SYNTHESIS OF LABDANE DITERPENOIDS

SYNTHESIS OF LABDANE DITERPENOIDS

by

MICHAEL BARRY GRAVESTOCK, B.Sc., A.R.I.C.,

A Thesis
Submitted to the Faculty of Graduate Studies
in Partial Fulfilment of the Requirements
for the Degree
Doctor of Philosophy

McMaster University
September 1969

Doctor of Philosophy (1969)
(Chemistry)

McMaster University,
Hamilton, Ontario.

TITLE : Synthesis of Labdane Diterpenoids

AUTHOR : Michael Barry Gravestock, B.Sc. (Southampton University)
A.R.I.C.

SUPERVISOR : Professor R.A. Bell

NUMBER OF PAGES: xii, 202

SCOPE AND CONTENTS:

The previously known, 8-oxo-(13→17)-pentanorlabda-12,19-dioic acid 19-methyl ester 36, was synthesised via two routes following the extensive investigation of the dehydrobromination of bromo-ketone 48, and also partial ozonolysis of the phenolic ring of podocarpic acid.

This keto-acid 36 has been transformed to the corresponding 8-methylene compound in high yield. Application of the latter intermediate to diterpene synthesis has been demonstrated by the synthesis of 12-hydroxylabd-8(17)-en-19-oic acid 37 and methyl 12-ketolambertianate 61.

During investigation of other synthetic intermediates a selective reducing agent for carboxylic esters in the presence of the carboxylic acid function - sodium trimethoxyborohydride, has been discovered.

ACKNOWLEDGEMENTS

The author wishes to express his gratitude and deep appreciation to all those who have made this thesis possible. I am particularly indebted to:

Dr. R.A. Bell (Research Director), for his warm friendship, enthusiasm and guidance throughout this work. Drs. D.B. MacLean, J.W. Warkentin and J.J. McCullough for their interest and helpful discussions.

To my parents for their constant encouragement and interest, and finally to my wife Sally, for her constructive efforts in the completion of this thesis and for her patience and encouragement throughout the course of this work.

Financial support through McMaster University and the National Research Council of Canada is also gratefully acknowledged.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

GENERAL INTRODUCTION

Until the beginning of the nineteenth century, it was generally believed that organic compounds could only be produced in living organisms. A special power inherent in the living cell, the vital force, was thought to be essential for the formation of the complex substances occurring in the animal and vegetable kingdoms. However, following Friedrich Wöhler's success in transforming the inorganic compound ammonium cyanate into a well known organic compound urea, the science of modern organic chemistry can be considered to have been born.

There have been two definitions of organic chemistry. The first due to Berzelius, was -- "the chemistry of substances found in living matter", the second by Gmelin simply as -- "the chemistry of the carbon compounds". Both of these definitions is inadequate in itself. A very large number of the carbon compounds known to-day are of purely synthetic origin and do not, as far as we are aware, occur in living matter. But it is undoubtedly true that the study of substances which are found in living organisms has provided most of the major stimulus to the advance of organic chemistry throughout its history. The direct study of substances from living matter or, more briefly, of natural products is as old as chemistry itself. Its particular rise to prominence during the present century has been as a result of the many ways industry and medicine have been able to put its products to good use. The rise of the organic chemical industry and the growing outlets for new materials

encouraged work on natural materials, with the aim of producing synthetic analogues which might at once have their virtues, and be free of their defects, - as had been the case with the products of the dye industry. Finally, the steady development of medicine and the access to tropical colonial territories provided a major stimulus to the search for new natural drugs and their synthetic relations.

Of the many classes of natural products which arose from these investigations it was soon apparent that a certain group of substances was widely distributed throughout the plant and animal kingdom in exceptionally diversified forms, known collectively as terpenes. These were descriptively and precisely defined by Haagen-Smit as -- "all compounds which have a distinct architectural and chemical relation to the simple C_5H_8, isoprene molecule" i. The word terpene has become associated with fragrant, steam volatile substances from higher plants (essential oils) which contain the mono-($C_{10}H_{10}$) and sesqui-($C_{15}H_{24}$) terpenes based on multiples of two and three isoprene units respectively. Terpenes as we now know them may be based on eight or more such units, containing any number of different functional groups, and based on structural requirements may not exactly contain multiples of five carbon atoms.

Since the diterpenes consist of four isopentane units combined, the possibilities for structural complexity become quite large. These are reflected in the carbon skeletons shown in Figure 1 which represent nine of the basic cyclic hydrocarbons (apart from the rare monocyclic compounds) which have so far been found in nature. The cyclic diterpenes have presented a particularly challenging

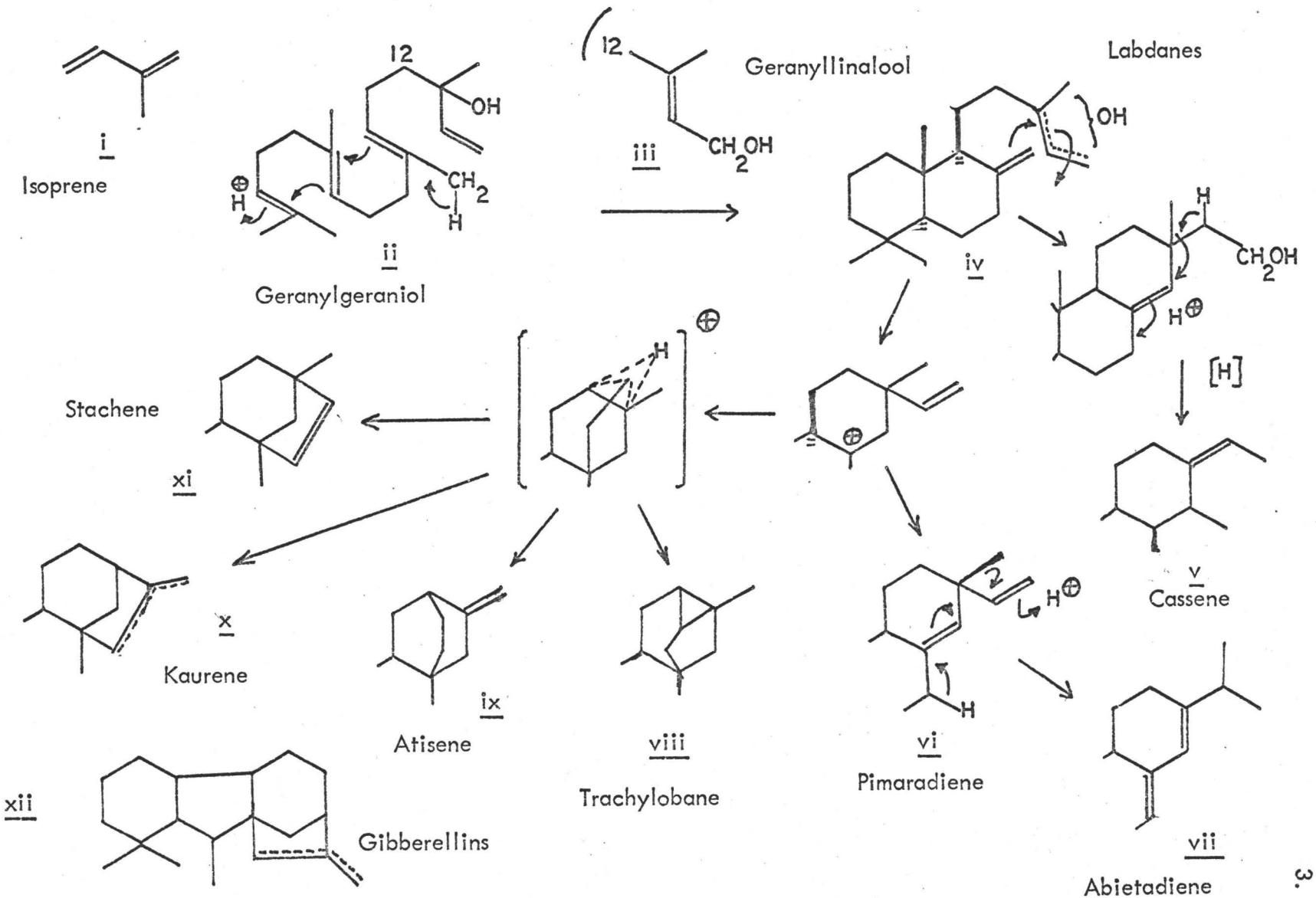


FIGURE 1 : Biogenesis of the Diterpenoids

field for research. Their occurrence in nature is limited to the plant kingdom, where some of them in the form of the gibberellins xii have already assumed great economic and scientific importance because of their apparent role in the stimulation of plant growth. The present basic concept of diterpene biogenesis stems from the suggestion of Ruzicka, and its important extension by Wenkert, involving cyclisation of an initial isoprenoid tetramer, geranylgeraniol ii (or geranyllinalool iii), to the bicyclic labdane alcohol iv, from which all of the known diterpenes subsequently develop by methyl migrations, characteristic of the terpene series. The general validity of the rule has been strikingly proven by numerous isotopic labelling studies.

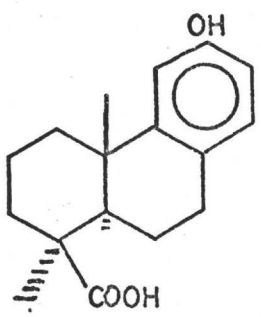
It is fascinating to speculate on the function of all these structural types in the plant. If one accepts the biosynthetic prodigality of plants as an example of evolution in progress then one may see merging at least one function for each main group of terpenoids. In the present case when, during evolution, the gibberellins emerged as essential plant hormones, the enzymes which evolved at the same time to convert the basic diterpenoid precursor, geranylgeranyl pyrophospate into the gibberellins, were either rather unspecific so that they also catalysed other slightly different reactions leading to related diterpenes, or they were one of a series of enzymes produced in a non-selective manner, which catalysed similar but different reactions. Possibly in the distant future plants may have 'settled down', evolutionary speaking, and will show far less biosynthetic individuality than they do to-day.

The objects of natural product synthesis in the laboratory are multifarious. The classical aims were mostly centred on confirmation of the structure of the product obtained from natural sources, since alternative physical and chemical means of determining molecular constitution were not well developed. Although this still remains an important goal of synthesis, many additional results have become apparent. In the course of a synthesis, unexpected intermediates or by-products may arise, shedding new light on mechanisms, and thus allowing the extension of synthetic methods to other systems. Additionally the increasing demand for, and hence development of, physical and/or spectroscopic forms of data on new and existing compounds, has accelerated the efficacy with which the results of a synthetic step can be characterised in further reactions. The increasing complexity of function and steric requirement of multi-functional molecules has led to a great expansion in the number of specifically directed and 'mild' reagents available for a given conversion.

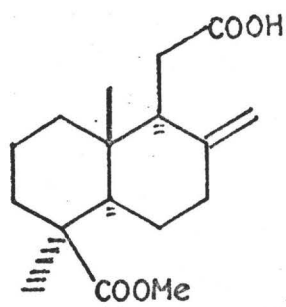
Two other, incidental but often dominant reasons for a synthesis emerge. The desired product or its progenitors may have a well known or possible, medical and economic utility and hence the need for an alternative supply to natural resources may be paramount where the latter are costly or uncertain. As many natural products have a complex and highly specific stereochemistry, and it has only been through an understanding of the stereoelectronic principles of reactions that their synthesis have been successfully planned and executed, the exercise of this understanding and its continuous development presents a considerable

motivation for intellectual challenge and satisfaction to the organic chemist.

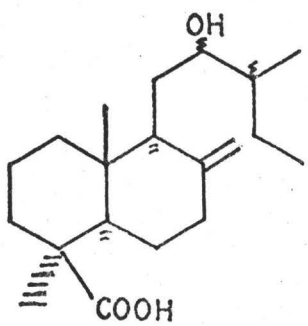
Briefly, the aim of a good synthesis is to produce the desired material, either from another readily available natural product of known structure, or from a cheap, simple precursor using the minimum of steps, each with the highest possible yield. The actual scheme may depend on the construction of the desired carbon skeleton and the placing of functional groups at the proper positions, or more usually two fairly complete, simpler units are combined by a key carbon-carbon bond forming reaction. The object of the present work was to devise practical partial syntheses of diterpenoids possessing the labdane skeleton iv, from the readily available podocarpic acid xiii as a starting material.



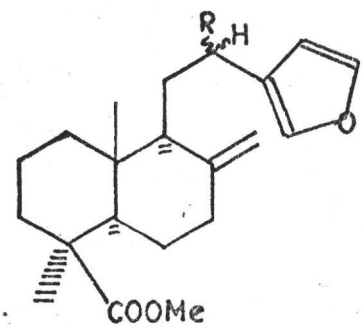
xiii



xiv



xv



xvi

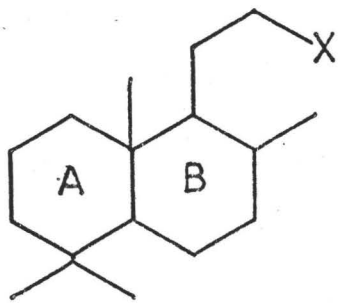
Several high yield, total syntheses of podocarpic acid xiii have been recorded, and thus such synthetic schemes would constitute formal total syntheses.

In the event a high yield, five step synthesis to the intermediate xiv has been achieved, which should be of general utility in the synthesis of several labdane type diterpenoids. Thus the synthesis of 12-hydroxy-labd-8(17)-en-19-oic acid xv has been completed. This 12-hydroxy compound - as a mixture of dextrorotatory, erythro-threo isomers at C-13, - has allegedly been isolated from Juniperus Phoenicea L. However we have found that the physical data described for the natural product do not agree with those obtained for the synthesised compound, and thus the structure of the natural material is in doubt. In addition the alcohol xvi (R = OH) has been obtained which is potentially convertable to methyl lambertianate xvi (R = H), the methyl ester of another natural product. The latter work has led to an improved procedure for 3-furyllithium useful for the synthesis of other, 3-furan- containing natural products. Finally, incidental studies have demonstrated the potential of sodium trimethoxyborohydride as a selective reagent for the reduction of esters in the presence of the carboxylic acid function.

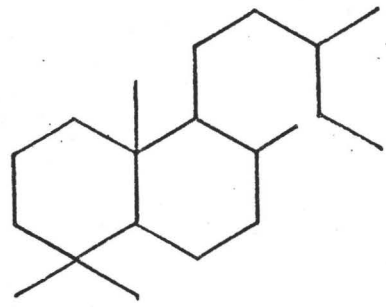
HISTORICAL INTRODUCTION

Bicyclic Diterpenoid Synthesis

The vast majority of the synthetic approaches to bicyclic diterpenes in the past have utilised the construction of the A, B and C rings of a tricyclic entity, followed by degradation of ring C to an A/B bicyclic with suitable functionalisation for further reaction. In many cases the tricyclic intermediate itself has been primarily intended as a precursor to a tricyclic or tetracyclic diterpenoid. The main problem which arises is that of achieving the correct configuration at the minimum, of four asymmetric centres which occur in these molecules. Thus one attempt has been recorded[1] to elaborate decalins of the type 1 from 2,2,6-trimethylcyclohexanone through an acetylenic intermediate, but without conspicuous success.



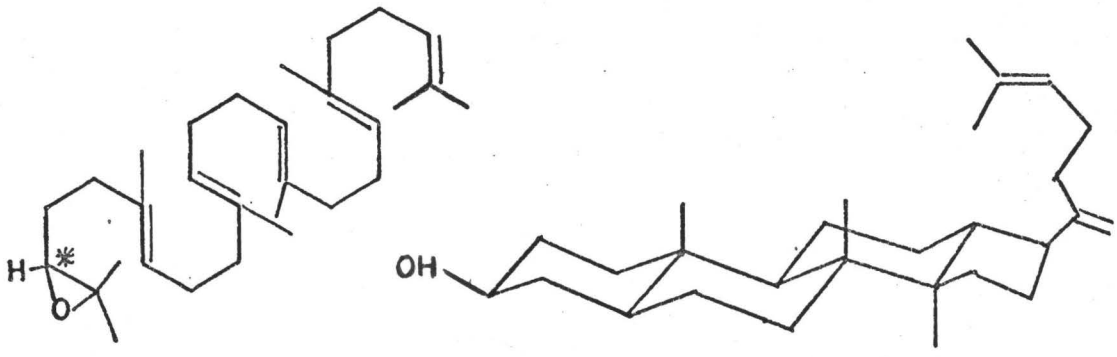
1



2

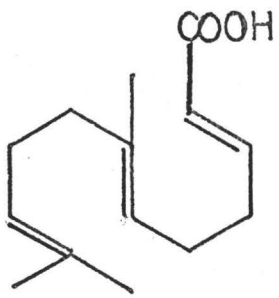
The utilization therefore of a tricyclic compound, with the correct stereochemistry at the C-4, C-5, C-8, C-9 and C-10 centres (see bicyclic LABDANE skeleton 2), is obviously a major factor in the successful synthesis of such molecules. A full review of the methods used in the past to build up such tricyclic intermediates, is beyond the scope of this introduction, but several major examples of the types of technique used will become apparent from the bicyclic diterpenoid syntheses to be discussed below.

Before reviewing these previous syntheses however, mention should be made of an alternative, and entirely different approach to the multicarbocyclic ring systems of the terpene (and steroid) series. The biosynthesis of these molecules takes place (as we have seen in the General Introduction) by enzyme catalysed cyclisations of poly-olefin type species in the plant. The most impressive aspect of these cyclisations is that a substrate such as squalene 2,3-oxide 3, with one asymmetric centre, is thus converted into a product dammaradienol 4, with no less than eight asymmetric centres, in a completely stereoselective manner[2].

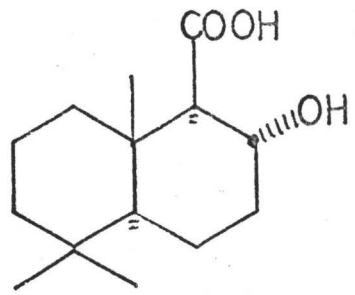


3 4

It is obvious that study of such processes to determine the feasibility of non-enzymic cyclisations in the laboratory would be of fundamental practical and theoretical importance, and accordingly the field has already achieved considerable attention. There were originally, good a priori reasons for supposing that all - trans, squalene - like, polyolefins should cyclise stereoselectively to products with the "natural" configuration[3], and in the ensuing years from 1955, considerable success was achieved with strong acid catalysed systems. Thus trans-desmethylfarnesic ester 5 gave the product 6 in 60 - 70% yield[4], with sulphuric/formic acids at 20°.



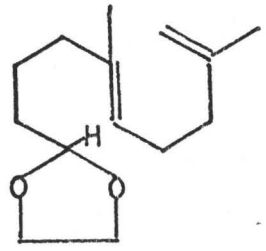
5



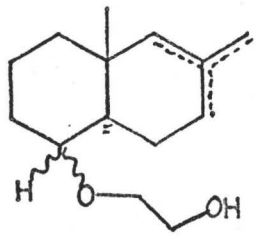
6

However these early studies were soon found to involve stepwise, monocyclic intermediates, and further, not to be of utility for polyenes containing more than three double-bonds (cyclising to tricyclic and higher materials). Subsequent work in this field has led to other more satisfactory methods which have been lucidly outlined by Johnson[2]. Early cyclisations involving acid solvolysis of sulphonate esters gave the desired stereochemical results but suffered from low yields and

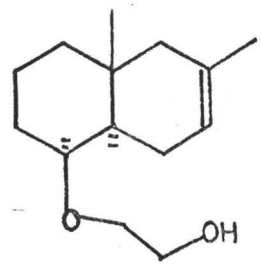
products, without functionalisation in ring A. Later, cyclisation of olefinic acetals showed considerable promise. The trans dienic acetal 7, on treatment at 25^{o2} with stannic chloride in benzene, underwent a very rapid reaction with the formation of trans-bicyclic material in 90% yield, which consisted of five isomers 8.



7



8

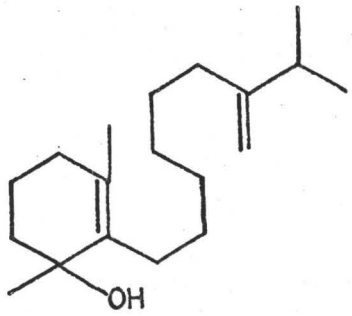


9

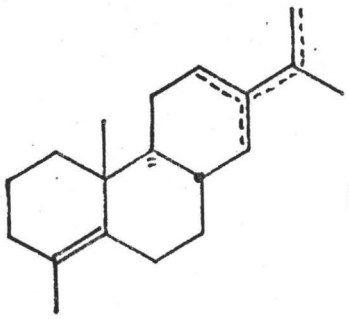
Nitromethane as a polar solvent gave 80% of the product as the isomer 9, as opposed to 60% in benzene. Further, the corresponding cis acetal gave the appropriate cis A/B ring junction products, also in high yield. The potential of the method for bicyclisation in high yield, with high selectivity as originally predicted was thus confirmed.

Additional work has also shown considerable success in the cyclisation to tri and tetracyclic materials, both by this method and by use of allylic cation promoted cyclisations. Thus on shaking 10 with formic acid for 11 min at room

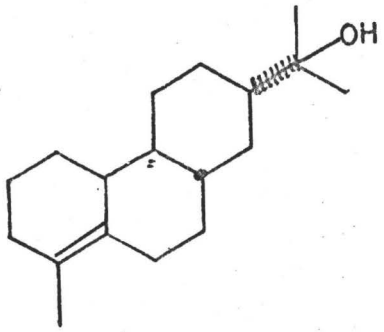
temperature, essentially quantitative conversion to tricyclic material took place[2], consisting of four isomeric hydrocarbons, 11, and an alcohol 12. These were all subsequently converted to dl-fichtelite, a natural resin acid, hydrocarbon. There is no doubt therefore that polyolefinic cyclisations will become of increasing importance in polycarbocyclic synthesis in the future.



10

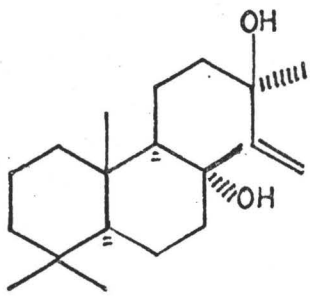


11

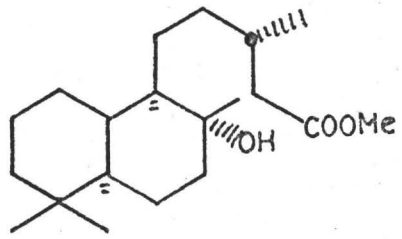


12

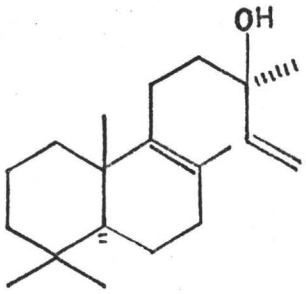
Previous syntheses of bicyclic diterpenes have used either synthetic tricyclic material or another natural product itself, also usually tricyclic, as basic starting material in the synthesis. The technique is well illustrated by Rogers and Barltrop et al's synthesis[5] of the diterpenes from the labdane group; sclareol 13, methyl labdanolate 14, and isomanool 15, from podocarp-8(14)-en-7-one 16. Compound 16 was ozonised to keto acid 17, (16 having been obtained from the corresponding phenol ether which was prepared by classical cyclisation procedures) - and treatment of this keto acid with methyl lithium followed by dehydration led through the hydroxy-ketone 18 to the unsaturated ketone 19 (R = Ac).



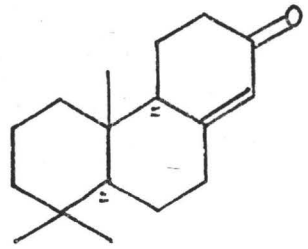
13



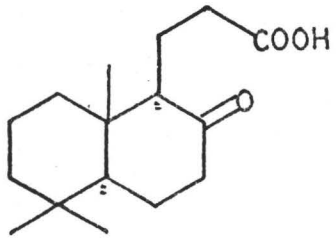
14



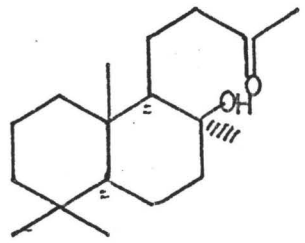
15



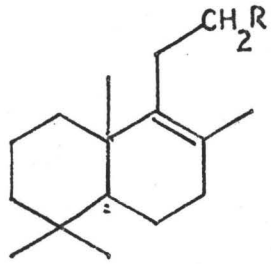
16



17

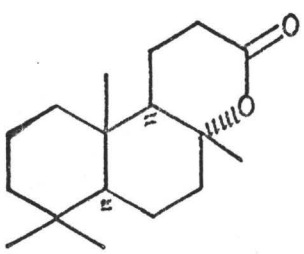


18

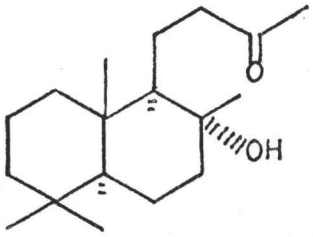


19

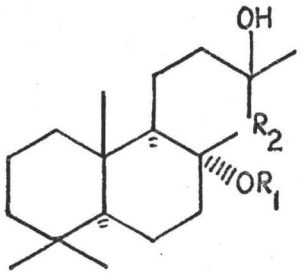
The ketone on hypoiodite oxidation gave the corresponding unsaturated acid 19 (R = COOH), which was cyclised under acidic conditions to (+)-ambreinolide 20. This compound, itself a natural product, served as a relay for further synthesis. (+)-Ambreinolide was hydrolysed to the lithium salt of the related hydroxy acid which with methyl-lithium gave the ketone 21. This ketone was converted to a mixture of epimeric acetoxyethynyl carbinols 22 (R_1 = Ac R_2 = -C ≡ CH), which on being separated, and reduced with lithium aluminium hydride gave rise to sclareol 13 and 13-episclareol. Dehydration of 13 gave isomanool 15. Ketone 21 was also converted to methyl labdanolate 14 and its 13-epimer by reaction with ethoxyacetylene, acid-catalysed rearrangement of the ethoxyethynylcarbinol 22 (R_2 = C≡C - OEt, R_1 = H) to the $\alpha\beta$-unsaturated ester and hydrogenation.



20



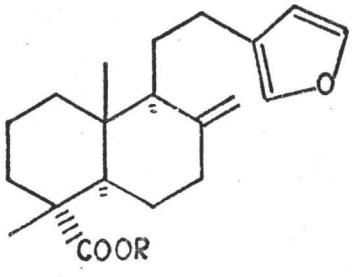
21



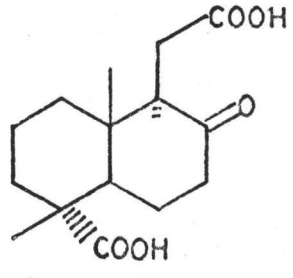
22

More recently, two partial syntheses have been achieved using degradation products from natural diterpenoids of known configurations. The problem of fixing configuration of at least three asymmetric centres was thus

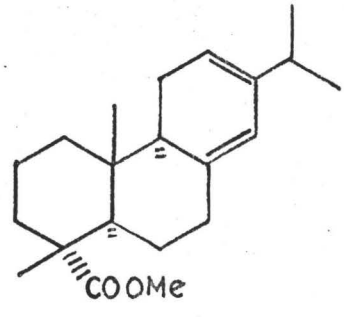
eliminated. In their synthesis of antipodal(+)-polyalthic acid 23 (R = H), Pelletier et al[6] started from the keto-acid 24, obtained by ozonolysis of methyl laevopimarate 25[7,8].



23



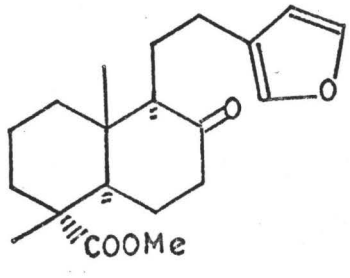
24



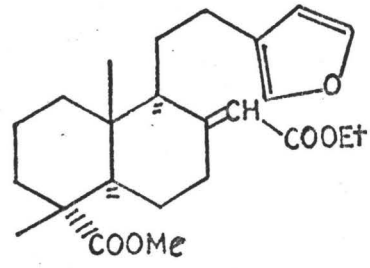
25

The acid 24 was coupled by the Kolbé electrolytic method with 3-furylacetic acid in low yield to give the intermediate 26. The exocyclic methylene group required was then elaborated by the Stork procedure. Condensation with lithium ethoxyacetylide and rearrangement in acidified methanol gave an $\alpha\beta$-unsaturated ester 27, which on hydrolysis and decarboxylation with copper chromite in quinoline gave methyl antipodal polyalthate 23 (R = CH_3). Potassium t-butoxide in dimethyl sulphoxide served to yield the parent acid 23 (R = H).

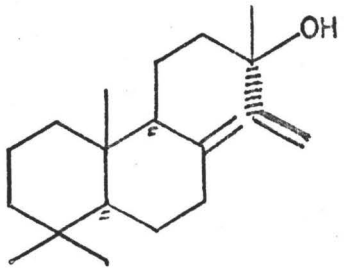
In their synthesis of manool[9] 28, Wenkert et al utilised sclareol 13 as a relay compound to a formal total synthesis of 28. The sclareol was synthesised by modifications to the unsaturated ketone 29 obtained as an ozonolysis product of neoabietic acid.



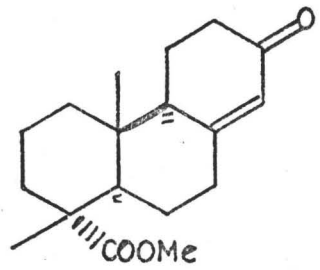
26



27



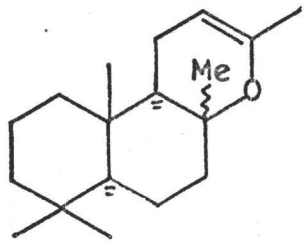
28



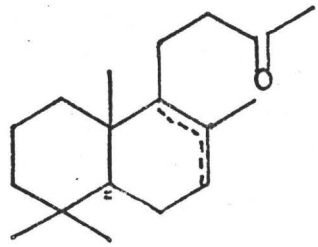
29

Protection of the carbonyl group, lithium aluminium hydride reduction and Saratt oxidation with CrO_3 in pyridine converted the C-4 ester to aldehyde. Huang-Minlon reduction and treatment with acid yielded the ketone 16 (previously obtained both by synthesis and degradation of sclareol itself). Their route then followed the same pathway as used above to the keto-alcohol 18 but the enol-lactone 30 was also

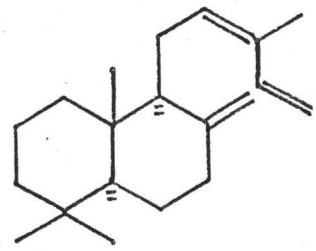
isolated with the present conditions. Dehydration of the enol-lactone gave a mixture of olefins 31, of which the $\Delta^{8,9}$ isomer was a major constituent, and which had been previously converted to 13 and hence to manool 28. The overall conversion was not notable for its yield.



30

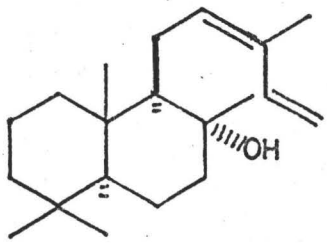


31

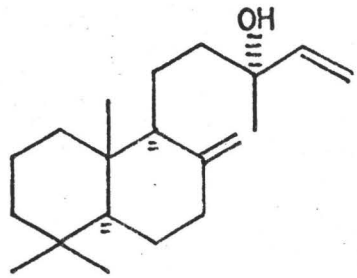


32

The only other recent bicyclic diterpene syntheses consist of one and two step conversions from other natural products. Cis-biformene 32 was obtained[10] by the dehydration of abienol 33 in pyridine at 0° with $POCl_3$ in 90% yield. Use of the same reagent on manool 28 gave three products including trans-biformene and sclarene. 13-Epimanool 34 was synthesised in a Russian study[11] from 13-episclareol by acetylation with acetyl chloride in dimethyl aniline and subsequent distillation of the diacetate at 175°. A mixture of sclaranes plus 13-epimanool acetate was obtained, the latter being subsequently hydrolysed to 34 with potassium hydroxide in ethanol.



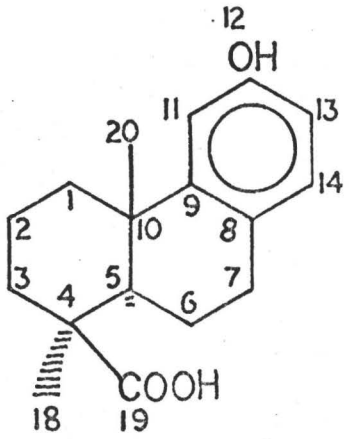
33



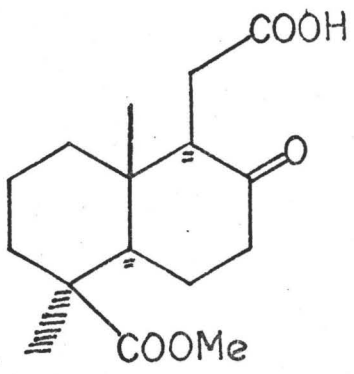
34

Podocarpic Acid as Starting Material in Synthesis

Podocarpic acid 35 occurs widely in certain trees of the southern hemisphere, notably in Podocarpus Dacrydium cupressinum Lamb. ("rimu") whence it was first isolated and in larger amounts in Podocarpus dacrydioides A Rich ("kahikatea"), where it frequently occurs in the heartshakes from which it can be collected in high purity without extraction[12]. The compound is not strictly a diterpenoid but is usually considered along with them because of its close biogenetic relationship and chemical importance. Total syntheses have been numerous[13], and will not be considered in detail here except to note that the main problem has been associated with the elaboration of the correct stereochemistry at C-4 (see for instance references 13g and 13i).



35



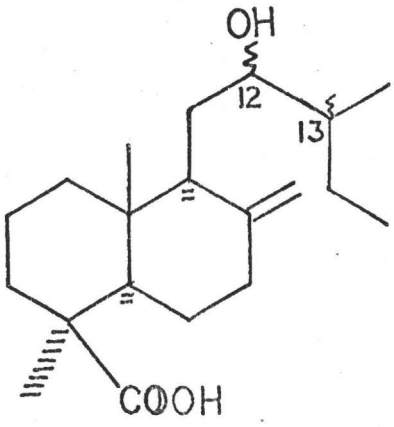
36

The compound is thus readily available naturally as well as synthetically and is of undisputed structure. It is therefore an ideal substrate for further synthetic manipulation, not least for the fact that its aromatic ring C leads to ready functionalisation of the molecule. That this point has not escaped the attention of other workers is demonstrated by the numerous conversions which have been performed, particularly on ring C. The more recent ones are listed under reference 14. Ring A has also received attention, either at the C-4 carboxyl[15], or also in conjunction with oxygenation at C-7 in ring B[16].

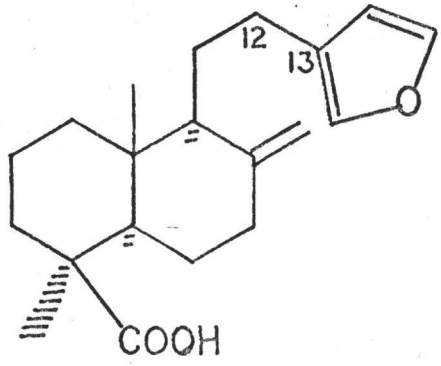
Proposed Synthetic Objectives

In planning the present work it was hoped that a basic intermediate, such as the keto-acid 36 could be produced (see Original Synthetic Plan, below), which would then be suitably modified at C-12 to produce a desired diterpene intermediate

by condensation with a suitable carbon-carbon bond forming reagent. Two diterpenes in particular seemed potentially easily derivable by this approach; 12-hydroxy labd-8(17)-en-19-oic acid 37 obtained from Juniperus phoenicea L.[17] and lambertianic acid ((+)-daniellic acid) 38, obtained from Pinus lambertiana Dougl. ("sugar pine")[18] and also from Pinus sibirica[19] together with its C-19 methyl ester.



37

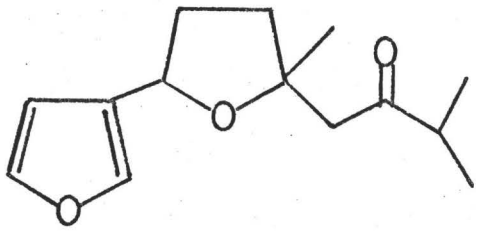


38

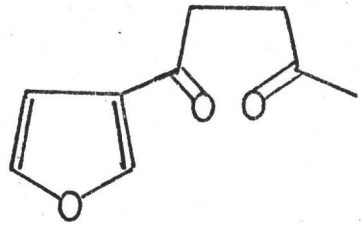
In general this scheme obviously required use of a sec-butyl lithium or similar reagent for synthesis of 37, and a similar 3-furyl reagent for 38. The configuration at C-13 in 37 was not specified, except that both configurations were present in the natural product so no problems were anticipated in obtaining the correct product, using commercially available sec-butyl lithium. The use of a 3-substituted furyl derivative for synthesis of 38 was less clear-cut however.

Although the 3-substituted furan ring occurs quite widely in nature, particularly in the terpenes, very few syntheses have been recorded of natural products containing this moiety. Prior to 1958, the three reported[20], utilised

3-furoic acid as starting material as typified by the synthesis of (+)-ipomeamarone 39[20c], and ipomeanine 40[20b]. Both 40 and 3-furoic acid occur in black-rotted sweet potatoes where the final product 39 is also found.

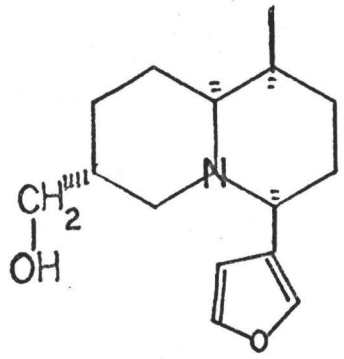


39

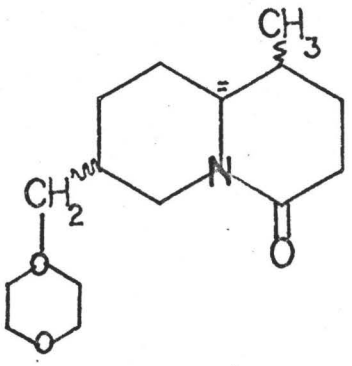


40

Since Gronowitz and Sorlin's work[21] in 1962 on a reasonably efficient route to 3-chloromercury furan, and hence to 3-furyl lithium, incorporation of a preformed 3-furyl carbon unit into a synthetic scheme has been feasible as an efficient one-step route for this structure. This work made 3-furyl lithium available by synthesis in reasonable quantity. Since that time two groups of workers have utilised it in synthesis. Bohlmann et al[22] obtained the sesquiterpene-alkaloid, dl-castoramin 41, which had been previously isolated from the glands of the Canadian beaver, by reaction of 3-furyl lithium with the precursor 42, followed by hydrolysis, dehydration and reduction with palladium/barium sulphate. The natural product 41 was obtained together with its epimers.

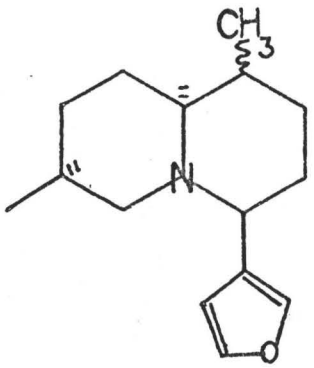


41

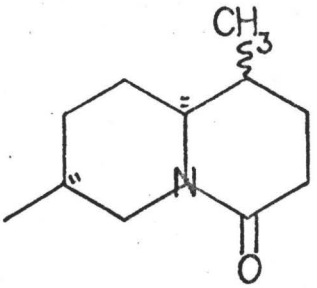


42

Working on the closely related nupharidine alkaloid systems, Wrobel et al[23] in the same year (1965), obtained dl-deoxynupharidine 43, by reaction of the amide 44 with 3-furyl lithium and reduction of the product with palladium/charcoal.



43



44

Finally, the synthesis[6] of antipodal(+)-polyalthic acid 23 (R = H) (see above) was reported during the course of the present work. Since this study had utilised a rather inefficient route to the 3-furyl moiety by converting 3-furyl lithium to

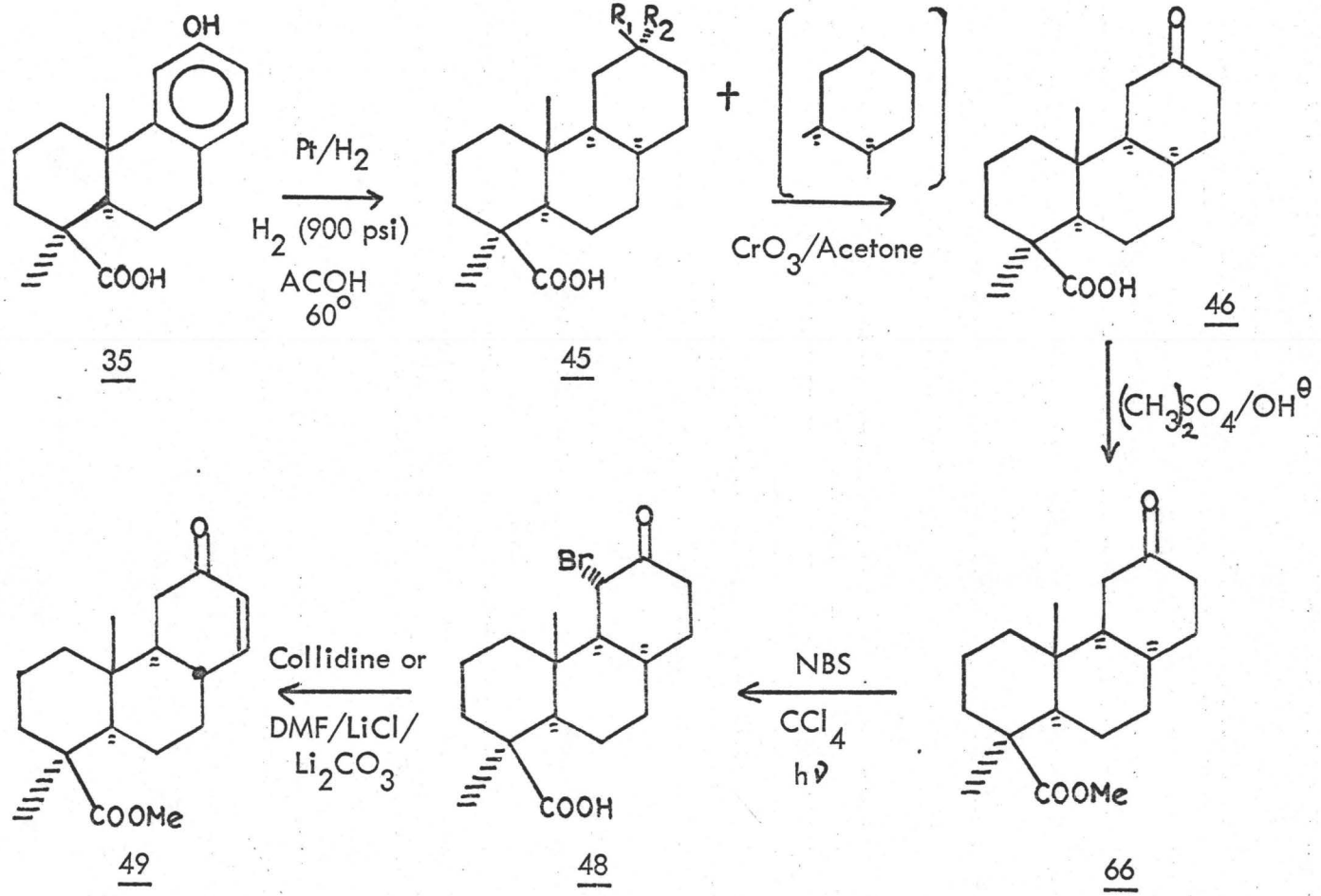


FIGURE 2 : Intermediates from Podocarpic Acid[24]

3-furyl acetic acid, via 3-furoic acid, and then coupling the latter compound in low yield to the keto-acid 24, it was concluded that the route to be explored here was also of value. However the utilisation of the keto-acid 24 by the other workers, had demonstrated the basic correctness of our original plans for use of the corresponding isomer 36 in the present epimeric series as a key intermediate.

Original Synthetic Plan

Following Bible and Burtner's study[24] on the reduction of ring C of podocarpic acid and derivation of various intermediates, it was decided to attempt to improve yields in those conversions, and to then progress from the $\alpha\beta$-unsaturated ketone 49. The reactions which they had performed which were of interest are recorded in Figure 2. It was felt that reduction of the aromatic ring by rhodium or ruthenium catalysts should markedly reduce the amount of hydrogenolysis found by Bible and Burtner. In addition, the yield of bromo-ketone 48 was thought to be improvable, as also was the yield of the $\alpha\beta$-unsaturated ketone 49 which was formed by an apparent 1,4-elimination mechanism.

