APPROACHES TOWARDS THE SYNTHESIS OF ROSENONOLACTONE

A Thesis

Presented for the Degree of

Doctor of Philosophy

in

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by

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CONTENTS

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SUMMARY.

The Birch reduction of O-methyl podocarpic acid has been carefully investigated and this has allowed the development of satisfactory methods for the preparation of 12-oxo-podocarp-8-en-16-oic acid and podocarp-8-en-16-oic acid. Two schemes for the synthesis of rosenonolactone have been developed based on these intermediates. One of these has given a satisfactory yield of 12-oxorosenonolactone.

The key reaction in these syntheses was the rearrangement of a suitably substituted epoxide with boron trifluoride. This allowed the introduction of the lactone bridge and the 9β-methyl group of rosenonolactone in one step and in a satisfactory yield (30-60%). Although the balance of material in these reactions was generally a complex mixture of acids, an exception was the rearrangement of 8α,9α-epoxy-podocarpan-16-oic acid which gave a spiroketone in a 60% yield. Some reactions of this compound have been investigated and the structure 5α,9β-dimethyl-2-oxo-decalin-1-spirocyclopentane-5β-carboxylic acid has been proposed.

Several literature methods have been investigated for the introduction of the C_{13} substituents of rosenonolactone.

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ACKNOWLEDGEMENTS

I wish to thank Dr. R.A. Massy-Westropp and Dr. L.N. Mander for their guidance and encouragement during this work. I should also like to thank my colleagues in the laboratory and my long-suffering wife and parents.

This research was carried out during the tenure of a Commonwealth Postgraduate Award, which I gratefully acknowledge.

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STATEMENT

This thesis contains no material previously submitted for a degree or diploma in any University, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

W.S. Hancock.

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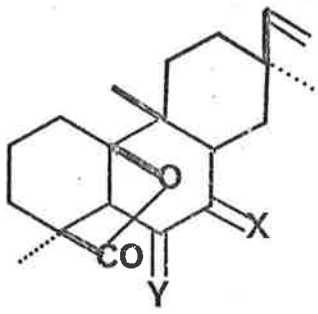
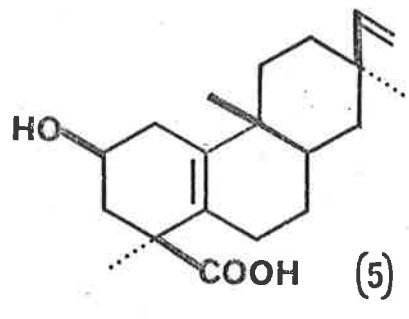
INTRODUCTION.

Rosenonolactone (1) was first isolated as the major constituent of the extract from the fungus Trichothecium roseum Link by Freeman and Morrison[1] in 1948. The determination of the structure of rosenonolactone was of great interest as the crude extract was shown to have significant antifungal activity. Robertson et al.[2] initiated chemical studies on rosenonolactone in 1949, and this was continued by Whalley et al.[3] who finally elucidated the structure in 1965. This work was confirmed by X-ray determination of the relative configuration of 15,16-dibromorosenonolactone.[4]

Other metabolites of Trichothecium roseum Link, deoxorosenonolactone (2),[5] rosolclactone (rosonolactone) (3),[6] 6β-hydroxyrosenonolactone (4)[7,8] and isorosenolic acid (5)[9] have been isolated and identified by correlation with rosenonolactone.

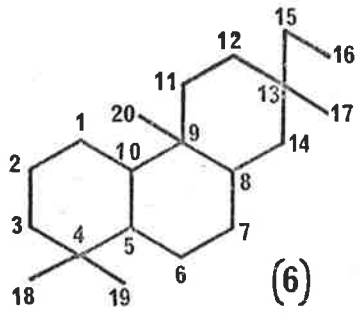




(5)

1. X = O; Y = H_2
2. X = H_2; Y = H_2
3. X = H_2; Y = β-OH, H
4. X = O; Y = β-OH,H

The numbering system for rosenonolactone derivatives in this thesis will be based on the rosane skeleton (6)[10] and will be in the same sense as for the podocarpane system (7).



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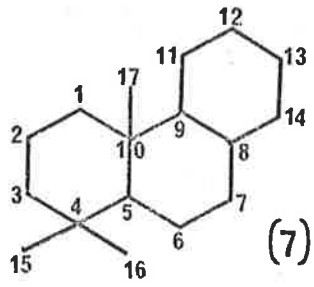
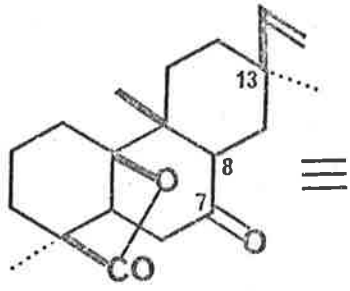


(7)

While rosenonolactone is a member of a large class of tricyclic diterpenes it has the distinguishing features of a trans, syn, trans backbone instead of the normal trans, anti, trans arrangement, and a methyl group at C_9 instead of C_{10}. Although the biosynthetic relationship of rosenonolactone to the general class of diterpenes is clear[11] its synthesis has not been achieved, and the attainment of this goal would be a useful addition to the chemistry of this fungal metabolite. This thesis will describe the various approaches to the synthesis that were developed, and while the synthesis itself was not completed, several compounds closely related to the natural product were prepared.

Before the synthetic scheme used in this thesis can be discussed, it is necessary to appreciate the problems associated with the synthesis of this diterpene. The trans, syn, trans back-



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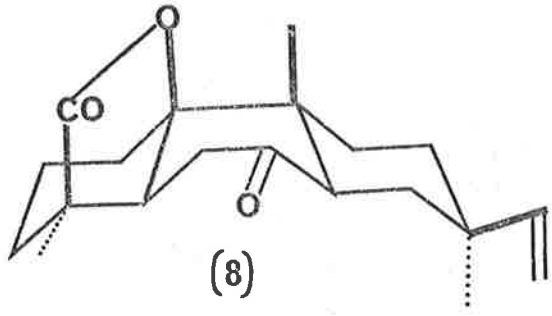
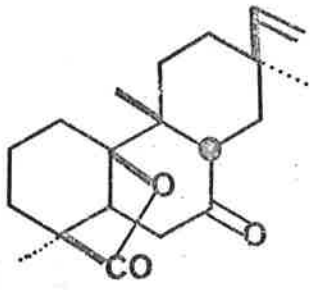


(8)

rosenonolactone (1)



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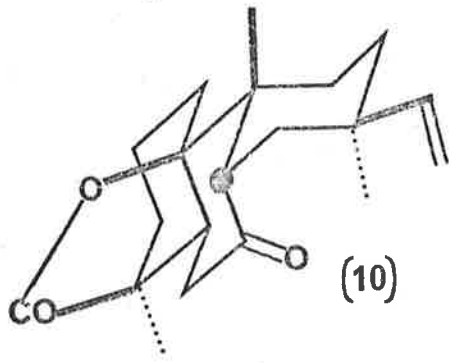


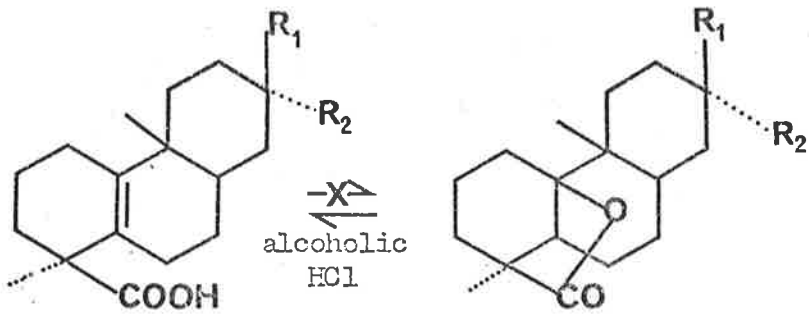
(10)

isorosenonolactone (9)

bone of rosenonolactone (1) forces ring B to adopt a boat conformation and the serious steric interactions due to this system (8) will present a barrier to any synthetic scheme. Once the carbonyl group is introduced at C_7. epimerisation at the C_8 centre may occur readily to give the more stable, all chair, trans, syn, cis system (10). An equilibrium mixture of the two forms is obtained only when substituents are present at C_{13} to

destabilise the trans, syn, cis system, such as in the interconversion of rosenonolactone (1) and iso-rosenonolactone (9).

Conversely, if a trans B:C ring junction was established during a synthesis, cyclisation of an intermediate such as (11) would not be expected to give the desired lactone. This prediction was verified by some degradative work on rosenonolactone, where lactonisation of the unsaturated acid (12) gave two new lactones.≠



(13)

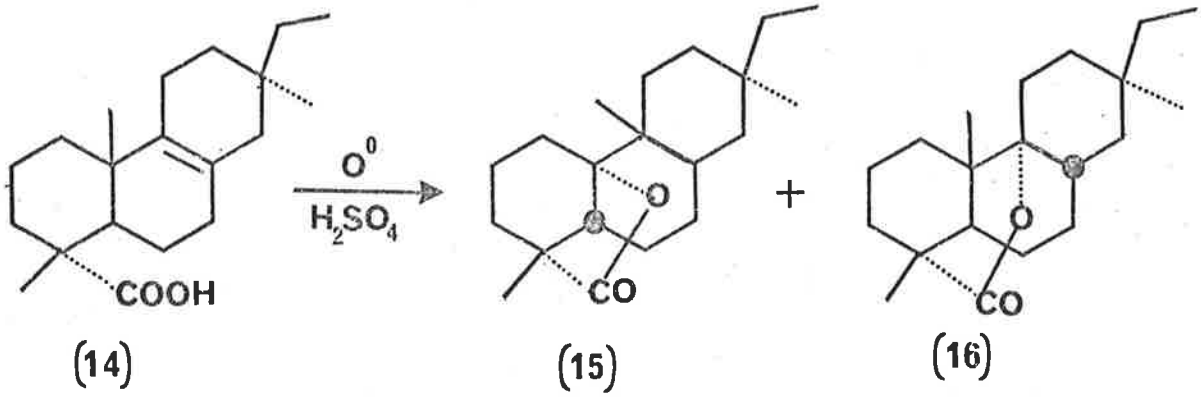
(11) $R_1 = R_2 = H$

(12) $R_1 = CH_3CH_2-$, $R_2 = CH_3-$

≠ While specific structures were not proposed for the lactones by the authors,[3] the evidence provided clearly rules out the formation of the trans, syn, trans lactone structure.

It was decided that a synthetic scheme which used a natural product as a starting material had a distinct advantage over a total synthesis, which must construct the basic tricyclic system as well as introduce the various functional groups. Furthermore, it seemed that the best solution to the problems involved in establishing the trans, syn, trans backbone of rosenonolactone was to introduce the lactone bridge as the first stage in the synthesis, and this conclusion led to the use of a resin acid as the starting material.≠

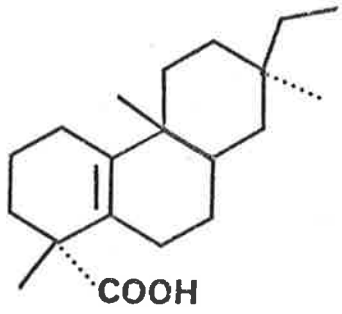
This approach had a decided advantage in that the lactonisation of resin acids had been studied extensively. Many of these lactonisations involved a methyl shift from C_{10} to C_9, as in the following example from the work of Wenkert.[13]



(14) (15) (16)

≠ This decision has been supported by a recent publication[12] in which the authors commented on the difficulties inherent in a total synthesis of rosenonolactone, and particularly in the introduction of the lactone bridge.

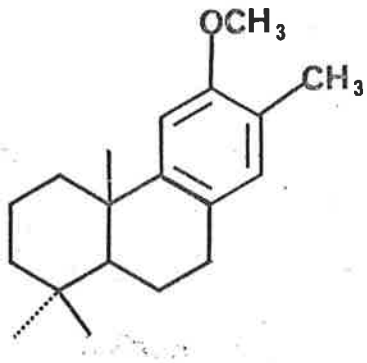
The all chair structures (15) and (16) were assigned to the products on the basis that they involved the least number of interactions and thus would be preferred.[14] The rearrangement must proceed via a $\Delta 5$ (10) acid as an intermediate, because the formation of structure (15) requires epimerisation at C_5 of the starting acid (14). If the lactonisation of the acid (14) was carried out with alcoholic hydrochloric acid[15,28] instead of sulphuric acid as the catalyst, the intermediate unsaturated acid (17) was isolated, which when further subjected to the reaction conditions, gave the γ-lactone (18).



(17)

However, these studies have only been carried out on resin acids which have the opposite stereochemistry at C_4 to rosenonolactone. It was not obvious that a similar rearrangement would occur for an acid which had a β-carboxyl group at C_4 (cis to the C_{10} methyl group), because the lactonisation could no longer be concerted with the migration of the methyl group.

Podocarpic acid (28) was chosen as the starting material for the synthesis described in this thesis, because it had several important advantages. It was readily available in large quantities, it had the same stereochemistry at C_4 as rosenonolactone, and its total synthesis had been achieved by Wenkert.[16] Because of this total synthesis any transformation of podocarpic acid into another diterpene constituted a formal total synthesis of the latter, and this concept had been used by Bible[17] in the synthesis of nimbiol (18).



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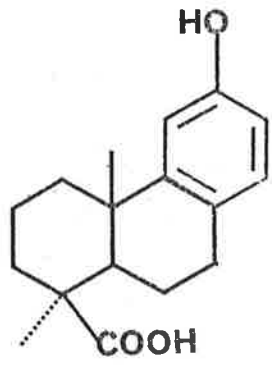
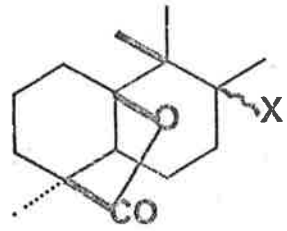


(28)

However, before podocarpic acid (28) could be used in the synthesis, it was necessary to determine if the desired rearrangement, with a methyl shift from C_{10} to C_9 and concomitant lactonisation, could be achieved. Section A of the discussion will describe the investigation of this rearrangement and will explain how an intermediate of the type (19) was made in one step, and in good yield from a suitable podocarpane precursor, with complete stereochemical control

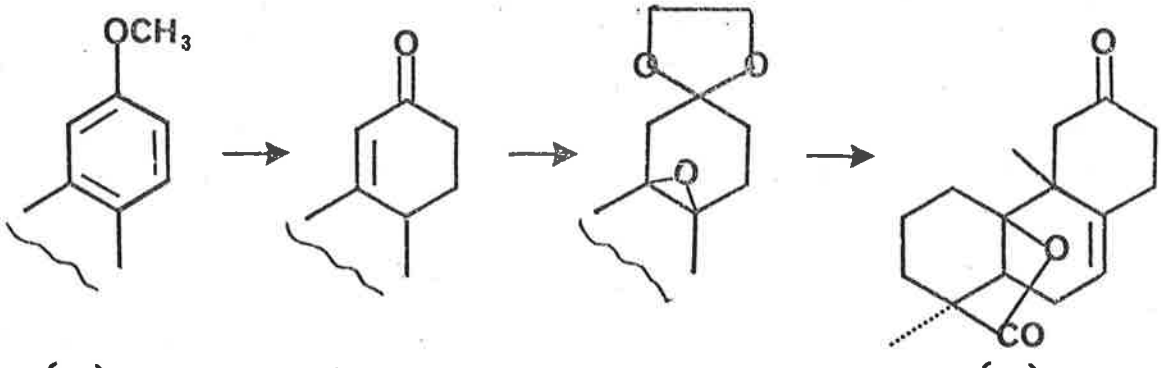
at C_5, C_9, and C_{10}.



(19)

X = H or OH

The first step in introducing the C_{13} substituents of rosenonolactone required the modification of ring C of O-methyl podocarpic acid (20), via a Birch reduction, to the unsaturated ketone (21). Further transformations gave the epoxyketal (22), which could be readily converted to the lactone (23) using the methods described in section A of the discussion.



(20) (21) (22) (23)

The carbonyl group at C_{12} could now be used as an activating group for the introduction of the substituents at C_{13}, and one could use one of the procedures that have been developed by Ireland.[18] It was also necessary to transform the double bond at C_7 into a ketone. Section B of the discussion will describe the execution of these steps while differentiating between the various functional groups.

CHAPTER I.

Introduction of the lactone bridge and the 10β methyl group of rosenonolactone.

1.1 Preparation of podocarpic acid derivatives.

1.2 Lactonisation of podocarpic acid derivatives.

1.3 Determination of the stereochemistry at C_5 of the unsaturated lactone (5).

1.4 Attempts at the functionalisation of the C ring.

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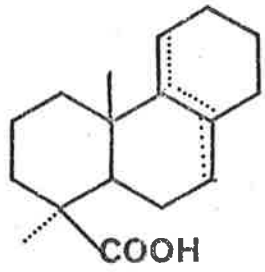
1.1 Preparation of podocarpic acid derivatives.

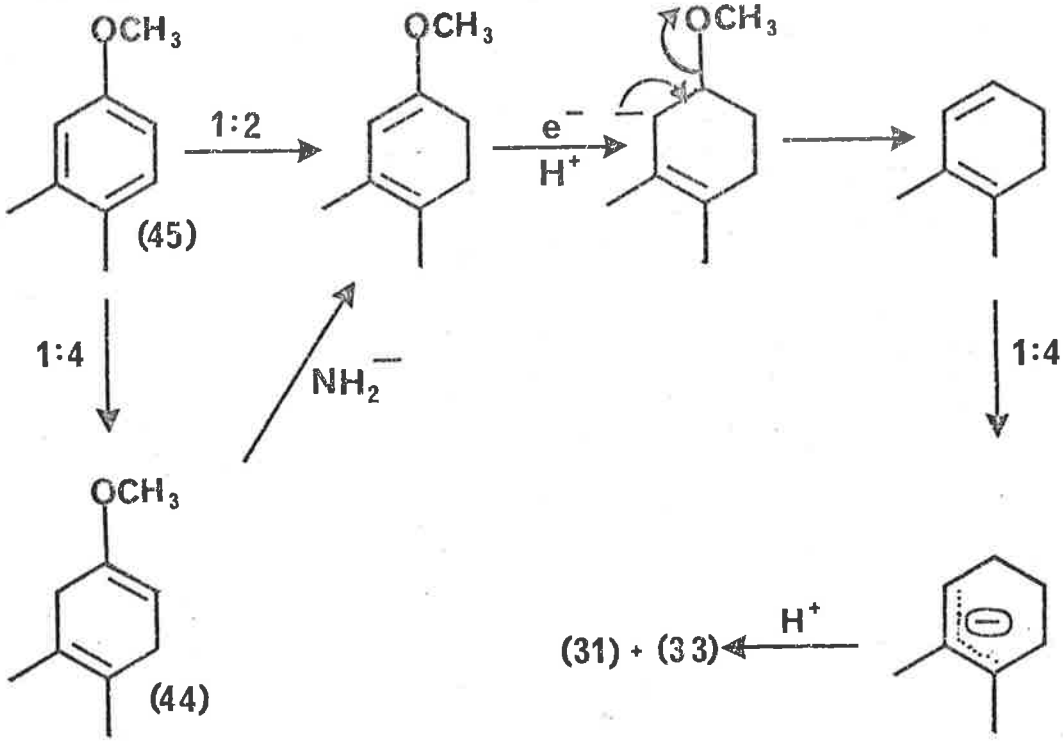
An unsaturated acid of the general structure (43) is required to determine if migration of the methyl group from C_{10} to C_9 with concomitant lactonisation will occur in the same manner for podocarpic acid derivatives as for the abietic acid series. In podocarpic acid (28) the C_4 carboxyl group is cis to the C_{10} methyl group, and hence lactonisation at C_{10} can not be concerted with the migration of the methyl group.



(43)

Although at that time, the reports[19-23] published on the Birch reduction of O-methyl podocarpic acid (29) were incomplete, several results encouraged us to expect a reasonable yield of the unsaturated acid (31) from this reaction. It was suggested[24] that the normal 1,4-reduction of the aromatic ring, which led to the dihydroanisole (44), was so retarded by steric hindrance at C_{11}, that 1,2-reduction could compete. This alternative mode of reduction led to the isomeric dihydroanisole (45) which, as a conjugated diene,

could be reduced further. Furthermore it was predicted that this steric effect would be accentuated by the use of an alcohol with a hindered hydroxyl group (such as t-butyl alcohol) to retard protonation of the radical anion at the more hindered position.



In our hands, the reduction of O-methyl podocarpic acid (29) with a mixture of lithium, ammonia, and an alcohol gave the products shown in scheme 1. As anticipated, the yield of unsaturated acids (31) and (33), was increased (from 10 to 30%) if t-butyl alcohol was used instead of ethanol, and a longer reaction time was used (8 hr). Conversely the best yield of the normal products, the unsaturated ketones (35) and (36) was obtained with a short reaction time ($\frac{1}{2}$ hr), and ethanol as the proton donor.

Although our results were consistent with the formation of the conjugated diene (45) by 1,2-reduction, the increase in yield of the unsaturated acids (31) and (33) with time suggested that (45) was arising also from the slow isomerisation of the 1:4 reduction product.

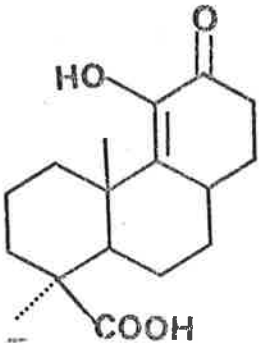
The optimum conditions for the isolation of the ketones (35) and (36) will be described here, although they are not of direct relevance to this section of the work. The importance of these compounds will become clear later in the thesis.

