PODOCARPIC ACID IN DITERPENE SYNTHESIS

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by

EJIOFOR NWABUNWANNE CHRISTOPHER OSAKWE, B. Sc., M. Sc.

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AUTHOR : Ejiofor Nwabunwanne Christopher Osakwe
(B.Sc. Lond., M.Sc. Ibadan)

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SCOPE AND CONTENTS :

The C→B→A ring formation sequence has been adopted towards a total synthesis of podocarpic acid, starting from 2,7-dihydroxynaphthalene. Experimental procedures which were developed by other workers have been modified to improve the yields and the purity of the products.

Using naturally occurring podocarpic acid, a reliable procedure has been explored for the functionalization of C-6 and C-7 positions in order to construct the 19,6-lactone ring in synthetically satisfactory yields. Catalytic reduction of the aromatic ring C, after functionalization of ring B, has been investigated with the aim of developing a pathway towards the elaboration of the C,D ring system of the kaurane skeleton.

ACKNOWLEDGEMENTS

I wish to express my thanks to Dr. R.A. Bell for his guidance throughout this work. I am also thankful to Professor D.B. MacLean for his interest in my personal progress while at McMaster.

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GENERAL INTRODUCTION

i. Natural Products Chemistry - a brief perspective

Almost the entire organic chemical industry originated in the study of organic compounds of plant and animal origin, generally referred to as natural products. One of the oldest branches of this industry is the dyestuffs industry - dating back about one hundred years.

Until the middle of the nineteenth centry, indigo and alizarin, both of vegetable origin, were the most important materials used for the dying of textile fibres. Around 1890, students of Baeyer had established the chemical constitution of these substances and performed their first technically usable syntheses. Thus began the world-wide development of the dyestuffs industry.

A new era in the study of natural substances began early this century when Willstatter and his school investigated the leaf-coloring matter, chlorophyll. They observed that this substance consisted partly of two green components chlorophyll α and chlorophyll β which were similar in composition and properties but which could not be separated by chemical methods. This led to the development of the technique of chromatography and the separation of mixtures by partitioning in non-miscible solvents.

It was also learned during the investigation of chlorophyll that certain substances called enzymes may occur in living cells which interacted, to some extent, with the natural products causing them to break down to simpler substances.

The chemistry of natural products and its industrial exploitation expanded remarkably following the research work on hormones, vitamins and antibiotics in the 1930's and 1940's. The composition and structure of insulin, the antidiabetic hormone, was elucidated by Sanger; and its total synthesis, reported in 1965 by scientists in Peoples Republic of China, constitutes an important development in modern medicine.

The so-called additives to nutrition, which are indispensable factors for growth and the normal metabolism of human and animal organs were considered of vital importance and were therefore called vitamins. In 1931 Karrer isolated vitamin A and determined its constitution. Later the anti-anaemic principle, vitamin B12, was structurally elucidated with the aid of x-ray studies carried out by Hodgkins at Oxford.

The discovery of penicillin in 1929, by Fleming, opened a new epoch in the treatment of infectious diseases. Countless soil samples were studied for strains of fungi and bacteria. As a result, a great number of substances which inhibit the growth of pathogenic organisms were isolated, although some of them were rendered useless by their high toxicity. Streptomycin and tetracyclin are examples of this class of compounds.

Most antibiotics have been found to be relatively low-molecular weight compounds, although in some instances they have complex structures. Consequently, even in those instances where synthesis has been effected on a laboratory scale, no attempts have been made to produce them on an industrial scale. This work is left to the micro-organisms, the optimum development of the antibiotics being

achieved by a suitable composition of the nutrient substrates and favourable physical conditions.

Before the recent discovery of antibiotics, vitamins and hormones, man had, for thousands of years depended on the use of certain plants as the only available means for the treatment and prevention of diseases. It was therefore, a natural development at the beginning of the nineteenth century, when modern chemistry and pharmacy began to develop, to study these medicinal plants.

The isolation of morphine, the hypnotic and anaesthetic principle of opium, led to the investigation of a whole series of other plants for similar products. Some of them were found to be complicated organic compounds of a basic nature. In view of their alkaline properties, which are due to their nitrogen content, they were called alkaloids.

The preparation of drugs from plants or animal organs has thus been going on for quite a long time. At first extracts, and later pure substances were prepared on an ever-increasing scale as the demand grew. Finally, they were prepared in small factories, and thus began research on the rational preparation and chemical elucidation of the active principles.

The vegetable kingdom provides us not only with alkaloids but also with many other highly active substances, for example, the cardiac glycosides obtained from Digitalis species, the therapeutic effect of which was first recognised in 1785. Today several of these natural glycosides are prepared on a large scale in industry. These preparations are becoming indispensable in view of the rising tide of cardio-vascular diseases.

The ergot alkaloids form another class of very valuable compounds which have been part of the major results of natural products chemistry. The experience gained in the study of chlorophyll facilitated the isolation of ergotamine, one of the highly sensitive principles in this class. Subcutaneous injections of a fraction of a milligram of this compound elicit a rapid contraction of the uterus, thus stopping life-endangering haemorrhage. Ergotamine not only exerts a constrictor effect on smooth muscle fibres, but also exerts a marked effect on the autonomic nervous system. In the course of time, it has been widely used in internal medicine and neurology, for instance, in migraine and in gastro-intestinal atony.

A whole series of active principles similar to ergotamine have been isolated and the heterocyclic ring system of lysergic acid is known to be common to all of them. One of the most potent substances known today, lysergic acid diethylamide (LSD) belongs to this class of compounds. The extraordinarily violent effect of LSD has been an obstacle to the more widespread use of this substance in therapeutics. At present, its use is confined to psychoanalytical research.

Until recently, ergot, appearing as a poisonous weed in cereals, was often the cause of serious large-scale poisoning of the population. After a long period of detailed investigations it has evolved as the essential basic material for the production of important drugs, and today it must be cultivated in order to satisfy the needs of industry and medicine. Natural products chemistry has thus transformed an enemy of man into an indispensable friend!

Currently under rigorous investigations is the lycopodium group of alkaloids, known to exist in many parts of the world. The unique structural constitution of this

group is a point of major academic interest, although they might in future become of pharmacological importance. Professor MacLean of McMaster is well known for his leading contributions in this area of the subject.

Studies of the natural products not only increase and deepen our scientific knowledge, but also provide a basis for a highly developed industry which in turn promotes the living standards of man and helps to treat or prevent disease. Thus excellent services are rendered to humanity through these studies. One of the most noteworthy endeavours of scientific research in general is providing the benefits of its splendid achievements to ever-widening circles of the world's population.

II. Synthesis : Scope and Effectiveness

The over-riding aim in synthetic organic chemistry is to produce in the laboratory, through rational assemblies of reactions, organic compounds discovered in nature. Successful synthesis of a natural product is usually regarded as a confirmation of the structure which had been deduced by degradative reactions of the substance.

Considerable effort has also been expended on the synthesis of some unusual structures, which may not occur in nature, in order to gain further insight into molecular geometry and reactivity. Noteable examples are P. E. Eaton's synthesis of cubane, and the current attempts to synthesise tetrahedrane, "Dewar" benzene, and prismane.

A particular organic compound may be synthesised for any of a number of reasons. There are rough correlations between structures of compounds and physical chemical or biological properties. Thus research chemists can frequently draw structures of compounds as yet unknown, which, when prepared, have a calculable chance of possessing a desired property. Such properties are then put to either scientific or commercial use. Sometimes an organic compound is prepared in the attempt to originate or substantiate a theory, to discover new properties or correlations, or to study a reaction mechanism.

Occasionally, intricate syntheses are conceived and executed simply to satisfy a scientist's urge to construct a complex molecule. The synthesis of

reserpine, reported quite recently by Woodward is an example of such an undertaking, since it is still more economical to obtain the compound from the roots of Rauwolfa.

Most organic compounds can be prepared by different routes, and criteria are needed to select the best method. Generally, the best synthesis of a substance involves the conversion of the most available and cheapest starting materials into the desired product by the least number of steps and in the highest overall yield. In commercial syntheses, costs of starting materials and economy of operations play a dominant role, whereas in many syntheses carried out for academic purposes, the dispatch with which a compound can be obtained is more important.

In many cases, an excellent synthesis, in principle, has to be abandoned for practical reasons. Occasionally, reactions are too hazardous for anything but small-scale work. Sometimes an intermediate, although produced in good yield, is too difficult to purify. Possibly an intermediate is too unstable for storage or too insoluble in any medium to permit confinement of the reaction to reasonable volumes. In other cases, yields vary because reaction rates are highly sensitive to impurities, reaction conditions, solvent, catalyst grade, or other variables. Difficulties of this sort are hard to anticipate and sometimes not easy to overcome.

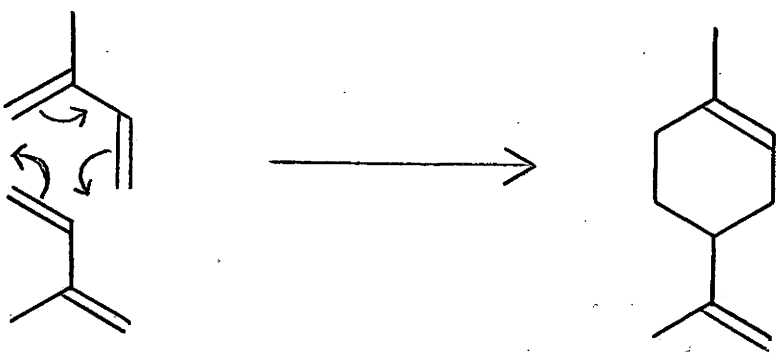
Conception of organic syntheses for compounds of any complexity usually involves a stepwise procedure of working backward from the structure of the product to the structure of available starting materials. Final possible reactions that might lead to the desired product are first considered. Compounds needed for these reactions are next examined and treated as if they were the desired product. This procedure is repeated until available compounds are encountered. At every step,

reactions are chosen that allow the desired (final or intermediate) compound to be made from the simplest starting material.

From the point of view of synthetic utility, organic reactions fall into two general and sometimes overlapping classes. In the first of these, carbon chains or skeletons are elaborated; in the second, functional groups are interconverted. Any systematic problem can be analysed in terms of construction of the required carbon skeleton and placement of functional groups at the proper positions on the skeleton.

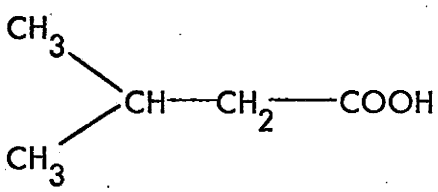
III. Terpenes

A large number of natural plant products have been found to be related in that they are built up of one or more units of isoprene C_5H_8 i. For example, the terpene dipentene ii, the racemic form of limonene, can be made by heating isoprene.



i ii

Isoprene itself has never been encountered in nature although isovaleric acid iii is a natural product.



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It was observed that the thermal decomposition of almost all terpenes gave isoprene as one of the products. It was therefore suggested that the skeleton of all naturally occurring terpenes can be built up of isoprene units. Although this concept, generally referred to as the isoprene rule, has not proved correct in every case, it remains a useful guide in structural studies of natural products where the carbon content is a multiple of five.

Monoterpenes, compounds of molecular formula $C_{10}H_{16}$, and sesquiterpenes, $C_{15}H_{24}$, are the common constituents of the essential oils - the volatile oils obtained from the sap and tissues of certain plants and trees. These oils have been used in perfumery from the earliest times. Diterpenes, $C_{20}H_{32}$, and triterpenes, $C_{30}H_{48}$, which are not steam volatile, are obtained from plant and tree gums and resins.

Terpenes consisting of five or seven isoprene units, $C_{25}H_{40}$ or $C_{35}H_{56}$, have not been encountered although many tetraterpenes, $C_{40}H_{64}$, usually treated as a separate class (the carotenoids) are known. The most important polyterpene is rubber. In addition to the terpene hydrocarbons, there are oxygenated derivatives of each class which also occur naturally, and these are mainly alcohols, aldehydes, ketones, or carboxylic acids.

Early investigations, aimed at the isolation and structure elucidation of mono- and sesquiterpenes, were beset by special difficulties because these substances are liquid and occur in mixtures with closely related compounds. However, by 1887, Wallach succeeded in preparing the first pure individual terpenes by using reagents, particularly nitrosyl chloride (NOCl), which form with terpenes solid addition compounds suitable for characterisation.

In general there are four methods of extraction of the terpenes:

(i) expression

(ii) steam distillation

(iii) extraction by means of volatile solvents

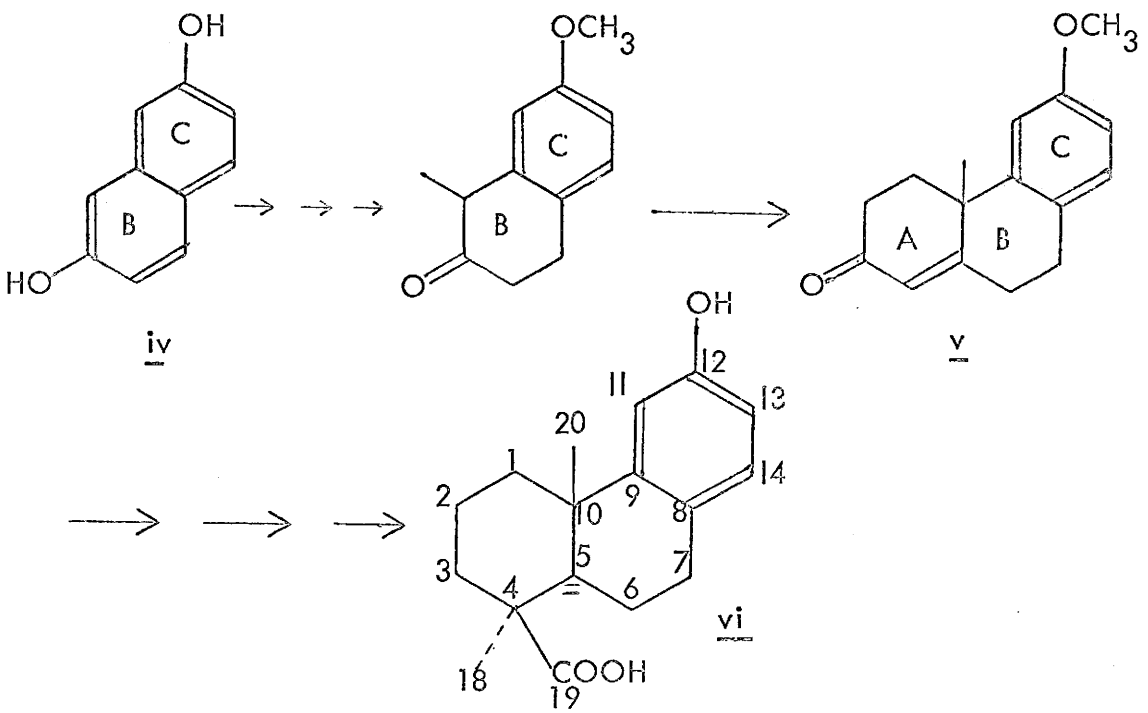
(iv) adsorption in purified fats.

The hydrocarbons usually have lower boiling points than their oxygenated derivatives.

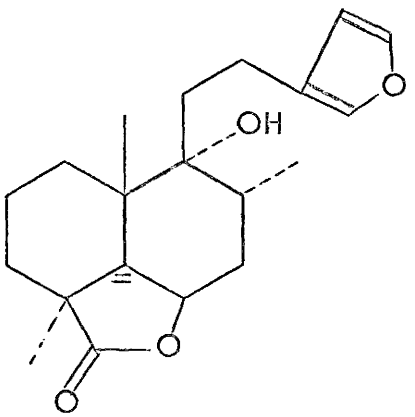
IV Outline of This Thesis

This thesis records a synthesis of podocarpic acid, vi, starting with the naphthalene derivative, iv, as the potential rings B and C of the final product.

The procedure involves the modification of ring B by selective hydrogenation and the attachment of a four-carbon chain with ultimate cyclization leading to the tricyclic skeleton, v. This intermediate contains the functional groups necessary for its further transformation to podocarpic acid vi.



Attempts have also been made to explore the synthetic routes to the naturally occurring bitter principle, marrubiin vii; and to the optical antipode, viii, of naturally occurring 7β-hydroxykaurenolide, a known precursor of gibberellic acid.



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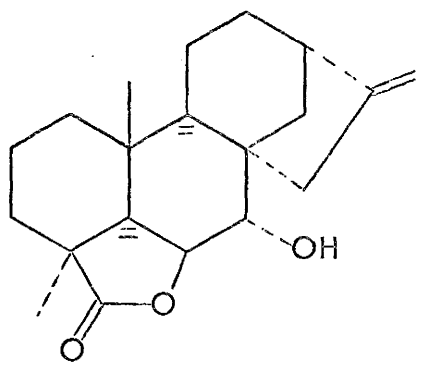

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HISTORICAL INTRODUCTION

1. Podocarpic Acid - Structure and Related Derivatives

Podocarpic acid was first isolated by Oudemans in 1873, from the resin Podocarpus cupressinum[1,2]. It was later found to occur in much larger quantities in other members of the Podocarpus Dacrydium species[3].

Oudemans[1] had shown that the compound is a monobasic hydroxyacid (molecular formula $C_{17}H_{22}O_3$) capable of nitration and sulfonation, and yielded 1-methylphenanthrene, $C_{15}H_{12}$, on distillation with zinc dust.

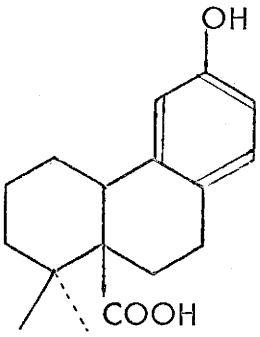
Sherwood and Short[4,5] established the phenolic character of podocarpic acid, and by means of molecular refraction studies, indicated a tricyclic system containing three ethylenic linkages. The production of 6-methoxy-1-methyl-phenanthrene by dehyodrogenation of the O-methyl ether of the compound was explained by formula 1 or 2 (R=R'=H) of which the former was preferred on account of the inert character of the carboxylic group in podocarpic acid.

Fieser and Campbell[6] suggested that the structure 2 (R=R'=H) had several advantages, and that 13-isopropyl-podocarpic acid might be identical with 12-hydroxy dehydroabiatic acid 3. Campbell and Todd[7] converted methyl O-methylpodocarpate 2 (R=R'=Me) into 13-isopropylpodocarpic acid which was found to differ from 3. Subsequently it was shown[8] that the two acids both gave ferruginol 4 when the carboxyl group was converted, via the aldehyde, into a methyl group.

Consequently, podocarpic acid was considered to be represented either by 2 (R=R'=H) or by an alternative obtained by interchanging the carboxyl and the angular methyl groups. The reduction of podocarpic acid to the corresponding carbinol, followed by a Wagner-Meerwein rearrangement and selenium dehydrogenation, gave 6-methoxy-1-ethyl-phenanthrene 5. It was concluded, therefore, that podocarpic acid and dehydroabietic acid[9] both contain the trans-decalin structure at the A/B ring junction but differ in configuration at carbon atom 4. To account for the marked difference in the acidities of podocarpic and abietic acids, the structure 6 (R=R'=H) was suggested, in which the carboxyl group is axial and on the same side as the angular methyl group and therefore subject to severe steric hindrance.

Thus podocarpic acid would have identical stereochemistry with agathene dicarboxylic acid 7[10] in the A ring, with the carboxyl group on the opposite side of the molecule as the carboxyl group of abietic acid 8.

Haworth and Moore[11] later confirmed the position of the carboxyl group in podocarpic acid by synthesis, using a modification of the earlier method[12] used for the synthesis of racemic dehydroabietic acid. The Grignard reagent from β-(4-methoxylphenyl)ethyl bromide was reacted with ethyl 2,6-dimethylcyclohexanone-2-carboxylate to give 9 after dehydration with formic acid. Cyclization of the cyclohexene derivative was effected by prolonged boiling in acetic-sulfuric acid. The resultant 6-methoxy-1,12-dimethyloctahydrophenanthrene-1-carboxylic acid 2 (R=H, R'=Me) was smoothly demethylated by boiling in hydriodic acid and acetic anhydride in an atmosphere of carbon dioxide to give the compound 2 (R=R'=H)



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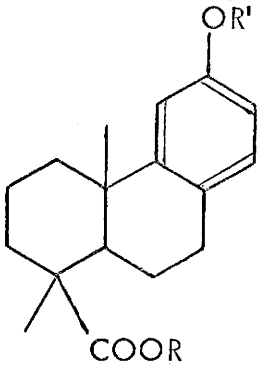

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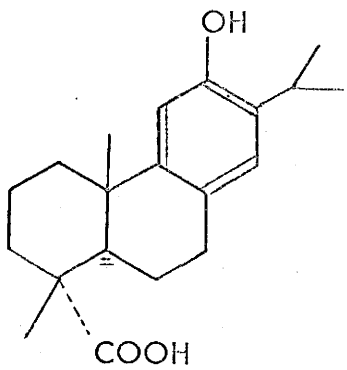

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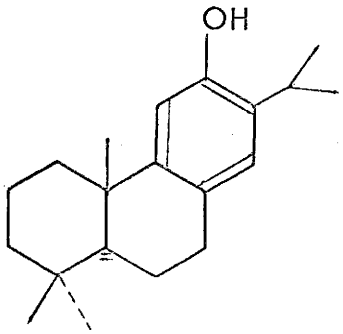

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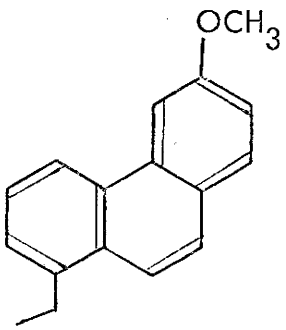

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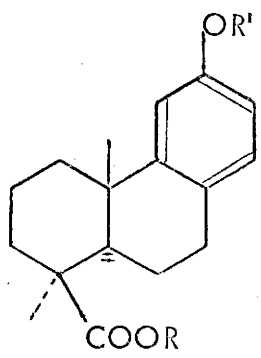

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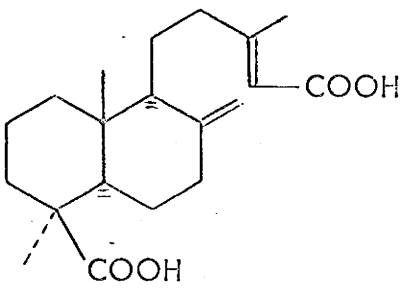

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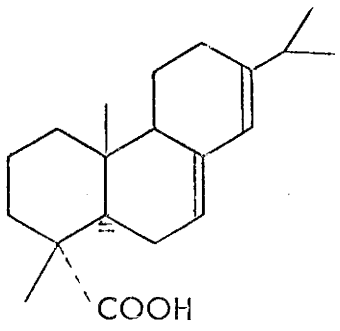

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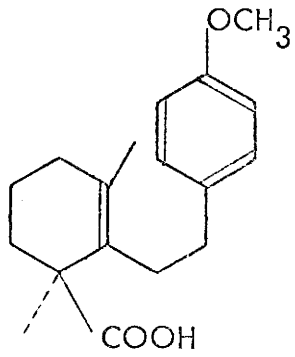

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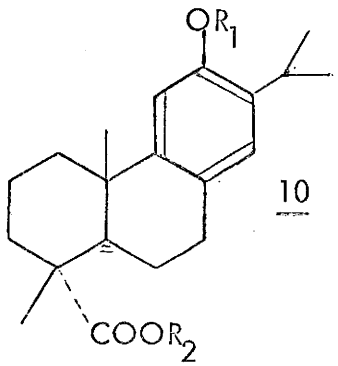


10

a $R_1 = R_2 = H$

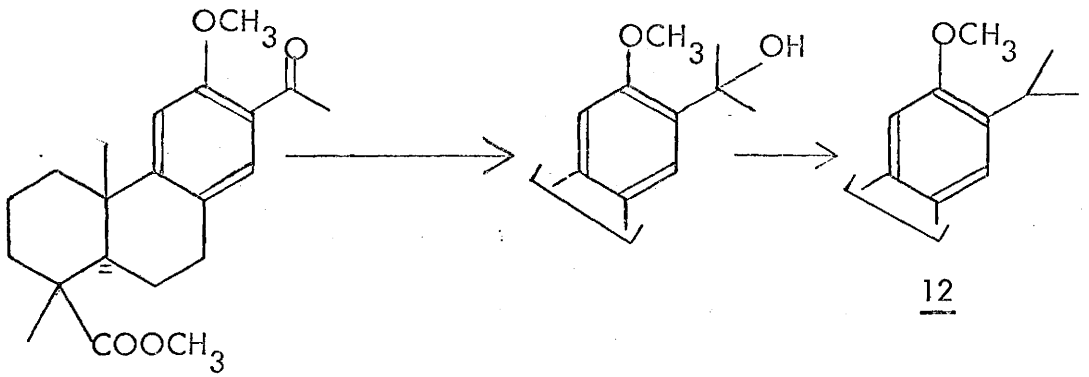
b $R_1 = R_2 = CH_3$

which proved to be identical, in chemical properties, with naturally occurring podocarpic acid.

Final proof of the stereochemical formula of podocarpic acid was provided in 1957 by Campbell and Todd[13], who prepared the phenol acid 10a via the corresponding sulfonate of dehydroabietic acid. Methylation of the phenol by the action of methyl sulfate on the magnesio-chloride derivative gave, after esterification with diazomethane, the compound 10b. Acetylation of methyl O-methyl podocarpate led to the ketone 11 which, on Grignard methylation and hydrogenolysis of the resulting alcohol gave the compound 12, isomeric with, but not identical with, 10b. By transformation of both esters through the acid chlorides to the aldehydes and Wolff-Kishner reduction of the carbonyls to methyl groups, compound 13 was obtained in both cases. The corresponding phenol is a naturally occurring diterpenoid, ferruginol, the major component of the resin of the miro tree[14].

King and his co-workers[15] had earlier confirmed the structure of ferruginol by synthesis. Using a slight modification of their method they also confirmed the structure of podocarpic acid by synthesis[16]. The method, summarised in scheme II, employed the reaction of 2-ethoxycarbonyl-2,6-dimethylcyclohexanone 14 and the Grignard reagent from p-methoxyphenylacetylene 15 to give the compound 16 in 57% yield. The acetylene bond was catalytically hydrogenated and cyclization was achieved using polyphosphoric acid at 80° for 45 minutes, to give racemic ethyl O-methylpodocarpate 6 (R=Et, R'=Me).

