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STRATEGIES TOWARDS THE SYNTHESIS OF PROSTAGLANDIN ANALOGUES

BY

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Thesis
Presented for the Degree of
DOCTOR OF PHILOSOPHY

In the
Department of Chemistry
University of Cape Town

APRIL 2006
ABSTRACT

Different strategies for the synthesis of cyclopentenone prostaglandins and their analogues have been explored. The key transformation critical to the success of each of the described routes involves a Lewis-acid mediated retro Diels-Alder (rDA) reaction as the final step in liberating a 4, 5 disubstituted cyclopent-2-ene-1-one under extremely mild conditions. The first approach involves installation of the α-chain followed by base-mediated methodology to affect regiospecific enolate generation. Effective trapping of the enolate generates the requisite target. Within the context of this strategy both 2- and 3-component coupling protocols have been elaborated. Having demonstrated that the α- and β- sidechains could be installed, the key rDA reaction has been used to generate target analogues.

The second approach utilizes a Diels-Alder cycloaddition reaction as the key step. The thermal and Lewis-acid catalysed Diels-Alder reactions between tricyclo[5.2.1.02.6]dec-8-en-3-one and 3-hydroxytricyclo[5.2.1.02.6]dec-8-ene with butadiene and butadiene sulfone have been investigated. While reaction between the enone and the dienophiles proved to be low yielding, the reaction between the allylic alcohol and butadiene sulfone proceeded readily and in high yield. The derived cycloadduct represents a late-stage intermediate for the synthesis of isoprostanes. Methodologies to perform cis-hydroxylation followed by oxidative cleavage of the cyclohexene moiety have been successfully implemented.

Finally, a synthesis was designed for generating oxygen analogues of the prostaglandin targets. This involved the generation of (3-exo, 4-endo)-5-oxatetracyclo[6.2.1.02.7.04.6]undec-9-en-3-01. Nucleophilic epoxide opening formed the basis for the installation oxygen on the ring. Methods for the succesful synthesis of both exo and endo epoxides of this nature have been demonstrated and the comparative opening of both structures has been investigated with the endo-epoxide producing the most promising results.
# CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>2. TWO AND THREE COMPONENT COUPLING APPROACHES</td>
<td>20</td>
</tr>
<tr>
<td>2.1 Synthetic Approach</td>
<td>20</td>
</tr>
<tr>
<td>2.2 Synthesis of the starting decadienone</td>
<td>21</td>
</tr>
<tr>
<td>2.3 Strategies for the synthesis of disubstituted 3-oxodicyclopentadiene</td>
<td>24</td>
</tr>
<tr>
<td>2.4 Three component coupling approach</td>
<td>44</td>
</tr>
<tr>
<td>2.5 Enol Silyl Ether Approach</td>
<td>66</td>
</tr>
<tr>
<td>2.6 Conclusion</td>
<td>72</td>
</tr>
<tr>
<td>3. THE CYCLOADDITION APPROACH</td>
<td>73</td>
</tr>
<tr>
<td>3.1 Introduction</td>
<td>73</td>
</tr>
<tr>
<td>3.2 Results and discussion</td>
<td>80</td>
</tr>
<tr>
<td>3.2.1 Cycloadditions of 3-oxodicyclopentadiene with butadiene</td>
<td>80</td>
</tr>
<tr>
<td>3.2.2 Cycloadditions with 3-exo-hydroxydicyclopentadiene as dienophile</td>
<td>84</td>
</tr>
<tr>
<td>3.3 Further Transformations</td>
<td>87</td>
</tr>
<tr>
<td>3.4 Conclusion</td>
<td>89</td>
</tr>
<tr>
<td>4. SYNTHESIS OF OXYGEN ANALOGUES</td>
<td>90</td>
</tr>
<tr>
<td>4.1 Oxygen Analogues of cyclopentenone prostaglandins</td>
<td>90</td>
</tr>
<tr>
<td>4.2 Conclusion</td>
<td>108</td>
</tr>
<tr>
<td>5. EXPERIMENTARY</td>
<td>109</td>
</tr>
<tr>
<td>6. REFERENCES</td>
<td>173</td>
</tr>
</tbody>
</table>
1.1. Background:
Prostaglandins (PG's) are a group of naturally occurring compounds that are generated \textit{in vivo} from arachidonic acid \textit{via} the membrane-bound cyclooxygenase enzyme system.\textsuperscript{1,2,3}

The central structural element of PG's is prostanoic acid (Figure 1.1). There are several different types of PG's comprising the prostaglandin alphabet and they are classified alphabetically from A-J (Figure 1.2). The letters identify the functional groups of the cyclopentane ring with a three-numerical subscript series indicating the number of double bonds in the sidechains. The PGF family (Figure 1.2) is further subdivided by means of a subscript $\alpha$ and $\beta$ to distinguish the relative configuration of the hydroxyl group at position 9.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Figure 1.1}
\end{figure}
These primary prostaglandins and their analogues display a broad spectrum of biological activities, which renders specific target selectivity difficult to achieve. Nevertheless, some such compounds have proved to be commercially viable. For example, Limaprost ⁴ has proved to be a successful drug for the treatment of gastrointestinal problems while Mexiprostil ⁵, whose synthesis is described below (Scheme 1.2), is used for the treatment of cardiovascular disease.

![Prostaglandin structures]

PG₁ series, R¹ = (CH₂)₆CO₂H; PG₂ series, R¹ = CH₂CH=CH(CH₂)₂CO₂H, Z-alkene, R²=CH=CHCH(OH)C₅H₁₁ (S configuration) except for PGG when R²=CH=CH(CH(OOH)C₅H₁₁

**Figure 1.2** The prostaglandin alphabet.

Cyclopentenone prostaglandins, cyPG’s, (prostaglandins of the A and J series Figure 1.3) have been shown to inhibit viral replication and hence have emerged as a new class of potentially therapeutic agents.⁶
They exhibit at least a component of their activity by induction of heat shock protein synthesis\textsuperscript{7} (via activation of Heat Shock Factor (HSF)) and inhibition of the nuclear transcription factor NF-\textkappa B (Figure 1.4).\textsuperscript{8-9} Heat-shock proteins (HSP) are known to protect mammalian cells against a wide range of toxic conditions, including extreme temperatures, oxidative stress, exposure to heavy metals or cytotoxic drugs, glucose deprivation and viral infection. This defence mechanism involves producing large amounts of these proteins which have a cytoprotective function. It requires the activation and translocation of HSF to the nucleus. HSF exists in an inactive, non-DNA binding form. Upon exposure of the cell to heat shock or other stimuli, it is rapidly converted into the DNA binding.\textsuperscript{10} In the nucleus, it then binds to specific heat shock elements and activates transcription. Cyclopentenone PG's are potent activators of HSF.
The second mode of activity is exhibited in the suppression of the nuclear transcription factor NF-κB. NF-κB is a regulator of the immediate early pathogen response and the activation of the immune system. It is known to play a critical role in the regulation of the body's inflammatory and immune responses. This transcription factor exists as part of an inactive cytoplasmic complex (called IKK). In the complex it is bound to an inhibitory protein of the IκB family, usually IκBα, and is activated in response to pathogenic stimuli. Stimulation triggers phosphorylation of the IKK complex, degrading IκBα which results in NF-κB translocation to the nucleus. In the nucleus, NF-κB binds to DNA inducing a variety of genes encoding signalling proteins. Inhibiting NF-κB suppresses the synthesis of viral proteins. Cyclopentenone prostaglandins suppress NF-κB by inhibiting the kinase enzyme IKK responsible for NF-κB activation.

These cyclopentenone PG's have been shown to inhibit a range of viruses including poliovirus and human immunodeficiency virus (HIV) via the cytoprotective activity mentioned above.¹¹⁻¹³
The cyclopentenone ring structure is key to their activity and serves as a Michael acceptor involved in reacting with thiol groups of key proteins.\textsuperscript{14}

Another series of prostaglandin-like compounds, with interesting biological properties, which have emerged are the isoprostanes.\textsuperscript{15,16} Isoprostanes are the products of a non-enzymatic free radical initiated peroxidation arachidonic acid in the mammalian cell. This contrasts with the cyclooxygenase mediated process for the formation of PG's. They hence serve as markers of oxidative stress.\textsuperscript{17,18} They have also been shown to be potent vasoconstrictors as well as platelet aggregation factors\textsuperscript{19} and while little is really known of their biological activity, their increased formation during kidney failure and severe liver disease has been reported.\textsuperscript{20} Isoprostanes A and J are the C12- and C8-epimers of PG's of the A and J series respectively (Figure 1.5). Isoprostanes can be distinguished from other PG's by two structural features, firstly the thermodynamically less stable cis-stereochemistry of the two sidechains and secondly, that they are generated in racemic form which is consistent with a non-enzymatic radical mediated pathway.\textsuperscript{21} Isoprostanes of the A\textsubscript{2} and J\textsubscript{2} series have been shown to be active against a range DNA and RNA viruses, including HIV-1 and influenza virus. They are generated through dehydration of E\textsubscript{2} and D\textsubscript{2} isoprostanes respectively.
1.2. Synthesis of cyclopentenone prostaglandins

Cyclopentenone PG's emerged as an attractive class of prostanoids in the early 1990's. To date, there have been a number of synthetic approaches to these analogues with the most popular methodology being Nyori's three component coupling (3CC) approach. This multicomponent coupling strategy involves a "one-pot" process that combines three or more substrates simultaneously. Hence, this constitutes a direct route to PG's.

Nyori's three component strategy has been one of the most widely utilized strategies for accessing trans-1,2-substituted cyclopentane PG's and was initially designed to gain access to the PGE series. The strategy involves a tandem conjugate addition to a cyclic enone followed by trapping of the resulting enolate with a reactive electrophile. The general strategy makes use of organocuprates in the conjugate addition phase and proceeds smoothly with cyclopentenones. However, trapping of the lithium enolate proved low-yielding. This has been attributed in large part to enolate equilibration. This led, over
time, to the investigation of the efficiency of a number of alternative metal-enolates, generated either by the nature of the conjugate addition adduct or via a transmetallation of the generated enolate. Tin enolates were found to be successful as exemplified in the synthesis of PGE₁. In this example, a phosphine-complexed organocuprate is transmetallated with triphenyltin chloride to give the tin enolate under conditions which utilize HMPA (Scheme 1.1).

Scheme 1.1 Reagents and conditions: (i) t-BuLi, Et₂O, -95 to -78°C, 3 h, (ii) Cul, PPh₃, THF, -78°C, 10 min, (iii) 5, THF, -78°C, (iv) HMPA, Ph₃SnCl, (v) 7 in HMPA, -30°C, 39 h.

The use of triorganozinc allowed the process to occur through a zinc enolate intermediate. This resulted in comparable yields to those of the organocopper route but isolation of the product was easier. The use of dimethylzinc eliminated the need for the phosphine/copper complex or triphenyltin chloride.²³

The multigram preparation of Mexiprostil (Scheme 1.2) uses the vinylstannane of the lower side chain 11. The vinylstannane is treated with n-BuLi and copper
iodide to afford the organocopper reagent (12). Sequential treatment of the enone with the cuprate (12) and aldehyde (10) gave a mixture of diastereomers of the hydroxyl PGE\textsubscript{1} derivative (14).

\begin{center}
\[10\]
\end{center}

\begin{center}
\[11\]
\end{center}

\begin{center}
\[12\]
\end{center}

\begin{center}
\[13\]
\end{center}

\begin{center}
\[14\]
\end{center}

\textbf{Scheme 1.2 Reagents and conditions:} (i) n-BuLi, Bu\textsubscript{3}P, Cul, 11, -78° C, 50%.

Lipshutz and Wood have described the use of a zincate reagent Bu\textsubscript{2}ZnLi to produce a reactive zinc enolate in the synthesis of PG analogues (Scheme 1.3). They had previously demonstrated alkyne hydrozirconation to a cyclopentenone and \textit{in situ} transmetallation to generate a higher order cyanocuprate. Following this, attempts at transmetallation and ensuing conjugate addition with the zincate reagent was attempted. Following hydrozirconation of the alkyne (15), the Zr-Cl bond is substituted with MeLi to give 17. Transmetallation with a catalytic amount of the cyanocuprate Me\textsubscript{2}Cu(CN)Li\textsubscript{2} in the presence of the zincate reagent with slow enone (5) addition, leads to the conjugate addition product (18) which is transformed \textit{via}
Cu-to-Zn transmetallation to the zinc enolate (19). The electrophile then traps the enolate to generate the three component coupling product (20).

Scheme 1.3 Reagents and conditions: (i) Cp₂ZrHCl, THF, rt, (ii) MeLi, -78°C, (iii) Me₂Cu(CN)₂Li₂, MeLi, Me₃ZnLi, (iv) 18, slow addition at -78°C, (v) R₂CHO or R₂OTf, -78°C.

Zwannenburg et al described the enantio- and stereoselective synthesis of clavulone (26) form the PG intermediate γ-hydroxycyclopentenone (24) (Scheme 1.4).²⁴ Nucleophilic octynylzinc addition to the carbonyl group of 22 was followed by reductive opening of the oxirane. Cycloreversion of 23, selective oxidation of the secondary hydroxyl group and reduction of the alkyne moiety afforded 25 from which 26 was obtained in three steps.
Scheme 1.4 Reagents and conditions: (i) \( \text{H}_2\text{O}_2, \text{OH}^-, \text{rt}, 100\%\), (ii) \( \text{RZnBr}, \text{rt}, 90\%\), (iii) \( \text{LiAlH}_4\), rt, 3 days, 77\%, (iv) \( \text{FVT}, 500^\circ\text{C}, 10^{-2} \text{mbar}, 72\%\), (v) \( \text{PCC}, \text{DCM}, 91\%\), (vi) \( \text{H}_2\), Lindlar cat, toluene.

The use of the so-called Corey lactone or derivatives thereof has also been widely employed in the synthesis of cyclopentenone PG's. This can be exemplified in the synthesis of PGA\(_2\). Hodgson and Gibbs\(^{25}\) generated the diol (28) by stereoselective rearrangement of the epoxide (27) with an optically active base. The diol (28) is converted in 3 steps to 29 which is transformed to the key PG intermediate (30) in two steps. This intermediate was used by Grieco and Corey in the synthesis of PGA\(_2\) (Scheme 1.5).\(^{26}\)
In an alternative PG synthesis, the sulfide-directing Pauson-Khand cycloaddition of 1, 2 disubstituted alkenes, was used by Corey for the synthesis of PGA₂ (Scheme 1.6). The key intermediate for the synthesis was the acetal (33). It was generated in 5 steps from the trans-4,5-disubstituted cyclopentenone (32).²⁷

**Scheme 1.6 Reagents and conditions:** (i) [(trimethylsilyl)acetylene]hexacarbonyldicobalt complex, PhCH₃, 95°C, 30 h, 79%. 

²⁷ University of Cape Town
1.3. Synthesis of Isoprostanes

Synthetic routes towards both prostanes and isoprostanes are largely based on three strategies, the Corey synthesis, the two-component coupling and three-component coupling; although a number of other approaches have been adapted.

Much work has been done on the synthesis of isoprostanes of the F-series. Corey et al have described a biomimetic route to 8-epi-PGF$_{2\alpha}$ from arachidonic acid. 28 Mulzer et al have demonstrated the utility of a stereocontrolled biomimetic free radical 8, 12 cyclization in the synthesis of ent-12-epi-PGF$_{2\alpha}$. 29 Rokach et al had prior to this demonstrated using this methodology to generate the all cis-Corey lactone. 30,31 The Corey lactone has also been transformed to 12-epi-PGF$_{2\alpha}$. 32 Larock et al have used a Pd promoted intermolecular coupling of three different alkenes to generate 12-epi-PGF$_{2\alpha}$. 33 Taber et al 34 have developed a novel strategy towards the synthesis of racemic 8-epi-PGF$_{2\alpha}$ ethyl ester (Scheme 1.7). Cyclisation of 34 with rhodium (II) octanoate proceeds to give the bicyclic ketone (35) with 77:23 selectivity for the cis-2, 3 arrangement. Boron trifluoride etherate-mediated addition of thiophenol to 35 under neutral low temperature conditions produces 36a and 36b with a diastereoselectivity ratio of 90:10 for 36a to 36b. The isoprostane (37) was revealed after a few functional group interconversions,
Cha et al have synthesized 12-epi-PGF$_2\alpha$ and its C-15 epimer. Their strategy involves the use of the Corey lactone 39. Key to their approach is the Sml$_2$ induced reductive ring opening of the epoxy ester 40. The resulting dienolate is trapped with an aldehyde for construction of the lower side chain. The requisite cis-dialkyl stereochemistry is established by stereocontrolled hydrogenation occurring at the less hindered convex face of the bicyclic lactone 41. The upper side chain is then installed via Wittig olefination. A few functional group manipulations furnished the isoprostane 12-epi-PGF$_2\alpha$ (42) and its epimer at C-15 (Scheme 1.8).
Scheme 1.8
Snapper et al.\textsuperscript{26} utilized a ring opening metathesis approach as the key transformation in the stereodivergent synthesis of diastereomers of the 15-F\textsubscript{2}-IsoPs 49 (Scheme 1.9).

Scheme 1.9 Stereodivergent synthesis of diastereomers of the 15-F\textsubscript{2}-IsoPs 49
In a total synthesis of 8-epi-PGF$_{2\alpha}$ 60, Rokach and co-workers$^{37}$ have selected a synthetic design based on a Diels-Alder approach as a means of generating the cis-relationship between the sidechains (Scheme 1.10). Key to this approach was control of the facial selectivity of the diene. This involved compelling the diene to approach from the less hindered face of the dienophile so as to obtain the two hydroxyl groups on the ring a to the plane of the ring and the sidechains cis to one another and anti to the hydroxyl groups. To achieve this, the hydroxyl group of the proposed diene was protected as a TBDPS group in a bid to encouraging facial discrimination by the diene. The Diels-Alder reaction produced a mixture of products 52 - 54 with a 92:8 ratio of product resulting from attack of the diene from the less hindered side to product resulting from attack on the more hindered side of the dienophile. The relevant products 52 and 53 were transformed to a gem methoxy derivative 55 via allylic rearrangement. This was converted in two steps to the cis diol 56. Cleavage of the diol 56 with sodium peridate followed by treatment with diisopropylamine and methyl iodide afforded the methyl ester aldehyde 57. At this point, the lower side chain was introduced using Wittig methodology followed by formation of the $\alpha$ aldehyde to give 58. A two-carbon extension of the aldehyde introduced the upper sidechain affording 59. Some functional group manipulation was then required to yield the isoprostane 8-epi-PGF$_{2\alpha}$ 60.
Scheme 1.10 Diels Alder methodology for the synthesis of 8-epi-PGF$_2$α, 60
While much work has been done on the synthesis of isoprostanes of the F-series, the cyclopentenone isoprostanes of the A and J series' have not been widely explored.

Vadari et al\textsuperscript{38} have established a route towards the synthesis of the A\textsubscript{2}- and J\textsubscript{2}-cyclopentenone isoprostanes (67) and (73) respectively. Their approach utilizes two key steps for the formation of both the A\textsubscript{2}- and J\textsubscript{2}- isoprostanes. The first is the stereoselective assembly of the cis-disubstituted cyclopentene moiety (66). The second critical point is the E-stereoselective Julia-Lythgoe olefination employed in the installation of the lower side chain (Scheme 1.11). The third key transformation, only for the formation of the J\textsubscript{2} isoprostane, involves 1, 3 allylic transposition of the C-9 hydroxyl group and oxidation to the ketone (Scheme 1.12).

In the first step, known lactone (61) is converted in two steps to the sulfone lactone (62) with maintenance of initial stereochemistry.\textsuperscript{39} The lactone (62) was then protected as a MIP lactol to which the lower side chain 68 is added to yield 63. This reaction utilizes the Julia-Lythgoe olefination and ensures preservation of the defined stereochemistry as well as E stereochemistry at the $\Delta^{13}$ double bond. Installation of the upper side chain exploits Wittig methodology with a non-stabilized Wittig reagent (69) and well known PG chemistry\textsuperscript{40} to give the Z-olefin in the upper side chain. Oxidation followed by TBS deprotection yields the A\textsubscript{2} isoprostane (67).
Scheme 1.11 Synthesis of cis-disubstituted cyclopentene 66 towards $A_2$ isoprostane 67 and $J_2$ isoprostane 73.

The final key transformation in the formation of $J_2$ isoprostane is the 1, 3 allylic transposition of the C-9 hydroxyl group and oxidation to the ketone (Scheme 1.12). This is followed by functional group manipulation to afford the isoprostane 73. The [2, 3] sigmatropic rearrangement of the secondary selenide 71 afforded the alcohol 72. This was converted in three steps to the $J_2$ isoprostane 73.
Scheme 1.12 Final transformation in the synthesis of J2 isoprostane 73.

1.4. Aims and Objectives

Given the biological activity of both the cyclopentenone prostaglandins and the isoprostanes, it has become necessary to find efficient synthetic routes to cyPG's with a view to evaluating their biological properties. The challenges involved in the synthetic pursuit of these molecules include the difficulty in installing the two sidechains with thermodynamically less favoured cis-dialkyl stereochemistry and as well as the propensity for epimerization of the labile stereogenic centres at C-8 and C-12 (PG numbering). Thus the synthesis of these molecules is not only challenging but also necessary as a means of obtaining sufficient material for biological studies.8
2.1 SYNTHETIC APPROACH

The synthesis of enantiopure cyPG's with the C7- and C6-sidechains orientated cis to each other presents a significant synthetic challenge considering the propensity of these compounds to undergo epimerisation, at the position α to the carbonyl group, in the presence of either acid or base.

The envisaged synthetic approach encompasses the synthesis of the decadienone scaffold (21) in a 3-step sequence from dicyclopentadiene (74) (Scheme 2.1). This involves allylic oxidation of (74) to yield the acetate (77). Hydrolysis of the acetate furnishes the corresponding alcohol (78) which is then oxidised to 21. Installation of the first side chain takes place in a Michael sense followed by electrophilic trapping of the second side chain α to the ketone to give 75 (Scheme 2.1).

The obligatory orientation of the newly installed sidechains is determined by the architecture of the dienone 21 which dictates that addition occurs exclusively from the exo-face of the tricyclic system. This is reminiscent of the Noyori three-component coupling employed for the synthesis of prostaglandins (Scheme 2.2). The second key step in the synthetic sequence involves a Lewis-acid mediated retro Diels-Alder reaction. This allows for the late-stage unveiling of the α, β-unsaturated system of the cyclopentenone PG (76) under mild conditions allowing for the preservation of the relative stereochemistry.
Scheme 2.1 Synthetic approach towards the synthesis of iPG's A-J.

Scheme 2.2 Three-component coupling approach.

2.2 SYNTHESIS OF THE STARTING DECADIENONE 21

Ogasawara and co-workers have illustrated the synthetic utility of 77 and 78 as precursors for the synthesis of 21 (Scheme 2.3). Previous routes to 21
employed selenium dioxide oxidation of 74 to afford 78 hence rendering the oxygen functionality at the requisite position. However, the toxicity of the oxidants led to exploration of alternative procedures by the authors. Preparation of the racemic acetate (77) involves the allylic oxidation of 74. This was achieved through the use of manganese (III) acetate, prepared in situ, in the presence of warm acetic acid, acetic anhydride and catalytic potassium bromide. The result afforded the acetate, in a stereospecific manner, with a yield of 50%. The yields obtained are comparable with those obtained for the selenium dioxide method which yields the 3-hydroxydicyclopentadiene (78) in 57% yield. The exo approach of the acetate group can be rationalized in terms of the sterically congested concave face 74. Spectral data of 77 were identical to those reported by Takano and co-workers. The diagnostic singlet for the methyl group of the acetate resonates at $\delta$ 2.02 in the $^1$H NMR spectrum while the presence of the carbonyl moiety has been confirmed by the IR peak at 1720 cm$^{-1}$.

Hydrolysis of exo-3-acetoxydicyclopentadiene with K$_2$CO$_3$ in methanol for 18 h afforded the allylic alcohol (78). Its $^1$H NMR spectrum showed a new signal for H-3 at $\delta$ 4.07 which corresponds to the signal expected for a proton attached to a hydroxyl bearing carbon. The proposed structure is confirmed by the loss of the signal for the acetate methyl group in the $^1$H NMR spectrum. The C-3 signal resonates at $\delta$ 79.2 in the $^{13}$C NMR spectrum while the signal for the C=O carbon has disappeared. A broad IR absorption band at 3430 cm$^{-1}$ supported the presence of hydroxyl functionality.

Oxidation of 78 to 21 was achieved using pyridinium chlorochromate adsorbed on alumina (PCC/alumina). The reagent is prepared by adding alumina to a pyridinium chlorochromate (PCC) solution and removing the pyridine under reduced pressure. The reaction is performed by stirring excess oxidant with the alcohol 78 in a suitable solvent at room temperature. The use of alumina
reduces the reaction workup to simple filtration. The facile production of the reagent, the clean manner in which the reaction proceeds and simple isolation of the product makes this an attractive alternative for the effective oxidation of primary and secondary alcohols to aldehydes and ketones. The $^{13}$C NMR provided evidence of the carbonyl carbon with a signal resonating at $\delta$ 210.6. This was confirmed by the carbonyl stretching frequency present at 1693 cm$^{-1}$ in the IR spectrum.

The olefinic region of the $^1$H NMR spectrum of 21 has four signals. Of these, H-4 and H-5 appear at $\delta$ 5.77 (doublet of doublets) and $\delta$ 7.36 (doublet of doublets) respectively. This marked difference in chemical shift is attributed to the conjugative electronic displacement of the $\alpha,\beta$-unsaturated carbonyl substructure.

Scheme 2.3 Reagents and conditions: (a) Mn(OAc)$_3$, KMnO$_4$, KBr (cat.), AcOH, Ac$_2$O 70°C, 1 h, 50%; (b) K$_2$CO$_3$, MeOH, rt, 18 h, 85%; (c) PCC on alumina, hexane, rt, 18 h, 96%.
2.3 STRATEGIES FOR THE SYNTHESIS OF DISUBSTITUTED 3-OXODICYCLOPENTADIENE (21)

As illustrated (Figure 2.1), three alternative paths were explored to provide insight into the best synthetic method for elaborating 21 to yield the key intermediate 75. Path A involves the stepwise installation of the first sidechain R1, to generate the ketone 79, followed by base-mediated installation of R2 leading to 75. The first step in Path B is the envisaged generation of the enol silyl ether (80) via conjugate nucleophilic addition followed by trapping of the enolate. The enolate is then liberated and electrophilic trapping by R2 is expected to lead to 75. A three component coupling (3CC) approach, first used by Nyori et al.\(^{48,42}\) was to be explored in Path C in the transformation of 21 to 75 via the metal enolate 81. Common to the first step in all three of the proposed routes is the conjugate addition of the side chain, R1.
2.3.1 BASE MEDIATED APPROACH:

2.3.1.1 Conjugate addition of organocuprate Bu₂CuLi

Butyl ketone (82) was to be used as a model template in the synthesis of isoprostanes of PG's A-J (84) (Scheme 2.4). It was envisaged that the butyl R¹ chain could be used to develop the methodology as it provided an easily accessible form of the R¹ group. Furthermore, one of the aims of this programme is to investigate the use of an unfunctionalised chain in examining the effect of the prostaglandin R¹ group on the biological activity in these compounds.
From this investigation, we hoped to gain insight into the preferred synthetic methods for the synthesis of these compounds.

Scheme 2.4 Reagents and conditions: (i) n-BuLi, Cul, Et₂O, 0°C to rt, 2 h, 62%.

Organocuprate reagents are highly reactive and were expected to chemoselectively transfer ligands exclusively at the β-position of the enone (21) as well as stereospecifically to give the exo substituted tricyclodecanone. Carruthers⁴⁹ has illustrated that the factors that govern the stereochemical outcome of the addition of organocuprates to (poly)cyclic enones are not completely understood. It is accepted that approach of the reagent is in general perpendicular to the plane of the enone and is sensitive to both steric and stereoelectronic factors. Zwannenburg et al⁶⁰ have shown that in both 1, 2- and 1, 4-additions of organometallic compounds to 82, addition invariably occurs from the convex face of the tricyclic skeleton. They propose that this is mainly as a result of the three dimensional structure of 21 and attribute this to the steric control exerted by the C8-C9 ethylene bridge. Hence, the compound 21 undergoes facile and stereoselective 1, 4-conjugate addition with the organocuprate.

Attractions between nucleophiles and electrophiles are governed by two related interactions.⁵¹ The first is the electrostatic interaction between positive and negative charges and the second the orbital overlap between the HOMO of the
nucleophile and the LUMO of the electrophilic species. Both factors play a role but which factor dominates is dependent on the nature of the nucleophile and electrophile involved. Small, highly electronegative nucleophiles are subjected to electrostatic control while the reactions of larger nucleophiles are dominated by orbital overlap. These two types of reagents have been called hard and soft respectively. Hard nucleophiles have a higher charge density while the softer nucleophiles can be uncharged or have larger atoms with higher energy. Electrophiles can also be classified as hard or soft and in general hard nucleophiles prefer to react with hard electrophiles while soft nucleophiles react with soft electrophiles. In the case of the carbonyl moiety, the carbon is considered to be hard due to the partial positive charge that resides on the carbon as a result of the polarization of the C=O bond. It will react with hard nucleophiles. In the case of an α, β-unsaturated carbonyl system, conjugation leads to stabilizing interaction and the π-bonds now react as a single, conjugated system as opposed to separate functional groups. This delocalization of the π-electrons in the conjugated system polarises the structure and renders the C=C bond electrophilic at the β-position. There are now potentially two positions of nucleophilic attack, one of which is hard and the other is soft. Here, the β-carbon does not have a high partial positive charge and is the site of the largest coefficient in the LUMO. Hence the β-carbon is a soft electrophile and is likely to react well with soft nucleophiles such as organocopper reagents in a 1, 4 addition manner.

The gross structure of 82 was deduced from its mass, IR and NMR data. The $^{13}$C NMR spectra showed a diagnostic peak at δ 220.9 thus confirming the presence of the carbonyl moiety. Inspection of the $^1$H NMR of 82, a two bond geminal coupling of 18.4 Hz is observed between the H-$4_{\text{exo}}$ and H-$4_{\text{endo}}$ protons. This type of coupling is indicative of diastereotopic nature of these two protons and hence their magnetic non-equivalence. The assignment H-$4_{\text{exo}}$ has been deduced from the long range four bond “W” coupling that it experiences
with H-2 (Figure 2.2). Mass spectroscopy further confirmed the presence of the proposed 1, 4-addition product.

![Chemical structure](image)

**Figure 2.2** Selected coupling constants for 82 ($J$ values in Hz).

### 2.3.1.2 Alkylation with LDA as base:

With 82 in hand, we turned our attention to the installation of the $\alpha$-sidechain. Following literature procedures, our initial endeavours focused on the use of a kinetic base as a means of installing $R^2$. While the initial choice of the structural entity 21 was made in order to support exo-alkylation at positions 4 and 5 (Scheme 2.2), it was also expected that such a bridged system would suppress enolisation occurring at C-2. Under conditions of both thermodynamic and kinetic control, enolisation to C-2 is not expected to occur on the basis of statistical reasons. Furthermore, it is expected that the bridged system would suppress enolate equilibration which is the major obstacle in conjugate addition approaches to prostanoids. It is anticipated that if such equilibration does occur, it would be slow and protonation thereof would result in formation of the butyl ketone (82) (Scheme 2.5). Hence, regiospecific enolate generation is expected to occur from the corresponding ketone. Alkylation of the requisite regiospecific enolate affords the cis-dialkyl product.
Johnson and Penning\textsuperscript{52} have shown that reactive halides could be used in effecting this alkylation process. Hence, our studies focused on using the highly reactive iodides as the electrophiles in this substitution procedure. They along with others\textsuperscript{53-54} have also demonstrated the importance of the presence of HMPA in these reactions. Suzuki \textit{et al} have shown that the structure and reactivity of the lithium enolate of cyclopentenone are strongly influenced by co-existing co-solvent HMPA.\textsuperscript{55}
Scheme 2.6 Reagents and conditions: (i) LDA, THF, -78°C (ii) Bu₃SnCl, HMPA, Mel, 62%.

Initial alkylation studies were carried out using iodomethane. The required kinetic enolate was generated with LDA and Bu₃SnCl in THF and the enolate successfully alkylated with Mel. The tributylstannyl chloride was used to transmetalate the lithium enolate generated by enolisation of 82, which has been reported to produce a slower yet cleaner reaction with fewer by-products. Its ¹H NMR was used to verify the relative stereochemistry at positions 4 and 5 of 86. H-4 in 86 appears at δ 2.19. This corresponds to the chemical shift for H-4_endo (δ 2.20) in 82. Hence, one can deduce that addition occurred at the concave face of 82 to yield the cis-product. An alternative procedure to the same compound has been explored and will be discussed later (Scheme 2.14).

Having demonstrated that the two sidechains could be installed with control of regio- and stereoselectively, we sought to extend this methodology to different groups which could be manipulated to yield PG’s A and J and analogues thereof. Despite the success achieved with the relatively sterically undemanding methyl-substrate, it was anticipated that larger substrates might provide a stiffer synthetic challenge. A number of different activated alkyl substituents were investigated for installation of R₂, the first being 5-(tetrahydro-2’-pyranyloxy)-1-iodo-pentane (87). With our substrate, this result proved elusive but to some extent the problem was overcome using conditions of thermodynamic control (Scheme 2.10). These findings are elucidated below.
Attempts with various other reactive sidechains proved unsuccessful which led to the exploration of alternative methods for constructing these molecules.

In pursuit of generating analogues of these structures, efforts were made to install a sidechain similar to that found in the PGA- and J-series', only one carbon atom shorter.

The reactive alkyl agent utilized was the tosylate (91) which was generated from ethyl 6 hydroxy-hexanoate (90) (Scheme 2.7). The reaction of 91 with the butyl ketone (82) proved unsuccessful. This led to an investigation into the effects of a shorter R¹-chain on the reaction. As such, the butyl-chain was substituted with an ethyl chain. The ethyl ketone (88) was synthesized using magnesium cuprate methodology to install the ethyl group in the β-position of 21 (Scheme 2.7).

**Scheme 2.7 Reagents and conditions:** (i) C₂H₅Br, Mg, Cul, Et₂O, 80% (ii) LDA, 91, THF, 8% (iii) TsCl, Et₃N, CH₂Cl₂, 66%.

![Diagram showing the reaction of compounds 21, 88, and 89](image-url)
Analysis of the NMR data indicates formation of the trans rather than the required cis-product. This is supported by considering the chemical shifts of the H-4 protons in 88. These have been shown to resonate at \( \delta 1.89-1.96 \) (H-4exo) and \( \delta 2.20 \) (H-4endo). The presence of H-4 at \( \delta 1.54-1.80 \) as part of a 12 proton multiplet in the \(^1\)H NMR spectrum of the addition product 89 indicates that the stereochemical outcome of this reaction is the trans-product as depicted. Repeating the reaction using a larger excess of base (2.5 equiv) improved the yield only slightly to 15%.

The base-mediated addition of ethyl-6-oxohexanoate (95) to 94 was investigated. The species containing the prostaglandin side chain in the \( \beta \)-position 94 was synthesized via a 1, 4 conjugate addition of 93 to 21 (Scheme 2.8). The enol silyl ether (93) is derived from the silylation of 1-octyn-3-ol. It has been demonstrated in the literature that this side chain can be inserted by use of the vinylstannane of 93.\(^{56,57}\) However, it is important to note that the preparation of E-vinylstannanes, formed via hydrostannylation of 1-alkynes is neither regio- nor stereospecific for generation of the E-isomer. Hydrozirconation of 1-alkynes using the Schwartz reagent provides a route towards stereo- and regiodefined E-isomer formation. The alkenylzirconate is transmetalated to give the cyanocuprate\(^{58}\) (See Scheme 1.3). Thereafter conjugate addition of the cuprate to 21 inserts the \( \beta \)-chain to yield 94. Treatment of 94 with LDA generated the enolate which was quenched by the aldehyde 95 to give 96 with the expected exocyclic olefinic bond in only 4% yield (Scheme 2.8). The reaction yielded a number of by-products at first assumed to be diastereomeric \( \alpha,\beta \)-hydroxy ketones. Attempts, however, to encourage these to form the \( \alpha,\beta \)-unsaturated ketone failed. Attempts at the three component coupling approach produced similar results (Scheme 2.27). The longer \( \beta \)-sidechain could account for the low yielding result. NMR evidence does however support the structural assignment.
Scheme 2.8 Reagents and conditions: (i) TBDMScI, imidazole, DMF, rt, 18 h, 78%, (ii) Cp₂Zr(H)Cl, MeLi, CuCN, THF, -50 to 0°C, 50%, (iii) LDA, THF, -78°C to rt, 4%.