Careful acidification of the mixture from the Birch reduction with oxalic acid gave 12-oxo-podocarp-8-en-16-oic acid (36) together with products formed by the reduction of the dihydroanisole system (45). However, the Δ8-ketoacid (36) could not be obtained crystalline even after careful chromatography, due to the presence of a small quantity of 12-oxo-podocarpan-16-oic acid (37). In fact, these two ketones were so similar in properties, that they could not be separated, and their structures could only be deduced from a study of the corresponding alcohols. Reduction of the ketones with lithium aluminium tri-t-butoxy hydride gave a mixture of the alcohols (41) and (42), which were separated by careful chromatography. The saturated alcohol (42) was a known compound[19] while 12-hydroxy-podocarp-8-en-16-oic acid (41) was identified from its elemental analysis and spectra. Saturated ketones have been observed before[21,25] in the Birch reduction of other podocarpic acid derivatives.

If the reduction product was acidified with hydrochloric acid instead of oxalic acid, the α,β-unsaturated ketone (35) was formed. The mixture of products was separated by fractional crystallisation of the sodium salts from water. The first crop of crystals consisted of a 3:1 mixture of the two unsaturated acids (31) and (33) respectively (the ratio was determined from the integration of the nuclear magnetic resonance (n.m.r.) spectrum). The α,β-unsaturated ketone (35), contaminated with a trace of the β,γ-isomer (36), was obtained in the second crop.

Recrystallisation of the respective crops gave a pure sample of podocarp-8-en-16-oic acid (31) and 12-oxo-podocarp-9(11)-en-16-oic acid (35), but not podocarp-9(11)-en-16-oic acid, because samples of the latter were always contaminated with the Δ8-isomer. The two products (31) and (35) were converted into known compounds by standard methods (see scheme 1).

It is worthwhile to note that the unsaturated ketones (35) and (36) are difficult to crystallise because of their ready oxidation to the hydroxyketone (43), the diosphenol (44), and podocarpic acid (45). The first product (43) has also been observed by Rogers[20] from reduction of the corresponding hydroperoxide during the chromatography of the α,β-unsaturated ketone (35). Also the chemistry of these products has been the subject of another investigation.[26]



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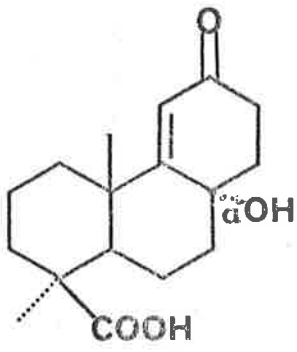

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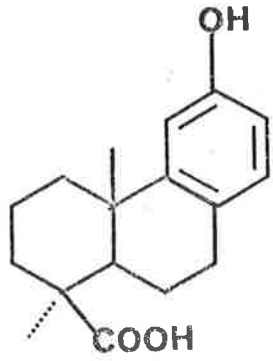

(28)

A pure sample of the minor unsaturated acid could only be obtained by desulphurisation of the thioketal (39) which was formed from the α,β-unsaturated ketone (35). However the corresponding methyl ester (34) was readily identified in the product from the Birch reduction by vapour phase chromatography (v.p.c.) of the mixture of methyl esters. The structure (33) of the unsaturated acid was confirmed by the n.m.r. spectrum which exhibited a one proton triplet at τ4.58, and by its oxidation with selenium dioxide to the α,β-unsaturated ketone (35).

1.2 Lactonisation of podocarpic acid derivatives.

(a) Lactonisation of podocarp-8-en-16-oic acid (31).

(b) Lactonisation of 8α,9α-epoxy-podocarp-8-en-16-oic acid (51).

(c) The structure of the hydroxylactone (52).

(d) The structures of the unsaturated lactones (53) and (54).

(e) Possible mechanisms for the rearrangement of the epoxyacid (51).

(f) Lactonisation of the mixture of epoxides (51) and (69).

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(a) Lactonisation of podocarp-8-en-16-oic acid (31).

Now that the unsaturated acid (31) was available, the study of the rearrangement and lactonisation of podocarpic acid derivatives could start. When the major unsaturated acid (31) was treated with boron trifluoride etherate ($BF_3 \cdot Et_2O$) a saturated γ-lactone ('BF_3-lactone') (ν_{max} 1770 cm^{-1}) was formed. An isomeric γ-lactone ('H_2SO_4-lactone') was obtained if the major or the minor unsaturated acid (31) or (33), or the 'BF_3-lactone' (46) was treated with sulphuric acid. This suggested that the 'BF_3-lactone' (46) was the kinetic product and the 'H_2SO_4-lactone' (47) was the thermodynamic product from the lactonisation of an intermediate Δ5(10) acid (48).

This conclusion was supported by the observation that, if the $BF_3 \cdot Et_2O$ catalysed lactonisation was left for a much longer time, a significant quantity of the thermodynamic product, the 'H_2SO_4-lactone' (47), was formed. With the rearrangement catalysed by $BF_3 \cdot Et_2O$, the migration of the C_{10} methyl group should be concerted with the protonation of the Δ8-olefin and therefore the 'BF_3-lactone' should have a trans B:C ring junction. Since the 'BF_3-lactone' was the kinetic product, it would be expected to have a trans A:B ring junction,[27,28] and therefore it would be best described by structure (46). Of the three remaining possible structures (47), (67), and (68), from an examination of molecular models, it appeared that (47) had the structure which was most thermodynamically stable, and therefore was

assigned to the 'H_2SO_4-lactone'. This assumption was verified by later work - see section 1.3.

The trans, syn, trans backbone of the 'BF_3-lactone' (46) forces ring B to adopt the boat conformation - see scheme 3, and could be expected to isomerise on treatment with sulphuric acid to the all-chair structure (47). It is interesting to note that while the 'BF_3-lactone' could be formed directly from the unsaturated acid (31), the 'H_2SO_4-lactone' must be formed via the $\Delta 5(10)$ unsaturated acid (48) to allow epimerisation at C_5 to occur.

These results were most encouraging, for it had been shown that the rearrangement and lactonisation of podocarpic acid derivatives could be achieved, and that the stereochemistry at C_5 of the product could be controlled by the correct choice of a Lewis acid for a catalyst. However the two saturated lactones (46) and (47) could not be used in the synthesis of rosenonolactone, because they did not have a functional group that would allow the introduction of the C_7 and C_{13} substituents.

Furthermore, if a suitably functionalised lactone could be prepared, it was essential that the stereochemistry at C_5 could be unambiguously assigned at an early stage.

(b) Lactonisation of 8α,9α-epoxy-podocarpan-16-oic acid (51).

An intermediate of the desired type was prepared by the lactonisation of the epoxyacid (51), which was prepared in quantitative yield from the major unsaturated acid (31) by treatment with m-chloroperbenzoic acid. As the α-face of the unsaturated acid was markedly less hindered, the epoxide was assigned to the α-stereochemistry.

$BF_3.Et_2O$ was a much better catalyst than sulphuric acid for this rearrangement, as the latter gave variable yields of lactone material, and also the resulting mixture could not be readily separated.

The epoxyacid (51) was treated very briefly with $BF_3.Et_2O$ and the products from the reaction were separated into an acidic and a neutral fraction. Chromatography of the neutral fraction (30% yield) gave two unsaturated lactones (53) and (54) (25% yield) and a hydroxylactone (52) (5% yield) - see scheme 4. The acidic fraction contained one major product, but as this compound was not relevant to the synthetic scheme, its chemistry will be discussed in an appendix.

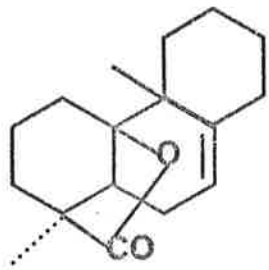
(c) The structure of the hydroxylactone (52).

The hydroxylactone, $C_{17}H_{26}O_3$ (ν_{max} 3580, 1760 cm^{-1}) gave an n.m.r. spectrum which showed only one lowfield signal at τ7.39 (broad singlet, removed by exchange with deuterium oxide) which was assigned to a hydroxylic proton. If these lactones are formed by a shift of the methyl group from C_{10} to C_9 with lactonisation at C_{10}, the tertiary alcohol must be formed by opening of the epoxide, and therefore can only be at C_8. This argument, together with the other evidence, defines (52) as the structure of the hydroxylactone.

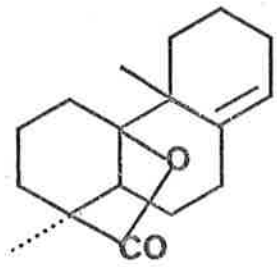
The hydroxylactone (52) was found to be remarkably resistant to dehydration, presumably due to the extreme steric hindrance of the alcohol (ν_{max} 3580 cm^{-1}), but it could be acetylated by a mixture of p-toluene sulphonic acid and acetic anhydride (normal conditions were unsuccessful). Pyrolysis of the acetate (58) gave a good yield of the unsaturated lactone (53).

(d) The structures of the unsaturated lactones (53) and (54).

The major unsaturated lactone (53), which analysed for $C_{17}H_{24}O_2$, had two salient features in its spectra. The infrared (i.r.) spectrum showed only lactone absorption (1760 cm^{-1}), while the n.m.r. spectrum contained a doublet at τ5.03 p.p.m. corresponding to one olefinic proton. This data was consistent with either structure (53) or (54) for the unsaturated lactone.



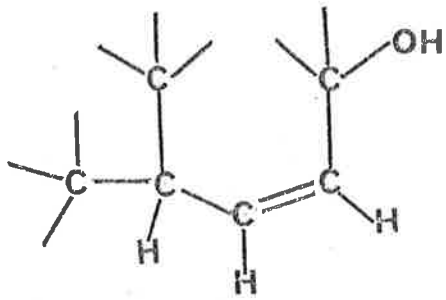
(53)



(54)

Careful chromatography of the oily residues from the recrystallisation of the unsaturated lactone gave a pure sample of an isomeric unsaturated lactone. As before, the n.m.r. spectrum contained an absorption due to a single olefinic proton (at τ4.72 p.p.m.), while the almost identical mass spectral fragmentation patterns clearly demonstrated the isomeric relationship between the two unsaturated lactones.

Oxidation of the major unsaturated lactone (53) with selenium dioxide gave an unsaturated hydroxylactone, $C_{17}H_{24}O_3$ (ν_{max} 3570, 1770 cm^{-1}), whose n.m.r. spectrum included signals that were assigned to two olefinic protons (τ4.39 p.p.m., broad singlet), one allylic proton (τ7.74 p.p.m., broad singlet), and one hydroxylic proton (τ7.5 p.p.m., broad singlet, removed on exchange with deuterium oxide), but no signals that could be attributed to protons bound to carbon-bearing oxygen. These features are best accommodated by the following partial structure (a) and this led to structure (55)



(a)

for the selenium dioxide oxidation product. The oxidation must have occurred with concomitant allylic rearrangement from structure (53) and not (54), and this was presumably a consequence of the hindered environment of the C_6 carbon atom.

The possibility that the selenium dioxide oxidation had occurred with skeletal rearrangement[29] was discounted by the reaction sequence outlined in scheme 5, which converted the oxidation product back to the unsaturated lactone (53). Structure (53) could now be confidently assigned to the major unsaturated lactone and (54) to the minor isomer.

Hydrogenation of the unsaturated hydroxylactone (55) gave the hydroxylactone (52), and this result again established the relationship between the two rearrangement products, the hydroxylactone (52) and the unsaturated lactone (53). Also this result indicated that the C_8 hydroxyl group of both the hydroxylactone (52) and the unsaturated hydroxylactone (55) had the same stereochemistry. Up

to this stage the hydroxyl group has been assumed to have the α-configuration and it is now time to present some evidence for this assumption.

(e) Possible mechanisms for the rearrangement of the epoxyacid (51).

Two possible mechanisms for the rearrangement of the epoxy-acid (51) are shown in scheme 6. The hydroxyl group of the hydroxy-lactone (52) will have the α-configuration if it is formed by path A, but if it is formed by path B, then no conclusion can be made about the stereochemistry of the hydroxyl group.

Good evidence for path B was obtained by the isolation of the fluorolactone (64) (in a low yield, 1%). The analysis and n.m.r. spectrum, which had no lowfield absorptions, were consistent with the proposed structure (64). The molecular ion of the mass spectrum occurred at m/e 280, and this together with the presence of ions at m/e 261 and 260 (consistent with the loss of $F^{\bullet}$ and HF), confirmed the structure of the fluorolactone. If the fluorolactone (64) was treated under the reaction conditions, a good yield of the unsaturated lactone (53) was obtained. This result suggested that the unsaturated lactone (53) was formed by path B≠ and not by path A via dehydration

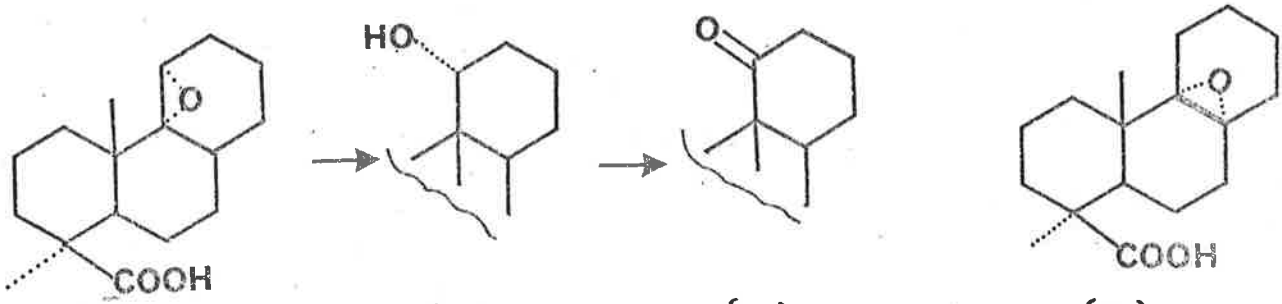
≠ This assumption is of course true only if the rearrangement occurs via one of the proposed pathways (A or B).

of the hydroxylactone (52), (or some boron derivative). This was consistent with the difficulty experienced in dehydrating the hydroxylactone (52), and especially its stability to $BF_3.Et_2O$.

Although it was probable that the hydroxylactone (52) was not formed from the fluorolactone (64), it was necessary to have definite proof of this assumption, and this was provided by the following experiment. It was found that the rearrangement would not occur in the absence of water, but normally sufficient water was present if the reaction was carried out in sodium dried benzene but the apparatus was not dried. If the water was replaced with H_2O^{18} (80% labelled), it was found that there was none of the label present in the hydroxylactone (52), which therefore could not have been formed by hydrolysis of the fluorolactone (64). The hydroxylactone (52) must have been formed directly from the epoxide, and the hydroxyl group should therefore have the α-configuration corresponding to that of the epoxyacid (51).

(f) Rearrangement of the mixture of epoxides (51) and (69).

Because of the difficulty in the separation of the unsaturated acids (31) and (33) or their corresponding epoxides, it was not practicable to use a pure sample of the epoxide (51) for a large scale lactonisation reaction.



(69) (70) (71) (51)

A new hydroxylactone, $C_{17}H_{26}O_3$ (ν_{max} 3490, 1740 cm^{-1}), was obtained from the $BF_3.Et_2O$ catalysed rearrangement of either a pure sample of the isomeric epoxide (69) or the mixture of epoxides (in the latter case together with the products from the other epoxide (51)). Fortunately this extra product was not a problem to the large scale work as the mixture of lactones was easily separated.

The n.m.r. spectrum of the hydroxylactone indicated the presence of a secondary hydroxyl group, with a one-proton doublet at τ6.23, which was not removed on exchange with deuterium oxide. This data suggested the structure (70) because the hydroxyl group could only be placed at C_{11} from the opening of the epoxide ring. The n.m.r. spectrum of the corresponding ketone (71) confirmed this assumption as the C_9 methyl group was strongly deshielded (0.24 p.p.m.)

relative to the hydroxylactone (70).

1.3 Determination of the stereochemistry at C_5 of the unsaturated lactone (53).

(a) Hydrogenation of the unsaturated lactone (53).

(b) Epoxidation of the unsaturated lactone (53).

(c) Hydroboration of the unsaturated lactone (53).

(d) Sodium borohydride reduction of the ketolactone (72).

***

1.3 Determination of the stereochemistry at C_5 of the unsaturated lactone (53).

There are two possible structures for the unsaturated lactone (53), depending on whether the A:B ring juntion is cis (66) or trans (65). On examination of the corresponding models it is clear that preferential reaction will occur from the β-face of (66), while reaction can occur from either face of (65) although one can expect some preference for reaction from the β-face.

It was decided to investigate the steric control of reactions occurring at the Δ7-olefin in the hope that the results would distinguish between the two structures (65) and (66). The common synthetic procedures hydrogenation, epoxidation, and hydroboration were chosen. Hydrogenation was a particularly useful method because the product, a saturated lactone, could be readily correlated with the two other saturated lactones (46) and (47).

(a) Hydrogenation of the unsaturated lactone (53).

Catalytic hydrogenation of the unsaturated lactone (53) with platinum oxide as the catalyst gave a saturated lactone (the 'H_2-lactone'). The spectral data clearly indicated that this new lactone was different from both the previously obtained lactones (46) and (47), and the almost identical mass spectral fragmentation patterns of the three lactones reinforced their stereoisomeric

inter-relationship.

As is shown in scheme 7 the saturated lactone can have one of three possible structures (46), (67), or (68), however structure (46) can be discounted as the 'H_2-lactone' is isomeric with the 'BF_3-lactone'. Also the hydrogenation product can not have structure (67) as it is stable to a prolonged exposure to $BF_3.Et_2O$. Structure (67), with a cis, syn, cis backbone, has particularly severe non-bonded interactions between the hydrogen atoms bound to C-1, C-12, and C-14, and will be readily isomerised to the more stable structure (68) with a trans, syn, cis backbone (i.e. the third possibility for the structure of the 'H_2-lactone'), particularly as $BF_3.Et_2O$ has been found to equilibrate the 'BF_3-lactone' (46) to the 'H_2SO_4-lactone' (47). Thus the 'H_2-lactone' has structure (68) and the unsaturated lactone structure (65). This important result can be summarised by these two deductions:

(1) the unsaturated lactone has a trans A:B ring junction,

(2) reaction has occurred from the β-face.

When the 'H_2-lactone' (68) was treated with sulphuric acid the 'H_2SO_4-lactone' (47) was readily formed. This isomerisation must involve protracted rearrangements (presumably 1,2-shifts) but does lead to a product with fewer non-bonded interactions (calculations on an exact model suggest an energy different of about 2kcal/mole between the two systems).[30]

(b) Epoxidation of the unsaturated lactone (53).

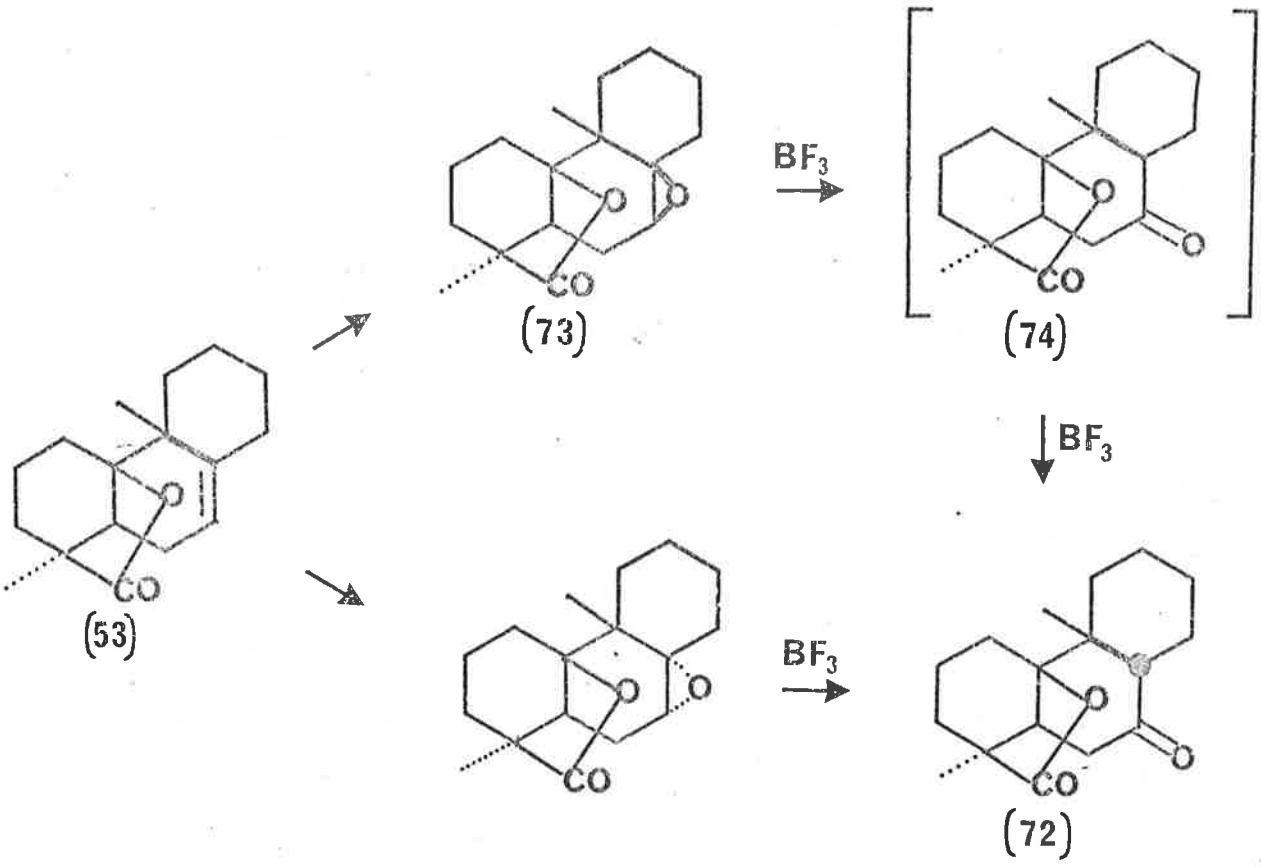
Epoxidation of the unsaturated lactone (53) lacked the specificity of hydrogenation, as it gave a crystalline 1:1 mixture of the two epimeric epoxides - see scheme 8. This result was consistent with the proposed structure (65) of the unsaturated lactone because it was unlikely that the alternative structure (66), with a cis A:B ring junction, would allow epoxidation from the α-face of the molecule.