Strictly speaking, podocarpic acid, a C_{17} compound, is not a diterpene. It is, however, usually included among the diterpenes since its chemistry is closely



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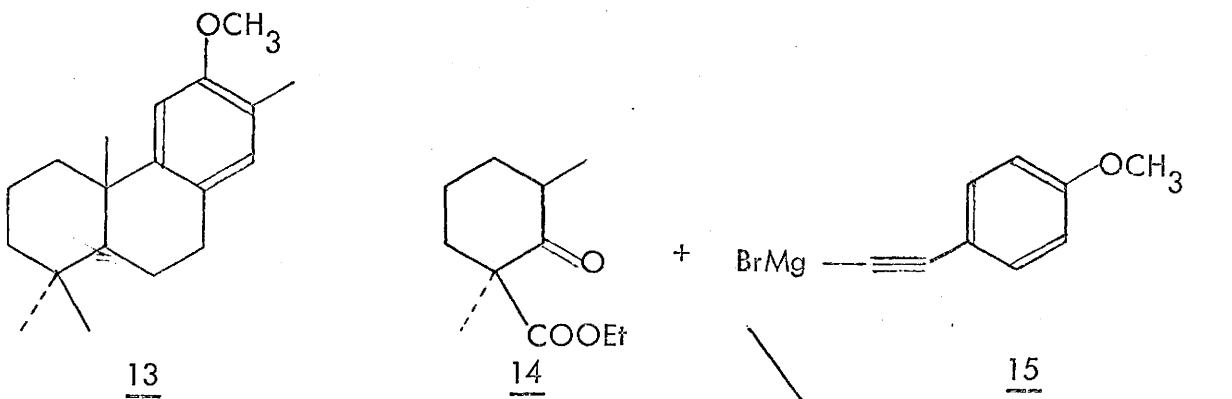
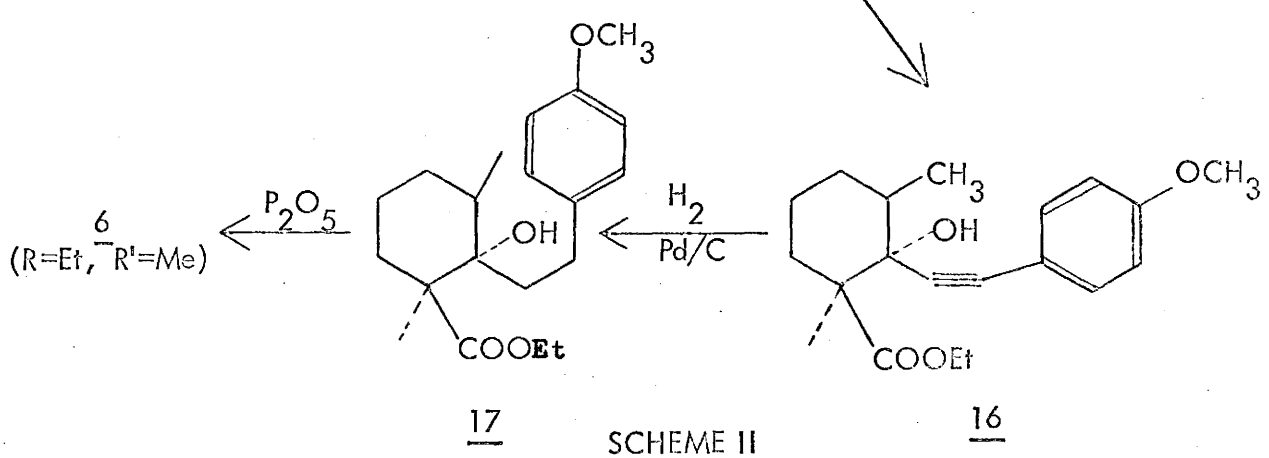
SCHEME I

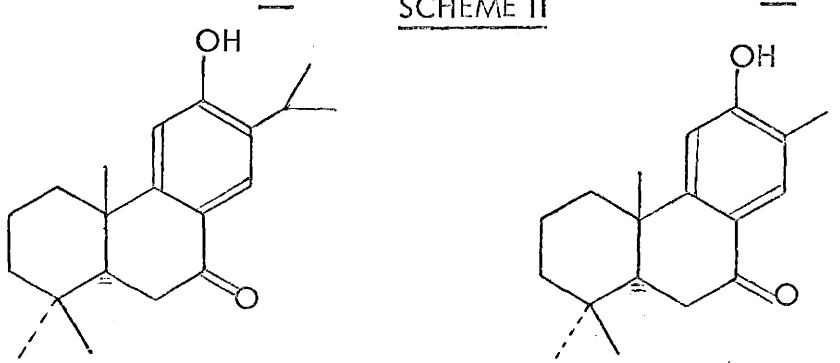


13 14 15



17 16

SCHEME II



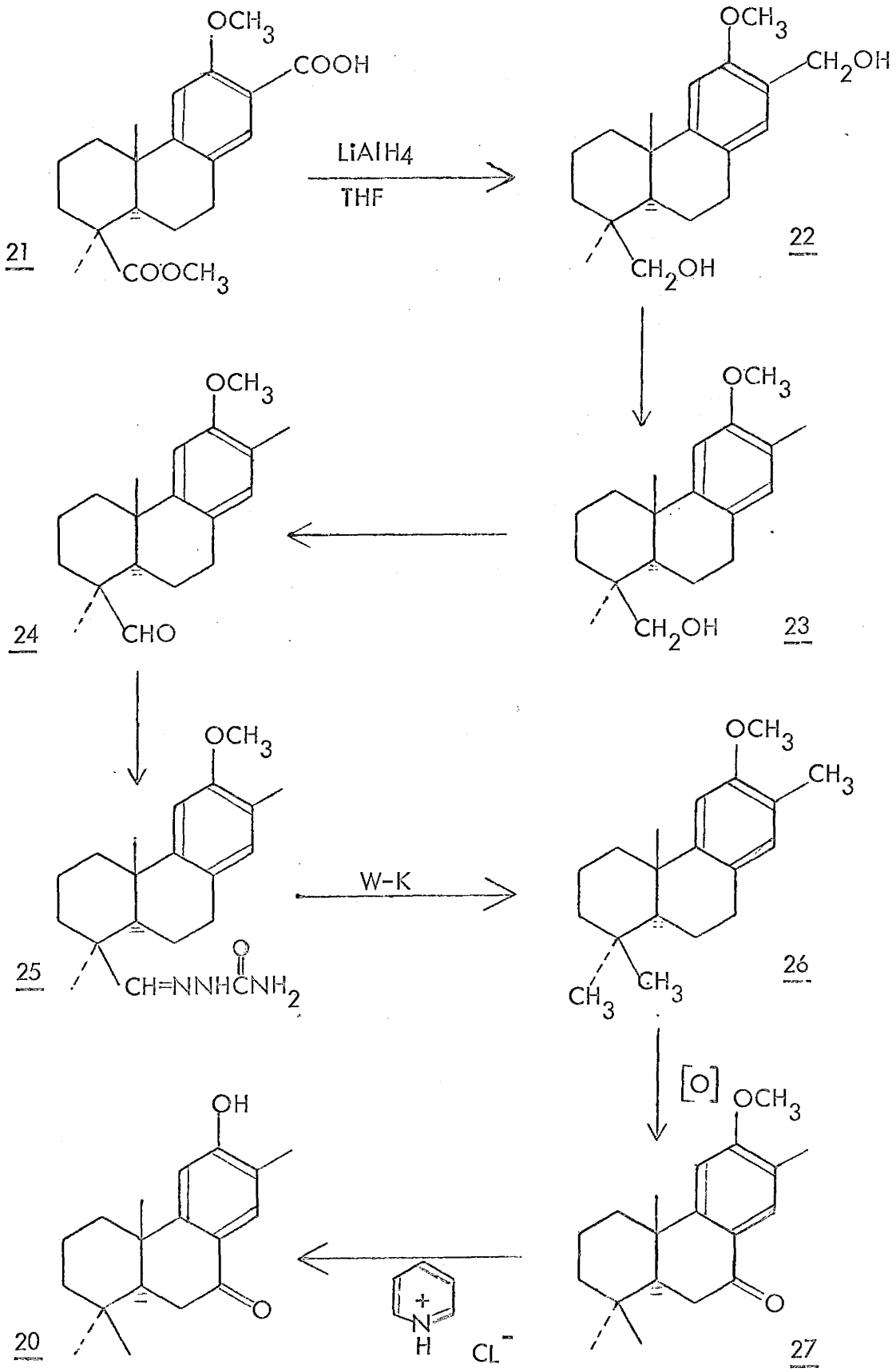
19 20

associated with these substances. Its established constitution and conversion to ferruginol suggested it as an excellent starting material for the preparation of other naturally occurring compounds with similar structural features.

Brandt and Thomas[17] observed that the oxidation product of ferruginol was identical with sugiol, a substance isolated from Cryptomeria japonica and to which the structure 19 had been assigned[18,19].

Two independent groups of workers[20,21] succeeded in converting podocarpic acid to nimbiol, a compound isolated[22] from the trunk bark of Melia azadiracta Linn and which had been assigned the structure 20[23,24]. The procedure of Bible[21], summarised in scheme III, begins with the lithium aluminum hydride reduction of methyl O-methyl-7-carboxypodocarpate 21, a compound readily available by the Baeyer oxidation of methyl O-methyl-7-acetylpodocarpate[7], to the diol 22. The hydroxymethylene on the aromatic ring in 22 is smoothly converted to a methyl group by selective hydrogenolysis over palladium/charcoal in the presence of hydrochloric acid. The resulting alcohol 23 is then converted to the aldehyde 24 with chromic acid-sulfuric acid in acetone. The crude product from Wolff-Kishner reduction of the aldehyde, via its semicarbazone 25, is remethylated in view of the anticipated demethylation of the ether, and the product 26 is then oxidized to the 9-keto compound 27, the corresponding phenol of which is nimbiol.

Wenkert and co-workers[25] have developed another method for the introduction of the C-13 methyl group in the conversion of podocarpic acid to nimbiol. Mannich reaction of methylpodocarpate, formaldehyde and dimethylamine afforded a near quantitative yield of the dimethyl-aminomethyl compound 28, lithium-


OCH3
COOH
LiAlH4
THF
21
COOCH3
OCH3
CH2OH
22
CH2OH
OCH3
CH2OH
23
OCH3
24
CHO
OCH3
25
CH=NNHCNH2
O
W-K
OCH3
CH3
26
CH3
CH3
[O]
OCH3
27
O
OH
20
O
+
N
H
CL-

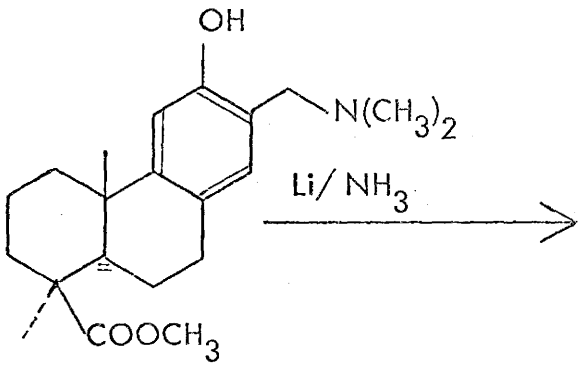
SCHEME III

in-liquid-ammonia reduction of which gave a mixture of 29 and 30 with the former as the major product.

Brandt and Ross[28] have prepared podocarpinol 31 by Rosenmund reduction of O-acetyl podocarpyl chloride to the corresponding aldehyde which on copper chromite reduction followed by acetate hydrolysis gave the alcohol. Preliminary physiological tests have indicated that podocarpinol possesses oestrogenic activity.

The complete stereochemistry of the naturally occurring 6,7-diketonic diterpene, xanthopherol 32, was established on the basis of its unusual properties[29], similar to those of the diketone 33. During their extensive investigations of the diterpenoid acids, Wenkert and co-workers[30] observed that the deisopropylation of dehydroabietonitrile 34 under the stimulus of aluminum chloride in benzene solution led to a mixture of products from which a crystalline compound 35a, present in the largest amount (39%) was readily isolated. Chromic acid oxidation of this component led to a mixture of three crystalline compounds, one an acid, another a monoketone whose carbonyl was conjugated with the aromatic ring, and the third, established as an α-diketone. Previous oxidations of hydrophenanthrenes had been observed to lead to monoketones only[31,32,33,34], while under drastic conditions acids were obtained[35,36]. Detailed investigation revealed that the α-diketone had the structure 35d thus suggesting that the starting material for the oxidation reaction was 5-iso-desoxypodocarponitrile enantiomer, 35a. The acid and the monoketone would be 35b and 35c respectively.

On selenium dioxide oxidation, a reaction known to convert 7-keto hydrophenanthrenes exclusively to their 5,6-dehydro derivatives eg 36 -> 37[37],



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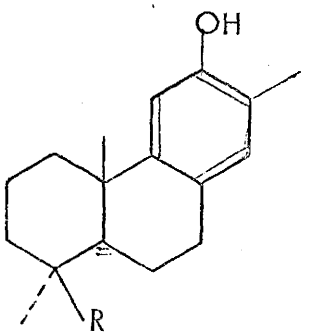
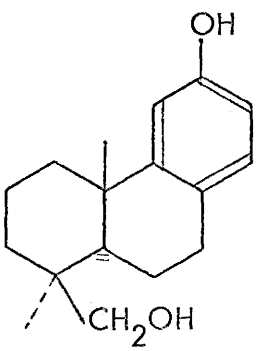


29 R = COOH

30 R = CH_2OH

SCHEME IV



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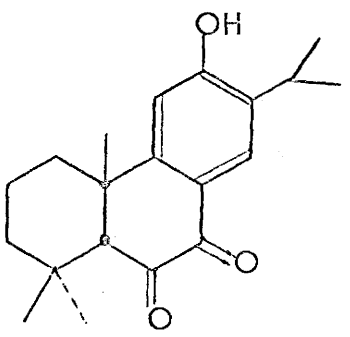

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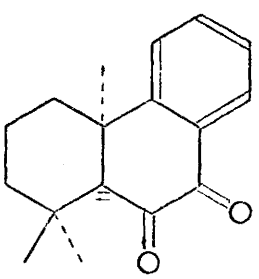

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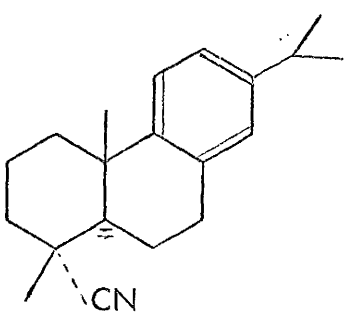

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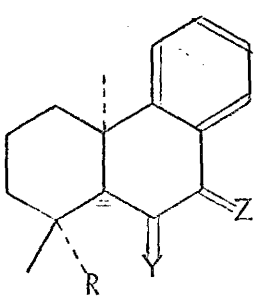
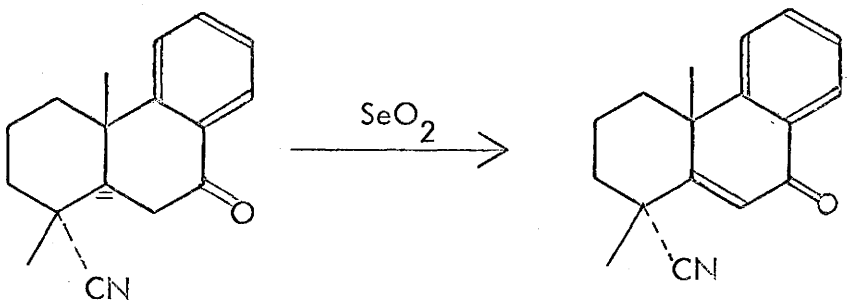


35	R=	Y=	Z=
a	CN	H_2	H_2
b	COOH	H_2	H_2
c	CN	H_2	O
d	CN	O	O

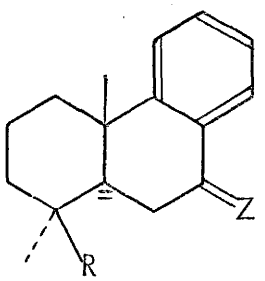
the monoketone 35c yielded a mixture of unsaturated ketone and the α-diketone 35d. It was thought, therefore, that the formation of an α-diketone in the ring B of perhydrophenanthrenes was possible only when the molecule had a cis A/B ring junction. Similar results were obtained by other workers[38]. Thus selenium dioxide oxidation can be employed as a powerful diagnostic tool in elucidating the nature of the A/B ring junction of a monobenzenoid tricarbocylic diterpene system.

The Kenner desoxygenation[39], which comprises the lithium-in-liquid ammonia reduction of a phosphorylated phenol, has been successfully applied[40] to podocarpic acid, the methyl ester of which yielded a mixture of 38a, 38b and 38c. The conversion of desoxypodocarpinol, 38c, to the corresponding aldehyde 38d and Wolff-Kishner reduction of the aldehyde afforded a hydrocarbon, which on controlled oxidation, produced 7-ketodesoxy podocarpane 38e[41]. Nitration of α-tetralone had been reported[42] to yield a mixture of 7-nitro and 5-nitro-α-tetralone in the ratio of 97:3. The expectation that the ketone 38e, would, on nitration yield 39a was justified; only one product was actually obtained. Removal of the keto group led to 13-amino desoxypodocarpane 39b which, on diazotization and alkaline hydrolysis, was readily converted to the phenol 39c.

ApSimon and Edwards[43] have constructed the cyclic amino ring E of the garrya alkaloids by the photolysis of podocarpyl azide, the product being the enomtiomer of the phenol 40, obtained from degradation of natural atisine 41. Attempts to build the appropriate C, D ring system and complete the synthesis of the enontiomer of natural atisine, starting with podocarpic acid, failed because the double bond necessary for the introduction of the C-15 and C-16 substituents was

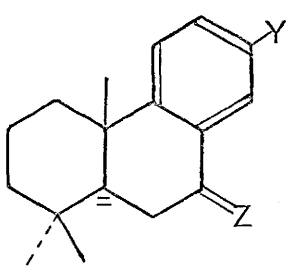


36 37



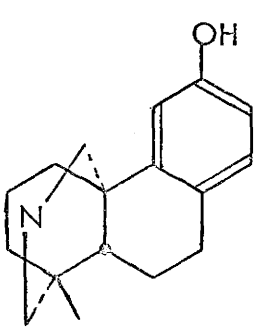
38

a	R = COOH	;	Z = H_2
b	R = $COOCH_3$	;	Z = H_2
c	R = CH_2OH	;	Z = H_2
d	R = CHO	;	Z = H_2
e	R = CH_3	;	Z = O
f	R = COCl	;	Z = H_2
g	R = $CONH_2$	;	Z = H_2
h	R = CN	;	Z = H_2



39

a	Y = NO_2	;	Z = O
b	Y = NH_2	;	Z = O
c	Y = OH	;	Z = H_2



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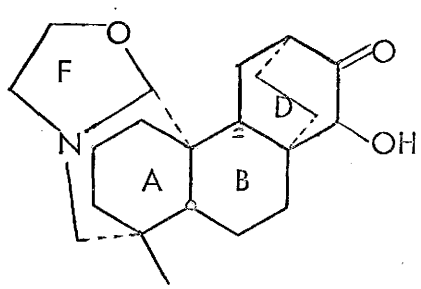


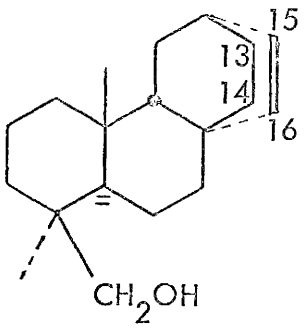
41

in the wrong position (42 and 43).

The transformation of podocarpic and other diterpenoid resin acids to their related compounds requires, in some cases, the conversion of the carboxylic acid to a methyl or hydroxymethylene group. The direct reduction of the carboxylic acid is usually attended by more or less difficulty, depending on the configuration of these groups at C-4. The trans acids, represented by abietic acid, are less hindered and therefore more easily reduced than the cis acids, represented by agathic and podocarpic acids, which are quite resistant to reaction owing to the extremely large effect of steric hindrance. Thus, while methyl abietate responds readily to a forced Bouvealt-Blanc reduction, methyl agathate is almost completely unaffected[45].

Campbell and Todd[8] used an indirect method for reducing O-methyl podocarpic acid to O-methyl podocarpinol via the acid chloride and the aldehyde. Zeiss and Slimowicz[46] later found that lithium aluminum hydride reduces podocarpic acid directly to podocarpinol in satisfactory (56%) yield. The ester and the acid chloride of O-methyl podocarpic acid were also observed to react with the reagent to give, after hydrolysis of the metal complex, O-methyl podocarpinol.

The formation of the acid 38a during the Kenner desoxygenation of methylpodocarpate[40] attracted some attention and required explanation. This novel hydrolysis of a methyl ester was seen as a reductive process and was given the formal interpretation in Scheme VI. Its successful competition with normal ester reduction was thought to be due to the great resistance of the axially oriented trigonal (sp^2) carbonyl carbon atom to expansion to the more sterically demanding



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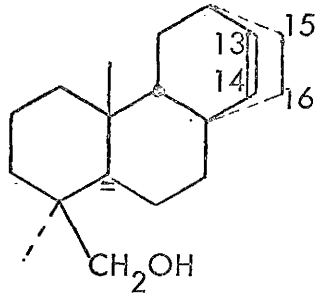

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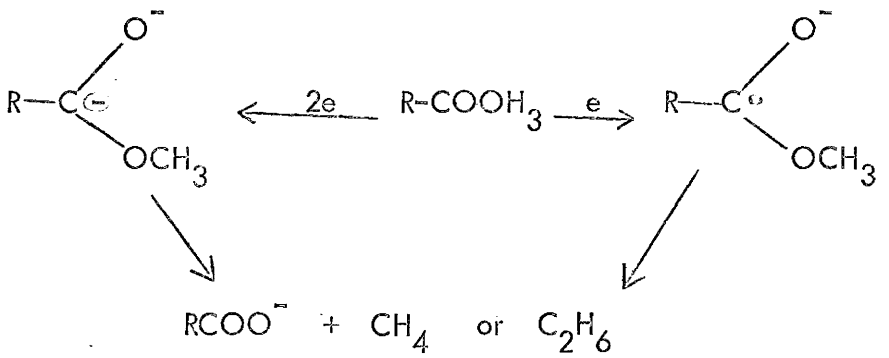
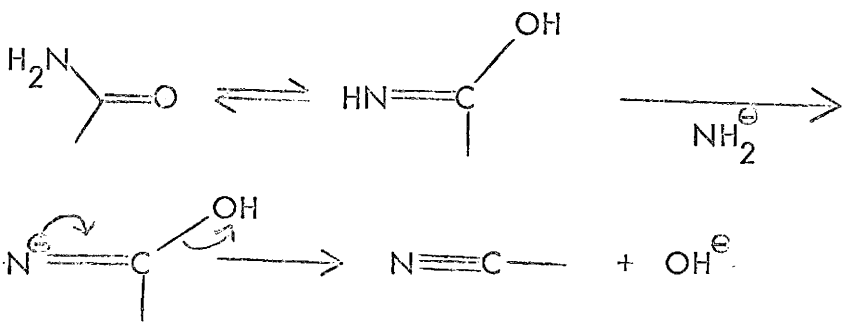


SCHEME VI



SCHEME VII

tetrahedral (sp^3) state. The fate of the methyl group has not been determined; most probably it is reduced to methane or ethane. The closest analogy to this reductive hydrolysis is the reported cleavage of alkyl aryl ethers to phenols[47].

Desoxypodocarpyl chloride, 38f, was observed to be inert to aqueous ammonia solution but could easily be transformed into a mixture of desoxypodocarpamide 38g and desoxypodocarponitrile, 38h, by the action of sodamide in liquid ammonia[30]. These results are also explicable on the basis of the resistance of the sp^2 carbonyl carbon towards expansion to the sp^3 configuration, and the apparent driving force towards the least sterically demanding linear (sp) configuration. They help to point out quite clearly the importance of steric factors in the reactivity of molecules. The nitrile formation has been rationalised as a slow base-catalysed dehydration of the iminol form of the initially produced amide according to scheme VII.

While the reductive process appeared to be useful as a simple, hydrolytic method for sterically hindered esters, it also suggested itself as a diagnostic tool for differentiating axial from equatorial carboxyl groups in rigid systems. Esters which are subject to less steric hindrance, are expected to reduce to alcohols, while sterically hindered axial esters should undergo reductive hydrolysis to the corresponding acids. This hypothesis has proved correct in several cases examined.

II. Synthetic Approaches to the Diterpenoid Resin Acids

Several groups of workers have explored the synthesis of the resin acids. The foremost problem has been the construction of the perhydrophenanthrene nucleus with the correct (trans) A/B ring junction, and the stereoselective introduction of methyl and carboxyl substituents at the quarternary C-4 position in the correct configuration relative to the angular C-10 methyl group.

Most synthetic approaches have been designed to deal with this stereochemical problem in one of two general ways:

a) by the generation of the angular C-10 asymmetric centre by closure of the 9,10-bond in an electrophilic aromatic alkylation process, after the C-4 substitution pattern has been established,

or

b) through stereoselective alkylation of a bi- or tricyclic 3-keto or Δ^4-3-keto derivative[52-59].

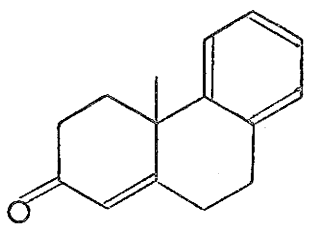
The former approach was first employed[48] in the synthesis of a racemic dehydroabietic acid. It was later modified[49] for the preparation of methyl O-methyl podocarpate as illustrated in Scheme II. The products from these and subsequent reactions[50,51] were invariably mixtures providing very low (ca 30%) yields of the desired compounds.

To explore the alternative general approach, the tricyclic enone, 44 was seen as the central intermediate in the synthesis of these resin acids. For the preparation of this compound, 1-methyl-2-tetralone 45 was required. This tetralone was prepared in two different ways. The first route[60] was a rather long one since at the time no suitable method was available for monomethylation of β-tetralones.

With the subsequent development of suitable monomethylation methods[61,62], a much shorter route became possible. Reduction of β-naphthol by the method of Birch[63,64] gave β-tetralone as a liquid which could be purified via its bisulfite adduct. Enamine alkylation of the pure tetralone led exclusively to the α-methyl β-tetralone which in the presence of methanolic potassium hydroxide added to methyl vinyl ketone with cyclization and accompanying dehydration to give the tricyclenone 44.