While, it has been demonstrated that the ketone could be alkylated by sequential treatment with LDA and the halide or tosylate, the yields obtained for these reactions were low. Furthermore, the reactions are characterized by the production of a number of by-products which, at times, made product isolation difficult, if not impossible. Longer reaction times and increased temperatures contributed to the amount of by-product formed. The length of the alkyl chains seem to have a significant impact on whether the reaction proceeds at all but the complexity of the mixtures obtained and the poor yields resulted in the exploration of alternate methods for the synthesis of these compounds.
2.3.1.3 Alkylation using thermodynamic conditions:

In light of the difficulties in conversion, and low yields, obtained with the use of a kinetic base, we sought to explore the influence of the base on the reaction outcome. In particular, we wanted to determine if the use of the more reactive thermodynamic bases would allow for improved yields and less by-product formation. The envisaged synthetic pathway makes use of a base catalysed reaction that proceeds via a metal enolate transition state. 5-(Tetrahydro-2'-pyranlyoxy)-1-iodo-pentane (87) was to be utilized as the electrophile for trapping of the enolate to give 97 (step (a), Scheme 2.9). It was expected that preferential approach of the iodide would take place on the sterically less demanding exo-face of 82. Step (b) would involve cleavage of the THP moiety, oxidation of the resulting primary hydroxyl group to an aldehyde followed by two-carbon Wittig homologation to reveal 98.

Scheme 2.9 Proposed synthetic route to 98.
As illustrated (Scheme 2.10), the requisite alkylation agent for this reaction scheme was synthesized by a number of different routes in an effort to obtain the best yield. This optimized synthesis was necessary considering the large excess of the alkylation agent, typically 2-5 equivalents, required in the substitution reaction. Taylor, in a comprehensive review on organocopper conjugate addition-enolate trapping, notes that such an excess is necessary as, in addition to the reagent required to react with the enolate, further reagent is needed to consume excess organometallic reagent, reactive ligands etc. Diorganic cuprates usually produce one equivalent of alkylcopper upon completion of conjugate addition, hence excess trapping reagent is required when such reagents are used.\textsuperscript{59}

In the first route (Scheme 2.10, step (i)-(iv)), 1,5-pentanediol (99) is first converted to the THP ether (101) in 57% yield, with the bis-protected product (100) being formed as the minor product. The hydroxyl functionality of 101 is then converted to the tosylate (102). The tosyate is then converted to the iodide (87) using NaI and acetone. The two step transformation from 101 to 87 can be performed in one step with the use of triphenylphosphine, iodine and imidazole. The second route, encompassing steps (v)-(viii), begins with the same starting 1, 5- pentanediol (99) which is stirred in the presence of Ag\textsubscript{2}O, TsCl and catalytic KI in dichloromethane to yield the tosylate (104).\textsuperscript{60} In this case, only 7% of the ditosylated product (104) is isolated. Stirring with sodium iodide and acetone led to the conversion of 104 to 106 in 31% yield.\textsuperscript{61-63} A by-product of this reaction is the acetal (105). This is formed from the reaction of the mono THP protected product with acetone and is a known by-product of the Finkelstein reaction.\textsuperscript{62} The \textsuperscript{1}H NMR demonstrates a C-2 symmetric product with a singlet at $\delta$ 2.04 illustrating the presence of the two CH\textsubscript{3} moieties adjacent to the oxygens of the acetal. These are clearly absent in 106. THP-ether formation is the final step in forming the iodo-THP protected alkyl chain. The
yield for this route over 3 steps is only 15%. It is improved to 43% with direct conversion of 1, 5-pentanediol (99) to 106 with cerium trichloride heptahydrate and sodium iodide in acetonitrile.\(^{64}\)

![Chemical Structures](image)

**Scheme 2.10** Reagents and conditions: (i) TsOH, DHP, CH\(_2\)Cl\(_2\), rt (ii) TsCl, Et\(_3\)N, CH\(_2\)Cl\(_2\), 0°C to rt (iii) Nal, (CH\(_3\))\(_2\)CO, reflux (iv) PPh\(_3\), I\(_2\), imidazole, Et\(_3\)O/CH\(_3\)CN, rt (v) Ag\(_2\)O, TsOH, KI, rt, (vi) Nal, (CH\(_3\))\(_2\)CO, reflux, (vii) TsOH, DHP, CH\(_2\)Cl\(_2\), rt (viii) CeCl\(_3\), 7H\(_2\)O, Nal, CH\(_3\)CN, reflux (ix) base as per table 2.1, THF.

Addition of the \(\alpha\)-sidechain to 82 was attempted with the use of a number of different bases, utilizing conditions of both thermodynamic (Table 2.1) and kinetic control. In all cases, the reactions were characterized by low yields, with entries 2 and 3 yielding both the cis- and trans-addition products. As the conditions for thermodynamic control allow for slower reactions to occur and
the formation of the most stable products,\(^5\) this could account for formation of the more thermodynamically stable \textit{trans}-product. However, once formation of the \textit{cis}-product has occurred, equilibration to the sterically demanding \textit{trans}-product is expected to be slow as this requires the deprotonation of H-4\textsubscript{endo}. It must, however be noted that while thermodynamic conditions afforded both \textit{cis}- and \textit{trans}-products, the yields obtained in these reactions were most promising for this set of reactions. Entry 1 illustrates the result obtained using potassium hydride as base. This reaction did not lead to complete conversion of the starting enone after 18 h with an excess of base. The most successful application utilized KOBu\(^t\) (entry 2). A mixture of \textit{cis}- and \textit{trans}-addition products were isolated with an overall product yield of 62 \%. A small amount of starting material (5\%) remained unreacted. Similar results were obtained using only 0.8 equivalents of the base. Entry 3 makes use of the dimethyl anion as base. This is generated \textit{in situ} by the reaction of NaH with DMSO.\(^{65,66}\) This reaction yielded 30\% of the required \textit{cis}-product. Unreacted starting material accounted for the majority of the material recovered (40\%).

<table>
<thead>
<tr>
<th>Base</th>
<th>Equiv.</th>
<th>Solvent</th>
<th>Temp ((^\circ)C)</th>
<th>Result</th>
<th>Ratio (\textit{cis}:\textit{trans})</th>
</tr>
</thead>
<tbody>
<tr>
<td>KH</td>
<td>1.5</td>
<td>THF</td>
<td>0(^\circ)C</td>
<td>8% (\textit{cis}) \textbf{97}</td>
<td>100:0</td>
</tr>
<tr>
<td>KOBu(^t)</td>
<td>1.1</td>
<td>DMSO</td>
<td>rt</td>
<td>27 %(\textit{cis}) \textbf{97} and 35% (\textit{trans}) \textbf{107}</td>
<td>1.3:1</td>
</tr>
<tr>
<td>MeSO(_2)CH(_2)(^+)</td>
<td>1.2</td>
<td>DMSO</td>
<td>rt</td>
<td>5% (\textit{trans}) \textbf{107} and 30% (\textit{cis}) \textbf{97}</td>
<td>5.4:1</td>
</tr>
</tbody>
</table>

*Dimethyl anion generated from NaH in DMSO

<table>
<thead>
<tr>
<th>Base</th>
<th>Equiv.</th>
<th>Solvent</th>
<th>Temp ((^\circ)C)</th>
<th>Result</th>
<th>Ratio (\textit{cis}:\textit{trans})</th>
</tr>
</thead>
<tbody>
<tr>
<td>KH</td>
<td>1.5</td>
<td>THF</td>
<td>0(^\circ)C</td>
<td>8% (\textit{cis}) \textbf{97}</td>
<td>100:0</td>
</tr>
<tr>
<td>KOBu(^t)</td>
<td>1.1</td>
<td>DMSO</td>
<td>rt</td>
<td>27 %(\textit{cis}) \textbf{97} and 35% (\textit{trans}) \textbf{107}</td>
<td>1.3:1</td>
</tr>
<tr>
<td>MeSO(_2)CH(_2)(^+)</td>
<td>1.2</td>
<td>DMSO</td>
<td>rt</td>
<td>5% (\textit{trans}) \textbf{107} and 30% (\textit{cis}) \textbf{97}</td>
<td>5.4:1</td>
</tr>
</tbody>
</table>

Structure elucidation was accomplished with the help of spectroscopic (Table 2.2) and analytical evidence which confirmed the proposed structures of \textbf{97} and \textbf{107}. Through nOe experiments, it has been confirmed that \textbf{97} is the \textit{cis}-product.
and 107 is the \textit{trans}-adduct. Irradiation of the signal assigned to H-4 ($\delta$ 1.93) of 107 shows an increase in intensity of the signals assigned to H-2 and H-6 as a result of through space relaxation. Since these protons are located on the \textit{exo}-face of the molecule, it can be concluded that H-4 must be \textit{exo} and 107 is the \textit{trans} addition product. Having confirmed the structures and their relative stereochemistry by nOe, we sought to explain the observed differences in the chemical shifts of H-8 and H-9 by conformational analysis of 97 and 107. In the \textit{trans}-isomer (107), the bulky C-4 alkyl group is arranged in the preferred pseudo-equatorial position. This results in a conformational change in the 5-membered ring resulting in the shift of the adjacent carbonyl group towards the C8-C9 bridge. H-9 therefore falls under the anisotropic effect of the carbonyl moiety which accounts for the observed downfield shift of H-9 in the \textit{trans}-isomer. The \textit{cis}-isomer (97) adopts a conformation which minimizes the eclipsing interactions between the alkyl groups on C-4 and C-5. This places the large C-4 alkyl group in a pseudo-equatorial position which shifts the carbonyl moiety towards the C-10 bridge in this case. As a result, the anisotropic influence of the carbonyl group is removed. Thus a relative upfield shift for H-9 is observed in the \textit{cis}-isomer. This interpretation has been confirmed by molecular modelling as illustrated in figure 2.3. Modelling confirmed a lower energy status of the \textit{trans} isomer 107 with an energy difference of 2.54 kcal/mol (10.63 kJ/mol) between the two isomers.
Figure 2.3 Conformations of 97 and 107 as determined by ab initio molecular dynamics calculations
The stereochemistry depicted for 97 and 107 was confirmed with NMR experiments. COSY spectra were used in the assignment of the diagnostic signals as evidenced in Table 2.2. Differences were observed in the chemical shifts of certain key signals of the two stereoisomers. There is a marked difference in the value of the chemical shift of the signals assigned to H-8 and H-9 in the cis-isomer (97) with H-8 appearing at δ 6.01 and H-9 at δ 5.96. By contrast, the corresponding signals in the trans-isomer (107) resonate at δ 6.02 and δ 6.13 respectively. Significantly, this constitutes an upfield shift of the H-9 signal by 0.17 ppm for the trans-isomer.

Table 2.2 Selected Data from the proton NMR spectra run in CDCl₃ of the stereoisomers 97 and 107

<table>
<thead>
<tr>
<th>Proton</th>
<th>97 (cis)</th>
<th>107 (trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-8</td>
<td>δ 6.01 (dd, J 5.7 and 3.0 Hz)</td>
<td>δ 6.02 (dd, J 5.8 and 3.0 Hz)</td>
</tr>
<tr>
<td>H-9</td>
<td>δ 5.96 (dd, J 5.7 and 3.2 Hz)</td>
<td>δ 6.13 (J 5.8 and 3.2 Hz)</td>
</tr>
<tr>
<td>H-1</td>
<td>δ 3.04-3.10 (m)</td>
<td>δ 3.12 (br m)</td>
</tr>
<tr>
<td>H-2</td>
<td>δ 2.87 (m)</td>
<td>δ 3.0 (m)</td>
</tr>
<tr>
<td>H-7</td>
<td>δ 2.87 (m)</td>
<td>δ 2.97 (br m)</td>
</tr>
<tr>
<td>H-6</td>
<td>δ 2.46 (m)</td>
<td>δ 2.54 (m)</td>
</tr>
<tr>
<td>H-2'</td>
<td>δ 4.58 (m)</td>
<td>δ 4.56 (m)</td>
</tr>
<tr>
<td>H-4</td>
<td>δ 1.81 (m)</td>
<td>δ 1.93 (m)</td>
</tr>
</tbody>
</table>

The assignment of the relative stereochemistry was further confirmed by examination of the COSY spectrum of 107 which revealed a cross-peak between H-2 and H-4. This correlation is a consequence of 4 bond "W"
coupling which is only observed for the cis-isomer. Examination of molecular models reveals that in the trans-isomer H-2 and H-4 are ideally orientated thus allowing for long range coupling. By contrast, the cis-isomer 97 lacks the requisite "W" configuration and consequently no cross-peak between H-2 and H-4 is observed. While H-4 resonates as a multiplet in both the cis- and trans-isomers, the observed coupling in the COSY of 107 can only be attributed to "W" coupling which can only occur in the cis-isomer. This very diagnostic signal of H-4 is more deshielded in the trans-product (δ 1.93) relative to its position in the cis-product (δ 1.81). An increase in steric compression is known to lead to an upfield proton shift relative to its former position.67,68 In the cis-addition product, H-4 is sterically more compressed, Hence, accounting for its upfield shift relative to the signal for the corresponding proton in the trans-addition product. The COSY spectrum of 107 was also able to indicate that H-4 does not couple to H-5 due to the dihedral angle between the two of 90°C in the trans-isomer. From inspection of molecular models, H-4 and H-5 should couple in 97 (dihedral angle =180°), although the large aliphatic quotient of the molecule makes it difficult to assign this proton absolutely.

In an attempt to investigate whether the protecting group of the α-sidechain affected the success of the reaction, 82 was treated under thermodynamic conditions with a base in the presence of a TBDMS protected five carbon iodide (108). Treatment of 82 with KOBu1 and alkylation of the resulting enolate of 82 with 108 rendered an inseparable mixture of cis- and trans-stereoisomers (Scheme 2.11). Based on an analysis of the integration for the signal for the H-8 and H-9 protons, it may be concluded that the cis:trans ratio is 2:3.

The reactive sidechain 108 was synthesized in two steps from 1, 5-pentanediol (99). The diol was heated in refluxing acetonitrile in the presence of sodium iodide and cerium trichloride to yield the iodo-alcohol (106). The hydroxyl group was protected as the TBDMS ether using TBDMSCI in the presence of triethylamine to afford 108.
At this point, we considered the use of allyl bromide as the electrophile for installing the $R^2$ sidechain. Allyl bromide is readily available rendering it ideal considering the large excess of alkylating agent required to install the $R^2$ sidechain.

While competing bis-alkylation could be predicted with a large excess of base and allyl bromide, the compromise lay between driving the reaction to completion and the aforementioned bis-alkylation. To that end, attempts were made to alkylate 82 with allyl bromide and an excess of potassium hydride. This however yielded only the bis-allylated product 110 (Scheme 2.12). NMR evidence lay in the integration of the olefinic region. A ratio of 1:1 for H-8 or H-9:H-4$^2$ is expected for the single alkylation product. The presence of 8 olefinic protons in the $^1$H NMR spectrum indicates the presence of two allyl...
groups in the molecule. Attempts using potassium hydride as base rendered a separable mixture of the bisallyl product 110 as well as the mono-allylated addition product 111. NMR inspection of 111 revealed H-8 and H-9 at $\delta$ 6.13 and $\delta$ 6.18. At this point the relative stereochemistry was not defined. We were however also able to synthesize the mono-allylated product using the triply convergent approach (Scheme 2.18) and at that point a full structural assignment was made (as described in section 2.4).

![Scheme 2.12 Reagents and conditions: (i) KH, allyl bromide, THF, 38%.](image)

Having demonstrated the applicability of KOBu$^+$ (Table 2.2) in generating the cis-addition products, its use was extended to the formation of potential analogues of PG's A-J as described above (Scheme 2.7). Alkylation of the enolate of 82 with 112 in the presence of KOBu$^+$ gave an inseparable mixture of the cis- and trans-stereoisomers 113 + 114 followed by the trans-product 114 which was isolated in only 11% yield (Scheme 2.13). The ratio of cis:trans in the mixture as determined by the NMR ratio is 1:1. The stereoisomers were assigned on the basis of evidence presented earlier wherein the signal for the H-9 proton experiences a marked downfield shift in the case of the trans-isomer relative to the corresponding signal in the cis-isomer. Assignment of the stereoisomers was confirmed at a later stage where the trans-isomer was unambiguously produced in a stereospecific manner (Scheme 2.24).
Scheme 2.13 Reagents and conditions: (i) TsCl, Et3N, CH2Cl2, 0°C to rt, 66% (ii) NaI, (CH3)2CO, reflux, 83%, (iii) KOBu, DMSO, rt.

The alkylating agent 112 was synthesized in two steps from commercially available ethyl 6 hydroxy-hexanoate (90) (Scheme 2.13). Tosylation of the hydroxyl moiety was followed by iodination with NaI in acetone.

2.4 THREE COMPONENT COUPLING APPROACH

Potentially the most 'synthetically flexible and direct' route to prostaglandin molecules has been the triply convergent approach as pioneered by Noyori et al. There is a large body of literature on the investigations into the feasibility and refinements of this synthetic protocol over time. In this approach, the entire framework of the prostaglandin is assembled in a one pot sequence. This involves β-alkylation of the 4-oxygenated 2-cyclopentenone derivatives, this
process relying on the Michael-acceptor properties of the cyclopentenone nucleus. The β-chain is introduced with concomitant enolate generation via organometallic induced conjugate addition. The enolate can, in principle, be trapped with an electrophile to allow for regioselective α-alkylation (Scheme 2.2).

We sought to extend this methodology to our didecadienone system, employing the three component strategy with the hope of affecting cis-alkylation directed by the architecture of 21 (Scheme 2.1).

Chapdelaine and Hulce have reported that copper and lithium enolates were unreactive relative to those bearing other gegenions. However, following the success reported by Johnson and Penning in a three component coupling (3CC) approach using Mel as electrophile on their substrate, we chose to repeat the reaction with our substrate 21 (Scheme 2.14). Thus we employed the 3CC strategy conditions elucidated by Johnson and Penning. As such, addition of dibutylcuprate to 21 followed by addition of HMPA and Mel at low temperature afforded the vicinally disubstituted 86 in 67% yield followed by the 1, 2-addition product 115 (30%) (Scheme 2.14).

![Scheme 2.14](image)

**Scheme 2.14 Reagents and conditions:** (i) Bu₂CuLi, THF, -78°C, (ii) HMPA, Mel, -78°C to rt.

NMR elucidation of 86 can be interpreted in a similar manner to that described earlier for this molecule (Scheme 2.6). The gross proposed structure of 115
was verified by spectroscopic and analytical data. The presence of four signals corresponding to the olefinic protons in the $^1$H NMR, as well as the $^{13}$C NMR, indicated that Michael addition did not take place. This is further supported by an absorption band characteristic of an OH which appears in the IR spectra. Given that cuprates, in general, do not undergo 1, 2 addition to α, β-unsaturated compounds, it is proposed that incomplete formation of the cuprate results in the formation of 115. This can be overcome by using the conditions which were used in the formation of 82 and stirring the Cul and n-BuLi at 0°C for a longer period of time.

A comparison using 87 (Scheme 2.10) as a source of the alkylating agent seemed prudent at this point. Addition of the lithium dibutylcuprate to 21, followed by HMPA and 87 afforded 97 (20%) and an inseparable mixture of 97 and 107 (8%) as well as unreacted 82 (30 %) (Scheme 2.15). Longer reaction times i.e. 4 days failed to improve the conversion.

Scheme 2.15 Reagents and conditions: (i) n-BuLi, Cul, THF, 0°C, (ii) HMPA, 87, -78°-0°C, 6 h.
The cis-product 97 has been hydrolysed using catalytic p-toluene sulfonic acid in methanol to give the free hydroxyl moiety in 116 which was then oxidized to the aldehyde (117) under Dess Martin conditions. While no further work was carried out on 117, this nonetheless provides a point of departure for the synthesis of iPG analogues. Wittig homologation of 117 would afford an analogue of PG-A or -J which would allow for testing of the effect of the double bond position on biological activity (Scheme 2.16).

Scheme 2.16 Reagents and conditions: (i) TsOH, CH₂OH, rt to 45°C, 79% (ii) Dess Martin periodinane, CH₂Cl₂, rt, quant.

The structural assignments for 97 and 107 were made using ¹H and ¹³C NMR spectra interpretation, similar to those described before for the assignment of 97 and 107 (Scheme 2.10). Relative stereochemistry was assigned on the basis of comparative Rf values to the already verified 97 and 107 as well as nOe studies. Conversion of 97 to 117 was confirmed by noting that aldehyde proton of 117 was shown to resonate at δ 9.74 as a singlet in its ¹H NMR
spectrum. The presence of a signal at $\delta 202.4$ in the $^{13}$C spectrum is further indication of the presence of the aldehyde carbon.

From these results, it emerges that the base-mediated approach using thermodynamic conditions provides us with a better recovered yield of the required cis-product. The drawback with all of these reactions, however, is that prolonged reaction times do not lead to complete conversion of the starting material but do lead to a larger observed decomposition and competing formation of the thermodynamically more stable trans-product. Furthermore, addition of excess base leads to bis $\alpha$-alkylation (Scheme 2.11). From this it is clear that further work would involve a study looking at the effect of the base stoichiometry on the reaction outcome with a view to improving the yield.

The reaction of lithium enolates with alkyl halides has been utilized widely for ketone alkylation although highly selective monoalkylation with strict exclusion of proton exchange has often remained difficult. Organozinc reagents have successfully been used as a transmetallation agents in the 3CC coupling protocol to overcome the difficulties encountered with the lithium and copper enolates. Suzuki et al.\textsuperscript{72} demonstrated that the reaction of equimolar amounts of the cyclopentenone species (5), a vinyllithium $\beta$-side chain (118) and dimethylzinc followed by addition of the reactive $\alpha$-sidechain (119) in excess would generate the triply coupled product (120) (Scheme 2.17).
Scheme 2.17 Reagent and conditions: (i) ZnEt₂, THF, 119, -78°C, 71%.⁷²

The applicability of this methodology to our system was investigated using allyl bromide as the source of reactive electrophile. Previous attempts to generate this product using base mediated methodology have proved unsuccessful (Scheme 2.12). The product of the reaction between n-BuLi and diethylzinc, generated in situ, was added to the enone (21).⁷⁴,⁷⁵ It is postulated that this reaction proceeds via a lithium methyl/butyl mixed zincate as the reactive species with only the sp² hybridized C-1 of 118 undergoing conjugate addition to the enone.⁷² This is followed by addition of HMPA and allyl bromide. The resulting complex mixture, after separation, revealed 2 major products 111 and 121 accompanied by a large amount of unconverted butyl ketone (82) after several hours (Scheme 2.18).
Scheme 2.18 Reagents and conditions: (i) n-BuLi, Zn(CH(CH₃)₂, THF, -78°C (ii) HMPA allylbromide, THF, -40°C to rt.

The $^1$H NMR spectra of both 111 and 121 indicate the presence of the vicinally disubstituted moiety with no indication of bis-allylation occurring as seen before (110, Scheme 2.12). In contrast to the previous examples in which the chemical shift of H-9 was diagnostic in the assignment of the relative stereochemistry, in this case this was not possible. Consequently, alternate methods were used for stereochemical assignment.

The signal for H-4² resonates as a dddd in the range $\delta$ 5.66 -5.79 ppm in both isomers. H-4³ is identified as a complex multiplet between $\delta$ 4.91-5.02. The signals that resonate at $\delta$ 2.56-2.60 and $\delta$ 2.58-2.65 ppm are assigned to H-6 in 111 and 121 respectively. These signals exhibit distinctly different coupling patterns and, by comparison, were invoked as a means of assigning the cis- and trans-isomers. H-6 in 111 is a much simpler signal than that of H-6 in 121. Structure modelling indicates that only the trans-isomer would be set up for long range "W" coupling between H-6 and H-4. In both isomers, H-6 is capable
of coupling to H-2 with a large coupling constant and two smaller couplings to H-5 and H-7. Only, in the trans-isomer is there a predicted coupling between H-6 and H-4. This additional coupling reveals itself in the complexity of the signal for H-6 in 121. The signal assigned to H-6 in 111 resonates as a ddd ($J = 10.0$ and $2 \times 4.0$ Hz) while H-6 in resonates as a dddd ($J = 9.0$ and $3 \times 4.0$ Hz) in 121. Furthermore, structure modelling indicates that only the trans-isomer would be set up for long range “W” coupling between H-4 and H-5$^2$. The weight of evidence allows us to conclude that 121 as the trans-isomer and 111 as the cis-isomer. The ratio of cis:trans is 3:1. The reaction does not proceed to completion and the butyl ketone (82) is isolated in 35% yield.

\[\text{cis-isomer: 111} \]
\[\text{trans-isomer: 121} \]

\textbf{Figure 2.3} Comparative couplings of H-6 of 111 and 121 ($J$ values in Hz).
Further to our study on the influence of the leaving group on the success of the challenging α-alkylation, we sought to use triflates as the reactive electrophile species. Their use has been well documented \(^{76,77,78}\) and hence, it was clear that the use of triflates as a means of installing the α-sidechain needed to be investigated.

Trifluoromethanesulfonic esters are typically prepared from the reaction of an alcohol with triflic anhydride in the presence of a non-nucleophilic base at low temperature. As alkyl triflates are highly electrophilic, the use of pyridine as a base in their preparation is precluded as alkylation of pyridine occurs during
this reaction.* The use of a hindered base such as 2, 6-di-tert-butyl-4-methylpyridine (DTBP) is preferred in their preparation. The advantage associated with using this base is that it forms a precipitate which can be removed by filtration to render fairly pure triflate. After attempting the reaction using more readily available bases as illustrated in the literature, we turned our attention to the use of this base in the synthesis of the alkyl triflates.

As indicated in the literature, alkyl triflates are sensitive groups and not particularly stable. Hence triflate formation is conducted simultaneously as the enolate generation. This allows for both mixtures to be maintained at the appropriate temperature and under inert conditions before the enolate is treated with a solution of the triflate transferred using a cannula. The enolate is generated by treatment of 21 with the trialkylzincate intermediate generated from n-BuLi and ZnCl₂.TMEDA. This zincate undergoes conjugate addition to the Michael acceptor 21. The use of a mixed zincate in 1, 4-addition reaction has been well illustrated by Watson and Kjonass. The enolate thus formed is quenched with a large excess of the triflate to afford 128 (Scheme 2.19).

* There are examples which make use of pyridine in the literature. Decico, C.P., Grover, P. *J. Org Chem.* 1996, 61, 3534
Scheme 2.19 Reagent and conditions: (i) n-BuLi, ZnCl₂, TMEDA, THF, -48°C to 0°C, (ii) HMPA, 127, -78°C to -40°C, 18 h, (iii) Tf₂O, Et₃N, CH₂Cl₂, -25°C, 10 min.

The ¹H NMR of 128 indicates the presence of the alkynic proton H-4$^5$ (δ 3.98). It also indicates the presence of the butyl chain. nOe studies were conducted by irradiation at one of the olefinic protons, C-8 or C-9 at δ 6.09. This revealed an enhancement of the signals corresponding to H-4. Thus H-4 is spatially close to H-8 or H-9, indicative of cis-product formation. The reactions attempted were characterized by low yields and large degree of decomposition. Attempts to generate these products from the enol silyl ether derived from the butyl ketone (82) are described below (Scheme 2.29). In this reaction, Et₃N was used as the base in the triflate generation. The above reaction was repeated using triethylamine and 2, 6 ditert-butylpyridine as base for generation of the triflate without any significant change in the outcome.

The coupling reaction was reproduced using the triflate generated from the alcohol (101). The triflate was prepared using the non-nucleophilic hindered
base, DTBP, under similar conditions as described above. A number of attempted couplings were made, all resulting in isolation of varying amounts of butyl ketone as the sole identifiable product.

**Scheme 2.20** Reagent and conditions: (i) n-BuLi, ZnCl₂, TMEDA, THF, -48°C to 0°C (ii) HMPA, 129, -78°C to -40°C, 18 h (iii) Tf₂O, DTBP, CH₂Cl₂, -25°C, 3 h.

Coupled with the extremely cautious conditions required for generation of the triflate, this did not emerge as the most viable route for preparation of these compounds.

While the traditional 3CC strategies focused on the use of the so-called reactive alkylating agents such as iodides or triflates, we were also interested in exploring the use of aldehydes as coupling partners.81-83 Eddolls and co-workers82 have explored the use of three component coupling methodology using aldehydes to install the α-functionality. They were able to show that a one pot three component coupling procedure could be employed on both
racemic and enantiopure substrates to give good yields of the exocyclic enones (Scheme 2.21).

Scheme 2.21

Our extension of this methodology was in the use of the $R^2$ chains employed in the successive one pot alkylocuprate addition/aldol condensation/dehydration route. A few $\alpha$ sidechains were investigated (Table 2.3). The reagents used were $Bu_2CuLi$ and $Bu_2ZnLi$ (Scheme 2.22). Reagent addition was followed by aldehyde quench of the enolate intermediate $131$. From the result obtained, dehydration occurs in the absence of any significant heating or acid.

Scheme 2.22 Reagents and conditions: (i) $n$-BuLi, Cul, ZnCl$_2$, TMEDA, Et$_2$O, -78°C (ii) $R_2CHO$, 0°C.
Table 2.3 Synthesis of exocyclic enones via one pot alkylcuprate addition/aldol condensation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cuprate reagent</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield, (%) (E/Z ratio)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu$_2$CuLi</td>
<td>CH$_3$CHO</td>
<td><strong>131</strong></td>
<td>(30) (100:0)</td>
</tr>
<tr>
<td>2</td>
<td>Bu$_2$CuLi</td>
<td>CH$_3$(CH$_2$)$_2$CHO</td>
<td><strong>132</strong></td>
<td>(59) (100:0)</td>
</tr>
<tr>
<td>3</td>
<td>Bu$_2$ZnLi*</td>
<td>CO$_2$Et(CH$_2$)$_2$CHO</td>
<td><strong>133</strong></td>
<td>(34) (100:0)</td>
</tr>
</tbody>
</table>

* was generated from ZnCl$_2$-TMEDA and n-BuLi in THF
** ratio determination-see page 61

Entry 1 uses the commercially available acetaldehyde as the $\alpha$-addition moiety. NMR evidence in support of the product was unambiguous and pointed to the fact that the postulated exocyclic olefinic group had indeed been installed. The presence of signal at $\delta$ 6.36 (qd, 3 x 7.5 and 2.1 Hz) in the $^1$H NMR indicated the presence of a new olefinic signal which could only be ascribed to H-4$^1$. The smaller coupling constant of 2.1 Hz is attributed to the allylic coupling between H-4$^1$ and H-5. A signal at $\delta$ 135.9 in the $^{13}$C NMR spectra further verifies the presence of the olefinic moiety.

Entry 2 illustrates the result obtained with hexanal as the aldehyde. Once again, the exocyclic olefinic proton, H-4$^1$, is identified as the most deshielded signal ($\delta$ 6.29, ddd, $J$ 8.4, 7.2 and 2.4 Hz) with a small allylic coupling to H-5. The $^{13}$C spectrum indicates the presence of three olefinic carbon signals resonating at $\delta$ 133.6, 135.9 and 137.2 with the latter being attributed to the newly generated C-4$^1$.

The third entry makes use of the aldehyde 95 generated via Swern oxidation of the readily available ethyl 6-hydroxy-hexanoate. The reaction is characterized by the production of a number of products. Included in these are presumably the four diastereomeric $\beta$-hydroxy ketones as well as the dehydrated form. Attempts to mesylate or tosylate the diastereomeric alcohols with a view to dehydrating these compounds were unsuccessful. The dehydrated product could however be isolated from the original reaction mixture in 34% yield.
Enone (133) was shown by $^1$H NMR to be a single diastereomer with a new olefinic resonance at $\delta$ 6.24 (ddd, $J$ 8.8, 6.8 and 2.2 Hz) accounting for the presence of a new olefinic proton H-4$^1$. The small coupling constant can be attributed to allylic coupling with H-5 which may be singled out in the COSY spectrum as resonating at $\delta$ 2.39. A cross peak from H-5 highlights H-6 ($\delta$ 2.52) which is shown to couple to both H-2 and H-7. The protons H-1 and H-7 are located as cross peaks from H-8 and H-9 ($\delta$ 5.94, 2H, $J$ 11.4, 5.6 and 2.6 Hz). Therefore H-7 can be identified as resonating at $\delta$ 3.00 and H-2 at 2.96 (dd, $J$ 8.9 and 5.0). The $^{13}$C assignment is verified by cross referencing using HSQC experiments. This is also seen for 132 and 131.

In this case, the alkyl moiety introduced in a 1, 4 addition sense was the trialkylzincate intermediate Bu$_3$ZnLi generated from the addition ZnCl$_2$.TMEDA to n-BuLi in THF and which may form an alkoxydialkylzincate.$^{84,85}$ Zinc enolates are thought to suppress the proton exchange between the enolate generated from the starting material and ketonic products. The ZnCl$_2$.TMEDA salt is a deliverable form of zinc and is more convenient to use than ZnCl$_2$ since it is non-hygroscopic.$^{86}$

| Table 2.4 Selected coupling constants for the enones the 131, 132 and 133 |
|-----------------|-----------------|-----------------|
|                 | H-4$^1$         | H-4$^2$         | H-5              |
| 131             | 6.36 (qd, $J$ 3 x 7.5 and 2.1 Hz) | 1.72 (dd, $J$ 7.5 and 1.2 Hz) | 2.40 (m)         |
| 132             | 6.29 (ddd, $J$ 8.4, 7.2 and 2.4 Hz) | 2.01-2.12 (m) | 2.50-2.54 (ddd, $J$ 8.8, 4.0 and 1.6 Hz) |
| 133             | 6.24 (ddd, $J$ 8.8, 6.8 and 2.2 Hz) | 2.02-2.14 (m) | 2.39 (m)         |
While the yields obtained for these reactions were not optimised, they were reproducible (Table 2.3). These exocyclic enone species were seen as key intermediates for the production of a number of different types of prostaglandins via different routes (Scheme 2.23). Route A involves a rDA performed under Lewis-acid conditions to reveal the \( \alpha, \beta \)-unsaturated cyclopentenone ring. This is a way into the formation of analogues of prostaglandins of this type. Route B involves a conjugate reduction with obligatory formation of the trans cyclopentenone prostaglandin. The initial step in route C, involves exo- to endo-cyclic isomerisation of the double bond. It is envisaged that at this point, reduction of this double bond would produce the analogue with the vicinal disubstitution being cis. A simple rDA would then give the cyclopentenone isoprostane.

Scheme 2.23
To this end, both 133 and 132 were subjected to conjugate reduction using the protocol developed by Stryker. (Scheme 2.23, Route B). Chemoselective conjugate reduction is effected with the use of the hexa-μ-hydrohexakis(triphenylphosphine) hexacopper complex in toluene.\(^8^7\)

This bulky reagent will approach the exo-face of the substrate and hence it is anticipated that the relative stereochemistry of the α- and β-side groups would be trans (Scheme 2.24). This was verified via NMR experiments. Irradiation of H-4 (δ 1.94) during nOe experiments on 140 lead to the enhancement of the signals corresponding to H-2, H-7 and H-6. It can therefore be deduced that the relative stereochemistry is indeed trans. Similarly, irradiation of H-6 (δ 2.54) in 141 enhances the signal corresponding to H-4. The relative positions of H-8 and H-9 in 141 were verified using the COSY spectrum.

