SOME ASPECTS OF TERPENOID CHEMISTRY

A thesis submitted to the

Board of the Faculty of Physical Sciences

in the

University of Oxford

in partial fulfilment of the requirements for

the degree

Doctor of Philosophy

by

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December 1971.

When you have eliminated alkaloids, carbohydrates, flavonoids, lignans, lipids, nucleosides, peptides, polyketides, quinones and steroids; whatever remains, however improbable, must be a terpene.

With apologies to

Sir Arthur Conan Doyle

ABSTRACT

The chemotaxonomy and the biosynthesis of tetranortriterpenes is briefly reviewed in chapter one and the partial syntheses of some of these products is described.

The work described in the first part of chapter two was directed towards a synthesis of the γ-lactone ring system in the side chain of flindissol, while that in the latter part involved studies of the allylic oxidation in ring D of some apotirucallol derivatives.

The acid constituents of Manila elemi resin were separated and methyl 3α-acetoxytirucalla-8,24-dien-21-oate (1) was then converted to 3β-acetoxy-tirucall-8,24-dien-21-oic acid. Bromination of this acid resulted in low yields of the dibromide and an explanation for this was put forward.

The action of ammonia on the acyl chloride of 3α-acetoxytirucalla-8,24-dien-21-oic acid followed by reaction with lead tetra-acetate and iodine led to formation of 3α-acetoxy(21-24)cyclotirucalla-7,9(11),24-trien-21-one. Reaction of 3α-acetoxytirucall-8-en-21-amide with lead tetra-acetate and iodine resulted in formation of 3α-acetoxytirucalla-7,9(11)-dien-21-isocyanate and explanations for these results are given.

Ozonolysis was used extensively during this work and the mechanism of ozonolysis is discussed. Treatment of a mixture of methyl 3α-acetoxytirucall-7 and 8-en-21-oate with ozone gave three products, methyl 3α-acetoxy-7α,8α-epoxytirucallan-21-oate (2), methyl 3α-acetoxy-7-oxotirucall-8-en-21-oate

and methyl 3α-acetoxy-7,11-dioxotirucall-8-en-21-oate. The 7α,8α-epoxide (2) was rearranged with boron trifluoride and acetylation of the product gave methyl 3α,7α-diacetoxyapotirucall-14-en-21-oate (3).

A crude mixture of dibromo elemi acid methyl esters was ozonised and reductive work up gave four products, (13αH)ursan-3,12-dione, methyl 3,7-dioxotirucalla-8,24-dien-21-oate, methyl 3,7,11-trioxotirucalla-8,24-dien-21-oate and methyl 7α-bromo-3,15-dioxo-(14αH)apotirucall-24-en-21-oate (4). Similarly ozonolysis of a crude mixture of methyl 3α-acetoxy-24,25-dibromotirucall-7 and 8-en-21-oate and reductive work up gave a mixture of seven products. Methyl 3β-acetoxy-12-oxo-(13βH)ursan-28-oate, methyl 3α-acetoxy-7α,8α-epoxytirucall-24-en-21-oate (5), methyl 3α-acetoxy-7α-bromo-15-oxo-(14αH)apotirucall-24-en-21-oate (6), methyl 3β-acetoxy-11-oxours-12-en-28-oate (7), methyl 3α-acetoxy-7,11-dioxotirucalla-8,24-dien-21-oate, methyl 3α-acetoxy-7-oxotirucalla-8,24-dien-21-oate and methyl 3α-acetoxy-14β,15β-epoxy-7α-hydroxyapotirucall-24-en-21-oate (8). The structure and mechanism of formation of (7) and (8) is discussed. The crude 7α,8α-epoxide (5) was rearranged with boron trifluoride and acetylation of the product gave methyl 3α,7α-diacetoxyapotirucalla-14,24-dien-21-oate (9). The structure and mechanism of formation of the two 7α-bromides (4) and (6) is discussed.

Reaction of methyl 3α-acetoxy-24,25-dibromotirucall-8-en-21-oate with tetramethylammonium acetate gave methyl 3α-acetoxy-24-bromotirucalla-

8,24-dien-21-oate which was reduced to 24-bromotirucalla-8,24-dien-3α,21-diol and reduction of this diol gave tirucall-8-en-3α,21-diol.

Oxidation of (1) with iodine and iodic acid in aqueous dioxan and acetylation of the products gave methyl 3α-acetoxy-24§,25-epoxytirucall-8-en-21-oate and methyl 3α,24§-diacetoxy-25-hydroxytirucall-8-en-21-oate which was hydrolysed to methyl 3α,24,25-trihydroxytirucall-8-en-21-oate.

Bromination of (9) gave methyl 3α,7α-diacetoxy-24,25-dibromoapotirucall-14-en-21-oate (10) in 38% yield. Oxidation of this dibromide with selenium dioxide gave what is thought to be the 14,15-diol and the mechanism of oxidation with selenium dioxide is discussed. Treatment of (3) with bispyridinechromium oxide and also with aqueous N-bromosuccinimide gave methyl 3α,7α-diacetoxy-16-oxoapotirucall-14-en-21-oate in good yield. Similarly oxidation of (10) with bispyridinechromium oxide gave the 14-en-16-one in good yield but after debromination, methyl 3α,7α-diacetoxy-16-oxoapotirucall-14,24-dien-21-oate decomposed on attempted purification.

Deoxygenation of havanensin triacetate with a zinc-copper couple deoxyhavanensin triacetate in good yield but attempts to oxidise this alkene with either selenium dioxide or bispyridinechromium oxide were unsuccessful. Oxidation of this alkene with aqueous chromic acid gave isophotodeoxyhavanensin triacetate.

The literature of the chemistry of some pentacyclic triterpene-12-ketones

is discussed in chapter three together with the structures of some new 12-ones and their o.r.d. curves and mass spectra.

The triterpene lupeol was used as a model system to construct the 1α,3α-diacetate group common to the meliacins and this work is described in chapter four. Lupeol benzoate was firstly converted to lupan-3-one. Treatment of lupan-3-one hydrazone with lead tetra-acetate gave 5(4 → 3)-abeolup-3-ene and the mechanism of this reaction is discussed. Bromination of lupan-3-one gave a mixture of 2(α and β)-bromolupan-3-ones which was dehydrobrominated to lup-1-en-3-one. Epoxidation of this enone with hydrogen peroxide gave 1α,2α-epoxylupan-3-one which on rearrangement with hydrazine gave lup-2-en-1α-ol. Epoxidation of this alcohol gave 2α,3α-epoxylupan-1α-ol which was reduced with lithium in ethylamine to lupan-1α,3α-diol. The yield of this diol was greater by this route than by reduction of 1α,2α-epoxylupan-3-one. The o.r.d. of some lupan-3-ones is also discussed.

The structure of a new diterpene furan and an attempt to synthesise this product from sclareol is described in chapter five.

Oxidation of sclareol with chromic acid in acetic acid gave norambreinolide and 8α-acetoxy-13,14,15,16-tetranorlabdan-12-oic acid. Methanolysis of norambreinolide gave a 1:1 mixture of starting material and methyl 8α-hydroxy-13,14,15,16-tetranorlabdan-12-oate and a synthetic route via this ester was not pursued.

Reduction of norambreinolide gave 13,14,15,16-tetranorlabdan-8α,12-diol which gave 8α-acetoxy-13,14,15,16-tetranorlabdan-12-yl acetate on acetylation. Dehydration of this acetate with phosphoryl chloride gave a mixture of 13,14,15,16-tetranorlabd-7 and 8(17)-en-12-yl acetates. Hydrolysis of this mixture and oxidation of the alcohols with silver carbonate gave a mixture of 13,14,15,16-tetranorlabd-7 and 8(17)-en-12-als. Reformatsky condensation of these aldehydes with ethyl α-bromoacetate gave a mixture of ethyl 12 - hydroxy-15,16-dinorlabd-7 and 8(17)-en-14-oates.

Treatment of this mixture of hydroxyesters with o-monoperphthalic acid gave pure ethyl 12§-hydroxy-15,16-dinorlabd-8(17)-en-14-oate, together with ethyl 7α,8α-epoxy-12§-hydroxy-15,16-dinorlabdan-14-oate. The C-12 epimers of these products were separated and their spectra and the configuration of these epimers at C-12 is discussed.

Oxidation of ethyl 12§-hydroxy-15,16-dinorlabd-8(17)-en-14-oate gave ethyl 12-oxo-15,16-dinorlabd-8(17)-en-14-oate. Reaction of this β-keto-ester with 1,2-dichloroethyl ethyl ether and aqueous sodium hydroxide gave only traces of a furan while in triethylamine, a mixture of products was obtained. From these results it was concluded that a different approach to synthesis of the furan ring may be necessary.

ACKNOWLEDGEMENTS

The author would like to thank

Professor Sir Ewart R.H. Jones F.R.S. for the opportunity of carrying out research work in the Dyson Perrins Laboratory, and for his interest in this work;

Dr. T. G. Halsall for his supervision;

Mrs. E. Richards for comments on the practical determination of n.m.r. spectra;

Dr. R. T. Aplin for comments on the interpretation of mass spectra;

Dr. P. M. Scopes, Westfield College, London, for the determination of o.r.d. and c.d. curves;

Miss P. A. Wilmot for typing this thesis; and

The Chemistry Division of the Department of Scientific and Industrial Research, New Zealand, for financial assistance.

NOMENCLATURE

The terpenoid nomenclature used in this thesis is that which has been tentatively proposed for steroids,[1] and the numbering system is shown for tirucalla-8,24-dien-3β-ol (1).

For the more highly oxidised triterpenes, those possessing an intact side chain and either a Δ^{7}-tirucallene or a Δ^{14}-apotirucallene nucleus, are referred to collectively as protoazadirane derivatives; those possessing an apotirucallane nucleus and a 17α-(β-furan) side chain, as azadiran es; those having the 17α-(β-furan) side chain, together with an intact ring A, and a ring D δ-lactone, as meliacins; and those meliacins which have undergone cleavage in ring A, as limonoids. Further differentiation for the aphanamixinin (109), mexicanolide (111), methyl angolensate (118) and nimbin (77) derivatives is unnecessary for this thesis.

The numbering system, used for lupane derivatives,[2] is shown for lup-20(29)-en-3β-ol (2) and that for ursane derivatives is shown for α-amyrin (3).

The numbering system for the diterpenoids is that which has been proposed by Rowe,[3] and is shown for labd-14-en-8α,13R-diol (sclareol) (4).

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CHAPTER ONE

THE INTRODUCTION

1.1 THE TETRANORTRITERPENES AND RELATED COMPOUNDS

The meliacin, limonoid[4] and simaroubalide[5] bitter principles are a class of degraded triterpenes,[6] which arise by considerable oxidation of a simple tetracyclic precursor and occur in nature, respectively in the Meliaceae, Rutaceae and Simaroubaceae, three closely related plant families (Table I).[7]

TABLE I

Order	Sub-order	Family
Rutales	Rutineae	Akaniaceae
		Picrodendraceae
		Cneoraceae
		Burseraceae
		Simaroubaceae
		Meliaceae
		Rutaceae
	Malpigiineae	
	Polygalineae	

The close relationship between the structures of the above compounds, affords striking evidence of the botanical affinity between these plant families. However, the genetic diversity of the three families, which is revealed by

differences in the morphological characters of the plants, is likewise revealed by the progressive structural variation in the triterpenoids from the three families. These compounds have many structural features in common, but differ in small, yet significant details,[8] which arise from a divergence of the final stages of metabolism in the three families. For example, the limonoids all have cleaved rings A and D, whereas the meliacins have an intact ring A, and rings B, C or D may be cleaved.[9] It is interesting to note that the protoazadirane, flindissol (40) which has been isolated from Flindersia species, is very moderately oxidised when compared with limonin (70) and this fact has consequently questioned[8] the real relationship of the Flindersia genus to the Rutaceae. Conversely, since the Burseraceae is botanically closely related to the Simaroubaceae, Meliaceae and the Rutaceae, one can speculate whether the chemical relationship between the latter three families, also extends into the Burseraceae. So far, no azadiranes, meliacins, limonoids or simaroubalides have been isolated from plants of the Burseraceae,[10] although the genus Canarium is the source of the elemi acids,[11] which are by-products from the biosynthesis of protoazadiranes. Likewise, the simaroubalides have not yet been isolated from plants of either the Meliaceae or the Rutaceae, even though plants of the Simaroubaceae are botanically very little differentiated from those of the Rutaceae.[7] Recently,[12] meliandiol (42) was isolated from Samadera madagascariensis, and this is the first known example of the occurrence of a Δ^{7}-protoazadirane in the Simaroubaceae.

