mg) as a yellow oil. Chromatography of this material on silica (4 g) with hexane:ethyl acetate (10:1, 5:1 then 2:1) gave the title compound (40a) (57.8 mg, 0.258 mmol, 95%) as a colourless oil: $\eta = 0.13$ (hexane:ethyl acetate (5:1)); (Found: $M^+$, 224.1050. $C_{12}H_{16}O_4$ requires $M^*$, 224.1049); $\nu_{max}$ (film) 2977, 2951, 2913, 2828, 1777, 1769, 1738, 1731, 1455 and 1377 cm$^{-1}$; $\delta$ (270 MHz, CDCl$_3$) 1.14 (3H, d, $J$ 7.5 Hz, C5-H$_3$), 1.44 (3H, s, C4-CH$_3$), 2.27-2.41 (1H, m, CS-H), 3.00 (1H, d, J 9.4 Hz, C3a-H), 3.09-3.22 (1H, m, C7a-H), 3.48 (1H, dd, J 7.7, 8.6 Hz, C1-H$^\prime$), 3.51 (1H, dt, J 10.1, 2.2 Hz, C7-H) and 5.72 (1H, ddd, J 2.4, 4.2, 10.1 Hz, C6-H); $\delta_C$ (68.1 MHz, CDCl$_3$) 17.2, 25.8, 35.0, 37.6, 44.4, 45.5, 51.7, 70.7, 123.1, 133.7, 174.4 and 176.3; m/z (EI, 70 eV) 224 (36%), 192 (29), 164 (49), 128 (54), 107 (69), 91 (47) and 80 (100).

\textit{rel}-methyl (3aS, 4R, 5R, 7aS)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (410)

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{410.png}
\caption{Structure of 410.}
\end{figure}

To a stirred solution of rel-(3aS, 4R, 5R, 7aS)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylic acid (40d) (23.2 mg, 0.110 mmol) in diethyl ether (10 mL) at -65° was added dropwise an ethereal solution of diazomethane\textsuperscript{173} (Section \textbf{6.6.3}). On completion of the addition the solvent was evaporated to give the crude product (25.0 mg) as a yellow oil. Chromatography of this material on silica (2 g) with hexane:ethyl acetate (10:1, 5:1 then 2:1) gave the title compound (410) (23.5 mg, 0.105 mmol, 95%) as a colourless oil: $\eta = 0.10$ (hexane:ethyl acetate (5:1)); (Found: $M^*$, 224.1049. $C_{12}H_{16}O_4$ requires $M^*$, 224.1049); $\nu_{max}$ (film) 3025, 2971, 1878, 1768, 1731 and 1454 cm$^{-1}$; $\delta$ (270 MHz, CDCl$_3$) 1.14 (3H, d, $J$ 7.5 Hz, C5-H$_3$), 1.41 (3H, s, C3a-CH$_3$), 2.59-2.72 (1H, m, C5-H), 2.73-2.85 (1H, m, C7a-H), 2.81 (1H, d, J 5.7 Hz, C4-H), 3.63 (3H, s, -CO$_2$CH$_3$), 4.17 (1H, dd, J 8.1, 9.9 Hz, C1-H), 4.56 (1H, dd, J 7.9, 9.9 Hz, C1-H$^\prime$), 5.57 (1H, dt, J 9.9, 2.0 Hz, C6-H) and 5.70 (1H, dt, J 9.9, 3.1 Hz, C7-H); $\delta_C$ (68.1 MHz, CDCl$_3$) 18.5, 26.5, 28.2, 41.2, 43.0, 50.3, 51.6, 69.9,
123.9, 129.9, 172.3 and 180.5; \textit{m/z} (EI, 70eV) 224 (26%), 193 (25), 164 (59), 120 (49), 107 (100) and 91 (42).

\subsection*{6.4.3 Preparation of \textit{exo} adducts}

\begin{center}
1-((2E,4E)-2,4-hexadien-1-yl) 4-methoxymethyl (2Z)-3-methyl-2-butenedioate (411)
\end{center}

To a stirred solution of 1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (38c) (57.4mg, 0.273mmol) in dichloromethane (1mL) at RT under argon was added triethylamine (189µL, 1.37mmol, 5eq) and chloromethyl methyl ether (51.9µL, 0.683mmol, 2.5eq). Stirring was continued for 10min then the reaction mixture was diluted with dichloromethane (10mL) and partitioned against saturated aqueous sodium bicarbonate (10mL), water (10mL), 10% aqueous hydrochloric acid (10mL), water (10mL) and brine (10mL) then dried, filtered and evaporated to give the crude product (61.9mg) as a yellow oil. Chromatography of this material on silica (3g) with hexane:ethyl acetate (10:1, 5:1 then 2:1) gave the \textbf{title compound} (411) (40.8mg, 0.160mmol, 59%) as a colourless oil: \(R_{f} = 0.43\) (hexaneethyl acetate (5:1)); (Found: \(M^+\), 254.1160. \(C_{13}H_{18}O_5\) requires \(M\), 254.1154); \(\nu\)max (film) 3000, 2956, 2852, 1724, 1654, 1445, 1350 and 1266cm\(^{-1}\); \(\delta_{\text{H}}\) (270MHz, CDCl\(_3\)) 1.76 (3H, d, \(J\ 6.8\text{Hz}, \text{C}6\text{-H}\)), 2.08 (3H, d, \(J\ 1.8\text{Hz}, \text{-CH=CCH}_3\text{-}\)), 3.51 (3H, s, \(-\text{CH}_2\text{OCH}_3\)), 4.62 (2H, d, \(J\ 6.8\text{Hz, C1-H}\)), 5.36 (2H, s, \(-\text{CH}_2\text{OCH}_3\)), 5.61 (1H, dt, \(J\ 14.9, 6.8\text{Hz, C2-H}\)), 5.75 (1H, dq, \(J\ 14.9, 6.8\text{Hz, C5-H}\)), 5.88 (1H, q, \(J\ 1.8\text{Hz, -CH=CCH}_3\text{-}\)), 5.97-6.10 (1H, m, \(C4\text{-H}\)) and (1H, dd, \(J\ 10.3, 14.9\text{Hz, C3-H}\)); \(\delta_{\text{C}}\) (68.1MHz, CDCl\(_3\)) 18.2, 20.5, 57.9, 65.3, 91.6, 120.8, 123.0, 130.2, 131.3, 135.1, 144.9, 164.4 and 168.2; \textit{m/z} (EI, 40eV) 254 (1%), 158 (9), 141 (18), 113 (18), 97 (56), 79 (13) and 45 (100).
rel-methoxymethyl (3aR, 4S, 5R, 7aS)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (412) and rel-methoxymethyl (3aS, 4R, 5R, 7aS)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (413)

To a stirred solution of 1-((2E,4E)-2,4-hexadien-1-yl) 4-methoxymethyl (2Z)-3-methyl-2-butenedioate (411) (35.4mg, 0.139mmol) in toluene (28.0mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (6.1mg, 0.014mmol, 0.1eq). The solution was warmed to reflux and heating was continued for 19h. Evaporation of the solvent gave the crude product (42.0mg) as a yellow oil. Chromatography of this material on silica (3g) with hexane:ethyl acetate (10:1, 5:1 then 2:1) gave the title compounds (412 and 413) (34.0mg, 0.134mmol, 96%, 412:413 (88:12)), vide infra.

rel-methoxymethyl (3aR, 4S, 5R, 7aS)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (412)

White needles; mp 89.4-90.5°C (from tert-butyl methyl ether); R_i = 0.44 (hexane:ethyl acetate (5:1)); (Found: M'-H_2O, 236.1053. C_{13}H_{16}O_4 requires M, 236.1049); ν_{max} (KBr disc) 3023, 2974, 2909, 2837, 1774, 1742, 1477 and 1451cm⁻¹; δ_1H (270MHz, CDCl₃) 1.04 (3H, d, J 7.5Hz, C5-CH₃), 1.58 (3H, s, C4-CH₃), 2.17 (1H, d, J 13.6Hz, C3a-H), 2.96-3.16 (2H, m, C5-H and C7a-H), 3.45 (2H, s, -CH₂OCH₃), 3.80 (1H, dd, J 7.9, 11.4Hz, C1-H), 4.43 (1H, dd, J 6.8, 7.9Hz, C1-H'), 5.26 (3H, s, -CH₂OCH₃) and 5.65-5.75 (2H, m, C6-H and C7-H); δ_C (68.1MHz, CDCl₃) 16.9, 19.6, 37.8, 38.7,
44.6, 46.4, 57.8, 69.8, 90.8, 121.9, 136.1, 173.9 and 174.4; m/z (EI, 70eV) 236 (0.2%), 164 (15), 133 (11), 119 (19), 105 (14), 91 (10) and 45 (100).

rel-methoxymethyl (3αS, 4R, 5R, 7αS)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (413)

\[ \text{MOM}_{2}O\text{C} \]