The originally proposed route to the diterpenes 37 and 38 from 49 is shown in Figure 3. Enol acetylation of 49 was assumed to give 50 as the majority product under thermodynamically controlled conditions[25]. It was then hoped that ozonolysis of 50 with oxidative work-up would lead to the keto-acid 36. Elaboration of the exocyclic double bond, or the side-chain moiety first, would then be possible, and as illustrated it was hoped to attach the side-chain via

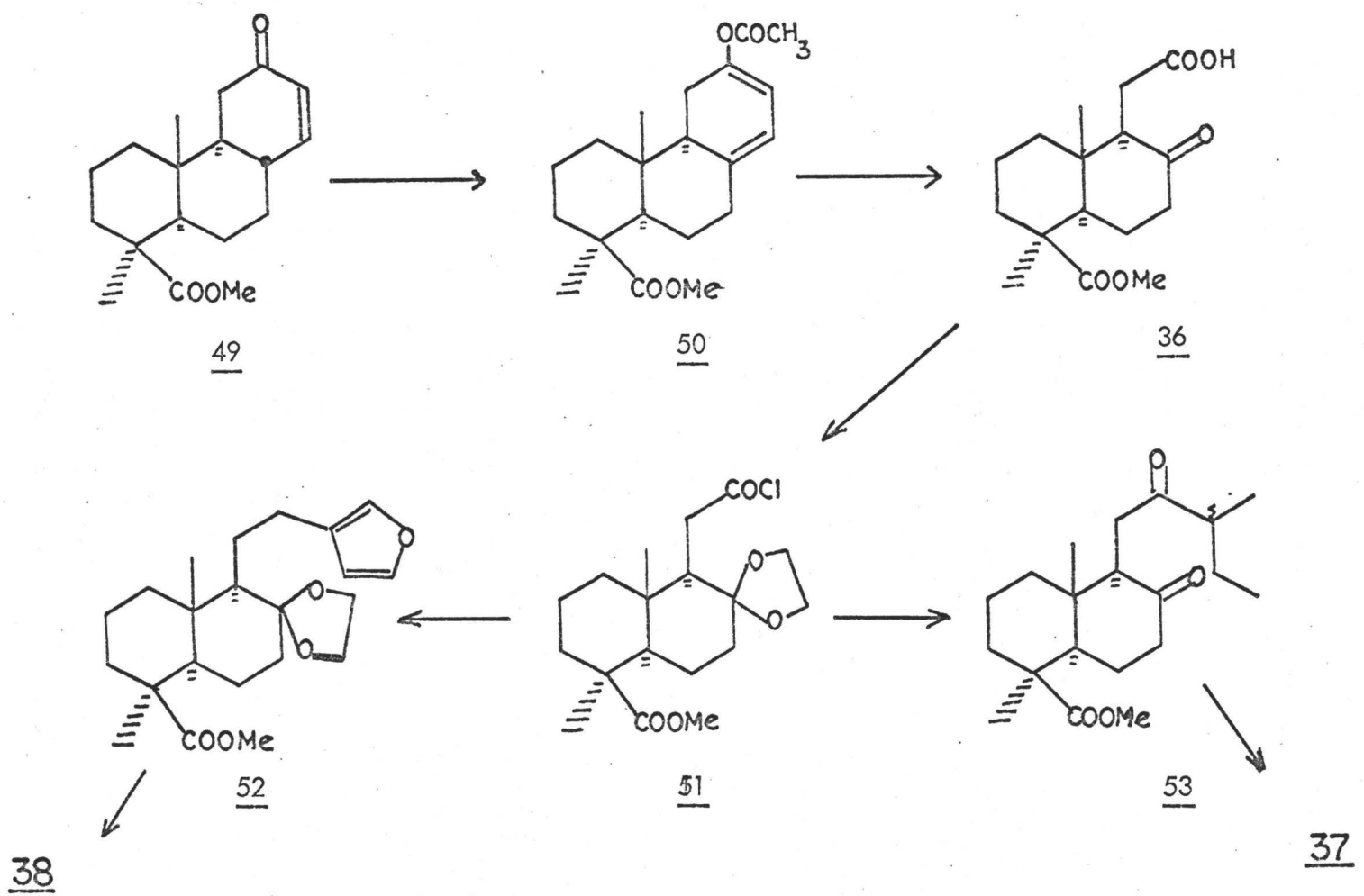


FIGURE 3 : Proposed Synthetic Route to Diterpenes 37 and 38

alkylcadmium attack on the acid-chloride 51, after ketal formation at C-8. It was hoped to be possible to prepare these cadmium derivatives[26] from the corresponding lithium compounds. Removal of the keto group at C-12 in 52 by Huang-Minlon or similar reduction and elaboration of the double bond by the Wittig method was presumed would lead to methyl lambertianate 38 whilst hydride reduction of the ketone 53 would lead to the alcohol(s) 37. In the event, studies took a very different course before final products had been reached, although the keto-acid 36 did in fact prove to be a key intermediate in the syntheses. Its subsequent conversion to the corresponding exocyclic double-bond compound 58, shown in Figure 4, gave a basic precursor for generation of a number of bicyclic diterpenes by attachment of a suitable carbon fragment at C-12, as had been originally hoped for. The subsequent routes taken to 12-hydroxylabd-8(17)-en-19-oic acid 37 and methyl 12-ketolambertianate 61 are also shown in Figure 4. Unfortunately we have not as yet been able to remove the C-12 keto group in the latter compound. The general significance of this problem and the general synthetic potential of the method are discussed in the main body of this thesis.

In the naming of compounds in the experimental section, the system of nomenclature proposed[27] by Dr. J.W. Rowe, now under consideration by an ad hoc committee of diterpene chemists for IUPAC, has been used. The need for a unifying systematic nomenclature for diterpenes has been evident for some time, since various independent previous attempts have led to further confusion.

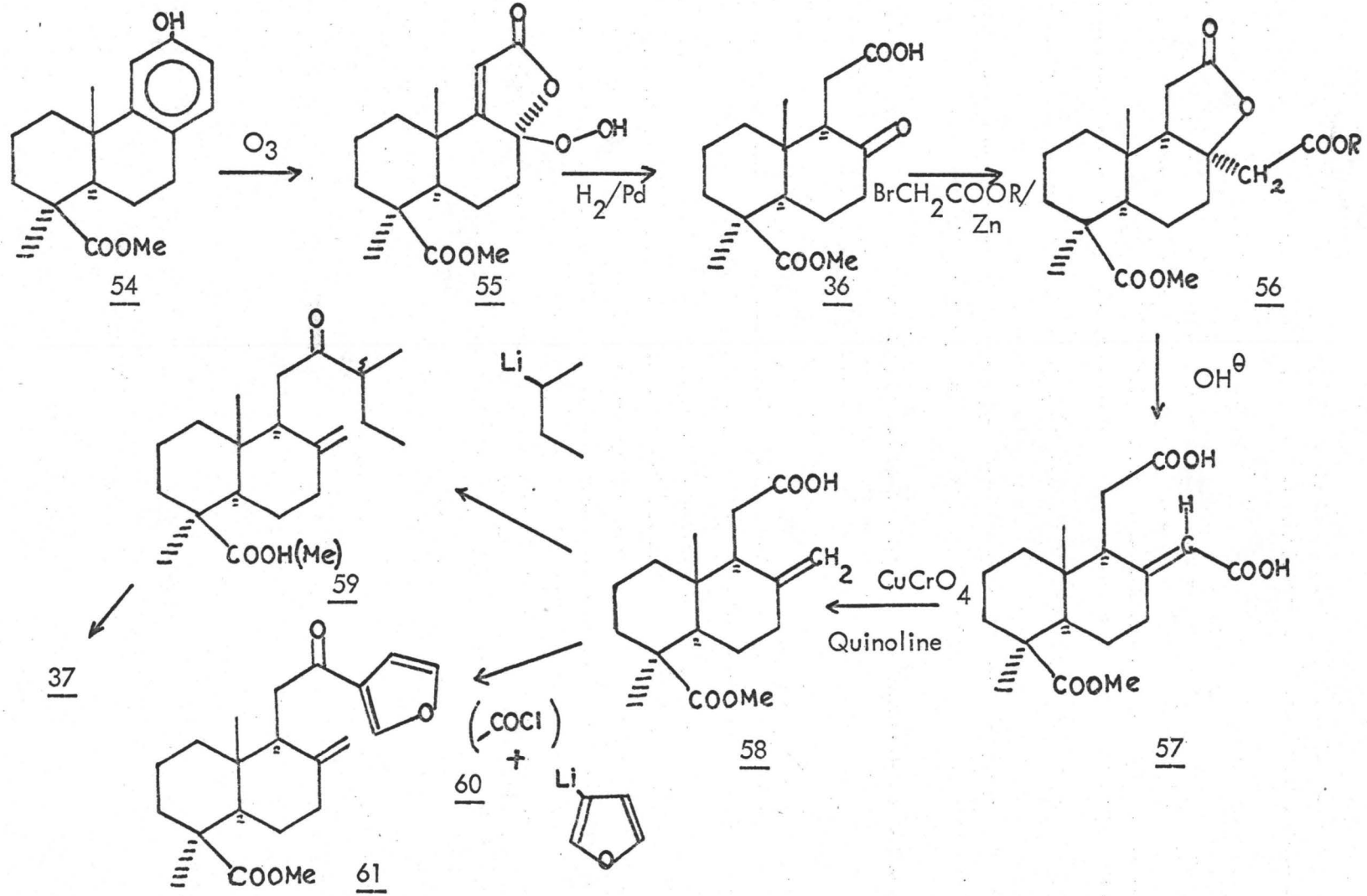
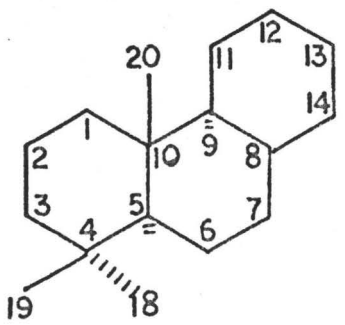
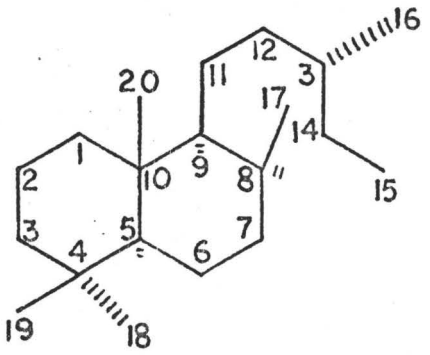


FIGURE 4 : Actual Synthetic Route to Precursor 58, and Then to Diterpene Products

The proposed[27] skeletons for the structures in this thesis are those of PODOCARPANE 62 and LABDANE 63 both hypothetical hydrocarbons, but biogenetically consistent and which have been found convenient to use.



62



63

DISCUSSION AND RESULTS

1. Degradation of Podocarpic Acid (via Reduction-Oxidation Sequence) to the Keto-Acid 36

Reduction of the aromatic ring of podocarpic acid 35, using platinum oxide in acetic acid, and medium pressure hydrogen as reported by Bible and Burtner[24], gave substantial quantities of desoxypodocarpic acid (see Figure 2) as a result of hydrogenolysis of the 12-hydroxyl function. In order to improve the procedure for reduction of the aromatic ring we thus turned to consideration of other catalyst systems. Rhodium metal on alumina as substrate, had been shown by Garcia-Munoz[28] in a study on hydroxy-naphthalenes, to give very little (<3%) hydrogenolysis of carbon-oxygen bonds. Other examples have also been well documented recently[29].

Use of this catalyst (5% Rhodium on Alumina; Englehard Industries Inc.) in the solvent found to be most effective previously[28] (namely one per cent acetic acid in ethanol) gave at most, two per cent hydrogenolysis when used on the podocarpic acid system, with one to three atmospheres hydrogen pressure. When one part catalyst to three parts substrate was used, reduction was complete after some forty-eight hours. Use of smaller or larger quantities of catalyst did not alter the proportion of trans-reduction of the B/C ring junction, which was consistently 15% of the product, but simply resulted in variation of the time to

completion.

It was found that the catalyst could be used a second time, without change in product character and using twice the previous amount to achieve reduction in the same time. Further, reactivation of the catalyst[28] by Soxhlet extraction with methanol for 24 h, acetic acid washing, and drying at 400° in a muffle furnace for 36 h, gave a product which was good for at least one further reduction at the 1:3 ratio. Second-time use and regeneration, represents a considerable economy on the use of this catalyst in view of its high initial cost.

When hydrogenations were performed with acetic acid in ethanol as above, but the pressure bottle used was heated to ca 50°, or when a few drops of concentrated perchloric acid were present in addition as a strong acid catalyst, the reduction rate was very slow or negligible. These results are interpreted as being due to ethyl acetate formation which had previously been found to give no reduction with this catalyst[28] when used alone as solvent. The reason for the apparent catalyst poisoning by this compound remains obscure.

The proton magnetic resonance (pmr) spectrum of the crude reaction product showed that the B/C cis ring-junction product was present in 85% yield, but as a mixture (5:3) of the 12α-hydroxy 45, (R_1 = OH, R_2 = H) and 12β-hydroxy 45 (R_1 = H, R_2 = OH), compounds respectively (see Figure 5). The product composition was further confirmed by pmr analysis of the mixture of the acetates derived from the crude hydrogenation product[30], and also by pmr analysis of the mixture of the ester-ketones, 65 and 66, obtained by direct oxidation and

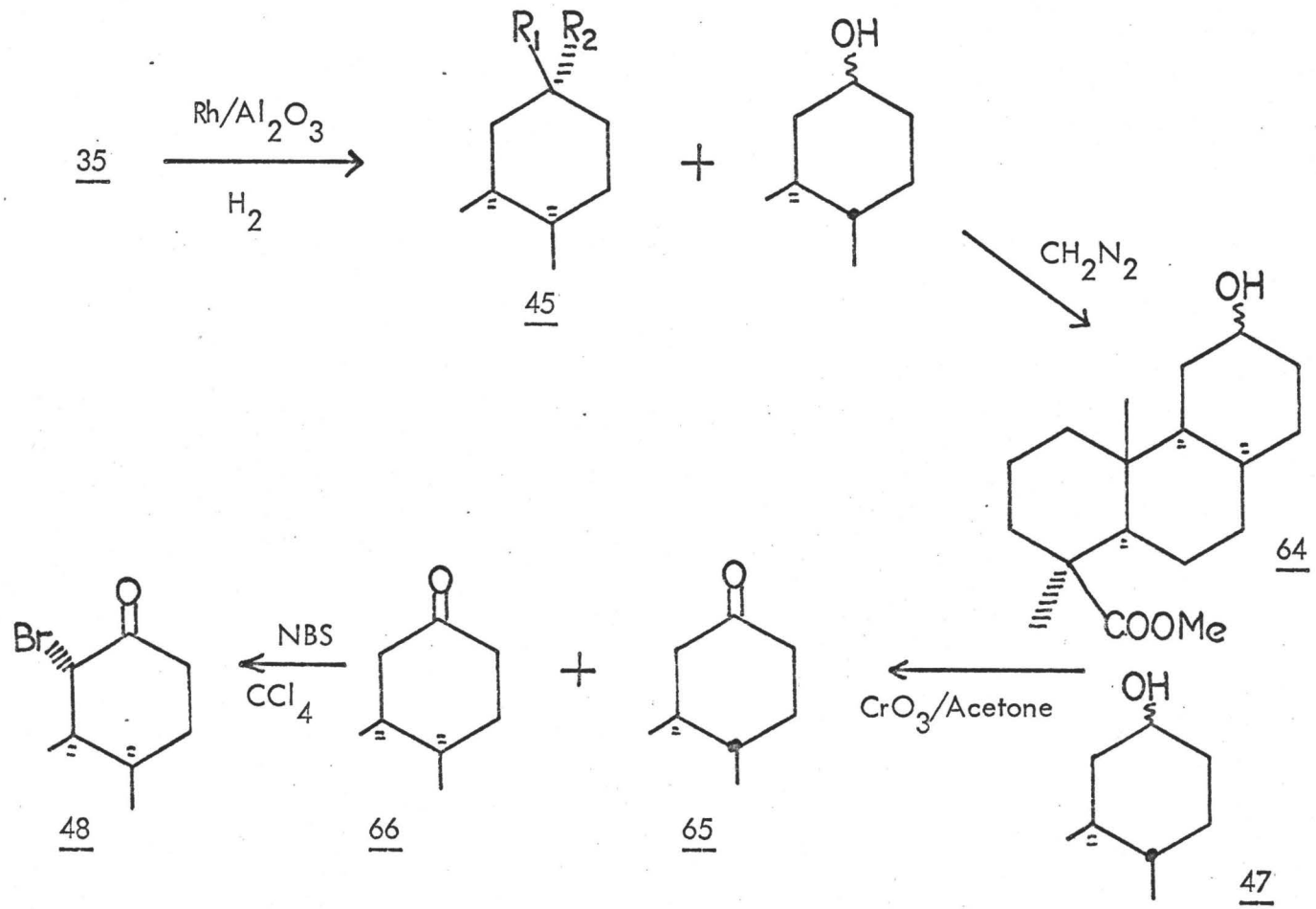


FIGURE 5 : Reductive Degradation of Podocarpic Acid

methylation of the crude hydrogenation product. The predominance of the B/C-cis ring juncture is expected on simple steric grounds, the α-face of the molecule being less sterically congested than the β-face. The minor formation of the B/C-trans ring juncture is also explicable if it is assumed that part or whole of the hydrogenation of the aromatic ring is a step-wise process and that the most difficult bond to saturate is the 8(9)-double bond. A number of other 8(9)-olefinic diterpenoids have been noted to yield B/C-trans products either predominantly[31] or exclusively on catalytic hydrogenation[32].

Methylation of the crude hydrogenation product 45, or of the pure, (mp 230 - 233°) cis hydroxy acid gave the hydroxy-methyl ester 64 as a near-colourless glass, which could not be obtained crystalline, as already noted by Bible[24]. This is most probably because the 'pure' compound is still a mixture of 12- α/β isomers and also that air oxidation of the 12-β compound to the ketone is extremely facile. Thus recrystallization of the original hydroxy-acids 45 must be performed under nitrogen to avoid oxidation. The extreme ease of this oxidation is apparently due to the large amount of steric relief obtained on going from an sp^3 to an sp^2 carbon at the 12-position, arising from interaction with the C-20 methyl group.

Subsequent oxidation of the crude methylated hydroxy esters with Jones reagent[33] (8N chromic acid in acetone) proceeded well at 15-25°, to give a mixture of keto-esters, 65 and 66, which was freed from traces of desoxy, phenolic and highly-coloured material by washing through alumina. A mixture of

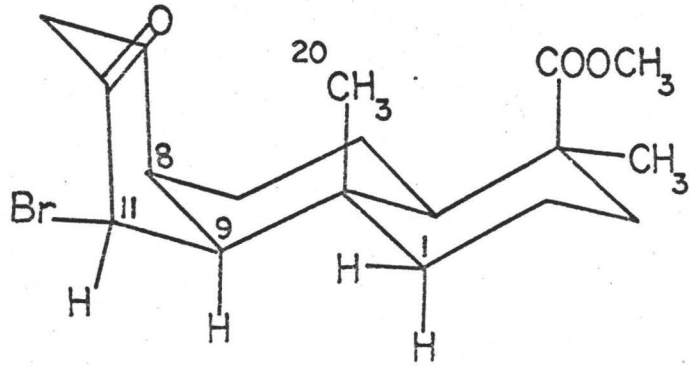
85% 66 and 15% 65 was obtained in this way.

Successful separation of high yields (70%) of the desired cis isomer 66 were finally achieved by fractional crystallisation from ethyl acetate-hexane, although previously, some success had been obtained by utilizing the selective reaction of the cis isomer 66 with Girard's 'T' reagent (Trimethylaminoaceto-hydrazide chloride). The reason for this selectivity remains obscure since on steric grounds the trans isomer 65 would be expected to possess the least hindered carbonyl group. It was thought at one point that the difference in reactivities was due to a subtle pH dependence of the condensation reactions. The reagent initially found to exhibit the selectivity was a sample from Fisher Chemical Co. Ltd. Refluxing with 1.5 - 2.0 moles of reagent in ethanol-acetic acid for 1 - 2 h in the usual manner gave ca 80% yield of the cis isomer 66 on acidification of the aqueous extract. However subsequent trials with reagents from Matheson, Coleman and Bell, and British Drug Houses Limited gave somewhat lower amounts of reaction and absolutely no selectivity between isomers. Investigation of the pH of these reagents alone in water revealed significant differences (ranging from pH 4.5 - 6.8) and it appeared that a correlation could be drawn between extent of reaction and pH of reagent (and hence perhaps of reaction medium). It thus seemed possible that the trans isomer 65 derivative, once formed, might be more sensitive to subsequent hydrolysis by acid back to starting material; but initial trials with additions of small quantities of hydrochloric acid proved fruitless and the problem

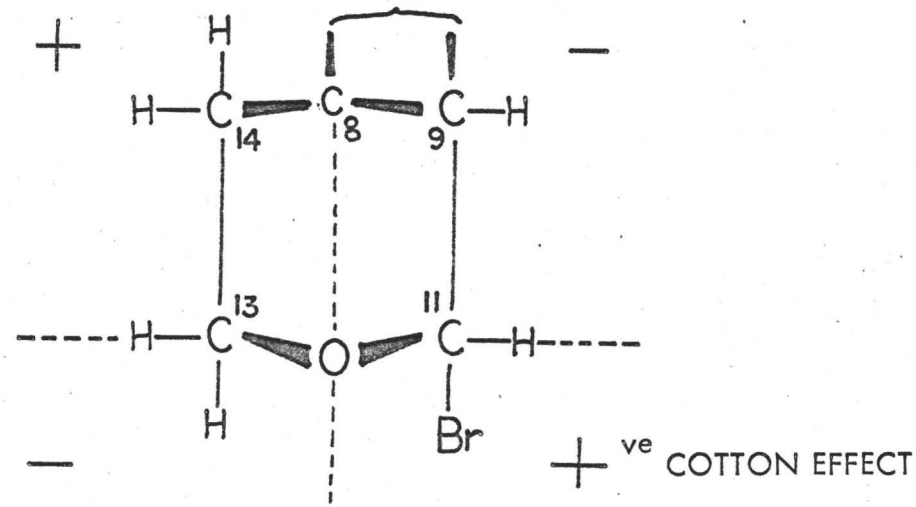
remains at present unresolved. It seems possible that specific catalysis by some unknown contaminant in the Fisher material cannot be ruled out.

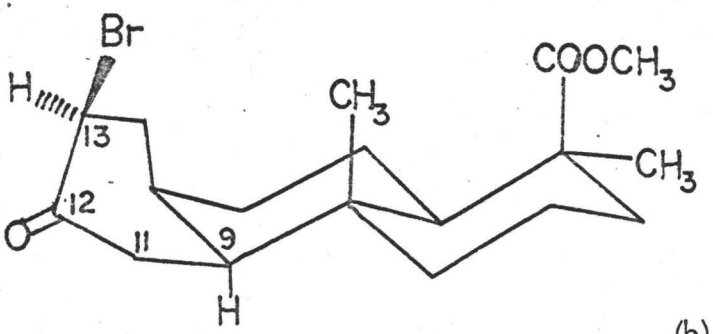
The cis keto-ester 66, obtainable by fractional crystallisation in considerably improved[24] overall yield from podocarpic acid, was next subjected to bromination with N-bromosuccinimide in carbon tetrachloride solution. The initial procedure of Bible[24] was modified by the use of more dilute solutions and initiation by a drop of hydrobromic acid instead of by ultraviolet light. When the reaction was thus performed, controlled-low bromine concentration - bromination took place to give a crude product containing some 90% of a single component.

This component was isolated and characterised as the bromo-ketone 48, by Bible and Burtner[24]. The 11α-configuration assigned to the bromine atom in this bromo-ketone was based on the long wavelength absorption at 310 mμ (ϵ, 130) in the ultraviolet spectrum, which is indicative of an axial bromine[34], and the strong positive Cotton effect observed in the Optical Rotatory Dispersion (ORD) curve. However, the inspection of a molecular model and application of the Octant Rule[35] to projections of the model (see Figure 6) shows that these spectroscopic properties can be satisfied by an 11α-bromine substituent with ring C in a chair conformation, (Figure 6a) as previously postulated, or, by a 13β-bromine with ring C in a twist conformation (Figure 6b). Since the subsequent dehydrobromination of this compound[24] gave more than 60% of the $\Delta^{13,14}$



(a)





(b)

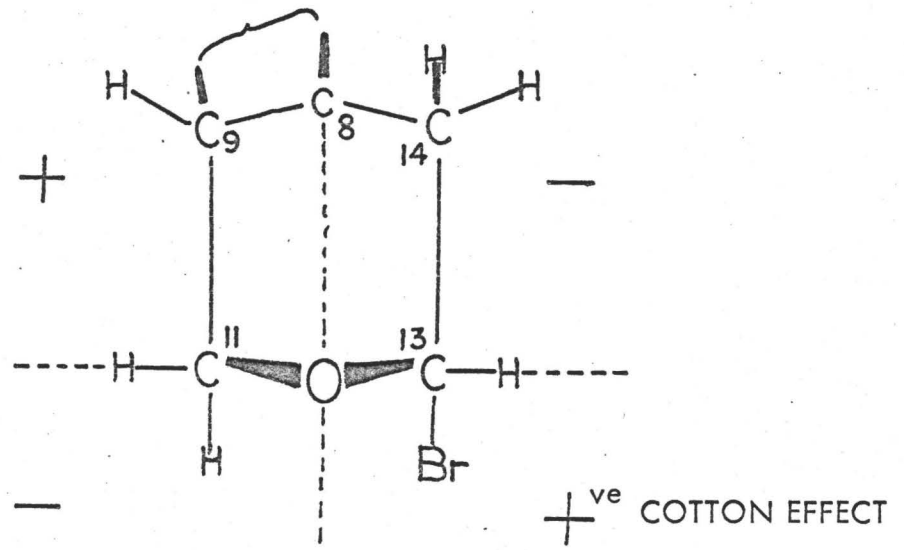


FIGURE 6: The Octant Rule Applied to Bromo-Ketone 48

unsaturated ketone 49, ie the 1,4-elimination product - (and the highest recorded example of 1,4-, versus the more usual, 1,2-elimination, was 40%[36]) - it was decided to distinguish unequivocally between the two possibilities by use of the nuclear Overhauser Effect (NOE).

The NOE properties of the proton adjacent to the bromine atom and carbonyl group (C-11 or C-13, - signal at 4.37 ppm) were examined. The basis for the effect lies in the contributions which neighbouring protons make to the longitudinal relaxation time T_1 of the proton of interest. As a general, qualitative rule[37], if the nearest neighbouring protons are within 3.6 Å of a carbon atom of a methyl group for example, then saturation of the methyl (or all) protons with a second rf field will result in an area increase for this proton.

Thus the α-proton of the bromo-ketone showed a 7% area increase (see Table I) when the C-20 methyl group was saturated.

Protons Saturated	ppm	Proton Observed	ppm	% Area Increase
C-20, CH_3	0.675	H-11	4.37	7
H-1, a	1.12	"	"	7
H-1, e	2.17	"	"	17
H-9	2.27	"	"	18
H-1, e*	2.17	"	"	37
H-9, *	2.17			

* Triple resonance experiment

TABLE I

Nuclear Overhauser Effects in 48

This clearly implies that the α-proton and the C-20 methyl carbon must be within 3.60° of one another. Measurement of this distance with the aid of a molecular model for an 11α-bromine substituent showed a separation of 3.36 Å for the α-(11β)-proton, whilst measurement of the equivalent distance for a 13β-bromine substituent, placed the α-(13α)-proton and the C-20 carbon 4.0 Å apart. It must therefore be concluded that the bromo-ketone possesses the 11α-configuration as in 48 and the original assignment of Bible and Burtner is correct.

On the basis of the structure 48 for the brom-ketone, other information on the chemical shifts of the neighbouring protons of the 11β-proton can be assigned from the Overhauser effect data. Thus it is possible to distinguish between the H-1 and H-9 protons by virtue of the coupling ($J_{9,11} \approx 1$ Hz) which exists between H-9 and H-11. When an rf field was applied which was sufficient to saturate H-9 then this was also sufficient to decouple[38] H-9 from H-11; the signal from H-11 accordingly not only increased in area but also decreased in line width[39]. The coupling constant, $J_{11,13} = 1.0$ Hz, was now also clearly visible by the splitting of the H-11 signal into a closely spaced doublet. The numerical values for the NOE's observed for the axial and equatorial protons at C-1 are subject to some doubt since the strong coupling between these two protons means that saturation of the transitions of the other occurs,[40] although this has been disputed[37]. However, it is possible to assign accurate chemical shifts in spite of this.

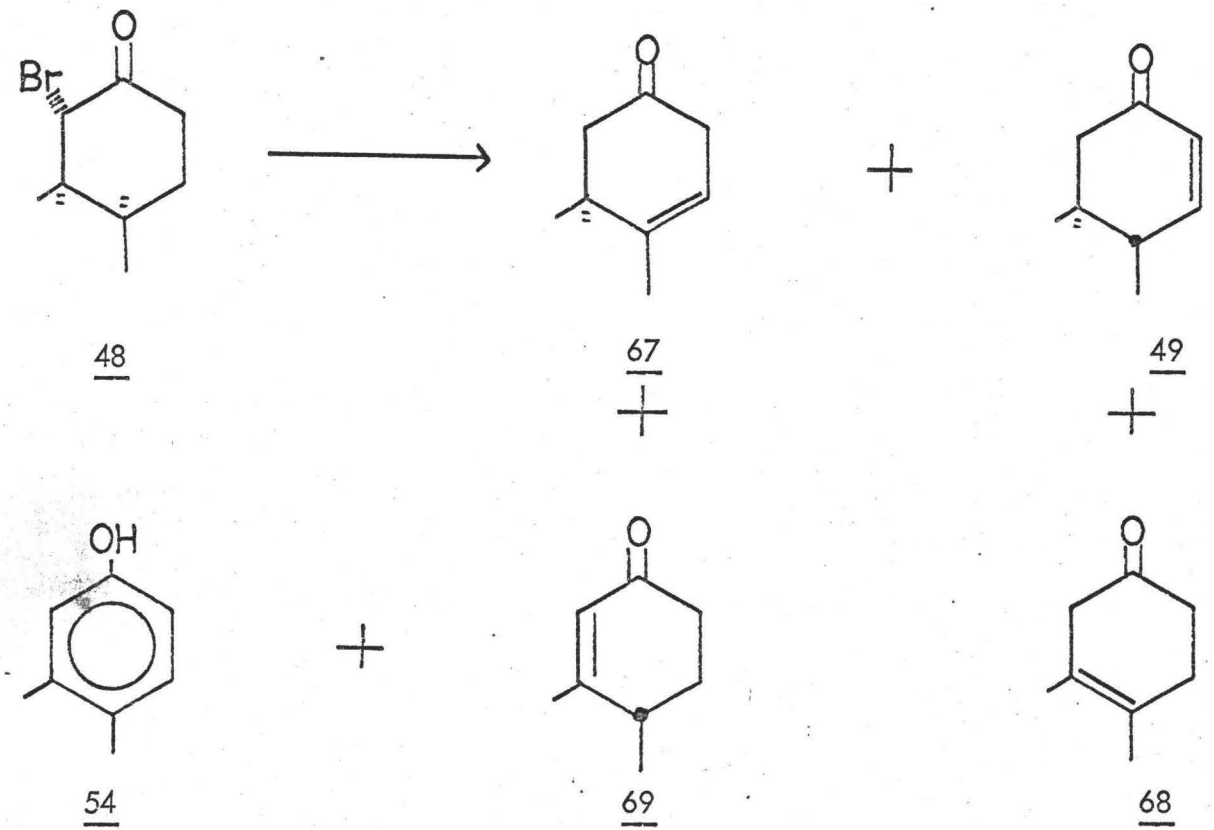


FIGURE 7 : Dehydrobromination of Bromo-Ketone 48

Having unequivocally established the stereochemistry of the bromo-ketone 48 our attention was next turned to its somewhat unusual behaviour on dehydrobromination in boiling dimethylacetamide (DMA) containing calcium-carbonate. Dehydrobromination of 48 for 30 minutes, (Table II) gave as the principal product the $\alpha\beta$-unsaturated ketone 49 which resulted from the elimination of hydrogen bromide in a 1,4-manner. Whilst such 1,4-eliminations have ample precedent[41] in the dehydrobromination of many bromo-ketones there are, as mentioned above, relatively few examples where the 1,4-elimination product is the principal product[36], except in those trivial cases where 1,2-elimination is rendered impossible by complete substitution at the β-carbon. The predominance of a 1,4-elimination pathway over the normal 1,2-pathway is usually a simple consequence of the 1,2-elimination being a high energy process because of steric or stereoelectronic reasons. In this respect the bromo-ketone 48 is no exception, for inspection of a molecular model (see Figure 6a) shows that the dihedral angle between the C-9 H bond and the C-11 Br bond is approximately 60 - 90° and ring C cannot achieve coplanarity of these two bonds without undergoing severe distortion. Thus, the activation barrier for a 1,2-elimination will be high[42] and the alternative 1,4-elimination pathway will be open to the molecule. An analogous situation is to be found in Reichstein's[43] work on 11α- and 11β-bromo-12-keto steroids. Dehydrobromination of 11β-bromo-ketones (a trans elimination with the C-9 α proton) was dramatically more facile than dehydro-

bromination of the 11α-bromo-ketones. In these examples of course only 1,2-elimination is possible.

Since the unsaturated ketone 49 possesses a trans B/C ring juncture, 49 cannot be the primary product of a 1,4-elimination process. In an attempt to find the B/C cis-fused ketone 72 (Figure 8), which would be the presumed initial product, 48 was exposed to refluxing DMA/$CaCO_3$[44] for various periods of time. The appearance of a highly shielded C-20 methyl group at 0.55 ppm in the pmr spectra of the products was observed as the reaction period decreased. This compound was the predominant product (60%, see Table II) after a reaction period of 10 minutes. Shorter reaction times down to a period of 5 minutes resulted in the recovery of unreacted bromo-ketone and no distinguishable change in the composition of the dehydrobromination products. When the principal product from the 10-minute reaction was isolated via silica gel or Florisil chromatography and its spectral properties examined, it was clear that it was not the cis-fused ketone 72, but the non-conjugated ketone 67.

Thus 67 showed only one vinylic proton at 5.44 ppm in its pmr spectrum, and only weak absorption at 282 mμ (ϵ, 100) in its ultra violet spectrum, characteristic of the 'borrowed' intensity of the n-π^* absorption of a $\alpha\beta$-unsaturated ketone[45]. Moreover, on treatment with alumina or dilute acid, 67 was transformed into a mixture consisting of 95% of 49 and 5% of 67. This equilibrium composition indicates that 49 is thermodynamically more stable than 67, although it should be noted that the equilibrium composition of 4-alkylcyclohexenones favours the

$\beta\gamma$-form as the size of the alkyl substituent increases[46].

A mechanism for the formation of 49 and 67 is shown in Figure 8. Although a number of mechanisms may be written for the initial steps of the 1,4-elimination[36c], the most straightforward is shown since this dehydrobromination offers no new information on this aspect of the process. The enol 70, can therefore, be considered to furnish the unsaturated enol 71 by 1,4-elimination. Proton transfer to C-11 of 71 via the enolate then leads to the elusive B/C cis-ketone 72. However the severe steric interaction between the C-20 methyl group and the C-14 carbon provides a strong driving force for base abstraction of the C-8 proton to give the conjugated enolate 73, where this steric interaction is completely removed. In addition the C-8 hydrogen of 72 is pseudo-axial with respect to ring C and therefore its removal by base should be further facilitated for stereo-electronic reasons[47]. Because of these two factors the C-8 hydrogen appears to be more acidic than normal, and even a weak base[48] such as DMA can rapidly abstract it although of course it is not necessary, or even likely, that DMA should be the only basic species involved in this proton removal. In other decalin systems, where excessive steric interactions are absent, the removal of a γ-hydrogen by DMA or other bases present appears to be a comparatively slow process and little or no isomerisation of the ring junction is observed[49].

The enolate 73 can undergo protonation at either C-13 or C-8. Under conditions of kinetic control, protonation will take place preferentially at the

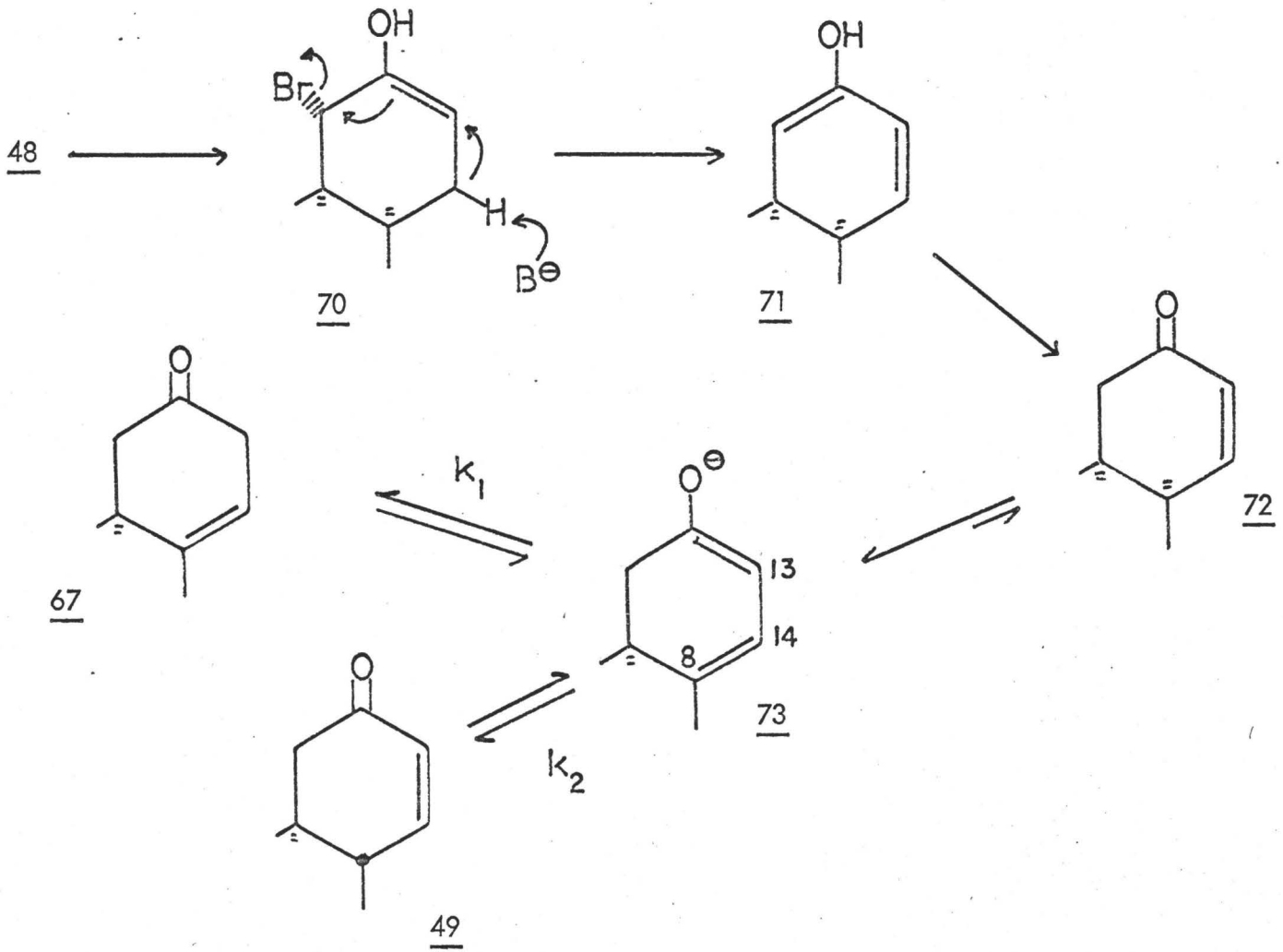


FIGURE 8 : Mechanism for the Formation of Dehydrobromination Products (I)

site of highest electron density[50], that is at C-13 (with the second order rate constant $k_1 > k_2$) and the non-conjugated ketone 67 will be formed. Under conditions of thermodynamic control, that is if there is an equilibrium between 67 and 49 the more stable ketone 49 will be formed. The predominant formation of 67 during the short reaction period shows that the reaction is largely kinetically controlled over this period. The longer, 30 minute reaction period results in principally thermodynamic control. Since the product ratio of 49 and 67 did not change appreciably for more extended reaction periods, the observed ratio of 60:14 for 49 to 67 probably represents the ratio of their stabilities in refluxing DMA.

Although the rate of the 1,2-elimination process is slow, as is noted above, it still occurs to the extent of 20% and, as in the case of 1,4-elimination, the intermediate 9(11)-conjugated ketone 74 possesses only a fleeting existence and is rapidly transformed by enolisation and protonation into the 9(11)-conjugated ketone 69, and the non-conjugated ketone 68. The ratio of 69 and 68 showed only a slight change with increasing reaction period (see Table II) and this is indicative of a situation which is approaching thermodynamic control very quickly. To achieve this, either the ketones 69 and 68 must be in equilibrium or the rate of protonation at C-11, must be comparable with the rate of protonation at C-8. The latter is considered more reasonable here, for despite the high electron density at C-11, the 11-position suffers steric interactions from both the C-20 methyl group and the

Reaction time, (min)	5	10	20	30	50
Product (%)					
Bromo-ketone 48	60	1	0	0	0
Δ-13(14)-ketone 49	1	14	40	60	60
Δ-8(14)-ketone 67	30	60	33	14	14
Δ-8(9)-ketone 68	7	16	16	16	14
Δ-9(11)-ketone 69	2	6	5	3	2
Methyl podocarpate 54	0	4	6	7	10

TABLE II

Dehydrobromination of 45 in DMA/$CaCO_3$ for various periods

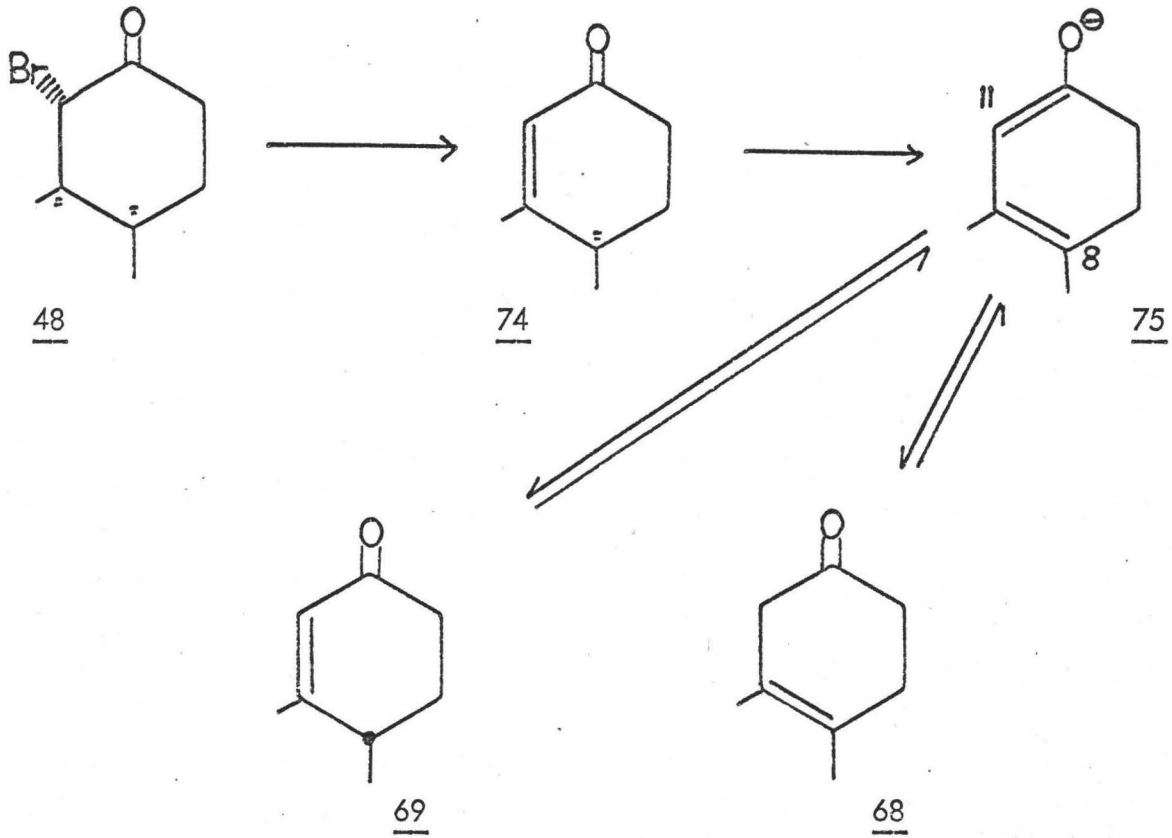


FIGURE 9 : Mechanism for the Formation of Dehydrobromination Products (11)

C-1 hydrogens, whilst the 8-position suffers only an interaction from the C-20 methyl. It is interesting to note that in contrast to the ratio of about 5:1 for 69 : 68 in refluxing DMA, the equilibrium in either acidic or basic media at room temperature is overwhelmingly in favour[24] of 69.

The only other product aside from the ketones 49, 67, 68 and 69 obtainable from the dehydrobromination of 48 was methyl podocarpate 54. It appeared to have its origin in the air-oxidation of the unsaturated ketones, since experiments performed with the reaction mixture open to the air resulted in greatly increased yields of 54 as well as polymeric materials. A consistent 3 - 4% yield of 54 appeared to be a lower limit and is probably a consequence of the experimental technique employed (see Experimental). All the products cited above had clearly resolved C-20 methyl resonance absorptions at 60MHz in their pmr spectra. The values observed are listed below in Table III (see also Table VI). Identification of the various assignments was achieved by isolation or by examination of samples from external sources as indicated.

As an additional study to determine optimum conditions for the preparation of the $\beta\gamma$-unsaturated ketone 67, and also to possibly shed light on the proton abstracting basic species in DMA, various other anions and solvent systems were investigated.

Dehydrohalogenation by high-boiling aprotic solvents was first introduced in 1953 by Holysz[51], and since that time the reaction has proved to be remarkably

Compound	C-20 CH_3 ppm*
Bromo-ketone 48	0.68
Δ-13(14)-ketone 49	0.71[a]
Δ-8(14)-ketone 67	0.55
Δ-9(11)-ketone 69	0.94[a]
Δ-8(9)-ketone 68	0.77[b]
Methyl podocarpate 54	0.97

TABLE III

Chemical Shifts of some C-20 methyl resonances

* TMS as internal standard, deuteriochloroform solutions.

a Pmr spectrum of an authentic sample from Dr. O. E. Edwards, National Research Council of Canada

b Sample from Dr. Goldsmith, Emory University

---

useful in organic synthesis[44,52]. Holysz's original findings showed that certain covalent halides such as lithium chloride and bromide promoted dehydrohalogenation in hot dimethyl formamide (DMF). He proposed that in the 4β-bromo-3-keto steroid which he was studying the chloride anion attacked the C_4-α position, whilst the small lithium cation, co-ordinated with the nucleophilic centre and served to pull off the departing bromine atom. After this halide inversion, trans E2 elimination was then facile with the β-C-5 proton. Joly and Warnant[53]

further observed that addition of lithium carbonate, (particularly with lithium bromide), further improved the reaction and reduced the extent of 1,4- over 1,2-elimination. In a later study on the kinetics of the lithium bromide reaction, other workers showed[54] that the rate determining step was attack of bromide ion on the hydrogen in the β-position to the carbonyl group.

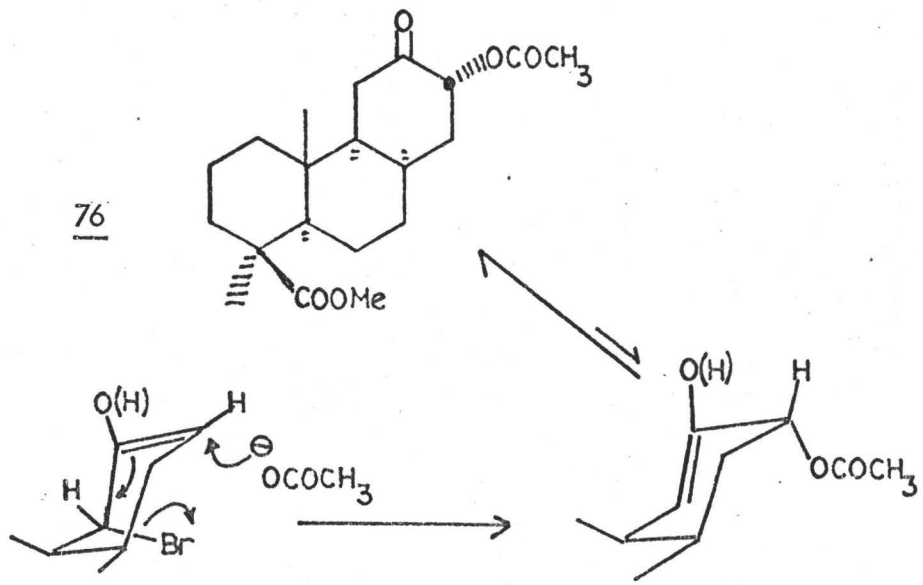
The use of calcium carbonate in the related aprotic solvent DMA, was introduced by Green and Long[44], and this system has been the subject of some study, including patent work on the crystalline form of the calcium carbonate used[55].