By inspection of this stereochemically homogeneous group of compounds, it is possible to trace a compelling route of biosynthesis, in which most of the steps can be illustrated by known naturally occurring products, beginning with a simple tetracyclic precursor and progressing to the most extensively oxidised compound. Very little definitive experimental work has been carried out to determine the course of the many secondary elaborations of these triterpenes. The present views[10] on the biosynthesis of the extensively degraded triterpenes are based on the assumption that these compounds can be derived by a rational series of structural alterations, of which specific examples are known within a particular plant group. To illustrate this argument, the compounds azadirone (59), azadiradione (62), epoxyazadiradione (63) and gedunin (66) all occur in the same plant, Melia azadirachta.

1.2 THE BIOSYNTHESIS OF TETRACYCLIC TRITERPENES

The biosynthesis of tetracyclic triterpenes is now well established,[13,14] and is outlined here for continuity to the next section.

Terpenoid biosynthesis is initiated (fig.1) by the condensation of two molecules of acetyl coenzyme A (5), which yields acetoacetyl CoA (6). Aldol condensation of a further unit of acetyl CoA to (6) gives 3S-hydroxy-3-methyl-glutaryl CoA (7), which is selectively reduced[15] to (R)-mevalonic acid (10). The intermediacy of the enzyme-bound intermediates (8) and (9) has been

invoked to account for the irreversibility of this reaction.[16] The discovery of mevalonic acid[17] and demonstration of the efficient incorporation[18] of its (R)-enantiomorph into cholesterol (36), led to the presently accepted mechanism of triterpene and sterol biosynthesis.

Stepwise phosphorylation of (10) (fig.2) gives mevalonic acid-5 OPP* (11).[19] Phosphorylation of the 3-hydroxyl group with a further molecule of ATP, concomittant decarboxylation, and elimination of the 3-phosphate group, gives 3-methylbut-3-en-1-yl (isopentyl) OPP (13),[20] the "biological isoprene unit", which is stereospecifically converted to 3-methylbut-2-en-1-yl (prenyl) OPP (14) by an isomerase.[21] If 2-^{14}C-mevalonic acid is used in studies of terpenoid biosynthesis, the labelled $=CH_2$ group in isopentyl OPP gives rise to the methyl group which is trans to the $-CH_2OPP$ group in prenyl OPP, and this label thus differentiates the seemingly equivalent methyl groups in (14).

Isopentyl OPP and prenyl OPP are linked together by an S_N2 reaction[22] (fig.3) which yields geranyl OPP (16)[23] and farnesyl OPP (17).[24] A (Lewis) base (probably an enzyme containing an active thiol group[25]) has been postulated to take part in this reaction.[26]

Robinson[27] initially postulated that sterols were synthesised in nature by the cyclisation of the hydrocarbon squalene (25). This postulate was revised

* OPP = abbreviation for pyrophosphate

by Woodward and Bloch[28] and was extended by Ruzicka[29,30,31] and by Stork and Burgstahler[32] to encompass the biosynthesis of all the different types of triterpene.

The complete degradation of squalene[33,34] and cholesterol,[35,36,37] which had been synthesised enzymatically from labelled acetate and again later from labelled mevalonate, fully supported the theoretical work and demonstrated that sterols and triterpenes are indeed formed from squalene,[38,39] which in turn is formed by the "tail to tail" coupling of two farnesol molecules. Cornforth and Popjak[40,41,42,43] showed that one of the protons at C_{12} or C_{13} in squalene is lost during coupling of the farnesyl OPP molecules, and following this work, many speculations were put forward concerning the mechanism of this coupling reaction.

Recently, Rilling[44,45,46] elucidated the structure of presqualene OPP (19), a cyclopropylcarbinol which closely resembles the terpene crysthanthemic acid (20). Rilling had previously shown that presqualene OPP is an intermediate in the biosynthesis of squalene,[47] and it has recently been converted into squalene by a yeast microsomal preparation. The coupling of two farnesyl OPP molecules (fig.4) can therefore be visualised as a base catalysed S_N2 reaction, followed by a trans 1,3 elimination reaction, which would yield the cyclopropylcarbinol. After the syntheses of presqualene alcohol by Crombie,[48] Altman[49] and Coates,[50] two different hypotheses have been proposed for its

conversion to squalene (fig.5). The first, due to van Tamelen[51] and Altman[49] involves the solvolytic cyclopropylcarbinyl (21), cyclobutyl (22), allyl (24) cation rearrangement, already a well documented reaction.[52] The second, due to Rilling[45,46] involves the two isomeric cyclopropylcarbinyl cations (21) and (23).

The cyclisation of squalene to form a small group of triterpenes, namely those occurring in the primitive plants,[53] the ferns, lichens and mosses, is initiated by protonation of squalene at C_3.[54,55] However, cyclisation of the great majority of triterpenes, was demonstrated by Corey[56] and van Tamelen[57] to be initiated by protonation of the epoxide group of 2,3-epoxysqualene (26), the epoxide oxygen atom being derived from molecular oxygen.[58]

The cation (27), one of the fundamental intermediates in triterpene biosynthesis,[30] is formed by the cyclisation of 2,3-epoxysqualene, while the latter is enzymically held in the chair-chair-chair-boat conformation (fig.6). This cation leads directly to dammardienol (31), while a series of concerted and stereospecific [1,2] migrations of methyl groups[59] and hydride ions,[60] as shown, yields euphol (32) and its epimer tirucallol (1). Alternatively, rearrangement of ring D gives rise to the large class of pentacyclic triterpenes. Moss[61] has recently demonstrated experimentally that triterpenes possessing a 3β-hydroxyl group, arise by cyclisation of 2,3S-epoxysqualene (26), while ring A is held in the chair conformation. Kitahara[62] and Cotterrell have

suggested that those triterpenes which possess a 3α-hydroxyl group arise from 2,3R-epoxysqualene, which is cyclised while ring A is held in the boat conformation.

Enzymic folding of 2,3-epoxysqualene in the chair-boat-chair-boat conformation (28) (fig.6) leads to the cation (29) which, after rearrangement to (30) as above, yields lanosterol (33), parkeol (34) or cycloartenol (35), depending on the biochemical system (see below). Although lanosterol is the precursor of sterols, e.g. cholesterol (36) in animal systems, Ourisson[63,64] and Goodwin[65] have shown that cycloartenol is the corresponding precursor of phytosterols, e.g. β-sitosterol (37). The alcohol (38), which occurs in the fungus Cephalosporium caerulens[66] is seen to arise directly from the cation (29), and similarly, Caspi[67] has shown that fusidic acid (39) is synthesised in the fungus Fusidium coccineum via the cation (29), and that no rearrangement occurs, after the initial formation of this intermediate.

In order to determine more precisely the function of the cyclase enzyme in sterol biosynthesis, van Tamelen[68] has demonstrated that the C_1-C_{12} fragment in 2,3-epoxysqualene represents the minimum requirement for cyclase action and therefore an important role of the enzyme, which is primarily to maximise π-orbital overlap in 2,3-epoxysqualene, is to control the stereochemistry at C_9 in the product sterol (fig.6).

1.3 THE POSTULATED BIOSYNTHESIS OF TETRANORTRITERPENES AND RELATED COMPOUNDS

Tirucallol (1) is generally considered to be the precursor of the tetranortriterpenes. However Ekong[69] recently showed that labelled euphol (32) is incorporated into nimbolide (78) in the leaves of Azadirachta indica, much more readily than is either of the isomeric compounds, butyrospermol (Δ^7-euphol), tirucallol or Δ^7-tirucallol. He also pointed out that since the biosynthetic pathway is postulated to go through a C_{21}-aldehyde, epimerisation can readily be achieved.

Oxidation of tirucallol at C_{21} and C_{23}, and cyclisation of the side chain would yield flindissol (40) [Flindersia dissosperma],[70] the simplest representative of the protoazadiranes. Modification of the C_{24} double bond and the functional group at C_3 would lead to further naturally occurring products in this series, e.g., Turraeanthin (41) [Turraeanthus africanus][71] and meliandiol (42) [Melia azedarach].[72]

The two groups of apotirucallanes which occur in nature, namely those with an intact side chain, for example, sapelin A (43)[73] and sapelin D (44) [Entandrophragma cylindricum],[74] and grandifoliolenone (45) and 16-oxo-grandifoliolenone (46) [Khaya grandifoliola],[75] and those with a furan side chain (fig.11), both arise from a similar precursor. While rings A, B, C and D undergo an identical transformation, the side chains differ in their elaboration.

The six membered ether ring of the sapelins is postulated to arise (fig.9) by the opening of a 24,25-epoxide (47) which would give the allylic alcohol (48). Oxidation at C_{21} and epoxidation of the new double bond would yield (50). Intramolecular attack at C_{24} by the primary alcohol would then yield the naturally occurring ring system (51). The furan ring can be envisaged (fig.10) as arising from the turraeanthin side chain,[71] by rearrangement of the 24-epoxide to a ketone (57), followed by Baeyer-Villiger oxidation of (57) which would yield (58). Hydrolysis of the ester, and dehydration of the product would then give the furan ring, which is intrinsic to all tetranortriterpenes. A further characteristic feature of this group of natural products is the 1-en-3-one group and the 1α,3α,7α group of substituents. Conversion of a 1-en-3-one to a 1α,3α-diacetate has been achieved in the present work.

The azadiranes differ only in ring D, and are thought to arise (fig.11) from azadirone (59) [Melia azadirachta][76] by epoxidation in ring D, e.g., havanensin triacetate (60) [Trichilia havanensis][77] and cedrelone (61) [Cedrela toona],[78,79,70] or by allylic oxidation at C_{16}, which would give azadiradione (62) [Melia azadirachta][76] and finally by epoxidation again in ring D, which would yield epoxyazadiradione (63) [Melia azadirachta][76] and khayanthone (64) [Khaya anthotheca].[81]

Baeyer-Villiger expansion of ring D would give rise to the meliacin series (fig.11) of which many khivorin (65) [Khaya ivorensis][82,83] and gedunin

(66) [Entandrophragma angolense][84,85] derivatives are known. Baeyer-Villiger expansion of ring A would then give rise to the fourth major class of products, the limonoids (fig.12). Hydrolysis of ring A of Obacunone (67) [Phellodendron amurense][86] and lactonisation of the 3-carboxyl group of obacunoic acid (68) [Dictamnus dasycarpus][87] with a C_{19} alcohol, would yield ichangin (69) [Citrus ichangensis],[88] which has been converted to limonin (70) in vitro, by dehydration with trifluoroacetic acid.[88] Michael addition of the hydroxyl group of (68) to C_1 (which has been achieved in vitro, with barium hydroxide[89]) gives veprisone (71) [Vepris bilocularis],[90] which on further oxidation at C_{19}, would yield limonin (70),[91,92] the major constituent of the seeds of most Citrus species.[8]

The biosynthesis of seco-ring B meliacins and bicyclononanolides has essentially been achieved in vitro and is outlined in the next section.

It can be seen that all the tetranortriterpenes discussed so far undergo a postulated Baeyer-Villiger expansion in ring A, ring B (next section), ring D and the side chain. Ring C is also thought to undergo expansion (fig.13). Oxidation of azadirone (59) at C_6 would give meldenin (72) [Melia azadirachta][93] which, on further oxidation at C_1, C_{12} and C_{30} would furnish nimbidinin (73) (Melia indica].[94] Baeyer-Villiger expansion of ring C, followed by a S_N2' reaction at C_{15} (74) would give rise to nimbidin acid (75) [Melia indica][94] and salanin (76) [Melia azadirachta].[95,96] Modification of ring A would then yield nimbin (77) [Melia azadirachta].[97] Convincing evidence of this pathway[97]

comes once again from the occurrence of these five compounds within the same genus.

With the sole exception of simarolide (89) [Simarouba amara],[98,99] all the simaroubalides, e.g., quassin (79) [Quassia amara],[100] chaparrin (80) [Castela nicholsonii][101,102,103] and samaderin B (81) [Samadera indica],[104] possess an oxygen function at C_{12}. Simarolide lacks this functional group, but retains the lactone side chain, corresponding to the furan of the meliacins. These features suggest that the biosynthesis[105,106,107] of the simaroubalides may follow the pathway envisaged in fig.14.

