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ROUTES TO DRIMANES FROM PODOCARPIC ACID

A THESIS PRESENTED TO

THE UNIVERSITY OF AUCKLAND

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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The synthesis and ozonolysis of the 6- and 7-substituted 12-hydroxypodocarpatrienes (26), (86), (90), and (98), as a possible route for the synthesis of drimanes from 12-hydroxypodocarpa-8,11,13-trien-19-oic acid (podocarpic acid) (9) has been investigated.

Modification of the aromatic ring of (9) has given 11- and 14-hydroxypodocarpatrienes which were ozonised to give the congeners (31), (34), and (36) of the naturally occurring drimanes confertifolin (6), isodrimenin (7), and winterin (8). The oxidation of a 12,13-dihydroxypodocarpatriene (37) and its dimethyl ether (38) have also been investigated.

Routes for the conversion of the enone (45) and oxime (230), derived from the ozonolysis products of methyl podocarpate (10), to drimanes have also been investigated.
NOTES ON NOMENCLATURE

The numbering of all diterpenoid derivatives of podocarpic acid in this thesis follows that proposed by J.W. Rowe in 'The Common and Systematic Nomenclature of Cyclic Diterpenoids', 3rd Revision, Oct. 1968.

Sesquiterpenoid derivatives are named as derivatives of the drimane parent skeleton shown below:

The abbreviation Bz is used throughout this thesis to represent a benzyl (Ph CH₂-) group.
INTRODUCTION

Drimanes are a class of bicyclic sesquiterpenes deriving their name from their abundant occurrence in the stembarks of trees of the genus *Drimys*.\(^1\) Several members of this class have been found to possess potent biological activity promoting interest in their synthesis. Warburganal (1)\(^2\) has been found to possess antifeedant activity against the African army worm *Spodoptera exempta*\(^2c\) and against fish,\(^2e\) anti-molluscidal activity including against the schistosome-carrying snail,\(^2c\) anti-fungal, anti-yeast, anti-tumour, broad anti-microbial activity, cytotoxicity and plant-growth regulatory properties.\(^3\) The related compounds polygodial (2),\(^4\) cinnamodial (3),\(^2a,5\) and muzigadal (4),\(^2b,6\) show similar properties, especially antifeedant activity.\(^7\)

![Chemical structures](image)

Studies\(^2c-e,3\) of these and related compounds show that both the enal and the 9β-aldehyde groups are required for anti-feedant activity with the active compounds possessing a hot taste.\(^2d-e\) The epimeric 9α-aldehydes are both tasteless and inactive. A 9α-hydroxyl group greatly enhances activity, substitution at C6 reduces it slightly, while substitution on the A-ring has no significant effect. The activity is attributed\(^8\) to an interaction between the dialdehyde functionality and a primary amine group (perhaps at lysine) of the taste receptors.

Owing to the difficulty of obtaining large quantities of these compounds from natural sources and the lack of a commercially viable synthesis of optically pure materials, none of these compounds are yet of commercial utility. Racemic material
cannot be used as the unnatural enantiomers are probably phytotoxic (the enantiomer of polygodial (2) shows phytotoxicity at 100 ppm\(^9\)).

A number of total syntheses of racemic (1) and (2) have been reported.\(^{10}\) The most efficient route to date is that of Ley\(^{11}\) which uses a Diels-Alder reaction to construct the B ring (Scheme 1).

\[\begin{align*}
\text{CHO} & \xrightarrow{a,b} \text{CHO} & \xrightarrow{c} \text{CHO} & \xrightarrow{d} \\
\text{CHO} & \xrightarrow{e} \text{CHO} & \xrightarrow{f} \text{CHO} & \xrightarrow{g-i} \\
\text{CHO} & \xrightarrow{g-i} \text{CHO} & \xrightarrow{g-i} \text{CHO} & \xrightarrow{g-i}\end{align*}\]

\[\begin{align*}
a) & \text{Me}_3\text{SiOCH}_2\text{MgBr}, \ b) p-\text{TsOH}, \ c) \text{MeO}_2\text{CC}≡\text{CCO}_2\text{Me}, 180°, \\
d) & \text{H}_2, \text{Pd} / \text{C}, \text{H}^+, \ e) \text{LiAlH}_4, \ f) \text{DMSO}, (\text{COCl})_2, \ g) \text{Ac}_2\text{O}, \text{py}, \\
h) & \text{SeO}_2, \ i) \text{K}_2\text{CO}_3, \text{MeOH}, \ j) \text{DMSO}, \text{TFAA}, \text{Et}_3\text{N}.
\end{align*}\]

**Scheme 1**

White and Burton\(^{12}\) have extended this work to a synthesis of racemic cinnamodial (3) (Scheme 2).
A synthesis of both enantiomers of polygodial (2) has been developed by Mori\textsuperscript{13} which utilises an asymmetric reduction with baker's yeast to place a chiral centre on the A ring prior to construction of the B ring thereby enabling separation of the diastereomeric products from the Diels-Alder reaction (Scheme 3).
(-)-Polygodial (2) has been prepared in 30% yield from naturally occurring (-)-drimenol (5) by Cortes et al.\textsuperscript{14} (Scheme 4).

a) PCC, b) CH\textsubscript{2}(CH\textsubscript{2}OH)\textsubscript{2}, H\textsuperscript{+}, c) SeO\textsubscript{2}, (MeOPh)\textsubscript{2}SeO, d) H\textsubscript{3}O\textsuperscript{+}.

Scheme 4.

The first synthesis of natural (-)-warburganal (1) was that of Ohno et al.\textsuperscript{15} starting from the resin acid (-)-abietic acid (Scheme 5).
The natural isomer has also been prepared from naturally occurring (-)-drimenol (5)\textsuperscript{16} and confertifolin (6)\textsuperscript{17} (Scheme 6).
More recently Nakano and co-workers\textsuperscript{18} have converted manool into (-)-warburganal (1) (Scheme 7).

Akita and Oishi\textsuperscript{19} have synthesised the naturally occurring drimane (+)-isodrimenin (7) from dehydroabietane by ozonolysis of an 11-hydroxy derivative (Scheme 8). Ozonolysis of 14-hydroxy derivatives gave the naturally occurring drimanes (+)-confertifolin (6), and (+)-winterin (8) (Scheme 9). As warburganal (1) has been prepared from both (6)\textsuperscript{17} and (7)\textsuperscript{20a} this completed a formal synthesis of (-)-warburganal (1) from dehydroabietane.
Scheme 7.

a) KMnO₄, b) hv, c) hv, O₂, mTPP, d) LiAlH₄, e) mCPBA, f) LiNEt₂, g) (ClOCl)₂, DMSO, Et₃N.

Scheme 8.

a) CH₃COCl, AlCl₃, b) mCPBA, c) H₂SO₄, d) HNO₃, AcOH, e) H₂, PtO₂, f) FeCl₃, g) H₂, Pd/C, h) O₃, NaBH₄.
To date the only synthesis of (+)-confertifolin (6) and (+)-isodrimenin (7) from a podocarpane is that of Wenkert and Strike\textsuperscript{21} which utilised a lengthy route involving removal of the C ring by ozonolysis followed by reconstruction of the B ring (Scheme 10).

Scheme 9.
Pelletier and Ohtsuka\textsuperscript{22} have synthesised (+)-winterin (8) by ozonolysis of an 11,14-dihydroxypodocarpane (Scheme 11).
As reduction of winterin (8) with sodium borohydride\textsuperscript{20b} has been shown to give confertifolin (6) (14\%) and isodrimenin (7) (81\%) this completes a formal synthesis of warburganal (1) from podocarpic acid (9).
**The Present Work.**

This thesis reports some investigations into new routes for the conversion of the naturally occurring resin acid 12-hydroxypodocarpa-8,11,13-trien-19-oic acid (podocarpic acid) (9)\textsuperscript{23} into congeners of the naturally occurring drimanes warburganal (1), polygodial (2), confertifolin (6), isodrimenin (7), and winterin (8). The starting materials for these investigations were methyl podocarpate (10), and methyl 12-methoxypodocarpate (11).

The first chapter concerns an investigation into the synthesis and ozonolysis of some 6- and 7-substituted podocarpatrienes. In many of the existing syntheses of \( \Delta^7 \)-drimanes the double bond at C7 has to be introduced by isomerisation of a \( \Delta^8 \)-alkene or by the opening of an 8,9-epoxide with a lithium dialkylamide. An alternative route for the introduction of this bond would be by dehydration of a 7-alcohol. As C7 in podocarpatrienes is benzylic, it can readily be oxidised, thus a ketone and hence a hydroxyl group can be introduced here early in the synthesis. This would need to be protected during the modification of the C ring to construct the drimane skeleton. Subsequent deprotection, and elimination would give a suitable intermediate for synthesis of congeners of warburganal (1) and polygodial (2) (Scheme 12).

A ketone has been introduced at C7 by benzylic oxidation of podocarpatrienes with chromium oxidants, e.g. Scheme 10. It has also been reported that treatment of the 12-methoxy methyl ester (11) with ozone at -78° gives the ketone (12).\textsuperscript{24} Reduction of the ketone group gives a 7\textbeta-alcohol, e.g. (12) is reduced to (13).\textsuperscript{25} Some 7\textalpha-acetoxy compounds have been isolated as minor products of the lead tetraacetate oxidation of podocarpic acid derivatives.\textsuperscript{25,26}
Little work has been done on the ozonolysis of 7-substituted podocarpatrienes. Cambie et al.\textsuperscript{27} reported that the 7-ketone (14) did not react with ozone at -78°, but gave a complex mixture at -20°, while ozonolysis of the 7-alcohol (15) at -78° also gave a complex mixture. An investigation into the ozonolysis of podocarpatrienes bearing a protected ketone or hydroxyl group, e.g. dithioacetal, at C7 was undertaken.

A number of naturally occurring drimanes, e.g. cinnamodial (3) bear oxygenated functionality at C6. An investigation into new routes for the introduction of such functionality at C6 in podocarpatrienes, in conjunction with an investigation of the conversion of podocarpatrienes into drimanes would produce a potential new route to the synthesis of such compounds.

A number of methods have been used to introduce a hydroxyl group at C6 in podocarpatrienes. Cambie et al.\textsuperscript{25-28} have synthesised 19-6β lactones which on hydrolysis or reduction gave 6β,7-dihydroxy compounds. They also prepared 6α,7-dihydroxy compounds by oxidation of C7 enol acetates\textsuperscript{28} (Scheme 13).
As a 7-hydroxy group can be removed by hydrogenation, these routes could be used to make 6-hydroxypodocarpatrienes. However, hydrogenation of some 6,7-disubstituted podocarpatrienes has been reported to be difficult and to give variable products. Mori et al. prepared methyl 6α-hydroxy desoxypodocarpate (16) by a route involving hydrogenation of a 6α,7α-epoxide (Scheme 14).
Scheme 14.

Epoxidation of the 14-methoxy alkene (17) with perbenzoic acid however, gave a mixture of the 7β-benzoyloxy (18) (16%) and 7α-benzoyloxy 6α-hydroxy (19) (15%) compounds, which both gave the 6α-hydroxy compound (20) on hydrogenation. Epoxidation of a Δ6-dehydroabietate (21)\(^{32}\) with perbenzoic acid is reported to give a mixture of the 6α-hydroxy 7α-benzoate (22) (43%) and the 7-ketone (23) (47%). Epoxidation of methyl 12-methoxypodocarpa-6,8,11,13-tetraen-19-oate (24) has been variously reported as giving the 6α,7α-epoxide (25),\(^{33}\) or a complex mixture.\(^{30}\)

It was decided to investigate the route shown in Scheme 15 as a possible synthesis of methyl 6α,12-dihydroxypodocara-8,11,13-trien-19-oate (26).
An alternative method for introducing a 6-hydroxy group is by hydroboration of a Δ₆-alkene. Hydroboration of abieta-6,8,11,13-tetraene (27)³² with diborane in tetrahydrofuran gives a mixture of 6α-hydroxy (28) (45%) and 7α-hydroxy (29) (55%) compounds. As an alternative to epoxidation the hydroboration of the alkene (30) was also investigated.

The second chapter concerns an investigation into the synthesis and ozonolysis of 11- and 14- hydroxy podocarpatrienes, as a route to the synthesis of congeners of confertifolin (6), isodrimenin (7), and winterin (8). Akita and Oishi¹⁹ have synthesised dehydroabietanes bearing hydroxyl groups at all possible sites on the aromatic ring. They found that ozonolysis resulted in the loss of two carbon atoms, with the direction of cleavage determined by the position of the hydroxyl group, with the products possessing a carbonyl group at this position. Thus ozonolysis of 11- or 14-hydroxy dehydroabietanes gave drimanes (see Schemes 8 and 9).

The strong o,p-directing properties of the 12-hydroxy group in podocarpic acid derivatives renders the direct introduction of a C14 substituent extremely difficult. Recently, Metzler³⁴ within this department has introduced alkyl substituents at C14 in
some 7-ketopodocarpatrienes by means of transition metal carbonyl complexes. Attempts to introduce a C14 hydroxyl group have proved unsuccessful.\textsuperscript{35} It was envisaged, therefore that introduction of such a group would require prior substitution at C13 with an \textit{o}-directing group. Oxidation of \textit{p}-substituted phenols or anilines with Frémy's salt (potassium nitrosodisulfonate)\textsuperscript{36} gives \textit{o}-quinones which can be reduced to \textit{o}-dihydroxy compounds. Hence the synthesis of the confertifolin congener (31) by the route shown in Scheme 16 was investigated.

\textbf{Scheme 16.}

The introduction of a substituent at C11 is also difficult, as although this site is electronically favourable for substitution, steric congestion due to the neighbouring angular methyl group makes substitution at the less congested C13 more favourable.
Therefore, to introduce a hydroxyl group at C11, prior substitution at C13 seemed necessary. An acetyl group which could be reduced to an ethyl group, seemed most suitable. An 11-hydroxyl could then be introduced by the method of Akita and Oishi\textsuperscript{19b} (Scheme 8). An alternative route would be that of Matsumoto \textit{et al.}\textsuperscript{36} who oxidised ferruginol (32) to the 11-hydroxy compound (33) with benzoyl peroxide.\textsuperscript{37} Thus the routes shown in Scheme 17 were investigated as possible syntheses of the isodrimenin congener (34).

\begin{center}
\begin{tikzpicture}
\begin{scope}[scale=0.8]
\node at (0,0) {\includegraphics[width=\textwidth]{scheme17.png}};
\end{scope}
\end{tikzpicture}
\end{center}

\begin{itemize}
\item[a)] CH\textsubscript{3}COCl\textsubscript{3}, AlCl\textsubscript{3},
\item[b)] AlCl\textsubscript{3}, \Delta,
\item[c)] Cu(NO\textsubscript{3})\textsubscript{2}, Ac\textsubscript{2}O,
\item[d)] H\textsubscript{2}, Pd/C,
\item[e)] Zn\textsubscript{i}Hg, H\textsuperscript{+},
\item[f)] (PhCO\textsubscript{2})\textsubscript{2},
\item[g)] NaIO\textsubscript{4},
\item[h)] OH\textsuperscript{-},
\item[i)] O\textsubscript{3},
\item[j)] NaBH\textsubscript{4}.
\end{itemize}

\textbf{Scheme 17.}

Davis and Watkins\textsuperscript{38} found that oxidation of methyl 12-methoxypodocarpate (12) with peracetic acid gave the 11,14-quinone (35) (9\%). As Pelletier and Ohtsuka\textsuperscript{22} have prepared winterin (8) by ozonolysis of an 11,14-dihydroxypodocarpatiene
(Scheme 11), it was decided to investigate the possible synthesis of the winterin congener (36) by the route shown in Scheme 18.

![Scheme 18](image)

Also investigated was the oxidation of the 12,13-dihydroxy compound (37), and its dimethyl ether (38). Oxidation of catechols with copper (I) chloride and oxygen in the presence of methanol gives monomethyl muconates, while ozonolysis of o-dimethoxybenzenes in the presence of boron trifluoride gives dimethyl muconates. It was envisaged that oxidation of (37) and (38) with these reagents would give derivatives of the muconic acid (39) which on decarboxylation might give compounds with a drimane skeleton. Researchers within this department are investigating the oxidation of the related catechol (40) as a route to nagilactones.

The third chapter concerns an investigation into the conversion of the ozonolysis products of methyl podocarpate (10) into drimanes. Ozonolysis of (10) gives the hydroperoxy lactone (41) which can be reduced to the keto-acid (42). Conversion of (42) into drimanes requires the loss of one carbon atom from the side-chain and the addition of a one-carbon side-chain at C8. The latter can be achieved by the use of a modified Oshima reaction to introduce a methylene group at C8, e.g. (43) is converted to (44) (82%). The chain-shortening has been achieved by means of a novel debromo-decarboxylation (Scheme 19).
It was decided to investigate the conversion of the enone (45) into compounds with drimane skeletons suitable for conversion into congeners of warburganal (1), by the routes shown in Scheme 20.

As the enone (45) is unstable, rapidly undergoing dimerisation27 it was decided to also investigate an alternative chain-shortening route shown in Scheme 21.
Brown and Weissman\textsuperscript{46} report that LiAlH(OMe)\textsubscript{3} will reduce esters but not oximes. Given the steric hindrance at C19, it was hoped that the ester group at C12 could be reduced selectively by the use of only 2 equivalents of hydride.

Scheme 21.

\textbf{Scheme 21.}

Brown and Weissman\textsuperscript{46} report that LiAlH(OMe)\textsubscript{3} will reduce esters but not oximes. Given the steric hindrance at C19, it was hoped that the ester group at C12 could be reduced selectively by the use of only 2 equivalents of hydride.
CHAPTER ONE

This chapter concerns an investigation into the low-temperature ozonolysis of some 6- and 7-substituted derivatives of podocarpic acid (9). As was shown in the introduction, many biologically active drimanes possess a C7 double bond which is usually introduced during synthetic studies by isomerisation of the A8-isomer, or by the opening of an 8,9- or 8,12-epoxide with a lithium dialkylamide. The introduction of a protected ketone or alcohol at C7 early in the synthesis presents an alternative to this functionality as shown in Scheme 12. In particular ozonolysis of a 7-substituted podocarpatiene offers a potential route to the triester (46) from which congeners of a number of naturally occurring drimanes could be prepared by previously established routes. The initial objective, therefore was to prepare and ozonise derivatives of (9) with a protected ketone or alcohol at C7.

1.1 The reaction of aromatic compounds with ozone.

The ozonation of aromatic compounds has been reviewed extensively by Bailey. The following brief review provides a summary of some aspects of the reaction of ozone with aromatic rings with specific regard to its synthetic utility, and a summary of some recent examples of this in the diterpene field.

The reaction of aromatic compounds with ozone has been little utilised in synthesis for two reasons. Firstly, aromatic rings are much less reactive towards ozone than olefinic double bonds; indeed the latter can be cleaved in the presence of the former, e.g. treatment of isoeugenol gives vanillin. Reaction is promoted by the presence of activating substituents on the ring. Even activated rings, however, are resistant to ozone; for example methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (11) when treated with ozone at -78° undergoes a benzylic oxidation to give the ketone
Kinetic studies by Wibaut and co-workers of the ozonation of substituted benzenes suggest an analogy between the addition of ozone to an aromatic ring and electrophilic substitution on it. They found that the reaction was catalysed by Lewis acids such as aluminium trichloride, presumably by complexation between the catalyst and the ozone causing polarisation of the latter and thus enhancing its electrophilicity.

Secondly, once a molecule of ozone has been added to the ring, the resulting diene is usually more reactive towards ozone, so that control of the amount of ozone addition is difficult with the usual result being the complete destruction of the ring, e.g. benzene gives a triozonide which can be reduced to give 3 moles of ethanediol. Disubstituted benzenes give products corresponding to equal attack by ozone on both Kekulé forms. As a result ozonolysis has been used to remove an aromatic ring from a molecule, e.g. in Wenkert and Strike’s synthesis of drimanes.

Oxidation of polycyclic phenols usually results in destruction of the hydroxyl-bearing ring. The choice of solvent has a profound effect on the products obtained. Ozonolysis of 2-naphthol in solvents such as chloroform which cannot react with the intermediate ozonide gives a mixture of phthalic acid, phthalaldehyde and a cinnamic acid, while in methanol the product is a benzodioxan.

There are some examples in the literature of the partial ozonolysis of aromatic rings. In these cases steric hindrance prevents further attack on the diene. Speyer and Popp found that ozonolysis of dihydrocodeine gave the ester (50) in 40% yield, which was improved to 75% by Rapoport and Payne. As part of their synthesis of strychnine, Woodward et al. converted the o-dimethoxy compound (51) into the diester (52) by treatment with ozone at -78°C in ethyl acetate. Recently, Isobe et al. have reported that ozonolysis of o-dimethoxybenzenes can be controlled by the presence of boron trifluoride-diethyl etherate, to give dimethyl muconates. Presumably the Lewis acid complexes to the dienes making them less susceptible to attack.
Bell and Gravestock\textsuperscript{42} found that ozonolysis of methyl 12-hydroxypodocarpa-
8,11,13-trien-19-oate (10) in dichloromethane-methanol gave the 8\(\beta\)-hydroperoxy lactone (41) in 68\% yield. Presumably, steric hindrance precluded oxidation of the 9(11)-double bond. They proposed the following mechanism for the reaction:

Subsequently, workers within this department reported that the ozonolysis of podocarpic acid (9) and the derivatives (53), (54) and (55) gave the hydroperoxy lactones (56) (57\%),\textsuperscript{27} (57) (95\%),\textsuperscript{57} (58) (60\%),\textsuperscript{58} and (59) (35\%) respectively. Treatment of (60) with ozone and subsequent reduction of the crude product with sodium hydrogensulfite gave a complex mixture of which only the dilactone (61) (29\%) could be identified.\textsuperscript{27} The ketolactone (14) was unreactive towards ozone at -78\textdegree, presumably due to the deactivating effect of the carbonyl group on the aromatic ring. Treatment of (14) with ozone at -15\textdegree gave a complex mixture, as did the ozonolysis of the 7\(\beta\)-hydroxylactone (15) at -78\textdegree.\textsuperscript{27}

An investigation has also been made within this department into the ozonolysis of derivatives of totarol (62).\textsuperscript{59} Totarol (62) was found to undergo extensive degradation, but treatment of the 12,13-dimethoxy derivative (63) with ozone (dimethyl sulfide workup) gave the dimethyl muconate (64) in 95\% yield. The catechol mono-
ethers (65) and (66) gave complex mixtures.
Akita and Oishi\textsuperscript{19} have investigated the ozonolysis of dehydroabietane derivatives bearing hydroxyl groups at all positions on the aromatic ring. They found that the oxidation proceeded with loss of 2 carbon atoms to give a hydroperoxy lactone with the carbonyl at the site of the original hydroxyl group, whose position determined the direction of cleavage. They did not attempt to isolate these compounds but characterised the products from their reduction. Ozonolysis of ferruginol (32) and subsequent reduction with zinc-acetic acid gave the keto-acid (67)\textsuperscript{57} (63\%). Ozonolysis of the 13-hydroxy compound (68) and subsequent reduction with sodium borohydride gave the lactone (69) (22\%) which was converted in 50\% yield into the marine natural product pallescensin A (70).\textsuperscript{60} Ozonolysis of the 14-hydroxy compounds (71) and (72) with subsequent reduction with borohydride gave confertifolin (6) in 11\% and 47\% yields respectively. Similarly, the 11-hydroxy compound (73) was converted into isodrimenin (7) in 26\% yield. Ozonolysis of (72) followed by reduction with sodium hydrogensulfite gave validiolide (74) (18\%) which was oxidised with Jones’ reagent to give winterin (8) (50\%). Winterin has also been prepared in 30\% yield by Jones oxidation of the product from ozonolysis of an 11,14-dihydroxy podocarpatiene (75).\textsuperscript{22} Ozonolysis\textsuperscript{19} of the 6α-hydroxy (76) and 6α-acetoxy (77) 14-hydroxy dehydroabietanes followed by reduction with borohydride in methanol gave the 6α-hydroxy (78) (48\%) and 6α-acetoxy (79) (54\%) confertifolins respectively. Also obtained from the ozonolysis of (77) was the 11-methoxy derivative (80) (11\%). The 6α-hydroxy compound (78) was converted into the naturally occurring drimanes (+)-fragolide (81)\textsuperscript{5} (100\%), and (+)-bemadienolide\textsuperscript{5} (82) (6\%).

1.2 Preparation and ozonolysis of a protected 7-ketone.

Methyl podocarpate (10)\textsuperscript{23} was prepared in 77\% yield by methylation of crude podocarpic acid (9) with dimethyl sulfate and sodium hydrogencarbonate. Treatment
with acetic anhydride and pyridine gave the 12-acetate (83)\(^{61}\) (94%) which was oxidised with chromium trioxide in acetic acid to the 7-ketone (84)\(^{62}\) (76%). Hydrolysis with methanolic sodium hydroxide gave the 12-hydroxy ketone (85)\(^{63}\) (87%). Oxidation of (83) with ozone at \(-78^\circ\) gave a mixture of the 12-acetoxy (84) (21%) and 12-hydroxy (85) (30%) ketones. The direct oxidation of (10) to (85) was found to be low-yielding due to competing oxidation of the aromatic ring, the best yield of (85) (40%) being obtained by use of chromium trioxide in acetic acid.

The 12-hydroxy ketone (85) was treated with ethanedithiol and boron trifluoride-etherate in acetic acid to give the dithioacetal (86) in 54% yield. In the mass spectrum of (86) the base peak was at \(m/z\) 318 (M-60) which probably arises from the following fragmentation pathway:

\[
\text{OH} \quad \text{CO}_2\text{Me} \quad m/z \ 378
\]

\[
\text{OH} \quad \text{CO}_2\text{Me} \quad m/z \ 318
\]

This is supported by the presence of a strong peak at \(m/z\) 60 corresponding to thirane.

The relatively low yield of (86) was due to the need during workup to remove the excess of thiol by extraction with base. Use of less than 2 equivalents of thiol was found to slow the reaction considerably so that contamination of the product with the diacetate of the thiol, a volatile solid with a most unpleasant odour, became significant. The reaction was found to be considerably, slower with chloroform as solvent, 25% of starting material being recovered after 4 days at reflux with 40% of (86).

Since the base solubility of (86) was the cause of the low yield, it was thought that formation of the 12-acetoxy dithioacetal (87) and subsequent hydrolysis would be a better route to (86), as the acetate group would lower the solubility in base. However, treatment of the 12-acetoxy ketone (84) with ethanedithiol and boron trifluoride-
etherate gave only (86) (34%). The yield was lowered by the need to remove a red coloured impurity by chromatography.

The acetate having proved too labile, the next reaction investigated was the demethylation of the 12-methoxy dithioacetal (88). Methylation of podocarpic acid (9) with dimethyl sulfate and sodium hydroxide gave methyl 12-methoxypodocarpate (11)23 (89%) which was oxidised with chromium trioxide-acetic acid to the 12-methoxy ketone (12)64 (71%). Treatment of (12) with ethanedithiol and boron trifluoride-etherate in refluxing chloroform for 5 days gave an oil from which (88) was obtained in 15% yield after chromatography on silica and repeated crystallizations from methanol. If the reaction was done in acetic acid, the product was found to be heavily contaminated with the diacetate of the thiol which could not be completely removed even by repeated chromatography on silica or recrystallizations. The mass spectrum of (88) also had as base peak a fragment ion M-60, corresponding to loss of thiirane. Treatment of (88) with boron tribromide at -78⁰65 gave the 12-hydroxy dithioacetal (86) in 35% yield with 25% recovery of starting material.

Ozonolysis of (86) and reduction of the crude ozonide with zinc and hydrochloric acid gave an oil which was separated into 9 compounds, all of which rapidly coloured in air with formation of multiple spots on t.l.c. analysis. No signals corresponding to aromatic protons could be detected in the ¹H n.m.r. spectrum of any of these compounds, nor could bands corresponding to a sulfoxide or sulfone group be detected in their i.r. spectra indicating that no oxidation of the sulfide linkages had occurred.66 The two largest components of the mixture had fragments of highest mass at m/z 570 in their mass spectra with M+1:M ratios suggesting they were C₃₅ species indicating dimeric structures. All of these compounds were too unstable to be characterised and the reaction was not further investigated. The ketone (85) was unreactive towards ozone at -78⁰ even in the presence of aluminium trichloride as catalyst.26c

Treatment of (85) with 2-mercaptoethanol gave a small amount of a material
which showed no ketone stretch band in the i.r. and which t.l.c. analysis showed to be a mixture of at least 2 compounds. All attempts to prepare the acetal (89) were unsuccessful.

1.3 Preparation and ozonolysis of a protected 7-alcohol.

Reduction of the 12-acetoxy ketone (84) with sodium borohydride in methanol gave the 7β,12-dihydroxy compound (90) (91%). The H7 signal in the 1H n.m.r. spectrum was a broad singlet with a $W_\frac{1}{2}$ of 15 Hz, indicating H7 was in the axial α position with a resultant widening of the signal due to the large 6ax-7ax coupling. If H7 were equatorial (β) this large coupling would be lacking and the signal would have a $W_\frac{1}{2}$ of 6-10 Hz. This indicates that reduction had occurred as expected from the less-hindered α-face. Attempts to prepare the 12-acetoxy 7-alcohol (91) by performing the reduction in tetrahydrofuran were unsuccessful, no reaction being observed even under reflux. The diol (90) could also be prepared in quantitative yield by reduction of the 12-hydroxy ketone (85) with borohydride. The diol (90) was unstable, colouring rapidly in air, and decomposed on attempted purification to give the alkene (92). No molecular ion could be detected in the mass spectrum, the fragment of highest mass being at $m/z$ 286 (M-18). Ozonolysis of (90) gave a complex mixture which was not further investigated.

Since the acetate had proved too labile under basic conditions, the use of the less base-labile benzoate group to protect the phenol was investigated. Treatment of methyl podocarpate (10) with benzoic anhydride and pyridine gave the benzoate (93) (79%) which was oxidised with chromium trioxide-acetic acid to the 12-benzoyloxy ketone (94) (73%). Treatment of (93) with ozone at -78° gave (94) in 29% yield with 45% recovery of starting material. Reduction of (94) with sodium borohydride in aqueous tetrahydrofuran gave the 7β-alcohol (95) in quantitative yield. The H7 signal
in the $^1$H n.m.r. spectrum was a doublet of doublets ($J$ 9, 6 Hz) indicating H7 was axial ($\alpha$).

Treatment of the alcohol (95) with $p$-toluenesulfonic acid in refluxing methanol gave a mixture of the crystalline 7$\alpha$-methoxy (96) (49%) and the oily 7$\beta$-methoxy (97) (11%) compounds. The stereochemistry at C7 was assigned on the basis of the H7 signals in the $^1$H n.m.r. spectra. The H7 signal for (96) was a broad singlet $\frac{1}{2}$ 8 Hz, indicating H7 was equatorial (β), while H7 in (97) had $\frac{1}{2}$ 14 Hz indicating it was axial (α). The product ratio suggests that the reaction proceeds via a C7 cation with preferential attack of methanol from the less-hindered α-face. Hydrolysis of (96) gave the desired 12-hydroxy-7$\alpha$-methoxy compound (98) which was an unstable oil that decomposed to the alkene (92) on attempted purification. The H7 signal in the $^1$H n.m.r. spectrum had a $\frac{1}{2}$ of 8 Hz indicating that H7 was β. Ozonolysis of (98) gave a complex mixture that was not further investigated.

The synthesis of a 12-hydroxy 7-acetate (99) was attempted next. Reduction of the 12-methoxy ketone (12) with sodium borohydride gave the 7$\beta$-alcohol (13) (80%) which was acetylated to give the 7$\beta$-acetate (100) (95%). Treatment of (100) with boron tribromide at -78° gave an oil which was a complex mixture by t.l.c. analysis. $^1$H n.m.r. analysis suggested that partial demethylation had occurred, while a signal at $\delta_H$ 6.3 suggested the presence of a $\Delta^6$-alkene.

The last route to 7-substituted 12-hydroxypodocarpatrienes investigated was the hydrogenation of 7-substituted 12-benzyloxy compounds. Though C7 is also benzylic it was hoped that hydrogenation might proceed more readily at C12 so that this position could be hydrogenated selectively. Methyl podocarpate was converted into its benzyl ether (101) in 79% yield using benzyl bromide and sodium hydroxide. Oxidation with chromium trioxide-acetic acid gave the ketone (102) (84%) which was also obtained in 34% yield from treatment of (101) with ozone at -78° with 35% recovery of starting material. Reduction with sodium borohydride gave the 7$\beta$-alcohol (103)
The H7 signal in the $^1$H n.m.r. spectrum was a doublet of doublets ($J\,10,\,6\,\text{Hz}$) indicating H7 was axial ($\alpha$). Methylation of (103) with potassium hydroxide and iodomethane in dimethyl sulfoxide gave the methyl ether (104) which was assigned the 7β structure as H7 showed similar coupling to H7 in (103). Treatment of (104) with 1 equivalent of hydrogen over a palladium catalyst gave (101) (46%) with 10% recovery of starting material. Acetylation of (103) with acetic anhydride and pyridine on a waterbath gave a mixture of epimeric 7-acetates (105). Of the two signals corresponding to the acetate protons in the $^1$H n.m.r. spectrum the more downfield ($\delta_{H}$$2.15$) was assigned to the β-acetate as $^1$H n.m.r. studies of 6 and 7 substituted podocarpatrienes show that 7β-acetate proton signals appear downfield of the corresponding 7α-acetate signals. Examination of models shows that in the most probable conformations the 7α-acetate protons are in a position to receive shielding from the aromatic π-system, while the 7β-acetate protons are not, and hence one expects the 7β-acetate proton signal to be further downfield. Comparison of the integrals for the acetate protons showed the mixture to contain 55% of the α-acetate (105a) and 45% of the β-acetate (105b). Comparison of the integrals for the H20 and H18 signals led to the more downfield signals at $\delta_{H}$$1.08$ and $\delta_{H}$$1.25$ respectively being assigned to the β-acetate (105b). Models show that the lone pairs on the carboxyl oxygen can deshield the protons at C20 when the acetate is β, but not when it is α, hence the H20 signal is more downfield for the β-acetate. Conversely, when the acetate is α the lone pairs can provide shielding for the protons at C18, hence the H18 signal is more upfield for the α-acetate (105a).

Hydrogenation of (105) also proceeded preferentially at C7 to give (101) in 46% yield with 11% recovery of starting material. $^1$H n.m.r. analysis of the recovered acetate mixture showed the β-acetate to be predominant indicating that the axial α-acetate had been reduced preferentially. As the hydrogenation of benzyl esters frequently proceeds faster than than that of benzyl ethers the formation of (101) from hydrogenation of (105) is not unexpected.
1.4 Preparation and ozonolysis of a 6-alcohol.

A number of naturally occurring drimanes bear oxygenated functionality at C6, e.g. mukaadial (106),\textsuperscript{69} 6β-hydroxyisodrimenin (107),\textsuperscript{70} cinnamodial (3),\textsuperscript{5} and fragolide (81).\textsuperscript{5} As part of the current work, the synthesis and ozonolysis of the 6α-hydroxy-podocarpatriene (26) as a potential route to 6-substituted drimanes was investigated.