Attempts at the stereoselective introduction of the C-4 substituents have led to the general expectation that alternation in the stepwise introduction of methyl and potential carboxyl functions in the tricyclic enone would selectively produce either the podocarpic or abietic acid sterochemistry. In the course of the synthesis of dehydroabietic acid, Stork and Schulenberg[53] proposed that the presence of the axial angular methyl group at C-10 in the rigid enolate ion 46 would be expected to make the transition state for alkylation in which the bromoester would approach from the β-side cis to the angular methyl group of higher energy than the alternative approach from the α-side. Thus the desired equatorial stereochemistry of the potential carboxyl group was predicted. The alkylation product was found to be exclusively the expected ketoester (Scheme VIII).

It has been emphasised that the stereochemical result of this reaction would not be so reliable without such rigidity as is present in the enolate ion, or with a much smaller alkylating agent. For example, while the alkylation of the hydroxy-ketone 47 with methyl allyl iodide led to the introduction of the methallyl group trans to the axial hydroxyl substituent, the related alkylation of the ketone 49 produced



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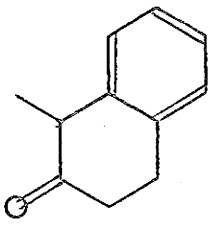

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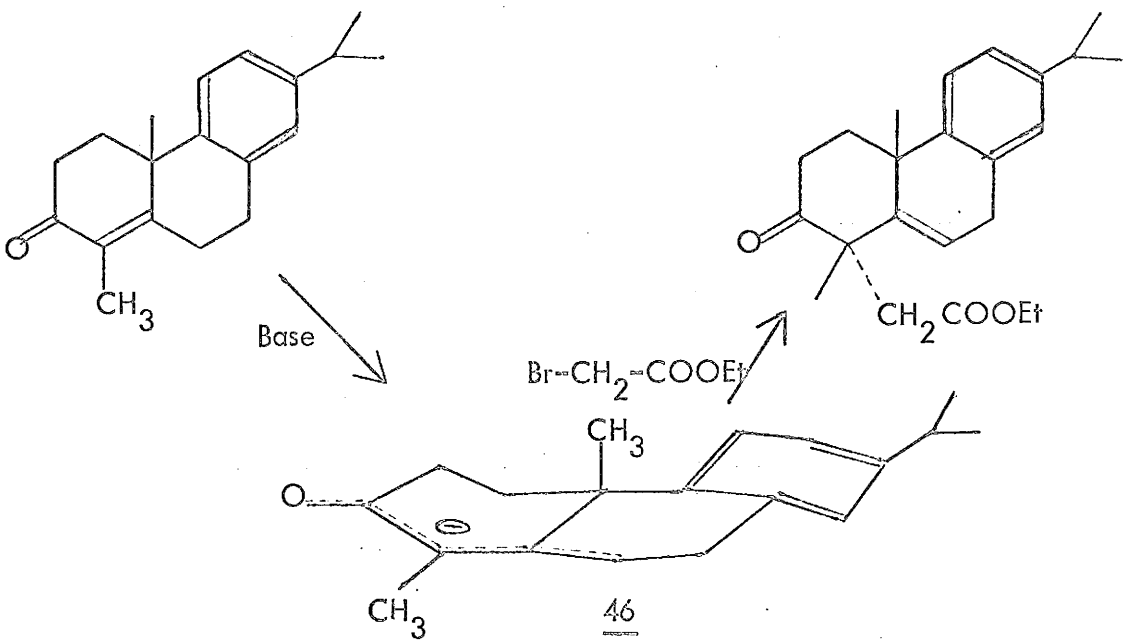

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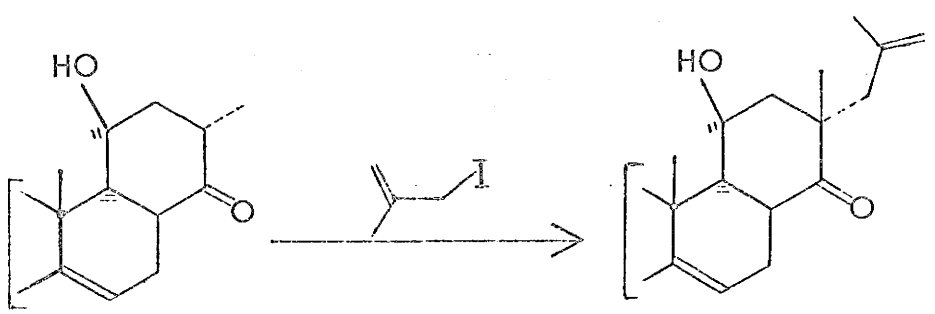
SCHEME VIII



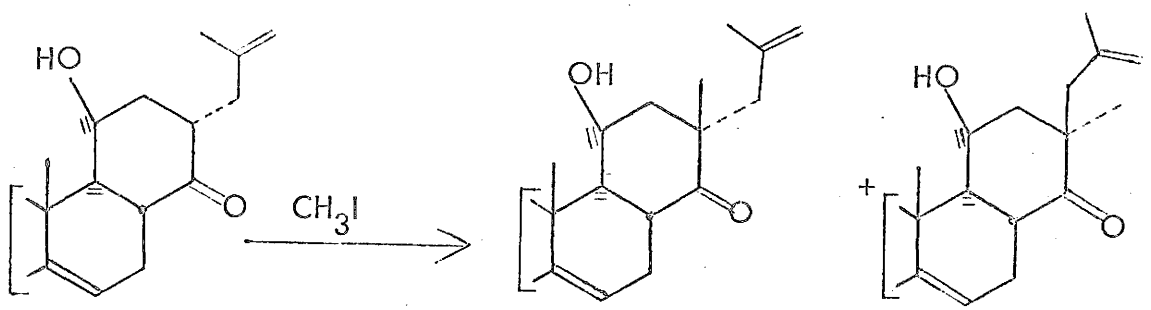
47

48

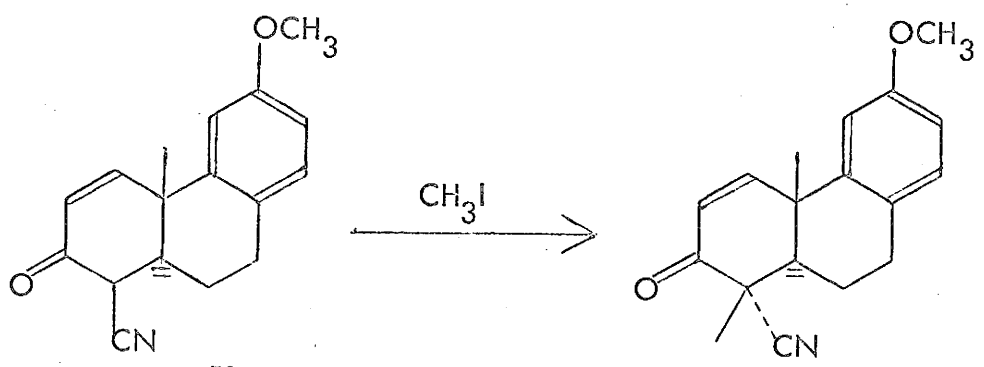
an almost inseparable mixture of epimers[65].

It would appear, therefore, that these alkylation reactions are controlled by two major factors, one electronic and the other steric. This hypothesis is born out by results of subsequent investigations. Thus Kuehne's observation[59] that the alkylation of the β-ketonitrile 52 with methyl iodide led to the entry of the methyl group cis to the axial methyl at C-10 (in 80% yield) was explicable on the basis of stereoelectronic control of the approach of the methyl group towards the corresponding enolate salt. The maximum charge overlap with the carbonyl and nitrile functions favours axial introduction of the electrophilic group, whereas steric repulsion by the axial angular methyl group should shield the enolate from axial attack and favour the equatorially alkylated product. Stereoelectronic direction to similar alkylations of carbonions has been observed with alkoxyl and acyloxy groups placed in potential 1,3-diaxial relationship[66,67].

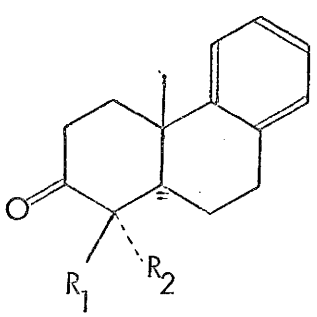
Wenkert[57] observed that methylation of the saturated ketoester, 54a, with methyl iodide and potassium t-butoxide led to a 2.4:1 mixture of the ketoesters 54b and 54c. In effect, the methylation had proceeded, contrary to expectation, in a nonselective manner and, in fact, had yielded more product of the abietic acid stereochemistry (axial methylation cis to C-10 methyl) than of the podocarpic acid type. He also examined alkylation at the C-2 position in the compounds 55 and 56 and obtained products which arise from axial methylation. He therefore concluded that the angular methyl group exerts much less potent 1,3-diaxial interference in the carbon-carbon bond-formation than was initially anticipated and that the alkylations generally proceeded by axial attack of the alkyl group on the enolate salt substrate.



49 50 51



52 53

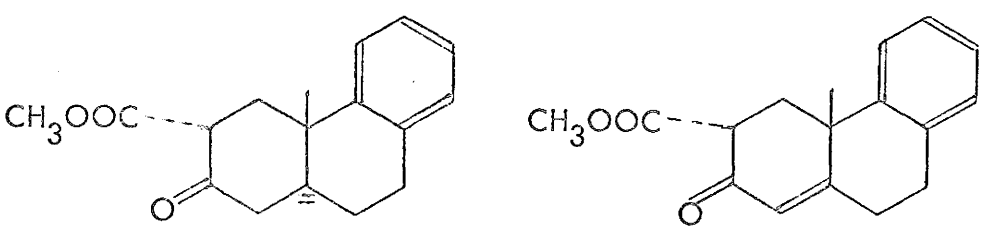


54

a R_1 = H ; R_2 = $COOCH_3$

b R_1 = CH_3 ; R_2 = $COOCH_3$

C R_1 = $COOCH_3$; R_2 = CH_3



55 56

When, however, he studied the methylation of the unsaturated ketoester 57, under similar conditions, with catalytic reduction of the resultant Δ^5-double bond, he observed that there was just one single product (in 75% yield) - of the podocarpic acid stereochemistry. He considered this result a clear illustration of the importance of the nature of the enolate (rather than the size of the alkylating agent) in determining the stereochemistry of alkylation. Furthermore, he suggested that if it be accepted that, in the absence of overpowering steric hindrance, stereo-electronic control (axial attack by the alkylating group) governs the stereochemistry of alkylation, then the anion of ketoester 57 must assume an A ring boat conformation in the transition state of its methylation.

Graham and McQuillin[67,68] have studied the benzyloxymethylation of bicyclic and tricyclic enones with a similar structural arrangement as 44 and have concluded from their results that stereoselectivity in alkylation depends on the principle of least hindered approach in simpler instances but the reaction course can be reversed by the presence of polar substituents at the C-10 position[69]. Selectivity is observed to depend also on minor structural changes, the aromatic residue introducing a steric constraint and, in comparison with bicyclic systems, removing two axial substituents.

Catalytic hydrogenation of the Δ^5-double bond in compound 58, and its analogues has led consistently to A/B trans compounds[53, 72]. As would be expected, a combination of the Δ^5-double bond and the benzenoid fragment confers a large measure of rigidity on the system, thus greatly favouring approach of the catalyst from the side of the molecule opposite to two axial substituents at

C-10 and C-4. Again, it is important to note that without the degree of rigidity which is present in the system, the course of the hydrogenation would not be readily predictable. For instance, it has been shown[70,71] that while the hydrogenation of the hydroxy enone 59 (R=H) produces a predominantly trans decalone system, similar hydrogenation of its acetate 59 (R=Ac) leads to predominantly cis stereochemistry in the ring junction.

The removal of the 3-keto group, if desired, is readily accomplished[73] by desulfurisation of the corresponding thioketal using special grade Raney nickel[74].

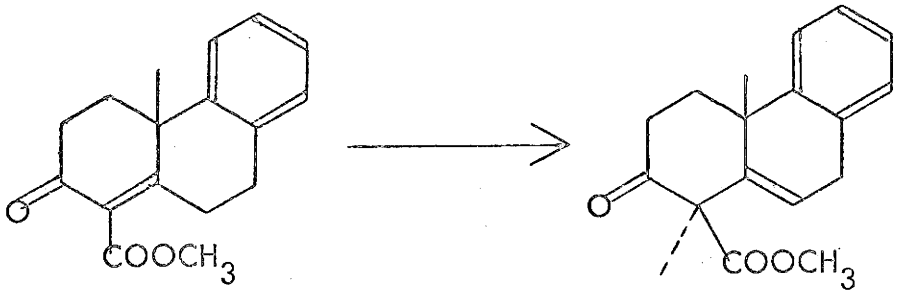
Wenkert's hypothesis of over-riding stereoelectronic control of the alkylation of substituted enones such as 57 is seriously contradicted by the results and opinions of Stork and McQuillin. These other investigators, however, used much bulkier alkylating agents than the methyl group, used by Wenkert. It became necessary, therefore, to reinvestigate Wenkert's exact procedure with a much closer examination of the entire alkylation product. This has been carried out and is reported in this thesis. Attempts have been made in the course of this work to improve the yields at the crucial stages of the reaction sequence.

III. Podocarpic Acid as a Central Intermediate in Diterpene Synthesis

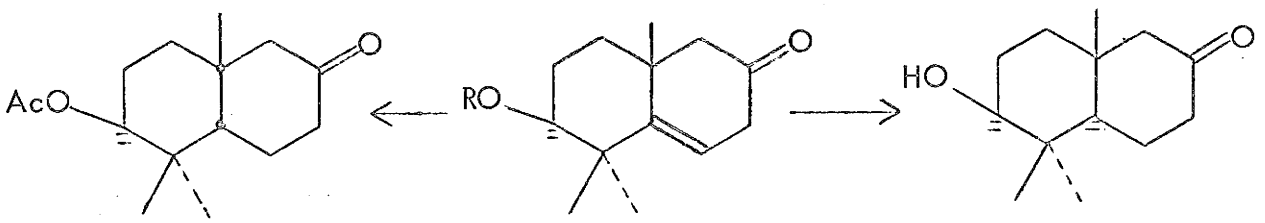
The availability of podocarpic acid whether from natural sources or by synthesis has become of considerable importance, in view of the numerous other natural products into which it has already been converted and many others which are theoretically derivable from it. Recently it has been found[75] that toxodone 60 and toxodione 61, both compounds theoretically derivable from podocarpic acid, and to a lesser extent sugiol 19 showed significant inhibitory activity against some forms of carcinoma in rats. The possibility that these compounds might play an important part in the treatment of human cancer makes their availability on a large scale a necessity.

During studies directed towards the total synthesis of diterpenoid natural substances, Wenkert and co-workers[76] investigated a number of tangential chemical problems of synthetic and/or mechanistic interest. In the attempts to prepare the Δ^5-dehydro derivatives of podocarpic acid by collidine treatment of the 6-bromo-7-keto derivatives, mixtures of unsaturated ketones and ketolactones, 62, (in about 30% yield) were obtained. Similar results had been reported by Bible and Grove[77].

In the search for compounds having biological activities, Bible and Burtner[78] investigated the reduction of the aromatic ring of podocarpic acid and found that it proceeds over platinum in acetic acid at 60-70° to give an easily-isolated perhydroderivative, the structure of which was proved to be 63, in addition to a small amount (7%) of C-12 desoxy acids. Oxidation of the resulting hydroxyacid gave the ketoacid 64 (R=H) which was easily converted to the corresponding ketoester. Bromination of the ketoester 64 ($R=CH_3$) with N-bromosuccinimide in carbon tetra-



57 58



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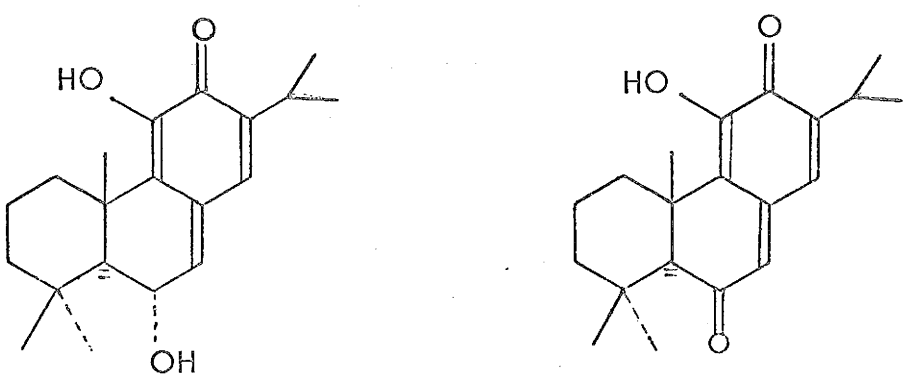
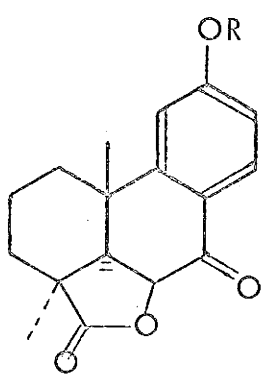


60 61



62

R = H, CH_3 or Ac

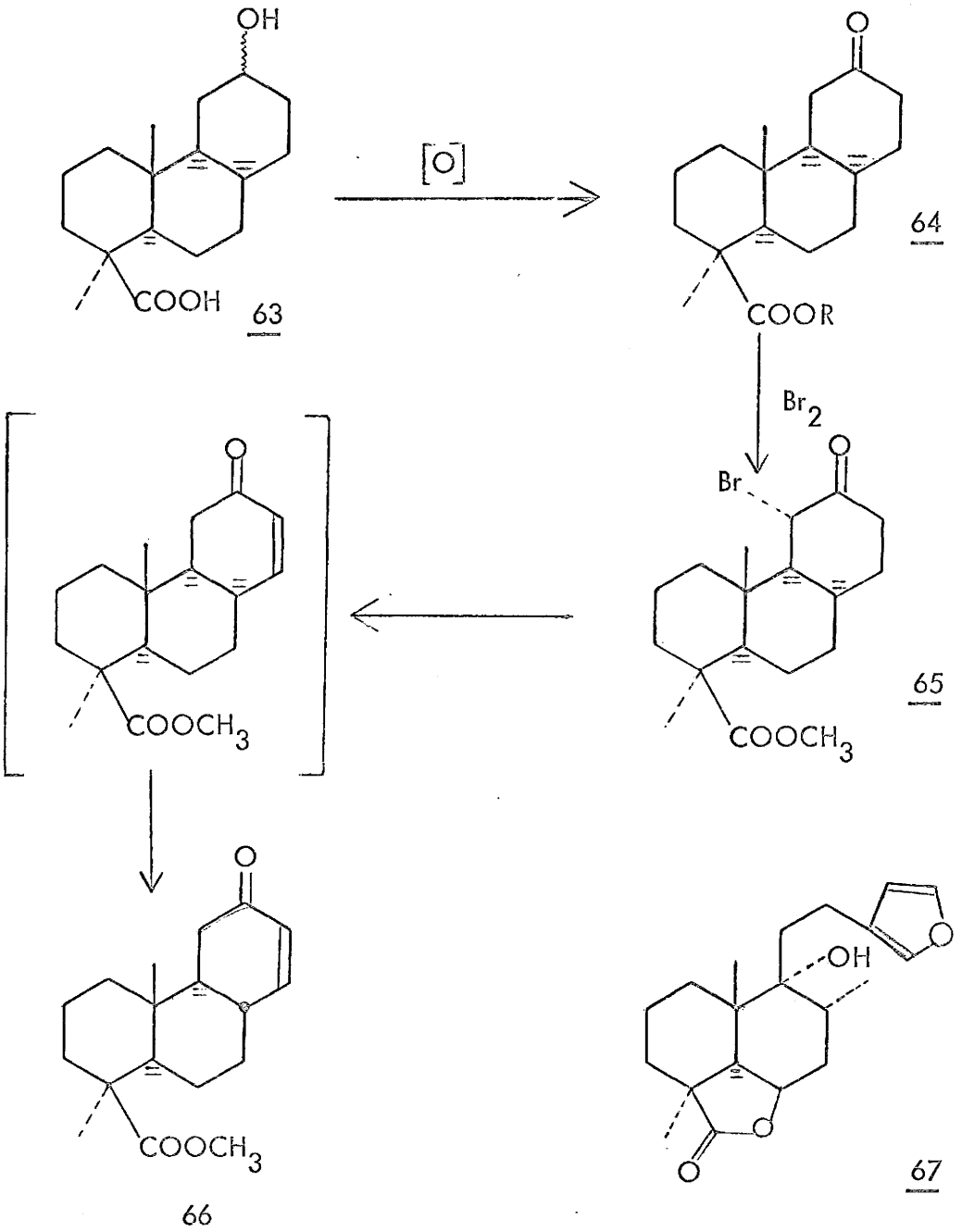
chloride at room temperature gave an axial bromo-ketone 65 which, on dehydrobromination either with lithium chloride-lithium carbonate or with collidine followed by equilibration over basic alumina gave the unsaturated ketoester 66.

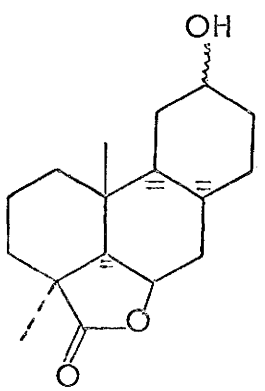
Recent studies of the aromatic ring reduction reveal that podocarpic acid is readily reduced on 5% rhodium/alumina in ethanol with 1% acetic acid at room temperature and three atmospheres of hydrogen. Similar results were obtained on bromination and dehydrobromination of the ketone corresponding to the reduction product[79].

The lactone-formation and aromatic ring-reduction results have spelled out good prospects of fairly easy approaches to known naturally occurring bicyclic diterpenes, by the degradation of the aromatic ring after it has been used to introduce the appropriate substitution pattern in ring B; and the tetracyclic diterpenes by the elaboration of the tricyclic system.

One example of the bicyclic systems to which easy access was conjectured is marrubiin 67, the bitter principle of horehound (marrubium vulgare) first described by Harris in 1842. The complete structure was established only very recently and several groups[82-85] have made unsuccessful attempts at its synthesis.

Catalytic hydrogenation of the keto-lactone 62 (R=H) would be expected to give the hydroxy-lactone 68 which on oxidation, bromination and dehydrobromination would give the unsaturated keto lactone 69. Ozonolysis of 69 would lead to compound 70 which has all the necessary ring substituents in the right places for conversion to marrubiin. The preparation of 3-furoic acid[86] and its successful conversion to 3-furylacetic acid[87] have been accomplished. Pelletier and



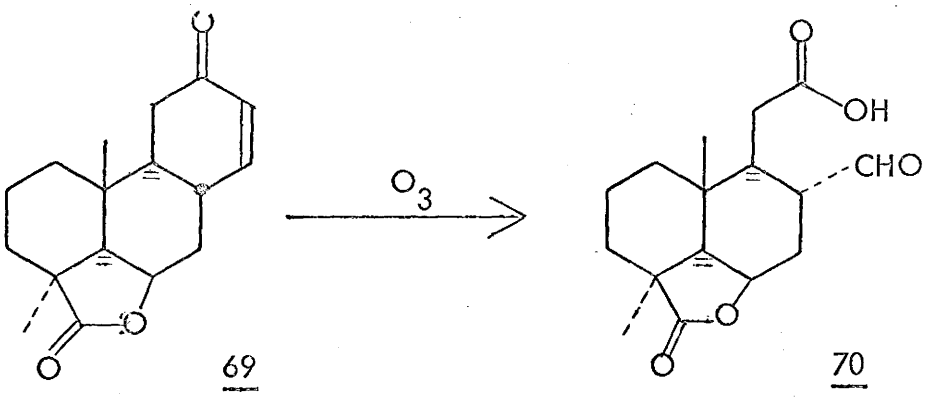
62 (R=H) $\xrightarrow{H_2/Rh\text{-}Al_2O_3}$  $\xrightarrow[(3)\ -HBr]{(1)\ [O]\quad (2)\ Br_2}$

co-workers[88], in the synthesis of antipoidal polyathic acid 76, have successfully attached the furan ring to the carbon chain at C-9 by Kolbe synthesis, using the ketoacid, 74, which was obtained from the ozonolysis of methyl levopinarate, 73, and 3-furylacetic acid 75. (Scheme IX). It was reasonable therefore to suppose that this reaction should be applicable in the approach to marrubiin.

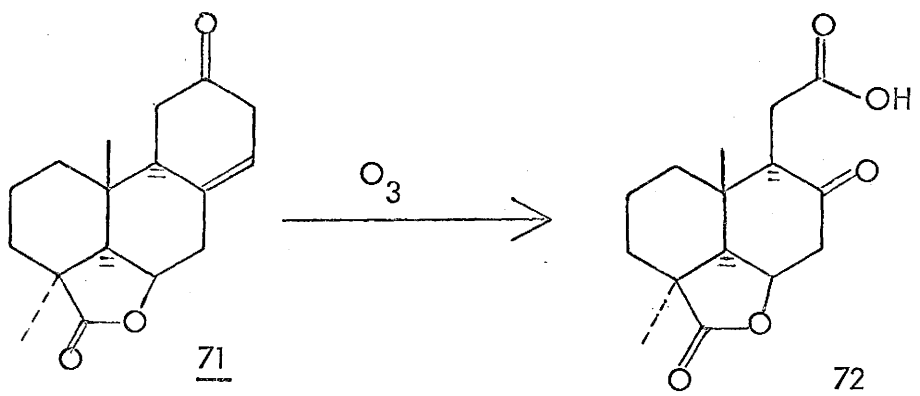
Much more recently, it has been shown[89] that methyl podocarpate, on ozonolysis in methanol/methylene chloride at -70°, after removal of solvent, affords the peroxy lactone 77 (90% yield), which on catalytic hydrogenation with palladised charcoal gives the ketoacid 78. This very new development promises to cut down the route to marrubiin by at least three steps.

A number of naturally occurring bicyclic, tricyclic and tetracyclic diterpenes have an oxygenated ring A. Since naturally occurring podocarpic acid cannot easily be functionalised in this ring, any synthetic approach which leads up to functionalised ring A becomes of great value in the approach to this class of compounds. Such compounds as 3-oxo marrubiin 79, isolated from marrubium incarium[90]; 1,3-dioxo ferruginyl methyl ether 80, from cupressus sempervirens[91]; and lanost-8-en-1,3-dione, 81 can be approached starting from 3-oxo podocarpic acid, the methyl O-methyl ester of which is a necessary intermediate in the synthesis of podocarpic acid via the enone alkylation method.