![Scheme 2.24](image)

**Scheme 2.24** Reagents and conditions: (i) [(Ph\(_3\)P)CuH]\(_6\), toluene, 18h.

In the elaboration of route A, 134, was treated with ethylaluminium dichloride in the presence of maleic anhydride at 50°C. This affords two products which are identified as the E-and Z-adducts (Scheme 2.25).
Differentiation of E-and Z-products was assigned on the basis of NMR interpretation (Table 2.5). The olefinic proton, H-6, resonates at δ 6.51 (tt, J 2 x 7.8 and 2 x 1.8 Hz) in the E-isomer 143 and at δ 6.01 (br t, J 2 x 7.6 Hz) in the Z-isomer 142. The relative chemical shifts can be explained on the basis of the anisotropic effect of the carbonyl group. It is clear from the structure that the E-isomer is set up for H-6 to experience this effect and hence the downfield shift of H-6 in 143 relative to that of 142. This signal can be regarded as a collapsed doublet of doublets in which H-6 of the Z-isomer 142 couples to the two H-5 protons. In the E-isomer H-6 resonates as a triplet of triplets coupling to both H-5 protons but also has a small allylic coupling to H-2'. This can be verified by a crosspeak from H-6 to H-2' in the COSY spectrum. H-3' resonates at δ 7.53 (ddd, J 6.0, 2.7 and 0.9 Hz) in 143 and δ 7.43 (dd, J 6.0 and 2.4 Hz) in 142. The large coupling constant in both cases refers to that with H-4' while the intermediate in 143 and the smallest in 142 indicate the coupling to H-2'. The smallest coupling in 143 is the long range “W” coupling experienced with H-6. From model structures, only the E isomer is set up for such “W” coupling. A cross peak in the COSY spectrum from H-3' to H-6 confirms this model structure elucidation. From this data 142 can be assigned as the Z-isomer and 143 as the E-isomer. The ratio of E/Z is 5:1.
Table 2.5 Selected chemical shifts and coupling constants for 142 and 143

<table>
<thead>
<tr>
<th></th>
<th>H-4'</th>
<th>H-3'</th>
<th>H-2'</th>
<th>H-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>142(Z)</td>
<td>6.23 (dd, J 6.0 and 1.7 Hz)</td>
<td>7.43 (dd, J 6.0 and 2.4 Hz)</td>
<td>3.27 (m)</td>
<td>6.01 (br t, J 2 x 7.6 Hz)</td>
</tr>
<tr>
<td>143(E)</td>
<td>6.32 (dd, J 6.0 and 2.0 Hz)</td>
<td>7.53 (ddd, J 6.0, 2.7 and 0.9 Hz)</td>
<td>3.48 (m)</td>
<td>6.51 (tt, J 2 x 7.8 and 2 x 1.8 Hz)</td>
</tr>
</tbody>
</table>

**Figure 2.5** Selected coupling constants of 142 and 144 (J values in Hz).

Differentiation of the E- and Z-isomers of 145 and 144 was based on interpretation of the $^1$H NMR in combination with structure modelling. A few key signals were used in this interpretation. The signal assigned to H-4 in 145 resonates as a ddd at $\delta$ 7.54 (J 6.2, 2.7 and 1.5 Hz). The same signal in 144 resonates as a dd at $\delta$ 7.63 (J 5.6 and 2.8 Hz). Structure modelling indicates that the extra coupling in 145 is due to H-4 interaction with H-2'. This is only
possible in the \(E\)-isomer configuration. This small coupling does not occur in \(\text{144}\) as the \(Z\)-isomer is not structurally set up for such "W" coupling. This is confirmed by the signal \(H-2^1\) which is shown to couple to \(H-2^2\), \(H-3\) and \(H-4\). This coupling of \(H-2^1\) to \(H-4\) is not present in \(\text{144}\) as the protons are not optimally aligned for such a long-range coupling to occur. From the above data, it is clear that \(\text{145}\) is the \(E\) isomer while \(\text{144}\) is the \(Z\)-product.

Table 2.6 Selected chemical shifts and coupling constants for \(\text{144}\) and \(\text{145}\)

<table>
<thead>
<tr>
<th></th>
<th>(H-2^1)</th>
<th>(H-4)</th>
<th>(H-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{145}(E))</td>
<td>6.55 (tt, (J 2 \times 7.8) and (2 \times 1.5) Hz)</td>
<td>7.54 (dd, (J 6.2), and (2 \times 1.5) Hz)</td>
<td>6.32 (dd, (J 6.2) and (1.7) Hz)</td>
</tr>
<tr>
<td>(\text{144}(Z))</td>
<td>6.64 (td, (J 7.8) and (2 \times 2.8) Hz)</td>
<td>7.63 (dd, (J 5.6) and (2.8) Hz)</td>
<td>6.14 (dd, (J 5.6) and (2.0) Hz)</td>
</tr>
</tbody>
</table>

Figure 2.5 Selected coupling constants of \(\text{144}\) and \(\text{145}\) (\(J\) values in Hz).
Both starting materials for the rDA reaction 133 and 132 are diastereomerically pure E-isomers with no evidence indicating any Z-isomer present. The rDA reaction, however, is seen to yield a mixture of both E- and Z-products. This can only be rationalized by concluding that partial isomerisation occurs during the course of the rDA reaction resulting in the formation of both the E- and Z-isomers. Facile isomerisation of \( \alpha, \beta \)-unsaturated ketones under both thermal\(^{88} \) and photochemical conditions\(^{89} \) has been reported in the literature. Lewis-acid complexation to the carbonyl oxygen is followed by electron migration to neutralise the positively charged oxygen. Regeneration of the \( \alpha, \beta \)-unsaturated ketone could see neutralization of the positively charged CH\(_2\) occurring from either face of the molecule (Scheme 2.26).

![Scheme 2.26](image)

Route C as described in Scheme 2.23 first involves an \textit{exo} to \textit{endocyclic} double bond isomerisation. Attempts at the isomerisation of 134 with concentrated hydrochloric acid in the presence of \( n\text{-BuOH} \)\(^{90} \) were unsuccessful, yielding only the starting three component addition product. A
second well known approach, which involves the use of zinc dust in the presence of acetic acid\textsuperscript{91} was attempted on 134 to effect this synthetic transformation. However, once again, stirring for 48 h only produced the starting material. Further efforts may involve the use of rhodium\textsuperscript{92,93} or potassium fluoride in the presence of Al\textsubscript{2}O\textsubscript{3}\textsuperscript{94} to render the endocyclic isomerisation product (137). It is then postulated that conjugate reduction of 20 will afford the cis vicinally disubstituted 138. Lewis-acid mediated rDA conditions are expected to reveal the isoprostane moiety 139.

This three component coupling approach was extended towards the use of 94 as the \( \beta \) chain, as is found in PG's A to J. Hydrozirconation of 1-alkynes using the Schwartz reagent provides a route towards stereochemical and regiochemical control of \( E \)-isomer formation\textsuperscript{95,96}. The alkenylzirconate of the alkyne is transmetallated to give the cyanocuprate generated \textit{in situ} as before (Scheme 2.8). Therefore conjugate addition of the cuprate to 21 inserts the \( \beta \)-chain and concomitantly generates the enolate species \textit{in situ} which was then quenched with the aldehyde 95 to give 96 in low yield (Scheme 2.27). The \( ^{1}H \) NMR spectrum of the product has olefinic resonances at \( \delta \) 6.01 (2H, m, H-8 and H-9), and \( \delta \) 6.39 (1H, m) indicating that the postulated exocyclic olefinic group had indeed been installed. The presence of signal at \( \delta \) 6.39 \( ^{1}HNMR \) indicated the presence of a new olefinic signal which could only be ascribed to H-4\textsuperscript{1}. Attempts to generate this compound using base-mediated methodology have been indicated earlier (Scheme 2.8).
Scheme 2.27 Reagents and conditions: (i) \( \text{Cp}_2\text{Zr(H)}\text{Cl} \) (ii) 93, MeLi, CuCN, THF, -50 to 0°C, 4%.

2.5 ENOL SILYL ETHER APPROACH

This indirect approach involving enol silyl ethers utilizes path C of Scheme 2.3. As previously described, this involves:

1) Formation of enol silyl ether via conjugate addition of \( R^1 \)
2) Liberation of the enolate
3) Trapping of the enolate with the reactive \( \alpha \)-sidechain

The enol silyl ether could be generated directly from 21 via cuprate mediated addition of the \( \beta \)-side chain and trapping of the resulting enolate as a TMS ether as in 146. Alternatively, the butyl ketone (82), upon treatment with a
base would give an enolate which could subsequently be trapped by TMSCl to give 146 (Scheme 2.28). Facile cleavage of the enol silyl ether on silica gel made purification and isolation difficult accounting for the use of crude enol silyl ether in many of these procedures. However, evaluation of the $^1$H NMR of the crude material indicates the presence of the TMS ether group as well as the butyl chain. In order to overcome this difficulty, the enol silyl ether was prepared and used without further purification.

Scheme 2.28 Reagents and conditions: (i) $n$-BuLi, CuCN, THF, -78°C, (ii) TMSCl, THF, 0°C, 46%, (iii) $n$-BuLi, Cul, Et$_2$O, 0°C to rt, 2 h, 62% (iv) LDA, THF, TMSCl, -78° to rt, 54%.

With the intermediate in hand, attempts were now made at $\alpha$-sidechain insertion through liberating the enolate and quenching it with various R$^2$ groups. The first reactive group that was investigated was the triflate leaving group.
Scheme 2.29 Reagents and conditions: (i) MeLi, THF, -25°C, (ii) R²-Otf, THF, -78 to -40°C, 13%.

Lithium enolate was regenerated from the enol silyl ether by treatment with MeLi in THF (Scheme 2.29). The triflate is simultaneously prepared by addition of Tf₂O to a mixture of the corresponding alcohol and 2, 6-diter-butylpyridine. A volume of hexane equivalent to that of THF was added and the resulting solution stirred at -78°C which formed a suspension. This was then filtered to afford a clear solution of the triflate.

Several attempts were made to optimize the yields. The use of 2, 6-di-tert-butyl-4-methylpyridine as opposed to triethylamine as base in formation of the triflate, did not contribute to a greater conversion of the enolate to the product. These reactions were characterized by large amounts of decomposition and products appeared to be contaminated. While the reactions proceeded, the yields obtained were very low and over time the integrity of the triflate can become compromised which does not allow for extended reaction times.

In an attempt to generate the target PG analogues via this methodology, the lower PG sidechain was reacted with enone 21 to give 94. In order to avoid the complications previously outlined associated with the use of vinyl stannane methodology, the Schwartz reagent is used to insert the β-chain and generate the required regiospecific enolate species as indicated above (page 34). Conjugate addition of the cuprate to 21 generates 94 (Scheme 2.30). LDA
treatment of 94 generates the required enolate which is then trapped by chlorotrimethylsilane to afford 147. Crude 147 was treated with MeLi to generate the enolate which was quenched with the tosylate 148 to insert the α-chain.

\[
\begin{align*}
&\text{21} & \overset{(i)}{\longrightarrow} & \overset{(ii)}{\text{93}} & \overset{(iii)}{\longrightarrow} & \overset{(iv)}{\text{147}} \\
&\overset{(i)}{\text{92}} & \overset{(ii)}{\text{TBDMS}} & \overset{(iii)}{\text{147}} & \overset{(iv)}{\text{TBDMSO}} & \overset{(v)}{\text{150}}
\end{align*}
\]

**Scheme 2.30** *Reagents and conditions:* (i) TBDMSCI, imidazole, DMF, rt, 18 h, 78% (ii) Cp₂Zr(H)Cl, 93, MeLi, CuCN, THF, -50 to 0°C, 50% (iii) LDA, TMSCI, THF, -78 to rt (iv) MeLi, 148, THF, -78 to -23°C, 5%.

While the resulting yield of the conversion of 147 to 150 is poor, NMR evidence indicates the presence of a hydroxyl group in the ¹H NMR which is further verified by the absorption band at 3673 cm⁻¹ in the IR spectrum. The poor yield
can be explained by the fact that a large percentage of the enolate is being quenched by the alcohol. This can be attributed to the basic enolate being quenched by the hydroxyl group of 148. Hence, a significant amount of 94 was isolated.

The following attempts involve the use of aldehydes to insert the α-sidechain. Generation of these adducts via a 3CC approach have been elucidated earlier (Schemes 2.14-2.27). Here we illustrate the success of installing the α-sidechain in a two step process as indicated in Scheme 2.28. The enolate generated from the corresponding enol silyl ether, is quenched with an aldehyde.97 The enol silyl ether was treated with MeLi to release the enolate. This lithium enolate was transmetallated with zinc in the form of ZnCl₂·TMEDA. The enolate was then trapped with the aldehyde to insert the α-sidechain (Scheme 2.31). Highly regioselective alkylation of the enolate generated from the corresponding enol silyl ether only occurs when the enolate reacts with an alkylation agent prior to equilibration (Scheme 2.5)

Scheme 2.31 Reagents and conditions: (i) MeLi (for 151) or BuLi (for 133), ZnCl₂·TMEDA, THF, -25°C, (ii) R²CHO, THF, -20°C to rt.
Table 2.7 Synthesis of exocyclic enones via MeLi mediated enolate generation followed by aldehyde quench

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield, %</th>
<th>(E/Z ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHO(CH₂)₄OTHP (152)</td>
<td>151</td>
<td>(28)</td>
<td>(100:0)</td>
</tr>
<tr>
<td>2</td>
<td>CO₂Et(CH₂)₄CHO(95)</td>
<td>133</td>
<td>(65)</td>
<td>(100:0)</td>
</tr>
</tbody>
</table>

Entry 1 (Table 2.7) makes use of the aldehyde (152) which was synthesized in two steps from 1, 5-pentanediol. Formation of the mono-THP protected adduct as described previously (Scheme 2.10) was followed by Swern oxidation to give the aldehyde. Following the coupling reaction, the ¹H NMR spectrum of 151 revealed the presence of a signal at δ 6.30 (ddd, J 8.6, 6.8 and 2.0 Hz) in the ¹H NMR spectrum and at δ 143.8 in the ¹³C spectrum indicates the presence of a newly installed olefinic moiety. Allylic coupling accounts for the coupling constant of 2.0 Hz for H-4. The result is supported by verifying HRMS. Entry 2 uses 95 as the aldehyde for addition of the α-group. The aldehyde was synthesized from ethyl 6-hydroxy-hexanoate as described before (page 30-31). As opposed to the result obtained using the 3CC approach, using this approach the reaction does not exhibit a large number of by-products. The presumed intermediate β-hydroxy-ketone product is not identified and dehydration seems to take place almost instantaneously (133, Scheme 2.22). The structure of the product is identified and elucidated in the same manner as its 3CC counterpart (Scheme 2.22).
2.6 Conclusion

The three pronged approach outlined in this chapter serves to demonstrate that access to both cyclopentenone prostaglandins and their isoprostane analogues is possible employing the methodology we have developed. Furthermore, the synthesis of cross-conjugated dienones has been described. Further elaboration of this divergent strategy starting from common precursor 21 will yield an array of diverse molecules suitable for biological testing. The control of diversity is governed by the choice of sidechains employed.
3.1 Introduction

The Diels-Alder reaction is one of the most commonly encountered strategies for the formation of multiple carbon-carbon bonds in both a regio- and stereoselective manner. A survey of the literature revealed surprisingly few reports detailing the use of the tricyclic decadienone 21 as dienophile in the [4 + 2] Diels-Alder cycloaddition reaction. The paucity of examples may potentially indicate that 21 is in fact a poor dienophile. Nevertheless, these examples proved to be informative in directing our work in the area. Strategically, our aim was to generate iPG-type molecules (A) using a Diels-Alder reaction to install the requisite cis-orientated C4- and C5-sidechains.

The successful synthesis of the target compound 157 is dependant on the regio- and stereoselective cycloaddition of 21 with butadiene to produce 154 (Scheme 3.1). Regioselective cis-hydroxylation of 154 will afford 155 which will be transformed into 156 over a number of steps. A Lewis-acid catalysed rDA reaction performed on 156, is envisaged to reveal the target compound 157.
Scheme 3.1 Proposed synthetic plan for the synthesis of 157 from 21.

The utility of 21 as a dienophile has been demonstrated as a key first step in the diastereoselective synthesis of (+)-estrone (160) (Scheme 3.2). This elegant synthesis makes use of chiral 21, which is accessible from racemic cyclopentadiene via lipase mediated asymmetric resolution, and 6-methoxy-1-vinyl-3,4-dihydronaphthalene (158). These are reacted under Lewis-acid conditions to give the cycloadduct (159). A four step sequence which included thermolysis as a key step revealed estrone (160).
Scheme 3.2 Diels Alder cycloaddition mediated synthesis of (+)-estrone 160.

It is recognized that the Alder endo-rule governs the stereochemical outcome of a Diels-Alder reaction. Lewis-acid catalysts are known to enhance regioselectivity in these cycloaddition reactions via complexation to the dienophile. This interaction is said to reduce the energy gap between the lowest unoccupied molecular orbital (LUMO) of the dienophile and the highest occupied molecular orbital (HOMO) of the diene. This decreases the activation energy required for the cycloaddition. This stabilization is greater in the endo-transition state than the exo transition state thus the use of Lewis-acids has been shown to favour endo-mode of addition over the exo-mode. Quinkert noted that the Lewis-acid may not only influences the reaction rate but also the topology of the transition state structure while, in a comprehensive review, Nicolaou and co-workers commented on the ability of a Lewis-acid to reverse the regiochemical outcome of a Diels-Alder addition reaction and generate products that would not have been observed in simple, thermally induced
reactions. The expectation is thus that the *endo*-addition of a dienophile to a diene is favoured.\(^{103}\)

In the reaction detailing the formation of estrone, however, complete and yet opposite stereoselectivity was observed. This has been attributed to the ‘preferential intervention’ of the *exo* mode of addition as opposed to the electronically favoured *endo* mode to alleviate steric strain which accompanies the *endo*-addition (Scheme 3.3).\(^ {104}\)

![Scheme 3.3 Lewis-acid interaction with dienophile.](image)

Following work by Cookson and co-workers,\(^ {105}\) Zwannenberg *et al.*\(^ {106}\) have observed the stereoselective *exo*-addition of 21 with cyclopentadiene. The reaction, carried out in the presence of AlCl\(_3\), afforded both the *endo*- and *exo*-cycloadducts with a strong preference for formation of the *exo* cycloadduct being exhibited (Scheme 3.4).
Scheme 3.4 Diels Alder cycloaddition of 21 and cyclopentadiene.

Their attempts at a thermal Diels-Alder cycloaddition \textit{i.e.} without the use of a Lewis-acid catalyst proved unsuccessful.

In light of the aforementioned literature precedence and the previously proposed hypothesis, which invokes the architecture of 21 as the dominant feature controlling the stereochemical outcome of additions (Scheme 2.2), the concept of utilizing the Diels-Alder cycloadduct as a key intermediate in the synthesis of the targeted prostaglandin analogues was considered worthy of investigation.

Our investigation into the thermal and Lewis-acid catalysed cycloadditions of 21 with butadiene and Danishefsky’s diene was characterized by low yields and large decomposition. In light of the inability to produce the cycloadduct in sufficient quantities for the development of this synthetic route, our focus was redirected towards employing the alcohol 78 as dienophile. While in theory this is electronically considered to be a less likely dienophile than 21, the Diels-Alder addition afforded a clean, stereoselectively privileged cycloadduct (164) (Scheme 3.5). The cycloadduct (164) contains an array of functional groups ideally positioned for conversion to the prostaglandin analogues. The proposed synthetic plan follows precisely as described earlier with the exception of including an oxidation of the alcohol to the enone in the conversion of 165 to 158.
Scheme 3.5 Proposed synthetic plan for the synthesis of 157 from 78.

The key transformations are outlined in the retrosynthetic analysis of iPG's A and J (Scheme 3.6).
Scheme 3.6 Retrosynthetic analysis for the conversion of 164 to PGA-J.

In examining the retrosynthetic analysis, it was envisaged that a Lewis-acid catalysed retro Diels-Alder reaction of 157 would reveal the α, β-unsaturated cyclopentenone of PG’s A and J. The following key step that was identified, involves homologation of 167 using Wittig methodology to give R1 and R2 as illustrated in 157. Ready lactolisation of the α-sidechain carbonyl moiety of 166 to 167 would allow chemodifferentiation of the carbonyl functionalities. This would be exploited to extend both chains differentially. It was thought that oxidative cleavage the triol (165) would afford 166. Initial cis-hydroxylation of the cycloadduct would reveal the triol that was required.
3.2 RESULTS AND DISCUSSION

3.2.1 Cycloadditions of oxodicyclopentadiene (21) with butadiene

Various methods for the generation of this cycloadduct were attempted. Initial attempts focused on the use of the thermally induced Diels-Alder cycloaddition between the enone (21) and butadiene 168. These compounds were heated in a sealed pressure tube in toluene at 160°C for 24 hours. This demonstrated that under these conditions, the attempted transformation to the cycloadduct yielded only starting material (Scheme 3.7).

![Scheme 3.7 Reagents and conditions: (i) toluene, 160°C, 24 h.]

The Diels-Alder adduct reaction between 21 and butadiene 168 under Lewis-acid catalysed conditions provided erratic results. An excess of butadiene was condensed into toluene. The enone (21) and Lewis-acid were added and the mixture stirred for 21 h in a sealed pressure tube. These reactions were performed using a number of different Lewis-acids in varying molar equivalents. The yields of the cyclization products were dependant on the choice of Lewis-acid used. Some of these results have been tabulated below (Scheme 3.8). The reactions were characterized by the production of complex mixtures which were often difficult to separate as well as an inability to drive the reaction to completion. As noted by Roush et al, that while the best product ratios are generally obtained with use of Lewis-acids, there are a number of
substrates which decompose and fail to undergo cycloaddition reactions upon exposure to Lewis-acid reagents.\textsuperscript{107}

<table>
<thead>
<tr>
<th>Compound</th>
<th>Lewis-acid</th>
<th>No. of Equiv.</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>154</td>
<td>BF\textsubscript{3}OEt\textsubscript{2}</td>
<td>1.0</td>
<td>18 %</td>
</tr>
<tr>
<td>154</td>
<td>TiCl\textsubscript{4}</td>
<td>0.2</td>
<td>33 %</td>
</tr>
<tr>
<td>154</td>
<td>SnCl\textsubscript{4}</td>
<td>0.2</td>
<td>18 %</td>
</tr>
</tbody>
</table>

\textbf{Scheme 3.8 Reagents and conditions:} (i) toluene, -78°C to 25°C, 21 h.

Mass spectral, and NMR spectral data were consistent with the assigned structure of the cycloadduct. Although yields of the cycloadducts obtained were poor, only one stereoisomer was detected. The signal for H-6 and H-7 resonated at \(\delta 5.68\) (2H, m) while those for H-12 and H-13 appeared at \(\delta 6.10\) and \(\delta 6.24\). Here, H-12 and H-13 are shifted downfield relative to their positions in the starting enone 21. Zwannenburg \textit{et al} in their synthesis of 162, report similar chemical shifts for these olefinic protons (\(\delta 6.14\) and 6.17).\textsuperscript{106}

Rationalization of the chemoselectivity could be inferred from the available spectral data. H-4 has been identified to be the most deshielded proton in the starting enone and resonates at \(\delta 7.36\). The disappearance of this signal in 154 is evidence that addition has taken place at the H-4/H-5 position of the enone. This result is to be expected. The proximity of the C-10 bridge has a subtle
influence on the chemoselective outcome of the Diels-Alder reaction. Furthermore, this is the more likely dienophilic position. Due to conjugation with the carbonyl group, it is less electron rich than its non-conjugated counterpart. For all these reasons, it was assumed, and shown, that addition would occur to give the assigned product.

The proposed stereoselectivity can be explained in terms of the concave structure of 21 which leads to the formation of the sterically favoured exo-isomer over that of the electronically favoured endo-isomer (Scheme 3.9). For the electronically favoured endo-addition to occur, the diene would have to add at the sterically congested or hindered concave face of 21. This steric interference directs the diene towards the more accessible exo-face of the molecule promoting the formation of the electronically less favoured but sterically more favoured exo product. Our architectural hypothesis combined with the spectroscopic findings provides convincing proof that this is indeed the case.

Literature precedent for these kinds of reactions points towards the use of Lewis-acids in the Diels-Alder cycloaddition with the tricyclic dienone (21) as dienophile. There are however few examples of this nature available for study which may indicate a level of difficulty involved in successfully implementing this chemical transformation.
Our investigations led to the use of butadiene sulfone as diene, which provides butadiene in situ which is released by extrusion of SO₂ under high temperature conditions (Scheme 3.10).

The thermal cycloaddition of the dienone (21) with butadiene sulfone (170) was investigated (Scheme 3.11). The most successful result afforded a mixture of inseparable products with less than 50% conversion of the starting material occurring after 6 days. The complexity of the product mixtures obtained using this strategy render it unsuitable for the preparation of these cycloadducts as a key intermediate in this synthesis.
Employing similar methodology with the addition of a Lewis-acid also proved unsuccessful. ZnCl₂.TMEDA provides a source of deliverable ZnCl₂ and ensures the integrity of the Lewis-acid delivered to the dienophile during the reaction. This procedure, however, was not encouraging as it resulted in no conversion to the cycloadduct after 24 hours.

3.2.2 Cycloadditions with 3-exo-hydroxydicyclopentadiene (78) as dienophile

We turned our attention to the use of the alcohol (78) as the dienophile. While allylic alcohols are considered to be unactivated dienophiles, there are examples in the literature where it has been successfully engaged as a dienophile. In a publication by Batey et al, they demonstrate the successful utilization of allylic and homoallylic alcohols as dienes in an intramolecular Diels-Alder reaction of 1, 3-dienylboronates under thermal conditions. In ionic Diels-Alder reactions, allylic alcohols and ethers have been shown to be useful precursors as dienophilic allyl cations.

While this is electronically a less likely dienophile than 21, it was envisaged that, with the use of butadiene sulfone as diene, a hydrogen bonding
interaction between the hydroxyl proton and the oxygen of the sulfone would assist preorganising the reagents thus facilitating this reaction (Scheme 3.12). To this end, 78 was heated in toluene at 160°C for 2 hours which delivered 170 in 72% yield. The successful outcome of this reaction was reproducible.

![Scheme 3.12](image)

**Scheme 3.12 Reagents and conditions:** (i) heat, toluene, 160°C, 2 h, 72%.

This proposed theory was further substantiated by the fact that the acetate 77 when reacted with butadiene sulfone (170) in the same manner, showed no conversion to the product (Scheme 3.13).

![Scheme 3.13](image)

**Scheme 3.13 Reagents and conditions:** (i) heat, toluene, 160°C, 21 h.

Spectroscopic and analytical evidence confirmed the structure of 164 but absolute chemo- and stereochemistry was difficult to definitively assign due to the complex nature of the NMR spectrum. Hence, 164 was oxidized to the corresponding ketone (154) (Scheme 3.14). The ¹H NMR was used to
unequivocally confirm the chemoselectivity indicating that the cycloaddition reaction had indeed taken place at C-4-C-5 double bond of the alcohol 78. H-6 and H-7 are seen to resonate at $\delta 5.78$ (ddd $J 9.5, 4.7$ and $1.3$ Hz) and $\delta 5.84$ (ddd, $J 9.5, 5.2$ and $0.9$ Hz) while H-12 and H-13 resonate as a multiplet at $\delta 5.94$ Hz.

\[ \text{Scheme 3.14 Reagents and conditions: (i) Dess Martin periodinane, CH}_2\text{Cl}_2, 25^\circ\text{C, 56%}. \]

The presence of H-6 and H-7 is diagnostic as had cycloaddition occurred at the alternative olefinic bond to give 171 (Scheme 3.15), the presence of protons relating to the $\alpha, \beta$-unsaturated moiety of the cyclopentane would clearly be evident with the much deshielded resonance of H-10 occurring in the region $\delta 7.2-7.4$ ppm. H-5 of 21 resonates at $\delta 7.36$. Comparison to the $^1\text{H}$ NMR spectrum of 154 reveals that the two compounds are identical serving as further confirmation.

\[ \text{Scheme 3.15 Alternative chemoselective product.} \]
3.3 Further Transformations on 164

Further chemistry focused on the identifying protocols for the transformation of 164 to the isoprostanes of PG's A and J as indicated in Figure 3.1.

Figure 3.1 Transformations required in converting 21 to into PG's A and J.

The retrosynthetic analysis (Scheme 3.5) highlighted the proposed intermediates in the synthesis plan. A description of the progress made towards this end is described below.

_Cis-hydroxylation_

_Cis-hydroxylation_ of the cycloadduct 164 utilized catalytic osmium tetroxide with N-morpholine-N-oxide as co-oxidant in acetone-water to give the triol 165 (Scheme 3.16).
Scheme 3.16 *Reagents and conditions:* (i) OsO₄, NMO, (CH₃)_₂CO·H₂O, 25°C.

Having proven that the *cis*-hydroxylation could be successfully affected and noting that the triol was difficult to handle given its polarity, an approach in which *cis*-hydroxylation is directly followed by oxidative cleavage without isolation was of the cyclohexanetriol (165) was adopted. Thus Ogasawara *et al.* have documented a procedure which reported very acceptable yields utilizing this methodology. As such the crude cyclohexanetriol was successfully cleaved with lead tetraacetate in dichloromethane to yield the lactol (167) (Scheme 3.17).

Scheme 3.17 Tandem osmylation of 164 followed by oxidative cleavage to give 167

The ^1^H NMR of 167 provides diagnostic signals for confirmation of the proposed structure. Firstly, the presence of H-10 and H-11 has been confirmed by the presence of a multiplet, integrating for two protons, resonating at δ 5.73 and δ 5.74. The signal for H-4 resonates at δ 5.35 (dd, J 3.9 and 3.2 Hz) and has couplings to the two protons at the 5-position. This downfield shift is
expected for a proton adjacent to a hydroxyl group. The signal assigned to H-3 resonates as a doublet of doublets at δ 5.14 with couplings to H-2 and H-6. The presence of the aldehyde is confirmed by the signal resonating at δ 9.94, an expected chemical shift for an aldehyde proton as well as the resonance at δ 202.8 in the 13C NMR spectrum.

3.4 Conclusion:

As indicated earlier (Schemes 3.5 and 3.6), the isolation of 167 provides the requisite cis-dialkyl stereochemistry of the two sidechains of the proposed PG targets. Simultaneously, it allows for chemoselective differentiation of these two sidechains for their extension. Installation of the α-sidechain (as seen in Chapter 2) is no longer necessary as it is built into the molecule. This also assists in circumventing the problem of epimerisation associated with moieties α to a carbonyl group. Elaboration of the sidechains using chemistry outlined by Larock et al111 and Corey is envisaged to render the target prostaglandin analogues.
4.1 Oxygen Analogues of cyclopentenone prostaglandins:

Within the scope of this project we sought to explore routes to oxygen analogues of the proposed targets of the cyclopentenone prostaglandins of the A- and J-series (Figure 4.1).

![Figure 4.1 Proposed Oxygen Analogues of the A and J series.](image)

It was envisaged that epoxidation of 78 would yield the cis-epoxide utilizing the well known cis-directing effects of allylic alcohols. The regioselective opening of the epoxide was investigated as a means of installing one of the sidechains. This would render a free hydroxyl group for manipulation to introduce the second sidechain to reveal analogues of the type we are interested in.
Scheme 4.1 Proposed synthetic strategy.

The cis-directing effects of allylic and homoallylic alcohols are well documented in the literature.\textsuperscript{112-114} Henbest and Wilson first observed that treatment of cyclic allylic alcohols with peracids resulted in epoxide formation cis to the hydroxyl group.\textsuperscript{115} It has been postulated that the participation of the hydroxyl group results in delivery of the electrophilic oxygen to the nucleophilic alkene face cis to the hydroxyl group. This face selectivity with allyl alcohols has been attributed to hydrogen bond formation between the allyl hydroxyl group and the most basic carbonyl oxygen of the peroxy acid resulting in a transition state resembling the Bartlett "butterfly" mechanism\textsuperscript{116} (Scheme 4.1). Henbest et al did however note that this directing effect is weak and thereby subject to steric interference for several allylic alcohols.\textsuperscript{115}
The use of transition metals as catalysts for epoxidation has been documented.\(^{117}\) Sharpless and Michaelson\(^{118}\) have demonstrated the synthetic utility of vanadium and molybdenum as catalysts for this reaction. They have further shown that vanadium and molybdenum catalysed epoxidations of allylic and homoallylic alcohols are stereospecific, at times in contrast with the results obtained using peracids for the same transformation.

![Scheme 4.1 Transition state resulting in delivery of peracid.](image)

The alcohol (78), generated from dicyclopentadiene (74), (Scheme 2.3), was chemoselectively epoxidised with VO(acac)\(_2\) in toluene to yield 172 (Scheme 4.2). The epoxidation results in the formation of the exo-epoxide. This can be attributed to the steric directing effects of the architecture of the molecule and the accessibility of the exo-face. This works in concert with the cis-directing effects of the allylic alcohol to produce the exo-epoxide.

Spectroscopic data were consistent with the assigned structure of 172. It’s \(^1\)H NMR spectrum showed the disappearance of two olefinic signals whilst the signals at \(\delta 3.28\) and \(\delta 3.43\), each integrating for one proton, indicated the presence of two new protons attached to the hydroxyl bearing carbons. The proton signal at \(\delta 3.28\) has been assigned to H-5 and resonates as a doublet. This is a result of a dihedral angle of nearly 90° between H-5 and H-6 resulting in \(J=0\) for that interaction. The \(^{13}\)C spectrum similarly showed the disappearance of the two olefinic signals relative to the starting alcohol. New
resonances at $\delta$ 63.4 and 62.8 concurred with the findings from the proton spectrum. The IR absorption band at 1221.7 supported the C-O stretch while an absorption band at 3019.0 indicated the presence of hydroxyl functionality. Attempts to affect the epoxidation using $m$-cpba rendered only 21, presumably via oxidation of the hydroxyl group to the ketone.

![Scheme 4.2](image)

Scheme 4.2 Reagents and conditions: (a) VO(acac)$_2$, t-BuOOH, toluene, rt to reflux, 40 min, 70% (ii) LAH, THF, rt to reflux, 2 h, 76% (ii). $m$-cpba, CHCl$_3$, reflux, 3 h.

The epoxide (172) was opened via hydride attack at position 4 to give the meso-diol (173) (Scheme 4.3). Evidence in support of the proposed structure was derived from the $^1$H NMR spectrum of (173). Given that the meso-diol is $C_2$ symmetric, the spectrum revealed a simplification of the signals consistent with the formation of a meso-diol.
Having demonstrated that opening of the exo-epoxy alcohol was feasible we sought to investigate this opening using other nucleophiles. The literature has numerous examples of BF$_3$.Et$_2$O promoted reactions of organolithiates with epoxides.$^{119-121}$ Yamaguchi et al have shown that the combination of organolithium with BF$_3$.Et$_2$O is well set up for the ring opening reaction of oxiranes and oxetanes.$^{122}$

Following literature procedures, treatment of the epoxide 172 with the anion derived from the reaction with alkyne with n-BuLi and BF$_3$.Et$_2$O in THF resulted in successful opening of the epoxide at C-5. This however only yielded the diol (174) in 9.5 % (Scheme 4.4) with recovery of the starting epoxide.

The regioselectivity is different to the opening by the hydride anion and can be attributed to the size of the incoming nucleophile. Fang et al indicate that, in the
case of a 2-substituted oxirane, ring opening usually occurs at the less hindered site. The regioselectivity of the opening was confirmed by spectroscopic data. The $^1$H NMR spectrum reveals the absence of a meso-diol confirming that ring-opening occurs via attack of the nucleophile at C5.

Further attempts at the regioselective opening of the exo-epoxide focused on the use of the Grignard reagent generated from 2-bromomethyl-1,3-dioxolane. Once installed, the dioxolane would then serve as a substrate for extension to the relevant sidechain (Scheme 4.5). Grignard addition of 2-bromomethylmagnesium 1, 3-dioxolane successfully opened the epoxide (172) at C5 rendering the diol (175) in 10% yield (Scheme 4.5). Once again, this is confirmed by spectroscopic data revealing the absence of a meso-diol as well as the characteristic signal for the proton attached to C5.

Scheme 4.5 Reagents and conditions (i) 2-bromomethyl 1,3-dioxolane, Mg turnings, THF, rt-50°C, 8h.
Benzyl protection of the free hydroxyl groups and deprotection of the aldehyde was thought to be the first step in pursuing the synthesis. It was envisaged that deprotection of this suitably protected dioxalane will yield the aldehyde which can be extended using Wittig methodology to yield the β-sidechain. Chemoselective debenzylation and extension will afford the α-sidechain. Oxidation of the deprotected 3-hydroxy group at position 3 followed by a rDA will yield the proposed target.

While having demonstrated that the opening of the exo-epoxide could be achieved for installation of the required sidechains, in light of the difficulty in achieving complete conversion and hence acceptable synthetic yields, we turned our attention to the synthesis of the endo-epoxide to be obtained from epoxidation of the corresponding endo-alcohol. In this case, the architecture of the starting alcohol and the cis-directing effects the allylic alcohols no longer work in concert. It was predicted that regioselective opening of the endo-epoxide would prove to be more facile as nucleophilic attack would be favoured with the incoming nucleophile experiencing unhindered approach from the sterically less congested exo-face. Envisaged chemoselective reduction of the enone (21) would afford the endo-alcohol (180) (Scheme 4.6). Several methods were employed to effect this reduction. The first method utilised was the well-known Luche reduction\textsuperscript{124} which utilises the Lewis-acid cerium trichloride as a means of potentiating the enone (21) for nucleophilic reduction by sodium borohydride, which is considered a mild and selective reducing agent.\textsuperscript{125} In our hands, attempts at utilizing a large excess of the Lewis-acid still only yielded several products, one of which has been identified as 179 resulting from exhaustive reduction of the α, β-unsaturated system.
Scheme 4.6 Reagents and conditions: (i) NaBH₄, CeCl₃·7H₂O (1eq), MeOH, rt to reflux (ii) NaBH₄, CeCl₃·7H₂O (2eq), MeOH, rt to reflux (iii) DIBAL-H, toluene, -78°C, 20 min, 77% (iv) VO(acac)₂, t-BuOOH, toluene, rt to reflux, m-cpba, CHCl₃, reflux, 3 h.