The starting materials for this investigation were the 12-benzyloxy (30) and 12-benzoyloxy (108) Δ⁶-alkenes. The 12-benzyloxy Δ⁶-alkene (30) was obtained by dehydration of the 7β-alcohol (103) with hydrochloric acid (81%). The alkene (30) was also obtained in 77% yield from treatment of (103) with acetic anhydride and an excess of pyridine. The 12-benzoyloxy alcohol (95) was more resistant to dehydration with 3% of starting material being recovered after treatment with \( p \)-toluenesulfonic acid in refluxing tetrahydrofuran for 16 h, together with the 12-hydroxy (92) (10%) and 12-benzoyloxy (108) (65%) Δ⁶-alkenes. Benzoylation of (92) gave (108) (75%). Treatment of (95) with acetic anhydride and pyridine on a waterbath, unlike the acetylation of (103), gave only the 7β-acetate (109) (63%). The acetate was assigned a β configuration on the basis of the \( ^1H \) n.m.r. spectrum. H7 appeared as a doublet of doublets at \( δ_H 5.98 \), with coupling constants of 10 and 7 Hz characteristic of an axial 7α-proton coupled to axial and equatorial H6 protons. The acetate protons appeared at \( δ_H 2.30 \). \( ^1H \) n.m.r. studies of other 7-acetoxy-podocarpatrienes\textsuperscript{28} show that 7β-acetate protons appear at \( δ_H 2.1-2.2 \), while 7α-acetate protons appear at \( ca. δ_H 2.0 \). Starting material was recovered quantitatively from treatment of both (105) and (109) with pyridine in refluxing tetrahydrofuran.

Unlike most derivatives of (+)-podocarpic acid (9), the Δ⁶-alkenes (30), (92), and (108) were laevorotatory. The vinylic proton signals for these alkenes appeared as broad singlets at \( ca. δ_H 6.3 \) in the \( ^1H \) n.m.r. spectrum. These properties have been observed for other 6,8,11,13-podocarpatetraenes with a C19 ester group.\textsuperscript{25,28,71,72} The
appearance of the vinyl protons as a singlet has been explained as being due to their similar chemical environments and an H5-H6 dihedral angle of ca. 90°. Δ⁶-Alkenes with a tetrahedral C19 atom show more complex H6 and H7 splitting patterns.

Epoxidation of the 12-benzyloxy Δ⁶-alkene (30) with m-chloroperbenzoic acid at 0° gave a complex mixture, the products isolated being the epimeric 6α-hydroxy 7β-(110) (13%) and 7α-(111) (26%) m-chlorobenzoates, the 6α,7α-diol (112) (9%), and a glass (12%) which was an inseparable mixture of the 7α-hydroxy-6α-m-chlorobenzoate (113) (77%) and the 7β-hydroxy-6β-m-chlorobenzoate (114) (23%). The structures of (110)-(114) were assigned on the basis of their ¹H n.m.r. spectra. The chemical shifts and coupling constants for H6 and H7 in (110)-(114) are shown in Table 1.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Shift</th>
<th>Coupling (Hz)</th>
<th>Assignment.</th>
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<tr>
<td>(114)</td>
<td>6.48 (5.1)*</td>
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<tr>
<td>(115)</td>
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<tr>
<td>(116)</td>
<td>4.30</td>
<td>4.67</td>
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</table>

*Obscured by benzyl protons.

Table 1.

The H6 signals for (110) and (111) appeared as doublets of doublets at δ₇H4.65 (J 11.0, 8.6 Hz) and δ₇H4.74 (J 10.1, 3.6 Hz) respectively, while the H7 signals appeared as doublets at δ₇H6.37 (J 8.6 Hz) and δ₇H6.48 (J 3.6 Hz) respectively. ¹H n.m.r. studies of some 6,7-dihydroxydipodocarpatiene monoacetates show that the proton geminal to the acetate appears at δ₇H5.6-5.65 in 6-acetates and at δ₇H5.6-6.0 in 7-acetates. As the greater electron-withdrawing power of a benzoate group causes the geminal proton
signal to shift 0.2-0.3 ppm downfield with respect to the corresponding acetate, the $m$-chlorobenzoate groups were assigned to C7. The large $J_{5,6}$ values indicate a diaxial relationship between H5 and H6. Thus the 6-alcohols were equatorial (α). The $J_{6,7}$ values of 8.6 Hz for (110) and 3.6 Hz for (111) indicate H7 is axial (α) in (110) and equatorial (β) in (111). In the $^1$H n.m.r. spectra of the similar 6α-hydroxy 7-benzoates (18) and (19), H6 appears a doublets of doublets ($J_{10, 8}$ Hz) at δ_H 4.62 for the 7β-benzoate(18), and as a doublet of doublets ($J_{10, 6}$ Hz) at δ_H 4.80 for the 7α-benzoate(19). For (112) H6 appeared as a doublet of doublets ($J_{10, 3.7}$ Hz) at δ_H 4.82. As the H6 and H7 splitting patterns for (111) and (112) were identical, (112) was assigned as the 6α,7α-diol. For (113) H6 appeared as a doublet of doublets ($J_{9.4, 3.9}$ Hz) at δ_H 6.28, and H7 as a doublet ($J_{3.9}$ Hz) at δ_H 5.03. As the H6 and H7 splitting patterns for (111) and (113) were similar, H6 and H7 were both assigned as β, while comparison of the chemical shifts showed that the $m$-chlorobenzoate was at C6. The change in coupling constants from (111) to (113) suggested a change in the conformation of the B-ring. The H6 signal for (114) appeared as a doublet of doublets ($J_{7.2, 3.5}$ Hz) at δ_H 6.48. The small (3.5 Hz) value of $J_{5,6}$ indicated that H6 was equatorial (α), while the value of 7.2 Hz for $J_{6,7}$ suggested that H7 was axial (α). Comparison of the integrals for the H6 signals of (113) and (114) indicated that the mixture contained 77% of (113) and 23% of (114).

The diol (112) was not detected by t.l.c. analysis of the reaction mixture prior to workup, suggesting that it was formed during workup, either by hydrolysis of (111) or by an $S_N2$ displacement of the $m$-chlorobenzoate group in (110). The formation of both (110) and (111) suggests that the epoxide initially formed opens by an $S_N1$-like process to produce an incipient C7-cation with subsequent nucleophilic attack by the $m$-chlorobenzoate proceeding preferentially from the less-hindered α-face.

Opening of epoxides usually proceeds with inversion via an $S_N2$ mechanism to give products with trans-stereochemistry. However, acyl or aryl substituted epoxides
often open with retention to give products with cis-stereochemistry.\textsuperscript{75} This has been explained as resulting from an $S_N1$-like mechanism with stabilisation of the incipient positive charge by the neighbouring group, and the direction of attack by the nucleophile being determined by steric effects.\textsuperscript{75b,c}

The product ratio from epoxidation of (30) was variable, the amount of (112) isolated being increased by the use of a greater excess of peracid. Presumably, the greater acidity of the reaction mixture causes greater hydrolysis of the esters. From one experiment the major product (34\%) was an inseparable mixture of (110) (60\%) and the 7\beta-hydroxy-6\alpha-m-chlorobenzoate (115) (40\%). The H6 signal for (115) appeared as a doublet of doublets ($J_{11.0, 8.2}$ Hz) at $\delta_H4.87$ while the H7 appeared as a doublet ($J_{8.2}$ Hz) at $\delta_H5.94$. As the H6 and H7 splitting patterns for (110) and (115) were virtually identical, H6 was assigned as β and H7 as α, while the chemical shifts indicated the m-chlorobenzoate was at C6. The composition of the mixture was determined by comparison of the integrals for the H7 signals. Also isolated from this experiment were the 6\alpha,7\alpha- (112) (6\%) and 6\beta,7\beta- (116) (2\%) diols. The H6 signal for (116) appeared as a broad doublet ($J_{8}$ Hz) at $\delta_H4.30$, while H7 appeared as a doublet ($J_{8}$ Hz) at $\delta_H4.67$. The small coupling constant $J_{5,6}$ (<2 Hz) showed that H6 was equatorial (α) with an H5-H6 dihedral angle of ca. 90°. The large $J_{6,7}$ value showed that H7 was axial (α) with a small H6-H7 dihedral angle. This suggests that the B-ring in (116) is in a half-boat like conformation which would allow for hydrogen-bonding between the hydroxyl groups.

Epoxidation of the 12-benzoyloxy $\Delta^5$-alkene (108) with m-chloroperbenzoic acid also gave a complex mixture, the identified products being the 7-ketone (94) (5\%),
an inseparable mixture (14%) of the 6α-hydroxy-7α-m-chlorobenzoate (117) (44%) and the 7α-hydroxy-6α-m-chlorobenzoate (118) (56%), the 6α,7α-diol (119) (15%), and the 6α,7β-diol (120) (8%). The structures of (117)-(120) were assigned on the basis of their ¹H n.m.r. spectra. The chemical shifts and coupling constants for (117)-(120) are shown in Table 2.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Shift</th>
<th>Coupling (Hz)</th>
<th>Assignment.</th>
</tr>
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<td>H7</td>
<td>J₅,₆</td>
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<tr>
<td>(120)</td>
<td>4.29</td>
<td>4.72</td>
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</table>

Table 2.

The H6 signals for (117) and (118) appeared as doublets of doublets at δH₄.82 (J 9.7, 3.7 Hz) and δH₆.43 (J 8.4, 4.2 Hz) respectively, while the H7 signals appeared as doublets at δH₆.54 (J 3.7 Hz) and δH₅.17 (J 4.2 Hz) respectively. The values for J₅,₆ and J₆,₇ indicated that in both compounds H6 was axial (β) and H7 equatorial (β). On the basis of the chemical shifts the m-chlorobenzoate was assigned to C7 in (117) and to C6 in (118). Comparison of the integrals for the H6 and H7 signals showed the mixture to consist of 44% of (117) and 56% of (118). The H6 signal for (120) appeared as a doublet of doublets (J 11.0, 9.0 Hz) at δH₄.29, the large values for J₅,₆ and J₆,₇ indicating that H6 and H7 were in the axial β and α positions respectively. The H6 signal for (119) appeared as a triplet of doublets (J 8.6, 4.5, 3.6 Hz) at δH₄.62, while H7 appeared as a doublet (J 3.6 Hz) at δH₄.90. The large J₅,₆ (8.6 Hz) showed that H6 was axial (β), while the small J₆,₇ (3.6 Hz) showed that H7 was equatorial (β). The third coupling of 4.5 Hz was to the C6-hydroxyl proton at δH₃.42. The smaller J₅,₆ in (119) than (120) suggests that the B-ring in the former is in a less chair-like conformation, thus permitting hydrogen-bonding between the hydroxyl groups. As the observation of
coupling between H6 and a C6-hydroxyl proton shows that the latter cannot be rotating freely about the oxygen it is proposed that (119) exists in the conformation shown:

![Chemical structure](image)

Also isolated was an oil tentatively identified as the 6-ketone (121) (4%). The fragment of highest mass was at m/z 406 corresponding to C<sub>25</sub>H<sub>26</sub>O<sub>5</sub>. There was a single broad carbonyl stretching band at 1720 cm<sup>-1</sup> in the i.r. spectrum. The 6-ketone (122)<sup>76</sup> shows bands at 1720 (ester) and 1700 cm<sup>-1</sup> (ketone). The H20 and H18 signals in the <sup>1</sup>H n.m.r. spectrum appeared at δ<sub>H</sub> 1.34 and δ<sub>H</sub> 1.41; the corresponding signals for (122) appear at δ<sub>H</sub> 1.30 and δ<sub>H</sub> 1.34.

The ketones (94) and (121) presumably arise from an acid-catalysed rearrangement of the initial epoxide:

![Chemical structures](image)

The formation of glycols and glycol monoesters during the epoxidation of alkenes can often be prevented by buffering of the solution with sodium carbonate or
sodium dihydrogen phosphate.\textsuperscript{77} The use of buffers in the epoxidation of (30) and (108) was not investigated however, as the major products had the desired 6α-hydroxy group.

Comparison of the products from epoxidation of the 12-methoxy Δ\textsuperscript{6}-alkene (24) in various solvents suggests that the formation of ring-opened products is dependent on the solvent used. Epoxidation of (24) in ether\textsuperscript{33} gives the α-epoxide (25) (87%), while epoxidation of (24) in chloroform and treatment of the crude product with aqueous acid gives the 6-ketone (122) (86%).\textsuperscript{76} Epoxidation of (24) in dichloromethane\textsuperscript{30} however, gives a mixture of seven products including hydroxy m-chlorobenzoates, which have not been obtained in pure form.

Hydrogenation of the 12-benzyloxy 6α-hydroxy compounds (110)-(112) gave the desired 6α,12-dihydroxy compound (26) in yields of 80%, 74%, and 83% respectively. The H6 signal in the \textsuperscript{1}H n.m.r. spectrum of (26) appeared as a triplet of doublets (J 9.0, 9.0, 5.2 Hz) at \(\delta_H\) 4.62. The large value for \(J_{5,6}\) showed that H6 was axial (β). Hydrogenation of the 12-benzoyloxy 6α,7α-diol (119) also gave (26) (77%). Ozonolysis of (26) and reduction of the crude ozonide with sodium borohydride in ethanol gave an oil which was shown to be a complex mixture by t.l.c. analysis and was not further investigated.

As an alternative route for the introduction of a 6-hydroxyl group, the hydroboration of the 12-benzyloxy Δ\textsuperscript{6}-alkene (30) was investigated. Hydroboration of (30) with borane-dimethyl sulfide afforded the alkane (101) (3%), the 7α-alcohol (123) (32%), and two 6α-hydroxy products, the 19-aldehyde (124) (27%) and the 19-alcohol (125) (10%). The structures of (123)-(125) were assigned on the basis of their \textsuperscript{1}H n.m.r. spectra. The H7 signal for (123) was a broad singlet at \(\delta_H\)4.81 with a half-width of 8 Hz characteristic of an equatorial 7β proton. In contrast to the equatorial 7β-alcohol (103), the molecular ion for (123) could not be detected in the mass spectrum, the fragment of highest mass being at M-18 corresponding to the alkene (30). Again, in
contrast to (103), the axial alcohol (123) underwent partial dehydration on attempted purification by sublimation (Kugelrohr) so that a correct analysis could not be obtained. These results suggest that elimination of the axial hydroxyl group proceeds more readily than for the corresponding equatorial hydroxyl group. That the alcohol was at C7 was proved by hydrogenation of (123) with ammonium formate and palladium on charcoal\(^\text{78}\) which gave methyl podocarpate (10) (80%). The C7 signal for (123) appeared at \(\delta_\text{C}=67.9\) compared with \(\delta_\text{C}=71.1\) for the C7 signal of the 7β-alcohol (103).

In the \(^1\text{H}\) n.m.r. spectra of (124) and (125) H6 appeared as triplets of doublets at \(\delta_\text{H}=4.69\) \((J=8.5, 6.1, 5.7 \text{ Hz})\) and \(\delta_\text{H}=4.51\) \((J=9.8, 9.4, 5.8 \text{ Hz})\) respectively. The values of 8.5 and 9.8 Hz for the coupling between H6 and the axial H5 indicate that H6 is axial (β). The smaller couplings between H6 and the axial H5 and H7\(\alpha\) protons in (124) than (125) indicates that the B-ring is in a less chair-like conformation in the former compound. Reduction of (124) with sodium borohydride gave (125) (80%).

That the alcohols in (123)-(125) are α indicates that the borane has attacked as expected from the less-hindered α-face. Brown and Sharp\(^\text{79}\) have suggested that the formation of ethylbenzenes from the hydroboration of styrenes is due solely to the hydrolysis of the α-boranes, in which case the product ratio above indicates a 37:35 preference for attack by boron at C6. By comparison, hydroboration of the abietatetraene (21)\(^\text{32}\) gives a 55:45 ratio of C7:C6 attack. The difference in the ratios of β (C6) to α (C7) attack can be accounted for by the different substitution patterns on the aromatic rings of (21) and (30). Studies of the hydroboration of substituted styrenes\(^\text{79,80}\) have shown a correlation between the Hammett \(\sigma^+\) values for the substituents and the ratio of β to α attack. Thus \(p\)-methoxystyrene \((\sigma^+ = -0.78)\) gives a ratio of 94:5 for \(\beta:\alpha\) attack, while \(m\)-methoxystyrene \((\sigma^+ = 0.05)\) gives a ratio of only 81:19. As (30) has a \(p\)-benzyloxy group which has similar electronic properties to a \(p\)-methoxy group \((\sigma^+ = -0.78)\), and (21) has a \(m\)-isopropyl group \((\sigma^+ = -0.07)\) one would expect a higher ratio of β to α attack for hydroboration of (30). The relatively high amounts of attack at the
α-carbon (C7) of both (21) and (30) are due to steric hindrance at C6.

The reaction of (30) with catecholborane\(^8\) was also investigated as the bulky substituent should preclude reduction of the C19 ester. However, no reaction was observed, even in the presence of Wilkinson’s catalyst, which has been shown to catalyse hydroboration of alkenes with this reagent.\(^8\) Presumably C6 is too hindered and C7 too unfavourable electronically to permit attack by this reagent.

Acetylation of the 7α-alcohol (123) on a waterbath gave a mixture of 7-acetates (105) (90%), which by \(^1\)H n.m.r. analysis was identical to the mixture obtained from acetylation of the 7β-alcohol (103) under the same conditions. That both isomers gave the same product mixture suggested that both reactions proceeded via a common intermediate. To account for the observed product ratio, and for the formation of the alkene (30) from one experiment in which a large excess of pyridine was used, it is proposed that the acetylations proceed via the 7-cation with preferential attack by acetic acid from the less-hindered α-face, with loss of a proton becoming competitive when an excess of pyridine is used.

The C12 benzyl ether is an activating, \(o,p\)-directing group, and thus there is a high electron density at C8 which can stabilise a C7 cation. By contrast, a C12 benzoate ester is a deactivating, \(m\)-directing group, and thus there is a low electron
density at C8 which cannot stabilise a C7 cation, and hence acetylation of the 12-benzyloxy 7β-alcohol (95) under these conditions gives only the 7β-acetate (109). A C12 methyl ether is also an activating, o,p-directing group, and it was found that treatment of the 12-methoxy 7β-alcohol (12) with acetic anhydride and an excess of pyridine on a waterbath gave a mixture which by 1H n.m.r. analysis contained the alkene (24)25 (40%), the 7β-acetate (100)25 (27%), and the 7α-acetate (126) (33%). The ratio of β:α-acetates (9:11) was identical to that observed from acetylation of both (103) and (123) under these conditions.

By contrast, as reported above, treatment of (12) with acetic anhydride and pyridine at room temperature gave only the 7β-acetate (100) (95%), which suggests that the reaction requires heating to overcome the energy barrier for formation of the cation. Acetylation of the 12-benzyloxy 7β-alcohol (103) at room temperature gave the 7β-acetate (105b) (72%), while acetylation of the 7α-alcohol (123) gave a mixture (105) which was identical to that obtained from acetylation at waterbath temperatures (60-80°). This indicates that there is a smaller energy barrier for cleavage of the axial C7-O7α bond than for cleavage of the equatorial C7-O7β bond.
CHAPTER TWO

This chapter concerns an investigation into the synthesis and ozonolysis of 11- and 14-hydroxy-podocarpatrienes as a route to the synthesis of drimanes from podocarpic acid (9). The synthesis and cleavage of a 12,13-catechol in this series is also investigated.

2.1 Synthesis of a confertifolin congener.

Akita and Oishi\(^\text{19}\) reported that ozonolysis of the 14-hydroxydehydroabietanes (62) and (71) and subsequent reduction with borohydride gave (+)-confertifolin (6) in 46% and 11% yields respectively. As (6) has been converted to (-)-warburganal (1)\(^\text{17}\) this completed a formal synthesis of (1) from dehydroabietic acid (127).

As part of the current work, the synthesis and ozonolysis of a 14-hydroxypodocarpatriene was investigated. As the direct introduction of a substituent at C14 is extremely difficult, it was necessary to introduce a group at C13 which could direct substitution to C14. Frémy's salt (potassium nitrosodisulphonate)\(^\text{83}\) oxidises phenols and anilines, a p-quinone being the usual product, with an o-quinone being formed if the para-position is blocked. Oxidation of a 12-substituted 13-hydroxy or 13-amino compound and reduction of the resulting o-quinone would thus give a 13,14-dihydroxy compound.

Friedel-Crafts acylation of methyl 12-methoxypodocarpate (11) with acetyl chloride and aluminium trichloride by the method of Matsumoto \textit{et al.}\(^\text{84}\) gave the 13-acetyl compound (128) (81%). Baeyer-Villiger oxidation with \textit{m}-chloroperbenzoic acid gave the 13-acetate (129) (58%), which was hydrolysed with methanolic sodium hydroxide to the 13-hydroxy compound (130) (86%, 41% from (11)). Oxidation of (130) with Frémy's salt in aqueous acetone gave the expected o-quinone (131) (80%).
The purple quinone (131) was red in solution with absorbances in the u.v. and i.r. spectra, and a strong M+2 peak in the mass spectrum characteristic of an o-quinone.\textsuperscript{86,87}

Nitration of (11) with copper(II) nitrate in acetic anhydride\textsuperscript{88} gave a mixture of the 11-nitro (132) (30%), 13-nitro (133) (38%), and 11,13-dinitro (134) (1%) compounds. The 11-nitro compound (132) was a crystalline solid with a sharp melting point, while the 13-nitro compound (133) was a glass with a broad melting point. Davis \textit{et al.}\textsuperscript{89} reported that nitration of methyl 12-methoxypodocarpa-8,11,13-triene (135) with this reagent gave the crystalline 11-nitro (136) (29%) and glassy 13-nitro (137) (61%) compounds. The 13-nitro compound (133) was also obtained in 96% yield from methylation of the 13-nitro phenol (138).\textsuperscript{90} Reduction of (133) with hydrazine hydrate and 10% palladium on charcoal\textsuperscript{91} gave the 13-amine (139) (79%). The amine (139) could also be obtained in 89% yield from reduction of (133) with tin(II) chloride, but material produced by this method was coloured and of lower melting point, presumably due to contamination with other reduction products.

Oxidation of the 13-amine (139) with Frémy's salt was found to be less efficient than for the 13-hydroxy compound (130). The order of addition was found to be important with the optimal yield of quinone (131) (54%) being obtained by the dropwise addition of a solution of the amine (139) to a stirred solution of oxidant. Addition of oxidant to the amine (139) gave a complex mixture from which (131) was obtained in a best yield of 25%; material is presumably lost in a reaction between the quinone (131) and unreacted amine (139). Diazotization of the amine (139) by the method of Mori and Matsui\textsuperscript{92} gave a low (20%) yield of the 13-hydroxy compound (130).

Reduction of the quinone (131) by hydrogenation gave the desired 13,14-dihydroxy compound (140) (100%) which was characterised as its diacetate (141). Ozonolysis of the catechol (140) and reduction of the crude ozonide with sodium borohydride gave a mixture from which the desired confertifolin 19-carbethoxy
congener (31) was isolated in 8% yield. This compound unlike the oily 18-carbomethoxy congener (142) was a crystalline solid, possessing similar physical and spectral properties to those of confertifolin (6). The lactone methylene protons (H11) appeared as an 8-line multiplet at $\delta_H 4.66$ ($J 16.9, 3.4, 1.6$ Hz), and a 6-line multiplet at $\delta_H 4.72$ ($J 16.9, 2.8, 2.8$ Hz). The corresponding protons for (6) appear as an 8-line multiplet at $\delta_H 4.65$ ($J 17.5, 3.5, 2$ Hz) and a 6-line multiplet at $\delta_H 4.72$ ($J 17.5, 3$, 3 Hz). From comparison of the coupling constants observed for (31) with those calculated for (6) ($J_{11\alpha,7\alpha} 5.0$, $J_{11\alpha,7\beta} 1.4$, $J_{11\beta,7\alpha} 3.9$, $J_{11\beta,7\beta} 2.7$ Hz) the more upfield multiplet was assigned as H11α.

### 2.2 Synthesis of a winterin congener.

Pelletier and Ohtsuka reported that ozonolysis of the 11,14-dihydroxy compound (75) and subsequent Jones oxidation gave (+)-winterin (8) (30%) which can be converted into (-)-warburganal (1). Oxidation of the 11-amine (143) would be expected to give the $p$-quinone (35) which could be reduced to a 11,14-dihydroxy compound.

Reduction of the 11-nitro compound (132) with hydrazine hydrate and palladium on charcoal gave the 11-amine (143) (82%). Reduction of (132) could not be obtained with tin(II) chloride, but hydrogenation in methanol containing a trace of hydrochloric acid gave (143) (79%). This latter material was coloured and possessed a lower melting point than that prepared with hydrazine hydrate and palladium.

The 11-amine (143) was somewhat resistant to oxidation with Frémy's salt, presumably due to steric congestion at C11 by the adjacent angular methyl group. Nearly half of the starting material was recovered with the product of oxidation being the $p$-quinone monoimine (144) (27%) instead of the expected quinone (35). This is unusual as normally the imine formed as the initial oxidation product is hydrolysed in the
acidic reaction medium. The isolation of (144) is presumably due to the steric congestion at C11 slowing hydrolysis and to its insolubility in the reaction mixture. The imine (144) showed strong C=O and C=N stretches at 1645 and 1625 cm⁻¹ in the i.r. and absorbance maxima at 276 and 335 nm in the u.v. spectrum. Hydrolysis of (144) with aqueous acid gave the yellow p-quinone (35)³⁸ (75%). Treatment of (143) with nitrous acid gave a complex mixture from which only (11) (16%) could be identified.

Given the low (4%) yield of (35) from (11) by the above route, the oxidation of (11) to (35) with peracid was investigated. The oxidation of phenols and their methyl ethers with peracids has been found to give a variety of oxygenated products. Phenols with a free para-position are oxidised to p-quinones.⁹⁶-⁸ If this position is blocked then either oxidation occurs here to give a quinol,⁹⁹ or hydroxylation occurs at an ortho-position followed by further oxidation with ring cleavage to give a muconic acid.¹⁰⁰-² Ferruginol (32) undergoes an unusual 2,5-oxidation with peracetic acid (in this work the term peracetic acid is used to refer to the mixture of acetic acid and hydrogen peroxide commonly called by this name¹⁰³) to give rolleyanone (145) in low yield.¹⁰⁴ Phenol methyl ethers can be hydroxylated in the ipso- and para-positions with displacement of the methoxy group to give a quinol, or if the 2 and 5 positions are free, oxidised to give a methoxy p-quinone.¹⁰⁵-⁶

Davis and co-workers³⁸,¹⁰⁷-⁸ within this department have investigated the neutral products from the peracetic acid oxidation of some 12-hydroxy and 12-methoxy podocarpatrienes. Oxidation of 12-hydroxypodocarpa-8,11,13-triene (53) gave a complex mixture whose major components were the acetate (146) (10%) and the 8β-hydroxydienone (147) (19%). The 8-hydroxy group in (147) was assigned a β-configuration as the signal corresponding to the protons on the angular methyl group (H₂₀) in the ¹H n.m.r. spectrum of (147) was shifted 0.2 ppm downfield of the corresponding signal for (53) due to a 1,3-diaxial interaction between the methyl and hydroxyl groups, which would not be seen for the 8α-epimer. The methyl ether (135)
was less reactive with 23% of starting material being recovered after 22h, and the major products being the quinol (147) (17%) and quinone (148) (7%). Oxidation with monoperphthalic acid was much slower, with 50% of (135) being recovered after 3 months, with both (147) and (148) being obtained in 24% yield. The 19-alcohol (149) was more reactive, treatment with peracetic acid for 22h giving the 19-acetate (150) (27%), 8β-hydroxydienone (151) (24%), and quinone (152) (14%). Methyl 13-ethyl-12-methoxypodocarpa-8,11,13-trien-19-oate (153) was very unreactive towards peracetic acid due to its low solubility in the reaction medium, 68% of starting material being recovered with an 8% yield of the 8β-hydroxydienone (154). The 19-alcohol (155) was more reactive giving the acetate (156) (28%), 8β-hydroxydienone (157) (26%), and quinone (158) (17%). Methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (11) was also somewhat unreactive, with 26% of starting material being recovered after 6 days, with the quinone (35) being obtained in 9% yield, and an 8-hydroxydienone (159), of undetermined stereochemistry, in 14% yield. The quinol (159) has also been obtained among the products from the oxidation of methyl podocarpate (10) with thallium(III) perchlorate.109

In the current work, oxidation of (11) with peracetic acid for 19h gave (35) (7%) and (159) (10%) with 5% recovery of (11). Oxidation of (11) with m-chloroperbenzoic acid in dichloromethane for 3 days gave in addition to unreacted (11) (1.6%), a number of oxygenated products including (35) (12%) and (159) (6%). The quinol (159) was assigned the 8β-hydroxy structure on the basis of the angular methyl group signal in the 1H n.m.r. spectrum. This was shifted 0.3 ppm downfield from that for (11) indicating a 1,3 -dixial relationship between the angular methyl and hydroxyl groups. In contrast to the majority of derivatives of (+)-podocarpic acid (9), (159) was laevorotatory, as are other quinols from oxidation of podocarpatrienes.107-8 Also isolated were the muconic acid anhydrides (160) (0.8%), and (161) (8%), the muconate half-ester (162) (4%), and a polar yellow compound (163) (0.6%). Unlike the crystalline (161), (160) was an
unstable oil which decomposed on attempted purification by sublimation (Kugelrohr). The second ester group in (162) was assigned to C12 on the basis of a COLOC experiment. This showed correlations (i.e. long-range couplings) between H13 (δH 6.4) and the methyl (δC 52.1) and carbonyl (δC 166.0) carbons of a methyl ester group. Also observed were correlations between C13 and H14, and between C4 and H5. An unusual feature of the 1H n.m.r. spectrum of (162) was that the more downfield of the H6 and H7 signals were those of the equatorial H6α and axial H7α protons. Study of the 1H n.m.r. spectra of podocarpatrienes reported in the current work, and by other workers28,110-112 indicates that usually the β-proton signals are downfield of the corresponding α-proton signals. Study of models shows that in the s-trans conformer of (162), the lone pairs on the C12 carbonyl oxygen can shield the H6α and H7α-protons. This would be expected to be the preferred conformer as in the s-cis conformer there is considerable steric congestion between the groups at C11 and C12.

The polar yellow compound was assigned the heterocyclic structure (163). The proposed structure was supported by the following spectral evidence. The fragment of highest mass appeared at m/z 318.1476 corresponding to a formula of C18H22O5, which was supported by the presence of 18 signals in the 13C n.m.r. spectrum, and an integral value for the 1H n.m.r. spectrum corresponding to 22H. Bands at 1670 and 1645 cm⁻¹ in the i.r. spectrum, and absorbance maxima at 245 and 363 nm in the u.v. spectrum indicated the presence of a quinone group, which was confirmed by the presence of signals at δC 182.0 and δC 187.0 in the 13C n.m.r spectrum. The presence of a tertiary ether group was shown by the C10 signal at δC 84.6. In the 13C n.m.r. spectrum of the similar heterocyclic compound (164), obtained by Ryan in 15% yield from the oxidation of totarol (62) with benzeneseleninic anhydride, C10 appears at δC 81.3. As the two vinyl proton signals are not coupled to each other, and as geometric constraints require that the ether linkage can only be between C10 and C9, the quinone carbonyls must be at C12 and C13.
These compounds arise from an initial electrophilic hydroxylation of (11). Hydroxylation at C13 leads to (160) and (163) (Scheme 22).

Scheme 22.

Hydroxylation at C11 leads to compounds (158), (161), and (162) (Scheme 23).

Scheme 23.

Hydroxylation at C8 leads to compound (159) (Scheme 24).
Study of models shows that the peracid carbonyl oxygen can interact with C12 concertedly with hydroxylation at C8 as shown in Scheme 24 above, but not with the methoxyl group, indicating that the formation of (159) must be a two-step process. That hydroxylation at C8 occurs from the sterically more congested β-face can be explained by consideration of the B-ring conformation in the transition state. Examination of models shows that for attack from the β-face this ring adopts a chair-like conformation, while for α-attack it it adopts the energetically less favourable boat conformer.

A similar route to that proposed for the formation of (160)-(162) has been proposed by Fernholz\(^{102}\) for the formation of a muconate monomethyl ester (165) from the oxidation of 2-methoxynaphthalene with perbenzoic acid in benzene. That this reaction involved an anhydride intermediate was shown by further experiments. Oxidation with aqueous peracetic acid gave the acid (47) while oxidation with perbenzoic acid in benzene-ethanol gave the monoethyl ester (166). The monomethyl ester (165) was also obtained from oxidation of 1-naphthol with perbenzoic acid in benzene-methanol.

Böeseken\(^{114}\) had previously obtained the acid (47) from oxidation of β-naphthoquinone (167) with peracetic acid, while Karrer and Schneider\(^{115}\) obtained the anhydride (168) from oxidation of (167) with perbenzoic acid in chloroform. In further papers Karrer\(^{116}\) showed that oxidation of other α-diketones with peracids gave anhydrides.

Some evidence for this mechanism was obtained in the present work. A trace of a compound of similar \(R_f\) to the quinones (35) and (131) and with the red colour typical
of an \(o\)-quinone could be detected in the reaction mixture by t.l.c. analysis, but could not be isolated. Further, oxidation of the 13-hydroxy compound (129) with \(m\)-chloroperbenzoic acid for 24 h gave the anhydride (160) in 22% yield with 25% recovery of starting material, supporting the intermediacy of (129) in the formation of (160).

The ratio of products (35), (161) and (162), to (160) and (163) indicates that the initial hydroxylation occurs preferentially at C11, rather than at C13 which is the usually preferred site for reaction on the C ring.

The mechanism of the oxidation of aromatic systems with peracids has not been fully elucidated. Friess et al.\(^{105}\) showed that the oxidation of 1,3,5-trimethoxybenzene to 2,6-dimethoxybenzoquinone with perbenzoic acid was first order in both substrate and oxidant which led them to propose the following mechanism:

\[
\begin{align*}
\text{MeO} & \quad \text{OH}^- \\
\text{MeO} & \quad \text{MeO} \\
\text{slow} & \quad \text{MeO} \\
\text{MeO} & \quad \text{OH} \\
\end{align*}
\]

Ogata et al.\(^{117}\) found that the hydroxylation of anisole with monoperphosphoric acid (\(H_3PO_5\)) was first order in anisole and second order in oxidant. The oxidation of phenol was second order in both substrate and oxidant, becoming first order in phenol upon addition of catalytic sulphuric acid. They explained these results as being due to a fast acid-catalysed dimerisation of the oxidant with the observed second-order kinetics for phenol being due to the formation of hydrogen-bonded pairs of phenol molecules. The ratio of \textit{ortho}- to \textit{para}-substitution was found to be higher for phenol (5:1), than for anisole (3.5:1) or toluene (2:1). A similar preference for \textit{ortho}-substitution has been observed for the hydroxylation of anisole and diphenyl ether with trifluoroperacetic acid,\(^{118}\) and for hydroxylation of phenol with peracetic acid.\(^{117,119}\) As the rates of oxidation of catechol and hydroquinone with monoperphosphoric acid were found to be equal, these ratios could not be due to more rapid further oxidation of the \(p\)-substituted products, and it was proposed that they were due to hydrogen-bonding
between the aromatic substituent and the peracid directing the oxidant to the ortho-position.