Treatment of this mixture with $BF_3.Et_2O$ gave only one ketolactone (72), because its C_8 epimer (74) formed from epoxide (73) was presumably isomerised to the more stable ketone (72) under the reaction conditions.[31]

(c) Hydroboration of the unsaturated lactone (53).

If the two deductions from hydrogenation are correct, then attack of diborane should occur from the β-face of the unsaturated lactone (53) to give the triol (75), which on oxidation with Jones's reagent≠ will give the ketolactone (72).

≠ The assumptions as to the structure of the ketolactone will be correct only if the oxidation of the triol does not epimerise the C_8 centre in the ketolactone. Although this possibility is unlikely because of the mild conditions of the oxidation,[32] the problem will be discussed later in the thesis (see section 1.3(d)) and good evidence will be presented for the absence of epimerisation in the formation of the ketolactone.

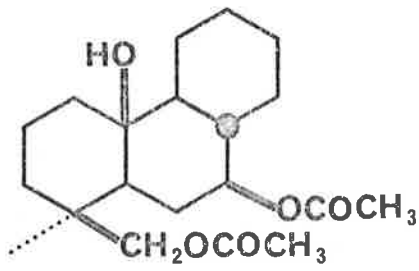


Scheme 8

If the first deduction is incorrect and the unsaturated lactone has a cis A:B ring junction, the ketolactone will have the structure (77), while if the diborane approaches from the α-face and the second deduction is wrong, the ketolactone will have the structure (76). However, an examination of molecular models indicates that structures (76) and (77) are both less stable than their C_8 epimers, (72) and (78) respectively (see scheme 9), and one would expect that on treatment with base (76) and (77) will be epimerised at C_8 to form the more stable epimers (72) and (78).

Therefore only one of the three possible structures for the keto-lactone will be stable to base, i.e. (72).

(83)



Hydroboration of the unsaturated lactone (53) gave the triol (75) which was characterised as its diacetate (83). Oxidation of the triol (75) gave the ketolactone≠ which was recovered unchanged from prolonged exposure to methanolic sodium methoxide. Following on from the previous discussion this result meant that

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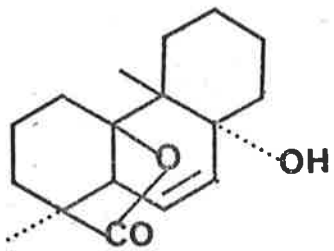
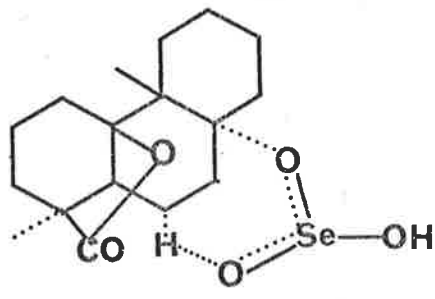
≠ The yield of ketolactone (72) from this sequence of reactions was comparable to the yield from the epoxidation of the unsaturated lactone (53) and rearrangement of the epoxide. However the hydroboration sequence was important in that it provided an alternative method for the introduction of the carbonyl group at C_7.

the ketolactone must have the trans, syn, cis backbone of structure (72), and was formed by the addition of diborane to the β-face of the unsaturated lactone (53).

Now that hydroboration has been proven to occur from the same face (β) as hydrogenation, it is interesting to note that the selenium dioxide oxidation must have followed the opposite stereochemical course so as to form the unsaturated hydroxylactone (55) in a rational manner. This difference may reflect the different mechanism of possibly a seven-centred transition state[33] (84) in the oxidation, versus a four-centred transition state for the other reactions.



(55)



(84)

Although we were confident that the arguments presented as proof of the stereochemistry of the unsaturated lactone (53) were sound, it was desirable to eliminate (78) as a possible structure for the ketolactone by an alternative method. Such a result would leave only one structure for the ketolactone which is stable to base, i.e. (72) - see scheme 9.

(d) Sodium borohydride reduction of ketolactone (72).

Sodium borohydride reduction of the ketolactone (72) gave a mixture of two epimeric alcohols (85) and (86), both of which were very useful in providing the final confirmation of the structure of the unsaturated lactone (53) - see scheme 10.

Reduction of the equatorial alcohol (85) with lithium aluminium hydride gave the same triol (75) as from the hydroboration of the unsaturated lactone (53), and this meant that no epimerisation at C_8 could have occurred when the triol (75) was oxidised to the ketolactone (72) - see section 1.3(c).

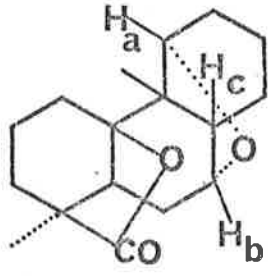
From scheme 9 it can be seen that there are only two

possible structures (72) and (78) for the ketolactone that are base stable. An excellent way of distinguishing between the two structures (90) and (91) for the corresponding alcohol is outlined in schemes 10 and 11. Lead tetra-acetate oxidation will give an ether, the structure of which should readily distinguish between the two possibilities (90) and (91) for the structure of the alcohol.

Oxidation of the axial alcohol (86) with lead tetra-acetate gave a cyclic ether which could be obtained in a pure form after careful chromatography. Of the two possibilities for the structure of the ether, (92) and (93), the n.m.r. spectrum, with signals assignable to two methyl groups (τ 8.93 and 8.84, singlets) and two single protons bound to carbon-bearing oxygen (τ 5.87 [triplet], 6.13 [pentuplet]), defined the structure as (92).

One would expect that the axial hydrogen atoms bound to C_{11} and C_{13} would be equidistant from the C_8 alcohol. However, the molecule would be distorted so as to relieve the serious interaction between the C_1 and C_{11} hydrogen atoms, and this distortion significantly decreased the distance between the C_{13} hydrogen atom and the C_8 alcohol. It was not surprising that only the C_{13} hydrogen atom was abstracted, and hence the ether (94) was not observed as a significant product. With the ether (94) the n.m.r. spectrum would be expected to be significantly different from the one obtained, because H_A and H_B should both give rise to a triplet (H_B is

orthogonal to H_c).



(94)

Now that the structure of the ketolactone had been unambiguously assigned, one could be confident that all the lactones described in this thesis had the same stereochemistry at the A:B ring junction as rosenonolactone (i.e. trans). The next step was the conversion of one of these compounds into a useful precursor that would facilitate the introduction of substituents at C_7 and C_{13}.

1.4 Attempts at the functionalisation of the C ring.

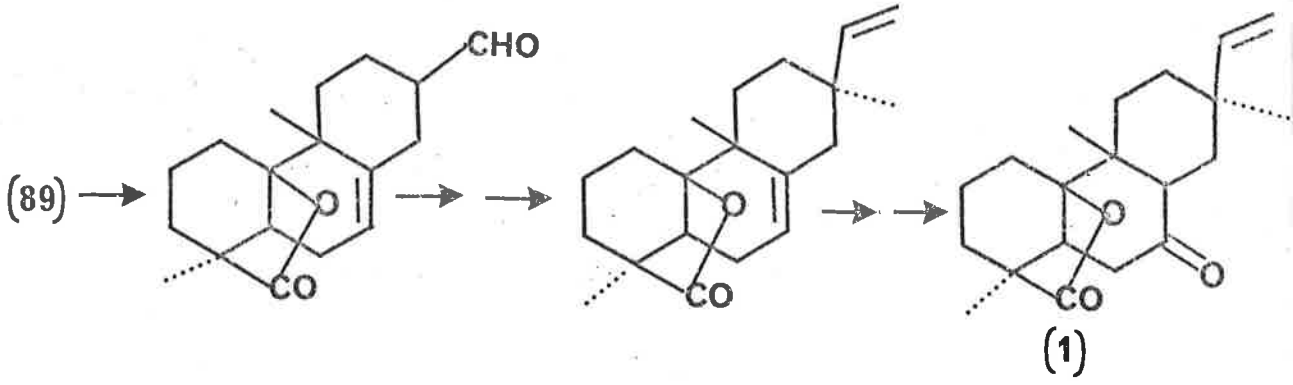
(a) Opening of the ether (87).

(b) Attempted synthesis of the bromoether (98).

***

(a) Opening of the ether (87).

The cyclic ether (87), with its oxygen bridge from C_7 to C_{13}, was an obvious choice for this precursor, provided that the ether bridge could be opened readily. Acetic acid and $BF_3.Et_2O$ have been used successfully in the opening of steroidal ethers[34a] and the usual product was the diacetate or an unsaturated acetate. If the unsaturated acetate (89) or the diacetate (88) could be obtained in a good yield, then the synthesis of rosenonolactone (1) could be approached by the sequence outlined below:



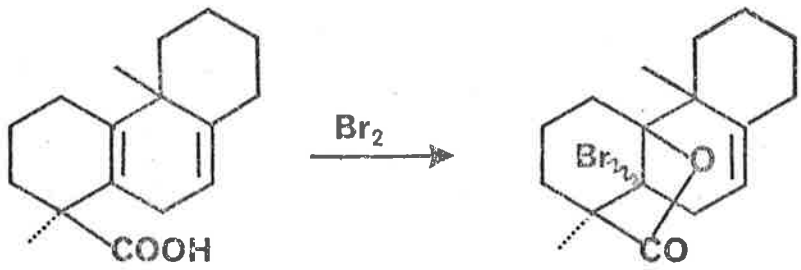
However the result from the opening of the ether was disappointing because the expected preference for the formation of the Δ7-unsaturated acetate (89) or the diacetate (88) did not occur. A complex mixture of acetates was obtained, and only a small sample of the expected products (88) and (89) could be obtained after careful chromatography.

(b) Attempted synthesis of bromoether (98).

If the bromoether (98) could be prepared, the problem of cleavage of the ether group would be solved, because reductive cleavage of the bromoether (98) would be expected to give the unsaturated acetate (89) as the only product.

For the bromoether (98) to be prepared as shown in scheme 12, it was necessary to obtain the bromohydrin (95), and this was prepared by the addition of hypobromous acid to the unsaturated lactone (53). The hypobromous acid was prepared by the addition of perchloric acid to either N-bromoacetamide or N-bromosuccinimide. Although a wide variety of conditions were used, the bromohydrin proved to be most unstable and decomposed the bromoketone (97) and the ketolactone (72) - see scheme 12. This instability was presumably due to the very hindered nature of the axial, tertiary bromine atom.

An interesting product, which did not form via the bromohydrin (95) was the bromolactone (96), which presumably arose from lactonisation of the unsaturated acid (98a) in the presence of bromine. There was some precedent for this reaction[16] but it was unusual for the lactone ring to open so readily in the presence of acid. The proposed structure (96) for the bromolactone was indicated by its spectral data and reductive cleavage to the unsaturated lactone (53). The n.m.r. spectrum had only one lowfield absorption

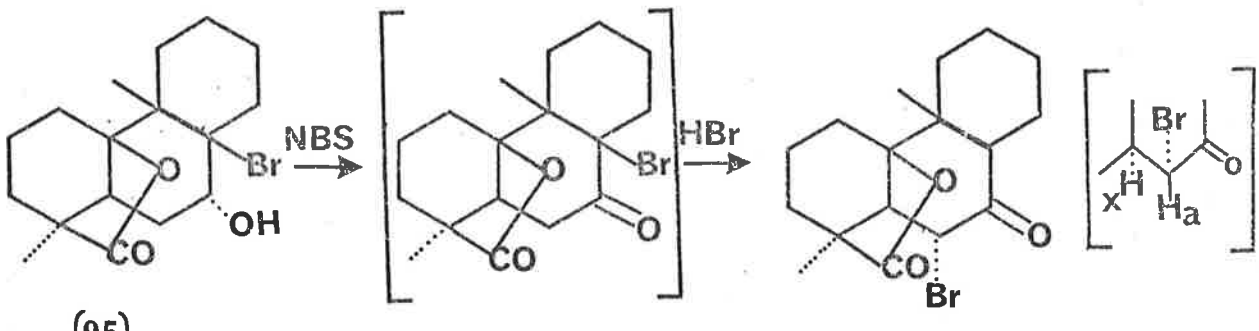


(98a) (96)

(τ5.05, doublet) which was assignable to an olefinic proton.

The bromoketone (97) was probably formed by the following sequence (scheme 13), especially as steroidal bromoketones have been observed[44] to rearrange in an identical manner in the presence of hydrobromic acid.

Scheme 13



(95) (97)

Once again the structure was assigned on the basis of physical evidence, and by reductive cleavage to the ketolactone (72). The n.m.r. spectrum featured two doublets at τ7.34 and τ4.73 respectively and these were assigned to H_X and H_A. The large coupling of 11 c.p.s. between the protons indicated that they were trans diaxially orientated, with the bromine therefore in the equatorial conformation.

The bromohydrin (95) could be isolated by careful chromatography of the reaction mixture, but in poor yield. When the product was subjected to the original reaction conditions, a good yield of the bromoketone (97) was obtained, and this observation was consistent with the mechanism outlined in scheme 13. The n.m.r. spectrum showed a single lowfield absorption at τ6.12 (a triplet) which was due to the proton bound to carbon-bearing oxygen, and this, together with the other physical data, was sufficient to assign the structure (95) to the bromohydrin. Unfortunately the low yield of the bromohydrin (95) precluded the use of the bromoether (98) in the synthesis and the approach was abandoned.

At this stage the synthetic scheme that was being used had obvious weaknesses, particularly as the yield in two steps was very low (see scheme 14). Also, it was clear that the introduction of a suitable functional group in the C ring would be difficult. One

solution to these problems was to use the major product, the unsaturated ketone (35), from the Birch reduction and section B of the discussion will describe the synthetic scheme developed, using this compound.

CHAPTER II.

Introduction of the C_7 and C_{13} substituents of rosenonolactone.

2.1 Preparation of the hydroxyketolactone (101).

2.2 Preparation of the unsaturated ketolactone (113).

2.3 Introduction of the C_{13} substituents of rosenonolactone.

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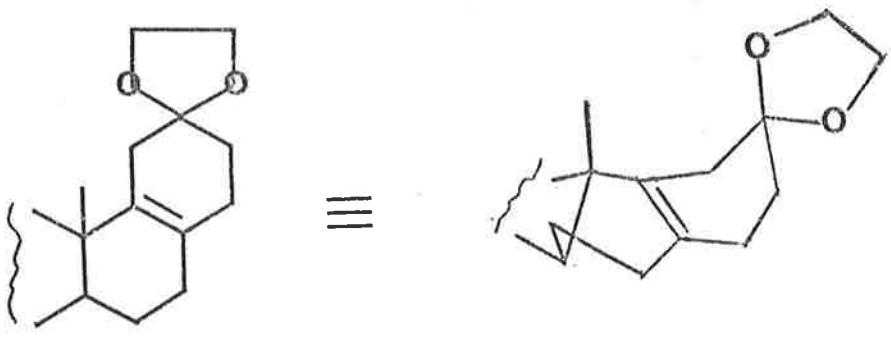
2.1 Preparation of the hydroxyketolactone (101).

(a) Preparation and rearrangement of the epoxyketal (100).

(b) Role of solvents in the rearrangement.

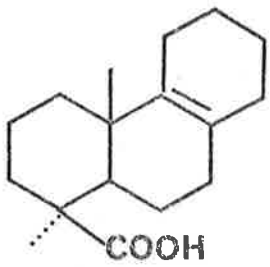
(a) Preparation and rearrangement of the epoxyketal (100).

The first step in improving the overall yield of the synthetic plan was to utilise the major product, the unsaturated ketone (36), from the Birch reduction of O-methylpodocarpic acid (29). The unsaturated ketone (36) was converted in an excellent overall yield to the epoxyketal (100) by the sequence of reactions outlined in scheme 15. From a consideration of models of all possible transition states based on the results of Levine et al.,[56] it was concluded that the stereochemical outcome of this reaction was due to the complexing of the peroxyacid with the ketal group[57] as indicated in the diagram below. As a consequence the epoxide

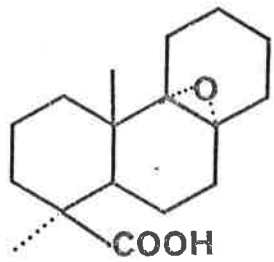


group of the epoxyketal (100) was found to have the opposite stereochemistry to that of the epoxyacid (51).≠

≠ Only this assignment was consistent with the product (101) that was obtained from the rearrangement of the epoxyketal (100) with $BF_3 \cdot Et_2O$ (see later).



(31)



(51)

The sequence of reactions outlined in scheme 15 could be carried out on the crude product from the Birch reduction, and the epoxyketal (51) was isolated by crystallisation of the final product. This allowed a significant increase in the overall yield of the sequence because the unsaturated ketone (36) was very readily oxidised and therefore could not be easily separated from the other products.

Once again $BF_3.Et_2O$ was found to be a much better catalyst than sulphuric acid for the rearrangement and lactonisation of an epoxyacid. If the epoxyketal (100) was treated with sulphuric acid, no rearrangement products were formed and a good yield of the keto-acid (105) was obtained.

Reaction of the epoxyketal (100) with $BF_3.Et_2O$, under exactly the same conditions as for the epoxyacid (51), gave a moderate yield of a single neutral compound. Elemental analysis and spectral data indicated that the product was a hydroxyketolactone, and its

structure was readily established as (101), with the stereochemistry at C_8 unknown, by the following sequence of reactions (scheme 15).≠ Desulphurisation of the thioketal (103) gave the hydroxylactone (104), and the latter compound was dehydrated with p-toluene-sulphonic acid and acetic anhydride to the known unsaturated lactone (53).

In an attempt to determine the configuration of the hydroxyl group in the hydroxyketolactone (101) the mechanism of the rearrangement of the epoxyketal (100) was investigated (see scheme 16 where two pathways[31,38] for the reaction are shown). If the hydroxy-ketolactone (101) was formed by one of these two pathways the hydroxyl group should have the β-configuration (same as the epoxide group of the epoxyketal (100)). When the lactonisation was carried out in the presence of H_2O^{18} no label could be detected in the hydroxy-ketolactone (101). While this result was consistent with the

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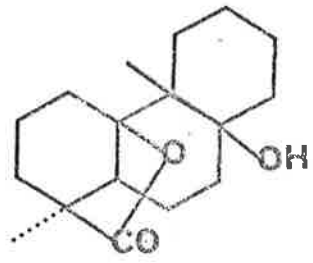
≠ Since the $BF_3.Et_2O$ catalysed lactonisation has not epimerised the C_5 centre, the hydroxyketolactone (101) has the correct stereochemistry for the synthesis of rosenonolactone.

formation of the product by either pathway,≠ it did indicate that the hydroxyl group was formed from the epoxide group.

The assignment of the β-stereochemistry to the hydroxyl group was confirmed by a comparison of the two hydroxylactones (52) and (104). A study of the corresponding models indicated that the hydroxyl group of the former alcohol should be more hindered, and this conclusion was substantiated by dilution studies on the i.r. spectra of both alcohols.

≠ Although it has been noted[31,35] that, in a $BF_3.Et_2O$ catalysed rearrangement, it does not seem to matter whether the migrating group is cis or trans to the epoxide group, this observation is difficult to reconcile with the fact that the energy requirement for the transition state (111) of the concerted migration should be less than for the non-concerted migration (106). However, if the rearrangement of the epoxides (51) and (100) occurs via a fluorohydrin as an intermediate,[36] the methyl group in both systems (62) and (109) is trans to the C_9 substituent and a concerted migration can occur.

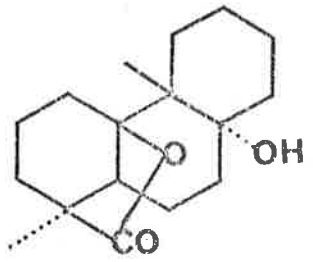


(104)

IR spectra (dilution studies)

3460, 3370

The intermolecular hydrogen bonding (ν_{max} 3370 cm^{-1}) disappeared on dilution.



(52)

3580 cm^{-1}

No hydrogen bonding at any concentrations.

(b) Role of solvents in the rearrangement.

It was found that if the rearrangement was carried out in a solvent of high dielectric constant (ε) the yield of the hydroxyketolactone (101) was increased - see Table 1. Presumably the more polar solvent preferentially stabilised the transition

state leading to intermediate (107) or (110) and thus allowed the lactonisation to compete more favourably with the other side reactions.

TABLE 1.

Solvent	Reaction time.	$[BF_3]^*$	ε^{37}	product	yield
benzene	3 min.	2	2.3	(101)	22%
ether	36 hr.	10	4.3	(102)	30%
acetonitrile	40 hr.	2	39	(101)	40%
nitromethane	$\frac{1}{2}$ hr.	2	36	(101)	55%

* = molar ratio of $BF_3.Et_2O$ to epoxyketal (100).

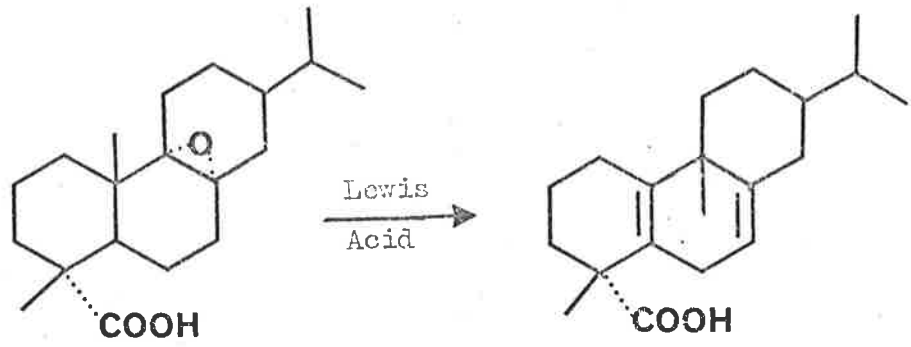
If ether was used as the solvent the reactivity of the $BF_3.Et_2O$ was greatly reduced, the reaction was very slow and a greater concentration of catalyst was needed. Under these milder conditions the ketal (102) was isolated, which on hydrolysis with p-toluene sulphonic acid gave the hydroxyketolactone (101). While other workers[35,36,38] have also noted the lower activity of $BF_3.Et_2O$ in an oxygenated solvent, they observed that ether as a solvent favoured the formation of fluorohydrins at the expense of rearranged product.