Thus in the present work it seemed of interest to try other anion-solvent combinations, besides the lithium chloride - lithium carbonate - dimethyl formamide combination used previously on this system. The results of using calcium carbonate - dimethyl acetamide have been covered extensively above. Surprisingly, however, the other two main combinations, calcium carbonate - dimethyl formamide and lithium carbonate-dimethylacetamide, both left the bromo-ketone totally unaffected after 10-15 minutes at reflux temperature. Plainly the reaction proceeds only as a result of a subtle balance between solvent, reflux temperature and nature of co-ordinating cation, since addition of lithium chloride to the lithium carbonate-dimethylacetamide combination which was normally unreactive, did promote dehydrobromination, although not as fast as for calcium carbonate-dimethylacetamide. The latter system apparently does not require added halide

ion for reaction, since addition of calcium chloride did not appreciably affect previous results. It is quite probable in the latter case that a small quantity of bromide ion is present in the bromo-ketone itself.

Because of the selective and rather unreactive behaviour of the bromo-ketone in aprotic solvents above, it was also of interest to determine the behaviour with certain substituted hydrazine reagents which bring about dehydrobromination, (after derivative formation with the carbonyl group) with most α-bromo-ketones[56]. With these reagents 1,2-elimination is reportedly almost exclusive, with 1,4-elimination reduced to 0.1 - 0.7% in some cases. Fairly strong steric hindrance, as for certain (C-12 and C-20) keto positions in the steroids for instance, however limits the use of the method[56].

Thus on heating the bromo-ketone with semicarbazide free base in tetrahydrofuran/t-butyl alcohol and a trace of HCl, also 2,4-dinitrophenyl hydrazine and Girard's Reagent 'T' in acetic acid buffered systems, three different but not unexpected results were obtained. The first reagent yielded unchanged starting material; in the second case a complex mixture was obtained from which no well-defined products resulted. In the third case a pure crystalline compound was isolated in 60 - 70% yield. Analysis and spectral examination left no doubt that the compound was the acetoxy-ketone 76. The pmr spectrum showed a clear triplet for the C-13β-proton as a result of an AB coupling with the C-14 protons. This product is apparently the result of a direct displacement by acetate anion as shown.



Finally, the inactivity of this bromo-ketone to 'normal', i.e. 1,2-elimination (or 1,4-elimination) was demonstrated by its behaviour with the tertiary amine, dehydrohalogenating agent, 1,5-Diazabicyclo[4,3,0]non-5-ene (DBN) which has been shown to be a potent reagent for dehydrohalogenation[57]. After heating in xylene solution at reflux temperature for 30 mins however, only 25% 1,4-elimination had taken place together with 25% aromatisation. It is of interest in this respect that Bible and Burtner obtained the conjugated ketone 49 in low yield[24] by heating for 6 h with the conventional, dehydrohalogenating amine, collidine.

Having thus obtained the $\beta\gamma$-unsaturated ketone 67 in good overall yield from the keto-ester 66 by bromination, dehydrobromination for 10 minutes and careful chromatography on silica gel, this $\beta\gamma$-unsaturated ketone was examined as a possible source of the desired key synthetic intermediate 36. It seemed

probable that oxidative degradation, by fission of the 8(14)-double bond would give an intermediate β-keto-aldehyde which would further cleave to the desired keto-acid 36.

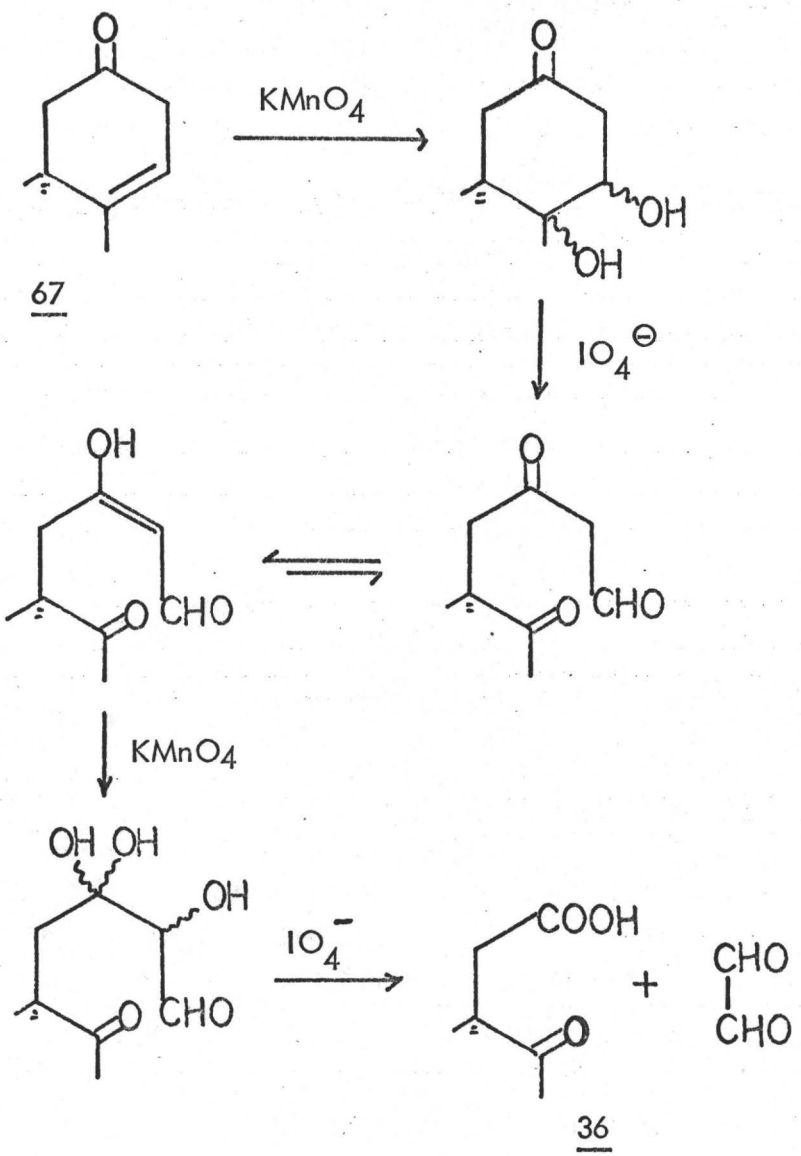


FIGURE 10 : Oxidative Cleavage of the $\beta\delta$-Unsaturated Ketone 67

This conversion was initially accomplished using the periodate-permanganate reagent of Lemieux and von Rudloff[58]. This reagent is presumed to oxidize olefins by vic-glycol formation by the permanganate at pH 7-8, followed by cleavage of the diol by the periodate. The periodate present also serves to regenerate the permanganate ion which is present in considerably less than molar amount. Although the original reactant concentrations and type of organic co-solvent[59], used with the method have been altered considerably since its innovation, it has remained a good procedure for a wide range of oxidations. Since two initial, trial ozonolyses of the $\beta\gamma$-ketone in ethyl acetate had proven unsatisfactory, our attention was turned to the Lemieux - von Rudloff reagent and a satisfactory procedure was devised whereby the keto-acid 36 was obtained in 70-80% yield. The reaction presumably proceeded by the route shown in Figure 10. This is the most straightforward mechanism to be drawn, although it is also possible to consider the cleavage of carbons 13, and 14 occurring as a stepwise process, involving two enolisations after the initial 8(14)-cleavage.

After some success with this reaction however, non-reproducibility and poor product quality/yield resulted. Similar difficulties have been noted[7] in the related system, laevopimaric acid, which was subsequently successfully converted to the appropriate products in a reproducible manner and good yield, by ozonolysis in ethyl acetate and oxidation of the product with Jones' reagent. In the present example a fresh successful procedure was worked-out, involving

ozonolysis in methanol as a participating solvent, followed by work-up with basic hydrogen peroxide. This new procedure consistently gave the keto-acid 36 in yields of 80% (crude product). The path of this reaction probably proceeds by hydroperoxide attack on the initially formed β-ketomethoxyhydroperoxide 77 (Figure 11; see Section II for further comment) followed by a 1,2 shift and hydrolysis of the resultant ester.

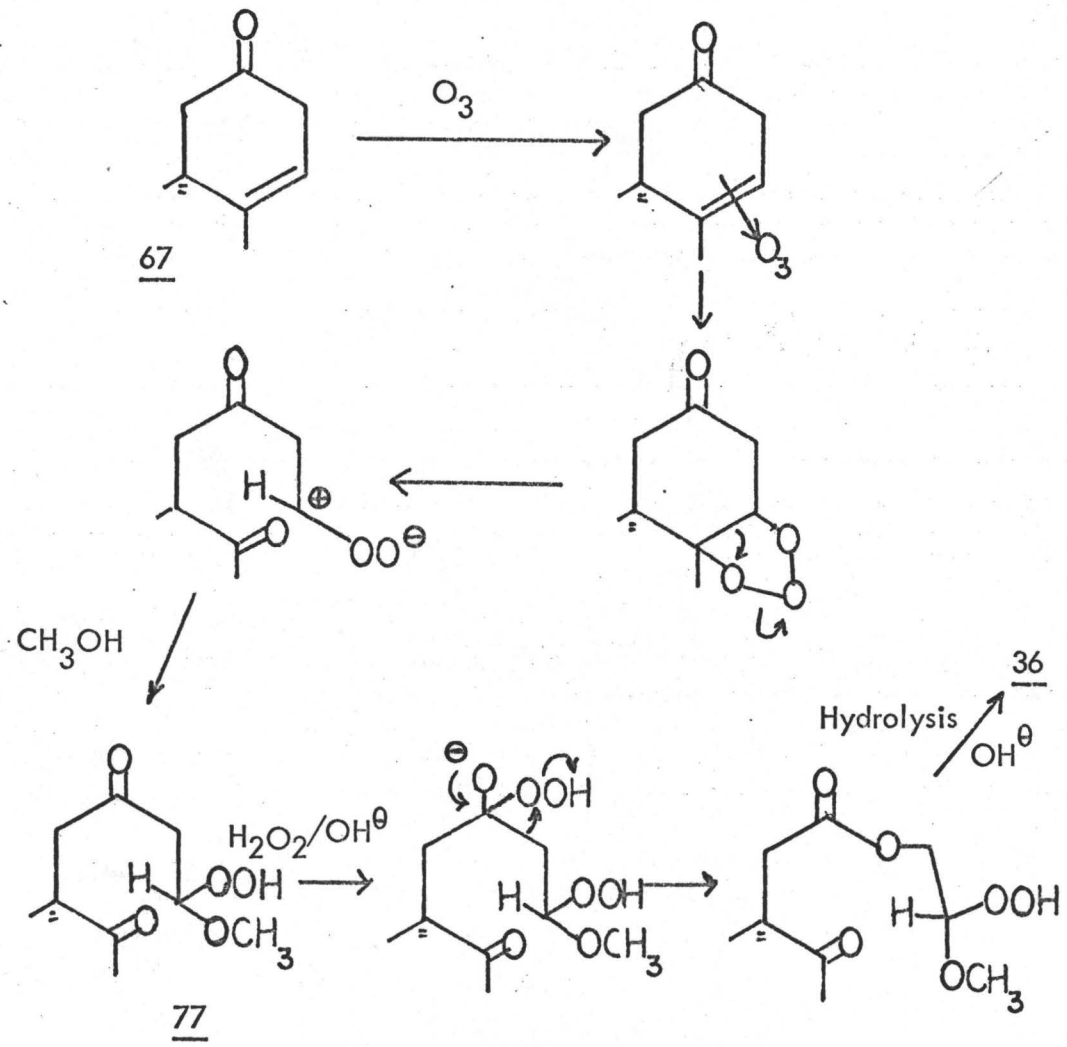
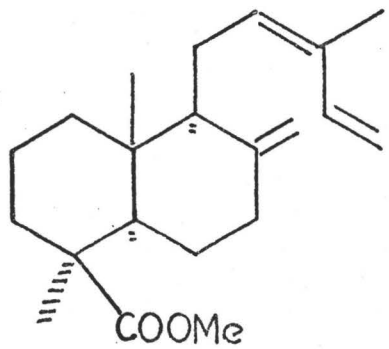


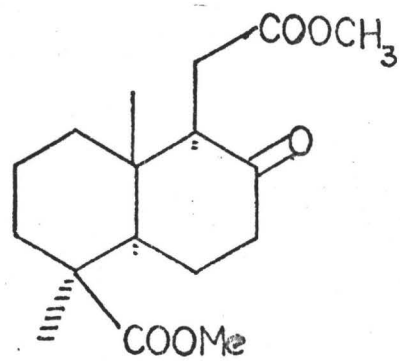
FIGURE 11 : Ozonolysis of the $\beta\gamma$-Unsaturated Ketone 67

Attempts in the present case to use ethyl acetate as ozonolysis solvent and subsequent Jones' reagent oxidation, did not give as consistently good results as found for the laevopimaric acid system[7].

The keto-acid 36 which resulted from these degradations was identical, as judged by melting-point and infra-red characteristics, with the material previously obtained[60] in 1961 as a degradation product of communic acid 78, and prior to that by Ruzicka[61].

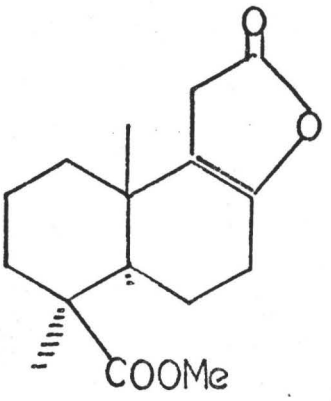


78



79

The methyl ester 79, which previously[60,61] had only been obtained as an oil has now been characterised as a solid, mp 96 - 97°. The compound forms a 2,4-dinitrophenylhydrazone as yellow needles mp 161 - 163°, in excellent agreement with the literature value[60]. The mass spectrum of the keto-acid 36 is interesting in that the parent ion at 278 is apparently due to the enol-lactone 80



80

II. Degradation of Podocarpic Acid (via Oxidation-Reduction Sequence) to the Keto-Acid 36

During investigation of the ozonolysis of the $\beta\gamma$-unsaturated ketone 67 above, in trial reactions where the total crude reaction mixture from the dehydrobromination of 48 was directly ozonised - rather than the pure compound, it was noticed that the small proportion of methyl podocarpate 54 present in the crude mixture (see Table II), disappeared during the ozonolysis reaction. It therefore seemed of interest to determine in a separate study, what products were being formed from this material.

Ozonolysis of phenols and phenoxy ethers seems in general to be a neglected field. The only example[62] of its synthetic use for selective degradation of a phenolic substrate is that recorded by Woodward et al in their synthesis of strychnine. Some studies have been made however on the behaviour of phenolic (naphthalene in particular) systems, where partial or total degradation of one ring to two carboxylic fragments has been achieved[63]. Normally phenol, and the simpler poly-hydroxy phenols are completely cleaved by ozone at room temperature to carbon dioxide, water, glyoxal, and similar fragments[64]. However as the temperature is lowered and the structure of the substrate becomes more sterically demanding the reactivity of the phenolic ring is reduced. Thus numerous examples are available in the literature where other reactive sites

(double-bonds) in a molecule have been cleaved in ozonolyses, with little or no attack on a phenol or phenolic ether present[65]. Indeed in some cases, investigators seem to have been more concerned with oxidation at the benzylic position of an aromatic ring, than attack on the ring itself[66].

Thus in general the unsubstituted aromatic ring is considered as fairly inert to ozone except where one of the aromatic 'double bonds' is effectively localised - as for example in phenanthrene[67]. The hydroxyl group in a phenol apparently also has the same effect in making the 'double bond' on which it is attached, more susceptible to electrophilic attack, and hence the first bond to react with ozone. This is born out by studies on the naphthalene phenols noted above[63c], where controlled reaction with one mole of ozone was used.

In the case of the present substrate methyl podocarpate 54, this also appears to be the course of reaction, although subsequent attack on the second 'double bond' of the ring is apparently also fast under the conditions investigated. Attempts to stop the reaction after one mole of ozone had been absorbed resulted only in products resulting from attack of two moles of ozone and unchanged starting material.

In the present section, only the results of the main synthetic sequence, that is ozonolysis of methyl podocarpate 54, and isolation of the stable hydroperoxide 55 as the initial product will be discussed. In a later part - Section V - the results of direct reductive and oxidative work-ups of the ozonolysis reaction mixture will be considered, when a number of other products were obtained.

Because of the relatively poor solubility of methyl podocarpate in methanol alone at -70°, various co-solvents were screened which combined inertness with high solvent power. In a 1945 study[68], carbon tetrachloride, chloroform, fluorotrichloromethane (Freon-11), and methylene chloride were rated as the most inert solvents to ozone in the -20-0° temperature range. Of these and other solvents used in admixture with methanol as solvent system for methyl podocarpate, methylene chloride at 1:1 ratio with methanol proved most satisfactory. Although Freon-11 is probably more chemically inert, its lower solvent power proved deleterious. This finding was a direct result of the observation that a certain minimum concentration of substrate in solution was necessary to react with all the ozone as it entered the solution. The use of too high an ozone concentration in the air stream also had the same effect of 'over-oxidising' the system. It seems in short that benzylic attack occurs if the rate of ozone flow is greater than that required for reaction with the two reactive bonds of the aromatic ring.

It is probable that the unique selectivity of ozone for the 12(13) and 14(15) bonds of the ring, leaving the 9(11) bond untouched, is due to considerable steric hindrance to the latter bond provided by the C-20 methyl group. The absorption of two moles of ozone only was quite clearly discernable when the contents of the reaction vessel started to turn pale blue due to excess ozone at the end of the reaction. It is notable that even continued passing of ozone into the system after this point, so that some considerable excess is present, did not

cause further reaction of the product, so that the general reproducibility, using standard voltage and gas flow settings on the ozonizer (see Experimental), was very good.

On removing excess ozone with nitrogen, and then solvent removal, an off-white, crystalline product was directly obtained. A considerable body of spectral and chemical information leads to the assigned hydroperoxide structure 55. The infrared shows conjugated five-membered lactone, 1765 and 1640 cm^{-1}, and hydroperoxide, 3500 and 927 (870) cm^{-1}, absorptions. Conjugation is confirmed by the 218 mμ (ϵ, 11,000) π-π^* transition in the ultraviolet and by the single unsplit vinylic proton in the pmr spectrum at 5.79 ppm. The pmr spectrum also clearly indicates one hydroperoxide proton at 9.08 ppm which is exchangeable but does not react with diazomethane. The chemical shift agrees well with the few examples on record[69] for this type of proton. The compound analysed for 98% active oxygen, by iodine determination.

Finally, nuclear Overhauser measurements show no area increase of the C-11 vinylic proton on irradiation of the C-20 methyl group. Inspection of a molecular model clearly shows that the C-11 proton and the C-20 carbon are 3.88 Å apart when ring-C is down, and the hydroperoxide group β to ring-B so that no NOE is expected (cf. discussion above) if this is the configuration. The distance is 3.2 Å if the hydroperoxide group were down, which would give a definite positive effect.

The mechanism of the formation of the hydroperoxide 55 can be rationalized by reference to the mechanism of Criegée[70], a refined version of which[71] is still considered the most successful for the interpretation of the more subtle stereochemical results of ozonolysis[72]. With most carbon-carbon double bonds, at least in protic solvents, the predominant initial ozone attack seems to be to give a π-complex 81 (Figure 12), followed by electron shifts to produce the five-membered, 1,2,3-trioxolane ring 82 intermediate[73]. The direction of cleavage of this ring is apparently controlled mainly by the inductive effects of the substituents on the ring[69a, 73] although the most recent work suggests that mesomeric effects may also have a part to play[72]. It seems clear that the zwitterion which is preferentially formed (83 or 84) is the one whose environment is better able to stabilise the positive change by increasing the electron density in the vicinity of the carbon cation, via inductive and mesomeric effects.

In the present example (Figure 12) the zwitterion from cleavage path b, 84, is probably favoured over that from path a, 83 since, although both can exist in tautomeric forms (86 and 88), the intermediate 83 also has the destabilizing influence of the electron withdrawing 12-hydroxy group. The argument against resonance stabilisation of the products[69a] is seen from a consideration of the highly exothermic nature of these decompositions (ie. ozonides from cis olefins are extremely unstable) so that the transition state would be expected to be very reactant-like by the Hammond postulate[74]. Hence

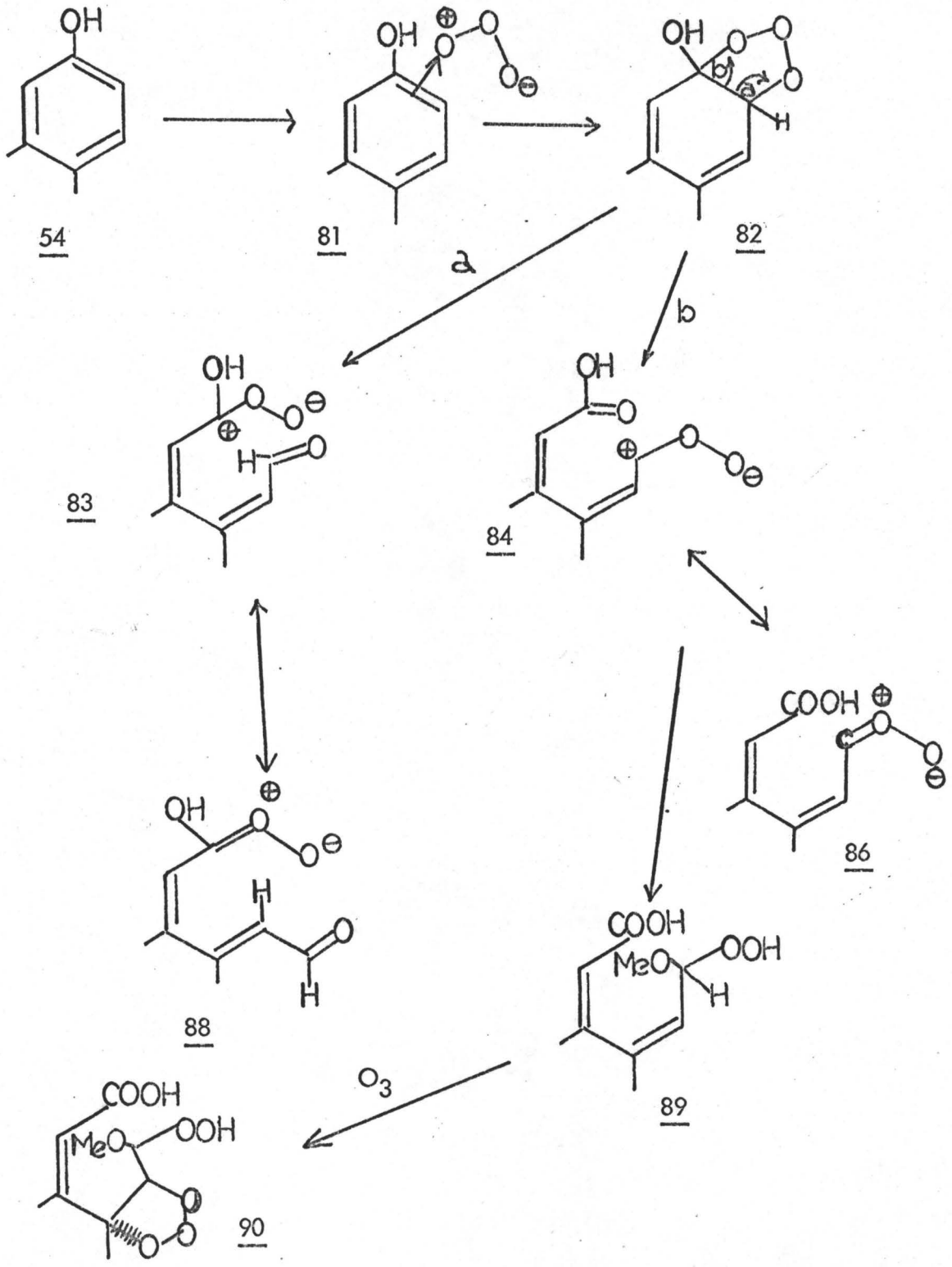


FIGURE 12 : Mechanism for the Formation of Hydroperoxide 55 (I)

relative resonance stabilities of the products should be almost irrelevant[69a].

It is also possible that methanol itself, by participation in the ring opening process and circumvention of the Criegée zwitterion, thus influences the direction of cleavage. However available evidence[69a, 72] suggests that the highly exothermic decomposition of the primary ozonide 82, precedes any possible interaction with methanol to 92, although the actual trapping of the zwitterion itself is very rapid.

Assuming that 89 is the primary stable product, a further mechanism for the mode of attack of the second mole of ozone must be deduced. Making the reasonable assumption that attack on the 8(14)-bond is from the much less sterically hindered, α-face of the molecule, 90 should be the initial ozonide formed. If as expected, decomposition to a zwitterion is fast, two possible paths, a and b, are again open. Presumably here the polarisation of the unsaturated acid system provides greater inductive stabilisation of 91, than occurs with the electron donating oxygens in the alternative two-carbon fragment from pathway a, and thus path b is preferred. It appears that subsequent internal quenching of the cationic centre by the carboxylate group to the final hydroperoxide 55, takes precedence over methanol participation since other products which would be expected by the latter process (as yet unidentified) make up only 15% or less of the reaction mixture.

It is interesting to note that the presence of the 9(11)-double bond is apparently the main factor stabilizing the cationic centre at C-8 leading to path

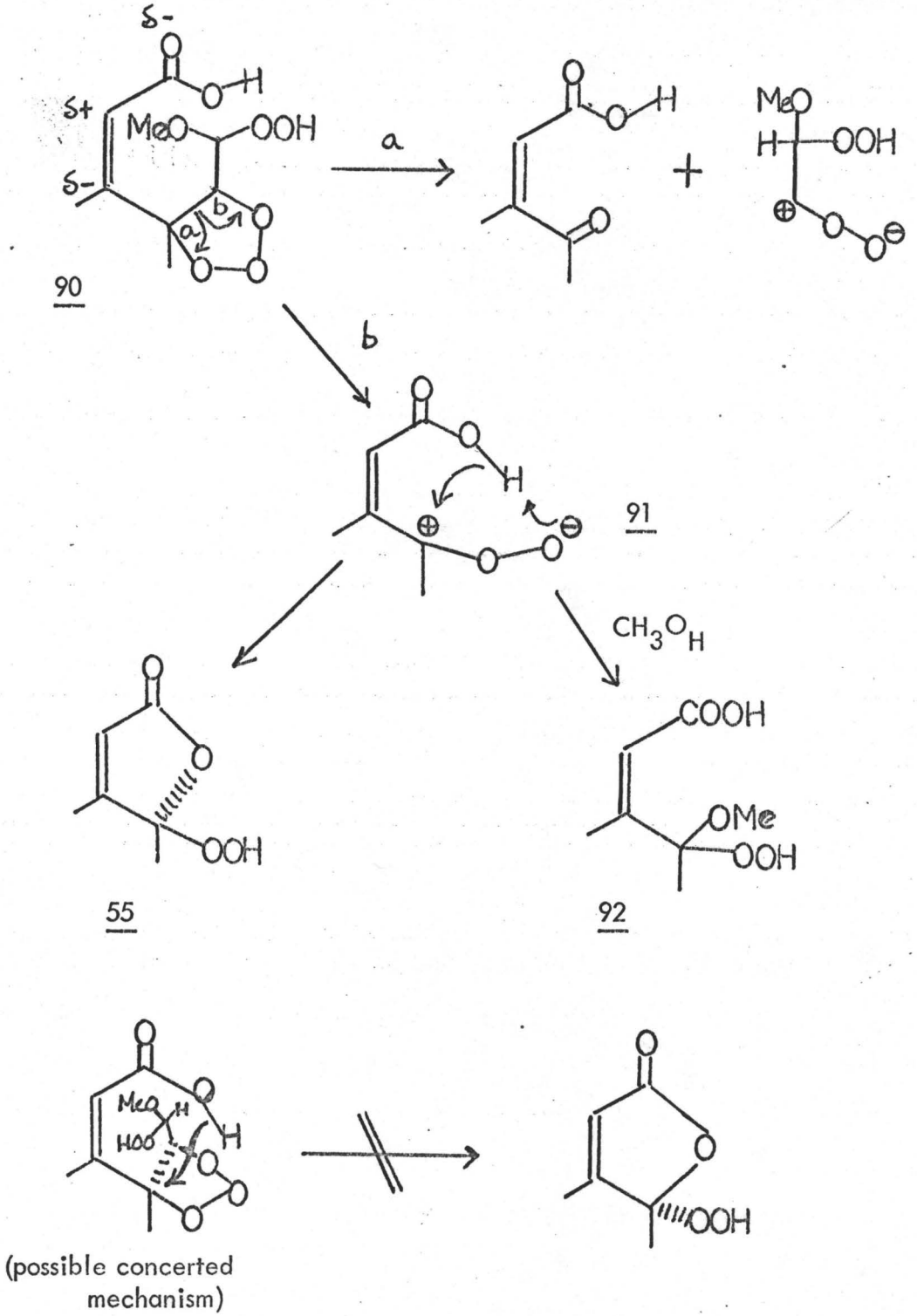


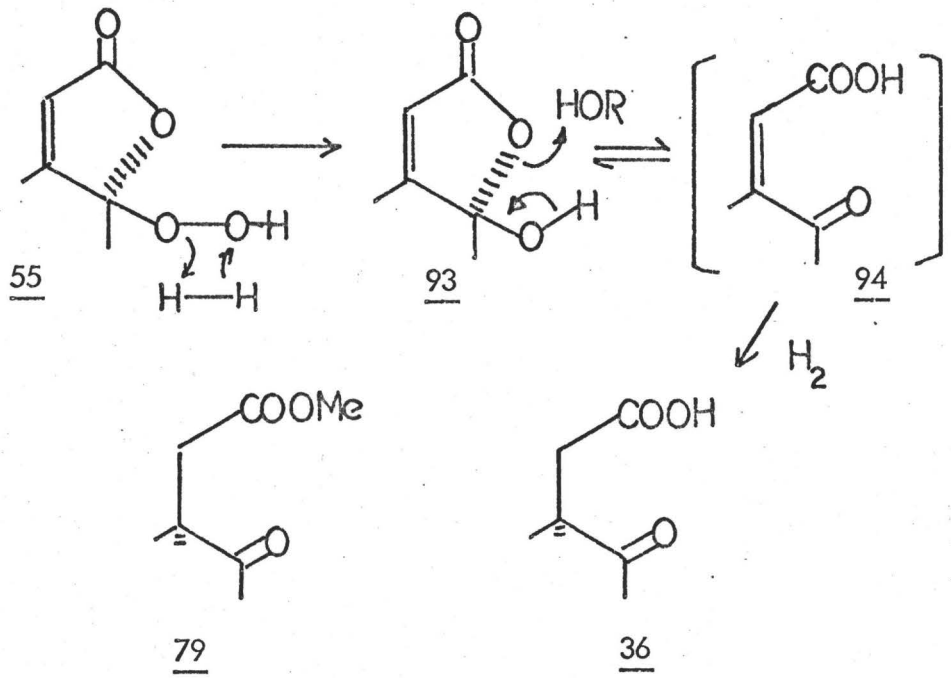
FIGURE 13 : Mechanism for the Formation of Hydroperoxide 55 (II)

b, since in the similar case without this unsaturation (see Section I, Figure 11) pathway a is preferred leading to a keto group at C-8. Significantly the final stereochemistry of the product requires underside attack by carboxylate anion leading to a β-hydroperoxide, and this would be impossible if such attack was a concerted mechanism on the α-ring ozonide itself (Figure 13) by the carboxylate group, without the intermediary of a zwitterion. An interesting example of a similar intramolecular alkoxy-hydroperoxide formation during ozonolysis, but in an 'inert' solvent - ethyl acetate, has been recently noted[75]. In the present case an experiment using ethyl acetate as solvent led to an unidentifiable mixture of products. This was probably due to the reactivity of the hydroperoxide itself together with decomposition products of the solvent.

The results of reaction of various reducing agents on the hydroperoxide are discussed elsewhere (Section V), however the catalytic reduction used to convert the hydroperoxide to the keto-acid will be discussed here in connection with the main synthetic goal.

Catalytic reduction as a means of conversion of hydroperoxides and ozonides to useful products has been used extensively[76]. Accordingly we elected to try palladium-on-charcoal reduction with hydrogen at low (1-3 atmospheres) pressure. Hydrogen was expected to cleave the peroxide bond, whereupon the lacto-hemiacetal 93 formed would open up in a protic solvent such as ethanol to give the keto compound 94 as its more stable isomer. Simple cis addition to the α-face by catalyst was presumed would lead to the desired

keto-acid 36. On performing the experiment we were therefore gratified to find that the keto-acid 36 was indeed produced in greater than 90% yield. This new sequence (ozonolysis and catalytic reduction) therefore achieved in two, high-yield steps, the synthesis of the desired synthetic intermediate 36, which previously (see Section I) had required six steps.



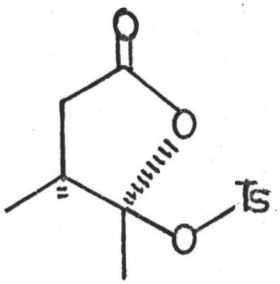
An interesting point arises concerning the mechanism of the above reaction however. Subsequent studies (see Section V) have shown that the lactone-hemiketal 93 - which has been isolated by sulphite reduction of 55, is quite stable itself, in the solid state or in aprotic solutions. Further, when the above catalytic reduction is carried out in methanol as solvent, the methyl ester 79 is produced albeit incompletely, rather than the acid. Since some examples

of esterification of isolated carboxyl groups by methanol/catalyst systems are known[77], it is assumed that solvent is probably not involved in the ring opening itself, and that the latter process occurs after reduction of the 9(11)-double bond. That is, the proposed mechanism above is incorrect, and the saturated lactone-hemiketal analogue of 93, ring-opens spontaneously to the keto-acid 36 (see Section V for further discussion on this point).

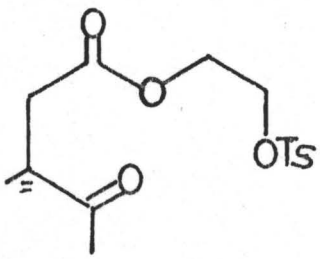
III. Conversion of the Keto-Acid 36 to 12-Hydroxylabd-8(17)-en-19-oic acid 37 and Methyl 12-Ketolambertianate 61

In the two previous sections the work performed to obtain the key intermediate, keto-acid 36 was described. It was shown that this compound may now be obtained in three steps, conveniently and quickly in 50-60% yield from podocarpic acid. As reported in the Historical Introduction, the initial synthetic plans consisted of protection of the C-8 carbonyl group of 36 as its ketal and elaboration of the required side chain at C-12, followed by final conversion of the carbonyl group, to the exocyclic methylene group of the appropriate diterpene. The difference between the projected sequence and the final, successful synthetic plan, bears eloquent testimony to the still primative state of the science of predicting organic reactions in structurally 'complex' molecules.

The initially projected step of ketalisation was approached in the usual way, by refluxing in toluene with excess ethylene glycol and p-toluenesulphonic acid as catalyst. Inspection of aliquots however revealed a very slow reaction rate and the reactions which had proceeded gave at least two compounds. Work-up and full examination after twenty-four hours reaction revealed 30% starting material and approximately equal quantities of the two major products which pmr and mass spectral analysis clearly indicated contained the toluenesulphonate moiety, and to be probably 95 and 96, although the evidence is not conclusive.



95



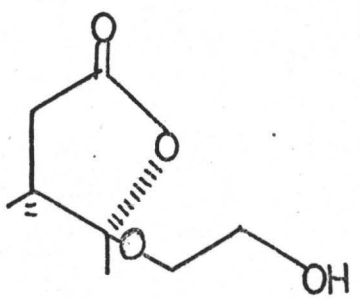
96

Further when the methyl ester 79 was reacted in a similar way a single product was obtained which pmr and mass spectral analysis showed could be the structure 97, although again this is not clear. The ease with which this system forms a five-membered lactone is noted elsewhere, but what was also apparent was the futility of trying to prepare a ketal of C-8. Hence consideration was next given to elaboration of the exocyclic methylene group before attachment of the side chain to the molecule.

The most obvious reagent to try first seemed to be the methylenetriphenylphosphorane ylid reagent of Wittig. The reagent is generated by addition of a strong base such as an alkyl lithium or potassium tertiary-butoxide to triphenylmethylphosphonium bromide[78]. Using a procedure[79] utilizing potassium tertiary-butoxide as base the keto-acid was reacted in tetrahydrofuran/tertiary butanol. Completely unchanged starting material was obtained. Failure

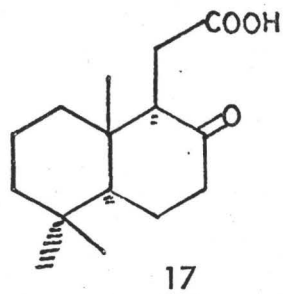
also resulted from reactions where heating was employed or where the ylid was generated with n-butyl lithium or methyl sulphinyl carbanion in dimethyl sulphoxide. This latter method of generation has been reported[80] to give much faster reaction with Wittig reagents, often with superior yields. However we again failed to obtain any reaction with the keto-acid 36. Also these conditions allow selective reaction with the ketonic function of keto-esters[80]. Accordingly the ester 79 was reacted but again to no avail.

It seems probable that the keto-acid 36 is behaving in a very similar fashion to the compound 17 which was found[5], even under forcing conditions of various refluxing solvents, to be completely inert.

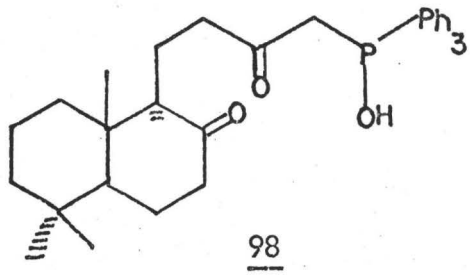


97

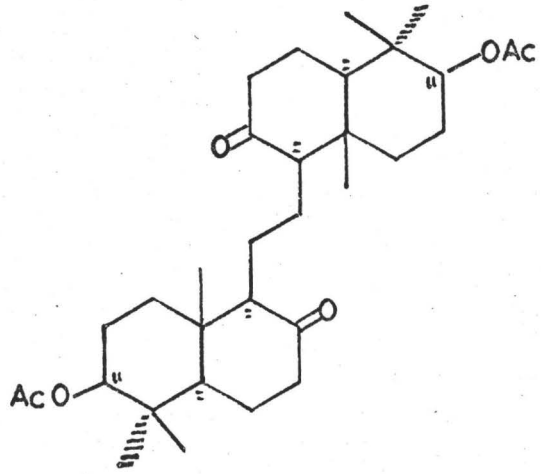
When the corresponding methyl ester was reacted[5] the organophosphorous compound 98 was obtained rather than ketone reaction. Stork has also noted[81] the failure of the Wittig reaction with the onocerin precursor 99.



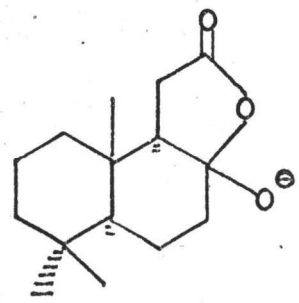
17



98



99

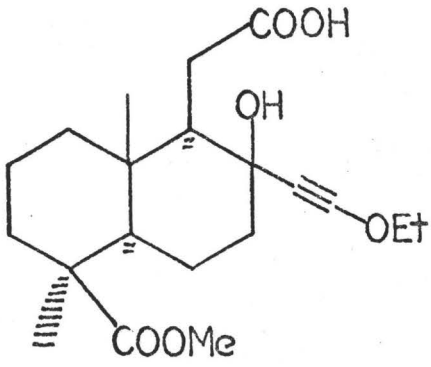


100

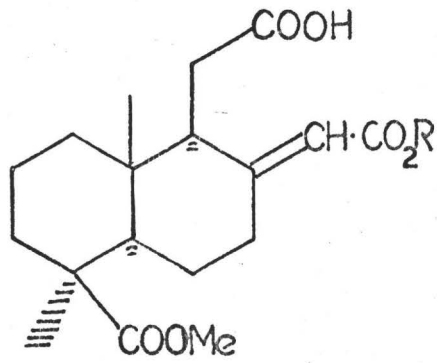
This failure of a 8-ketone to react even under forcing conditions may perhaps be attributed to the presence of the anion 100, enolate formation by the ketone, or simply to the large steric requirement of the Wittig ylid, with its three phenyl groups.

A recently reported[82] simple method for generation of exocyclic methylene groups, utilizing gem-organometallic derivatives such as methylene magnesium iodide $CH_2(MgI)_2$, generated from methylene iodide and magnesium analgram, was also attempted on the keto-acid 36 and its ester 79. However again pure starting material resulted. At this point, there seemed little hope of success -

with the two major types of condensation reactions involving carbanions - left to try; namely the phosphoric acid bis-amide reaction of Corey[83] and the 'formylolefination' method of Nagata[84]. We were thus resigned to the Stork procedure[81] involving treatment with lithium ethoxyacetylide at -20° to give an acetylenic carbinol 101, hydration to an $\alpha\beta$-unsaturated ester 102, base hydrolysis and decarboxylation. This procedure had been used previously in the synthesis[6] of the C_4-epimer to lambertianic acid 38, - antipodal polyalthic acid 23.



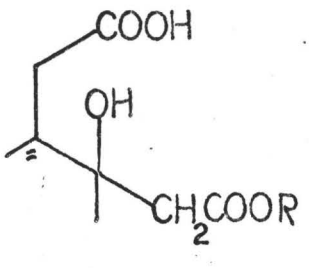
101



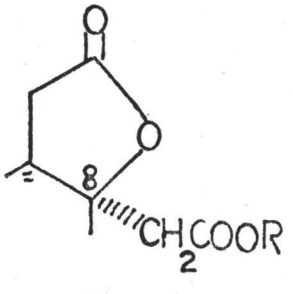
102

Before attempting the above conversion however it was decided to try a Reformatsky reaction as a more straightforward and cheaper route to the $\alpha\beta$-unsaturated ester 102. We were surprised and gratified therefore in view of the above evidence to find that the reaction proceeded readily, in benzene or toluene under reflux, with ethyl or methyl bromoacetate and activated zinc[85]. The product from the reaction was the five-membered lactone-ester 56 (R = CH_3).

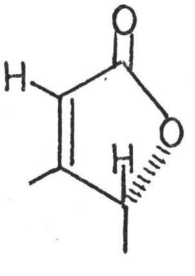
The configuration at the C-8 carbon is not certain but it seems probable that the ester group is down (α) from a consideration of the mechanism of its formation. The production of this lactone rather than the 'normal' hydroxy-ester 103, is easily rationalized by the mechanism shown below. Attack by the organometallic derivative is probably from the less hindered α-face of the molecule to give the anion complex, 105 which then undergoes anionic attack at the C-12 carbonyl with expulsion of $OH^{\ominus}$ ion, probably in its complexed form with zinc bromide as shown. The zinc bromide would be present in the reaction mixture from the beginning due to reaction between the metal and the bromo-ester.



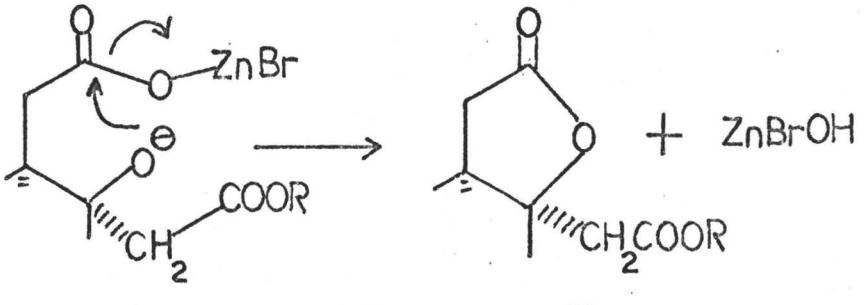
103



56

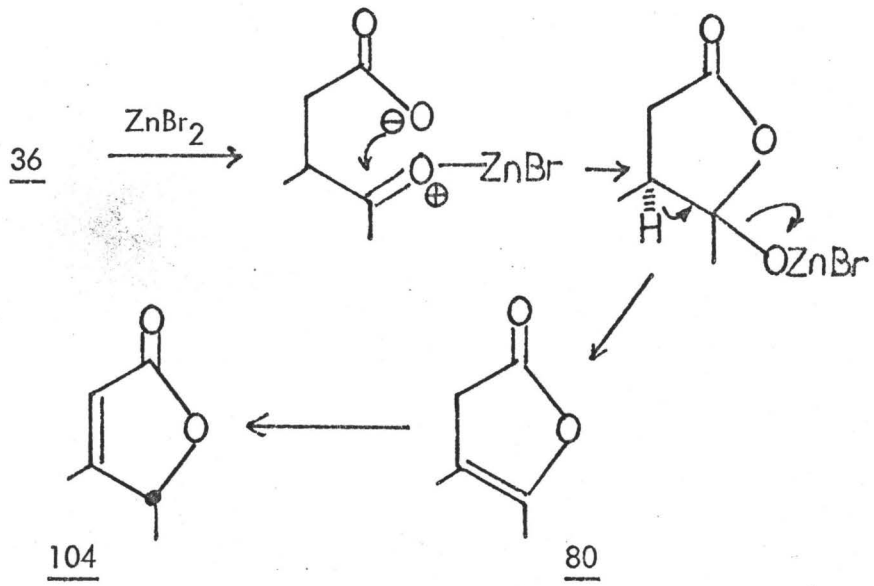


104



105 56

The results obtained using different solvents and esters are recorded in Table IV. A side-reaction is also apparently competing with the main reaction, which gives rise to the unsaturated lactone 104. The formation of the lactone 104 can be rationalized by attack of zinc bromide on the keto group of starting material followed by carboxylate participation to close the ring, 1,2-elimination with expulsion of -OZnBr and isomerisation to the conjugated product. It seems that the activation energy for this latter reaction overall is less than that for the main reaction since the proportion of lactone 104 increases on going to the higher boiling solvent toluene, from benzene (Experiments 4 and 3 respectively). Also, for the same reason, the side-reaction is favoured over the main reaction as the steric bulk of the attacking ester increases. It is interesting to note that the introduction of dimethoxyethane (DME) as co-solvent reduces lactone 104 formation to zero.