The exact nature of the oxygenating species in these oxidations is unknown. There is evidence that the initial reaction is an electrophilic aromatic hydroxylation with the peracid acting as an equivalent for $\text{OH}^+$. For example, treatment of mesitylene with trifluoroperacetic acid at $0^\circ$ for 24h gives 2,4,6-trimethylphenol (mesitol) (17%) and 2,3,5-trimethylbenzoquinone (3%) with 75% recovery of starting material.\textsuperscript{99} This reaction has been found to be greatly accelerated by boron trifluoride etherate with reaction being almost instantaneous at -40$^\circ$ and the yield of mesitol being nearly quantitative.\textsuperscript{120} The marked increase in rate is presumably due to complexation of the Lewis acid to the carbonyl group of the oxidant causing bond polarisation, thus enhancing the electrophilicity of the hydroxyl oxygen. The greater susceptibility of the phenols produced to substitution and/or oxidation than the starting materials, limits the utility of this reaction for synthesising phenols.\textsuperscript{121}

There is evidence for the intermediacy of arene oxides in these oxidations. For example, oxidation of 4-deuterotoluene with trifluoroperacetic acid at $0^\circ$ for 5 h gives 3-deutero-$p$-cresol with 68% retention of the label.\textsuperscript{122} The following mechanism has been proposed to explain this: Supporting this, treatment of the proposed epoxide intermediate (A) with dilute acid gives 3-deutero-$p$-cresol with 38-75% retention of the label. A similar 1,2-deuterium shift known as the NIH shift\textsuperscript{123} has been observed in the enzymatic hydroxylation of aromatic compounds, for which arene oxide intermediates have also been proposed.\textsuperscript{124-5} By contrast, no retention of label has been observed from hydroxylation of aromatic systems with other non-enzymatic reagents, or from other
aromatic electrophilic substitutions. \textsuperscript{126} Arene oxides may also be involved in the alkyl migrations that have been observed during some peracid oxidations. \textsuperscript{99,121}

In light of this evidence the intermediate in the hydroxylation is best represented as below:

The ratio of products (35), (161) and (162) to (160) and (163) indicates that the initial electrophilic attack occurs preferentially at C11 rather than the sterically less congested C13, which is the preferred site for other electrophilic substitutions on podocarpane. The degree of preference for C13 attack increases with the size of the electrophile as is shown by comparison of the products of halogenation of methyl podocarpate (10). Iodination of (10)\textsuperscript{92} gives only the 13-iodo compound (169), while bromination\textsuperscript{127} gives a mixture of the 13-bromo (170) (81\%) and 11,13-dibromo (171) (13\%) compounds. Recently within this department, Metzler\textsuperscript{34} has found that chlorination of (10) gives a mixture of the 11-chloro (172) (14\%), 13-chloro (173) (14\%), 11,13-dichloro (174) (52\%), and 8\beta-chloro (175) (7\%) compounds. The chlorine in (175) was assigned to the 8\beta position on the basis of a downfield shift of the H2O signal in the \textsuperscript{1}H n.m.r. spectrum similar to that observed for (159). These results and those for nitration and acetylation reported in the current work suggest that though C11 is an electronically favourable site for electrophilic attack, the steric hindrance caused by the adjacent angular methyl group, and to a lesser extent by the A ring, cause C13 to be the favoured site, especially for large electrophiles for whom the steric congestion involved in attack at C11 will be greater.
To account for the preference for C11 attack observed in the reaction with peracid it is suggested that the intermediate from electrophilic attack at C11, whose major resonance contributor is (A), is of lower energy than that for C13 attack whose major contributor is (B).

With relatively reactive electrophiles, such as NO$_2^+$ there is an early transition state which more closely resembles the starting materials than the intermediate σ-complex, so that the relative energies of (A) and (B) are of less importance in determining the reaction site than the relative steric accessibility of the two sites. Peracid, as is shown by the slow reaction rate, is a relatively unreactive electrophile and so it has a late transition state which more closely resembles the intermediate σ-complex with substantial charge on the ring, so that the relative energies of (A) and (B) become the decisive factor in determining the site of substitution. Some evidence supporting this proposal comes from studies on the reactions of 5,6,7,8-tetrahydro-2-naphthol (176). Electrophilic substitution of (176) occurs preferentially at C5$^\text{51}$ (nitration is an exception$^{128}$) while for 5-hydroxyindane (177) it occurs at C6.$^\text{51}$ This led Mills and Nixon$^\text{129}$ to propose that in benzene rings fused to cycloalkyl rings bond localisation occurs such that the resonance form with a double bond as a ring junction is favoured for a 6-membered alkyl ring and disfavoured for smaller rings. Since then evidence for $^\text{130}$ and against$^\text{131}$ this hypothesis has been presented. Calculations by Berthier and Pullmann$^\text{132}$ indicate that in (176) the electron density at C5 is greater than at C7 making the former the preferred site for electrophilic attack. Waters$^\text{133}$ has proposed that the substitution patterns seen in the reactions of (176) and (177) are due to bond localisation in the intermediate σ-complexes, i.e. (C) and (E) are of lower
energy than (D) and (F) respectively. Calculations by Longuet-Higgins and Coulson\textsuperscript{134} show that (E) is of lower energy than (F).

Reduction of the quinone (35) gave the hydroquinone (178) which was characterised as its diacetate (179). Dimethylaminopyridine had to be used as co-catalyst to achieve complete acetylation; presumably steric congestion at C11 makes this site resistant to acetylation. Burkinshaw and Davis\textsuperscript{107} converted the quinone (148) to the diacetate (180) by reductive acetylation with zinc and acetic acid. However, treatment of (35) with this reagent gave only the diol (178) (100\%). Ozonolysis of (178) gave the desired winterin congener (36) (26\%). Unlike the synthesis of (8) from (75),\textsuperscript{22} Jones oxidation of the crude ozonide was not required.

Treatment of (36) with methanol in the presence of the acidic catalyst amberlyst-15 gave a mixture of the 12-methyl (181) (66\%) and 11-methyl (182) (33\%) esters. No evidence of double bond migration was seen. Reduction of (36) with lithium aluminium hydride gave the isodrimenin congener (34) (63\%). Reduction with Red-Al was slower, \textsuperscript{1}H n.m.r. analysis showing the presence of only 50\% of (34) after 1 h, as well as the diol (183) (5\%). The diol (184), a congener of (183) has been converted into warburganal (1).\textsuperscript{17-18}

2.3 Synthesis of an isodrimenin congener.

Ozonolysis of the anhydride (161) and reduction of the crude ozonide with sodium borohydride gave the isodrimenin congener (34) (46\%). The lactone methylene protons (H12) appeared as a singlet at $\delta_H 4.57$ in the 60 MHz spectrum, which at 400 MHz was resolved as an AB quartet at $\delta_H 4.54, 4.61 (J 17 \text{ Hz})$. The corresponding
protons in isodrimenin (7) appear as a singlet at $\delta_H 4.55$ at 60 MHz,\textsuperscript{19} while in 6β-hydroxyisodrimenin (107)\textsuperscript{70} they appear as a singlet at $\delta_H 4.63$ in CDCl$_3$ and as an AB quartet at $\delta_H 4.46$, 4.68 ($J$ 17 Hz) in $d_5$-pyridine. Ozonolysis of the half-ester (162) and subsequent reduction with borohydride gave a complex mixture from which (34) was isolated in 8% yield.

Akita and Oishi\textsuperscript{19} reported that ozonolysis of an 11,12-dihydroxyabietatriene (73) and subsequent reduction with sodium borohydride gave isodrimenin (7) (26%). As the overall yield of (34) from methyl 12-methoxypodocarpate (11) by the above route was only 3%, the ozonolysis of an 11,12-dihydroxypodocarpatriene as an alternative route to (34) was investigated.

Friedel-Crafts acetylation of (11) and demethylation with aluminium trichloride in a one-pot process gave the 12-hydroxy-13-acetyl compound (185) (78%).\textsuperscript{90} Nitration with copper(II) nitrate and acetic anhydride\textsuperscript{88} gave the 11-nitro compound (186) (44%). Hydrogenation gave an oil which coloured rapidly in air. The absence of the NO$_2$ stretching band at 1535 cm$^{-1}$ in the i.r. spectrum indicated that this group had been completely reduced. The retention of the aryl ketone band at 1650 cm$^{-1}$ and of the acetyl proton signal at $\delta_H 2.53$ in the $^1$H n.m.r. spectrum indicated the partial survival of the acetyl group. Comparison of the integrals of the signal at $\delta_H 2.53$ and of the methyl ester signal at $\delta_H 3.63$, indicated a 70% retention of this group. On the basis of these spectra the product was identified as a mixture of methyl 13-acetyl-11-amino-12-hydroxypodocarpa-8,11,13-trien-19-oate (187) (70%), and methyl 11-amino-12-hydroxy-13-(1'-hydroxyethyl)-podocarpa-8,11,13-trien-19-oate (188) (30%). Oxidation of this mixture with iron(III) chloride gave an orange oil which was a complex mixture by t.l.c. analysis. Attempts to nitrate the 12-methoxy-13-acetyl compound (128) were unsuccessful.

As nitration and then reduction had proved to be an unsatisfactory route, the reduction of the acetyl group and subsequent nitration was investigated. Hydrogen-
ation of (185) was slow with 21% of starting material being recovered after 3 h, along with the desired 13-ethyl compound (189) (40%), and the 13-hydroxyethyl compound (190) (38%). A satisfactory analysis for (190) could not be obtained as it decomposed on attempted purification by sublimation (Kugelrohr). An accurate mass could not be obtained for the molecular ion, owing to its low intensity, but could be obtained for the fragment ion at M-18 produced by dehydration of the hydroxyethyl group. Clemmensen reduction of (185) gave (189) (91%). Similarly, hydrogenation of (128) gave a mixture of the 13-ethyl (153)\(^{107}\) (75%) and 13-hydroxyethyl (191)\(^{135}\) (10%) compounds, while Clemmensen reduction gave (153) (80%). The melting point of (191) was 100-105° as compared to the reported value of 150°,\(^{135}\) but the \([\alpha]_D\) and i.r. spectrum were identical. The \(^1\)H n.m.r. and mass spectra were also consistent with this structure.

Nitration of (189) with nitric acid and acetic anhydride gave the 11-nitro compound (192) (57%), which was reduced with hydrazine hydrate and palladium on charcoal\(^{91}\) to the unstable aminophenol (193) (44%). Oxidation of (193) with sodium periodate by the method of Stubbenrauch and Knuppen\(^{136}\) gave a complex mixture which was not investigated further. Nitration of (153) with nitric acid and acetic anhydride gave a mixture of the 12-methoxy-11-nitro (194) (10%) and 12-hydroxy-11-nitro (192) (46%) compounds. A similar partial demethylation was reported by Tahara et al.\(^{137}\) for the nitration of a 12-methoxydehydroabietane (195) with this reagent. They found that the amount of demethylation depended on the density of the nitric acid used, with less occurring with the use of denser (i.e. more concentrated) acid.

Next the oxidation of (189) with benzoyl peroxide was investigated.\(^{37}\) The oxidation of phenols with free \(o\)-positions with diacyl peroxides usually gives \(o\)-acyloxy phenols with the acyloxy group at either the original hydroxyl position or the \(o\)-position. Other products which have been obtained are \(o\)- or \(p\)-acyloxy dienones and products of aromatic coupling-usually at the \(p\)-position. Matsumoto et al.\(^{36}\) as part of a
synthesis of taxodione (196) oxidised the 12-hydroxydehydroabietate (197) with benzoyl peroxide to give the 12-benzoyloxy-11-hydroxy derivative (198) (61%), and the benzoyloxydienones (199) (2%), (200) (6%), and (201) (11%). Similarly oxidation of ferruginol (32) gave (33) (44%), (202) (2%), (203) (3%), and (204) (6%).

To account for the formation of acyloxy phenols and acyloxydienones in these reactions Barton et al.\textsuperscript{138} have proposed the following mechanism:

Oxidation of the 12-hydroxy-13-ethyl compound (189) gave the 12-benzoyloxy-11-hydroxy compound (205) (33%). This compound was assigned as the 12-benzoate on the basis of the C14 signal in the $^{13}$C n.m.r. spectrum, which appeared at $\delta_C$121.1 as compared to predicted values of $\delta_C$122.1 for the 12-benzoate and $\delta_C$124.5 for the 11-benzoate, calculated from the observed value of $\delta_C$129.5 for the C14 signal for (189) using standard additivity values. The byproduct was a yellow glass which was a complex mixture by $^1$H n.m.r. analysis. From one experiment in which only a slight
excess of oxidant was used the byproduct was a white solid with an ion of highest mass in the mass spectrum at m/z 750 corresponding to \( \text{C}_{47}\text{H}_{58}\text{O}_8 \), indicating a dimeric structure. Though homogeneous on t.l.c., \(^1\text{H}\) n.m.r. analysis showed it to be a mixture of at least two compounds.

Hydrolysis of (205) gave the catechol (206) (90%) as an unstable oil which darkened rapidly in air. Ozonolysis of (206) and reduction of the crude ozonide with sodium borohydride gave the isodrimenin congener (34) (20%).

2.4 Oxidation of a 12,13-dihydroxy and a 12,13-dimethoxypodocarpatriene.

A number of reagents have been reported to cleave oxidatively catechols or their dimethyl ethers to give muonic acid derivatives, including oxygen-copper(I) chloride,\(^{40}\) peracetic acid (copper(II) catalysis),\(^{139}\) chlorous acid,\(^{140}\) and ozone-boron trifluoride.\(^{41}\) As part of the current work an investigation of the oxidative cleavage of the 12,13-catechol (37) was made. This would be expected to give derivatives of the muonic acid (39) which on decarboxylation would give compounds with drimane skeletons. Other workers within this department are investigating the cleavage of the 14-isopropyl-12,13-catechol (40) as a potential route to nagilactones.

Reduction of the 13-nitrophenol (138) with hydrazine and palladium on charcoal\(^{39}\) gave the aminophenol (207) (75%). Oxidation with sodium periodate by the method of Stubbenrauch and Knuppen\(^{136}\) gave the catechol (37) in a best yield of 43%. The product (for which a satisfactory analysis was obtained) was subject to aerial oxidation particularly in solution. The melting point of freshly sublimed material was 216-220°. Johnson and co-workers\(^{39}\) have previously prepared (37) by hydrolysis of the 2'-benzoyl-4'-nitrophenyl ether (208). Initially\(^{39\text{a}}\) they reported the product to be the acid (209), m.p. 237-9°, on the basis of analytical figures of C 70.0, H 7.8% \( \text{C}_{17}\text{H}_{22}\text{O}_4 \) requires C 70.3, H 7.6%). Subsequently\(^{39\text{b}}\) they reported the product to be
the ester (37), m.p. 242-244°, on the basis of new analytical figures of C 70.7, H 7.5% (C₁₈H₂₄O₄ requires C 71.0, H 8.0%) and (unreported) n.m.r. data. Acetylation of their product gave the diacetate (210), while methylation gave the dimethyl ether (38) for both of which satisfactory analyses were obtained. In the current work oxidation of (207) and acetylation of the crude product gave the diacetate (210) (14%) which had identical physical properties to those reported.³⁹b As the oxidation of (207) gave variable yields of (37) and the product was usually contaminated with highly coloured impurities which were difficult to remove by chromatography or recrystallization, alternative routes to (37) were investigated.

The nitrophenol (138) was converted to the tosylate (211) (83%), which was reduced with hydrazine and palladium on charcoal to the amine (212) (80%). Treatment of (212) with nitrous acid by the method of Mori and Matsui⁹² gave a heterocyclic product (213) (10%). The yield was reduced considerably by the need for to remove an orange impurity. Despite repeated recrystallizations a satisfactory analysis could not be obtained, even though the material appeared to be pure by both t.l.c. and n.m.r. analysis. The product (213) presumably arises from attack by an aromatic cation on the aryl ring of the tosyl group. Geometrical constraints require attack to occur at the tosyl C2 rather than the electronically more favourable C3. Drieding models show that the two aromatic rings are at an angle of ca. 30° to each other.

The next route investigated was the synthesis of the diacetate (210). Acetylation of the 13-acetyl-phenol (185) gave the acetate (214) (86%). Baeyer-Villiger oxidation of (214) was much slower than for the 12-methoxy compound (128) with
23% of starting material being recovered after 6 weeks, with the diacetate (211) being obtained in 30% yield. Also isolated was the phenol (185) (3%) presumably formed by acid catalysed hydrolysis of (214). Hydrolysis of (210) gave the catechol (37) quantitatively.

Oxidation of (37) with \textit{m}-chloroperbenzoic acid gave the anhydride (160) (27%), while oxidation with oxygen and copper(I) chloride\textsuperscript{40} gave a complex mixture which was not further investigated.

Also investigated was the cleavage of the dimethoxy compound (38). Methyl-ation of the 12-methoxy-13-hydroxy compound (130) gave (38) (81%) as a solid. This compound has been previously\textsuperscript{39} reported as an oil. Isobe \textit{et al.}\textsuperscript{41} have reported that ozonolysis of \(\alpha\)-dimethoxybenzenes in the presence of boron trifluoride etherate gives dimethyl muconates in good yield. The boron trifluoride is thought to complex to the diene system deactivating it towards further attack by ozone. Oxidation of (38) by this reagent gave the trimethyl ester (215) (50%). Ozonolysis in the absence of the Lewis acid gave a complex mixture of which (215) was a minor component by t.l.c. and \(^1\)H n.m.r. analysis. The triester (215) decomposed on attempted purification by sublimation (Kugelrohr). Examination of models showed that the methyl ester groups at C12 and C13 are very close together and it would be expected that relief of this steric strain would make loss of one of these groups energetically favourable. This is supported by the presence of only a weak molecular ion in the mass spectrum with the base peak being at M-59 corresponding to loss of CO\(_2\)CH\(_3\).

Ozonolysis of the monomethyl ether (130) gave a complex mixture which was not further investigated.
CHAPTER THREE

This chapter concerns an investigation into the conversion of the hydroperoxy-lactone (41) produced by ozonolysis of methyl podocarpate (10) into compounds with drimane skeletons. Such a conversion involves shortening of the side-chain by one carbon atom and the introduction of a one-carbon side-chain atom at C8. Chain-shortening has been achieved previously by a debromodecarboxylation of the bromo acid (216) to give the enone (45). A one-carbon side-chain has been introduced at C8 by means of a modified Oshima reaction using diiodomethane, which converted the 8-ketones (43) and (217) into the 8-methylene compounds (46) (82%) and (218) (71%) respectively. Two routes were investigated in the present work. The first was the conversion of the enone (45) into compounds with drimane skeletons (Scheme 20). The second route investigated was chain-shortening with the C8 ketone protected as the oxime methyl ether.

3.1 Reduction of the Hydroperoxy-lactone (41).

Ozonolysis of methyl podocarpate (10) gave the hydroperoxy-lactone (41) (62%). Reduction of the crude hydroperoxide with zinc and hydrochloric acid in methanol by the method of Robertson gave the dimethyl ester (43) in a best yield of 47% from (10). The yield from this reaction was variable with the keto-acid (42) being isolated from some experiments in up to 15% yield. Reduction in ethanol gave the keto-acid (42) in 29-30% yield from (10) with the ethyl ester (219) being obtained in between 4% and 52% (crude) yield. A pale green colour was usually observed in the hydroperoxide solution upon addition of the zinc dust, which disappeared upon addition of the hydrochloric acid. During the addition of the acid a lilac colour was observed which disappeared overnight with subsequent contamination of the products with a...
dark-coloured impurity. The product required extensive purification to remove the impurity with consequent lowering of the yields. Moderation of the reaction temperature by slowing the rate of addition and/or cooling on an ice-bath reduced the formation of this impurity considerably, and also increased the proportion of the acid (42) in the product mixture. Reduction of (41) with zinc and acetic acid\(^\text{19}\) gave the keto-acid (42) (52%).

Hydrogenation of (41) under acidic conditions\(^\text{57}\) gave the hydroxy-lactone (220) in 45% yield from (10), while under basic or neutral conditions the product was the keto-acid (42) (43% from (10)). To achieve complete reduction of (41) to (42) it was found to be optimal to hydrogenate under basic conditions. From one hydrogenation performed in methanol both the acid (42) (45%) and methyl ester (43) (15%) were isolated. Goeth\(^\text{42}\) found that hydrogenation of the hydroperoxy-lactone (56) in ethanol gave the ethyl ester (221) (90%) and proposed that this product was formed by a nucleophilic attack by ethanol at the lactone carbonyl group. The hydroxy-lactone (220) was also obtained by reduction of (41) with sodium hydrosulfite\(^\text{27}\) (29%), or by working up the ozonolysis of (10) with dimethyl sulfide (40%). Reduction of (220) with hydrogen or zinc and acetic acid gave (42) in 90% and 86% yield respectively.

Hydrolysis of the dimethyl ester (43) and crude ethyl methyl ester (219) gave the acid (42) in yields of 70% and 65% respectively. Also isolated from the hydrolysis of (219) was a trace of the decalone (222).\(^\text{42}\) The identity of (222) was confirmed by comparison with a sample prepared from (220) (45%) by a reverse-aldol reaction.\(^\text{42}\)

Methylation of (42) with methanol using Amberlyst-15 as catalyst\(^\text{143}\) gave (43) (90%). The reaction was slow, requiring 24 h at reflux to reach completion. Although considerably slower than the use of diazomethane or dimethyl sulfate, this method avoids the potential hazards involved in the use of these highly toxic reagents.
3.2 Reactions of Methyl 8-Oxo-12-nordrim-9(11)-en-14-oate (45).

Bromination of the keto-acid (42) gave the 6α-bromo-acid (216)\(^{27}\) (95%). The presence of fragments at \(m/z\) 404 and 402 in the mass spectrum of (216) indicated the presence of a trace of the ethyl ester (223) which was presumably formed by reaction of (216) with the ethanol present in the chloroform solvent. Treatment of (216) with potassium carbonate in acetone gave a quantitative yield of the crude enone (45).\(^{27}\) \(^1\)H n.m.r. analysis showed the presence of a trace of the dimer (224).\(^{27}\) The enone (45) was unstable with respect to the dimer (224), especially upon heating, complete conversion being obtained by refluxing a solution of (45) in ethanol overnight. For this reason crude enone (45) was used in further work without purification.

Epoxidation of (45) with basic hydrogen peroxide gave the epoxide (225) (23%). The epoxide (225) was assigned an α-configuration as one would expect epoxidation to proceed from the less-hindered α-face. No significant n.O.e enhancement of the epoxide methylene protons (H11) signals at \(\delta_H 2.85\) and \(\delta_H 3.14\) was observed upon irradiation of the angular methyl group protons at \(\delta_H 0.90\). Attempts to rearrange the epoxide (225) with boron trifluoride\(^{77}\) or to open it with perchloric acid\(^{77}\) gave complex mixtures which were not investigated further.

An attempt to introduce a protected aldehyde group at C8 by treatment of (45) with 1,3-dithianyl lithium\(^{144}\) was unsuccessful, the only product isolated being the dimer (224). Hydroboration of (45) gave a complex mixture which was not investigated further.

Methylenation of (45) by a modified Oshima reaction\(^{44,45}\) was expected to give the diene (226), a congener of which (227) has been converted into warburganal (1)\(^{18}\) (Scheme 7). However, the major (27%) product was a mixture of the spirocyclopropanes (228) (67%) and (229) (33%). The structures of (228) and (229) were assigned on the basis of the \(^1\)H and \(^13\)C n.m.r. spectra, which were interpreted with the aid of COSY
and C-H correlation experiments. The presence of a cyclopropane group was shown by the presence of markedly upfield signals in the $^{13}$C n.m.r. spectrum at $\delta_C$ 4.9 and $\delta_C$ 10.4, which correlated to proton signals at $\delta_H$ -0.02, 0.50, 0.68, and 0.87. The observed chemical shifts and coupling constants for these proton signals and the presence of a C-H stretching band at 3030 cm$^{-1}$ in the i.r. spectrum are typical of a cyclopropane group, while the value of 1640 cm$^{-1}$ for the C=C stretching band is typical of a vinyl-cyclopropane.$^{145}$ The terminal alkene proton signals for (228) appeared as doublets ($J$ 1.5 Hz) at $\delta_H$ 4.51 and 4.60 in the $^1$H n.m.r. spectrum, while the corresponding protons in (229) appeared as doublets ($J$ 1.1 Hz) at $\delta_H$ 4.47 and 4.86. As a COSY experiment showed a correlation between the olefinic methylene protons of (228) and an H7 proton at $\delta_H$ 2.3, the terminal alkene group was assigned to C8. The corresponding group in (229) was assigned to C9 on the basis of correlations between the vinyl protons and the H1$\beta$ ($\delta_H$ 1.75) and H2$\beta$ ($\delta_H$ 1.85) protons. The composition of the mixture was determined by comparison of the integrals for the terminal alkene protons. The molecular ion was not seen in the mass spectrum. The major fragmentation was the formation of a fragment ion at $m/z$ 234 (M-28) for which the following fragmentation pathway is proposed:

$$\begin{align*}
\text{m/z 262} & \rightarrow \text{m/z 234} \\
\text{CO}_2\text{Me} & \rightarrow \text{CO}_2\text{Me} \text{ (M-28)}
\end{align*}$$

The rearrangement of vinylcyclopropanes to cyclopentenes is a well-known synthetic process.$^{146}$

Although the conversion of alkenes to cyclopropanes with diiodomethane and zinc (the Simmons-Smith reaction)$^{147}$ or diethylzinc$^{148}$ is well-known, no cyclopropanes have previously been reported among the products from treatment of carbonyl
compounds with the Oshima reagent.\textsuperscript{44} That the major product is the C9-cyclopropane (228) suggests that a significant amount of 1,4-attack by the reagent on (45) occurs, as on steric grounds one would expect the major product of cyclopropanation of the diene (226) to be the C8-cyclopropane (229).

Also isolated was an oil (15\%) which by \textsuperscript{1}H n.m.r. and t.l.c. analysis was a mixture whose major component was the dimer (224).

\textbf{3.3 Chain-shortening of the O-methyl Oxime (230).}

Treatment of the keto-ester (43) with methoxylamine hydrochloride and pyridine gave the O-methyl oxime (230)(83\%). The \textsuperscript{1}H and \textsuperscript{13}C n.m.r. spectra of (230) were fully assigned by means of a C-H correlation experiment. Comparison of the \textsuperscript{1}H n.m.r. spectra of (230) and (43)\textsuperscript{111} showed that the oxime had the (E)-configuration. The C9 and C7 axial protons in (230) were shielded by 0.3 and 0.6 ppm respectively, compared with (43) while the C7 equatorial proton was deshielded by ca. 0.8 ppm and the C11 proton signals were unaffected. If the oxime were (Z) the lone pairs on the oxygen would affect the C11 proton signals while the H7 signals would be unaffected.

Brown and Weissmann\textsuperscript{46} have reported that lithium trimethoxylaluminium hydride will reduce esters but not oximes. It was expected, therefore that reduction of (230) with this reagent would give the diol (231). However, reduction of (230) with an excess of this reagent gave only 8\% of (231), the major product being the hydroxylamine methyl ether (232) (75\%). The 8-methoxylamino group was assigned as axial (\(\beta\)) on the basis of the H8 signal in the \textsuperscript{1}H n.m.r. spectrum. This was a broad singlet at \(\delta_H 3.13\), a half-width of 12 Hz indicating that H8 was equatorial (\(\alpha\)). If H8 was axial, the two large axial-axial interactions to H7\(\alpha\) and H9 would cause H8 to have a \(W_\parallel\) of ca. 20 Hz. This indicates that the hydride had attacked from the less-hindered \(\alpha\)-face. Reduction of (230) with 2 equivalents of hydride gave the 12-alcohol (233) (21\%) and
the diol (231) (3%) with 54% recovery of starting material. The alcohol was assigned a 12-hydroxy structure on the basis of the H18 and H20 signals in the $^1$H n.m.r. spectrum, which were unshifted with respect to the corresponding signals for (230). A study$^{149}$ of the $^1$H n.m.r. spectra of podocarpic acid derivatives has shown that reduction of a C19 ester group to an alcohol causes an upfield shift of 0.16-0.23 ppm of the H18 signal, and a 0.1-0.15 ppm downfield shift of the H20 signal.

The reduction of oxime ethers to alkoxylamines has previously been achieved by use of borane-pyridine complex in the presence of acid.$^{150}$ This reagent, however, also reduces oximes to hydroxylamines.$^{151}$ One reason for the lack of syntheses of alkoxylamines from oxime ethers is that the former compounds are more readily reduced to amines than are hydroxylamines. For example, borane-dimethyl sulfide and borane-tetrahydrofuran complexes will reduce oximes to hydroxylamines which can be reduced to amines upon heating to 105-110$^\circ$, while these same reagents will reduce oxime ethers and esters to amines at 25$^\circ$. The use of lithium trismethoxy aluminium hydride would thus appear to offer a method for the selective reduction of oxime ethers in the presence of oximes.

No reaction was observed from treatment of the diol (232) with toluenesulfonyl chloride and pyridine by the method of Kabalka et al.,$^{153}$ while treatment of the alcohol (233) with methanesulfonyl chloride and triethylamine gave a complex mixture which was not investigated further. Attempts to prepare the oxime (234) and the acetal (235) were unsuccessful.

**CONCLUSION**

The routes discussed in this thesis, although low-yielding present convenient methods for the synthesis of optically active analogues of naturally occurring drimanes. These routes are capable of extension to provide syntheses of analogues of biologically active drimanes, e.g. warburganal.
SUMMARY

This section contains a summary of the current work in schematic form, comprising the following schemes.

**Scheme I**  Synthesis of the 12-hydroxy 7-dithioacetal (86) and 7-alcohol (90).

**Scheme II**  Synthesis of the 12-hydroxy 7α-methoxy compound (98).

**Scheme III**  Synthesis of 7-functionalised derivatives of the 12-benzyl ether (101).

**Scheme IV**  Epoxidation of the 12-benzyloxy Δ6-alkene (30).

**Scheme V**  Epoxidation of the 12-benzoyloxy Δ6-alkene (108).

**Scheme VI**  Hydroboration of the 12-benzyloxy Δ6-alkene (30).

**Scheme VII**  Synthesis of the confertifolin congener (31).

**Scheme VIII**  Peracid oxidation of methyl O-methyl podocarpate (11).

**Scheme IX**  Synthesis of the isodrimenin congener (34).

**Scheme X**  Synthesis of the 12,13-dihydroxy compound (37).

**Scheme XI**  Synthesis and reactions of the enone (45).

**Scheme XII**  Reduction of the oxime methyl ether (230).

All new compounds are labeled **NEW** where first shown.
Scheme I.
Scheme II.
Scheme III.
Scheme IV.
Scheme V.
Scheme VI.
Scheme VII.
Scheme VIII.
Scheme IX.
Scheme X.
Scheme XI.
Scheme XII.
EXPERIMENTAL

Melting points were recorded on a Reichert-Kofler block and are uncorrected. Optical rotations were measured using a Perkin Elmer 241 polarimeter in either chloroform or dichloromethane solutions.

Microanalyses were performed by the microanalytical laboratory, University of Otago.

Ultraviolet (u.v.) spectra were recorded on a Varian DMS 100 spectrophotometer in chloroform solution. Infrared (i.r.) spectra were recorded on either a Perkin Elmer 397 or a Shimadzu IR-27G spectrophotometer in chloroform solution.

60 MHz $^1$H n.m.r. spectra were recorded on either a Varian T60 or a Varian EM360L n.m.r. spectrometer in deuterochloroform solution using tetramethylsilane (tms) as internal reference. High field $^1$H n.m.r. (400 MHz) and $^{13}$C n.m.r. (100 MHz) spectra were recorded on a Bruker AM-400 n.m.r. spectrometer in deuterochloroform solution unless specified otherwise. $^1$H n.m.r. data are reported as chemical shift in ppm downfield of tms, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, quin=quintet, m=multiplet, br=broad), coupling constant(s) $J$ or half-width $W_\frac{1}{2}$, relative integral (integral values of $^1$H are not reported except for unassigned signals), and assignment. $^{13}$C n.m.r. spectra were assigned by use of DEPT-135 spectra and with the assistance of data compiled by Wehrli and Nishida.

Low resolution mass spectra were recorded on either a Varian-Mat CH7 or a Varian 7070 mass spectrometer using a normal beam energy of 70 eV. High resolution mass spectra were recorded on a Varian 7070 mass spectrometer at 5,000 or 10,000 nominal resolution using perfluorokerosene as internal reference.

Ozone was generated by a British Oxygen Company Mark II ozone generator. 1,3-Dithiane was prepared by the method of Corey and Seebach. Standard solutions of lithium aluminium hydride and of Red-Al (sodium bis(2-methoxyethoxy)aluminium hydride) were standardised by injection of measured aliquots into a 5% v/v solution of sulfuric acid in 50% aqueous tetrahydrofuran and measurement of the volume of hydro-
gen produced.

Column chromatography on silica was performed on Kieselgel S (230-400 mesh, Riedel de Haen). Analytical thin-layer chromatography (t.l.c.) was performed on 0.2 mm plates of Kieselgel PF$_{254}$ (Merck) with visualisation of bands by irradiation with u.v. light or by spraying with anisaldehyde solution. Preparative thin-layer chromatography (p.l.c.) was performed on 1 mm plates of Kieselgel PF$_{254+366}$ (Merck).


All new (i.e. unlisted in Chemical Abstracts) compounds have their names written in *italics* where first reported with all spectral data.
CHAPTER ONE

Methyl 12-Hydroxypodocarpa-8,11,13-trien-19-oate (10)

Crude podocarpic acid (9) was methylated with sodium hydrogencarbonate and dimethyl sulfate23 to give methyl 12-hydroxypodocarpa-8,11,13-trien-19-oate (10), m.p. 208-9° (lit.23 208°) (77%) (correct i.r. and $^1$H n.m.r. spectra).

Methyl 12-Acetoxypodocarpa-8,11,13-trien-19-oate (83)

Acetylation of methyl 12-hydroxypodocarpa-8,11,13-trien-19-oate (10) with acetic anhydride and pyridine61 gave methyl 12-acetoxypodocarpa-8,11,13-trien-19-oate (83), m.p. 123-5° (lit.61 125-125.5°) (94%) (correct i.r. and $^1$H n.m.r. spectra).

Methyl 12-Acetoxy-7-oxopodocarpa-8,11,13-trien-19-oate (84)

a) Oxidation of methyl 12-acetoxypodocarpa-8,11,13-trien-19-oate (83) with chromium trioxide in acetic acid62 gave methyl 12-acetoxy-7-oxopodocarpa-8,11,13-trien-19-oate (84), m.p. 133-4° (lit.62 132-6°) (76%) (correct i.r. and $^1$H n.m.r. spectra).

b) Treatment of the 12-acetate (83) (0.54 g) with ozone at -78° followed by workup with dimethyl sulfide gave an oil which was separated by chromatography on silica into the 12-acetoxy ketone (84) (0.12 g, 21%) and methyl 12-hydroxy-7-oxopodocarpa-8,11,13-trien-19-oate (85) (0.18 g, 30%).

Methyl 12-Hydroxy-7-oxopodocarpa-8,11,13-trien-19-oate (85)

a) Hydrolysis of methyl 12-acetoxy-7-oxopodocarpa-8,11,13-trien-19-oate (84) with sodium hydroxide solution63 gave methyl 12-hydroxy-7-oxopodocarpa-8,11,13-trien-19-oate (85), m.p. 233-4° lit.63 235-7°) (87%) (correct i.r. and $^1$H n.m.r. spectra).
b) Oxidation of methyl podocarpate (10) with chromium trioxide in acetic acid gave the ketone (85) (40%).