If the hydroxyketolactone (101) was formed via the fluorohydrin (109) the role of the more polar solvents may be to reduce the activity of the $BF_3.Et_2O$ rather than to increase the stability of the transition state leading to the intermediate (107). It has been reported[39] that careful purification of the $BF_3.Et_2O$ suppressed the formation of fluorohydrins and it was suggested that fluoroboric acid was responsible for this product. However, for the lactonisations described in this thesis, it was essential for a good yield that the $BF_3.Et_2O$ was freshly distilled from calcium hydride, and this presumably removed any fluoroboric acid that may have been present in the reagent.

Nitromethane was finally chosen as the best solvent for the rearrangement of the epoxyketal (100) because the hydroxy ketolactone (101) was formed in a good yield (60%)≠ with only a trace of other neutral products. Johnson[40] has used nitromethane as a solvent for Lewis acid catalysed rearrangements of unsaturated epoxides, although it was not explained why this solvent was used.

≠ The yield of hydroxyketolactone was most gratifying, particularly as Herz[41] has reported a very low yield for the rearrangement shown in scheme 18.

Scheme 18.



2.2 Preparation of the unsaturated ketolactone (113).

(a) Dehydration of the hydroxyketolactone (101).

(b) Rearrangement of the epoxyketal (100) with a large excess of boron trifluoride.

(c) Rearrangement of 12-hydroxy-8α,9α-epoxy-podocarpan-16-oic acid (117) with boron trifluoride.

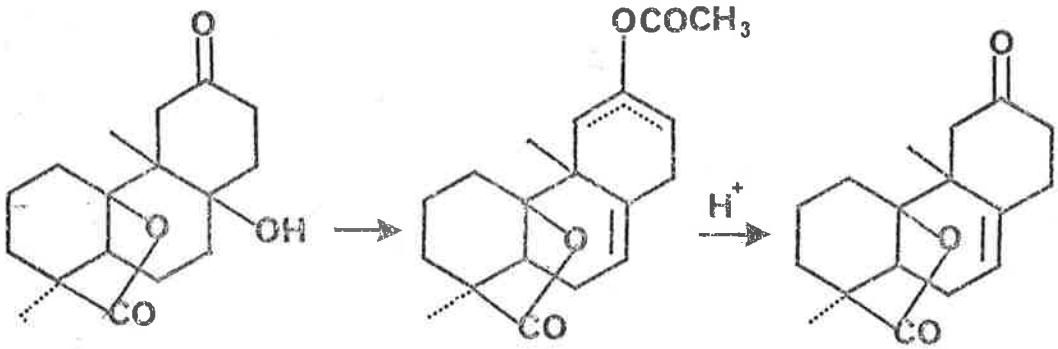
(a) Dehydration of the hydroxyketolactone (101).

At this stage the new synthetic plan was most satisfactory as the yield of both the unsaturated ketone (36) and the hydroxyketolactone (101) was three times that of the corresponding intermediates (the unsaturated acid (31) and the unsaturated lactone (53)) in the partial synthesis described in Chapter I.

One could now consider the problems involved in introduction of the C_7 and C_{13} substituents of rosenonolactone. If the hydroxyketolactone (101) could be dehydrated to the $\Delta 7$-ketolactone (113), the C_7 carbonyl group could be introduced by the Brown hydroboration procedure or by the rearrangement of the corresponding epoxide of the olefin with $BF_3.Et_2O$. It was decided to investigate the dehydration at this stage of the synthesis, when there was ample material available because it was difficult to predict whether the $\Delta 7$ or $\Delta 8(14)$-olefin would predominate. This was especially true as an examination of the molecular models of the isomeric hydroxylactones (52) and (104) indicated that there was no marked preference for dehydration to occur in one direction, and yet both alcohols gave a 90% yield of the $\Delta 7$-olefin.

It was found that the tertiary hydroxyl group of the hydroxyketolactone (101) required forcing conditions for its dehydration. Even the method of choice (outlined in scheme 19) was not

particularly satisfactory as it gave a low yield of the unsaturated ketolactone (101), after hydrolysis of the crude mixture of enol acetates and chromatography of the product. The n.m.r. spectrum of



(101) (113)

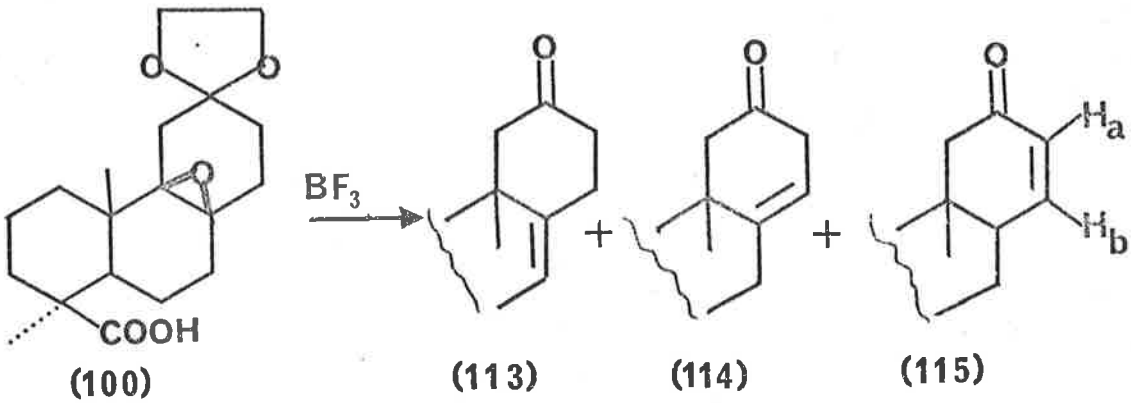
Scheme 19.

the product exhibited a lowfield absorption (broad triplet) at $\tau 4.45$, which was assigned to a single olefinic proton. The trisubstituted double bond could only be placed at C_7, because the compound was found to be stable to acid, and the $\Delta 8(14)$-isomer (β,γ-unsaturated ketone) would have equilibrated with the α,β-unsaturated ketone under these conditions.≠

≠ It will be proved later that the $\Delta 8(14)$-isomer did undergo this equilibration when treated with acid.

(b) Rearrangement of the epoxyketal (100) with a large excess of boron trifluoride.

Because of the low yield in the dehydration of the hydroxy-ketolactone (101), it was decided to reinvestigate the $BF_3 \cdot Et_2O$ catalysed rearrangement of the epoxyketal (100) in an attempt to form the unsaturated ketolactone (113) directly. If the epoxyketal (100) was treated with a vast excess of $BF_3 \cdot Et_2O$ the hydroxylactone (101) (or a precursor) was dehydrated under the reaction conditions, but the yield of lactone material was reduced by the formation of tar. Also a considerable amount of the Δ8(14)-olefin (114) was formed, which under the acidic reaction conditions, was isomerised to a mixture of the Δ8(14) and Δ13-olefins.



(100) (113) (114) (115)

Further acid treatment did not affect the ratio of the isomeric olefins, and this confirmed that the product was an

equilibrium mixture. Careful chromatography of the mixture separated the Δ7- and Δ8(14)-isomers, while the Δ13(14)-olefin could only be obtained as a 1:1 mixture with the Δ8(14)-isomer. The elemental analyses and the almost identical mass spectral fragmentation patterns established that the three olefins were isomeric, while the i.r. spectra distinguished between the conjugated ketone (ν_{max} 1680 cm^{-1}) and the unconjugated ketones (ν_{max} 1700 cm^{-1}). If the Δ8(14)-isomer was treated with base it was isomerised to the equilibrium mixture of the Δ8(14)- and Δ13-isomers. The n.m.r. spectrum of the Δ7- and Δ8(14)-unsaturated ketones (113) and (114) each had one lowfield absorption (doublet) due to a single olefinic proton at τ4.45 and 4.44 respectively, while the Δ13-isomer (115) had two lowfield absorptions due to the two olefinic protons (H_A and H_B) at τ4.13 (doublet) and 3.09 (quartet) respectively.

(c) The rearrangement of 12-hydroxy-8α,9α-epoxy-podocarpan-16-oic acid (117).

The results above clearly indicated that dehydration of the β-hydroxyl group of the hydroxyketolactone (101) would not give a satisfactory yield of the Δ7-compound. A possible solution to this difficulty was to prepare the α-alcohol in the hope that its dehydration would give a better yield of the required olefin.

Reduction of the β,γ-unsaturated ketone (36) with lithium tri-t-butoxyaluminium hydride gave the alcohol (41), the hydroxyl group of which should have the α-configuration as the reagent could be expected to give an equatorial hydroxyl group.[34(c)] Epoxidation of this alcohol (41) should now occur from the α-face as the hydroxyl group should not influence the direction of epoxidation.

These deductions proved to be correct, for when the epoxide (117) was treated with $BF_3.Et_2O$ in nitromethane, a reasonable yield of the unsaturated hydroxylactone (119) was obtained - see scheme 20. The same sequence of reactions was carried out on the corresponding Δ8-acetate (116) in the hope that, with the hydroxyl group protected as the acetate, a higher yield would be obtained for the $BF_3.Et_2O$ catalysed rearrangement of the acetoxyepoxide (118). However, the slight increase in yield that was obtained, was not sufficient to make the extra steps worthwhile. The unsaturated hydroxy- and acetoxylactones (119) and (120) were readily converted to the unsaturated ketolactone (113) by the reactions shown in scheme 20.

Fortunately the sequence of reactions from compound (36) to (117) (in scheme 20) could be carried out on the crude product from the Birch reduction. This eliminated the need for isolation of the β,γ-unsaturated ketone (36), which was difficult to handle because it was easily oxidised or equilibrated.

It was particularly convenient that the neutral fraction from the rearrangement crystallised readily, and therefore all the reactions in scheme 20 could be readily carried out on a large scale.

2.3. Introduction of the C_{13} substituents of rosenonolactone.

(a) General discussion.

(b) Attempted preparation of the β-ketoester (140).

(c) Preparation of the ethylidene ketone (144).

(d) Synthesis of 12-oxorosenonolactone (149).

(a) General Discussion.

The unsaturated ketolactone (113) was now readily available in useful quantities and attention was directed to the synthesis of rosenonolactone. It was decided to introduce the substituents at C_{13} before the carbonyl group at C_7, because if the latter was introduced too early it would be difficult to distinguish between the C_7 and C_{13} carbonyl groups, unless both groups were protected as different derivatives - and this would involve too many extra reactions.

There are two basic approaches for the introduction of the C_{13} substituents. One can either shift the oxygen function from C_{12} to C_{13} and follow the sequence of reactions outlined in scheme 21 (via compound (124)), or use an activating group at C_{13}. Although there are several well-established approaches[18,39] for the introduction of the carbonyl group at C_{13} they are rather tedious and the yields are only moderate. The use of an activating group was far more direct but did have the problem of the removal of the C_{12} carbonyl group at the end of the sequence. It was necessary for =CRX to be an activating group (see scheme 21) so that alkylation would occur at C_{13} and not C_{11}. Fortunately C_{11} was extremely hindered and alkylation or acylation of the enolate of the C_{11} ketone should give (125) as the thermodynamic product. Monoalkylation of this system (125) should not be difficult to achieve, again because of the hindered environment at the C_{11} position.

Alkylation of either system (124) or (125) can give two isomeric products and the ratio will depend on whether the methyl group is introduced preferentially from the α- or β-face. The alkylation of enolate systems has been extensively studied and rules have been established[42,43] that can predict the direction of approach of the alkylating reagent. In general, if one side of a cyclohexanone enolate anion is substantially more hindered than the other side, alkylation will occur from the less hindered side. However, the difference in structure that is required to change the direction of alkylation is often very slight, and this is illustrated by some examples from the work of Ireland[18,44] (see scheme 22). Although system (132) is only slightly less hindered on the α-face than the other systems (130) and (131), the alkylation ratios change dramatically from 1:1 to 6:1 and 100:0 respectively (β:α-alkylation).

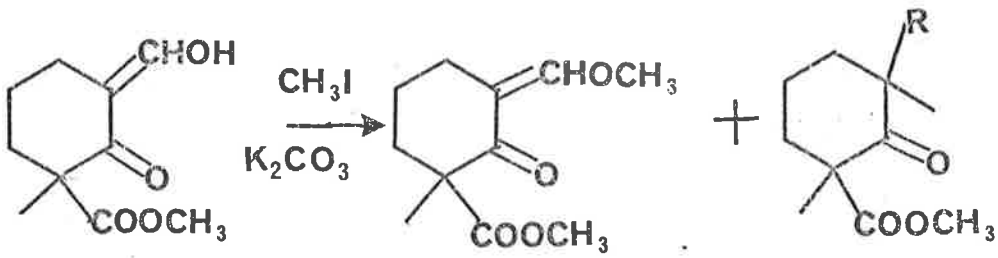
Depending on the actual synthetic scheme that is used, there are three possible systems (133), (134), and (135) that would have to be alkylated. For the synthesis of rosenonolactone (1) alkylation must occur from the α-face, and it is clear that system (133) is more accessible on the α-face. Therefore the best synthetic scheme must be the one that leads to this intermediate. Although it is difficult to make comparisons, system (133) is about as

hindered on the α-face as (132) and therefore one could hope for a reasonable yield of the alkylation product (126). However, the α-face of the two alternatives (134) and (135) are certainly no more accessible than that of (130), and alkylation of these enolates could well give isomer (129) as the sole product.

These considerations unfortunately placed rigid limits on the synthesis and meant that alkylation could not be carried out on a derivative of the hydroxyketolactone (i.e. 134, X = OH). Furthermore, the approach via the C_{13} ketone (123) was inadvisable as this led to the aldehyde (124), and thence to the enolate (135).

This left the second approach as the method of choice and initially three activating groups (a formyl, carboethoxy, or ethylidene group) were considered, although on closer examination it was found that the formyl group had serious disadvantages. A literature search[45-48] revealed that the alkylation of the formyl-ketone system (136) was a complex reaction with O-alkylation of the ketone competing with C-alkylation. Also the product (137) was difficult to isolate because the formyl group was readily cleaved by nucleophiles. In one example[47] the undesired side-reactions predominated to such an extent, that none of the normal product (138) was isolated. These difficulties, together with the problem of the selective removal of the carbonyl group at C_{12} in the alkylated product (137),

indicated that this approach was unsatisfactory.



(138) R=CHO

(138a) R=H

(b) Attempted preparation of the ketoester (140).

It was decided to investigate the second approach by preparing the ketoester (140), which should not have any of the difficulties encountered with the formyl-ketone (136). The alkylation of the ketoester (140) should be achieved in a good yield because O-alkylation of this system does not occur readily. Another advantage is that the carbonyl group can be easily removed in the presence of an ester.

Initially diethyl carbonate was used as the acylating reagent, but it was too unreactive. However the more reactive diethyl oxalate formed the glyoxalate ester (141) when allowed to react with the unsaturated ketolactone (113). While decarbonylation

of the glyoxalate ester (141) occurred readily, the product, the β-ketoester (140), was so unstable under the conditions of the reaction that a good yield of the unsaturated ketolactone (113) was obtained, even when the reaction vessel was completely freed of acid or base.

(c) Preparation of the ethylidene ketone (144).

The difficulties encountered with the other approaches meant that the preparation of the ethylidene ketone (144) was of considerable importance. Although this approach had the advantage of directness, previously the anticipated difficulties in the preparation of the ethylidene ketone had prompted the investigation of alternative routes.

Several methods[49-51] have been developed for use in an aldol condensation between a ketone and acetaldehyde, and have been reasonably successful with simple unhindered ketones, despite the ease with which acetaldehyde polymerises. However, when these methods were applied to the unsaturated ketolactone (113), in the hope that the ethylidene ketone would be formed (see scheme 23a), the desired aldol reaction was found to be much slower than the self-condensation of the acetaldehyde, and no useful products could be isolated.

The enolate of the unsaturated ketolactone (113) (formed

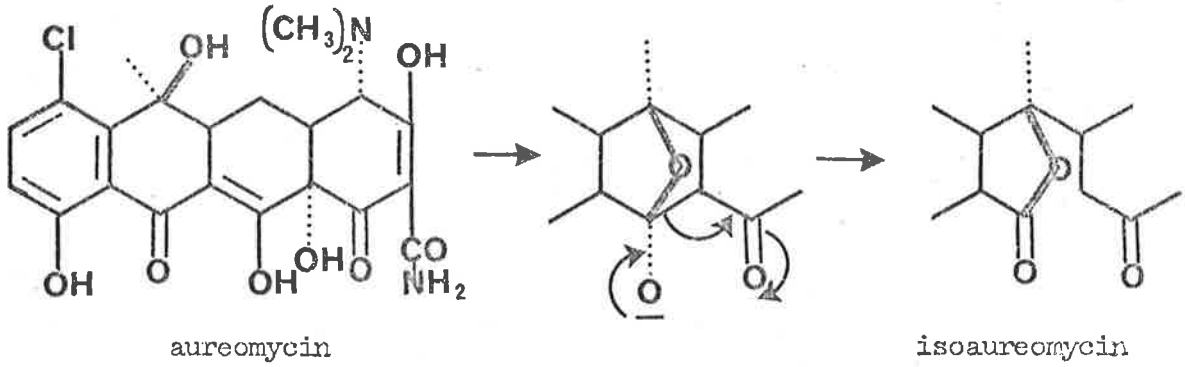
by reaction of the ketone with one mole of potassium t-butoxide) was reacted either with acetaldehyde or the corresponding Mannich base (formed from the reaction of acetaldehyde with pyrrolidine) in the hope that polymerisation of the acetaldehyde would be prevented. However only the starting ketone (113) together with some polymeric material could be isolated, although the reaction was carried out under a variety of conditions.

The second method (scheme 23b) has been used by Ireland[18] in the synthesis of pimaradiene where the sequence worked extremely well. In this synthesis, however, the 1,4-addition of the Grignard reagent to the pyrrolidine enamine (148) had to be carried out selectively in the presence of the lactone moiety, and because of this problem, it had been decided previously to try the alternative approaches first. Of course, when these methods failed, Ireland's procedure was re-examined, and it was found that a selective Grignard reaction might be possible on this system, particularly as the lactone group in a similar compound has been shown[28] to be rather unreactive to methyl magnesium iodide.

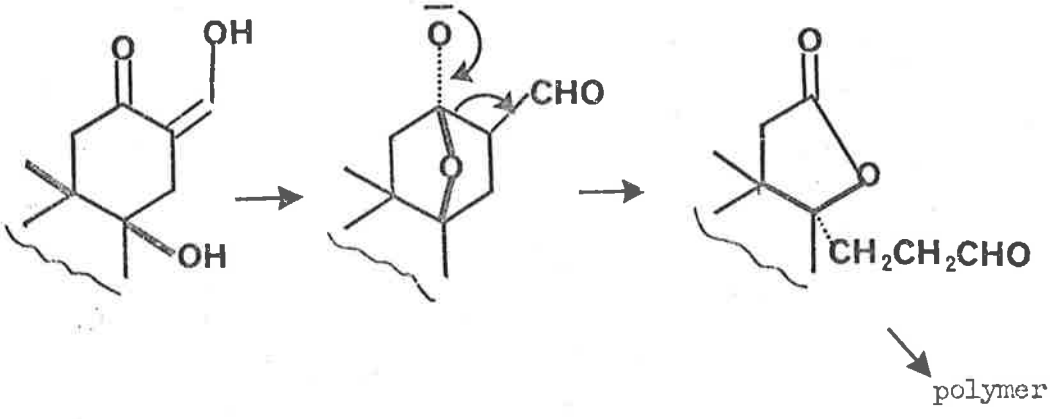
In the event, it was found that the sequence worked extremely well, with an overall yield of 70% for the ethylidene

ketone (144). The formylketone (136)≠ and the pyrrolidine enamine (148) were prepared successfully, while selective addition to the enamine, using short reaction times, gave the ethylidene derivative (144).

≠ If the hydroxyketolactone (101) was reacted under exactly the same conditions as for the formylation of the unsaturated keto-lactone (113), a polymeric material was obtained (ν_{max} 1760 cm^{-1}). An excellent analogy for this reaction was the degradation of aureomycin with base[58] and allowed the proposal of the following mechanism.



aureomycin isoaureomycin

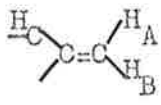
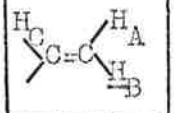
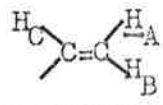
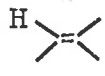


polymer

(d) Synthesis of 12-oxorosenonolactone.

Alkylation of the ethylidene ketone (14) was achieved in a satisfactory yield, by using the method developed by Ireland[18] in which the ketone was completely enolised by a vast excess of potassium t-butoxide (160-fold excess) before the methyl iodide was added. This excess of base displaced the equilibrium between the ketone and its enolate so much in the direction of the enolate that polymerisation via Michael-type addition of the enolate to un-ionised ketone was prevented. In the event, the reaction gave a single product, together with some polymeric material. The spectral data indicated that the alkylation had been successful, particularly as the n.m.r. spectrum had the following absorptions - see Table 2.

TABLE 2.

Compound		J cis	J trans		J trans
(a)	5.0	10	17.5	5.02	17.5
(b)	5.82	10	17.5	4.9	17.5
		J cis			
(a)	3.8	10	4.46		
(b)	4.88	10	-		

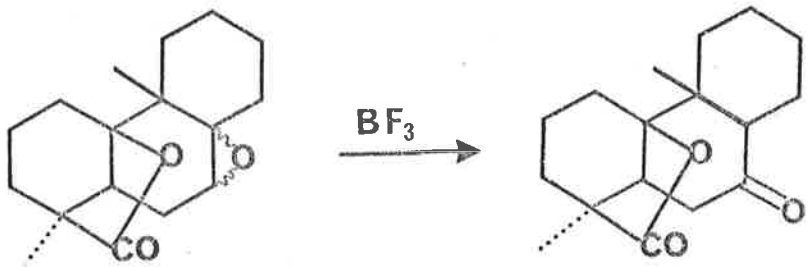
(a) = alkylation product, (b) = rosololactone.