A survey of the literature revealed that Ogasawara et al.¹²⁶ had successfully utilized DIBAL-H to effect the above chemical transformation. Chemoselective reduction of the enone (21) rendered the required endo-alcohol (180) in a yield of 77%. Spectroscopic and analytical evidence confirmed the structure of 180 and the presence of the endo alcohol. Spectroscopic data were consistent with the assigned structure. Elucidation of the ¹H NMR spectrum revealed the appearance of a new signal at δ 4.67 could be attributed to H-3. A comparison with the exo-alcohol (78) indicated a downfield shift of H-3 which resonates at δ 4.07 in this species. Further confirmation was acquired from the characteristic IR OH stretching frequency at 3599.
Table 4.1 NMR data of 78 and 185

<table>
<thead>
<tr>
<th>Proton</th>
<th>Exo alcohol 78</th>
<th>Endo alcohol 180</th>
<th>Carbon Exo alcohol 78</th>
<th>Carbon Endo alcohol 180</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-1</td>
<td>3.36 (m)</td>
<td>2.89-2.98 (m)</td>
<td>C-1 44.9*</td>
<td>46.9</td>
</tr>
<tr>
<td>H-2</td>
<td>3.04 (m)</td>
<td>3.29 (dd, J 7.2 and 3.9 Hz)</td>
<td>C-2 54.8*</td>
<td>54.0</td>
</tr>
<tr>
<td>H-3</td>
<td>4.07 (m)</td>
<td>4.67 (br d, J 8.1 Hz)</td>
<td>C-3 79.2</td>
<td>75.9</td>
</tr>
<tr>
<td>H-4</td>
<td>5.93 (dd, J 5.8 and 3.2 Hz)</td>
<td>6.15 (dd, J 5.7 and 2.4 Hz)</td>
<td>C-4 135.4</td>
<td>135.2</td>
</tr>
<tr>
<td>H-5</td>
<td>5.60 (br d, J 6.0 Hz)</td>
<td>5.81 (dd, J 5.6 and 3.2 Hz)</td>
<td>C-5 138.0</td>
<td>135.2</td>
</tr>
<tr>
<td>H-6</td>
<td>2.53 (m)</td>
<td>2.89-2.98 (m)</td>
<td>C-6 53.7*</td>
<td>52.5</td>
</tr>
<tr>
<td>H-7</td>
<td>2.8 (m)</td>
<td>2.89-2.98 (m)</td>
<td>C-7 51.4*</td>
<td>47.0</td>
</tr>
<tr>
<td>H-8</td>
<td>5.77 (br d, J 5.6 Hz) or 5.84 (dd, J 5.6 and 3.2 Hz)</td>
<td>5.59 (2H, m)</td>
<td>C-8 134.8</td>
<td>134.6</td>
</tr>
<tr>
<td>H-9</td>
<td>5.77 (br d, J 5.6 Hz) or 5.84 (dd, J 5.6 and 3.2 Hz)</td>
<td>5.59 (2H, m)</td>
<td>C-9 132.4</td>
<td>133.4</td>
</tr>
<tr>
<td>H-10</td>
<td>1.37 (br d, J 8.12 Hz) and 1.55 (br d, J 8.12 Hz)</td>
<td>1.48 (br d, J 8.4 Hz) and 1.57 (dt, J 2 x 8.4 and 1.8 Hz)</td>
<td>C-10 44.8</td>
<td>44.7</td>
</tr>
</tbody>
</table>

* Not unambiguously assigned

Attempts at formation of the epoxide using VO(acac)$_2$, yielded only starting enone (21), presumably via oxidation of the allylic alcohol by t-butylhydroperoxide. The use of m-cpba rendered the product which was identified as 183. Although initial analysis of the spectroscopic data was
thought to indicate the presence of the epoxide 181, attempts at opening of the epoxide using both lithium aluminium hydride and the grignard reagent ethyl magnesium bromide did not validate this. Further analysis of the data led to the conclusion that 183 had formed rather than the expected epoxide. Formation of 183 must occur via the intermediate epoxy-alcohol (182) which undergoes an intramolecular opening via nucleophilic attack by the free hydroxyl group (Scheme 4.7). The alcohol of the cyclic ether (183) was acetylated as a means of further validation to yield 184. Disappearance of the signal corresponding to the hydroxy proton in the $^1$H NMR provided further evidence of it's presence in 183.

Scheme 4.7 Reagents and conditions: (i) m-cpba, CHCl$_3$, reflux, 3 h, 77% (ii) Ac$_2$O, DMAP (cat), pyridine, rt, 20 h, 49%.

The proton NMR was fully assigned with the aid of the COSY spectrum (Figure 4.2). The characteristic proton for H-3 resonates at $\delta$ 4.66 as a doublet of
doublets \((J = 5.2 \text{ and } 1.8 \text{ Hz})\). This is confirmed by a cross peak in the COSY from H-4 which is the only olefinic proton with coupling to a proton on an oxygen-bearing proton. Hence H-4 is assigned as the most deshielded proton resonating at \(\delta 5.91\) \((J = 5.2 \text{ and } 1.8 \text{ Hz})\) with a large coupling to H-5 \((\delta 5.75, \text{ br dd, } J = 5.2 \text{ and } 2.0)\). A cross peak from H-3 allowed for allocation of H-2 which resonates as a multiplet at \(\delta 2.99\) and a small “W” coupling of H-3 to H-6 is also observed. The position of H-6 is confirmed by the cross peak from H-5 which reveals H-6 as a multiplet at \(\delta 2.90\). H-2 is expected to couple to H-1 and hence H-1 can be located from its cross peak. H-1 resonates at \(\delta 2.69\). A cross peak from H-6 reveals the location of the distinctly shielded H-7 resonating at \(\delta 2.13\) and further verifies the position of H-2 via long range coupling. H-8 and H-9 were unambiguously assigned. The H-8 proton was located using the COSY spectrum as a cross peak from H-7 \((\delta 2.13)\) and resonates at \(\delta 3.88\) in the \(^1\text{H}\) NMR spectrum. As a result of the dihedral angle of approximately 90° between H-8 and H-9, the COSY spectrum shows no cross coupling peaks between these two protons. However, H-9 can be assigned on the basis of it being the only other olefinic proton \((\delta 4.07)\) as well as its coupling to H-1 \((\delta, J = 4.4)\). The protons for H-10 could also be assigned and were shown to resonate as doublets at \(\delta 2.23\) \((J = 10.4 \text{ Hz})\) and \(\delta 1.82\) \((J = 10.4 \text{ Hz})\). These are allocated as a cross peak from H-1 which is shown to couple to both H-10\(_a\) and H-10\(_b\). H-8 reveals a long range coupling to either H-10\(_a\) or H-10\(_b\).

Assignment of the \(^{13}\text{C}\) NMR spectrum was verified using HSQC experiments. These couplings have been illustrated in Figure 4.3. High resolution MS results proposed a molecular ion with \(M^+ 164.0141\). The proposed structure has been unequivocally confirmed by crystal structure analysis (Figure 4.4).
Figure 4.2 Cosy spectrum of 183.
Following this, an alternative approach was attempted. This involved chemoselective reduction of the C8/C9 double bond of the enone (21) without reducing the $\alpha,\beta$-unsaturated system (Scheme 4.8). Thus (21) was hydrogenated at atmospheric pressure in the presence of palladium on carbon for 18 h. This led to the reduction of both double bonds as in 185 which was
verified by the complete disappearance of all olefinic signals in the $^1$H and $^{13}$C NMR spectra. Reducing the time of the reaction to 1 h afforded the target 186. The chemoselective reduction has been verified by the presence of the much deshielded H-4 proton, (ddd, $\delta$ 7.57), in the $^1$H NMR spectrum. C-4 is clearly present in the $^{13}$C NMR spectrum resonating at a similar position to where it was located in the 21 $^{13}$C spectrum, $\delta$ 162.7. The HRMS results proposed a parent molecular ion with $M^+$ 148.0868. All of these data confirm the above structure. Diisobutylaluminium hydride (DIBAL-H) reduction yielded the endo-alcohol (187). The $^1$H NMR spectrum of the product carried a signal implying the presence of the hydroxyl moiety (doublet, $\delta$ 4.88). The $^{13}$C NMR spectral interpretation verified this hydroxyl group with C-3 resonating at $\delta$ 76.5. Rationalisation of the stereochemistry of the product lies in the sterically congested endo-face of the molecule which directs the reducing agent to the exo-face resulting in formation of the proposed endo-alcohol. Attempted VO(acac)$_2$ mediated epoxidation afforded 188 while m-cpba mediated epoxidation rendered an as yet unidentifiable species.
Scheme 4.7: (i) Pd/C, H₂, rt, 20 h, 80% (ii) Pd/C, H₂, rt, 1 h, 64% (iii) DIBAL-H, toluene, -78°C, 20 min, 80% (iv) m-cpba, CH₂Cl₂, 80% (v) VO(acac)₂, toluene, reflux.

Payne rearrangement

The next method that was attempted for formation of the endo-epoxide involved performing a Mitsunobu inversion of the exo-epoxyalcohol (172) to generate the exo-epoxy-endo-ester (189) which, after hydrolysis, was expected to undergo a Payne rearrangement to give the endo-epoxy-exo-alcohol (190) (Scheme 4.9). Facile opening of the epoxide would then be expected on the basis of exo-approach of the incoming nucleophile.

The secondary alcohol (172) was subjected to an enhanced Mitsunobu reaction in which 172 was treated with DIAD in the presence of triphenylphosphine and p-nitrobenzoic acid as nucleophile (Scheme 4.10). Historically the use the activated carboxylic acid, p-nitrobenzoic acid, as opposed to benzoic acid has been shown to increase the efficiency of the reaction threefold. 127 While Zibari et al. 128 reported higher yields of the inverted
product using benzene rather than THF as solvent, in our hands, the use of THF produced perfectly acceptable yields.

\[ \text{Mitsunobu inversion} \]

\[ \text{Hydrolysis and Payne rearrangement} \]

**Scheme 4.9** Proposed synthetic plan for the synthesis of the *endo*-epoxy alcohol (190).

The \(^1\text{H} \) NMR of the epoxy ester (189) indicates a downfield shift (δ 5.64) of H-3 relative to its position in the epoxy alcohol (172) (δ 3.79). H-3 resonates as a ddd (J 5.3, 4.4 and 0.6 Hz) with couplings to H-2, H-4 and "W"-coupling to H-6. The signal is much less diagnostic in 172 resonating as a broad singlet. A key signal in ascertaining whether inversion of the alcohol had indeed taken place, is H-2. H-2 resonates at δ 2.61 (dddd, J 10.2, 4.4, 1.2 and 1.0 Hz). These couplings can be assigned to the interaction of H-2 with H-3, which would produce the large coupling, H-6 and H-1. The smallest coupling constant can be attributed to its interaction with H-7 in which we see a long range "W" coupling. Considering model structures, it is clear that this coupling could not have occurred if H-2 was *endo*. Hence, we can conclude that the *endo*-ester has been generated. Subsequent chemical transformation of 189 supported this assignment.

Thus, the epoxy-ester (189) was then hydrolysed with potassium carbonate in methanol and underwent the Payne rearrangement (Scheme 4.10).
Scheme 4.10 Reagents and conditions: (i) DIAD, PPh₃, p-nitrobenzoic acid, THF, 60°C, 4 h, 81%; (ii) K₂CO₃, MeOH, 25°C, 4 h.

Nucleophilic opening of the epoxide by the oxygen anion is a reversible process with the thermodynamic equilibrium favouring formation of the endo-epoxide-exo-alcohol (Scheme 4.11).

Scheme 4.11 Thermodynamic equilibration of the payne rearrangement.
The presence of the assigned structures of 190 and 191 were confirmed by NMR with the minor product being assigned as the one in which the hydroxyl group is endo. The signal attributed to H-3 was exploited in this assignment. H-3 resonates as at $\delta 4.86$ (dd, $J_{6.8}$ and $2.8$ Hz) in 190 while it is found at $\delta 4.87$ (ddd, $J_{6.6}$, $2.8$ and $0.6$ Hz) in 191. H-3 has an extra coupling in 191 which is attributed to the "W" coupling to H-6. This coupling is only possible in the example in which H-3 is endo. Hence, 191 is assigned as the exo-alcohol which is the minor product obtained in only 7 % yield.

Direct comparison with the opening of the exo-epoxide-exo-alcohol (172) was made by treating 190 with the anion derived from alkyne (Scheme 4.12), used in the opening of the exo-epoxide in Scheme 4.4. The good yield obtained relative to one obtained with the exo-epoxide (172) opening serves as further confirmation for the formation of the endo-epoxide.

![Scheme 4.12](image)

Scheme 4.12 Reagents and conditions: (i) n-BuLi, THF, 78°C, 6 h, 66 %.

The regioselectivity of the nucleophilic opening was assigned by inspection of the H-5 proton which resonates at $\delta 2.78$ (dd, $J_{9.1}$ and $8.4$ Hz), diagnostic for a proton $\alpha$ to a triple bond. Furthermore, if generation of the opposite regioisomer had occurred, the proton adjacent to the alkyne group would be seen to couple to both of the protons adjacent to the two hydroxyl bearing carbons. The exo approach of the nucleophile is confirmed by the trans-
relationship between H-4 and H-5 which is revealed by the large coupling constant of 9.1 Hz between the two. This is indicative of a H4-H5 dihedral angle approaching 180°.

4.2 Conclusion

With the *endo* epoxide synthesis in place and facile opening thereof established, this creates a platform for elaboration to produce the requisite oxygen analogue targets. The system is now well set up for extension as indicated in Figure 4.2. It allows for variation of the nucleophiles installed for evaluation of the biological properties thereof.

![Diagram](image)

**Figure 4.5** Points of elaboration for formation of oxygen analogues of PG's.

It is envisaged that 173 may be converted to enantiopure enone *via* an enzyme-mediated desymmetrisation. This would allow for asymmetric synthesis of the envisaged analogues.
CHAPTER 5

EXPERIMENTAL

General:
Melting points were determined on a Reichert-Jung Thermovar and a Fischer-Johns hot stage microscope and are uncorrected. Proton nuclear magnetic resonance spectra were recorded using trimethylsilane as an internal standard on a Varian VXR-200 (200MHz), Varian Mercury (300MHz) or a Varian Unity Spectrometer (400MHz). Carbon –13 nuclear magnetic resonance spectra were determined on the same instruments at 50, 75 or 100MHz (using trimethylsilane as an internal standard). Infrared spectra were recorded in solutions specified using a Perkin Elmer Paragon 1000 FT-IR spectrometer. Elemental analyses were performed using a Fisons EA 1108 CHNS-O instrument. Mass spectra were recorded on a VG micromass 16F spectrometer operating at 70eV with an accelerating voltage of 4kV. Accurate masses were determined using a VG-70E spectrometer at the University of the Witwatersrand.

All reactions were monitored by thin layer chromatography using aluminium-backed silica gel 60F_{254} plates (Merck). The plates were visualised by a combination of ultraviolet light (254nm) and either anisaldehyde spray [prepared from a 2.5% solution of p-methoxybenzaldehyde (20cm³) and 18 M sulphuric acid (1 cm³)] or cerium (IV) ammonium sulfate in 8 M sulphuric acid and baking at 200°C. Column chromatography was carried out on silica gel (Merck Kieselgel 60: 70-230 mesh for gravity and 230-400 mesh for flash chromatography).

All solvents used were dried by the appropriate technique. Tetrahydrofuran and diethyl ether were dried over sodium wire prior to use using benzophenone
as indicator. Triethylamine was dried over and distilled from calcium hydride and it was stored over potassium hydroxide pellets. Dichloromethane was dried over phosphorous pentoxide and distilled. Solvents not mentioned which were used in reactions were anhydrous unless stated otherwise.

**exo-3-Acetoxytricyclo[5.2.1.0^2.6]-deca-4, 8-diene (77)**

Acetic anhydride (61 cm$^3$) was added to a solution of manganese (III) acetate (40 g, 165 mmol) in acetic acid added (160 cm$^3$) and the mixture was refluxed for 20 minutes. Potassium permanganate (6.5 g, 40.9 mmol) was added portion wise to this hot solution and the mixture was then refluxed for a further 30 minutes. After cooling to 70°C, dicyclopentadiene (19.6 cm$^3$, 146 mmol) was added followed by potassium bromide (2.95 g, 24.8 mmol) and the reaction mixture stirred at that temperature until the dark colour of the manganese (IV) ion had faded (~2 h). After cooling, the solution was filtered through a Celite pad, diluted with water and extracted with ethyl acetate (3 x 75 cm$^3$). The organic extract was washed successively with saturated NaHCO$_3$, H$_2$O and brine, dried over magnesium sulfate and evaporated under reduced pressure. Column chromatography on a silica gel column using ethyl acetate-hexane (1:9) afforded the acetate 77 (14 g, 50%) as colourless oil; $\delta_H$ (200 MHz, CDCl$_3$): 1.39 (1H, d, $J_{8.2}$ Hz, H-10$_a$), 1.58 (1H, d, $J_{8.2}$ Hz, H-10$_b$), 2.02 (3H, s, CH$_3$), 2.59 (1H, m, H-7), 2.82 (1H, br m, H-6), 3.1 (1H, br m, H-2), 3.40 (1H, m, H-1), 4.90 (1H, m, H-3), 5.60 (1H, dd, $J_{5.6}$ and 2.8 Hz, H-8), 5.89-5.83 (2H, m, H-5 and H-9) and 6.02 (1H, dd, $J_{5.6}$ and 2.8 Hz, H-4).

**exo-3-Hydroxydicyclopentadiene (78)**

The acetate 77 (14 g, 74 mmol) in was stirred with potassium carbonate (32 g, 368.5 mmol) in methanol (125 cm$^3$) at 24°C for 18 h. The mixture was filtered
through a Celite pad and washed with methanol (3 x 75 cm\(^3\)) and the methanol removed under reduced pressure. The residue was partitioned between ethyl acetate and water and the organic product extracted into ethyl acetate (3 x 75 cm\(^3\)), dried over magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel using ethyl acetate-petroleum ether (3:7) afforded the alcohol 78 (9.3g, 85%) as a crystalline solid; m.p. 72-73°C (from hexane) (lit 71.5-72 °C); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3430 (OH); \(\delta_H\) (400 MHz, CDCl\(_3\)) 1.37 (1H, br d, \(J\) 8.1 Hz, H-10\(a\) or H-10\(b\)), 1.55 (1H, br d, \(J\) 8.1 Hz, H-10\(a\) or H-10\(b\)), 2.53 (1H, m, H-6), 2.8 (1H, m, H-7), 3.04 (1H, m, H-2), 3.36 (1H, m, H-1), 4.07 (1H, m, H-6), 5.60 (1H, br d, \(J\) 6.0 Hz, H-5), 5.77 (1H, br d, \(J\) 5.6 Hz, H-8 or H-9), 5.84 (1H, dd, \(J\) 5.6 and 3.2 Hz, H-8 or H-9) and 5.93 (1H, dd, \(J\) 5.8 and 3.2 Hz, H-4); \(\delta_C\) (100 MHz, CDCl\(_3\)) 44.8 (C-10), 44.9, 51.4, 53.7, 54.8, 79.2 (C-3), 132.5, 134.8, 135.5 and 138.0; (Found M\(^+\) 148.0889; C\(_{10}\)H\(_{12}\)O requires 148.0888).

### Synthesis of Pyridinium Chlorochromate (PCC) on alumina

To a solution of chromium trioxide (8.4 g, 84.45 mmol) and 6N HCl (14.1 cm\(^3\)), pyridine (6.7 g, 85.45 mmol) was added at 40°C within 10 minutes. The mixture was then kept at 10°C for 30 minutes resulting in the formation of a yellow-orange solid. Reheating to 40°C yielded a solution to which alumina (70 g) was added. After evaporation under reduced pressure, the orange solid was dried under vacuum for 2 h at 24°C.

### 3-Oxodicyclopentadiene (21)

PCC supported on alumina (84.45 mmol) was added to a flask containing a solution of the alcohol 78 (5 g, 33.8 mmol) in \(n\)-hexane (80 cm\(^3\)). The mixture was stirred at 24°C for 18 h. The solid was filtered through a Celite pad and washed with diethyl ether (3 x 75 cm\(^3\)). The combined filtrate was dried over
magnesium sulfate and evaporated. Column chromatography on silica gel using ethyl acetate-petroleum ether, (3:7) yielded the ketone 21 (4.7g, 96%) as a white crystalline solid; m.p. 74-75°C (from hexane) (lit 76°C); $^{13}$O$_{\text{max}}$/cm$^{-1}$ 1693 cm$^{-1}$ (Found: C, 82.1; H, 6.9; C$_{10}$H$_{10}$O requires C, 82.3; H, 6.8); $\delta$$_{\text{H}}$ (300 MHz, CDCl$_3$): 1.62 (1H, d, J 8.6 Hz, H-10$_a$ or H-10$_b$), 1.74 (1H, d, J 8.6 Hz, H-10$_a$ or H-10$_b$), 2.78 (1H, m, H-6), 2.96 (1H, m, H-2), 3.22 (1H, m, H-7), 3.41 (1H, m, H-1), 5.77 (1H, dd, J 5.5 and 2.8 Hz, H-4), 5.95-5.91 (2H, m, H-8 and H-9) and 7.36 (1H, dd, J 5.5 and 2.4 Hz, H-5); $\delta$$_{\text{C}}$ (100 MHz, CDCl$_3$) 44.3, 45.2, 48.5, 50.4, 52.9 (C-1, C-2, C-6, C-7, C-10), 132.5 (C-8), 132.8 (C-9), 137.2 (C-4), 164.6 (C-5) and 210.6 (CO).

**exo-5-n Butyl-tricyclo[5.2.1.0$^{2,6}$]-dec-8-ene-3-one (82)**

n-Butyl lithium (1.6 M in hexane, 6.3 cm$^3$) was added gradually to a suspension of copper iodide (1.4 g, 7.4 mmol) in dry ether (10 cm$^3$) at 0°C. The mixture was stirred at this temperature for 15 minutes. The ketone (21) (375 mg, 2.6 mmol) in dry ether (10 cm$^3$) was added gradually to the reaction vessel and the solution was allowed to warm to 24°C. The mixture was stirred at 24°C for 2 h. Saturated aqueous ammonium chloride was added and the aqueous phase extracted with ether (2 x 50 cm$^3$). The combined organic extracts were washed with water, dried over magnesium sulfate and the solvent evaporated under reduced pressure. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:9) yielded the alkyl ketone (82) (327 mg, 62%) as a clear oil; $\nu_{\text{max}}$/ cm$^{-1}$ 1734 (CO); (Found: M$^+$, 204.1517. C$_{14}$H$_{20}$O requires 204.1514); $\delta$$_{\text{H}}$ (400 MHz, CDCl$_3$) 0.90 (3H, t, J 6.8 Hz, CH$_3$), 1.25-1.43 (7H, m, 3 x CH$_2$ and H-10$_a$ or H-10$_b$), 1.54 (1H, br d, J 4.4 Hz, H-10$_a$ or H-10$_b$), 1.68 (1H, m, H-5), 1.93 (1H, ddd, J 18.4 , 6.8 and 2.0 Hz, H-4$_{\text{exo}}$), 2.20 (1H, dd, J 18.4 and 7.8 Hz, H-4$_{\text{endo}}$), 2.64 (1H, dt, J 2 x 9.4 and 4.2 Hz, H-6), 2.92 (1H, ddd, J 9.4, 4.8 and 2.0 Hz, H-2), 3.01 (1H, m, H-7), 3.16 (1H, m, H-1) and 6.13 (2H, m, H-8 and H-
9); δC (100 MHz, CDCl₃) 13.9 (CH₃), 22.6 (CH₂), 22.7 (CH₂), 36.8 (C-5), 37.5 (CH₂), 6.1 (C-1), 47.1 (C-7), 48.3 (C-4), 48.75 (C-6), 52.3 (C-10), 54.8 (C-2), 135.2 (C-8), 136.1 (C-9) and 220.9 (CO).

5-n-Butyl-4-methyl-tricyclo[5.2.1.0₂⁻]deca-8-ene-3-one (86)

1. n-Butyllithium (2.5M in hexane, 0.43 cm³) was added to a stirred solution of diisopropylamine (0.15 cm³, 1.18 mmol) in dry tetrahydrofuran (8 cm³) at -78°C under nitrogen. The resulting solution was warmed to 0°C and stirred for 30 min. The solution was cooled to -78°C and a solution of 82 (200 mg, 0.98 mmol) in tetrahydrofuran (4 cm³) was added. After stirring at this temperature for 30 min tributyltin(1) chloride was added and stirring was continued for a further 30 min. Hexamethlphosphorotriamide (0.44 cm³, 2.5 mmol) and iodomethane (0.18 cm³, 2.94 mmol) were added consecutively and the reaction was stirred for another 30 min at -78°C, then warmed to ambient temperature and stirred for 23 h. The mixture was diluted with saturated aqueous ammonium chloride and extracted with diethyl ether (3 x 20 cm³). The organic extract was washed consecutively with water and sodium thiosulfate, dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:19) as eluent yielded 86 (132 mg, 62%); νmax/cm⁻¹ 1716 (CO); δH (300 MHz, CDCl₃) 0.92 (6H, t, J 7.2 Hz, 2 x CH₃), 1.28-1.64 (9H, m, H-5, 2 x H-10, 3 x CH₂), 2.19 (1H, m, H-4), 2.58 (1H, quintet, J 9.9 and 4.6 Hz, H-6), 2.98 (2H, m, H-2, H-7), 3.15 (1H, m, H-1) and 6.14 (2H, m, H-8, H-9); δC (100 MHz, CDCl₃) 11.4 (CH₃), 14.3 (CH₃), 23.2 (C-10), 30.0 (CH₂), 31.4 (CH₂), 40.3 (CH₂), 46.1 (C-5), 46.5, 47.1, 50.5, 52.9 (C-1, C-6, C-7, C-2), 53.4 (C-4), 135.6 (C-8 or C-9) and 136.4 (C-8 or C-9); (Found M⁺-C₅H₆ 218.1617) followed by 82 (45 mg, 23%).
2. *n*-Butyl lithium (2.5 M in hexane, 0.68 cm³) was added to a suspension of copper iodide (160 mg, 0.85 mmol) in dry tetrahydrofuran (4 cm³) at -78°C. The solution was allowed to warm to -20°C and stirred for 1-2 min before being recooled to -78°C. A solution of the enone (21) (100 mg, 0.68 mmol) in dry tetrahydrofuran (2 cm³) was added and the reaction stirred at -78°C for 30 min. Addition of hexamethylphosphorotriamide (0.50 cm³) and iodomethane (0.20 cm³, 3.2 mmol) was followed by stirring at the same temperature for 30 min and then allowing the reaction to warm to 24°C. The reaction was quenched with saturated aqueous ammonium chloride and the organic product extracted into diethyl ether (1 x 30 cm³, 2 x 10 cm³), dried over sodium sulfate and concentrated under reduced pressure. The crude material (135 mg) was chromatographed on silica gel using ethyl acetate-petroleum ether (3.97) to yield 86 (99 mg, 67%); \( \nu_{\text{max}} / \text{cm}^{-1} = 1716, \text{CO} \); \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 0.92 (6H, m, 2 x CH₃), 1.19-1.44 (7H, m, H-10a, 3 x CH₂), 1.56 (1H, dt, J 2 x 8.0 and 1.8 Hz, H-5), 1.67 (1H, m, H-10b), 2.19 (1H, quintet, J 15.6 and 7.8 Hz, H-4), 2.58 (1H, quintet, J 10.0 and 4.7 Hz, H-6), 2.98 (2H, m, H-2, H-7), 3.15 (1H, m, H-1) and 6.14 (2H, ddd, J 14, 5.6 and 3.2 Hz, H-8, H-9); \( \delta_{\text{C}} \) (100 MHz, CDCl₃) 11.4 (CH₃), 14.3 (CH₃), 23.2 (C-10), 30.0 (CH₂), 31.4 (CH₂), 40.3 (CH₂), 46.1 (C-5), 46.5, 47.1, 50.5, 52.9 (C-1, C-6, C-7, C-2), 53.4 (C-4), 135.6 (C-8 or C-9) and 136.4 (C-8 or C-9); (Found M⁺-C₅H₆ 152.1218 C₁₅H₂₂O requires 218.1617) the 1,2 addition product (116) (41 mg, 39%); \( \nu_{\text{max}} / \text{cm}^{-1} = 3590.0 \) (OH); \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 0.90 (3H, m, CH₃), 1.31-1.37 (6H, m, 3 x CH₂), 1.44 (1H, br d, J 7.6 Hz, H-10a), 1.53-1.59 (1H, m, H-10b), 2.61 (1H, dd, J 8 and 4.2 Hz, H-6), 2.89 (2H, m, H-2, H-7), 3.26 (1H, m, H-1), 5.47 (2H, ddd, J 22.5, 5.6 and 1.7 Hz, H-4, H-5), 5.85 (1H, dd, J 5.7 and 3.2 Hz, H-8 or H-9) and 6.17 (1H, dd, J 5.7 and 3.2 Hz, H-8 or H-9); \( \delta_{\text{C}} \) (100 MHz, CDCl₃) 14.3 (CH₃), 23.4 (C-10), 26.1 (CH₂), 43.2 (CH₂), 45.5 (CH₂),
5-(Tetrahydro-2'-pyranyloxy)-1-iodo-pentane (87)

1) Iodine (2.0 g, 16 mmol) was added to a stirred solution of the mono-THP protected alcohol (101) (1.0 g, 5.3 mmol), imidazole (1.1 g, 16 mmol) and triphenylphosphine (4.2 g, 16 mmol) dissolved in ether: acetonitrile (1:3, 60 cm³). The mixture was stirred at 24°C for 3.5 h and the solvent was then removed under reduced pressure. Column chromatography gave the iodinated product 87 (0.134 mg, 67%) as pale orange oil; $\nu_{\text{max}}$cm$^{-1}$; $\delta_H$(400 MHz, CDCl$_3$) 1.46-1.89 (12H, m, 6 x CH$_2$), 3.20 (2H, t, J 7.0 Hz, H-1), 3.39 (H, dt J 2 x 9.5 and 6.3 Hz, H-5), 3.50 (H, m, H-6'), 3.75 (H, dt, J 2 x 9.5 and 6.7 Hz, H-5), 3.86 (H, m, H-6') and 4.57 (H, dd, J 4.4 and 2.8 Hz, H-2'); $\delta_C$(100 MHz, CDCl$_3$) 7.0 (C-1), 19.9, 25.7, 27.5, 28.9, 31.0, 33.6 (C-3'-C-5' and C-2-C-4), 67.4, 62.6 and 99.1 (C-6', C-5, C-2'); (Found M$^+$ 298.0441 C$_{10}$H$_{19}$I$_2$O$_2$ requires 298.0430).

2) Sodium iodide (1.97 g, 13.1 mmol) was added to a solution of 102 (2.97 g, 10.1 mmol) in acetone (50 cm³). The mixture was refluxed for 21 h. The reaction was quenched by adding water and the crude organic product was extracted into ethyl acetate (3 x 20 cm³). The organic phases were combined, dried over anhydrous magnesium sulfate, filtered and concentrated at reduced pressure. Column chromatography of the residue on silica gel with ethyl acetate-petroleum ether (1:9) as eluent gave adduct 87 (1.50 g, 50%); $\nu_{\text{max}}$cm$^{-1}$; $\delta_H$(400 MHz, CDCl$_3$) 1.46-1.89 (12H, m, 6 x CH$_2$), 3.20 (2H, t, J 7.0 Hz, CH$_2$-l), 3.39 (H, dt J
exo-5-Ethyl-tricyclo-[5.2.1.0²,⁶]-dec-8-en-3-one (88)

Bromoethane (0.3 cm³, 4.00 mmol) was added gradually to magnesium turnings (78.3 mg, 3.22 mmol) in dry ether (10 cm³) and the mixture was stirred until the magnesium had been consumed. To the turbid mixture was added dry CuI (20 mg, 0.11 mmol) and the resulting green-yellow mixture stirred at 0°C for 30 minutes. The mixture was cooled to -78°C and a solution of enone (21) (100 mg, 0.68 mmol) in ether (10 cm³) was added drop wise over a period of 5 min. After stirring for 1 h at -78°C, the reaction mixture was quenched with a saturated aqueous ammonium chloride solution. The aqueous phase was extracted with ether and the combined organic phase washed with water, dried (MgSO₄), and the solvent evaporated under reduced pressure. Column chromatography on silica-gel (10 g, ethyl acetate-hexane; 1:10) gave 88 (96.5 mg, 80%) as a colourless oil. IR 1725 cm⁻¹ (C=O). (Found: M⁺, 176.1201. C₁₂H₁₆O requires 176.1201). δH (300 MHz; CDCl₃): 6.13 (2H, m, H-8 and H-9), 3.18-3.12 (1H, m, H-1), 3.04-2.98 (1H, m, H-7), 2.90 (1H, ddd, J = 9.5, 4.4, 1.8 Hz, H-2), 2.60 (1H, dt, J = 9.5, 4.0 Hz, H-6), 2.18 (1H, dd, J = 18.7, 9.5 Hz, H-4endo), 1.91 (1H, ddd, J = 18.7, 6.6, 1.8 Hz H-4exo), 1.66-1.56 (1H, m, H-5), 1.53 (1H, d, J = 8.4 Hz, H-10a or H-10b), 1.46-1.55 (2H, m, CH₂), 1.40 (1H, d, J = 8.75 Hz, H-10a or H-10b), 0.94-0.86 (3H, t, J = 7.32 Hz, CH₃). δC (75 MHz; CDCl₃): 11.9 (CH₃), 30.5 (CH₂), 38.5 (CH₂), 46.2 (CH), 47.2 (CH), 47.9 (CH), 48.5 (CH), 52.3 (CH), 54.9 (C-10), 135.2 (C-8 or C-9), 136.0 (C-8 or C-9), 220.9 (CO); (Found M⁺ 176.1201; C₁₂H₁₆O requires 176.1201).
n-Butyllithium (2.5 M in hexane, 0.27 cm$^3$) was added to a solution of diisopropylamine (0.1 cm$^3$, 0.73 mmol) in dry tetrahydrofuran (2 cm$^3$) at -78°C. The reaction mixture was stirred at 0°C for 30 min, and then recooled to -78°C. A solution of 88 (100 mg, 0.52 mmol) in dry tetrahydrofuran (1 cm$^3$) was added and stirring continued for 15 min at this temperature. 91 (440 mg, 1.56 mmol) in dry tetrahydrofuran (1 cm$^3$) was then added and the reaction mixture was allowed to warm to 0°C over 3 h. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (3 x 20 cm$^3$). The extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude material was chromatographed on silica gel using ethyl acetate-petroleum ether (1:9) as eluent and gave 89 (13 mg, 8%); $\delta$H (300 MHz, CDCl$_3$) 0.87 (3H, t, J 7.5 Hz, CH$_3$), 2.24 (3H, t, J 7.1 Hz, -OCH$_2$CH$_3$), 1.54-1.80 (12H, m, 4 x CH$_2$, H-4 and H-5, 2 x H-10), 2.11 (2H, -O(CO)CH$_2$CH$_3$), 2.49 (1H, m, H-6), 2.79 (1H, m, H-7), 2.90, (1H, m, H-1), 2.99 (1H, dd, J 9.9 and 3.9 Hz, H-2), 4.18 (2H, q, J 7.2 Hz, -(CO)OCH$_2$CH$_3$), 6.13 (1H, dd, J 5.6 and 3.0 Hz, H-8 or H-9) and 6.31 (1H, dd, J 5.6 and 3.0 Hz, H-8 or H-9); followed by 88 (48 mg, 52%); $\nu$$_{max}$/cm$^{-1}$ 1725 (CO); 0.91 (3H, t, J 7.2 Hz, CH$_3$), 1.38-1.48 (3H, m, CH$_2$ and H-10a), 1.54 (1H, d J 8.4 Hz, H-10b), 1.61-1.64 (1H, m, H-5), 1.89-1.96 (1H, ddd, J 18.6, 6.6 and 2.0 Hz, H-4exo), 2.20 (1H, dd, J 18.6 and 9.0 Hz, H-4endo), 2.61 (1H, dt, J 9.6 and 4.0 Hz, H-6), 2.91 (1H, ddd, J 9.6, 4.4 and 2.0 Hz, H-2), 3.02 (1H, m, H-7), 3.16 (1H, m, H-1), 6.12 (1H, dd, J 5.6 and 2.8 Hz, H-8 or H-9) and 6.15 (1H, dd, J 5.6 and 3.0 Hz, H-8 or H-9); (Found M$^+$ 176.1201; C$_{12}$H$_{16}$O requires 176.1201).
Ethyl-6-{[(4-methylphenyl) sulfonyl] oxy}-hexanoate (91)

&p-Toluenesulfonylchloride (97.8 g, 41 mmol) in dichloromethane (20 cm³) was added to a mixture of ethyl 6-hydroxy hexanoate (90) (3.0 g, 18.7 mmol) and triethylamine (7.8 cm³, 56.1 mmol) in dry dichloromethane (10 cm³) at 0°C. The solution was stirred at this temperature for 20 min, then at 24°C for 2 h. The reaction was quenched with 1M hydrochloric acid and the aqueous layer extracted with dichloromethane. The combined organic phase was washed with saturated aqueous sodium carbonate, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Column chromatography on silica gel with ethyl acetate-petroleum ether yielded the tosylate 91 (3.9 g, 66%); \( \delta_H \) (400 MHz, CDCl₃) 1.22 (3H, t, J 7.2 Hz, -CH₂CH₃), 1.33 (2H, m, CH₂), 1.56 (2H, quintet, J 7.6 Hz, CH₂), 1.64 (2H, m, CH₂), 2.23 (2H, t, J 7.4 Hz, H-2), 2.43 (3H, s, ArCH₃), 4.00 (2H, t, J 6.4 Hz, H-6), 4.09 (2H, q, J 7.2 Hz, -CH₂CH₃), 7.32 (2H, d, J 8.2 Hz, 2 x Ar-CH) and 7.76 (2H, d, J 8.2 Hz, 2 x Ar-CH); \( \delta_C \) (100 MHz, CDCl₃) 14.1 (PhCH₃), 21.5 (-CH₂CH₃), 24.2 (CH₂), 24.8 (CH₂), 28.5 (CH₂), 33.9 (C-2), 60.2 (-CH₂CH₃), 70.2 (C-6), 127.8 (ArC), 129.7 (ArC), 133.2 (ArC), 144.6 (ArC) and 173.20 (CO).