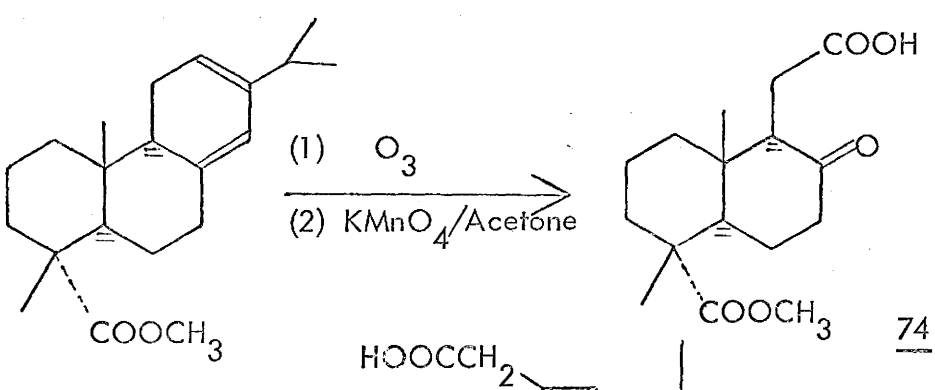
A number of tetracyclic diterpenes which are theoretically derivable from podocarpic acid are known to occur in nature. These compounds are characterised by the phyllocladane (or kaurane) carbon skeleton, 82, with the same A/B rings pattern as the resin acids. Another class of tetracyclic compounds, characterised



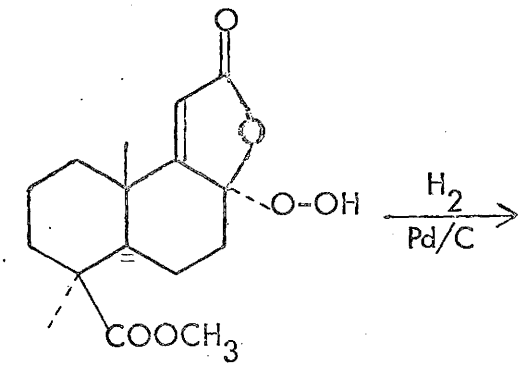
69 70



71 72



73 74 75 76



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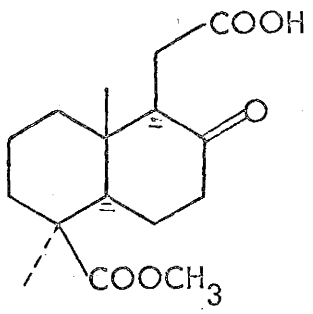

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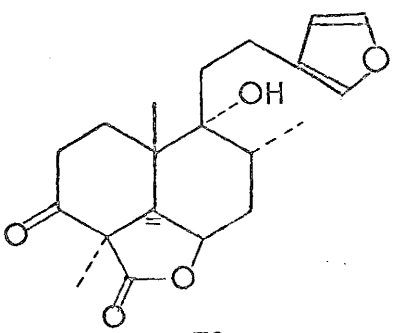

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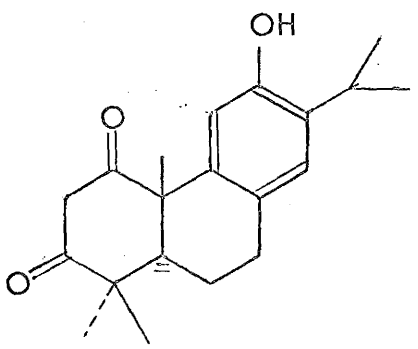

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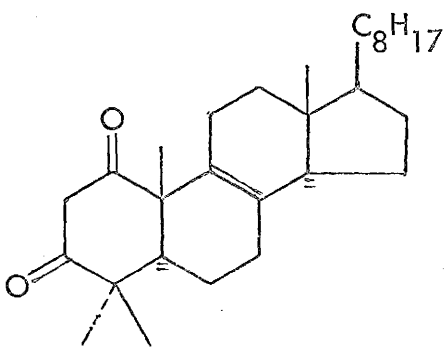

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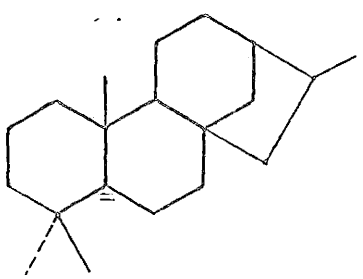


82

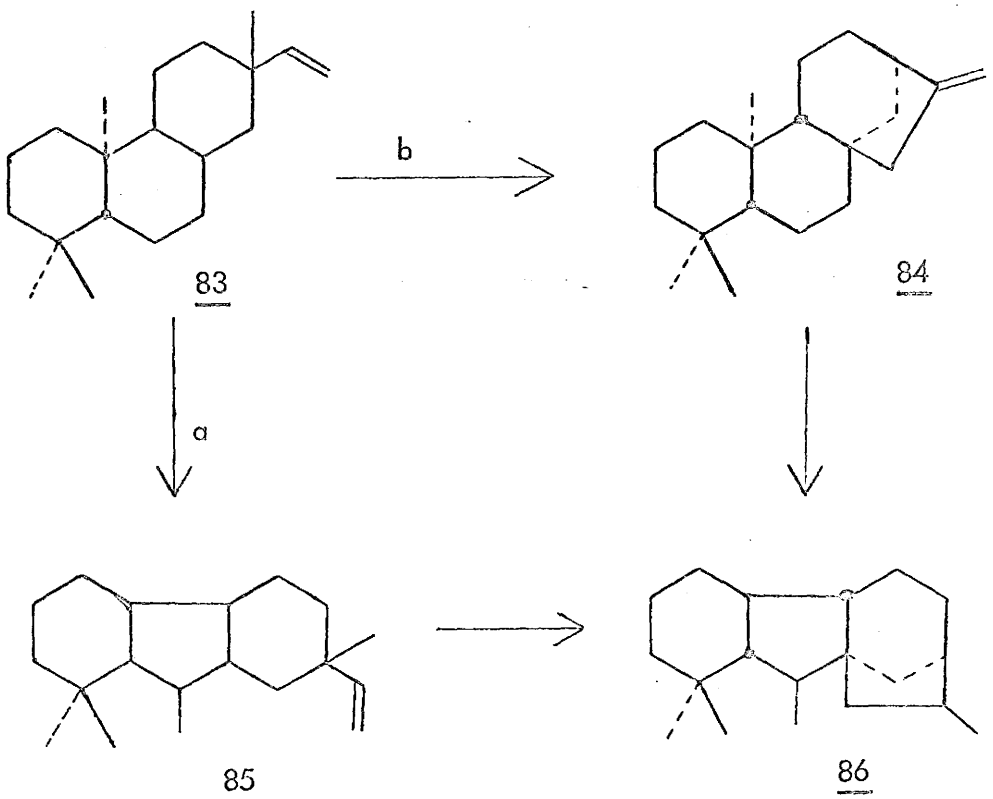
by the gibbane skeleton, 86, have also been extensively examined.

The widespread and varied effects of the later group (generally known as the gibberellins) on many aspects of higher plants growth and development[92-94] have attracted much attention. Studies carried out with gibberellic acid[95,96] isolated from the fungus, Gibberella fujikuroi[97,98] have shown the gibberellins to be diterpenoids in which, in addition to other structural modifications, contraction of ring B of the primarane skeleton 83 have occurred with extrusion of one carbon atom as a carboxyl group[99,100]. Furthermore, it has been shown[101] that (-)-kaurene, 84, acts as a precursor of gibberellic acid and that rearrangement of 83 to form a tetracyclic intermediate takes place before oxidative attack and subsequent contraction of ring B and the accompanying loss of C-10 angular methyl group.

The isolation of (-)-7 -hydroxy-kaurenolide 87a and 7,18-dihydroxy-kaurenolide 87b from the culture of Gibberella fujikuroi[101] led to the suggestion that these might be intermediates probably derived from 84 by microbial oxidation during the biosynthesis of gibberellic acid 88.

A number of ingeneous methods have been used in the synthetic elaboration of the C,D ring system of some diterpenes and diterpene alkaloids. The bicyclo (2,2,2) octane C,D ring system of the Garrya alkaloids[102] has received much attention in recent years.

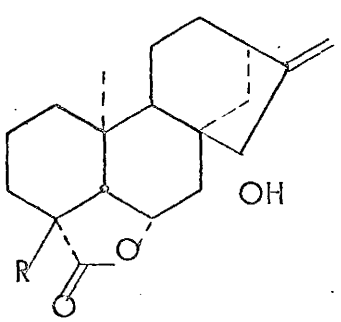
Pelletier and Parthasarathy[103] accomplished a partial synthesis of atisine by reconverting the mono-acid monoester 89, a degradation product of atisine, to the C,D ring system of atisine by homologation of the free carboxyl group followed by Dieckmann cyclization and then further transformations to introduce the C-15 and



83 84 85 86

SCHEME X

a R = CH_3
b R= CH_2OH



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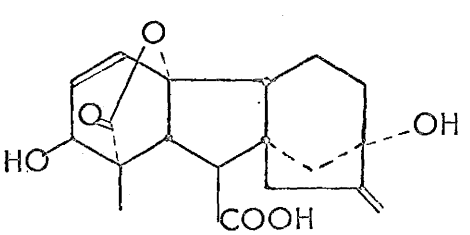


88

C-16 functions. (Scheme XI).

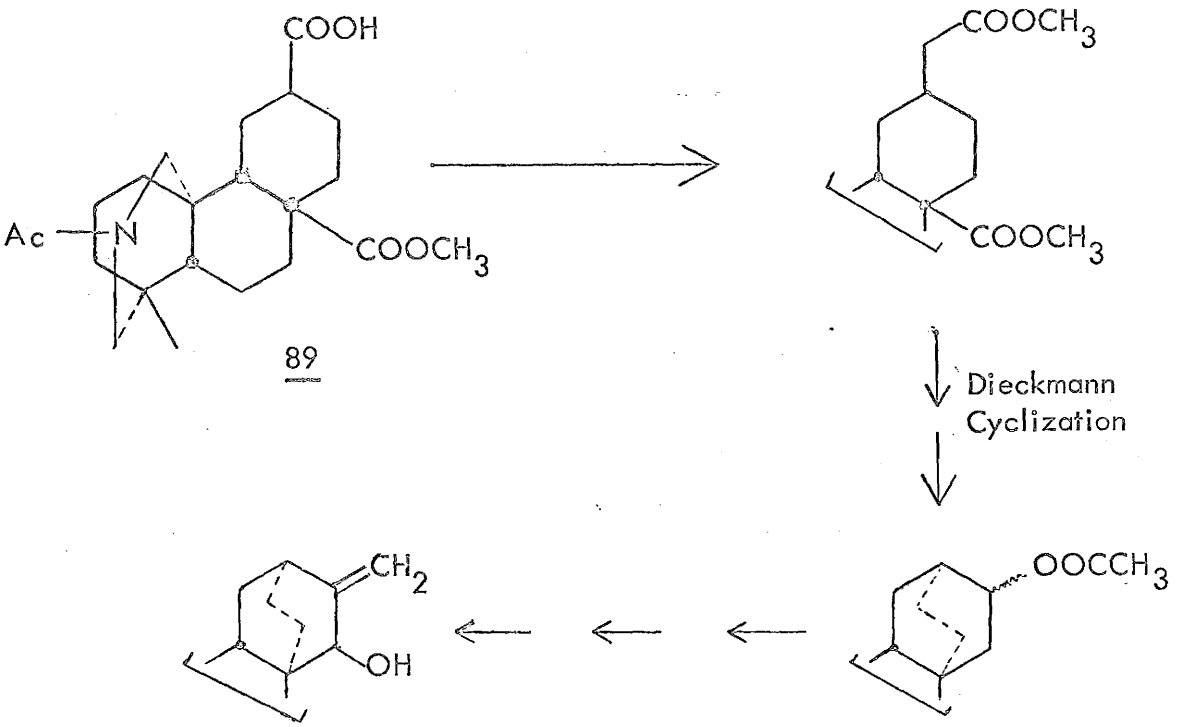
Bell and Ireland[104,105] have used an acid-catalysed aldol-type condensation to construct the C,D ring systems of atisine and garryfoline, with (-)-kaurene as an intermediate on the route to garryfoline.

In the total synthesis of atisine, Nagata and co-workers[106] used the displacement method to build the C,D ring system by t-butoxide-catalysed cyclization shown in Scheme XII. This method is similar to the one applied by Turner and his co-workers[107] to achieve the synthesis of phyllocladene

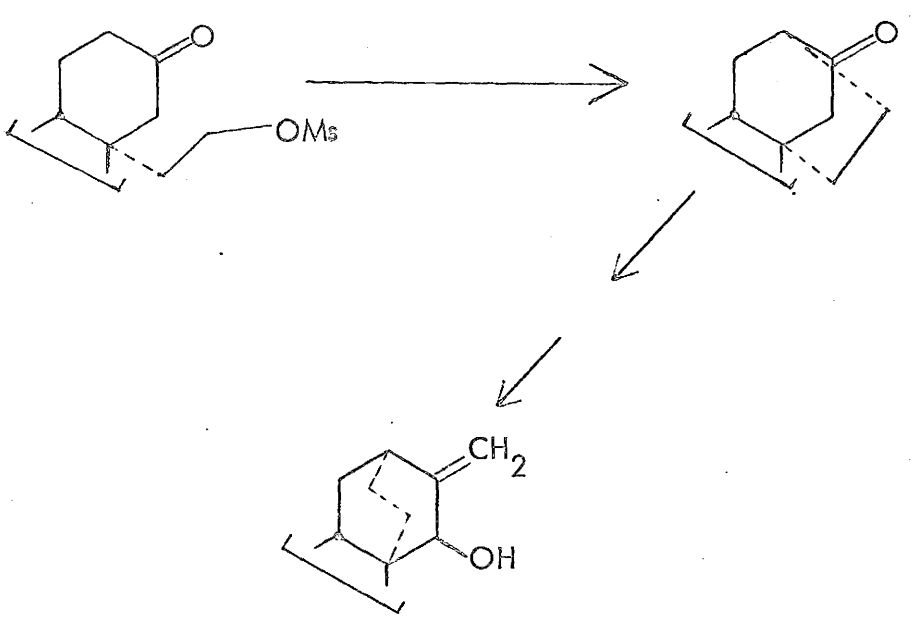
Other groups of investigators[108-111] have approached the same problem by way of Diels-Alder addition of a dienophile to the appropriate diene in ring C. This method is summarised by the reaction of levopimaric acid and maleic anhydride. (Scheme XIII). The addition is generally on the α-side of the tricyclic ring system.

Much work has also been done on the direct elaboration of the bicyclo (3,2,1) octane C,D ring system characteristic of the kaurane skeleton. Masamune[112] contrived the cyclization reaction in which the aromatic ring is converted to the nucleophile during the detosylation reaction of Scheme XIV. Application of this reaction to compound 90 afforded very satisfactory yields (>90%) of the compound 91, which was transformed in eight steps to dl-16-keto-10-carboxy-17,20-bisnor-kaurane 92. This product has been used to synthesise (-)-kaurene, and is observed to be the degradation product of veatchine, a major alkaloid of Garrya Lauriforia[114]. Masamune has also synthesised garryine starting from 92 and has converted garryine and veatchine to atisine[115].

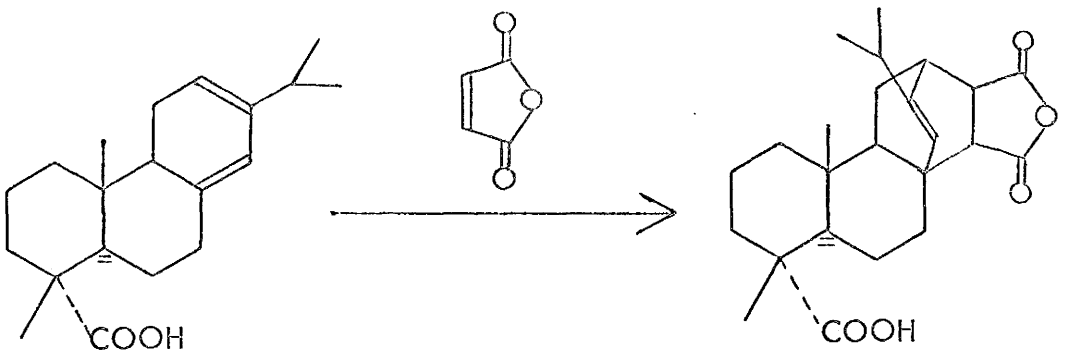
A photochemical approach to the C,D ring system of atisine has also been



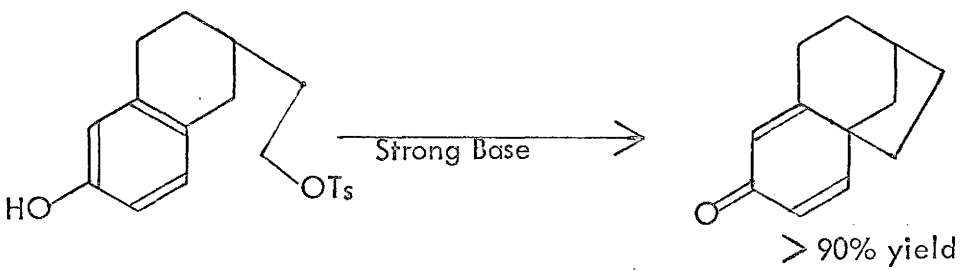
SCHEME XI



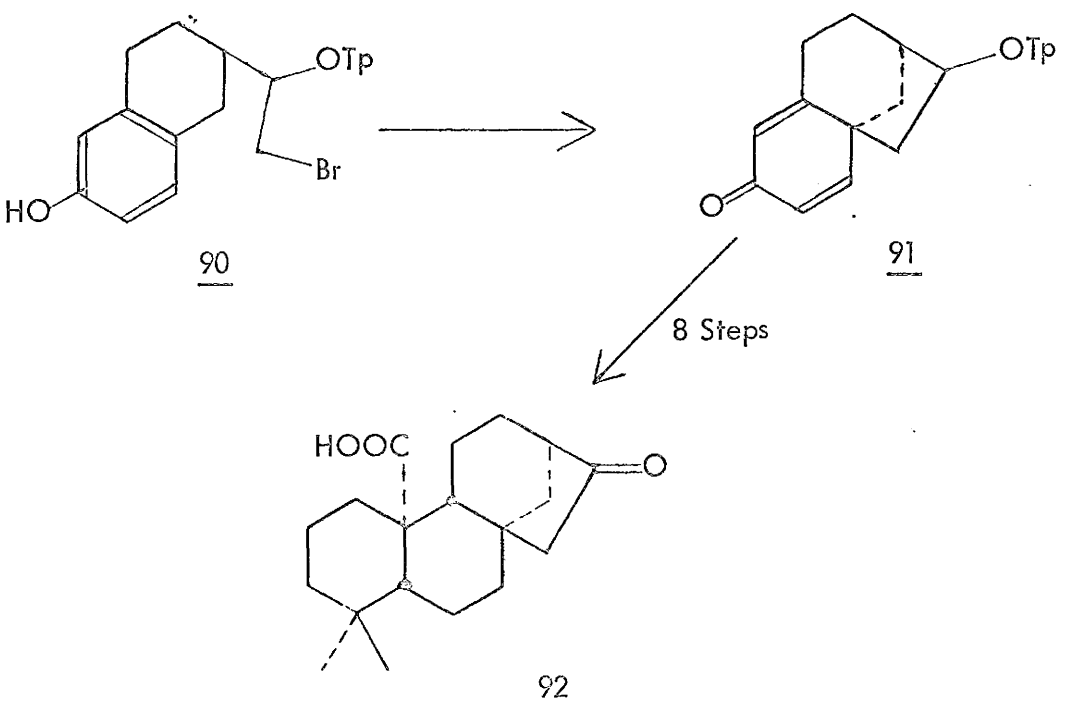
SCHEME XII



SCHEME XIII



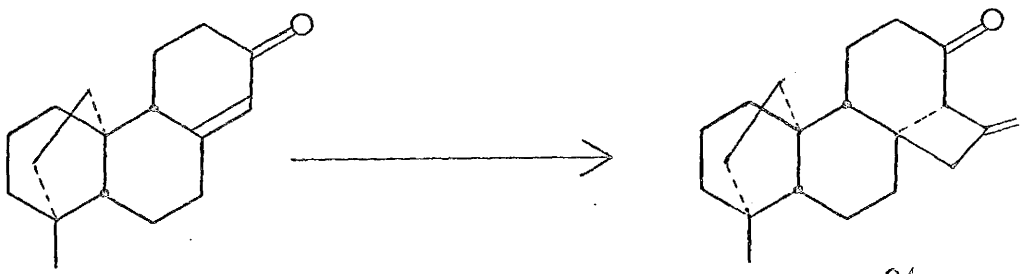
SCHEME XIV



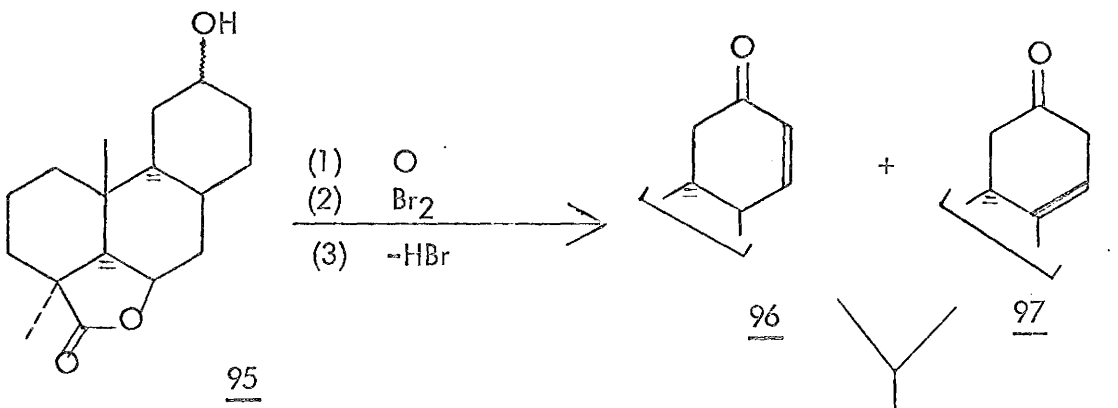
successfully employed by Valenta and his colleagues[116]. Irradiation of a 1% solution of the ketone 93 in dry tetrahydrofuran in presence of large excess of allene at -80° for 13 hrs. resulted in a complete conversion to the compound 94 which has also been transformed to the C,D ring system of atisine.

In view of the accomplishments summarised above, it was projected that successful hydrogenation of the aromatic ring in the keto-lactone 62 (R=H) with preservation of the oxygen functions at least in C-6 and C-12 positions would set the stage for an easy approach to (+)-7-hydroxykaurenolide, via the allylation of C-8 of the diketone corresponding to the diol from hydrogenation reaction; and then cyclization by a S_N2 displacement method. If, on the other hand, the C-7 oxygen was lost by hydrogenolysis, the resultant hydroxylactone 95 would, on Jones oxidation, bromination and dehydrobromination, lead to the unsaturated ketone 96 or 97 or a mixture of both. Either of these enones would be readily convertible to the dienol acetate 98 which should undergo a Diels-Alder addition with such compound as 1-cyanoethylene acetate[117] to afford the adduct 99. Further transformations of this intermediate would be expected to lead to the desired (+)-7α-hydroxykaurenolide 100.

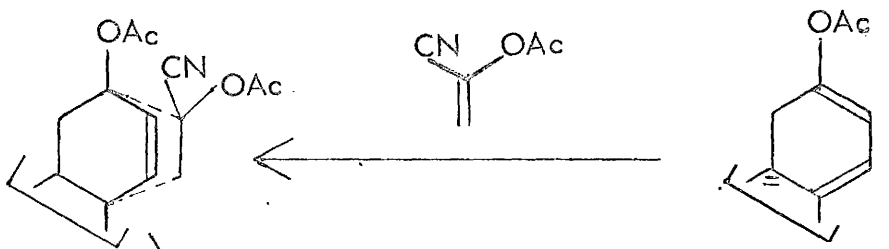
A similar application of 1-cyanoethylene acetate in the construction of the C,D ring system has recently been reported[118]. The reagent is observed to add readily to the conjugated dienol ether 101. This is obtained from the Birch reduction of methyl O-methyl podocarpate followed by t-butoxide isomerisation of the reduction product in dimethyl sulfoxide. (Scheme XV).