The precursor of this class of compounds is considered to be the lactone (82). Rings A, B, C and D will have evolved along a pathway identical to that of deoxyhavanensin triacetate (cf. 60), while the side chain will have followed the pathway, outlined in fig.9. Hydrolysis of the epoxide (50) would give the tetrol (52), which could be cleaved to give the aldehyde (53). Intramolecular hemi-acetal formation would then lead to the γ-lactone (55). Conversion of (82) to (84) follows the pathway described above, and has essentially been achieved in vitro (see below). Reduction of the unsaturated lactone would give rise to (85). Hydrolysis of C_7 and C_{16} and lactonisation of these groups would yield the key intermediate (86). Oxidative elimination in ring A [cf. khivorin (65) $\longrightarrow$ isogedunin (88)][83] together with oxidation at C_{30}, would yield (87) [cf. nimbin (77)]. Decarboxylation at C_4 followed by modification of ring A

via the 2α,3α-epoxide, together with hydroxylation at C_{11}, would finally yield simarolide (89). Further oxidation at C_{12} and cleavage of the β-diketone system (90) would yield the basic simaroubalide nucleus (91). Further oxidation of the 8β-methyl group is common within the simaroubaceae but is unknown within the Meliaceae and Rutaceae. The biosynthesis of the simaroubalides along the pathway shown has been substantiated[108] by the isolation of labelled glaucarubolone (92) from Simarouba glauca having the expected labelling pattern for a natural product which had been derived from tirucallol.

1.4 IN VITRO SYNTHESES OF TETRANORTRITERPENES

The important rearrangement of a Δ^7-tirucallane to a Δ^{14}-apotirucallane, which was outlined in the previous section, has been achieved in vitro (fig.15).[109] Wriglesworth prepared the Δ^7-epoxide (94) by ozonolysis of (93) and subsequently rearranged this epoxide with boron trifluoride in benzene, to the alcohol (95) in high yield. A similar result was obtained by Lavie, using tin (IV) chloride.[110]

A further transformation required to convert a protoazadirane to an azadirane is formation of the furan ring from the hemi-acetal group. Buchanan[111] achieved this step in vitro, as shown in fig.16. Treatment of turraeanthin (41) or its epimer (96) with sodium metaperiodate in aqueous dioxan with a trace of perchloric acid, gave the hydroxyhemi-acetals (97) which were readily dehydrated to the furans (98) with toluene sulphonic acid in benzene. Compounds having

this tetranor-Δ^7-tirucallane nucleus have not yet been isolated as natural products. The furans (98) were converted to the epoxides (99) with m-perphthalic acid in ether[111] and were rearranged, as above, with boron trifluoride to the simple azadiranes (100).[111] Bromination of (100e) with cupric bromide in THF, followed by dehydrobromination of the product with DBN gave the naturally occurring triterpene,[112] azadirone (59). Lavie converted azadirone (59) to azadiradione (62) with selenium dioxide.[76] Further discussion of this reaction is given in chapter two. Baeyer-Villiger oxidation of khayanthone (64) has given[112] the meliacin, khivorin (65).

Connolly has recently synthesised mexicanolide (111) and methyl angolensate (118), in vitro, along routes, which closely follow those postulated for the in vivo biosynthesis of these compounds.[113]

Mexicanolide was synthesised from 7-deacetyl-7-oxokhiverin (101) [Khaya senegalensis][114] along the route[115] shown in fig.17. Oxidation of this ketone with peracetic acid gave the ring B ϵ-lactone (104). Alkaline hydrolysis, followed by methylation gave the alcohol (105). Dehydration of this alcohol with thionyl chloride gave the meliacin (106) in good yield. Mild hydrolysis of (106) and oxidation of the diol (107) gave the 1,3-dione (108). A very similar meliacin, aphanamixinin (109) has been isolated from Apharamixis pdystachya.[116] Deoxygenation of (108) with chromous chloride (fig.18) gave the unsaturated lactone (110) and treatment of this with mild base caused michael addition of

C_2 to the exomethylene group and yielded the naturally occurring mexicanolide (111) [Cedrela odorata].[117,118,119] An essentially identical route to mexicanolide has been elaborated by Ekong[120] (fig. 17). Treatment of the oxime (102) with thionyl chloride gave the lactam (103) which then yielded the ε-lactone (104) with sodium nitrite in cold acetic acid-acetic anhydride. Many derivatives of mexicanolide occur in nature and swietenine (112) [Swietenia macrophylla][113,121] is typical. Utilin (113) [Entandrophragma utile][122] is one of the most highly oxidised triterpenes known.

Methyl angolensate (118) was synthesised from 7-deacetyl-7-oxokhivorin (101) along the route[123] shown in fig. 19. Deoxygenation of the lactone (101) with chromous chloride gave the unsaturated lactone (114), which upon Baeyer-Villiger oxidation gave the dilactone (115). Mild hydrolysis of (115) and dehydration of the alcohol with toluene sulphonic acid, followed by methylation, gave the unsaturated lactone (116). A similar class of seco-ring B compounds can be obtained[124] by treatment of the vinylogous β-ketone system of (119), with alkali (fig. 20). Hydrolysis of the diacetate (116) and acidification of the product, gave the ether (117), which yielded methyl angolensate (118) [Entandrophragma angolense][124,125,126] upon oxidation.

Synthesis of the γ-lactone side chain of simarolide,[12,127] has been achieved by a reaction sequence (fig. 21) similar to that described above for the synthesis of a furan ring. Reduction of meliandiol (42) with sodium borohydride

gave the pentol (121), which upon treatment with sodium metaperiodate gave the hemi-acetal (122). Mild oxidation of (122) with silver carbonate led to the γ-lactones (123) and (124) which have the carbonyl group at C_{23}, as in simarolide. Further reaction of this lactone (124) as described above, yielded[12] the unsaturated δ-lactone (126) [cf. (84)].

1.5 STEPS IN THE BIOSYNTHESIS OF THE TETRANORTRITERPENES, YET TO BE ACHIEVED IN VITRO

From the postulated biosynthetic steps, outlined in section 1.3, and those which have been achieved in vitro, the conversions yet to be accomplished in vitro, are as follows:

(a) tirucallol to flindissol

(b) gedunin to khivorin

(c) havanensin triacetate to khayanthone

(d) gedunin to obacunone

(e) obacunoic acid to ichangin

(f) veprisone to limonin.

No synthetic work has been carried out to convert an azadirane to the ring C seco-triterpenes, nimbin and salanin, and much difficult work remains to synthesise a naturally occurring simaroubalide.

An attempt has been made for this thesis, using model systems, to achieve the first three of these steps.

CHAPTER TWO

A DISCUSSION OF THE CHEMISTRY OF SOME TETRACYCLIC TRITERPENES

2.0 INTRODUCTION

One of the current fields of interest in the chemistry of the tetracyclic triterpenes is the synthesis of some naturally occurring products along routes which mirror in vitro, the probable biogenetic routes to these compounds and in particular, elaboration of the side chain of the protoazadiranes flindissol (40) and turraeanthin (41). Since Buchanan[111] has converted turraeanthin into azadirone (59), it appeared attractive to attempt to complete in vitro the early stages of the biosynthesis of the hemi-acetal side chain of flindissol.

The naturally occurring elemi acids[11] were used as starting materials for this work since they possess a carboxyl group at C-21 and this functionality is essential if the difficult task of oxidising the inert C-21 methyl group of tirucallol is to be avoided. The work described in the first part of this thesis was directed towards a synthesis of the γ-lactone (127). A protoazadirane (128) which has this lactone moiety has been isolated from Melia azedarach.[128]

2.1 ROUTES TOWARDS A SYNTHESIS OF THE SIDE CHAIN OF FLINDISSOL

Several synthetic routes to the γ-lactone are available. One suggested by Cotterrell[129] is shown in fig. 22. Epoxidation of the 24,25-double bond and rearrangement of the epoxide would yield the 24-ketone, which could be converted to a 24-exomethylene group by a Wittig condensation. Hydrolysis of the 21-ester and reaction of the acid with selenium dioxide would result in allylic

oxidation and subsequent lactonisation to the required lactone. This lactonisation was elaborated[130] during structural studies on eburicoic acid (129). Ozonolysis of the alkene would yield the potentially useful ketolactone.

This route suffers from the disadvantage that selenium dioxide very readily effects dehydrogenation of Δ^7 or Δ^8-tetracyclic triterpenes to 7,9(11)-alkenes[131] and a strong reducing agent is required to convert a conjugated diene back to either a Δ^7 or Δ^8 compound.[132]

A similar sequence has been elaborated by Cotterrell[129] (fig.23). The 24,25-epoxide was opened with acidified methanol and the alcohol was oxidised to the methoxyketone. Bromination of the ketone and reaction of the bromoketone with lithium bromide gave the ketolactone. If this method is to be used for a synthesis of (127), a nucleophile less inert than a methoxyl group would have to be used to block the C-25 position.

Reaction of an elemi acid or its methyl ester with N-bromosuccinimide also results in considerable dehydrogenation of Δ^7 and Δ^8 compounds to dienes.[131,133]

A further series of reactions which lead to the γ-lactone (127) involve photolysis of reactive intermediates. All these reactions produce radical species which will also cause dehydrogenation as above.

Homolysis of the hypohalite (fig.24) formed from the alcohol by lead tetra-acetate and iodine[134] would give an iodoalcohol, which upon treatment with base would yield a cyclic ether. This ether could then be oxidised to a γ-lactone.

Reaction of the primary alcohol (fig. 25) with lead tetra-acetate in a neutral non-polar solvent would also yield the five-membered ether ring by way of a homolytic fragmentation.[135]

Yet a further route to the cyclic ether (fig. 26) is photolysis of the nitrite of a primary alcohol.[136,137] Hydrolysis of the resultant oxime and reduction of the ketone would yield a diol, which could be dehydrated to the ether with either phosphoryl chloride[138] or copper chromite.[139]

The most direct route to the required lactone is photolysis of an N-iodo-amide which can be prepared from the corresponding amide with lead tetra-acetate and iodine.[140]

Of the possible routes discussed, that chosen for investigation was photolysis of the N-iodoamide. Wriglesworth[133] attempted to prepare the required amide for this reaction from the corresponding acid chloride but repeatedly obtained the parent acid. This result is surprising since Jeger had prepared an azide and a hydrazide from the same acid chloride.[141] It was of interest therefore to reinvestigate this apparently anomalous reaction. Completion of the synthesis of the five membered cyclic hemi-acetal from the γ-lactone could be accomplished by reduction with diborane.[142]

2.2 THE ISOLATION AND SEPARATION OF THE ACID CONSTITUENTS OF MANILA ELEMI RESIN

The method for the isolation and separation of the elemi acids, which was

developed by Cotterrell[11] was followed closely in the present work.

The acids were extracted with aqueous sodium hydroxide from an ethereal solution of commercial Manila elemi resin, obtained from Canarium luzonicum. The acids were methylated and the esters were then separated on a column of alumina.

Methyl 3α-acetoxytirucalla-8,24-dien-21-oate (130) and methyl 3-oxotirucalla-8,24-dien-21-oate (135) were eluted first followed by α-amyrin. The fourth fraction which contained two compounds was acetylated, the two components were separated and were found to be β-amyrin acetate and methyl 3α-acetoxytirucalla-8,24-dien-21-oate (130). Similarly the fifth fraction was acetylated, the two components were separated and identified as methyl 3β-acetoxyurs-12-en-28-oate (136) and methyl 3α-acetoxytirucalla-7,24-dien-21-oate (137). Ursolic acid has not previously been identified in the resin.

2.3 THE PREPARATION OF 3β-ACETOXYTIRUCALLA-8,24-DIEN-21-OIC ACID

The work described in this section was directed towards a satisfactory preparation of the acetoxy acid (143). The abundant Δ^8-ester (133) was used for this investigation. The initial problem encountered was hydrolysis of the C-21 acid methyl ester to the corresponding acid. The severe steric hindrance of the C-21 ester was noted during early work on the elemi acids.[143]

Reaction conditions which have been used to effect hydrolysis of sterically hindered triterpene acid methyl esters include 25% potassium hydroxide in ethylene glycol,[144] boron trichloride in dichloromethane,[145] lithium iodide in 2,4,6-trimethylpyridine[146] and lithium iodide in dimethylformamide.[147] In the present work, lithium bromide in dimethylformamide was used in an attempt selectively to hydrolyse the ester (133) to the acetoxy acid (132), but over a period of 5 hours these conditions proved to be ineffective.