3-t-Butylsilyloxy-octyn-1-yne (93)

t-Butyl dimethylsilyl chloride (3.6 g, 23.8 mmol) in dimethylformamide (20 cm³) was added to a solution of 1-octyn-3-ol (92) (3 g, 23.8 mmol) and imidazole (2.4 g, 35.7 mmol) in dimethylformamide (10 cm³) at 24°C. The solution was stirred at this temperature for 18 h. The reaction was quenched with water before being extracted into ethyl acetate (3 x 20 cm³). The combined organic extracts were washed with water and then dried over magnesium sulfate, filtered and concentrated. Column chromatography on silica gel using ethyl
acetate-petroleum ether (3:97) yielded 93 (4.5 g, 78%) as a clear oil; 

\[ \nu_{\text{max}} / \text{cm}^{-1} \]

3300 (CH), 1066.7 (SiO); \[ \delta_{\text{H}} (300 \text{ MHz}, \text{CDCl}_3) 0.11 (3\text{H}, \text{s, CH}_3), 0.13 (3\text{H}, \text{s, CH}_3), 0.90 (12\text{H}, \text{s, } t\text{-Bu and H-8}), 1.26-1.70 (8\text{H}, \text{m, H-4-H-7}), 2.36 (\text{H, d, J 2.1 Hz, H-1}) \text{ and } 4.33 (\text{H, td, J 6.6 and 2 x 2.1 Hz, H-3}); \delta_{\text{C}} (75\text{MHz, CDCl}_3) -5.1 (\text{Si-CH}_3), -4.6 (\text{Si-CH}_3), 14.0 (\text{C-8}), 18.23 (\text{CH}_2), 22.6 (\text{CH}_2), 24.8 (\text{C-1}), 25.8 (t\text{-Bu}), 31.4 (\text{CH}_2), 38.6 (\text{CH}_2), 62.8(-\text{C(CH}_3)_2), 71.8 (\text{C-3}) \text{ and } 85.8 (\text{C-2}); 

(Found: M+240.1914; C_{14}H_{28}OSi requires 240.1909).

5-\((3'-t\text{-Butylidimethylsilyloxy}-1'-\text{oct-1-enyl})\text{-tricyclo[5.2.1.0^{2,5}]deca-8-ene-3-one (94)}

A reaction vessel was charged with Schwartz reagent \([\text{Cp}_2\text{Zr( H)Cl]}\) (1.2 g, 4.6 mmol) in dry tetrahydrofuran (7 cm\(^3\)) under nitrogen. A solution of the octyne (93) in dry tetrahydrofuran (15 cm\(^3\)) was added and the reaction stirred for 30 min at 24°C. The reaction mixture was then cooled to -50°C and the cooled mixture treated with methyl lithium (1.4 M in diethyl ether, 6.0 cm\(^3\)) and stirred at this temperature for 10 min. This mixture was added to copper cyanide (376 mg, 4.2 mmol) in a flame-dried vessel at -50°C and stirred for 15 min. Addition of methyl lithium (1.4 M in diethyl ether, 3 cm\(^3\)) was followed by stirring at -50°C for a further 15 min. A solution of enone \((21)\) (613 mg, 4.2 mmol) in dry tetrahydrofuran (10 cm\(^3\)) was added and the reaction stirred at the same temperature for a further 30 min. The solution was allowed to warm to 0°C before being quenched with saturated aqueous ammonium chloride. The organic product was extracted into ethyl acetate (3 x 15 cm\(^3\)) and filtered through Celite before being washed with brine and dried over anhydrous magnesium sulphate. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:9) yielded the substituted enone (94) (789 mg, 50%) as a clear oil; 

\[ \nu_{\text{max}} / \text{cm}^{-1} \]

3682.1 (SiO), 1669.1 (CO); \[ \delta_{\text{H}} (400 \text{ MHz, CDCl}_3) 0.040 (6\text{H, m, Si( CH}_3)_2), 0.90 12 \text{H, t, J 3.0 Hz, } t\text{-Bu and CH}_3), 1.26-1.58 (10\text{H, m, H-}}
5 to H-5, 2 x H-10), 2.09-2.18 (1H, dddd, J 18.0, 8.0, 6.4 and 1.8 Hz, H-4exo), 2.26 (1H, ddd, J 18.0, 8.8 and 2.8 Hz, H-4endo), 2.34 (1H, m, H-5), 2.76 (1H, m, H-6), 2.95 (1H, m, H-2), 3.07 (1H, m, H-7), 3.18 (1H, m, H-1), 4.04 (1H, ddd, J 12.4 and 6 Hz, H-5), 5.37 (1H, dddd, J 15.2, 6.8, 2.0 and 1.0 Hz, H-5), 5.59 (1H, ddt, J 15.2, 7.2 and 2 x 1.0 Hz, H-5), and 6.18 (2H, s, H-8 and H-9); δC(100 MHz, CDCl₃) -4.7 (SiCH₃), -4.2 (SiCH₃), 13.9 (CH₃), 22.5 (C-10), 24.9 (CH₂), 25.8 (t-Bu), 31.7 (CH₂), 38.3 (CH₂), 39.5 (C-4), 45.9 (C-7), 46.24 (C-1), 47.8 (C-5), 48.8 (C-6), 54.4 (C-2), 73.3 (C-5), 132.7 (C-5), 133.5 (C-5), 135.1 (C-90), 136.34 (C-8) and 219.2 (CO).

**Ethyl-6-oxohexanoate (95)**

Oxalyl chloride (1.79 cm³, 20.6 mmol) was added to a solution of dimethyl sulfoxide (2.9 cm³, 41.2 mmol) in dry dichloromethane (50 cm³) at -60°C under nitrogen and the mixture stirred for 15 min. Ethyl 6-hydroxy-hexanoate (90) (3.02 cm³, 18.7 mmol) was added and stirring continued for a further 15 min before the addition of triethylamine (13 cm³). The mixture was stirred for 15 min allowing it to warm to 24°C, then quenched with 1M HCl and the mixture extracted with dichloromethane (3 x 25 cm³). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Flash chromatography of the residue on silica gel using ethyl acetate-heptane (3:7) gave the aldehyde 95 (2.38 g, 80%); δH (400 MHz, CDCl₃) 1.25 (3H, t, J 7.2 Hz, CH₃), 1.68 (4H, quintet, J 3.6 Hz, 2 x CH₂), 2.35 (4H, dt, J 2 x 21.2 and 7.0 Hz, H-2 and H-5), 4.13 (2H, q, J 7.2 Hz, -OCH₂-); δC (100 MHz, CDCl₃) 14.2 (CH₃), 24.1 (CH₂), 24.3 (CH₂), 33.5 (C-2), 33.9 (C-5), 60.3 (-O-CH₂), 173.8 (CO) and 179.6 (CO); (Found M⁺ 158.0887; C₈H₁₄O₃ requires 158.0943).
Ethyl(3E)-6-(4-(3′t-butyldimethylsilyloxy1′-oct-1-enyl)-3-oxotricyclo[5.2.1.02,6]dec-8-en-4-ylidene)hexanoate (96)

1) n-Butyllithium (1.6M in hexane, 0.09 cm³) was slowly added to a stirred solution of diisopropylamine (0.020 cm³, 0.15 mmol) in dry tetrahydrofuran (1 cm³) at -78°C. After 30 min stirring at 0°C the mixture was then recooled to -78°C and a solution of 94 (50 mg, 0.13 mmol) in tetrahydrofuran (1.5 cm³) was added and the resulting solution was stirred for 30 min. A solution of the aldehyde (95) in tetrahydrofuran (1 cm³) was added and the mixture was stirred at ambient temperature for 48 h without effecting complete conversion of the starting enone. Saturated aqueous sodium chloride was added and the mixture was extracted with ether (2 x 10 cm³). The organic extract was dried over anhydrous magnesium sulphate and the solvent was removed under reduced pressure to give a yellow oil. Chromatography on silica gel using ethyl acetate-hexane (1:19) as eluent afforded the addition product 96 (3 mg, 4%); δH (300 MHz, CDCl₃) 0.013 (6H, m, Si(CH₃)₂), 0.88 (12H, t-Bu + CH₃), 1.22-1.65 (19H, m, 7 x CH₂, CH₃, 2 x H-10), 2.04 (2H, m, H-4²), 2.26 (2H, t, J 7.4 Hz, -CH₂CO₂-), 2.57 (1H, m, H-5), 2.99 (2H, m, H-2 and H-6), 3.10 (1H, m, H-1), 3.25 (1H, m, H-7), 4.03 (1H, dd, J 12.1 and 6.2 Hz, H-5³), 4.12 (2H, q, J 7.1 Hz, -CO₂CH₂CH₃⁻), 5.23-5.36 (1H, H-5⁵), 5.45-5.55 (1H, H-5¹), 6.01 (2H, m, H-8 and H-9) and 6.39 (1H, m, H-4¹); (Found M⁺ 528.3672; C₃₂H₅₂O₄Si requires 528.3635). (Found M⁺ 528.3672; C₃₂H₅₂O₄Si requires 528.3635).

2) A reaction vessel was charged with Schwartz reagent [Cp₂Zr(H)Cl] (600 mg, 2.3 mmol) in dry tetrahydrofuran (5 cm³) under nitrogen. A solution of the octyne 93 (510 mg, 2.1 mmol) in dry tetrahydrofuran (10 cm³) was
added and the reaction stirred for 30 min at 24°C. The reaction mixture was then cooled to -50°C and the cooled mixture treated with methylthiium (1.4 M in diethyl ether, 2.9 cm³) and stirred at this temperature for 10 min. This mixture was added to copper cyanide (190 mg, 2.1 mmol) in a flame-dried vessel at -50°C and stirred for 15 min. Addition of methylthiium (1.4 M in diethyl ether, 1.5 cm³) was followed by stirring at -50°C for a further 15 min. A solution of enone (21) (300 mg, 4.2 mmol) in dry tetrahydrofuran (3 cm³) was added and the reaction stirred at the -40°C for a further 1 h, then at ambient temperature for 20 h. The solution was allowed to warm to 0°C before being quenched with saturated aqueous ammonium chloride. The organic product was extracted into ethyl acetate (3 x 15 cm³) and filtered through Celite before being washed with brine and dried over anhydrous magnesium sulphate. Column chromatography on silica gel using ethyl acetate-petroleum ether (1: 4) yielded 96 (42.8 mg; 4%); δH (300 MHz, CDCl₃) 0.013 (6H, m, Si(CH₃)₂), 0.88 (12H, t-Bu + CH₃), 1.22-1.65 (17H, m, 7 x CH₂, CH₃), 2.04 (2H, m, H-4), 2.26 (2H, t, J 7.4 Hz, -CH₂CO₂⁻), 2.57 (1H, m, H-5), 2.99 (2H, m, H-2 and H-6), 3.10 (1H, m, H-1), 3.25 (1H, m, H-7), 4.03 (1H, dd, J 12.1 and 6.2 Hz, H-5), 4.12 (2H, q, J 7.1 Hz, -CO₂CH₂CH₃⁻), 5.23-5.36 (1H, H-5), 5.45-5.55 (1H, H-5'), 6.01 (2H, m, H-8 and H-9) and 6.39 (1H, m, H-4'); (Found M⁺ 528.3672; C₃₂H₅₂O₄Si requires 528.3635).

Addition of 2-[5-iodopentyl] oxy] tetrahydro-2H-pyran (87) to give 97 and 107

1) Mediated by potassium-t-butoxide

The butyl ketone (82) (50 mg, 0.25 mmol) in dry dimethylsulfoxide (4 cm³) was added to a suspension of potassium-t-butoxide (34 mg, 0.28 mmol) in
dry dimethylsulfoxide (4 cm$^3$) at 24°C under an inert nitrogen atmosphere. The mixture was stirred at this temperature for 20 min prior to the addition of 87 (102 mg, 0.34 mmol) in dry dimethylsulfoxide (1 cm$^3$). Stirring was continued for 2 h after which the reaction was quenched with water and the resulting mixture extracted with ethyl acetate (3 x 15 cm$^3$). The combined organic extracts were washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and concentrated in vacuo. Column chromatography on silica gel using ethyl acetate-hexane (1:19) as eluent gave the cis addition product (4-exo, 5-exo)-5-butyl-4-(5'-(tetrahydro-2H-pyran-2'-yloxy)pentyl)tricycle[5.2.1.0$^{2,6}$]dec-8-en-3-one (97) as a clear oil (25 mg, 27%); $\nu_{\text{max}}$ cm$^{-1}$ 1669 (CO); $\delta_H$ (300 MHz, CDCl$_3$) 0.88 (3H, t, $J$ 6.9 Hz, CH$_3$), 1.23-1.76 (23 H, m, 10 x CH$_2$, 2 x H-10, H-5), 1.81 (1H, m, H-4), 2.24 (1H, m, H-6), 2.87 (1H, m, H-7), 3.0 (1H, m, H-2), 3.07 (1H, m, H-1), 3.36 (1H, dt, $J$ 2 x 9.0 and 6.4 Hz, H-6'), 3.46-5.54 (1H, m, H-4$^5$), 3.70 (1H, m, H-6'), 3.85 (1H, m, H-4$^5$), 4.58 (1H, m, H-2'), 5.96 (1H, dd, $J$ 5.7 and 3.2 Hz, H-9) and 6.01 (1H, $J$ 5.7 and 3.0 Hz, H-8); $\delta_C$ (75 MHz, CDCl$_3$) 14.1 (CH$_3$), 19.7 (CH$_2$), 22.5 (CH$_2$), 22.7 (CH$_2$), 25.5 (CH$_2$), 29.5 (CH$_2$), 29.8 (C-5), 30.8 (CH$_2$), 32.6 (CH$_2$), 36.9 (CH$_2$), 37.7 (CH$_2$), 46.1(C-1), 47.2 (C-2), 48.3 (C-7), 48.8 (C-6), 52.3 (CH$_2$), 54.8 (CH$_2$), 62.4 (C-6$'$), 62.9 (CH), 67.5 (C-4$^5$), 98.9 (C-2'), 135.7 (C-8 or C-9), 136.3 (C-8 or C-9) and 220.9 (CO); (Found M$^+$ 374.2834 C$_{24}$H$_{38}$O$_3$ requires 374.2821); followed by 82 (2.6 mg, 5%) followed by the trans addition product (4-endo,5-exo)-5-butyl-4-(5'-(tetrahydro-2H-pyran-2''-yloxy)pentyl)tricycle[5.2.1.0$^{2,5}$]dec-8-en-3-one (107) as a clear oil (33 mg, 35%); $\nu_{\text{max}}$ cm$^{-1}$ 1669 (CO); $\delta_H$ (300 MHz, CDCl$_3$) 0.94 (3H, t, $J$ 6.9 Hz, CH$_3$), 1.23-1.59 (23 H, m, 10 x CH$_2$, 2 x H-10, H-5), 1.93 (1H, m, H-4), 2.54 (1H, m, H-6), 2.97 (1H, m, H-7), 3.00 (1H, m, H-2), 3.10 (1H, m, H-1), 3.36 (1H, dt, $J$ 2 x 9.6 and 6.8 Hz, H-6'), 3.49 (1H, m, H-4$^5$), 3.70 (1H, dt, $J$ 2 x 9.6 and 6.9 Hz, H-6'), 3.85 (1H, m, H-4$^5$), 4.56 (1H, m, H-2'), 6.02 (1H, dd, $J$ 5.8 and 3.0 Hz, H-8) and 6.13 (1H, dd, $J$ 5.8 and 3.2 Hz, H-9); $\delta_C$ (75 MHz,
CDC\textsubscript{3}) 14.1 (CH\textsubscript{3}), 19.7 (CH\textsubscript{2}), 22.9 (CH\textsubscript{2}), 25.5 (CH\textsubscript{2}), 26.6 (CH\textsubscript{2}), 27.1 (CH\textsubscript{2}), 27.4 (CH\textsubscript{2}), 29.6 (CH\textsubscript{2}), 30.0 (CH\textsubscript{2}), 30.8 (CH\textsubscript{2}), 36.5 (CH\textsubscript{2}), 43.4 (C-5), 44.5 (C-1), 46.5 (C-6), 47.0 (C-7), 52.5 (C-10), 55.3 (C-2), 58.6 (C-4), 62.3 (C-4\textsuperscript{5}), 67.6 (C-6'), 98.8 (C-2'), 135.5 (C-8), 137.1 (C-9) and 219.6 (CO); (Found M\textsuperscript{+} 374.2834 \text{C}_{24}\text{H}_{38}\text{O}_3 \text{requires } 374.2821).

2) Mediated by potassium hydride

Potassium hydride (35% suspension in mineral oil, 15 mg, 0.38 mmol) was washed with dry hexane to remove the oil, then dried by the passage of nitrogen over the hydride and finally suspended in dry tetrahydrofuran. \text{82} in dry tetrahydrofuran was added and the resulting mixture stirred at 0°C for 5 min prior to the addition of \text{87} (210 mg, 0.70 mmol) in dry tetrahydrofuran (2 cm\textsuperscript{3}). The mixture was then stirred at ambient temperature for 18 h. The reaction was quenched by the slow addition of water and the aqueous layer extracted with ethyl acetate (3 x 15 cm\textsuperscript{3}). The combined organic extracts were washed with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The crude product was subjected to column chromatography on silica gel with ethyl acetate-petroleum ether (1:32) affording (4-exo, 5-exo)-5-butyl-4-(5'-((tetrahydro-2H-pyran-2''-yloxy)pentyl)tricycle[5.2.1.0\textsuperscript{2,6}]dec-8-en-3-one (97) (7.4 mg, 8%).

3) Mediated by sodium hydride

Sodium hydride (60 % suspension in mineral oil, 12 mg, 0.30 mmol) was washed with dry pentane to remove the oil, then dried by the passage of nitrogen over the hydride and finally suspended in dry dimethylsulfoxide (2 cm\textsuperscript{3}). This suspension was heated at 60°C for 1 h and then cooled to
ambient temperature. Butyl ketone (82) (50 mg, 0.25 mmol) in dry dimethylsulfoxide (2 cm³) was added and the mixture stirred for 15 min at this temperature. 87 in dry dimethylsulfoxide was added with stirring. The resultant mixture was stirred for a further 15 min at this temperature, then water was added and the mixture extracted into ethyl acetate (3 x 15 cm³), dried over anhydrous sodium sulfate and concentrated. Column chromatography on silica gel with ethyl acetate-petroleum ether (1:19) as eluent gave (4-exo, 5-exo)-5-butyl-4-(5'-(tetrahydro-2H-pyran-2'-yloxy)pentyl)tricycle[5.2.1.0²⁶]dec-8-en-3-one (97) (28 mg, 30%) followed by 82 (20 mg, 40%) followed by (4-endo, 5-exo)-5-butyl-4-(5'-(tetrahydro-2H-pyran-2'-yloxy)pentyl)tricycle[5.2.1.0²⁶]dec-8-en-3-one (107) (2.6 mg, 5%).

5-(Tetrahydro-2'-pyranyloxy) pentan-1-ol (101)

To a reaction vessel charged with 1, 5-pentanediol (200 mg, 1.92 mmol) in dichloromethane (10 cm³), p-toluenesulfonic acid (37 mg, 0.192 mmol) and 3, 4-dihydro-2H-pyran (0.12 cm³, 1.3 mmol) was added. The solution was stirred at 24°C for 18 h and the reaction mixture diluted with water. The organic product was extracted into ethyl acetate (3 x 30 cm³) and dried over anhydrous magnesium sulfate. Column chromatography on silica gel using ethyl acetate-petroleum ether as eluent (1:1) yielded 1,5-bis(tetrahydro-2H-pyran-2'-yloxy)pentane (100) (168 mg, 46%) as a clear oil; $\nu_{\text{max/cm}^{-1}}$ 1128.0 (COC); $\delta_{\text{d}}$(400MHz, CDCl$_3$) 1.39-1.84 (18H, m, 9 x CH$_2$), 3.39 (2H, dt, J 2 x 9.6 and 6.6 Hz, H-6'), 3.48 (2H, m, H-6'), 3.72 (2H, tt, J 2 x 9.6 and 6.75 Hz, H-1 or H-5), 3.86 (2H, m, H-1 and H-5) and 4.6 (2H, dd, J 4.7 and 2.5 Hz, H-2'); $\delta_{\text{c}}$ (100 MHz, CDCl$_3$) 19.6, 22.95, 25.5, 29.6, 30.8 (C-3', C-4', C-5', C-2, C-3, C-4), 62.2, 67.45 (C-6', C-1 and C-5) and 98.8 (C-2'); (Found M$^+$ 272.198; C$_{15}$H$_{26}$O$_4$ requires 272.198) followed by the alcohol 101 as a clear oil (143 mg, 57%); $\nu_{\text{max/cm}^{-1}}$ 3683.8 (OH), 1050.9 (COC); $\delta_{\text{d}}$(300 MHz, CDCl$_3$) 1.39-1.84 (12H, m,
4-(Tetrahydro-2H-pyran-2'-yloxy)pentyl 4'-methylbenzenesulfonate (102)

The alcohol (101) (200 mg, 1.06 mmol) was dissolved in dry dichloromethane (5 cm³) under a nitrogen atmosphere. To the solution was added triethylamine (0.4 cm³, 3.18 mmol) and the mixture was cooled to 0°C. Tosyl chloride (400 mg, 2.3 mmol) in dry dichloromethane (5 cm³) was added, the reaction temperature was raised to 24 °C and stirring was continued for 24 h. The mixture was washed with 6 N hydrochloric acid (2 x 10 cm³) and saturated aqueous sodium carbonate (2 x 20 cm³). The organic residue was dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography on silica gel with ethyl acetate-petroleum ether (1:9) as eluent afforded 102 (0.24 g, 80%); 1.40-1.71 (12 H, m, 6 x CH₂), 2.44 (3H, s, CH₃), 3.33 (1H, dt, J 2 x 9.6 and 6.3 Hz, H-1), 3.49 (1H, m, H-3'), 3.69 (1H, dt, J 2 x 9.6 and 6.6 Hz, H-1), 3.83 (1H, m, H-3'), 4.03 (2H, t, J 6.2 Hz, H-5), 4.53 (1H, br, t, J 3.6 Hz, H-2'), 7.34 (2H, dd, J 8.4 and 0.8 Hz, 2 x Ar) and 7.78 (2H, d, J 8.4 Hz, 2 x Ar); δC (75 MHz, CDCl₃) 19.7, 21.6, 22.3, 25.5, 28.7, 29.1, 30.7 (CH₂), 62.4, 67.1, 70.5 (C-3', C-1, C-5), 98.9 (C-1'), 127.9, 129.8, 133.3 and 144.6 (4 x Ar-C).

5-Hydroxypentyl 4'-methylbenzenesulfonate (104)
Silver (II) oxide (3.5 g, 15 mmol) [freshly prepared from silver (I) nitrate with sodium hydroxide in water heated to 80-90°C] was added to a solution of 1,5 pentane diol (1.0 g, 10 mmol) in dichloromethane (30 cm³), followed by p-toluenesulfonic acid (2.1 g, 11 mmol) and potassium iodide (330 mg, 2 mmol). The reaction mixture was stirred at 24°C for 4 h. The mixture was then filtered through silica gel, washed successively with ethyl acetate and the solvent removed under reduced pressure. Column chromatography on silica gel using ethyl acetate-petroleum ether (3:7) yielded the ditosylate 5-[(4'-methylphenyl)sulfonyl]oxy] pentyl 4'-methylbenzenesulfonate (103) (271 mg, 7%) as colourless solid; m.p. 71-74°C (from chloroform), (Found: C, 55.1; H, 6.0; S, 15.0; C₁₉H₂₄O₅S₂ requires C, 55.3; H, 5.9; S, 15.5); νₘₐₓ/cm⁻¹ 1311.2 (SO₂), 1083.1 (SO₂); δ_H(300 MHz, CDCl₃) 1.32-1.40 (2H, m, CH₂), 1.55-1.65 (4H, m, 2 x CH₂), 2.45 (6H, s, 2 x CH₃), 3.97 (4H, t, J 6.5 Hz, 2 x CH₂-OTs), 7.34 (4H, d, J 8.1 Hz, 4 x Ar) and 7.76 (4H, d, J 8.1 Hz, 4 x Ar); δ_C (100MHz, CDCl₃) 21.7 (CH₃), 21.8 (CH₂), 28.4 (2 x CH₂), 70.2 (2 x C-OTs), 128.1 (4 x Ar), 130.1 (4 x Ar), 133.3 (C-CH₃) and 145.0 (C-SO₂) followed by the monotosylate 104 (2.06 g, 80%) as a colourless oil; νₘₐₓ/cm⁻¹ 3682.9 (OH), 1306.1 (SO₂), 1076.6 (SO₂); δ_H(300MHz, CDCl₃) 1.36-1.45 (2H, m, CH₂), 1.48-1.55 (2H, m, CH₂), 1.63-1.73 (2H, m, CH₂), 1.79 (3H, s, CH₃), 3.60 (2H, t, J 6.3 Hz, H-5), 4.03 (2H, t, J, 6.3 Hz, H-1), 7.34 (2H, d, J 8.3 Hz, H-2' and H-3') and 7.80 (2H, d, J 8.4 Hz, H-5' and H-6'); δ_C (100MHz, CDCl₃) 21.5 (CH₃), 21.6 (CH₂), 28.55 (CH₂), 31.8 (CH₂), 62.4 (C-5), 70.3 (C-1), 127.8 (C-2' and C-3'), 129.7 (C-5' and C-6'), 133.1 (C-4') and 144.6 (C-1'); (Found M⁺ 258.0934; C₁₂H₁₈O₄S requires 258.0926).

5- Iodopentan-1-ol (106)

1) The monotosylate (105) (0.875 g, 3.39 mmol) was suspended in acetone (20 cm³) and sodium iodide (1.02 g, 6.78 mmol) was added. The mixture was refluxed for 18 h, diluted with water and the organic product extracted into ethyl acetate (2 x 15 cm³), dried over anhydrous
magnesium sulfate and concentrated. The crude material was chromatographed on silica gel using ethyl acetate-petroleum ether (1:9) as eluent yielding 1-ido-5-(2'-(5''-iodopentyloxy) propan-2'-yl) pentane (105) (218 mg, 14%); ν\text{max}/cm\(^{-1}\) 1187.0 (CH\(_2\)), 1128.6 (COC); δ\(_H\) (400MHz, CDCl\(_3\)) 1.43-1.52 (4H, m, 2 x CH\(_2\)), 1.65 (4H, quintet, J 7.0 Hz, 2 x CH\(_2\)), 1.85 (4H, quintet, J 7.2 Hz, 2 x CH\(_2\)), 2.04 (6H, s, 2 x CH\(_3\)), 3.19 (4H, t, J 7.0 Hz, 2 x CH\(_2\)-I) and 4.07 (4H, t, J 6.6 Hz, 2 x CH\(_2\)-O-); δ\(_C\) (100 MHz, CDCl\(_3\)) 6.65 (2 x CH\(_2\)-I), 21.2 (2 x CH\(_3\)), 27.1 (2 x CH\(_2\)), 27.8 (2 x CH\(_2\)), 33.2 (2 x CH\(_2\)), 63.3 (2 x CH\(_2\)-O-) and 171.4 (C); (Found M\(^+\) 468.0019; C\(_{13}\)H\(_{26}\)I\(_2\)O\(_2\) requires 468.0022) followed by the iodoalcohol (106) (0.226g, 31%) as an orange oil; ν\text{max}/cm\(^{-1}\) 3681.9 (OH), 1205.7 (CH\(_2\)); δ\(_H\) (400 MHz, CDCl\(_3\)) 1.4-1.51 (2H, m, CH\(_2\)), 1.55-1.62 (2H, m, CH\(_2\)), 1.86 (2H, quintet, J 7.2 Hz, CH\(_2\)), 3.2 (2H, t J 7.0 Hz, CH\(_2\)), 3.2 (2H, t J 7.0 Hz, H-5) and 3.6 (2H, t, J 6.4 Hz, H-1); δ\(_C\) (75 MHz, CDCl\(_3\)) 6.6 (C-5), 26.8 (CH\(_2\)), 31.6 (CH\(_2\)), 33.2 (CH\(_2\)) and 62.6 (C-1); (Found M\(^+\) 213.9845 C\(_5\)H\(_{11}\)I\(_2\)O requires 213.9855).

2) Cerium (III) trichloride heptahydrate (13.5 g, 41.3 mmol) was added to a stirred suspension of 1, 5 pentane diol (99) (3 cm\(^3\), 27.5 mmol) and sodium iodide (4.95 g, 33.0 mmol) in acetonitrile (55 cm\(^3\)) and the mixture heated to reflux for 5 h. The solution was cooled to ambient temperature and diluted with water. The mixture was extracted with ethyl acetate and the combined organic extracts washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate. The resulting crude residue (5.2 g) chromatographed on silica gel using ethyl acetate-petroleum ether (1:4) as eluent afforded the iodoalcohol (106) (4.1 g, 70%); ν\text{max}/cm\(^{-1}\) 3681.9 (OH), 1205.7 (CH\(_2\)); δ\(_H\) (400 MHz, CDCl\(_3\)) 1.4-1.51 (2H, m, CH\(_2\)), 1.55-1.62 (2H, m, CH\(_2\)), 1.86 (2H, quintet, J 7.2 Hz, CH\(_2\)), 3.2 (2H, t J 7.0 Hz, CH\(_2\)), 3.2 (2H, t J 7.0 Hz, H-5) and 3.6 (2H, t, J 6.4 Hz, H-1); δ\(_C\) (75 MHz, CDCl\(_3\)) 6.6 (C-5), 26.8 (CH\(_2\)), 31.6 (CH\(_2\)), 33.2 (CH\(_2\)) and 62.6 (C-1); (Found M\(^+\) 213.9845 C\(_5\)H\(_{11}\)I\(_2\)O requires 213.9855).
5-lodo-1-(t-butyldimethylsilyloxy)pentane (108)

To a solution of 106 (100 mg, 0.47 mmol), triethylamine (7 μl, 0.51 mmol) and 4-dimethylaminopyridine (DMAP) (2 mg, 0.02 mmol) in dry dichloromethane (6 cm³) was added t-butyldimethylsilyl chloride (0.18 g, 1.18 mmol). The solution was stirred at 24°C for 2 h, and the reaction quenched with 1M HCl. The aqueous phase was extracted with hexane (2 x 15 cm³) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue chromatographed on silica gel with ethyl acetate-petroleum ether (1:9) giving 108 (0.12 g, 78%); δH (400 MHz, CDCl3) 0.05 (6H, s, 2 x CH₃), 0.89 (9H, s, t-Bu), 1.42-1.57 (4H, m, 2 x CH₂), 1.85 (2H, quintet, J 7.2 Hz, CH₂), 3.19 (2H, t, J 7.0 Hz, CH₂I) and 3.61 (2H, t, J 6.2 Hz, CH₂OSi); δC (100 MHz, CDCl3) -5.3 (2 x CH₃), 6.9 (CH₂I), 25.9 (t-Bu), 26.9 (CH₂), 31.7 (CH₂), 33.4 (CH₂) and 62.8 (CH₂OSi); (Found M⁺-TBDMS 212.9776; C₁₁H₂₅OSi requires 328.0719).

5-Butyl-4-(4⁵-t-butyldimethylsilyloxy)pent-4'-yl)-tricyclo[5.2.1.0².⁶]dec-8-en-3-one (109)

Butyl ketone (82) (50 mg, 0.25 mmol) in dry dimethylsulfoxide (2 cm³) was added to a suspension of potassium-t-butoxide (34 mg, 0.28 mmol) in dry dimethylsulfoxide 2 cm³) at 24°C under an inert nitrogen atmosphere. The mixture was stirred at this temperature for 30 min prior to the addition of 108 (115 mg, 0.35 mmol) in dry dimethylsulfoxide (2 cm³). Stirring was continued for 18 h after which the reaction was quenched with water and the resulting
mixture extracted with ethyl acetate (3 x 10 cm$^3$). The combined organic extracts were dried over anhydrous magnesium sulfate, concentrated in vacuo and the crude material subjected to column chromatography on silica gel using hexane as eluent to yield 109 as a mixture of cis and trans products (1:3); $\nu_{\text{max}}$/cm$^{-1}$ 1278 (c-O) and 1822 (CO); $\delta_H$ (300 MHz, CDCl$_3$) 0.05 (3H, s, CH$_3$), 0.07 (3H, s, CH$_3$), 0.89 (9H, s, t-Bu), 1.26-1.77 (overlapping signals), 1.96 (1H, dd, $J$ 6.9 and 2.1 Hz, H-4), 2.03-2.21 (1H, m, H-4), 2.24-2.27 (1H, m, H-6), 2.60-2.63 (1H, m, H-6), 2.80 (1H, m, H-7 or H-2), 2.85 (1H, m, H-7 or H-2), 3.02 (1H, m, H-1), 3.13 (1H, m, H-1), 5.5-3.67 (2H, m, H-45), 3.73-3.83 (2H, m, H-45), 5.92-6.02 (3H, m, 2 x H-8 and H-9 or 2 x H-9 and H-8), 6.14 (1H, s, H-8 or H-9); (Found M$^+$ 404.3161; C$_{25}$H$_{44}$O$_2$Si requires 404.3111).