**Methyl 7-Ethylendithio-12-hydroxypodocarpa-8,11,13-trien-19-oate (86)**

Boron trifluoride etherate (2.0 ml, 15 mmol) was added to a stirred solution of methyl 12-hydroxy-7-oxopodocarpa-8,11,13-trien-19-oate (85) (1.5 g, 5.0 mmol) and 1,2-dithioethane (1.1 ml, 12.5 mmol) in acetic acid (75 ml). The solution was left for 21 h, poured into ice-water (500 ml), and extracted with ether. The extract was washed with cold 10% sodium hydroxide solution and water, dried, and concentrated to give methyl 7-ethylendithio-12-hydroxypodocarpa-8,11,13-trien-19-oate (86) as needles (from aqueous methanol) (1.0 g, 54%), m.p. 242.5-245.5°, [α]D\text{17}^{+167°} (c, 1.5) (Found: C 63.5, H 7.0, S 16.7%. C_{20}H_{26}O_{3}S_{2} requires C 63.5, H 6.9, S 16.9%). ν\text{max} 3600 (OH), 2950, 1735 (ester), 1600 cm\text{−1} (C=C). δH 1.08, s, 3H, H20; 1.25, s, 3H, H18; 3.68, s, 3H, CO₂CH₃; 6.5-7.5, m, 3H, aryl H. δC 19.5, C2; 22.0, C20; 27.4, C18; 36.9, C3; 38.2, C10; 38.9, C1; 39.5, 40.7, CH₂S; 41.3, C6; 43.2, C4; 51.0, C5; 51.1, CO₂CH₃; 70.6, C7; 110.6, C13; 113.6, C11; 128.6, C8; 132.5, C14; 149.8, C9; 154.7, C12; 177.6, C19. m/z 378 (M, 24%), 318 (M-C₂H₂S, 100), 243 (30), 225 (44), 203 (79), 190 (70), 171 (38), 60 (63), 59(68).

The dithioacetal (86) was also obtained in 34% yield from treatment of the 12-acetoxy ketone (84) with 1,2-ethanediithiol and boron trifluoride etherate.

**Methyl 12-Methoxypodocarpa-8,11,13-trien-19-oate (11)**

Podocarpic acid (9) was methylated with sodium hydroxide and dimethyl sulfate\textsuperscript{23} to give methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (11), m.p. 128-9° (lit.\textsuperscript{23} 128°) (89%) (correct i.r. and ¹H n.m.r. spectra).
Methyl 12-Methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (12)

Oxidation of methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (11) with chromium trioxide in acetic acid\(^6\) gave methyl 12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (12), m.p. 122-3\(^\circ\) (lit.\(^6^4\) 122-4\(^\circ\)) (71\%) (correct i.r. and \(^1\)H n.m.r. spectra).

Methyl 7-Ethylenedithio-12-methoxypodocarpa-8,11,13-trien-19-oate (88)

Boron trifluoride etherate (5 ml) was added to a solution of the 12-methoxy ketone (12) (4.2 g, 13.3 mmol) and 1,2-dithioethane (2 ml, 22.7 mmol) in chloroform (70 ml). The mixture was refluxed for 5 days and then poured into water. The layers were separated, the aqueous layer was extracted with dichloromethane, and the combined organic fractions were washed with 10\% sodium hydroxide solution (x2), and 10\% hydrochloric acid, dried, and concentrated to give an oil (5 g) which was absorbed onto silica. Elution with hexane-ether (3:1) gave an oil which when crystallised from methanol (x2) gave methyl 7-ethylenedithio-12-methoxypodocarpa-8,11,13-trien-19-oate (88) as prisms (0.81 g, 15\%), m.p. 118-120\(^\circ\), [\(\alpha\)]\(^D\)\(^{18}\) +140\(^\circ\) (c, 1.0) (Found: C 64.3, H 7.4, S 16.2\%. C\(_2\)\(_{23}\)H\(_{28}\)O\(_3\)S\(_2\) requires C 64.3, H 7.2, S 16.2\%). \(v_{\text{max}}\) 2950, 1730 (ester), 1600 (C=\(\equiv\)), 1150 cm\(^{-1}\) (C-O). \(\delta\)\(_\text{H}\) 1.05, s, 3H, H20; 1.30, s, 3H, H18; 3.70, s, 3H, CO\(_2\)CH\(_3\); 3.80, s, 3H, ArOCH\(_3\); 5.6-6.9, m, 3H, aryl H. \(\delta\)\(_\text{C}\) 19.6, C2; 22.1, C20; 27.5, C18; 37.0, C3; 38.5, C10; 39.1, C1; 39.6, 40.8, CH\(_2\)S; 41.4, C6; 51.1, C5; 51.2 CO\(_2\)CH\(_3\); 55.2, ArOCH\(_3\); 70.7, C7; 109.6, C13; 111.8, C11; 128.8 C8; 132.4, C14; 149.6, C9; 158.6, C12; 177.4, C19. \(m/z\) 392 (M, 41\%), 332 (M-C\(_2\)H\(_2\)S, 100), 316 (24), 299 (14), 257 (20), 239 (35), 227 (26), 217 (27), 206 (45), 185 (25).

Demethylation of the 12-Methoxy Dithioacetal (88)

A solution of boron tribromide in dichloromethane (1 ml, 2.46 M, 2.46 mmol)
was added to a stirred solution of the 12-methoxy dithioacetal (88) (0.1 g, 0.25 mmol) in dry dichloromethane (10 ml) at -78° under a nitrogen atmosphere. The mixture was warmed to room temperature over a 1 h period with stirring, and then poured into water. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic fractions were washed with 10% hydrochloric acid and water, dried, and concentrated to give a pink solid which was separated by p.l.c. (hexane-ether, 1:2) into (i) starting material (25 mg); and (ii) the 12-hydroxy dithioacetal (86) (34 mg, 35%).

**Ozonolysis of the 12-Hydroxy Dithioacetal (86).**

Treatment of the 12-hydroxy dithioacetal (86) (1.3 g, 3.4 mmol) with ozone at -78°, followed by reduction with zinc dust (2.2 g, 34 mmol) and concentrated hydrochloric acid (35 ml) gave a brown oil (1.02 g) which was separated by chromatography on silica into 9 components, all of which coloured rapidly in air with consequent production of multiple spots on t.l.c. analysis.

**Reaction of the 12-Hydroxy Ketone (85) with 2-Mercaptoethanol**

Boron trifluoride etherate (0.5 ml) was added to a solution of the 12-hydroxy ketone (85) (75 mg, 0.25 mmol) and 2-mercaptoethanol (40 µl, 0.57 mmol) in acetic acid (10 ml), and the solution was stirred for 24 h, poured into water, and extracted with dichloromethane. The extract was washed with sodium hydrogen carbonate solution and water, dried, and concentrated to give a solid (60 mg) which was separated by p.l.c. (hexane-ether, 1:2) into: (i) a crystalline material (10 mg) which contained at least 2 components by t.l.c. analysis. ν<sub>max</sub> 3450 (OH), 3000, 1730 (ester), 1600 cm<sup>-1</sup> (C=C); and (ii) starting material.
Methyl 7β,12-Dihydroxypodocarpa-8,11,13-trien-19-oate (90)

a) Sodium borohydride (30 mg, 0.8 mmol) was added to a solution of the 12-acetoxy ketone (84) (0.1 g, 0.3 mmol) in ethanol (20 ml), and the mixture was stirred for 2 h. The mixture was concentrated under reduced pressure to a small volume and the residue partitioned between dichloromethane and 10% hydrochloric acid. The aqueous layer was extracted with dichloromethane and the combined organic fractions were washed with sodium hydrogen carbonate solution and water, dried, and concentrated to give methyl 7β,12-dihydroxypodocarpa-8,11,13-trien-19-oate (90) as a glass (from dichloromethane-hexane) (80 mg, 91%) which coloured rapidly in air. $\nu_{\text{max}}$ 3350 (OH), 2950, 1720 (ester), 1600 cm$^{-1}$ (C=C). $\delta_{H}$ 1.00, s, H20; 1.35, S, 3H, H18; 3.70, S, 3H, CO$_2$CH$_3$; 4.50, br s, W$_{\alpha}$ 15 Hz, H7α; 6.30, br s, OH; 6.6-7.1, M, 3H, aromatic H. $m/z$ 286 (M-H$_2$O, 25%), 236 (20), 213 (35), 179 (75), 149 (70), 57 (100).

An attempted purification by sublimation (Kugelrohr) resulted in formation of the alkene (92) (identical to sample prepared below).

b) A solution of sodium borohydride (0.19 g, 5 mmol) in tetrahydrofuran (5 ml) and water (2 ml) was added with stirring to a solution of the 12-hydroxy ketone (85) (0.5 g, 1.7 mmol) in tetrahydrofuran (20 ml). The mixture was stirred for 16 h and worked up as above to give the crude diol (90) (0.5 g, 100%) which was used without further purification.

Treatment of the crude diol (90) (56 mg, 0.16 mmol) with ozone at -78° gave a yellow oil (50 mg) which was a complex mixture by t.l.c. analysis.

Methyl 12-Hydroxypodocarpa-6,8,11,13-tetraen-19-oate (92)

A solution of the crude diol (90) (0.5 g, 1.7 mmol) in methanol (25 ml) and concentrated hydrochloric acid (3 ml, 33 mmol) was refluxed for 4 h. The alkene (92) which precipitated from the cooled solution was collected by filtration and washed with water, while further material was obtained by dilution of the combined filtrate and
washings with water and extraction with dichloromethane. Crystallisation from methanol gave methyl 12-hydroxypodocarpa-6,8,11,13-tetraen-19-oate (92) as needles (0.31 g, 65%), m.p. 165-170°, [α]_D^{17} -36° (c, 1.2) (Found: M⁺ 296.1579. C₁₈H₂₂O₃ requires M⁺ 286.1570.) v_max 3350 (OH), 2950, 1730 (ester), 1660 cm⁻¹ (conj. C=C). δ_H 0.80, s, 3H, H20; 1.35, s, 3H, H18; 3.70, s, 3H, CO₂CH₃; 6.35, s, 2H, H6,7; 6.5-7.0, m, 3H, aromatic H. δ_C 19.2, C20; 19.6, C2; 27.8, C18; 35.9, C3; 37.3, C1; 38.0, C10; 43.4, C4; 51.1, C5; 51.7, CO₂CH₃; 110.2, C13; 112.5, C11; 124.9, C6; 125.8, C8; 127.2, C14; 127.5, C7; 148.3, C9; 155.2, C12; 178.0, C19. m/z 286 (M, 72%), 254 (16), 211 (54), 171 (100).

Methyl 12-Benzovloxypodocarpa-8,11,13-trien-19-oate (93)

A solution of methyl 12-hydroxypodocarpa-8,11,13-trien-19-oate (10) (2.0 g, 6.9 mmol) and benzoic anhydride (1.9 g, 8.4 mmol) in pyridine (4 ml) was warmed on a waterbath for 5 h, poured into sodium hydrogen carbonate solution, and extracted with dichloromethane. The extract was washed with 2M hydrochloric acid and water, dried, and concentrated to give methyl 12-benzovloxypodocarpa-8,11,13-trien-19-oate (93) as needles (from methanol) (2.15 g, 79%), m.p. 144-6°, [α]_D^{17} +169° (c, 1.7) (Found: C 76.7, H 7.4%. C₂₅H₂₈O₄ requires C 76.5, H 7.2%). v_max 2950, 1720 cm⁻¹ (ester). δ_H 1.10, s, 3H, H20; 1.30, s, 3H, H18; 3.70, S,3H, CO₂CH₃; 6.9-8.3, m, 8H, aryl H. δ_C 19.9, C2; 20.9, C6; 23.0, C20; 28.5, C18; 31.5, C7; 37.6, C3; 38.6, C10; 39.3, C1; 44.0, C4; 51.3, C5; 52.5, CO₂CH₃; 118.5, C13; 118.8, C11; 128.5, 2C, benzoate C3,C5; 129.8, C8; 130.0, C14; 130.1, 2C, benzoate C2,C6; 133.0 benzoate C1; 133.5 benzoate C4; 140.0 C9; 149.5, C12; 165.4, PhCO₂; 177.8 C19. m/z 392 (M, 9%), 317 (8), 288 (5), 213 (11), 105 (100), 77 (30).

Methyl 12-Benzoyloxy-7-oxopodocarpa-8,11,13-trien-19-oate (94)

a) A solution of chromium trioxide (1.25 g, 12.5 mmol) in 80% acetic acid (20
ml) was added to a stirred solution of methyl 12-benzylxypodocarpa-8,11,13-trien-19-oate (93) (3.4 g, 8.5 mmol) in acetic acid (180 ml). The mixture was stirred for 90 h, poured into water and extracted with dichloromethane. The extract was washed with sodium hydrogen carbonate solution and water, dried, and concentrated to give methyl 12-benzoyloxy-7-oxopodocarpa-8,11,13-trien-19-oate (94) as needles (from methanol) (2.57 g, 73%), m.p. 83-5°, [α]D 17° +140° (c, 1.2) (Found: C 74.1, H 6.7%. C25H26O5 requires C 73.9, H 6.5%). νmax 2950, 1720 (ester), 1680 (ketone), 1600 cm⁻¹ (C=C). δH 1.15, s, 3H, H20; 1.30, s, 3H, H18; 3.70, s, 3H, CO₂CH₃; 7.1-8.3, m, 8H, arylH. δC 19.5, C2; 21.4, C20; 27.9, C18; 37.4, C6; 37.5, C3; 38.4, C1; 38.9, C10; 43.9, C4; 50.0, C5; 51.7, CO₂CH₃; 118.1, C13; 120.1, C11; 128.4, C8; 128.7, 2C, benzoate C3,C5; 129.2, C14; 130.2, 2C, benzoate C2,C6; 133.0, benzoate C1; 133.9, benzoate C4; 155.4, C9; 156.4, C12; 164.7, PhCO₂; 177.0, C19; 197.7, C7. m/z 406 (M, 2%), 105 (100), 77 (21).

b) Treatment of the benzoate (93) (0.1 g, 0.26 mmol) with ozone at -78° followed by workup with dimethyl sulfide gave an oil, which was separated by chromatography on silica into starting material (45 mg) and the ketone (94) (30 mg, 29%).

Methyl 12-Benzyloxy-7β-hydroxypodocarpa-8,11,13-trien-19-oate (95)

A solution of sodium borohydride (50 mg, 1.3 mmol) in tetrahydrofuran (5 ml) and water (1 ml) was added to a stirred solution of the 12-benzyloxy ketone (94) (0.5 g, 1.25 mmol) in tetrahydrofuran (20 ml). The mixture was stirred for 72 h, and then concentrated to small volume. The residue was partitioned between dichloromethane and 2M hydrochloric acid. The aqueous layer was extracted with dichloromethane, and the combined organic fractions were washed with water, dried, and concentrated to give methyl 12-benzyloxy-7β-hydroxypodocarpa-8,11,13-trien-19-oate (95) as a glass (from ether-hexane), (0.5 g, 100%), m.p. 55-65°, [α]D 18° +80° (c, 0.3) (Found: C 73.4, H 6.9%. C25H28O5 requires C 73.5, H, 6.9%). νmax 3350 (OH), 1710 (ester), 1600 cm⁻¹
A solution of the 7β-alcohol (95) (0.135 g, 0.33 mmol) and p-toluenesulfonic acid (75 mg) in methanol (20 ml) was refluxed for 4 h and then poured into water, and extracted with dichloromethane. The extract was washed with sodium hydrogen-carbonate solution and water, dried, and concentrated to give an oil (0.113 g) which was on separation by p.l.c. (hexane-ether, 1:2) gave: (i) methyl 12-benzoyloxy-7α-methoxypodocarpa-8,11,13-trien-19-oate (96) as prisms (from ether-hexane) (68 mg, 49%), m.p. 114-5°, [α]D17 +103° (c, 1.4) (Found: C 74.1, H 6.9%. C26H30O5 requires C 73.9, H, 7.2%). νmax 2950, 1720 (ester), 1600 (C=C), 1170 cm⁻¹ (C-O). δH 1.05, s, 3H, H20; 1.35, s, 3H, H18; 3.50, s, 3H, ROCH₃; 3.70, s, 3H, CO₂CH₃; 4.3, br s, W 8 Hz, H7β; 6.9-8.3, m, 8H, aryl H. δC 20.0, C2; 21.8, C20; 24.4, C6; 28.3, C18; 37.3, C3; 38.8, C10; 38.8, C1; 43.6, C4; 45.3, C5; 51.4, CO₂CH₃; 56.5, ROCH₃; 79.1, C7; 118.4, C13; 119.4, C11; 128.5, 2C, benzoate C3,C5; 129.6, C8; 130.2, 2C, benzoate C2,C6; 132.0, benzoate C1; 132.1, C14; 133.5, benzoate C4; 150.2, C9; 150.9, C12; 165.2, PhCO₂; 178.0, C19. m/z 422 (M, 3%), 391 (M-CH3O, 4), 331 (8), 254 (5), 105 (100), 77 (20); and (ii) methyl 12-benzoyloxy-7β-methoxypodocarpa-8,11,13-trien-19-oate (97), an oil (15 mg, 11%), [α]D18 +52° (c, 1.0) (Found: M⁺ 422.2090. C26H30O5 requires M⁺ 422.2093). νmax 2950, 1720 (ester), 1600 (C=C), 1170 cm⁻¹ (C-O). δH 1.15, s, 3H, H20; 1.35, s, 3H, H18; 3.50, s,3H, ROCH₃; 3.70, s, 3H, CO₂CH₃; 4.3, br s, W 14 Hz, H7α; 6.9-8.3, m, 8H, aryl H. m/z 422 (M, 1%), 391 (M-CH3O, 1), 331 (4), 251 (3), 105 (100), 77 (30).
Methyl 12-Hydroxy-7α-methoxypodocarpa-8,11,13-trien-19-oate (98)

A solution of methyl 12-benzoyloxy-7α-methoxypodocarpa-8,11,13-trien-19-oate (96) (0.45 g, 1.1 mmol) and potassium hydroxide (0.28 g, 5 mmol) in methanol (20 ml) was stirred for 72 h, and then poured into water, neutralised with 2M hydrochloric acid, and extracted with dichloromethane. The extract was washed with water, dried, and concentrated to give methyl 12-hydroxy-7α-methoxypodocarpa-8,11,13-trien-19-oate (98) as an oil (0.34 g, 100%) which coloured rapidly in air (Found: M-32 286.1555. C_{19}H_{28}O_4 requires M-CH$_3$OH 286.1569). δ$_H$ 0.95, s, 3H, H20; 1.25, s, 3H, H18; 3.45, s, 3H, ROCH$_3$; 3.60, s, 3H, CO$_2$CH$_3$; 4.35, br s, W 8 Hz, H7β; 6.5-6.8, m, 3H, aryl H. m/z 318 (M, 1.5%), 286 (M-CH$_3$OH, 100), 211 (50).

Treatment of (98) with ozone at -78° gave an oil (0.25 g) which was a complex mixture by t.l.c. analysis.

Methyl 7β-Hydroxy-12-methoxypodocarpa-8,11,13-trien-19-oate (13)

Reduction of methyl 12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (12) with sodium borohydride in aqueous tetrahydrofuran gave methyl 7β-hydroxy-12-methoxypodocarpa-8,11,13-trien-19-oate (13), m.p. 104-6° (lit. 33 100-6°, 25 110-2°) (80%) (correct i.r. and $^1$H n.m.r. spectra).

Methyl 7β-Acetoxy-12-methoxypodocarpa-8,11,13-trien-19-oate (100)

Treatment of the 12-methoxy alcohol (13) with acetic anhydride and pyridine gave methyl 7β-acetoxy-12-methoxypodocarpa-8,11,13-trien-19-oate (100), an oil, [α]$_D^{18}$ + 160° (c, 0.9) (lit. 25 [α]$_D^{25}$ +168° (c, 0.17)) (95%) (correct i.r. and $^1$H n.m.r. spectra).
Demethylation of the 12-Methoxy Acetate (100)

A solution of boron tribromide in dichloromethane (0.5 ml, 2.46 M, 1.23 mmol) was added to a solution of the 12-methoxy acetate (100) (0.1 g, 0.3 mmol) in dry dichloromethane (10 ml) at -78° under nitrogen. The mixture was warmed to room temperature over 1 h and worked up to give a light-brown oil (70 mg) which was a complex mixture by t.l.c. analysis. ¹H n.m.r. analysis showed partial demethylation had occurred.

Methyl 12-Benzyl oxypodocarpa-8,11,13-trien-19-oate (101)

A solution of methyl 12-hydroxypodocarpa-8,11,13-trien-19-oate (10) (2.5 g, 8.8 mmol) and sodium hydroxide (1.6 g, 40 mmol) in 50% aqueous methanol (150 ml) was refluxed for 1 h. Benzyl bromide (4.9 ml, 41 mmol) was added slowly via the condenser and the mixture was refluxed for a further 19 h, cooled, neutralised with 10% hydrochloric acid, diluted with water and extracted with dichloromethane to give methyl 12-benzyl oxypodocarpa-8,11,13-trien-19-oate (101) as needles (from methanol) (2.6 g, 79%), m.p. 103-6°, [α]D²⁰ +125° (c, 0.9) (lit. 35 m.p. 106-8°, [α]D²⁰ +147° (c, 0.41)) (Found: C 79.0, H, 8.2%. C2₅H₃₉O₃ requires C 79.4, H 7.9%) (correct i.r. and ¹H n.m.r. spectra).  δC 20.0, C2; 21.1, C6; 22.9, C20; 28.5, C10; 31.2, C7; 37.6, C3; 38.6, C10; 39.4, C1; 44.0, C4; 51.2, C5; 52.8, CO₂CH₃; 70.1, PhCH₂; 112.1, C13; 112.2, C11; 127.5, 2C, benzyl C3,C5; 127.8, benzyl C4; 127.9, C8; 128.5, 2C, benzyl C2,C6; 129.8, C14; 137.3, benzyl C1; 149.3, C9; 157.0, C12; 177.9, C19. m/z 378 (M, 8%), 227 (5), 213 (5), 91 (100).

Methyl 12-Benzyl oxy-7-oxopodocarpa-8,11,13-trien-19-oate (102)

a) A solution of chromium trioxide (0.95 g, 9.5 mmol) in 80% acetic acid (10 ml) was added to a stirred solution of methyl 12-benzyl oxypodocarpa-8,11,13-trien-
19-oate (101) (2.58 g, 6.9 mmol) in acetic acid (80 ml). The mixture was stirred for 22 h, poured into water, and extracted with dichloromethane. The extract was washed with sodium hydrogen carbonate solution and water, dried, and concentrated to give methyl 12-benzyl-7-oxopodocarpa-8,11,13-trien-19-oate (102) as needles (from methanol) (2.25 g, 84%), m.p. 112-4°C, [α]D17 +83° (c, 1.2). (Found: C 76.1, H 7.0%. C25H28O4 requires C 76.5, H 7.2%). νmax 2950, 1725 (ester), 1670 (ketone), 1600 (C=C), 1070 cm⁻¹ (C-O). δH 1.10, s, 3H, H20; 1.25, s, 3H, H18; 3.67, s, 3H, CO2CH3; 5.07, s, PhCH2. ν, oil. δC 19.6, C2; 21.3, C20; 28.0, C18, 37.4, C6; 37.4, C3; 38.4, C1; 38.8, C10; 43.9, C4; 50.2, C5; 51.6, CO2CH3; 70.1, PhCH2; 111.0, C13; 112.6, C11; 124.5, C8; 127.6, 2C, benzyl C3,C5; 128.3, benzyl C4; 128.7, 2C, benzyl C2,C6; 129.8, C14; 136.2, benzyl C1, 156.9, C9; 163.3, C12; 177.1, C19; 197.6, C7. m/z 392 (M, 1%), 378 (M-CH2, 7), 316 (7), 241 (10), 91 (100).

b) Treatment of (101) (0.1 g, 0.26 mmol) with ozone at -78°C followed by workup with dimethyl sulfide gave an oil, which was separated by p.l.c. (hexane-ether, 1:2) into starting material (35 mg) and the ketone (102) (35 mg, 14%).

Methyl 12-Benzyl-7β-hydroxypodocarpa-8,11,13-trien-19-oate (103)

A solution of sodium borohydride (58 mg, 1.5 mmol) in tetrahydrofuran (5 ml) and water (1 ml) was added to a stirred solution of the 12-benzylketo ketone (102) (0.15 g, 0.35 mmol) in tetrahydrofuran (10 ml), and the mixture was stirred for 24 h, then concentrated to small volume. The residue was partitioned between dichloromethane and 2M hydrochloric acid. The aqueous layer was extracted with dichloromethane and the combined organic fractions were washed with sodium hydrogen carbonate solution and water, dried, and concentrated to give methyl 12-benzyl-7β-podocarpa-8,11,13-trien-19-oate (103) as a glass (from ether-hexane) (0.14 g, 91%), m.p. 133-5°C, [α]D17 +169° (c, 1.0) (Found: C 76.2, H 7.7%. C25H30O4 requires C 76.2, H 7.6%). νmax 3350 (OH), 2950, 1720 (ester), 1600 (C=C), 1060 cm⁻¹ (C-O). δH 1.05, s, 3H, H20; 1.20, s, 3H, H18; 3.60, s, 3H, CO2CH3; 4.60, dd, J7α,6β 10 Hz,
A suspension of powdered potassium hydroxide (0.1 g, 1.8 mmol) in dimethyl sulfoxide (1 ml) was stirred for 5 min. A solution of the 12-benzyloxy alcohol (103) (0.15 g, 0.4 mmol) in dimethyl sulfoxide (4 ml) was added, followed immediately by iodomethane (0.12 ml, 2 mmol). The mixture was stirred for 30 min, poured into water, neutralised with 2M hydrochloric acid and extracted with dichloromethane. The extract was washed with water, dried, and concentrated to give an oil which was absorbed onto silica. Elution with hexane-ether (2:1) gave methyl 12-benzyloxy-7β-methoxypodocarpa-8,11,13-trien-19-oate (104) as an oil (72 mg, 46%), [α]D18 +80° (c, 0.7) (Found: M+ 408.2279. C26H32O4 requires M+ 408.2301). v_max 2950, 1720 (ester), 1060 cm⁻¹ (C-O). δH 1.05, s, 3H, H20; 1.25, s, 3H, H18; 3.45, s, 3H, ROCr; 3.65, s, CO2CH3; 4.40, dd, J7α,6β 10 Hz, J7α,6α 6 Hz, H7α; 5.05, s, 2H, PhCH2; 6.7-7.5, m, 8H, aryl H. δC 19.6, C2; 22.7, C20; 26.2, C6; 28.4, C18; 37.5, C3; 39.0, C10; 39.3, C1; 43.9, C4; 49.9, C5; 51.4, CO2CH3; 55.3, ROCH3; 70.0, PhCH2; 79.1, C7; 111.7, C13; 112.4, C11; 127.5, 2C, benzyl C3,C5; 127.9, benzyl C4; 128.4, 2C, benzyl C2,C6; 128.7, C14; 128.9, C8; 137.1, benzyl C1; 149.7, C9; 158.0, C12; 177.6, C19. m/z 408 (M, 1%), 394 (M-CH2, 1), 376 (M-CH3OH, 11), 317 (M-C7H7, 8), 300 (14), 241 (11), 225 (26), 185 (25), 150 (30), 91 (100).

Hydrogenation of (104) gave starting material (10%) and methyl 12-benzyloxy-podocarpa-8,11,13-trien-19-oate (101) (46%).
Methyl 7\(\varepsilon\)-Acetoxyl-12-benzylloxy-podocarpa-8,11,13-trien-19-oate (105)

A solution of the 12-benzyloxy alcohol (103) (0.11 g, 0.28 mmol) in acetic anhydride (5 ml) and pyridine (2 drops) was warmed on a waterbath for 4 h to give methyl 7\(\varepsilon\)-acetoxyl-12-benzylloxy-podocarpa-8,11,13-trien-19-oate (105) as a glass (86 mg, 71%), m.p. 48-55° (Found: M-60 376.2039. C\(_{27}\)H\(_{32}\)O\(_5\) requires M-CH\(_3\)CO\(_2\)H 376.2038). \(\nu_{\text{max}}\) 2950, 1720 (ester), 1160 cm\(^{-1}\) (C-O). \(\delta H\) 0.95, s, H20 (7\(\alpha\)-acetate); 1.08, s, H20 (7\(\beta\)-acetate); 1.23, s, H18 (7\(\alpha\)-acetate); 1.25, s, H18 (7\(\beta\)-acetate); 2.05, s, 7\(\beta\)-O\(_2\)CCH\(_3\); 2.15, S, 7\(\alpha\)-O\(_2\)CCH\(_3\); 3.65, s, 3H, CO\(_2\)CH\(_3\)); 5.05, s, PhCH\(_2\); 6.0, br s, W\(_4\) 18 Hz, H7; 6.6-7.4, m, aryl H. \(m/z\) 436 (M, 0.1%), 376 (M-CH\(_3\)CO\(_2\)H, 10), 91 (100).

Hydrogenation of (105) gave methyl 12-benzyloxy-podocarpa-8,11,13-trien-19-oate (101) (46%) and starting material (12%).

In a repeat experiment, treatment of the alcohol (103) (45 mg, 0.11 mmol) with acetic anhydride (8 ml) and pyridine (0.1 ml, 1.1 mmol) as above for 3 h gave the alkene (30) (33 mg, 77%) (identical to sample prepared below).

Starting material was recovered quantitatively from treatment of the acetate mixture (105) (22 mg, 50 \(\mu\)mol) with pyridine (50 \(\mu\)l, 0.6 mmol) in refluxing tetrahydrofuran (5 ml) for 5 h.

Methyl 12-Benzylloxy-podocarpa-6,8,11,13-tetraen-19-oate (30)

A solution of the 12-benzyloxy 7\(\beta\)-alcohol (103) (0.75 g, 1.8 mmol) in methanol (30 ml) and 10% hydrochloric acid (5 ml) was refluxed for 5 h, poured into water, and extracted with dichloromethane to give methyl 12-benzyloxy-podocarpa-6,8,11,13-tetraen-19-oate (30) as prisms (from methanol), m.p. 81-83°, [\(\alpha\)]\(_D\)\(^{17}\) -53° (c, 1.0) (Found: C 79.9, H 7.6%. C\(_{25}\)H\(_{28}\)O\(_3\) requires C 79.8, H 7.5%). \(\nu_{\text{max}}\) 1720 (ester), 1600 (C=C), 1060 cm\(^{-1}\) (C-O). \(\delta H\) 0.87, s, 3H, H20; 1.30, s, 3H, H18; 3.65, s, 3H, CO\(_2\)CH\(_3\); 4.98, s, 2H, PhCH\(_2\); 6.3 br s, 2H, H6,7; 6.5-7.4, m, 8H, aryl H. \(\delta C\) 19.3, C20; 19.7, C2;
A solution of methyl 12-benzoyloxy-7β-hydroxy podocarpa-8,11,13-trien-19-oate (95) (0.41 g, 1.0 mmol) and p-toluenesulphonic acid (0.15 g) in tetrahydrofuran (25 ml) was refluxed for 16 h, poured into water and extracted with dichloromethane. The extract was washed with sodium hydrogen carbonate solution, dried, and concentrated to give an oil which was absorbed onto silica. Elution with dichloromethane gave methyl 12-benzoyloxy podocarpa-6,8,11,13-tetraen-19-oate (108) as a glass (from dichloromethane-hexane) (0.26 g), m.p. 48-53°, [α]D24 -25° (c, 0.2) (Found: M+ 390.1836. C26H26O4 requires M 390.1831). νmax 2950, 1720 (ester), 1600 cm⁻¹ (C=C). δH 0.95, s, 3H, H20; 1.32, S, 3H, H18; 3.67, s,3H, CO₂CH₃; 6.45, br s, 2H, H6,7; 6.9-8.3, m, 8H, aryl H. δC 19.3, C20; 19.5, C2; 22.7, C18; 35.9, C3; 37.2, C1; 38.1, C10; 43.4, C4; 50.9, CO₂CH₃; 51.6, C5; 116.3, C13; 119.1, C11; 124.7, C6; 127.1, C7; 128.5, 2C, benzoate C3,C5; 129.6, C8; 129.9, C14; 130.1, 2C, benzoate C2,C6; 130.5, benzoate C1; 133.5, benzoate C4; 147.8, C9; 150.2, C12; 165.3, PhCO₂; 177.4, C19. m/z 390 (M, 11%), 330 (3), 315 (5), 105 (100), 77 (17).

Further elution with dichloromethane gave the 12-hydroxy Δ⁶-alkene (92) (30 mg, 10%), while elution with 2% ethyl acetate in dichloromethane gave starting material (10 mg).

Treatment of (92) with benzoic anhydride and pyridine gave (108) (75%).
**Methyl 7β-Acetoxy-12-benzoyloxypodocarpa-8,11,13-trien-19-oate (109)**

Treatment of methyl 12-benzoyloxy-7β-hydroxypodocarpa-8,11,13-trien-19-oate (95) (0.1 g, 0.25 mmol) with acetic anhydride (8 ml) and pyridine (5 drops) on a waterbath for 5 h gave an oil which was absorbed onto silica. Elution with dichloromethane gave methyl 7β-acetoxy-12-benzoyloxypodocarpa-8,11,13-trien-19-oate (109) (0.1 g, 83%) as needles (from dichloromethane-hexane) (60 mg), m.p. 149-153°, [α]D24 +99° (c, 1.5) (Found: C 72.2, H 6.9%. C27H39O6 requires C 72.0, H 6.7%). νmax 2950, 1720 (ester), 1600 cm⁻¹ (C=C). δH 1.13, s, 3H, H20; 1.30, s, 3H, H18; 2.20, s, 3H, CH₃CO₂; 3.72, s, 3H, CO₂CH₃; 5.98, dd, J7α,6β 10, J7α,6α 7 Hz, H7α; 6.8-8.3, m, 8H, aryl H. δC 19.7, C2; 21.5, CH₃CO₂; 22.7, C20; 27.3, C6; 28.4, C18; 37.4, C3; 39.0, C10; 39.2, C1; 43.8, C4; 49.6, C5; 51.5, CO₂CH₃; 72.7, C7; 118.5, C13; 119.5, C11; 128.2, 2C, benzoate C2,C6; 129.5, benzoate C1; 130.2, 2C, benzoate C3,C5; 131.6, C8; 133.6, benzoate C4; 150.3, C9; 150.6, C12; 165.2, PhCO₂; 171.2, CH₃CO₂; 177.3, C19. m/z 450 (M, 2%), 408 (M-CH₂CO, 1.5), 390 (M-HOAc; 10), 105 (100), 77 (18).

Further elution with dichloromethane gave starting material (5 mg). Starting material was recovered quantitatively from treatment of the acetate (109) (45 mg, 0.1 mmol) with pyridine (0.1 ml, 1.2 mmol) in refluxing tetrahydrofuran (5 ml) for 5 h.