The large deshielding of H_A and H_C in the n.m.r. spectrum of the product relative to rosololactone suggested that the vinyl group was in the plane of the C_{12} carbonyl group, corresponding to the equatorial conformation and therefore β-configuration. The product was therefore expected to be 12-oxorosenonolactone.

Although the structure of the alkylation product was not assigned unambiguously, it was decided to continue with synthesis in the hope that on completion of the project, the configuration at C_{13} could be established by comparison with rosenonolactone.≠ It was proposed to follow the sequence of reactions outlined in scheme 23.

After removal of the C_{12} carbonyl group, one could be confident that the diene (151) could be converted to the mono-epoxide (152) by selective epoxidation of the trisubstituted olefin, because there was ample precedent for this type of reaction in the literature.[52,53] The rearrangement of the epoxide (152) to the ketone (153) should occur in good yield, especially as the keto-lactone (72) has been obtained previously from the reaction of $BF_3.Et_2O$ with the epoxide (73).

≠ As the structure of rosenonolactone had been established by X-ray diffraction,[4] the aim of the project was not a structure-proof, but the development of general synthetic methods.



(73) (72)

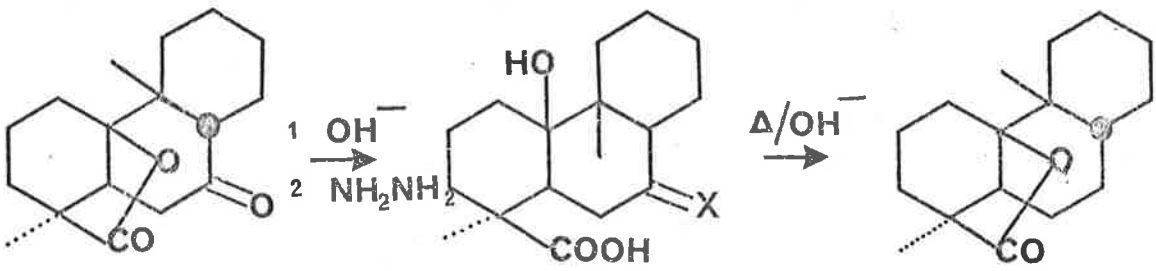
While there were many procedures available for the conversion of a carbonyl group to a methylene group, the presence of a reactive vinyl group in the system (149) restricted the choice of suitable methods to those shown in scheme 24.

The first method via the tosyl hydrazone appeared to be the most suitable, because other workers[55] have reported that the reduction of tosyl hydrazones with sodium borohydride gave high yields of reduction products under mild conditions.

The C_{12} carbonyl group was found to be extremely hindered and the tosyl hydrazone (154) could only be formed when the forcing conditions developed by Nagata[54] for the formation of hydrazones were used. Once again extreme conditions (heated under reflux in dioxan for 50 hr) were required to reduce the tosyl hydrazone, and in these circumstances, no useful products could be isolated.

It was then decided to try the more vigorous conditions of the Wolff-Kishner reduction[34d], but this had a further complication

in that the lactone could react with the hydrazine. Because of this difficulty, the ketolactone (72) was used as a trial compound, and the lactone was protected as the hydroxy-acid (156)≠ before the hydrazine was added. After formation of the hydrazone (157), the reaction mixture was heated at 215° for an extended period of time. Although the lactone survived the reaction, none of the expected product (68) was formed, and it was concluded that the hydrazone had not reacted even under these extreme conditions. Because of this lack of success, the reaction was not tried on the ketone (149), especially as there was a possibility that the vinyl group would not survive the reduction.



(72) (156) X=O (157) X=NHNH₂ (68)

≠ Robertson et al.[2] had observed that the lactone bridge in rosenonolactone could be opened to the corresponding hydroxy-acid by heating a solution of the compound in the presence of base. If the hydroxy-acid was treated with acid it readily relactonised to the original lactone.

The thioketal (158) of the ketone was reduced with a specially prepared Raney nickel catalyst, which was reported[34b] to achieve a selective reduction of a thioketal in the presence of a reactive aromatic system. However, a n.m.r. spectrum of the crude product indicated that the 15,16-vinyl group had been reduced as well as the thioketal.

At this stage the synthetic work described in this thesis was concluded, and although the trial reactions for the removal of the C_{12} carbonyl group were carried out on a small scale so as to conserve the ketone (149), the results obtained were conclusive in that they showed that the 15,16-vinyl group was too reactive to survive the forcing conditions necessary for the removal of the hindered C_{12} carbonyl group.

A possible approach for the completion of the synthesis is outlined in scheme 25, and while it is longer than those described in scheme 23 and scheme 24, at least one does not have the problem of the reactive 15,16-vinyl group.

The difficulties observed in the last few steps were presumably a consequence of the use of a natural product as a starting material. While this has many advantages, one is forced to accept the limitations of such an approach, where often the starting functional groups are not exactly in the correct place. In podocarpic acid, of course, it was the oxygenation of the C-ring that led to these final difficulties.

CHAPTER III

Experimental

General.

Melting points were determined on a Kofler heating stage and were uncorrected. Optical rotations were measured in an ethanol solution on a Hilger polarimeter. The wavelength used was the D line of the sodium emission spectrum. Infrared spectra were determined with Perkin-Elmer 337 and Unicam SP200 instruments, and the infrared absorption maxima refer to nujol mulls, unless otherwise specified. Ultraviolet spectra were recorded in ethanol on a Perkin-Elmer 137 instrument. All mass spectra were determined by Mr. D.B. Cobb with an Hitachi Perkin-Elmer RMU 6D double focussing mass spectrometer. The nuclear magnetic resonance spectra were recorded by Mr. R.L. Paltridge on a Varian DA-60-IL spectrometer operating at 60 mc/s with tetramethyl silane as an internal reference. In the spectra all signals were found to integrate for the correct number of protons. Analyses were carried out by the Australian Microanalytical Service, Melbourne.

Whatman S.G.31 silica gel was used for column chromatography, while thin-layer chromatography (t.l.c.) was carried out on 0.3 mm silica gel plates. Light petroleum refers to the fraction of b.p. 60-80°.

Compounds were identified by m.p., mixed m.p., and a comparison of their infrared spectra. The expression 'work-up in the normal manner' implies that the organic layer was washed with

water, dried over anhydrous magnesium sulphate, and concentrated under reduced pressure.

The preparations described in the experimental are listed in the order of the number designated to the product. The reactions which are not carried out as a preparation but as confirmation of a structure are listed under the number designated to the structure.

***

Preparation of O-methyl podocarpic acid (29).

The method used was adapted from the work of Cambie.[60] Podocarpic acid (28) (137 g, 0.5 m) was dissolved in aqueous sodium hydroxide (5%, 3 l) and to this dimethyl sulphate (310 ml, 3.3 m) was added in a slow stream. The solution was cooled to keep the temperature below 40°. After 20 min the addition of dimethyl sulphate was complete and the product was removed by filtration. Acidification of the product gave a precipitate of the free acid (29) and its corresponding methyl ester (30). The mixture was then dissolved in chloroform (500 ml) and the organic layer separated. The sodium salt of O-methyl podocarpic acid (29) was precipitated from this solution by the addition of aqueous sodium hydroxide (30%, 500 ml) and then the salt was removed by filtration. Acidification of the sodium salt gave the free acid, which was dried by the azeotropic removal of water from a chloroform solution (100 ml). Addition of light petroleum (300 ml) caused crystallisation to occur, and the product was then removed by filtration (95 g, 77%). This product was pure enough to use in the Birch reduction. Normal work-up of the chloroform layer gave a crystalline solid (27 g, 20%). Recrystallisation from a mixture of light petroleum and chloroform (20:1) gave pure methyl o-methyl podocarpate (30) (24 g, 18%). Acidification of the aqueous layer gave a small quantity of podocarpic acid (1.5 g, 1%).

Preparation of the unsaturated ketones (35) and (36) and the unsaturated acids (31) and (33) by lithium and ammonia reduction of O-methyl podocarpic acid (29).

Method (a) - with t-butyl alcohol as the proton donor.

O-methyl podocarpic acid (58 g, 0.2 m) was dissolved in a mixture of ether (200 ml), t-butyl alcohol (600 ml, 3.2 m), and liquid ammonia (2 l). Lithium (40 g, 5.6 g atoms) was added over a period of $\frac{1}{2}$ hr to the stirred reaction mixture. The reaction had decolourised after 45 min, and more lithium (20 g, 2.8 g atoms) was added. After 8 hr the excess lithium was decomposed with methanol (400 ml) and the ammonia was removed by heating the flask with hot water. Water (1 l) was added to dissolve most of the inorganic salts, and the product was extracted into ether (2 x 500 ml). The combined ether extracts were washed with dilute hydrochloric acid (20%) until the washings remained acidic. The organic layer was separated, and work-up in the normal manner gave a light yellow oil (59.5 g). The product was then dissolved in a mixture of ethanol (500 ml) and dilute hydrochloric acid (5%, 10 ml), and the resulting solution was heated under reflux for $\frac{1}{2}$ hr. The ethanol was removed under reduced pressure, water (200 ml) was added, and the product was extracted into ether (2 x 200 ml). Separation of the organic layer and work-up in the normal manner gave a light yellow oil (59 g), ν_{max} 3200-2700 (-COOH), 1705 (-CO-), 1695 (-COOH), 1640 (-C=CH-CO),

1610 (-C=CH-) cm^{-1}. T.l.c. (1:1, ether : light petroleum) indicated the presence of three products.

Podocarp-8-en-16-oic acid (31).

The product from the Birch reduction was dissolved in hot (60°) aqueous sodium hydroxide (2%, 350 ml) and on cooling to 30° colourless flakes separated and were removed by filtration (14.5 g, 25%). The free acid was obtained by acidification of the sodium salt. A pure sample of the unsaturated acid (31) was obtained by recrystallisation from acetone, m.p. 156-157°; $[\alpha]_{22}$ 163° (C1.64); ν_{max} 3200-2800 (-COOH), 1700 (-COOH) cm^{-1}; mass spectrum M^+, m/e 262; τ9.6 (singlet, C_{10} -CH_3), 8.77 (singlet, C_4 -CH_3). (Found: C, 77.4; H, 9.79. $C_{17}H_{26}O_2$ requires C, 77.8; H, 10.0%.)

12-Oxo-podocarp-9(11)-en-16-oic acid (35).

When the filtrate was cooled to 0° a second crop of crystals was obtained (23 g, 40%), and the corresponding acid was obtained by acidification of the sodium salt. A pure sample of the ketone was obtained by recrystallisation from a mixture of acetone and light petroleum, m.p. 197-198°; ν_{max} 3300-2850 (-COOH), 1710 (-COOH), 1690 (-CO-), 1600 (-C=CH-) cm^{-1}; λ_{max} 249 mμ (ε 12,000); mass spectrum M^+, m/e 276; (Found: C, 73.7; H, 8.97. $C_{17}H_{24}O_3$ requires C, 73.9; H, 8.75%).

Purification of the non-crystalline residue.

Acidification of the filtrate from the crystallisation of the α,β-unsaturated ketone (35) gave an oily precipitate which was purified by chromatography on silicic acid, and gave the following compounds:

Compound	yield g	yield %	m.p.	literature m.p.	eluant *1
Unsaturated acid (31) *2	4	8	156-157°	-	A:B, 1:25
o-Methylpodocarpic acid (29)	2	4	126-127°	128° [61]	A:B, 1:10
α,β-Unsaturated ketone (35)	6	12	197-198°	-	B:C, 1:20
Diosphenol (44)	*3		204-205°	-	B:C, 1:5
Hydroxyketone (43)	*3		191-193°	189° [20]	B:C, 2:5
Podocarpic acid (28)	*3		192-193°	193.5° [61]	B:C, 1:1

*1 A = petroleum ether; B = benzene; C = ether.

*2 contaminated with the 9(11) isomer.

*3 the yield of these compounds was variable but normally the combined yield was about 5%.

The compounds from the column were recrystallised from a mixture of acetone and light petroleum.

The α,β-unsaturated ketone (35) had the following physical constants, m.p. 197-198°; ν_{max} 3200-2700 (-COOH), 1705 (-COOH), 1635 (-CO-), 1590 (-C=CH-) cm^{-1}; λ_{max}^{240} mμ (ε15,000); mass spectrum M^+, m/e 276; (Found: C, 73.7; H, 8.97. $C_{17}H_{24}O_3$ requires C, 73.9; H, 8.75%).

The diosphenol (44) had the following physical constants, m.p. 204-205°; $[\alpha]_{15}$ 440° (C 0.66);

ν_{max} 3300 (-C(OH)=C-), 3150-2600 (-COOH), 1700 (-COOH), 1600 (-CO-) cm^{-1}; λ_{max} 292 mμ (ε 9,600); mass spectrum M^+, m/e 292; the n.m.r. spectrum could not be determined because of the insolubility of the compound; satisfactory analytical figures could not be obtained because the solvent of crystallisation could not be removed completely.

Method (b) - with ethanol as the proton donor.

O-methyl podocarpic acid (29) (29 g, 0.2 m) was dissolved in a mixture of ether (100 ml) and liquid ammonia (1 l). Lithium (20 g, 2.8 g atoms) was added quickly to the stirred reaction mixture, and ethanol (200 ml, 3.6 mm) was added carefully over a period of 30 min. The work-up procedure was the same as used for method (a), except that the ether extracts were acidified with aqueous oxalic acid instead of hydrochloric acid. Work-up in the normal manner gave a colourless oil (29 g).

Purification of 12-oxo-podocarp-8-en-16-oic acid (36).

The crude product (5 g) was chromatographed on silicic acid and the desired ketone (36) was eluted with a 50% ether and light petroleum mixture, and obtained as a colourless glass (3 g, 60%), ν_{max} 3200-2800 (-COOH), 1700 (-COOH and -CO-) cm^{-1}. However this product was still contaminated with small quantities of 12-oxo-podocarpan-16-oic acid (37).

The preparation of methyl podocarp-8-en-16-oate (32).

The major unsaturated acid (31) was esterified with diazomethane, (see compound 40), and gave the corresponding methyl ester (32) in quantitative yield. Recrystallisation from light petroleum gave a pure sample, m.p. 75-77°; ν_{max} 1720 (-COOCH$_3$) cm^{-1}; mass spectrum M$^+$, m/e 276; τ9.21 (singlet, C_{10} -CH$_3$), 8.85 (singlet, C_4 -CH$_3$), 6.47 (singlet, -COOCH$_3$); (Found: C, 78.1; H, 10.2. $C_{18}H_{28}O_2$ requires C, 78.2; H, 10.2%).

Preparation of the unsaturated acid (33) by desulphurisation of the thioketal (39).

Sodium (2 g, 0.087 g atoms) was added to a solution of the thioketal (39) (1.7 g, 5 mm) in dry ether (10 ml) and liquid ammonia (200 ml). Absolute ethanol (100 ml) was added slowly over a period of ½ hr until the blue colour was discharged. The ammonia was allowed to evaporate, the inorganic salts were dissolved in water (300 ml), and the resulting suspension was acidified. Extraction of the reaction mixture with chloroform (200 ml) and work-up in the normal manner, gave a crystalline solid, the desired unsaturated acid (33), (1.24 g, quantitative). A pure sample was obtained by recrystallisation from light petroleum, m.p. 170-171°; $[\alpha]_{18}$° 1.6° (C 0.8); ν_{max} 3200-2700 (-COOH), 1685 (-COOH) cm^{-1}; mass spectrum,

M^+ m/e 262; τ9.07 (singlet C_{10} $-CH_3$), 8.8 (singlet, C_4 $-CH_3$), 4.58 (singlet, $-C=CH-$); (Found: C, 77.8; H, 10.0. $C_{17}H_{26}O_2$ requires C, 77.7; H, 9.76%).

Selenium dioxide oxidation of olefinic acid (33).

The minor unsaturated acid (33), (0.260 g, 1 mm) and selenium dioxide (0.115 g, 1.1 mm) were dissolved in acetic acid (70%, 60 ml) and heated under reflux. After 60 hr the dark red solution was cooled, diluted with water (250 ml) and extracted with ether (250 ml). Work-up in the normal manner gave a yellow oil (0.186 g, 72%) of which t.l.c. indicated the presence of starting material and a product of lower R_f contaminated with some highly-coloured material. The reaction mixture was converted to the corresponding methyl esters by reaction with diazomethane - (see compound 40). Preparative t.l.c. (with an 80% ether and light petroleum mixture), followed by recrystallisation from light petroleum, gave a pure sample of the product (0.028 g, 11%); which was shown to be identical with methyl 12-oxo-podocarp-9(11)-en-16-oate by comparison with an authentic sample.

The preparation of methyl podocarp-9(11)-en-16-oate (34).

The minor unsaturated acid (33) was esterified with diazomethane (see compound 40), and gave the corresponding methyl ester

(34) in quantitative yield. Recrystallisation from light petroleum gave a pure sample, m.p. 77-79°; ν_{max} 1715 (-COOCH$_3$) cm^{-1}; mass spectrum M$^+$, m/e 276; (Found: C, 78.4; H, 10.3. $C_{18}H_{28}O_2$ requires C, 78.2; H, 10.2%).

Preparation of the thioketal of the unsaturated ketone (39).

The unsaturated ketone (35) (1.2 g, 4.3 mm) was added to a mixture of ethane dithiol (0.8 ml, 9.4 mm) and glacial acetic acid (10 ml). The stirred mixture was cooled to 5° and $BF_3.Et_2O$ (0.6 ml, 4.6 mm) was added dropwise over 10 min. The reaction mixture was stirred at room temperature for 1 hr, then cooled in an ice-bath until no more product crystallised. The product was removed by filtration (1.5 g, 95%) and a pure sample of the thioketal (39) was obtained by recrystallisation from acetone, m.p. 186-188°; $[\alpha]_{15}$ 23° (C 0.82); ν_{max} 3200-2600 (-COOH), 1680 (-COOH) cm^{-1}; mass spectrum M$^+$, m/e 352; τ 9.08 (singlet, C_{10} -CH$_3$), 8.83 (singlet, C_4 -CH$_3$), 6.73 (singlet, -SCH$_2$-CH$_2$S-), 4.47 (singlet, -C=CH-), -0.33 (broad multiplet, $^w/_2$= 7.5 , -COOH); (Found: C, 64.6; H, 8.09. $C_{19}H_{28}O_2S_2$ requires C, 64.7; H, 8.00%).

The preparation of methyl 12-oxo-podocarp-9(11)-en-16-oate (40).

The acid (0.145 g, 0.5 mm) was dissolved in ether (10 ml), cooled to 0°, and to the stirred solution, excess diazomethane (in

ether) was added. After 10 min the excess diazomethane was decomposed by the dropwise addition of acetic acid, and the solvent was removed under reduced pressure yielding a crystalline solid (0.150 g, quantitative). Recrystallisation from light petroleum gave a pure sample of the methyl ester (40), m.p. 114-115° (lit.[19] 115-121°); $[\alpha]_{23}$ -3° (C 0.6) (lit.[19] $[\alpha]$ -9°); ν_{max} 1720 (-COOCH$_3$), 1680 (-CO-), 1600 (-C=CH-) cm^{-1}; λ_{max} 238 mμ (ε 14,000); mass spectrum M$^+$, m/e 290; τ9.03 (singlet, C_{10} -CH$_3$), 8.85 (singlet, C_4 -CH$_3$), 6.4 (singlet, -COOCH$_3$), 4.3 (doublet, J=2, -C=CH-).

Preparation of the alcohol (41) by reduction of 12-oxo-podocarp-8-en-16-oic acid.

The keto acid (36) (13.9 g, 0.05 m) was added to a stirred suspension of lithium tri-t-butoxyaluminium hydride (28 g, 0.12 m) in tetrahydrofuran (200 ml). The reaction mixture was allowed to stand overnight (14 hr), the excess hydride was decomposed with wet ether, and then water (400 ml) was added carefully. The cold solution was acidified with dilute hydrochloric acid (10%) and the product was extracted into chloroform (300 ml). Work-up in the normal manner gave a semi-crystalline solid (14.0 g, quantitative), ν_{max} 3500 (-OH), 3250-2700 (-COOH), 1700 (-COOH) cm^{-1}. The β,γ-unsaturated alcohol (41), was contaminated with a small quantity of the saturated alcohol (42) which was removed by chromatography on silicic acid.

Elution with a solvent mixture of 20% ether and light petroleum gave the β,γ-unsaturated alcohol (41) (10 g, 70%), while 25% ether and light petroleum gave the saturated alcohol (42) (1.2 g, 8%).

β,γ-Unsaturated alcohol (41).

Recrystallisation from acetone gave a pure sample, m.p. 177-179°; [α] 240° (C 0.4); ν_{max} 3400 (-OH), 3250-2700 (-COOH), 1700 (-COOH) cm^{-1}; mass spectrum M^+, m/e 278; the n.m.r. spectrum could not be obtained because of the insolubility of the compound; (Found: C, 73.3; H, 9.41. $C_{17}H_{26}O_3$ requires C, 73.1; H, 9.46%).

Saturated alcohol (42).

Recrystallisation from acetone gave a pure sample, m.p. 248-250° (lit.[19] 248-250°); [α] 43° (C 0.9), (lit.[19] [α] 41.4°); ν_{max} 3300 (-OH), 3500-2700 (-COOH), 1700 (-COOH) cm^{-1}.

Preparation of the 'BF_3-lactone' (46).