The mechanism of this reaction involves attack of the halide anion at the methyl group of the acid methyl ester function. The failure of this halogenolysis is interesting since if the elemi acid side chain or ring D possesses a suitably placed functional group, then hydrolysis can be induced to occur. This was demonstrated by Cotterrell[129] who found that reaction of the bromoketones (145) with lithium chloride and lithium carbonate in dimethylformamide gave the ketolactones (146) (fig. 27) This result also demonstrates the steric hindrance at C-21 and C-23 since the expected dehydrobromination did not occur. Similarly under the same reaction conditions, the bromoketones (147) yielded the enone (149) while use of the milder base 1,5-diazabicyclo(3,4,0)-non-5-ene gave only the enones (148).

Further methods for effecting the hydrolysis of esters include finely divided sodium hydroxide in dimethylsulphoxide,[148] and dimsyl potassium,[149] which can be prepared by the addition of potassium t-butoxide to dimethyl-

sulphoxide.[150] This latter reagent readily hydrolysed the severely hindered ester methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (140) whereas the former reagent was ineffective. In the present work, hydrolysis of (133) at 100° with potassium t-butoxide in dimethylsulphoxide resulted in a 35% yield of the hydroxyacid (130). The mechanism of hydrolysis of the acid methyl ester and of the acetate group is given in figs. 29 and 30 respectively.[149] The difference in these mechanisms again illustrates the hindrance of the C-21 carbonyl group. If this reaction had been carried out at the boiling point of dimethylsulphoxide (189°), a higher yield of hydroxyacid would undoubtedly have been obtained.

Finally, hydrolysis of the ester (133) with potassium hydroxide in refluxing ethylene glycol resulted in a 77% yield of the hydroxyacid (130). The good yield achieved by this method of hydrolysis is most probably due to the high solvating power of ethylene glycol[151] together with the high temperature at which the reaction was carried out.

Oxidation of the hydroxyacid (130) with dipyridine chromium oxide in dichloromethane[152,153] gave the naturally occurring acid (134) in 16% yield. The major products from this oxidation[154] were the enone (150), the enedione (152), and the diene (154). These products were not isolated from this reaction but the corresponding methyl esters (151) and (153) and methyl 3α-acetoxy-tirucalla-7,9(11),24-trien-21-oate (225) were isolated and characterised during the course of later work. The low yield of the ketoacid (134) from this oxidation

was thought to be due, in addition to the formation of these unsaturated compounds, to salt formation between the carboxyl group and pyridine and so oxidation of the hydroxyester (131) was investigated.

Hydrolysis of the acetoxyester (133) with potassium hydroxide in methanol gave the hydroxyester (131). Oxidation of this latter ester as above gave the ketoester (135) in 37% yield, which was more than twice that obtained using the carboxylic acid.

Reduction of the ketoester (135) with sodium borohydride gave the axial alcohol (131) in 13% yield and the equatorial alcohol (142) in 75% yield. The equatorial alcohol then gave the acetoxyester (144) upon acetylation.

Hydrolysis of the hydroxyester (142) with potassium hydroxide in ethylene glycol gave the hydroxyacid (141) in 86% yield. The lower yields of the hydroxy acids obtained during earlier work and by previous workers are thought to be due to the partial solubility of these polar products in mixtures of hydroxylic solvents and water. An improved work up procedure was developed which involved dilution of the reaction mixture with a large volume of water and saturation of the neutralised aqueous solution with solid sodium chloride. Extraction with ethyl acetate then gave a very good yield of the hydroxyacid. Acetylation of the hydroxyacid (141) finally gave 3β-acetoxytirucalla-8,24-dien-21-oic acid (143).

2.4 BROMINATION OF THE 24,25-DOUBLE BOND AND RELATED ELECTROPHILIC REACTIONS

Wriglesworth[133] found that reaction of the acetoxyacid (132) in acetone with concentrated aqueous ammonia, or in a mixture of benzene and dimethylsulphoxide with sodamide gave the epimeric unsaturated ketones (155). Protection of the 24,25-double bond was therefore necessary if this cyclisation was to be avoided and so bromination was investigated, since the double bond could be regenerated with either zinc dust or sodium iodide at a later stage.

T.l.c. of the product from addition of bromine to the acetoxy acid (143) in either chloroform or ether, showed that both acid and neutral products had been formed; however these products could not be adequately separated. Hydrogen bromide gas was evolved during the reaction. Addition of bromine to the acetoxyacid (143) in methyl acetate gave a 15% yield of the dibromoacetoxyacid (157) as the major product. When methyl acetate was used as the solvent, decolourisation of the reaction mixture occurred more rapidly than when either chloroform or ether was used and less hydrogen bromide gas was generated, although hydrolysis of the methyl acetate could have "absorbed" much of this gas.

Two explanations are proposed to account for the low yield of the dibromoacid (157).

In a non-polar solvent, which will have a small dipole moment, the side chain of the elemi acids will exist in a coiled conformation as in (158), in order

to minimise the disruption of solvent dipole-dipole interactions. After initial formation of a bromonium ion (159), lactonisation can readily occur to give the six and seven membered bromolactones (161) and (162). Analogous compounds occur in nature, for example sapelins D (44) and E (163).[74] The methyl ester (160) in chloroform would also have the conformation shown but the methyl group of the acid methyl ester is less easily abstracted at room temperature than is the proton of the carboxylic acid and requires much stronger conditions. This hypothesis explains the formation of neutral products and the production of hydrogen bromide gas during bromination.

Wriglesworth[133] found that reaction of the diol (164) in chloroform with perbenzoic acid gave, in addition to the expected 24,25-epoxide, the epimeric ethers (165) and similarly reaction of the mixture of isomeric acids (166) with perbenzoic acid in chloroform gave the lactone (167) in low yield.

In a very polar solvent the carboxyl group of (158) will be solvated. This "blanketing" effect will prevent the 24,25 π-bond from approaching the carboxyl group and a greater yield of the dibromide should result. In solvents of intermediate polarity competition will exist between carboxyl (or primary alcohol)-solvent dipole interaction and solvent-solvent dipole interaction and only moderate yields of the dibromoacid would be expected.

The dipole moment of a solvent is related to its dielectric constant and hence this constant can be used as a criterion of polarity.[155] It can be seen

from Table 2 that bromination in either chloroform or ether should result in similar yields of the dibromide, while in methyl acetate a slightly increased yield of the dibromide is expected. Since the acetoxyacid (143) is insoluble in acetonitrile it will be difficult to find suitable solvents to investigate these effects further but the experimental results so far are in accord with this hypothesis.

TABLE 2

SOLVENT	DIELECTRIC CONSTANT	SOLVENT	DIELECTRIC CONSTANT
Hexane	1.89	t-Butanol	10.9 +
Cyclohexane	2.02 *	Pyridine	12.3 *
1,4-Dioxan	2.21 *	Isopropanol	18.3 *
Carbon tetrachloride	2.24	Butan-2-one	18.5
Benzene	2.28	Acetone	20.70 *
Carbon disulphide	2.64	Ethanol	24.30 *
Diethyl ether	4.34	Methanol	33.62
Chloroform	4.81 *	Nitrobenzene	35.74 **
Ethyl acetate	6.02 *	Dimethylformamide	38 **
Acetic acid	6.15 *	Acetonitrile	38 **
Methyl acetate	6.68 *	Dimethylsulphoxide	45 ++
Ethyl formate	7.1 *	Formic acid	58.5
Methyl formate	8.5	Water	80.37
Dichloromethane	9.08	Formamide	109

The values are from reference 156, and at 20°C unless otherwise indicated. (*) at 25°. (+) at 30°. (**) from reference 157. (++) at 16°.

Isomerisation of the Δ^8 double bond is another explanation for the low yield of the dibromoacid (157). Wriglesworth[133] found that addition of

concentrated hydrochloric acid to a solution of the hydroxyester (131) and its Δ^7 isomer in methanol, resulted in an increased proportion of the Δ^7 isomer. This isomerisation is in agreement with the work of Swayne,[154] who showed that the characteristic euphol-isoeuphol rearrangement[158] does not take place with the elemi acids. The hydrobromic acid liberated during bromination would probably give rise to an equilibrium mixture of Δ^7 and Δ^8 isomers and it could also effect hydrolysis of the 3β-acetate.

Bromination of the acetoxyester (133) in chloroform gave an excellent yield of the dibromide (168) which showed that the carboxylic acid group was indeed responsible for the results discussed above.

In the n.m.r. spectrum of the dibromide (168), the signal of one of the two C-25 methyl groups occurred as a doublet (J 2 Hz). This splitting is due to long range W coupling.[159] Bromination of the 24,25 double bond gives rise to both R and S epimers at C-24 and both of these epimers will exist in various conformations. However the most stable conformation of the R epimer will be the fully staggered conformer (169) and likewise the most stable conformation of the S epimer will be (170). If the asymmetry of the remainder of the side chain is neglected, then the two conformers shown of the R and S epimers will be enantiomeric and therefore only two methyl resonance signals will be seen instead of four. For the conformer (169) of the R epimer, the methyl groups at C-25 are magnetically different and will have different chemical shifts, but

owing to the unequal conformer population[160] (the fully staggered conformer (169) will predominate) the protons of the methyl group marked * will be coupled to the C-24 proton, while the protons of the other methyl group can only be coupled to the C-24 proton in a less favourable conformation.

2.5 THE ATTEMPTED PREPARATION OF 3(α AND β)-ACETOXY-TIRUCALLA-8,24-DIEN-21-AMIDE

The acyl chloride of the dibromoacid (157) was prepared with thionyl chloride and reaction of this acyl chloride with gaseous ammonia gave the amide as a gum. Attempted purification of this amide by p.l.c. resulted in hydrolysis to the parent dibromoacid. The i.r. spectrum of the amide showed characteristic NH_2 bands at 3500 and 3400 cm^{-1} and $CONH_2$ bands[161] at 1675 and 1590 cm^{-1}. The amide was more polar on silica gel than the parent carboxylic acid even though the amide nitrogen atom is devoid of basic properties. This polarity must therefore be due to hydrogen-bonding. Owing to the steric hindrance of a C-21 group towards bimolecular reactions, hydrolysis of the amide will proceed via an A 1 reaction. The strong H-bonding between the amide and silica must be responsible for the apparently facile hydrolysis observed, since in most cases hot concentrated acid is required to hydrolyse an amide.[162]

The "amide" of a mixture of the acetoxyacid (132) and its Δ^7 isomer was prepared as above. Since it was slightly discoloured this "amide" was used

for a photolysis reaction without purification and characterisation. Reaction of the "amide" with lead tetra-acetate and iodine and photolysis of the "N-iodoamide" gave a complex mixture of products. The major non-polar product was isolated pure after extensive chromatography and was shown to be the acetoxytrienone (156).

The large negative optical rotation of this compound indicated the presence of the nuclear diene chromophore.[163] The u.v. spectrum showed that the trienone possessed two chromophores (see Appendix I). The triplet absorption at lower wavelength is typical of a 7,9(11)-diene in the tirucallene series,[163] while the higher wavelength of absorption (257.5 nm) agreed with that observed by Swayne[154] for this type of five membered ring unsaturated ketone, and with the calculated value (254 nm). The i.r. spectrum showed two carbonyl bands at 1710 and 1700 cm^{-1} for an acetate group and a five membered ring unsaturated ketone and the relatively intense band at 1627 cm^{-1} is characteristic of a s-cis unsaturated ketone.[164] The n.m.r. spectrum had signals at 4.67 τ (2H) for the C-7 and C-11 protons, 5.28 τ (1H) for the 3β-proton, 7.75 τ (1H) for the epimeric C-20 proton and the C-26 and C-27 protons characteristically coalesced at 8.15 τ [cf. 8.18 τ for (155)].[133] The mass spectrum was readily interpreted as shown in fig.31. Loss of a methyl group and acetic acid from the molecular ion will yield one group of fragments and a second group will be generated by cleavage of the bond β to the carbonyl group.[165] The base peak at m/e 124

will arise from a McLafferty rearrangement[166] and fission of the side chain as shown.

Formation of the unsaturated ketone is envisaged in fig.32. Ionisation of the acid chloride to the acylium ion (171) followed by reaction with ammonia would yield the protonated Mannich base (172), which would lose ammonia to yield to the ketone. This cyclisation reaction would be facilitated by the conformational coiling of the side chain discussed above. Abstraction of a proton from one of the allylic positions in rings B or C (fig.33) with either lead tetra-acetate or an iodide radical would give an intermediate such as (173) which would readily rearrange to the nuclear diene. Both the unsaturated ketone and the diene group will undergo extensive rearrangement and polymerisation on photolysis.

Formation of the nuclear diene under these conditions verified the assumption made in section 2.1 and the low yield of isolable products makes this photolysis an unattractive preparative method for this work. Cyclisation of the acyl chloride of the acetoxyacid (132) with ammonia was also observed by Wriglesworth[133] (see above) and hence further attempts to prepare an iodoamide were made using a 24,25-dihydro compound.