**Epoxidation of Methyl 12-Benzzyloxypodocarpa-6,8,11,13-tetraen-19-oate (30)**

A solution of m-chloroperoxybenzoic acid (0.2 g, 0.9 mol) in dichloromethane (5 ml) was added to a stirred solution of methyl 12-benzzyloxypodocarpa-6,8,11,13-tetraen-19-oate (30) (0.2 g, 0.53 mmol) in dichloromethane (5 ml) at 0°. The mixture was stirred at 0° for 90 min, then at room temperature for 30 min. The mixture was diluted with dichloromethane, washed with potassium iodide solution, sodium hydrogensulfite solution, sodium hydrogen carbonate solution, and brine, dried, and concentrated to give an oil (0.2 g) which was absorbed onto silica. Elution with hexane-ether (1:1) and separation of a mixed fraction on a Chromatotron (hexane-ether, 3:2) gave (in order of
elution): (i) methyl 12-benzyloxy-7β-(3'-chlorobenzoyloxy)-6α-hydroxypropodocarpa-8,11,13-trien-19-oate (110) as a glass (from ether-hexane) (35 mg, 12%), m.p. 63-68°, [α]D 21 +30° (c, 1.5) (Found: C 69.3, H 6.0%; M-156 392.1489. C30H33ClO5 requires C 70.0, H 6.1%; M-C6H4ClO2H 392.1888). νmax 3450 (OH), 2950, 1715 (ester), 1600 (C=C), 1060 cm⁻¹ (C-O). δH 1.17, s, 3H, H20; 1.20, td, J3α,3β=J1α,2β 13.9, J1α,2α 4.2 Hz, H3α; 1.41, td, J1α,1β=J1α,2β 13.3, J1α,2α 3.7 Hz, H1α; 1.50, s, 3H, H18; 1.62, dm, H2α; 1.84, d, J5α,6β 11.0 Hz, H5; 1.90, qt, J2β,2α=J2β,3α 13.9, J2β,1α 13.3, J2β,3β 3.5, J2β,1β 3.3 Hz, H2β; 2.22, br d, J1α,1β 13.3 Hz, H1β; 2.28, br d, J3β,3α 13.9 Hz, H3β; 3.33, br s, OH; 3.77, s, 3H, CO2CH3; 4.65, dd, J6β,5α 11.0, J6β,7α 8.6 Hz, H6β; 5.03, s, 2H, PhCH2; 6.37, d, J7α,6β 8.6 Hz, H7α; 6.82, dd, J13,14 8.5, J13,11 2.5 Hz, H13; 6.88, d, J11,13 2.5 Hz, H11; 7.13, d, J14,13 8.5 Hz, H14; 7.35, tt, J4,3=J4,5 6.9, J4,4=J4,6 1.8 Hz, benzyl H4; 7.38, t, J3,2=J3,4 6.9 Hz, 2H, benzyl H3,H5; 7.42, dd, J2,3 6.9, J2,4 1.8 Hz, 2H, benzyl H2,H6; 7.45, t, J5,4=J5,6 8.0 Hz, benzoate H5; 7.54, ddd, J4,5 8.0, J4,4 2.1, J4,6 1.3 Hz, benzoylate H4; 8.05, dt, J6,5 8.0, J6,2 1.7 Hz, benzoate H6; 8.10, t, J2,4 2.1, J2,6 1.7 Hz, benzoate H2. δC 19.6, C2; 23.6, C20; 32.4, C18; 38.6, C3; 39.5, C1; 40.5, C10; 44.5, C4; 52.3, C5; 55.4, CO2CH3; 70.1, PhCH2; 72.0, C6; 77.8, C7; 111.6, C13; 112.8, C11; 125.2, C8; 127.5, 2C, benzyl C3,C5; 128.0, benzyl C4, 128.1, benzoate C6; 128.6, 2C, benzyl C2,C6; 129.0, C14; 129.6, benzoate C5; 129.9, benzoate C2; 132.2, benzoate C1, 132.9, benzoate C4; 134.4, benzoate C3; 136.8, benzyl C1; 149.3, C9; 158.7, C12; 166.0, ArCO2; 178.6, C19. m/z 392 (M-C6H4ClO2H, 11%), 139 (C26H4CO, 8), 91 (100).

(ii) methyl 12-benzyloxy-7α-(3'-chlorobenzoyloxy)-6α-hydroxypropodocarpa-8,11,13-trien-19-oate (111) as a glass (from ether-hexane) (75 mg, 26%), m.p. 60-65°, [α]D 21 +140° (c, 2.0) (Found: C 70.0, H 6.3%. C29H33ClO5 requires C 70.0, 6.1%). νmax 3450 (OH), 2950, 1715 (ester), 1600 (C=C), 1060 cm⁻¹ (C-O). δH 1.07, S, 3H, H20; 1.22, td, J3α,3β=J3α,2β 14.0, J3α,2α 3.5 Hz, H3α; 1.28, td, J1α,1β=J1α,2β 13.9, J1α,2α 4.4 Hz, H1α; 1.54, s, 3H, H18; 1.69, dm, J2α,2β 14.1 Hz, H2α; 1.93, qt, J2β,2α 14.1, J2β,3α 14.0, J2β,1α 13.9, J2β,1β=J2β,3β 3.5 Hz, H2β; 2.23, br d, H1β; 2.29, d, J5α,6β 10.1 Hz, H5; 2.33, br d, H3β; 3.40, br s, OH; 3.78, s, 3H, CO2CH3; 4.74, dd, J6β,5α
10.1, J_{6\beta,7\beta} 3.6 Hz, H6\beta; 5.04, s, 2H, PhCH2; 6.48, d, J_{7\beta,6\beta} 3.6 Hz, H7\beta; 6.84, dd, J_{13,14} 8.4, J_{13,11} 2.5 Hz, H13; 6.92, d, J_{11,13} 2.5 Hz, H11; 7.31, J_{14,13} 8.4 Hz, H14; 7.34, td, J_{4,3}=J_{4,5} 6.8, J_{4,2}=J_{4,6} 1.7 Hz, benzyl H4; 7.38, t, J_{3,4} 7.0, J_{3,2} 6.8 Hz, 2H, benzyl H3,H5; 7.38, t, J_{5,4} 8.0, J_{5,3} 7.8 Hz, benzoate H5; 7.42, dd, J_{2,3} 7.0, J_{2,4} 1.7 Hz, 2H, benzyl H2,H6; 7.51, ddd, J_{4,5} 8.0, J_{4,2} 2.1, J_{4,6} 1.1 Hz, benzoate H4; 7.98, dt, J_{6,5} 7.8, J_{6,2} 1.4, J_{6,4} 1.1 Hz, benzoate H6; 8.06, t, J_{2,4} 2.1, J_{2,6} 1.4 Hz, benzoate H2.

\( \delta_C \) 19.7, C2; 22.7, C20; 31.8, C18; 38.5, C3; 39.3, C1; 40.5, C10; 44.2, C4; 52.2, CO\_2CH\_3; 52.4, C5; 69.8, C6; 70.0, PhCH\_2; 73.9, C7; 111.6, C11; 112.6, C13; 124.7, C8; 127.5, 2C, benzyl C3,C5; 128.0, benzyl C4; 128.3, benzoate C6; 128.6, 2C, benzyl C2,C6; 129.6, C14; 129.8, benzoate C5; 131.5, benzoate C2; 132.5, benzoate C1; 132.9, benzoate C4; 134.4, benzoate C3; 136.7, benzyl C1; 149.4, C9; 159.3, C12; 165.3, ArCO\_2; 178.8, C19.

m/z 392 (M-CIC\_6H\_4CO\_2H, 14%), 139 (22), 91 (100).

(iii) a glass (35 mg, 12%), m.p. 58-62\(^\circ\), which by \(^1\)H n.m.r. analysis was a mixture of methyl 12-benzyloxy-6α-(3'-chlorobenzyloxy)-7α-hydroxypodocarpa-8,11,13-trien-19-oate (113) (77%) and methyl 12-benzyloxy-6β-(3'-chlorobenzyloxy)-7β-hydroxypodocarpa-8,11,13-trien-19-oate' (114) (23%). \( \nu_{\text{max}} \) 3450 (OH), 2950, 1715 (ester), 1600 (C=C), 1060 cm\(^{-1}\) (C-O). \( \delta_H \) 1.09, s, 3H, H20; 1.21, td, J_{3α,3β}=J_{3α,2β} 13.6, J_{3α,2α} 4.3 Hz, H3α; 1.40, s, H18(113); 1.49, s, H18(114); 1.56, td, J_{1α,1β}=J_{1α,2β} 13.8, J_{1α,2α} 3.8 Hz, H1α; 1.65, dm, H2α; 1.92, qm, J_{2β,2α} 14.1, J_{2β,1α} 13.8, J_{2β,3α} 13.6 Hz, H2β; 2.22, br d, H1β; 2.30, d, J_{5α,6α} 3.5 Hz, H5(114); 2.32, br d, H3β; 2.35, d, J_{5α,6β} 9.4 Hz, H5(113); 3.64, s, 3H, CO\_2CH\_3; 5.03, d, J_{7β,6β} 3.9 Hz, H7β(113); 5.06, s, 2H, PhCH\_2; 6.28, dd, J_{6β,5α} 9.4, J_{6β,7β} 3.9 Hz, H6β(113); 6.48, dd, J_{6α,7α} 7.2, J_{6α,5α} 3.5 Hz, H6α(114); 6.84, dd, J_{13,14} 8.5, J_{13,11} 2.5 Hz, H13; 6.89, d, J_{11,13} 2.5 Hz, H11; 7.31, d, J_{14,13} 8.5 Hz, H14; 7.35, br t, J_{4,3}=J_{4,5} 7.0 Hz, benzyl H4; 7.39, t, J_{5,4}=J_{5,6} 8.0 Hz, benzoate H5; 7.39, t, J_{3,2}=J_{3,4} 7.0 Hz, 2H, benzyl H3,H5; 7.43, br d, J_{2,3} 7.0 Hz, 2H, benzyl H2,H6; 7.54, ddd, J_{4,5} 8.0, J_{4,2} 2.1, J_{4,6} 1.0 Hz, benzoate H4; 7.93, dt, J_{6,5} 8.0, J_{6,2} 1.3, J_{6,4} 1.0, benzoate H6; 8.01, t, J_{2,4} 2.1, J_{2,6} 1.3 Hz, benzoate H2. \( \delta_C \) 19.6, C2; 22.8, C20; 30.1, C18; 38.6, C3; 39.2, C1; 40.4, C10; 44.1, C4; 49.9, C5; 51.8, CO\_2CH\_3; 68.8, C7; 70.1, PhCH\_2; 75.0, C6; 111.5, C13; 112.6, C11;
126.9, C8; 127.6, 2C, benzyl C3,C5; 127.9, benzyl C4; 128.0, benzoate C6; 128.6, 2C, benzyl C2,C6; 129.6, benzoate C5; 129.8, 2C, C14, benzoate C2; 132.2, benzoate C1; 133.1, benzoate C4; 134.7, benzoate C3; 148.0, C9; 159.0, C12; 164.9, ArCO2; 177.2, C19. \( m/z \) 392 (M-ClC6H4CO2H, 2%), 139 (ClC6H4CO, 12), 91 (100).

(iii) methyl 12-benzylxy-6α,7α-dihydroxypodocarpa-8,11,13-trien-19-oate as a glass (from ether-hexane) (112) (20 mg, 9%), m.p. 45-50°, [α]_D^{21} +18° (c, 0.2) (Found: M-18 392.1970. C_{18}H_{30}O_5 requires M-H2O 392.1988). ν_{max} 3500 (OH), 3030, 1720 (ester), 1600 (C=C), 1025 cm^{-1} (C-O).

In a repeat experiment treatment of the alkene (30) (0.86 g, 2.3 mmol) with \( m \)-chloroperbenzoic acid (1.25 g, 5 mmol) as above gave:

(i) the 6α,7α-diol (112) (51 mg, 6%).

(ii) methyl 12-benzyloxy-6β,7β-dihydroxypodocarpa-8,11,13-trien-19-oate (116) as an oil (22 mg, 2%), [α]_D^{21} +46° (c, 0.5) (Found: M^+ 410.2100. C_{18}H_{30}O_5 requires M^+ 410.2093.) ν_{max} 3450 (OH), 3000, 1720 (ester), 1600 (C=C), 1020 cm^{-1} (C-O). δ_H 1.07, s, 3H, H20; 1.53, s, 3H, H18; 3.77, s, 3H, CO_2CH_3; 4.30, br d, J_{6α,7α} 8 Hz, H6α; 4.67, d, J_{7α,6α} 8 Hz, H7α; 5.00, s, 2H, PhCH_2; 6.6-7.4, m, 8H, aryl H. \( m/z \) 410 (M, 1%), 392 (M-H2O, 6), 378 (M-CH_3OH, 2), 360 (2), 91 (100).
(iii) an oil (0.43 g, 34%) which by $^1$H n.m.r. analysis was a mixture of (110) (60%) and methyl 12-benzyl oxy-6α-(3'-chlorobenzyloxy)-7β-hydroxypodocarpa-8,11,13-trien-19-oate (115) (40%). $\delta_H$ 1.32, s, 3H, H20; 1.50, s, 3H, H18; 2.13, d, $J_{5\alpha,6\beta}$ 11.0 Hz, H5; 3.77, s, 3H, CO$_2$CH$_3$; 4.87, dd, $J_{6\beta,5\alpha}$ 11.0, $J_{6\beta,7\alpha}$ 8.3 Hz, H6$\beta$; 5.04, s, 2H, PhCH$_2$; 5.94, d, $J_{7\alpha,6\beta}$ 8.3 Hz, H7$\alpha$; 6.84, dd, $J_{13,14}$ 8.4, $J_{13,11}$ 2.8 Hz, H13; 6.87, d, $J_{11,13}$ 2.8 Hz, H11; 7.23, $J_{14,13}$ 8.4 Hz, H14; 7.3-7.5, m, 6H, benzyl H2-6, benzoate H5; 7.60, m, benzoate H4; 7.95, m, benzoate H6; 8.16, t, $J_{2,4}=J_{2,6}$ 1.8 Hz, benzoate H2. m/z 392 (M-CIC$_6$H$_4$CO$_2$H, 1%), 91 (100).

**Epoxidation of Methyl 12-Benzoyloxy-podocarpa-6,8,11,13-tetraen-19-oate (108)**

A solution of m-chloroperbenzoic acid (0.2 g, 0.5 mmol) in dichloromethane (4 ml) was added to a stirred solution of methyl 12-benzoyloxy-podocarpa-6,8,11,13-tetraen-19-oate (108) (0.2 g, 0.5 mmol) in dichloromethane (9 ml) at 0°C. The mixture was stirred at 0°C for 2 h, then at room temperature for 4 h. Workup gave a solid which was absorbed onto silica. Elution with dichloromethane gave the 7-ketone (92) (11 mg, 5%). Further elution with dichloromethane gave an oil (96 mg) which was separated by p.l.c. (hexane-ether, 1:2) into:

(i) *methyl 12-benzyl oxy-6-oxopodocarpa-8,11,13-trien-19-oate* (121) (7 mg, 3%) an oil, $[\alpha]_D^{21}$ +15° (c, 0.7) (Found: M$^+$ 406.1775. C$_{25}$H$_{26}$O$_5$ requires M$^+$ 406.1781.) $v_{max}$ 2950, 1720 (C=O), 1600 cm$^{-1}$ (C=C). $\delta_H$ 1.34, s, 3H, H20; 1.41, s, 3H, H18; 2.47, s, H5; 3.66, 2s, 2H, H7; 3.72, s, 3H, CO$_2$CH$_3$; 7.07, dd, $J_{13,14}$ 8.1, $J_{13,11}$ 2.2 Hz, H13; 7.16, d, $J_{11,13}$ 2.2 Hz, H1; 7.18, d, $J_{14,13}$ 8.1 Hz, H14; 7.53, t, $J_{3,5}$ 7.8, $J_{3,4}$ 7.4 Hz, 2H, benzoate H3,H5; 7.66, t, $J_{4,3}=J_{4,5}$ 7.4 Hz, benzoate H4; 8.22, d, $J_{2,3}$ 7.8 Hz, 2H, benzoate H2,H6. m/z 406 (M, 7%), 203 (15), 139 (9), 105 (100), 77 (23).

(ii) a glass which by $^1$H n.m.r. analysis was a mixture of *methyl 12-benzyl oxy-7α-(3'-chlorobenzyloxy)-6α-hydroxy-podocarpa-8,11,13-trien-19-oate* (117) (44%) and *methyl 12-benzyl oxy-6α-(3'-chlorobenzyloxy)-7α-hydroxy-podocarpa-8,11,13-trien-19-oate* (118) (56%). $v_{max}$ 3450 (OH), 2950, 1720 (ester), 1600 cm$^{-1}$ (C=C). $\delta_H$ 1.12,
Further elution with dichloromethane gave an oil (75 mg) which was separated by p.l.c. (hexane-ether, 1:4) into:

(i) methyl 12-benzoyloxy-6α,7α-dihydroxypodocarpa-8,11,13-trien-19-oate (119) as a glass (from ether-hexane) (28 mg, 15%), m.p. 68-73°, [α]D22 +56° (c, 0.3) (Found: M-18 406.1785. C25H28O6 requires M-H2O 406.1781). νmax 3450 (OH), 2950, 1725 (ester), 1600 (C=C), 1060 cm⁻¹ (C-O). δH 1.04, s, 3H, H20; 1.20, rd, J3α,3β=J3α,2β 13.8, J3α,2α 4.3 Hz, H3α; 1.50, s, 3H, H18; 1.51, td, J1α,1β=J1α,2β 12.8, J1α,2α 4.2 Hz, H1α; 1.64, dm, J2α,2β 13.9 Hz, H2α; 1.92, qt, J2β,2α 13.9, J2β,3α 13.8, J2β,1α 12.8, J2β,1β=J2β,3β 3.5 Hz, H2β; 2.07, d, J5α,6β 8.6 Hz, H5; 2.16, br d, H1β; 2.30, br d, J3β,3α 13.9 Hz, H3β; 3.06, br s, 7α-OH; 3.42, d, J 4.5 Hz, 6α-OH; 3.67, s, 3H, CO2CH3; 4.62, dt, J6β,5α 8.6, J6β,OH 4.5, J6β,7β 3.6 Hz, H6β; 4.90, d, J7β,6β 3.6 Hz, H7β; 7.10, d, J11,13 1.5 Hz, H11; 7.11, dd, J13,14 7.4, J13,11 1.5 Hz, H13; 7.50, d, J14,13 7.4 Hz, H14; 7.50, dd, J3,2 8.3, J3,4 7.4 Hz, 2H, benzoate H3,H5; 7.63, tt, J4,3=J4,5 7.4, J4,2=J4,6 1.3 Hz, benzoate H4; 8.19, dd, J2,3 8.3, J2,4 1.3 Hz, 2H, benzoate H2,H6. δC 19.6, C2; 22.5, C20; 31.3, C18; 38.3, C3; 38.9, C10; 39.2, C1; 44.1, C4; 51.8, C5; 52.1, CO2CH3; 70.2, C6; 70.8, C7; 117.7, C13; 119.8, C11; 128.5, 2C, benzoate C3,C5; 129.5, C8; 130.1, 2C, benzoate C2,C6; 130.6, C14; 132.5, benzoate C1; 133.4, benzoate C4; 148.7, C9; 150.9, C12; 165.2, PhCO2; 178.7, C19.
m/z 406 (M-H$_2$O, 12%), 374 (4), 105 (100), 77 (35).

(iv) methyl 12-benzyloxy-6α,7β-dihydroxypodocarpa-8,11,13-trien-19-oate (120) as a glass (15 mg, 8%), m.p. 55-60°, [α]$^D_{22}$ +70° (c, 0.5) (Found: M=18 406.1777. C$_{25}$H$_{28}$O$_6$ requires M-H$_2$O 406.1781). $\nu_{\text{max}}$ 3450 (OH), 2950, 1730 (ester), 1600 (C=C), 1060 cm$^{-1}$ (C-O). δ$_H$ 1.10, s, 3H, H20; 1.18, td, $J_{3\alpha,3\beta}$=$J_{3\alpha,2\beta}$ 13.9, $J_{3\alpha,2\alpha}$ 4.4 Hz, H3α; 1.44, td, $J_{1\alpha,1\beta}$=$J_{1\alpha,2\beta}$ 13.2, $J_{1\alpha,2\alpha}$ 3.8 Hz, H1α; 1.54, s, 3H, H18; 1.61, dm, $J_{2\alpha,2\beta}$ 13.9 Hz, H2α; 1.76, $J_{5\alpha,6\beta}$ 11.0 Hz, H5; 1.89, qt, $J_{2\beta,2\alpha}$=$J_{2\beta,3\alpha}$ 13.9, $J_{2\beta,1\alpha}$ 13.2, $J_{2\beta,1\beta}$=$J_{2\beta,3\beta}$ 3.5 Hz, H2β; 2.18, br d, $J_{1\beta,1\alpha}$ 13.2 Hz, H1β; 2.27, br d, $J_{3\beta,3\alpha}$ 13.9 Hz, H3β; 3.30, br s, 6α-OH; 3.74, br s, 7β-OH; 3.79, s, 3H, CO$_2$CH$_3$; 4.29, dd, $J_{6\beta,5\alpha}$ 11.0, $J_{6\beta,7\alpha}$ 9.0 Hz, H6β; 4.72, d, $J_{7\alpha,6\beta}$ 9.0 Hz, H7α; 7.05, d, $J_{11,13}$ 2.3 Hz, H11; 7.10, dd, $J_{13,14}$ 8.5, $J_{13,11}$ 2.3 Hz, H13; 7.50, t, $J_{3,2}$ 8.0, $J_{3,4}$ 7.5 Hz, 2H, benzoate H3,H5; 7.63, tt, $J_{4,3}$=$J_{4,5}$ 7.5, $J_{4,2}$=$J_{4,6}$ 1.4 Hz, benzoate H4; 7.68, dd, $J_{2,3}$ 8.0, $J_{2,4}$ 1.4 Hz, 2H, benzoate H2,H6. δ$_C$ 19.6, C2; 23.9, C20; 32.3, C18; 38.4, C1; 39.4, C3; 41.0, C10; 44.4, C4; 52.4, C5; 54.7, CO$_2$CH$_3$; 74.2, C6; 75.2, C7; 117.8, C13; 120.0, C11; 128.6, 2C; benzoate C3,C5; 129.6, C8; 130.2, 2C, benzoate C2,C6; 133.2, benzoate C1; 133.6, benzoate C4; 147.8, C9; 150.4, C12; 165.2, PhCO$_2$; 178.8, C19. m/z 406 (M-H$_2$O, 9%), 374 (8), 105 (100), 77 (20).

**Methyl 6α,12-Dihydroxypodocarpa-8,11,13-trien-19-oate (26)**

10% Palladium on charcoal (60 mg) was added to a solution of methyl 12-benzyloxy-6α,7α-dihydroxypodocarpa-8,11,13-trien-19-oate (112) (82 mg, 0.2 mmol) and ammonium formate (63 mg, 1 mmol) in methanol, and the mixture was refluxed for 1 h. The cooled solution was filtered and concentrated to give *methyl 6α,12-dihydroxypodocarpa-8,11,13-trien-19-oate* (26) as a glass (from methanol) which coloured in air, (50 mg, 83%), m.p. 73-78°, [α]$^D_{20}$ +57° (c, 1.0) (Found: M$^+$ 304.1696. C$_{18}$H$_{24}$O$_4$ requires M$^+$ 304.1675). $\nu_{\text{max}}$ 3350 (OH), 2950, 1720 (ester), 1600 (C=C), 1030 cm$^{-1}$ (C-O). δ$_H$ 1.01, s,3H, H20; 1.15, td, $J_{3\alpha,3\beta}$=$J_{3\alpha,2\beta}$ 14.0, $J_{3\alpha,2\alpha}$ 4.3 Hz, H3α; 1.50, s, 3H, H18; 1.50, m, H1α; 1.59, d, $J_{5\alpha,6\beta}$ 9.0 Hz, H5; 1.62, dm, H2α,
1.91, q, \( J_{2\beta,2\alpha}=J_{2\beta,3\alpha} \) 14.0, \( J_{2\beta,1\alpha} \) 13.7, \( J_{2\beta,1\beta}=J_{2\beta,3\beta} \) 4.0 Hz, H2\( \beta \); 2.16, br d, H1\( \beta \); 2.27, br d, H3\( \beta \); 2.82, dd, \( J_{7\alpha,7\beta} \) 15.8, \( J_{7\alpha,6\beta} \) 9.0 Hz, H7\( \alpha \); 3.15, dd, \( J_{7\beta,7\alpha} \) 15.8, \( J_{7\beta,6\beta} \) 5.2 Hz, H7\( \beta \); 3.67, s, 3H, CO\(_2\)CH\(_3\); 4.62, td, \( J_{6\beta,5\alpha}=J_{6\beta,7\alpha} \) 9.0, \( J_{6\beta,7\beta} \) 5.2 Hz, H6\( \beta \); 6.63, dd, \( J_{13,14} \) 8.2, \( J_{13,11} \) 1.3 Hz, H13; 6.72, d, \( J_{11,13} \) 1.3 Hz, H11; 6.96, d, \( J_{14,13} \) 8.2 Hz, H14. \( m/z \) 304 (M, 37%), 302 (M-2H, 56), 286 (M-H\(_2\)O, 25), 270 (48), 211 (68), 105 (100).

The dihydroxy compound (26) was also obtained by hydrogenation of the 6\( \alpha \)-hydroxy compounds (110) (80%), (111) (74%), and (119) (77%).

**Ozonolysis of Methyl 6\( \alpha \)-12-Dihydroxypodocarpa-8,11,13-trien-19-oate (26)**

Ozone was passed through a solution of methyl 6\( \alpha \),12-dihydroxypodocarpa-8,11,13-trien-19-oate (26) (60 mg, 0.2 mmol) in dichloromethane-methanol (1:1, 25 ml) at -78\( ^\circ \) until the blue colour persisted (15 min). The solution was purged with oxygen and a solution of sodium borohydride (38 mg, 1 mmol) in 50% aqueous ethanol (5 ml) was added. The mixture was stirred for 2.5 h, then worked up to give an oil (40 mg) which coloured in air, and which was a complex mixture by t.l.c. analysis.

**Hydroboration of Methyl 12-Benzylloxypodocarpa-6,8,11,13-tetraen-19-oate (30)**

A solution of the alkene (30) (0.3 g, 0.8 mmol) and borane-dimethyl sulfide (90 \( \mu \)l, 10M, 0.9 mmol) in dry tetrahydrofuran (15 ml) was stirred under a nitrogen atmosphere for 3.5 h. Water (0.6 ml) was added, followed by 3M sodium hydroxide solution (0.3 ml, 0.9 mmol). The solution was cooled to 0\( ^\circ \) and 27% hydrogen peroxide solution (0.23 ml, 1.8 mmol) was added dropwise. The mixture was warmed to 50\( ^\circ \) for 1 h, then worked up to give an oil which was absorbed onto silica.

Elution with dichloromethane gave methyl 12-benzyloxypodocarpa-8,11,13-trien-19-oate (101) (10 mg, 3%).

Elution with 1% ethyl acetate in dichloromethane and separation of a mixed
fraction on a Chromatotron gave (in order of elution):

(i) 12-benzyloxy-6α-hydroxypodocarpa-8,11,13-trien-19-al (124) as a glass (from dichloromethane-hexane) (80 mg, 27%), m.p. 40-45°C, [α]D^21 +15° (c, 1.0) (Found: C 78.9, H 7.8%. C_{24}H_{28}O_3 requires C 79.1, H 7.7%). \( \nu_{\text{max}} \) 3450 (OH), 2950, 1710 (CHO), 1600 (C=C), 1060 cm\(^{-1} \) (C-O). \( \delta_H \) 1.02, s, 3H, H20; 1.10-1.30, m, 2H, H1α, H3α; 1.30, s, 3H, H18; 1.45-1.55, m, H2α; 1.59, d, J_{5\alpha,6\beta} 8.5 Hz, H5; 1.68-1.80, m, H2β; 2.18, br d, J_{1\beta,1\alpha} 13.2 Hz, H1β; 2.28, br d, H3β; 2.81, dd, J_{7\alpha,7\beta} 16.1, J_{7\alpha,6\beta} 6.1 Hz, H7α; 3.28, dd, J_{7\beta,7\alpha} 16.1, J_{7\beta,6\beta} 5.8 Hz, H7β; 4.69, dt, J_{6\beta,5\alpha} 8.5, J_{6\beta,7\alpha} 6.1, J_{6\beta,7\beta} 5.8 Hz, H6β; 5.02, s, 2H, PhCH\(_2\); 6.78, dd, J_{13,14} 8.3, J_{13,11} 2.5 Hz, H13; 6.89, d, J_{11,13} 2.5 Hz, H11; 7.04, J_{14,13} 8.3 Hz, H14; 7.32, dt, J_{4,3}=J_{4,5} 6.9, J_{4,2}=J_{4,6} 2.3 Hz, benzyl H4; 7.38, J_{3,2}=J_{3,4} 6.9 Hz, 2H, benzyl H3,H5; 7.43, dd, J_{2,3} 6.9, J_{2,4} 2.3 Hz, 2H, benzyl H2,H6; 9.15, s, CHO. \( \delta_C \) 19.1, C2; 23.5, C20; 26.8, C18; 36.2, C7; 38.4, C3; 39.3, C10; 39.4, C1; 48.5, C4; 58.3, C5; 67.3, C6; 70.1, PhCH\(_2\); 111.2, C13; 111.9, C11; 125.9, C8; 127.5, 2C, benzyl C3,C5; 127.9, benzyl C4; 128.5, 2C, benzyl C2,C6; 129.9, C14; 137.1, benzyl C1; 148.5, C9; 157.6, C12; 207.8, C19. m/z 364 (M, 11%), 91 (100).

(ii) methyl 12-benzyloxy-7α-hydroxypodocarpa-8,11,13-trien-19-oate (123) as a glass (0.1 g, 32%), m.p. 45-50°C, [α]D^21 +104° (c, 0.4) (Found: M-18 376.2055. C_{25}H_{30}O_4 requires M-H\(_2\)O 376.2038). \( \nu_{\text{max}} \) 3400 (OH), 3050, 1715 (ester), 1600 (C=C), 1060 cm\(^{-1} \) (C-O). \( \delta_H \) 0.87, td, J_{3\alpha,3\beta}=J_{3\alpha,2\beta} 13.8, J_{3\alpha,2\alpha} 3.8 Hz, H3α; 0.95, s, 3H, H20; 1.15, td, J_{1\alpha,1\beta}=J_{1\alpha,2\beta} 13.4, J_{1\alpha,2\alpha} 4.2 Hz, H1α; 1.29, s, 3H, H18; 1.29, br d, J_{5\alpha,6\beta} 12.7 Hz, H5; 1.47, dm, J_{2\alpha,2\beta} 15.0 Hz, H2α; 1.59, br s, OH; 1.63-1.71, m, H2β; 1.96-2.00, m, H6α; 2.19, ddd, J_{6\beta,6\alpha} 14.5, J_{6\beta,5\alpha} 12.7, J_{6\beta,7\beta} 3.7 Hz, H6β; 2.19, br d, H1β; 2.30, br d, H3β; 3.66, s, 3H, CO\(_2\)CH\(_3\); 4.81, br s, W\(_\frac{1}{2} \) 8 Hz, H7β; 5.04, s, 2H, PhCH\(_2\); 6.83, dd, J_{13,14} 8.4, J_{13,11} 2.5 Hz, H13; 6.90, d, J_{11,13} 2.5 Hz, H11; 7.23, d, J_{14,13} 8.4 Hz, H14; 7.32, t, J_{4,3}=J_{4,5} 7.1 Hz, benzyl H4; 7.38, t, J_{3,4}=J_{3,5} 7.1, J_{3,2} 6.8 Hz, 2H, benzyl H3,H5; 7.42, d, J_{2,3} 2H, benzyl H2,H6. \( \delta_C \) 19.9, C2; 21.8, C20; 28.3, C18; 29.8, C6; 37.5, C3; 38.7, C10; 38.9, C1; 43.6, C4; 45.4, C5; 51.3, CO\(_2\)CH\(_3\); 67.9, C7; 70.0, PhCH\(_2\); 112.0, C13; 112.8, C11; 127.5, 2C, benzyl C3,C5; 128.0, benzyl C4;
128.6, 2C, benzyl C2, C6; 129.1, C8; 131.3, C14; 137.0, benzyl C1; 150.0, C9; 158.7, C12; 177.9, C19. m/z (M-H2O, 40%), 91 (100).

Elution with 5% ethyl acetate in dichloromethane gave 12-benzyloxypodocarpa-8,11,13-triene-6α,19-diol (125) as a glass (from dichloromethane-hexane) (0.1 g, 32%), m.p. 47-52°, [α]D21 +60° (c, 0.6) (Found: M’+ 366.2200. C24H36O3 requires M’+ 366.2196). υmax 3200 (OH), 3050, 1715 (ester), 1600 (C=C), 1060 cm⁻¹ (C-O).

Reduction of (124) with sodium borohydride in aqueous tetrahydrofuran gave (125) (80%). Hydrogenation of (123) with ammonium formate and 10% palladium on charcoal gave methyl podocarpate (10) (80%).

**Acetylation of the 7α-Alcohol (123)**

A solution of methyl 12-benzyloxy-7α-hydroxypodocarpa-8,11,13-trien-19-oate (123) (20 mg, 0.05 mol) in acetic anhydride (1 ml) and pyridine (1 drop) was warmed on a waterbath for 5 h. Workup gave a mixture of 7-acetates (105), which by ¹H n.m.r. analysis were identical to the mixture obtained from acetylation of the 7β-alcohol (103) under the same conditions. The mixture (105) was also obtained from treatment of (123) (20 mg) with acetic anhydride (2 ml) and pyridine (2 drops) at
room temperature for 16 h.

**Acetylation of the 12-Methoxy 7β-Alcohol (12)**

A solution of methyl 7β-hydroxy-12-methoxypodocarpa-8,11,13-trien-19-oate (12) (32 mg, 0.1 mmol) in acetic anhydride (2 ml) and pyridine (5 drops) was warmed on a waterbath for 5 h. Workup gave an oil which by $^1$H n.m.r. analysis was a mixture of methyl 12-methoxypodocarpa-6,8,11,13-tetraen-19-oate (24) (40%), methyl 7α-acetoxy-12-methoxypodocarpa-8,11,13-trien-19-oate (126) (33%), and the 7β-acetate (100) (27%). $\delta_H$ 0.80, s, H20(24); 0.97, s, H20(126); 1.08, s, H20(100); 1.25, 1.28,2s, H18; 2.02, s, 7α-O2CCH3; 2.18, s, 7β-O2CCH3; 3.63, s, CO2CH3; 3.75, s, ArOCH3; 6.27, H6,H7(24); 6.6-7.2, m, aryl H.

**Methyl 7β-Acetoxy-12-benzyloxypodocarpa-8,11,13-trien-19-oate (105b)**

Treatment of methyl 12-benzyloxy-7β-hydroxy podocarpa-8,11,13-trien-19-oate (103) (40 mg, 0.1 mmol) with acetic anhydride (2 ml) and pyridine (2 drops) at room temperature for 16 h gave methyl 7β-acetoxy-12-benzyloxypodocarpa-8,11,13-trien-19-oate (105b) as an oil (32 mg, 72%), $[\alpha]_D^{21}$ +60° (c, 1.8). $\delta_H$ 1.08, s, 3H, H20; 1.25, s, 3H, H18; 2.15, s, 3H, O2CCH3; 3.65, s, 3H, CO2CH3; 5.05, s, 2H, PhCH2; 5.75, dd, $J_{7\alpha,6\beta}$ 10, $J_{7\alpha,6\alpha}$ 8 Hz, H7α; 6.6-7.4, m, aryl H. $\delta_C$ 19.8, C2; 21.6, CH3CO2; 22.6, C20; 27.4, C6; 28.4, C18; 37.4, C3; 38.9, C10; 39.2, C1; 43.7, C4; 49.8, C5; 51.4, CO2CH3; 70.0, PhCH2; 72.9, C7; 111.9, C13; 112.6, C11; 126.6, C8; 127.5, 2C, benzyl C3,C5; 128.0, benzyl C4; 128.2, C14; 128.6, 2C, benzyl C2,C6; 136.9, benzyl C1; 150.2, C9; 158.4, C12; 171.3, CH3CO2; 177.4, C19.
CHAPTER TWO

Methyl 13-Acetyl-12-methoxypodocarpa-8,11,13-trien-19-oate (128)

Treatment of methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (11) with acetyl chloride and aluminium chloride in dichloromethane\(^8\) gave methyl 13-acetyl-12-methoxypodocarpa-8,11,13-trien-19-oate (128), m.p. 118-9\(^0\), (lit.\(^8\) 118-9\(^0\)) (81%) (correct i.r. and \(^1\)H n.m.r. spectra). \(\delta_C\) 19.9, C2; 20.9, C6; 22.7, C20; 28.5, C18; 30.9, C7; 31.8, CH\(_3\)CO; 37.5, C3; 39.1, C10; 39.3, C1; 44.0, C4; 51.3, C5; 52.5, CO\(_2\)CH\(_3\); 55.5, ArOCH\(_3\); 108.6, C11; 125.8, C13; 127.7, C8; 131.0, C14; 154.3, C9; 177.9, C19; 199.5, CH\(_3\)CO.