Colourless oil; \( R_f = 0.34 \) (hexane:ethyl acetate (5:1)); (Found: \( M^+ \), 254.1148. \( C_{13}H_{18}O_{5} \) requires \( M \), 254.1154); \( \nu_{\text{max}} \) (film) 2975, 2916, 2850, 1770, 1773, 1738, 1732, 1455 and 1375cm\(^{-1}\); \( \delta_{\text{H}} \) (270MHz, CDCl\(_3\)) 1.21 (3H, d, \( J 7.5\text{Hz} \), C5-CH\(_3\)), 1.51 (3H, s, C4-CH\(_3\)), 2.34-2.47 (1H, m, C5-H), 3.08 (1H, d, \( J 9.2\text{Hz} \), C3a-H), 3.13-3.25 (1H, m, C7a-H), 3.50 (3H, s, -CH\(_2\)OCH\(_3\)), 4.16 (1H, dd, \( J 4.0, 8.8\text{Hz} \), C1-H), 4.41 (1H, dd, \( J 7.5, 8.8\text{Hz} \), C1-H\(^*\)), 5.31 (1H, B of AB, \( J_{AB} 6.2\text{Hz} \), -CHH'OCH\(_3\)), 5.34 (1H, A of AB, \( J_{AB} 6.2\text{Hz} \), -CHH'OCH\(_3\)), 5.55 (1H, dt, \( J 10.1, 2.2\text{Hz} \), C6-H) and (1H, ddd, \( J 2.4, 4.2, 10.1\text{Hz} \), C7-H); \( \delta_{\text{C}} \) (68.1MHz, CDCl\(_3\)) 17.3, 26.1, 35.1, 37.6, 44.4, 44.7, 58.0, 70.8, 91.1, 123.2, 134.0, 173.7 and 176.3; m/z (EI, 80eV) 254 (1%), 165 (9), 121 (15), 105 (17), 91 (15) and 45 (100).

rel-(3αR, 4S, 5R, 7αS)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylic acid (39c)

\[ \text{HO}_{2}\text{C} \]

To a stirred solution of rel-methoxymethyl (3αR, 4S, 5R, 7αS)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (412) (17.5mg, 0.0688mmol) in dichloromethane (3.0mL) at RT under argon was added trifluoroacetic acid (54.1μL, 0.688mmol, 10eq). Stirring was continued for 18h then the solvent was evaporated to give the crude product (20.0mg) as a yellow oil. Chromatography of this
material on silica (2g) with hexane:ethyl acetate (2:1) then hexane:ethyl acetate:methanol:acetic acid (60:30:0.45:0.45) gave the title compound (39c) (13.9mg, 0.0661mmol, 96%) as a crystalline solid: mp 138-140°C (from tert-butyl methyl ether); Rf = 0.32 (hexane:ethyl acetate:methanol:acetic acid (60:30:0.45:0.45)); (Found: M+OH, 193.0865. C11H13O3 requires M, 193.0865); νmax (KBr disc) 3398, 2980, 2965, 2918, 1790, 1692 and 1467cm⁻¹; δH (270MHz, CDCl3) 1.05 (3H, d, J 7.3Hz, C5-CH3), 1.59 (3H, s, C4-CH3), 2.14 (1H, d, J 13.4Hz, C3a-H), 2.91-3.04 (1H, m, C5-H), 3.14-3.30 (1H, m, C7a-H), 3.81 (1H, dd, J 7.9, 11.4Hz, C1-H), 4.45 (1H, dd, J 7.0, 7.9Hz, C1-H'), 5.65-5.75 (2H, m, C6-H and C7-H); δc (68.1MHz, CDCl3) 17.0, 20.0, 37.9, 38.4, 44.6, 45.9, 69.7, 122.2, 135.9, 174.0 and 181.3; m/z (EI, 40eV) 193 (0.5%), 164 (47), 121 (100), 105 (67), 91 (36), 79 (21) and 41 (18).

rel-methyl (3aR, 4S, 5R, 7aS)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofuran-3-carboxylate (39a)

![39a]

To a stirred solution of rel-(3aR, 4S, 5R, 7aS)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofuran-3-carboxylic acid (39c) (9.2mg, 0.044mmol) in diethyl ether (5mL) at -65°C was added dropwise an ethereal solution of diazomethane (Section 6.6.3). On completion of the addition the solvent was evaporated to give the crude product (9.5mg) as a yellow oil. Chromatography of this material on silica (2g) with hexane:ethyl acetate (5:1 then 2:1) gave the title compound (39a) (6.2mg, 0.028mmol, 64%) as a crystalline solid; mp 108-109°C (from tert-butyl methyl ether) (lit.98 94-96°C); Rf = 0.55 (hexane:ethyl acetate (2:1)); (Found: M+, 224.1058. C12H16O4 requires M, 224.1049); νmax (KBr disc) 3025, 2995, 2916, 2849, 1786, 1730, 1465 and 1369cm⁻¹; δH (270MHz, CDCl3) 1.03 (3H, d, J 7.5Hz, C5-CH3), 1.54 (3H, s, C4-CH3), 2.13 (1H, d, J 13.6Hz, C3a-H), 2.95-3.11 (2H, m, C5-H and C7a-H), 3.71 (3H, s, -CO2CH3), 3.79 (1H, dd, J 7.9, 11.4Hz, C1-H), 4.43 (1H, dd, J 7.3, 7.9Hz, C1-H') and 5.62-5.75 (2H, m, C6-H and C7-H); δc (68.1MHz, CDCl3) 16.9, 19.8, 38.0, 38.7, 44.9, 46.1, 52.3, 69.6, 122.0, 136.1, 173.9 and 175.4; m/z (EI, 70eV) 224 (2%), 193 (3), 178 (7), 164 (58), 119 (100), 105 (68), 91 (43), 79 (21) and 41 (20).
1-((2E,4E)-2,4-hexadien-1-yl) 4-methoxymethyl (2Z)-2-methyl-2-butenedioate (414)

To a stirred solution of 1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-2-methyl-2-butenedioate (38d) (34.8mg, 0.167mmol) in dichloromethane (1mL) at RT under argon was added triethylamine (57.4µL, 0.414mmol, 2.5eq) and chloromethyl methyl ether (15.1µL, 0.199mmol, 1.2eq). Stirring was continued for 5min then the reaction mixture was diluted with dichloromethane (10mL) and partitioned against saturated aqueous sodium bicarbonate (10mL), water (10mL), 10% aqueous hydrochloric acid (10mL), water (10mL) and brine (10mL) then dried, filtered and evaporated to give the crude product (46.8mg) as a yellow oil. Chromatography of this material on silica (3g) with hexane:ethyl acetate (10:1 then 5:1) gave the title compound (414) (36.6mg, 0.144mmol, 86%) as a colourless oil: Rf = 0.43 (hexane:ethyl acetate (5:1)); (Found: M+, 254.1159. C15H18O5 requires M+, 254.1154); νmax (film) 3001, 2957, 2852, 1734, 1654, 1446, 1350 and 1265cm⁻¹; δH (270MHz, CDCl₃) 1.76 (3H, d, J 6.8Hz, C6-H), 2.07 (3H, d, J 1.5Hz, -CH==CCH3-), 3.44 (3H, s, -CH₂OCH₃), 3.72 (2H, d, J 6.8Hz, C1-H), 5.26 (2H, s, -CH₂OCH₃), 5.66 (1H, dt, J 15.2, 6.8Hz, C2-H), 5.77 (1H, dq, J 14.9, 6.8Hz, C5-H), 5.87 (1H, q, J 1.5Hz, -CH=CCH3-), 5.99-6.12 (1H, m, C4-H) and 6.28 (1H, dd, J 10.3, 15.2Hz, C3-H); δC (68.1MHz, CDCl₃) 18.2, 20.6, 57.7, 66.0, 90.8, 120.3, 122.9, 130.2, 131.4, 135.4, 146.2, 164.0 and 168.3; m/z (EI, 40eV) 254 (1%), 158 (7), 141 (12), 113 (16), 97 (63), 81 (45) and 45 (100).
To a stirred solution of 1-((2E,4E)-2,4-hexadien-1-yl) 4-methoxymethyl (2Z)-2-methyl-2-butenedioate (414) (34.9mg, 0.137mmol) in toluene (28.0mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (6.0mg, 0.027mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 22h. Evaporation of the solvent gave the crude product (36.6mg) as a yellow oil. Chromatography of this material on silica (3g) with hexane:ethyl acetate (5:1 then 2:1) gave the title compounds (415 and 416) (34.5mg, 0.136mmol, 99%, 415:416 (93:7), vide infra. (Adduct 416 was unable to be isolated and characterised. The structure of this compound is speculative and based on limited proton NMR analysis of mixtures only.)

\[ \text{rel-methoxymethyl} \ (3aR, \ 4S, \ 5R, \ 7aS)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate \ (415) \]

Colourless oil; \( R_f = 0.18 \) (hexane:ethyl acetate (5:1)); (Found: \( M^+ \), 254.1141. \( C_{13}H_{15}O_5 \) requires \( M \), 254.1154); \( \nu_{\text{max}} \) (film) 2969, 2935, 2878, 1778, 1731 and 1454cm\(^{-1}\); \( \delta_H \) (270MHz, CDCl\(_3\)) 1.07 (3H, s, C3a-CH\(_3\)), 1.32 (3H, d, J 7.5Hz, C5-CH\(_3\)), 2.48 (1H, d, J 3.3Hz, C4-H), 2.49-2.62 (1H, m, C5-H), 3.48 (3H, s, -CH\(_3\)OCH\(_3\)), 3.51-3.63 (1H, m, C7a-H), 4.10 (1H, dd, J 8.3, 12.1Hz, C1-H), 4.46-4.54 (1H, m, C1-H’), 5.17 (1H, B of AB, J\(_{AB}\) 6.0Hz, -CHH’OCH3), 5.35 (1H, A of
To a stirred solution of rel-methoxymethyl (3aR, 4S, 5R, 7aS)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate \((415)\) (29.3mg, 0.115mmol) in dichloromethane (5.0mL) at RT under argon was added trifluoroacetic acid (90.6µL, 1.15mmol, 10eq). Stirring was continued for 6h then the solvent was evaporated to give the crude product (35.0mg) as a yellow oil. Chromatography of this material on silica (3g) with hexane:ethyl acetate (10:1, 5:1 then 2:1) then hexane:ethyl acetate:methanol:acetic acid (50:50:0.5:0.5) gave the title compound \((39d)\) (21.4mg, 0.102mmol, 89%) as a crystalline solid: mp 157-160°C (from tert-butyl methyl ether); Rf = 0.19 (hexane:ethyl acetate (2:1)); (Found: \(M^+\)H, 211.0978. \(C_{11}H_{15}O_4\) requires \(M\), 211.0970); \(\nu_{\text{max}}\) (KBr disc) 2975, 2937, 2913, 2880, 1773, 1767, 1704, 1698 and 1435cm\(^{-1}\); \(\delta_H\) (270MHz, CDCl\(_3\)) 1.06 (3H, s, C3a-CH\(_3\)), 1.33 (3H, d, \(J\,7.7\text{Hz},\ C5-CH\(_3\)) ), 2.48 (1H, d, \(J\,3.1\text{Hz},\ C4-H\)), 2.55-2.70 (1H, m, C5-H), 3.46-3.59 (1H, m, C7a-H), 4.09 (1H, dd, \(J\,8.3, 11.9\text{Hz},\ C1-H\)), 4.47-4.54 (1H, m, C1-H\('\)), 5.68 (1H, ddd, \(J\,2.4, 3.1, 9.9\text{Hz},\ C7-H\)) and 5.80 (1H, dt, \(J\,9.9, 3.1\text{Hz},\ C6-H\)); \(\delta_C\) (68.1MHz, CDCl\(_3\)) 17.1, 23.3, 34.6, 39.0, 43.7, 50.8, 68.7, 122.1, 134.1, 178.2 and 178.9; \(m/z\) (EI, 70eV) 211(1%), 164 (17), 121 (100), 105 (77), 91 (42), 77 (19) and 41 (18).
rel-methyl (3aR, 4S, 5R, 7aS)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (417)