$^1$Given the complexity of the $^{13}$C NMR spectrum due to overlap of signals of the two diastereoisomers, the $^{13}$C data is not included

4-Allyl-5-butyltricyclo[5.2.1.0$^{2,6}$]dec-8-en-3-one (111)

Potassium hydride (35% suspension in mineral oil, 12 mg, 0.30 mmol) was washed with dry hexane to remove the oil, then dried by the passage of nitrogen over the hydride and finally suspended in dry tetrahydrofuran. 82 (50 mg, 0.25 mmol) in dry tetrahydrofuran (2 cm$^3$) was added and the resulting mixture stirred at 0°C for 5 min prior to the addition of allyl bromide (0.07 cm$^3$, 0.75 mmol). The mixture was then stirred at ambient temperature for 18 h. The reaction was quenched by the slow addition of water and the aqueous layer extracted with ethyl acetate (3 x 15 cm$^3$). The combined organic extracts were washed with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The crude product was subjected to column chromatography on silica gel with ethyl acetate-petroleum ether (1:32) affording the bisallylated product 110 (18 mg, 25%); $\delta_H$ (300 MHz, CDCl$_3$) 0.93 (3H, t, $J$ 7.0 Hz, CH$_3$), 1.24-1.54 (7H, m, 3 x
CH$_2$, H-10$_a$), 1.58-1.62 (1H, dt, J 2 x 10.8 and 2.4 Hz, H-10$_b$), 1.86 (1H, dd, J 19.0 and 12.2 Hz, H-4$^1$), 2.02 (1H, dd, J 19.0 and 11.0 Hz, H-4$^4$), 2.17-2.25 (1H, dddt, J 18.8, 8.8 and 1.8 Hz, H-4$^1$), 2.28-2.36 (1H, dddt, J 18.8, 7.2 and 2.0 Hz, H-4$^1$), 2.47-2.55 (1H, ddd, J 14.0, 10.8 and 5.2 Hz, H-6), 2.96 (1H, m, H-7), 3.01 (1H, dd, H 14.0 and 6.0 Hz, H-2), 3.17 (1H, m, H-1), 4.88-5.03 (4H, m, 2 x H-4$^3$), 5.45-5.69 (2H, m, 2 x H-4$^2$), 6.00 (1H, dd, J 5.7 and 3.0 Hz, H-8) and 6.12 (1H, dd, J 5.7 and 2.7 Hz, H-9); $\delta$C (75 MHz, CDCl$_3$) 14.1 (CH$_3$), 22.9 (CH$_2$), 30.1 (CH$_2$), 30.5 (CH$_2$), 37.2 (CH$_2$), 38.0 (CH$_2$), 44.0 (CH), 44.1 (CH), 46.0 (CH), 47.2 (CH), 52.6 (CH), 54.7 (CH), 60.3 (C-10), 117.0 (C-8 or C-9), 117.9 (C-8 or C-9), 133.4, 135.2, 135.7, 136.8 (2 x C-4$^2$ and 2 x C-4$^3$) and 218.9 (CO); (Found M$^+$ 284.2154; C$_{20}$H$_{28}$O requires 284.2140) followed by 111 (15 mg, 25%) $\delta$H (300 MHz, CDCl$_3$) 0.92 (3H, t J 7.2 Hz, CH$_3$), 1.30-1.55 (3 x CH$_2$, H-10$_b$), 1.59 (1H, dt J 2 x 8.4 and 1.8 Hz, H-10$_a$), 1.77 (1H, m, H-5), 2.03-2.11 (1H, m, H-4), 2.18-2.32 (1H, m, H-4$^4$), 2.58 (1H, m, H-6), 2.92 (1H, dd, J 9.8 and 4.6 Hz, H-2), 2.99 (1H, m, H-7), 3.16 (1H, m, H-1), 4.93-5.01 (2H, m, H-4$^3$), 5.69-5.71 (1H, m, H-4$^2$), 6.13 (1H, m, H-8 or H-9), 6.18 (1H, dd, J 5.6 and 3.2 Hz, H-8 or H-9); $\delta$C (100 MHz, CDCl$_3$) 24.0 (CH$_3$), 38.2, 39.7, 40.6, 45.6, 47.1, 49.6, 52.1, 52.7, 53.7, 55.1, 56.2 (CH$_2$), 115.6 (C-8 or C-9), 116.2 (C-8 or C-9), 135.8 (C-4$^2$ or C-4$^3$), 136.5 (C-4$^2$ or C-4$^3$) and 218.9 (CO); (Found M$^+$ 244.1839; C$_{17}$H$_{24}$O requires 244.1827) followed by 83 (6 mg, 12%).

4, 4-Diallyl-5-butyltricyclo[5.2.1.0$^{2,6}$]dec-8-en-3-one (110)

Butyl ketone (82) (50 mg, 0.25 mmol) in dry tetrahydrofuran (2 cm$^3$) was added to a stirred suspension of potassium hydride (32 mg, 0.80 mmol) in dry tetrahydrofuran (2 cm$^3$) and the mixture was stirred at 24°C for 1 h. Allyl bromide (0.07 cm$^3$, 0.75 mmol) was added and stirring continued for 1 h. The mixture was slowly transferred to a separating funnel containing water and the aqueous phase extracted into ethyl acetate (2 x 10 cm$^3$), dried over anhydrous magnesium sulfate and the solvent removed under reduced
Column chromatography on silica gel with ethyl acetate-petroleum ether (1:32) yielded 110 (23 mg, 32%); $v_{\text{max}}/\text{cm}^{-1}$ 1570 (C=C) and 1734 (CO); $\delta_H$ (300 MHz, CDCl$_3$) 0.93 (3H, t, J 7.0 Hz, CH$_3$), 1.24-1.54 (7H, m, 3 x CH$_2$, H-10$_a$), 1.58-1.62 (1H, dt, J 10.8 and 2.4 Hz, H-10$_b$), 1.86 (1H, dd, J 19.0 and 12.2 Hz, H-4$^1$), 2.02 (1H, dd, J 19.0 and 11.0 Hz, H-4$^2$), 2.17-2.25 (1H, dddt, J 18.8, 8.8 and 1.8 Hz, H-4$^3$), 2.28-2.36 (1H, dddt, J 18.8, 7.2 and 2.0 Hz, H-4$^4$), 2.47-2.55 (1H, ddd, J 14.0, 10.8 and 5.2 Hz, H-6), 2.96 (1H, m, H-7), 3.01 (1H, dd, H 14.0 and 6.0 Hz, H-2), 3.17 (1H, m, H-1), 4.88-5.03 (4H, m, 2 x H-4$^2$), 5.45-5.69 (2H, m, H-4$^3$), 6.00 (1H, dd, J 5.7 and 3.0 Hz, H-8 or H-9) and 6.12 (1H, dd, J 5.7 and 2.7 Hz, H-8 or H-9); $\delta_C$ (75 MHz, CDCl$_3$) 14.1 (CH$_3$), 22.9 (CH$_2$), 30.1 (CH$_2$), 30.5 (CH$_2$), 37.2 (CH$_2$), 38.0 (CH$_2$), 44.0 (CH), 44.1 (CH), 46.0 (CH), 47.2 (CH), 52.6 (CH), 54.7 (CH), 60.3 (C-10), 117.0 (C-8 or C-9), 117.9 (C-8 or C-9), 133.4, 135.2, 135.7, 136.8 (2 x C-4$^2$ and 2 x C-4$^3$) and 218.9 (CO); (Found M$^+$ 284.2154; C$_{26}$H$_{28}$O requires 284.2140) followed by 83 (4.6 mg, 9%).

**Ethyl-6-iodohexanoate (112)**

Sodium iodide (190 mg, 1.2 mmol) was added to a solution of 91 (300 mg, 0.96 mmol) in acetone (20 cm$^3$). The reaction was refluxed for 18 h rendering a white suspension. This was quenched with saturated aqueous sodium chloride and the organic product extracted into ethyl acetate (2 x 30 cm$^3$), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:9) as eluent gave 112 (210 mg g, 83%); $\delta_H$ (300 MHz, CDCl$_3$) 1.24 (3H, t, J 7.1 Hz, CH$_3$), 1.43 (2H, m, CH$_2$), 1.64 (2H, quintet, J 7.4 Hz, H-3), 1.83 (2H, quintet, J 7.2 Hz, CH$_2$), 2.30 (2H, t, J 7.0 Hz, H-6) and 4.12 (2H, q, J 7.1 Hz, -CH$_3$); $\delta_C$ (100 MHz, CDCl$_3$) 6.4 (CH$_3$), 14.2 (C-6), 23.8 (CH$_2$), 29.9
Ethyl 6-(5-butyl-3-oxotricyclo[5.2.1.0\(^2,6\)]dec-8-en-4-yl)hexanoate (113 and 114)

A solution of 82 (214 mg, 0.80 mmol) in dimethyl sulfoxide (1 cm\(^3\)) was added to a suspension of potassium-t-butoxide (76 mg, 1.1 mmol) in dimethyl sulfoxide (5 cm\(^3\)). The resulting suspension was stirred at 25°C for 15 min. 112 in dimethyl sulfoxide (1 cm\(^3\)) was then added and the reaction stirred at this temperature for 50 min. Water was slowly added to quench the reaction and the mixture was extracted with ethyl acetate (2 x 20 cm\(^3\)). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The product was purified by chromatography on silica gel with ethyl acetate-petroleum ether (1:19) as eluent to give a mixture of stereoisomers in 113 and 114 (14 mg, 8%); \(\delta_H\) (300 MHz, CDCl\(_3\)) 0.89 (3H, t, \(J = 6.0\) Hz, CH\(_3\)), 1.24 (3H, t, \(J = 7.0\) Hz, CH\(_3\)), 1.28-1.63 (17H, m, 7 x CH\(_2\), 2 x H-10, H-5), 1.81 (1H, m, H-4), 2.31 (2H, t, \(J = 7.6\) Hz, -CH\(_2\)CO\(_2\)-), 2.59-2.64 (1H, m, H-6), 2.87 (1H, m, H-7), 2.93 (1H, ddd, \(J = 9.8, 4.6\) and 1.8 Hz, H-2), 3.02 (1H, m, H-7), 3.07 (1H, m, H-2), 3.16 (1H, m, H-1), 4.13 (2H, q, \(J = 7.0\) Hz, -CO\(_2\)CH\(_2\)-), 5.95 (1H, dd, \(J = 5.8\) and 3.0 Hz, H-8 or H-9), 6.00(1H, dd, \(J = 5.6\) and 3.0 Hz, H-8 or H-9) and 6.14 (2H, m, H-8 and H-9), followed by 115 (19 mg, 11%); \(\delta_H\) (400 MHz, CDCl\(_3\)) 0.94 (3H, t, \(J = 7.2\) Hz, CH\(_3\)), 1.24 (3H, t, \(J = 7.2\) Hz, CH\(_3\)), 1.28-1.63 (17H, m, 7 x CH\(_2\), 2 x H-10, H-5), 1.93 (1H, m, H-4), 2.26 (2H, t, \(J = 7.6\) Hz, -CH\(_2\)CO\(_2\)-), 2.54 (1H, ddd, \(J = 10.3, 6.0\) and 4.0 Hz, H-6), 2.96 (1H, m, H-7), 3.01 (1H, ddd, \(J = 10.3, 4.6\) and 2.4 Hz, H-2), 3.12 (1H, m, H-1), 4.12 (2H, q, \(J = 7.2\) Hz, -CO\(_2\)CH\(_2\)-), 6.02 (1H, dd, \(J = 5.6\) and
3.2 Hz, H-8 or H-9) and 6.12 (1H, dd, J 5.6 and 3.0 Hz, H-8 or H-9); δc (100 MHz, CDCl3) 14.1 (CH3), 14.2 (CH3), 22.9 (CH2), 24.8 (CH2), 26.8 (CH2), 27.2 (CH2), 29.5 (CH2), 30.0 (CH2), 34.3 (CH2), 36.5 (CH2), 43.4 (CH2), 44.4 (CH2), 46.5 (CH), 47.0 (CH), 52.5 (CH), 55.3 (CH), 58.6 (CH), 60.1 (CH), 135.1 (C-8 or C-9), 137.1 (C-8 or C-9), 196.1 (CO) and 219.4 (CO); (Found M+ 346.2537; C22H34O3 requires 346.2508).

5-Butyl-4-(5'-(tetrahydro-2H-pyran-2''-yloxy)pent1yl)tricycle[5.2.1.02,6]dec-8-en-3-one (97 and 107)

A reaction vessel was charged with copper iodide (260 mg, 1.37 mmol) and flame dried. Dry tetrahydrofuran (4 cm³) was added and the suspension cooled to 0°C and n-butyllithium (2.5 M in hexane, 2.72 mmol) was added slowly. The mixture was stirred at 0°C for 15 min. Enone (21) (100 mg, 0.68 mmol) in dry tetrahydrofuran (2 cm³) was added and the mixture stirred at ambient temperature for 5 min. A separate flame-dried flask was charged with hexamethylphosphoric triamide (20% vol of THF, 1.6 cm³) and 87 (810 mg, 2.72 mmol) in dry tetrahydrofuran (8 cm³) at -78°C. This solution was added to the cuprate mixture via cannula and the resultant solution stirred at -78°C for 2 h, then at 0°C for 4 h. After 4 days at this temperature and still no further conversion, the reaction mixture was quenched with saturated aqueous ammonium chloride and the mixture extracted with diethyl ether (3 x 20 cm³). The organic extract was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude residue was chromatographed on silica gel using ethyl acetate-petroleum ether (1:19) as eluent and yielded a mixture of cis and trans addition products 5-butyl-4-(5'-(tetrahydro-2H-pyran-2''-yloxy)pent1yl)tricycle[5.2.1.02,6]dec-8-en-3-one (97 and 107) (21 mg, 8%) 0.88 (6H, m, 2 x CH3), 1.27-3.86 (overlapping signals), 4.57 (2H, m, H-2'), 5.95-6.01 (2H, m, H-8 and H-9) and 6.13 (2H, m, H-8 and H-9)*; followed by 82 (41
mg, 30%) followed by the cis addition product (4-exo, 5-exo)-5-butyl-4-(5'-(tetrahydro-2H-pyran-2"-yloxy)pentyl)tricycle[5.2.1.02\;2']-dec-8-en-3-one (97) (50 mg, 20%); \( \nu_{\text{max}}/\text{cm}^{-1} \) 1669 (CO); \( \delta_H \) (400 MHz, CDCl\(_3\)) 0.94 (3H, t, J 6.9 Hz, CH\(_3\)), 1.21-1.57 (23 H, m, 10 x CH\(_2\), 2 x H-10, H-5), 1.82 (1H, m, H-4), 2.55 (1H, m, H-6), 2.92 (1H, overlapping signals, dd, H-7), 2.96 (1H, m, H-2), 3.13 (1H, m, H-1), 3.36 (1H, m, H-6'), 3.48 (1H, m, H-4\( ^5 \)), 3.71 (1H, m, H-6'), 3.85 (1H, m, H-4\( ^5 \)), 4.55 (1H, m, H-2') and 6.12 (2H, m, H-8 and H-9); \( \delta_C \) (75 MHz, CDCl\(_3\)) 14.1 (CH\(_3\)), 19.7 (CH\(_2\)), 22.5 (CH\(_2\)), 22.9 (CH\(_2\)), 25.5 (CH\(_2\)), 29.6 (CH\(_2\)), 30.8 (CH\(_2\)), 32.6 (CH\(_2\)), 36.5 (CH\(_2\)), 37.7 (CH\(_2\)), 46.5 (C-1), 47.0 (C-2), 48.3 (C-7), 48.8 (C-6), 52.5 (C-10), 55.3 (CH\(_2\)), 62.3 (C-6'), 62.9 (CH), 67.6 (C-4\( ^5 \)), 98.8 (C-2'), 135.5 (C-8 or C-9), 137.1 (C-8 or C-9) and 219.6 (CO); (Found M\(^+\) 374.2827 \( C_{14}H_{20}O \) requires 374.2821).

*Given the complexity of the \(^{13}\)C NMR spectrum due to overlap of signals of the two diastereoisomers, the \(^{13}\)C data is not included.

5-(3'-t-Butyldimethylsilyloxy-1'-oct-1-enyl)-4, -(5-hydroxy-pentyl)-tricyclo[5.2.1.02\;2']-deca-8-ene-3-one (116)

\( p \)-Toluene sulfonic acid (2.8 mg, 0.015 mmol) was added to a solution of 97 (27.5 mg, 0.074 mmol) in methanol (5 cm\(^3\)) and the reaction mixture was stirred at 25°C for 1 h, then at 45°C for 2 h. The solvent was removed \( \text{in vacuo} \) and saturated aqueous ammonium chloride was added. The organic product was extracted with ethyl acetate (2 x 5 cm\(^3\)) and the extract dried over anhydrous sodium sulfate and concentrated. Column chromatography of the product on silica gel with ethyl acetate-petroleum ether (1:4) as eluent gave 116 (17 mg, 79%); \( \delta_H \) (CDCl\(_3\)) 0.91 (3H, t, J 6.9 Hz, CH\(_3\)), 1.21-1.69 (18H, m, 7 x CH\(_2\), 2 x H-10, H-4 and H-5), 1.94 (1H, m, OH), 2.56 (1H, m, H-6), 2.93-2.97 (2H, m, H-
2 and H-7), 3.13 (1H, m, H-1), 3.61 (2H, t, J 6.6 Hz, H-4 and H-5) and 6.13 (2H, m H-8 and H-9).

5-Butyl-4-(4\textsuperscript{5}-oxopent-4\textsuperscript{1}-yl)tricycle[5.2.1.0\textsuperscript{2,6}]dec-8-en-3-one (117)

Dess-Martin periodinane (23 mg, 0.050 mmol) was added to a solution of 116 in dichloromethane (4.5 cm\textsuperscript{3}). The mixture was stirred for 30 min at 25°C after which it was diluted with ether (5 cm\textsuperscript{3}) , washed with 0.1 M sodium thiosulfate, saturated sodium hydrogen carbonate and water. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Chromatography on silica gel using ethyl acetate-petroleum ether (3:7) afforded the aldehyde quantitatively; \( \delta \text{H} (400 \text{ MHz, CDCl}_3) 0.91 (3\text{H, t, } J 7.0 \text{ Hz, CH}_3), 1.20-1.63 (16\text{H, 6 x CH}_2, 2 \times \text{H-10, H-4 and H-5}), 2.40 (2\text{H, td, } J 7.3 \text{ and } 2 \times 1.7 \text{ Hz, H-4}), 2.56 (1\text{H, m, H-6}), 2.93 (1\text{H, dd, } J 9.9 \text{ and } 4.6 \text{ Hz, H-2}), 2.97 (1\text{H, m, H-7}), 3.13 (1\text{H, m, H-1}), 6.12 (1\text{H, dd, } J 5.6 \text{ and } 2.9 \text{ Hz, H-8 or H-9}), 6.15 (1\text{H, dd, } J 5.6 \text{ and } 3.1 \text{ Hz, H-8 or H-9}) \text{ and } 9.74 (1\text{H, s, CHO}); \delta \text{C (75 MHz, CDCl}_3) 14.1 \text{ (CH}_3), 22.1 \text{ (CH), 22.9 \text{ (CH), 25.5 \text{ (CH), 27.1 \text{ (CH), 29.7 \text{ (CH), 30.9 \text{ (CH), 39.6 \text{ (CH}_2, 43.7 \text{ (CH}_2, 45.8 \text{ (CH}_2, 46.2 \text{ (CH}_2, 46.8 \text{ (CH}_2, 52.6 \text{ (CH}_2, 53.5 \text{ (CH}_2, 135.28 \text{ (C-8 or C-9), 136.4 \text{ (C-8 or C-9), 202.4 \text{ (CHO) and 220.42 \text{ (CO).}}}

4-Allyl-5-butyltricyclo[5.2.1.0\textsuperscript{2,6}]dec-8-en-3-one (111 and 121)

\( n \)-Butyllithium (2.5M in hexane, 0.28 cm\textsuperscript{3}) was added to dry tetrahydrofuran (4 cm\textsuperscript{3}) at -78°C. After addition of diethylzinc (1.1M in toluene, 0.65 cm\textsuperscript{3}), the reaction mixture was stirred at 0°C for 15 min. The solution was recooled to -
78°C and a solution of 21 (100 mg, 0.68 mmol) in dry tetrahydrofuran (4 cm³) was added over a 60 min period at this temperature. Stirring was continued for a further 15 min. Hexamethylphosphoric triamide (1.18 cm³, 6.8 mmol) was added and stirring continued for another 15 min. Allyl bromide (0.29 cm³, 3.4 mmol) was added dropwise and the reaction was stirred at -40°C for 10 h, then at ambient temperature for 8 h. The reaction was quenched with saturated aqueous ammonium chloride and the organic product extracted into diethyl ether (3 x 10 cm³), dried over anhydrous magnesium sulfate and concentrated in vacuo. Column chromatography on silica gel using ethyl acetate-petroleum (1:32) ether as eluent afforded 111 (21.1 mg, 13%); νmax/cm⁻¹ 1587(C=C) and 1717(CO); δH (400 MHz, CDCl₃) 0.92 (3H, t, J 7.2 Hz, CH₃), 1.55-1.61 (8H, m, 3 x CH₂ and H-10ₐ and H-10ₜ), 1.67-1.74 (1H, m, H-5), 2.01-2.09 (1H, m, H-4), 2.18-2.33 (2H, m, H-4'), 2.56-2.60 (1H, ddd, J 10.0 and 2 x 4.0 Hz, H-6), 2.91 (1H, dd, J 9.8 and 4.6 Hz, H-2), 2.99 (1H, m, H-7), 3.16(1H, m, H-1), 4.91- 5.02 (2H, m, H-4'), 5.69-5.79 (1H, overlapping signals dddd, H-4²), 6.11 (1H, dd, J 5.6 and 2.8 Hz, H-8 or H-9) and 6.19 (1H, dd, J 5.6 and 3.0 Hz, H-8 or H-9); δC ( 100 MHz, CDCl₃) 24.0 (CH₃), 38.2, 39.7, 40.6, 40.9, 45.6, 47.1, 49.6, 52.1, 52.7, 53.7, 55.1, 56.2 (CH₂), 115.6 (C-8 or C-9), 116.2 (C-8 or C-9), 135.8 (C-4² or C-4³), 136.5 (C-4² or C-4³) and 218.9 (CO); (Found M+ 244.1839; C₁₇H₂₄O requires 244.1827) followed by 121 (6.3 mg, 4%) δH (400 MHz, CDCl₃) 0.93 (3H, t, J 7.4 Hz, CH₃), 1.51-1.53 (7H, m, 3 x CH₂ and H-10ₐ), 1.56 (1H, dt, J 2 x 8.0 and 1.8 Hz, H-10₉), 1.66-1.75 (1H, m, H-5), 2.04-2.09 (1H, H-4), 2.19-2.26 (2H, m, H-4'), 2.56-2.65 (1H, ddd, J 9.0 and 3 x 4.0 Hz, H-6), 2.91 (1H, dd, J 9.8 and 4.6 Hz, H-2), 3.01 (1H, m, H-7), 3.16 (1H, m, H-1), 4.91- 5.02 (2H, m, H-4'), 5.66-5.78 (1H, overlapping signals dddd, H-4²), 6.14 (1H, dd, J 5.8 and 2.8 Hz, H-8 or H-9) and 6.20 (1H, dd, J 5.8 and 3.0 Hz, H-8 or H-9); δC ( 100 MHz, CDCl₃) 24.0 (CH₃), 38.2, 39.7, 40.6, 45.6, 47.1, 49.6, 52.1, 52.7, 53.7, 55.1, 56.2 (CH₂), 115.6 (C-8 or C-9), 116.2 (C-8 or C-9), 135.8 (C-4² or C-4³), 136.5 (C-4² or C-4³) and 218.9 (CO); (Found M+ 244.1839; C₁₇H₂₄O requires 244.1827) followed by 82 (48 mg, 35%).
5-Butyl-4-pent-4-ynltricyclo[5.2.1.0²⁶]dec-8-en--one (128)

1) The synthesis of triflate (reaction A) and enolate (reaction B) were conducted simultaneously as described below:

**Reaction A:**

A reaction vessel was charged with dry dichloromethane (3 cm³) at -25°C under an inert nitrogen atmosphere. Trifluoromethane sulfonic anhydride (1.2 cm³, 7.1 mmol) was slowly added with stirring followed by mixture of pent-4-yn-1-ol (0.33 cm³, 3.4 mmol) and triethylamine (0.58 cm³, 4.1 mmol) in dry dichloromethane (2 cm³) which was added over a 10 min period. Stirring was continued for 5 min after which the mixture was filtered under nitrogen through anhydrous sodium sulfate and washed with dry hexane. The resulting solution was cooled to -78°C and flushed with nitrogen gas. It was maintained under these conditions until implementation in the reaction B.

**Reaction B:**

*n-Butyllithium* (1.6 M in hexane, 1.4 cm³) was added to a solution of ZnCl₂·TMEDA (0.19 g, 0.75 mmol) [prepared from ZnCl₂ and TMEDA in dry tetrahydrofuran]¹⁵ in dry tetrahydrofuran (3 cm³) and the mixture stirred at 0°C for 15 min. The reaction mixture was then cooled to -78°C and a solution of enone 21 (100 mg, 0.68 mmol) was added in dry tetrahydrofuran (4 cm³) over a 40 min period. Stirring was continued at this temperature for 15 min prior to the
addition of HMPA (1.2 cm³, 6.8 mmol). After another 10 min the triflate (3.4 mmol in hexane) from reaction A was added via cannula with the temperature of both solutions being maintained at -78°C. The reaction mixture was then stirred at -40°C for 18 h before being quenched with saturated aqueous ammonium chloride. The resulting mixture was extracted with ethyl acetate (5 x 10 cm³) and the combined organic phase washed with brine, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Column chromatography in petroleum ether gave 128 (17 mg, 9%); \( \delta_H (300 \text{ MHz, CDCl}_3) 0.92 (3 \text{H, t, } J 6.8 \text{ Hz, CH}_3), 1.26-1.36 (8 \text{H, m, } 4 \times \text{CH}_2), 1.51-1.74 (8 \text{H, m, } 2 \times \text{H-10, 2 x CH}_2, \text{H-4 and H-5}), 2.72 (1 \text{H, ddd, } J 10.3, 7.4 \text{ and } 4.3 \text{ Hz, H-6}), 2.98 (1 \text{H, m, H-7}), 3.16 (1 \text{H, m, H-1}), 3.39 (1 \text{H, dd, } J 10.3 \text{ and } 4.3 \text{ Hz, H-2}), 3.98 (1 \text{H, d, } J 5.1 \text{ Hz, H-4}), 6.09 (1 \text{H, dd, } J 5.8 \text{ and } 3.0 \text{ Hz, H-8 or H-9}) \text{ and } 6.19 (1 \text{H, dd, } J 5.8 \text{ and } 2.7 \text{ Hz, H-8 or H-9}); \delta_C (75 \text{ MHz, CDCl}_3) 13.95 (\text{CH}_3), 22.8, 29.5, 30.6, 33.9, 34.2, 42.9, 44.2, 45.3, 46.7, 51.8, 53.0, 60.0, 61.0, 68.0, 92.1 (\text{CHCHCH}_2^-), 135.5 (\text{C-9 or C-9}), 136.9 (\text{C-8 or C-9}) \text{ and } 218.6 (\text{CO}); (\text{Found M}^+ 270.1967 \text{ C}_{19}H_{26}O \text{ requires 270.1984})

2) The synthesis of triflate (reaction A) and enolate (reaction B) were conducted simultaneously as described below:

**Reaction A:**

A reaction vessel was charged with dry dichloromethane (3 cm³) at -25°C under an inert nitrogen atmosphere. Trifluoromethane sulfonic anhydride (1.2 cm³, 7.1 mmol) was slowly added with stirring followed by mixture of pent-4-yne-1-ol (0.33 cm³, 3.4 mmol) and triethylamine (0.58 cm³, 4.1 mmol) in dry dichloromethane (2 cm³) which was added over a 10 min period. Stirring was continued for 5 min after which the mixture was filtered under nitrogen through anhydrous sodium sulfate and washed with dry hexane. The resulting solution
was cooled to -78°C and flushed with nitrogen gas. It was maintained under these conditions until implementation in the reaction B.

**Reaction B:**

\(n\)-Butyllithium (1.6 M in hexane, 1.4 cm\(^3\)) was added to a solution 146 (135 mg, 0.49 mmol) in dry tetrahydrofuran (3 cm\(^3\)) and the mixture stirred at -25°C for 2 h. The reaction mixture was then cooled to -78°C and the triflate (3.92 mmol in hexane) from reaction A was added via cannula with the temperature of both solutions being maintained at -78°C. The reaction mixture was then stirred at -40°C for 18 h before being quenched with saturated aqueous ammonium chloride. The resulting mixture was extracted with ethyl acetate (5 x 10 cm\(^3\)) and the combined organic phase washed with brine, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Column chromatography in petroleum ether gave 128 (17 mg, 13%); \(\delta_H\) (300 MHz, CDCl\(_3\)) 0.92 (3H, t, \(J_{6.8}\) Hz, CH\(_3\)), 1.26-1.36 (8H, m, 4 x CH\(_2\)), 1.51-1.74 (8H, m, 2 x H-10, 2 x CH\(_2\), H-4 and H-5), 2.72 (1H, ddd, \(J_{10.3, 7.4}\) and 4.3 Hz, H-6), 2.98 (1H, m, H-7), 3.16 (1H, m, H-1), 3.39 (1H, dd, \(J_{10.3}\) and 4.3 Hz, H-2), 3.98 (1H, d, \(J_{5.1}\) Hz, H-4\(^5\)), 6.09 (1H, dd, \(J_{5.8}\) and 3.0 Hz, H-8 or H-9) and 6.19 (1H, dd, \(J_{5.8}\) and 2.7 Hz, H-8 or H-9); \(\delta_C\) (75 MHz, CDCl\(_3\)) 13.95 (CH\(_3\)), 22.8, 29.5, 30.6, 33.9, 34.2, 42.9, 44.2, 45.3, 46.7, 51.8, 53.0, 60.0, 61.0, 68.0, 92.1 (CHCHCH\(_2\)) , 135.5 (C-9 or C-9), 136.9 (C-8 or C-9) and 218.6 (CO).

\((4E)-5\)-\(n\)-Butyl-4-ethylidenetricyclo[5.2.1.0\(^2\),2\]dec-8-ene-3-one (131)

\(n\)-Butyllithium (1.6 M in hexane, 1.0 cm\(^3\)) was added to a stirred suspension of copper (I) iodide (160 mg, 0.82 mmol) in diethyl ether (9 cm\(^3\)) cooled to -78°C and stirred at this temperature for 3 h. A solution of enone (21) (100 mg, 0.68 mmol) in dry diethyl ether (6 cm\(^3\)) was added dropwise over 5 min and the
reaction stirred at this temperature for 1.5 h. After addition of acetaldehyde (0.1 cm$^3$, 2.04 mmol) the reaction mixture was warmed to 0°C and stirring continued for 18 h. The reaction was quenched with saturated aqueous sodium chloride, extracted into diethyl ether (3 x 15 cm$^3$), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Column chromatography on silica gel with ethyl acetate-petroleum ether (1:19) as eluent gave 131 (45 mg, 29%); $\delta_H$ (300 MHz, CDCl$_3$) 0.90 (3H, t, $J$ 6.3 Hz, CH$_3$), 1.27-1.41 (7H, m, 3 x CH$_2$, H-10$_a$), 1.47 (1H, dt, $J$ 2 x 8.2 and 2.0, H-10$_b$), 1.72 (3H, dd, $J$ 7.5 and 1.2 Hz, CH$_3$), 2.40 (1H, m, H-5), 2.52 (1H, ddd, $J$ 8.8, 4.4 and 2.0 Hz, H-6), 2.95 (1H, dd, $J$ 8.7 and 4.8 Hz, H-2), 3.0 (1H, m, H-7), 3.22 (1H, m, H-1), 5.93 (1H, dd, $J$ 5.6 and 2.9 Hz, H-8 or H-9), 5.96 (1H, dd, $J$ 5.6 and 2.9 Hz, H-8 or H-9) and 6.36 (1H, qd, $J$ 3 x 7.5 and 2.1 Hz, H-4$^1$); $\delta_C$ (75 MHz, CDCl$_3$) 14.1 (CH$_3$), 14.9 (CH$_3$), 22.8 (CH$_2$), 29.1 (CH$_2$), 35.8 (CH$_2$), 40.3 (C-10), 44.3 (C-5), 47.36 (CH), 47.4 (CH), 51.5 (CH), 53.8 (CH), 131.5 (C-8 or C-9), 133.4 (C-8 or C-9), 135.9 (C-4$^1$), 145.8 (C-4) and 209.0 (CO).

**4E)-5-Butyl-4-hexylidenetricyclo[5.2.1.0$^{2,6}$]dec-8-en-3-one (132)**

$n$-Butyllithium (1.6 M in hexane, 2.8 cm$^3$) was added to a solution of ZnCl$_2$-TMEDA (380 mg, 1.51 mmol) in dry tetrahydrofuran (10 cm$^3$) at 0°C and the mixture was stirred at this temperature for 15 min. The solution was then cooled to -40°C and the enone (21) (200 mg, 1.37 mmol) in dry tetrahydrofuran (6 cm$^3$) was added portionwise over 20 min. The solution was stirred at -40°C for 30 min. The aldehyde, hexanal, (685 mg, 6.85 mmol) was then added and the mixture stirred at this temperature for 1 h before being quenched with saturated aqueous ammonium chloride. The organic product was extracted into diethyl ether (3 x 15 cm$^3$), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Column chromatography on silica gel using hexane followed by ethyl-acetate-hexane
(3:97) as eluent yielded the dehydrated double addition product 132 (232 mg, 59%); δH (400 MHz, CDCl₃) 0.90 (6H, m, 2 x CH₃), 1.26-1.43 (14H, m, 7 x CH₂), 1.47 (1H, t, J 1.6 Hz, H-10ₐ or H-10ₐ), 1.49 (1H, t, J 1.6 Hz, H-10ₐ or H-10ₐ), 2.01-2.12 (2H, m, H-4²), 2.40 (1H, m, H-6), 2.50-2.54 (1H, ddd, J 8.8, 4.0 and 1.6 Hz, H-5), 2.94-2.98 (1H, dd, J 8.8 and 4.8 Hz, H-2), 3.01 (1H, m, H-7), 3.23 (1H, m, H-1), 5.92-5.97 (2H, m, H-8 and H-9) and 6.29 (1H, ddd, J 8.4, 7.2 and 2.4 Hz, H-4¹); δC (100 MHz, CDCl₃) 14.06 (CH₃), 14.1 (CH₃), 22.5 (CH₂), 22.9 (CH₂), 28.4 (CH₂), 29.1(CH₂), 29.3(CH₂), 31.6(CH₂), 36.5 (CH₂), 40.5 (C-5), 44.6 (CH), 47.5 (CH), 51.6 (CH), 53.9 (CH), 133.6 (C-9), 135.9 (C-8) and 137.2 (C-4¹).

**Ethyl (5E)-6-(5-butyl-3-oxotricyclo[5.2.1.0²⁶]dec-8-en-4-ylidene)hexanoate (133)**

1) n-Butyl lithium (1.6 M in hexane, 2.8 cm³) was added to a solution of ZnCl₂-TMEDA (380 mg, 1.51 mmol) in dry tetrahydrofuran (10 cm³) at 0°C and the mixture was stirred at this temperature for 15 min. The solution was then cooled to -40°C and the enone (21) (200 mg, 1.37 mmol) in dry tetrahydrofuran (6 cm³) was added portionwise over 20 min. The solution was stirred at -40°C for 30 min. The aldehyde 95 (1.1 g, 6.85 mmol) was added and the reaction was stirred at this temperature for 1 h before being quenched with saturated aqueous ammonium chloride. The organic product was extracted into diethyl ether (3 x 15 cm³), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Column chromatography on silica gel using hexane followed by ethyl-acetate-hexane (3:97) as eluent yielded the dehydrated double addition product 133 (160 mg, 34%); δH (300 MHz, CDCl₃) 0.90 (3H, t, J 6.8 Hz, CH₃), 1.25 (3H, t, J 7.2 Hz, CH₃), 1.30-1.65 (12H, m, 2 x H-10, 5 x CH₂), 2.02-2.14 (2H, m, H-
4^2), 2.28 (2H, t, J 7.4 Hz, H-4^5), 2.39 (1H, m, H-5), 2.52 (1H, ddd, J 8.8, 4.0 and 1.6 Hz, H-6), 2.96 (1H, dd, J 8.9 and 5.0, H-7), 3.0 (1H, m, H-2), 3.23 (1H, m, H-1), 4.12 (2H, q, J 7.2 Hz, (CO)-O-CH2), 5.94 (1H, dd, J 11.4, 5.6 and 2.6 Hz, H-8 or H-9), 5.97 (1H, dd, J 5.6 and 2.8 Hz, H-8, H-9) and 6.24 (1H, ddd, J 8.8, 6.8, 2.2 Hz, H-4^1); δ_c (100 MHz, CDCl3) 14.0 (CH3), 14.2 (CH3), 22.8 (CH2), 24.7 (C-4^2), 28.1 (CH2), 28.9 (CH2), 29.0 (CH2), 34.1 (C-4^5), 36.4 (C-10), 40.5 (C-5), 44.3 (C-6), 47.4, (C-1 and C-7), 51.5 (CH2), 53.8 (C-2), 60.2 (-CO2CH2CH3), 133.5 (C-9), 135.9 (C-8 or C-4^1), 136.0 (C-8 or C-4^1), 145.0 (C-4), 173.3 (CO) and 209.2 (CO); (Found M^+-C6H5 278.1832; C22H32O3 requires 344.2351).