2.6 THE PREPARATION OF 3α-ACETOXYTIRUCALL-8-EN-21-AMIDE AND PHOTOLYSIS OF THE "N-IODOAMIDE"

A mixture of the hydroxyacids (130) and (139) was hydrogenated and the two isomeric products (174) and (176) were separated by multiple elution p.l.c. The Δ^8-acid (174) was acetylated and the amide (177) was prepared as above from (175) in 88% yield. The use of very pure thionyl chloride[167] gave a colourless acid chloride and consequently the amide did not require purification. The i.r. spectrum of this amide showed bands at 3525, 3490 and 3405 cm^{-1} due to the NH_2 group and bands at 1712 cm^{-1} for the acetate group and at 1671 and 1585 cm^{-1} for the $CONH_2$ group. The amide NH_2 protons resonated at 3.99 τ and 4.45 τ ($w_{\frac{1}{2}}$ 16 Hz) in the n.m.r. spectrum and the existence of two distinct signals is due to the partial double bond character of the amide group.[168] The broadness of the signals is due firstly to slow proton exchange and secondly to the partial averaging of the spin-spin coupling of the protons to nitrogen.[169]

Barton[140] used two different methods for the preparation and photolysis of an N-iodoamide. Firstly an N-iodoamide was formed in situ prior to photolysis by the gradual addition of iodine to a solution of the amide and lead tetra-acetate and the second method involved photolysis of a solution of an amide, lead tetra-acetate and iodine. The first of these two procedures was used in the present work, so that photolysis of the N-iodoamide could be followed by t.l.c.

Photolysis of the product from reaction of the amide (177) with lead tetra-acetate and iodine gave a gum from which only one unstable compound could be isolated and this was identified as the isocyanate (178) by the strong absorption band at 2270 cm^{-1} in its i.r. spectrum.[170] The formation of this isocyanate instead of the desired γ-lactone is envisaged in fig 34.

Baumgarten,[171] and later Beckwith[172] demonstrated that reaction of a primary amide with lead tetra-acetate (179) will yield a secondary amide (180) which will undergo intramolecular decomposition to a nitrene (181). The nitrene will then spontaneously rearrange to an isocyanate which will yield an amine, a carbamic acid, a urethane or a urea depending on the nature of the solvent. This mechanism is very similar to that of the Hofmann rearrangement.[173]

An N-iodoamide (183) must form via a transition state such as (182) upon reaction of the secondary amide (180) with iodine. For an alternative mechanism see reference 134b. Barton[140] demonstrated that photolysis of an N-iodoamide (183) will cause homolysis of the N-I bond which will result in formation of a γ-iodoamide (184). Spontaneous cyclisation of this γ-iodoamide will yield a salt (185) which will decompose to an iminolactone (186). Hydrolysis of (186) will then yield a γ-lactone. That this mechanism is correct was demonstrated by photolysis of a pure N-iodoamide whereupon iodine was liberated and only a 50% yield of a γ-lactone was obtained. Yields in excess of 50% can only be obtained if excess oxidant is present to recycle the primary amide.

The steric hindrance at C-21 of the amide (177) is such that the transition state (182) cannot form and a nitrene, and then an isocyanate is formed instead.

One of the difficult problems encountered in the chemistry of Δ^{14}-azadirene compounds which have a furan side chain, is allylic oxidation at C-16. Lavie[76] effected this oxidation with selenium dioxide but several workers have been unable to repeat this result.[174] Cotterrell[129] obtained a 40% yield of a 14-en-16-one by oxidation of methyl 3α,7α-diacetoxyapotirucall-14-en-21-oate (187) with chromic acid in acetic acid and it therefore appeared that a 16-oxoazadirene could be prepared by allylic oxidation of a protoazadirene followed by elaboration of the side chain. Of the procedures outlined in section 2.1, only the "dehydrobromination" sequence seemed to be of preparative use. The apotirucallol derivatives (187) and (188) were used for this investigation. The key step in the preparation of these compounds was ozonolysis of a mixture of the dibromides of the acetoxy esters (133) and (137) and the mechanism of ozonolysis is discussed in the next section.

2.7 THE MECHANISM OF OZONOLYSIS

Cotterrell and Wriglesworth[109] used ozone to prepare the 7α,8α-epoxide (209) from a mixture of the dibromides of the isomers (133) and (137). This was a particularly convenient method since it avoided the necessity of separating the

Δ^7 and Δ^8-isomers prior to ozonolysis. The 7α,8α-epoxide was less polar than and hence easily separated from the unsaturated ketones (212) and (213) which are formed from the Δ^8 isomer.

The mechanism of ozonolysis has been discussed in a recent review[175] and more recently Story[176] has put forward a new concept of this mechanism which explains many of the anomalous results obtained upon reaction of alkenes with ozone. His proposals are shown in fig.35.

The initial ozone-alkene adduct is thought to be the π-complex (189) which can rearrange to either the trioxolane (190) or the molozonide (191). The molozonide may then rearrange to either the trioxolane (190) or undergo cleavage to the Criegee zwitterion[177] (192) which gives rise to the ozonide (193).

Ozonolysis of hindered alkenes is known to yield epoxides and to effect cleavage of the carbon-carbon single bond adjacent to the olefinic bond. An example of this type of reaction is ozonolysis of the diterpene Araucarolone diacetate (194).[178] The initial π-complex (195) can lose oxygen to yield the epoxide (196) and can also undergo an intramolecular reaction[179] as shown to yield the keto-zwitterion (197) [cf. (192)], which then yields the aldehyde (198).

Evidence for the existence of a molozonide is provided by the ozonolysis of trans-t-butylethylene.[180] If propionaldehyde is added to the reaction mixture (fig.37) after excess ozone has been removed, pivaldehyde and propionic acid are formed. The propionic acid is thought to be formed by a Baeyer-Villiger

reaction (199).[181]

Evidence for the existence of a zwitterion is provided by the ozonolysis of alkenes in the presence of alcohols or carboxylic acids, when alkoxy and acyloxy hydroperoxides are formed (fig.38).[177]

Halsall[109] has suggested that formation of an enone and an enedione such as (201) and (202) from a Δ^8-alkene occurs by way of the nuclear diene (fig.39). Formation of the diene may occur by epoxidation of the 8,9-double bond followed by rearrangement, and elimination of water.[131] Epoxidation of the diene and further rearrangement will yield an enone.[182] An enedione is the major product on prolonged ozonolysis and since there is always a large proportion of unozonised oxygen present during this reaction, then an enedione is most likely to arise by peroxidation of the allylic position at C-11 by triplet oxygen.

Since oxidation of an alcohol with oxygen usually requires a platinum catalyst[183] then oxidation of an alcohol to a ketone during ozonolysis[197] will most likely go via a mechanism such as that in fig.40 which is analogous to that proposed by Littler[184] for the oxidation of alcohols with bromine or mercury (II).

2.8 THE PREPARATION OF METHYL 3α,7α-DIACETOXYAPOTIRUCALL-14-EN-21-OATE

A mixture of methyl 3α-hydroxytirucalla-7 and 8,24-dien-21-oates was

acetylated and the products were hydrogenated. Ozonolysis of the mixture of acetoxyesters gave the epoxide (94) in 77% yield, based on the approximate content of the Δ^7 isomer in the initial mixture, together with the enone (201) and the enedione (202). Rearrangement of the 7α, 8α-epoxide with boron trifluoride etherate in benzene gave the alcohol (95) which upon acetylation yielded the diacetate (187).

The n.m.r. spectra of apotirucallene compounds characteristically show two methyl signals grouped together approximately 10 Hz downfield from the remaining methyl signals. These signals are from the 8β and 13α-methyl groups which are deshielded by the 14,15-double bond.[185]

Halsall[109] has pointed out that the selectivity of the tirucallol-apotirucallol rearrangement is due to abstraction of the 15α proton by the 7α oxygen group, and this would initiate a concerted rearrangement. A similar conclusion was reached by ApSimon[186] but these arguments are incorrect, since the 7α, 8α-epoxide oxygen atom is too distant from the 15α proton for it to be able to abstract the 15α proton. Evidence for this is provided by the failure of a 15-ketone to abstract a 7β proton[202] in a McLafferty rearrangement and these two groups are closer together than are the 7α oxygen and the 15α proton. The selectivity of the rearrangement is more likely to be due to an unfavourable cis 1,3-diaxial interaction which would exist between the 7α oxygen group and the 14α methyl group if the 13α methyl group were to shift to the 14α position.

This 1,3 interaction will also be the basis of the havanensin-neohavanensin rearrangement.[187]

The diacetate (187) was used later for studies of allylic oxidation at C-16.

2.9 THE ATTEMPTED PREPARATION OF METHYL 3-OXOAPOTIRUCALLA-14,24-DIEN-21-OATE

A crude mixture of elemi acid methyl esters was used for this preparation since ozonolysis of both the Δ^8-3-ketone (135) and the Δ^8-3-alcohol (131) was expected to yield the two unsaturated ketones (204) and (205) from which the epoxide (207) could be separated. The 24,25 double bond was protected by bromination since it could be regenerated during the reductive work up after ozonolysis.

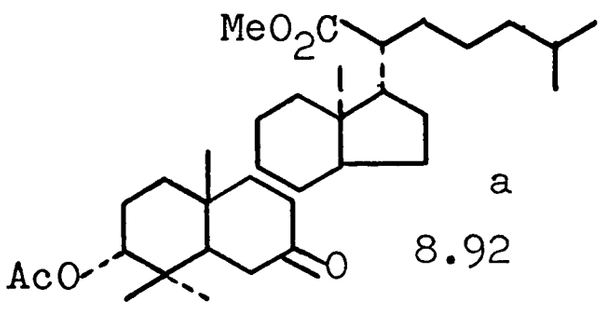
Chromatography of the product from ozonolysis of the mixture of dibromides gave four fractions (chart I). The polar third and fourth fractions were not investigated since they contained compounds which were more polar than an authentic sample of the desired epoxide (207). The partially crystalline second fraction was shown by t.l.c. to contain mostly the enone (205) and likewise was not investigated. The components of the crystalline first fraction were separated by column chromatography.

The enone (205) was isolated from fraction 1/3 and the corresponding

enedione (204) was isolated from fraction 1/2. These unsaturated ketones were readily identified by their u.v. spectra.[154] The chemical shifts of the most deshielded methyl group of some enones and some enediones have been collected in Table 3 . Comparison of the chemical shifts of this methyl group in the pairs of compounds a and b, c and d, and f and g shows that this methyl group is strongly deshielded by the 11-ketone group. Similarly comparison of the chemical shifts in the pairs of compounds b and d, c and e, and g, h and i shows that this methyl group is also strongly deshielded by the 3-ketone group. The 10β methyl group is the only one which can be deshielded by both the 3 and the 11-ketone groups. The strong deshielding of the 10β methyl group by the 11-ketone group is unexpected on consideration of the possible anisotropic effects of the ketone group.[188] This deshielding has been noted in the steroid field[189] and it is thought to be due to a lack of conformational parity between those compounds which do not have an 11-ketone group and those compounds which do have an 11-ketone group. This lack of parity is caused by interaction of the 1β proton with the 11-ketone group.[188]

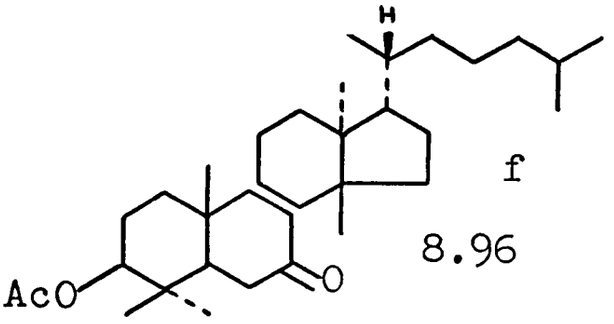
The diketone (206) was isolated from the mother liquors of crystallisation of the two unsaturated ketones (see chart 1). The constitution of this compound remained unknown for some time and a discussion of the elucidation of its structure is given in section 2.11.