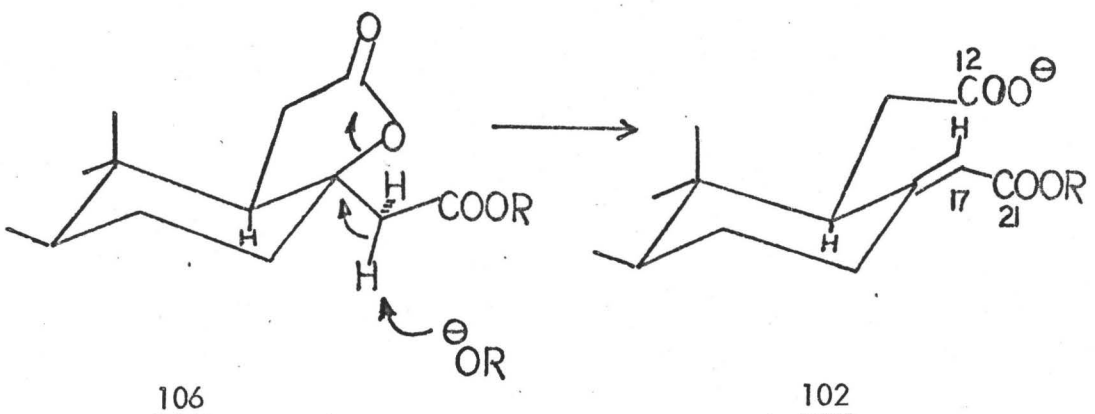
Experiment No.	α-bromoester	Solvent	Product (%)		
			lactone-ester 56	unsat. lactone 104	st. material 36
1	$BrCH_2COOCH_3$	Benzene	75-80	5	10
2	"	Benzene/DME (3:1)	90-95	0	5
3	$BrCH_2COOC_2H_5$	Benzene	70	5	20-25
4	"	Toluene	10	50	40
5	$BrCH_2COO^tBu$	Benzene	20	40	20

TABLE IV

Results of Reformatsky Reactions on the Keto-Acid 36

This is taken as confirming the fact that $ZnBr_2$ or a similar Lewis acid species is involved. Here DME is an excellent co-ordinating solvent and would be expected to effectively isolate Lewis acid species from co-ordinating reactions such as that shown above.

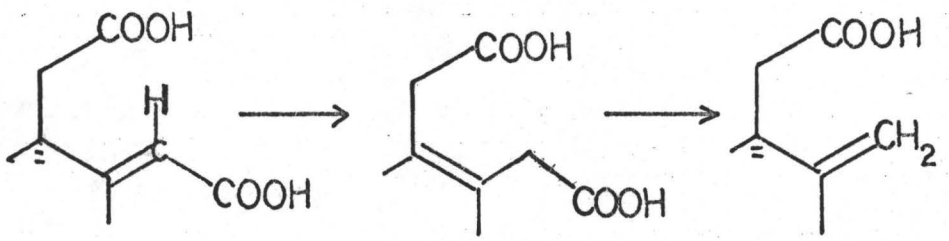
Since the keto acid 36 could now be converted in high yield to the lactone-ester 56 (R = CH_3), this new, two carbon chain extended intermediate, was of great interest as a potential source of the $\alpha\beta$-unsaturated ester 102 (R = CH_3) previously planned via the lithium ethoxyacetyline route. Accordingly both the methyl and ethyl esters were treated in their respective dry alcohols with sodium metal for two hours at reflux. Spectral analysis and thin-layer chromatography, which revealed formation of the desired product in high yield, also indicated that the 8(17) double-bond isomer distribution was at least 95% in the direction indicated below 102, although the melting-point range of the analytical sample showed that a little of the double bond isomer was present.



106 102

The elimination is thus apparently highly stereospecific resulting from proton removal by $^{\ominus}OR$ when the ester side-chain is in the configuration shown as 106, when steric interactions between the ester and lactone ring are at a minimum.

The parent diacid 57, of acid-ester 102 was obtained easily by base hydrolysis of either the lactone-ester 56 directly or of the acid-ester 102. Again, elimination with the lactone-ester 56 by hydroxide ion, as with alkoxide, led to at least 95% of the double bond isomer shown as 57, as detectable by pmr analysis. Hydrolyses of both compounds gave as 5% of the reaction mixture an unknown compound which had no vinylic protons and C-20 methyl absorption at 0.80 ppm which suggested an 8(9)-double bond (see Section VI). That the compound was the isomeric $\beta\gamma$-unsaturated acid 107, later became clear when it was found to be an intermediate in the decarboxylation of 57.

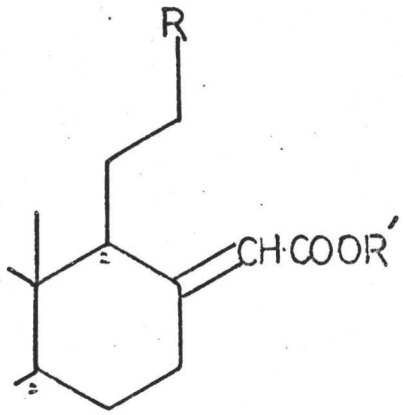


57 107 58

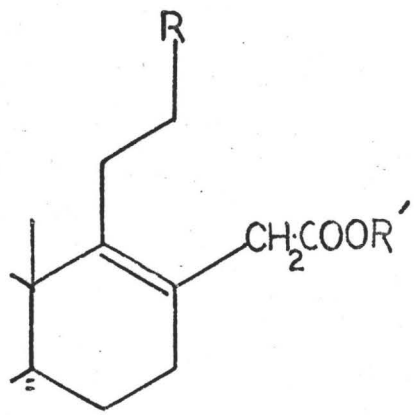
The decarboxylation of the diacid 57 was successfully carried out on a scale of 20 mg - 2.0 g, (using a procedure similar to Stork's[81]) - which utilized copper chromite catalyst in quinoline near the boiling point (238°). There seems no a priori reason why the scale of this reaction cannot be considerably increased

further without loss of yield or purity. The reaction was found to proceed with the best overall yield of product 58, when the temperature was at 230°, with a minimum of catalyst (2.5%) and reaction time was for approximately 1.25 hours. Examination of the reaction mixture after shorter periods of time at this temperature, revealed substantial quantities of the intermediate acid 107 mentioned above. That this acid was indeed the principal intermediate of the reaction, was demonstrated by its disappearance as the reaction proceeded.

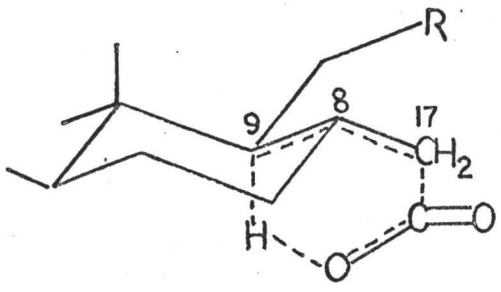
The above observation is in accord with the likely mechanism for the reaction. $\alpha\beta$-Unsaturated acids are known[86] to decarboxylate thermally, via their $\beta\gamma$-unsaturated isomers. Thus in the onocerin precursor of Stork[81] 108, the most stable $\beta\gamma$-isomer (of the two possibilities) is the 8(9) isomer 109. On decarboxylation, stereospecific introduction of the carboxyl proton at C-9 in the axial (α) position allows continuous overlap of the developing sp^3 orbital at C-9 with the p-orbitals of the incipient C-17 methylene group (116), and this process is therefore thought to be favoured[81], leading to clear formation of one isomer only. The same considerations apparently hold in the present example 111, and in another reported related system[6]. It will be noted that in the present example, the other C-12 carboxyl group is also in a $\beta\gamma$-position for elimination when the double bond is at the 8(9)-ring juncture. The apparently overwhelming preference for C-17 over C-12 decarboxylation, may be explained on steric grounds. With the C-12 carboxyl group in the best conformation for proton



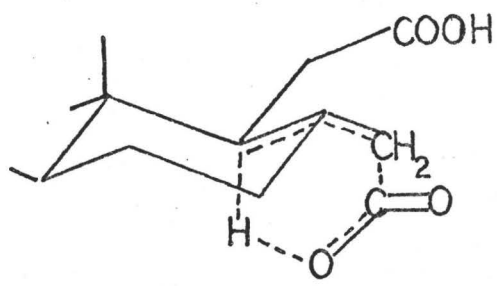
108



109



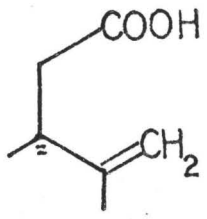
110



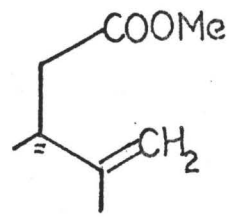
111

addition at C-8, from above (axial) or below (equatorial), - a severe interaction (within the van der Waal's radii) between the C-1 equatorial and C-11 protons takes place. Further if the argument above for axial proton transfer is valid - (which has to take place from the top β-face at C-8) - then an additional steric interaction between the C-20 methyl group and the incoming carboxyl must occur. The net effect of these interactions is thus to reduce the rate of this reaction pathway to negligible proportions.

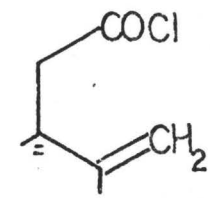
Experimentally, under the conditions cited above, some 10 - 20% hydrolysis of the C-19 methyl ester occurs; this is not a serious drawback however since the product 58 is most easily purified and isolated as its methyl ester 112.



58



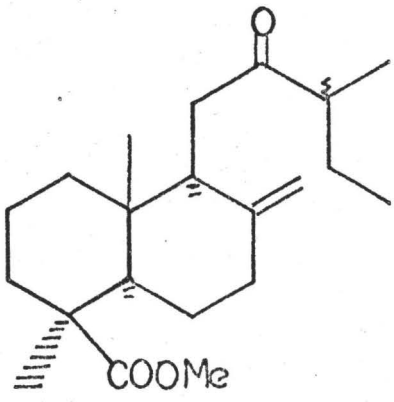
112



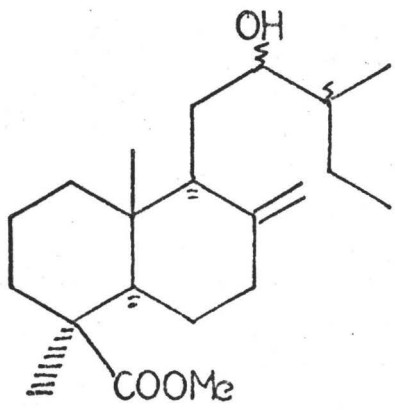
60

Thus treatment of the crude acid product with diazomethane and chromatography on Florisil served to give a 61% yield of pure crystalline ester 112, which could be quantitatively rehydrolysed to the olefinic-acid intermediate 58. The 40 - 50% overall yield thus obtained from the keto-acid 36, compared more than favourably with the ca. 30% yield obtained for the exocyclic double bond synthesis by Pelletier's group[6], with the antipodal polyalthic system 24 using the lithium ethoxyacetylide route.

The first and principle aim of the work had thus been achieved with formulation of a high yield five step synthesis of the olefin-acid 58 from methyl podocarpate 54. It now remained to demonstrate the potential of 58 as a precursor to labdane diterpenoids by elaboration of the C-12 side chain. As intimated in the Historical Introduction the first example chosen for synthesis was 12-hydroxylabd-8(17)-en-19-oic acid[17] 37, in view of the simplicity of the side chain in this molecule. The natural product was reported[17] isolated as a mixture of two, erythro and threo, alcohols and was characterised as a mixture of C-19 methyl esters. It was envisaged that use of sec-butyl lithium (Alpha Inorganics, Inc.) should yield a ketone mixture enantiomeric at C-13, 53. Reduction of the ketone with a suitable complex hydride reducing agent was then planned to yield the methyl ester of the natural product 113 as a major or minor part of a mixture of alcohols.



53



113

Two methods were first considered possible for elaboration of the ketones 53 from 58. Principally, reaction of the acid chloride 60 with sec-butyl cadmium, derivable in principle[87] from sec-butyl lithium by exchange with anhydrous cadmium chloride should yield the appropriate ketone 53 with no further attack at the ketonic function[87]. More simply, certain ketones have been prepared by direct reaction between carboxylic acids and alkyl lithiums. This simple and facile reaction seems to have met with very little exploitation since its initial observation in the 1930's[88]. In a study[89] with methyl lithium, Tegner found that reaction with cinnamic acid or its preformed lithium salt gave equal (70%) yields of ketone in ether at reflux, and demonstrated the general utility of the method for many although not all types of carboxylic acids with methyl lithium.

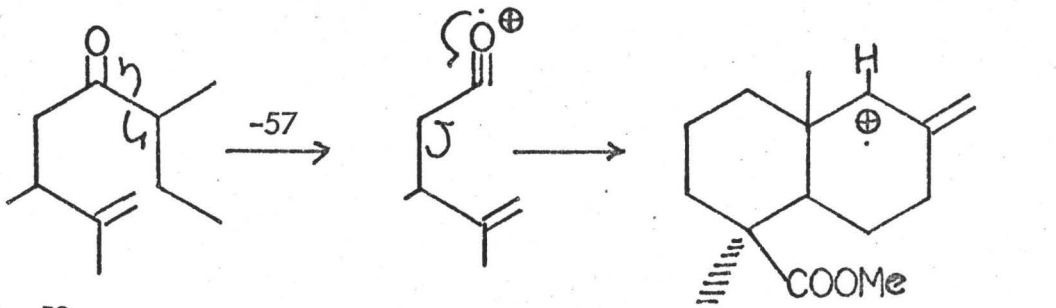
It seemed appropriate therefore to attempt this straightforward reaction first of all. Accordingly a sample of 58 was stirred with four moles excess sec-butyl lithium in ether for one hour at 0° plus a further hour at room temperature. Pmr inspection of the acidified product showed 80% of the starting material together with 20% of a new component. Further experimentation showed that an optimum of 60% of the product was obtained after reaction with one addition of excess reagent overnight at room temperature. In one experiment utilising several repeated additions of fresh reagent, a small amount of side reaction to unknown products took place and no improvement in yield resulted. Bicarbonate extraction of the product in order to remove starting material met with difficulty however,

even when the crude product was stirred for some thirty minutes in an aqueous, ethanolic solution. The use of bicarbonate only for this extraction was necessary since the C-19 ester in both components had been totally hydrolysed to acid by excess sec-butyl lithium in the course of the reaction, and this acid function is soluble at pH above ca 9. The latter somewhat unexpected process apparently proceeds by displacement at carbon in analogy to the behaviour of hindered esters with other strong bases in aprotic systems[90], although precedent in the case of alkyl lithiums is not readily available.

The apparently low acidity of the C-12 carboxyl function in the starting material 58, as evidenced by incomplete extraction by bicarbonate, had been previously experienced also in preliminary work-up of crude decarboxylation products from 57. Accordingly in the present case the crude reaction product containing 58 and ketone-acid 114 was esterified with diazomethane and chromatographed on 'Florisil' to give 50-60% of the ketones 53 as an oil. This mixture of 13R and S - ketones had identical C-20 methyl chemical shifts in the pmr spectrum. The mass spectrum gave good evidence for the assigned structure, showing a molecular ion at 334 and peaks corresponding to loss of methyl, carbomethoxy, butyl ($C_4H_9^+$) arising from C-12, C-13 cleavage and a base peak at m/e 235 which corresponds to the stable ion 115. Further prominant peaks at m/e 175/177 were visible due to loss of the C-19 carbomethoxy group from 115.

Having established the structure of 53 we undertook to reduce it to the natural product 37. In an attempt to produce a preponderance of one alcoholic

isomer (ie. that arising from attack of reagent from the direction of least steric hindrance) - in the hope of identifying the alcohols in the natural product, the highly sterically demanding, lithium tritertiarybutoxyaluminium hydride was used first.



53 → 115 + $CH_2=C=O$

On reduction in dimethoxyethane, overnight at room temperature, using two moles excess reagent only, some 30% reduction had taken place as judged by pmr inspection. The reduction was more conveniently carried out with excess sodium boronhydride at 50°.

The product showed two distinct sets of exocyclic methylene absorptions in the ratio of 7:3, a proton α to the C-12 hydroxyl group at 3.6 ppm (and very broad), presumably due to multiple coupling, and the OH peak under the methylene envelope, detected by exchange with D_2O. The C-20 methyl peak was indistinguishable from that of a pure compound with a half-height width of 1.5Hz at 60 MHz.

However the spectrum of the methylated sample was markedly different from that in our possession[91], obtained for the methyl ester of the natural product. In particular, the exocyclic methylene absorption exhibited different chemical

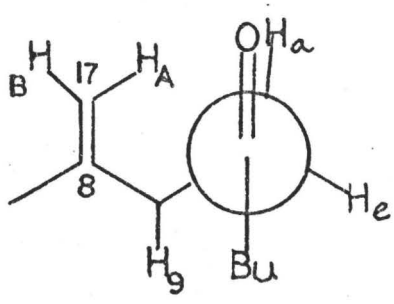
shifts and also more markedly, the proton absorption α to the hydroxyl function was totally different. In the natural product this absorption occurs as a doublet J=7Hz, 4.14 ppm for one isomer together with a broad singlet at 3.71 ppm for the other. The two isomers were present in a 65:35 ratio respectively. The rest of the spectra for the natural and synthesised products were very similar but not superimposable.

Unfortunately at the time of writing, further detailed spectral data or a sample for comparison of the natural product were not available. Thus until such data are available definite conclusions cannot be drawn; at this time however it appears that the isolated[17] natural product is not 12-hydroxylabd-8(17)-en-19-oic acid 37 and that the hydroxyl function is elsewhere in the molecule. The detailed spectral results obtained for the synthetic methyl ester of 37 (113) are recorded in the Experimental section, but it is relevant to point out here the mass spectral evidence for the assigned structure, which must in any case follow from the structure of the precursors. The spectrum showed a molecular ion 336 (at 200°), M-H_2O, M-methyl and a prominant peak of M-C_4H_9 showing facile C-12, C-13, α-cleavage to the alcoholic function. In addition to peaks showing simultaneous loss of water, C_4H_9 and carbomethoxy, and α C-11, C-12 cleavage, a base peak at m/e 235, the ion 115, was observed as found in the case of the ketone 53. In this case dehydration is followed by facile allylic cleavage of the C-9, C-11 bond to ion m/e 235.

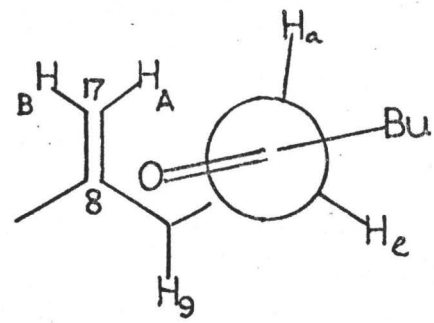
Before leaving these two alcohols consideration of their relative configurations at C-12 and C-13 is in order and the question of their relative

abundance as a result of hydride reduction of the ketone 53. A detailed consideration of the conformations available to the side chain in 53 and 113 leaves no doubt that the 11(12) bond is orientated towards the right (as drawn in conventional two dimensional diagram 113) where the 11 protons are in axial and equatorial positions in the same manner as if the side chain were part of a normal six membered (chair) ring.

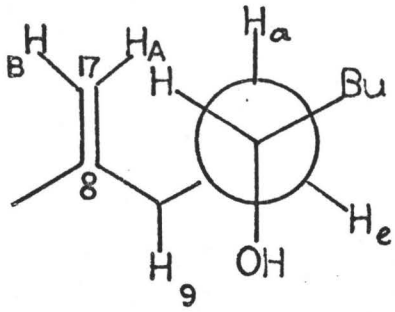
This conformation gives rise to the minimum of interactions with C-1 protons and the C-20 methyl group. It then leads to two basic conformations only for the ketone 116 and 117, and the alcohols 118 and 119. Hydride attack on 116 can only occur from the right giving rise to threo (12R) (13S) or erytho (12R) (13R) isomers 118. Since there is no obvious reason for a preferred butyl configuration an equal mixture should result. Similarly hydride attack on 117 can only be from the underside giving a (12S) threo or erythro alcohol 119. The essential difference then lies in hydride attack of rotamer 116 or 117.



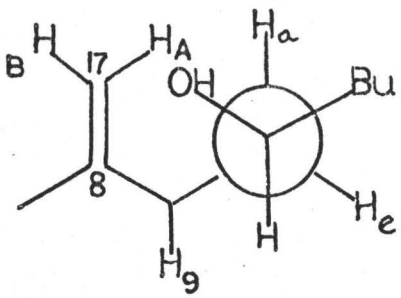
116



117



118



119

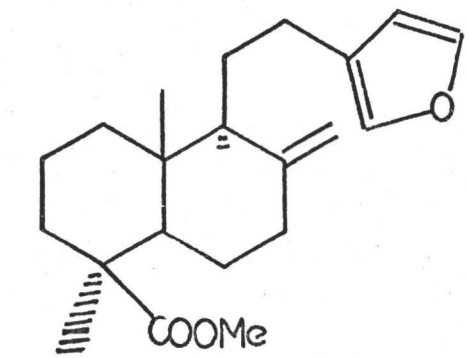
Since 116 leads to a gauche C-9⇔C-13 interaction compared to rotamer 117 (which has the butyl side chain between the C-11 hydrogens, rotamer 117 should be favoured by some 0.8 - 0.9 Kcals. Both transition states force the developing hydroxyl against the C-17 vinylic proton (H_{17A}) and this factor should therefore approximately cancel. This energy difference at 70-80° leads to a predicted isomer distribution of ca 70:30 in favour of 119.

It will be recalled that experimentally, an isomer distribution of 7:3 is precisely what was observed! - the alcohol in preponderance showed a marked deshielding of the C-17H_A— vinylic proton. This effect is directly attributable to the close proximity of the C-O bond (and the oxygen atom) in isomer 119 and therefore this is considered to be the majority product. Alcohol 118 will have the preferred conformation shown where the OH is down, since the controlling factor in both structures is avoidance of a gauche 1,3 interaction between the H_9 hydrogen and the side chain butyl group.

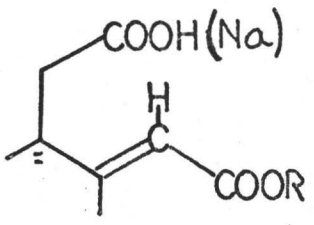
After the successful demonstration of the utility of the synthetic scheme for labdane type structures as shown by the synthesis of 37 above (and the general utility of synthesis for confirmation - or otherwise - of natural structures) the synthesis of methyl lambertianate 38 was attempted.

The immediate synthetic plan was firstly to convert the C-12 carboxylate of 102 into its acid chloride 120 by the exchange reaction with oxalyl chloride. This could be achieved without rearrangement and attack on ester[92], using either, the free acid itself or its sodium salt[93]. This acid chloride was then to be reacted with 3-furyl cadmium to give the ketone 121. The furyl cadmium was theoretically derivable by exchange with cadmium chloride[87], from 3-furyl lithium, which had been previously prepared[21]. The rather laborious preparation of 3-furyl lithium is described below and in the Experimental section. When it had been obtained and mixed with cadmium chloride at -70°, warmed to room temperature, and the freshly-prepared acid chloride added however, the result of work-up revealed only unreacted starting acid 102 ($R = CH_3$).

Subsequent investigation revealed that no appreciable cadmium derivative formation takes place at -70°, and that on warming-up the lithium derivative decomposed before the cadmium chloride reacted. The only synthetic possibility therefore was to use the lithium derivative directly and experimental trials were made with the acid-ester 102 and the acid chloride-ester 120. As suspected the C-21 ester group ($R = CH_3$) was more reactive than the C-12

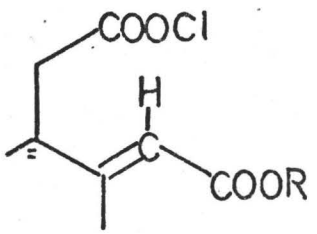


38

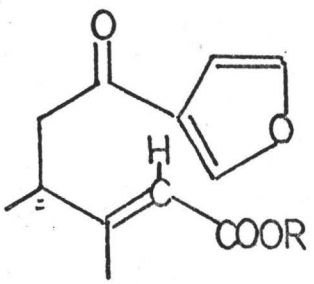


102

$(COCl_2)$

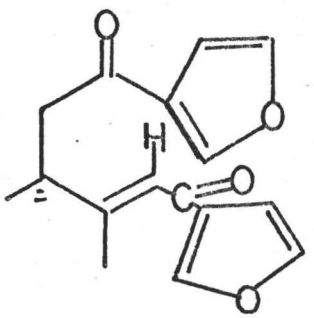


120



121

+



carboxylic acid in 102, and an alcoholic product with two furan rings at C-21 was obtained. The acid chloride 120 showed more promise, in that with one mole of lithium reagent to one mole of sbustrate, the product obtained showed partial reaction at the acid chloride position with apparently only one furan ring being attached. That is, the ketone formed after reaction with one molecule was apparently not very reactive to further attack. This was in contrast to the ketone produced at C-21 (see above). However in the present case, some reaction still occurred at the latter C-21 ester position, so further investigation was needed.

The above results suggested two other initial approaches. Firstly to use the corresponding acid-tertiarybutyl ester 102 ($R = t_{Bu}$), which might be more hindered to lithium alkyl attack at C-21, and give the acid chloride reaction an opportunity to go to completion. However as we have seen above, synthetic studies towards preparing this particular ester were not encouraging, and the proposition has not been explored. Secondly though, the possibility that the C-12 acid chloride 60 might react specifically with one mole of reagent in the presence of pre-formed exocyclic 8(17) double bond, seemed reasonable in view of the above evidence. Two basic fragments were therefore required. Firstly, the acid chloride 60, was easily and efficiently prepared by hydrolysis of the ester 112, solution in sodium bicarbonate 9-10%excess) and treatment of the sodium salt with oxalyl chloride. We were reasonably certain that no acid catalysed migration of the exocyclic double bond would occur under these conditions from previous examples[94,95].

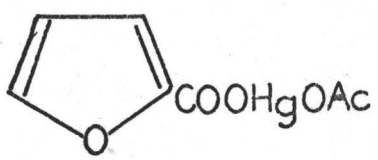
The second reactant, 3-furyllithium has been alluded to above. Its efficient preparation constitutes something of a thesis in itself, and only certain aspects of the problem can be discussed here. The compound was first prepared in 1962 from 3-iodofuran[21], and was shown to have considerable potential for the synthesis of 3-substituted furans in general and of 3-substituted furan-containing natural products in particular (for examples see Historical Introduction). The preparation of the lithium derivative is simply accomplished by exchange with an alkyl lithium and 3-iodofuran at -70° followed by insitu reaction.

The prime intermediate is therefore 3-iodofuran. Very few such 3-substituted furans have been prepared. For the few early examples involving partial decarboxylation of polycarboxyfurans and other tedious procedures, Gronowitz and Sorlin's paper[21] should be consulted. Other more recent, but usually non-general types of reaction are, cyclisations of enol ethers[96], rearrangement of epoxy-acetals[97,98] and a very recent interesting method of value[99], involving acetylenic epoxides cyclising through diols to 3-substituted furans. Under normal conditions, electrophilic substitution of furans is always in the 2-position. Use of 2-carbonyl substituted furans and blockage by complex formation with aluminium chloride has been one method of obtaining 3-orientation[100], but this is of little value in the present case.

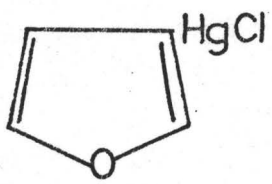
3-Iodofuran itself was originally prepared by Gilman and Wright[101] by selective aluminium amalgam reduction of tetraiodofuran. However Gilman

also prepared the compound by iodine oxidation of 3-chloromercuryfuran in better yield, by an analogous method to the process by which the tetraiodo compound had been formed[102,103]. This procedure for 3-chloromercuryfuran itself and subsequent iodine oxidation, is the technique improved by Gronowitz and Sorlin[21], and Wrobel[23]. The method was reported[103] as the best to date in 1966, for these intermediates, and used in the present study, where it has been improved still further.

The preparation consists of precipitation of the mixed 2-(acetoxy-mercuric)-furoate salt 122 from mercuric acetate and 2-furoic acid, followed by pyrolysis of the (dry) powdered salt. The product of this pyrolysis is then treated with glacial acetic acid and sodium chloride solution which on work-up gives the 3-chloromercuryfuran 123 in low yield.



122



123

Gilman's early ideas on the mechanism[101] are hardly correct although some useful observations were made, including the fact that some furan and carbon dioxide were evolved during the reaction, but that no acetic acid was formed. His proposed[101] mechanism is outlined in Figure 14, the key intermediate being the bicyclic 125, formed after disproportionation. Even if this species can form the rest of the

mechanism is distinctly dubious.

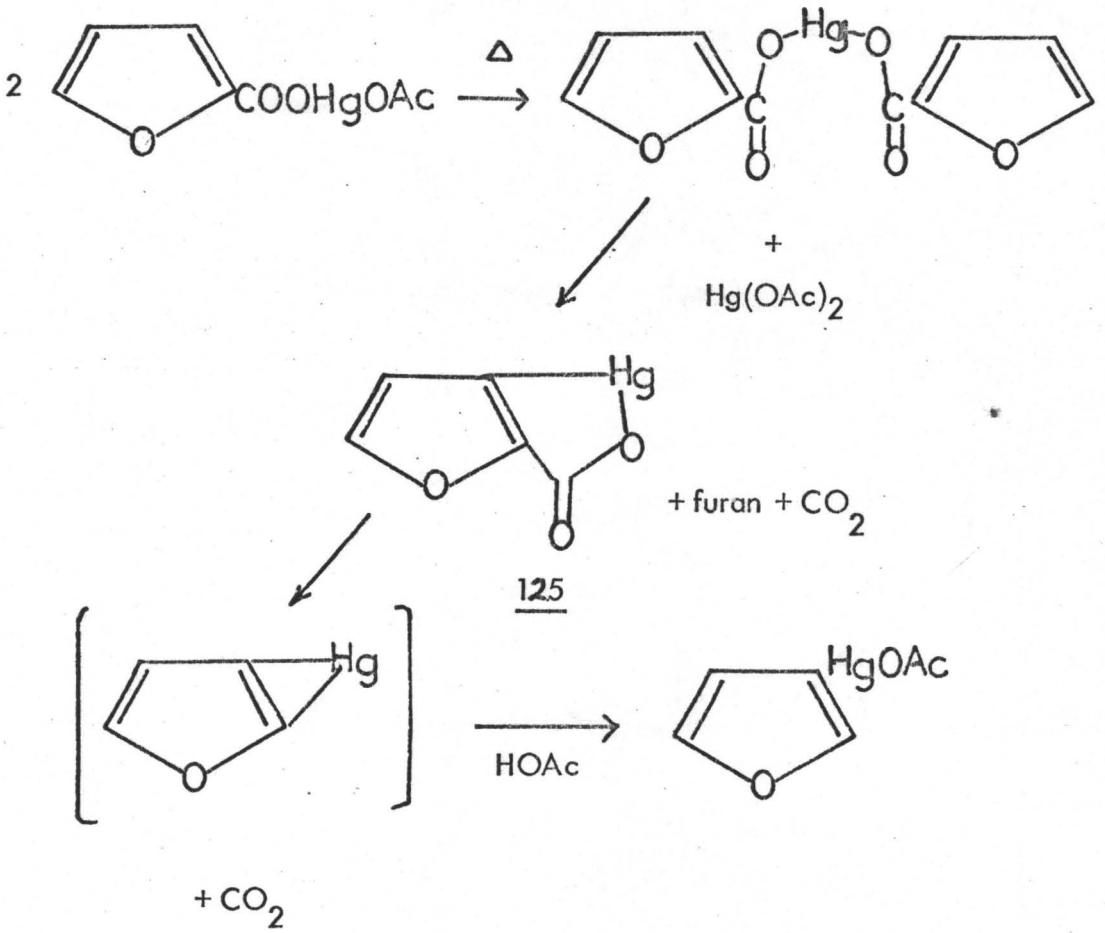


FIGURE 14 : Mechanism for the Formation of 3- Chloromercuryfuran 123 (Gilman[101])

A more plausible route is suggested below in Figure 15, although no direct evidence exists for this. There is some precedent for the ortho-mercurial rearrangement observed in this system. Kharasch showed in very early work[104] that certain substituted benzoic acid mercury salts which do not lose carbon dioxide readily, undergo ortho substitution by mercury, in an analogous manner to give the corresponding biphenyl. The initial disproportionation seems reasonable

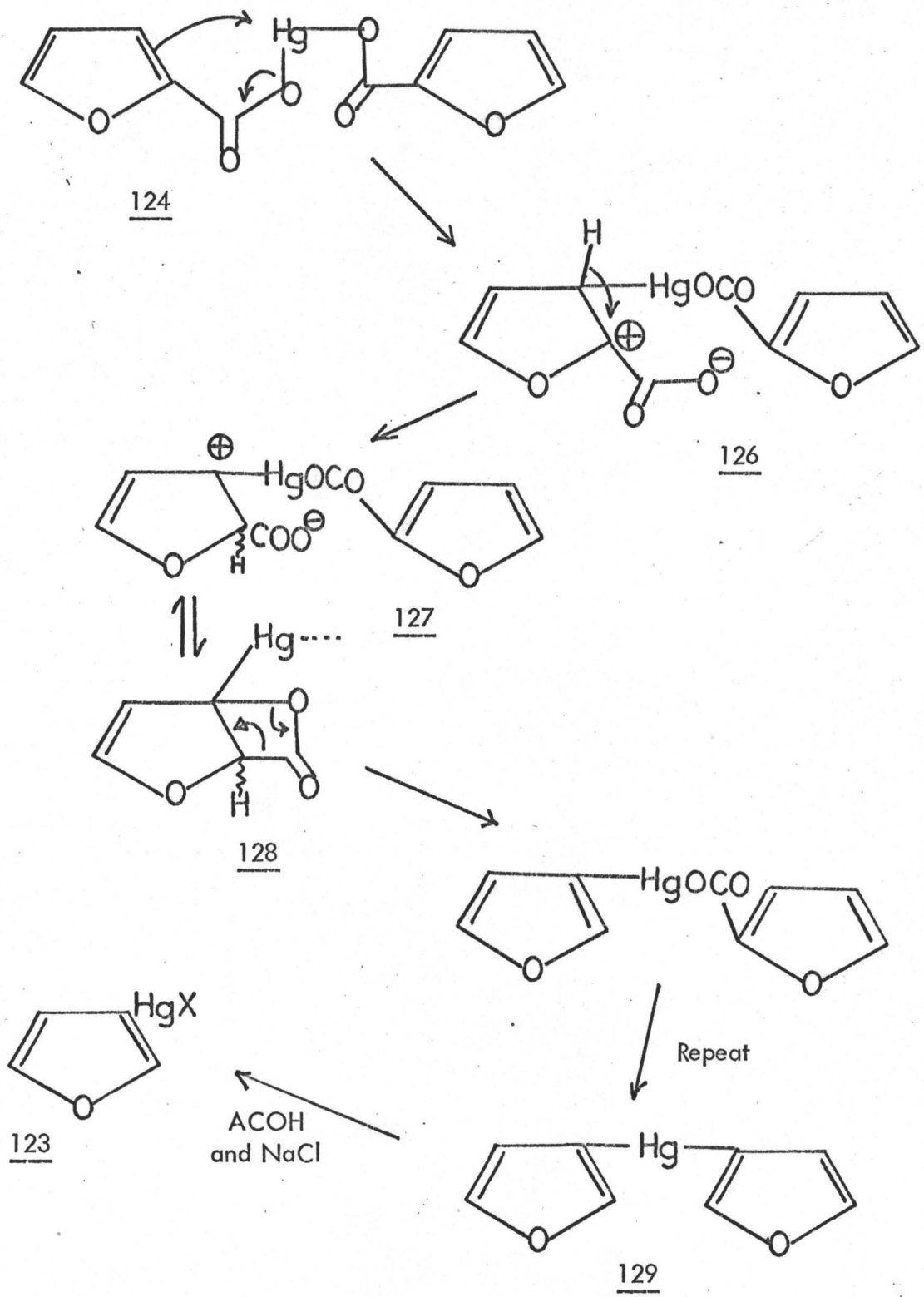
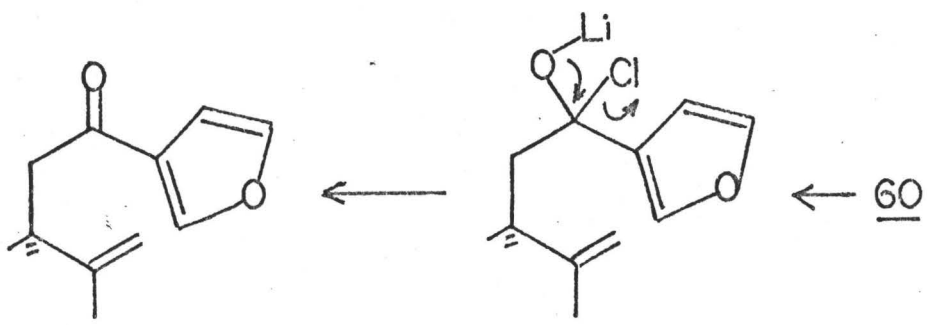


FIGURE 15 : Proposed Mechanism for the Formation of 3-Chloromercuryfuran 123

particularly as the crude product seems to be at least 50% mercuric acetate, and a cyclic electrophilic substitution reaction can then be drawn for the furoic salt 124. The zwitterion 126 can be considered to undergo a 1,2-hydride shift to the mercury atom stabilized cation 127, or its ring closed form 128. The formal separation of cationic charges is not necessarily correct of course. Expulsion of carbon dioxide and a repeat of the process leads to the β-bifuryl mercury analogue 129 of the biphenyls mentioned above. Work-up with acetic acid and sodium chloride then gives product 123. It is probable that in experiments such as Gilman's where no precaution to remove all acetic acid was taken, the latter step could also occur initially during the pyrolysis. Gronowitz and Sorlin's procedure[21] produced the 3-chloromercury derivative in 15% yield from 2-furoic acid. Their infrared analysis showed the material to contain 5% of the 2-isomer after one recrystallization, however, material of this purity was adequate since the 3-iodofuran obtained from it was found to contain considerably less 2-isomer. In the present procedure one modification was performed based on Wrobel's work[23]. The pyrolysis itself was performed in xylene rather than as a dry powder, giving a more reproducible and safer procedure. The acetic acid work-up of the product in the present case however was reduced to a minimum time of three hours, from twenty-four in the other studies[21,23]. This reduction seemed to have the effect of lessening further product degradation or rearrangement, since the overall yield obtained of final product was considerably higher than before. Extraction of the crude mixture of mercuri-chlorides and mercuric acetate from the pyrolysis and

work-up, showed that the proportion of 2-isomer increased as extraction was prolonged. By this procedure it was possible to obtain some 31% overall yield of 3-chloromercuryfuran containing only 6% 2-isomer, and therefore suitable for further reaction without recrystallisation.

Having thus obtained 3-iodofuran in synthetically useful quantities, the coupling reaction between the acid chloride 60 and 3-furyllithium was attempted. The alkyl lithium was prepared by reaction between methyl lithium and 3-iodofuran at -70° for one hour. The solution of the acid chloride, which had been freshly prepared was then syringed into the alkyl lithium solution as quickly as possible to achieve maximum possible reaction between the two, before the incipient carbonyl group could react further. Contrary to pessimistic expectations, the reaction proceeded well! Even use of a 50% molar excess of the alkyl lithium, led to no further observable reaction of the newly formed C-12 ketone in 61.



61 130 60

The ketone 61 comprised 80% of the crude product. Starting material (as the free acid) consisted of 10% of the product and could be base extracted and recycled. The remaining 10% consisted of minor materials none of which seemed to contain furanoid absorption in their pmr spectra. The keto-furan was obtained pure as an oil from chromatography on Florisil, but has not to date been obtained crystalline. However a high resolution mass spectrum confirms the assigned structure. Methyl lambertianate is also an oil[18], and therefore the non-crystalline nature of the keto-furan is not unexpected in view of the probable similarity of 'close packing' of the two molecules.

The pmr spectrum of 61 was consistent with the 3-substituted furan structure. In addition to the two vinylic C-17 protons at 4.31 and 4.66 ppm, essentially unchanged from starting material, the three furan proton chemical shifts, had altered from their values in 3-iodofuran. Where previously the two α-protons next to the ether oxygen were deshielded and downfield at an approximately common chemical shift, the α-proton (C-16) to the ether oxygen which was now also β to the $\alpha\beta$-unsaturated ketone at C-12, was further deshielded and appeared at considerably lower field. The question as to why the C-12 carbonyl is so apparently inert to further attack by reagent is not straightforwardly answered. The initially formed adduct 130 almost certainly eliminates chloride ion as shown, fairly soon after it is formed, so ketone would be present from the early stages of the reaction. It is probable that formation of the unreactive enolate of the ketone

prevents further reaction and that this is the main competing process although the steric bulk of the furyllithium may simply prevent further attack at the hindered 12-ketone (see condensation results below). It is known that low temperatures suppress the reaction of Grignard reagents with ketones more than their reactions with acyl chlorides, and also that steric hindrance[105] can be very significant with the organomagnesium reagents. Alkyl lithiums however are usually rather reactive despite steric hindrance.

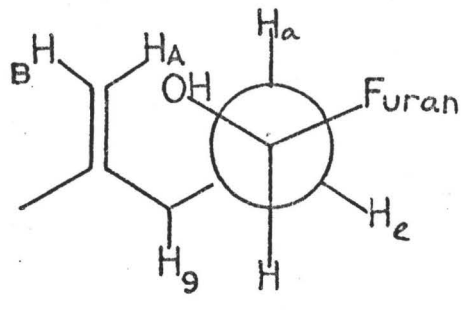
That the 12-keto group in 61 was indeed inert to further attack, became evident when attempts were made to form derivatives suitable for conversion to the hydrocarbon, methyl lambertianate 38. It had been originally broadly planned to remove the ketone function in 61 by base catalysed reactions such as the Wolf-Kishner reaction. However an initial reaction with this method using lower than normal temperatures[106] on the supposedly reactive[107] α-furyl ketone produced extensive degradation including reduction of the furan ring.

The same unfortunate story was repeated with all the types of substituted hydrazine derivatives tried, including p-toluene sulphonyl hydrazine[108], semicarbazone[109], and hydroxylamine hydrochloride[110]. When conditions were mild no reaction resulted, but if forcing conditions were attempted further degradation of the molecule took place with still no evidence for carbonyl reaction. Thus in attempts to prepare the tosyl hydrazone for elimination by sodium borohydride[108], under the temperature of refluxing ethanol, the reagent apparently partially breaks down to diimide[111] and reduction of the exocyclic double bond took place. For

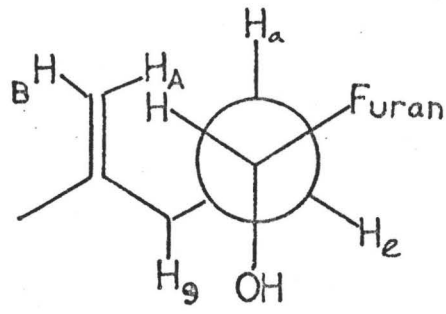
full details of these reactions, the Experimental section must be consulted.

As an alternative approach we then attempted preparation of the C-12 thioketal[112], to be reductively removed by deactivated[113] Raney nickel. Boron trifluoride catalysed addition gave a fairly pure compound, the pmr spectrum and identity of which have not been interpreted. Preliminary experiments with deactivated Raney nickel did not lead to desulfurisation however and some double bond reduction took place. It is probable that the product from the original ketalisation is a rearrangement product arising from cation formation at C-12.

At the time of writing all further efforts to remove the oxygen function via the alcohol have failed. Sodium borohydride reduction of the ketone 61 yields a mixture of two epimeric alcohols in the approximate ratio of 6:4, which are separable by 'Florisil' chromatography, the major isomer being crystalline. By analogy to the arguments applied to the labdane alcohols 118 and 119 above this latter alcohol is assumed to be the 12(S)-epimer 131 corresponding to 119.



131

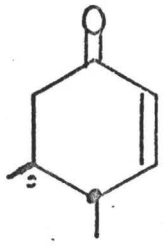


132

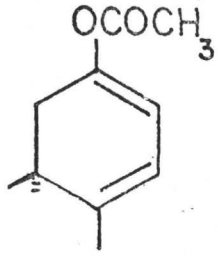
Reaction of these alcohols with tosyl or brosyl chloride in pyridine at 0^{o} or room temperature leads only to starting material. Formation of the lithium salts with methyl lithium and subsequent quenching with brosyl chloride also had no effect. Removal of this oxygen function remains therefore unaccomplished, but it is felt that there may still be scope for further investigation, possibly via the C-12 halide 114 which in principal, is removable by tri-n-butyltin hydride in a free-radical process.

IV. Derivation of Other Synthetic Intermediates from the $\alpha\beta$-Unsaturated Ketone 49

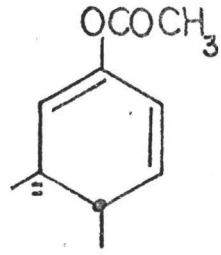
In the original synthetic plan, the keto-acid 36, which has since been obtained by two alternative routes as elaborated in Sections I and II; was to have been prepared, by ozonolysis of the enol acetate 50, which was predicted to be the major product from thermodynamically controlled enol acetylation of the $\alpha\beta$-unsaturated ketone 49. By an appropriate choice of reaction conditions, it is possible to convert an unsymmetrical ketone (eg 49) predominantly to either the more highly substituted 50 or the less highly substituted 133 enol acetate.



49



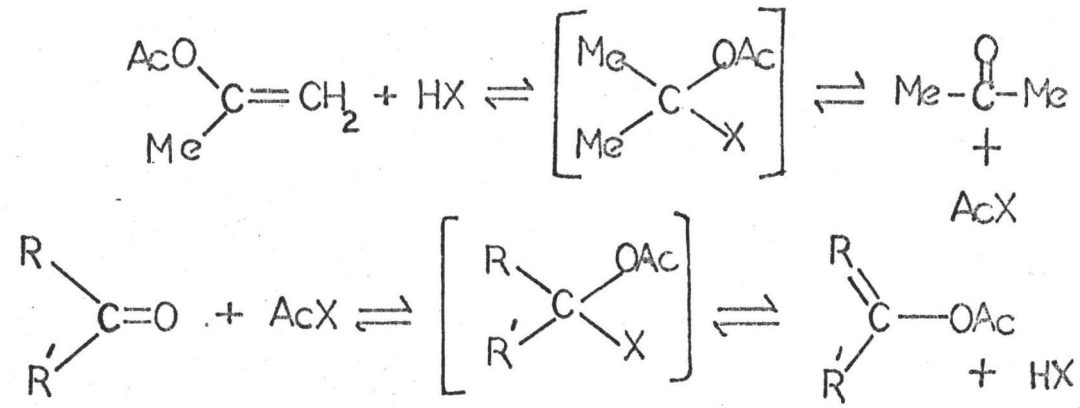
50



133

Thus the more highly substituted enol acetate 50 was expected to be formed by using acetic anhydride and p-toluene sulphonic acid as reagent, under which conditions "thermodynamic control" is expected to take place[115], and the less highly substituted isomer 133 should be produced by the action of isopropenyl acetate with a trace of acid catalyst which was known to produce conditions of "kinetic control"[115].