Methyl 13-Acetoxy-12-methoxypodocarpa-8,11,13-trien-19-oate (129)

A solution of methyl 13-acetyl-12-methoxypodocarpa-8,11,13-trien-19-oate (128) (2.2 g, 6.45 mmol) and \(m\)-chloroperbenzoic acid (1.5 g, 7 mmol) in dichloromethane (15 ml) containing \(p\)-toluenesulfonic acid (few crystals) was left at 4\(^0\) for 6 days and then filtered. The precipitate was washed with dichloromethane, and the combined filtrate and washings were washed successively with potassium iodide, sodium hydrogensulfite, and sodium hydrogencarbonate solutions, and water. The dried solution was filtered through a short column of silica and concentrated to give methyl 13-acetoxy-12-methoxypodocarpa-8,11,13-trien-19-oate (129) as needles (from methanol) (1.34 g, 58%), m.p. 147-150\(^0\), [\(\alpha\)]\(_D\)\(^17\) +115\(^0\) (c, 1.3) (Found: C 69.6, H 8.1%. C\(_{21}\)H\(_{28}\)O\(_5\) requires C 70.0, H 7.8%). \(\nu_{\text{max}}\) 2950, 1720 (ester), 1060 cm\(^{-1}\) (C-O). \(\delta_H\) 1.07, s, 3H, H20; 1.30, s, 3H, H18; 2.30, s, 3H, O\(_2\)CCH\(_3\); 3.67, s, 3H, CO\(_2\)CH\(_3\); 3.77, ArOCH\(_3\); 6.70, s, H14; 6.83, s, H11. \(\delta_C\) 19.9, C2; 20.7, CH\(_3\)CO; 20.9, C6; 22.9, C20; 28.5, C18; 31.1, C7; 37.6, C3; 38.6, C10; 39.5, C1; 44.0, C4; 51.3, C5; 52.6, CO\(_2\)CH\(_3\);...
55.9, ArOCH₃; 109.6, C11; 122.5, C14; 128.1, C8; 137.5, C13; 146.4, C9; 148.9, C12; 169.4, CH₃CO₂; 177.9, C19. m/z 360 (M, 13%), 318 (M-C₂H₂O, 85), 303 (77), 243 (100), 43 (33).

**Methyl 13-Hydroxy-12-methoxypodocarpa-8,11,13-trien-19-oate (130)**

A solution of methyl 13-acetoxy-12-methoxypodocarpa-8,11,13-trien-19-oate (129) (1.3 g, 3.6 mmol) in methanol (50 ml) and 2M sodium hydroxide solution (12 ml, 24 mmol) was warmed on a water bath for 4 h. The mixture was poured into water, acidified, and extracted with dichloromethane to give methyl 13-hydroxy-12-methoxypodocarpa-8,11,13-trien-19-oate (130) as needles (from methanol) (0.99 g, 86%), m.p. 132-4°, [α]D¹⁷ +138° (c, 1.1) (Found: C 71.6, H 8.5%. C₁₉H₂₆O₄ requires C 71.7, H 8.3%). vₘₐₓ 3550 (OH), 2950, 1720 (ester), 1050 cm⁻¹ (C-O). δH 1.00, s,3H, H20; 1.25, s, 3H, H18; 3.63, s, 3H, CO₂CH₃; 3.75, s, 3H, ArOCH₃; 5.93, br s, OH; 6.53, s, H14; 6.67, s, H11. δC 20.0, C2; 21.1, C6; 22.9, C20; 28.5, C18; 31.4, C7; 37.6, C3; 38.2, C10; 39.8, C1; 44.0, C4; 51.2, C5; 52.9, CO₂CH₃; 56.0, ArOCH₃; 107.8, C11; 114.1, C14; 128.4, C8; 139.7, C9; 143.3, C13; 144.8, C12; 178.0, C19. m/z 318 (M, 33%), 303 (M-CH₃, 51), 271 (12), 243 (100).

**Methyl 12-Methoxy-13,14-dioxopodocarpa-8,11-dien-19-oate (131)**

A solution of potassium nitrosodisulfonate⁸³ (1.27 g, 4.75 mmol) in 0.016M potassium dihydrogen phosphate solution (55 ml) was added slowly to a stirred solution of methyl 13-hydroxy-12-methoxypodocarpa-8,11,13-trien-19-oate (130) (0.75 g, 2.36 mmol) in acetone (50 ml). The mixture was stirred for 5 h, diluted with water, and extracted with dichloromethane to give methyl 12-methoxy-13,14-dioxopodocarpa-8,11-dien-19-oate (131) as purple needles (from chloroform-hexane) (0.63 g, 80%).
m.p. 160-2°, [α]D17 +95° (c, 1.0) (Found: C 68.4, H 7.5%. C19H24O5 requires C 68.6, H 7.3%). λmax 240 (log ε 3.49), 490 nm (2.87). νmax 2970, 1720 (ester), 1660, 1640 (quinone), 1580 cm⁻¹ (C=C). δH 0.98, s, 3H, H20; 1.25, s, 3H, H18; 3.60, s, 3H, CO₂CH₃; 3.67, s, 3H, ROCH₃; 5.82, s, H11. δC 17.3, C20; 19.2, C2; 19.4, C6; 22.7, C7; 28.3, C18; 35.6, C3; 37.2, C1; 39.5, C10; 43.9, C4; 51.5, C5; 52.3, CO₂CH₃; 55.5, ROCH₃; 108.8, C11; 128.3, C8; 151.2, C9; 156.1, C12; 176.0, C13; 177.4, C19; 179.5, C14. m/z 334 (M+2, 58%), 332 (M, 33), 319 (30), 259 (100).

**Nitration of Methyl 12-Methoxypodocarpa-8,11,13-trien-19-oate (11)**

Powdered copper(II) nitrate trihydrate (0.45 g, 1.8 mmol) was added to a stirred solution of methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (11) (1.0 g, 3.31 mmol) in acetic anhydride (50 ml), and the mixture was stirred for 8 h, poured into sodium hydrogen carbonate solution, and extracted with ether. The extract was washed with water, dried, and concentrated to give a yellow solid which was absorbed onto silica. Elution with dichloromethane-hexane (4:1) and separation of mixed fractions on a Chromatotron gave: (i) *methyl 12-methoxy-11-nitropodocarpa-8,11,13-trien-19-oate* (132) as pale yellow needles (from methanol) which slowly reddened on exposure to air (0.31 g, 30%), m.p. 143-6°, [α]D18 +150° (c, 0.6) (Found: C 65.7, H 7.3, N 3.9%. C₁₉H₂₅N⁵O₅ requires C 65.7, H 7.3, N 4.0%). λmax 270 nm (log ε 2.7). νmax 2950, 1710 (ester), 1600 (C=C), 1525 (NO₂), 1320 cm⁻¹. δH 1.20, s, 3H, H20; 1.27, s, 3H, H18; 3.62, s, 3H, CO₂CH₃; 3.75, s, 3H, ArOCH₃; 6.70, d, J 8 Hz, H13; 6.97, d, J 8 Hz, H14. δC 19.7, C2; 20.2, C20; 20.5, C6; 29.0, C18; 32.3, C7; 35.5, C3; 37.0, C1; 40.5, C10; 44.1, C4; 51.4, C5; 53.1, CO₂CH₃; 56.6, ArOCH₃; 110.6, C13; 129.6, C8; 131.6, C14; 138.6, C11; 141.7, C9; 149.5, C12; 177.4, C19. m/z 347 (M, 100%), 330 (M-OH, 56), 272 (72), 256 (30), 254 (31) 237 (30), 176 (41), 115 (46).

(ii) *methyl 12-methoxy-13-nitropodocarpa-8,11,13-trien-19-oate* (133) as a yellow
glass (from chloroform-hexane) (0.44 g, 38%), m.p. 45-55°, [α]D18 +125° (c, 1.0) (Found: C 65.6, H 7.3, N 4.1%. C19H25NO5 requires C 65.7, H 7.3, N 4.0%). λmax 267 nm (log ε 2.67). vmax 2950, 1710 (ester), 1600 (C=C), 1525 (NO2), 1320 cm⁻¹. δH 1.03, s, 3H, H20; 1.23, s, 3H, H18; 3.63, s, 3H, CO2CH3; 3.87, s, 3H, ArOCH3; 6.87, s, H11; 7.47, s, H14. δC 19.8, C2; 20.7, C6; 22.8, C20; 28.4, C18; 30.8, C7; 37.4, C3; 39.3, C1; 40.5, C10; 44.0, C4; 51.4, C5; 52.1, CO2CH3; 56.5, ArOCH3; 110.8, C11; 126.1, C14; 128.2, C8; 137.2, C13; 151.2, C12; 155.4, C9; 177.6, C19. m/z 347 (M, 30%), 302 (22), 272 (100), 227 (29).

(iii) methyl 12-methoxy-11,13-dinitropodocarpa-8,11,13-trien-19-oate (134) as an orange glass (from chloroform-hexane) (15 mg, 1%), m.p. 45-50°, [α]D17 +64° (c, 0.5) (Found: M⁺ 392.1579. C19H24N2O7 requires M⁺ 392.1584). λmax 267 nm (log ε 2.8). vmax 2950, 1710 (ester), 1600 (C=C), 1525 (NO2), 1320 cm⁻¹. δH 1.23, s, 3H, H20; 1.30, s, 3H, H18; 3.70, s, 3H, CO2CH3; 3.90, s, 3H, ArOCH3; 7.73, s, H14. m/z 392 (M, 4%), 375 (M-OH, 32), 347 (46), 317 (21), 272 (100).

Methyl 12-Hydroxy-13-nitropodocarpa-8,11,13-trien-19-oate (138)

Nitration of methyl 12-hydroxy podocarpa-8,11,13-trien-19-oate (10) with copper(II) nitrate and acetic anhydride⁹⁰ gave methyl 12-hydroxy-13-nitropodocarpa-8,11,13-trien-19-oate (138), m.p. 146° (lit.⁹⁰ 147°) (83%) (correct i.r. and ¹H n.m.r spectra). δC 19.7, C2; 20.6, C6; 22.8, C20; 28.4, C18; 30.9, C7; 37.2, C3; 39.0, C1; 39.4, C10; 43.9, C4; 51.4, C5; 51.9, CO2CH3; 116.4, C11, 124.7, C14; 128.5, C8; 131.4, C13; 152.7, C12; 159.8, C9; 177.4, C19.

Methylation of the 13-Nitrophenol (138)

Dimethyl sulfate (0.5 ml, 0.5 mmol) was added slowly via the condensor to a
refluxing solution of the 13-nitrophenol (138) (0.1 g, 0.3 mmol) and potassium carbonate (0.2 g, 1.5 mmol) in acetone (15 ml). The mixture was refluxed for 1 h, poured into water, and extracted with dichloromethane to give methyl 12-methoxy-13-nitropodocarpa-8,11,13-trien-19-oate (133) (0.1 g, 96%).

Methylation of (138) with iodomethane and potassium hydroxide in dimethyl sulfoxide gave (133) (70%).

**Methyl 13-Amino-12-methoxypodocarpa-8,11,13-trien-19-oate (139)**

10% Palladium on charcoal (30 mg) was added in portions to a hot solution of methyl 12-methoxy-13-nitropodocarpa-8,11,13-trien-19-oate (133) (0.21 g, 0.66 mmol) and hydrazine hydrate (0.2 ml, 4 mmol) in ethanol (20 ml). Upon cessation of the resulting effervescence the mixture was refluxed for 2 h. The cooled mixture was filtered and concentrated to give methyl 13-amino-12-methoxypodocarpa-8,11,13-trien-19-oate (139) as needles (from methanol) (0.15 g, 78%), m.p. 149-152°, [α]D\text{18} +200° (c, 0.8) (Found: C 72.1, H 8.9, N 4.4%. C_{19}H_{27}NO_{3} requires C 71.9, H 8.6, N 4.4%). v\text{max} 3650, 3600 (NH₂), 3020, 1715 (ester), 1600 cm⁻¹ (C=C). δH 1.08, s, 3H, H20; 1.33, s, 3H, H18; 3.73, s, 3H, CO₂CH₃; 3.87, s, 3H, ArOCH₃; 6.42, s, H14; 6.70, s, H11. δC 20.0, C2; 21.2, C6; 22.9, C20; 28.5, C18; 31.4, C7; 37.7, C3; 38.1, C10; 39.8, Cl; 44.0, C4; 51.2, C5; 53.1, CO₂CH₃; 55.6, ArOCH₃; 107.6, C11; 114.9, C14; 127.7, C8; 133.8, C13; 138.3, C9; 146.0, C12; 178.0, C19. m/z 317 (M, 80%), 302 (M-CH₃, 100), 270 (9), 242 (60).

Reduction of (133) with tin(II) chloride gave (139) m.p. 146-150° (89%).

**Diazotization of the 13-Amine (139)**

A solution of the 13-amine (139) (50 mg, 0.17 mmol) in pyridine (3 ml) was
added over 25 min to a stirred solution of sodium nitrite (0.1 g, 1.6 mmol) in 80% sulfuric acid (5 ml) at 0°. The mixture was stirred at 0° for 15 min then treated with ice (3 g) over 15 min. A solution of urea (1 g) in water (10 ml) was added dropwise, and the mixture was poured into water and extracted with dichloromethane. The extract was washed with dilute hydrochloric acid and water, dried, and concentrated to give a red oil which was separated by p.l.c. (dichloromethane) into methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (11) (8 mg, 17%) and methyl 13-hydroxy-12-methoxypodocarpa-8,11,13-trien-19-oate (130) (10 mg, 20%).

Oxidation of the 13-Amine (139)

A solution of the 13-amine (139) (0.41 g, 1.3 mmol) in dimethylformamide (50 ml) was added dropwise to a stirred solution of potassium nitrosodisulfonate (0.8 g, 2.9 mmol) in 0.05M potassium dihydrogen phosphate solution (60 ml) over 15 min. The mixture was stirred for 30 min, then diluted with water, and extracted with ether to give a red oil which was absorbed onto silica. Elution with dichloromethane gave the quinone (131) (0.23 g, 54%) m.p. 161-2°.

Methyl 13,14-Diacetoxy-12-methoxypodocarpa-8,11,13-trien-19-oate (141)

A solution of the quinone (131) (50 mg, 0.16 mmol) in methanol (10 ml) was hydrogenated over 10% palladium on charcoal (10 mg) at 1 atm. for 30 min. Concentration of the filtered solution gave crude methyl 13,14-dihydroxy-12-methoxypodocarpa-8,11,13-trien-19-oate (140) as an oil which coloured on exposure to air (50 mg, 100%). δ_H 1.04, s, 3H, H20; 1.27, s, 3H, H18; 3.63, s, 3H, CO2CH3; 3.77, s, 3H, ArOCH3; 6.30, s, H11.

Treatment of the crude diol (140) with acetic anhydride (5 ml) and pyridine (50
(0.75 g, 2.25 mmol) in methanol (65 ml) was hydrogenated over 10% palladium on charcoal (0.1 g) at 1 atm, for 50 min. Workup gave the crude diol (0.75 g, 100%) which was treated with ozone in dichloromethane-methanol (1:1, 60 ml) at -78°C until the blue colour persisted (35 min) then flushed with oxygen and warmed to room temperature. A solution of sodium borohydride (0.23 g, 6 mmol) in 50% ethanol (20 ml) was added and the mixture was stirred for 2 h, concentrated to small volume, neutralised with 2M hydrochloric acid, and extracted with dichloromethane to give a brown oil which was absorbed onto silica. Elution with 2% ethyl acetate in dichloromethane gave 14-methyl hydrogen 11-hydroxydrim-8-ene-12,14-dioate 11,12-lactone (31) (52 mg, 8%) as prisms (from hexane-ether) (38 mg), m.p. 166-9°C, [α]D18 +102° (c, 0.6). (Found: C 68.8, H 8.1%; M+ 278.1531. C16H22O4 requires C 69.0, H 8.0%; M+ 278.1518). \( \lambda_{\text{max}} \) 241 nm (log \( \varepsilon \) 2.58). \( \nu_{\text{max}} \) 2950, 1750 (lactone), 1720 (ester), 1665 (C=C), 1200 cm\(^{-1}\). δH 0.98, s, 3H, H20; 1.26, s, 3H, H18; 3.56, s, 3H, CO\(_2\)CH\(_3\); 4.66, ddd, \( J_{11}\alpha,11\beta \) 16.9, \( J_{11}\alpha,7\alpha \) 3.4, \( J_{11}\alpha,7\beta \) 1.6 Hz, H11α; 4.72, dt, \( J_{11}\beta,11\alpha \) 16.9, \( J_{11}\beta,7\alpha \) 2.8, \( J_{11}\beta,7\beta \) 2.8 Hz, H11β. δC 18.8, C15; 19.0, C2; 20.1, C6; 22.0, C7; 28.3, C13; 36.6, C3; 37.0, C10; 37.7, C1; 43.6, C4; 51.3, C5; 52.3, CO\(_2\)CH\(_3\); 68.4, C11; 109.4, C8; 124.2, C9; 169.2, C12; 177.3, C14. \( m/z \) 278 (M, 30%).
Methyl 11-Amino-12-methoxypodocarpa-8,11,13-trien-19-oate (143)

10% Palladium on charcoal (30 mg) was added in portions to a warm solution of methyl 12-methoxy-11-nitropodocarpa-8,11,13-trien-19-oate (132) (0.27 g, 0.76 mmol) and hydrazine hydrate (0.2 ml, 4 mmol) in ethanol (25 ml). Upon cessation of the resulting effervescence, the mixture was refluxed for 4 h. The cooled mixture was filtered and concentrated to give methyl 11-amino-12-methoxypodocarpa-8,11,13-trien-19-oate (143) as needles (from methanol) (0.19 g, 82%), m.p. 152.5-155°, [α]D18 +100° (c, 1.3) (Found: C 72.0, H 9.0, N 4.0%. C19H27NO3 requires C 71.9, H 8.6, N 4.4%). νmax 3670, 3600 (NH2), 3050, 1720 (ester), 1600 (C=C), 1230 cm⁻¹. δH 1.17, s, 3H, H20; 1.27, s, 3H, H18; 3.67, s, 3H, CO2CH3; 3.98, s, 3H, ArOCI3; 6.31, d, J 8 Hz, H13; 6.85, d, J 8 Hz, H14. δC 15.9, C20; 19.6, C2; 21.0, C6; 29.0, C18; 33.5, C7; 35.0, C3; 37.5, C1; 39.5, C10; 44.0, C4; 51.2, C5; 55.8, CO2CH3; 56.6, ArOCH3; 108.3, C13; 118.8, C14; 129.8, C8; 131.8, C9; 134.1, C11; 146.0, C12; 178.1, C19. m/z 317 (M, 100%), 302, (M-CH3, 46), 242 (63).

Hydrogenation of (132) over 10% palladium on charcoal in methanol containing a trace of hydrochloric acid gave the amine (143), m.p. 134-140° (79%).

Oxidation of the 11-Amine (143)

A solution of the 11-amine (143) (0.13 g, 0.4 mmol) in dimethylformamide (1.5 ml) was added dropwise over 15 min to a stirred solution of potassium nitrosodisulfonate (0.32 g, 1.2 mmol) in 0.55M potassium dihydrogen phosphate solution (24 ml). The mixture was stirred for 75 min, poured into water, and extracted with dichloromethane to give a yellow solid which was absorbed onto silica. Elution with
dichloromethane gave starting material (56 mg) and methyl 11-imino-12-methoxy-14-oxopodocarpa-8,12-dien-19-oate (144) as pale yellow needles (from dichloromethane-hexane) (35 mg, 27%), m.p. 207-211°, [α]_D^{18} +198° (c, 0.3) (Found: M+: 331.1785. C_{19}H_{25}NO_{4} requires M+: 331.1784). \( \lambda_{max} \) 276 (log ε 3.36), 335 nm (3.05). \( \nu_{max} \) 3050, 1720 (ester), 1645 (C=O), 1625 (C=N), 1590 cm\(^{-1}\) (C=C). δ_H 1.10, s, 3H, H20; 1.23, s, 3H, H18; 3.60, s, 3H, CO₂CH₃; 3.72, s, 3H, ROCH₃; 5.65, s, H13. \text{m/z} \ 331 (M, 100%), 288 (26), 256 (49), 227 (26).

**Methyl 12-Methoxy-11,14-dioxopodocarpa-8,12-dien-19-oate (35)**

A solution of the imine (144) (33 mg, 0.1 mmol) in methanol (10 ml) was stirred with water (0.1 ml) and 2M hydrochloric acid (5 drops) for 20 min. The mixture was diluted with water, and extracted with dichloromethane to give methyl 12-methoxy-11,14-dioxopodocarpa-8,12-dien-19-oate (35) as yellow needles (from acetone) (25 mg, 75%), m.p. 210-212° (lit.\textsuperscript{38} 210-211.5°), [α]_D^{18} +155° (c, 0.4) (correct i.r. and \textsuperscript{1}H n.m.r. spectra.) δ_C 17.4, C20; 19.0, C2; 19.3, C6; 26.4, C7; 28.6, C18; 36.1, C3; 37.4, C1; 39.2, C10; 43.6, C4; 51.3, C5; 53.4, CO₂CH₃; 56.1, ROCH₃; 105.8, CI3; 143.7, C8; 148.0, C9; 158.8, CI2; 177.4, C19; 181.4, CI1; 187.6, CI4. \text{m/z} 334 (M+2, 6%), 332 (M, 38), 272 (29), 257 (44), 218 (57), 121 (100).

**Diazotization of the 11-Amine (143)**

A solution of the 11-amine (143) (75 mg, 0.25 mmol) in pyridine (5 ml) was added dropwise over 15 min to a stirred solution of sodium nitrite (0.1 g, 1.6 mmol) in 80% sulfuric acid (5 ml) at 0°. The mixture was stirred at 0° for 20 min then ice (3 g) was added over 15 min. Excess of nitrous acid was destroyed with urea (0.5 g) in water (10 ml), then the mixture was poured into water, and extracted with dichloromethane to
give an orange oil (30 mg) which was separated by p.l.c. (dichloromethane) into:

(i) methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (11) (11 mg, 16%); and (ii) an oil (8 mg). \( m/z \) 344 (67%), 332 (37), 329 (76), 317 (41), 269 (100), 257 (30), 242 (39), 240 (51), 227 (72).

**Peracid oxidation of Methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (11)**

Methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (11) (5.0 g, 16.7 mmol) was added to a solution of \( m \)-chloroperbenzoic acid (12.1 g, 55 mmol) in dichloromethane (200 ml) and the resulting yellow solution was left in the dark for 66 h, then filtered and the precipitate washed with dichloromethane. The combined filtrate and washings were washed successively with potassium iodide solution, sodium hydrosulfite solution, sodium hydrogencarbonate solution, and water, dried, and concentrated to give a yellow solid which was absorbed onto silica. Elution with dichloromethane and separation of mixed fractions on a Chromatotron gave (in order of elution): (i) starting material (0.16 g, 3%).

(ii) 19-methyl dihydrogen 12,13-seco-podocarpa-8(14),9(11)-diene-12,13,19-trioate anhydride (160), an oil which slowly darkened in air (40 mg, 0.8%) \([\alpha]_D^{18} +120^\circ\) (c, 0.4) (Satisfactory analysis not obtained). \( \nu_{\text{max}} \) 3000, 1770 (anhydride), 1715 cm\(^{-1}\) (ester). \( \delta_H \): 0.86, s, 3H, H20; 1.21, s, 3H, H18; 3.64, s, 3H, \( \text{CO}_2\text{CH}_3 \); 6.34, s, H14; 6.55, s, H11. \( \delta_C \) 17.7, C20; 19.3, C2; 25.2, C6; 28.5, C18; 31.9, C7; 36.4, C3; 37.8, C1; 41.3, C10; 44.1, C4; 51.6, C5; 54.9, \( \text{CO}_2\text{CH}_3 \); 127.8, C8; 132.5, C11; 133.4, C14; 138.3, C9; 159.4, C13; 159.6, C12; 176.9, C19. \( m/z \) 318(M, 1%), 290 (M-CO, 3), 273 (M-CO\(_2\)H, 23), 247 (100).

(iii) 19-methyl dihydrogen 11,12-seco-podocarpa-8,13-diene-11,12,19-trioate anhydride (161), as needles (from dichloromethane-hexane) (0.4 g, 8%), m.p.130-134\(^\circ\), \([\alpha]_D^{18} +425^\circ\) (c, 0.4) (Found: C 68.0, H 7.0%. \( \text{C}_{18}\text{H}_{22}\text{O}_5 \) requires C 68.0, H 7.0%). \( \nu_{\text{max}} \) 3000,
(anhydride), 1715 cm⁻¹ (ester). δ_H 1.04, td, J_3β,3α=J_3α,2β 13.5, J_3α,2α 4.2 Hz, H3α; 1.15, s, 3H, H20; 1.21, s, 3H, H18; 1.31, td, J_1α,1β=J_1α,2β 12.7, J_1α,2α 4.4 Hz, H1α; 1.33, dd, J_5α,6β 12.6, J_5α,6α 1.6 Hz, H5α; 1.55, dt, J_2α,2β 14.2, J_2α,1α 4.4, J_2α,3α 4.2, J_2α,1β=J_2α,3β 2.9 Hz, H2α; 1.78, br d, J_1β,1α 12.7 Hz, H1β; 1.88, qt, J_2β,2α 14.2, J_2β,3α 13.5, J_2β,1α 12.7, J_2β,1β =J_2β,3β 3.8 Hz, H2β; 1.92, ddd, J_7α,7β 18.5, J_7α,6β 12.5, J_7α,6α 6.5 Hz, H7α; 2.10, br dd, J_6α,6β 14.1, J_6α,7α 6.6 Hz, H6α; 2.25, br d, J_3β,3α 13.5 Hz, H3β; 2.28, ddd, J_6β,6α 14.2, J_6β,5α 12.6, J_6β,7α 12.5, J_6β,7β 6.5 Hz, H6β; 2.36, ddd, J_7β,7α 18.5, J_7β,6β 6.5, J_7β,6α 1.1 Hz, H7β; 3.64, s, 3H, CO₂CH₃; 6.17, d, J_13,14 12.0 Hz, H13; 6.44, d, J_14,13 12.0 Hz, H14. δ_C 18.4, C20; 19.0, C2; 19.5, C6; 28.2, C18; 31.2, C7; 36.7, C3; 37.3, C1; 39.1, C10; 43.5, C4; 51.4, CO₂CH₃; 51.4, C5; 121.6, C13; 134.3, C9; 141.7, C14; 143.2, C8; 159.2, C12; 161.1, C11; 177.0, C19. m/z: 318 (M, 6%), 290 (M-CO, 14), 273 (M-CO₂H, 100), 259 (M-CO₂CH₃, 73), 213 (94), 199 (26), 195 (27).

(iv) 12,19-dimethyl hydrogen 11,12-seco-podocarpa-8,13-diene-11,12,19-trioate (162), an oil (0.24 g, 4%), b.p. 120-130°/0.08 mm Hg, [α]_D +210° (c, 0.6) (Found: C 65.1, H 7.5%; C₁₉H₂₆O₆ requires C 65.1, H 7.45%). v_max 3000, 1720 cm⁻¹ (ester). δ_H 0.93, s, 3H, H20; 1.07, td, J_3α,3β=J_3α,2β 13.5, J_3α,2α 4.4 Hz, H3α; 1.23, s, 3H, H18; 1.27, td, J_1α,1β=J_1α,2β 13.1, J_1α,2α 4.2 Hz, H1α; 1.57, dt, J_2α,2β 13.7, J_2α,3α 4.4, J_2α,1α 4.2, J_2α,3β=J_2α,1β 2.8 Hz, H2α; 1.58, dd, J_5α,6β 12.5, J_5α,6α 1.7 Hz, H5α; 1.72, br d, J_1β,1α 13.1 Hz, H1β; 1.80, qt, J_2β,2α 13.7, J_2β,3α 13.5, J_2β,1α 13.1, J_2β,1β=J_2β,3α 3.8 Hz, H2β; 1.87, ddd, J_6β,6α 13.8, J_6β,5α 12.5, J_6β,7α 12.2, J_6β,7β 5.4 Hz, H6β; 2.08, br dd, J_6α,6β 13.8, J_6α,7α 6.0 Hz, H6α; 2.20, br dd, J_7β,7α 16.8, J_7β,6β 5.4 Hz, H7β; 2.24, br d, J_3β,3α 13.5 Hz, H3β; 2.37, dd, J_7α,7β 16.8, J_7α,6β 12.0, J_7α,6α 6.0 Hz, H7α; 3.66, s, 3H, C(19)O₂CH₃; 3.72, s, 3H, C(12)O₂CH₃; 5.81, d, J_14,13 12.0 Hz, H14; 6.40, d, J_13,14 12.0 Hz, H13; 7.93, s, CO₂H. δ_C 16.8, C20; 18.8, C2; 20.3, C6; 28.1, C18; 28.6, C7; 34.8, C3; 37.3, C1; 39.3, C10; 43.4, C4; 51.4, C(19)O₂CH₃; 51.5, C5; 52.1, C(12)O₂CH₃; 121.6, C13; 140.5, 2C, C9,14; 150.0, C8; 159.9, C11; 166.0,
Cl₂; 177.3, C19. m/z 350 (M, 7%), 332 (M-H₂O, 12), 322 (M-CO, 18), 305 (M-CO₂H, 97), 292 (M-CO₂CH₃, 36), 290 (52), 262 (32), 247 (62), 230 (39), 219 (51), 187 (93), 123 (76), 41 (100).

(v) methyl 12-methoxy-11,14-dioxopodocarpa-8,12-dien-19-oate (35) (0.62 g, 12%).

Elution with ethyl acetate and separation of mixed fractions by p.l.c. (5% ethyl acetate in dichloromethane) gave (in order of elution):

(vi) methyl 9,10-epoxy-12,13-dioxo-9,10-seco-podocarpa-8(14),9(11)-dien-19-oate (163) as yellow prisms (from ethyl acetate-hexane) (30 mg, 0.6%), m.p.183-187°, [α]D23-10° (c, 0.5) (Found: M⁺ : 318.1476. C₁₈H₂₂O₅ requires M⁺ : 318.1467). λ_max 245 (log ε 3.78), 363 nm (2.94). ν_max 2950, 1760 (ester), 1670, 1645 (quinone), 1600 cm⁻¹ (C=C). δ_H 1.22, s, 3H, H20; 1.46, s, 3H, H18; 1.51-1.79, m, 8H; 1.87, br dd, J 14.4, 4.0 Hz, 1H; 2.38-2.54, m, 2H; 3.81, s, 3H, CO₂CH₃; 5.91, s, H14; 6.48, s, H11. δ_C 18.1, C20; 19.6, C2; 22.1, C18; 25.2, C6; 27.8, C7; 36.4, C3; 36.6, C1; 48.4, C4; 55.1, C5; 56.3, CO₂CH₃; 84.6, C10; 107.7, C14; 130.7, C11; 149.7, C9; 158.6, C8; 179.9, C19; 182.0, C13; 187.0, C12. m/z 318 (M, 10%), 290 (M-CO, 8), 153 (100).

(vii) methyl 8β-hydroxy-12-oxopodocarpa-9(11),13-dien-19-oate (159) as needles (from aqueous acetone) (0.3 g, 6%), m.p.203-206° (lit.13 209-212°, 18 206-207°), [α]D24 -63° (c, 1.0). ν_max 3400 (OH), 1720 (ester), 1660 (conj. C=O), 1620 cm⁻¹ (C=C). δ_H 1.20, s, 3H, H20; 1.21, s, 3H, H18; 3.68, s, 3H, CO₂CH₃; 4.05, br s, OH; 5.93, dd, J₁₃,₁₄ 10, J₁₃,₁₁ 2 Hz, H13; 5.95, d, J₁₁,₁₃ 2 Hz, H11; 6.62, d, J₁₄,₁₃ 10 Hz. m/z 304 (M, 10%), 286 (M-H₂O, 20), 244 (M-HCO₂CH₃, 95), 227 (30), 213 (39), 121 (100).

Oxidation of (11) with peracetic acid for 24 h gave starting material (5%), the quinone (35) (7%), and the quinol (159) (10%).
Peracid Oxidation of Methyl

13-Hydroxy-12-methoxypodocarpa-8,11,13-trien-19-oate (130)

*m*-Chloroperbenzoic acid (0.14 g, 0.63 mmol) was dissolved in a solution of methyl 13-hydroxy-12-methoxypodocarpa-8,11,13-trien-19-oate (130) (0.1 g, 0.32 mmol) in dichloromethane (5 ml) and the resulting red solution was kept in the dark for 16 h. Workup gave a red oil which was absorbed onto silica. Elution with dichloromethane gave: (i) 19-methyl dihydrogen 12,13-seco-podocarpa-8(10),9(11)-dien-12,13,19-trioate (160) (20 mg, 20%) and (ii) starting material (25 mg).

A repeat of this reaction on the same scale gave the anhydride (160) (10 mg, 10%) and starting material (50 mg).

Methyl 11,14-Diacetoxo-12-methoxypodocarpa-8,11,13-trien-19-oate (179)

Zinc dust (0.13 g, 2 mmol) was added to a solution of the quinone (35) (40 mg, 0.12 mmol) in acetic acid (1 ml) and the mixture was left for 30 min. Workup gave crude methyl 11,14-dihydroxy-12-methoxypodocarpa-8,11,13-trien-19-oate (178) as an off-white solid which turned yellow in air (40 mg, 100%). δH 1.17, s, 3H, H2O; 1.23, s, 3H, H18; 3.67, s, 3H, CO2CH3; 3.77, s, 3H, ArOCH3; 5.20, br s, 2H, ArOH; 6.30, s, H13.