The major component of fraction 1/1 had the same t.l.c. R_F as an authentic



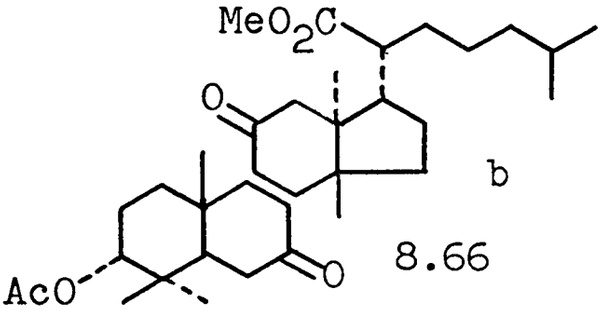
a

8.92



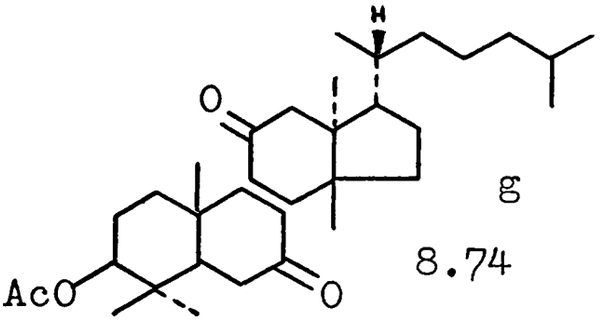
f

8.96



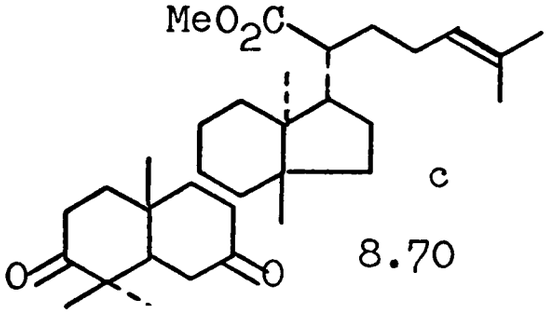
b

8.66



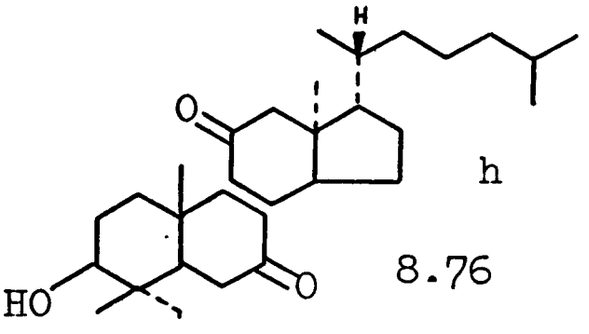
g

8.74



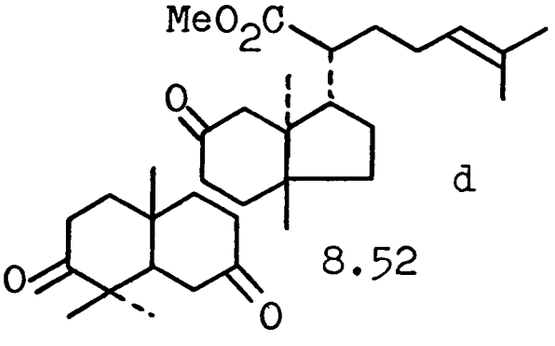
c

8.70



h

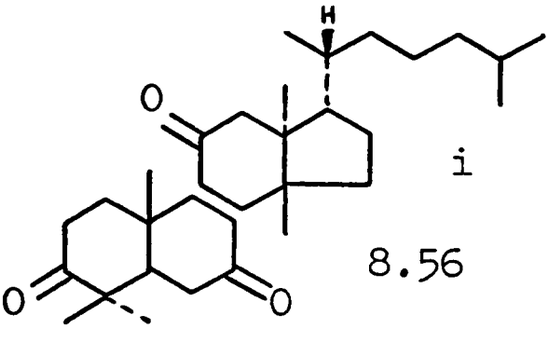
8.76



d

8.52

$CDCl_3$



i

8.56

CS_2

Ref. 190.

TABLE 3

Δ ab = -26
Δ cd = -18
Δ fg = -22

Δ bd = -14
Δ ac = -22
Δ gi = -18
Δ hi = -20

sample of the ketoepoxide (207). However addition of boron trifluoride to this fraction produced no apparent change in its composition. Chromatography of the product yielded (13αH)ursan-3,12-dione (203) which will have been formed from α-amyrin, one of the components of the crude acid starting material. A discussion of the structure of this dione and of some other pentacyclic triterpene 12-ketones is given in chapter three.

The reason why the ketoepoxide (207) was not isolated was not immediately obvious but it became apparent later after the structure of the diketone (206) had been elucidated.

2.10 THE PREPARATION OF METHYL 3α,7α-DIACETOXYAPOTIRUCALLA-14,24-DIEN-21-OATE

A crude mixture of elemi acid methyl esters was acetylated and the product was treated with bromine The dibromides were then ozonised as before. Chromatography of the product from ozonolysis gave an oil, the major component of which, by t.l.c., was of similar polarity to that of the epoxide (209). P.l.c. of a small portion of this oil yielded a mixture of 3β-acetoxy(13α and 13βH)ursan-12-ones (see chapter three). Addition of boron trifluoride etherate to this fraction produced no apparent change in its composition (t.l.c.) which confirmed the absence of the desired epoxide (209).

Since a large number of products was most likely to have been formed

during the above ozonolysis, separation of a crude mixture of the Δ^7 and Δ^8-isomers (131) and (138) from α-amyrin and the ketone (135) was desirable.

A crude mixture of the elemi acid methyl esters (131) and (138) was acetylated and the product was treated with bromine. Ozonolysis of a mixture of the dibromides gave an oil which was separated into its components as shown in chart II.

The first fraction yielded methyl 3β-acetoxy-12-oxo(13βH)ursan-28-oate (see chapter three), the second fraction yielded the desired epoxide (209) and the third fraction was a mixture of five compounds which was separated by p.l.c.

Fraction 3/1 yielded the 7α-bromo-15-ketone (210) (see section 2.11) and fraction 3/2 gave methyl 3β-acetoxy-11-oxours-12-en-28-oate (211). Fractions 3/3 and 3/4 yielded the enedione (212) and the enone (213) respectively and finally fraction 3/5 gave the epoxide (214).

In the n.m.r. spectrum of the oxoursene (211), the 14α methyl group resonated at 8.70 τ in agreement with the chemical shift calculated (8.68 τ) by Askam.[191] The signal from the C-12 proton was a sharp singlet and therefore the proton at C-18 has the β configuration.[192] The stereochemistry at C-18 can also be determined by consideration of the mechanism of formation of the enone group.

The C-11 position will probably not be oxidised directly as it would be with chromic acid (see the discussion on allylic oxidation in section 2.13) but

as discussed in section 2.7, the enone will be formed via the 11,13(18)-diene as shown in fig.41. Reaction of methyl 3β-acetoxyurs-12-en-28-oate with ozone will yield the epoxide (215) which can rearrange to either the 12-ketone or to the allylic alcohol (216) which will lose water to give the stable heteroannular diene (217). Support for this mechanism is given by the formation of olean-11,13(18)-diene upon treatment of olean-12β,13β-epoxide with dilute acid.[193] Epoxidation of the less hindered double bond of the diene (217) (hydrogenation of olean-11,13(18)-diene yielded olean-13(18)-ene[193]) from the less hindered α face will yield the epoxide (218). Rearrangement of this allylic epoxide will yield the βγ-unsaturated ketone (219). The allylic epoxide (218) can rearrange to either the 11 or the 12 position but an 11-ketone will be considerably less hindered than a 12-ketone. The 13(18) double bond of (219) will then move into conjugation with the 11-ketone to yield the αβ-unsaturated ketone (211).

Barton[194] showed that methyl 3β-acetoxy-11-oxoolean-12-en-28-oate can be isomerised to the more stable 18αH-isomer whereas methyl 3β-acetoxy-11-oxours-12-en-28-oate cannot be isomerised. The three methyl groups on ring E of the 18αH-isomer of (211) will all have an axial configuration while those on ring E of (211) will all have an equatorial configuration and hence the C-18 proton will adopt the β-configuration. The stability of ring E will therefore be responsible for the stereoselectivity of the rearrangement (219) to (211).

The hydroxyepoxide (214) is thought to arise (fig.42) by rearrangement of the epoxide (220) which will yield the apoalcohol (221). Further oxidation of this alcohol and a reductive work up will give the epoxide (214). An almost identical epoxide (223) has been prepared by Cotterrell,[129] by ozonolysis of the diacetate (187). Models show that the β face of ring D is less hindered than the α face and oxidation with ozone is therefore expected to yield a β-epoxide.

The o.r.d. curve of the hydroxyepoxide (214) is a plain negative curve similar to that of (223). The i.r. spectrum showed a band at 3515 cm^{-1} consistent with dimeric H-bonding of the 7α-alcohol. The n.m.r. spectrum showed a poorly resolved triplet at 6.89 τ which has been assigned to the 7β proton. The chemical shift of this proton is greater ($\Delta\sigma$, +29 Hz) than that for a proton geminal to a 3α-alcohol and this must be caused by the shielding of the 14β,15β-epoxide ring (224).[195] The C-15 proton resonated as a singlet at 6.94 τ. The mass spectrum of the hydroxyepoxide (214) was dominated by two intense peaks at m/e 349 (71%) and 319 (45%). These arise from the fragmentation shown in fig.43, which is caused by cleavage of either the 6-7 or the 7-8 bonds adjacent to the hydroxyl group. Transfer of the 5α-proton to C-9 will then generate the two major ions.

Boron trifluoride etherate was added to the crude epoxide (209) and the products were separated by column chromatography. The first compound to be eluted was the diene (225), which will have been formed from the epoxide (209) by traces of acid in the boron trifluoride.[196] The second compound was the

bromoketone (210) which had been present in the crude epoxide mixture, as also had been the third component, methyl 3β-acetoxy-12-oxo(13αH)ursan-28-oate (see chapter three). The fourth compound was the desired apoalcohol (226) which was converted to the ketone (227) with Jones reagent and to the diacetate (188).

2.11 THE STRUCTURE OF METHYL 7α-BROMO-3,15-DIOXO(14αH)APO-TIRUCALL-24-EN-21-OATE AND THAT OF THE CORRESPONDING 3α-ACETATE

The isolation of these two bromides was described in sections 2.9 and 2.10. Since ozonolysis will have effected oxidation of a 3α-hydroxyl group to a ketone,[197] then elemental analysis and mass spectral molecular weight of the diketone (206) indicated that one oxygen atom and one bromine atom had been introduced to either methyl 3α-hydroxytirucalla-7 or 8,24-dien-21-oate. The i.r. spectrum showed bands at 1725, 1197, 1174 and 1161 cm^{-1} for the acid methyl ester and a band 1700 cm^{-1} for the 3-ketone. The five membered ring ketone absorption band was hidden under the ester carbonyl band. In addition to the signals from the C-24 olefinic proton, the two C-25 olefinic methyl groups, the $-CO_2Me$ group and the five tertiary methyl groups, the n.m.r. spectrum of the diketone showed a triplet signal at 5.18 τ (J, 3 Hz) and a singlet signal at 7.30 τ. Similarly the n.m.r. spectrum of the acetate (210)

showed a triplet signal at 5.26 τ, the signal from the 3β proton at 5.34 τ and a singlet signal at 7.26 τ.

Since an isolated oxygen atom in this case can only form a tertiary alcohol, an epoxide or a ketone (which would have arisen by rearrangement of an epoxide), then the low field signal must be from a proton geminal to the bromine atom and the chemical shifts at 5.18 τ and 5.26 τ are in the range expected for a proton geminal to an axial bromine atom. These low field signals were identical in shape to that from an equatorial 3β proton and therefore the bromine atom can only occupy the 7α position.

Chemical evidence in support of the assignment of the position and configuration of the bromine atom was given by dehydrobromination of the acetoxybromide (210) with 1,5-diazabicyclo(3,4,0)non-5-ene which yielded the acid (228). The i.r. spectrum of this acid now had three carbonyl bands at 1742, 1730 and 1708 cm^{-1} for a 5 membered ring ketone, an acetate and an acid respectively. The n.m.r. spectrum of this acid showed an AB (H-6, H-7) quartet (J, 10 Hz) of which the A proton was further coupled to another (5α-H) proton (J, 3 Hz). The ease of dehydrobromination is consistent with a trans diaxial elimination of hydrogen bromide. Demethylation of the acid methyl ester during this reaction showed that the bicyclononene is a stronger base than halide ion which did not effect demethylation under the same conditions.