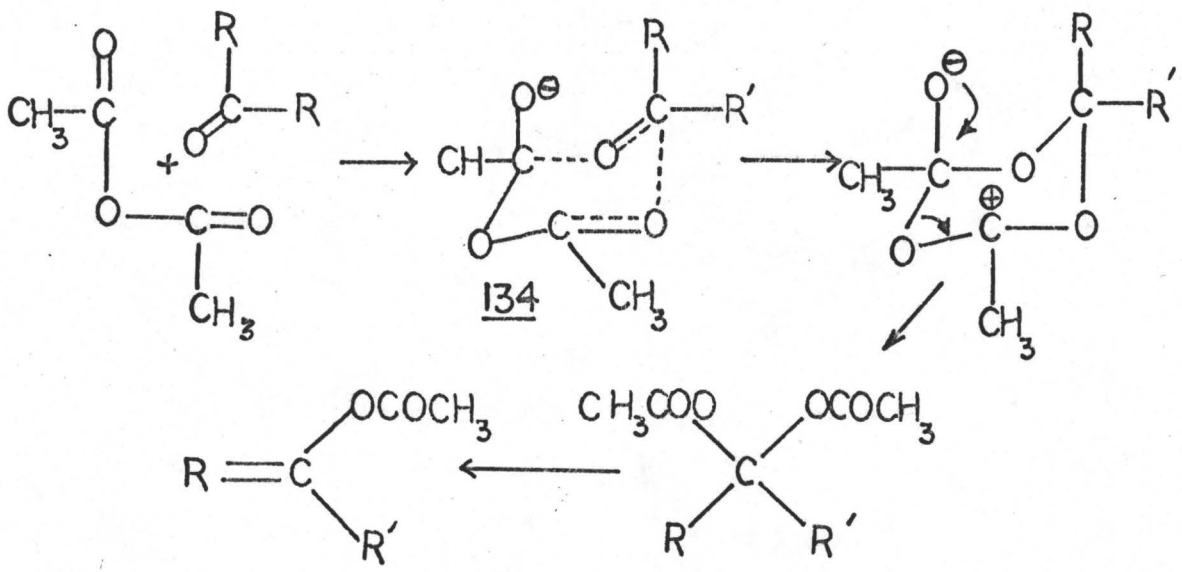
Before discussing the outcome of initial experiments on these lines it is worth considering the postulated mechanisms for these reactions, in view of the confusion (even until recently[116]) which still prevailed on the subject. It was proposed by Satchell et al[116] that the active species in enol acylation of ketones with isopropenyl acetate and acids were mixed anhydrides, formed from the two reagents. It was suggested that these mixed anhydrides then reacted with the enol form of the ketone. However in two recent interesting papers, Libman and Mazur[117] have produced compelling evidence that the mixed anhydrides attack the ketone and not the enol form, leading to a gem-diester. The latter would subsequently eliminate one molecule of acid resulting in enol acetates. Thus their scheme is as shown below.



Accordingly different acid catalysts with isopropenyl acetate will result in different gem disubstituted intermediates. It was found that as acid strength increased the "kinetic ratio" of products turned to the "thermodynamic ratio", the ratio of the isomeric enol acetates being dependent on the nature of the

transition states involved in the elimination of the acid molecules from these gem-diester intermediates.

Further additional work using acetic anhydride with sulphuric and perchloric acids as catalysts showed that although the stronger acid gave much quicker conversion to enol acetates, the ratio of isomeric acetates formed was constant at any given percentage conversion and equilibrated on further treatment with the reagent in favour of the "thermodynamic ratio". This evidence was interpreted to mean that the reactive species here was protonated acetic anhydride; ie. the same reagent for any acid but present in differing amounts according to acid strength. The protonated acetic anhydride was envisaged to add to ketone and the resulting geminal diacetate to eliminate acetic acid to give the enol acetate. A six-centred transition state 134 which may assume chair geometry is possible in this addition.



We may thus tentatively apply the above interpretations to results obtained with the $\alpha\beta$-unsaturated ketone 49. Refluxing the ketone 49 with acetic anhydride and p-toluene sulphonic acid for three to four hours with concomitant slow distillation, led to a product containing the enol acetates 50 and 133 in a 3:2 ratio, together with some starting material, methyl podocarpate 54 and 5% of an initially unidentified compound (see below). Despite considerable adjustment of conditions, no improvement in the yield of the desired isomer 50 could be obtained. Thus, increased reaction time led only to increased amounts of the aromatised product 54, use of sulphuric acid as catalyst gave almost identical results and perchloric acid, using several suggested methods[118], gave considerable charring of the product[119]. Chromatographic purification was of limited success and although the enol acetate 50 could ultimately be obtained pure by crystallization, it was only in 28% yield.

In order to throw further light on the above reaction mixture which apparently represented the relative thermodynamic stabilities of the two isomers 50 and 133, the alternative reaction conditions using isopropenyl acetate were tried. The use of p-toluene sulphonic acid as catalyst yielded as expected, some 90% of the kinetic isomer 133 alone, together with 10% starting material after four to five hours reaction. When the pure compound, isolated by crystallisation, was reheated in acetic anhydride with a trace of acid catalyst, the same mixture of 3:2, 50 to 133 was obtained as previously. House and Kramar in a study[25] on direction of enolisation of unsymmetrical ketones were

able to prepare mixtures of enolates, representing the true thermodynamic ratio of their stabilities, by dissolution of ketones in the strong base triphenylmethyl potassium in dimethoxyethane, followed by quenching as enol acetates in acetic anhydride. It was hoped to obtain additional information in the present system using the same technique but a trial experiment led only to base catalysed condensation products possibly due to Michael addition, and the desired information of possible effect of cation size and solvent[25] on the equilibrium was not obtainable.

Djerassi has suggested[120] that two main factors operate in determining the direction of enol acetylation and (probably) enolisation, in 3-oxo-5α-steroids. The first is steric, arising from angular methyl interactions while the second is hyperconjugative. House demonstrated in the above mentioned study[25] that small energy differences of 1-2 Kcal/mole due to α-substituents etc., were sufficient to explain all observed equilibria, and finally Liston[119] has demonstrated using calculations of non-bonded interactions in 3-oxo-5α-steroids that the direction of enolisation is also governed by steric forces in the absence of any hyperconjugative effect.

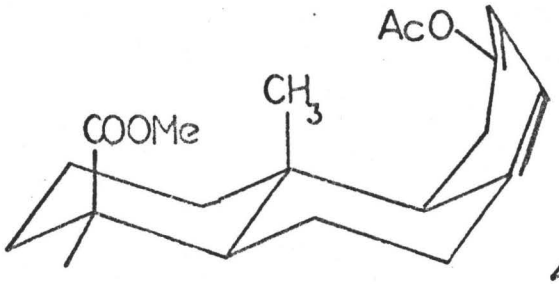
In order to ascertain the actual conformation of the diene rings in the present two enol acetates with a view to explaining the observed equilibrium between the two in terms of such non-bonded interactions, we examined the optical rotatory dispersion spectra (ORD) of the two compounds. A fundamental analysis[121] of the Cotton effect associated with 1,3-cyclohexadienes has

revealed that the skewness (helicity) imposed on such dienes by structural factors constitutes the major element of asymmetry responsible for the Cotton effect. The helicity of the diene makes a contribution to optical activity far outweighing that of adjacent asymmetric centres. It has been shown theoretically and confirmed experimentally[121] that the sign of the Cotton effect of skewed cisoid dienes depends upon the sense of helicity of the diene system. A right-handed helix 135 produces a positive Cotton effect associated with the π-π^* absorption bond; a left-handed helix 136 produces a negative effect.

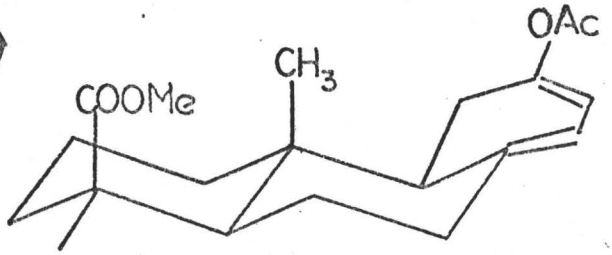
135 136

An examination of the ORD spectra of the two compounds 50 and 133 in methanol gave results of considerable interest. A strong negative Cotton effect (molecular amplitude = 443) was produced for the 8(14),12(13)-diene 50. Ring C can reside in two conformations in this molecule represented as the folded form 137, and the extended form 138. It thus appears that the situation is totally analogous to the very similar compound, laevopimaric acid, where precisely the same effect is observed[122]. Considerable steric repulsion between the C-1β and C-11β protons is relieved by folding the ring up as shown 137 leaving the C-11β proton down and away from C-1 and the diene system with a

left-handed skew.



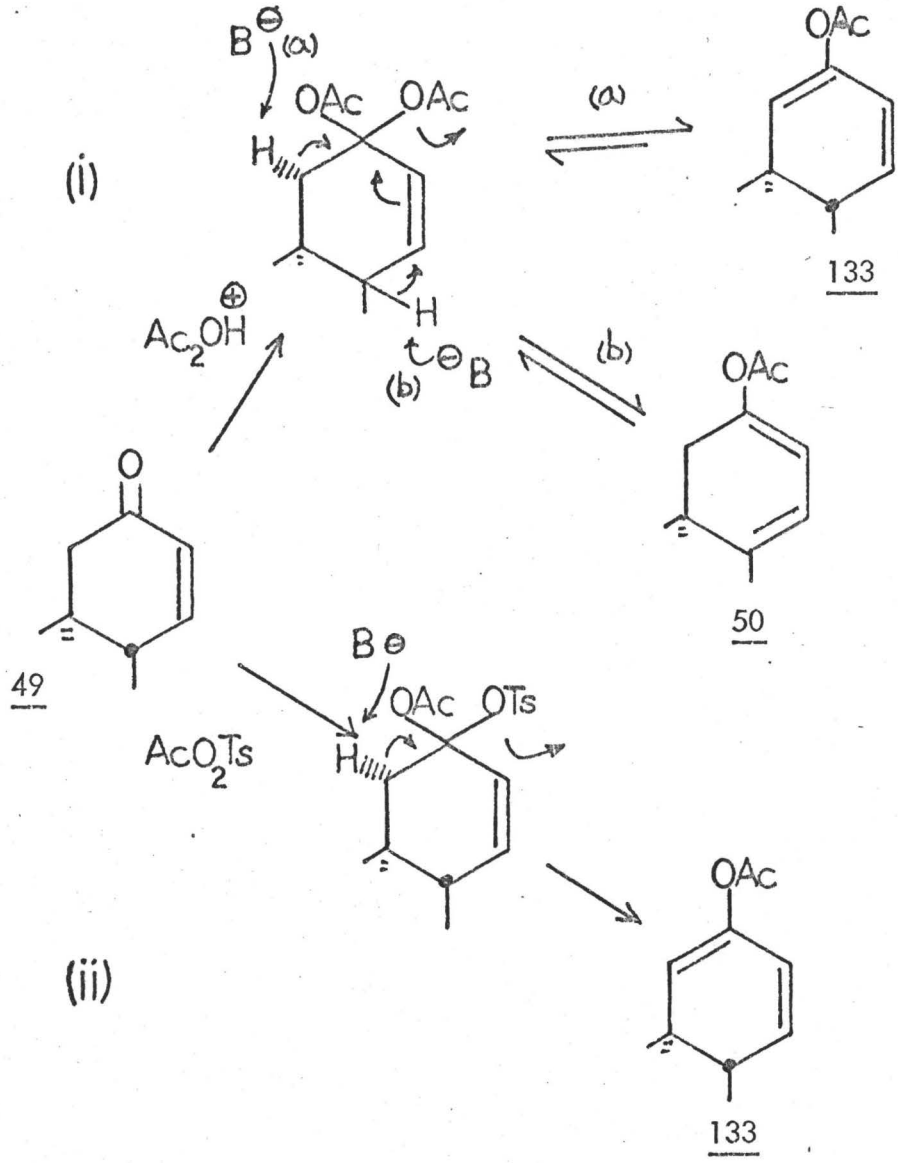
137



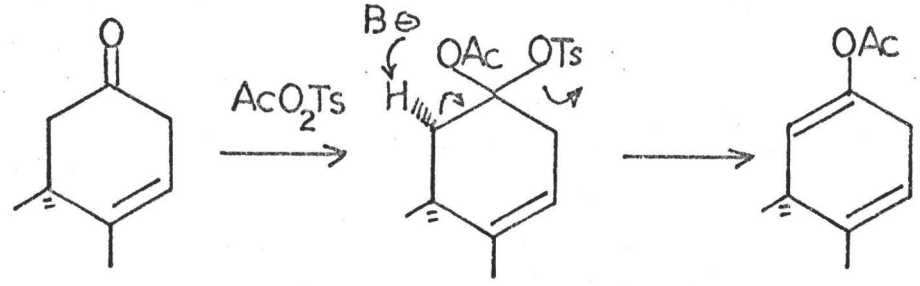
138

A somewhat unexpected result was obtained for the 11(12),13(14)-diene 133, viz. a plain positive curve with no Cotton effect, showing that the diene system is at, or very near, planarity. Examination of a model shows that to achieve planarity, distortion of the C-11 carbon atom up (β), does in fact remove a quite severe interaction between the C-1β proton and the C-11 vinylic proton, and so this conformation is therefore very reasonable. This particular distortion also has the effect of relieving interactions between the C-20 methyl group and the axial β-proton on C-8. The combination of these two steric reliefs may well therefore explain the unexpectedly high proportion of this 'kinetic' isomer in the equilibrium mixture. Although the stabilizing influence (in reducing overall energy) of the trisubstituted double bond in the other isomer 50, is obviously predominant, it is now obvious that the rather subtle relief of steric strain - not obvious a priori from models - in the kinetic isomer, leads to its relatively favourable proportion in the mixture.

The mechanism for the formation of these two enol acetates may readily be rationalised using the mechanism of Libman and Mazur[117] above. Presumably the reason that no further equilibration takes place in mechanism (ii) is that all the acid catalyst is taken up as mixed anhydride and is thus not available for protonation.



When later in the work the βγ-ketone 67 (see Section I) was obtained it was expected that this ketone on treatment in kinetic conditions should produce the enol acetate 133 as the initial product. Surprisingly however, on heating 67 with isopropenyl acetate and p-toluene sulphonic acid, a new compound was obtained, as 60% of a mixture containing also methyl podocarpate 54, 15% and enol acetate 50, 20%. Unfortunately despite 'Florisil' chromatography, thin layer chromatography and repeated crystallisation, we have not been able to obtain better than a 83%/17% 50 mixture (by pmr). It has been possible to tentatively assign the structure 139, on the evidence to hand however. Analysis shows the mixture to be isomeric with enol acetate 50. The ultraviolet was featureless except for the characteristic peaks due to 50, with extinction coefficient corresponding to 17% concentration. The infrared also showed no conjugation but CO absorption at 1760 cm^{-1}, and finally the pmr showed an acetoxy group at 2.05 ppm plus two vinylic protons centred at 5.35 ppm as overlapping multiplets, with a multiplet at 2.5 - 2.8 ppm, due to two protons, suggestive of allylic absorption.



67 140 139

iii

The apparent stability of this non-conjugated 1,4-diene is somewhat surprising, particularly to 'Florisil' and silica gel. It is possible though that the failure to achieve good purification on crystallization is due to a slow conversion of 139 to 50. The original formation presumably proceeds through a gem-diester intermediate 140 as shown above, where surprisingly C-11 proton removal is favoured (to the extent of 4:1)- over a proton from C-13.

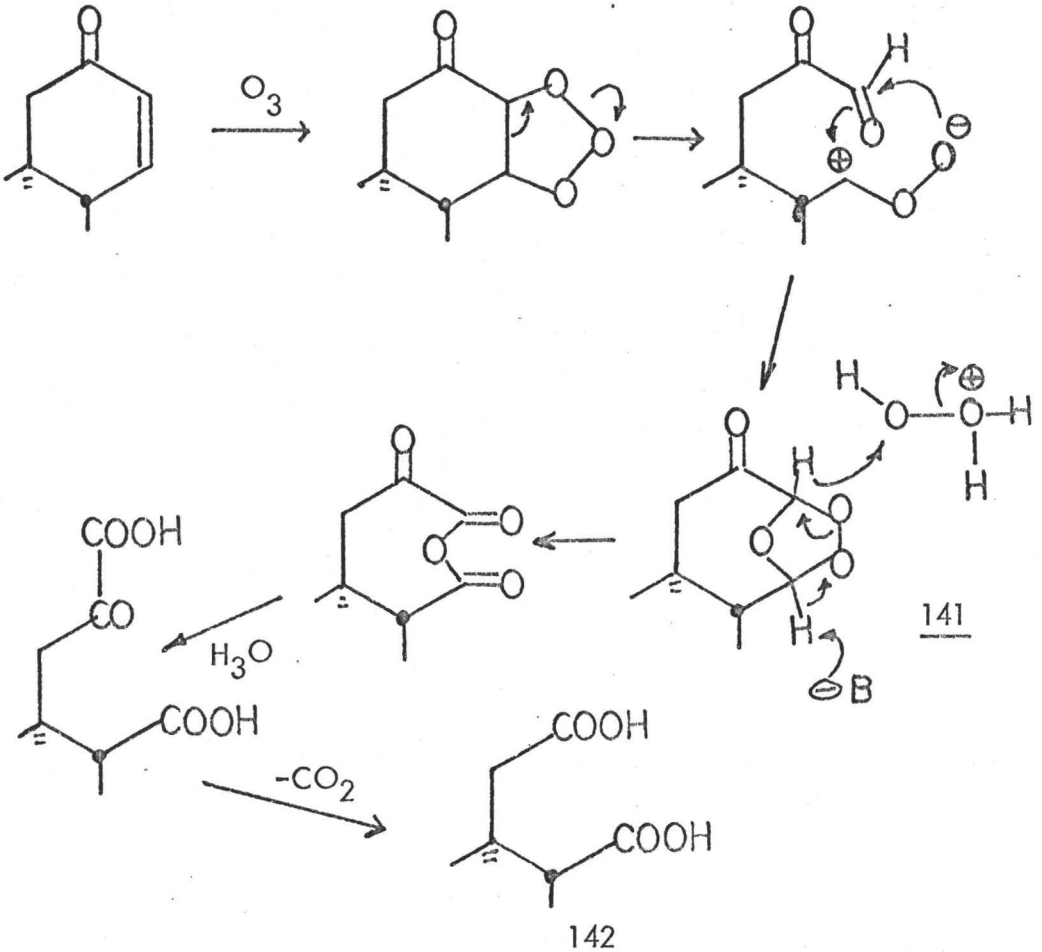
A final note is in order concerning the pmr spectra of these enol acetates. The 8(14),12(13)-diene 50, shows an AB quartet at 5.40 ppm due to its two (13 and 14) vinylic protons with J_{AB}= 6.3 Hz and δ_{AB}=3.9Hz (at 60 MHz). This is as expected for such a system. However in a related steroid ring - A diene[123], the analogous two protons are stated to be 'magnetically equivalent' - (which they almost certainly are not) and to give a broadened singlet (Wh/2 = 2Hz at 60 MHz), which is at distinct variance to the present results. The 11(12),13(14)-diene 133, shows an unresolved multiplet (Wh/2 = 5Hz at 60 MHz) at 5.70 ppm due to the C-13 and C-14 vinylic hydrogens and a sharp doublet at 5.87 ppm, J =1.0Hz presumably due to homo-allylic coupling with the C-13 vinylic proton.[124] Approximately zero coupling with the axial C-9 proton is expected since they are at, or near, 90°[125]. Finally the proposed 8(14),11(12)-diene shows a semi-triplet character to part of its vinylic multiplet, perhaps due to the C-14, C-13 proton pair, which are apparently equivalent since the ring is quite flexible. The absorption of the C-11 proton is too 'buried' under the signals to allow proper analysis however. Garbisch has recently commented[126] on the magnitude of

allylic-allylic coupling in 1,4-cyclohexadienes. Further comment on the relative shielding of the C-20 methyl group in these compounds is made in Section VI.

Following the initial studies on the enol acetates, other possible intermediates were sought from the $\alpha\beta$-unsaturated ketone 49, since the previously desired enol acetate 50 was not available in synthetically useful amounts as a potential source of the keto-acid 36, otherwise unavailable at the time. The alternative synthetic route thus planned involved use of intermediates still containing the C-14 fragment as a potential precursor to the exocyclic 8(17)-double bond. Such intermediates seemed theoretically derivable from the $\alpha\beta$-unsaturated ketone 49 by direct oxidative fission at the 13(14)-double bond. The results of such preliminary studies and the unexpected general chemical information thus obtained are recorded below.

The $\alpha\beta$-unsaturated ketone 49 was found to be successfully cleaved by ozonolysis to the diacid 142. The general procedure adopted was that of Engel and Rakhit[127] using dry ethyl acetate alone at 0° (rather than with acetic acid as co-solvent at -10° which appeared to reduce product purity slightly). Similarly the one reaction using methanol as participating solvent at -30°, which was attempted, led to some precipitation during reaction and an inferior product. It is probable that use of methanol:methylene chloride mixtures at -70 might well improve the overall yield. The ozonide 141 which is presumably formed in ethyl acetate as a non-participating solvent[67], was cleaved to diacid 142 by the method of W.S. Johnson[128], utilizing acidified hydrogen peroxide in acetic acid. The overall mechanism can be written in a straightforward manner. The direction of

opening is expected to be as shown[69], although this does not alter the structure of the intermediate ozonide 141.



142

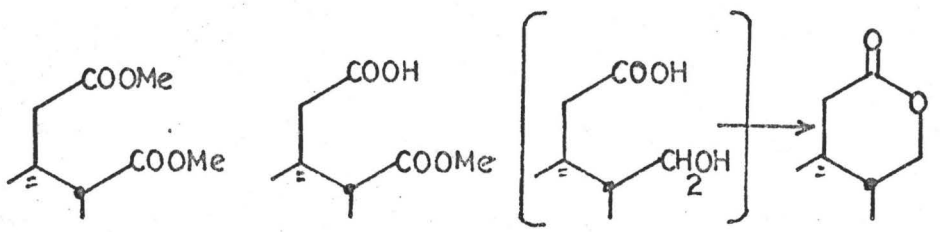
The diacid 142 on treatment with ethereal diazomethane smoothly gave the corresponding diester 143. The pmr spectrum of this compound showed the three methyl ester absorptions at 3.53, 3.50 and 3.48 ppm respectively for the tertiary, secondary and primary groups (assignments based on subsequent hydrolysis). The selective hydrolysis of the diester was hoped to yield a reasonable proportion of the acid-ester 144, where only the primary ester had been attacked. It was

known from previous examples[129] that with one equivalent of sodium hydroxide at less than 1N concentration, that this was possible in good yield. In the event, refluxing 143 in aqueous methanol with 1 mole of 0.05N sodium hydroxide for four hours, produced 90% of an acid fraction which pmr analysis showed to contain >95% of the desired compound 144. The product showed clearly two 'clean' ester absorptions in the pmr at 3.57 and 3.54 ppm.

The final aim of the initial studies was now to convert the acid-ester 144 to the hydroxy-acid 145, by selective reduction of the C-17 ester. The best reagent to use for this purpose was not immediately obvious. Sodium borohydride in large excess (10 - 20 moles) in methanol[130] reduces aromatic carboxylic esters to alcohols in good yields, but results with aliphatic and alicyclic esters were less satisfactory. Lithium borohydride on the other hand reduces esters well, but also attacks carboxylic acids to varying extents[131,132] so that selective reduction of esters in the presence of acids is rarely possibly in synthetically good yields. Also lithium aluminium hydride, at the other extreme from sodium borohydride, rapidly reduces practically all functional groups[133]. Introduction of alkoxy groups onto the aluminium atom considerably diminishes the reducing power of this hydride, so that the tri-t-butoxy derivative[134] has activity approaching only that of sodium borohydride. Lithium trimethoxyaluminohydride however is nearer lithium aluminium hydride in its activity since it reduces esters, acids and other groups easily[135].

On the other hand introduction of alkoxy substituents onto the borohydrides

increases their reactivity[136]. The differing effects of alkoxy substitution on the reactivities of these two reducing agents have been attributed to a combination of resonance interaction and inductive effects[137]. It thus seemed possible that sodium trimethoxyborohydride would be of sufficient reactivity to reduce the secondary ester in 144, without affecting the primary carboxyl function. To our satisfaction this rational was born out in practice, using a commercial sample of reagent which was on hand[138]. Refluxing the acid-ester 144 in dimethoxyethane (DME) as solvent, together with a three mole-equivalent excess of sodium trimethoxyborohydride produced the ester-acid-alcohol 145 in 95% yield, either as the free alcohol or more usually in the form of its δ-lactone 146. Careful examination of the crude reaction product by pmr showed that the C-19 carbomethoxy group had suffered no observable reduction. The carboxyl function at C-12 was likewise completely unaffected as demonstrated by quantitative lactone formation.



143 144 145 146

In Brown's early report[139] it was observed, that this reagent reacted only slowly with esters in ethyl or n-butyl ethers at reflux, and we suspected

a specific catalytic effect in the present substrate 144. To examine the general utility of sodium trimethoxyborohydride in dimethoxyethane as a reagent for ester reductions, the rates of reaction of the esters, methyl 3-phenylpropionate, methyl cyclohexylcarboxylate, and methyl abietate 147 were measured using the same procedure as above with three mole-equivalents excess of reagent. Reduction times and products are summarised in Table V. The expected alcohols were all produced in essentially quantitative yield and were characterised by their pmr spectra and as their 3,5-dinitrobenzoate derivatives.

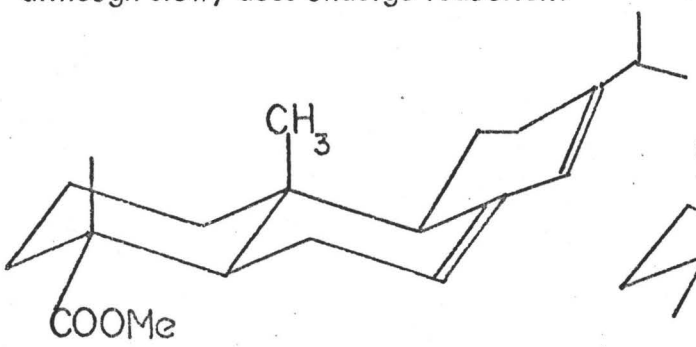
Ester	Time for 50% reduction (min)	Time for 100% reduction (min)	Product
Methyl 3-phenyl-propionate	17	40	3-phenylpropanol
Methyl cyclohexyl-carboxylate	27	60	Cyclohexylcarbinol
Acid-ester 144	32	75	Acid-alcohol 145
Methyl abietate 147	255	600	Abietenol

TABLE V

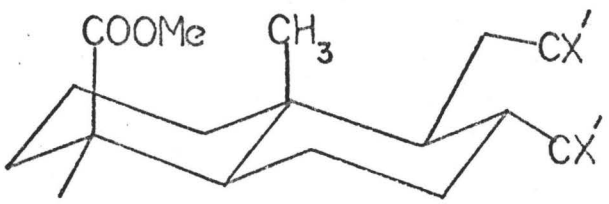
Reduction of Esters with Sodium Trimethoxyborohydride

Since sodium trimethoxyborohydride does not react with the carboxyl group group[131,139] (except to form the carboxylate anion) it would seem that the selective reduction of esters in the presence of carboxylic acids is readily achieved with this reagent[140]. The relative rates of reduction of the primary and secondary

esters, methyl 3-phenylpropionate and methyl cyclohexanecarboxylate (1.6:1 respectively for 50% reduction) show that some selectivity (ca. 60%) may be achieved between them[141]. This selectivity could be improved considerably by operating at lower temperatures, for example 0°. The very slow rate found for the tertiary ester, methyl abietate 147, indicates that excellent selectivity can be achieved between primary and secondary esters in the presence of tertiary esters and that the reagent should also be of synthetic use in these areas. The total non-reaction of the axial C-19 ester, in the ester-acid 144 (148) arises because of the severe 1,3-diaxial interaction with the C-20 methyl group. This may be compared with the more normal behaviour of the tertiary, equatorial methyl ester in 147, which although slow, does undergo reduction.



147



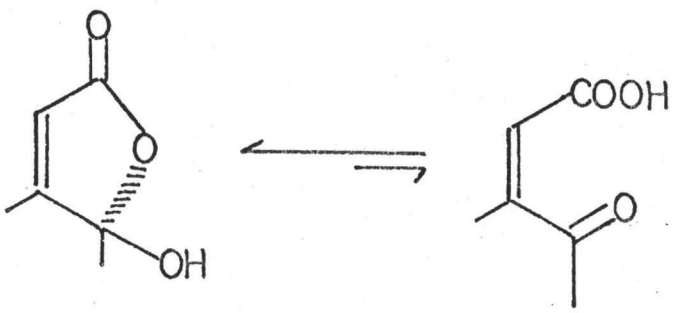
148

In view of Brown's report[139] of none - or very slow reduction, using other mono ethers it is possible that dimethoxyethane is giving a specific solvent effect with this reagent. The investigation of this possibility and the effect of different alcohol moieties in the ester group must await further experimentation.

V. - Derivation of Other Synthetic Intermediates from the Hydroperoxide 55

The rationale leading up to the ozonolysis of methyl podocarpate, and the subsequent isolation, by direct removal of solvent, of the hydroperoxide 54 have been recorded in Section II. The results of direct reduction of the crude ozonolysis reaction mixtures by sodium borohydride, direct oxidative work-up with basic hydrogen peroxide, and further examination of the hydroperoxide 55, are now considered.

Initial examination of the effect of mild reducing agents such as dimethyl sulphide and triphenylphosphine on the isolated, crude hydroperoxide gave superficially surprising results. Examination of the pmr spectra of the products from these reactions revealed apparently no change at all - except that the hydroperoxide proton absorption had moved and the vinylic absorption at 5.79 ppm had moved upfield to 5.63 ppm. Subsequently, when a pure sample of the hydroperoxide was obtained and reduced with aqueous methanolic sodium sulphite - a similar mild reducing agent for the hydroperoxide bond - the same product was obtained as before, but on this occasion as a crystalline solid. Its infrared was identical to that of 55. Analysis and other spectral data leave no doubt that the compound isolated is the unusually stable lactone hemi-ketal 93. When this lactone hemi-ketal was reduced catalytically over palladium, the keto-acid 36 was produced in high yield.



93 94

An interesting point of comparison between the saturated keto-acid 36 and the unsaturated keto-acid 94 is the observation that 94 exists entirely in the lactone-hemiketal form 93, whereas 36 exists only in the keto-acid form. The factors causing this unusual change in equilibrium between the two keto-acids are most reasonably a combination of bond angle changes introduced by the 9(11)-double bond, and steric interactions between the C-11 hydrogen and the hydrogens at C-1[142]. In 36 rotation about the 9,11-bond can enable the side chain to adopt suitable conformations which minimise the C-1, C-11 hydrogen interactions. However, keto-acid 94 has no such possibilities open to it and inspection of a molecular model places the C-11 hydrogen only 1.9 Å away from the C-1 equatorial hydrogen (sum of the van der Waal's radii of two hydrogens 2.4 Å) and 2.3 Å from the axial hydrogen. This interaction with the C-1 equatorial hydrogen is removed

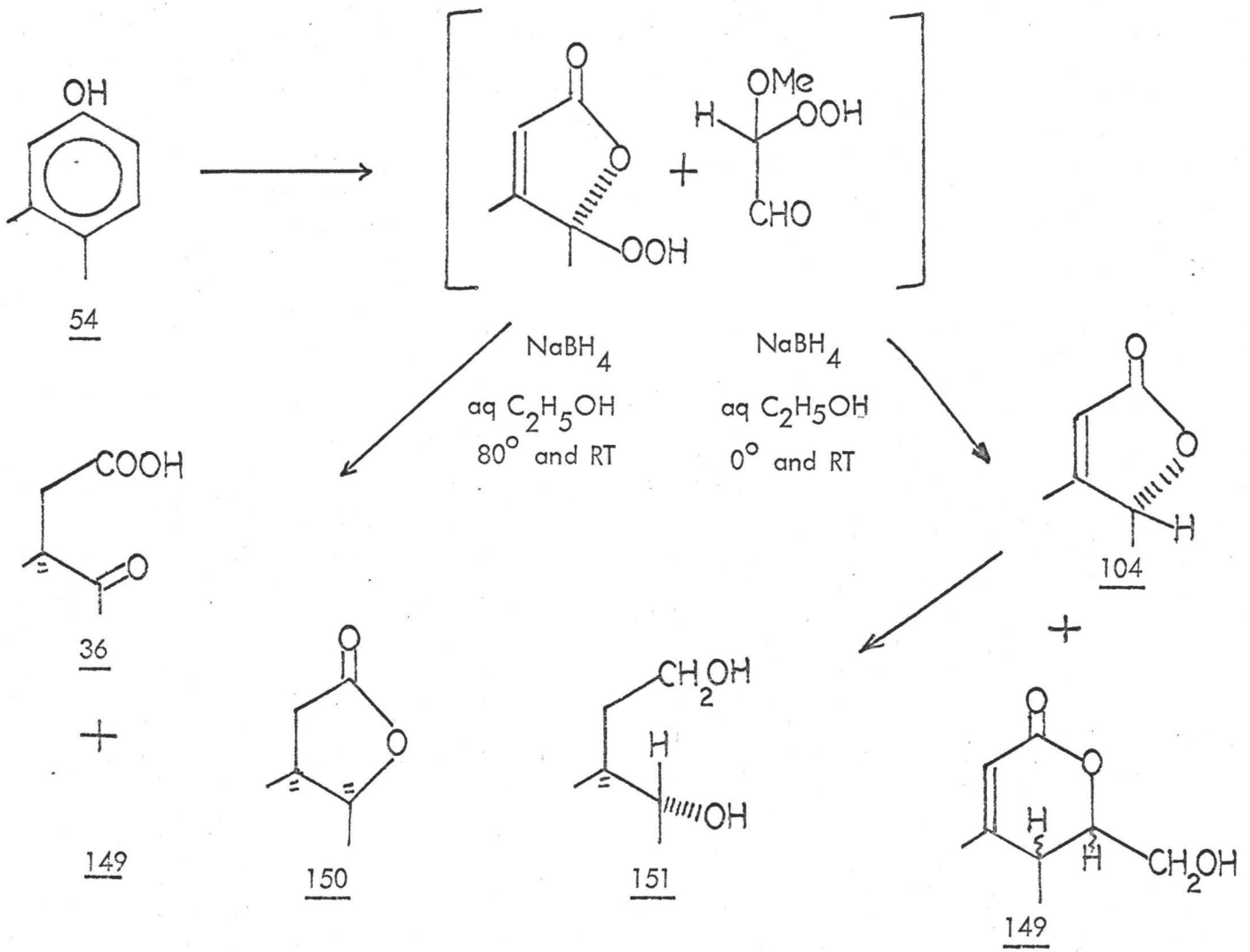


FIGURE 16 : Sodium Borohydride Reduction of the Ozonolysis Product from Methyl Podocarpate 54

in the lactone-hemiketal form 93 and examination of a molecular model places the C-11 hydrogen midway between the C-1 axial and equatorial protons and at distances of 2.3 and 2.5 Å respectively. It seems certain that the lactone-hemiketal 93 is the direct intermediate in catalytic reduction of the hydro-peroxide 55, and that 93 suffers further reduction itself before ring opening.

The results of sodium borohydride reduction of the crude ozonolysis mixture or of the pure hydroperoxide lead to a considerable diversity of products, depending upon the exact conditions used. The results are summarised in Figure 16. The origin of the five products obtained in variable amounts is most reasonably rationalised on the basis of hydroperoxide 55 being the sole precursor. The low temperature experiment is of significance in this respect, where the unsaturated lactone 104 was obtained in yields of as high as 85% when borohydride was added directly to the reaction mixture at -78°, followed by warming to room temperature and isolation. It thus seems that the lactone 104 is formed by reduction of the keto function of 94, obtained directly from the hydroperoxide structure, already in solution at -78°, via the lactone-hemiketal 93.

The structure of the unsaturated lactone 104 follows from the several results. It shows a single olefinic absorption at 6.20 ppm in its pmr spectrum (Figure 17) a γ-lactone band at 1755 cm^{-1} in its infrared spectrum, and is reduced with excess sodium borohydride in hot ethanol to the diol 151. The absolute configuration of the C-8 proton in 104 was determined by pmr and nuclear Overhauser

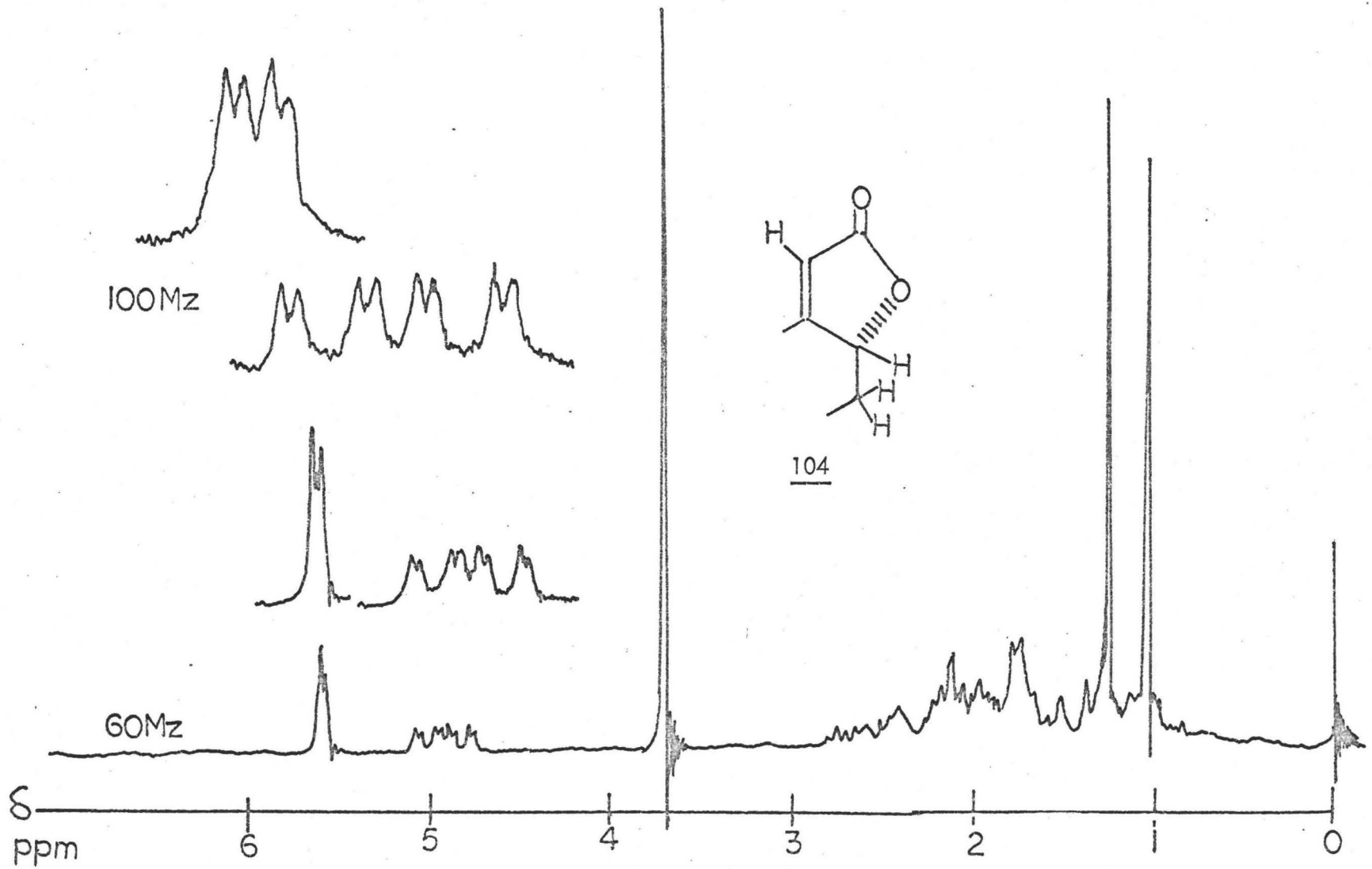


FIGURE 17 : Pmr Spectrum of Lactone 104

effect data. Examination of the pmr spectrum of 104 at 100 MHz revealed, (Figure 17) absorption due to the 8β-proton (a) at 4.86 consisting of two quartets J_{AB}=11.5Hz, J_{AC}= 7.5Hz, and J_{AD}=1.5Hz. The coupling constants J_{AB} and J_{AC} are consistent with the dihedral angles[143a] between the geminal C-7, α- and β-protons respectively and the 8β-proton. Also the coupling constant of 1.5Hz between the latter proton and the vinylic C-11 proton (d) is that expected for an allylic 4-bond coupling at 90°.[143b] Finally closer examination of the apparent doublet J_{AD}- 1.5Hz due to the vinylic proton (d) at 5.53 ppm, revealed at 100 Hz sweep width that the absorption was in fact a quartet with further splitting, J_{DB}=0.6Hz. This homo-allylic coupling probably arises from 'W-plan' interaction with the C-7β proton (c) which is most favourably placed for such coupling[143c, 144]. These coupling constants were confirmed by appropriate spin-decoupling experiments.

Since it appeared more reasonable, on inspection of a molecular model, to explain these results with the C-8 proton in the β configuration, rather than the expected α-configuration, we undertook to measure any observable nuclear Overhauser effect between the C-8 proton at 5.53 ppm and the C-20 methyl group. In the β-configuration the distance between these two nuclei is 3.16 Å so that an observable effect would be expected. Alternatively in the expected α-configuration no observable NOE would be possible as the C-20 methyl and the C-8 proton are then 4.5 Å apart. The experimental result was a

substantial NOE of some 18%. The β-configuration of the C-8 proton as represented in 104 is therefore taken to be correct.

Since this unsaturated lactone 104 was also formed as a side-product in the Reformatsky reaction discussed in Section III it appears that the enol-lactone 80 is the intermediate to 104 and that 104 is formed preferentially in a protonation-conjugation equilibrium from 80 in that process. It is certainly true that the lactone, and ring B in 104 are less strained than is the case in the alternative structure with C-8 proton-α. This therefore apparently results in the structure of greatest stability when a 9(11)-double bond is present which has the effect of tilting the C-9 and C-8 carbons away from the C-20 methyl group. The latter observation explains the preferred mode of β-attack by hydride on 94 to give 104 whereas in the same reaction on the saturated structure 36, α-attack is preferred yielding the known[60] saturated lactone 150.

When crude ozonolysis mixtures were reductively treated with boro-hydride direct, the two lactones 104 and 150 were produced by the above competing 1,2 and 1,4 reductions of 94 and 93, but were also sometimes accompanied by another product 149. This minor component was obtained from reductions of the crude ozonolysis product over a wide temperature range (-60 to +80°) in yields of 15-35%, which from its high resolution mass spectrum and analysis had molecular formula $C_{18}H_{26}O_5$. The proposed lactone-alcohol structure 149 is compatible with the recorded spectroscopic data. Thus 149 showed in its pmr spectrum the vinylic C-11 proton at 6.07 ppm, the C-17 proton

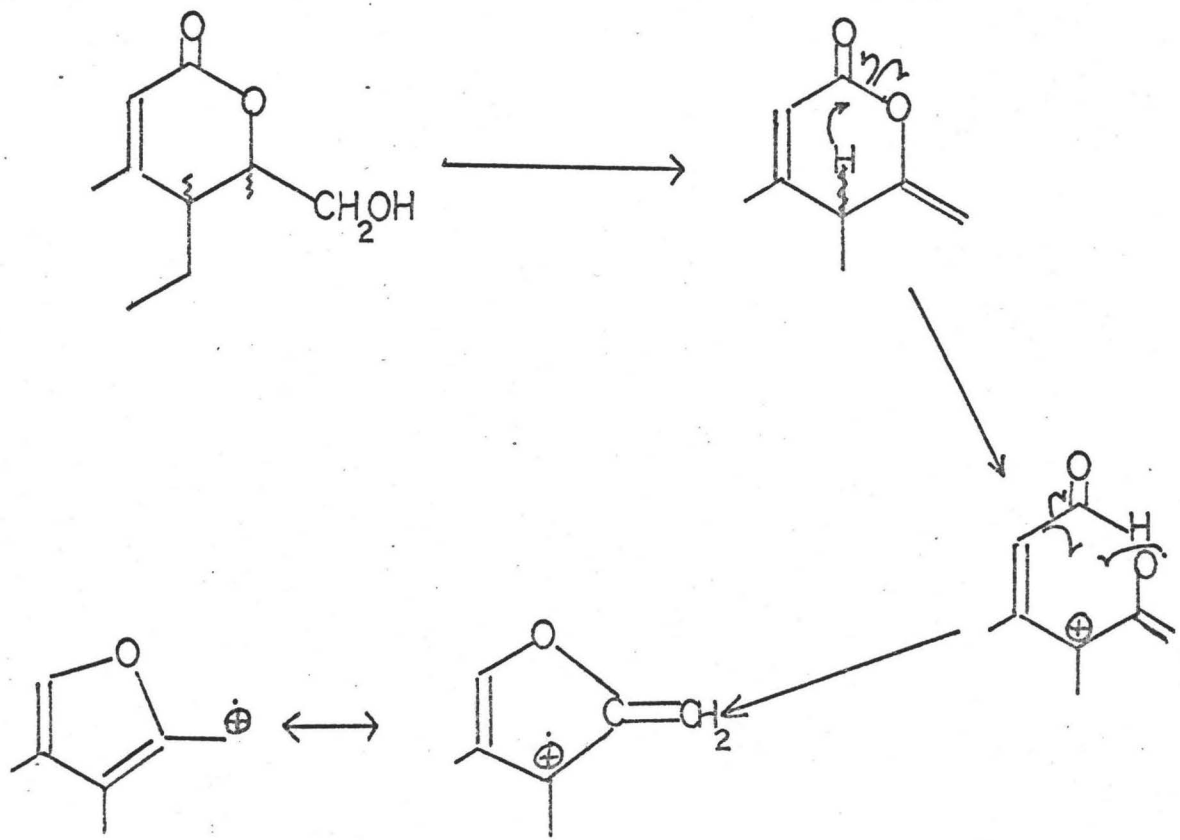


FIGURE 18 : Cleavage of Lactone Alcohol 149 in the Mass Spectrum

as a triplet (J = 5.5 Hz) at 4.68 ppm, and the hydroxymethylene protons as a doublet (J = 5.5Hz) at 3.82 ppm. The coupling of the C-17 proton and the hydroxymethylene protons were conclusively established by spin decoupling experiments. The infrared spectrum of 149 showed the hydroxyl absorption at 3610 and 3500 cm^{-1}, the C-19 ester and (12→17)-lactone carbonyl stretching at 1730 cm^{-1} and the ultraviolet spectrum showed a maximum of 214 mu (ϵ, 10,000) suggestive of a 9(11)-unsaturated lactone system (cf the maximum of 214 mu (ϵ, 10,400) for the lactone-acid 152). The high resolution mass spectrum was also consistent with the proposed structure of 149 (see Figure 18) and the molecular ion (intensity temperature dependent) showed an M-18 peak which corresponded with the ion $C_{18}H_{24}O_4$, indicating the loss of a molecule of water. This ion gave rise to an M-46 (base peak) which corresponded to the ion 151 $C_{17}H_{24}O_3$. This stable aromatic ion 151 results from the loss of a hydrogen atom and carbon monoxide from 150 and is a reasonable fragmentation for a cyclic lactone[145].