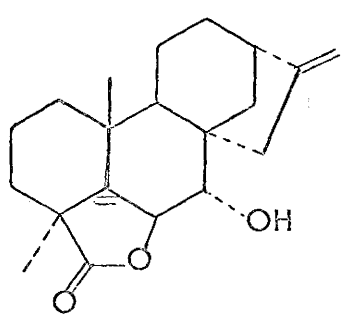
93 94



95 96 97



99 98



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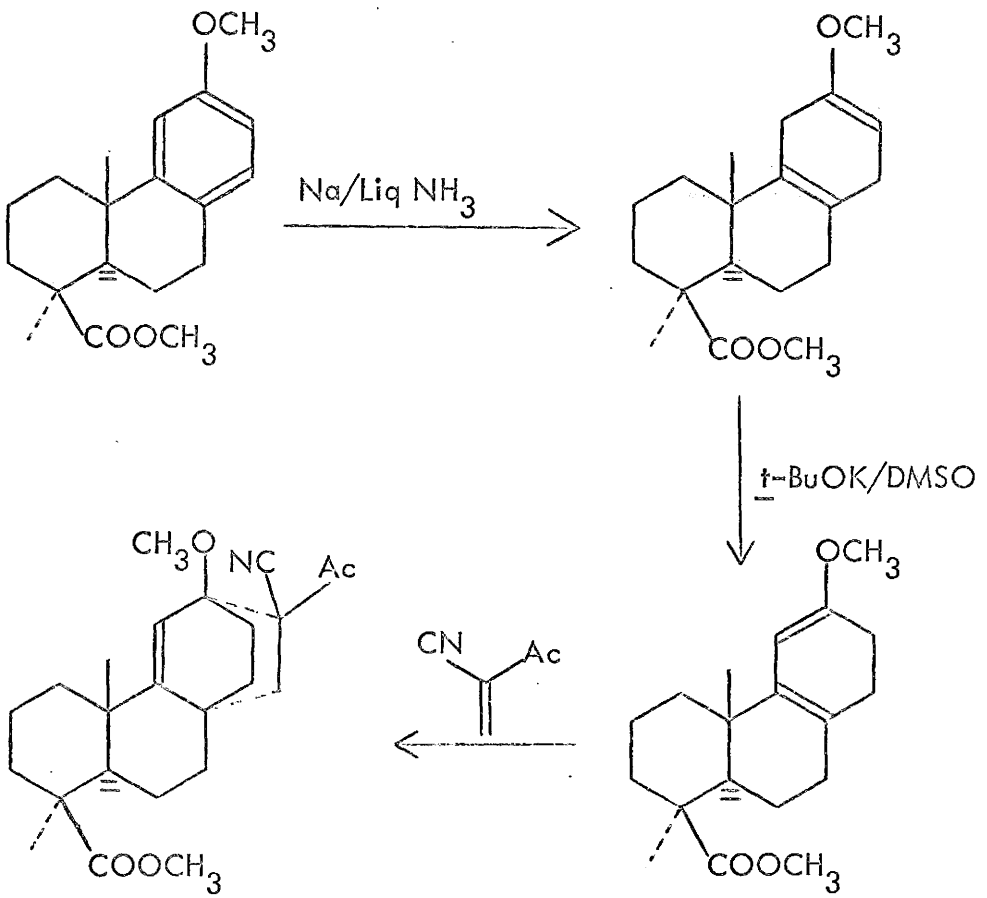


101

SCHEME XV

EXPERIMENTAL

All melting points were determined on a Kofler Hot Stage.

All proton magnetic resonance spectra were recorded on a Varian A60 spectrometer, at 37° with tetramethylsilane as internal standard in deuteriochloroform except where otherwise stated. The nuclear Overhauser effect experiments were carried out on a Varian HA 100.

All infrared spectra were recorded on a Beckmann IR5 double beam spectrophotometer 5000 - 630 cm^{-1}, using sodium chloride transmittance material.

All ultraviolet spectra were recorded on Cary 14 spectrophotometer.

All microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

2,7-Dimethoxynaphthalene 103

To two litres of 3N sodium hydroxide, continuously stirred in a 5-l three-necked flask which was fitted with a condenser, was added 160 g (1 mole) of 2,7-dihydroxynaphthalene which was purified by recrystallization of commercially available material. The hot solution was then treated with 700 g (5.5 moles) of dimethyl sulfate, added dropwise over a period of 2.5 h. The reaction was stirred overnight (18 h) and was gently warmed to 50° for 2 h. The mixture, which was strongly basic (pH 14), was allowed to cool to room temperature and filtered. The residue was washed on the filter with five litres of 1 N sodium hydroxide and then with water until the washing was no longer basic, and was then air-dried. The ash-grey crude product (185 g) was taken up in 700 ml of benzene and the resulting jet-black solution was filtered through 500 g of alumina using two litres of benzene. The volume of the faintly-coloured eluate was reduced to 250 ml by evaporation at reduced pressure and, on cooling, 123 g of 2,7-dimethoxynaphthalene, mp 138°, separated as cream-colored flakes. The mother liquors was evapored almost to dryness and the residue dissolved in boiling ethanol. On cooling, an additional 43 g of 103, mp 138.5° was obtained. Concentration of the filtrate yielded a further 15 g of the same material (total yield 96%). Literature[59] mp 139°.

7-Methoxy-2-tetralone 104

The method of Birch[47] was employed for the selective reduction of one ring by limiting the amount of sodium used.

A solution of 40 g (0.22 mole) of 2,7-dimethoxynaphthalene in 200 ml

tetrahydrofuran was added to a mixture of three litres of liquid ammonia, one litre of sodium-dried ether, and 165 ml of absolute ethanol. The mixture was constantly stirred while 12.3 g (0.5 mole) of sidum was added in small lumps, each addition being made after the blue coloration due to the previous one had disappeared (total time taken : 90 min.). The reaction mixture was stirred overnight (14 h) to allow much of the ammonia to evaporate. It was then treated with 10 g solid ammonium chloride, and 800 ml of tap water was added. The ethereal layer was separated and the aqueous phase extracted four times with 150 ml portions of ether. The combined ethereal layer was washed twice with 300 ml portions of water and dried with saturated sodium chloride solution. The ether was removed by evaporation over a steam bath, firstly at atmospheric pressure, and then under reduced pressure. The 37.5 g of crude product was dissolved in 50 ml acetone and treated with 30 ml of 3 N hydrochloric acid. The mixture was refluxed for 30 min over a steam bath and the acetone removed by evaporation. Some 200 ml of water was added and the organic material was extracted three times with 250 ml portions of ether. The combined extract was washed repeatedly with dilute sodium bicarbonate solution until there was no more effervescence, then twice with 300 ml portions of water and finally with saturated sodium chloride solution. Evaporation of the ether at reduced pressure afforded 37 g of crude product which was purified via the bisulfite adduct.

Purification of 7-Methoxy-2-tetralone

A solution of 37 g of crude tetralone in 50 ml of ethanol was gently added to a vigorously stirred solution of 87 g of sodium bisulfite in 152 ml of water. Within

30 sec. a bulky precipitate formed in the mixture. Stirring was continued for another 5 min and the reaction flask then allowed to stand at 0° for 18 h. The precipitate was filtered off and washed first with 100 ml of 1:1 ethanol-water, then with 100 ml of absolute ethanol, 200 ml of ether and finally with 100 ml of benzene. The precipitate was air-dried at the filter pump for 2 h. It was suspended in 300 ml of water and treated with a solution of 100 g of sodium bicarbonate in 300 ml of water until the mixture became basic (pH 9). The mixture was stirred at room temperature for 1 h and the organic material which separated extracted with 4 x 100 ml portions of ether. The ethereal extract was washed twice with saturated sodium chloride solution. The ether was removed by evaporation and 50 ml of benzene introduced and then evaporated under reduced pressure to yield 29 g (78%) of pure 7-methoxy-2-tetralone, bp 103° (0.1 mm); $\nu_{max}^{CHCl_3}$ 1710 cm^{-1} (C=O), 1610 cm^{-1} (enhanced aromatic), 1260 cm^{-1} (C-O-C); reported[119, 120], bp 123 - 125 (0.4 mm).

1-Methyl-7-methoxy-2-tetralone 105

The method of Stork [121] for the monomethylation of ketones was employed.

A mixture of 22 g (0.125 mole) of 7-methoxy-2-tetralone and 41 ml (ca 0.5 mole) of anhydrous pyrrolidine (distilled under nitrogen) in 150 ml of dry benzene was heated at reflux under nitrogen with a Dean-Stark water separator for 6 h. A total of 2.8 ml of water (theoretical 2.5 ml) was collected. The benzene and excess pyrrolidine were distilled off, firstly at atmospheric pressure and finally at reduced pressure - care being taken to ensure that the enamine was under nitrogen at all times. The light-brown oil was then dissolved in 100 ml of anhydrous methanol

purified by refluxing in iodine-activated magnesium turnings and distilling in an atmosphere of dry nitrogen)[122] and the solution was treated with 70 g (0.5 mole) of methyl iodide. The mixture was refluxed for 24 h and the immonium salt was decomposed by the addition of 20 ml of glacial acetic acid in 100 ml of water and refluxing for a further 30 min. After cooling to room temperature, the organic material was isolated by extraction of the diluted (excess water) solution with an ether/benzene mixture and the extract washed with water and dried with saturated sodium chloride solution. Evaporation of the solvent afforded 21 g (89%) of crude 1-methyl-7-methoxy-2-tetralone, bp 100° (0.02 mm); pmr δ 1.38 (3H,d,J=7 cps, C-1-CH_3), 2.38 (2H, m, C-4-CH_2-), 2.92 (2H,t,J=6cps, C-3 -CH_2-), 3.39 (1H, q, J=7 cps, C-1 H), 3.75 (3H, s, -OCH_3), 6.6 - 7.2 (3H, m, aromatic); reported[59]: bp 123 - 124° (0.25 mm).

1-Piperidino-3-butanone, PB

The method of Wilds and Werth[123] was used.

A mixture of 243 g (0.2 mole) of piperidine hydrochloride, mp 242 - 244°, 9.4 g (0.28 mole) of paraformaldehyde, 60 ml (0.82 mole) of acetone, and 40 ml ethanol was refluxed on the steam bath for 20 h (longer heating reduced the yield considerably). The cloudy solution was filtered and concentrated under reduced pressure. After adding 50 ml of water, the solution was treated with excess of 4.5% potassium hydroxide solution and saturated with potassium carbonate. The organic material was isolated by extraction with ether and the extract washed with saturated brine and further dried with anhydrous sodium sulfate. Removal of

the ether under reduced pressure gave 35.7 g of liquid residue which was distilled in vacuo to give 26 g (87%) of 1-piperidino-3-butanone, bp 42° (0.01 mm); n_D^{24} 1.4627; $\nu_{max}^{CHCl_3}$ 1710 cm^{-1} (C=O); reported[123] bp 89 - 90° (7 mm), n_D^{25} 1.4628. The product was found to be homogeneous by TLC.

6-Methoxy-12-methyl-2,3,4,9,10,12-hexahydrophenanthrene-2-one 106

The procedure of Conforth and Robinson[124] was followed with slight modification.

To 15 g (0.1 mole) of 1-N-piperidino-3-butanone gently swirled in a 1l flask cooled in an ice bath was added 15 g (0.1 mole) of methyl iodide in portions over a period of 30 mm. The swirling was regulated so as to obtain the crystalline methiodide as an even coating on the walls of the flask. When no more liquid remained, the flask was kept in ice for 30 min and then under tap water (27°) for 45 min. A solution of 17 g (0.09 mole) of 1-methyl-7-methoxy-2-tetralone in 100 ml of dry thiophene-free benzene was added, air being excluded from the flask by means of a current of dry nitrogen. A solution of 7 g of potassium in 120 ml of absolute ethanol (prepared by refluxing with diethylphthalate for 6 h and distilling in a current of dry nitrogen) was then added with ice-cooling. Swirling was continued until the methiodide had all dissolved (ca 30 min) and was replaced by a precipitate of potassium iodide. After it had been kept in ice for another hour, the mixture was boiled gently for 25 min. An excess of 2 N sulfuric acid was then added to (ph 1) and the nitrogen stream cut off. After the addition of enough water to dissolve the potassium sulfate, the benzene layer was separated

and the aqueous layer extracted twice with ether. The united extract was washed with water, clarified with a little magnesium sulfate and evaporated. The warm residue (22.6 g) was triturated with ether until the total weight was about 35 g. Crystallization set in almost immediately and was allowed to proceed at 0° overnight. The first crop was collected by filtration and washed with chilled ether to give 12 g (57%) of the tricyclenone 106 as bright yellow prisms, mp 79°; $\nu_{max}^{CHCl_3}$ 1660 cm^{-1} (αβ-unsaturated ketone), 1245 cm^{-1} (C-O-C); λ_{max}^{EtoH} 227 mμ (ε, 17,000); pmr δ 1.52 (3H, s, C-12-CH_3), 3.78 (3H, s, -OCH_3); 5.9 (1H, s, C-1 vinyl H). reported[59] mp 78.5 - 79. The yield as determined from the proton magnetic resonance spectrum of the crude product was 85%.

1-Carbomethoxy-6-methoxy-12-methyl-2,3,4,9,10,12-hexahydrophenanthrene-2-one 107

The method of Wenkert[55] was extensively modified for the introduction of the carboxyl function in the appropriate position. Every care was taken to protect the reaction from the slightest trace of moisture.

Into a three-necked specially designed flask, still warm with oven-drying, and continuously flushed with nitrogen (dried first, by bubbling through concentrated sulfuric acid and then through a six-inch column of phosphorus pentoxide in a U-tube), 2.3 g (5 equivalents) of 50% sodium hydride dispersed in mineral oil was introduced. 100 ml of anhydrous (sodium-dried) ether was then added and the mixture stirred for 15 min and allowed to settle. After the supernatant solvent was carefully removed by means of a pipette, 2.4g(0.01 mole) of 6-methoxy-12-methyl-2,3,4,9,10,12-hexahydro-2-phenanthrenone was added and the mixture covered with 150 ml of

dimethoxy ethane-DME- (dried by refluxing over calcium hydride and distilled in an atmosphere of dry nitrogen). The mixture was first stirred at room temperature for 12 h and then gently warmed for 30 min. On cooling to room temperature, the reaction vessel was immersed in a mixture of Dry Ice and carbon tetrachloride (ca - 50°) and the stream of nitrogen was replaced with carbon dioxide (carefully dried in a similar manner) which was bubbled through the reaction mixture with continuous stirring for 7 h. With the temperature of the reaction mixture still maintained at -50°, the excess sodium hydride was decomposed by the gradual introduction of crushed ice until the ice was in excess. The cold bath was then removed and the mixture diluted with ice-cold water to 200 ml and extracted twice with 35 ml of a chilled 1:1 ether/benzene mixture. The combined organic extract was in turn washed three times with ice-cold 2% sodium hydroxide solution and the combined aqueous layers (kept ice-cold with the occasional addition of crushed ice) was acidified with the addition of ice-cold 10% sulfuric acid (to pH 1). This solution was immediately extracted five times with chilled ether. The ethereal extract was washed twice with ice-cold water, once with saturated sodium chloride solution and then treated with an excess of ethereal diazomethane. After stirring for 5 min, the excess diazomethane and solvent were removed under reduced pressure to give 2.52 g (84%) of a light yellow gum which readily afforded 2.2 g of crystalline 107 on tituration with ether. The unsaturated keto-ester, after recrystallization from ether, showed: mp 89.5°; $\nu_{max}^{CHCl_3}$ 1730 cm^{-1} ($\alpha\beta$ -unsaturated ester), 1670 cm^{-1} ($\alpha\beta$ -unsaturated ketone), 1245 cm^{-1} (C-O-C); λ_{max}^{EtOH} 280 mμ (ε, 18,000); pmr δ 1.61 (3H,

s, C-12 -CH_3), 1.81 (3H, s, -OCH_3), 1.87 (3H, s, -$COOCH_3$), 6.6 - 7.2 (3H, m, aromatic).

It was found necessary to decompose the excess sodium hydride at sub-zero temperature and to maintain the potential product at ice-temperature at all stages before esterification. Failure to do so resulted in extensive decarboxylation of the intermediate acid and gave very low yields of the keto-ester 107.

The neutral extract, containing the alkali-insoluble fraction, was dried (anhydrous magnesium sulfate) and evaporated to dryness whereby 300 mg of the starting ketone 106 was obtained. The overall yield of keto-ester 107 based on ketone 106 was 96%.

Methyl 3-Keto-Δ^5-O-methylpodocarpate 108

The procedure of Wenkert[57] was followed without serious modification.

A solution of 1.1 g (3.4 mmoles) of the β-keto-ester in 25 ml of dry t-butyl alcohol was added to a solution of 200 mg (5.1 mmoles; 1.5 equiv.) of potassium in 10 ml dry t-butyl alcohol and the mixture was refluxed under nitrogen for 30 min. The solvent was removed under reduced pressure and three 25 ml portions of dry benzene were introduced and removed. A solution of 6 ml (excess) of methyl iodide in 30 ml dry benzene was then introduced over a stream of nitrogen and the mixture refluxed for 18 h. The solution was then washed with cold water and dried (Na_2SO_4) before the solvent was evaporated off, to give, after drying in vacuo, 1.15 g (98%) crude product. The proton magnetic resonance spectrum of this crude methylated keto-ester showed it to be a mixture of two compounds in the ratio of 4:1 (see discussion and results). On trituration with ether the crude product afforded

600 mg of the major component, 108, in crystalline form, mp 110°; pmr δ 1.32 (3H, s, C-10, CH_3), 1.54 (3H, s, C-4 CH_3), 3.45 (2H, d, J=5 cps, C-7 -CH_2-), 3.78 (3H, s, O-CH_3), 3.83 (3H, s, -$COOCH_3$), 6.11 (1H, t, J=5 cps, C-6 vinylic proton), 6.7 - 7.3 (3H, m, aromatic). $\nu_{max}^{CHCl_3}$ 1745 cm^{-1} (-$COOCH_3$), 1720 cm^{-1} (C=O).

Methyl 3-Keto-O-methylpodocarpate 109

A solution of 500 mg of 108 in 20 ml glacial acetic acid was introduced into an hydrogenation flask containing 200 mg of 5% palladium-on-charcoal in 10 ml acetic acid already saturated with hydrogen. After stirring for 12 h under 1 atm of hydrogen at room temperature, the catalyst was filtered off and washed on the filter with benzene. The combined filtrate was evaporated almost to dryness on the water bath at reduced pressure. The residue was dissolved in 50 ml benzene and the solution washed twice with 5% aqueous sodium bicarbonate to remove the last trace of acetic acid, once with water and finally with saturated sodium chloride solution. The benzene was evaporated under reduced pressure affording 496 mg of methyl 3-keto-O-methylpodocarpate as the sole product, mp 166 - 167°; pmr δ 1.33 (3H, s, C-10 - CH_3), 1.48 (3H, s, C-4 - CH_3), 3.74 (3H, s, -OCH_3), 3.80 (3H, s, -$COOCH_3$), 6.7 - 7.3 (3H, m, aromatic).

Methyl O-Methylpodocarpate 111

The 3-keto group of compound 109 was removed by the method of Fieser[73] This consisted of conversion of the keto group to the thioketal and desulfurisation of the thioketal by means of specially prepared Raney nickel.

A solution of 100 mg of methyl 3-keto-O-methylpodocarpate and 0.25 ml of ethanedithiol in 3 ml of hot (80°) glacial acetic acid was treated with 0.3 ml boron trifluoride etherate with constant stirring. On cooling to room temperature (27°) colorless, fine-crystals separated which were collected by filtration and washed with cold methanol to give 85 mg (68%) of the thioketal 110. Without further purification the thioketal was dissolved in 10 ml of warm absolute ethanol and the solution refluxed overnight (20 h) with excess 200 mg) of special grade Raney nickel (see below). The catalyst was filtered off and washed on the filter with ethanol. The combined filtrate was evaporated almost to dryness and 10 ml of water was added. The solid which separated was isolated by extraction with ether. Evaporation of the dried ethereal extract gave 65 mg (68%) of methyl-O-methylpodocarpate, mp 118°; pmr δ 102 (3H, s, C-10, $-CH_3$), 1.27 (3H, s, C-4 $-CH_3$), 2.8 (2H, m, benzylic proton) 3.67 (3H, s, $-OCH_3$), 3.86 (3H, s, $-COOCH_3$), 6.56 - 7.12 (3H, m, aromatic). This pmr was identical with that of authentic compound.

Preparation of Raney Nickel

This was prepared by the method of Burgstahler and Abdel-Rahman[74]

A solution of 0.52 g of sodium hydroxide in 2 ml of water was maintained at 75° with stirring and 400 mg of Raney nickel alloy was gradually added portion-wise over a period of 30 min. Digestion was allowed to continue at a gradually decreasing temperature for an additional 30 min. The mixture was allowed to settle and the supernatant solution was decanted. The residue was transferred with distilled water to a 1-l graduate cylinder placed in a sink. A 7-mm glass tube, reaching to the bottom of the cylinder, was connected to the distilled water tap,

and the flow of water was adjusted so that the metal rose to within 3 inches of overflowing the top of the cylinder. After 15 min., the washings were found to be neutral to pH paper. The water was decanted and the residue was washed several times with absolute ethanol before it was transferred, with the aid of a small quantity of absolute ethanol, to the thioketal solution.

12-Acetoxypodocarpic Acid 112

The method of Sherwood and Short[5] was employed with slight modification.

A mixture of 50 g (0.18 mole) of podocarpic acid mp 193°, 70 g (0.75 mole) of acetic anhydride and 1 g of anhydrous sodium acetate was refluxed for 1 h and the excess acetic anhydride destroyed by warming with 100 ml of water for 20 min. The mixture was stirred into 3l of cold water (4°) and the solid which separated was filtered off and washed at the filter pump with a further 500 ml of water. An ethereal solution of the residue was dried using anhydrous sodium sulfate and the solution concentrated to a total volume of about 120 ml. Crystallization which set in almost immediately was allowed to continue at 0° affording 54 g (95%) of 12-acetoxypodocarpic acid, mp 183° $\nu_{max}^{CHCl_3}$ ~ 3200 cm^{-1} (-COOH), 1750 cm^{-1} (CH_3CO-), 1700 cm^{-1} (-COOH), 1280 cm^{-1} (C-O-C). pmr δ 1.12 (3H, s, C-10 $-CH_3$), 1.33 (3H, s, C-4 $-CH_3$), 2.25 (3H, s, CH_3CO-), 6.70 - 7.17 (3H, m, aromatic). literature:[125] mp 180 - 182°.

7-Keto-12-acetoxypodocarpic Acid 113

A solution of 15 g (0.05 mole) of O-acetylpodocarpic acid in 100 ml of glacial acetic acid was treated with a solution of 11.5 g (5 equivalents) of

chromium trioxide in 300 ml of acetic acid containing 10 ml of water and the mixture stirred at room temperature for 40 h. The volume of the reaction solution was reduced to about 100 ml by evaporation on a water bath under reduced pressure and the resultant dark-green solution poured into 3l of cold water with stirring. The organic material which separated was isolated by extracting several times with ethyl acetate. The combined organic extract was washed twice with water and dried (anhydrous $MgSO_4$) Evaporation of the solvent afforded 17.7 g of dark-green product which was purified by passing through a column of 500 g of silica gel using 2l of 15% ethyl acetate/ benzene. Evaporation of the solvent gave 15.3 g (98%) of the keto-acetate 113 (homogeneous by TLC), which was recrystallized from ether, mp 178°; λ_{max}^{EtoH} 256 mμ (ε, 10,560); pmr δ 1.23 (3H, s, C-10 $-CH_3$), 1.35 (3H, s, C-4 $-CH_3$), 2.30 (3H, s, CH_3CO-), 3.1 (2H, d, J=3.5 cps, C-6 methylene). 7.0 - 7.25 (2H, m, C-11 and C-13 protons), 7.85 (1H, d, J=9 cps, C-14 H).

6α-Bromo-7-keto-12-acetoxypodocarpic Acid 114

The procedure of Wenkert[76] was employed without modification.

A solution of 5.7 g (1.1 equiv.) of bromine in 10 ml acetic acid was added dropwise to a stirred solution of 10 g (0.03 mole) of 7-keto-12-acetoxy-podocarpic acid in 30 ml of acetic acid to which three drops of 15% hydrobromic acid had been added. Care was taken to add each drop after the colour due to the previous addition had disappeared. The mixture was then stirred for a further 15 min at room temperature and all the acetic acid was removed over a steam bath under reduced pressure. The resulting residue was taken up in 15 ml of warm methanol and

the solution allowed to stand. On cooling 11.8 g (96%) of 6$_\alpha$-bromo-7-keto-12-acetoxypodocarpic acid was obtained, mp 89 - 92°; pmr δ 0.98 (3H, s, C-10 -CH_3), 1.65 (3H, s, C-4 -CH_3), 2.33 (3H, s, -CO-CH_3), 2.6 (1H, d, J=7 cps, C-5 H), 6.1 (1H, d, J=7 cps, C-6 H), 7 - 7.25 (2H, m, C-11 and C-13 protons), 7.85 (1H, d, J=9 cps, C-14 H).

6β-Hydroxy-7-keto-12-acetoxypodocarpic-19,6-lactone 115 (R = Ac)

A solution of 10 g (0.025 mole) of 6-bromo-7-keto-12-acetoxypodocarpic acid in 25 ml of chloroform was treated with 1 ml of pyridine. After the mixture was stirred overnight (15 h) at room temperature it was washed with 30 ml of 1% hydrochloric acid and then twice with water and finally with saturated sodium chloride solution. On evaporation of the solvent, 7.8 g (96%) of the lactone was obtained as the sole product. This material was recrystallized from a 2:1 mixture of ethyl acetate and hexane giving the lactone mp 163 - 164°; $\nu_{max}^{CHCl_3}$ 1770 cm^{-1} (γ-lactone), 1700 cm^{-1} (aromatic ketone), 1190 cm^{-1} (C-O-C); λ_{max}^{EtoH} 260 m (ε, 12,780); pmr δ 1.09 (3H, s, C-10 -CH_3), 1.34 (3H, s, C-4 -CH_3), 2.31 (3H, s, CH_3CO-) 2.42 (1H, d, J=5.5 cps, C-5 H), 4.96 (1H, d, J=5.5 cps, C-6 H), 7.0 - 7.24 (2H, m, C-11 H and C-13 H), 7.88 (1H, d, J=9 cps, C-14 H). literature:[76] mp 161 - 164°.

7-Keto-podocarpic-19,6-lactone 115 (R=H)

A solution of 500 mg of 7-keto-12-acetoxypodocarpic-19,6-lactone, 115 (R = Ac), in 50 ml of warm isopropyl alcohol (IPA) was treated with 1.5 ml conc. sulfuric acid in 40 ml of water and was allowed to stand on the steam bath for 30 min.

The isopropyl alcohol was evaporated under reduced pressure and the resultant mixture was diluted by the addition of 250 ml of water. The organic material which separated was extracted in 3 x 50 ml portions of benzene and the extract washed twice with water and dried (anhydrous $MgSO_4$). On evaporation of the benzene and tituration of the residue with ether, 375 mg (86%) of colorless, fine crystals of the phenol-lactone 115 (R=H) separated, mp 193 - 195°; ν_{max}^{nujol} 1755 cm^{-1} (γ -lactone), 1660 cm^{-1} (C=O); λ_{max}^{EtoH} 285 mμ (ε, 12,000); pmr (in perdeuterio-acetone) δ 1.15 (3H, s, C-10 $-CH_3$), 1.39 (3H, s, C-4 $-CH_3$), 2.43 (1H, d, J=6 cps, C-5 H), 5.08 (1H, d, J=6 cps, C-6 H), 6.6 - 6.95 (2H, m, C-11 and C-13 protons) 7.81 (1H, d, J=8 cps, C-14 H). Reported[76]: mp 161 - 164°.