The signal at 7.30 τ in the n.m.r. spectrum of the ketone (206) and at

7.26 τ in that of the acetate (210) was attributed to the 14α proton of a 15-ketone. Both a tertiary alcohol and an epoxide were ruled out when no reaction occurred on addition of phosphoryl chloride to the acetate (210). Since this reagent is relatively bulky, the acetate (210) was treated with toluene-p-sulphonic acid whereupon a slow but quantitative reaction occurred which yielded the alkene (229). The n.m.r. spectrum of this alkene showed that the signals from the 3β proton and the acetate group of (210) had vanished and had been replaced by a "doublet" at 4.58 τ from the protons at C-2 and C-3. This doublet is consistent with a cis-disubstituted double bond of which the two protons are in a very similar environment. Under these conditions, $\Delta\sigma$ is small and the AB pattern observed for the alkene (229) will approach an A_2 (singlet) pattern.[198] This phenomenon had previously been observed in the n.m.r. spectrum of lup-2-ene.[199] Trans diaxial elimination is a common, but not a characteristic reaction of 3α-oxygenated triterpenes.[200]

The n.m.r. spectrum of (229) also showed a signal at 7.29 τ from the 14α proton and hence the chirality at C-14 had not altered. Similarly, Taylor has shown that neotrichilenone (230) is not isomerised under basic conditions.[77] Models show that a cis fusion of rings C and D is more stable than a trans ring fusion since in the former, ring C will adopt a boat conformation while in the latter, ring C will have a skew boat conformation with consequent strain in both rings C and D. The CD curve (see below) shows that a chair conformation

of ring C is most improbable.

The 15-ketone was shown to be particularly hindered since reduction with sodium borohydride failed, whereas reduction with lithium aluminium hydride removed the bromine atom and also gave a mixture of 15α and β-alcohols.

The apotirucallane nucleus and the presence of a 14αH-15-ketone group in the two bromides (206) and (210) was clearly established by comparison of the o.r.d. and c.d. curves of these two compounds with those of the ketone (231) which had been obtained as a minor product from ozonolysis of the diacetate (187).[129] The o.r.d. curves of the acetates (210) and (231) [see appendix II] were particularly complex, but were completely superimposable. The differential dichroic absorption of the 15-ketones (206) and (210) was also superimposable but the diketone showed an additional positive absorption due to the 3-ketone group. This positive Cotton effect was identical with that observed for 3-oxo-triterpenes which possess an 8β methyl group (see lupan-3-one, chapter 4).

The negative Cotton effect of the 14αH-15-ketone group is interesting since a strong positive effect is given by 14αH-15-oxosteroids.[201] The difference in this case is due to the presence of a 7α functional group. If ring C adopts a chair conformation, then ring D would lie in a plane perpendicular to rings A B and C (232), there would be a cis 1,3-diaxial interaction between the 8β methyl group and ring D, and rings A, B and C and the 7α-substituent would lie in a positive octant of the carbonyl group. This conformation would lead

to a strong positive Cotton effect as observed for the steroids. If ring C adopts a boat conformation, then ring D would lie more in the plane of rings A, B and C (233), there would be no interaction between the 8β methyl group and ring D, and the 7α-substituent would now lie in a negative octant. This conformation would therefore lead to a weak negative Cotton effect and this was observed for the diketone (206), the bromoketone (210) and the diacetate (231). The origin of the fine structure of the o.r.d. and c.d. curves is unknown but it is an excellent means by which these compounds may be distinguished.

The mass spectra of the diketone (206) and the acetoxyketone (210) also provided strong evidence for the location of the ketone group at C-15. The origin of the ions observed in the high mass region of the spectra of these two compounds is shown in fig.44.

The origin of the ion at m/e 251, which was observed in the spectra of both compounds is shown in fig.45. Djerassi[202] showed that this fragmentation is characteristic of steroidal 14αH-15-ketones and it gave rise to the base peak in the spectra of these compounds. He also demonstrated that the same fragment does not arise from a McLafferty rearrangement, since the 7β proton is too distant from the 15-ketone to take part in such a rearrangement.

The mechanism by which these bromides must be formed is shown in fig.46. Bromination of the Δ^7-alkene will yield a bromonium ion which will rearrange to an apotirucallene tribromide. The stereoselectivity of this

rearrangement was mentioned in section 2.8. Oxidation of this tribromide with ozone will yield an epoxytribromide, which on reductive work up will yield the bromoketone.

This mechanism explains why so little of the desired Δ^7-epoxides was isolated from the products of ozonolysis. It is particularly interesting because Cotterrell[109] used ether as a solvent for bromination and obtained only a 24,25-dibromide, whereas chloroform was used in the present work. The selectivity of bromination in the side chain in ether is identical with the behaviour of aromatic peracids towards the two double bonds. Ourisson[203] showed that in ether, p-nitroperbenzoic acid selectively epoxidised the 24,25-double bond of euphol, while in chloroform both the 24,25 and the 8,9 double bonds were oxidised.

Proof that the bromoketones were formed from the Δ^7-alkene (137) was provided by the bromination, in chloroform, of a pure sample of this alkene. Ozonolysis of the product and reductive work up gave a mixture of two products, the more polar of which was the enone (213). This enone cannot have arisen as in fig.39 but must have been formed by the pathway shown in fig.47. This is yet a further way in which the amount of isolable epoxide will have been reduced. Addition of boron trifluoride to the less polar product from above left it unchanged. The product was isolated and was found to be the bromoketone (210).

2.12 FURTHER STUDIES OF THE CHEMISTRY OF THE 24,25-DOUBLE BOND

A suitable method for protecting the 24,25-double bond now had to be found so that allylic oxidation in ring D of the apotirucallenes (187) and (188) could be effected. An epoxide appeared to be an attractive protecting group since it could be converted into a methoxyketone (fig.23) after which allylic oxidation could be carried out, followed by completion of the formation of the lactone ring. The difficulty to be overcome was that both the 14,15 and 24,25-double bonds are trisubstituted and were expected to be equally reactive towards electrophilic reagents. However, the 14,15-double bond is more hindered than that in the side chain and this property was therefore investigated. Direct epoxidation of (188) was not possible since Lavie[128] had shown that epoxidation of (234) to (235) could be achieved with perbenzoic acid which is the least reactive of the aromatic peracids and hence an indirect method of epoxidation was required.

The first method investigated was substitution of a 24-bromide atom of a 24,25-dibromide by an acetate group using tetramethylammonium acetate in boiling acetone. Under these conditions the acetate group was expected to be a relatively strong nucleophile. Treatment of the bromoacetate with base should have yielded an epoxide. The dibromide (168) was used as a model compound and reaction with tetramethylammonium acetate gave the enol bromide (236) in high yield.

Elemental analysis of this enol bromide showed that dehydrobromination had occurred. The n.m.r. spectrum showed no signals from protons geminal to a bromine atom and no signals from an olefinic proton. The two methyl groups at C-25 had chemical shifts of 8.14 and 8.26 τ compared with 8.32 and 8.42 τ for those of an isopropylidene group and 8.04 and 8.20 τ for those of a 24,25-dibromide.

Oxidation of the enol bromide with potassium permanganate and sodium metaperiodate[204] failed but this may merely have been due to a slow rate of reaction in a solution containing a high proportion of organic solvent.[205] Ozonolysis of the enol bromide gave a large number of products which were not investigated.

Reduction of the enol bromide with lithium aluminium hydride gave the diol (237). Elemental analysis indicated that the bromine atom was still present and the chemical shifts of the C-25 methyl groups (8.14, 8.23 τ) showed that the enol bromide group had been unaffected by this reagent. Hydrogenation of the diol (237) gave tirucall-8-en-3α,21-diol (238).

Of the factors which determine whether substitution or elimination will take place,[206] temperature is the most important. Although the temperature of the attempted substitution reaction was not high (56°), it may have been high enough to cause elimination in this case. Alternatively the strength of the acetate group as a base may have been greater than its strength as a nucleophile

under these conditions, or finally, the steric hindrance of the dibromide group may be such that elimination of a bromide ion from C-25 will occur irrespective of the conditions used.

The preparation of an epoxide by way of an iodohydrin[207] was also investigated since iodine was not expected to attack a Δ^{14}-double bond. The ester (133) was oxidised with iodine and iodic acid in aqueous dioxan and the product was treated with potassium hydroxide in methanol. Acetylation of the hydrolysis product finally gave three products. The least polar was starting material and the second product was the epoxide (239) which was isolated in 7% yield. The most polar product was the diacetate (240) which was isolated in 17% yield.

The i.r. spectrum of (240) showed an OH band at 3585 cm^{-1} ($\Delta\nu$, 35 cm^{-1}) indicative of hydrogen bonding,[208] and the n.m.r. spectrum showed signals from two acetoxyl groups, a signal at 5.31 τ from the 3β proton and a broad signal at 5.21 τ from the C-24 proton geminal to an acetate group. The two methyl groups at C-25 resonated coincidentally at 8.85 τ, in close agreement with those of t-butyl alcohol (8.78 τ).

Alkaline hydrolysis of the diacetate (240) gave the triol (241) as a mixture of two products of very similar polarity which were thought to be C-24 epimers. The n.m.r. signal of one of the two C-25 methyl groups occurred as a doublet. This phenomenon is due to long range W coupling[159] between this

methyl group and the C-24 proton (242). The 24,25-diol group will be held in a near eclipsed conformation by H-bonding, which will give rise to the coupling observed.

This epoxidation reaction has much potential but the conditions need to be optimised. If aqueous iodine had been used then the strongest nucleophile in solution would have been an iodide ion and an alkyl diiodide would have been formed. In addition, iodide ions and iodine would have combined to form tri-iodide ions. The reaction was therefore carried out in dilute solution and at an elevated temperature to avoid diiodide formation and iodic acid was added in order to oxidise iodide ions back to iodine. Under these conditions, water will now be the strongest nucleophile and it will attack an iodinium ion to form an iodohydrin. Cornforth[207] used calcium hydroxide to form an epoxide from an iodohydrin but this base was ineffective in the present case and alcoholic potassium hydroxide had to be used. Release of strain in the epoxide ring resulted in formation of a diol and the use of sodium aluminate in an aprotic solvent has been suggested in order to avoid this reaction.

The ketolactone (fig. 23) was prepared via a methoxyketone. A methoxy group is rather inert and formation of a diol would be more suitable. A mild oxidising agent (e.g. silver carbonate) could be used to oxidise the C-24 hydroxyl group to a ketone in the presence of the C-25 hydroxyl group. A diol could be prepared by the action of base on a 24,25 epoxide as above, or

alternatively acid catalysis could be used. Perchloric acid in butan-2-one has been used to prepare a steroid diol from an epoxide.[209] Addition of water was shown to impede the rate of the hydrolysis and so water was not added in the present case.

Addition of perchloric acid to the epoxide (239) in butan-2-one gave a quantitative yield of the ketone (243). The chemical shift of the C-25 methyl groups was 8.92 τ (J, 7 Hz) compared to 8.91 τ in the ketone (244).[133] The result of this reaction would appear to indicate that there is a fine boundary between what constitutes insufficient water, and what is too much water. 72% perchloric acid was used in the present case while Meakins' group used 61% acid.

The mechanism of this epoxide rearrangement must be concerted[210] since if it had been a stepwise mechanism, a diol would have been formed. By comparison of this reaction with the boron trifluoride catalysed rearrangement of a 24,25-epoxide in the euphol[190] and the lanosterol series,[211] two products were expected (fig.48). Migration of the 24-proton would yield a ketone while migration of the 23-alkyl group would yield an aldehyde (245). However no signal from an aldehyde proton could be detected in the n.m.r. spectrum of the ketone (243). Formation of an aldehyde by this method has been utilised in a recent synthesis of the natural product cycloneolitsin (246).[212]

It had initially been assumed that bromination of the apodiacetate (188) would result in attack at the Δ^{14}-double bond but since indirect epoxidation of

the 24,25-double bond had not been particularly successful, bromination was finally investigated. Addition of bromine to the diacetate (188) in chloroform gave the dibromide (247) in 38% yield. The moderate yield of this reaction indicated that the above assumption had been correct.

2.13 SOME STUDIES OF ALLYLIC OXIDATION

Oxidation of the allylic position at C_{16} in the apodiacetate (247) was the next major objective. A variety of reagents is available for this oxidation, for example:

(i) ozone, ethyl acetate.