The stereochemistry at C-8 and C-17 of 149 is uncertain although the very small coupling (J = 1 Hz) between the C-8 and C-17 protons implies a dihedral angle of approximately 90°. The equatorial nature of the 8,17-bond with respect to ring B is substantiated by the observation that 149, although soluble in dilute base, immediately relactonised on mild acidification and this behaviour is paralleled by the saturated lactone 145 obtained previously (see Section IV).

The actual structure of 149 remains uncertain in view of our inability

to derive a mechanism for its formation from glyoxylic or other fragments, and hydroperoxide 55, as a result of base catalysed reactions. Since the potential of a structure such as 149 is obvious, in synthesis of the present type of diterpenes, further investigation should be worthwhile.

We can now consider the product of oxidative work-up of the crude hydroperoxide containing ozonolysis mixture, namely the seven-membered lactone-acid 152, which was obtained in high yield (90%), by treatment of pure (or crude) hydroperoxide with basic hydrogen peroxide in methanol at reflux for thirty minutes. The structure of 152 follows from its infrared spectrum which showed absorption for a carboxyl group at 1720 cm^{-1} and a δ -lactone at 1730 cm^{-1}, and its pmr spectrum which showed the C-11 proton as a single sharp singlet, at 6.22 ppm and the two protons at C-7 as a multiplet at 4.20 ppm. This multiplet showed a variable line shape pattern in the temperature range 30-70°, and was thus assumed to be present in a flexible ring system. In addition the ultraviolet spectrum of 152 showed maxima at 214 mu (ϵ, 10,400) and 280 mu (ϵ, 190) consistent with the conjugation of the system proposed.

The origin of 152 was disclosed by the results of further experiment. Since it is possible to derive a mechanism for formation of the lactone 152, without involving hydroperoxide ion, but simply base alone, it was deemed of interest to determine the effect of base alone on the hydroperoxide 55 and the lactone-hemiketal 93. Refluxing of these two substances in aqueous/ethanolic sodium hydroxide for four to six hours led to yields of from 50-70%

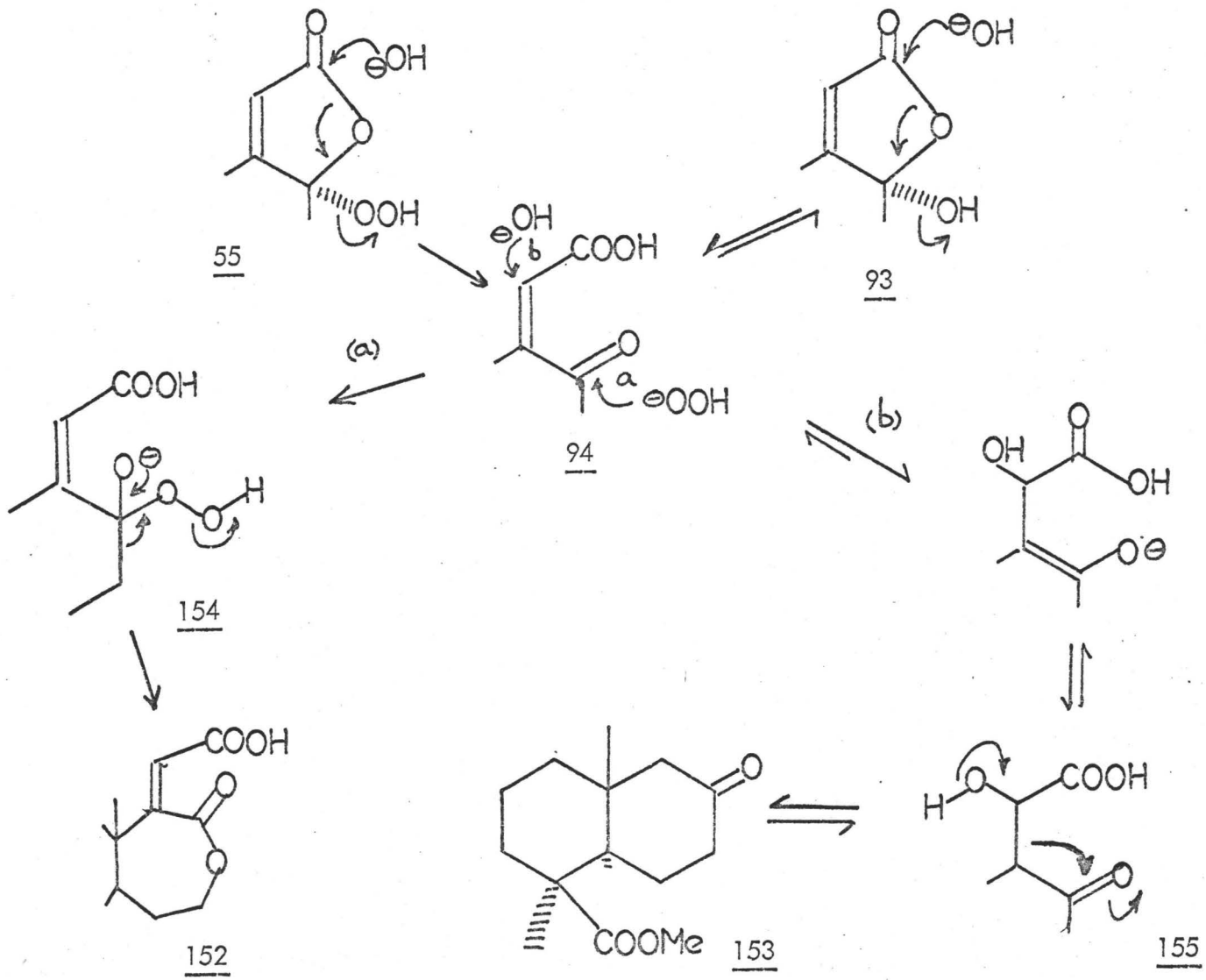


FIGURE 19 : Mechanism of Formation of (a) Lactone-Acid 152 and (b) of Decalone 153

of the substituted 6-decalone 153. The results of these experiments together with that of hydrogen peroxide attack can be explained by the presence of the common intermediate 94, the open-chain acid form of the lactone-hemiketal 93, which is presumably present in significant amount in strongly basic solution Attack on this species can follow two paths, namely pathway (a), by hydroperoxide ion addition to the lactone 152, or pathway (b), by hydroxide ion addition to the 9(11)-double bond leading to the decalone 153.

Hydroperoxide attack is fast at the C-8 carbonyl (a) (reaction over in 30 minutes or less), giving the anionic intermediate 154 which undergoes a 1,2-shift onto oxygen of the C-7, C-8 bond leading to product. The slower (reversible) attach at C-11 of 94 by hydroxide ion, gives the hydroxy-ketone 155, which can undergo reverse oldol condensation eliminating the C-11, C-12 carbon unit to give the decalone 153. It is also possible that some hydroxide attack can occur α, at C-9 giving an α-diketone 156 which would undergo benzylic acid type of rearrangement to the acid 157.

156 157

This could account for one or more of the acidic components also produced in the base reactions.

The formation of the decalone 153 in good yield, is of considerable interest in view of the effort which has been expended in total synthesis of its 5, and 7-ketonic isomers[146]. These compounds, containing the same or antipodal stereochemistry at C-1 (C-4 diterpenoid numbering), have been of considerable value in synthesis of certain tricyclic resin acids[146,147]. It is thus possible that decalone 153 could be a valuable synthetic intermediate, if base catalysed condensations can be effected at C-5 without retro-aldol condensations. The compound has not apparently been described before in the literature.

VI. - C-20 Methyl Chemical Shifts of Diterpenoids

It has been noted by a large number of authors that the resonance frequencies of the tertiary methyl groups of steroids and terpenes in their pmr spectra, constitute a sensitive method for structure determination because of their easily discernable nature in otherwise complex spectra. A large number of steroids have been examined and as a result of consideration of some 260 examples of known structure, it has been possible to derive with few exceptions, self-consistent chemical shifts for C-18 and C-19 methyl groups, caused by specific functional groups at the various skeletal locations[148]. The results allow, on the assumption of the additivity of chemical shifts, an immediate check of any proposed structure, using the four saturated, androstane hydrocarbons, as reference compounds in these cases.

Several approaches have since been made to derive, and collate data, for a similar set of values for diterpenes[149]. Such attempts have so far only met with limited success, even though such studies have been restricted to certain groups of diterpenes such as the resin acids. In many diterpene acids it is well established[150] that methyl groups attached to a carbon atom which also bears a carboxyl group resonate at a lower field than do isolated methyl groups. Thus in the present examples, the C-20 methyl group is consistently more than 0.15 ppm up-field of the C-18 methyl group at C-4 to which the β C-19 carboxyl is attached.

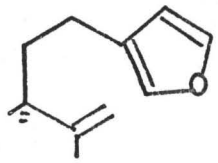
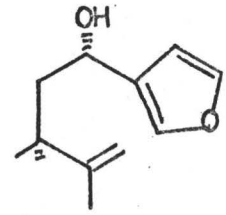
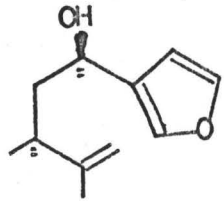
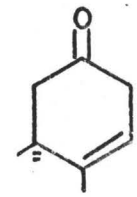
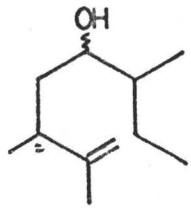
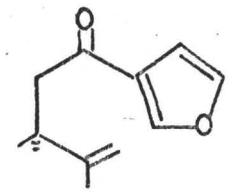
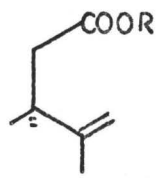
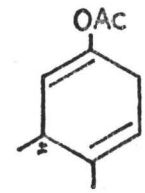
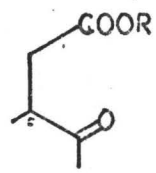
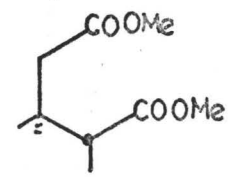
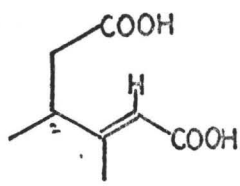
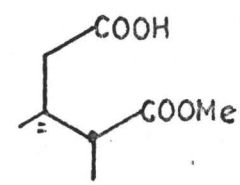
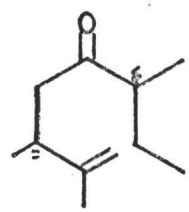
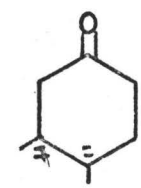
In addition to this inductive effect, transannular shielding of the C-20 methyl by the C-19 carboxyl occurs[151]. This effect is most marked when the acid is esterified (methyl ester in recorded examples), and results in an up-field shift of 0.20 ppm in podocarpic acid 35, for instance.

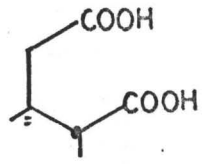
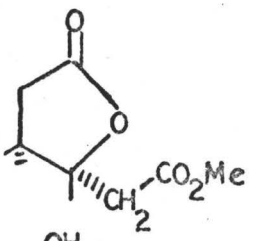
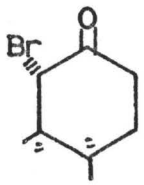
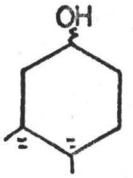
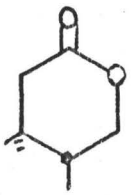
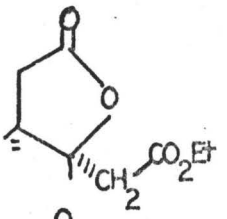
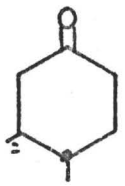
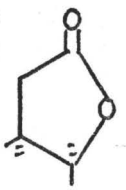
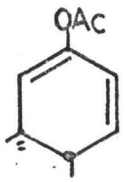
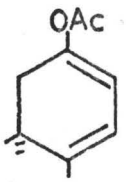
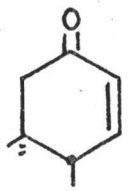
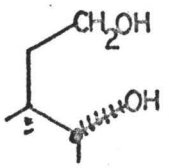
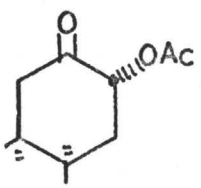
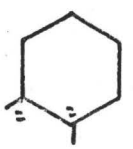
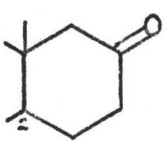
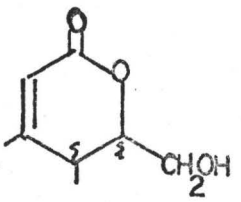
Recent calculations by ApSimon et al[152] on the anisotropies of carbon-carbon single, and double bonds, and the carbon-oxygen double bond[153] however, have led to satisfactory agreement with calculated and observed shift values for the resin acids and their hydrogenated derivatives. Although no such attempt has been made in the present study, to correlate C-20 methyl chemical shifts, nonetheless some interesting and regular trends have been noted, particularly with regard to the influence of the carbon double bond and carbonyl group in ring C. In Table VI the majority of the compounds encountered directly or indirectly in this thesis have been listed in order of decreasing shielding of the C-20 methyl group.

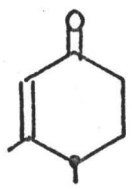
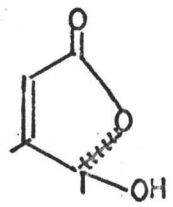
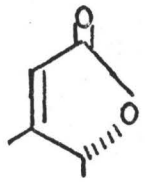
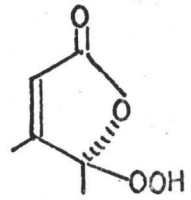
Several generalisations may be made on a superficial examination of the data. The strong shielding influence of a 8(14) - or 8(17)- double bond or 8-carbonyl group, is easily seen by comparing early entries in the table with the desoxy-hydrocarbon 158. Further that this influence is virtually independent of other structural modifications emphasizes its powerful influence. Likewise the strong, deshielding influence of a 9(11)-double bond is apparent from several examples. On the other hand a 8(9)-double bond between the B/C rings has only a mild shielding influence. Table VI reveals some initial, semi-quantitative predictions of the effect at C-20 methyl of variously placed functional groups, but emphasis should be made at this

TABLE VI

Chemical Shifts of C-20 Methyl Resonances Correlated with Structure (β, C-19 Methyl Esters in all cases)

Code		Signal	Code		Signal
38		28.0	131		32.5
132		31.0	67		33.0
37		31.0	61		35.5
58/112		32.0	139		36.0
36/112		32.5	143		37.0
57		32.5	144		38.0
53		32.5	66		41.5

142		39.5	56		44.5
48		40.5	64		45.0
146		41.0	56		45.5
65		43.0	150		46.5
133		41.5	50		47.0
49		42.5	151		50.0
76		43.0	158		52.0
153		43.0	149		55.0

69		56.0	93		67.5
104		59.5	55		68.5
54		63.0			

stage that these observations are inductive rather than decisive.

Several illustrations of how such information may be of use in the structural identification of new intermediates can be briefly given.

(a) As was pointed out in Section I, the early evidence for the structure of bromo-ketone 48 was not unequivocal. The possibility existed that the α-bromine atom was 11-α, or 13-β with ring C in a twist form. Consideration of the close similarity of the chemical shifts of the bromo-ketone 48 and the parent keto-ester 66 in Table V, reveals that the strong deshielding influence expected for a bromine-carbon bond at C-13[154] is not present, and therefore this structure is unlikely.

(b) The chemical shift of the C-20 methyl group in the enol acetate 50 is unusually deshielded. As this compound has an 8(14)-double bond and as the 12(13)-double bond's effect is weak (see Table VI), for effect of double bond at 11(12), and 13(14) positions, a fairly strong shielding effect would be expected. Since none is observed and the compound on balance is deshielded some other effect is obviously in operation. Just such an effect was alluded to above in Section IV, with regard to the ORD spectra of enol acetate 50 and laevopimaric acid; i.e. the suggestion that there may be a specific interaction between the conjugated diene system and the C-20 methyl group in 50, causing a net downfield shift in the pmr spectrum, and also stabilising the somewhat unusual conformation, used to explain the ORD Cotton Effect in 50, and in laevopimaric acid. This point is obviously purely speculative and in analogy to Burgstahler et al's[110] argument for laevopimaric acid.

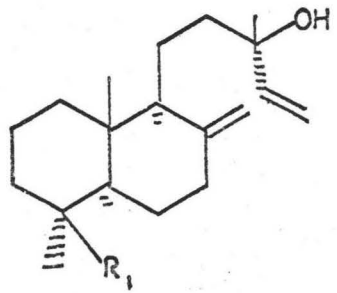
GENERAL CONCLUSIONS AND POTENTIAL SYNTHETIC SCOPE

The synthesis of 12-hydroxylabd-8(17)-en-19-oic acid 37 outlined above was derived from two key intermediates, keto-acid 36 and the olefinic acid 58. In addition, condensation of 3-furyl lithium with the acid chloride 60, derived from 58, led to the ketone precursor 59, of methyl lambertianate 38 ($R = CH_3$).

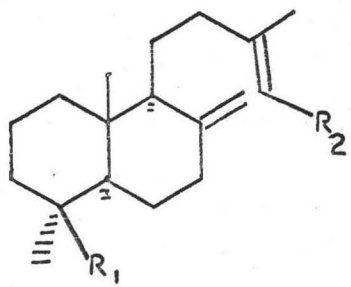
It may be recalled from the General Introduction that cyclisation of geranyl geraniol ii or geranyl linalool iii (as phosphate esters by enzymes in plants) leads to the bicyclic alcohol(s) iv, with the labdane skeleton, from which all diterpenoids are postulated to be derived. Over the last decade a striking number of oxygenated diterpenoids have been isolated from various plant sources, which may be considered derived from the initial alcohol(s) iv. Those which contain an oxidised C-19 carbon atom, including the derivatives corresponding to iv, cupressic 159 ($R_1 = COOH$) and isocupressic 160 acids ($R_1 = COOH$, $R_2 = CH_2OH$), are shown in Figure 20.

Utilising the synthetic intermediates 36 and 58, a number of straightforward conversions to many of these substances is now possible. A few examples must suffice here.

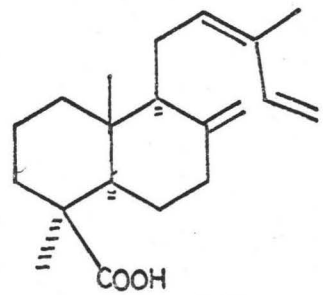
(a) Cupressic 159 ($R_1 = COOH$), isocupressic 160 ($R_1 = COOH$, $R_2 = CH_2OH$), agatholic 160 ($R_1 = CHO$, $R_2 = COOH$), agathic 160 ($R_1 = R_2 = COOH$), communic 161, elliotinoic 162, imbricatol 163, sciadopic 164 - acids, and



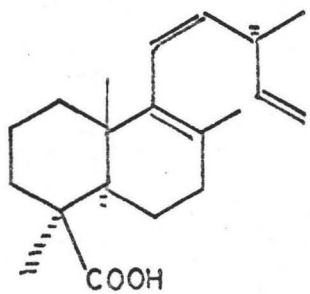
159



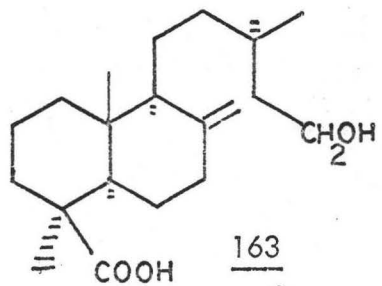
160



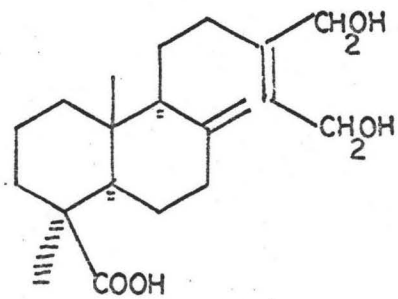
161



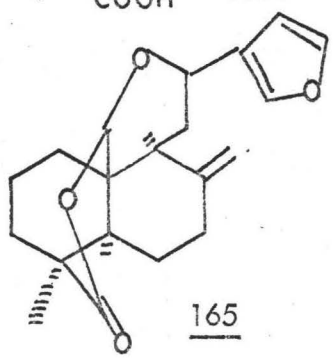
162



163



164



165

FIGURE 20 : Some β, C-19 Oxygenated Diterpenes with the Labdane Skeleton

torulosol 159 ($R_1 = CH_2OH$) should all in principle be derivable from analogues of the acid chloride 60 by condensation of the appropriate lithium derivative (or cadmium analogue where stable and necessary). Products would then result by reduction, elimination or reductive elimination of the C-12 carbonyl so formed.

(b) Photochemical functionalisation of the C-20 methyl group, and similar treatment with the furan sequence above, followed by lactonisation could lead to the sciadin structure 165. Thus it seems reasonable to expect further synthetic application by the routes indicated.

Finally, sodium trimethoxyborohydride in preliminary investigations, has been shown to be a good selective reducing agent for the carboxylic ester function, particularly in the presence of carboxylic acids which are not attacked.

EXPERIMENTAL

Apparatus, Methods and Materials

Melting points were determined on a Kofler micro hot-stage apparatus and are uncorrected unless otherwise stated.

Infrared spectra were obtained on Beckmann IR-5 and Perkin-Elmer 337 infrared spectrophotometers in chloroform solution or as nujol mulls.

Proton magnetic resonance (pmr) spectra were recorded on Varian Associates HA-100, A-60 and T-60 spectrometers in deuterochloroform solution, using tetramethylsilane as internal standard. Unless otherwise stated the spectra refer to 60 MHz. The Nuclear Overhauser Effect (NOE) experiments were kindly performed by Mr. J. Saunders of this department. The symbols s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet are used below in the recording of spectra.

Optical Rotatory Dispersion (ORD) measurements were performed in methanol or cyclohexane solution on a JASCO ORD - UV - 5 instrument at the University of Toronto by kind permission of Dr. J.B. Jones.

Mass spectra were determined on an Hitachi Perkin-Elmer RMU-6A spectrometer and also on a C.E.C. 21-110 high resolution mass spectrometer. 'Mass matching' measurements on the latter instrument were kindly performed by Drs. G.E.F. Gracey and L. Baczynsj of this department. Ultraviolet spectra

were obtained in methanol solution using a Carey-14 spectrophotometer.

Carbon, hydrogen, and oxygen microanalyses were performed by Spang Microanalytical Laboratories, P.O. Box 1111, Ann Arbor, Michigan, 48106, USA.

In the experimental descriptions to follow, the phrase "--- worked-up in the usual way---" refers to the following procedure. - The organic extract (in the specified solvent) was washed once with water, once with saturated brine and dried by filtration through granular anhydrous sodium sulphate. Solvent was then removed in vacuo from the resultant extract, on a Buchi-Rotavapor 'R' - rotary evaporator, using a water bath at 50 - 70°. - Any modification or addition to this procedure is so stated where appropriate.

Analysis of product compositions in all cases was by examination of their pmr spectra - in particular the C-20 methyl absorption region. The number of components present were usually readily estimated and their relative proportions obtained by direct integration. In the numerous experiments where diazomethane was used in small or large quantities, the procedure of Th. J. de Boer and H.J. Backer[156] was used, utilizing Diazald (Aldrich) (N-methyl-N-nitroso-p-toluenesulphonamide). Small quantities of ethereal-alcoholic diazomethane so obtained could be stored at -20° in the dark for up to a week without serious deterioration.

A - Conversion of Podocarpic Acid to the Keto-acid 36, Via Reduction and Subsequent Ring Fission

1. 12β-Hydroxy-8α-podocarpan-19-oic acid 45 (R_1 = OH; R_2 = H)

The general procedure of Meyers et al[28] was used. Fifty grams (0.182 mol) of podocarpic acid, (obtained from Timber Processing Cpy. Ltd., Auckland, New Zealand - recrystallized from 10% aq. methanol to mp 192-193° and dried in vacuo at 80° for 24 h to remove methanol of crystallization) - was added to a mixture of 12.5 g of 5% rhodium-on-alumina, (Engelhard Industries Inc.) and 200 ml of 95% ethanol containing 1% acetic acid, and the mixture shaken under hydrogen (40 - 50 psi) at RT in a Parr apparatus. Uptake of hydrogen effectively ceased after 48 h.

The reaction mixture was filtered under reduced pressure, the filter pad being washed well with methanol, and the filtrate evaporated to dryness in vacuo to give 50.5 g of crude hydroxy-acid as a colourless solid. Because of the insolubility of the compound and its susceptibility to air oxidation, dissolution in ethyl acetate for crystallization was performed under nitrogen at reflux temperature. One further crystallization in a similar manner gave 25.0 g (50%) of the cis(β)-hydroxy acid 45 (R_1 = OH; R_2 = H), mp 230-234°, lit.[24] mp 234.5-236°, pmr (60 MHz, pyridine/CS_2) δ 0.97 (s, 3H, C-20 CH_3), 1.26 (s, 3H, C-18 CH_3), 3.68 (s, broad, 2H, C-19 COOH and C-12 OH) ppm.

The crude hydroxy-acid obtained in this reduction has been shown[30],

by methylation and acetylation in pyridine and pmr examination, to consist of the cis-12α- and cis-12β-alcohols in an approximate ratio of 3:5 respectively. These acetates were identified by an independent synthesis[30].

In addition to the cis B/C ring junction alcohols which compose some 82% of the reaction mixture, there is 15% of trans B/C ring junction alcohols present, and approximately 3% of deoxygenated material. This analysis was derived from the direct oxidation-methylation sequence described below.

2. 12-Oxo-8α-podocarpan-19-oic acid 46

The crude cis-12 -hydroxy acids 45, mp 225-230°, 25 g, were dissolved in 1.2 l acetone, the solution cooled to 10° and Jones'[23] reagent added dropwise until excess reagent was present as evidenced by an orange colouration. After destruction of excess reagent with isopropanol, the majority of solvent was removed in vacuo at 40°, the residue diluted with water and benzene extracted (3 x 100 ml). Usual work-up gave 25.1 g crude crystalline keto-acid which on recrystallisation from hexane : ether (50:50) yielded 18.3 g (73%), keto-acid 46, mp 170-173°, (>98% pure, lit.[24] 168-174°; pmr (60 MHz) δ 0.79 (s, 3H, C-20 CH_3), 1.25 (s, 3H, C-18 CH_3), 10-11 (s, broad, C-19 COOH) ppm; mass spectrum, m/e 278, 260, 234, 232, 217, (mol wt. 278).

The keto-acid could also be recovered in good yield by crystallization from the mother liquors of 45 above; formed by air oxidation.

3. Methyl 12β-Hydroxy-8α-podocarpan-19-oate 64

Five grams of twice crystallized hydroxy-acid 45 mp 230-234° were

dissolved in (R) methanol and ethereal diazomethane added dropwise until excess was present. The ether-methanol was then removed in vacuo to give 5.24 g of a near-colourless gum, pmr (60 MHz) δ 0.75 (s, 3H, C-20 CH_3), 1.15 (s, 3H, C-18 CH_3), 3.56 (s, 3H, C-19 CH_3) ppm. The sample contained 5% of 12α-hydroxy B/C-cis isomer plus 15% keto-ester 64 resulting from air oxidation in handling.

4. Methyl 12-Oxo-8α-podocarpan-19-oate 66

A slurry of 50.5 g of the crude hydroxy-acid 45, direct from reduction, was treated with portions of ethereal diazomethane at RT until the yellow colour of excess reagent had been present for 15 min. The solvent was then removed in vacuo to give 53.0 g of the crude hydroxy-ester 64 + 47, as a pale yellow gum. The gum was dissolved in 500 ml of (R) acetone and Jones' reagent added dropwise to the well stirred solution maintained at 10-25° with an ice-bath. When excess reagent was visible as a permanent orange colouration, the reaction was arrested by the addition of isopropanol and the bulk of the acetone removed in vacuo at 30-40°. The residue was diluted with 500 ml water and extracted with ether (2 x 200 ml) and benzene (1 x 100 ml). The combined organic extracts were worked-up as usual to give 52.0 g (98%) of pale yellow-green crystals. The pmr spectrum showed the product to consist mainly of the desired cis-keto-ester 66, together with some trans-keto-ester 65, and traces of other components.

The mixture was washed through 300 g alumina in benzene, when the majority of the colour and non-oxidized and aromatic material was removed, giving 50 g (95%) of a crystalline mixture of 66 and 65. Integration of the 100 MHz

pmr spectrum of the C-19 $COOCH_3$ absorptions, at 3.63 and 3.66 ppm respectively, showed that this mixture consisted of 85% 66 and 15% 65.

Separation of the ketones 66 and 65

a) Direct fractional crystallization. The above mixture of keto-esters (50 g) was dissolved in 200 ml of boiling ethyl acetate: hexane (1:3) and the solution seeded with pure cis-keto-ester 66 and cooled slowly to room temperature. After standing for 48 h at room temperature, 33 g (62% from podocarpic acid) of the cis-keto-ester 66 was obtained as colourless slabs, mp 120-122°; pmr (60 MHz) δ 0.69 (s, 3H, C-20 CH_3), 1.17 (s, 3H, C-18 CH_3), 3.63 (s, 3H, C-19 $COOCH_3$) ppm; lit.[24], mp 120-121.5°. The mother liquors, after evaporation and dissolution in 50 ml ether - 5 ml ethyl acetate - 15 ml hexane at the boiling point, seeding, and standing at room temperature, yielded a further 4.2 g of cis-keto-ester 66, (8% from podocarpic acid) mp 118-120° (purity 95% by pmr).

b) Girard's Reagent 'T' Extraction. For some time, several separations were achieved as detailed in a specimen run below, using reagent 'T' (trimethyl aminoacetylhydrazide chloride) obtained from Fisher Chemical Company. However using reagent 'T' from Matheson Coleman and Bell Company, and British Drug Houses Limited gave totally different results. The trans-keto-ester reacted as fast as the cis-keto-ester so that no effective separation resulted. See 'Results and Discussion' for further comments on this problem.

A typical procedure was: - Crude keto-esters mixture 25.0 g, was dissolved in 200 ml of 95% ethanol containing 20 ml acetic acid and refluxed

(stirring under N_2) - with 20 g Girard's reagent 'T' for 1.5 h. After cooling the reaction mixture was poured into 600 ml water containing 220 ml 1N sodium hydroxide, and extracted with ether (3 x 150 ml). The aqueous layer was then treated with 80 ml conc. hydrochloric acid and stood at room temperature for 1 h. Work-up via benzene gave 18.25 g (69% from podocarpic acid) of pure cis-keto-ester 66 mp 121-122°; mass spectrum (80 ev) m/e 292, 260, 233, 218 and 215; (mol. wt. 292).

5. Methyl 12-Oxo-podocarpan-19-oate 65

The mother liquors from the above crystallizations contained approximately 60% of the trans-keto-ester 65. In one experiment, careful seeding with a sample of pure 65 (obtained by hydrogenation of the trans α/β-unsaturated ketone 49, using 5% Pd/C[24]) gave 65 as colourless crystals, mp 110-115° (>90% pure by pmr spectroscopy); pmr δ 0.715 (s, 3H, C-20 CH_3), 1.17 (s, 3H, C-18 CH_3), 3.65 (s, 3H, C-19 $COOCH_3$) ppm. lit.[24] mp 116-121.5°.

6. Methyl 11α-Bromo-12-oxo-8α-podocarpan-19-oate 48

To a solution of 39.3 g (0.135 mol) of cis-keto-ester 66, mp 120-124°, in 1500 ml of dry carbon tetrachloride (molecular sieves) was added 25.5 g (0.140 mol) of N-bromosuccinimide and one drop of 48% hydrobromic acid. An immediate liberation of bromine as an orange colouration vanished after 30 sec. and after stirring at RT for 2-4 h the reaction was complete as evidenced by the supernatant succinimide present and the absence of any N-bromosuccinimide. The solution was washed free of succinimide and hydrogen bromide by shaking with

water (3 x 300 ml), filtered through anhydrous sodium sulphate and evaporated in vacuo at 40°. Drying at 0.5 mm overnight gave ca 50 g (100%) of crude bromo-ketone. The pmr spectrum of the crude reaction product showed the presence of 85-90% of the desired compound together with 5% unreacted starting material and 5-10% other stereoisomeric bromo-ketones (mainly mono-brominated). Crystallization from hexane-ether at 0° yielded 35.0 g (70%) of bromo-ketone 48 as colourless crystals, mp 145-150°. A second crystallization gave 30 g of 48 mp 151-152°; pmr δ 0.68 (s, 3H, C-20 CH_3), 1.17 (s, 3H, C-18 CH_3), 3.1 (m, 1H, C-13 axial H), 3.57 (s, 3H, C-19 $COOCH_3$), 4.37 (s, broad Wh/2 = 4Hz, 1H, C-11 equatorial H) ppm. lit.[24] mp 152-153°.

Nuclear Overhauser Effect measurements were obtained on a carefully degassed 0.16 M-solution of 48 in deuterioacetone. The experiments were performed at 100 MHz in frequency-sweep mode. The second saturating rf field applied was of the order of 0.75 - 1.0 milligauss[37], and area integrations were repeated at least 25 times for each signal. We have found area increases down to as low as 3% to be quite reproducible with current instrumentation. Many such small area increases have been noted in compounds on unequivocal structure[37] giving increased confidence in the application of the method in the present study.

7. Dehydrobromination Experiments

a) Dimethyl acetamide (DMA) - Calcium Carbonate. - The general procedure of Green and Long[44] was used. To determine the change in product composition with the time of the reaction, a number of small scale runs were

carried out. Two grams of bromo-ketone 48, mp 151-152°, were added portionwise over 2 min to 40 ml of refluxing dimethylacetamide (dried over calcium hydride) containing 4 g of precipitated calcium carbonate. The additions were made through a vertical side-arm in the flask connected to a wide-neck powder funnel, and the boiling solution was protected from atmospheric oxygen by a positive pressure of dry nitrogen. Further reflux was continued under nitrogen for 3, 8, 18, 28, and 48 min in five successive runs. Each run was quenched by cooling rapidly in an ice-bath, filtering under pressure with the filter-pad being well washed with ether, the filtrate diluted with twice its volume of water and the whole extracted with ether. The dried and evaporated extracts yielded pale yellow oily or crystalline products which were examined by pmr spectroscopy. The components were identified by the chemical shifts of their C-20 methyl absorptions. The assignments of these absorptions were made from the pmr spectra of authentic samples of each compound and are recorded in Table III (see Discussion).

The individual compounds were either prepared and isolated as given below or obtained from separate sources. The differences between the chemical shifts of the C-20 methyl groups were sufficient to permit the determination of the product composition either by direct integration or simple triangulation and weighing. The relative intensities of the bromo-ketone C-11 proton, and the various vinylic absorptions were also helpful. The product composition results were found to be reproducible to within + 3% and are shown in Table II (see Discussion).

b) Other Dehydrobromination Reagent Trials. -

(i) Calcium carbonate-dimethyl formamide (DMF). Dry dimethyl formamide 40 ml, and 4 g calcium carbonate (precipitated) were brought to reflux under N_2 and 2.0 g of 48 added in the usual manner over 3 min and the whole refluxed with stirring for further 7 min.

Cooling and usual work-up gave 1.98 g white crystalline solid, which pmr analysis showed to be unchanged starting material.

(ii) Lithium carbonate-dimethylacetamide. The same procedure as in (i), with 2.0 g of 48, 2 g lithium carbonate, and 50 ml DMA was used. The product on work-up was unreacted starting material.

(iii) Lithium carbonate-lithium chloride-dimethyl acetamide. The same procedure as for (ii) was used and in addition 2.0 g of dried (110°) lithium chloride was added. Refluxing was continued for 15 min. Pmr analysis showed 5% unreacted starting material, 10% $\alpha\beta$-unsaturated ketone 49, 15% $\alpha\beta$-unsaturated ketone 69, 7% $\beta\gamma$-unsaturated ketone 68, 55% $\beta\gamma$-unsaturated ketone 67, and ca 3% methyl podocarpate 54.

(iv) Calcium carbonate-calcium chloride-dimethyl acetamide. Bromoketone 48, 2 g, calcium carbonate 2g, and calcium chloride (anhydrous-powdered) 2 g were used in 40 ml DMA, refluxing for 3 min (addition time 3 min). Usual work-up and pmr showed, 65% unreacted starting material, approximately 10% each of ketones 69, and 49, 10% of 67 and less than 5% of 68.

(v) Dimethyl acetamide alone - No added base. Two grams of bromoketone 48 were added to 50 ml refluxing DMA in the usual way (2 min) and

refluxed for 15 min. Usual work-up and pmr analysis showed, 14% methyl podocarpate 54, 16% 69, 5% each of 68, and 67, 15% unreacted 48 and 45% 49.

(vi) 1,5-Diazobicyclo 4.3.0 non-5-ene (DBN). The bromo-ketone 48 2.0 g (5.38 mmol) was dissolved in 20 ml of dry benzene and brought to reflux under nitrogen. 0.73 g (5.9 mmol) DBN[57] in 7 ml dry benzene was added dropwise over 2 min. After 1 h of refluxing under N_2, the reaction mixture was cooled, washed three times with 5% NaH_2PO_4 solution and worked-up in the usual way. The product showed some 20% 67, and 80% starting material. Repetition of the experiment using xylene rather than benzene gave after 30 min reflux, 50% starting material, 25% 67, and 25% methyl podocarpate 54.

(vii) Substituted hydrazine derivatives. Attempted elimination of bromine using these reagents in acetic acid gave mainly the C-13 acetoxy substituted ketone 76, by displacement. Thus Girard's reagent 'T' gave a 70% yield of this compound (see below), 2,4-dinitrophenylhydrazine gave some starting material, possibly some 76, and several other products which were unidentified. Semicarbazide (free base) gave a mixture of products including 76, but no olefinic material.

Typically, 2.0 g of bromo-ketone 48, was refluxed in 20 ml ethanol containing 2 ml acetic acid and 2 g of Girard's reagent 'T' for 45 min under N_2. The cooled mixture was poured into water and ether extracted. The aqueous extract was acidified with 10 ml concentrated hydrochloric acid and stood at room temperature for 30 min, and then isolated via benzene to give 1.53 g yellow oil which pmr analysis indicated to be new compound (90% purity). Two

crystallizations from 5% ethyl acetate -hexane methyl 13α-acetoxy-12-oxo-8α-podocarpan-19-oate 76 as off-white needle-clusters mp 115-116° ir ν_{max} 2950, 1745, 1725, 1370, 1210(b), 1158 cm^{-1}; pmr δ 0.72 (s, 3H, C-20 CH_3), 1.15 (s, 3H, C-18 CH_3), 2.05 (s, 3H, -$OCOCH_3$), 3.60 (s, 3H, C-19 $COOCH_3$), 4.95 (t, $J_{apparent}$=3.5Hz, 1H, C-13β H) ppm. Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63; O. 228.83. Found : C, 68.50; H, 8.55; O. 22.98.

When the reaction with semicarbazide was conducted in tetrahydrofuran: butanol with a trace of HCl, no reaction occurred in 3 h at reflux temperature. Similarly attempted preparation of the Girard 'T' derivative using Amberlite IRC '50' acid exchange resin[163] in t-butyl alcohol gave completely unchanged starting material.

8. Methyl 12-Oxopodocarp-8(14)-en-19-oate 67

Ten grams (27.0 mmol) of the bromo-ketone 48, mp 147-152°, were added portionwise over a period of two minutes to a mixture of 200 ml of dry, refluxing DMA and 20 g precipitated calcium carbonate, and the whole refluxed for a further 8 min under nitrogen. The products were isolated via ether extraction as described above and yielded 7.72 g (99%) of a pale yellow oil the composition of which is recorded in Table II (10 min reaction). The material was transferred onto a column of 400 g of Silica Gel (11-200 mesh, Davidson Chemical Company) in 1:1 benzene-petroleum ether (30-60°).

The chromatogram was developed with 500 ml of the same solvent and 1 l of benzene. Elution with 1% ethyl acetate in benzene afforded 50 mg of

unreacted bromo-ketone and elution with 2% ethyl acetate yielded 4.6 g (60%) of the $\beta\gamma$-unsaturated ketone 67 as a colourless crystalline solid (purity 90%). Two recrystallizations from 10% ethyl acetate in hexane gave the analytical sample as colourless prisms, mp 99-100°; ir ν_{max} 2940, 2850, 1712 cm^{-1}; uv λ_{max} 282 (100) mμ; pmr δ 0.55 (s, 3H, C-20 CH_3), 1.14 (s, 3H, C-18 CH_3), 2.32 (m, Wh/2 = 4Hz, 2H, C-11 CH_2), 2.70 (m, Wh/2 = 7Hz, 2H, C-13 CH_2), 3.56 (s, 3H, C-19 $COOCH_3$), 5.44 (t, $J_{apparent}$ = 7Hz, C-14 H) ppm.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44, H, 9.03. Found : C, 74.42; H, 8.99.

Crude bromo-ketone could be used in this preparation with a corresponding considerable improvement in overall yield from the original cis-keto-ester 66. In such cases unreacted 66, and minor brominated components were eluted first. The major impurity in the crude bromo-ketone, a compound with C-20 methyl absorption at 0.64 ppm, is apparently the equatorial C-11 bromo isomer or the α,β-C-13 mono-bromo compound, since it is substantially dehydrobrominated to the same products under the above conditions.

9. Methyl-12-Oxopodocarp-13-en-19-oate 49

The crude dehydrobromination product obtained by refluxing 10.0 g of 48 in a mixture of 200 ml of DMA and 20 g of calcium carbonate for 30 min and isolation in the same manner as above, was dissolved in 250 ml of acetone containing 25 ml of 3N hydrochloric acid and refluxed under nitrogen for 2 h. The majority of the acetone was removed in vacuo, the residue diluted with water and isolated with ether to give 7.7 g of a pale yellow crystalline solid,

containing 70% 49, 6% 67, 15% 69, 2% 68 and 7% methyl podocarpate 54. Chromatography on Silica-Gel in 1:1 benzene-petroleum ether (30-60°) and elution with 2% ethyl acetate in benzene gave the majority of 67, 68 and some of 54. Further elution with 5% ethyl acetate in benzene gave crystalline 49, 4.5 g (58%) mp 120-123°. Recrystallization from methanol gave the conjugated ketone as glistening plates, mp 127-130.5°; uv λ_{max} 230 (10,500) mμ; pmr δ 0.715 (s, 3H, C-20 CH_3), 1.15 (s, 3H, C-18 CH_3), 3.64 (s, 3H, C-19 $COOCH_3$), 5.85 (q, $J_{13,14}$ = 10Hz, $J_{14,15}$ = 2.6Hz, C-13 H), 6.65 (q, $J_{13,14}$ = 10Hz, $J_{11,13}$ = 1.6Hz C-14 H) ppm; lit.[24] mp 126.5-129°; λ_{max} 230 (8,710) mμ.

The $\Delta^{9,11}$ α,β-unsaturated ketone 69 present was unusually polar and although part of the material was found in the late 49 fractions, the majority of the compound was eluted last in pure ethyl acetate and ethyl acetate-acetone, giving 1.14 g (90% pure by pmr). Recrystallization from 1:4 ethyl acetate-hexane gave 0.80 g of methyl 12-oxo-podocarp-9(11)-en-19-oate 69 as needle-clusters mp 110-112°; pmr δ 0.94 (s, 3H, C-20 CH_3), 1.17 (s, 3H, C-18 CH_3), 3.70 (s, 3H, C-19 $COOCH_3$), 5.73 (d, J=2Hz, 1H, C-11 vinylic) ppm; lit.[24] mp 111-112°.

10. Oxidative degradation of methyl 12-oxopodocarp-8(14)-en-19-oate 67, to 8-oxo-(13→17)-pentanorlabdan-12,19-dioic acid 19-methyl ester 36

Two methods, ozonolysis and potassium permanganate-sodium periodate oxidation, were employed to degrade 67, to the keto-acid 36. Both methods gave yields of 36 of the same order of magnitude, but the permanganate-periodate

reagent gave surprisingly inconsistent results whereas ozone gave reasonably reproducible yields.

Permanganate-Periodate Oxidation

Five grams (17.2 mmol) of $\beta\gamma$-unsaturated ketone 67, mp 97-100° (purity >98%) were dissolved in 375 ml of t-butyl alcohol. A further 375 ml t-butyl alcohol was stirred with 1250 ml of stock oxidant (containing 23.7 g $NaIO_4$ and 0.74 g $KMnO_4$ in litre of water; for 1 mmol 67, this contains 8 mmol (1.718 g) $NaIO_4$ and 0.34 mmol (0.0537 g) $KMnO_4$) together with 5 g anhydrous potassium carbonate. After 10 min, the pH of the mixture was 8.0 and some solid had precipitated. This mixture was then added to the stirred organic phase over 5 min, washing in the precipitated solid with ca 150 ml water. The pH of the final solution after addition was 8.2 and the colour, a deep burgandy-red. After a few minutes the pH had dropped to 7.7 and after stirring for 2 h had finally stabilized at 7.4. The colour of the solution was then orange-red.

Solid sodium carbonate and sodium metabisulphite ($Na_2S_2O_5$ or Na_2SO_3) were added portionwise until the solution was colourless, (I_2 and $KMnO_4$ free) and alkaline. If sufficiently alkaline the majority of the t-butyl alcohol separated and could be drawn off and evaporated. The residue was taken up in the main aqueous fraction, washed twice with ether and acidified with 2N sulphuric acid. Benzene extraction (3 x 200 ml) and usual work-up gave 4.30 g (85%) of a near colourless oil which crystallised on standing. Pmr analysis showed 90-95% of

keto-acid 36. Recrystallisation from 1:3 ethyl acetate-hexane gave the keto-acid as needles mp 170-172°; lit.[60], mp 171-172°.

Early success with this procedure gave way to varying pH values and poor quality product in later runs. Numerous variations in oxidant strength, pH adjustment and solvent balance did not give consistent improvement so the method was abandoned in favour of the ozonolysis procedure below.