To a stirred solution of rel-(3aR, 4S, 5R, 7aS)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylic acid (39d) (8.9mg, 0.042mmol) in diethyl ether (5mL) at -65°C was added dropwise an ethereal solution of diazomethane\textsuperscript{173} (Section 6.6.3). On completion of the addition the solvent was evaporated to give the crude product (9.7mg) as a yellow oil. Chromatography of this material on silica (2g) with hexane:ethyl acetate (5:1 then 2:1) gave the title compound (417) (9.4mg, 0.042mmol, 100%) as a colourless oil: $\nu_{\text{max}}$ (film) 3030, 2967, 2919, 2876, 2849, 1779, 1731 and 1435cm$^{-1}$; $\delta_{\text{H}}$ (270MHz, CDCl$_3$) 1.06 (3H, s, C3a-CH$_3$), 1.29 (3H, d, $J$ 7.5Hz, C5-CH$_3$), 1.25 (1H, d, $J$ 3.3Hz, C4-H), 2.47-0.25 (1H, m, C5-H), 3.52-3.65 (1H, m, C7a-H), 3.71 (3H, s, -CO$_2$CH$_3$), 4.09 (1H, dd, $J$ 8.3, 12.1Hz, C1-H), 4.46-4.54 (1H, m, C1'-H'), 5.67 (1H, dt, $J$ 9.7, 2.9Hz, C6-H) and 5.80 (1H, dt, $J$ 9.7, 2.9Hz, C7-H); $\delta_{\text{C}}$ (68.1MHz, CDCl$_3$) 17.3, 23.0, 34.5, 39.3, 44.0, 51.2, 52.0, 68.5, 122.2, 134.1, 174.0 and 178.0; $m/z$ (EI, 70eV) 224 (4%), 193 (12), 164 (22), 121 (100), 105 (51) and 91 (30).

6.4.3 Attempted DA reactions

Attempted ETDA reaction of 1-((2S,3S,4E,6E)-1,2-0-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2Z)-2-methyl-2-butenedioate (401)
To a stirred solution of 1-((2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2Z)-2-methyl-2-butenedioate (401) (37.0 mg, 0.0840 mmol) in toluene (16.8 mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (3.7 mg, 0.017 mmol, 0.2 eq). The solution was warmed to reflux and heating was continued for 12 h. Evaporation of the solvent gave the crude product (40.7 mg) as a yellow oil. Chromatography of this material on silica (5 g) with hexane:ethyl acetate (5:1) gave (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)-oxy-4,6-octadien-1,2,8-triol (228) (16.7 mg, 0.0508 mmol, 61%), vide supra.

Attempted ETDA reaction of 1-((2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (402)

To a stirred solution of 1-((2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (402) (9.4 mg, 0.021 mmol) in toluene (4.2 mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (0.9 mg, 0.004 mmol, 0.2 eq). The solution was warmed to reflux and heating was continued for 24 h. Evaporation of the solvent gave the crude product (10.4 mg) as a yellow oil. Chromatography of this material on silica (2 g) with hexane:ethyl acetate (2:1) gave (2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)-oxy-4,6-octadien-1,2,8-triol (228) (3.9 mg, 0.012 mmol, 57%), vide supra.
Attempted ETDA reaction of 1-((2S,4E,6E)-1,2-O-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2Z)-2-methyl-2-butenedioate (403)

To a stirred solution of 1-((2S,4E,6E)-1,2-O-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2Z)-2-methyl-2-butenedioate (403) (14.8mg, 0.0477mmol) in toluene (9.5mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (2.1mg, 0.0095mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 12h. Evaporation of the solvent gave the crude product (17.0mg) as a yellow oil. Chromatography of this material on silica (4g) with hexane:ethyl acetate (2:1) gave (2S,4E,6E)-1,2-O-isopropylidene-4,6-octadiene-1,2,8-triol (235) (5.9mg, 0.030mmol, 63%), vide supra.

Attempted ETDA reaction of 1-((2S,4E,6E)-1,2-O-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (404)

To a stirred solution of 1-((2S,4E,6E)-1,2-O-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (404) (7.4mg, 0.024mmol) in toluene (4.7mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (1.0mg, 0.0045mmol, 0.2eq). The solution was warmed to reflux and was heating continued for 5h. Evaporation of the solvent gave the crude product (8.5mg) as a yellow oil. Chromatography of this material on silica (2g) with hexane:ethyl acetate (2:1) gave (2S,4E,6E)-1,2-O-isopropylidene-4,6-octadiene-1,2,8-triol (235) (2.6mg, 0.013mmol, 54%), vide supra.
Attempted ETDA reaction of 1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-2-methyl-2-butenedioate (38d) and 1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (38c) (64:65, 1:1)

A stirred solution of 1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-2-methyl-2-butenedioate (38d) and 1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (38c) (38d:38c (50:50)) (96.3mg, 0.458mmol) in xylene (3.98mL) was warmed to reflux under argon and heating was continued for 15h.98 The solvent was evaporated, the residue was redissolved in CDCl₃ and proton NMR analysis was carried out. The crude material contained compounds 40c, 39c, 40d and 39d (40c:39c:40d:39d (51:16:27:6)) (mass balance = 90.6mg, 94%) as a yellow oil. To a stirred solution of the crude material in dichloromethane (8.3mL) at RT under argon was added trifluoroacetic acid (1.97mmol, ca. 5eq). Stirring was continued for 24h and then the solvent and trifluoroacetic acid were evaporated. The residue was redissolved in CDCl₃ and proton NMR analysis was carried out. The crude material contained compounds 40c, 39c, 40d and 39d (40c:39c:40d:39d (50:14:28:8)) (mass balance = 83.0mg, 89%) as a yellow oil.

Attempted ETDA reaction of 1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-2-methyl-2-butenedioate (38d)

A stirred solution of 1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-2-methyl-2-butenedioate (38d) (16.7mg, 0.0794mmol) in xylene (0.69mL) was warmed to reflux under argon and heating was continued for 15h.98 The solvent was evaporated, the residue was redissolved in CDCl₃ and proton NMR analysis was carried out. The crude material contained compounds 40c, 39c, 40d and 39d (40c:39c:40d:39d
(55:7:28:10)) as a yellow oil. To a stirred solution of the crude material in dichloromethane (1.7mL) at RT under argon was added trifluoroacetic acid (31µL, 0.39mmol, ca. 5eq). Stirring was continued for 24h and then the solvent and trifluoroacetic acid were evaporated. The residue was redissolved in CDCl3 and proton NMR analysis was carried out. The crude material contained compounds 40c, 39c, 40d and 39d (40c:39c:40d:39d (53:11:29:7)) (mass balance = 15.2mg, 91%) as a yellow oil.

**Attempted ETDA reaction of 1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (38c)**

![Diagram of 38c reaction](image)

A stirred solution 1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (38c) (69.6mg, 0.331mmol) in xylene (2.90mL) was warmed to reflux under argon and heating was continued for 15h. The solvent was evaporated, the residue was redissolved in CDCl3 and proton NMR analysis was carried out. The crude material contained compounds 40c, 39c, 40d and 39d (40c:39c:40d:39d (54:11:24:11)) as a yellow oil. To a stirred solution of the crude material in dichloromethane (7.0mL) at RT under argon was added trifluoroacetic acid (129µL, 1.64mmol, ca. 5eq). Stirring was continued for 24h and then the solvent and trifluoroacetic acid were evaporated. The residue was redissolved in CDCl3 and proton NMR analysis was carried out. The crude material contained compounds 40c, 39c, 40d and 39d (40c:39c:40d:39d (52:12:29:7)) (mass balance = 62.5mg, 90%) as a yellow oil.

**Attempted BDA reaction of (2E,4E)-2,4-hexadien-1-ol (301) and citraconic anhydride (406)**

![Diagram of 301 and 406 reaction](image)
A stirred solution \((2E,4E)-2,4\text{-hexadien-1-ol} (301)\) (50.7mg, 0.517mmol) and citraconic anhydride \((406)\) (46.3μL, 517mmol, 1eq) in xylene (4.50mL) was warmed to reflux under argon and heating was continued for 15h. The solvent was evaporated, the residue was redissolved in CDCl₃ and proton NMR analysis was carried out. The crude material contained compounds \(40c, 39c, 40d\) and \(39d\) (\(40c:39c:40d:39d\) (57:7:30:6)) as a yellow oil. To a stirred solution of the crude material in dichloromethane (10.9mL) at RT under argon was added trifluoroacetic acid (202μL, 2.57mmol, ca. 5eq). Stirring was continued for 24h and then the solvent and trifluoroacetic acid were evaporated. The residue was redissolved in CDCl₃ and proton NMR analysis was carried out. The crude material contained compounds \(40c, 39c, 40d\) and \(39d\) (\(40c:39c:40d:39d\) (58:7:29:7)) (mass balance = 108.7mg, 95%) as a yellow oil.