The major unsaturated acid (31) (0.130 g, 0.5 mm) was dissolved in benzene (20 ml) and the solution was cooled to 0°. $BF_3.Et_2O$ (5 ml, 38.5 mm) was added to the solution with stirring, and after 30 hr at room temperature the reaction was diluted with ether (100 ml). The excess $BF_3.Et_2O$ and any unreacted unsaturated acid (31) were removed by washing the ether successively with

aqueous sodium bicarbonate (saturated, 10 ml) and aqueous sodium hydroxide (5%, 2 x 50 ml). Work-up in the normal manner gave a crystalline solid (0.088 g, 68%), which was recrystallised from light petroleum to give the 'BF_3-lactone' (46), m.p. 122-124°; $[\alpha]_{22}$ -70° (C 0.74); ν_{max} 1760 (-CO-O-) cm^{-1}; mass spectrum M^+, m/e 262; τ9.18 (C_9 -CH_3), 8.97 (C_4 -CH_3) cm^{-1}; (Found: C, 77.6; H, 9.71. $C_{17}H_{26}O_2$ requires C, 77.8; H, 10.0%). If the reaction was left for a further 50 hr the yield of lactone material was much lower (0.041 g, 31%). V.p.c. of the crude product indicated that there was a considerable amount of the 'H_2SO_4-lactone' (47) now present (approximately 30%). This lactone could also be detected in the n.m.r. spectrum of the crude product.

Isomerisation of the 'BF_3-lactone' (46) or the 'H_2-lactone' (68) to the 'H_2SO_4-lactone' (47).

The lactone (46) or (68) (0.130 g, 0.5 mm) was treated with sulphuric acid, (see compound (31)), and gave a semi-crystalline solid (0.108 g, 83%). Recrystallisation from light petroleum gave a pure sample, m.p. 77-78°, which was shown to be identical with the 'H_2SO_4-lactone' (47) on comparison with an authentic sample.

Preparation of the 'H_2SO_4-lactone' (47) from either unsaturated acid (31) or (33).

The acid (31) or (33) (0.130 g, 0.5 mm) was dissolved, with stirring, in concentrated sulphuric acid (20 ml) at 2°, and the reaction mixture was maintained at this temperature for 1 hr. The reaction mixture was allowed to warm to room temperature, and poured on to ice (50 g). The resulting solution was extracted with ether (50 ml), and the ether extract was washed with aqueous sodium hydroxide (5%, 2 x 10 ml). Normal work-up gave a crystalline solid, the 'H_2SO_4-lactone' (47), (0.128 g, quantitative) and recrystallisation from light petroleum gave a pure sample, m.p. 76-77°; $[\alpha]_{22}$ +27.5° (C 1.88); ν_{max} 1760 (-CO-O-) cm^{-1}; mass spectrum M^+, m/e 262; τ8.99 (singlet, C_9 -CH_3), 8.87 (singlet, C_4 -CH_3); (Found: C, 78.1; H, 10.0. $C_{17}H_{26}O_2$ requires C, 77.8; H, 10.0%).

The preparation of 8α,9α-epoxy-podocarp-8-en-16-oic acid (51).

m-Chloroperbenzoic acid (0.230 g, 1.33 mm) was added to a solution of the major unsaturated acid (31) (0.340 g, 1.3 mm) in chloroform (50 ml) and the reaction mixture was left at room temperature for 6 hr. The solution was then washed successively with aqueous sodium bisulphite (saturated, 10 ml), and aqueous sodium bicarbonate (saturated, 4 x 10 ml). Normal work-up gave the epoxide (51) (0.380 g). Recrystallisation from a mixture of acetone

and light petroleum gave a pure sample, m.p. 188-189°; $[\alpha]_{22}$ 23° (C 1.64); ν_{max} 3200-2800 (-COOH), 1710 (-COOH) cm^{-1}; mass spectrum M^+, m/e 278; τ9.1 (singlet, C_9 -CH_3), 8.8 (singlet, C_4 -CH_3); (Found: C, 73.2; H, 9.36. $C_{17}H_{26}O_3$ requires C, 73.3; H, 9.41%).

Preparation of the hydroxylactone (52) and the unsaturated lactones (53). and (54).

The pure epoxyacid (51) (0.4 g, 1.44 mm) was dissolved in dry benzene (50 ml) and $BF_3.Et_2O$ (0.4 ml, 3 mm) was added dropwise to the stirred solution. After 5 min the reaction was terminated by the addition of aqueous sodium bicarbonate (saturated, 20 ml). The reaction mixture was then washed with aqueous sodium hydroxide (5%, 2 x 50 ml). Work-up in the normal manner gave a semi-crystalline solid (0.237 g, 63%) of which t.l.c. indicated the presence of two products. The crude product was purified by chromatography on silicic acid and the following compounds were eluted from the column:- the unsaturated lactone (53) (0.102 g, 25%) with a 15% ether and light petroleum mixture, and the hydroxylactone (52) (0.019 g, 5%) with a 40% ether and light petroleum mixture. However the unsaturated lactone (53) obtained directly from the column contained a small quantity (approximately 5%) of the isomeric unsaturated lactone (54) which could only be removed by recrystallisation. Thus the actual yield of unsaturated lactone (53) that was pure enough

to be used further in the synthetic scheme, was only 20%. If the oily residue from crystallisation of the unsaturated lactone (53) was chromatographed carefully on silicic acid, a crystalline solid, the minor unsaturated lactone (53), was obtained in low yield (3%).

The unsaturated lactone (53) was recrystallised from light petroleum to give a pure sample, m.p. 135-136°; $[\alpha]_{22}$ 69° (C 0.52); ν_{max} 1760 (-CO-O-) cm^{-1}; mass spectrum M^+, m/e 260; τ8.92 (singlet, C_9 $-CH_3$), 8.82 (singlet, C_4 $-CH_3$), 4.75 (doublet, J=5, $-\overset{|}{C}=CH-$); (Found: C, 78.1; H, 9.16. $C_{17}H_{24}O_2$ requires C, 78.4; H, 9.30%).

The unsaturated lactone (54) was recrystallised from light petroleum to give a pure sample, m.p. 140-141°; ν_{max} 1760 (-COO-) cm^{-1}; mass spectrum M^+, m/e 260; τ9.04 (singlet, C_9 $-CH_3$), 8.88 (singlet, C_4 $-CH_3$), 4.72 (multiplet, $^w/_2$ = 7, $-\overset{|}{C}=CH-$); (Found: C, 78.1; H, 9.26. $C_{17}H_{24}O_2$ requires C, 78.4; H, 9.29%).

The hydroxylactone (52) was recrystallised from ether to give a pure sample, m.p. 156-157°; $[\alpha]_{22}$ 49.0° (C 0.94); ν_{max} 3580 (-OH), 1765 (-CO-O-) cm^{-1}; mass spectrum M^+, m/e 278; τ8.87

(singlet, C_9 $-CH_3$), 8.80 (singlet, C_4 $-CH_3$), 7.39 (broad singlet which was removed on D_2O exchange, -OH); (Found: C, 73.4; H, 9.50. $C_{17}H_{26}O_3$ requires C, 73.3; H, 9.41%).

Acidic products. When the sodium hydroxide extract was acidified, an oily precipitate was formed which was readily extracted into chloroform. Normal work-up gave a yellow oil (2.7 g, 67%), and although t.l.c. indicated only one significant product, the oil could not be induced to crystallise.

Rearrangement of the epoxyacid (51) in the presence of H_2O.[18]

Epoxyacid (51) (0.1 g, 0.38 mm) was dissolved in dry benzene (50 ml) and H_2O^{18} (0.010 g, 0.6 mm) was added. $BF_3.Et_2O$ (0.2 ml, 1.5 mm) was reacted with the epoxyacid (51) under exactly the same conditions as

for the normal run. Normal work-up and chromatography gave a pure sample of the hydroxylactone (52) (0.010 g, 10%). The sample was recrystallised from ether until the m.p. was constant at 156-157°.

Acetylation of the hydroxylactone (52).

The hydroxylactone (52) (0.250 g, 0.71 mm) was dissolved in acetic anhydride (5 ml) and p-toluenesulphonic acid (0.025 g) was added. The reaction ~~mixture~~ was left at 40° for 14 hr and then terminated by the addition of ice. After 4 hr the product was extracted into chloroform (50 ml.) and the organic layer was washed with aqueous sodium bicarbonate (saturated, 3 x 20 ml.). Normal work-up gave a crystalline solid (0.260 g) of which t.l.c. indicated the presence of two products. The minor one had the same R_f as the unsaturated lactone (53). The unsaturated lactone (53) (0.020 g, 8%) and the acetoxylactone (58) (0.210 g, 73%) were isolated by preparative t.l.c. with a solvent mixture of 50% ether and light petroleum.

A pure sample of the unsaturated lactone (53) was obtained by recrystallisation from ether and was identified by comparison with an authentic sample. Recrystallisation from ether gave a pure sample of the acetoxylactone (58), m.p. 161.5-162.5°; $[\alpha]_{17}$ -24° (C 1.88); ν_{max} 1760 (-CO-O-), 1710 (-CO-CH_3) cm^{-1}; mass spectrum M^+, m/e 320; τ8.93 (singlet, C_9 -CH_3), 8.76 (singlet, C_4 -CH_3), 8.04 (singlet, -COCH_3); (Found: C, 71.0; H, 8.67. $C_{19}H_{28}O_4$ requires C, 71.2; H, 8.81%).

Conversion of the acetoxylactone (58) to the unsaturated lactone (53).

The acetoxylactone (58) (0.160 g, 0.5 mm) was heated at 160° for 10 min, and then the product was distilled from the reaction mixture at 160°/0.1 mm to give a semicrystalline solid (0.118 g, 85%) which was purified by recrystallisation from ether. The product was shown to be the unsaturated lactone (53) by comparison with an authentic sample. However when the acetylation of the hydroxylactone (52) was carried out at 100° for 12 hr the unsaturated lactone was formed directly (72% yield).

Preparation of the unsaturated hydroxylactone (55).

The major unsaturated lactone (53) (0.260 g, 1 mm) was treated with selenium dioxide (0.115 g, 1.1 mm) (see compound 33 - reaction time 5 hr), and gave a light yellow solid (0.205 g, 90%). Recrystallisation from light petroleum gave pure material, the unsaturated hydroxylactone (55), m.p. 150-152°; $[\alpha]_{22}$ 54° (C 0.34); ν_{max} 3570 (-OH), 1780-1760 (-CO-O-), 1650 (-CH=CH-) cm^{-1}; mass spectrum M^+, m/e 276; τ8.82 (singlet, C_9 -CH_3), 8.80 (singlet, C_4 -CH_3), 7.72 (broad singlet, C_5 -H), 6.63 (broad singlet, which was removed by D_2O exchange, -OH), 4.37 (broad singlet, -CH=CH-); (Found: C, 73.7; H, 8.69. $C_{17}H_{24}O_3$ requires C, 73.9; H, 8.75%).

Lithium and ammonia reduction of the unsaturated hydroxylactone (55).

The unsaturated hydroxylactone (55) (0.050 g, 0.18 mm) was dissolved in a mixture of t-butyl alcohol (0.3 g, 0.41 mm) and liquid ammonia (100 ml). Lithium (0.1 g, 0.014 g atoms) was added to the stirred reaction mixture, and after 5 hr the excess lithium was destroyed by the addition of methanol (10 ml). The ammonia was allowed to evaporate and water (20 ml) was added. The product was extracted into ether (40 ml), and work-up in the normal manner gave a colourless oil (0.050 g). The i.r. spectrum of the product indicated that the lactone ring had been reduced, and therefore the oil was oxidised with Jones's reagent, using the same procedure as for compound (75). The product was a light yellow oil (0.045 g) of which t.l.c. indicated the presence of some unsaturated lactone (53) as well as starting material. Preparative t.l.c. (with a 50% ether and light petroleum mixture), followed by recrystallisation from light petroleum, gave a pure sample of the unsaturated lactone (53) (0.008 g, 16%), which was identified by comparison with an authentic sample.

Hydrogenation of the unsaturated hydroxylactone (55).

The alcohol (55) (0.014 g, 0.05 mm) was dissolved in ethanol (10 ml) and to this was added platinum oxide (0.005 g). After $2\frac{1}{2}$ hr at atmospheric pressure, the hydrogenation was complete

and the catalyst was removed by filtration. Evaporation of the solvent gave a crystalline solid (0.015 g, quantitative), which on recrystallisation from light petroleum gave a pure sample. This product was shown to be identical with the hydroxylactone (52) by comparison with an authentic sample.

Isolation of the fluorolactone (64).

Chromatography on silicic acid of a large quantity (25 g) of the crude mixture from the rearrangement of the epoxyacid (51) with $BF_3.Et_2O$, and elution with a solvent mixture of 20% ether and light petroleum gave the fluorolactone (64) (0.250 g, 1%). Recrystallisation from ether gave a pure sample, m.p. 167-169°; ν_{max} 1760 (-COO-) cm^{-1}; mass spectrum M^+, m/e 280, M^+-F° m/e 261, M^+-HF, m/e 260; τ8.92 (C_9 -CH_3), 8.82 (C_4 -CH_3); (Found: C, 72.8; H, 8.99. $C_{17}H_{25}O_2F$ requires C, 72.8; H, 8.84%).

Reaction of the fluorolactone (64) with boron trifluoride.

Fluorolactone (64) (0.140 g, 0.5 mm) was treated with $BF_3.Et_2O$ (0.2 ml, 1.5 mm) under exactly the same conditions as for the epoxyacid (51). Normal work-up gave a semicrystalline solid (0.150 g, quantitative) of which t.l.c. indicated the presence of one main product which had the same R_f as the unsaturated lactone (53). Chromatography of the product on silicic acid gave the

unsaturated lactone (53) (0.1 g, 70%) as the only crystalline product.

Preparation of the 'H_2-lactone' (68).

The unsaturated lactone (53) was hydrogenated (see compound 55) for 2 hr with 5% palladium on carbon as the catalyst. The product, the saturated lactone (68), was formed in quantitative yield, and recrystallisation from light petroleum gave a pure sample, m.p. 78-79°, $[\alpha]_{22}$ 28° (C 0.26); ν_{max} 1760 (-CO-O-) cm^{-1}; mass spectrum M^+, m/e 262; τ9.02 (singlet, C_9 -CH_3), 8.96 (singlet, C_4 -CH_3); (Found: C, 77.6; H, 10.1. $C_{17}H_{26}O_2$ requires C, 77.8; H, 10.0%).

Isomerisation of the 'H_2-lactone' (68) to the 'H_2SO_4-lactone' (47).

This experiment was described in the section on the 'BF_3-lactone' (46).

Equilibration of the 'H_2-lactone' (68) with boron trifluoride.

The lactone (68) (0.262 g, 1 mm) was dissolved in benzene (20 ml) and equilibrated with $BF_3.Et_2O$ (0.3 ml, 3.9 mm) - see compound (46). Normal work-up after 10 hr gave a crystalline solid (0.260 g, quantitative), which was shown to be the unchanged lactone (68) by comparison with an authentic sample.

Preparation of 9α,11α-epoxy-podocarpan-16-oic acid (69).

The minor unsaturated acid (33) (1.6 g, 6.1 mm) was epoxidised with m-chloroperbenzoic acid (2 g, 11.1 mm) - see compound (31). After 16 hr, work-up in the normal manner gave an oil (1.7 g) which was purified by preparative t.l.c. (with a solvent mixture of 60% ether and light petroleum) to give a crystalline solid (0.98 g, 60%). Recrystallisation from ether gave a pure sample of the epoxide (69), m.p. 149-150°; ν_{max} 3150-2700 (-COOH), 1695 (-COOH) cm^{-1}; mass spectrum M^+, m/e 278; τ9.03 (singlet, C_{10} -CH_3), 8.83 (singlet, C_4 -CH_3), 6.9 (triplet, J=2, -C(O)-CH-), -1.0 (multiplet, $W/_2$=7½, -COOH); (Found: C, 73.3; H, 9.44. $C_{17}H_{26}O_3$ requires C, 73.3; H, 9.41%).

Preparation of the hydroxylactone (70).

The epoxyacid (69) (0.139 g, 0.5 mm) was dissolved in benzene (5 ml) and rearranged with $BF_3.Et_2O$ (0.2 ml, 2.6 mm) for 5 min - see compound (51). Normal work-up gave a crystalline solid (0.037 g, 28%), which on recrystallisation from ether gave a pure sample of the hydroxylactone (70), m.p. 164-165°; $[\alpha]_{22}$ 1.2° (C 1.84); ν_{max} 3490 (-OH), 1740 (-CO-O-) cm^{-1}; mass spectrum M^+, m/e 278; τ8.9 (singlet, C_4 and C_9 -CH_3), 6.23 (broad singlet, -CHOH); (Found: C, 73.3; H, 9.16. $C_{17}H_{26}O_3$ requires C, 73.3; H, 9.41%).

Preparation of the ketolactone (71).

The hydroxylactone (70) (0.069 g, 0.25 mm) was oxidised with excess Jones's reagent - see compound (75). Work-up in the normal manner gave a crystalline solid (0.068 g, quantitative), which on recrystallisation from light petroleum gave the ketolactone (71), m.p. 113-115°; ν_{max} 1760 (-CO-O-), 1700 (-CO-) cm^{-1}; mass spectrum M^+, m/e 276; τ9.0 (singlet, C_4 -CH_3), 8.5 (singlet, C_9 -CH_3); (Found: C, 73.7; H, 9.00. $C_{17}H_{24}O_3$ requires C, 73.9; H, 8.75%).

Preparation of the ketolactone (72).

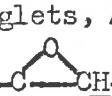
The triol (75) (0.28 g, 1 mm) was dissolved in acetone (20 ml, freshly distilled from potassium permanganate) and Jones's reagent[62] was added until a red colour persisted. After 10 min the excess reagent was destroyed with isopropanol, then water (100 ml) and ether (100 ml) were added to the reaction mixture. The organic layer was separated, and work-up in the normal manner gave a crystalline solid (0.288 g), of which t.l.c. showed one product contaminated with some low R_f material. The product was purified by chromatography on silicic acid, and the desired ketolactone (72) was eluted with a solvent mixture of 25% ether and light petroleum. Recrystallisation from a mixture of acetone and light petroleum gave pure material (0.190 g, 65%); m.p. 194.5-195.5°, $[\alpha]_{30}$ 124° (C 0.94); ν_{max} 1765

(-CO-O-), 1705 (-CO-) cm^{-1}; mass spectrum M^+, m/e 276; τ8.91 (singlet, C_9 -CH_3), 8.67 (singlet, C_4 -CH_3); (Found: C, 73.6; H, 8.61. $C_{17}H_{24}O_3$ requires C, 73.9; H, 8.75%).

Base equilibration of the ketolactone (72).

Sodium methoxide was prepared by the addition of sodium (0.010 g) to dry methanol (10 ml), and to this solution the ketone (0.013 g, 0.05 mm) was added. After 10 hr the reaction mixture was diluted with water (50 ml) and extracted with ether (100 ml). Work-up in the normal manner gave a crystalline solid (0.012 g, quantitative), which was shown to be identical with an authentic sample of the ketolactone (72).

Preparation of the epoxide (73) of the unsaturated lactone (53).

The unsaturated lactone (53) (0.1 g, 0.38 mm) was converted to the corresponding epoxide (73) (0.122 g, quantitative) - see compound (51) (14 hr reaction time). Recrystallisation from ether gave a pure sample of a 1:1 mixture of the two epoxides, m.p. 94-95°; ν_{max} 1755 (-COO-) cm^{-1}; mass spectrum M^+, m/e 276; τ8.95, 8.88, 8.80, 8.73 (singlets, 4X -CH_3), 7.25 (doublet, J=4, ), 7.02 (doublet, J=3, ); (Found: C, 73.6; H, 8.96. $C_{17}H_{24}O_3$ requires C, 73.9; H, 8.75%).

Action of boron trifluoride on the epoxide (73).

The epoxide (73) (0.6 g, 0.22 mm) was rearranged with $BF_3.Et_2O$ (0.2 ml, 0.23 mm) - see compound (51) (reaction time of 5 min). Work-up in the normal manner gave a semicrystalline solid (0.050 g, 83%), which on recrystallisation from acetone gave pure ketolactone (72) (0.030 g, 50%). The ketolactone was identified by comparison with an authentic sample.

Preparation of the triol (75).

A stirred suspension of sodium borohydride (1.6 g, 42 mm) in dry tetrahydrofuran (50 ml) under dry nitrogen, was cooled to 0°, and freshly distilled $BF_3.Et_2O$ (5 ml, 40 mm) was added dropwise. After 4 hr the unsaturated lactone (53) (2.6 g, 10 mm) was added and the reaction mixture was stirred overnight (12 hr). The reaction mixture was cooled to 0°, and successively, aqueous potassium hydroxide (10%, 26 ml, 46 mm) and hydrogen peroxide (27%, 25 ml, 20 mm) were added cautiously. After stirring for 2 hr the reaction mixture was diluted with water (250 ml) and the product was extracted into chloroform. Normal work-up gave a crystalline solid (0.235 g, 90%) of which t.l.c. showed one major product. Preparative t.l.c. (with ether as a solvent) and recrystallisation from dichloromethane gave a pure sample of the triol (75), m.p. 215-216°, $[\alpha]_{22}$ 0° (c 0.32); ν_{max} 3300 (-OH) cm^{-1}; mass spectrum M^+-H_2O, m/e 262.

Preparation of the acetate (83).

The triol (75) (0.140 g, 0.5 mm) was dissolved in a mixture of pyridine (5 ml) and acetic anhydride (1 ml) and the reaction mixture was left overnight (16 hr). The excess acetic anhydride was hydrolysed with water (50 ml) and the product was extracted into chloroform (50 ml). The organic layer was then washed successively with aqueous sodium bicarbonate (saturated, 2 x 30 ml) and dilute hydrochloric acid (5%, 3 x 10 ml). Work-up in the normal manner gave a crystalline solid, the acetate (83), (0.163 g, 90%), which on recrystallisation from light petroleum gave the pure product (83), m.p. 155-156°; ν_{max} 3450 (-OH), 1740 (-COCH$_3$) cm^{-1}; mass spectrum M$^+$-CH_3COOH, m/e 286; τ9.06 (singlet, C_9 -CH$_3$), 9.00 (singlet, C_4 -CH$_3$), 8.0 (singlet, 2x -COCH$_3$), 5.79 (quartet, J=5.5 and 17, -CH$_2$OCOCH$_3$), 4.94 (multiplet, $^W/_2$= 18, -CHOCOCH$_3$); (Found: C, 68.9; H, 9.51. $C_{21}H_{34}O_5$ requires C, 68.8; H, 9.35%).