6,7-Dihydroxypodocarpic-19,6-lactone 116

A solution of 6.4 g (0.02 mole) of 6β-hydroxy-7-keto-12-acetoxypodocarpic lactone in 35 ml of 95% ethyl alcohol was cooled in an ice bath with stirring for 10 min, and was then treated with a suspension of 1.5 g (0.04 mole) of sodium borohydride. The mixture was stirred at ice temperature for 1 h and then overnight (15 h) at room temperature. After the volume of ethanol had been considerably reduced with the minimum of heating, about 500 ml of cold 1% hydrochloric acid was added and the mixture was saturated with sodium chloride and extracted several times with chloroform. The extract was washed with water and dried (anhydrous $MgSO_4$). On evaporation of solvent 4.9 g (89%) of 6,7-dihydroxypodocarpic-19,6-lactone (homogeneous by TLC), was obtained, mp 206 - 208°; ν_{max}^{nujol} 3485, 3370 cm^{-1} (-OH), 1765 cm^{-1} (γ-lactone); λ_{max}^{EtoH} 230 mμ (ε, 9,000);

pmr (in perdeuterio-acetone) δ 1.28 (3H, s, C-10 $-CH_3$), 1.36 (3H, s, C-4 $-CH_3$), 2.25 (1H, d, J=6 cps, C-5 H, X part of an ABX), 2.95 (1H, broad s, C-7 -OH), 5.12 (2H, m, C-6 H and C-7 H, AB part of an ABX), 6.54 - 6.78 (2H, m, aromatic C-11 and C-13 protons), 7.14 (1H, d, J=9 cps, aromatic C-14). Two recrystallizations from ethyl acetate provided an analytical sample. Calculated for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99%. Found: C, 70.73; H, 6.80%.

6,7-Dihydroxypodocarpic Acid 117

Hydrolysis of the lactone was carried out according to the method used by Tahara and co-workers[126].

Methyl alcohol was added to a mixture of 2.8 g (0.01 mole) of the hydroxy-lactone 116 and 45 ml of 15% sodium hydroxide solution until the solid completely dissolved. The resulting solution was heated at reflux for 4 h and the methanol evaporated. The mixture was cooled under tap water, acidified with 10% hydrochloric acid (to pH 1) and, after saturation with sodium chloride, was extracted several times with ethyl acetate. The extract was washed once with distilled water and dried with anhydrous sodium sulfate. Evaporation of the solvent provided 3.1 g of light yellow residue (mostly a single compound by TLC) which was purified by passage through a column of 100 g of silica gel with 25% ethyl acetate in benzene. Evaporation of the eluate gave 2.7 g (90%) of the dihydroxy-acid as a colourless solid which crystallized from methanol-benzene, mp 203 - 205°; ν_{max}^{nujol} 3275, 3125 cm^{-1} (-OH), 1685 cm^{-1} (-COOH), 1610 cm^{-1} (enhanced aromatic).

The compound was fully characterised as its methyl ester, mp 143 - 144°;

$\nu_{max}^{CHCl_3}$ 3550, 3300 cm^{-1} (-OH), 1750 cm^{-1} ($-COOCH_3$); pmr δ 1.05 (3H, s, C-10 $-CH_3$), 1.3 (3H, s, C-4 $-CH_3$), 2.33 (1H, d, J=6 cps, C-5 H, X part of an ABX), 3.71 (3H, s, $-COOCH_3$), 4.78 (2H, m, C-6 H and C-7 H, AB part of an ABX), 6.08 (1H, s, phenolic H), 6.68 - 6.88 (2H, m, aromatic C-11 H and C-13 H), 7.55 (1H, d, J=9 cps, C-14 H). Two recrystallizations from ethyl acetate provided an analytical sample. Calculated for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55%. Found : C, 67.58; H, 7.60%.

Hydrogenation of 6,7-Dihydroxypodocarpic Acid

To a mixture of 300 mg of 5% rhodium-on-alumina and 20 ml of glacial acetic acid saturated with hydrogen was added a solution of 1.3 g of 6,7-dihydroxy-podocarpic acid in 80 ml of glacial acetic acid. The whole mixture was treated with 0.36 ml of 70% perchloric acid (making the total solution 0.25% in perchloric acid) and subjected to 3.5 atm of hydrogen at room temperature for 48 h with constant shaking. The catalyst was filtered off and washed on the filter with some benzene. The combined filtrate was evaporated with gentle warming under reduced pressure. The residue was treated with 15 ml of 5% sodium hydroxide with addition of methyl alcohol to achieve complete dissolution and the mixture heated on the steam bath for 30 min. Methyl alcohol was removed by evaporation at reduced pressure, and the mixture was acidified (to pH 1) with 2N hydrochloric acid. After saturation of the aqueous phase with sodium chloride, the resulting precipitate was extracted with ether. The extract was further dried using anhydrous magnesium sulfate before it was treated with excess ethereal diazomethane. The mixture was stirred at room

temperature for 5 min and excess diazomethane and ether were evaporated off to give 1.1 g.of colourless crystalline material. This was found to be a mixture of many compounds by TLC. Chromatography of the residue on 75 g of silica gel and elution with benzene afforded 700 mg of one component identified as methyl 8α-podocarp-19-oate, 118, which was recrystallized from ether-hexane to give oily crystals, mp 49°; $\nu_{max}^{CHCl_3}$ 1720, 1240 cm^{-1} (-COOMe); pmr δ 0.87 (3H, s, C-10 $-CH_3$), 1.16 (3H, s, C-4,$-CH_3$), 3.62 (3H, s, $-OCH_3$). The proton magnetic resonance spectrum was identical to that of an authentic sample, mp 45°, prepared[127] in the same laboratory by the Wolff-Kishner reduction of methyl 12-keto-8α-podocarpan-19-oate. Anal. Calculated for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86%. Found : C, 77.52; H, 10.75%.

Further elution with 5% ethyl acetate-in-benzene gave 215 mg of another component identified as methyl 12-keto-8α-podocarpan-oate, 119, which was recrystallized from ether-hexane to give colourless crystals, mp 107 - 109°; $\nu_{max}^{CHCl_3}$ 1720 cm^{-1} (-COOMe), 1695 cm^{-1} (C=O), 1235 cm^{-1} (C-O-C); pmr δ 0.7 (3H, s, C-10 $-CH_3$), 1.2 (3H, s, C-4 $-CH_3$), 2.4 (4H, m, C-11 and C-13 methylenes), 3.65 (3H, s, $COOCH_3$). The proton magnetic resonance spectrum was identical to that of an authentic sample, obtained[128] by Jones oxidation of the hydroxy-ester product from catalytic hydrogenation of methyl podocarpate.

Continued elution with some solvent provided about 100 mg of solid the infrared spectrum of which showed it to be a mixture of a lactone and a hydroxyacid which could not be separated by fractional crystallization from hexane.

DISCUSSION AND RESULTS

A. THE TOTAL SYNTHESIS OF PODOCARPIC ACID

The sequence of reactions used is summarized in scheme XVI.

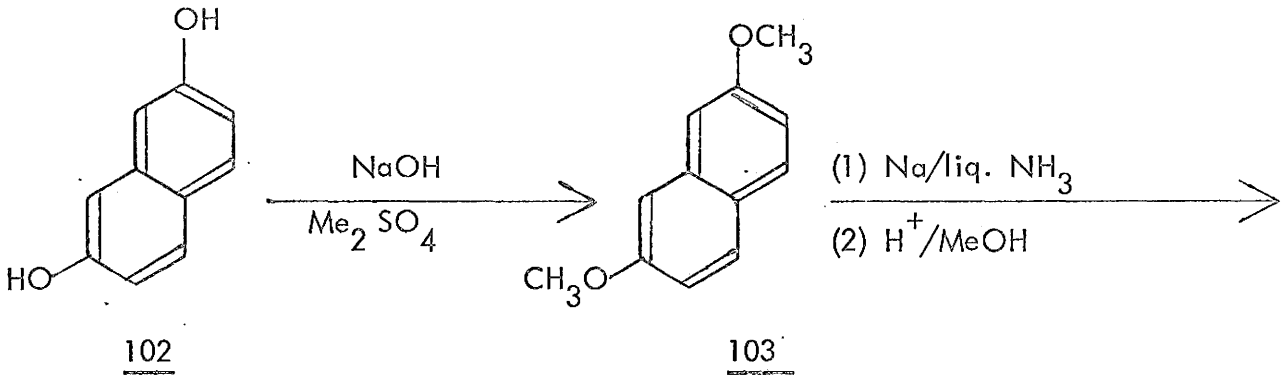
i. Construction of the Tricyclic Carbon Skeleton

A convenient starting material for the approach, selected in this work, to the perhydrophenanthrene nucleus was 2,7-dihydroxynaphthalene. It was readily converted to the corresponding dimethyl ether by the treatment of its solution in strong alkali with excess dimethyl sulfate. This reaction consistently afforded more than 90% of the theoretical yield.

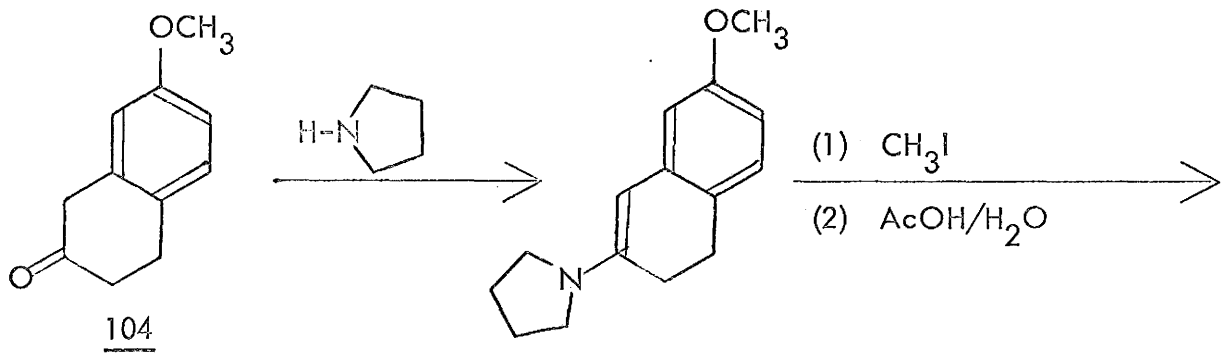
Further transformation of the dimethyl ether required the modification of one of the two rings. This was achieved by selective reduction using the method of Birch. The essential feature of this reaction is the use of a solution of an alkali metal in liquid ammonia to provide a source of electrons which can be added stepwise to an aromatic ring. The interaction of the resulting radical anions with proton donors in the reaction mixture leads to the irreversible reduction of the aromatic ring. The extent to which reduction proceeds is determined by the number of mole equivalents of the alkali metal used.

The addition of two electrons to one ring of the naphthalene nucleus leads to the desired stage of reduction according to the following formulation.

However, the possibility of the addition of more than two electrons to the same molecule cannot be completely avoided. Further addition of electrons can



102 103



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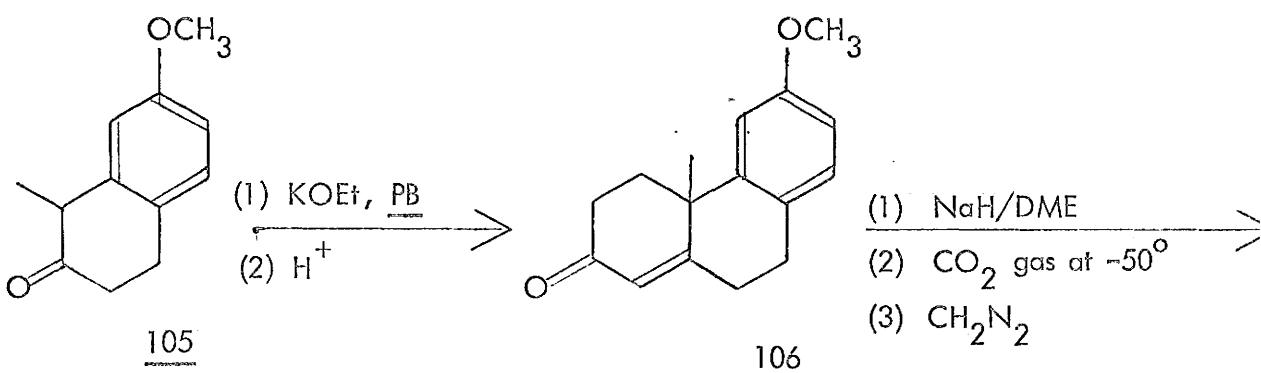

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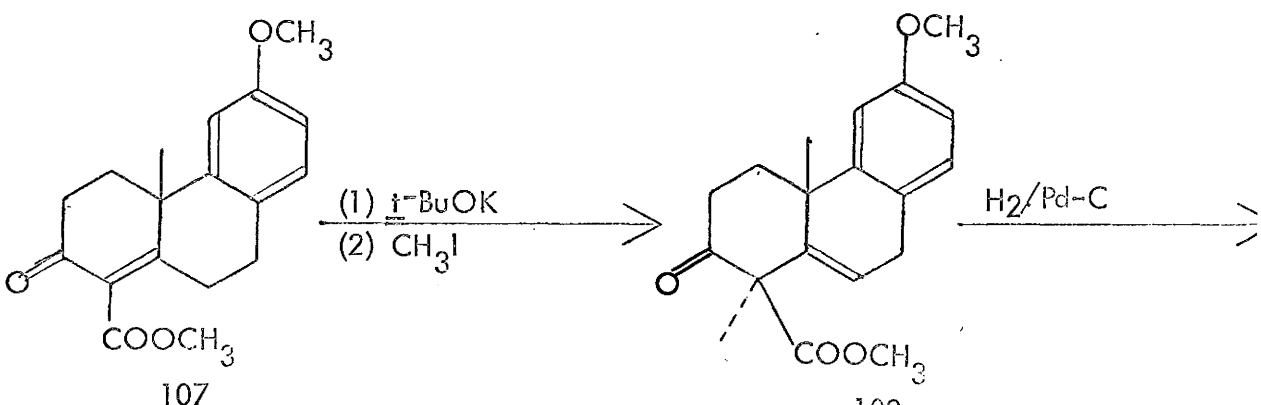

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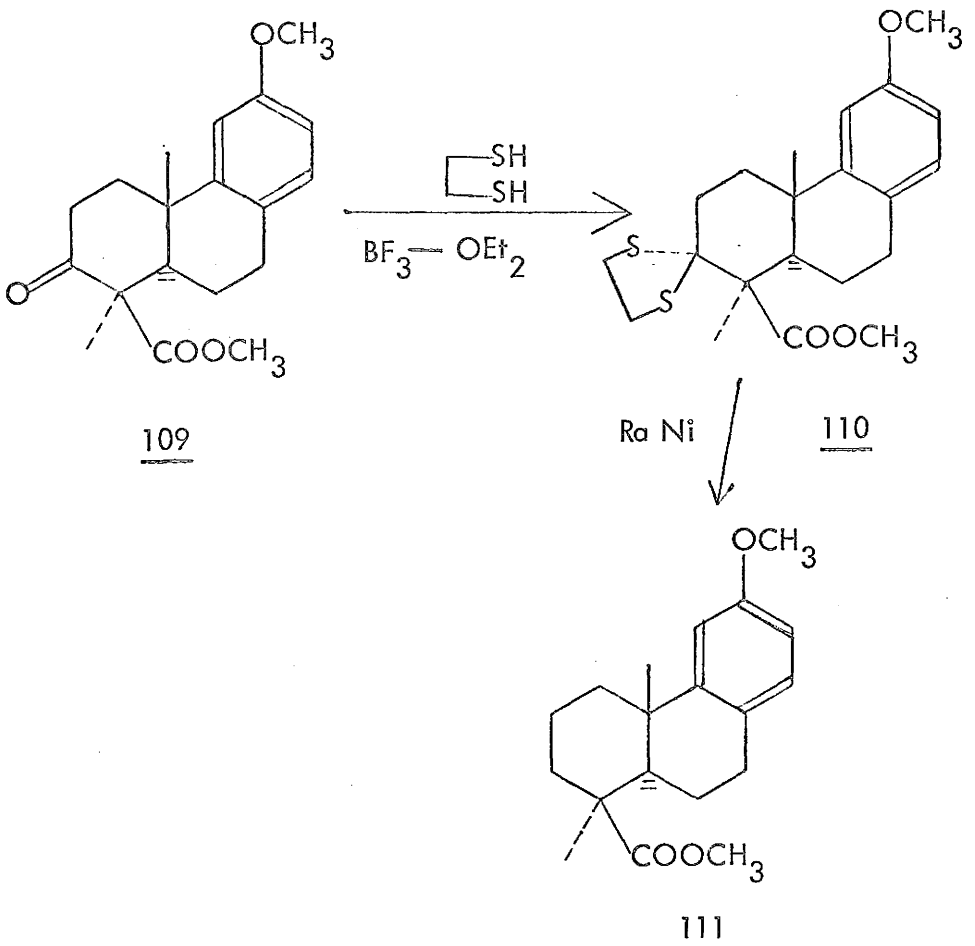

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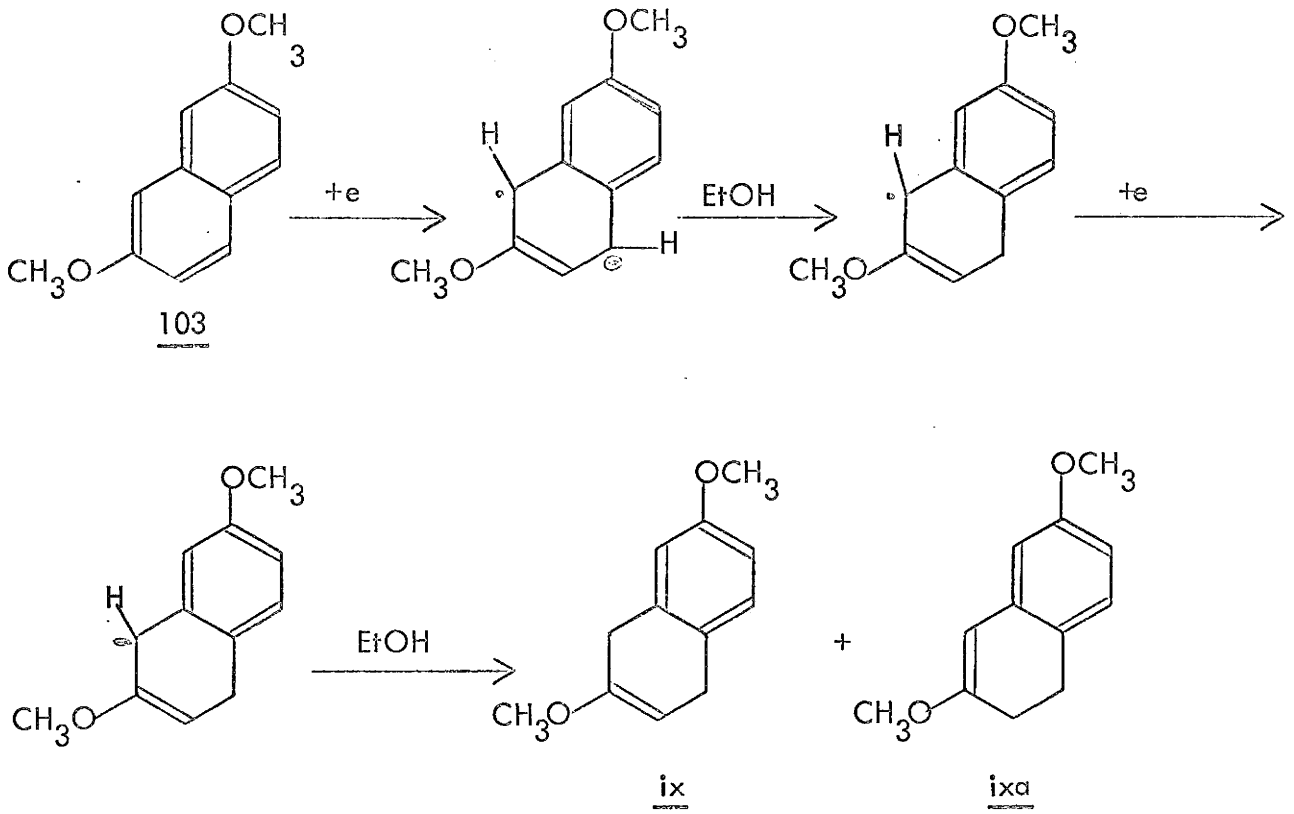
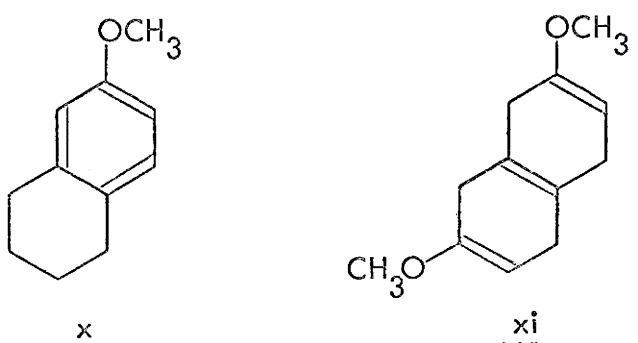
SCHEME XVI



occur very facilely to the conjugated isomer ixa resulting in the elimination of the methoxyl group and eventual complete saturation of the ring giving the tetralin x. The addition of electrons to the second aromatic ring ix is difficult, but can take



x xi

place and the tetrahydro intermediate xi results. The formation of x and xi in experiments using 2 mole equivalents of alkali metal made the recovery of some of the starting naphthalene inevitable. The use of excess alkali metal led to an enormous increase in the percentage of products due to over-reduction.

A series of trial experiments was carried out on a small scale to ascertain the number of gram-equivalents of sodium which afforded the highest percentage yield of the dihydro intermediate, ix. The results, summarized in Table I indicate that this was achieved with nearly 2.4 gram-equivalents of sodium. Product analysis was conducted by vapour phase chromatography in all cases.

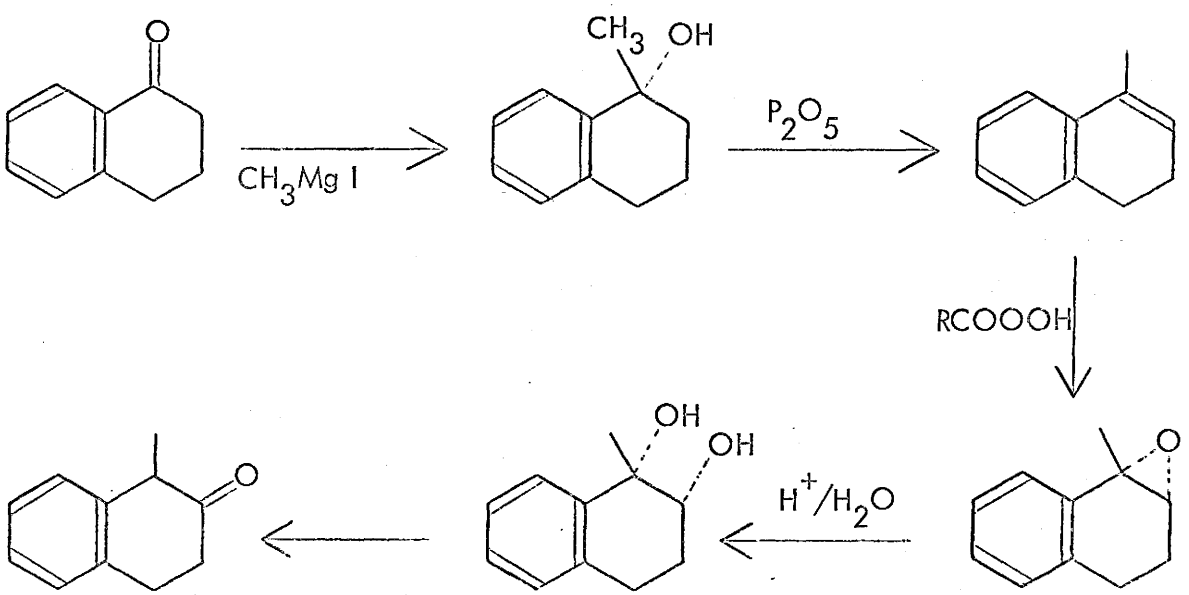
TABLE I

Equiv. of Na used	% of ix	% of x	% of xi	% 103 recovered
1.9	71.7	3.4	1.4	23.6
2.2	79.	3	3.5	14.5
2.35	80	5	4.5	10.5
2.6	77	6	10.5	6.5
3.0	67.5	6.5	25	< 1.

During large-scale reactions it was observed that when more than 40 g of the starting material was used in three litres of liquid ammonia the yield of the intermediate ix was very low. Additional care to improve the yield was taken by

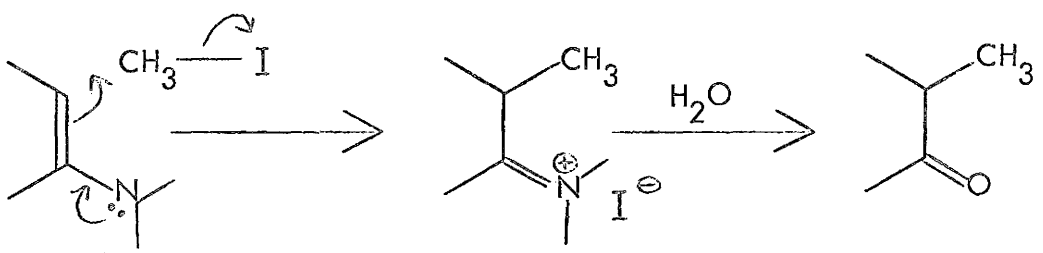
introducing the alkali metal in very small portions and allowing the reaction due to each addition to proceed to completion before the following addition was made. The reduction product was hydrolysed immediately after isolation to avoid possible air oxidation.

The monomethylation of β-tetralones in the α-position by ordinary methods had been found extremely difficult to achieve[129 - 131]. Thus earlier preparations of α-methyl β-tetralones[132 - 135] involved the circiutous procedure of the Grignard methylation of α-tetralones, dehydration of the resultant alcohols and peracid oxidation of the 4-methyl-1,2-dihydronaphthalene derivatives followed by acid-catalysed hydrolysis of the epoxides as shown below:



Low overall yields, based on the starting α-tetralone derivatives were invariably obtained.