Proton NMR experiment on 1-\((2E,4E)-2,4\text{-hexadien-1-yl}) 4\text{-hydrogen (2Z)-2-methyl-2-butenedioate} (38d)

\[
\begin{align*}
\text{HO}_2\text{C} & \rightarrow \Delta \\
& \text{ds-toluene} \\
38d
\end{align*}
\]

To 1-\((2E,4E)-2,4\text{-hexadien-1-yl}) 4\text{-hydrogen (2Z)-2-methyl-2-butenedioate} (38d) (20.2mg, 0.0961mmol) was added \(d_8\)-toluene (835μL) under argon at RT. The resulting solution was transferred to an NMR tube and this was heated to 110°C. At specific time intervals (0min, 15min, 30min, 45min, 60min, 90min, 2h, 4h, 8h, 16h, 24h, 48h, 70h, 93h and 140h), the reaction mixture was quenched in ice water and a proton NMR spectrum was recorded. Stack plots of these spectra are illustrated in Figures 4.11 and 4.12 (Section 4.5.2).

Proton NMR experiment on 1-\((2E,4E)-2,4\text{-hexadien-1-yl}) 4\text{-hydrogen (2Z)-3-methyl-2-butenedioate} (38c)

\[
\begin{align*}
\text{HO}_2\text{C} & \rightarrow \Delta \\
& \text{ds-toluene} \\
38c
\end{align*}
\]
To 1-((2E,4E)-2,4-hexadien-1-yl) 4-hydrogen (2Z)-3-methyl-2-butenedioate (38c) (18.8mg, 0.0894mmol) was added d₆-toluene (777μL) under argon at RT. The resulting solution was transferred to an NMR tube and this was heated to 110°C. At specific time intervals (0min, 15min, 30min, 45min, 60min, 90min, 2h, 4h, 8h, 16h, 24h, 48h, 70h, 93h and 140h), the reaction mixture was quenched in ice water and a proton NMR spectrum was recorded. Stack plots of these spectra are illustrated in Figures 4.13 and 4.14 (Section 4.5.2).

ETDA reaction of 1-((2E,4E)-2,4-hexadien-1-yl) 4-methyl (2Z)-2-methyl-2-butenedioate (405)

To a stirred solution of 1-((2E,4E)-2,4-hexadien-1-yl) 4-methyl (2Z)-2-methyl-2-butenedioate (405) (50.0mg, 0.223mmol) in toluene (45mL) at RT under argon was added 2,6-di-tert-butyl-4-methylphenol (9.8mg, 0.44mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 24h. Evaporation of the solvent gave the crude product (60.0mg) as a yellow oil. Chromatography of this material on silica (4g) with hexane:ethyl acetate (5:1 then 2:1) gave recovered starting material (405) (2.8mg, 0.012mmol, 5%) followed by the ETDA adducts (417 and 410) (33.4mg, 0.149mmol, 71% (at 95% conversion), 417:410 (93:7)), vide supra.

ETDA reaction of 1-((2E,4E)-2,4-hexadien-1-yl) 4-methyl (2Z)-3-methyl-2-butenedioate (38a)

To a stirred solution of 1-((2E,4E)-2,4-hexadien-1-yl) 4-methyl (2Z)-3-methyl-2-butenedioate (38a) (45.0mg, 0.201mmol) in toluene (40.1mL) at RT under argon was
added 2,6-di-tert-butyl-4-methylphenol (8.8mg, 0.040mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 24h. Evaporation of the solvent gave the crude product (53.9mg) as a yellow oil. Chromatography of this material on silica (4g) with hexane:ethyl acetate (10:1 then 5:1) gave the ETDA adducts (39a and 40a) (29.2mg, 0.130mmol, 65%, 39a:40a (84:16)), vide supra.

6.5 Experimental for Chapter Five

6.5.1 Preparation of precursors

\((2S,3S,4E,6E)-3-(1\text{-tert-butyl-1,1-dimethylsilyl})\text{oxy-1,2-dihydroxy-4,5-octadien-8-yl hydrogen maleate (515)}\)

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{TBSO} & \quad \text{CO:O} \\
\end{align*}
\]

To a stirred solution of \((2S,3S,4E,6E)-1,2-O-isopropylidene-3-(1\text{-tert-butyl-1,1-dimethylsilyl})\text{oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (236)}\) (26.1mg, 0.0615mmol) in dichloromethane (5mL) at 0°C under argon was added dropwise trifluoracetic acid (50µL, 0.62mmol, 10eq). On completion of the addition the solution was warmed to RT and stirring was continued for 20min. The solvent was evaporated to give the crude product (25.0mg) as a yellow oil. Chromatography of this material on silica (2g) with hexane:ethyl acetate:methanol:acetic acid (50:50:0.5:0.5) gave the title compound (515) (13.9mg, 0.0360mmol, 59%) as a colourless oil: \([\alpha]_D^{19.5} = -0.70^\circ \text{ (c = 0.42, dichloromethane)}; R_f = 0.11 \text{ (hexane:ethyl acetate:methanol:acetic acid (50:50:0.5:0.5)); (Found: } M^+-(H_2O+C_4H_9), 311.0955. \text{ C}_{14}H_{19}O_6Si \text{ requires } M, 311.0951); \nu_{\text{max}} \text{ (film) 3431, 2953, 2925, 2887, 2857, 1729, 1644, 1472 and 1462cm}^{-1}; \delta_\text{H} \text{(270MHz, CDCl}_3) \text{ 0.055 and 0.095 (6H, 2 x s, -Si(CH}_3)_2^-, 0.915 (9H, s, -C(CH}_3)_3^-, 3.50-3.75 (3H, m, C1-H and C2-H), 4.22 (1H, t, J 6.3Hz, C3-H), 4.80 (2H, d, J 7.0Hz, C8-H), 5.72-5.87 (2H, m, C4-H and C7-H), 6.18-6.46 (2H, m, C5-H and C6-H) and 6.37 and 6.46 (2H, 2 x d, B and A of AB, } J_{AB} \text{ 13.0Hz, } -CH=CHCO_2H; \delta_\text{C} \text{(68.1MHz, CDCl}_3) \text{ -4.78, -3.96, 18.2, 25.9, 62.9, 66.7, 73.7, 74.8, 125.2, 128.9, 130.6, 134.8 (2 x C), 135.8, 164.7 and 167.1; } m/z \text{ (EI, 70eV) 386 (0.2%), 311 (0.2), 281 (4), 227 (19), 117 (17), 95 (20), 75 (100), 59 (82) and 41 (65).} \)
To a stirred solution of (2S,3S,4E,6E)-1,2-o-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-4,6-octadien-1,2,8-triol (228) (1.015 g, 3.09 mmol) in dichloromethane (20 mL) at RT under argon was added Dess-Martin periodinane\(^{167}\) (Section 6.6.1) (1.442 g, 3.40 mmol, 1.1 eq). Stirring was continued for 30 min then saturated aqueous sodium bicarbonate (10 mL) and saturated aqueous sodium thiosulphate (5 mL) were added. The organic phase was partitioned against saturated aqueous sodium bicarbonate (10 mL), water (10 mL) and brine (10 mL) then dried, filtered and evaporated to give the crude product (1.091 g) as a yellow oil. Chromatography of this material on silica (30 g) with hexane:ethyl acetate (5:1) gave the title compound (518) (0.833 g, 2.55 mmol, 83%) as a yellow oil: \([\alpha]_D^{21} = -30.4^\circ\) (c = 0.70, dichloromethane); \(R_t = 0.34\) (hexane:ethyl acetate (5:1)); (Found: \(M^+\text{-CH}_3\), 311.1675. \(C_{16}H_{27}O_4\)Si requires \(M\), 311.1679); \(v_{\text{max}}\) (film) 2986, 2955, 2931, 2887, 2858, 1730, 1693, 1682, 1644, 1472, 1462, 1381, 1371 and 1255 cm\(^{-1}\); \(\delta_H\) (270 MHz, CDCl\(_3\)) 0.061 and 0.085 (6H, 2 x s, -Si(CH\(_3\))\(_2\)-), 0.904 (9H, s, -C(CH\(_3\))\(_3\)), 1.33 and 1.40 (6H, 2 x s, -C(CH\(_3\))\(_2\)-), 3.80 (1H, dd, \(J = 5.8, 8.7\) Hz, C\(_8\)-H), 3.97 (1H, dd, \(J = 6.7, 8.7\) Hz, C\(_8\)-H'), 4.11-4.19 (1H, m, C\(_7\)-H), 4.44 (1H, td, \(J = 5.1, 1.3\) Hz, C\(_6\)-H), 6.16 (1H, dd, \(J = 8.0, 15.3\) Hz, C\(_2\)-H), 6.29 (1H, dd, \(J = 5.1, 15.2\) Hz, C\(_5\)-H), 6.56 (1H, dd, \(J = 1.3, 10.9, 15.2\) Hz, C\(_4\)-H), 7.13 (1H, dd, \(J = 10.9, 15.3\) Hz, C\(_3\)-H) and 9.58 (1H, d, \(J = 8.0\) Hz, C\(_1\)-H); \(\delta_C\) (68.1 MHz, CDCl\(_3\)) -4.79, -4.64, 18.3, 25.0, 25.8, 26.3, 65.0, 72.6, 78.0, 109.5, 129.0, 131.7, 142.9, 150.9 and 193.5; \(m/z\) (EI, 80 eV) 311 (4%), 269 (25), 226 (100), 211 (33), 129 (21), 101 (95), 73 (74), and 43 (35).