Preparation of the hydroxylactones (85) and (86).

The ketolactone (72) (0.685 g, 2.4 mm) was dissolved in ethanol (50 ml) and to this sodium borohydride (0.350 g, 9.2 mm) was added. After 4 hr the ethanol was removed under reduced pressure, and the reaction mixture was diluted with water and extracted with ether (2 x 50 ml). Work-up in the normal manner gave a crystalline solid (0.660 g, 96%). T.l.c. of the product indicated that both

epimeric alcohols had been formed, and the mixture was separated by chromatography on silicic acid. The axial alcohol (86) (0.473 g, 70%) was eluted with a 40% ether and light petroleum mixture, and the equatorial alcohol (85) (0.140 g, 20%) with a 80% ether and light petroleum mixture.

Axial alcohol (86).

A pure sample was obtained by recrystallisation from ether, m.p. 183.5-185°; $[\alpha]_{25}$ -4.7 (C 0.64); ν_{max} 3540 (-OH), 1760 (COO-) cm^{-1}; mass spectrum M^+, m/e 278; τ8.97 (singlet, C_9 $-CH_3$), 8.88 (singlet, C_4 $-CH_3$), 6.12 (sextuplet, J=2, 5, and 5, $-CHOH$); (Found: C, 73.1; H, 9.42. $C_{17}H_{26}O_3$ requires C, 73.3; H, 9.41%).

Equatorial alcohol (85).

A pure sample was obtained by recrystallisation from ether, m.p. 148-150°; $[\alpha]_{34}$ 39° (C 0.62); ν_{max} 3460 (-OH), 1740 (-COO-) cm^{-1}; mass spectrum M^+, m/e 278; τ8.92 (singlet, C_9 $-CH_3$), 8.85 (singlet, C_4 $-CH_3$), 6.0 (multiplet, $^w/_2$= 5, $-CHOH$); (Found: C, 73.5; H, 9.30. $C_{17}H_{26}O_3$ requires C, 73.3; H, 9.41%).

Reduction of hydroxylactone (85) with lithium aluminium hydride.

The hydroxylactone (85) (0.1 g, 0.32 mm) was dissolved in dry ether (50 ml) and lithium aluminium hydride (0.074 g, 2 mm) was added. The reaction mixture was heated under reflux for 4 hr, then

cooled to room temperature, and the excess lithium aluminium hydride was decomposed by the addition of hydrated sodium sulphate (0.2 g). The organic layer was decanted and the precipitate was washed with chloroform (2 x 20 ml). Work-up in the normal manner gave a crystalline solid (0.103 g, quantitative), which was shown to be identical with the triol (75) by comparison with an authentic sample.

Preparation of the ether (87).

Cyclohexane was washed with concentrated sulphuric acid, heated under reflux with potassium permanganate, and then carefully fractionated. The hydroxylactone (86) (0.350 g, 1.3 mm) was dissolved in cyclohexane (150 ml) under nitrogen, and excess lead tetra-acetate (2.5 g, 5.6 mm) was added. The reaction mixture was irradiated for $2\frac{1}{2}$ hr, then cooled, and ether (200 ml) was added. The solution was then washed with aqueous sodium bisulphite (1%, 50 ml) and aqueous sodium hydroxide (1%, 50 ml). Work-up in the normal manner gave a colourless oil (0.380 g); ν_{max} 1760 (-COO-), 1710 ($-COCH_3$) cm^{-1}. The acetate band at 1710 cm^{-1} was probably due to insertion products from reaction of the lead tetra-acetate with the solvent. T.l.c. indicated the presence of two products of slightly lower R_f than the starting material, and the mixture was separated by chromatography on silicic acid. The ether (87) (0.055 g, 40%) was eluted with a 20% ether and light petroleum mixture. Recrystallisation from a mixture

of acetone and light petroleum gave pure material, m.p. 119-121°; $[\alpha]_{34}$ -32.5° (C 0.4); ν_{max} 1765 (-COO-) cm^{-1}; mass spectrum M^+, m/e 276; τ 8.93 (singlet, C_9 $-CH_3$), 8.84 (singlet, C_4 $-CH_3$), 6.13 (pentuplet, J=4,4,4, -CH-O-), 5.86(triplet, J=4,3.5 -CH-O-); (Found: C, 73.3; H, 9.16. $C_{17}H_{24}O_3$ requires C, 73.9; H, 8.75%). The second and minor product from the column could not be obtained in a pure form and was not further investigated.

Preparation of the diacetate (88).

The ether (87) (0.138 g, 0.5 mm) was dissolved in acetic anhydride (1 ml) and $BF_3.Et_2O$ (0.1 ml, 1.3 mm) was added with stirring. After 6 min the reaction was terminated by pouring the reaction mixture on to ice, and the product was extracted into chloroform (100 ml). The organic layer was washed with aqueous sodium bicarbonate (3 x 30 ml) and work-up in the normal manner gave a light yellow oil (0.135 g); ν_{max} 1760 (-COO-), 1720 ($-COCH_3$) cm^{-1}. T.l.c. indicated the presence of two products, one of higher and one of lower R_f, than starting material. The product was purified by chromatography on silicic acid, and the unsaturated acetate (89) (0.050 g, 36%) was eluted with a 40% ether and light petroleum mixture. The diacetate (88) was eluted with a 60% ether and light petroleum mixture.

Unsaturated acetate (89).

The material eluted from the column was still contaminated with isomeric products and only a small sample could be obtained crystalline. Recrystallisation from ether gave a pure sample of the unsaturated acetate (89), m.p. 149-150°; ν_{max} 1760 (-COO-), 1720 (-COCH$_3$) cm^{-1}; mass spectrum M$^+$, m/e 318, which was consistent with the formula $C_{19}H_{26}O_3$; τ8.77 (singlet, C_9 -CH$_3$), 8.76 (singlet, C_4 -CH$_3$), 8.06 (singlet, CH$_3$CO-), 5.1 (multiplet, $^w/_2$=7, -CHOCOCH$_3$), 4.82 (multiplet, -C=CH-); insufficient compound was available for analytical figures to be obtained.

Diacetate (88).

Recrystallisation from ether gave a pure sample, m.p. 171-173°; ν_{max} 1760 (-COO-), 1720 (-COCH$_3$) cm^{-1}; mass spectrum M$^+$-CH$_3$COOH, m/e 318; τ8.97 (singlet, C_9 -CH$_3$), 8.78 (singlet, C_4 -CH$_3$), 8.06 and 8.03 (singlets, 2X -COCH$_3$), 5.0 (multiplet, $^w/_2$=9, 2X -CH-OCOCH$_3$); (Found: C, 66.6; H, 8.13. $C_{21}H_{30}O_6$ requires C, 66.6; H, 7.99%).

Preparation of the bromohydrin (95), the bromolactone (96), and the bromoketone (97).

Method I - with N-bromosuccinimide.

The unsaturated lactone (0.203 g, 0.78 mm) and N-bromosuccinimide (0.9 g, 5.1 mm) were dissolved successively in a mixture

of dioxane (70 ml) and water (5 ml). The temperature of the stirred reaction mixture was maintained between 1-3°, while perchloric acid (10%, 8 ml.) was added dropwise. After the addition was complete the light yellow reaction mixture was allowed to warm to room temperature (22°) and stirred for a further 45 min. The reaction was then terminated by the addition of aqueous sodium bisulphite (saturated, 10 ml), and the reaction mixture was diluted with water (200 ml). The product was extracted into ether (150 ml) and normal work-up gave a light yellow oil (0.259 g) of which t.l.c. indicated the presence of three products (one of same R_f as starting material). The crude product was chromatographed on silicic acid and the following products were eluted from the column: bromolactone (96) (0.051 g, 19%) with a 30% ether and light petroleum mixture; bromoketone (97) (0.133 g, 50%), 80% ether and light petroleum mixture; bromohydrin (95) (0.080 g, 30%), 100% ether.

Bromolactone (96) was recrystallised from ether to give a pure sample, m.p. 128.5-130°; ν_{max} 1760 (-COO-) cm^{-1}; mass spectrum M^+, m/e 340, 338; τ8.87 (singlet, C_9 $-CH_3$), 8.5 (singlet, C_4 $-CH_3$), 5.05 (doublet, J=2, $-C=CH$); satisfactory analytical figures could not be obtained because removal of the solvent of crystallisation caused decomposition of the compound.

Bromoketone (97) was recrystallised from ether to give a pure

sample, m.p. 155-156°; $[\alpha]_{34}$ -42.3 (C 1.56); ν_{max} 1770 (-COO-), 1720 (-CO-) cm^{-1}; mass spectrum M^+, m/e 356, 354; τ8.61 (singlet, C_4 -CH_3), 8.5 (singlet, C_{10} -CH_3), 7.35 (doublet, J=10, C_5 -H), 4.73 (doublet, J=10, -CHBr); satisfactory analytical figures could not be obtained because removal of the solvent of crystallisation caused decomposition of the compound.

Bromohydrin (95) was recrystallised from acetone to give a pure sample, m.p. 195-197°; ν_{max} 3400 (-OH), 1740 (-COO-) cm^{-1}; mass spectrum M^+ -HBr, m/e 260; τ8.97 (singlet, C_9 -CH_3), 8.89 (singlet, C_4 -CH_3), 6.12 ~~(broad triplet, J=3)~~ (broad triplet, J=3, -CHOH); satisfactory analytical figures could not be obtained because removal of the solvent of crystallisation caused decomposition of the compound.

Method II - with N-bromoacetamide.

Reaction of the unsaturated lactone (53) (0.160 g, 0.62 mm) with N-bromoacetamide (0.168 g, 1.4 mm) and perchloric acid (10%, 2 ml) for 1½ hr, with the same method as in the previous experiment, gave a semicrystalline oil (0.175 g). Recrystallisation from ether gave a pure sample of the ketolactone (72), which was identified by comparison with an authentic sample. T.l.c. of the oily residues indicated the presence of the bromoketone (97) and the bromohydrin (95).

Zinc and acetic acid reduction of the bromoketone (97).

The bromoketone (97) (0.018 g, 0.05 mm) was dissolved in acetic acid (2 ml) and added to a suspension of zinc dust (0.010 g) in acetic acid (20 ml). The reaction mixture was stirred for 3 hr, then diluted with water (100 ml). The product was extracted into chloroform (50 ml) and the organic layer was washed with aqueous sodium bicarbonate (saturated, 3 x 20 ml). Normal work-up gave a crystalline solid (0.014 g, quantitative) which was purified by recrystallisation from ether, and was shown to be identical with an authentic sample of the ketolactone (72).

Zinc and acetic acid reduction of the bromolactone (96).

The bromolactone (96) was reduced in quantitative yield to the unsaturated lactone (53) with the method outlined for compound (97).

Oxidation of the bromohydrin (95) to the bromoketone (97).

The bromohydrin (95) (0.085, 0.25 mm) was treated under exactly the same reaction conditions as for the addition of hypobromous acid to the unsaturated lactone (53). Work-up in the normal manner gave a semicrystalline solid (0.090 g) which was purified by chromatography and recrystallisation to give a pure sample of the bromoketone (97) (0.045 g, 55%).

Preparation of the ketal (99).

The unsaturated ketone (36) (10 g, 36.2 mm) was dissolved in benzene (200 ml) and to this ethane diol (1.6 g, 40 mm) and p-toluene sulphonic acid (0.1 g, 0.7 mm) were added. The solution was heated under reflux (Dean Stark water separator) for 3 hr and work-up in the normal manner gave the ketal (99) (12.2 g, quantitative). A pure sample was obtained by recrystallisation from a mixture of acetone and light petroleum, m.p. 159-160.5°; $[\alpha]_{15}$ 137° (C 3.2); ν_{max} 3150-2750 (-COOH), 1700 (-COOH) cm^{-1}; mass spectrum M^+, m/e 320; τ9.17 (singlet, C_{10} -CH_3), 8.76 (singlet, C_4 -CH_3), 6.1 (broad singlet, -OCH_2CH_2O-), -0.61 (multiplet, $^W/_2$= 5, -COOH); (Found: C, 70.9; H, 8.79. $C_{19}H_{28}O_4$ requires C, 71.2; H, 8.81%).

Preparation of the epoxyketal (100).

The ketal (99) (5 g, 15 mm) was converted to the corresponding epoxide (100) (6 g, quantitative) - see compound (51), 6 hr reaction time. A pure sample of the epoxyketal (100) was obtained by recrystallisation from acetone, m.p. 188-189.5°; $[\alpha]_{15}$ 114° (C = 1.1); ν_{nujol} 3150 (-COOH), 1700 (-COOH) cm^{-1}; mass spectrum M^+, m/e 336; τ9.06 (singlet, C_{10} -CH_3), 8.82 (singlet, C_4 -CH_3), 6.13 (broad singlet, -OCH_2CH_2-O-), 0.6 (multiplet, $^W/_2$=5, -COOH); (Found: C, 67.6; H, 8.30. $C_{19}H_{28}O_5$ requires C, 67.8; H, 8.39%).

Preparation of the hydroxyketolactone (101).

(a) benzene. The epoxyketal (100) (0.2 g, 0.45 mm), dissolved in benzene (50 ml), was reacted with $BF_3.Et_2O$ (0.15 ml, 1.1 mm) for 5 min. Work-up, as described for compound (53), gave a crystalline solid (0.051 g, 22%), which on recrystallisation from acetone, gave pure hydroxyketolactone (101), m.p. 262.5-263.5°; $[\alpha]_{17}$ 45° (C 0.96); $\bar{\nu}_{max}$ 3450 (-OH), 1750 (-COO-), 1705 (-CO-) cm^{-1}; mass spectrum M^+, m/e 292; τ9.0 (singlet, C_9 -CH_3), 8.93 (singlet, C_4 -CH_3), 8.05 (broad singlet, removed by exchange with D_2O, -OH); (Found: C, 69.9; H, 8.27. $C_{17}H_{24}O_4$ requires C, 69.8; H, 8.27%).

(b) ether. The epoxyketal (100) (0.2 g, 0.45 mm), dissolved in ether (sodium dried, 50 ml), was reacted with $BF_3.Et_2O$ (0.6 ml, 4.6 mm) for 50 hr. Work-up, as described for compound (53) gave a crystalline solid (0.063 g, 35%), which on recrystallisation from acetone gave pure ketal (102), m.p. 202-204°, ν_{max} 3500 (-OH), 1720 (-COO-) cm^{-1}; mass spectrum M^+, m/e 336; satisfactory analytical figures could not be obtained, because the solvent of crystallisation could not be removed.

(c) nitromethane. The epoxyketal (100) (16 g, 12 mm), dissolved in nitromethane (800 ml), was reacted with $BF_3.Et_2O$ (2.8 ml, 22 mm) for ½ hr. The reaction was terminated as usual, by the addition of aqueous sodium bicarbonate, then the aqueous layer was separated and

the nitromethane removed under reduced pressure. Work-up as for compound (53) gave the hydroxyketolactone (101) as a crystalline solid (6.6 g, 55%).

Hydrolysis of ketal (102).

The ketal (0.020 g, 0.063 mm) was dissolved in acetone (10 ml) and p-toluenesulphonic acid (0.001 g) was added. The solution was left overnight (14 hr), then the solvent was removed under reduced pressure and the product was extracted into ether (50 ml). The ether was washed with water (10 ml) and work-up in the normal manner gave a crystalline solid (0.018 g, quantitative). Recrystallisation from a mixture of acetone and light petroleum gave a pure sample, which was shown to be identical with an authentic sample of hydroxyketolactone (101).

Preparation of the thioketal (103) of the hydroxyketolactone.

The hydroxyketolactone (101) (0.6 g, 2 mm) was converted to the corresponding thioketal (0.760 g, quantitative) - see compound (39). Recrystallisation from acetone gave a pure sample of the thioketal, m.p. 254-256°d,; $[\alpha]_{17}$ 23° (C 0.3); $\nu_{max}^{CH_2Cl_2}$ 3460 (-OH), 1760 (-COO-) cm^{-1}; mass spectrum M^+, m/e 368; τ8.97 (singlet, C_9 -CH_3), 8.78 (singlet, C_4 -CH_3), 6.76 (singlet, -SCH_2CH_2-S-); (Found: C, 61.9; H, 7.61. $C_{19}H_{28}O_3S_2$ requires C, 61.9; H, 7.66%).

Preparation of the hydroxylactone (104).

The thioketal (103) (0.15 g, 0.41 mm) was dissolved in ethanol (50 ml) and excess Raney nickel was added to the solution. The reaction mixture was heated under reflux for $\frac{1}{2}$ hr, cooled, and celite (10 g) was added. The reaction mixture was then filtered and evaporation of the solvent, under reduced pressure, gave a colourless solid. The organic material was extracted with hot ether (2 x 100 ml). Work-up in the normal manner gave the hydroxylactone (104) (0.120 g, quantitative). Recrystallisation from ether gave a pure sample, m.p. 207.5-210°; $[\alpha]_{17}$ 68° (C 0.44); ν_{max} 3460 (-OH), 1740 (-COO-) cm^{-1}; mass spectrum M^+, m/e 278; τ8.95 (singlet, C_9 -CH_3), 8.92 (singlet C_4 -CH_3); (Found: C, 73.0; H, 9.49. $C_{17}H_{26}O_3$ requires C, 73.3; H, 9.41%). This product was shown to be isomeric with the hydroxylactone (52) by i.r. and n.m.r. spectroscopy, and mixed m.p.

Dehydration of the hydroxylactone (104).

The hydroxylactone (104) (0.065 g, 0.22 mm) was dissolved in acetic anhydride (20 ml), and to this p-toluenesulphonic acid (0.001 g, 0.06 mm) was added. The reaction mixture was heated at 60° for 12 hr, and the reaction was terminated by the addition of water (100 ml). The product was extracted into chloroform (100 ml) and work-up in the normal manner gave a semicrystalline solid

(0.070 g, 93%); ν_{max} 1760 (-COO-), 1705 (-$COCH_3$) cm^{-1}. T.l.c. indicated the presence of two products, which correspond in R_f to the unsaturated lactone (53) and the expected acetate. The mixture was pyrolysed by sublimation at 160°/0.1 mm to a light yellow oil (0.06 g, 98%). Preparative t.l.c. of the product (with a solvent mixture of 60% ether and light petroleum), gave a crystalline solid (0.035 g, overall yield 58%), which was identified as the unsaturated lactone (53) by comparison with an authentic sample.

Preparation of the unsaturated ketolactone (113) by dehydration of the hydroxyketolactone (101).

The hydroxyketolactone (101) (0.150 g, 0.5 mm) was dissolved in acetic anhydride (5 ml), p-toluenesulphonic acid (0.005 g) was added, and the reaction mixture was heated at 50° for 16 hr. The reaction mixture was poured on to ice and left for 2 hr, then the product was extracted into chloroform (80 ml), and the chloroform layer was washed with aqueous sodium bicarbonate (saturated, 3 x 50 ml). Normal work-up gave a semicrystalline oil (0.160 g, quantitative) which contained two major products (by t.l.c.); ν_{max} 1770 - 1760 (-COO- and -CH=C(-)-$OCOCH_3$), 1725 (-$COCH_3$) cm^{-1}.

Hydrolysis of the mixture of enolacetates.

The acetylation product (0.160 g) was dissolved in acetone (10 ml), p-toluenesulphonic acid (0.005 g) was added, and

the reaction mixture was left overnight (14 hr). Work-up in the normal manner gave a light yellow oil (0.150 g) which contained one major product (by t.l.c.); ν_{max} 1760 (-COO-), 1720 ($-COCH_3$) cm^{-1}.

Pyrolysis of the crude acetate.

The crude mixture was pyrolysed at 140°/0.1 mm to give a semicrystalline oil (0.120 g). Purification of the product by preparative t.l.c. (with a solvent mixture of 60% ether and light petroleum) gave pure unsaturated ketolactone (113) (0.030 g, 20% overall yield).

Preparation of the isomeric unsaturated ketones (113), (114), and (115).

The epoxyketal (4 g, 11.8 mm) was dissolved in nitromethane (250 ml) and $BF_3.Et_2O$ (12 ml, 92 mm) was added. After ½ hr the reaction was terminated and the neutral fraction of the reaction mixture was isolated as a colourless oil (2.35 g, 59%); ν_{max} 3500 (OH), 1760 (-COO-), 1700 (-CO-), 1680 ($-\overset{|}{C}=CH-CO-$) cm^{-1}. T.l.c. indicated the presence of unsaturated ketolactone (major compound) and some products of slightly lower R_f. The product was chromatographed on silicic acid and the unsaturated ketolactone (113) (1.2 g, 33%) was eluted with a 40% ether and light petroleum mixture. The Δ8(14)-isomer (114) (0.4 g, 11%) was also eluted with the same solvent mixture, however the latter fractions were contaminated with

a small quantity of the Δ13-isomer (115) (0.12 g, 3.3%).

Unsaturated ketolactone (113). Recrystallisation from a mixture of acetone and light petroleum gave a pure sample, m.p. 173-175°; $[\alpha]_{17}$ -92° (C 0.36); ν_{max} 1750 (-COO-), 1700 (-CO-) cm^{-1}; mass spectrum M^+, m/e 274; τ8.7 (singlet, C_4 and C_9 $-CH_3$), 4.45 (doublet, J=2.5, -C=CH-); (Found: C, 74.2; H, 8.40. $C_{17}H_{22}O_3$ requires C, 74.4; H, 8.08%).

Δ(13)-isomer (115). Recrystallisation from acetone gave a pure sample, m.p. 163-164°; ν_{max} 1760 (-COO-), 1670 (-C=CH-CO-) cm^{-1}; mass spectrum M^+, m/e 274; τ8.9 (singlet, C_9 $-CH_3$), 8.82 (singlet, C_4 $-CH_3$), 4.13 (doublet, J=10, -CH=CH-CO-), 3.09 (quartet, J=10 and 6, -CH=CH-CO-); (Found: C, 74.8; H, 7.74. $C_{17}H_{22}O_3$ requires C, 74.4; H, 8.08%).