The recent method for monomethylation of carbonyl compounds, developed by Stork[121] provided excellent yields of 1-methyl 7-methoxy-2-tetralone. The formation of the enamine double bond exclusively in the 1,2-position could be predicted on the basis of the strongly acidic α-protons and the potential conjugation with the aromatic ring. Treatment of the enamine with methyl iodide followed by decomposition of the resulting immonium salt with aqueous acetic acid afforded the desired compound. The reaction is rationalized according to the following scheme:



The methylation reaction was initially attempted using the method of Kuehne[59]. This involved refluxing the enamine in excess of methyl iodide for five days followed by the decomposition of the immonium salt with aqueous acetic acid. The yields from three different attempts were remarkably lower than that reported (91%) by Kuehne. However, when the reaction was repeated by refluxing the enamine with an equivalent amount of methyl iodide in anhydrous methanol, a reproducible yield of about 90% was obtained.

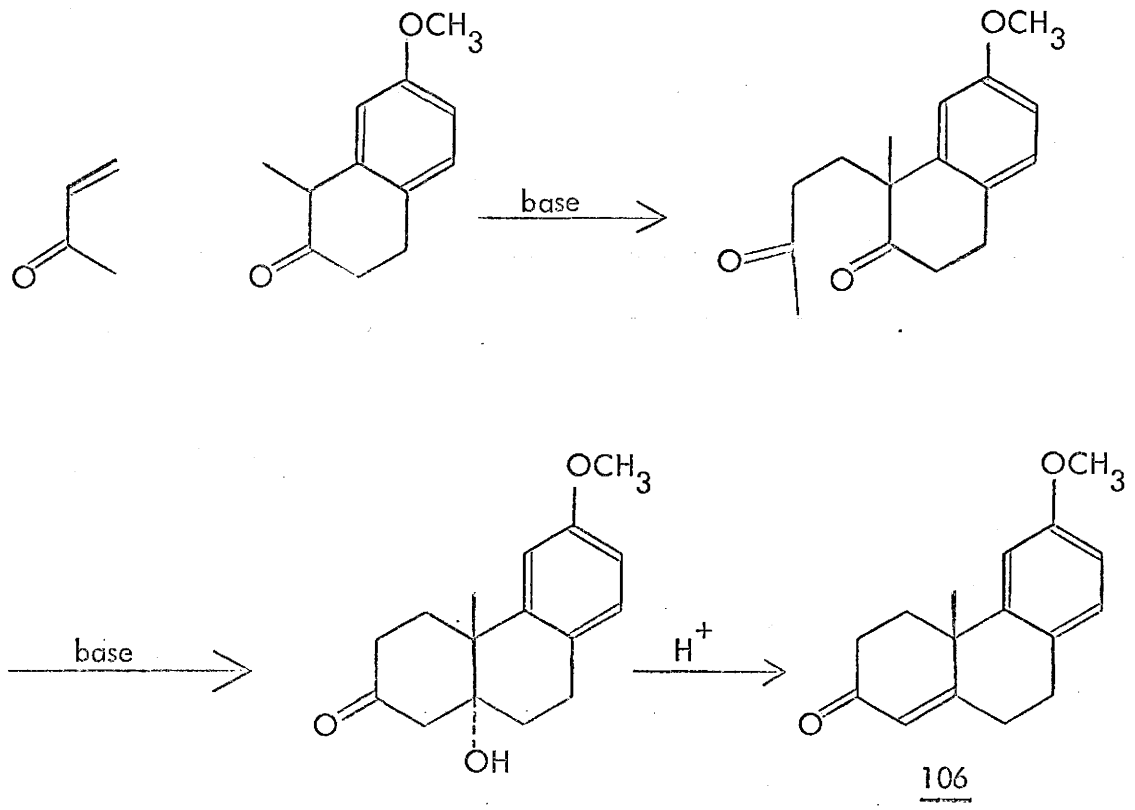
A possible explanation for this trend is that in the absence of a solvent medium, quarternization of the enamine nitrogen would occur by direct displacement on carbon thus removing the lone pair of electrons necessary for the release of the π-electrons of the enamine double bond in C-alkylation.

Initial attempts to construct the tricyclic carbon skeleton 106, led to unsatisfactory results. The Robinson annelation reaction which was used comprises three stages:

(a) the Michael addition of 7-methoxy-1-methyl-2-tetralone to methyl ketone in the presence of a strong base,

(b) cyclization by an intramolecular aldol condensation and

(c) subsequent dehydration of the resulting tertiary alcohol leading to the tricyclic enone.

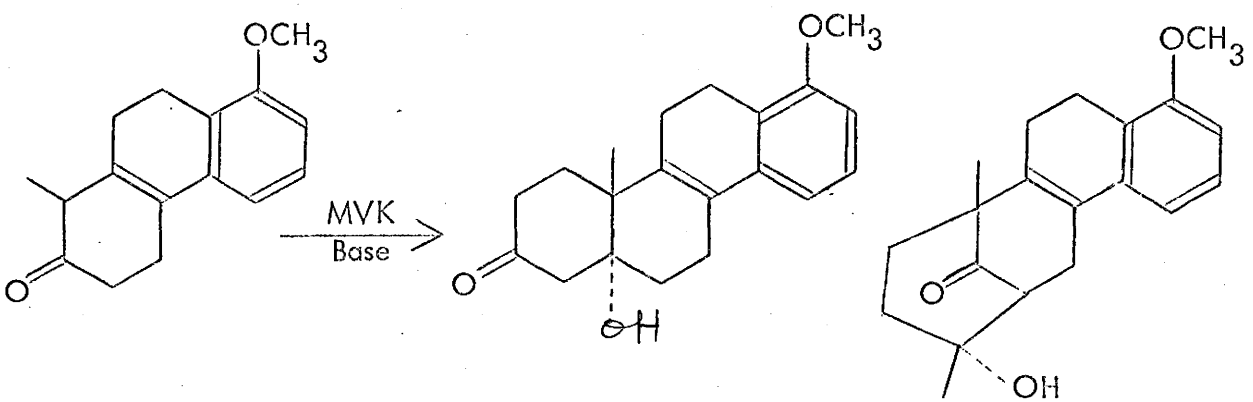


106

The acidity of the C-1 protons and potential conjugation of the double bond with the carbonyl group lead to formation of the double bond exclusively in ring A.

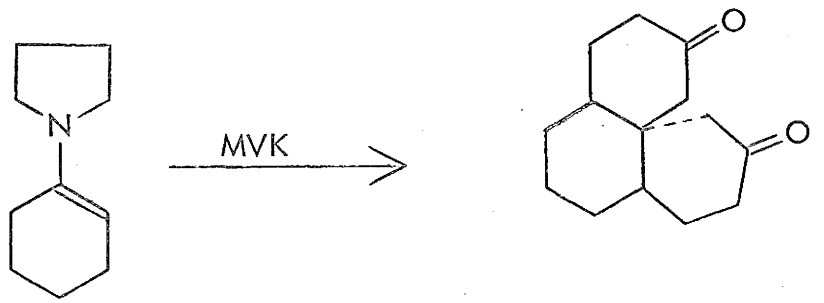
The procedure adopted initially consisted of the introduction of all of the required amount of freshly-distilled methyl vinyl ketone at the beginning of the reaction. This led to much self-condensation of the butenone and, to a considerable extent, the addition of two molecules of butenone to one molecule of the tetralone. The product in most cases was an intractable mixture of the starting material, some of the desired tricyclenone and other compunds of high molecular weight as determined by mass spectrometry. Distillation of such products left sizeable amounts of polymeric material as residue.

Earlier investigators had reported the isolation of anomalous products from similar Michael reactions. These products are easily seen to arise from the addition of two molecules of methyl vinyl ketone to one molecule of the substrate or from lack of cyclization and/or subsequent dehydration in cases where only one molecule of the butenone had added to the substrate. W.S. Johnson and co-workers[136] have identified the compounds xiii and xiv as the products from the Michael addition of the ketone xii to methyl vinyl ketone (MVK).



xii xiii xiv

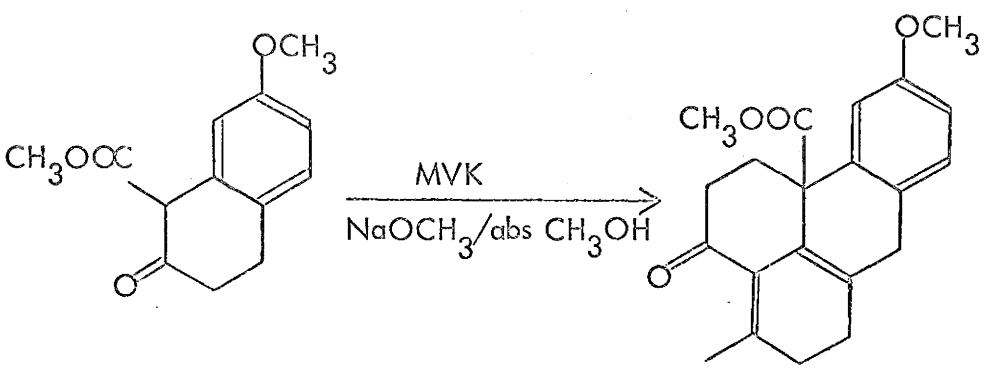
The reaction of the pyrrolidine enamine of cyclohexanone with methyl vinyl ketone in benzene was observed[137] to yield, in addition to the expected products, the saturated diketone xv.



xv

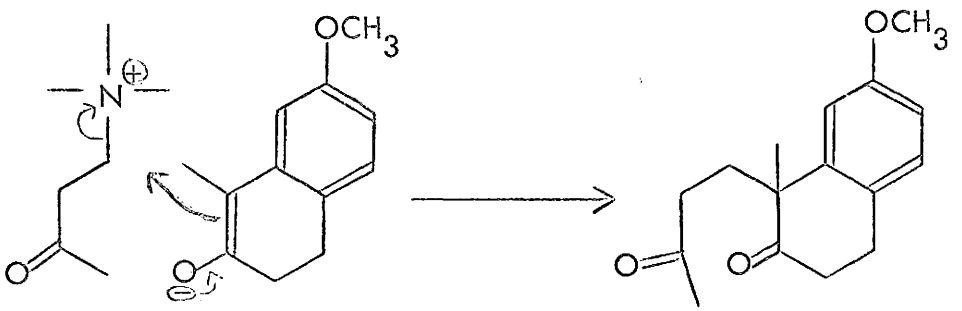
The yield of xv was found to increase in the absence of any solvent.

In the attempted Michael addition of methyl vinyl ketone to the keto-ester xvi Ommen[138] observed that an appreciable proportion of the product was a high molecular weight compound, the spectral data of which suggested the structure xvii.



xvi xvii

The formation of these anomalous products and the accompanying self-condensation of methyl vinyl ketone have been attributed to the high concentration of the butenone in the reaction mixture. To obviate these side reactions, a simple way was devised[124] for generating the four-carbon unit in situ. This involved the initial preparation of 1-N-dialkylamino-3-butanone methiodide as an even coating on the walls of the reaction vessel, followed by the addition of a benzene solution of the substrate and then the dropwise introduction of a solution of an equivalent amount of potassium in excess of anhydrous methanol. The procedure is thought to create the conditions for a direct S_N2 displacement of the amino group by the enolate of the substrate as the first stage in the reaction, thus:



However, Ferry and McQuillin[139] maintain, on the basis of kinetic studies, that the β-keto-alkyl quarternary halide decomposes rapidly in the presence of alkoxides to the butenone. The butenone then sets up an equilibrium with the alcohol in solution and gradually reacts with the enolate of the substrate.

For sometime, diethylaminobutanone was most widely used for this type of reaction until it was observed[123] that piperidinobutanone was a superior reagent

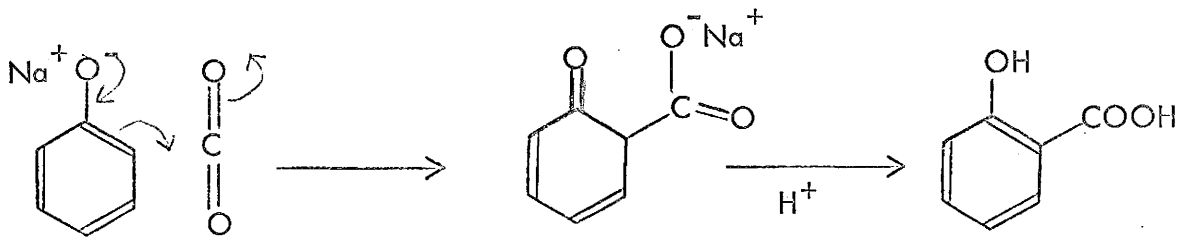
for the generation of butenone. 1-N-Piperidino-3-butanone was prepared in satisfactory yield and the modified procedure afforded consistently good yields (80 - 85%) of tricyclic enone.

ii. Transformations of the Tricyclic Enone

In view of the theoretical considerations already outlined in the introduction (Section II) and the results of earlier investigations, it was necessary to introduce the carboxyl function first at the C-4 position. This approach was expected to ensure that in the event of two stereoisomers arising from the introduction of the methyl group at the C-4 position, the major product would be of the podocarpic acid stereochemistry.

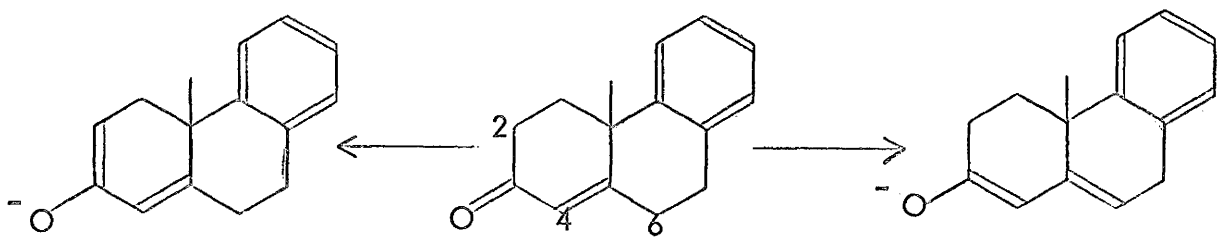
The most effective procedure for the direct introduction of a carboxyl function is the generation of a carbanion at the appropriate centre followed by treatment with carbon dioxide. This procedure has been in use since it was observed that the carbonyl group of carbon dioxide is subject to nucleophilic attack by Grignard reagents and alkyl- or aryllithium compounds. It is currently the basis of the industrial preparation of salicylic acid - the Kolbe-Schmidt reaction[140]. In this case, a solution of phenol in aqueous alkali is evaporated to a dry powder, and the sodium phenolate is saturated with carbon dioxide at 4-7 atmospheres of pressure and heated to 125°, free salicylic acid is liberated on acidification of an aqueous solution of the cooled melt and is obtained in close to the theoretical amount.

The mechanism of this reaction is similar to that postulated for the ortho-alkylation of phenols:



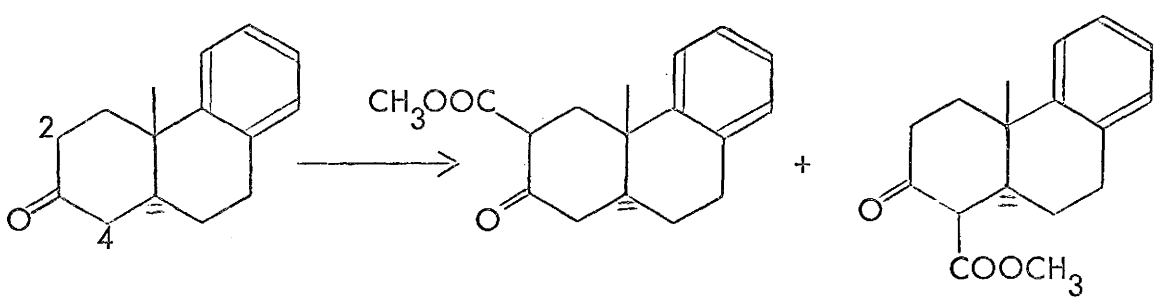
Although reports (eg.[141, 142]) abound in the literature on the alkylation of systems comparable to the tricyclic enone 106, only three publications[55,143,144] have so far been encountered on the direct carbonation of similar systems. The procedure of Wenkert[55] which was essentially the same as that of Robinson and co-workers[143], involved the use of triphenylmethide anion for the generation of the enolate in ethereal solution. These conditions were expected to lead to the irreversible formation of the enolate anion, and in fact were used originally to provide mechanistic information on the first step of the much-utilised t-butoxide-catalysed alkylation reactions of the tricyclic enones.

The possibility that the tricyclic enone xviii could enolize in two different directions, leading to either the homoannular (HM) or the heteroannular (HT) dienoid systems, implied that the enolate anions would undergo carbonation at the C-2, C-4, or C-6 positions (diterpenoid numbering system used). From the kinetically-controlled reaction, Wenkert and co-workers[55] isolated only two crystalline compounds which were identified as products of C-2 and C-4 carbonation,



HM xviii HT

in about equal amounts, with a combined yield of about 50%. This result was not in accord with expectations since the more acidic proton at C-2 was expected to be attacked faster than its counterpart at C-6. Similar carbonation of the saturated ketone xix led to a 7:1 mixture of the products of carbonation at C-2 and C-4, xx and xxi respectively.



xix xx xxi

According to Wenkert's hypothesis, if the transition state of the enolate formation depended on the nature of the starting material, the steric and electronic similarity of the α-hydrogens at C-2 and C-4 in xix would lead to the prediction

that the rates of the production of the enolates leading to xx and xxi would be comparable. If, however, the transition state is mostly dependent on product stability, the enolate leading to xx would be produced more rapidly, and thus high yields of xx could be predicted. It was therefore expected that the thermodynamic control of the carbonation of 106 would lead to predominantly the C-4 carbonation product.

Recent studies[145 - 147] of alkylations in solvents such as dimethylformamide, dimethyl sulfoxide, and 1,2-dimethoxy ethane have shown that substantial increases in the rates of reaction of enolate anions with alkylating agents result from their use in preference to alcohols or inert solvents. Their advantage over protonic solvents lies in the fact that they presumably do not solvate the enolate anions as "tightly" as the protonic solvents do and consequently, do not diminish the enolates' reactivity as a nucleophile. They also, have the ability to solvate the cation, separating it from the cation-enolate ion-pair more efficiently and leaving a relatively free anion in the reaction mixture. The free anion would thus be a more reactive nucleophile. There is convincing evidence that enolate anions exist as ion pairs with cations in the observations[148, 149] that the reactivity of an enolate anion is often influenced by the nature of the cation present.

For the purposes of the investigations discussed herein, it was decided to carry out the carbonation of the enone 106. in the heterogenous system of sodium hydride and 1,2-dimethoxyethane. This procedure was expected to serve the dual purpose of enhancing the predominant formation of the thermodynamically more stable

enolate anion as well as increase its reactivity.

In most of the reactions carried out, a large excess (about 5 equivalents) of sodium hydride was used to ensure the complete conversion of the enone to the enolate anion. It was, therefore, necessary to decompose the unreacted base before the isolation of the carbonated product.

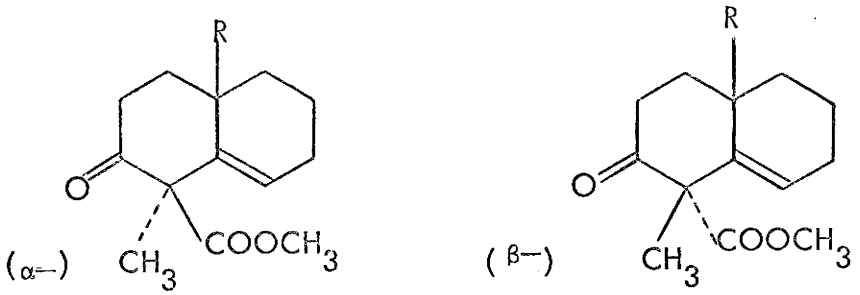
The initial experiments afforded disappointingly low yields of acidic products which were further complicated by the contamination with the starting material although the work-up procedure was aimed at a complete separation of the carbonated products from any possible unreacted material. It was thought that the method of the decomposition of the excess sodium hydride, by the introduction of crushed ice into the reaction mixture at room temperature, might be responsibile for these unsatisfactory results. When the decomposition of sodium hydride was therefore carried out at the temperature (-50°) of the carbonation reaction, there was a remarkable and reproducible improvement both in the yield (of more than 90%) and the purity (complete absence of starting material) of the product.

The unsatisfactory results of the initial experiments must be, therefore, due to extensive decarboxylation of the potential product induced by the heat generated during the decomposition of sodium hydride. Product analysis was conducted mainly by the observation of the proton magnetic resonance spectra of the crude isolated materials. In no case was there evidence of product arising from carbonation at the C-2 position. The yields from the improved reactions suggested that almost complete enolization of the substrate was achieved in the

medium employed.

The methylation of the C-4 keto-ester was carried out under the same conditions as Wenkert[57] used since it was intended, at the start of this work, to examine his hypothesis of stereoelectronic control of alkylation in such systems. The proton magnetic resonance spectrum of the crude methylation product (obtained in about 95% yield) showed the presence of two components in the ratio of 4:1. The major component, 108 was shown to be of the podocarpic acid stereochemistry in view of its subsequent transformations to a product which was identical with that of authentic methyl O-methylpodocarpate - obtained from natural sources.

The minor product was assigned the abietic-type (β-CH_3 at C-4) stereochemistry on the following grounds: Previous similar alkylations induced with potassium t-butoxide were not observed to lead to C-2 alkylations. The sole formation of the enolate anion involving the Δ^4-double bond is further enhanced by the carbomethoxyl substituent at C-4. Finally, support for such an assignment comes from the recent observations of Bottom and McQuillin[69] that compounds with similar arrangements of rings A and B as in the diterpenoid resin acids, but differing only in their stereochemistry at the C-4 position can be distinguished on the basis of the chemical shift of the C-4 methyl group. The α-methyl (podocarpic-type stereochemistry) invariably appears at a lower magnetic field strength than the β-methyl (abietic-type) as in the following examples. A similar trend was also observed[150] in the chemical shifts of α- and β- C-4 methyls of the 3-keto A/B trans compounds in the resin acid field.



R	α - CH_3(δ)	β-CH_3 (δ)
CH_3	1.26	1.08
COOH	1.32	1.18

The C-4 methyl of the minor product appeared at 1.48 ppm while that of the major product appeared at 1.52 ppm in the pmr spectrum of the crude methylation product. It has not been possible to obtain a crystalline sample of the minor component to rigorously establish its stereochemistry. Enriched non-crystalline samples found in the mother liquors always contained large amounts of the major isomer.

Hydrogenation of the Δ^5-double bond of 108 was readily accomplished with palladised charcoal in glacial acetic acid at atomspheric pressure, and afforded a single component (by TLC). This on thioketalization followed by desulfurization of the thioketal by active Raney nickel in absolute ethanol afforded a single compound the pmr spectrum of which was identical with that of authentic methyl

O-methylpodocarpate.

In view of the facility with which methyl O-methylpodocarpate is converted to podocarpic acid, in quantitative yield, by refluxing in acetic acid in the presence of 48% hydrobromic acid, the sequence constitutes a total synthesis of Podocarpic Acid.