2) Methylolithium (1.6M in diethyl ether, 0.045 cm^3) was added to a stirred solution of the enol silyl ether (146) (20 mg, 0.072 mmol) in dry tetrahydrofuran (2 cm^3) at -20°C and the solution stirred for 1 h. The mixture was warmed to 0°C and the zinc chloride-TMEDA complex (18 mg, 0.072 mmol) [prepared from a saturated solution of zinc chloride salt in THF to which tetramethyl ethylene diamine was added] was added. The solution was recooled to -20°C and a solution of the aldehyde 95 (68 mg, 0.43 mmol) in dry tetrahydrofuran (2 cm^3) was added. The reaction was stirred at this temperature for 1.5 h, then saturated aqueous ammonium chloride was added and the mixture was extracted with diethyl ether (3 x 15 cm^3). Flash chromatography of this residue on silica gel with ethyl-acetate-heptane (1:9) as eluent gave 133 (16.1 mg, 65%); δ_h (300 MHz, CDCl3) 0.90 (3H, t, J 6.6 Hz, CH3), 1.25 (3H, t, J 7.2 Hz, CH3), 1.29-1.50 (8H, m, 2 x H-10, 3 x CH2), 1.57-1.65 (4H, m, 2 x CH2), 2.03-2.13 (2H, m, H-4^5), 2.28 (2H, t, J 7.5 Hz, H-4^5), 2.39 (1H, m, H-6), 2.52 (1H, ddd, J 8.7, 3.9 and 1.8 Hz, H-5), 2.96 (1H, dd, J 8.9 and 5.0, H-2), 3.00 (1H, m, H-7), 3.22 (1H, m, H-1), 4.12 (2H, q, J 7.2 Hz, (CO)-O-CH2), 5.95 (2H, ddd, J 11.4, 5.6 and 2.6 Hz, H-8 and H-9) and 6.24 (1H, ddd, J 8.7, 6.9, 2.3 Hz, H-4); δ_c (75 MHz, CDCl3) 14.2
Ethyl 6 (5-butyl-3-oxotricyclo[5.2.1.0<sup>2,6</sup>]dec-8-4-yl)hexanoate (140)

A solution of 133 in dry toluene (3 cm³) was deoxygenated by bubbling nitrogen gas through it for 10 min. Stryker's reagent, Hexa-μ-hydrohexakis(triphenylphosphine) hexacopper complex (120 mg, 0.062 mmol), was added and the reaction was stirred at ambient temperature for 17 h. A further addition of Stryker's reagent (120 mg, 0.062 mmol) and continued stirring did not effect any further change in the reaction. The reaction mixture was opened to air and stirred for 1 h before being filtered through Celite, washed with diethyl ether and the solvent removed under reduced pressure. Column chromatography on silica gel using ethyl-acetate-petroleum ether (1:9) as eluent gave the reduced product 140 (9 mg, 42%); δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 0.95 (3H, t, J = 7.1 Hz, CH₃), 1.25 (3H, t, J = 7.1 Hz, CH₃), 1.29-1.62 (17H, 7 x CH<sub>2</sub>, 2 x H-10 and H-5), 1.94 (1H, m, H-4), 2.27 (2H, t, J = 7.6 Hz, -CH₂CO₂-), 2.54 (1H, ddd, J = 10.3, 6.1 and 4.2 Hz, H-6), 2.97 (1H, m, H-7), 3.01 (1H, ddd, J = 10.3, 4.5 and 2.4 Hz, H-2), 3.13 (1H, m, H-1), 4.12 (2H, q, J = 7.1 Hz, -CO₂CH₂CH₃-), 6.03 (1H, dd, J = 5.7 and 3.0 Hz, H-8 or H-9) and 6.13 (1H, dd, J = 5.7 and 2.9 Hz, H-8 or H-9); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 14.1 (CH₃), 14.2 (CH₃), 22.9 (CH₂), 24.8 (CH₂), 26.8 (CH₂), 27.2 (CH₂), 29.5 (CH₂), 30.0 (CH₂), 34.3 (CH₂), 36.5 (CH₂), 43.4 (CH₂), 44.4 (CH₂), 46.5 (CH), 47.0 (CH), 52.5 (CH), 55.3 (CH), 58.6 (CH), 60.1 (CH), 135.1 (C-8 or C-9), 137.1 (C-8 or C-9), 196.1 (CO) and 219.4 (CO); (Found M⁺-C₆H₅ 278.1926; C₂₂H₃₄O₃ requires 346.2351).
5-Butyl-4-hexyltricyclo[5.2.1.0²⁶]dec-8-en-one (141)

A solution of 132 (20 mg, 0.070 mmol) in dry toluene (2 cm³) was deoxygenated by purging with nitrogen for 10 min. The triphenylphosphine copper hydride hexamer complex (340 mg, 0.062 mmol) was added and the resulting reaction mixture was stirred at ambient temperature for 18 h. The reaction was quenched with water and the mixture extracted with ethyl acetate (3 x 10 cm³). The extracts were dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude product was chromatographed on silica gel using ethyl acetate-hexane (1:9) as eluent afforded the reduced product 141 (12.8 mg, 63%); \( \nu_{\text{max}}/\text{cm}^{-1} \) 1731 (CO); \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 0.86 (3H, t, \( J = 6.9 \) Hz, CH₃), 0.94 (3H, t, \( J = 7.1 \) Hz, CH₃), 1.21-1.36 (17H, m, 8 x CH₂, H-5), 1.44 (1H, br d, \( J = 7.8 \) Hz, H-10a), 1.58 (1H, dt, \( J = 2 \times 8.2 \) and 1.8 Hz, H-10b), 1.93 (1H, m, H-4), 2.54 (1H, ddd, \( J = 10.3, 6.1 \) and 4.1 Hz, H-6), 2.96 (1H, m, H-7), 3.00 (1H, ddd, \( J = 10.3, 4.5 \) and 2.4 Hz, H-2), 3.13 (1H, m, H-1), 6.02 (1H, dd, \( J = 5.8 \) and 2.9 Hz, H-9) and 6.13 (1H, dd, \( J = 5.8 \) and 2.9 Hz, H-8); \( \delta_{\text{C}} \) (100 MHz, CDCl₃) 14.1 (2 x CH₃), 22.7 (CH₂), 22.95 (CH₂), 27.3 (CH₂), 27.5 (CH₂), 29.7 (CH₂), 30.0 (CH₂), 31.8 (CH₂), 36.6 (CH₂), 43.5 (CH₂), 44.5 (CH), 46.6 (CH), 47.1 (CH), 52.5 (CH), 55.3 (CH), 58.7 (CH), 135.5 (C-9), 137.1 (C-8) and 209.2 (CO); (Found M⁺ 288.246; C₂₀H₃₂O requires 288.2453).

Ethyl (6Z)-6-(2'-n-butyl-5'-oxocyclopent-3'-en-1-ylidene) hexanoate (142) and ethyl (6E)-6-(2'-n-butyl-5'-oxocyclopent-3'-en-1-ylidene) hexanoate (143)
A solution of 133 (80 mg, 0.23 mmol) and maleic anhydride (56 mg, 0.58 mmol) in 1, 2 dichloroethane (2.9 cm³) was treated with ethylaluminium dichloride (1.0 M solution in hexane, 0.4 cm³) at ambient temperature. The solution was then stirred at 50°C for 1.5 h and then quenched with saturated aqueous sodium hydrogen carbonate. The organic product was extracted into diethyl ether and the combined organic extract dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Column chromatography on silica gel using ethyl-acetate-hexane (1:4) as eluent gave the prostaglandin ethyl (6Z)-6-(2'-n-butyl-5'-oxocyclopent-3'-en-1-ylidene) hexanoate (142) (10.2 mg, 16%); δ_H (300 MHz, CDCl_3) 0.90 (3H, t, J 7.2 Hz, CH3), 1.24 (3H, t, J 7.2 Hz, CH3), 1.28-1.35 (4H, m, 2 x CH2), 1.441.72 (7H, m, 3 x CH2), 2.32 (2H, t, J 7.4 Hz, H-5), 2.83 (2H, m, H-2), 3.27 (1H, m, H-2'), 4.12 (2H, q, J 7.2 Hz, ((CO)-O-CH2) 6.01 (1H, br t, J 2 x 7.6 Hz, H-6), 6.23 (1H, dd, J 6.0 and 1.7 Hz, H-4') and 7.43 (1H, dd, J 6.0 and 2.4 Hz, H-3'); δ_C (75 MHz, CDCl_3) 13.9 (CH3), 14.3 (CH3), 22.9 (CH2), 24.6 (CH2), 26.8 (CH2), 28.5 (CH2), 28.9 (CH2), 33.3 (CH2), 34.1 (C-5), 45.4 (C-2'), 60.2 ((CO)-O-CH2), 136.3 (C-6 or C-4'), 139.4 (C-6 or C-4'), 160.3 (C-3') and 198.2 (CO); Found M⁺ 278.1908; C_{17}H_{26}O_2 requires 278.1882; followed by Ethyl (6E)-6-(2'-n-butyl-5'-oxocyclopent-3'-en-1-ylidene) hexanoate (143) (51.2 mg, 80%); δ_H (300 MHz, CDCl_3) 0.88 (3H, t, J 7.1 Hz, CH3), 1.25 (3H, t, J 7.2 Hz, CH3), 1.44-1.86 (10, m, 5 x CH2), 2.22-2.30 (1H, m, H-2), 2.31 (2H, t, J 7.2 Hz, H-5), 3.48 (1H, m, H-2'), 4.12 (2H, q, J 7.2 Hz, ((CO)-O-CH2), 6.32 (1H, dd, J 6.0 and 2.0 Hz, H-4'), 6.51 (1H, tt, J 2 x 7.8 and 2 x 1.8 Hz, H-6) and 7.53 (1H, ddd, J 6.0, 2.7 and 0.9 Hz, H-3'); δ_C (100 MHz, CDCl_3) 13.9 (CH3), 14.3 (CH3), 22.9 (CH2), 24.8 (CH2), 28.2 (2 x CH2), 28.8 (CH2), 30.6 (CH2), 32.2 (CH2), 34.2 (C-5), 43.3 (C-2'), 60.3 ((-CO2CH2-)), 134.8 (C-4' or C-6), 138.4 (C-4' or C-6), 161.9 (C-3'), 169.4 (C-5), 173.4 (CO) 196.9 (CO) and 217.2 (CO); (Found M⁺ 278.1882; C_{17}H_{26}O_2 requires 278.1882).
A solution of 132 (80 mg, 0.28 mmol) and maleic anhydride (68 mg, 0.70 mmol) in 1, 2 dichloroethane (2.9 cm³) was treated with ethylaluminium dichloride (1.0 M solution in hexane, 0.48 cm³) at ambient temperature. The solution was then stirred at 50°C for 1.5 h and then quenched with saturated aqueous sodium hydrogen carbonate. The organic product was extracted into diethyl ether and the combined organic extract dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Column chromatography on silica gel using ethyl-acetate-hexane (1:4) as eluent gave the prostaglandin (5Z)-4-butyl-5-hexylidenecyclopent-2-en-1-one (144) (7 mg, 11%); ν_max/cm⁻¹ 1639 (CO) and 1713 (CO); δ_H (300 MHz, CDCl₃) 0.91 (6H, m, 2 x CH₃), 2.31-2.39 (1H, m, H-2²), 1.26-1.79 (12H, m, 6 x CH₂), 2.91 (1H, m, H-3), 6.14 (1H, dd, J 5.6 and 2.0 Hz, H-5), 6.64 (1H, td, J 7.8 and 2 x 2.8 Hz, H-2¹) and 7.63 (1H, dd, J 5.6 and 2.8 Hz, H-4); δ_C (75 MHz, CDCl₃) followed by (5E)-4-butyl-5-hexylidenecyclopent-2-en-1-one (145) (41 mg, 67%); ν_max/cm⁻¹ 1627 (CO) and 1723 (CO); δ_H (300 MHz, CDCl₃) 0.90 (6H, m, 2 x CH₃), 1.23-1.37 (8H, m, 4 x CH₂), 1.45-1.89 (4H, m, 2 x CH₂), 2.17-2.35 (2H, m, H-2²), 3.45-3.50 (1H, ddd, J 8.4, 3.9 and 2.1 Hz, H-3), 6.32 (1H, dd, J 6.2 and 1.7 Hz, H-5), 6.55 (1H, tt, J 2 x 7.8 and 2 x 1.5 Hz, H-2¹) and 7.54 (1H, ddd, J 6.2, 2.7 and 1.5 Hz, H-4); δ_C (75 MHz, CDCl₃) 13.90 (CH₃), 13.94 (CH₃), 22.5 (CH₂), 22.8 (CH₂), 28.0 (CH₂), 28.3 (CH₂), 29.1 (CH₂), 21.6 (CH₂), 32.1 (CH₂), 43.3 (C-3), 134.8 (C-5 or C-2'), 135.8 (C-5 or C-2'), 161.8 (C-4) and 197.0 (CO).
1) *n*-Butyllithium (1.6 M in hexane, 0.34 cm³) was added to a heterogeneous mixture of copper cyanide (25 mg, 0.27 mmol) in dry tetrahydrofuran (4 cm³) at -78°C. The mixture was allowed to warm to ambient temperature until the copper cyanide had dissolved and then recooled to -78°C. Enone (21) (20 mg, 0.14 mmol) in dry tetrahydrofuran (2 cm³) was added and the solution was stirred at this temperature for 30 min. Chlorotrimethylsilane (0.02 cm³, 0.19 mmol) was then added and the solution was stirred at 0°C for 20 min before being quenched with saturated aqueous sodium bicarbonate. The organic product was extracted into diethyl ether (2 x 10 cm³), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Flash chromatography of the crude residue on silica gel using ethyl acetate-heptane (1:9) yielded the *enol silyl ether* (146) (17.9 mg, 47%); δ_H (300 MHz, CDCl₃) 0.21 (9H, s, 3 x CH₃), 0.91 (3H, t, J 6.8 Hz, CH₃), 1.21-1.31 (7H, m, 3 x CH₂, H-10a), 1.51 (1H, br dt, J 2 x 8.0 and 1.7 Hz, H-10b), 1.80 (1H, m, H-6), 2.25 (1H, m, H-5), 2.84-2.86 (1H, m, H-2), 2.88-2.90 (1H, m, H-7), 2.95-3.01 (1H, m, H-1), 4.39 (1H, br m, H-4) and 6.03 (1H, br m, H-8, H-9).

2) The reaction vessel was charged with diisopropylamine (0.5 cm³, 3.74 mmol) in dry tetrahydrofuran (15 cm³) and cooled to -78°C. *n*-Butyl lithium (1.6M in hexane, 2.1 cm³) was added and the reaction stirred for 30 min at -78°C. The alkyl ketone (82) (700 mg, 3.4 mmol) was added slowly to the reaction mixture which was stirred for a further 30 minutes before addition of chlorotrimethylsilane (1.5 g, 10.2 mmol). Stirring was continued at -78°C for 1 h, then at 24°C for 18 h. The reaction was quenched with saturated aqueous sodium bicarbonate (5 cm³) and the organic material extracted into ethyl acetate (2 x 15 cm³), dried over magnesium sulfate and evaporated under reduced pressure. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:99)
afforded the enol silyl ether (146) as a colourless oil (510 mg, 47%); δH (300 MHz, CDCl3) 0.21 (9H, s, 3 x CH3), 0.91 (3H, t, J 6.8 Hz, CH3), 1.21-1.31 (7H, m, 3 x CH2, H-10a), 1.51 (1H, br dt, J 2 x 8.0 and 1.7 Hz, H-10b), 2.25 (1H, m, H-6), 1.80 (1H, m, H-5), 2.84-2.86 (1H, m, H-2), 2.88-2.90 (1H, m, H-7), 2.95-3.01 (1H, m, H-1), 4.39 (1H, br m, H-4) and 6.03 (1H, br m, H-8, H-9).

2-Hydroxyethyl 4-methylbenzenesulfonate (148)

Silver (II) oxide (14.8 g, 120.3 mmol) [freshly prepared from silver (I) nitrate with sodium hydroxide in water heated to 80-90°C131] is added to a solution of ethylene glycol (7.0 g, 109.2 mmol) in dichloromethane (50 cm3) at ambient temperature, followed by the addition of p-toluenesulfonic acid (2.28 g, 120.1 mmol) and potassium iodide (1.99 g, 12.0 mmol). The reaction mixture was stirred at this temperature for 4.5 h. The mixture was then filtered through silica gel, washed successively with ethyl acetate and the solvent removed under reduced pressure. The crude material (28.1 g) was chromatographed on silica gel using ethyl acetate-petroleum ether (1:19) and yielded 2-[(4’-methylphenyl)sulfonyl]oxy)ethyl-4”-methylbenzenesulfonate (149) (9.3 g, 23%) as a colourless solid; m.p. 122-125°C (from ethyl acetate-hexane); (Found: C, 51.9; H, 5.0; S, 17.0; C16H18O6S2 requires C, 51.9; H, 4.9; S, 17.3); νmax/cm⁻¹ 1424.9 (SO₂), 1031.1 (SO₂) ; δH (400MHz, CDCl3) 2.45 (6H, s, 2 x CH₃), 4.18 (4H, s, 2 x CH₂), 7.33 (4H, d, J 8.3 Hz, 4 x Ar) and 7.73 (4H, d, J 8.3 Hz, 4 x Ar); δC (400MHz, CDCl3) 21.9 (2 x CH₃), 66.9 (2 x CH₂), 128.2 (4 x Ar), 130.2 (4 x Ar), 132.7 (2 x C-4’ and C-4”) and 145.5 (C-1’ and C-1”) followed by the monotosylate 148 (16.0 g, 68%) as a colourless solid; (Found : C, 50.1; H, 5.2; S, 15.6; C₉H₁₂O₄S requires C, 50.0; H, 5.6; S, 14.8); νmax/cm⁻¹ 3576.6 (OH), 1424.9 (SO₂), 1030.8 (SO₂); δH (400 MHz, CDCl₃) 2.35 (H, br s, OH), 2.4 (3H, s, CH₃), 3.79 (2H, br m, H-2), 4.12 (2H, t, J 4.5 Hz, H-1), 7.34 (2H, d, J 8.1
Hz, H-2' and H-3') and 7.79 (2H, d, J 8.1, H-5' and H-6'); \( \delta_c \) (100 MHz, CDCl₃)
21.9 (CH₃), 66.9 (C-1), 71.8 (C-2), 128.2 (C-2' and C-3'), 130.2 (C-5' and C-6'),
133.2 (C-4') and 145.5 (C-1').

5-(3'-t-Butyldimethylsilyloxy-1'-oct-1-enyl)-4-(ethyl alcohol)-tricyclo[5.2.1.0².⁶]-deca-8-ene-3-one (150)

Methyllithium (1.4 M in diethyl ether, 1.6 cm³) was added to a solution of crude 147 (250 mg, 0.54 mmol) in dry tetrahydrofuran (2 cm³) at -78°C. The solution was warmed to -23°C and stirred at this temperature for 20 min. The mixture was then cooled to -78°C and a solution of the tosylate (148) in dry tetrahydrofuran (2 cm³) was slowly added. Stirring was continued for 10 min at -78°C, then for 10 min at -23°C. The reaction did not proceed to completion after several hours and quenched with saturated aqueous ammonium chloride and the organic product extracted into diethyl ether (2 x 15 cm³) and dried over anhydrous magnesium sulfate. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:19) gave ketone (94) (73 mg, 39%) followed by (150) (11 mg, 5%); \( \nu_{max}/\text{cm}^{-1} \) 3063 (OH), 1651.9 (CO); \( \delta_H \) (300 MHz, CDCl₃)
0.125 (6H, s, Si(CH₃)₂), 0.89 (12H, d, J 3.0 Hz, t-Bu and CH₃), 1.26-1.65 (15H, m, 6 x CH₂, 2 x H-10, OH), 1.74 (1H, m, H-4), 1.94 (1H, dd, J 12.9 and 6.5 Hz, H-5), 2.54 (2H, m, H-6 and H-7), 2.76 (1H, m, H-2), 2.86 (1H, m, H-1), 4.01 (1H, dd, J 12.3 and 6.4 Hz, H-5'), 5.34 (1H, dd, J 15.4 and 6.5 Hz, H-5'), 5.48 (1H, ddd, J 15.4, 6.4 and 3.2, H-5'), 6.17 (1H, m, H-9) and 6.44 (1H, dd, J 5.4 and 3.0 Hz, H-8); \( \delta_c \) (75 MHz, CDCl₃) -4.7 (SiCH₃), -4.1 (SiCH₃), 14.0 (CH₃),
22.6 (C-10), 21.7 (CH₂), 25.0 (CH₂), 25.1 (CH₂), 26.0 (t-Bu), 31.8 (CH₂), 38.4 (CH₂), 39.5 (C-4), 52.2 (C-7), 52.2 (C-1), 54.8 (C-5), 55.0 (C-6), 58.7 (C-2),
78.8 (C-5'), 132.9 (C-5'), 133.1 (C-5'), 135.2 (C-9), 136.9 (C-8) and 216.2 (CO); (Found M⁺ 432.3101 C₈₅H₄₄O₃Si requires 432.3060).
Methyllithium (1.6 M in diethyl ether, 0.05 cm³) was added dropwise to a solution of the enol silyl ether (146) in dry tetrahydrofuran (2 cm³) at -20°C and the mixture stirred at this temperature for 30 min. ZnCl₂·TMEDA (18 mg, 0.072 mmol) [prepared from zinc chloride and tetramethylethylenediamine] was then added and the mixture was stirred at 0°C for 15 min and then re-cooled to -20°C. The aldehyde 152 (80 mg, 0.29 mmol) in dry tetrahydrofuran (2 cm³) was added at this temperature and the solution stirred temperature for 1 h at -20°C before being allowed to warm to 24°C and stirred for a further 6 h. The reaction was quenched with saturated aqueous ammonium chloride, extracted into diethyl ether (2 x 15 cm³) and dried over anhydrous sodium sulfate. Flash chromatography of the crude residue on silica gel using ethyl acetate-heptane (1:19) as eluent 151 (7.5 mg, 28%); δ_H (300 MHz, CDCl₃) 0.92 (3H, J 7.1 Hz, CH₃), 1.21-1.61 (16H, m, 8 x CH₂), 2.12 (2H, overlapping signals, 2 x H-4³), 2.29 (1H, m, H-6), 2.42 1H, ddd, J 8.7, 4.1 and 1.6 Hz, H-5), 2.97 (1H, dd, J 8.7 and 4.8 Hz, H-7), 3.02 (1H, m, H-2), 3.25 (1H, m, H-1), 3.39 (1H, dt, J 2 x 9.7 and 6 Hz, H-4₉a), 3.53 (1H, m, H-4₉b), 3.73 (1H, m, H-4₅a), 3.87 (1H, m, H-4₅b), 4.58 (1H, t, J 3.3 Hz, H-4⁷), 5.97 (2H, m, H-7, H-8) and 6.30 (1H, ddd, J 8.6, 6.8 and 2.0 Hz, H-4¹); δ_C (500 MHz, CDCl₃) 13.1 (CH₃), 18.6, 21.9, 24.5, 28.0, 28.4, 28.5, 28.7, 29.8, 35.4, 37.4, (CH₂), 39.5 (C-6), 43.3 (C-5), 46.4 (C-2), 50.5(C-1), 52.8 (C-7), 61.3 (C-9¹), 66.2 (C-4⁵), 97.9 (O-C-O), 134.9, 135.6, 143.8 (C-8, C-9 and C-4¹) and 208.4 (CO); (Found M⁺ 372.2664; C₂₄H₃₆O₃ requires 372.2660).
5-(Tetrahydro-2H-pyran-2'-yloxy)pentenal (152)

Oxalyl chloride (1.4 cm³, 16.1 mmol) was added to a solution of dimethyl sulfoxide (2.3 cm³, 32 mmol) in dry dichloromethane (30 cm³) at -60°C under nitrogen and the mixture stirred for 15 min. 101 (2.7 g, 14.6 mmol) was added in dry dichloromethane (20 cm³) and stirring continued for a further 15 min before the addition of triethylamine (10 cm³, 73 mmol). The mixture was stirred for 15 min allowing it to warm to 24°C, then quenched with 1M HCl and the mixture extracted into dichloromethane (3 x 30cm³), dried over anhydrous magnesium sulfate and the organic extracts concentrated under reduced pressure. Flash chromatography of the residue on silica gel using ethyl acetate-heptane (3:7) gave the aldehyde 152 (2.27 g, 84%); νmax/cm⁻¹ 1642 (CO); δH (300 MHz, CDCl₃) 1.50-1.83 (10 H, m, 5 x CH₂), 2.48 (2H, td, J2 x 1.4 and 7.1 Hz, H-2), 3.36-3.43 (1H, dt, J 2 x 9.7 and 6.1 Hz, H-6'), 3.46-3.56 (1H, m, H-5), 3.72-3.80 (1H, J 10.4 and 2 x 6.2 Hz, H-6'), 3.85 (1H, ddd, J10.4, 7.5 and 3.5 Hz, H-5), 4.56 (1H, br t, J 3.2 Hz, H-2') and 9.77 (1H, s, COH); δC (100 MHZ, CDCl₃) 19.7, 21.7, 25.5, 29.1, 30.8 (C-3', C-4', C-5', C-3, C-4), 62.3, 63.0, 67.0 (C-2, C-5, C-6'), 98.9 (C-2') and 193.2 (CO); (Found M⁺ + Na 209.1; C₁₀H₁₈O₃Na requires 209.1154).

General procedure for cycloadditions of enone HH3 with butadiene (a) thermally induced cycloadditions

Tetracyclo [9.2.1.0.²¹.⁴.⁹] tetradeca-6,12-diene-3-one (169)

A solution of the enone (21) (100 mg, 0.68 mmol) in dry toluene (4 cm³) was introduced into a pressure tube and purged with nitrogen. Butadiene was condensed into the tube which was sealed and the mixture was heated at 160°C for 24 h (CAUTION-explosion risk). The tube was cooled to 25°C and
then opened. Observation using TLC indicated only the presence of 21. The solvent was evaporated and the residue chromatographed on silica gel using ethyl acetate-petroleum ether as eluent to give 21 quantitatively.

**General procedure for cycloadditions of enone (21) (b) Lewis-acid-catalysed conditions**

An excess of 1, 3 butadiene (168) was bubbled through toluene (3 cm$^3$) under an inert atmosphere at -78°C. A solution of enone (21) (100 mg, 0.68 mmol) in toluene (1.5 cm$^3$) was added to the reaction mixture. The Lewis-acid was slowly added at this temperature and the reaction mixture was allowed to warm to room temperature with stirring for 21 h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate and the organic product extracted into ethyl acetate (3 x 25 cm$^3$). The combined organic extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* to give the cycloadduct (169) which was purified on silica gel using ethyl acetate-petroleum ether.

a) The reaction using boron trifluoride-diethyl ether (0.1 cm$^3$, 0.68 mmol) as Lewis-acid gave an oil (0.21 g) after workup. Chromatography on silica gel (20 g) using ethyl acetate-petroleum ether (1:32) afforded *etracyclo [9.2.1.0$^{2,10}$ 7.4, 9.8.0$^{6,12}$] tetradeca-6, 12-dien-3-one* 169 as a colourless oil (0.024 g, 18%); $\delta$H (75 MHz, CDCl$_3$) 2.11 (1H, m, H-14a), 1.60 (1H, m, H-14b), 1.94 (1H, m, H-8), 1.99 (1H, m, H-5), 2.21 (1H, m, H-9), 2.28 (1H, m, H-10), 2.32 (1H, m, H-5), 2.40 (1H, m, H-8), 2.63 (1H, m, H-4), 3.19 (1H, m, H-1), 3.42 (1H, m, H-2), 3.42 (1H, m, H-11), 5.78 (1H, ddd, J 9.5, 4.7 and 1.3 Hz, H-6 or H-7), 5.84 (1H, ddd, J 9.5, 5.2 and 0.9 Hz, H-7 or H-6), 5.94 (2H, m, H-12 and H-13); $\delta$C (75 MHz, CDCl$_3$) 27.2 and 31.4 (C-5 and C-8), 46.6, 46.9, 47.4, 47.5, 49.5, 52.3, 54.0, 124.5 and 124.9 (C-6 and C-7), 135.8 and 136.0 (C-12 and C-13), 215.8 (C-7)
b) The reaction using Titanium (IV) chloride \(0.28 \text{ cm}^3, \ 0.14 \text{mmol}\) as Lewis-acid yielded an oily residue post workup. Column chromatography on silica gel using ethyl acetate-petroleum ether \(1:19\) as eluent gave the cycloaddition product tetracyclo \([9.2.1.0^2.1^4.0^4.5]\) tetradeca-6, 12-dien-3-one 169 as a colourless oil \(0.045 \text{g}, \ 33\%\).

c) The reaction with Tin (IV) chloride \(0.28 \text{ cm}^3, \ 0.14 \text{mmol}\) as Lewis-acid gave a dark oil after workup. Column chromatography on silica gel with ethyl acetate-petroleum ether \(1:32\) as eluent yielded tetracyclo \([9.2.1.0^2.1^4.0^4.9]\) tetradeca-6, 12-dien-3-one 169 as a colourless oil \(0.025 \text{g}, \ 18\%\).

**Attempted cycloaddition of 21 with butadiene sulfone under a) thermally induced conditions**

Tetracyclo \([9.2.1.0^2.1^4.0^4.9]\) tetradeca-6, 12-diene-3-one (169)

a) The enone \((21)\) \((50 \text{ mg}, \ 0.34 \text{ mmol})\) was added to a solution of butadiene sulfone \((200 \text{ mg}, \ 1.70 \text{ mmol})\) in dry toluene \((5 \text{ cm}^3)\) under nitrogen. The mixture was heated at 110°C for 24 h. There was no conversion of starting material after 24 h as observed by TLC. A further aliquot of butadiene sulfone was added \((200 \text{ mg}, \ 1.70 \text{ mmol})\) and the solution transferred to a sealed tube and heated at 160°C (oil bath) for further 24 h. No reaction was observed and only starting enone was recovered.

b) A solution of the enone \((21)\) \((1.00 \text{ g}, \ 6.76 \text{ mmol})\) in dry toluene \((5 \text{ cm}^3)\) was introduced into a pressure tube and purged with nitrogen. Butadiene sulfone \((1.99 \text{ g}, \ 16.9 \text{ mmol})\) was added to the tube which was sealed and the mixture was heated at 110°C for 18 h. The tube was cooled to 25°C and then opened.
Observation using TLC indicated only the presence of 21. The solvent was evaporated and the residue chromatographed on silica gel using ethyl acetate-petroleum ether as eluent to give 21 quantitatively.

c) A solution of the enone (21) (212 mg, 1.45 mmol) in dry toluene (5 cm$^3$) was introduced into a pressure tube and purged with nitrogen. Butadiene sulfone (857 mg g, 7.26 mmol) was added to the tube which was sealed and the mixture was heated at 150°C for 6 days. The tube was cooled to 25°C and then opened. The toluene was removed under reduced pressure and the crude material chromatographed on silica gel with ethyl acetate-hexane (1:19) as eluent. Attempted separation yielded a mixture of inseparable products and 21 (119 mg, 41%).

**Attempted cycloaddition of 21 with butadiene sulfone (170) under a) Lewis-acid induced conditions**

A solution of the enone 21 (120 mg, 0.82 mmol) in dry toluene (5 cm$^3$) was introduced into a pressure tube and purged with nitrogen. Butadiene sulfone (485 mg, 4.11 mmol) was added to the tube followed by ZnCl$_2$.TMEDA complex. The tube was then sealed and the mixture was heated at 110°C for 24 h. The tube was cooled to 25°C and then opened. Observation using TLC indicated only the presence of 21. The solvent was evaporated and the residue chromatographed on silica gel using ethyl acetate-petroleum ether as eluent to give 21 quantitatively.

**Tetracyclo [9.2.1.0$^2$.10.4.9] tetradeca-3-hydroxy, 6, 12-diene (164)**

A solution of the alcohol (78) (1.05 g, 7.2 mmol) and butadiene sulfone (170) (1.3 g, 10.8 mmol) in dry toluene was purged with nitrogen and then heated in a sealed tube at 160°C (oil bath) for 2 h. The cooled residue was evaporated
under reduced pressure and the resulting crude residue (1.23 g) chromatographed on silica gel (100 g) using ethyl acetate-petroleum ether (1:9) as eluent gave the cycloadduct (164) (1.04 g, 72%); νmax(cm⁻¹ 1525 C=C) and 3366 (OH); δH (300 MHz, CDCl₃) 0.80-1.26 (6H, m, H-4, H-5, H-8 and H-9), 1.42 (1H, d, J 2.7 Hz, H-14a), 1.58 (1H, br dt, H-14a), 2.60-2.68 (1H, H-10), 2.78 (1H, m, H-11), 3.01 (1H, m, H-1), 3.37 (1H, m, H-2), 3.92 (1H, m, H-3), 5.61 (1H, m, H-6, H-7, H12 or H-13), 5.78 (1H, m, H-6, H-7, H12 or H-13), 5.88 (1H, m, H-6, H-7, H12 or H-13) and 5.98 (1H, m, H-13); δC (100 MHz, CDCl₃) 29.55 (CH₂), 44.50 (CH₂), 44.84 (CH₂), 45.11 (CH), 50.62 (CH), 50.76 (CH), 51.24 (CH), 54.64 (CH), 84.41 (CH), 84.56 (CH), 132.25, 132.90, 135.43 and 137.66 (C-6, C-7, C-12 and C-13);

Tetracyclo [9.2.1.0₂.⁴.⁸] tetradeca- 6, 12-diene-3-one (169)

Dess Martin periodinane (50 mg, 0.12 mmol) was added to a solution of the cycloadduct (16 mg, 0.08 mmol) in dry chloroform at 25° C. The mixture was stirred at 25° C for 5 h, water added and then extracted with dichloromethane (4 x 5 cm³). The combined organic extracts were washed with saturated aqueous sodium thiosulfate, water and brine, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude material was chromatographed on silica gel (2 g) using ethyl acetate-hexane (1:4) as eluent to give the ketone (169) (9 mg, 56%).

Tetracyclo [9.2.1.0₂.⁴.⁸] tetradeca- 3, 6, 7-hydroxy- 12-ene (165)

A solution of the cycloadduct (164) (55 mg, 0.27 mmol) in acetone: water (5 cm³, 4:1) was treated with osmium tetroxide (14 mg, 0.05 mmol) followed by N-morpholine-N-oxide (28 mg, 0.28 mmol). The green/grey solution was stirred at
25° C for 3 h, then saturated aqueous sodium sulfite (5 cm³) was added and stirring continued for 2 h. The mixture was then extracted with dichloromethane (4 x 10 cm³), the combined extracts washed with water and brine, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude material (63 mg) was chromatographed on silica gel (7 g) using ethyl acetate-hexane (1:1) as eluent to give 165 (48 mg, 76 %) as a colourless solid m.p 178 – 181° C (from CHCl₃-MeOH); νmax/cm⁻¹ 3468 (OH); δH (CDCl₃/D₂O) 1.00-2.24 (8H, m, H-4, H-5, H-8, H-9 and 2 x H-14), 2.40 – 2.50 (1H, m, H-10), 2.56 (3H, m, OH), 2.47-3.16 (3H, m, H-1, H-2, H-11), 5.09 (2H, m, H-6 and H-7) 5.38 (1H, m, H-3) and 6.07 (2H, m, H13 and H-13); δC (CDCl₃/D₂O) 36.1 (2 x CH₂), 1, 44.1, 45.5, 45.5, 47.3, 48.8, 48.8, 50.2, 66.6 and 68.5 (C-6 and C-7), 80.1 (C-3), 136.3 and 139.1 (C-12 and C-13).