methyl (2E,4E,6E,8E,10S,11S)-11,12-O-isopropylidene-10-(1-tert-butyl-1,1-dimethylsilyl)oxy-11,12-dihydroxy-2,4,6,8-dodecataenoate (519)
To a stirred solution of \((2E,4E,6S,7S)-7,8-\text{-isopropylidene}-2,4\text{-octadienial (518)}\) \((2.435\text{g, 7.46mmol})\) in dichloromethane \((20\text{mL})\) at RT under argon was added methyl 4-(triphenylphosphoranylidene)-(2E)-2-butoenate\(^{168}\) \((4.03\text{g, 11.2mmol, 1.5eq})\). On completion of the addition the solution was warmed to reflux and stirring was continued for 3h. The reaction mixture was diluted with hexane \((80\text{mL})\) and passed through a silica plug \((4\text{cm diameter x 14cm deep})\) which was saturated with hexane. The silica was then eluted with hexane:ethyl acetate \((3:1)\) to give the crude product \((2.826\text{g})\) as a yellow oil. Chromatography of this material on silica \((60\text{g})\) with hexanecethyl acetate \((19.5:1\text{ then 9:1})\) gave compound \(519\) as a mixture of \(Z\)- and \(E\)-stereoisomers \((1.406\text{g, 3.44mmol, 46%})\).

**Isomerisation.**

To a stirred solution of the \(Z\)- and \(E\)-stereoisomers of compound \(519\) \((1.406\text{g, 3.44mmol})\) in dichloromethane \((60\text{mL})\) at room temperature under argon was added a solution of iodine \((25.0\text{mmol/L in dichloromethane, 1.52mL, 0.0380, 0.011eq})\). On completion of the addition the reaction mixture was place in the dark for 2h then in direct sunlight for 1h. Two further aliquots of iodine solution \((0.250\text{mol/L in dichloromethane, 1.52mL, 0.380mmol, 0.11eq})\) were added at 1h intervals. The reaction mixture was partitioned against saturated aqueous sodium thiosulphate \((50\text{mL})\), water \((50\text{mL})\), brine \((50\text{mL})\) then dried, filtered and evaporated to give the crude product \((1.604\text{g})\) as a yellow oil. Chromatography of this material on silica \((48\text{g})\) with hexane:ethyl acetate \((19.5:1\text{ then 9:1})\) gave the **title compound (519)** \((0.8340\text{g, 2.04mmol, 59%})\) as a yellow oil: \([\alpha]_D^{20} = -45.1^\circ\) \((c = 1.97, \text{ dichloromethane}); R_t = 0.36 \text{ (hexanecethyl acetate (9:1))};\) (Found: \(M^+\), 408.2333. \(C_{22}H_{36}O_{3}Si\) requires \(M, 408.2333\); \(\nu_{\text{max}}\) \((\text{film})\) 2987, 2953, 2991, 2886, 2857, 1714, 1620, 1598, 1472, 1462, 1379, 1380 and 1260cm\(^{-1}\); \(\lambda_{\text{max}}\) \((\text{methanol})/\text{nm} 329 (e/Lmol\(^{-1}\)cm\(^{-1}\) 5.22 x 10\(^4\)); \(\delta_{H} (270\text{MHz, CDCl}_{3})\) 0.050 and 0.070 \((6\text{H}, 2 \times s, -\text{Si(}CH_{3} \text{)}_{2}^{2-}), 0.896 \text{ (9H, s, -C(}CH_{3} \text{)}_{3}), 1.325 \text{ and 1.383 (6H, 2 s, -C(}CH_{3} \text{)}_{2}^{2-}), 3.74 \text{ (3H, s, -CO}_{2}\text{CH}_{3}), 3.78 \text{ (1H, dd, J 6.2, 8.5Hz, C12-H)}, 3.94 \text{ (1H, dd, J 6.7, 8.5Hz, C12-H\text{'}), 4.05-4.13 (1H, dd, J 6.2, 8.5Hz, C12-H\text{'}), 4.29-4.35 (1H, m, C10-H), 5.82 \text{ (1H, dd, J 5.9, 14.2Hz, C9-H)}, 5.87 \text{ (1H, d, J 15.5Hz, C2-H), 6.21-6.64 (5H, m, C4-H, C5-H, C6-H, C7-H and C8-H) and 7.31 \text{ (1H, dd, J 11.3, 15.5Hz, C3-H}); \(\delta_{C} (68.1\text{MHz, CDCl}_{3})\) -4.75, -4.53, 18.3, 25.2, 25.8, 26.4, 51.5, 65.2, 73.4, 78.6, 109.4, 120.2, 129.9, 131.2, 131.7, 134.6, 136.3, 140.4, 144.4 and 167.3; \(m/z \) (EI, 70eV) 408 (7%), 351 (9), 333 (9), 308 (43), 101 (100) and 73 (34).
(2S,3S,4E,6E,8E,10E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyloxy-1,2-dihydroxy-4,6,8,10-dodecatriene-12-ol (520)

To a stirred solution of methyl (2E,4E,6E,8E,10S,11S)-11,12-O-isopropylidene-10-(1-tert-butyl-1,1-dimethylsilyloxy)-11,12-dihydroxy-2,4,6,8-dodecatrieneanoate (519) (385.2 mg, 0.943 mmol) in dichloromethane (10 mL) at -10°C under argon was added dropwise diisobutylaluminium hydride (1.5 mol/L in toluene, 1.38 mL, 2.07 mmol, 2.2 eq). On completion of the addition the reaction mixture was warmed to -80°C. Hexane (20 mL) then ethyl acetate (4 mL) was cautiously added then the reaction mixture was eluted through a silica plug (4 cm diameter x 7 cm deep) which was saturated with hexane. The silica was then eluted with hexane:ethyl acetate (2:1) to give the crude product (399.0 mg) as a yellow oil. Chromatography of this material on silica (20 g) with hexane:ethyl acetate (5:1 then 2:1) gave the title compound (520) (317.5 mg, 0.834 mmol, 88%) as a colourless oil: [α]D 20.5 = -47.5° (c = 2.77, dichloromethane); Rf = 0.46 (hexane:ethyl acetate (2:1)); (Found: M+, 380.2384. C21H36O4Si requires M, 380.2383); νmax (film) 3415, 2986, 2954, 2929, 2885, 2856, 1645, 1609, 1471, 1462, 1380, 1370 and 1254 cm⁻¹; λmax (methanol)/nm 314 (ε/L mol⁻¹ cm⁻¹ 5.19 x 10⁴), 300 (5.95 x 10⁴) and 288 (4.14 x 10⁴); δH (270 MHz, CDCl₃) 0.049 and 0.067 (6H, 2 x s, -Si(CH₃)₂⁻), 0.893 (9H, s, -C(CH₃)₃), 1.33 and 1.38 (6H, 2 x s, -C(CH₃)₂⁻), 1.81 (1H, s, -OH), 3.78 (1H, dd, J 6.2, 8.5 Hz, C1-H), 3.93 (1H, dd, J 6.7, 8.5 Hz, C1-H'), 4.04-4.12 (1H, m, C2-H), 4.14-4.24 (2H, m, C12-H), 4.24-4.31 (1H, m, C3-H), 5.94-5.61 (2H, m, C4-H and C11-H) and 6.14-6.37 (6H, m, C5-H, C6-H, C7-H, C8-H, C9-H and C10-H); δC (68.1 MHz, CDCl₃) -4.74, -4.49, 18.3, 25.3, 25.8, 26.4, 63.3, 65.3, 73.6, 78.7, 109.4, 131.3, 131.7, 132.0, 132.1, 132.3, 132.5, 132.6 and 132.9; m/z (EI, 70 eV) 380 (9%), 323 (7), 305 (8), 279 (100), 101 (85) and 73 (55).

diethyl (2E,6E)-2,6-octadienedioate (523)
To a stirred solution of succinaldehyde \( \text{Section 6.6.4} \) (150mL, from the total volume (300mL)) in dichloromethane (150mL, from the total volume (300mL)) at RT under argon was added ethyl (triphenylphosphoranylidene)ethanoate (26.4g, 0.0728mol). On completion of the addition the solution was warmed to reflux and stirring was continued for 64h. The solvent was evaporated and the crude product extracted from the solid material with pentane (3 x 200mL). Evaporation of the pentane gave the crude product (9.22g) as a yellow oil. Kugelrhor distillation of this material (200°C/0.05mmHg) gave the **title compound** (523) (7.22g, 0.0319mol, 88%) as a colourless oil: \( R_t = 0.36 \) (hex:ac:ethyl acetate (5:1)); (Found: \( M^+ \), 226.1212. \( C_{12}H_{18}O_4 \) requires \( M, 226.1205 \)); \( \nu_{\max} \) (film) 2981, 2937, 2904, 1719, 1654, 1367 and 1269cm\(^{-1}\); \( \delta_H \) (270MHz, CDCl\(_3\)) 1.29 (3H, t, \( J = 7.1 \)Hz, \(-CO_2CH_2CH_3\)), 2.34-2.42 (2H, m, C4-\( H \)), 4.12 (2H, q, \( J = 7.1 \)Hz, \(-CO_2CH_2CH_3\)), 5.86 (1H, \( J = 15.6 \)Hz, C2-\( H \)) and 6.88-6.99 (1H, m, C3-\( H \)); \( \delta_C \) (68.1MHz, CDCl\(_3\)) 14.2, 30.4, 60.1, 12.2, 146.5 and 166.0; \( m/z \) (EI, 70eV) 226 (1%), 181 (96), 152 (77), 107 (41), 85 (100), 79 (82) and 68 (57).