Δ8(14)-isomer (114). Recrystallisation from acetone gave a 1:1 mixture of the isomers (114) and (115). A study of the spectra of the mixture allowed the deduction of the following data for the Δ13-isomer; ν_{max} 1760 (-COO-), 1700 (-CO-) cm^{-1}; mass spectrum M^+, m/e 274; τ8.9 (singlet, C_4 and C_9 $-CH_3$), 4.44 (doublet, J=4, -C=CH-); (Found: C, 74.6; H, 8.28. $C_{17}H_{22}O_3$ requires C, 74.4; H, 8.08%).

Action of base on the unsaturated ketolactone (113).

The unsaturated ketolactone (113) (0.010 g, 0.024 mm) was dissolved in methanol (5 ml) and aqueous sodium hydroxide (5%, 0.05 ml) was added. The reaction mixture was heated under reflux for 1 hr and the methanol was removed under reduced pressure. The product was extracted into ether (20 ml), and work-up in the normal manner gave a crystalline solid (0.010 g, quantitative) which was shown to be identical with an authentic sample of the unsaturated ketolactone (113).

Preparation of the Δ8-acetate (116).

The alcohol (41) (0.140 g, 0.5 mm) was converted to the corresponding acetate (0.160 g, quantitative) - see compound (83). Recrystallisation from a mixture of acetone and light petroleum gave a pure sample, m.p. 202-204°; ν_{max} 3230 (-COO<u>H</u>), 1720 (-O<u>C</u>OCH$_3$), 1695 (-<u>C</u>OOH) cm^{-1}; mass spectrum M$^+$, m/e 320; τ9.15 (singlet, C$_{10}$ -C<u>H</u>$_3$), 8.77 (singlet, C$_4$ -C<u>H</u>$_3$), 8.0 (singlet, -OCOC<u>H</u>$_3$), 5.25 (multiplet, $^W/_2$=10, -C<u>H</u>-OCOCH$_3$), -1.09 (multiplet, $^W/_2$=11, -COO<u>H</u>); (Found: C, 71.0; H, 8.77. $C_{19}H_{28}O_4$ requires C, 71.2; H, 8.81%).

Preparation of the hydroxyepoxide (117) and its rearrangement with boron trifluoride.

The Δ8-unsaturated alcohol (41) (0.560 g, 2 mm) was

converted to the corresponding epoxide (117) - see compound (51). However it was not possible to separate the m-chlorobenzoic acid from the epoxide by washing with aqueous sodium bicarbonate, as both products were of comparable solubility.

$BF_3.Et_2O$ rearrangement.

After the epoxidation was complete the chloroform was evaporated under reduced pressure and nitromethane (50 ml) was added. $BF_3.Et_2O$ (0.6 ml, 4.6 mm) was added dropwise to the stirred reaction mixture. After $\frac{1}{2}$ hr the reaction was terminated and the neutral fraction (0.196 g, 32%) was isolated using the method outlined for compound (53). Recrystallisation from acetone gave a pure sample of the unsaturated hydroxylactone (119), m.p. 207-208°; ν_{max} 3400 (-OH), 1760 (-COO-) cm^{-1}; mass spectrum M^+, m/e 276; τ8.9 (singlet, C_9 $-CH_3$), 8.55 (singlet, C_4 $-CH_3$), 5.83 (multiplet, $W/_2$=6, $-\underset{|}{C}HOH$), 4.66 (triplet, J=2, $-C=CH-$); (Found: C, 74.0; H, 8.59. $C_{17}H_{24}O_3$ requires C, 73.9; H, 8.75%).

Preparation of the acetoxyepoxide (118) and its rearrangement with boron trifluoride.

The Δ8-unsaturated acetate (116) (0.640 g, 2 mm) was converted to the corresponding epoxide (118) which was treated with $BF_3.Et_2O$ (0.6 ml, 4.6 mm) - see compound (51). Work-up in the normal manner gave a crystalline solid, the unsaturated acetoxylactone (120)

(0.210 g, 35%), and recrystallisation from a mixture of acetone and light petroleum gave a pure sample, m.p. 164-166°; ν_{max} 1760 (-COO-), 1720 (-OCOCH$_3$) cm^{-1}; mass spectrum M$^+$, m/e 318; τ8.96 (singlet, C$_9$ -CH$_3$), 8.87 (singlet, C$_4$ -CH$_3$), 7.94 (singlet, -OCOCH$_3$), 4.93 (broad triplet, -CHOCOCH$_3$), 4.62 (doublet, J=4, -CH=CH-); (Found: C, 72.3; H, 8.75. $C_{19}H_{26}O_4$ requires C, 71.6; H, 8.23%).

Oxidation of the unsaturated hydroxylactone (119) with Jones's reagent to the unsaturated ketolactone (113).

The unsaturated hydroxylactone (119) (0.140 g, 0.5 mm) was oxidised with Jones's reagent to the corresponding ketone (113) (0.140 g, quantitative) - see compound (72). This product was readily identified with an authentic sample of unsaturated keto-lactone (113).

Hydrolysis of the unsaturated acetoxylactone (120).

The unsaturated acetoxylactone (120) (0.159 g, 0.5 mm) was hydrolysed with potassium hydroxide (0.2 g) dissolved in ethanol (10 ml). After 16 hr the reaction mixture was diluted with water (100 ml) and the product was extracted into chloroform (20 ml). Work-up in the normal manner gave the unsaturated hydroxylactone (113), (0.150 g, quantitative), which was identical with the previously obtained material.

Preparation of the formyl-ketone (136).

Sodium ethoxide was prepared from sodium (0.5 g) and anhydrous ethanol (30 ml). The alcohol was removed under reduced pressure (0.05 mm) at 200° for 2 hr. The sodium ethoxide was suspended in dry benzene (100 ml) under nitrogen, and ethyl formate (1 ml) was added. A solution of the unsaturated ketolactone (113) (0.250 g, 0.92 mm) in dry benzene (30 ml) was added dropwise to the suspension, and the reaction mixture was stirred overnight (16 hr). The addition of dilute sulphuric acid (5%, 20 ml) terminated the reaction, and work-up in the normal manner gave a yellow crystalline solid, the formyl-ketone (136) (0.280 g, quantitative). A pure sample was obtained by recrystallisation from acetone, m.p. 188-190°; $[\alpha]_{20}$ 180°, (C 1.24); ν_{max} 1760 (-COO-), 1640,1600 (-CO-CHO) cm^{-1}; λ_{max} 282 mμ (ε 9,500), mass spectrum M^+, m/e 302; τ8.86 (singlet, C_9 $-CH_3$) 8.77 (singlet, C_4 $-CH_3$), 6.98 (doublet, J=16, C_{14} $-CH_2-$), 4.5(doublet, J=2, $-\overset{|}{C}=CH-$), 1.3 (broad singlet, =CHOH), -4.2 (broad singlet, removed on D_2O exchange, =CHOH); (Found: C, 71.3; H, 7.24. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.33%).

Preparation of glyoxalate ester (141).

The unsaturated ketolactone (0.3 g, 0.73 mm) dissolved in benzene (sodium dried, 20 ml), was added dropwise to a suspension of sodium hydride (0.2 g, 8.3 mm) in dry benzene (100 ml) and

dimethyloxalate (1 ml, 7.3 mm) under nitrogen. The reaction mixture was stirred for 6 hr, then terminated by the successive addition of methanol (10 ml) and dilute sulphuric acid (5%, 20 ml). Work-up in the normal manner gave a yellow oil (0.430 g, quantitative) which slowly crystallised. The product was chromatographed on silicic acid and the glyoxalate ester (141) was eluted with a 2% ether and benzene mixture. Recrystallisation from a mixture of acetone and light petroleum gave pure material (0.210 g, 51%), m.p. 150-152°; $[\alpha]_{28}$ -190 (C 1.04); ν_{max} 1760 (-COO-), 1730 (-COOMe), 1600 (-CO-) cm^{-1}; λ_{max} 311 mμ (ε 7,880), mass spectrum M^+, m/e 360; τ8.87 (singlet, C_9 -CH_3), 8.73 (singlet, C_4 -CH_3), 6.91 (doublet, J=16, C_{14} -CH_2-), 6.12 (singlet, -COOCH_3), 5.48 (doublet, J=4, -C=CH-), -5.1 (singlet, -OH); (Found: C, 66.8; H, 6.74. $C_{20}H_{24}O_6$ requires C, 66.7; H, 6.71%).

Decarbonylation of glyoxalate ester (141).

All apparatus used in this reaction was carefully washed with distilled water to ensure that it was free of traces of acid or base. Glyoxalate ester (141) (0.2 g, 0.56 mm) was carefully mixed with powdered glass (0.1 g) and the mixture was heated under nitrogen for 2 hr at 180°. The product was extracted with dichloromethane (30 x 10 ml) and the combined extracts were filtered. Removal of solvent under reduced pressure gave an oil (0.180 g). T.l.c. of the crude product indicated that the main constituent was the

unsaturated ketolactone (113), which was purified by chromatography on silicic acid. Unsaturated ketolactone (113) (0.096 g, 51%) was eluted with a 2% ether and benzene mixture, and was the only crystalline material obtained from the reaction.

Preparation of the ethylidene ketone (144).

All of the solvents used in this reaction were distilled from lithium aluminium hydride. Methyl magnesium iodide (0.150 mm) was prepared under nitrogen from magnesium (0.036 g), methyl iodide (0.265 g), and ether (100 ml). After the Grignard reagent had formed, most of the ether was removed under reduced pressure. Pyrrolidine enamine (0.2 g, 0.67 mm) dissolved in dry toluene (250 ml), was added dropwise to the stirred reaction mixture. After 20 min the reaction was terminated by the addition of dilute sulphuric acid (5%, 20 ml) and work-up in the normal manner gave a crystalline solid (0.170 g, quantitative). The product was chromatographed on silicic acid and the ethylidene ketone (144) was eluted with a 20% ether and light petroleum mixture. Recrystallisation from a mixture of acetone and light petroleum gave a pure sample, m.p. 180-181°; $[\alpha]_{25}$ 121° (C 0.9); ν_{max} 1760 (-COO-), 1680 (-CO-), 1620 (-C=CH-) cm^{-1}; λ_{max} 244 mμ (ε 7,600); mass spectrum M^+, m/e 300; τ8.83 (singlet, C_9 $-CH_3$), 8.73 (singlet, C_4 $-CH_3$), 7.83 and 7.63 (singlets,

=CH-C$\underline{H}_3$), 7.05 (broad singlet, C_{14} -C$\underline{H}_2$-), 4.47 (doublet, J=4, -C=C$\underline{H}$-), 3.2 (multiplet, $^{W}/_{2}$=20, =C$\underline{H}$-CH_3); (Found: C, 75.7; H, 8.16. $C_{19}H_{24}O_3$ requires C, 76.0; H, 8.05).

Preparation of pyrrolidine enamine (148).

The formyl-ketone (136) (0.1 g, 0.33 mm) was dissolved in a mixture of benzene (200 ml) and pyrrolidine (0.052 g, 0.33 mm). The reaction mixture was heated under reflux for 2 hr, then the solvent was evaporated under reduced pressure to give a yellow crystalline solid (0.1 g, quantitative). Crystallisation from a mixture of acetone and light petroleum gave the pyrrolidine enamine (148), m.p. 246-248°; ν_{max} 1760 (-C$\underline{O}$O-), 1640 (-C$\underline{O}$-) cm^{-1}; λ_{max} 348 mμ (ε 18,000); mass spectrum M^+, m/e 355; τ8.88 (singlet, C_9 -C$\underline{H}_3$), 8.76 (singlet, C_4 -C$\underline{H}_3$), 6.53 (multiplet, $^{W}/_{2}$=22, -N-(C$\underline{H}_2$)$_4$-), 4.065 (doublet, J=2, -C=C$\underline{H}$-), 2.33 (broad singlet, =C$\underline{H}$-N-); (Found: C, 74.0; H, 8.08. $C_{22}H_{29}O_3N$ requires C, 74.3; H, 8.22%).

Preparation of the alkylated ketone (149).

Potassium t-butoxide (236 g, 1.32 mm) was prepared from the reaction of potassium (42 g) with t-butanol (dried over calcium hydride, 1400 ml) under nitrogen. Ethylidene ketone (2.5 g, 8.3 mm) dissolved in dry benzene (200 ml) was added in a slow stream to the stirred reaction mixture. However, just before the addition, the

system was carefully degassed and then placed under an atmosphere of oxygen-free nitrogen. After 5 min, methyl iodide (70 ml, 1.1 m) was added slowly, and 20 hr later, a further aliquot (14 ml, 0.22 m) was added. Finally, after an extra 25 hr, the reaction was terminated by the addition of water ($2\frac{1}{2}$ l) and the product was extracted into chloroform (1 l). Normal work-up gave a semicrystalline solid, the alkylated ketone (149) (2.7 g, quantitative), which was chromatographed on silicic acid. Elution with a solvent mixture of 25% ether and light petroleum gave a crystalline solid (1.7 g, 65%). Recrystallisation from acetone gave a pure sample of the alkylated ketone (149), m.p. 230-231°; ν_{max} 1760 (-COO-), 1700 (-CO-) cm^{-1}; mass spectrum M^+, m/e 314; τ8.87 (singlet, C_4, C_9, and C_{17} $-CH_3$), 5.02 (triplet, J=10 and 10, $H\rangle C=C\langle H$), 5.01 (quartet, J=10 and 18, $H\rangle C=C\langle H$), 4.45 (doublet, J=4, $-C=CH$), 3.81 (quartet, J=10 and 18, $H\rangle C=C\langle H$); (Found: C, 76.1; H, 9.00. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.40%).

Preparation of the tosyl hydrazone (154).

The alkylated ketone (149) (0.157 g, 0.5 mm) was dissolved in ethanol (10 ml), tosyl hydrazide (0.560 g, 3 mm) was added, and the reaction mixture was heated under reflux for 60 hr. The solvent was removed under reduced pressure and gave a crystalline solid

(0.72 g); ν_{max} 1760 (-CO-O-), 1630 (w, -C=N), 1600 (aromatics) cm^{-1}.

Reduction of the tosyl hydrazone (154) with sodium borohydride.

The crude tosyl hydrazone (154) was dissolved in dry dioxan (50 ml), sodium borohydride (0.38 g, 10 mm) was added, and the reaction mixture was heated under reflux for 60 hr. Most of the solvent was removed under reduced pressure and water (10 ml) was added. The product was extracted into chloroform, and the organic layer was washed with dilute sulphuric acid (1%, 2 l). Work-up in the normal manner gave an oil (0.140 g), which was chromatographed on silicic acid. Elution with a 25% ether and light petroleum mixture gave an oil (0.060 g, 40%); ν_{max} 1760 (-COO-) cm^{-1}, which was homogeneous by t.l.c. However, the n.m.r. spectrum indicated that the product was a mixture, and that there were no olefinic protons in the product.

Preparation of the hydrazone (157) and the Wolff-Kishner reduction of the ketolactone (72).

The ketolactone (72) (0.0135 g, 0.05 mm) was dissolved in a mixture of diglyme (25 ml) and water (1 ml). Sodium hydroxide (0.1 g) was added, the system degassed carefully and placed under oxygen-free nitrogen, and the reaction mixture was heated at 90° for 3 hr. Hydrazine hydrate (0.5 ml) was added and the reaction mixture was

heated at 120° for 3 hr, and then at 215° for 6 hr. The reaction mixture was allowed to cool, and extracted into chloroform (20 ml). Work-up in the normal manner gave an oil (0.015 g, quantitative); ν_{max} 1760 (-C<u>O</u>O-), 1620 (<u>C</u>=N) cm^{-1}, of which t.l.c. (80% ether and light petroleum), indicated the presence of only low R_f material.

Preparation of the thioketal (158).

The alkylated ketone (0.015 g, 0.05 mm) was dissolved in ethane dithiol (1 ml) and $BF_3.Et_2O$ (0.05 ml, 0.3 mm) was added. After 34 hr the reaction mixture was diluted with chloroform (20 ml), and washed with aqueous sodium hydroxide (5%, 2 x 20 ml). Work-up in the normal way gave a semicrystalline solid (0.25 g, quantitative); ν_{max} 1760 cm^{-1}.

Reduction of the thioketal (158) with Raney nickel alloy.

The crude thioketal (158) was dissolved in ethanol (20 ml), excess Raney nickel alloy was added, and the reaction mixture was heated under reflux for 10 min. The reaction mixture was treated in the same manner as for compound (104), and gave a semicrystalline oil (0.015 g, quantitative); ν_{max} 1760 cm^{-1}; τ 8.96, 8.93, 8.74 (singlets, C_4, C_9, and C_{17} -C<u>H</u>$_3$) 4.74 (broad doublet, -C<u>H</u>=C-).

APPENDIX.

Some reactions of the spiroketo-acid (159).

The acidic products from the rearrangement of the various epoxides with $BF_3.Et_2O$ were usually not investigated as they were often complex mixtures and of little relevance to the synthetic project. However, the high yield of acidic products (65%) from the reaction of the epoxyacid (51) was an important problem in the early stages of the synthetic work. After extensive efforts to increase the yield of lactonic material from this rearrangement had failed, it was decided to investigate the acidic fraction, particularly as it was mainly one compound.

The i.r. spectrum of the major acidic product, $C_{17}H_{26}O_3$, indicated the presence of a ketone (ν_{max} 1660 cm^{-1}), and this was confirmed by reduction of the carbonyl group with sodium borohydride to the corresponding alcohol. The n.m.r. spectrum of the alcohol (162) exhibited a one-proton multiplet at τ6.42 which was attributed to a proton bound to carbon bearing oxygen.

Spiroketones have been frequently observed[59] as products from the rearrangement of epoxides with $BF_3.Et_2O$ and if the product from this reaction was a spiroketo-acid, it could have one of four possible structures (159), (163), (164), or (165). An examination of molecular models of the various transition states for the rearrangement indicated that the formation of (163) would be preferred, and therefore the structure 5α,9β-dimethyl-2-oxo-decalin-1-spirocyclopentane-5β-carboxylic acid (163) was proposed for the

spiroketo-acid.

The important feature of this structure was that similar ketones[59] have been found to rearrange when the corresponding alcohol was dehydrated. Thus when the hydroxyspiro-ester (161) was treated with phosphorus oxychloride, a good yield of the unsaturated ester (32) was obtained. This meant that, if necessary, the low yield of lactone material for the rearrangement of the epoxyacid (51) could be overcome by the conversion of the acidic fraction back to the unsaturated acid (31).

Isolation of the spiroketo-acid (159).

The crude acidic fraction (5 g) was chromatographed on silicic acid, and the spiroketo-acid was eluted with a 20% ether and light petroleum mixture. Recrystallisation from a mixture of acetone and light petroleum gave a pure sample of the spiroketo-acid, (159), m.p. 173.5-174°; ν_{max} 3250-2650 (-COOH), 1695 (-COOH), 1660 (-CO-) cm^{-1}; mass spectrum M^+, m/e 278; τ9.14 and 8.8 (singlets, C_5 and C_9 $-CH_3$), -1.3 (multiplet, $^W/_2$ =5, -COOH); (Found: C, 72.5; H, 9.94. $C_{17}H_{28}O_3$ requires C, 72.8; H, 10.06%).

Preparation of the spiroketo-ester (160).

The spiroketo-acid (159) was esterified with diazomethane (see compound (31)), and gave a quantitative yield of the corresponding methyl ester (160). Recrystallisation from light petroleum gave a pure sample of the spiroketo-ester (160), m.p. 74-75°; ν_{max} 1720 ($-COOCH_3$), 1695 (-CO-) cm^{-1}; $[\alpha]_{25}$ -41° (C 1.74); mass spectrum M^+, m/e 292; τ9.26 and 8.87 (singlets, C_5 and C_9 $-CH_3$), 6.37 ($-COOCH_3$); (Found: C, 73.7; H, 9.46. $C_{18}H_{28}O_3$ requires C, 73.9; H, 9.65%).

Preparation of the hydroxyspiro-ester (161).

The hydroxyspiro-acid (162) was esterified with diazomethane (see compound (31)), and gave a quantitative yield of the

corresponding methyl ester. Recrystallisation from light petroleum gave a pure sample of the hydroxyspiro-ester (161), m.p. 129-131°; $[\alpha]_{23}$ 38.0° (C 1.86); ν_{max} 3520 (-OH), 1710 (-COOCH$_3$) cm^{-1}; mass spectrum M$^+$, m/e 294; τ9.39 and 8.83 (singlets, C_5 and C_9 -CH$_3$), 6.37 (singlet, -COOCH$_3$), 6.23 (broad triplet, -CHOH); (Found: C, 73.1; H, 10.0. $C_{18}H_{30}O_3$ requires C, 73.4; H, 10.3%).

Dehydration of the hydroxyspiro-ester (161).

The hydroxyspiro-ester (161) (0.145 g, 0.55 mm) was dissolved in pyridine (2 ml), and phosphorus oxychloride (0.5 ml) was added. The reaction mixture was then left for 2 hr, then poured on to ice, and the product was extracted into chloroform. The chloroform layer was washed with dilute hydrochloric acid (5%, 2 x 50 ml) and work-up in the normal manner gave a semicrystalline solid (0.105 g, 75%). Recrystallisation from light petroleum gave a pure sample of the unsaturated ester (32), which was identified by comparison with an authentic sample.

Preparation of the hydroxyspiro-acid (162).

The spiroketo-acid (159) (0.292 g, 1 mm) was reduced with excess sodium borohydride (see compound (85)), and gave the corresponding alcohol (0.280 g, 95%). Recrystallisation from ether gave a pure sample of the hydroxyspiro-acid (162), m.p. 80-82°; ν_{max}

3400 (-OH), 3200-2800 (-COOH), 1690 (-COOH) cm^{-1}; mass spectrum M^+, m/e 280; τ9.31 and 8.83 (singlets, C_5 and C_9 $-CH_3$), 6.42 (multiplet, $W/_2$ =6, $-\underset{|}{C}HOH$); (Found: C, 72.5; H, 9.94. $C_{17}H_{28}O_3$ requires C, 72.8; H, 10.1%).

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