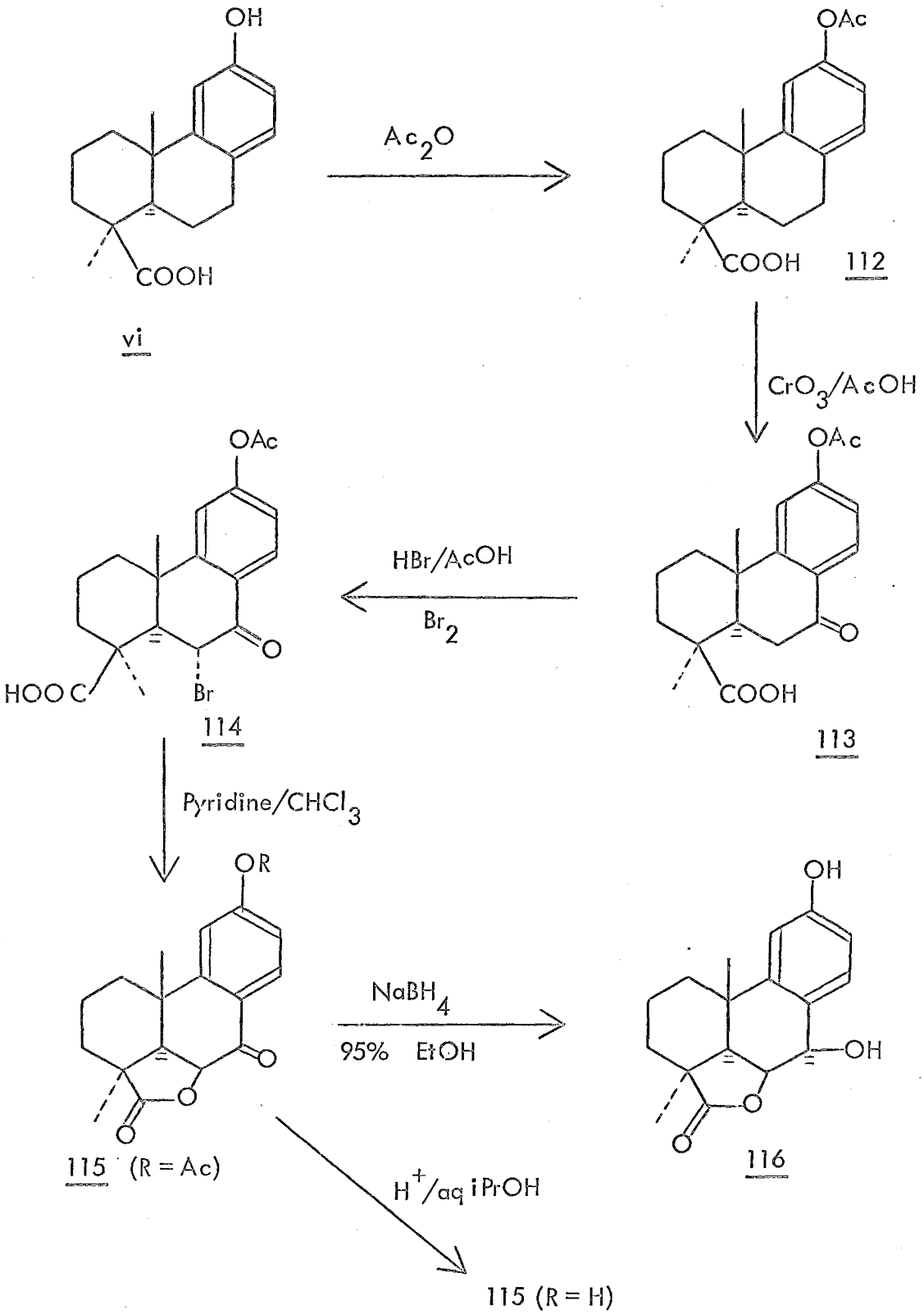
B. TRANSFORMATIONS ON PODOCARPIC ACID

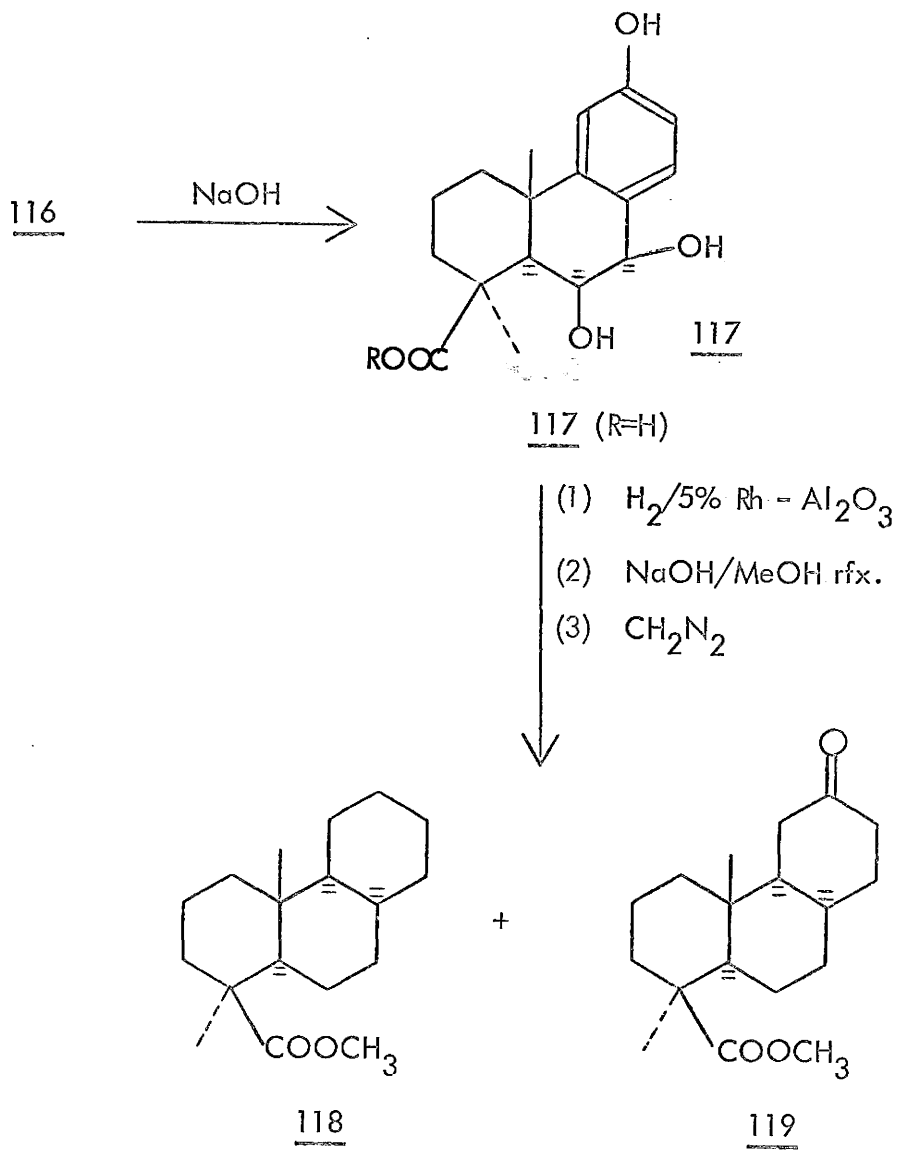
In view of the recent discoveries of lactonic diterpenoids structurally related to podocarpic acid in the A/B ring system, it became worthwhile to develop a reliable procedure for the functionalization of ring B with the aim of constructing the 19,6-lactone ring in satisfactory yield. For this purpose, the naturally occurring podocarpic acid vi was employed as the starting material since it was readily available[151] in appreciable quantity.

The reaction sequence explored is summarized in scheme XVII.

The allylic C-7 position was considered the best point of entry intro ring B by oxidation. Since phenols and aromatic amines are readily oxidized to quinones and, with excess oxidant, to carbon dioxide and water[152], the successful selective oxidation of the C-7 position depended on the protection of the phenolic group. This was readily achieved by acetylation using the procedure of Sherwood and Short[5] which invariably afforded satisfactory (90%) yield.

Chromic acid oxidation of the acetoxy product,[112], was carried out by the method of Wenkert and Jackson[30]. Except for the problem of purifying the crude product from the contaminating chromium salts, this reaction consistently afforded very satisfactory yields (95%) of the 7-keto derivative 113. On one occasion when chloroform was used to extract the crude oxidation product, it was impossible to obtain a pure sample of the keto-compound by any means.


OH
COOH
vi
Ac_2O
OAc
COOH
112
CrO_3/AcOH
OAc
COOH
113
HBr/AcOH
Br_2
OAc
HOOC
Br
114
Pyridine/$CHCl_3$
OR
115 (R = Ac)
$NaBH_4$
95% EtOH
OH
OH
116
H^+/aq iPrOH
115 (R = H)


116
NaOH
OH
OH
OH
ROOC
117
117 (R=H)
(1) H_2/5% Rh - Al_2O_3
(2) NaOH/MeOH rfx.
(3) CH_2N_2
COOCH$_3$
COOCH$_3$
+
118
119

SCHEME XVII

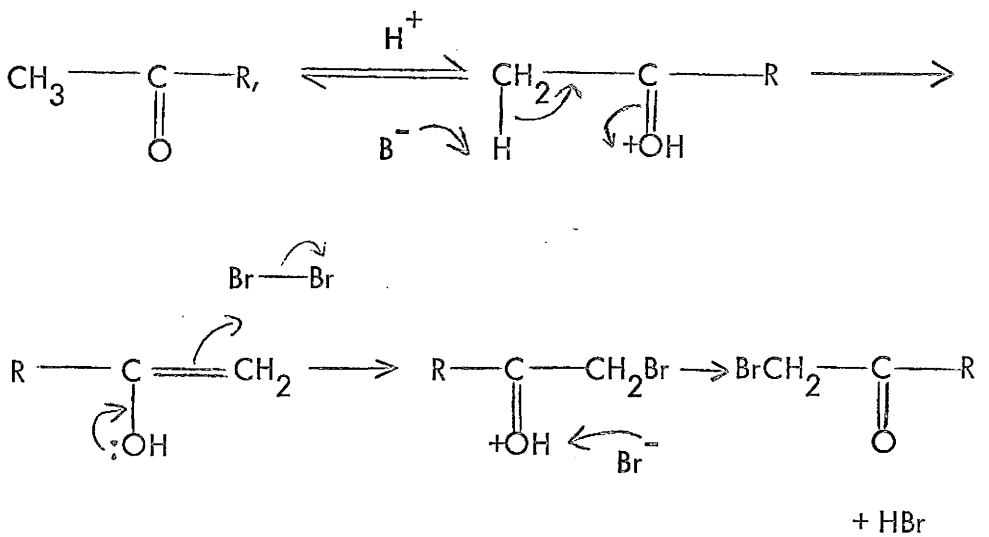
In the attempts to prepare 7-keto derivatives of similar monobenzenoid tricyclic compounds, Mori and Matsui[153, 154] considerably modified Wenkert's procedure by the addition of disproportionately large volume of water and in addition heating the oxidation mixture to about 65° for one hour. The desired 7-keto compounds were obtained in remarkably low yields due to excessive oxidation leading to 5α-hydroxy-6,7-diketo derivatives.

At about the same time as this work was in progress, other workers[155] reported the attempts to introduce the oxygen function into the C-7 position of O-methyl-podocarpic acid by lead tetra-acetate oxidation. These attempts invariably led to mixture of several compounds in very low yield.

The reproducible high yield of the 7-keto derivative, 113, obtained in this work (with the acetoxy group on the aromatic ring) is worthy of note. This is in remarkable contrast to the results obtained with a methoxyl in place of the acetoxy group. A satisfactory explanation has not been deduced for this observation.

During earlier attempts to prepare the 5,6-dehydro derivatives of the methyl esters of the resin acids, Wenkert[76] observed that the collidine treatment of the 6-bromo-7-keto esters led to mixtures of keto-lactones and the expected unsaturated .....

ketones. These unusual dehydrobromination results thus led to the suggestion that the bromine atom in these compounds was most probably in an α-configuration. This stereochemistry is predictable on the basis of the accepted mechanism for the bromination of ketones. The reaction of a ketone with bromine is generally accepted as proceeding by the acid-catalysed enlozation of the ketone followed by electrophilic attack of the enol by a bromine molecule. Loss of a proton from the intermediate oxonium ion leads to the bromo-ketone, according to the following scheme.



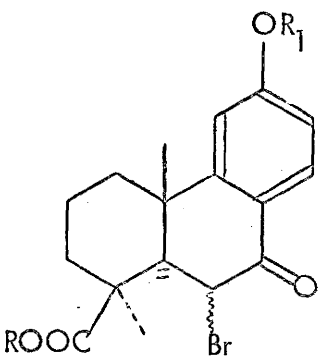
In the bromination of podocarpic acid, the resulting 6,7-enol would be susceptible to attack by the bromine molecule mainly from the α-side of the molecule in view of the prohibitive steric interference due to the axial C-4 carboxyl function and the C-10 methyl group. On the basis of the above considerations, bromination of the

6-position of 7-keto-12-acetoxypodocarpic acid, 113 was expected to yield predominantly the α-bromo derivative.

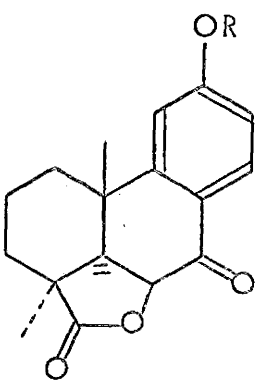
Bromination in the aromatic ring, already substantially inhibited by the presence of the acetate and the carbonyl substituents on the ring, was further prevented by the introduction into the reaction mixture, of a solution of small amounts of sodium thiosulfate and sodium acetate to destroy the slight excess of bromine with which the reaction had been stirred for ten minutes at room temperature. This was followed by further dilution of the reaction solution with a large excess of water leading to complete precipitation of the product. The products of these reactions, however, were invariably a mixture of the desired bromo-ketone and what was identified from its infrared spectrum to be a lactone ($\nu_{max}^{CHCl_3}$ 1770 cm^{-1}). Stirring this mixture in some 10% aqueous acetic acid for a few hours led to complete lactonization.

It became necessary to modify the procedure in order to obtain a pure sample of the bromo-ketone, Wenkert's original procedure, of evaporating the excess bromine together with the solvent (acetic acid), at reduced pressure on a lukewarm water bath, was adopted. The bromo-ketone of the free acid was obtained pure and in quantitative yield. The proton magnetic resonance spectrum of the pure bromo-ketone showed, among others, the C-6 proton as the doublet centred at 6.1 ppm with a coupling constant of 7 Hz (due to coupling with the C-5 hydrogen). These results were in firm agreement with those of Bible[77] and those of Cambie and co-workers[156].

While the orientation of the bromine atom in these 6-bromo derivatives of the diterpenoid resin acids was not conclusively established, all available evidence led to the general assumption of an α-configuration. This assumption was recently questioned by Wheeler[157]. Not long after, an x-ray structure determination of methyl 6-bromo-7-keto-O-methylpodocarpate xxii ($R=R_1=CH_3$) showed unequivocably that in the solid state of the molecule, the bromine atom possesses an α-configuration and the central ring (ring B) adopts a classical boat conformation[158].



xxii



115

It has also been established in this work[159] by nuclear Overhauser experiments that the C-6 bromine in a related compound, xxii ($R=CH_3$, R_1=AC), has the α-configuration in solution.

Until recently, the kinds of information which organic chemists have used from nmr spectroscopy have been restricted to chemical shift and spin-sping coupling data. It is now realized that there is additional valuable information available from spectral properties which have their origin in magnetic relaxation. The so-called Nuclear Overhauser Effect (NOE)[160 - 163] is one such property.

Specifically, the spin-dipole relaxation time constant, T_1 (longitudinal relaxation time), for a given nucleus has contributions from a number of sources such as inter- and intramolecular dipoles, external fluctuating fields, external paramagnetic species etc. If any of these sources of relaxation of a nucleus be perturbed, or even completely removed, changes in the observed value of T_1 will result. Although it is possible to measure values of T_1, for example by spin-echo techniques, it is more convenient experimentally to observe other parameters which are related to T_1. One such parameter is the area under an absorption signal.

Thus, if, for example, the spectrum of a compound is recorded under frequency sweep conditions and the areas of the signals carefully measured, it is observed that the application of a second saturating rf field to a particular signal results in changes in the areas of some of the remaining signals. This is one of the observable results of a nuclear Overhauser effect. This effect is found to operate (at least in proton systems) if there are protons which are within 3.0 Å of each other, but not observable for protons which are more than this distance apart.

What is done experimentally is to change (increase) the spin-lattice relaxation time T_1 for a proton H_A by saturating one of its neighbouring protons, H_B, and therefore removing H_B as a source of dipole relaxation. If the two protons are in the same molecule, an intramolecular Overhauser effect operates, and if they are in different molecules it is an inter-molecular Overhauser effect. The interpretation of the latter effect is complicated by the fact that the relative positions of H_A and H_B will be time-dependent, although its further study should prove of great value in

the problem of solvent-solute interactions. The intramolecular Overhauser effect is relatively more easily examined especially in the case of organic molecules with fairly rigid structures in which the relative positions of the protons are invariant.

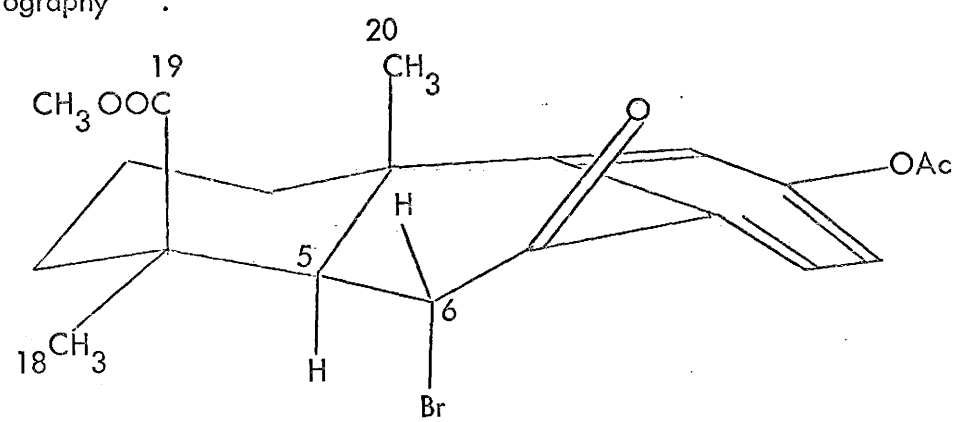
The observation of intramolecular NOEs in xxii ($R=CH_3$, R_1=Ac) served not only to define precisely the configuration of the 6-bromine atom but also to give invaluable information on the preferred conformation of ring B in solution. In this particular case, the area of the C-6 hydrogen was measured while a second saturating field was applied to the transitions of spatially proximate nuclei. The outcome of these investigations have been a further demonstration of the power of this method in stereochemical and conformational analysis.

The data which were obtained for an 0.21 M solution of xxii ($R=CH_3$, R_1=Ac) in carbon tetrachloride and for an 0.2M solution in perdeuterio-acetone were essentially identical and are shown in Table II.

Protons Saturated	% Area Increase of C-6 proton	Internuclear Distance Å *
C-5H	4-5	2.95
20 - CH_3	10	2.6
18 - CH_3	21	2.3
O - CH_3	2-3	3.0

* As measured from a Drieding Molecular Model.

The fact that any NOE was observed on saturation of the 20-methyl absorption indicates that the 6-proton must be on the same side of the molecule as the 20-methyl group, that is, the bromine possesses an α-configuration. To place the bromine atom in a β-configuration would mean that the 20-methyl and the C-6 hydrogen would be at least 3.5Å apart and this distance is too great to permit any observable NOE[160]. The 21% NOE observed on saturation of the 18-methyl group is considerably greater than the 10% observed with the 20-methyl group. This implies that the C-6 proton is closer to the 18-methyl than to the 20-methyl group and therefore that the preferred conformation of ring B in solution must be a boat or a twist-boat conformation (see diagram below) as has been found in the solid state by x-ray crystallography[158].



The above configurational and conformational assignments are further supported by the chemical reactivity of the parent acid, xxii (R=H, R_1=Ac), which could be isolated from carefully controlled bromination reactions and recrystallized from methanol as has been commented on above. The ease with which the bromo-acid undergoes quantitative lactonization in mildly acidic or basic solutions, at

room temperature, is typical[164] of an intramolecular S_N2 displacement reaction. Here the carboxyl oxygen can readily adopt a collinear position with the breaking carbon-bromine bond. The inspection of a molecular model indicated that this requirement can be met if the bromine possesses an α-configuration and if ring B exists either in a boat conformation or can adopt such a conformation with the expenditure of very little energy.

The preparation of the lactone 115 (R=Ac) via xxii (R=H, R_1=Ac) is by far the most satisfactory procedure for preparing similar (19,6-) γ-lactones of the resin acids. Most other approaches reported in the literature were often characterized by remarkably low yields or by the formation of desired lactone as one in, sometimes, a difficultly separable product mixture. Wenkert's collidine treatment of the bromo-keto-ester xxii ($R=R_1=CH_3$)[76] afforded about 30% of the lactone 115 ($R=CH_3$) as part of a mixture of the starting material and the 5,6-dehydro derivative. Application of Wenkert's procedure by Wheeler and his group[157] le d to similar results.

Other investigators[155, 165, 166] have attempted the preparation of similar γ-lactones of the diterpenoid resin acids by the application of the photochemical lactonization reaction of saturated and unbrominated acids, developed independetly by Barton[167] and Petterson[168]. This method involves the conversion of the acids, through the acid chlorides, to amides. These are then irradiated in dry benzene with low pressure mercury lamps in the presence of lead tetraacetate-iodine reagent. The yields were invariably poor (less than 10%) and were, in some cases, complicated by the formation of δ-lactones involving the 20-carbon atom. These poor results

cannot be explained in terms of lack of stability of the 19,6-lactone group since that of 115 (R=Ac) is stable to sodium borohydride reduction mixture (pH 11) at room temperature for 24 hours.

The reduction of a large number of cyclic ketones with metal hydrides have been studied in the past, but the stereochemical outcome of these reactions has always been difficult to predict. Two factors were initially suggested[169] to be important: steric hindrance to the approach of the carbonyl function, called steric approach control; and the stability of the final product, called product-development control. An alternative rationalization based on pure steric approach was also put forward[170] independently at about the same time.

Recent investigations[171, 172], however, have led to the interpretation of the product composition in these reactions on the basis of eclipsing effects and torsional strain arising from partial bonds in the transition states of the reactions. The more recent kinetic studies of Eliel and co-workers[173], tend to support this later interpretation.

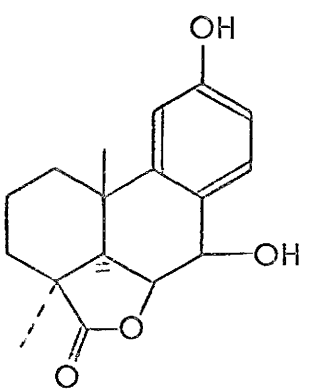
The sodium borohydride reduction of the keto-lactone 115 (R=Ac) consistently afforded a single product in more than 90% yield. Considering that the β-side of the molecule is highly hindered by the presence of three axial substituents, it has been assumed that the only approach of borohydride to the carbonyl is from the α-side, thus leading to the β-(equatorial) hydroxyl group at C-7. The relative stability of the lactone ring is demonstrated by the fact that, in all cases, the phenol acetate was hydrolysed to the phenol during the borohydride

reduction reaction while the lactone was unaffected.

The hydrogenation of the aromatic ring C of 6- and 7-oxygenated podocarpic acids posed a serious problem in view of the highly probable hydrogenolysis of these oxygen functions. Several groups of investigators[174 - 178] had noted the ease with which allylic and benzylic amines and alcohols are hydrogenolysed in the presence of the most common catalysts. However, rhodium and rhuthenium catalysts were observed[179 - 182] to effect satisfactory reduction of aromatic rings with minimum hydrogenolysis of benzylic-oxygen and nitrogen functions.

Stocker[180] reported satisfactory to excellent results in the reduction of benzyl alcohol to cycloheyxyl carbinol using 1.5 g of 5% rhodium-on-alumina for every 50 mmoles of the compound, at 3-4 atmospheres of hydrogen and room temperature, in 95% ethanol containing 1% of glacial acetic acid. Higher percentages of water was observed to lead to considerable deactivation of the catalyst.

Initial attempts at the hydrogenation of the aromatic ring in the hydroxy-lactone 116 were therefore carried out according to the procedure of Stocker but without success.



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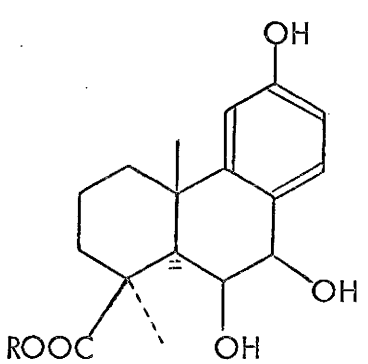

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The conditions of the reaction were gradually altered, one at a time, without significant improvement in the results. When the reaction was carried out at about 70° in glacial acetic acid, complete reduction of the aromatic ring was achieved as could be seen from the pmr spectrum of the product, but the multiplet pattern due to the C-6 and C-7 hydrogens of the hydroxy-lactone (δ 4.5 - 5.1 ppm) had disappeared. This suggested that extensive hydrogenolysis, not only of the C-7 hydroxyl, but also of the C-6 lactone, had occurred. The infrared spectrum of the acetic acid-free reduction product showed that the carbonyl absorption had moved from 1770 cm^{-1} to about 1680 cm^{-1}.

Both 7-keto and 7-hydroxypodocarpic acid were in turn subjected to the initial reduction conditions and complete hydrogenation of the aromatic ring was invariably accompanied by complete hydrogenolysis of the C-7 oxygen function. However the observation that these non-lactonic derivatives hydrogenated under much milder conditions than the lactonic derivatives prompted the speculation that the presence of the lactone ring on the β-side of the molecule heightened the importance of steric effects in the hydrogenation of the aromatic ring.

Early studies by Linstead[183] and by Fieser[184] of the hydrogenation of phenanthrene and diphenic acid derivatives over platinum catalyst led to the concept that the less hindered side of an unsaturated molecule is adsorbed on the catalyst surface. The adsorption was thought to be followed by the simultaneous transfer of two or more hydrogen atoms from the catalyst to the adsorbed molecule and subsequent desorption of the reduced molecule. This concept led to the useful generalization that catalytic hydrogenation of a multiple bond results in the cis

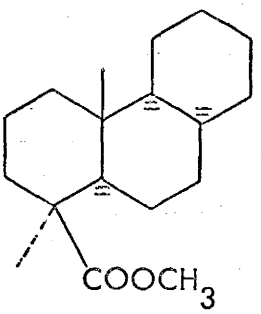
addition of two hydrogen atoms from the less hindered side of the multiple bond.

The considerable unreactivity of the lactone derivatives towards the hydrogenation reactions was interpreted as due to lack of sufficient contact between the aromatic ring and the catalyst surface. This would arise from steric factors. Considering that the β-side of the molecule is excessively crowded, it is quite obvious that the approach of the molecule to the catalyst surface from this side would be extremely difficult. Furthermore, the five-membered lactone ring would tend to pull rings A and B towards each other on the β-side. Thus a tendency for the aromatic ring to "bend away" from the severely crowded side of the molecule, along the 8,9-bond, would render the α-side of the aromatic ring difficultly accessible to the catalyst surface.

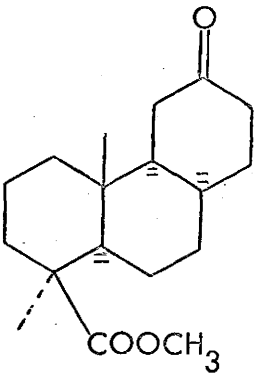
Opening of the lactone ring was considered a possible way of relieving the steric constraint as the molecule would flatten out. This was readily achieved by the procedure of Tahara and co-workers[126].

Attempts to reduce the 6,7-dihydroxy acid, 117 (R=H) under the same initial conditions as for the lactone were unsuccessful. When hydrogenation was carried out in glacial acetic acid in the presence of 0.25% of perchloric acid, at room temperature and three atmospheres of hydrogen for 48 hours, the product was found to be a mixture, the two main components of which were identified as 118 (65%) and 119 (20%)

Thus it would appear, from the experience gained in this work, that catalytic reduction of the aromatic ring of C-6 and C-7 functionalized podocarpic acid



118



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derivatives does not provide a satisfactory pathway towards the elaboration of the C,D ring system of the kaurane skeleton. The aromatic ring of podocarpic acid is readily reduced under relatively mild conditions; but when the functional groups have been introduced in the C-6 and C-7 positions, the minimum conditions required to achieve the reduction of the aromatic ring are so drastic that these functional groups are also removed.

Alternative approaches to the reduction of the aromatic ring are readily envisaged, for example Birch reduction, but these methods were not explored in this work.

SUMMARY

A total synthesis of Podocarpic Acid has been accomplished. The reactions used in the sequence were improved to afford more than 80% of the intermediate products. The results of the methylation of the unsaturated keto-ester 107 were not in accord with Wenkert's hypothesis of stereoelectronic control of the alkylation of similar systems.

A reliable procedure has been developed for the introduction of functional groups in the C-6 and C-7 positions in ring B. Nuclear Overhauser experiments were employed to establish unequivocally, that the bromine atom in the 6-bromo-7-keto derivative xxii ($R=CH_3$, $R_1=Ac$) has the α-configuration in solution.

The construction of the 19,6-lactone ring in quantitative yields has opened up avenues towards the syntheses of recently discovered bicyclic and tetracyclic lactonic diterpenoids.

The results of attempted catalytic reduction of the aromatic ring C after the functionalization of ring B suggest that steric factors become so great as to prevent hydrogenation under the same conditions in which podocarpic acid is readily reduced. The conditions required for the successful catalytic reduction of the aromatic ring were so drastic that the functional groups present in ring B were also removed.

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