**\( 2E,6E \)-2,6-octadienedioic acid (524)**

To a stirred solution of diethyl \( (2E,6E)-2,6\)-octadienedioate (523) (1.00g, 4.42mmol) in tetrahydrofuran (11mL) at RT was added aqueous potassium hydroxide solution (1.0mol/L, 44mL, 44mmol, 10eq). Stirring was continued for 2h then the reaction mixture was partitioned against diethyl ether (50mL). The aqueous layer was titrated with 10% aqueous hydrochloric until it was pH 1, then it was filtered. The crude product was rinsed with acetone (3 x 50mL) and dried to constant mass on high vacuum to give the **title compound** (524) (0.514g, 3.02mmol, 68%) as a white powder: mp 255-259°C (dec.) (lit.\(^{243} \) 250-252°C (dec.)); \( R_t = 0.08 \) (ethyl acetate:methanol:acetic acid (100:0.5:0.5)); (Found: \( M^++\text{NH}_4^+ \), 188.0918. \( C_8H_{14}NO_4 \) requires \( M, 188.0923 \)); \( \nu_{\max} \) (KBr disc) 2921, 1685, 1636 and 1430cm\(^{-1}\); \( \delta_H \) (270MHz, \( d_\sigma^-\text{DMSO/} \text{internal reference} 2.50 ppm) 2.27-2.41 (2H, m, C4-\( H \)), 5.80 (1H, \( J = 15.6 \)Hz, C2-\( H \)) and 6.71-6.85 (1H, m, C3-\( H \)); \( \delta_C \) (68.1MHz, \( d_\sigma^-\text{DMSO/} \text{internal reference} 39.7 ppm) 30.6, 123.3, 148.3 and 167.7; \( m/z \) (Cl/\( \text{NH}_3 \), 70eV) 188(0.4%), 167 (6), 153 (12), 124 (100), 79 (56), 68 (41) and 39 (24).
triisopropylsilyl hydrogen (2E,6E)-2,6-octadienedioate (525) and **bis-triisopropylsilyl (2E,6E)-2,6-octadienedioate (526)**

\[
\begin{align*}
\text{TIPS}_2\text{C} & \quad \text{CO}_2\text{H} + \quad \text{TIPS}_2\text{C} & \quad \text{CO}_2\text{TIPS} \\
525 & & 526
\end{align*}
\]

To a stirred solution of (2E,6E)-2,6-octadienedioic acid (524) (0.502g, 2.95mmol) and triethylamine (430μL, 3.10mmol, 1.05eq) in tetrahydrofuran (200mL) at RT under argon was added triisopropylsilyl chloride (632μL, 2.95mmol, 1eq) via syringe pump over the course of 1h. On completion of the addition silica (6g) was added and the solvent evaporated. This material was loaded onto a silica column (30g) and eluted with hexane:ethyl acetate (5:1 then 1:1) then ethyl acetate:methanol:acetic acid (100:0.5:0.5) to give **title compounds 525** (0.445g, 1.36mmol, 44%) and 526 (0.314 g, 0.650mmol, 22%), *vide infra*, followed by recovered starting material (524) (0.100g, 0.588mmol, 20%), *vide supra*.

**triisopropylsilyl hydrogen (2E,6E)-2,6-octadienedioate (525)**

Crystalline solid: mp 74-75°C (from hexane/diethyl ether); R_f = 0.47 (hexane:ethyl acetate (1:1)); (Found: M^+ -C,H_2, 283.1361. C_{14}H_{23}O_3Si requires M, 283.1366); ν_{max} (KBr disc) 3367, 3063, 2946, 2868, 2717, 1697, 1641, 1465, 1427 and 1321 cm⁻¹; δ_H (270MHz, CDCl_3) 1.09 (18H, d, J 7.3Hz, -Si(CH(CH_3)_2)_3), 1.24-1.42 (3H, m, -Si(CH(CH_3)_2)_3), 2.36-2.46 (4H, m, C4-H and C5-H), 5.87 (2H, d, J 15.6Hz, C2-H and C7-H) and 6.84-7.15 (2H, m, C3-H and C6-H); δ_C (68.1MHz, CDCl_3) 12.1, 17.9, 30.2, 30.7, 121.5, 123.9, 147.0, 149.7, 165.8 and 171.2; m/z (EI, 70eV) 283 (100%), 265 (8), 237 (28), 223 (25), 131 (24), 103 (29), 75 (35) and 61 (18).

**bis-triisopropylsilyl (2E,6E)-2,6-octadienedioate (526)**

\[
\begin{align*}
\text{TIPS}_2\text{C} & \quad \text{CO}_2\text{TIPS} \\
526
\end{align*}
\]
Yellow oil: \( R_r = 0.95 \) (hexane:ethyl acetate (5:1)); (Found: \( M^+\cdot C_{13}H_{11}, 439.2695 \). \( C_{23}H_{43}O_4Si_2 \) requires \( M, 439.2699 \)); \( \nu_{\text{max}} \) (film) 2945, 2892, 2867, 1698, 1650, 1464, 1384, 1368 and 1283 cm\(^{-1}\); \( \delta_H \) (270 MHz, CDCl\(_3\)) 1.09 (18H, d, \( J 7.3\) Hz, \(-\text{Si}(\text{CH}(\text{CH}_3)_2)_3\)), 1.22-1.42 (3H, m, \(-\text{Si}(\text{CH}(\text{CH}_3)_2)_3\)), 2.36-2.41 (2H, m, C4-H), 5.85 (1H, d, \( J 15.4\) Hz, C2-H) and 6.84-6.98 (1H, m, C3-H); \( \delta_C \) (68.1 MHz, CDCl\(_3\)) 12.1, 17.9, 30.4, 123.8, 147.2 and 165.7; \( m/z \) (EI, 70 eV) 439 (100%), 198 (11), 157 (10), 115 (22), 87 (10) and 59 (13).

\( \overset{(2S,3S,4E,6E,8E,10E)}{-}1,2-O\text{-isopropylidene-3-}(1\text{-tert-butyl-1,1-dimethylsilyl})\text{oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl triisopropylsilyl} \ (2E,6E)\text{-2,6-octadienedioate (527)} \)

To a stirred solution of \( (2S,3S,4E,6E,8E,10E)\text{-1,2-O-isopropylidene-3-}(1\text{-tert-butyl-1,1-dimethylsilyl})\text{oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-ol (520)} \) (0.255g, 0.670mmol) in dichloromethane (2.3mL) at 0°C under argon was added 2,6-di-tert-butyl-4-methylphenol (29.5mg, 0.134mmol, 0.2eq), triisopropylsilyl hydrogen \((2E,6E)\text{-2,6-octadienedioate (525)} \) (0.273g, 0.836mmol, 1.25eq), dicyclohexylcarbodiimide (0.207g, 1.00mmol, 1.5eq) and N,N-dimethylaminopyridine (12.2mg, 0.100mmol, 0.15eq). Stirring was continued for 3h then the reaction mixture was diluted with hexane (10mL) and passed through a silica plug (4cm diameter x 5cm deep) which was then eluted with hexane:ethyl acetate (10:1, 5 x 50mL) then hexane:ethyl acetate (10:1, 3 x 50mL) and the solvent was evaporated to give the crude product (0.336g) as a yellow oil. Chromatography of this material on silica (15g) with hexane:ethyl acetate (20:1, 10:1 and 5:1) gave the title compound (527) (0.157g, 0.228mmol, 34%) as a yellow oil: \( [\alpha]_D^{25} = -25.1^\circ \) (c = 0.89, dichloromethane); \( R_r = 0.58 \) (hexane:ethyl acetate (5:1)); (Found: \( M^+, 688.4205 \). \( C_{35}H_{64}O_{10}Si_2 \) requires \( M, 688.4191 \)); \( \nu_{\text{max}} \) (film) 2948, 2893, 2867, 1723, 1698, 1650, 1473, 1463, 1380, 1370 and 1283 cm\(^{-1}\); \( \lambda_{\text{max}} \) (methanol)/nm \( 316 (\varepsilon/\text{Lmol}^{-1}\text{cm}^{-1}, 4.07 \times 10^4), 302 (4.74 \times 10^4), 289 (3.45 \times 10^4) \) and 199 (1.47 \times 10^5); \( \delta_H \) (270 MHz, CDCl\(_3\)) 0.057 and 0.076 (6H, 2 x s, \(-\text{Si}(\text{CH}_3)_2\)\(_2\)), 0.902 (9H, s, \(-\text{C}(\text{CH}_3)_3\)), 1.09 (18H, d, \( J 7.3\) Hz, \(-\text{Si}(\text{CH}(\text{CH}_3)_2)_2\)), 1.18-1.45 (3H, m, \(-\text{Si}(\text{CH}(\text{CH}_3)_2)_2\)), 1.34 and 1.39 (3H, 2 x s, \(-\text{C}(\text{CH}_3)_2\)\(_2\)), 2.36-2.42 (4H, m, \(-\text{CH}_2\text{CH}_2\)),
3.79 (1H, dd, J 6.2, 8.5Hz, C1-H), 3.94 (1H, dd, J 6.7, 8.5Hz, C1-H'), 4.04-4.13 (1H, m, C2-H), 4.29 (1H, t, J 5.7Hz, C3-H), 4.68 (2H, d, J 6.5Hz, C12-H), 5.51-5.93 (2H, m, C4-H and C11-H), 5.88 and 5.86 (2H, 2 x dd, J 15.7Hz, 2 x -CH=CH-CO2-), 6.08-6.44 (6H, m, C5-H, C6-H, C7-H, C8-H, C9-H and C10-H), and 6.82-7.04 (2H, m, 2 x -CH=CH-CO2-); δ_C (68.1MHz, CDCl3) -4.72, -4.49, 12.1, 17.8, 18.3, 25.3, 25.9, 26.4, 30.3, 30.6, 64.6, 65.3, 73.7, 78.7, 109.3, 122.0, 123.9, 126.6, 128.2, 131.6, 131.7, 132.4, 133.0, 133.9, 134.3, 147.1, 147.2, 165.7 and 165.8; m/z (EI, 70eV) 688 (2%), 613 (5), 587 (48), 283 (24), 262 (81), 101 (100) and 73 (49).