(4-Hydroxytricyclo[5.2.1.0⁴₈, ⁸₈]-dec-6-en-[1.2-b]furan-4-yl) acetaldehyde (167)

A solution of the cycloadduct (164) (223 mg, 1.10 mmol) in acetone: water (8 cm³, 4:1) was treated with osmium tetroxide (28 mg, 0.11 mmol) followed by N-morpholine-N-oxide (112 mg, 1.1 mmol). The green/grey solution was stirred at 25° C for 3 h. The starting material was judged to be consumed by TLC. The acetone was removed in vacuo and additional water was added (5 cm³). The mixture was then extracted with ethyl acetate (5 x 10 cm³), the combined extracts dried over anhydrous magnesium sulfate. The crude extract was then dissolved in dichloromethane. Lead tetraacetate (488 mg, 1.1 mmol) was then added and the resulting mixture stirred at ambient temperature for 2.5 hours. Water was added and the mixture was extracted with ethyl acetate (4 x 10 cm³), dried under anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude material was chromatographed on silica gel (7 g) using ethyl acetate-hexane (2:3) as eluent to give 167 (133 mg, 52%);
\( \nu_{\text{max}} / \text{cm}^{-1} \) 1252 (C-O), 1688 (CO) and 3385 (OH); \( \delta_{\text{H}} (300 \text{ MHz, CDCl}_3/\text{D}_2\text{O}) \)

1.35 (1H, m, H-9\(_a\)), 1.49 and 1.53 (2H, m, 2 x H-3), 1.70 (1H, m, H-9\(_b\)), 2.04 (1H, m, H-3\(_a\)), 2.41 and 2.47 (2H, each m, 2 x H-4\(^1\)), 3.16 (1H, m, H-8\(_a\)), 3.32 (1H, m, H-4), 3.52 (1H, m, H-5), 3.58 (1H, m, H-8), 3.80 (1H, ddd, \( J 10.2, 8.9, 5.0 \) Hz, H-4\(_a\)), 5.14 (1H, dd, \( J 6.6 \) and 4.0 Hz, H-8\(_b\)), 5.35 (1H, dd, \( J 3.9 \) and 3.2 Hz, H-2), 5.73 and 5.74 (2H, H-6 and H-7), 9.94 (1H, dd, \( J 3.3 \) and 2.2 Hz, H-4\(^2\)); \( \delta_{\text{H}} (75 \text{ MHz, CDCl}_3) \) 28.8 (C-4), 34.5 (C-3), 43.9, 46.5, 46.6, 46.9, 48.8, 50.0, 54.2, 77.6 (C-8\(_b\)), 98.5 (C-2), 136.2 and 136.4 (C-6 and C-7), 202.8 (C-4\(^2\)).

\((3\text{-exo, 4\text{-exo}})\text{-5-Oxatetracyclo[6.2.1.0.27.04.6]undec-9-en-ol} (172)\)

Vanadium acetyl acetonate (20 mg, 0.8 mmol) was added to a solution of 78 (580 mg, 3.9 mmol) in toluene (4 cm\(^3\)), at 24°C. \( \iota \)-butylhydrogenperoxide (0.7 cm\(^3\), 5.1 mmol) was added slowly and the solution was refluxed for 40 min. The reaction mixture was allowed to cool and the organic product was extracted into ethyl acetate (3x 15 cm\(^3\)) from water. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:1) yielded the epoxide 172 as a colourless oil (450 mg, 70%); \( \nu_{\text{max}} / \text{cm}^{-1} \) 1221.7 (COC) and 3019.0 (OH); (Found 164.0810 C\(_{19}\)H\(_{12}\)O\(_2\) requires 164.0837); \( \delta_{\text{H}} (400\text{MHz, CDCl}_3) \) 1.31 (1H, br dt, H-11\(_a\)), 1.48 (1H, dt, \( J 2 x 8.4 \) and 1.8 Hz, H-11\(_b\)), 1.73 (1H, br s, OH), 2.27 (1H, ddd, \( J 2.4, 4.7 \) and 7.8 Hz, H-7), 2.90 (1H, m, H-8), 3.00 (1H, br dd, \( J 4.1 \) and 7.7 Hz, H-2), 3.04 (1H, m, H-1), 3.28 (1H, d, \( J 2.7 \) Hz, H-6), 3.43 (1H, t, \( J 2.0 \) x 2.3 Hz, H-4), 3.79 (1H, br s, H-3) and 6.10 (2H, m, H-9 and H-10); \( \delta_{\text{C}} (75\text{MHz}) \), 44.5 (C-7), 45.2 (C-2), 51.2 (C-1), 51.5 (C-11), 53.1 (C-7), 62.8 (C-6), 63.4 (C-4), 74.9 (C-3), 134.8 (C-9) and 135.2 (C-10).

158
exo-3,5-Dihydroxy tricyclo[5.2.1.0²⁶]deca-, 4-8-diene (173)

Lithium aluminium hydride (50 mg, 1.3 mmol) was added to a solution of epoxide 172 (50 mg, 0.3 mmol) in dry tetrahydrofuran (6 cm³) at 0°C under nitrogen. The reaction mixture was brought to reflux for 2 h. The reaction was quenched with water and the same amount of 15% aqueous sodium hydroxide. The solution was filtered through Celite and washed with ethyl acetate. The organic washings were dried over magnesium sulfate. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:1) yielded the diol, (38 mg, 76 %) δₕ (300 MHz, CD₃OD) 1.41 (1H, br dt, H-10a), 1.55 (1H, dt, J 2 x 8.1 and 1.6 Hz, H-10b), 1.74 (1H, dt, J 2 x 11.8 and 8.8 Hz, H-4exo), 2.1 (1H, dt, J 2 x 11.8 and 6.0 Hz, H-4endo), 2.70 (2H, m, H-2 and H-6), 2.8 (2H, m, H-1 and H-7), 3.51 (2H, m, H-3 and H-5) and 6.18 (2H, t, J 2 x 2.0 Hz, H-8 and H-9), δc (100MHz) 29.47 (C-10), 44.5 (C-4), 53.0 (C-1 and C-7), 56.2 (C-2 and C-6), 73.0 (C-3 and C-5) and 136.4 (C-8 and C-9).

(3-exo,4-exo,5-endo)-[3-(Benzyloxy)prop-1-ynyl]tricyclo[5.2.1.0²⁶]dec-8-ene-3,4-diol (174)

n-Butyllithium (1.6 M solution in hexane, 0.55 cm³) was added to a solution of (prop-2-ynyloxy)benzene (49 mg, 0.34 mmol) in tetrahydrofuran (10 cm³) cooled to -78°C. The mixture was stirred at this temperature for 30 min then epoxy-alcohol (172) (50 mg, 0.31 mmol) was added dropwise and stirring continued at -78°C for 6 h. The solution was allowed to warm to 25°C and then saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate; the combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude material was chromatographed on silica gel using ethyl acetate-hexane as eluent to give 174 (9.5 mg, 9.5%); δₕ (400 MHz, CDCl₃) 1.33 (1H, br d, J 8.2 Hz, H-10), 1.44-1.47 (1H, dt, J 2 x...
8.1 and 1.8 Hz H-10), 2.08 (2H, br s, 2 x OH), 2.12 (2H, m, H-3 and H-4), 2.82-2.85 (1H, ddd, J 8.8, 4.5 and 1.4 Hz, H-6), 2.98-3.01 (2H, m, H-2 and H-7), 3.20 (1H, dd, J 8.9 and 4.1 Hz, H-1), 3.73 (1H, ddd, J 5.1, 3.0 and 1.5 Hz, H-5), 4.22 (2H, s, -OCH2), 4.59 (2H, s, -OCH2), 6.03 (1H, dd, J 5.7 and 3.1 Hz, H-8 or H-9), 6.23 (1H, dd, J 5.7 and 2.9 Hz, H-8 or H-9) and 7.35 (5H, m, PhH); δC (100 MHZ, CDCl3) 45.5 (CH2), 46.0 (CH), 52.2 (CH), 52.4 (CH), 57.0 (CH), 59.2 (CH), 74.2 C-3 or C-4, 74.3 (C-3 or C-4), 84.3 (OCH2), 95.3 (OCH2), 122.9, 128.3, 128.5, 131.6, 133.7 and 137.4 (Ph and C-8 and C-9);

(3-exo,4-exo,5-endo)-5-(1,3-Dioxalane-2-ylmethyl)tricyclo[5.2.1.02,6]dec-8-ene-3,4-diol (175)

The epoxide (172) (0.050 g, 0.30 mmol) was added to a solution of 1, 3 dioxalane, 2-magnesium bromide [prepared from 2-bromomethyl 1, 3 dioxalane (0.1 cm3, 0.90 mmol) and magnesium turnings (0.023 g, 0.96 mmol)] in tetrahydrofuran (5 cm3) and the reaction was stirred 24°C for 18 h, followed by heating at 50°C for 8 h. Although complete conversion of the starting epoxide had not been effected at this time, the reaction was quenched with water and the organic product extracted into dichloromethane (2 x 15 cm3). The combined organic extracts were washed with water and dried over magnesium sulfate. The recovered crude material (0.075 mg) was chromatographed silica gel using ethyl acetate-petroleum ether (2:8) yielded the grignard product 175; δH (400 MHz, CD3OD) 1.28-1.42 (2H, m, 2 x H-10), 1.62-1.79 (2H, m, H-51), 2.53 (1H, m, H-5), 2.78, 1H, dd, J 8.6 and 4.6, H-6), 2.95 (1H, m, H-7), 3.02 (1H, m, H-1), 3.06 (H, dd, J 8.6 and 4.0, H-6), 3.51 (H, br d, J 5.4, H-3), 3.86 (2H, t, J 9.8, -OCH2), 3.97 (1H, dd, J 9.6 and 5.4, H-4), 4.21 (2H, t, J 9.8, -OCH2), 6.15 (H, dd, J 5.6 and 3.0, H-9), 6.27 (1H, t, J 1.8, H-52), 6.36 (H, dd, J 5.6 and 3.0, H-8).
**endo-3-Hydroxydicyclopentadiene (180)**

Di-isobutylaluminium hydride (1.5M solution in toluene, 0.88 mmol) was added dropwise to a stirred solution of the enone (21) (0.1g, 0.68 mmol) in dry toluene at -78°C. After 20 min at this temperature, the reaction mixture was diluted with diethylether (8 cm³) and then treated with 25% ammonium hydroxide at 0°C. The mixture was then stirred for 2 h at rt before being filtered through Celite. The filtrate was extracted using dichloromethane (2 x 40 cm³), washed with brine (10 cm³), dried over magnesium sulfate and concentrated. The crude material was chromatographed on silica gel using ethyl acetate-petroleum ether (1:9) to yield the *endo alcohol* (180) (77 mg, 77%) as a colourless solid, m.p. 82-83°C (from chloroform); $\nu_{max}$/cm$^{-1}$ 3599 (OH); $\delta_H$ (300 MHz, CDCl$_3$) 1.48 (1H, br d, J 8.4, H-10$_a$ or H-10$_b$), 1.57 (1H, dt J 2 x 8.4 and 1.8, H-10$_a$ or H-10$_b$), 2.89-2.98 (3H, m, H-1, H-6, H-7), 3.29 (1H, dd, J 7.2 and 3.9, H-2), 4.67 (1H, br d, J 8.1, H-3), 5.59 (2H, s, H-8 and H-9), 5.81 (1H, dd, J 5.6 and 3.2, H-5) and 6.15 (1H, dd, J 5.7 and 2.4, H-4); $\delta_C$ (75 MHz, CDCl$_3$) 44.7 (C-10), 46.9 (C-1), 47.0 (C-7), 52.5 (C-6), 54.0 (C-2), 75.9 (C-3), 133.4 (C-9), 134.6 (C-8), 135.2 (C-5) and 135.2 (C-4). (Found: C, H, N. C$_{18}$H$_{21}$O requires C, 81.1%; H, 8.1%).

**8-Hydroxy-11-oxatetracyclo [5.2.1.1$^{3}$,7.1$^{3}$,9.$^{2}$] undec-4-ene (183)**

$m$-cpba (90 mg, 0.41 mmol) in chloroform (2 cm³), was added dropwise to a flask containing *endo alcohol* (180) (50 mg, 0.34 mmol) in chloroform (5 cm³). The reaction mixture was heated to reflux for 3 h, thereafter cooled to 24°C and washed with saturated aqueous sodium bisulfite (15 cm³), saturated aqueous sodium hydrogen carbonate (3 x 15 cm³) and brine (15 cm³). The organic product was dried over anhydrous magnesium sulfate, filtered and
concentrated. The recovered material (44 mg) was chromatographed on silica gel ethyl acetate-pet ether (3:7) to yield the cyclic ether (183) (43 mg, 77%) as a colourless solid; m. p. 110-113°; (Found: C, 73.3; H, 7.4%; C_{10}H_{12}O_{2} requires C, 73.2; H, 7.4%); ν_{max} (chloroform)/cm\(^{-1}\) 3609 (OH), 1220 (C-O-C); δ_{H} (400 MHz, CDCl\(_3\)) 1.85 (H, br d, J 10.4 Hz, H-10\(_a\) or H-10\(_b\)), 1.90 (1H, br s, OH), 2.13 (H, m, H-7), 2.23 (H, d, J 10.4 Hz, H-10\(_a\) or H-10\(_b\)), 2.69 (H, m, H-1), 2.90 (H, m, H-6), 2.99 (H, m, H-2), 3.88 (H, s, H-8), 4.06 (H, d, J 4.4 Hz, H-9), 4.66 (H, dd, J 5.2 and 1.8 Hz, H-3), 5.75 (H, dd, J 5.2 and 1.8 Hz, H-5) and 5.91 (H, br dd, J 5.2 and 1.8 Hz, H-4); δ_{C} (75 MHz, CDCl\(_3\)) 38.7 (C-10), 45.3 (C-7), 46.6 (C-1), 49.8 (C-2), 50.5 (C-6), 75.6 (C-8), 85.3 (C-3), 90.8 (C-8), 134.4 (C-5) and 134.6 (C-4); (Found: M\(^+\) 164.0141 C_{10}H_{12}O_{2} requires 164.0837).

8-Acetoxy-11-oxatetracyclo [5.2.1.1\(^3\).1\(^3\).9.0\(^2\).6\(^6\)] undec-4-ene (184)

To a stirred solution of the cyclic ether (183) (0.050 g, 0.31 mmol) in pyridine (3 cm\(^3\)) was added catalytic dimethylaminopyridine and acetic anhydride (0.044 cm\(^3\), 0.47 mmol). After stirring for 20 h at 24°C, the reaction mixture was washed with 1M HCl (2 x 15 cm\(^3\)) and extracted with ethyl acetate (2 X 15 cm\(^3\)). The organic product was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulfate and concentrated. Column chromatography on silica gel with ethyl acetate-pet ether (3:7) yielded the acetate (184) (0.034g, 49%); ν_{max}/cm\(^{-1}\) 1225.0 (CO) and 1260.5 (COC); δ_{H} (400MHz, CDCl\(_3\)) 1.84 (1H, dd, J 10.8 and 1.6 Hz, H-10\(_a\)), 1.99 (3H, s, CH\(_3\)), 2.09 (1H, dt, J 2 x 10.8 and 1.6 Hz, H-10\(_b\)), 2.24 (1H, dq, J 4.2, 2.8 and 2 x 1.6, H-1), 2.70 (1H, t, J 4.8, H-7), 2.93 (1H, m, H-6), 3.03 (1H, dt, J 8.8, 5.6 and 2 x 3.2, H-2), 4.17 (H, d, J 4.8, H-8), 4.70 (H, br s, H-9), 4.70 (H, dd, J 5.6 and 2.2, H-3), 5.82 (H, ddd, J 6 and 2.4 and 0.8, H-4) and 5.97 (H, dd, J 6 and 2.4, H-5) and; δ_{C} (75MHz, CDCl\(_3\)) 21.1 (CH\(_3\)), 38.8 (C-10), 43.1 (C-1), 46.6 (C-7), 49.7 (C-2), 50.5 (C-6), 78.4 (C-9 or C-8), 85.4 (C-3), 88.0 (C-8 or
C-9), 134.3 (C-5), 134.8 (C-4) and 169.9 (CO); (Found M+ 206.0947 C12H14O2 requires 206.0943).

Tricyclo [5.2.1.02-6]-deca-3-one (185)

To a solution of 21 (200 mg, 1.37 mmol) in ethyl acetate (10 cm³) was added 10% palladium suspended on carbon (290 mg, 2 mol %) and the suspension stirred at ambient temperature at atmospheric pressure in the presence of hydrogen gas. After 18 h, the suspension was filtered through Celite and the filtrate evaporated under reduced pressure. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:19) yielded the exhaustively hydrogenated product 185 (0.164g, 80 %) as a colourless solid; v max/cm⁻¹ 1700 (CO), 1176 (C-CO-C); δ_H (400MHz, CDCl₃) 1.24-1.54 (6H, m, H-5, H-9 and H-10), 1.8-1.99 (2H, m, H-8), 2.12-2.34 (3H, m, H-4 and H-7), 2.49 (H, dt, J 2 x 4.2 and 1.6 Hz, H-1), 2.53 (H, m, H-6) and 2.73 (H, m, H-2); (Found M+ 150.1038; C10H14O requires 150.1045).

Tricyclo [5.2.1.02-6]-dec-4-ene-3-one (186)

To a solution of 21 (200 mg, 1.37 mmol) in ethyl acetate (10 cm³) was added 10% palladium suspended on carbon (290 mg, 2 mol %) and the suspension stirred at ambient temperature at atmospheric pressure in the presence of hydrogen gas. After stirring for 1 h at 24°C, the suspension was filtered through Celite and the solvent removed under reduced pressure. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:19) yielded the exhaustively hydrogenated product 185 (39 mg, 19 %) as a colourless solid; m. p. 85-88°; v max/cm⁻¹ 1700 (CO), 1176 (C-CO-C); δ_H (400MHz, CDCl₃) 1.24-1.54 (6H, m, H-5, H-9 and H-10), 1.8-1.99 (2H, m, H-8), 2.12-2.34 (3H, m, H-4 and H-7), 2.49 (H, dt, J 2 x 4.2 and 2 x 1.6 Hz, H-1), 2.53 (H, m, H-6) and 2.73
(H, m, H-2) followed by 186 (130 mg, 64%) as a colourless solid; m. p. 88-91°; $\nu_{\text{max}/\text{cm}^{-1}}$ 1638.1 (CO); $\delta_H$ (300MHz, CDCl$_3$) 1.15 (H, m, H-10$_a$), 1.41 (H, m, H-10$_b$), 1.60 (H, dt, J 2 x 9.5 and 1.7, H-8), 1.69 (H, dt, J 2 x 9.5 and 1.7, H-9), 2.49 (H, m, H-6), 2.57 (H, ddd, J 2 x 6.6, and 1.8 Hz, H-2), 2.61 (H, m, H-7), 3.22 (H, m, H-1), 6.08 (H, dd, J 7.6 and 1.7 Hz, H-5) and 7.57 (H, ddd, J 5.4, 3 and 0.8 Hz, H-4); $\delta_C$ (100MHz, CDCl$_3$) 21.4 (C-8 and C-9), 35.15 , 36.3, 38.9, 47.1, 49.3 (C-1, C-2, C-6, C-7, C-10), 131.5 (C-5), 162.7 (C-4) and 209.9 (CO); (Found M$^+$ 148.0868; C$_{10}$H$_{12}$O requires 148.0888).

3-endo-Hydroxytricyclo [5.2.1.0$^{2,5}$]-dec-4-ene (187)

Di-isobutylaluminium hydride (1.5 M solution in toluene, 0.59 cm$^3$) was added to a stirred solution of the enone (21) (100 mg, 0.68 mmol) in dry toluene (3 cm$^3$), the mixture was cooled to -78°C and stirred at that temperature for 20 min, before being allowed to warm to 24°C. The reaction mixture was diluted with diethyl ether (8 cm$^3$) and treated with saturated aqueous ammonium hydroxide (1 cm$^3$) at 0°C and subsequently for 2 h at 24°C before being filtered through a Celite pad, extracted with CH$_2$Cl$_2$ (2 X 10 cm$^3$), washed with brine and dried over magnesium sulfate. Chromatography on silica gel using ethyl acetate–petroleum ether (3:7) yielded the endo alcohol (187) (81 mg, 80%) as a colourless solid; (Found; C, 77.52; H, 9.35; C$_{10}$H$_{13}$O requires C, 79.96; H, 9.39 ; $\nu_{\text{max}/\text{cm}^{-1}}$ 3682.2 (OH); $\delta_H$ (400MHz, CDCl$_3$) 1.30-1.59 (6H, m, H-8, H-9 and 2 x H-10), 1.61 (H, br s, OH), 2.34 (br m, H-2 and H-6), 2.62 (H, tdd, 2 x 9.2, 4.2 and 1.6 Hz, H-7), 2.83 (H, m, H-1), 4.88 (H, br d, J 8.4 Hz, H-3), 5.73 (H, dt, J, 5.6 and 2 x 1.8 Hz, H-5) and 5.80 (H, dtd J 5.6, 2 x 1.8 and 0.4 Hz, H-4); $\delta_C$ (75MHz, CDCl$_3$) 24.3 (C-9), 24.9 (C-8), 38.8 (C-10), 41.0 (C-1), 41.4 (C-7), 47.7 (C-6), 51.1 (C-2), 76.5 (C-3), 133.8 (C-5) and 134.7 (C-4).
(3-endo,4-exo)-5-oxatetracyclo[6.2.1.0^2,7.0^4,6]undec-9-en-3-yl 4-nitrobenzoate (189)

To the epoxide (172) (440 mg, 2.68 mmol), dissolved in dry tetrahydrofuran (10 cm^3), was added triphenylphosphine (1.76 g, 6.7 mmol), followed by p-nitrobenzoic acid (1.11 g, 6.7 mmol). The solution was cooled to 0° C and then di-isopropylazodicarboxylate (542 mg, 2.68 mmol) was added. The solution was then heated to 60° C for 4h, cooled and added to water (15 cm^3). The mixture was extracted with ethyl acetate (3 x 15 cm^3), the combined extracts washed with saturated aqueous sodium hydrogen carbonate, water and brine. The organic phase was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to give crude epoxy-ester (978 mg).

This crude material was chromatographed on silica gel (100 g) using ethyl acetate-hexane (1:9) as eluent to give 189 (680 mg, 81 %) as a colourless solid. m.p 142 - 144°C (from CHCl_3-MeOH) δ_H (300 MHz, CDCl_3/D_2O) 0.36 (1H, m, H-11_a), 0.72 (1H, m, H-11_b), 2.61 (1H, dddd, J 10.2, 4.4, 1.2, and 1.0 Hz, H-2), 2.70 (1H, dd, J 1.3 and 4.5 Hz, H-6), 3.02 (1H, J 10.2, 1.2, 1.0, and 1.3 Hz, H-7), 3.08 (1H, m, H-8), 3.10 (1H, dd, J 5.3 and 4.5 Hz, H-4), 3.30 (1H, m, H-1), 5.64 (1H, ddd, J 5.3, 4.4 and 0.6 Hz, H-3), 5.85 (2H, m, H-9 and H-10), 7.45 - 7.68 (4H, m, H-2', H-3', H-5' and H-6'); δ_C (75 MHz, CDCl_3) 44.1, 44.1, 46.7 and 46.7 (C-1, C-2, C-7 and C-8), 50.0 (C-11), 57.3 (C-6), 60.2 (C-4), 77.6 (C-3), 128.8, 128.8, 129.1, 129.8, 129.8, 133.5, 133.7 and 136.0 (C-9 and C-10), 165 (C=O).

Payne Rearrangement

The epoxy-ester (189) (600 mg, 1.92 mmol) was dissolved in methanol (15 cm^3) and solid potassium carbonate (1.32 g, 9.57 mmol) was added. The mixture was stirred at 25° C for 4 h followed by removal of the methanol under
reduced pressure. The solid material was diluted with water (20 cm³) and extracted with ethyl acetate (3 x 15 cm³). The combined organic extracts were washed with water and brine, dried (MgSO₄) and the solvent removed under reduced pressure. Chromatography of the crude material (324 mg) on silica gel (50 g) using ethyl acetate-hexane (1:4) as eluent gave \((3\text{-endo}, 4\text{-exo})\)-5-oxatetracyclo[6.2.1.0²7.0.4'undec-9-en-3-ol (191) (22 mg, 7 %), \(\delta_H(300\ \text{MHz, CDCl₃/D}_2\text{O})\ 0.47\ (1\text{H, m, H-11}_a), 0.55\ (1\text{H, m, H-11}_b), 2.59\ (1\text{H, m, H-2}), 2.64\ (1\text{H, dd, } J\ 4.5\ \text{and 0.7 Hz, H-6}), 2.83\ (1\text{H, } J\ 6.6\ \text{and 4.5 Hz, H-4}), 3.03\ (1\text{H, dddd, } J\ 10.2, 1.4, 0.9\ \text{and 0.7 Hz, H-7}), 3.08,\ (1\text{H, m, H-1}), 3.14\ (1\text{H, m, H-8}), 4.87\ (1\text{H, ddd, } J\ 6.6, 2.8\ \text{and 0.7 Hz, H-3}), 5.85\ (2\text{H, m, H-9 and H-10}); \delta_C(75\ \text{MHz, CDCl₃}) 44.5, 44.9, 46.7\ \text{and 45.8 (C-1, C-2, C-7 and C-8), 49.9 (C-11), 56.9 (C-6), 61.2 (C-4), 76.6 (C-3), 132.3\ \text{and 135.3 (C-9 and C-10) followed by (3-exo, 4-exo)-5-oxatetracyclo[6.2.1.0²7.0.4'undec-9-en-3-ol (190) (214 mg, 68 %); \(\delta_H(300\ \text{MHz, CDCl₃/D}_2\text{O})\ 0.55\ (1\text{H, m, H-11}_a), 0.67\ (1\text{H, m, H-11}_b), 2.62\ (1\text{H, m, H-2}), 2.63\ (1\text{H, dd, } J\ 4.5\ \text{and 0.7Hz, H-6}), 2.81\ (1\text{H, } J\ 6.6\ \text{and 4.5 Hz, H-4}), 3.07\ (1\text{H, dddd, } J\ 10.2, 1.4, 0.9\ \text{and 0.7 Hz, H-7}), 3.11,\ (1\text{H, m, H-1}), 3.17\ (1\text{H, m, H-8}), 4.86\ (1\text{H, dd, } J\ 6.8\ \text{and 2.8, H-3}), 5.77\ (2\text{H, m, H-9 and H-10}); \delta_C(75\ \text{MHz, CDCl₃}) 44.1, 44.3, 46.7\ \text{and 46.9 (C-1, C-2, C-7 and C-8), 48.2 (C-11), 57.1 (C-6), 60.2 (C-4), 77.2 (C-3), 136.0 and 136.7 (C-9 and C-10).}

\((3\text{-exo,4-exo,5-exo)-[3-(Benzyloxy)prop-1-yny]tricyclo[5.2.1.0²7.0.4']dec-8-ene-3,4-diol (192)}\)

\(n\)-Butyllithium (1.6 M solution in hexane, 0.68 cm³) was added to a solution of (prop-2-ynyloxy)benzene (160 mg, 1.1 mmol) in tetrahydrofuran (10 cm³) cooled to -78° C. The mixture was stirred at this temperature for 30 min then epoxy-alcohol 190 (150 mg, 0.914 mmol) was added dropwise and stirring continued at - 78° C for 6 h. The solution was allowed to warm to 25° C and
then saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate; the combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude material was chromatographed on silica gel using ethyl acetate-hexane as eluent to give 192 (187 mg, 66 %) as a pale yellow oil; \( \nu_{\text{max}}/\text{cm}^{-1} \) 2480 (CC) and 3085 (OH); \( \delta_\text{H} \) (300 MHz, CDCl\(_3\)/D\(_2\)O) 1.39 (1H, H-10\(_a\)), 1.73 (1H, H-10\(_b\)), 2.74 (1H, m, H-2), 2.78 (1H, dd, \( J \) 9.1 and 8.4 Hz, H-5), 3.44 (1H, ddd, \( J \) 10.2, 8.4 and 5.1 Hz, H-6), 3.44 (1H, m, H-1), 3.48 (1H, dd, \( J \) 9.1 and 6.3 Hz, H-4), 3.62 (1H, m, H-7), 4.15 (1H, dd, \( J \) 6.3 and 4.0 Hz, H-3), 4.25 and 4.30 (2H, each d, \( J \) 12.5 Hz, H-5\(^3\)), 4.44 – 4.46 (2H, m, OCH\(_2\)), 5.84 (1H, m, H-8), 5.73 (1H, H-9), 7.21 – 7.31 (5H, Ar-H); \( \delta_\text{C}(75 \text{ MHz, CDCl}_3) \) 43.7 (C-1, C-2, C-6 and C-7), 44.1, 46.4, 46.9, 48.8 (C-5), 50.4 (C-10), 62.0 (C-5\(^3\)), 73.5 (OCH\(_2\)), 80.3 (C-3 and C-4), 80.6, 82.1(C-5\(^5\)), 84.0 (C-5\(^1\)), 127.7 (Ar-C, C-8 and C-9), 128.1,128.8, 135.6, 136.0 and 137.5.

5.2 MOLECULAR MODELLING

GAMESS-UK\(^{132}\) was used for all \textit{ab initio} calculations. Both geometrical minimisations and single point energy calculations were made at the Hartree-Fock level with the STO-3G basis set.

5.3 CRYSTAL STRUCTURE DETERMINATION OF 183

Data were collected at 203K using a Nonius Kappa CCD with 1.5 kW graphite monochromated Mo radiation. The strategy for the data collection was evaluated using \textit{COLLECT}.\(^{133}\) The detector to crystal distance was 40 mm. Exposure times of 40 s per frame and scan widths of 1° were used throughout the data collection. Three sets of data were collected: a 182° \( \Phi \)-scan and two \( \omega \)-scans. The data were scaled and reduced using \textit{DENZO-SMN}.\(^{134}\) Unit cell dimensions were refined on 1291 strong. Well-measured reflections in the 0-
range 3.82° to 27.47° (resolution between 20.00 Å and 0.77 Å). The chiral space group P-1 was chosen on the basis of systematic absences. The structure was solved and refined using SHELX97. Hydrogen atoms were placed in calculated positions and refined as riding atoms. Molecular graphics were generated using X-SEED.

Details of the data collection and refinement are given in Table 5.1. Atomic coordinates for non-hydrogen atoms are listed in Table 5.2. Selected bond lengths are listed in Table 5.2, and torsion angles on Table 5.4.
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Goodness-of-fit on $F^2$  

1.047

Final R indices [$\text{l}>2\sigma(\text{I})$]  

$R_1 = 0.0385$, \text{wR}2 = 0.0908

R indices (all data)  

$R_1 = 0.0473$, \text{wR}2 = 0.0963

Largest diff. peak and hole  

0.299 and -0.158 eÅ$^3$

Table 5.2 Atomic coordinates (x 10$^4$) and equivalent isotropic displacement parameters (Å$^2$ x 10$^3$) for 183. \text{U} (eq) is defined as one third of the trace of the orthogonal \text{U}$_i^J$ tensor

<table>
<thead>
<tr>
<th></th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(12)</td>
<td>2652(2)</td>
<td>7949(1)</td>
<td>6964(1)</td>
<td>37(1)</td>
</tr>
<tr>
<td>O(11)</td>
<td>5495(2)</td>
<td>12708(1)</td>
<td>5616(1)</td>
<td>28(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>3473(2)</td>
<td>11108(2)</td>
<td>5975(1)</td>
<td>26(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>4311(2)</td>
<td>12765(2)</td>
<td>8988(1)</td>
<td>26(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>2924(2)</td>
<td>10591(2)</td>
<td>8586(1)</td>
<td>27(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>7786(2)</td>
<td>14364(2)</td>
<td>7928(2)</td>
<td>30(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>3791(2)</td>
<td>13672(2)</td>
<td>7559(1)</td>
<td>26(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>3905(2)</td>
<td>9964(2)</td>
<td>7271(1)</td>
<td>24(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>5968(2)</td>
<td>14271(2)</td>
<td>6742(1)</td>
<td>26(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>6874(2)</td>
<td>13527(2)</td>
<td>9137(1)</td>
<td>30(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>717(2)</td>
<td>10575(2)</td>
<td>7802(2)</td>
<td>35(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>1925(2)</td>
<td>11958(2)</td>
<td>6625(2)</td>
<td>30(1)</td>
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</table>
Table 5.3 Selected bond lengths for 183

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length (Å)</th>
<th>Bond</th>
<th>Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(12)-C(2)</td>
<td>1.4275(14)</td>
<td>C(3)-H(3)</td>
<td>0.9900</td>
</tr>
<tr>
<td>O(12)-H(12)</td>
<td>0.90(2)</td>
<td>C(6)-C(5)</td>
<td>1.3238(19)</td>
</tr>
<tr>
<td>O(11)-C(1)</td>
<td>1.4381(14)</td>
<td>C(6)-C(7)</td>
<td>1.5032(18)</td>
</tr>
<tr>
<td>O(11)-C(7)</td>
<td>1.4621(14)</td>
<td>C(6)-H(6)</td>
<td>0.9400</td>
</tr>
<tr>
<td>C(1)-C(9)</td>
<td>1.5363(17)</td>
<td>C(8)-C(7)</td>
<td>1.5319(17)</td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.5554(17)</td>
<td>C(8)-C(9)</td>
<td>1.5374(17)</td>
</tr>
<tr>
<td>C(1)-H(1)</td>
<td>0.9900</td>
<td>C(8)-H(8)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(4)-C(5)</td>
<td>1.5007(18)</td>
<td>C(2)-H(2)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(4)-C(3)</td>
<td>1.5494(16)</td>
<td>C(7)-H(7)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(4)-C(8)</td>
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<td>C(5)-H(5)</td>
<td>0.9400</td>
</tr>
<tr>
<td>C(4)-H(4)</td>
<td>0.9900</td>
<td>C(10)-C(9)</td>
<td>1.5314(19)</td>
</tr>
<tr>
<td>C(3)-C(2)</td>
<td>1.5313(16)</td>
<td>C(10)-H(10A)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(3)-C(10)</td>
<td>1.5372(19)</td>
<td>C(10)-H(10B)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(9)-H(9)</td>
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Table 5.4 Selected torsion angles for 183

<table>
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<tr>
<th>Bonds</th>
<th>Angle (°)</th>
<th>Bonds</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(7)-O(11)-C(1)-C(9)</td>
<td>34.62(12)</td>
<td>C(7)-O(11)-C(1)-C(2)</td>
<td>-78.50(11)</td>
</tr>
<tr>
<td>C(5)-C(4)-C(3)-C(2)</td>
<td>-47.46(14)</td>
<td>C(8)-C(4)-C(3)-C(2)</td>
<td>65.11(12)</td>
</tr>
<tr>
<td>C(5)-C(4)-C(3)-C(10)</td>
<td>-153.22(11)</td>
<td>C(8)-C(4)-C(3)-C(10)</td>
<td>-40.65(11)</td>
</tr>
<tr>
<td>C(5)-C(4)-C(8)-C(7)</td>
<td>19.06(11)</td>
<td>C(3)-C(4)-C(8)-C(7)</td>
<td>-103.73(10)</td>
</tr>
<tr>
<td>C(5)-C(4)-C(8)-C(9)</td>
<td>130.72(10)</td>
<td>C(3)-C(4)-C(8)-C(9)</td>
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</tr>
<tr>
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</tr>
<tr>
<td>C(10)-C(3)-C(2)-C(1)</td>
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<tr>
<td>O(11)-C(1)-C(2)-O(12)</td>
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<td>105.62(10)</td>
</tr>
<tr>
<td>O(11)-C(1)-C(2)-C(3)</td>
<td>105.11(11)</td>
<td>C(9)-C(1)-C(2)-C(3)</td>
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<tr>
<td>C(1)-O(11)-C(7)-C(6)</td>
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<td>C(1)-O(11)-C(7)-C(8)</td>
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<td>C(5)-C(6)-C(7)-O(11)</td>
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<td>C(5)-C(6)-C(7)-C(8)</td>
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<tr>
<td>C(9)-C(8)-C(7)-O(11)</td>
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</tr>
<tr>
<td>C(9)-C(8)-C(7)-C(6)</td>
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<td>-19.76(11)</td>
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<tr>
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<td>C(8)-C(4)-C(5)-C(6)</td>
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<tr>
<td>C(3)-C(4)-C(5)-C(6)</td>
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<td>C(2)-C(3)-C(10)-C(9)</td>
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<tr>
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<tr>
<td>C(3)-C(10)-C(9)-C(8)</td>
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<td>O(11)-C(1)-C(9)-C(10)</td>
<td>-146.13(10)</td>
</tr>
<tr>
<td>C(2)-C(1)-C(9)-C(10)</td>
<td>-25.85(12)</td>
<td>O(11)-C(1)-C(9)-C(8)</td>
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<tr>
<td>C(2)-C(1)-C(9)-C(8)</td>
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<tr>
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<td>C(7)-C(8)-C(9)-C(1)</td>
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<tr>
<td>C(4)-C(8)-C(9)-C(1)</td>
<td>-79.03(10)</td>
<td></td>
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</table>
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