Ozonolysis

A solution of 1.60 g of $\beta\gamma$-unsaturated ketone 67, mp 95-98° (purity 90-95%) in 80 ml of dry methanol (molecular sieves) was treated with ozone (from a Welsbach 'T-408' ozonizer settings :- 0.55 LPM, 115 v, 7-8 psi, at -65 - 75° until the solution assumed a pale blue colour. Nitrogen was bubbled through to remove excess ozone and the solution transferred to a 500 ml flask in a total volume of 200 ml of methanol. This solution was then refluxed with 20 ml of 30% hydrogen peroxide and 50 ml of 10% sodium hydroxide for 30 min under nitrogen.

The majority of the methanol was then removed in vacuo and the residue diluted with 300 ml of water and ether extracted. The ethereal extracts were counter-washed once with water and the combined aqueous phases acidified to pH 1 with 2N sulphuric acid. The liberated acidic product was extracted with benzene (3 x 100 ml) and the extracts worked-up in the usual way to give 1.40 g of 36, as an oil which crystallized on standing. The pmr spectrum indicated that the desired product was present in about 80% yield. Recrystallization from 10% ethyl acetate-hexane gave 0.84 g (52%) of 8-oxo-(13→17)-pentan-

norlabdan-12,19-dioic acid 19-methyl ester 36 as colourless needles, mp 168-170°; pmr δ 0.55 (s, 3H, C-20 CH_3), 1.25 (s, 3H, C-18 CH_3), 3.70 (s, 3H, C-19 $COOCH_3$), 10.6 (s, broad Wh/2 = 15Hz, 1H C-12 COOH) ppm; mass spectrum (80 ev) m/e 296 (very small), 278 (enol-lactone-parent), 219, 263, 202 (mol.wt. 296.40); lit.[60] mp 171-172°.

11. Dimethyl 8-Oxo-(13→17)-pentanorlabdan-12,19-dioate 79

Crude (90%) βγ-unsaturated ketone 67, 1.6 g, direct from chromatography was ozonized as above and the crude product esterified with ethereal diazomethane. After removal of solvent the product was chromatographed on 50 g of 'Florisil' in 1:1 benzene-petroleum ether and elution with benzene yielded 1.25 g (73%) of the keto-ester 79, (purity 95% by pmr) which was crystallized from 5% ethyl acetate-hexane to give 0.95 g (56%) of 79 as colourless prisms, mp 96-97°; pmr δ 0.54 (s, 3H, C-20 CH_3), 1.27 (s, 3H, C-18 CH_3), 3.60 (s, 6H Wh/2 = 1.0Hz C-19 and C-12 $COOCH_3$'s superimposed) ppm; mass spectrum (80 ev) m/e 310 (mol ion); lit.[60] compound reported as oil only.

The 2,4-dinitrophenylhydrazone of the ester-ketone crystallized from aqueous ethanol as yellow needles mp 161-163°; lit.[60] mp 161-163°.

B - Conversion of Podocarpic Acid to the Keto-acid 36, Via the Ozonolysis Route

1. Methyl Podocarpate 54

Recrystallized podocarpic acid 35, mp 192-193°, 65 g, was dissolved in approximately 400 ml (R) methanol, and stirred at room temperature whilst ethereal diazomethane (prepared from 85 g 'Diazald', 90 ml of 95% ethanol, 20 g potassium hydroxide and 30 ml water) was added dropwise. After excess diazomethane (detected by a yellow-green colouration) was present for 15 min, solvent was removed in vacuo to give ca 400-500 ml of a white crystalline slurry which was stood overnight at 0°. Filtration under pressure, reduction of volume of the mother liquors, and further cooling gave a total of 58-60 g of pure white needles of methyl podocarpate 54: mp 207-210°; lit.[24] 205-208°; pmr δ 1.05 (s, 3H, C-20 CH_3), 1.30 (s, 3H, C-18 CH_3), 2.84 (m, 2H, C-7 CH_2), 3.70 (s, 3H, C-19 $COOCH_3$), 4.5 - 5.5 (s broad, 1H, C-12 OH), 6.80 (m, 3H, C-11 C-14 aromatic) ppm.

2. 8β-Hydroperoxy-8α-hydroxy-(13→17)-pentanorlabd-9(11)-ene-12,19-dioic acid 19-methyl ester 8α→12-lactone 55

Methyl podocarpate 54, mp 208-210°, 10.0 g (34.8 mmole) was dissolved by warming in 100 ml (R) methylene chloride plus 100 ml (R) methanol - both dried over molecular sieves - in a 250 ml gas absorption vessel fitted with a fritted-glass gas bubbler. After cooling to -70° in a 'Dry Ice'-acetone bath, ozonised dry air containing 2 mg O_3/liter gas - (± 10% - determined by I_2 liberation and titration with standard thiosulphate) - was passed through the

solution at a rate of 0.5 liters/min. The ozone was generated from a Welsbach - 'T408' ozonizer run at 7-8 psi gas pressure, and 80 volts primary potential.

Excess ozone was present, - as indicated by a pale blue colour in the solution, - after 6 h of gas flow. At this time nitrogen was passed through the solution for 15 min at -70°, and a further 15 min with the cold bath removed. The solution was then transferred to a flask with the aid of methanol, and solvent removed in vacuo at 30-40° to give a white crystalline slurry of crude hydroperoxide 55.

The slurry was dissolved in 200 ml chloroform and washed with 500 ml water, 200 ml brine, filtered through Na_2SO_4 and evaporated in vacuo at ca 40° to give after vacuum drying, 10.75 g (100%) off-white crystalline hydroperoxide 55, of 80-90% purity by pmr analysis. Solution of the solid in chloroform, reduction of volume to 50 ml at the boiling point and addition of 100 ml hexane initiated spontaneous crystallisation which after 24 h at 0° gave 7.30 g (68%) of white micro-crystalline solid of purity 95%; mp 183-187°d. One further crystallization from the same solvent gave the analytical sample as colourless prisms, mp 185-187°d; ir max 3500, 3250, 2950, 1765, 1725, 1640, 1235, 1210, 1160, 1097, 1085, 1040, 1008, 978, 927, 870 cm^{-1}; uv λ_{max} 218 (11,000) mu, (no n-π^* visible); pmr δ 1.135 (s, 3H, C-20 CH_3), 1.22 (s, 3H, C-18 CH_3), 3.72 (s, 3H, C-19 $COOCH_3$), 5.79 (s, 1H, C-11 vinylic H), 9.08 (s, Wh/2 = 2.0Hz, 1H, C-8 OOH) ppm; mass spectrum (80 ev) m/e 308/306, 291, 275, 247. Mol.wt. 310. Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15;

O, 30.93. Found: C, 61.86, H, 7.14;), 30.86.

Iodometric Determination of Peroxidic Oxygen[157]

Three 50 mg (0.161 mmol) samples of twice crystallized hydroperoxide mp 185-187°d were dissolved each, in 10 ml (R) isopropanol containing 0.5 ml acetic acid, 0.2 ml acetic anhydride, and 3 ml of a saturated solution of sodium iodide in (R) isopropanol added. After heating to bp for 5 mins the samples were titrated with standard sodium thiosulphate solution. The mean titre was ≡ 0.0200 g I_2. But 0.161 mmol hydroperoxide liberates 0.161 mmol I_2 = 0.0204 g. Therefore compound 55 has 0.0200/0.204 = 98% (+ 2%) active oxygen. It was found that reaction was essentially quantitative in two min. Since cyclic peroxides react much more slowly under these conditions, 55 is likely to be a hydroperoxide as formulated.

3. 8-Oxo-(13→17)-pentanorlabda-12,19-dioic acid 19-methyl ester 36

The hydroperoxide 55 mp 183-187°, 7.3 g, was added in 75 ml 95% ethanol to a pressure bottle containing a suspension of 0.7 g 5% Pd/C catalyst in 75 ml 95% ethanol, which had been prehydrogenated for 15 min. The mixture was shaken under 1-3 atm of hydrogen overnight. Filtration through 'Celite' efficient washing of the filter pad with methanol, and evaporation in vacuo gave 6.8 g (98%) of colourless crystalline keto-acid 36 which was 90-95% pure by pmr analysis. Recrystallization from 1:2 ethyl acetate:hexane gave 36 as colourless needles, mp 171-172°; lit.[60] 171-172°. See above, A-10, for further characterisation.

C - Synthesis of Labdane Structures from the Keto-acid Intermediate 36

1. 17-Carbomethoxy-8β-hydroxy-(13→16)-tetranorlabda-12,19-dioic acid 19-methyl ester 8β,12-lactone 56 (R = CH_3)

(i) Method using benzene as solvent:- Granulated zinc (20 mesh) was activated by the procedure of W. S. Johnson and L. F. Fieser[85]. After the metal had been heated in concentrated sulphuric acid containing a few drops of nitric acid at 100° for about 10 min, the majority of the acid was decanted off, and water added. After vigorous H_2 evolution for a few min, all traces of acid were removed by repeated washing with water, followed by acetone, ether and then drying at 110°.

The keto-acid 36, mp 171-172°, 5.00 g (16.9 mmol) was dissolved in 250 ml anhydrous benzene in a dry 500 ml three-necked flask fitted with a mechanical stirrer and reflux condenser (a magnetic stirrer bar gave adequate agitation in smaller scale runs). Then 5.20 g (34 mmol) of methylbromoacetate (R) (Eastman), 5 g activated zinc and 50 mg iodine were added, and the stirred mixture brought rapidly to reflux under nitrogen. Two further additions of, 2.60 g methyl bromo-acetate, 5 g zinc and a crystal of iodine, were made after 6 and 12 h reflux.

After 24 h total reflux, the reaction mixture was cooled, the zinc complex destroyed in 2N sulphuric acid and the acidified mixture extracted with benzene (2 x 100 ml) after removal of the initial benzene layer. The combined benzene extracts on usual work-up gave 6.25 g dark yellow oil. Pmr analysis

indicated some 5% of non-diterpenoid reagent condensation products, 75-80% lactone-ester 56 (R = CH_3), 10% starting material, 5% of unsaturated lactone 104, and a few per cent of an unknown compound with a C-20 methyl absorption at 38Hz (60 MHz).

Extraction of an ethereal solution of the product with saturated $NaHCO_3$ solution served to remove starting material and the unknown component. Two crystallizations of a portion from 2:1, hexane : ethyl acetate gave the analytical sample as colourless needles mp 104.5-105°; ir ν_{max} 3025, 3000, 2955, 2855, 1775, 1735, 1720, 1440, 1220(b), 1142, 985, 940, 925 cm^{-1}; pmr δ 0.74 (s, 3H, C-20 CH_3), 1.22 (s, 3H, C-18 CH_3), 3.65 and 3.72 (s and 3H each, C-19 and C-21 $COOCH_3$'s) ppm; Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.71; H, 8.01.

(ii) Method using benzene and dimethoxyethane as co-solvent:-

The keto-acid 36, 3.50 g (12.5 mmol, ca 95% pure) was dissolved in 160 ml dry benzene and 40 ml dry dimethoxyethane (distilled from calcium hydride) and 3.80 g (25 mmol) of methylbromoacetate, 3 g zinc and a crystal of iodine added. The mixture was mechanically stirred under reflux and a nitrogen atmosphere for 12 h and then a further 3.0 g (20 mmol) methylbromoacetate, 3g zince and crystal of iodine added. After a further 6 h reflux the reaction mixture was cooled and worked up in similar manner to (i), to give 3.97 g yellow oil. The pmr spectrum revealed no discernable unsaturated lactone 104, 90-95% pure lactone-ester 56 (R = CH_3) and some 5% starting material.

The oil was chromatographed on 160 g 'Florosil' in 50:50 benzene-petroleum ether (30-60°) and the chromatogram developed with benzene and 5% ethyl acetate/benzene which yielded ca 100 mg of yellow oil which by odour and pmr analysis appeared to be methyl phenylacetate. Further elution with 10% ethyl acetate-benzene gave a total of 2.98 g (75%) of pure (>98%) lactone-ester 56, mp 103-105°.

2. 17-Carboethoxy-8β-hydroxy-(13 16)-tetranolabda-12,19-dioic acid 19-methyl ester 8β→12-lactone 56 (R = Et)

Precisely the same procedure was followed as above 1(i) for the carbomethoxy ester, utilising 5.70 g (2 mol equivalents) ethyl bromo-acetate initially and two subsequent additions of 2.85 g (1 mole equivalent). However the extent of conversion was poorer than in 1(i) and pmr analysis indicated some 70% product, 20-25% starting material, and a 5% of unsaturated lactone 104.

Sodium bicarbonate extraction and two crystallizations gave an analytical sample of 56 (R = Et), mp 74-75°; ir ν_{max} 3025, 3000, 2955, 2855, 1778, 1732, 1722, 1455, 1230(b), 1142, 985, 940, 925 cm^{-1}; pmr δ 0.76 (s, 3H, C-20 CH_3), 1.22 (s, 3H, C-18 CH_3), 1.28 (t, J=7.0Hz, 3H, ester $-CH_2.CH_3$), 3.65 (s, 3H, C-19 $COOCH_3$); 4.20 (q, J=7.0Hz, 2H, ester $-CH_2.CH_3$) ppm; Anal. Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found : C, 65.72; H, 8.09.

t-Butylbromoacetate[158]

To a solution of 139 g (1 mol) $BrCH_2COOH$ (BDH) in 100 ml ether and 7.5 ml concentrated sulphuric acid was added 112 g (2 mol) of isobutylene

condensed in a 500 ml pressure bottle and cooled in 'Dry Ice". The bottle was sealed and kept at room temperature for 24 h.

After recooling, the bottle was opened and the contents poured into 400 ml ice-water containing 100 g sodium hydroxide. After swirling, the layers were separated, and the aqueous portion washed twice with ether. The combined ethereal extracts were dried over K_2CO_3 and filtered into a 1 l flask. Ether and isobutylene were removed by rotary evaporator at 20-30°. The residue of ca. 120 ml was poured into a 250 ml flask (prewashed with concentrated ammonium hydroxide and dried) and distilled in vacuo from magnesia, bp 50-60°/10-20 mm. Yield, 120 g (60%); 99% pure by pmr analysis

3. Attempted preparation of 17-carbotert-butoxy-8β-hydroxy-(13 16)-tetranorlabda-12,19-dioic acid 19-methyl ester 8β→12-lactone 56 (R = t-Bu).

The same procedure as before was used utilising two mole equivalents reagent initially and two subsequent additions of 1 mole equivalent each. However after 18 h reaction, and work-up, the pmr spectrum showed some 40% unsaturated lactone 104, 40% starting material and 20% of (presumably) the desired compound with C-20 methyl absorption at 51.0 Hz (60 MHz).

It had been found in the preparation of the methyl and ethyl ester analogues, that use of the higher bp solvent, toluene led to substantially greater quantities (up to 50%) of the elimination product 104. Consequently it seemed possible in the present case, that use of a lower bp solvent such as benzene: ether and the more reactive metal magnesium might lead to more extensive reaction.[159] However initial trials with these reagents led purely to starting material, and

ester self-condensation, so further investigation was abandoned.

4. 17-Carbomethoxy-(13→16)-tetranorlabd-8(17)E-ene-12,19-dioic acid 19-methyl ester 102 (R = CH_3)

The lactone-ester 56 (R = CH_3), 3.00 g (8.5 mmol, 95% pure - obtained by direct bicarbonate washing and one crystallization from ethyl acetate-hexane (1:3, at -20°) was dissolved in 50 ml of methanol (dried over Mg $(OCH_3)_2$),[160] and added to a solution of 0.50 g clean sodium metal (22 mmol - 2.5 equivalents) in 50 ml of $Mg(OCH_3)_2$- dried methanol under N_2. The solution was heated at reflux under N_2 for 2 h, cooled and poured into 1 l of 0.5 N sulphuric acid, and extracted with benzene (3 x 150 ml). The extracts on usual work-up gave 2.90 g pale yellow 'foam' (96.5%). The pmr spectrum indicated a product of 90-95% purity with traces of a component with C-20 methyl absorption at 40 Hz (60 MHz). Recrystallisation from methyl acetate-hexane (1:2) gave 2.63 g of off-white needles, mp 150-160°. A second recrystallisation gave the analytical sample of 102 as colourless needles, mp 152-160°; ir ν_{max} 3600 - 2400, 2950, 1725, 1715, 1705, 1640, 1425, 1250, 1170 cm^{-1}; uv λ_{max} 227 (16,000) (Calcd. 224(+ 5)) mμ; pmr δ 0.527 (s, 3H, C-20 CH_3), 1.22 (s, 3H, C-18 CH_3), 2.51 (s, broad, Wh/2 = 3Hz, 2H, C-11 CH_2), 3.64 and 3.69 (s and 3H each, C-19 and C-21 $COOCH_3$'s), 4.08 (m, 1H?, C-7 H?), 5.55 (s, broad, Wh/2 = 2.5Hz, 1H, C-17 vinylic), 9-11 (s, broad, Wh/2 = 10-60 Hz, C-12 COOH) ppm; Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found : C, 64.58; H, 8.11. (The mp range is apparently due to small quantities - ca 5% of the Z -$\Delta^{8,17}$ double bond stereoisomer which is not resolvable by pmr analysis or

tlc at this concentration.

5. 17-Carboethoxy-(13→16)-tetranorlabd-8(17)E-ene-12,19-dioic acid 19-methyl ester 102 (R = Et)

A similar procedure to the above was followed, utilizing 300 mg (0.82 mmol) 95% pure lactone 56 (R = Et), 38 mg (1.64 mmol) sodium metal, and 10 ml ethanol. The ethanol used was dried by treatment of 800 ml absolute ethanol with 6 g sodium and 24 g dibutylphthalate, refluxing for 1 h, and distilling. The product obtained (290 mg 95% yield) of ca 95% purity was recrystallised from ethyl acetate-hexane (1:2), giving off-white needles (250 mg). A second crystallisation gave the analytical sample, mp 75-82° (about 5% of Z, 8(17)-double bond isomer present); ir ν_{max} 3000 - 2400, 1720, 1710, 1640, 1440, 1260, 1170 cm^{-1}; uv λ_{max} 226 (12,800) mμ; pmr δ 0.53 (s, 3H, C-20 CH_3), 120 (s, 3H, C-18 CH_3), 1.25 (t, J=7.0Hz, 3H, ester $-CH_2.CH_3$), 2.46 (s, broad, Wh/2 = 3Hz, 2H, C-11, CH_2), 3.64 (s, 3H, C-19 $COOCH_3$) 4.10 (m, 1H?, C-7 H?), 4.18 (q, J=7.0Hz, 2H, ester $-CH_2.CH_3$), 5.50 (s, broad, Wh/2 = 3Hz, 1H, C-17 vinylic) 9-11 (s, broad, Wh/2 = 10-60 Hz) ppm; the analytical data for this compound were unsatisfactory.

6. 17-Carboxy-(13→16)-tetranorlabd-8(17)E-ene-12,19-dioic acid 19-methyl ester 57

(i) By hydrolysis of αβ-unsaturated ester 102 (R = CH_3). The αβunsaturated ester 102 (R = CH_3) 2.00 g (5.65 mmol) mp 150-160° (containing a minimum of 90% of the 'E' double bond isomer) was dissolved in 150 ml (R) methanol together with 50 ml of 1N sodium hydroxide solution and refluxed under nitrogen for 2 h.

The majority of the methanol was removed in vacuo and the residue poured into 250 ml of 1N sulphuric acid. The liberated acid was extracted with benzene (3 x 75 ml) and the extracts worked up in the usual way to give 1.94 g (100%) of an off-white crystalline solid. The pmr spectrum showed at least 90% 'E' double bond isomer, unsaturated diacid 57, with 5% 107 (see below).

(ii) By hydrolysis of lactone-ester 56 (R = CH_3). The lactone ester, 2.98 g (mp 103-105°, 98% pure - direct from chromatography of the above reaction product (C.1(ii))) was dissolved in 225 ml (R) methanol and 75 ml 1N sodium hydroxide added. The whole was refluxed under N_2 for 2 h. The majority of the methanol was removed in vacuo and the residue diluted with water, washed twice with ether and the aqueous extracts acidified with 2N sulphuric acid. The acidified solution was extracted with benzene (3 x 100 ml) which on usual work-up gave 2.85 g (99%) of a near colourless 'foam'. The pmr spectrum indicated some 95% of unsaturated diacid 57, plus 5% of the $\beta\gamma$-unsaturated isomer 107. This latter compound was also present as a decarboxylation intermediate and the crude reaction mixture could thus be used directly for decarboxylation (see below). Two crystallizations of a portion from ethyl acetate-hexane (1:2) gave the analytical sample as colourless crystalline clusters mp 216-220° (d. at 205°); ir ν_{max} 3500 - 2500(b), 3010, 1705, 1690, 1640, 1250, 1240(b), 1155, 930 cm^{-1}; uv λ_{max} 220 (12,800) mμ; pmr δ 0.54 (s, 3H, C-20 CH_3), 1.22 (s, 3H, C-18 CH_3), 2.52 (s, broad Wh/2 = 4Hz, 2H, C-11 CH_2), 3.60 (s, 3H, C-19 $COOCH_3$), 4.05 (m, 1H, C-7 H),

5.52 (s, broad Wh/2 = 3Hz, 1H, C-17 vinylic), 9-11 (s, broad (15Hz), 2H, C-12 and C-21 COOH's) ppm. Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.88, H, 7.74. Found : C, 63.60; H, 7.81.

7. (13→16)-Tetranorlabd-8(17)-ene-12,19-dioic acid 19-methyl ester 58

The $\alpha\beta$-unsaturated diacid 57 (containing 5% $\beta\gamma$-isomer 107) 2.00 g (5.90 mmol) was dissolved in 20 ml quinoline (distilled and degassed under nitrogen) together with 50 mg of copper chromite catalyst (see below) in a dry 50 ml flask containing a magnetic stirring bar. The flask was sealed with a reflux (air) condenser and a three-way trap to nitrogen and a water pump. The flask was evacuated with stirring at room temperature flushing the contents twice with nitrogen, and then finally evacuated while the temperature was raised to 100°. It was then filled with nitrogen and the temperature raised to 230° (silicone oil bath). The mixture was stirred under nitrogen at 230° (± 2°) for 1.25 h and then withdrawn from the bath and allowed to cool to room temperature. After diluting the contents of the flask with 200 ml of 1:4 benzene-ether, the whole was extracted with 10% sodium hydroxide solution (4 x 25 ml) and 25 ml water. The extracts were poured onto crushed ice, acidified with 80 ml of 2N sulphuric acid and benzene extracted (3 x 100 ml). Usual work-up of the extracts gave 1.54 g (88%) of a pale yellow oil. The pmr spectrum indicated 80% methylene vinylic absorption at 4.45 and 4.80 ppm due to 58 (C-20 CH_3 absorption at 0.53 ppm), and also the corresponding C-19 demethylated compound (C-20 CH_3 absorption at 0.63 ppm). In addition there was 10% of unreacted inter-

mediate 107, and 10% of other minor components. In the main synthetic sequence the product was purified and fully characterized as the methyl ester 112, (see below). However material from one run was isolated by two crystallizations from (1:3) ethyl acetate-hexane, giving off-white flakes mp 153-155° (>98% pure); ir $\hat{\nu}_{max}$ 3500-2400(b), 2940, 2855, 1715, 1645, 1460, 1150, 890, 680 cm^{-1}; pmr δ 0.53 (s, 3H, C-20, CH_3), 1.20 (s, 3H, C-18 CH_3), 3.60 (s, 3H, C-19 $COOCH_3$), 4.45 and 4.80 (s, and 1H each both Wh/2 = 3Hz, C-17 vinylic CH_2), 9-11 (s, broad Wh/2 = 10Hz, 1H, C-12 COOH) ppm.

Preparation of Copper Chromite Catalyst

The method of Sherrill and Mellock[161] was essentially used. Concentrated ammonium hydroxide was added to a solution of 63 g (0.25 mol) of ammonium dichromate in 250 ml water until the solution was yellow (chromate). A solution of 120.8 g (0.5 mol) of cupric nitrate dihydrate in 150 ml water was then added in a slow stream to the well stirred chromate solution. The orange-brown precipitate was filtered off under pressure and dried overnight at 110°.

After pulverising to a fine powder it was then heated slowly in a porcelain basin over a small flame. After spontaneous decrepitation had ceased it was then roasted strongly so that a fine black powder was finally produced. The powder was suspended in 10% acetic acid in water, filtered and the process repeated three times in water. The product was finally dried at 110° to give 65 g of '$CuCrO_4$' as a fine black powder.

8. Dimethyl(13→16)-Tetranorlabd-8(17)ene-12,19-dioate 112

The crude unsaturated acid 58 (from the decarboxylation of 2g of diacid 57) 1.54g was esterified with ethereal diazomethane, to give 1.60 g (87% from 57) of crude methyl ester 112, containing some 80% of the desired compound, as a dark yellow oil. The oil was chromatographed on 64 g of Florosil in 50:50 benzene-petroleum ether (30-60°) and the chromatogram developed with the same solvent. Elution with benzene yielded a total of 1.12 g (61% from 57) of pure (>98%) crystalline unsaturated ester 112. The sample for analysis was crystallized from 1:9 ethyl acetate-hexane giving colourless prisms, mp 109-110°; ir ν_{max} 3020, 2950, 2850, 1735, 1720, 1645, 1440, 1225(b), 1160, 910, 710 cm^{-1}; pmr δ 0.53 (s, 3H, C-20 CH_3), 1.19 (s, 3H, C-18 CH_3), 2.40 (s, 2H, C-11 CH_2), 3.60 and 3.625 (s, and 3H each C-19 and C-12 $COOCH_3$'s), 4.46 and 4.75 (s, and 1H each, both broad Wh/2 = 3Hz, C-17 vinylic CH_2) ppm; mass spectrum (high resolution) m/e Calcd. for $C_{18}H_{28}O_4$, 308.198747; Found : 308.200294 (mol ion), 249 (M-59). Anal. Calcd for $C_{18}H_{28}O_4$: C, 70:10; H, 9.15. Found: C, 70.28; H, 9.24.

9. Methyl 12-Ketolabd-8(17)-en-19-oate 53

Olefin-acid 58, 114 mg (0.39 mmol) was dissolved in 5 ml of anhydrous ether in a flask under nitrogen sealed with a septum inlet. Two millilitres of sec-butyl lithium (2.4 mmol) in hexane were added to the stirred solution cooled to 0° in an ice-bath, and after stirring for 6 h at 0° a further 1 ml of reagent was added, and the stirred solution allowed to warm to room temperature overnight.

The product was quenched in 5% NaH_2PO_4 solution, extracted with benzene and worked-up in the usual way to give 130 mg colourless oil. Pmr analysis showed some 60% of the desired ketone 53 and 40% starting material accompanied by some quantity of butyl telomeric material. Since prolonged bicarbonate extraction failed to remove all starting material, the oil was esterified with diazomethane and chromatographed on 'Florisil'. Elution with 50% petroleum ether (30/60°) : benzene gave unwanted telomer, and benzene elution yielded 65 mg (50%) of the ketone(s) 53 (epimeric at C-13) as a colourless oil; ir ν_{max} 3015, 2940, 2880, 2855, 1720, 1650, 1470, 1220, 1165, 878 cm^{-1}; uv λ_{max} 265 (40); pmr δ 0.54 (s, 3H, C-20 CH_3), 1.20 (s, 3H, C-18 CH_3), 3.60 (s, 3H, C-19 $COOCH_3$), 4.30 and 4.73 (s and 1H each, both broad Wh/2 = 3Hz, C-17 vinylic H's) ppm; mass spectrum m/e 334 (mol. ion), 319 (M-15), 302 (M-32), 275 and 277 (M-59/57) ($COOCH_3$ and sec-C_4H_9), 235 (M-57-42), 175/177 (M-57-42-59).

10. Methyl 12-Hydoxylabd-8(17)-en-19-oate 37 (R=CH_3)(113)

Ketone 53 30 mg (0.09 mmol) was dissolved in 2 ml dry dimethoxyethane, cooled to 0° and 75 mg (0.3 mmol) lithium tritertiarybutoxyaluminium hydride added. The mixture was stirred at 0° for 2 h and allowed to warm to room temperature overnight. On acidification with NaH_2PO_4 solution and benzene extraction the product showed only ca 30% reduction.

Reduction of the ketone 53 with excess sodium borohydride in refluxing

ethanol for thirty minutes and then working-up in the above fashion gave 31 mg colourless oil. The pmr spectrum revealed a clean mixture of two alcohols 37. Triangulation of the vinylic absorptions of the two alcohols showed them to be present in a ratio of 7:3. The alcohols showed, ir ν_{max} 3670, 3500, 3010, 2950, 2925, 2875, 2850, 1720, 1645, 1470, 1208, 1160, 1035, 895 cm^{-1}; uv (featureless); pmr δ 0.515 (s, 3H, C-20 CH_3), 1.18 (s, 3H, C-18 CH_3), 3.58 (m, 1H, broad Wh/2 = 30 Hz, C-12 H α to OH), 3.60 (s, 3H, C-19 $COOCH_3$), 4.40 (H_A) and 4.80 (H_B) (s and 0.15 H each, broad Wh/2=4Hz, C-17 vinylic H's (12(R)-118 epimer), 4.70(H_A) and 4.87 (H_B) (s and 0.35 H each, broad Wh/2 = 3Hz, C-17 vinylic H's, 12(S)-119 epimer) ppm; mass spectrum (200°) m/e 336 (mol.ion), 321 (M-15), 318 (M-18), 279 (M-57), 277 (M-59), 261 (M-18-57), 259 (M-18-59), 235 (M-18-101) (allylic 9(11) bond cleavage).

11. 12-Hydroxylabd-8(17)-en-19-oic acid 37 (R=H)

A 20 mg sample of 37 (R=CH_3) (C-19 easter-alochols 113 (118/119) from above was treated with 2 ml of sec-butyl lithium in anhydrous ether at 0° for two hours (as in 9.) in order to hydrolyse the ester. On quenching the product with water and work-up as before, 18 mg colourless oil was obtained. The pmr spectrum revealed complete demethylation of the 19-methyl ester. The acids showed, ir ν_{max} 3600-2800, 3550, 2960, 2870, 1720, 1690, 1640, 1460, 1230, 1160, 900 cm^{-1}; uv (featureless); pmr δ 0.565 (s, 3H, C-20 CH_3), 1.18 (s, 3H, C-18 CH_3) 3.56 (m 1H, broad Wh/2 = 30Hz, C-12 H α to OH), 4.40 and 4.80 (s and 0.15 H each, broad Wh/2 = 4Hz, each, C-17 vinylic H's - 12(R)-epimer, 4.70 and

4.87 (s and 0.35 H each, broad Wh/2 (H_B) = 3.5Hz, (H_A) = 4.5Hz, C-17 vinylic H's - 12(S) epimer) ppm. The COOH/OH peak was at 1.5-1.7 ppm under the methylene envelope.

12. Preparation of 3-Iodofuran

The basic procedure of Gronowitz and Sorlin[21] was used, with further modifications due to the work of Wrobel[23] and as a result of present investigations.

2-Furoic acid, 224 g (2 mol) was dissolved in 3 l of warm (35°) water and added dropwise over 1 h to a well stirred solution of 320 g (1 mol) mercuric acetate in 5 l water at room temperature. The precipitated solid resulting was filtered under pressure and dried at 0.1 mm/room temperature for two days to give 316 g (0.81 mol) of 2-(acetoxymercuric)-furoate 122 as a buff powder (81%). This material was pyrolysed following an adaption of Wrobel's[23] procedure.

2-(Acetoxymercuric)-furoate, 200 g (0.512 mol) was suspended in 350 ml xylene in a 1 l three-necked flask, fitted with a Herschberg stirrer, thermometer and a Dean-Stark trap with reflux condenser. The mixture was stirred and heated over 30 min to reflux temperature (ca. 140°), and kept at reflux for 1 h, when the trap contained water, xylene/water azeotrope and acetic acid. The temperature was then reduced to 135° and heating and stirring continued for 23 h. After cooling in an ice-bath, 250 ml of 95% acetic acid was added and stirring continued at room temperature for 3 h only (see Discussion). By this time nearly all solid matter had dissolved to a dark brown solution which was then poured into 1.7 l

water and sodium chloride added until no further precipitation took place. After stirring overnight the mixture was filtered under pressure to give a tan solid which was washed well with water and dried at 0.1 mm/room temperature for 36 h, to give 133 g of a tan solid (crude 3-(chloromercuric)-furan, plus a little 2-isomer and mercuric acetate).

The crude material was extracted with ether in a Soxhlet apparatus. The results of the extraction were examined in lots. Thus after 48 h, 34 g of 3-(chloromercuric)-furan were obtained, the pmr spectrum of which showed the presence of 5-6% of the 2-isomer. Another 24 h gave 7.5 g material containing 7-8% 2-isomer. Another 36 h gave 7 g material containing 8-9% of 2-isomer. Further prolonged extraction gave only 3 g containing 30-40% 2-isomer. Batches one to three, combined thus gave 48.5 g of 3-(chloromercuric)-furan 123, containing ca. 6% of the 2-isomer, pmr (DMF, ppm rel . to centre of DMF doublet) δ 3.8 (1H, d, β-H), 4.7 (1H, d, αH) 5.0 (1H, m, α'-H to O and Hg). This was of a purity comparable to that previously obtained by crystallization of the extracted product[21], and is of adequate purity for final reaction by iodine oxidation. The overall yield from 2-(acetoxymercuric)-furan is thus 51% (assuming initial disproportionation to mercuric acetate and mercuric difuroate (see Discussion), and 31% from starting material. This represents twice the yield previously obtained[21].

3-(Chloromercuric)-furan 33.5 g (0.11 mol) from the above was suspended in 400 ml water and a solution of 28.0 g (0.11 mol) iodine (I_2), in 36.5 g potassium iodide and 400 ml water was added dropwise to the stirred suspension at room

temperature. After the addition was complete, excess iodine was destroyed with sodium thiosulphate and the 3-iodofuran present steam distilled from the reaction mixture by boiling for ca. 2 h, (500 ml distillate). The distillate was extracted with ethanol-free ether (3 x 100 ml), and the extracts washed twice with brine, filtered through anhydrous sodium sulphate and evaporated in vacuo at 35° (maximum temperature) to give 16.16 g (75%) of 3-iodofuran as a pale yellow oil. The pmr spectrum indicated 5% of the 2-isomer[21]. The substance can be redistilled in vacuo but was sufficiently pure for purposes of the present synthesis. It is stable indefinitely at -20° in the dark, pmr (see also ref. 21), δ 6.55 (m, 1H, β-H), 7.3 - 7.6 (7.45 centre) (2H, m, α-H's).

13. Methyl 15,16-Epoxy-12-ketolabda-8(17),13(16),14-trien-19-oate 61

(a) Preparation of the acid chloride 60:- The crystalline unsaturated ester 112, 565 mg (1.83 mmol, > 98% pure) was refluxed in 90 ml methanol together with 30 ml 1N sodium hydroxide solution for 3 h under nitrogen. The methanol was removed in vacuo, the residue diluted with 300 ml water, washed once with 20% benzene in ether and then acidified with cold 2N sulphuric acid. Benzene extraction and usual work-up gave 530 mg (98%) of 98% pure unsaturated acid 58. A portion of the product 235 mg (0.80 mmol) was dissolved in 3 ml methanol in a 10 ml flask and 74 mg (0.88 mmol) (R) sodium bicarbonate added, together with 2 ml of water. After stirring at room temperature for 2h, when all carbon dioxide evolution had ceased, solvent was removed in vacuo on the rotary evaporator and the residue finally dried overnight at 0.1 mm/room temperature.

The product (255 mg sodium salt (0.80 mol, plus ca 8 mg sodium bicarbonate) was covered with 5 ml benzene containing 1% pyridine in the same 10 ml flask, cooled to partial freezing in an ice-bath, and treated dropwise with 340 mg (2.6 mmol) oxalyl chloride (Eastman) in 3 ml dry benzene. The mixture was stirred at the same temperature for 15 min and then allowed to warm to room temperature wtih stirring for a further 1.5 h. The solvent and the bulk of the oxalyl chloride was removed in vacuo at 30°, the residue flushed with a further 5 ml benzene and this too removed in the same way. Finally the residue was dried at 0.1 mm/room temperature for 15 min, and taken up in 2 ml anhydrous benzene - 3 ml anhydrous ether, for addition to the furyl lithium solution prepared below:-

(b) Preparation of 3-furyl lithium: Methyl lithium (2.40 M in ether), 0.50 ml (1.20 mmol), was syringed into a dry 20 ml flask equipped with septum inlet, under an atmosphere of nitrogen. Anhydrous ether 2 ml, was also syringed in, and the flask cooled to -70° in a "Dry Ice" - acetone bath. 3-Iodofuran, 235 mg (1.22 mmol) was then added dropwise by syringe in 5 ml of anhydrous ether and the solution stirred at -70° for 1 h, by which time 3-furyl lithium formation was complete. (n-Butyl lithium can also be used[21], when the formation time is faster, but the reagent is more difficult to keep at stable concentration).

At this time the acid chloride 60 solution (from A, above) was taken up in a 10 ml syringe (size 19 needle to prevent possible bloackage by precipitated sodium chloride present) and introduced into the 3-furyl lithium solution in a fast stream over one to three seconds. The resultant mixture was then stirred at -70°

for a further 30 min and allowed to warm to room temperature over 1-2 h by removal of the cold bath. The product was quenched in 5% sodium dihydrogen phosphate solution, benzene extracted (3 x 75 ml) and worked-up in the usual manner to give 260 mg (95%) of a dark yellow oil. The pmr spectrum showed 80% of the desired keto-furan 61, (furanoid and C-20 methyl absorption) 10% starting material 58, and 10% of minor components (the principal contaminant has a C-20 methyl absorption at 0.50 ppm).

The product was eluted onto 10.5 g 'Florosil' in 50:50 benzene-petroleum ether (30-60°) and developed with the same solvent, finally eluting with pure benzene giving a total of 182 mg (66%), of 97% pure keto-furan 61 as a near-colourless oil. (The oil has so far resisted all attempts at crystallization which is not unexpected since methyl lambertianate 38 (R=CH_3) itself is an oil). ir ν_{max} 2970, 2940, 2875, 1720, 1680, 1645, 1560, 1500, 1210 (broad), 1156, 888, 872 cm^{-1}; uv λ_{max} 251 (245) (π-π^*, B); 210 (7200) (end absorption, π-π^*, K); n-π^*, R, band too small to measure; pmr 0.59 (s, 3H, C-20 CH_3), 1.18 (s, 3H, C-18 CH_3), 3.65 (s, 3H, C-19 $COOCH_3$), 4.31 and 4.66 (s, and 1H each, broad Wh/2 = 3Hz, C-17 vinylic CH_2), 6.66 (m, 1H, C-14 β-furanoid H), 7.29 (m, 1H, C-15 α-furanoid H), 7.98 (m, 1H, C-16 α-furanoid H) ppm; High resolution mass spectrum m/e: Calcd. for $C_{21}H_{28}O_4$: 344.198747; Observed: 344.199064 (mol ion), 249 (M-95, β-ketone cleavage).

14. Attempts to Form C-12 Ketone Derivatives of 61

(a) p-Toluene sulphonyl hydrazone. — The ketone 61 was kept with excess p-toluene sulphonyl hydrazone in solutions of dry dimethoxyethane : ethanol at room temperature, 50° and 80°. Even when these mixtures were left for up to ten days at room temperature no reaction occurred, as evidenced by direct insitu reaction of the products with sodium borohydride which gave only the alcohols 131/132 resulting from reduction of the starting material. At ethanol reflux temperature extensive reduction of the 8(17)-double bond took place apparently due to diimide production[111].

Use of p-toluene sulphonic acid as a catalyst and isolation of the product revealed two components as judged by pmr inspection, one of which showed fresh (31.0Hz) C-20 methyl absorption. However, sodium borohydride at 60° failed to produce any effect on the mixture. Prolonged refluxing with sodium borohydride in isopropanol overnight gave a complex mixture probably as a result of Bamford-Stevens[162] reaction via the diazo compound.

(b) Semicarbazone. — Heating the ketone at 45° with semicarbazide hydrochloride in methanol : DMF with sufficient sodium bicarbonate to provide the right pH[109] produced an ill-defined product resulting from apparent degradation of the furan ring. No reaction occurred overnight at room temperature with this reagent.

(c) Oxime. — Boiling hydroxylamine hydrochloride in aqueous pyridine at 110° for twenty hours (conditions shown to give reaction with very hindered 11-keto

steroids[110]) gave an essentially homogeneous product which may be a mixture of two oximes although it has not been fully characterised. This derivative (if formed) maybe of future utility by reduction to amine and hydrogenolysis of the trimethyl derivative. Also the conditions of formation(?) may give better results with other reagents.

(d) Thioketal.—— The ketone 61, 20 mg (0.058 mmol) was placed in 5 ml 'pear'-tube and 5 drops (116 mg, 1.12 mmol) ethandiol added together with two drops (20 mg) of boron trifluoride ethereate. The solution was held at room temperature overnight. The product was diluted with benzene, washed with 5% sodium hydroxide solution, water, brine and evaporated to give a dark-pink oil, 22 mg. Pmr showed essentially one compound containing mixed furanoid absorption, and the vinylic protons had shifted downfield each showing a 4Hz splitting!

When the product was added to 400 mg W-2 Raney nickel (deactivated by refluxing for one hour in acetone) and stirred at room temperature for 30 min, the final result showed some sulfur removal but considerable double bond reduction.

15. Methyl 15,16-Epoxy-12-hydroxylabda-8(17),13(16),14-trien-19-oate (12(S)-131 and 12(R)-132)

Ketone 61 50 mg, was stirred with excess sodium borohydride in aqueous ethanol overnight at room temperature. The solution was then poured into 5% NaH_2PO_4 solution and benzene extracted. Usual work-up gave 49 mg colourless oil which pmr inspection showed to a mixture of the two alcohols 131 and 132 in the approximate ratio of 6:4 . (This same mixture was obtained from borohydride

reaction in the abortive tosylations above) ir ν_{max} 3620, 3400, 2920, 2850, 1720 (1730 sh), 1640, 1470, 1230, 1160, 1025, 895 and 875 cm^{-1}.

The mixture was chromatographed at 100:1 on 'Florisil' in 50:50 petroleum ether (30/60°) - benzene. Elution with benzene gave 15 mg of the 12(R) - 132 alcohol as a colourless oil, pmr δ 0.515 (s, 3H, C-20 CH_3), 1.18 (s, 3H, C-18 CH_3), 3.58 (s, 3H, C-19 $COOCH_3$), 4.48 (H_A) and 4.86 (H_B) (s and 1H each, broad Wh/2 = 3Hz, C-17 vinylic H's), 4.71 (d, J=7Hz, C-12 H, α to OH), 6.37 (m, 1H, C-14 furanoid H), 7.3 (m, 2H, C-15/16 furanoid) ppm. 5% ethyl acetate-benzene gave 20 mg of crystalline solid, 12(S) - 131 alcohol, pmr δ 0.530 (s, 3H, C-20 CH_3), 1.13 (s, 3H, C-18 CH_3), 3.55 (s, 3H, C-19 $COOCH_3$) 4.72 (H_A), and 4.88 (H_B) (s and 1H each, Wh/2 = 3Hz (H_B) or 4.5Hz (H_A), C-17 vinylic H's), 4.78 (d, J=14Hz, 1H, 12-H α to OH), 6.37 (m, 1H, C-14 furanoid H), 7.3 (m, 2H, C-15/16 furanoid) ppm.

D. - Additional Synthetic Intermediates

1. Methyl 12-Acetoxypodocarpa-8(14),12(13)-dien-19-oate 50

p-Toluene sulphonic acid monohydrate 80 mg, was refluxed in 15 ml acetic anhydride in a flask fitted with a Dean-Stark trap until 5 ml of distillate was obtained. Then 240 mg (0.83 mmol) of $\alpha\beta$-unsaturated ketone 49 (mp 126-130°) was added in 10 ml acetic anhydride and distillation continued for 3.5 h in such a manner that some 10 ml of distillate was collected. The reflux ratio was controlled by a positive pressure of nitrogen.

After cooling, the reaction mixture was diluted with hexane and washed with saturated sodium bicarbonate solution, saturated brine, and filtered through anhydrous sodium sulphate. Evaporation of the solvents in vacuo gave 280 mg (98%) of a light brown oil. Pmr analysis showed 10% unreacted starting material, 50% enol acetate 50, 30% enol acetate 133, 5% enol acetate 139, and 5% methyl podocarpate 54

Attempted chromatography on Silica Gel was of limited success and led only to removal of aromatic material and starting ketone, on elution with 2% ethyl acetate-benzene. The resulting (3:2) mixture of enol acetates 50 : 133, represents the thermodynamic distribution of the two (see below). Solution in methanol and cooling at -20° yielded 80 mg (28%) of almost pure enol acetate 50. The analytical sample obtained by a second cyrstallization from the same solvent, as clusters of needles, mp 96-97°; ir ν_{max} 2940, 2850, 1755, 1730, 1680, 1630,

1215, 1140 cm^{-1}; uv λ_{max} 257 (shoulder) (5200), 273.5 (7700), 282.5 (7800), 295 (shoulder)(5000) mμ; ord (concn. 0.10 mg/ml, CH_3OH), 22°; $[\phi]_{650}$ 0°, $[\phi]_{589}$ -1550°, $[\phi]_{290}$ -21,300°; $[\phi]_{232}$ +23,000°, $[\phi]_{650}$ 0°, $[\phi]_{589}$ -1550°, $[\phi]_{290}$ - 21,300°, $[\phi]_{232}$ + 23,000°, $[\phi]_{210}$ + 15,600°, mol.amplitude a = 443; pmr δ 0.78 (s, 3H, C-20 CH_3), 1.19 (s, 3H, C-18 CH_3), 2.08 (s, 3H, C-12 $-OCOCH_3$), 3.58 (s, 3H, C-19 $COOCH_3$), 5.40 (q, 2H, J_{AB}=6.3 Hz, δ_{AB} =3.9Hz) ppm; mass spectrum m/e 332, 314, 290, 288, 230, (metastable at 254). Mol.wt.332. Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found : C, 72.23; H, 8.44.

2. Methyl 12-Acetoxypodocarpa-11(12),13(14)-dien-19-oate 133

p-Toluene sulphonic acid monohydrate 300 mg, was refluxed with 1.00 g $\alpha\beta$-unsaturated ketone 49, (mp 126-130°) in 30 ml of isopropenyl acetate (R grade, Eastman) for 4.5 h, using the same apparatus and technique as in 1. above. Some 20 ml of distillate (acetone and reagent) were obtained in this manner. The product was taken up in hexane, washed with saturated sodium bicarbonate solution, brine and filtered through anhydrous sodium sulphate to give on evaporation in vacuo, 1.13 g, (95%) of a yellow oil. The pmr spectrum showed the product to consist of 90% of the desired enol acetate 133, together with 10% of the starting ketone. Crystallization from dry hexane at 0° gave 0.80 g (70%) crystalline material mp 75-78°. A further crystallization of a portion in cyclohexane gave the analytical sample of 133 as colourless needles, mp 78-80°; ir ν_{max} 2960, 2850, 1760, 1730, 1650, 1600, 1210, 1170 cm^{-1}; uv λ_{max} 262 (3400 mμ); ord (concn.