\[(2S,3S,4E,6E,8E,10E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl \text{hydrogen (2E,6E)-2,6-octadienedioate (529)}\]

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

\[
529
\]

To a stirred solution of \((2S,3S,4E,6E,8E,10E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl triisopropylsilyl (2E,6E)-2,6-octadienedioate (527) (63.6mg, 0.0923mmol) in methanol (25mL) at RT under argon was added anhydrous potassium carbonate (25.4mg, 0.184mmol, 2eq). Stirring was continued for 10 min then the reaction mixture was diluted with diethyl ether (100mL) and partitioned against saturated aqueous ammonium chloride (50mL). The aqueous layer was extracted with diethyl ether (50mL) and the combined extracts were washed with water (10mL) and brine (10mL) then dried, filtered and evaporated to give the crude product (70.4mg) as a yellow oil. Chromatography of this material on silica (3.5g) with hexane:ethyl acetate (2:1) then hexane:ethyl acetate:methanol:acetic acid (66:33:0.5:0.5 then 50:50:0.5:0.5) gave the title compound (529) (49.0mg, 0.0920mmol, 100%) as a yellow oil: \([\alpha]_D^{20} = -26.2^\circ \ (c = 2.3, \text{dichloromethane}); R_f = 0.53 \ \text{(hexane:ethyl acetate:methanol:acetic acid 50:50:0.5:0.5)}\). (Found: \(M^+, 532.2901\). \(C_{29}H_{44}O_7Si\) requires \(M, 532.2856\)); \(v_{\text{max}}\) (film) 3164, 2985, 2856, 2953, 2930, 2886, 2856, 1721, 1697, 1651, 1472, 1462, 1422, 1380, 1370 and 1257cm\(^{-1}\); \(\lambda_{\text{max}}\) (methanol)/nm 316 (e/Lmol\(^{-1}\)cm\(^{-1}\) 8.92 x 10\(^4\)), 302 (1.02 x 10\(^5\)), 289 (7.32 x 10\(^4\)) and 197 (1.20 x 10\(^5\)); \(\delta_H\) (270MHz, CDCl\(_3\)) 0.054 and 0.073 (6H, 2 x s, -Si(CH\(_3\))\(_2\)); 0.899
(9H, s, -C(CH₃)₃), 1.34 and 1.39 (6H, 2 x s, -C(CH₃)₂-, 3.79 (1H, dd, J 6.2, 8.5Hz, C1-H), 3.94 (1H, dd, J 6.6, 8.5Hz, C1-H'), 4.04-4.13 (1H, m, C2-H), 4.29 (1H, t, J 6.3Hz, C3-H), 4.68 (2H, d, J 6.3Hz, C12-H), 5.65-5.94 (2H, m, C4-H and C11-H), 5.87 and 5.89 (2H, 2 x d, J 15.7Hz, 2 x -CH=CH-CO₂-), 6.11-6.14 (6H, m, C5-H, C6-H, C7-H, C8-H, C9-H, C10-H) and 6.88-7.12 (2H, m, 2 x -CH=CH-CO₂-); δC (68.1MHz, CDCl₃) -4.69, -4.44, 18.3, 25.3, 25.9, 26.5, 30.4, 30.6, 64.7, 65.3, 73.7, 78.8, 109.4, 121.7, 122.1, 126.6, 131.6, 131.7, 132.4 (2 x C), 133.0, 133.9, 134.3, 147.0, 149.4, 165.8 and 170.7; m/z (EI, 70eV) 532 (0.5%), 431 (5), 262 (19), 101 (80), 75 (100), 57 (26) and 41 (42).

6.5.1 Attempted macrocyclisations, deprotections and TIMDA reactions

Attempted macrocyclisation of (2S,3S,4E,6E)-1,2-O-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl hydrogen maleate (237)

![Structure of 237 and 513](image)

To a stirred solution of (2S,3S,4E,6E)-1,2-O-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl hydrogen maleate (237) (57.7mg, 0.185mmol) in toluene (18mL) at RT under argon was added triethylamine (38.4µL, 0.277mmol, 1.5eq) and 2,4,6-trichlorobenzoyl chloride (31.8µL, 0.204mmol, 1.1eq). On completion of the addition the solution was stirred for 2h then N,N-dimethylaminopyridine (45.1mg, 0.370mmol, 2eq) was added and stirring continued for a further 10min. The reaction mixture was diluted with diethyl ether (50mL), 2,6-di-tert-butyl-4-methylphenol (9.4mg, 0.040mmol, 0.2eq) was added and then it was partitioned against 10% aqueous hydrochloric acid (50mL), saturated aqueous sodium bicarbonate (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (61.3mg) as a yellow oil. Radial chromatography (1mm plate) was carried out on this material with hexane:ethyl acetate (1:1), but compound 513 could not be identified (by proton NMR analysis) in any of the fractions isolated.
Attempted macrocyclisation of $(2S,3S,4E,6E)-3-(1$-$ tert$-$butyl$-$1,1$-$dimethylsilyl)oxy$-$1,2$-$dihydroxy$-$4,5$-$octadien$-$8$-$yl hydrogen maleate (515)

Method A

To a stirred solution of $(2S,3S,4E,6E)-3-(1$-$ tert$-$butyl$-$1,1$-$dimethylsilyl)oxy$-$1,2$-$dihydroxy$-$4,5$-$octadien$-$8$-$yl hydrogen maleate (515) (6.4mg, 0.017mol) in toluene (1.7mL) at RT under argon was added triethylamine (3.4μL, 0.025mol, 1.5eq) and 2,4,6-trichlorobenzoyl chloride (3.1μL, 0.020mmol, 1.2eq). On completion of the addition the solution was stirred for 18h then N,N-dimethylaminopyridine (45.1mg, 0.370mmol, 2eq) was added and stirring continued for a further 3h. The reaction mixture was diluted with diethyl ether (50mL) and partitioned against 10% aqueous hydrochloric acid (50mL), saturated aqueous sodium bicarbonate (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (7.1mg) as a yellow oil. Mass spectral analysis of the crude material (EI, 70eV) recorded fragments with relative molecular masses greater than 700amu, indicating that polymerization may have occurred.

Method B

To a stirred solution of dicyclohexylcarbodiimde (235mg, 1.14mmol, 20eq), N,N-dimethylaminopyridine (348mg, 2.85mmol, 50eq) and trifluoromethanesulphonic acid (101μL, 1.14mmol, 20eq) in chloroform (19.1mL) at RT under argon was added a solution of $(2S,3S,4E,6E)-3-(1$-$ tert$-$butyl$-$1,1$-$dimethylsilyl)oxy$-$1,2$-$dihydroxy$-$4,5$-$octadien$-$8$-$yl hydrogen maleate (515) (22.0mg, 0.0569mmol) in chloroform (3.7mL) via syringe pump over 8h. The reaction mixture was diluted with diethyl ether to precipitate urea and the filtrate was partitioned against 10% aqueous hydrochloric acid (50mL), water (50mL), saturated aqueous sodium bicarbonate (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (150mg) as an amorphous solid. Chromatography was carried out on this material on silica (5g) with hexane:ethyl acetate (10:1 and 2:1) then hexane:ethyl acetate:methanol:acetic acid...
(50:50:0.5:0.5), but compound 516 could not be identified (by proton NMR analysis) in any of the fractions isolated.

**Attempted deprotection of (2S,3S,4E,6E,8E,10E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl triisopropylsilyl (2E,6E)-2,6-octadienedioate (527)**

![Chemical structure of 527](image)

To a stirred solution of (2S,3S,4E,6E,8E,10E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl triisopropylsilyl (2E,6E)-2,6-octadienedioate (527) (14.3mg, 0.0208mmol) in dichloromethane (2.1mL) at 0°C under argon was added trifluoroacetic acid (16.5μL, 0.208mmol, 10eq). Stirring was continued for 30min and then the solvent was evaporated to give the crude product (8.1mg) as a yellow oil. Compound 529 could not be identified in the crude material by proton NMR analysis.

**Attempted deprotection of (2S,3S,4E,6E,8E,10E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl hydrogen (2E,6E)-2,6-octadienedioate (529)**

![Chemical structure of 528](image)

**Method A**

To a stirred solution of (2S,3S,4E,6E,8E,10E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl hydrogen
(2E,6E)-2,6-octadienedioate (529) (5.0mg, 9.8µmol) in dichloromethane (0.9mL) at RT under argon was added trifluoroacetic acid (3.7µL, 47µmol, 5eq). Stirring was continued for 30min then the solvent was evaporated to give the crude product (4.0mg) as a yellow oil. Compound 529 could not be identified in the crude material by proton NMR analysis.

**Method B**

To a stirred solution of (2S,3S,4E,6E,8E,10E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl hydrogen (2E,6E)-2,6-octadienedioate (529) (6.1mg, 7.7µmol) in tetrahydrofuran (1.0mL) at RT under argon was added acetic acid:water (3:1, 4mL). Stirring was continued for 24h then toluene (2 x 20mL) was added sequentially and the solution was concentrated to remove the acetic acid. The crude product (3.8mg) was absorbed onto silica (200mg) then chromatography was carried out on silica (1g) with ethyl acetate:hexane:ethyl acetate:acetic acid:methanol (50:50:0.5:0.5) and ethyl acetate:acetic acid:methanol (100:0.5:0.5). Compound 529 could not be positively identified by proton NMR analysis in any of the fractions isolated.