Treatment of the crude diol (178) with acetic anhydride (3 ml), pyridine (0.2 ml), and 4-dimethylaminoypyridine (18 mg) on a waterbath for 5 h gave methyl 11,14-diacetoxo-12-methoxypodocarpa-8,11,13-trien-19-oate (179) (30 mg, 55%) as prisms (from methanol) (20 mg, 37%), m.p. 60-3°, [α]D23 +100° (c, 0.2) (Found: C 66.5, H 7.2%. C23H30O7 requires C 66.0, H 7.2%). νmax 2950, 1750 (acetate), 1720 cm⁻¹ (ester). δH 1.07, s, 3H, H2O; 1.23, s, 3H, H18; 2.27, s, 6H, CH3CO2; 3.63, s, 3H, CO2CH3; 3.72, ArOCH3; 6.65, s, H13. m/z 418 (M, 2%), 376 (M-C2H2O, 9), 334
A solution of the quinone (35) (0.665 g, 2 mmol) in ethyl acetate (115 ml) was hydrogenated at 1 atm. over 10% palladium on charcoal (30 mg) for 1 h to give the crude diol (178) (0.67 g, 100%). Ozone was passed through a solution of the crude diol (178) in dichloromethane-methanol (1:1, 60 ml) at -78° until the blue colour persisted (~20 min). Workup gave a solid (0.7 g) which was absorbed onto silica. Elution with dichloromethane gave 14-methyl dihydrogen drim-8-ene-11,12,14-trioate anhydride (36) (0.2 g, 35%) as needles (from dichloromethane-hexane) (0.15 g, 26%), m.p. 205-8°, [α]D 24 +9° (c, 0.2) (Found: C 65.7, H 6.9%. C16H20O5 requires C 65.7, H 6.9%). λ_max 258 nm (log ε 3.52). ν_max 3050, 1845, 1770 (anhydride), 1720 (ester), 1660 cm⁻¹ (C=O). δ_H 1.06, s, 3H, H15; 1.10, td, J_3a,3b=J_3a,2a 13.6, J_3a,2a 4.4 Hz, H3a; 1.27, s, 3H, H13; 1.32, td, J_1a,1b=J_1a,2a 13.4, J_1a,2a 4.2 Hz, H1a; 1.42, br s, J_5a,6b 12.7 Hz, H5; 1.62, dtt, J_2a,2b 13.8, J_2a,3a 4.4, J_2a,1a 4.2, J_2a,1a=J_2a,3b 2.8 Hz, H2a; 1.85-1.98, m, 2H; 2.24-2.32, m, 3H; 2.46, br d, J_3b,3a 13.6 Hz, H3b; 2.62, br dd, J_7b,7a 18.2, J_7b,6b 5.4 Hz, H7b; 3.68, s, 3H, CO₂CH₃. δ_C 17.8, C15; 18.6, C2; 19.5, C6; 22.8, C7; 28.4, C13; 34.7, C3; 36.8, C10; 37.4, C1; 43.5, C4; 51.5, C5; 52.3, CO₂CH₃; 143.6, C8; 152.2, C9; 163.1, C12; 164.6, C11; 176.8, C14. m/z 292 (M, 7%), 260 (M-CH₃OH, 46), 247 (M-CO₂H, 53), 232 (M-HCO₂CH₃, 41), 159 (45), 1107 (46), 91 (56), 41 (100).

**Methanolysis of the Anhydride (36)**

A solution of the anhydride (36) (20 mg, 6.8x10⁻⁵ mol) in methanol (5 ml) was refluxed over Amberlyst-15 (8 mg) for 6 h. Concentration of the filtered solution gave
a solid (23 mg), m.p. 200-205°, which by ¹H n.m.r. analysis was a mixture of 12,14-dimethyl hydrogen drim-8-ene-11,12,14-trioate (181) (67%) and 11,14-dimethyl hydrogen drim-8-ene-11,12,14-trioate (182) (33%). $\nu_{\text{max}}$ 3200 (OH), 2950, 1760 (ester), 1710 cm⁻¹ (acid). $\delta_H$ 1.05, s, 3H, H15; 1.09, td, $J_{3\alpha,3\beta}=J_{3\alpha,2\beta}$ 13.6, $J_{3\alpha,2\alpha}$ 4.4 Hz, H3a; 1.26, s, 3H, H13; 1.27, td, $J_{1\alpha,1\beta}=J_{1\alpha,2\beta}$ 12.8, $J_{1\alpha,2\alpha}$ 4.2 Hz, H1a; 1.40, dd, $J_{5\alpha,6\beta}$ 12.4, $J_{5\alpha,6\alpha}$ 2.0 Hz, H5a; 1.50-1.60, m, H2a; 1.75-1.95, m, 2H; 2.20-2.35, m, 3H; 2.45, br d, $J_{3\beta,3\alpha}$ 13.6 Hz, H3b; 2.61, br dd, $J_{7\beta,7\alpha}$ 18.3, $J_{7\beta,6\beta}$ 5.4 Hz, H7b; 3.65, s, 3H, C(19)O₂CH₃; 3.67, s, 2H, C(12)O₂CH₃; 3.72, s, C(11)O₂CH₃.

Reduction of the Anhydride (36)

a) With LiAlH₄- A solution of the anhydride (36) (75 mg, 0.25 mmol) in dry tetrahydrofuran (5 ml) was added dropwise to a stirred solution of lithium aluminium hydride in tetrahydrofuran (1.0 ml, 1.3M in hydride, 1.3 mmol hydride), and the mixture was stirred under nitrogen for 2 h, then 2M hydrochloric acid (1 ml) was added. Extraction with dichloromethane gave a solid which was absorbed onto silica. Elution with dichloromethane-methanol (99:1) gave the isodrimenin congener (34) (45 mg, 63%) (identical to sample prepared below).

b) With Red-Al- A solution of the anhydride (36) (60 mg, 0.2 mmol) in dry tetrahydrofuran (3 ml) was added dropwise to a stirred solution of Red-Al in toluene (0.1 ml, 9.4M in hydride, 0.94 mmol hydride) diluted with dry tetrahydrofuran (0.5 ml) and the mixture was stirred under nitrogen for 1 h. Workup gave a solid (55 mg) which by ¹H n.m.r. analysis was a mixture containing the isodrimenin congener (34) (50%) and methyl 11,12-dihydroxydrim-8-en-14-oate (183) (5%). $\delta_H$ 0.81, 1.04, 2s, H15; 1.15, 1.22, 2s, H13; 3.64, s, CO₂CH₃; 4.05, 4.11, 4.17, 4.20, 4d, $J_{12.0}$ Hz, CH₂OH; 4.54, 4.61, 2d, $J_{17.0}$ Hz, lactone CH₂.
Ozonolysis of the 11,12-Anhydride (161)

Ozone was passed through a solution of the anhydride (161) (0.475 g, 1.5 mmol) in dichloromethane-methanol (1:1, 30 ml) at -78° until the blue colour persisted (~15 min). The solution was purged with oxygen, then a solution of sodium borohydride (75 mg, 2 mmol) in 50% ethanol (10 ml) was added. The mixture was stirred for 3 h, then concentrated to small volume. The residue was partitioned between 2M hydrochloric acid and dichloromethane, and the aqueous layer was extracted with dichloromethane. The combined organic fractions were dried and concentrated to give a white solid which was absorbed onto silica. Elution with dichloromethane gave 14-methyl hydrogen 12-hydroxyhydrin-8-ene-11,12-dioate 11,12-lactone (34) as needles (from dichloromethane-hexane) (0.19 g, 46%), m.p. 189-191°, [α]D 24° +142° (c, 0.6) (Found: C 69.3, H 7.7%. C₁₆H₂₂O₄ requires C 69.0, H 7.0%). λ max 238 nm (log ε 2.46). v max 3000, 1755 (lactone), 1720 (ester), 1660 cm⁻¹ (C=O). δH 0.95, s, 3H, H15; 1.07, td, J 3α,3β=J 3α,2β 13.6, J 3α,2α 4.4 Hz, H3α; 1.15, td, J 1α,1β=J 1α,2β 13.5, J 1α,2α 4.2 Hz, H1α; 1.23, s, 3H, H13; 1.34, dd, J 5α,6β 12.3, J 5α,6α 1.5 Hz, H5; 1.51, dtt, J 2α,2β 13.9, J 2α,3α 4.4, J 2α,1α 4.2, J 2α,1β=J 2α,3β 2.8 Hz, H2α; 1.63, br d, J 1β,1α 13.5 Hz, H1β; 1.86, qt, J 2β,2α 13.9, J 2β,3α 13.6, J 2β,1α 13.5, J 2β,1β=J 2β,3β 3.8 Hz, H2β; 1.92, ddd, J 7α,7β 18.4, J 7α,6β 12.0, J 7α,6α 4.9 Hz, H7α; 2.18, br dd, J 6α,6β 14.3, J 6α,7α 4.9 Hz, H6α; 2.27, dtd, J 6β,6α 14.3, J 6β,5α 12.3, J 6β,7α 12.0, J 6β,7β 5.5 Hz, H6β; 2.43, br dd, J 7β,7α 18.4, J 7β,6β 5.5 Hz, H7β; 2.57, br d, J 3β,3α 13.6 Hz, H3β; 3.65, s, 3H, CO₂CH₃; 4.54, 4.61, 2d, J 17.0 Hz, 2H, H12. δC 17.4, C15; 18.8, C2; 20.0, C6; 25.7, C7; 28.5, C13; 34.6, C3; 35.2, C10; 37.8, C1; 43.4, C4; 51.3, C5; 53.2, CO₂CH₃; 70.6, C12; 134.4, C8; 159.4, C9; 172.3, C11; 177.3, C14. m/z 278 (M, 23%), 263 (M-CH₃, 8), 246 (M-CH₃OH, 20), 219 (M-CH₃CO₂, 36), 203 (93), 44 (100).
Ozonolysis of the 12,19-Diester (162)

Ozone was passed through a solution of the 12,19-dieste (162) (0.24 g, 0.67 mmol) in dichloromethane-methanol (1:1, 20 ml) at -78° until the blue colour persisted (~10 min). The solution was purged with oxygen then a solution of sodium borohydride (5 mg, 1.5 mmol) in 50% ethanol (10 ml) was added. The mixture was stirred for 4 h, then worked up to give an oil (0.21 g) which was absorbed onto silica. Elution with dichloromethane and purification of a mixed fraction by p.l.c. (dichloromethane-ethyl acetate, 99:1) gave the isodrimenin congener (34) (15 mg, 8%).

Methyl 13-Acetyl-12-hydroxypodocarpa-8,11,13-trien-19-oate (185)

Treatment of methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (11) with acetyl chloride and aluminium chloride, followed by refluxing with aluminium chloride in dichloromethane gave methyl 13-acetyl-12-hydroxypodocarpa-8,11,13-trien-19-oate (185), m.p. 153-4° (lit. 153-4°) (78%) (correct 1H n.m.r. spectrum). δC 19.9, C2; 21.0, C6; 22.7, C20; 26.5, CH3CO; 28.5, C18; 31.2, C7; 37.4, C3; 39.0, C1; 39.3, C10; 43.0, C4; 51.3, C5; 52.4, CO2CH3; 114.8, C11; 118.0, C13; 126.3, C8; 131.1, C14; 158.0, C12; 160.0, C9; 177.6, C19; 203.9, CH3CO.

Methyl 13-Acetyl-12-hydroxy-11-nitropodocarpa-8,11,13-trien-19-oate (186)

Powdered copper(II) nitrate trihydrate (0.36 g, 1.5 mmol) was added to a stirred solution of methyl 13-acetyl-12-hydroxypodocarpa-8,11,13-trien-19-oate (185) (0.5 g, 1.5 mmol) in acetic anhydride (25 ml). The mixture was stirred for 4 h, then poured into water, stirred for a further 30 min, and extracted with dichloromethane. The extract was washed with sodium hydrogencarbonate solution, water, dried and
concentrated to give methyl 13-acetyl-12-hydroxy-11-nitropodocarpa-8,11,13-trien-19-oate (186) as yellow needles (from methanol) which darkened in air (0.23 g, 44%), m.p. 187°, [α]D<sup>18</sup> +272° (c, 0.5) (Found: C 64.3, H 6.8, N 3.6%. C<sub>20</sub>H<sub>25</sub>NO<sub>6</sub> requires C 64.0, H 6.7, N 3.7%). ν<sub>max</sub> 2950, 1720 (ester), 1645 (ketone), 1535 (NO<sub>2</sub>), 1320 cm<sup>-1</sup> (NO<sub>2</sub>). δ<sub>H</sub> 1.18, s, 3H, H20; 1.27, s, 3H, H18; 2.60, s, 3H, CH<sub>3</sub>CO; 3.63, CO<sub>2</sub>CH<sub>3</sub>; 7.40, s, H14. m/z 375 (M, 13%), 358 (M-OH, 7), 341 (8), 326 (7), 300 (9), 43 (100).

Reduction of the 11-Nitro Compound (186)

A solution of methyl 13-acetyl-12-hydroxy-11-nitropodocarpa-8,11,13-trien-19-oate (186) (0.1 g, 0.27 mmol) in methanol-acetic acid (9:1, 15 ml) was hydrogenated over 10% palladium on charcoal at 1 atmos. for 19 h. Concentration of the filtered solution gave a mixture of methyl 13-acetyl-11-aminod-12-hydroxypodocarpa-8,11,13-trien-19-oate (187) (70%) and methyl 11-aminod-12-hydroxy-13-(1'-hydroxyethyl)podocarpa-8,11,13-trien-19-oate (188) (30%) as an oil which darkened in air (95 mg). ν<sub>max</sub> 3400 (NH<sub>2</sub>, OH), 2950, 1715 (ester), 1650 cm<sup>-1</sup> (ketone). δ<sub>H</sub> 1.15, s, H20; 1.28, s, H18; 2.33, s, CH<sub>3</sub>CO; 3.63, s, CO<sub>2</sub>CH<sub>3</sub>; 4.23, br s, W<sub>½</sub> 14 Hz; 7.13, s, H14 (188); 7.35, s, H14 (187).

Oxidation of this mixture with iron(III) chloride gave an orange oil which was a complex mixture by t.l.c. analysis.

Reduction of Methyl 13-Acetyl-12-hydroxypodocarpa-8,11,13-trien-19-oate (185)

a) With zinc-hydrochloric acid- Zinc amalgam prepared from zinc dust (10 g, 0.15 mol) and mercury(II) chloride (1 g) was added to a solution of methyl 13-acetyl-12-hydroxypodocarpa-8,11,13-trien-19-oate (185) (5.0 g, 15.2 mmol) in ethanol (180 ml) followed by concentrated hydrochloric acid (7.5 ml), and the mixture was refluxed
for 2 h. The cooled mixture was filtered and the filtrate poured into water to give methyl 13-ethyl-12-hydroxypodocarpa-8,11,13-trien-19-oate (189) as needles (from methanol) (4.36 g, 91%), m.p. 163-6°, [α]D18° +138° (c, 0.9) (Found: C 75.8, H 9.3%; M+: 316.2032. C20H28O3 requires C 75.9, H 8.9%; M+: 316.2038). v_{\text{max}} 3350 (OH), 2950, 1710 cm\(^{-1}\) (ester). δ_H 1.00, s, 3H, H20; 1.20, s, 3H, H18; 1.23, t, J 4 Hz, 3H, ArCH\(_2\)CH\(_3\); 2.51, q, J 4 Hz, 2H, ArCH\(_2\)CH\(_3\); 3.53, s, 3H, CO\(_2\)CH\(_3\); 6.53, s, H14; 6.67, s, H11. δ_C 15.9, ArCH\(_2\)CH\(_3\); 20.0, C2; 21.2, C6; 22.5, ArCH\(_2\)CH\(_3\); 22.8, C20; 28.5, C18; 31.2, C7; 37.6, C3; 38.2, C10; 39.5, C1; 44.0, C4; 51.3, C5; 52.9, CO\(_2\)CH\(_3\); 111.9, C11; 127.4, 2C, C8,13; 129.5, C14; 146.8, C9; 151.5, C12; 178.1, C19. m/z 316 (M, 51%), 301 (M-CH\(_3\), 13), 241 (100), 185 (14).

b) With hydrogen- A solution of the ketone (185) (0.25 g, 0.77 mmol) in methanol-ethyl acetate (3:1, 46 ml) and acetic acid (2 ml) was hydrogenated over 10% palladium on charcoal (30 mg) at 1 atmos. for 3 h. Concentration of the filtered solution gave an oil (0.25 g) which was absorbed onto silica. Elution with dichloromethane gave (in order of elution): (i) starting material (53 mg, 21%).

(ii) methyl 13-ethyl-12-hydroxypodocarpa-8,11,13-trien-19-oate (189) (96 mg, 40%).

Elution with 5% ethyl acetate in dichloromethane gave methyl 12-hydroxy-13-(1'-hydroxyethyl)-podocarpa-8,11,13-trien-19-oate (190) as needles (from chloroform-hexane) (96 mg, 35%), m.p. 105-110°, [α]D18° +85° (c, 0.7) (Found: M-18 314.1877. C\(_{20}\)H\(_{28}\)O\(_4\) requires M-H\(_2\)O 314.1881). v_{\text{max}} 3350 (OH), 2950, 1710 cm\(^{-1}\) (ester). δ_H 1.09, s, 3H, H20; 1.27, s, 3H, H18; 1.55, d, J 6 Hz, 3H, ArCH(OH)CH\(_3\); 3.65, s, 3H, CO\(_2\)CH\(_3\); 4.97, q, J 6 Hz, ArCH(OH)CH\(_3\); 6.67, s, H14; 6.73, s, H11; 7.90, br s, ArOH. m/z 332 (M, 0.6%), 314 (M-H\(_2\)O, 56), 239 (100).

**Methyl 13-Ethyl-12-hydroxy-11-nitropodocarpa-8,11,13-trien-19-oate (192)**

A mixture of concentrated nitric acid (ρ 1.54 g cm\(^{-3}\)) and acetic anhydride (1:9,
0.25 ml, 0.4 mmol) was added to a stirred solution of methyl 13-ethyl-12-hydroxypodocarpa-8,11,13-trien-19-oate (189) (0.1 g, 0.32 mmol) in acetic anhydride (10 ml) at 0°. The mixture was stirred at 0-10° for 1 h, then poured into ice-water and extracted with dichloromethane to give a red solid (0.11 g) which was absorbed onto silica. Elution with dichloromethane gave methyl 13-ethyl-12-hydroxy-11-nitropodocarpa-8,11,13-trien-19-oate (192) as yellow needles (from methanol) which turned red in air (40 mg, 35%), m.p. 145-150°, [α]D 18 +367° (c, 1.1) (Found: M+ 361.1913. C20H27NO5 requires M+ 361.1889). νmax 3350 (OH), 3050, 1720 cm⁻¹ (ester). δH 1.05, s, 3H, H20; 1.20, s, 3H, H18; 1.25, t, J 6 Hz, 3H, ArCH2CH3; 2.51, q, J 6 Hz, 2H, ArCH2CH3; 3.65, s, 3H, CO2CH3; 6.98, s, H14. δC 13.5, ArCH2CH3; 19.6, C2; 20.2, 2C, C6,20; 22.7, ArCH2CH3; 29.0, C18; 31.9, C7; 35.5, C3; 37.0, C1; 39.9, C10; 44.0, C4; 51.5, C5; 53.4, CO2CH3; 129.5, C13; 130.7, C8; 132.3, C14; 137.2, C11; 140.7, C9; 144.6, C12; 177.5, C19. m/z 361 (M, 50%), 328 (41), 316 (47), 286 (58), 270 (40), 268 (38), 241 (100), 215 (48).

**Methyl 11-Amino-13-ethyl-12-hydroxypodocarpa-8,11,13-trien-19-oate (193)**

10% Palladium on charcoal (50 mg) was added in portions to a warm solution of methyl 13-ethyl-12-hydroxy-11-nitropodocarpa-8,11,13-trien-19-oate (192) (0.25 g, 0.7 mmol) and hydrazine hydrate (0.3 ml, 6 mmol) in ethanol (30 ml). Upon cessation of the resulting effervescence the mixture was refluxed for 3 h, then filtered to give a red solid which was absorbed onto silica. Elution with dichloromethane-ethyl acetate (99:1) gave starting material (19 mg). Elution with dichloromethane-ethyl acetate (98:2) gave **methyl 11-amino-13-ethyl-12-hydroxypodocarpa-8,11,13-trien-19-oate** (193) as a glass which rapidly turned red in air (0.1 g, 44%) (Found: M+ 331.2121. C20H29NO3 requires M+ 331.2147.) νmax 3600 (NH2), 3350 (OH), 3050, 1720 cm⁻¹ (ester). δH 1.00, s, 3H, H20; 1.17, s, 3H, H18; 1.23, t, J 6 Hz, 3H, ArCH2CH3; 2.50, q,
$J_6$ Hz, 2H, ArCH$_2$CH$_3$; 3.65, S, 3H, CO$_2$CH$_3$; 4.20, br s, 2H, NH$_2$; 6.43, s, H14. m/z 331 (M, 68%), 329 (M-2H, 100), 256 (34), 254 (57), 214 (34).

This compound was unstable and was used without further purification.

**Oxidation of the 11-Amine (193)**

A solution of 11-amino-13-ethyl-12-hydroxypodocarpa-8,11,13-trien-19-oate (193) (85 mg, 0.25 mmol) in acetic acid (20 ml) was added over 5 min to a stirred solution of sodium metaperiodate (0.8 g, 3.7 mmol) in 0.1M hydrochloric acid (20 ml). The mixture was stirred for 5 min then extracted with dichloromethane. The extract was shaken with a solution of potassium iodide (0.25 g, 1.5 mmol) in acetic acid (20 ml) for 5 min then worked up to give an orange oil (65 mg) which was a complex mixture by t.l.c. analysis.

**Reduction of Methyl 13-Acetyl-12-methoxypodocarpa-8,11,13-trien-19-oate (128)**

a) With zinc-hydrochloric acid- Clemmensen reduction of the ketone (128)$^{107}$ gave methyl 13-ethyl-12-methoxypodocarpa-8,11,13-trien-19-oate (153) m.p. 112-3$^\circ$ (lit.$^{107}$ 111-112.5$^\circ$) (80%) (correct $^1$H n.m.r. spectrum). $\delta_C$ 14.1, ArCH$_2$CH$_3$; 20.0, C2; 21.2, C6; 22.7, ArCH$_2$CH$_3$; 22.8, C20; 28.6, C18; 31.2, C7; 37.7, C3; 38.5, C10; 39.6, C1; 44.0, C4; 51.2, C5; 53.0, CO$_2$CH$_3$; 55.4, ArOCH$_3$; 107.2, C11; 127.0, C13; 129.2, C14; 130.1, C8; 146.2, C9; 155.6, C12; 178.0, C19.

b) With hydrogen- A solution of the ketone (128) (0.25 g, 0.7 mmol) in methanol (25 ml) and acetic acid (5 ml) was hydrogenated over 10% palladium on charcoal (30 mg) at 1 atmos. for 4 h. Concentration of the filtered solution gave an oil which was absorbed onto silica. Elution with dichloromethane gave (i) methyl 13-ethyl-12-methoxypodocarpa-8,11,13-trien-19-oate (153) (0.18 g, 75%) m.p. 109-112$^\circ$; and
(ii) methyl 13-(1'-hydroxyethyl)-12-methoxypodocarpa-8,11,13-trien-19-oate (191) as needles (from ether-hexane) (25 mg, 10%), m.p. 100-5°, [α]D218 +86° (c, 0.5) (lit.155 150°, [α]D21 +93° (c, 1.0)) (correct i.r. spectrum). δH 1.07, s, 3H, H20; 1.30, s, 3H, H18; 1.47, d, J 6 Hz, 3H, ArCH(OH)CH3; 3.65, s, 3H, CO2CH3; 3.80, s, 3H, ArOCH3; 5.05, q, J 6 Hz, ArCH(OH)CH3; 5.8, br s, OH; 6.78, s, H14; 7.02, s, H11. m/z 346 (M, 7%), 328 (M-H2O, 77), 255 (100).

Nitration of Methyl 13-Ethyl-12-methoxypodocarpa-8,11,13-trien-19-oate (153)

Concentrated nitric acid (0.2 ml, ρ 1.42 g cm⁻³, 3.2 mmol) was added to a solution of methyl 13-ethyl-12-methoxypodocarpa-8,11,13-trien-19-oate (153) (0.1 g, 0.3 mmol) in acetic anhydride (10 ml) at 0°. The mixture was stirred at 0° for 30min, then poured into ice-water and extracted with dichloromethane to give a yellow solid which was absorbed onto silica. Elution with dichloromethane gave:

(i) methyl 13-ethyl-12-methoxy-11-nitropodocarpa-8,11,13-trien-19-oate (194) as pale yellow needles (from methanol) which turned red in air (11 mg, 10%), m.p. 115-120°, [α]D218 +196° (c, 0.5) (Found: M⁺ 375.2047. C21H28NO3 requires M⁺ 375.2046). νmax 3050, 1720 (ester), 1530 (NO2), 1320 (NO2), 1060 cm⁻¹ (C-O). δH 1.17, s, 3H, H20; 1.27, s, 3H, H18; 1.28, t, J 6 Hz, 3H, ArCH2CH3; 2.83, q, J 6 Hz, 2H, ArCH2CH3; 3.67, s, 3H, CO2CH3; 3.75, s, 3H, ArOCH3; 7.0, s, H14. m/z 375 (M, 92%), 358 (M-OH, 17), 326 (17), 300 (100).

(ii) methyl 13-ethyl-12-hydroxy-11-nitropodocarpa-8,11,13-trien-19-oate (192) (50 mg, 46%).
Oxidation of Methyl 13-Ethyl-12-hydroxypodocarpa-8,11,13-trien-19-oate (189)

A solution of methyl 13-ethyl-12-hydroxypodocarpa-8,11,13-trien-19-oate (189) (0.8 g, 2.5 mmol) and benzoyl peroxide (1.0 g, 4.2 mmol) in chloroform (80 ml) was refluxed under a nitrogen atmosphere for 4 h. The cooled mixture was diluted with ether and a little acetic acid, then washed with potassium iodide solution, sodium hydrosulphite solution, sodium hydrogencarbonate solution, and water, dried, and concentrated to give a yellow solid which was absorbed onto silica. Elution with dichloromethane gave methyl 12-benzoyloxy-13-ethyl-11-hydroxypodocarpa-8,11,13-trien-19-oate (205) as plates (from methanol-hexane) (0.37 g, 33%), m.p. 180-5°, [α]D^18 +55° (c, 1.0) (Found: C 74.1, H 7.4%. C_{27}H_{32}O_5 requires C 74.3, H 7.4%). \nu_{max} 3400 (OH), 3000, 1720 (ester), 1600 cm^{-1} (C=C). \delta_H 1.18, s, 3H, H120; 1.27, s, 3H, H18; 1.28, t, J 6 Hz, 3H, ArCH_2CH_3; 2.40, q, J 6 Hz, 2H, ArCH_2CH_3; 3.65, s, 3H, CO_2CH_3; 5.33, s, OH; 6.60, s, H14; 7.3-8.3, m, 5H, aromatic H. \delta_C 13.8, ArCH_2CH_3; 17.2, C20; 19.8, C2; 20.9, C6; 23.0, ArCH_2CH_3; 29.0, C18; 33.5, C7; 36.0, C3; 37.7, C1; 39.8, C10; 44.0, C4; 50.8, C5; 51.2, CO_2CH_3; 121.2, C14; 128.4, C9; 128.8, 2C, benzoate C3,5; 130.4, 2C, benzoate C2,6; 133.0, benzoate C1; 133.5, C8; 134.1, benzoate C4; 135.4, C12; 135.8, C13; 146.2, C11; 164.9, PhCO_2; 178.3, C19. m/z 436 (M, 6%), 129 (3), 105 (100), 77 (10).

Further elution gave a yellow glass (0.3 g) which was a complex mixture by \^1H n.m.r. analysis.

Methyl 13-Ethyl-11,12-dihydroxypodocarpa-8,11,13-trien-19-oate (206)

A solution of methyl 12-benzoyloxy-13-ethyl-11-hydroxypodocarpa-8,11,13-trien-19-oate (205) (0.22 g, 0.5 mmol) in methanol (10 ml) was refluxed over sodium hydrosulphite (0.4 g, 5 mmol) for 90 min, Solvent was removed under reduced
pressure and the residue partitioned between ether and water. The aqueous layer was extracted with ether and the combined organic fractions were washed with sodium hydrogencarbonate solution, dried, and concentrated to give crude methyl 13-ethyl-11,12-dihydroxypodocarpa-8,11,13-trien-19-oate (206) as an oil (0.145 g, 90%). The product rapidly coloured in air and was used without further purification.

**Ozonolysis of the 11,12-Catechol (206)**

Ozone was passed through a solution of the crude catechol (206) (0.145 g, 0.45 mmol) in dichloromethane-methanol (1:1, 20 ml) at -78° until the blue colour persisted (12 min). The solution was purged with oxygen, then a solution of sodium borohydride (58 mg, 1.5 mmol) in 50% ethanol (5 ml) was added. The mixture was stirred for 2 h, then worked up to give a blue oil which was absorbed onto silica. Elution with dichloromethane gave the isodrimenin congener (34) (25 mg, 20%).

**Methyl 13-Amino-12-hydroxypodocarpa-8,11,13-trien-19-oate (207)**

10% Palladium on charcoal (50 mg) was added in portions to a hot solution of the nitrophenol (137) (0.38 g, 1.13 mmol) and hydrazine hydrate (0.4 ml, 8 mmol) in ethanol (40 ml). Upon cessation of the resulting effervescence the mixture was refluxed for 2 h. The cooled mixture was filtered and concentrated to give methyl 13-amino-12-hydroxypodocarpa-8,11,13-trien-19-oate (207) as needles (from methanol) (0.26 g, 75%), m.p. 203-8°, [α]D18 + 87° (c, 0.6) (Found: C 71.1, H 8.3, N 4.4%. C18H29NO3 requires C 71.3, H 8.3, N 4.6%). \( \nu_{\max} \) 3350 (NH2, OH), 2950, 1600 cm\(^{-1}\) (C=C). \( \delta_H \) 0.97, s, 3H, H20; 1.27, s, 3H, H18; 3.2, br s, 2H, NH2; 3.67, s, 3H, CO2CH3; 6.40, s, H11; 6.65, s, H14. \( \delta_C \) (dms-o-d6) 19.7, C2; 21.1, C6; 22.8, C20; 28.0, C18; 30.9, C7; 37.1, C3; 39.4, C1; C10 (obscured by solvent); 43.3,C4; 51.1, C5; 52.5, CO2CH3;
110.0, C11; 114.0, C14; 125.2, C8; 134.1, C13; 135.9, C9; 142.4, C12; 177.1, C19. \( m/z \) 303 (M, 74%), 288 (M-CH₃, 100), 222 (80).

**Oxidation of the Aminophenol (207)**

A solution of the aminophenol (207) (0.1 g, 0.33 mmol) in acetic acid (30 ml) was added dropwise over 5 min to a stirred solution of sodium metaperiodate (1.0 g, 4.7 mmol) in 0.1M hydrochloric acid (70 ml). The mixture was stirred for 3 min then extracted with dichloromethane. The extract was washed with brine then shaken with a solution of potassium iodide (0.3 g, 1.8 mmol) in acetic acid (30 ml) for 2 min. The dichloromethane layer was washed with sodium hydrosulfite solution, and brine, dried, and concentrated to give methyl 12,13-dihydroxypodocarpa-8,11,13-trien-19-oate (37) as prisms (from methanol) which darkened in air (43 mg, 43%), m.p. 216-220° (lit. 237-9°, 242-4°), [\( \alpha \)]D \( ^{18} \) +15° (c, 0.4) (Found: C 71.2, H 8.0%. \( \text{C}_{18}\text{H}_{24}\text{O}_{4} \) requires C 71.0, H 8.0%). \( \nu_{\text{max}} \) 3300 (OH), 1720 cm\(^{-1} \) (ester). \( \delta_{\text{H}} \) 0.80, s, 3H, H20; 0.95, s, 3H, H18; 3.67, s, 3H, CO\(_2\text{CH}_3\); 6.0, br s, 2H, ArOH; 6.47, s, H11; 6.57, s, H14. \( \delta_{\text{C}} \) (dmso-d\(_6\)) 19.7, C2; 21.0, C6; 22.8, C20; 28.0, C18; 30.8, C7; 37.3, C3; C1,C10 (obscured by solvent); 43.3, C4; 51.2, C5; 52.3, CO\(_2\text{CH}_3\); 112.3, C11; 115.0, C14; 125.3, C8; 138.4, C9; 143.0, C13; 143.2, C12; 177.1, C19. \( m/z \) 304 (M, 45%), 302 (M-2H, 39), 289 (M-CH₃, 40), 229 (100), 227 (42), 187 (43).

In a repeat experiment oxidation of the aminophenol (207) (0.634 g, 2 mmol) with sodium metaperiodate (6.3 g, 29.4 mmol) and subsequent reduction with potassium iodide (18 g, 10.8 mmol) as above gave an orange solid (0.5 g). Acetylation with acetic anhydride and pyridine with 4-dimethylaminopyridine as co-catalyst, followed by chromatography on silica gave the diacetate (210) (0.11 g, 14%) (identical to sample prepared below).
Methyl 13-Nitro-12-toluene-\textit{p}-sulfonoylxyloxydopocarpa-8,11,13-trien-19-oate (211)

Treatment of the nitrophenol (137) with \textit{p}-toluenesulfonyl chloride and potassium carbonate\textsuperscript{90} gave the toluene-\textit{p}-sulfonate ester (211) m.p. 129-130\degree (lit.\textsuperscript{90} 128-130\degree) (83\%) (correct $^1\text{H}$ n.m.r. spectrum).

Methyl 13-Amino-12-toluene-\textit{p}-sulfonoylxyloxydopocarpa-8,11,13-trien-19-oate (212)

10\% Palladium on charcoal (40 mg) was added in portions to a warm solution of the 13-nitro 12-tosylate (211) (0.61 g, 1.25 mmol) and hydrazine hydrate (0.4 ml, 8 mmol) in ethanol (25 ml). Upon cessation of the resulting effervescence the mixture was refluxed for 2 h. Concentration of the cooled, filtered mixture gave the 13-amine 12-tosylate (212) (0.46 g, 80\%) m.p. 128-9\degree (lit.\textsuperscript{90} 128-9\degree) (correct i.r. and $^1\text{H}$ n.m.r. spectra).

Diazotization of the 12-Toluene-\textit{p}-sulfonoyloxy-13-amine (212)

A solution of the amine (212) (0.5 g, 1.3 mmol) in pyridine (10 ml) was added over 40 min to a stirred solution of sodium nitrite (0.5 g, 8.2 mmol) in 80\% sulfuric acid (25 ml) at 0\degree. The mixture was stirred at 0-5\degree for a further 20 min and then ice (8 g) was added over 30 min. A solution of urea (1.3 g) in water (6 ml) was added and the mixture was poured into water and extracted with dichloromethane. The extract was filtered through a short silica column and concentrated to give an orange solid (0.13 g). Three recrystallisations from methanol gave methyl \textit{7b,8,9,10,11,11a\beta,12,13-octahydro-2,7b\alpha,11\beta-trimethylbenzo[c]-phenanthro[2,3-e]-[1,2]-oxathiin-11\alpha-carboxylate 5,5-dioxide} (213) as needles (50 mg, 10\%), m.p. 235-236.5\degree, $[\alpha]_D^{18} +150\degree$ (c, 0.4) (Found: $M^+$ 440.1666. $C_{25}H_{28}SO_5$ requires $M^+$ 440.1657). $\nu_{\text{max}}$ 3050, 1720 (ester),
Treatment of methyl 13-acetyl-12-hydroxypodocarpa-8,11,13-trien-19-oate (185) (2.35 g, 7.1 mmol) with acetic anhydride (15 ml) and pyridine (0.5 ml) for 3 h gave methyl 12-acetoxy-13-acetylpodocarpa-8,11,13-trien-19-oate (214) as needles (from methanol) (2.27 g, 86%), m.p. 121-3°, [α]D17 +128° (c, 0.9) (Found: C 71.2, H 7.9%. C22H28O5 requires C 70.9, H 7.6%). ν max 3050, 1750 (acetate), 1710 (ester), 1680 cm⁻¹ (ketone). δH 1.03, s, 3H, H20; 1.30, s, 3H, H18; 2.33, s, 3H, CH3CO2; 2.53, s, 3H, CH3CO; 3.68, s, 3H, CO2CH3,6.93, s, H11; 7.50, s, H14. δC 19.7, C2; 20.7, C6; 21.2, CH3CO2; 22.7, C20; 28.4, C18; 29.1, CH3CO; 31.4, C7; 37.4, C3; 38.9, C10; 39.0, C1; 43.9, C4; 51.4, C5; 52.1, CO2CH3; 120.8, C11; 127.6, C13; 131.4, C14; 133.4, C8; 147.2, C12; 154.4, C9; 169.9, CH3CO2; 177.6, C19; 197.2, CH3CO. m/z 372 (M, 1%), 330 (M-CH2CO, 100), 255 (70), 43 (60).