0.1 mg/ml. CH_3OH), 22°, $[\phi]_{650}$ +1000°, $[\phi]_{589}$ +1500°, $[\phi]_{400}$ +5000°, $[\phi]_{250}$ +7000°, $[\phi]_{220}$ +12,600°, (positive plain curve); pmr δ 0.69 (s, 3H, C-20 CH_3), 1.22 (s, 3H, C-18 CH_3), 2.18 (s, 3H, C-12 $OCOCH_3$), 3.77 (s, 3H, C-19, $COOCH_3$), 5.70 (m, Wh/2 = 4Hz (unresolved at 100 MHz), 2H, C-13 and C-14 vinylic H's), 5.87 (d, J = 1.0Hz, 1H, C-11 vinylic H) ppm; Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49, Found: C, 72.40, H, 8.38.

3. Additional Studies on the Enol Acetates

When the kinetically formed enol acetate 133 was refluxed in acetic anhydride for 1-2 h in the presence of a crystal of p-toluene sulphonic acid, cooled and worked up in the same manner as 1. above, the thermodynamic mixture of 62% 50 and 38% 133 was obtained. This mixture was identical to that obtained by chromatography of the reaction mixture from the $\alpha\beta$-unsaturated ketone.

In another experiment, in an attempt to prepare enol acetate 50, directly from the $\beta\gamma$-unsaturated ketone without equilibration, a third isomeric enol acetate was produced. The $\beta\gamma$-unsaturated ketone 67, 100 mg (purity >95%) was refluxed with 25 mg p-toluene sulphonic acid monohydrate, and 5 ml of isopropenyl acetate in the same apparatus as previously until 3.0 ml of distillate were obtained in 3 h. The product was cooled, diluted with hexane and washed with saturated sodium bicarbonate solution and worked-up in the usual way to give 108 mg of a semi-crystalline oil. The pmr spectrum showed the presence of 15% methyl podocarpate, 25% enol acetate 50 and 60% of an unknown compound with vinylic absorption in the same region as 133 and a C-20 methyl absorption at 0.60 ppm.

Chromatography on 'Florosil' served to remove methyl podocarpate but did not achieve spearation of the two main components. Tlc on silica gel was similarly unsuccessful. Crystallization of the mixture led to enrichment of the unknown compound, but after four crystallizations from hexane the compound still contained 17% of enol acetate 50. ir ν_{max} 2950, 2850, 1760, 1730, 1222, 865 cm^{-1} uv (featureless except for absorption due to enol acetate 50 at 17% of ϵ) pmr 0.60 (s, 1H, C-20 CH_3), 1.15 (s, 1H, C-18 CH_3), 2.05 (s, 3H, C-12 $OCOCH_3$); 2.5 - 2.85 (m, 2H, C-14 allylic); 3.58 (s, 3H, C-19 $COOCH_3$), 5.35 (m, 2H, C-11 and C-14 vinylic) ppm. Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26, H, 8.49. Found: C, 72.12; H, 8.67. The overall evidence thus suggests that the compound is methyl 12-acetoxy-podocarpa-11(12),8(14)-dien-19-oate 139.

4. (13 → 16)-Tetranor-8β-labda-12,17,19-trioic acid 19-methyl ester 142

The α/β-unsaturated ketone 49, 1.00 g (3.45 mmol) mp 124-126° was dissolved in 25 ml dry (R) ethyl acetate, cooled to 0° in an ice-bath and ozonized oxygen (ca 2% from a 'Welsboch T-408 Ozonizer' run at 0.5 SLPM, 115 v, 7-8 psi) was passed through the solution via a fritted-glass gas dispersion tube for 30 mins. After removal of excess ozone with a nitrogen stream, solvent was removed in vacuo at 40°. Then 30 ml acetic acid, 20 ml of 30% hydrogen peroxide and ten drops of concentrated hydrochloric acid were added and the mixture stirred at room temperature overnight, and finally for 1.5 h on the steam bath. The product was taken up in benzene, washed thoroughly with water, three 40 ml portions of saturated sodium carbonate solution and finally once with 50 ml of water. The

combined alkaline washings were acidified with 2N sulphuric acid and extracted with benzene. Usual work-up gave 0.90 g (80%) of the diacid 142 as an oil which crystallized slowly on standing. Recrystallization from hexane-ethyl acetate (4:1) gave the diacid as colourless needles, mp 182-184°; ir ν_{max} 3500 -- 2500 (broad), 2950, 1730--1700, 1440, 1225 (broad), 1165 cm^{-1}; pmr δ 0.66 (s, 3H, C-20 CH_3), 1.20 (s, 3H, C-18 CH_3), 3.66 (s, 3H, C-19 $COOCH_3$), 10.5 - 11.5 (s, broad, 2H, C-12 and C-17 COOH's) ppm. Anal. Calcd. for $C_{17}H_{26}O_6$: C, 62.56, H, 8.03. Found: C, 62.64; H, 8.11.

5. Trimethyl (13→16)-Tetranor-8β-labda-12,17,19-trioate 143

Ethereal diazomethane was added dropwise to a stirred solution at room temperature of 0.650 g (2 mmol) of diacid 142 in ether-methanol. Evaporation of the solvent in vacuo afforded 0.705 g (99-100%) of the crystalline triester 143. Recrystallization of a portion from hexane-ethyl acetate (9:1) yielded 143 as colourless prisms, mp 91.5-92.5°; ir ν_{max} 2950, 1740, 1735, 1725, 1220 (broad) 1165 cm^{-1}; pmr δ 0.59 (s, 3H, C-20 CH_3), 1.16 (s, 3H, C-18 CH_3), 3.60 (s, 9H, C-12,17, and 19 esters), 3.53, 3.50 and 3.48 (s, and 3H each, C-19, C-17 and C-12, $COOCH_3$'s respectively in CCl_4 solution) ppm; mass spectrum m/e 354, 322, 294. Anal. Calcd. for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.44; H, 8.11.

6. (13→16)-Tetranor-8β-labda-12,17,19-trioic acid 17,19-dimethyl ester 144

Triester 143, 1.00 g (2.83 mmol) mp 89-91°, was dissolved in 32 ml of

methanol, and 2.85 ml of 1N sodium hydroxide and 57.0 ml water added (making the total solution 0.05 N in sodium hydroxide). The mixture was refluxed for 3.5 h under nitrogen with stirring. After removal of the majority of the methanol in vacuo, the aqueous residue was washed with ether (3 x 50 ml) and the ethereal washings counterwashed once with 50 ml of water. The aqueous phases were then combined and acidified with 2N sulphuric acid and extracted with benzene. Usual work-up of the extracts gave 875 mg (91%) of acid-ester 144, as an oil which crystallized on standing. Pmr analysis showed it to be 95% pure. Crystallization of a portion from hexane-ethyl acetate (9:1) gave 144 as colourless plates, mp 138-139°; ir ν_{max} 3600 - 2600 (broad), 2950, 2870, 1735, 1717 1165, 1220 cm^{-1}; pmr δ 0.63 (s, 3H, C-20 CH_3), 1.16 (s, 3H, C-18 CH_3), 3.57 and 3.54 (s and 3H, each C-19, and C-17 $COOCH_3$'s) ca 11.3 (s, broad Wh/2 = 3Hz, 1H, C-12 COOH) ppm. Anal. Calcd. for $C_{18}H_{28}O_6$: C, 63.51, H. 8.29, Found : C, 63.54; H, 8.21.

7. Methyl (13→16)-Tetranor-8β-labda-19-oate-12,17-olide 146

A solution of 0.500 g (1.47 mmol) of acid-ester in 50 ml dimethoxyethane (freshly distilled from calcium hydride) was added dropwise to 2.25 g (5.85 mmol) of sodium trimethoxyborohydride (Alpha Inorganics Inc.) in a 200 ml flask under a nitrogen atmosphere. After a short period of frothing and hydrogen evolution, the mixture was stirred and brought to reflux for 75 min. After cooling, the reaction mixture was poured into cold water, acidified with 2N sulphuric acid and the liberated product extracted with benzne. The benzene extracts after washing

with water and usual work-up gave 0.45 g (98%) of crystalline hydroxy acid 145 or lactone 146. The presence of the hydroxy-acid was never fully established since lactonisation to 146, occurred on or before subsequent crystallisation. However the sample from one run on evaporation at RT showed ir ν_{max} 3600 - 2550, 1730, 1720 cm^{-1}; pmr δ 8.70 (s, 2H, broad C-12 COOH and C-17 OH) ppm. On crystallization from hexane-ethyl acetate, colourless plates of the lactone 146 were obtained, mp 136-137°; ir ν_{max} 2945, 2850, 1730, 1725, 1240, 1195, 1160 cm^{-1}; pmr δ 0.675 (s, 3H, C-20 CH_3), 1.16 (s, 3H, C-18 CH_3), 3.72 (s, 3H, C-19 $COOCH_3$) 3.66 and 4.20 (m, 2H, AB part of an ABX, J_{AB}=11Hz, J_{AX}=5Hz, and J_{BX}=11Hz, C-17 CH_2) ppm; mass spectrum m/e 294, 262, 235, 220. Anal. Calcd. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.38, H, 8.83.

8. Investigation of Reducing Ability of Sodium Trimethoxyborohydride on other Methyl Esters

Three esters were selected as typical primary, secondary and tertiary examples with suitable pmr absorptions so that they could be measured for extent of reduction easily. They were methyl 3-phenylpropionate, methly cyclohexyl-carboxylate and methyl abietate 147. The same general procedure as used above was followed. To a solution of 5 mmoles of ester in 50 ml dimethoxyethane was added 20 mmol of sodium trimethoxyborohydride and the mixture stirred under reflux under a nitrogen atmosphere. Five millilitre aliquots were withdrawn at appropriate times, quenched in dilute acid and examined by pmr spectroscopy for the extent of reduction. In all three cases it was possible to observe the rate of

disappearance of the ester group by integrating the area under the ester-methyl absorption and comparing it with the area under absorptions common to starting material and product. The results are shown in Table V (Section IV). The 3,5-dinitrobenzoates of the alcoholic products were prepared in pyridine and gave satisfactory melting points. The pmr spectra of the alcohols were also consistent with the expected products.

9. 8-Dihydroxy-(13→17)-pentanorlabd-9(11)-ene-12,19-dioic acid 19-methyl ester -8α→12-lactone 93

Hydroperoxide 55, mp 203-207° (>95%) 0.50 g was stirred in 50 ml of 95% ethanol and 0.5 g sodium sulphite added in 20 ml water. The mixture was stirred at room temperature and then poured into 500 ml water and extracted with b benzene (3 x 100 ml) in the usual way to give 465 mg (98%) of crystalline lactone hemi-ketal 93, which pmr analysis showed to be >95% pure. Recrystallisation from chloroform-hexane (1:1) gave colourless plates mp 198-201°(d); ir ν_{max} 3570, 3350(b), 2955, 1760, 1725, 1640, 1240, 1168, 1110, 1095, 1038, 1018, 978, 960, 930, 870 cm^{-1}; uv λ_{max} 220 (11,200), 280 sh (19) mμ; pmr δ 1.125 (s, 3H, C-20 CH_3), 1.22 (s, 3H, C-18, CH_3), 3.71 (s, 3H, C-19 $COOCH_3$), 4.1 - 4.9 (s, broad Wh/2 = 5Hz, 1H C-8 OH), 5.63 (s, 1H, C-11 vinylic) ppm; Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53; O, 27.15. Found: C, 65.38; H, 7.47;). 27.15.

10. 8α-Hydroxy-(13→17)-pentanorlabd-9(11)ene-12,19-dioic acid 19-methyl ester 8α-12-lactone 104

Methyl podocarpate 2.00 g (6.9 mmol) was dissolved in 40 ml of (1:1)

methanol-methylene chloride cooled to -78°, and ozonised air (80 v, 7-8 psi, 0.5 SLPM) passed through (as described above) the solution until it was pale blue (55 minutes). The still cold (-78°) solution was then treated with 1.5 g sodium borohydride in 20 ml of 50% aqueous ethanol, stirred (magnetic stirrer bar), and allowed to warm to room temperature. After further stirring at room temperature for 30 min the reaction mixture was poured into 200 ml water, filtered and the filtrate and sodium borate residue extracted with ether-benzene (3:1) (3 x 75 ml). Usual work-up gave 1.70 g (90%) of the unsaturated lactone 104 as a crystalline solid, which pmr analysis indicated to be ca 90% pure.

The aqueous residues from the above extraction were acidified with 2N sulphuric acid and extracted with benzene. Work-up gave 0.25 g (11%) of the δ-lactone-alcohol 149 (see below).

The unsaturated lactone 104 was crystallised from ethyl acetate-hexane (1:3) to give colourless slabs mp 144-145°, ir ν_{max} 3014, 2950, 1750, 1720, 1635, 1220, 1000 cm^{-1}; uv λ_{max} 218 (18,000), 280 (40) mμ; pmr (100 MHz) (see Figure 17) δ 0.99 (s, 3H, C-19 CH_3), 1.22 (s, 3H, C-18 CH_3), 3.66 (s, 3H, C-19 $COOCH_3$), 4.86 (two quartets, J_{AB}= 11.5Hz, J_{AC}=7.5Hz, J_{AD}=1.5Hz, 1H, C-8β-H), 5.53 (q, J_{AD}- 1.5Hz, $J_{DC?}$=0.6Hz, 1H, C-11 vinylic) ppm, mass spectrum (80 ev) m/e 278, 263 (M-15), 248 (M-30), 234 (M-45), 219 (M-59). Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97; Found: C, 68.88; H, 8.22.

11. 17α-Hydroxymethylene-17-hydroxy-(13→17)-tetranorlabd-9(11)-ene-12,19-dioic acid 19-methyl ester 12→17-lactone 149

In an identical manner to the above preparation (10) 1.0 g (3.45 mmol) methyl podocarpate was ozonised at -78° and after nitrogen had been bubbled through the solution for five minutes, 1.05 g sodium borohydride (27.6 mmol) was added in 10 ml of 50% aqueous ethanol to the still cold (-50→-20°) solution. After stirring until the solution warmed to room temperature and then for 30 min, the whole was heated on the steam bath for a further 30 min. After solvent had been removed in vacuo the product was acidified with 5% NaH_2PO_4 solution and extracted with benzene. Usual work-up yielded 0.80 g oil. Pmr analysis showed essentially two components. These were the keto-acid 36, ca 55% and the δ-lactone-alcohol 149. After esterification with diazomethane the mixture was chromatographed on Florosil. Elution with 5% ethyl acetate-benzene gave the keto-ester 79 400 mg, and then with 15% ethyl acetate-benzene gave 300 mg of 149. Crystallisation of the latter from 1:9 ethyl acetate-hexane gave a white micro-crystalline solid, mp 119-120°; ir ν_{max} 3590, 3410, 2950, 2850, 1730, 1570, 1470, 1238, 1068, 1036 cm^{-1}; uv λ_{max} 227 (8,300), 280 (40) mμ; pmr (100 MHz) δ 0.92 (s, 3H, C-20 CH_3), 1.23 (s, 3H, C-18 CH_3), 3.64 (s, 3H, C-19 $COOCH_3$), 3.82 (d, J= 5.5Hz, 2H, C-21 CH_2O), 3.5 - 5.5 (variable) (broad s, 1H, OH), 4.68 (t, J=5.5Hz, 1H, C-17 H), 6.07 (s, 1H, C-11 vinylic) ppm; mass spectrum (high resolution) m/e 322.1780, $C_{18}H_{26}O_5$ (mol.ion), 304.1674 $C_{18}H_{24}O_4$ ($M-H_2O$), 291.1596 $C_{17}H_{23}O_4$ ($M-CH_3O.$ or CH_2OH),

275.1647 $C_{17}H_{23}O_3$ ($M-H_2O-HCO$) (see Discussion), 263.1647 $C_{16}H_{23}O_3$ ($M-COOCH_3$), 229.128 $C_{15}H_{17}O_2$ ($M-COOCH_3 + H_2O + H + CH_3$); mol.wt. 322. Anal. Calcd. for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.10; H, 8.31.

N.B. Although the above data are consistent with the proposed structure 149, its genesis is in doubt (see Discussion).

12. 8β-Hydroxy-(13→17)-pentanorlabdan-12,19-dioic acid 19-methyl ester 12→8-lactone[60] 150

The lactone 150 was obtained on two separate occasions:

(a) By reduction of Keto-Ester 79. Treatment of 250 mg of keto-ester 79 in 25 ml dry dimethoxyethane with sodium trimethoxyborohydride (824 mg) at room temperature, gave the following results (on withdrawal and acidification of aliquots): 30 min, 38% 150, 62% 79; 1.5 h, 60% 150, 40% 79, 4 h 90% 150, 0% 79 and minor products.

(b) By reduction of crude ozonolysis mixture. The product from ozonolysis of 1.0 g methyl podocarpate (see above) was treated with excess sodium borohydride added in 20 ml of 50% aqueous ethanol. After stirring for 30 minutes at room temperature and then refluxing for 1.0 h, the reaction mixture was cooled, poured into water, benzene extracted and the aqueous phase acidified with 2N sulphuric acid and benzene extracted. Usual work-up gave 540 mg neutral fraction and 430 mg of acid fraction. The neutal fraction contained, as judged by pmr, a mixture of 104, 150 and 151 in the ratio 4:4:2 respectively. Chromatography on 'Florisil' gave the lactone 104 in benzene, followed by 200 mg of 150, using 5% ethyl acetate-benzene

as an oil which crystallised spontaneously. Crystallisation from hexane-ethyl acetate (9:1) gave a sample mp 160-161° (lit.[60] 163-164°) ir ν_{max} 3050, 2950, 2850, 1775, 1725, 947, 910 cm^{-1}; pmr δ 0.77 (s, 3H, C-20 CH_3), 1.23 (s, 3H, C-18 CH_3), 2.5 (m, 2H, C-11 CH_2), 3.66 (s, 3H, C-19 $COOCH_3$), 4.5 (m, 1H, C-8 H) ppm; mass spectrum (80 ev) m/e 280, 262 (M-18), 248 (M-32) 234 (M-46), 221 (M-59). mol.wt. 280.

13. 8α,12-Dihydroxy-(13→17)-pentanorlabdan-19-oic acid 19-methyl ester 151

The third component from the above chromatography, eluting with 10% ethyl-acetate-benzene was the diol 151, 110 mg as an oil. The same compound was obtained in a separate experiment where 100 mg of 104 were reduced with sodium borohydride in aqueous ethanol at reflux for 30 min. In both cases crystallisation from hexane-ethyl acetate (4:1) gave the analytical sample as glistening needles, mp 112-113°; ir ν_{max} 3615, 3420(b), 300, 2950, 1725, 1240-1210(b), 1155, 1035, 1000 cm^{-1}; pmr δ 0.83 (s, 3H, C-20 CH_3), 1.18 (s, 3H, C-18 CH_3), 3.65 (s, 3H, C-19 $COOCH_3$), 3.75 (m, 2H, C-12 CH_2O), 4.03 (m, 1H, C-8( ) CHO), 1.75 - 4.25 (concentration dependent, s, broad Wh/2 = 5Hz, 2H, C-12 and C-8 OH's) ppm, mass spectrum (80 ev) m/e no mol.ion, 292, 275, 266 (not interpreted). Anal. Calcd. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93. Found: C, 67.35; H, 10.25.

14. 1β-Carbomethoxy-1α,10β-dimethyldecal-6-one 153

The hydroperoxide 55, mp 203-207° (95%), 200 mg, was dissolved in

10 ml of ethanol and heated with 10 ml of 1N sodium hydroxide solution on the steam bath, under nitrogen, for 4h. The cooled reaction mixture was diluted with 200 ml water and extracted with benzene (3 x 50 ml) and usual work-up gave 106 mg colourless oil (70%) which pmr analysis showed to be a single component essentially analytically pure. Crystallisation of the sample from hexane at -20° gave 60 mg of colourless plates of the bicyclic ketone 153, mp 62-63° (softening at 54°+), ir ν_{max} 3110, 2950, 2850, 1720, 1705, 1460, 1240(b), 1160, 1150, 1095, 985 cm^{-1}; uv λ_{max} (featureless except for low n- π^* C=O at 290 mμ); pmr δ 0.715 (s, 3H, C-10 CH_3), 1.23 (s, 3H, C-4 CH_3), 3.55 (s, 3H, C-4 $COOCH_3$) ppm; mass spectrum m/e 238 (mol.ion), 223 (M-15), 179 (M-59) mol.wt 238; Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: H, 70.61, H, 9.46.

The base soluble fraction from the above reaction was acidified and extracted with benzene to give 42 mg colourless oil. Pmr analysis showed it to be a mixture of 45% lactone-hemiketal 93, 25% of an unknown component (C-20 CH_3 absorption at 1.03 ppm), and 30% of an acid at 0.85 ppm (C-20 CH_3) (see Discussion). Similar treatment of the lactone-hemiketal 93 in aqueous ethanolic base at reflux gave 5% (of total) of the above acid after 1.3 h and after 6 h, 30% of the acid and 60% of 153.

15. 7-Hydroxy-(13→17)-pentanor-7,8-secolabd-9(11)-ene-8,12,19-trioic acid 12,19-dimethyl ester 7,8-lactone 152 (R=CH_3)

The hydroperoxide 55, mp 203-207° (>95%) 0.50 g, was dissolved in

25 ml methanol together with 10 ml of 30% hydrogen peroxide, and 25 ml of 10% sodium hydroxide solution. After heating at reflux under nitrogen for 30 min the reaction mixture was cooled and poured into 2N sulphuric acid and the liberated organic material was extracted with benzene (3 x 50 ml). Usual work-up gave 0.50 g (95%) of colourless crystalline solid which pmr analysis showed to be 95% pure lactone-acid 152 (R=H). The compound absorbed 1 mole of hydrogen (catalytic hydrogenation with Pd/C) to give a colourless oil, and diazomethane gave a mono-ester 152 ($R=CH_3$), mp 95-96°. The compound was characterised as its methyl ester 152 ($R=CH_3$) originally since it had been obtained directly, crude (80%) from methyl podocarpate, and methylation and chromatography were necessary for purification. ir ν_{max} 3040, 3004, 2960, 1742, 1730, 1720, 1640, 1175 cm^{-1}; uv λ_{max} 214 (10,400), 280 (190, shoulder) mμ; pmr (100 MHz) δ 0.97 (s, 3H, C-20 CH_3), 1.20 (s, 3H, C-18 CH_3), 3.65 and 3.70 (s, and 3H each, C-19 and C-12 $COOCH_3$'s), 4.14 (m, 2H, C-7 CH_2O unresolved at 30°; at other temperatures: 40° t, J=5Hz, 50° m-4 lines; 70° m-6 lines), 5.85 (s, 1H, C-11 vinylic) ppm; mass spectrum (80 ev) m/e - no apparent mol. ion, 280 (M-44), 253 (m-71), 211 (M-113); mol. wt. 324. Anal. Calcd. for $C_{17}H_{24}O_6$: C, 62.95, H, 7.46; 0, 29.60. Found: C, 63.09; H, 7.28; 0, 29.39.

REFERENCES

1. S. Blake and G. Jones, J.Chem.Soc. 3012 (1965)

2. W.S. Johnson, Acc.Chemical Res. 1, 1 (1968)

3. G. Stork and A.W. Burgstahler, J.Amer.Chem.Soc. 77, 5068 (1955); P.A. Stadler, A. Eschenmoser, H. Schinz and G. Stork, Helv.Chim.Acta. 40, 2191 (1957)

4. P.A. Stadler, A. Nechvatal, A.J. Frey, and A. Eschenmoser, Helv.Chim.Acta. 40, 1373 (1957)

5. D.B. Bigley, N.A.J. Rogers, and J.A. Barltrop, J.Chem.Soc. 4613 (1960)

6. S.W. Pelletier, L.B. Hawley, Jr., and K.W. Gopinath, Chem.Commun. 96 (1967)

7. S.W. Pelletier, K.N. Iyer, C.W.J. Chang, and A. Ogiso, Tet.Lett. 3819 (1968)

8. A. Ogiso and S.W. Pelletier, Chem.Commun. 94 (1967)

9. E. Wenkert, J.R. Mahajan, M. Nussim and F. Schenker, Can.J.Chem. 44, 2575 (1966)

10. R.M. Carmen and N. Dennis, Aust.J.Chem. 20, 157 (1967)

11. P.F. Vlad, A.G. Russo and G.V. Lazurevskii, Khim. Prirodn Socdin. Akad. Nauk. Uz.S.S.R. 2 (1) 29 (1966). C.A. 65, 754a (1966)

12. L.H. Briggs, R.C. Cambie, R.N. Seelye and A.D. Warth, Tetrahedron, 7 270 (1959); see also S.G. Brooker, R.C. Cambie and M.A. Jones, Trans.Roy.Soc. N.Z. 1, 205 (1966)

13a B.K. Bhattacharya, J.Indian.Chem.Soc. 22, 105 (1945);

13b R.D. Haworth and B.P. Moore, J.Chem.Soc. 633 (1946)

13c F.E. King, T.J. King, and J.G. Topliss, Chem.and Ind. 113 (1956)

13(d) U. R. Ghatak, Tet. Lett . 19 (1959)

13(e) U. R. Ghatak, D. K. Datta and S. C. Ray, J. Amer. Chem. Soc. 82, 1728 (1960)

13(f) W. L. Meyer and K. K. Maheswari, Tet. Lett . 2643, (1964).

13(g) E. Wenkert, A. Afonso, J. B-son Bredenberg, C. Kaneko and A. Tahara, J. Amer. Chem. Soc. 86, 2038 (1964)

13(h) T. A. Spencer, R. J. Friary, W. W. Schmiegel, J. F. Simeone, and D. S. Watt, J. Org. Chem., 33, 719 (1968).

13(i) E. N. C. Osakwe, Ph.D. Thesis, McMaster University (1969).

14(a) H. L. Dryden, G. M. Webber, R. R. Burtner, and J. A. Cella, J. Org. Chem. 26, 3237 (1961)

14(b) F. A. Sondheimer and M. Gibson, Bull. Res. Council, Israel, 9A 204 (1960) C. A. 55, 6520 (1961)

14(c) E. Wenkert, V. I. Stenberg and P. Beak, J. Amer. Chem. Soc., 86, 96 (1964)

14(d) N. N. Girota and L. H. Zalkow, Tetrahedron, 21, 101 (1965)

14(e) K. Mori and M. Matsui, Tet. Lett. 2347 (1965)

14(f) K. Crowshaw, R. C. Newstead, and N. A. J. Rogers, Tet. Lett . 2307 (1964)

14(g) G. F. Burkinshaw and B. R. Davis, Tetrahedron 23, 4147 (1967)

14(h) B. R. Davis and W. B. Watkins, Tetrahedron 24, 2165 (1968)

15. C.R. Bennett, R. C. Cambie and T. J. Fullerton, Aust. J. Chem. 21, 2473 (1968)

16. R. A. Bell and E. N. C. Osakwe, Chem. Commun. 1093 (1968)

17. C. Tabacik-Wlotzka and Y. Laporthe, Tet. Lett. 3141 (1968)

18. W. G. Dauben and V. F. German, Tetrahedron, 22, 679 (1966)

19. R. Mayr, N. K. Kashtanova, A. I. Lisina, A. K. Dizizenko, and V. A. Pentegova, Isvest. Sibirsk. otdel Akad. Nauk. Ser. Khim. Nauk. 4, 126 (1967); C. A. 67, 64571c (1967)

20a T. Reichstein, A. Zschokke and A. Geog, Helv. Chim. Acta. 14, 1370 (1931)

20b A.J. Birch, R.A. Massey-Wintrapp, S.E. Wright, K. Matsuura, and H.D. Sutherland, Chem. Ind. 902 (1954)

20c T. Kubota and T. Matsuura, Chem. Ind. 521 (1956)

21. S. Gronowitz and G. Sorlin, Arkiv Kemi 19, 515 (1962)

22. F. Bohlmann, E. Winterfeldt, H. Laurent, and W. Ude, Tetrahedron, 19, 195 (1963)

23. J.T. Wrobel and Z. Dabrowski, Roczniki. Chemii Ann. Soc. Chim. Polonanim, 39, 1239 (1965). ibid. 40, 503 (1966)

24. R.H. Bible Jr., and R.R. Burtner, J. Org. Chem. 26, 1174 (1961)

25. H.O House and V. Kramar, J. Org. Chem. 28, 3362 (1963)

26. D.A. Shirley, Org. Reactions, 8, 28 (1954)

27. The Common and Systematic Nomenclature of Cyclic Diterpenes, 2nd Revision, April 1968. J.W. Rowe (Forest Products Laboratory, Forest Service, U.S. Department of Agriculture, Madison, Wisconsin 53705)

28. A.I. Meyers, W. Beverung and G.A. Garcia-Munoz, J. Org. Chem. 29, 3427 (1964). I.A. Kaye and R.S. Matthews, J. Org. Chem. 28, 325 (1963)

29. for examples see: H.O. House, "Modern Synthetic Reactions", W.A. Benjamin Inc. New York, N.Y. 1965. Ch. 1; P.N. Rylander "Catalytic Hydrogenation over Platinum Metals", Academic Press, New York and London

30. R.A. Bell and J.W. Easton, Unpublished observations.

31. O.E. Edwards, Private communication

32. J.W. ApSimon, P.V. Demarco and J. Lemke, Can. J. Chem. 43, 2793 (1965)

33. K. Bowden, I.M. Heilbron, E.R.H. Jones and B.C.L. Weedon, J. Chem. Soc. 39 (1946)

34. R.C. Cookson, J. Chem. Soc. 282 (1954)

35. W. Moffitt, R.B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, J. Amer.Chem.Soc. 83, 4013 (1961)

36a B.J. Magerlein, J.Org.Chem. 24, 1564 (1959), see also for other examples

36b M. Yanagita and K. Yamakawa, J.Org.Chem. 22, 291 (1957)

36c F.G. Bordwell and K.M. Wellman, J.Org.Chem., 28, 2544 (1963)

37. R.A. Bell and J.K. Saunders, Can.J.Chem., (in press)

38. J.D. Baldischweiler and E.W. Randall, Chem.Rev. 81 (1963)

39. M.C. Woods, I. Miura, Y. Nakadaira, A. Terehara, M. Maruyama, and K. Nakarushi, Tet.Lett. 321 (1967)

40. B.M. Fung, J.Amer.Chem.Soc., 90, 219 (1968)

41. J.J. Beereboom and C. Djerassi, J.Org.Chem. 19, 1196 (1954). C. Djerassi and D. Marshall, J.Amer.Chem.Soc., 80, 3986 (1958). M.E. Kuchne, J.Amer.Chem.Soc., 83, 1492 (1961).

42. C.H. DePuy, R.D. Thurn and G.F. Morris, J.Amer.Chem.Soc., 84, 1314 (1962). J.Hine, J.Amer.Chem.Soc., 88, 5525 (1966).

43. E. Seebeck and T. Reichstein, Helv.Chim.Acta, 26, 536 (1943)

44. G.F.H. Green and A.G. Long, J.Chem.Soc., 2532 (1961)

45. R.C. Cookson and N.S. Wariyar, J.Chem.Soc., 2302 (1956)

46. K.G. Lewis and G.J. Williams, Tet.Lett. 4573 (1965)

47. H.E. Zimmerman in "Molecular Rearrangements", P. deMayo Ed. Vol.1, Wiley-Interscience, New York, N.Y. 1963, pp 345-372.

48. E.M. Arnett, Progress in Physical Organic Chemistry, 1, 223 (1963)

49. J.A. Marshall, and N.H. Andersen, J.Org.Chem., 31, 667 (1966)

50. S.K. Malholtra and H.J. Ringold, J.Amer.Chem.Soc., 86, 1997 (1964). C.K. Ingold, "Structure and Mechanism in Organic Chemistry",

Cornell University Press, Ithaca, N.Y. 1953 p.565.
J. Warkentin and L.K.M. Lam, Can.J.Chem. 42, 1676 (1964).

51. R.P. Holysz, J.Amer.Chem.Soc., 75, 4432 (1953)

52a See for example: J.A. Marshall and D.J. Schaeffer, J.Org.Chem. 30 3642 (1965)

52b J.A. Marshall, W.I. Fanta, and H. Roebke, J.Org.Chem. 31, 1016 (1966)

52c T.A. Spencer, R.M. Villarica, D.L. Storm, T.D. Weaver, R.J. Friary, J. Posler, and P.R. Schafer, J.Amer.Chem.Soc. 89, 5497 (1967)

52d C. Berger, M. Frank-Neumann, and G. Ourisson, Tet.Lett. 3451 (1968)

53. R. Joly and J. Warnant, Bull.Soc.Chim. France 367 (1958)

54. V. Delaroff, R. Smolick, M. Bolla, and M. Legrand, Bull.Soc.Chim. France, 966 (1963)

55. C.M. Siegmann and W.J. van d Burg, U.S. Pat. 3053860 (1962); A.G. Long, S. Eardley and G.F.H. Green, U.S. Pat. 3, 060,199 (1962)

56. W. McGuckin and E.C. Kendall, J.Amer.Chem.Soc., 74, 5811 (1952); V.R. Mathox and E.C. Kendall, J.Biol.Chem. 188, 287 (1951)

57. H. Oediger, H.J. Kabbe, F. Moeller, and K. Eiter, Chem.Ber. 99, 2012 (1966); H.J. Kabbe, E. Truscheit and K. Eiter, Ann.682, 62 (1965)

58. R.U. Lemieux and E. von Rudloff, Can.J.Chem. 33, 1701, 1710 (1955) et seq.

59. E. von Rudloff, Can.J.Chem. 34, 1413 (1956); J.T. Edward, D. Holder, H. Lunn and I. Puskas, Can.J.Chem.39, 599 (1961) M.E. Wall and S. Serota, J.Org.Chem. 24, 741 (1959); B. Berkoz, L. Cuellor, R. Grezemkovsky, N.V. Avita, J.A. Edwards and A.D. Cross, Tetrahedron, 24, 2851 (1968)

60. V.P. Arya, C. Enzell, H. Erdtman and T. Kubota, Acta.Chem.Scand. 15, 225 (1961)

61. L. Ruzicka, E. Bernold and A. Tallicket, Helv.Chem.Acta. 24, 223 (1941)

62. R.B. Woodward, M.P. Cava, W.D. Ollis, A. Hunger, H.U. Daeniker, and K. Schenker, J.Amer.Chem.Soc., 76, 4749 (1954)

63a P.S. Bailey, S.S. Bath, F. Dobinson, F.J. Garcia-Sharp and C.D. Johnson, J.Org.Chem., 29, 697, 703 (1964)

63b E. Bernatek and C. Frengen, Acta.Chem.Scand. 16, 2421 (1962)

63c J.J. Pappas, W.P. Keaveney, M. Berger and R.V. Rush, J.Org.Chem., 33, 787 (1968)

64. E. Bernateck and C. Frengen, Acta.Chem.Scand. 15, 471 (1961); E. Bernateck, J. Moskaland and K. Valen, Acta.Chem.Scand. 15, 1454 (1961)

65. See for example: R.B. Turner, G.D. Diana, G.E. Fodor, K. Gebert, D.C. Simmons, A.S. Rao, O. Roos and W. Wirth, J.Amer.Chem.Soc., 88, 1786 (1966)

66. W.L. Meyer, D.D. Cameron and W.S. Johnson, J.Org.Chem., 27, 1130 (1962)

67. P.S. Bailey, J.Amer. Chem.Soc., 78, 3815 (1956)

68. F.L. Greenwood, J.Org.Chem., 10, 414 (1945)

69a W.P. Keaveney, M.G. Berger and J.P. Pappas, J.Org.Chem., 32, 1537 (1967)

69b S. Fujiwara and M. Katayama, Bull.Chem.Soc., Japan, 32, 657 (1959)

70. R. Criegee, Record Chem.Progr. 18, 111 (1957)

71. N.L. Bauld, J.A. Thompson, C.E. Hudson and P.S. Bailey, J.Amer.Chem. Soc., 90, 1822 (1968)

72. S. Fliszár and M. Granger, J.Amer.Chem.Soc., 91, 3330 (1969)

73. P.S. Bailey, S.B. Mainthia and C.J. Abshire, J.Amer.Chem.Soc., 82, 6136 (1960)

74. G.S. Hammond, J.Amer.Chem.Soc., 77, 334 (1955)

75. R.M. Carmen and D.E. Cowley, Tet.Lett. 2723 (1968)

76. For a summary see: A.G. Davies, "Organic Peroxides", Butterworths, London, 1961

77. Dr. D.B. MacLean, Personal communication

78. A. Maercker, Organic Reactions, 14, 270 (1965)

79. R.A. Bell, R.E. Ireland and L.N. Mander, J.Org.Chem., 31, 2537 (1966)

80. R. Greenwald, M. Chaykovsky and E.J. Corey, J.Org.Chem., 28, 1128 (1963)

81. G. Stork, A. Meisels and J.E. Davies, J.Amer.Chem.Soc., 85, 3419 (1963)

82. G. Cainelli, F. Bertini, P. Grasselli and G. Zubiani, Tet.Lett. 5153 (1967)

83. E.J. Corey and G.T. Kwiatkowski, J.Amer.Chem.Soc., 90, 6816 (1968)

84. W. Nagata and Y. Hayasi, Tet.Lett. 4359 (1968)

85. W.S. Johnson and L.F. Fieser, J.Amer.Chem.Soc., 62, 575 (1940)

86. R.T. Arnold and M.J. Danzig, J.Amer.Chem.Soc., 79, 892 (1957)

87. J. Cason, Chem.Reviews, 40, 15 (1947), see also ref. 26.

88. 'The Chemistry of the Carbonyl Group', S. Patai, Interscience, London, 1966, p.325

89. C. Tegner, Acta.Chem.Scand. 6, 782 (1952)

90. F. Elsinger, J. Schreiber and A. Eschenmoser, Helv.Chim.Acta., 43, 113 (1960)

91. Obtained from the authors: ref. 17.

92. J.E.H. Hancock and R.P. Linstead, J.Chem.Soc., 3490 (1953)

93. A.L. Wilds and C.H. Shurk, J.Amer.Chem.Soc., 70, 2427 (1948)

94. M. Miyano, J.Amer.Chem.Soc., 87, 3958 (1965)

95. G. Stork and F.H. Clarke, Jr., J.Amer.Chem.Soc., 83, 3120 (1961)

96. T.M. Harris, C.M. Harris and J.C. Cleary, Tet.Lett. 1427 (1968)

97. D.M. Burness, J.Org.Chem., 21, 102 (1956)

98. J.W. Cornforth, J.Chem.Soc., 1310 (1958)

99. D. Miller, J.Chem.Soc., (c) 13 (1969)

100. J.A.L. Goldfarb, J. B. Volkenstein and L.I. Belenkij, Angew.Chem. internat. Edit. 7, 519 (1968)

101. H. Gilman and G.F. Wright, J.Amer.Chem.Soc., 55, 3302 (1933)

102. H. Gilman and R.R. Burtner, J.Amer.Chem.Soc., 55, 2903 (1933)

103. M.A. Gianturco and P. Friedel, Can.J.Chem., 44, 1083 (1966)

104. M. Kharasch, J.Amer.Chem.Soc., 43, 2238 (1921)

105. S.T. Ioffe and A.N. Nesmeyanov, "Methods of Elemento-Organo Chemistry", Vol.2, North-Holland Publishing Cpy. Amsterdam, 1967

106. M. Gates and G. Tschudi, J.Amer.Chem.Soc., 78, 1380 (1956)

107. D. Todd, Org.Reactions, 4, 378 (1948)

108. L. Caglioti and P. Grasselli, Chem.Ind., 153 (1964)

109. M.F. Grundon, H.B. Herbest, and M.D. Scott, J.Chem.Soc.,1855 (1963)

110. E.B. Hershberg, E.P. Oliveto and R. Rausser, Chem.Ind., 1477 (1958)

111. R.S. Dewey and E.E. van Tamelin, J.Amer.Chem.Soc., 83, 3729 (1961)

112. L.F. Fieser, J.Amer.Chem.Soc., 76, 1945 (1954)

113. G.R. Pettit and E.E. van Tamelin, Org.Reactions, 12, 356 (1967)

114. G.J. van der Kerk and J.G. Noltes, J.Appl.Chem., 9, 106 (1959)

115. see H.O. House and H.W. Thompson, J.Org.Chem., 26, 3729 (1961); and leading references therein.

116. D.P.N. Satchell, J.Chem.Soc., 1752 (1960)

117. J. Libman, M. Sprecher and Y. Mazur, Tetrahedron, 25, 1679 (1969); J. Libman and Y. Mazur, ibid 25, 1699 (1969)

118. B.E. Edwards and P.N. Rao, J.Org.Chem., 31, 324 (1960)

119. A.J. Liston, J.Org.Chem., 31, 2105 (1966)

120. B. Berkoz, E.P. Chavez, and C. Djerassi, J.Chem.Soc., 1323 (1962); see also M.P. Hartshorn and E.R.H. Jones, J.Chem.Soc., 1312 (1962) (joint paper)

121. A. Moscowitz, E. Charney, U. Weiss and H. Ziffer, J.Amer.Chem.Soc., 83, 4661 (1961)

122. ibid, 83, 4460 (1961)

123. R. Wiechert and G. Schulz, Ber. 98, 3165 (1965)

124. H. Gunther, Tet. Lett. 2967 (1967)

125. E.W. Garbisch, Jr., J.Amer.Chem.Soc., 86, 5561 (1964)

126. E.W. Garbisch, Jr., and M.G. Griffith, J.Amer.Chem.Soc.,90, 3590 (1968).

127. C.R. Engel and S. Rakhit, Can.J.Chem., 40, 2153 (1962)

128. K.V. Yorka, W.L. Truett and W.S. Johnson, J.Org.Chem., 27, 4580 (1962)

129. L.A. Paquetti and N.A. Nelson, J.Org.Chem., 27, 2272 (1962)

130 M.S. Brown and H. Rapoport, J.Org.Chem., 28, 3261 (1963)

131. E. Schenker, Angew Chem. 73, 81 (1961) and references therein

132. R. Paul and N. Joseph, BullSoc.Chim., France, 758 (1963)
R.F. Nystrom, S.W. Chaikin and W.G. Brown, J.Amer.Chem.Soc., 71 3245 (1949);
H.C. Brown, E.J. Mead, and B.C. Subba Rao, J.Amer.Chem.Soc.77, 6209 (1955)

133. R.F. Nystrom and W.G. Brown, J.Amer.Chem.Soc., 69, 1197, 2548 (1947)

134. H.C. Brown and R.F. McFarlin, J.Amer.Chem.Soc., 78, 252 (1956); 80, 5372 (1958)

135. H.C. Brown and P.M. Weissman, J.Amer.Chem.Soc., 87, 5614 (1965)

136. H.C. Brown, E.J. Mead and C.J. Shoaf, J.Amer.Chem.Soc., 78 3613 (1956)

137. H.O. House, "Modern Synthetic Reactions",W.A. Benjamin, Inc., New York, Amsterdam, 1965, p.26

138. Courtesy of Dr. D.B. MacLean, Chemistry Department, McMaster Univ.

139. H.C. Brown and E.J. Mead, J.Amer.Chem.Soc., 75, 6263 (1953)

140. R.A. Bell and M.B. Gravestock, Can.J.Chem., 47, 2099 (1969)

141. C.K. Ingold and F.R. Shaw, J.Chem.Soc., 2918, (1927)

142. W. Nagata, T. Terasawa and K. Tori, J.Amer.Chem.Soc.68, 3746 (1964)

143a Applications of NMR Spectroscopy in Organic Chemistry, N.S. Bhacca and D.H. Williams, Holden-Day Inc., San Francisco, 1964, p.51

143b ibid, p.108

143c ibid, p.110

144 S. Sternhell, Quart.Revs., 23, 236 (1969)

145. 'Mass Spectrometry of Organic Compounds', H. Budikiewicz, C. Djerassi and D.H. Williams, Holden-Day Inc., San Francisco, 1967, p.206.

146. T.A. Spencer, M.A. Schwartz and K.B. Sharpless, J.Org.Chem., 29 782 1964 ; see also ref. 13h.

147. See for example: W.L. Meyer and C.W. Sigel, Tet.Letts., 2485 (1967) W.L. Meyer, G.B. Clemans and R.B. Huffman, Tet.Lett. 4255 (1966)

148a R.F. Zurcher, Helv.Chim.Acta., 44, 1380 (1961)

148b R.F. Zurcher, ibid., 46, 2054 (1963)

149 See for example: E. Wenkert, A. Afonso, P. Beak, R.W.J. Carney, P.W. Jeffs, and J.D. McChesney, J.Org.Chem., 30, 713 (1965)
P.V. Demarco., M.Sc., Thesis, Carleton University (1964);
J.W. Chien, J.Amer.Chem.Soc., 82, 4762 (1960)

150. See for example: J.W. ApSimon, O.E. Edwards and R. Howe, Can.J.Chem., 40, 630 (1962);
W.A. Ayer, C.E. McDonald and J.B. Stothers, Can.J.Chem., 41, 1113 (1963)

151. R.W.J. Carney, Ph.D. Thesis, Iowa State University (1962)

152. J.W. ApSimon, W.G. Craig, P.V. Demarco, D.W. Mathieson and W.B. Whalley, Tetrahedron, 23, 2375 (1967); and references therein

153. J.W. ApSimon, W.G. Craig, P.V. Demarco, D.W. Mathieson, A.K.G. Nasser, L. Saunders and W.B. Whalley, Chem.Commun.754(1966)

154. "Applications of NMR Spectroscopy in Organic Chemistry", N.S. Bhacca and D.H. Williams, Holden-Day Inc., San Francisco (1964), p.20

155. L. Ruzicka, Proc.Chem.Soc., 341 (1959);
E. Wenkert, Chem.Ind.(London), 282 (1955)
A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, Helv.Chim.Acta., 39, 1890 (1959)

156. Th.J. de Boer and H.J. Backer, Rec. Trav. Chim., Pays-Bas., 73, 229 (1954)

157. C.D. Wagner, R.H. Smith and E.D. Peters, Anal.Chem.19, 976 (1947)

158. W.S. Johnson, R.W. Kluiber, A.L. McCloskey and G.S. Fonken, Org.Syn. 34, 26 (1954)

159. T. Moriwake, J.Org.Chem., 31, 983 (1966)

160. A.I. Vogel, "Practical Organic Chemistry", 3rd ed. Longmans Green and Company Limited, London, 1964, p.169.

161. M.L. Sherrill and E.S. Mellock, J.Amer.Chem.Soc., 59, 2134 (1937); see also W.A. Lazier and H.R. Arnold, Org.Syn. Coll vol.2, 142 (1943)

162. W.R. Bamford and T.S. Stevens, J.Chem.Soc. 4735 (1952)

163. C.L. Teitelbaum, J.Org.Chem., 23, 646 (1958)