**Attempted TIMDA reaction of (2S,3S,4E,6E,8E,10E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl triisopropylsilyl (2E,6E)-2,6-octadienedioate (527)**

A solution of (2S,3S,4E,6E,8E,10E)-1,2-O-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl triisopropylsilyl (2E,6E)-2,6-octadienedioate (527) (7.1mg, 0.010mmol) in d₆-DMSO (1.0mL) at RT under argon was transferred to an NMR tube and heated to 110°C for 11h. Destruction of the starting material was observed.
Attempted TIMDA reaction of \((2S,3S,4E,6E,8E,10E)-1,2-O\)-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecataen-12-yl hydrogen \((2E,6E)-2,6\)-octadienedioate (529) ...}

To \((2S,3S,4E,6E,8E,10E)-1,2-O\)-isopropylidene-3-(1-tert-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecataen-12-yl hydrogen \((2E,6E)-2,6\)-octadienedioate (529) (5.3mg, 9.9μmol) and 2,6-di-tert-butyl-4-methylphenol (0.412mg, 1.88μmol, 0.2eq) at RT under argon was added aqueous sodium bicarbonate solution (5.0mmol/L, 2.0mL, 0.010mol, 1eq). Sodium carbonate (7.6mg, 0.090mmol, 9.0 eq) was added to dissolve the starting material and the resulting solution was heated at reflux temperature for 5d. No reaction was observed.

6.6 Preparation of reagents

6.6.1 Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one)\(^{167, 244, 245}\)

Part A\(^{244}\)

To a vigorously stirred solution of 2-iodobenzoic acid (42.6g, 0.172mol) in dilute aqueous sulphuric acid (0.730mol/L, 365mL) at 55°C was added potassium bromate (38.0g, 0.228mol, 1.33eq) in twelve equal portions over 1h. On completion of the addition the solution was warmed to 70°C and stirring was continued for 3h. The reaction mixture was cooled on ice and the precipitate was filtered then rinsed with water (500mL), ethanol (3 x 25mL) and diethyl ether (3 x 25mL) and dried under vacuum to give 1-hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide (41.0g, 0.146mol, 83%) as a crystalline white solid.
Part B

To a stirred solution of 1-hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide (41.0g, 0.146mol) in acetic anhydride (200mL, 2.12mol, 14.5eq) at RT under a calcium chloride drying tube was added para-toluenesulphonic acid monohydrate (0.250g, 1.31mmol, 8.97 x 10^-3eq). On completion of the addition the solution was warmed to 80°C and stirring was continued for 2h. The reaction mixture was cooled on ice then rapidly filtered. The precipitate was rinsed with diethyl ether (5 x 25mL) then dried under vacuum to give 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (50.5g, 0.119mol, 82%) as a crystalline white solid.

6.6.2 Ethyl 4-(triphenylphosphoranylidene)-(2E)-2-butenoate

Part A

To a stirred solution of ethyl (2E)-4-bromo-2-butenoate (20.0g, 0.104mol) in diethyl ether (200mL) at RT under argon was added triphenylphosphine (27.2 g, 0.104mol, 1eq). On completion of the addition the solution was warmed to reflux and stirring was continued for 3d. The reaction mixture was cooled on ice and filtered, then the precipitate was rinsed with diethyl ether (3 x 50mL) to give ((2E)-4-ethoxycarbonyl-2-propenyl)triphenylphosphonium bromide (31.7g, 0.0696mol, 67%) as a crystalline white solid.

Part B

To a stirred solution of ((2E)-4-ethoxycarbonyl-2-propenyl)triphenylphosphonium bromide (31.7g, 0.0696mol) in water (1L), cooled in ice, was added aqueous sodium hydroxide solution (2mol/L) until a sample tested basic with phenolphthalein indicator solution. The reaction mixture was filtered and the precipitate washed with water (4 x 50mL) then freeze dried for 4d to give the title compound as a yellow powder (22.7g, 0.609mol, 88%).

(A similar procedure was used to prepare methyl 4-(triphenylphosphoranylidene)-(2E)-2-butenoate from methyl (2E)-4-bromo-2-butenoate.)
6.6.3 **Diazomethane**\(^{173}\)

To a stirred solution of potassium hydroxide (3.37g, 0.0600mol) in water (5mL) at RT was added aqueous ethanol (96%, 17mL). This solution was warmed to 65°C and a solution of N-methyl-N-nitroso-para-toluenesulphonamide (14.3g, 0.0667mol, 1.11eq) in diethyl ether (85mL) was added dropwise. The diazomethane and diethyl ether were distilled from the reaction mixture and condensed using a dry ice/acetone trap. Further diethyl ether (10mL) was added and distillation continued until the vapour produced was colourless. The solution was refrigerated and used as required.

6.6.4 **Succinaldehyde**\(^{11}\)

To a stirred solution of 2,5-dimethoxytetrahydrofurane (10g, 0.0757mol) was added dilute aqueous hydrochloric acid (0.6mol/L, 50mL) at RT and stirring was continued for 45min. The solution was extracted with dichloromethane (3 x 15mL), then adjusted to pH 1 and extracted with further dichloromethane (15mL). The pH adjustment and extraction was repeated five times and then the combined dichloromethane fractions were dried, filtered and the volume made up to 300mL. Evaporation of the solvent was not carried out since neat succinaldehyde polymerizes on standing and it is volatile (bp 50-60°C/12mmHg\(^{11}\)). The solution was refrigerated and used as required.
Appendix 1

1.1 Summary of two dimensional NMR experiments

1.1.1 COSY spectra

39a, 40a, 228, 238c, 241a:242a (66:34), 241b, 241c, 241d, 242b, 246, 247, 252, 270:271 (50:50), 305, 310, 314, 315, 320, 321, 408, 410 and 417.

1.1.2 NOESY spectra

39a, 40a, 238c, 241a:242a (66:34), 241b, 241c, 241d, 242b, 246, 247, 252, 310, 314, 315, 320, 321, 408, 410 and 417.

1.1.3 HETCOR spectra

38a, 228, 236, 238c, 241b, 241c, 241d, 305, 314 and 405.

1.1.4 HMQC spectra

39a, 40a, 240, 246, 247, 303, 306, 310, 315, 410 and 417.

1.1.5 HSQC spectra

242b and 320.

1.1.6 ROESY spectrum

321.
1.2C  COSY spectrum of 241b
1.2N NOESY spectrum of 241b
1.3C COSY spectrum of 242b
1.3N NOESY spectrum of 242b
1.4C  COSY spectrum of 314
1.4N NOESY spectrum of 314
1.5C  COSY spectrum of 315
1.5N NOESY spectrum of 315
## Appendix 2

### 2.1 Crystal data and structure refinement for compound 39a.

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<th>Value</th>
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</thead>
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<td>Temperature</td>
<td>293(2) K</td>
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<tr>
<td>Wavelength</td>
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</tr>
<tr>
<td>Crystal system</td>
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</tr>
<tr>
<td>Space group</td>
<td>P2(1)/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
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<tr>
<td></td>
<td>b = 13.331(3) Å</td>
</tr>
<tr>
<td></td>
<td>c = 8.068(2) Å</td>
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<tr>
<td></td>
<td>α = 90°</td>
</tr>
<tr>
<td></td>
<td>β = 95.17(3)°</td>
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<tr>
<td></td>
<td>γ = 90°</td>
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<td>Volume</td>
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<td>Z</td>
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<td>Density (calculated)</td>
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<td>Absorption coefficient</td>
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<td>F(000)</td>
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<td>Crystal size</td>
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<td>Theta range for data collection</td>
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<td>Independent reflections</td>
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<td>Completeness to theta = 25.00°</td>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F$^2$</td>
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<td>Goodness-of-fit on F$^2$</td>
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<td>Final R indices [I&gt;2sigma(I)]</td>
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<tr>
<td>R indices (all data)</td>
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<tr>
<td>Extinction coefficient</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.138 and -0.159 e.Å$^3$</td>
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2.2 Atomic coordinates (x $10^4$) and equivalent isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for 39a. U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

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<th>x</th>
<th>y</th>
<th>z</th>
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<td>4945(2)</td>
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### 2.3 Bond lengths [Å] and angles [°] for 39a.

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<td>Bond:</td>
<td>Angle (°)</td>
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<tr>
<td>-----------------------------</td>
<td>-----------</td>
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### 2.4 Anisotropic displacement parameters ($\text{Å}^2 \times 10^3$) for 39a.

The anisotropic displacement factor exponent takes the form:

$$ -2p^2 [ h^2 a^*^2 U^{11} + ... + 2hk a^* b^* U^{12} ] $$

<table>
<thead>
<tr>
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References

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218 P. L. Huang, P. L. Huang, P. Huang, H. I. Huang and S. Lee-Huang, Chem. and Ind., 1992, 290-293.


Errata

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Experimental (pages 135-225)

The first letter of each of the compound names should be capitalised, except where the name forms part of a sentence.

The TBS group in compounds 224-228, 236, 238c, 241e, 242e, 304-307, 310, 311, 314, 315, 320, 321, 401, 402, 407-409, 515, 518-520, 527 and 529 should be referred to as tert-butyldimethylsilyloxy instead of 1-tert-butyl-1,1-dimethyisilyloxy.

The side chain numbering in compounds 241b, 242b, 241c, 242c, 241d, 242d, 246-249, 251, 270, 271, 310, 311, 314, 315, 320 and 321 should begin with the carbon attached to the bicyclic ring system. Propargyl should be replaced with propyl.

The side chain numbering in compounds 236, 237, 238a-d, 239, 240, 304-307, 401-404, 515, 527 and 529 should begin with the carbon attached to the bridging oxygen of the ester.