Methyl 12,13-Diacetoxypodocarpa-8,11,13-trien-19-oate (210)

A solution of methyl 12-acetoxy-13-acetylpodocarpa-8,11,13-trien-19-oate (214) (1.1 g, 3 mmol) and m-chloroperbenzoic acid (0.9 g, 4 mmol) in dichloromethane
(20 ml) containing p-toluenesulfonic acid (few crystals) was left at 4° for 7 weeks. Precipitated m-chlorobenzoic acid was removed by filtration and washed with dichloromethane. The combined filtrate and washings were washed with potassium iodide solution, sodium hydrogensulfite solution, sodium hydrogencarbonate solution, and water, dried, and concentrated to give an oil which was absorbed onto silica. Elution with dichloromethane gave (in order of elution):

(i) methyl 13-acetyl-12-hydroxypodocarpa-8,11,13-trien-19-oate (185) (28 mg, 3%);
(ii) methyl 12,13-diacetoxy podocarpa-8,11,13-trien-19-oate (210) as needles (from methanol) (0.34 g, 30%), m.p. 129-131° (lit.39 130-2°), [α]D18 +67° (c, 0.9) (correct i.r. and 1H n.m.r. spectra). δC 19.8, C2; 20.6, 20.7, CH3CO2; 20.7, C6; 23.0, C20; 28.5, C18; 31.5, C7; 37.5, C3; 38.4, C10; 39.3, C1; 43.9, C4; 51.3, C5; 52.2, CO2CH3; 120.4, C11; 123.0, C14; 134.3, C8; 139.4, C12; 139.9, C13; 146.7, C9; 168.6, 2C, CH3CO2; 177.8, C19. m/z 388 (M, 5%), 346 (M-CH2CO, 24), 304 (M-2CH2CO, 100), 289 (42), 43 (37); and (iii) starting material (0.26 g, 23%).

**Hydrolysis of the Diacetate (210)**

Treatment of the diacetate (210) with sodium hydroxide in aqueous methanol on a waterbath for 30 min gave the 12,13-catechol (37) (100%).

**Oxidation of the 12,13-Catechol (37)**

a) With m-chloroperbenzoic acid- A solution of m-chloroperbenzoic acid (40 mg, 0.2 mmol) and the catechol (37) (30 mg, 0.1 mmol) in dichloromethane (2 ml) was left in the dark for 18 h. Workup gave an oil which was absorbed onto silica. Elution with dichloromethane gave the 12,13-anhydride (160) (9 mg, 29%).

b) With copper(I) chloride and oxygen- Copper(I) chloride (33mg, 0.33 mmol)
was added in portions to a stirred mixture of pyridine (2 ml) and methanol (33 μl, 0.8 mmol) under a nitrogen atmosphere, and the mixture was stirred under an oxygen atmosphere for 5 min. A solution of the catechol (37) (0.1 g, 0.33 mmol) in pyridine (2 ml) and methanol (30 μl, 0.8 mmol) was added dropwise over 40 min with stirring. Workup gave a red oil which was a complex mixture by t.l.c. analysis.

**Methyl 12,13-Dimethoxypodocarpa-8,11,13-trien-19-oate (38)**

A solution of methyl 13-hydroxy-12-methoxypodocarpa-8,11,13-trien-19-oate (130) (0.2 g, 0.6 mmol) and sodium hydroxide (60 mg, 1.5 mmol) in methanol-water (2:1, 15 ml) was refluxed for 30 min. Dimethyl sulfate (0.15 ml, 1.5 mmol) was added via the condenser and the mixture was refluxed for a further 1 h. Sodium hydroxide was added to the cooled mixture and the mixture was refluxed for 30 min. Dimethyl sulfate (0.15 ml, 1.5 mmol) was added via the condenser and the mixture was refluxed for 1 h, then poured into water and extracted with dichloromethane to give methyl 12,13-dimethoxypodocarpa-8,11,13-trien-19-oate (38) as needles (from chloroform-hexane) (0.18 g, 81%), m.p. 75-9° (lit.39 oil, b.p. 160-170°/0.1 mm Hg), [α]D17 +106° (c, 1.2) (Found: C 72.0, H 8.8%. C20H28O4 requires C 72.25, H 8.4%). (Correct i.r. spectrum.) δH 1.02, s, 3H, H20; 1.25, s, 3H, H18; 3.62, s, 3H, CO2CH3; 3.78, s, 6H, ArOCH3; 6.38, s, H11; 6.62, s, H14. δC 20.0, C2; 21.1, C6; 22.8, C20; 28.5, C18; 31.7, C7; 37.6, C3; 38.2, C10; 39.7, C1; 44.0, C4; 51.3, C5; 52.9, CO2CH3; 55.7, 56.0, ArOCH3; 108.8, C11; 111.3, C14; 127.6, C8; 140.0, C9; 146.9, C13; 147.1, C12; 177.9, C19. m/z 332 (M, 100%), 317 (M-CH3, 32), 191 (12), 177 (15), 41 (11).

**Ozonolysis of the Dimethoxy Compound (38)**

Ozone was passed through a solution of the dimethoxy compound (38) (0.1 g, 0.3
mmol) and boron trifluoride etherate (37 µl, 0.3 mmol) in dry dichloromethane (15 ml) at -78°C for 5 min. The solution was purged with oxygen, warmed to room temperature, washed with water and brine, dried, and concentrated. The residue (0.1 g) was absorbed onto silica and eluted with dichloromethane to give trimethyl 12,13-seco-podocarpa-8(14),9(11)-dien-12,13,19-trioate (215) as an oil (55 mg, 50%), [α]D24 +25° (c, 0.2) (Found: M+ 364.1886. C20H28O6 requires M+ 364.1886). v_max 1720 (ester), 1650 cm⁻¹ (C=C). δ_H 0.90, s, 3H, H20; 1.05, td, J_3α,3β=J_3α,2β 13.5, J_3α,2α 3.7 Hz, H3α; 1.19, s, 3H, H18; 1.22, td, J_1α,1β=J_1α,2β 15.3, J_1α,2α 5.2 Hz, H1α; 1.41, dd, J_5α,6β 10.1, J_5α,6α 5.6 Hz, H5; 1.55-1.75, m,2H; 1.71, br d, J_1β,1α 15.3 Hz, H1β; 1.98, qt, J_2β,1α 15.3, J_2β,2α 14.5, J_2β,3α 13.5, J_2β,1β=J_2β,3β 3.5 Hz, H2β; 2.11-2.30, m, 3H; 2.60, dt, J_7β,7α 11.7, J_7β,6β 3.3, J_7β,6α 2.6 Hz, H7β; 3.54, s, 3H, C(13)O2CH3; 3.62, S, 3H, C(12)O2CH3; 3.65, s, 3H, C(19)O2CH3; 5.57, s, H14; 5.82, s, H11. δ_C 16.1, C20; 19.8, C2; 26.2, C6; 28.7, C18; 37.0, C7; 38.0, C13; 39.7, C1; 44.6, C10; 44.7, C4; 51.0, C(13)O2CH3; 51.1, C(12)O2CH3; 51.4, C(19)O2CH3; 56.0, C5; 112.1, C11; 115.2, C14; 155.8, C8; 162.6, C9; 166.0, C13; 167.0, C12; 177.1, C19. m/z 364 (M, 2%), 349 (M-CH3, 1), 305 (M-CO2CH3, 100), 69 (20).

Ozonolysis of (38) in the absence of boron trifluoride gave a complex mixture of which (215) was a minor component by ¹H n.m.r. analysis. Oxidation of (38) with m-chloroperbenzoic acid gave a complex mixture which did not contain (215).
CHAPTER THREE

Ozonolysis of Methyl 12-Hydroxypodocarpa-8,11,13-trien-19-oate (10)

Treatment of methyl 12-hydroxypodocarpa-8,11,13-trien-19-oate (10) with ozone at -78° gave methyl hydrogen 8β-hydroperoxy-8α-hydroxy-(13-17)-pentanorlabd-9(11)-ene-12,19-dioate 12,8α-lactone (41), m.p. 181-5° (lit. 185-7°) (62%).

Zinc-acid Reduction of the Hydroperoxy-lactone (41)

a) In methanol-Treatment of methyl podocarpate (10) with ozone at -78° followed by reduction of the crude hydroperoxy-lactone (41) with zinc and hydrochloric acid in methanol gave dimethyl 8-oxo-(13-17)-pentanorlabdane-12,19-dioate (43), m.p. 95-8° (lit. 96-7°) (42%) (correct 1H n.m.r. spectrum).

b) In ethanol-Treatment of methyl podocarpate (10) with ozone at -78° followed by reduction of the crude hydroperoxy-lactone (41) with zinc and hydrochloric acid in ethanol gave 19-methyl hydrogen 8-oxo-(13-17)-pentanorlabdane-12,19-dioate (42), m.p. 169-170° (lit. 171-2°) (27%) (correct 1H n.m.r. spectrum) and crude 12-ethyl 19-methyl 8-oxo-(13-17)-pentanorlabdane-12,19-dioate (219) as a brown oil (52%) which was used without further purification.

The yields and product ratios from these reductions were variable as shown in Table 3.
<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Scale (g)</th>
<th>%Yield</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(43)</td>
<td>(42)</td>
</tr>
<tr>
<td>MeOH</td>
<td>1.0</td>
<td>19 (^\text{b})</td>
</tr>
<tr>
<td>MeOH</td>
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<td>15 (^\text{c})</td>
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<td>19 (^\text{c})</td>
</tr>
<tr>
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<td>47</td>
</tr>
<tr>
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<td>27</td>
</tr>
<tr>
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<td>8.0</td>
<td>32</td>
</tr>
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<td>–</td>
</tr>
<tr>
<td>EtOH</td>
<td>8.0</td>
<td>–</td>
</tr>
</tbody>
</table>

- a) amount of (10) ozonised
- b) (41) purified before reduction
- c) crude product treated with dimethyl sulfate
- d) crude yield

Table 3.

c) In acetic acid-Zinc dust (2.0 g, 32 mmol) was added to a solution of the hydroperoxy-lactone (41) (2.2 g, 61 mmol) in acetic acid (40 ml) and the mixture was stirred for 2.5 h. Workup gave the keto-acid (42) (1.1 g, 52%).

Hydrogenation of the Hydperoxy-lactone (41)

- a) Under acidic conditions-Hydrogenation of crude hydroperoxy-lactone (41) in acetic acid\(^\text{57}\) gave methyl hydrogen 8\(\alpha\),8\(\beta\)-dihydroxy-(13-17)-pentanorlabd-9(11)-ene-
12,19-dioate (220), m.p. 199-200° (lit.\(^\text{42}\) 198-201°) (45% from (10)) (correct \(^1\text{H}\) n.m.r. spectrum).

b) Under basic conditions-Hydrogenation of crude hydroperoxy-lactone (41) (8.3 g, 26 mmol) in methanol (120 ml) and 10% sodium hydroxide solution (10 ml, 24 mmol) gave the keto-acid (42) (3.52 g, 43% from (10)) m.p. 171-2°.

**Reduction of the Hydroperoxy-lactone (41) with Sulfur Reagents**

a) With sodium hydrogensulfite-Reduction of the hydroperoxy-lactone (41) with sodium hydrogensulfite\(^{27}\) gave the hydroxy-lactone (220) (29%).

b) With dimethyl sulfide-Treatment of methyl podocarpate (10) with ozone at -78° followed by workup with dimethyl sulfide gave the hydroxy-lactone (220) (40%).

**Reduction of the Hydroxy-lactone (220)**

Hydrogenation\(^{57}\) of the hydroxy-lactone (220) gave the keto-acid (42) (90%). The keto-acid (42) was also obtained in 86% yield from the reduction of (220) with zinc and acetic acid.

**Hydrolysis of the Dimethyl Ester (43)**

A solution of the dimethyl ester (43) (2.1 g, 6.8 mmol) and sodium hydroxide (3.0 g, 75 mmol) in methanol (100 ml) and water (15 ml) was heated under reflux for 9 h, poured into water, acidified, and extracted with dichloromethane. The extract was washed with water, dried, and concentrated to give the keto-acid (42) as needles (from acetone-hexane) (1.4 g, 70%), m.p. 171-3°.
Hydrolysis of the Ethyl Methyl Ester (219)

A solution of crude ethyl methyl ester (219) (4.7 g, 14.3 mmol) and sodium hydroxide (3.0 g, 75 mmol) in ethanol (100 ml) and water (15 ml) was refluxed for 18 h, and then worked up to give the keto-acid (42) as needles (from acetone-hexane) (2.8 g, 65%), m.p. 169-171°.

Also isolated was the decalone (222) (47 mg, 1%) (identical to a sample prepared below).

Methyl 8-Oxo-11,12-dinordriman-14-oate (222)

A solution of the hydroxy-lactone (220) (50 mg, 0.17 mmol) in methanol and 1M sodium hydroxide solution (2 ml, 2 mmol) was refluxed under a nitrogen atmosphere for 18 h. The cooled mixture was poured into water and extracted with ether to give methyl 8-oxo-11,12-dinordriman-14-oate (222) as needles (from hexane) (18 mg, 45%), m.p. 62-4° (lit.42 62-3°) (correct i.r. and 1H n.m.r. spectra). Acidification of the aqueous layer and extraction with dichloromethane gave starting material (23 mg).

The decalone (222) was also obtained in 19% yield from treatment of the hydroperoxy-lactone (41) with methanolic sodium hydroxide as above.

Methylation of the Keto-acid (42)

A solution of the keto-acid (0.5 g, 1.67 mmol) in methanol (30 ml) was refluxed over Amberlyst-15 (0.12 g) for 24 h. Concentration of the filtered solution gave the dimethyl ester (43) (0.51 g, 100%) which crystallised from hexane as needles (0.45 g, 90%), m.p. 96-7°.
**Bromination of the Keto-acid (42)**

Treatment of the keto-acid (42) with bromine and hydrobromic acid\(^2^7\) gave 19-methyl hydrogen 7α-bromo-8-oxo-(13-17)-pentanorlabdane-12,19-dioate (216), m.p. 159-160° (lit.\(^2^7\) 158-160°) (correct \(^1\)H n.m.r. and mass spectra).

**Methyl 8-Oxo-12-nordrim-9(11)-en-14-oate (45)**

Treatment of the bromo-acid (216) with potassium carbonate in acetone\(^2^7\) gave crude methyl 8-oxo-12-nordrim-9(11)-en-14-oate (45) as an oil (lit.\(^2^7\) needles m.p. 226-8°) (100%) (correct \(^1\)H n.m.r. spectrum). \(^1\)H n.m.r. analysis showed the presence of a trace of the dimer (dimethyl 5β,7′α,8αα,10αβ-tetramethyl-2-oxo-1′,2′,3,4,4a,5,5′-6,6′,6a′,7,7′,8,8′,8a,9′,10′,10a′-octadecahydrospiro[naphthalene-1(2H),3′-[3H]naphtho[2,1-b]pyran]-5α,7β-dicarboxylate) (224).

The enone (45) was unstable with respect to the dimer (224) and was used without further purification.

**Dimerisation of the Enone (45)**

A solution of crude enone (45) (0.1 g, 0.4 mmol) in ethanol was refluxed for 16 h to give the dimer (224) as needles (from dichloromethane-hexane) (75 mg, 75%), m.p. 230-2° (lit.\(^2^7\) 230-2°) (correct \(^1\)H n.m.r. spectrum).

**Epoxidation of the Enone (45)**

30% Hydrogen peroxide solution (1.4 ml, 12 mmol) was added to a stirred solution of the crude enone (45) 0.2 g, 0.8 mmol) in methanol (20 ml) and 10% sodium
hydroxide solution (0.6 ml, 1.2 mmol) at 0°. The mixture was stirred at 0° for 5 h, poured into water and extracted with dichloromethane. The extract was washed successively with potassium iodide solution, sodium hydrgensulfite solution, sodium hydrogencarbonate solution, and water, dried, and concentrated to give a solid (0.15 g) which was absorbed onto silica. Elution with hexane-ether (2:1) gave methyl 9α,11α-epoxy-8-oxo-12-nordran-14-oate (225) as needles (from dichloromethane-hexane) (50 mg, 23%), m.p. 95-99°, [α]D21 -70° (c, 0.2). (Found: C 67.0, H 8.3%; M+: 266.1517. C13H22O4 requires C 67.6, H 8.4%; M+: 266.1519). νmax 2950, 1720 (ester, ketone), 1030 cm⁻¹ (C=O). δH 0.90, s, 3H, H15; 1.12, td, 3J1α,1β=J1α,2β 13.5, 3J3α,3β =J3α,2β 13.5, J1α,2α=J3α,2α 3.7 Hz, 2H, H1α,H3α; 1.29, s, 3H, H13; 1.47, dd, 1J5α,6β 13.5, 2J5α,6α=4J5α,2α 4.5 Hz, H5; 1.55, dq, 3J2α,2β 14.2, 1J2α,1α=J2α,3α 3.7, 1J2α,1β=J2α,3β 3.1 Hz, H2α; 1.85, qt, 2J2β,2α 14.2, 1J2β,1α=J2β,3α 13.5, 1J2β,1β=J2β,3β 3.3 Hz, H2β; 1.93, br d, 1J1β,1α 13.5 Hz, H1β; 2.20, dtd, 2J3β,3α 13.5, 2J3β,2β 3.3, 3J3β,2α 3.1, 1J3β,1β 1.4 Hz, H3β; 2.27-2.37, m, 2H, H6; 2.55, dt, 1J7β,7α 14.3, 1J7β,6β 3.8, 2J7β,6α 3.6 Hz, H7β; 2.62, ddd, 3J7α,7β 14.3, 1J7α,6α 11.0, 1J7α,6β 9.0 Hz, H7α; 2.85, 3.14, 2d, Δ 4.5 Hz, H11; 3.67, s, 3H, CO2CH3. δC 16.3, C15; 18.6, C2; 23.5, C6; 28.4, C13; 30.3, C7; 37.5, C3; 39.0, C10; 40.8, C1; 44.3, C4; 47.1, C11; 49.9, CO2CH3; 51.5, C5; 67.1, C9; 177.1, C14; 206.8, C8. m/z 266 (M, 28%), 251 (M-CH3, 19), 196 (17), 177 (17), 161 (21), 135 (20), 121 (100), 109 (89).

Treatment of the epoxide (225) with perchloric acid or boron trifluoride etherate
gave complex mixtures which were not investigated further.

**Attempted Addition of 1,3-Dithianyl Lithium to the Enone (45)**

Butyl lithium (0.25 ml of a 1.7M solution in hexane, 0.425 mmol) was added to a stirred solution of 1,3-dithiane\(^{155}\) (54 mg, 0.42 mmol) in dry tetrahydrofuran (1 ml) at -10° under a nitrogen atmosphere. The mixture was stirred at -10° for 2h, and a
solution of the enone (45) (0.1 g, 0.4 mmol) in dry tetrahydrofuran (2 ml) was added dropwise. The mixture was stirred at -10° for 0.5 h, and then left at 2° for 19 h. Workup gave the dimer (224) (86 mg).

**Attempted Methyleneation of the Enone (45)**

Freshly distilled diiodomethane (0.3 ml, 3.4 mmol) was added to a stirred suspension of zinc powder (0.6 g, 6.4 mmol) in dry tetrahydrofuran (5 ml), and the mixture was stirred under nitrogen for 30 min. A solution of freshly distilled titanium tetrachloride (0.18 ml, 1.7 mmol) in dry dichloromethane (5 ml) was added at 0°. The resulting black solution was stirred for 1 h. A solution of the enone (45) (0.2 g, 0.8 mmol) in dry tetrahydrofuran (5 ml) was then added. The mixture was stirred for 3 h, diluted with ether, washed successively with 2M hydrochloric acid, water, sodium hydrogen carbonate solution, and brine, dried, and concentrated to give an oil (0.15 g) which was absorbed onto silica. Elution with hexane-ether (1:1) gave an oil (56 mg, 27%), b.p. 110-120/0.15 mm Hg, which by n.m.r. analysis was a mixture of *methyl 5α,8α-dimethyl-2-methylene-3,4,4a,5,6,7,8,8a-octahydro[1H]-napthalene]-5β-carboxylate* (228) (67%) and *methyl 5α,8α-dimethyl-1-methylene-3,4,4a,5,6,7,8,8a-octahydro[1H]-napthalene]-5β-carboxylate* (229) (33%). \( \nu_{\text{max}} \) 3030, 2950, 1710 (ester), 1640 cm\(^{-1} \) (C=C). \( \delta_H \) -0.02, dt, \( J_{3'a,2'a} \) 9.8, \( J_{3'a,2'b} \) 4.5, \( J_{3'a,2'a} \) 4.4 Hz, H3'a; 0.50, dt, \( J_{2'b,3'b} \) 9.3, \( J_{2'b,2'a} \) 5.0, \( J_{2'b,3'a} \) 4.5 Hz, H2'b; 0.50, s, C8a-CH\(_3\)(228); 0.68, td, \( J_{2'a,3'a} \) 9.8, \( J_{2'a,2'b} \) 5.0, \( J_{2'a,3'b} \) 4.5 Hz, H2'a; 0.79, s, C8a-CH\(_3\)(229); 0.87, td, \( J_{3'b,2'b} \) 9.3, \( J_{3'b,2'a} \) 4.8, \( J_{3'b,3'a} \) 4.4 Hz, H3'b; 0.97, td, \( J_{6a,6b}=J_{6a,7b} \) 13.5, \( J_{6a,7a} \) 4.0 Hz, H6a; 1.00, td, \( J_{8a,8b}=J_{8a,7b} \) 13.4, \( J_{8a,7a} \) 3.9 Hz, H8a; 1.19, 1.20, 2s, C5-CH\(_3\); 1.43, dt, \( J_{7a,7b} \) 14.0, \( J_{7a,6a} \) 13.5, \( J_{7a,8a} \) 13.4, \( J_{7a,6b}=J_{7a,8b} \) 3.3 Hz, H7a; 1.49, dd, \( J_{4a,4b} \) 12.2, \( J_{4a,4a} \) 3.7 Hz, H4a; 1.85, qt, \( J_{7b,7a} \) 14.0, \( J_{7b,6a} \) 13.5, \( J_{7b,8a} \) 13.4, \( J_{7b,6b}=J_{7b,8b} \) 3.8 Hz, H7b;
1.90-2.10, m, H4; 2.15, br d, J8β,8α 13.4 Hz, Hz, H8β; 2.18, br d, J6β,6α 13.5 Hz, H6β; 2.34-2.44, m, H3(228); 3.07, td, J3α,3β 9.1, J3α,2β 8.8, J3α,2α 7.8 Hz, H3α(229); 3.34, td, J3β,βα 9.1, J3β,2β 8.5, J3β,2α 4.1 Hz, H3β(229); 3.62, s, CO2CH3(229); 3.63, s, CO2CH3(228); 4.47, 4.86, 2d, J 1.1 Hz, C=CH2(229); 4.51,4.60, 2d, J 1.5 Hz, C=CH2(228). δC 4.9 cyclopropyl CH2(228); 6.9 cyclopropyl CH2(229); 10.4 cyclopropyl CH2; 13.0, C8α-CH3(229); 18.1, C8α-CH3(228); 19.7, C7(228); 19.9, C7(229); 25.7, C4(228); 26.1, C4(229); 28.4, C5-CH3(228); 28.5, C5-CH3(229); 29.7, cyclopropyl C; 32.2, C8; 35.2, C8α(229); 35.8, C8; 37.1, C8α(228); 38.2, C6(229); 38.3, C6(228); 44.3, C5(229); 44.5, C5(228); 51.2, CO2CH3; 53.3, C4α; 105.4, C=CH2(228); 106.3, C=CH2(229); 147.1, C=CH2(229); 151.9, C=CH2(228); 177.6, CO2CH3(229); 177.7 CO2CH3(228). m/z 247 (M-CH3, 10%), 234 (M-C2H4, 87), 203 (30), 187 (42), 174 (100), 159 (26), 121 (80).

Further elution gave an oil (30 mg) which by t.l.c. and 1H n.m.r. analysis was a complex mixture whose major component was the dimer (224).

**Dimethyl 8-(E)-Methoxyimino-(13-17)-pentanorlabdane-12,19-dioate (230)**

A solution of the ketoester (43) (0.55 g, 1.8 mmol) and methoxylamine hydrochloride (0.35 g, 4 mmol) in pyridine (2 ml) was left at 75° for 22 h, poured into water, and extracted with dichloromethane. The extract was washed with dilute hydrochloric acid and water, dried, and concentrated to give an orange oil (0.57 g) which was absorbed onto silica. Elution with hexane-ether (1:2) gave dimethyl 8-(E)-methoxyimino-(13-17)-pentanorlabdane-12,19-dioate (230) as prisms (from ether-hexane) (0.44 g, 83%), m.p. 81-3°, [α]D +78° (c, 1.3) (Found: C 63.5, H 8.8%; M+ 339.2071. C18H29NO5 requires C 63.7, H 8.6%; M+: 339.2045). νmax 2950, 1720 cm⁻¹ (ester). δH 0.54, s, 3H, H20; 1.04, td, J3α,3β=J3α,2β 13.5, J3α,2α 4.0 Hz, H3α; 1.17, td, J1α,1β=J1α,2β 13.2, J1α,2α 4.0 Hz, H1α; 1.17, s, 3H, H18; 1.42, dd, J5α,6β 12.7,
$J_{5\alpha,6\alpha}$ 3.0 Hz, H5; 1.48, dquin, $J_{2\alpha,2\beta}$ 13.8, $J_{2\alpha,1\alpha}=J_{2\alpha,3\alpha}$ 4.0, $J_{2\alpha,3\beta}$ 3.2, $J_{2\alpha,1\beta}$ 3.0 Hz, H2α; 1.55, td, $J_{7\alpha,7\beta}$ 13.7, $J_{7\alpha,6\beta}$ 13.7, $J_{7\alpha,6\alpha}$ 5.6 Hz, H7α; 1.62, br d, H1β; 1.77, tdd, $J_{6\beta,6\alpha}$ 14.0, $J_{6\beta,7\alpha}$ 13.7, $J_{6\beta,5\alpha}$ 12.7, $J_{6\beta,7\beta}$ 4.3 Hz, H6β; 1.78, q, $J_{2\beta,2\alpha}$ 13.8, $J_{2\beta,3\alpha}$ 13.5, $J_{2\beta,1\alpha}$ 13.2, $J_{2\beta,1\beta}$ 3.5, $J_{2\beta,3\beta}$ 3.3 Hz, H2β; 2.00, ddt, $J_{6\alpha,6\beta}$ 14.0, $J_{6\alpha,7\alpha}$ 5.6, $J_{6\alpha,5\alpha}$ 3.0, $J_{6\alpha,7\beta}$ 2.5 Hz, H6α; 2.15, dtd, $J_{3\beta,3\alpha}$ 13.5, $J_{3\beta,2\beta}$ 3.3, $J_{3\beta,2\alpha}$ 3.2, $J_{3\beta,1\beta}$ 1.4 Hz, H3β; 2.23, dd, $J_{11\alpha,11\beta}$ 15.9, $J_{11\alpha,9\alpha}$ 3.6 Hz, H11α; 2.43, $J_{9\alpha,11\beta}$ 10.3, $J_{9\alpha,11\alpha}$ 3.6 Hz, H9α; 2.64, dd, $J_{11\beta,11\alpha}$ 15.9, $J_{11\beta,9\alpha}$ 10.3 Hz, H11β; 3.27, ddd, $J_{7\beta,7\alpha}$ 13.7, $J_{7\beta,6\beta}$ 4.3, $J_{7\beta,6\alpha}$ 2.5 Hz, H7β; 3.57, s, 3H, C(12)O2CH3; 3.59, s, 3H, C(19)O2CH3; 3.70, s, 3H, NOCH3. δC 12.9, C20; 19.6, C2; 23.3, C6; 25.8, C7, 28.8, C18; 38.1, C3; 38.9, C1; 40.1, C10; 44.1, C4; 51.3, C9; 51.3, C(12)O2CH3; 51.5, C(19)O2CH3; 55.2, C5; 61.3, NOCH3; 157.9, C8; 174.2, C12; 177.4, C19. m/z 339 (M, 27%), 324 (M-CH3, 22), 308 (M-CH3O, 29), 292 (33), 280 (20), 248 (23), 231 (24), 159 (100), 135 (22), 127 (38), 121 (48).

**Reduction of the Oxime Diester (230)**

a) With 6 equivalents of LiAl(OMe)3H-Dry methanol (1.5 ml, 37 mmol) was added to a stirred solution of lithium aluminium hydride in dry tetrahydrofuran (32 ml, 1.55M in hydride, 49.6 mmol hydride) under a nitrogen atmosphere. The mixture was stirred for 10 min, and a solution of the oxime diester (230) (0.7 g, 2.1 mmol) in dry tetrahydrofuran (30 ml) was added dropwise. The mixture was stirred for 3 h, and ethyl acetate (0.3 ml) was added, followed by 2M hydrochloric acid (10 ml) and dichloromethane (10 ml). The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic fractions were dried and concentrated to give a white solid which was absorbed onto silica. Elution with ethyl acetate gave:

(i) 8-methoxyiminoo-(13-17)-pentanorlabdane-12,19-diol (231) as needles (from dichloromethane) (44mg, 7.5%), m.p. 117-121°, [α]D18 +16° (c, 0.2) (Found: C 68.1, H 10.5,
N 4.95%. C_{16}H_{29}NO_3 requires C 67.8, H 10.1, N 4.9%). \nu_{\text{max}} 3350 (OH), 3000, 1600 cm\(^{-1}\) (C=\(C\)). \delta_H 0.69, s, 3H, H20; 0.90-0.96, m, 1H; 0.97, s, 3H, H18; 1.03-1.10, m, 1H; 1.31, d, J 12.9 Hz, 1H; 1.35, qd, J 12.9, 12.7, 12.7, 4.2 Hz, 1H; 1.44-1.57, m, 4H; 1.63-1.71, m, 1H; 1.76, br d, J 12.8 Hz, 1H; 1.82, br d, J 12.5 Hz, 1H; 1.82-1.94, m, 4H; 3.33, J_{7\beta,7\alpha} 13.1, J_{7\beta,6\beta} 4.0, J_{7\beta,6\alpha} 2.1 Hz, H7\beta; 3.36, d, J 10.8 Hz, H19; 3.51-3.57, m, 1H; 3.54, ddd, J_{12\beta,12\alpha} 9.9, J_{12\beta,11\beta} 6.4, J_{12\beta,11\alpha} 4.4 Hz, H12\beta; 3.65, ddd, J_{12\alpha,12\beta} 9.9, J_{12\alpha,11\beta} 7.0, J_{12\alpha,11\alpha} 3.5 Hz, H12\alpha; 3.71, d, J 10.8 Hz, H19; 3.78, NOCH_3. \delta_C 15.2, C20; 18.6, C2; 21.8, C6; 25.8, 26.0, C7,C11; 27.0, C18; 35.2, C3; 38.7, 2C, C1,C10; 40.3, C4; 55.3, C9; 55.6, C5; 61.2, NOCH_3; 62.9, C12; 64.6, C19; 160.7, C8. m/z 283 (M, 3%), 268 (M-CH_3, 4), 252 (M-CH_3O, 70), 224 (100).

(ii) 8\beta-methoxyamino-\(\text{(13-17)-pentanorlabdane-12,19-diol}\) (232) (0.52 g, 86%) as plates (from dichloromethane-hexane) (0.44 g, 75%), m.p. 138-142\(^\circ\), [\alpha]_D^{18} +15\(^\circ\) (c, 0.6) (Found: C 67.2, H 11.2, N 4.7%). C_{16}H_{31}NO_3 requires C 67.3, H 11.0, N 4.9%). \nu_{\text{max}} 3400 (OH, NH), 2950, 1040 cm\(^{-1}\) (C-O). \delta_H 0.79, s, 3H, H20; 0.80-0.90, m, 2H, H1\alpha,H3\alpha; 0.93, s, 3H, H18; 1.02, dd, J_{5\alpha,6\beta} 12.1, J_{5\alpha,6\alpha} 2.2 Hz, H5; 1.20-1.51, m, 6H; 1.52-1.70, m, 4H; 1.76, br d, J 13.5 Hz, 1H; 2.13, dd, J 13.6, 2.4 Hz, 1H; 3.13, br s, W \sim 12 Hz, H8\alpha; 3.41, d, J 10.9 Hz, H19; 3.47, s, 3H, NHOCCH_3; 3.60-3.72, , 3H; 3.73, d, J 10.9 Hz, H19; 5.5, br s, NHOCCH_3. \delta_C 16.6, C20; 17.0, C2; 18.1, C6; 26.9, C18; 28.0, 30.3, C7,C11; 35.4, C3; 37.4, C10; 38.5, C4; 39.0, C1; 50.4, C8; 56.9, C9; 57.5, C5; 61.6, C12; 61.9, NOCH_3; 65.1, C19. m/z 285 (M, 5%), 254 (M-CH_3O, 12), 95 (13), 86 (100).

b) With 2 equivalents of LiAl(O\(\text{Me}\))_3H- Dry methanol (0.34 ml, 8.8 mmol) was added to a stirred solution of lithium aluminium hydride in dry tetrahydrofuran (1.8 ml, 6.6M in hydride, 11.68 mmol) diluted with dry tetrahydrofuran (10 ml), under a nitrogen atmosphere. The mixture was stirred for 10 min, and a solution of the oxime diester (230) (0.39 g, 1.15 mmol) in dry tetrahydrofuran (15 ml) was added dropwise. The mixture was stirred for 22 h and then worked up to give an oil which was absorbed
onto silica. Elution with hexane-ether (4:1) gave starting material (0.184 g).

Elution with hexane-ether (1:1) gave methyl 12-hydroxy-8-methoxyimino-(13-17)-pentalabdan-19-oate (233) (76 mg, 21 %) as an oil, [α]D21 +96° (c, 0.5) (Found: M+ 311.2094. C17H29NO4 requires M+ 311.2097). νmax 3350 (OH), 2950, 1720 (ester), 1640 (C=N), 1070 cm⁻¹ (C-O). δH 0.57, s, 3H, H20; 1.23, s, 3H, H18; 3.63, s, 3H, CO₂CH₃; 3.83, s, 3H, NOCH₃. m/z 311 (M, 4%), 296 (M-CH₃, 3), 280 (M-CH₃O, 43), 252 (100).

Treatment of (233) with methanesulfonyl chloride and triethylamine gave a complex mixture which was not investigated further.
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STRUCTURES

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