(ii) selenium dioxide, water, dioxan.[213]

(iii) selenium dioxide, acetic anhydride, acetic acid.[213]

(iv) N-bromosuccinimide, lead tetra-acetate, benzene.[214]

(v) N-bromosuccinimide, water, calcium carbonate, dioxan, light.[215]

(vi) t-butyl perbenzoate, cuprous bromide, benzene.[216]

(vii) oxygen, sensitiser, pyridine, light.[217]

(viii) chromium trioxide, water, acetic acid.[218]

(ix) t-butyl chromate, carbon tetrachloride.[219]

(x) chromium trioxide, pyridine, dichloromethane.[220]

The methods investigated for the allylic oxidation of (247) were those which could also be used for oxidation of compounds with a furan side chain.

Ozonolysis of the apodiacetate (187) was shown[129] to yield the epoxide (223) in 60% yield, together with the ketone (231) and a ketoaldehyde as minor products.

Similarly, oxidation of the apodiacetate (187) with (iv) gave a number of products in low yield including the allylic acetate and the desired unsaturated ketone. Ramm[221] found that deoxyhavanensin triacetate (255) could not be oxidised with t-butyl perbenzoate at room temperature, and a complex product resulted when the reaction was carried out at the boiling point of benzene.

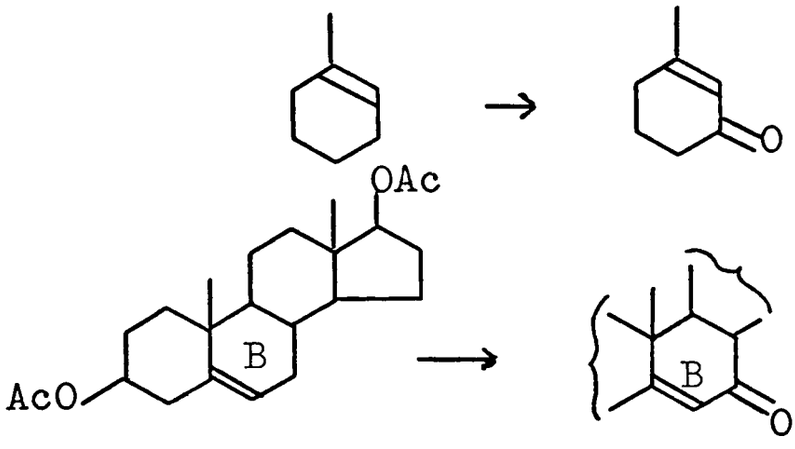
Photo-oxygenation (vii) of a furanoid compound is expected to result in oxidation of the furan ring.[222]

Cotterrell[129] used (viii) to oxidise the apodiacetate (187) and obtained the desired enone (248) in 40% yield, together with the 15-ketone (231) as a minor product. Acidic conditions however are unsuitable for oxidation of a furanoid compound (see section 2.14).

Dauben[220] has found that bispyridinechromium oxide in dichloromethane (X) is superior to both (viii) and (ix) for the allylic oxidation of alkenes (see Table 4) and these neutral conditions appeared to be applicable to the oxidation of a furanoid compound (see below).

The dibromide (247) could not be oxidised at room temperature with selenium dioxide in aqueous dioxan, while under reflux the "major product" was found to be starting material (11%).

TABLE 4

Reaction	Yield of Enone (viii)	(ix)	(x)
	20%	-	60%
	-	60%	76%

Trachtenberg[213] has given an extensive review of the oxidation of alkenes with selenium dioxide and the mechanism which he has proposed for this reaction shows that it will theoretically be difficult to effect oxidation at C-16 in an apotirucallene with this reagent. Guillemonat[223] has formulated a set of empirical rules for the oxidation of trisubstituted alkenes with selenium dioxide.

(a) Oxidation always occurs on the disubstituted side of a double bond if there is a non-bridgehead allylic hydrogen available there. This is in contrast to oxidation with chromium species.

(b) Oxidation of 1-alkylcyclohexenes occurs in the ring rather than in the side chain.

(c) Oxidation never occurs at a bridgehead position in bicyclic systems, falling within the limit of Bredt's rule.

(d) All other things being equal relative to the above rules, the preferred order

of reactivity is $CH_2 > CH_3 > CH$.

(e) If the preferred allylic position is tertiary, then a diene will generally be produced in preference to a tertiary carbinol.

(f) Allylic rearrangement products can and will be formed.

(g) Skeletal rearrangement can occur if the preferred allylic position is adjacent to a quaternary centre.

The mechanism of oxidation of (L)-menth-1-ene with selenium dioxide[224] is shown in fig.49. Markownikov addition of selenium dioxide to a double bond from the less hindered face of the molecule will yield the selenite ester (251). If this ester were to undergo a S_N1, S_N1' or a S_N2 reaction by water, then an essentially racemic mixture of the cis and trans alcohols would be expected. However there was a predominance of only partially racemised (L)-transcarvotan-acetol (252) and hence a S_Ni' or more probably a S_N2' reaction[225] must be responsible for the stereospecificity of this hydroxylation. Oxidation of the allylic alcohols is assumed to be similar to that by chromium oxide, but the allylic ester formed (fig.50) is capable of rearrangement and racemic carvotan-acetone is formed, particularly in strongly ionising solvents.

Application of this mechanism to the oxidation of the dibromide (247) is shown in fig.51. Markownikov addition of selenium dioxide to the Δ^{14}-double bond will yield the selenite ester (253). Neither the 8β methyl group, nor the 13α methyl group will be likely to migrate to C-14 and therefore a most probable

product from this reaction will be the diol (254). Tsutsumi[226] has shown that a diol will be formed from the oxidation of alkenes with selenium dioxide in acidic conditions. Further evidence for the formation of a diol in the present case was the observation that much polar material remained at the base line of p.l.c. plates used for isolation of the products from oxidation of the dibromide. In order to effect oxidation of an apotirucallene to the desired 14-en-16-one, anti-Markownikov addition to the Δ^{14}-double bond would have to occur, by the Trachtenberg mechanism, and this is unlikely since the buttressing effect of the 8β methyl group would prevent this type of addition, but since Lavie[76] has reported the oxidation of azadirone (59) to azadiradione (62) with selenium dioxide, then other factors may be involved.

Oxidation of the apodiacetate (187) with (v) was also investigated. During this reaction, bromine was observed to appear after fifteen minutes and to vanish after forty-five minutes. This reaction was particularly selective and gave only starting material in 45% yield and the enone (248) in 31% yield, while oxidation of (187) with anhydrous bispyridinechromium oxide in dichloromethane gave starting material in 40% yield and the enone (248) in 45% yield.

Similarly the dibromide (247) was oxidised with bispyridinechromium oxide. The product enone (249) was isolated but was not characterised, and was debrominated with zinc dust. However attempted purification of the desired enone (250) led to its decomposition with each elution on silica plates.

This decomposition was not observed with the enone (248) and it must therefore be due to some interaction between the 24,25-double bond and the enone function in ring D.

2.14 ATTEMPTED ALLYLIC OXIDATION OF HAVANENSIN TRIACETATE

Since allylic oxidation in ring D of an apotirucallene had been achieved under essentially neutral conditions, the same conditions were thought to be applicable to allylic oxidation of an azadirene.

From its n.m.r. spectrum, crude havanensin "triacetate" was found to be a mixture of diacetates and acetylation of this mixture gave the pure triacetate.

Recently a number of reagents have been shown to reduce epoxides to alkenes in good yields including chromous chloride,[227] trialkylphosphines,[228] magnesium bromide-magnesium amalgam,[229] chromium (II) ethylenediamine[230] and a zinc-copper couple.[231] Triphenylphosphine in dimethylformamide was ineffective but reduction of havanensin triacetate with a zinc-copper couple gave the alkene (255) in 68% yield which compares favourably with that obtained for the deoxygenation of cholesteryl epoxide.[231]

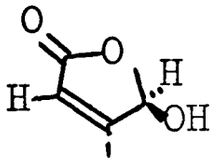
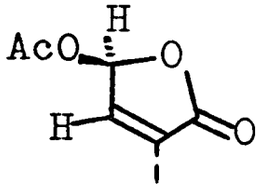
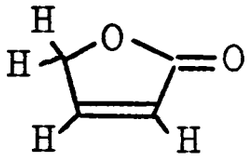
Oxidation of deoxyhavanensin triacetate with selenium dioxide in aqueous dioxan at 65° resulted in a 75% recovery of unreacted alkene and no enone could be detected. Surprisingly bispyridinechromium oxide was also unable to effect allylic oxidation of (255). Reaction of deoxyhavanensin triacetate with chromic

acid in acetone gave a mixture of products from which isophotodeoxyhavanensin triacetate (256) was isolated. The structure of this butenolide confirmed the assumption that acidic oxidising agents would attack a furan ring.

Elemental analysis and mass spectral molecular weight of (256) indicated that two oxygen atoms had been introduced to deoxyhavanensin triacetate. The i.r. spectrum of (256) showed bands for an alcohol, an acetate group (1721 cm^{-1}) and one for an $\alpha\beta$-unsaturated γ-lactone (1756 cm^{-1}). In the n.m.r. spectrum of (256), the two proton multiplet at 5.29 τ was assigned to the 1β and 3β protons, the one proton singlet at 4.78 τ to the 15-proton and the one proton multiplet at 4.57 τ to the 7β proton, by comparison with the n.m.r. spectrum of (255), which showed that rings A, B, C and D were identical with those of deoxyhavanensin triacetate. The signals from the three furan protons of (255) were absent but had been replaced by a broad one proton multiplet at 3.95 τ and a sharp one proton singlet at 4.07 τ which were assigned to the 21-proton and the 22-proton respectively.

The chemical shifts of the protons of the butenolide group of isophotodeoxyhavanensin triacetate (256), photogedunin acetate (257)[232] and of but-2-enolide[233] have been collected in Table 5 . These data clearly showed that (256) had a proton α to the carbonyl group and this established the position of both the carbonyl and the hydroxyl group. Acetylation of an alcohol usually shifts the signal from the proton geminal to an oxygen function downfield by

TABLE 5

Chemical shift (τ) of		α-proton	β-proton	γ-proton
	(256)	4.07	-	3.95
	(257)	-	2.62	2.94
		3.85	2.37	5.08

approximately 1.0 τ[234] and this agreed very well for the difference in chemical shift of the γ-protons in (256) and (257) [Table 5]. The broadness of the geminal proton signal in both cases lent further support to the assignment given above and also indicated that the γ-proton had an axial configuration. The uv spectrum of (256) showed a band at 213 nm for an αβ unsaturated butenolide[235] and on addition of aqueous sodium bicarbonate, gas was evolved, and a further band appeared in the spectrum at 255 nm and this behaviour is very characteristic of γ-hydroxy-αβ-unsaturated butenolides.[236]

The mechanism of addition of oxygen by photolysis is analogous to a Diels-Alder addition across a furan ring.[222] Reaction of furans with oxidising agents is also known to involve 1,4-addition at the carbon atoms adjacent to the oxygen atom. The exact mechanism is not known but is thought to go via the pathway shown in fig.52. The carbon atom farthest from ring D, i.e. C-23, is

expected to be oxidised to a higher level than C-21. This would explain the difference in the position of the carbonyl group in (256) and in photogedunin acetate (257).

The similar yields of the enone (248) obtained from N-bromosuccinimide and bispyridinechromium oxide oxidations of (187) are interesting since both reactions are thought to go via a radical mechanism. In the case of oxidation with N-bromosuccinimide[237] (fig.53), abstraction of an allylic proton by a bromide radical will yield an allylic bromide. Substitution by water will then yield a 14-en-16-ol which will be oxidised to an enone by N-bromosuccinimide.[238]

Unlike selenium dioxide, oxidation with chromium oxides always takes place at the carbon atom adjacent to the least substituted end of a trisubstituted alkene[239] (fig.54). This mechanism may possibly explain why bispyridinechromium oxide failed to effect allylic oxidation of deoxyhavanensin triacetate. If the C-17 position adjacent to the furan ring was more reactive than the C-16 position, then abstraction of the C-17 proton would yield either a resonance stabilised radical or a tertiary chromium ester, neither of which would undergo further oxidation.

In several sections of this work, reference has been made to the formation of epoxides during oxidation with chromium oxides. Initial formation of a Δ^{7}, Δ^{8} or $\Delta^{9(11)}$ epoxide is responsible for the production of a 7,9(11)-diene during oxidation of tetracyclic triterpenes with chromium(VI). Similarly the butyro-

spermol-apoeuphol rearrangement[240] (fig. 55) must involve the intermediacy of a Δ^7-epoxide. Rocek[241] has provided experimental evidence for the intermediacy of epoxides in the chromic acid oxidation of alkenes. Under anhydrous conditions, the mechanism of this reaction is thought to proceed as shown in fig. 56.[239]

Since allylic oxidation at C-16 of an apotirucallene cannot be satisfactorily achieved in the presence of either a 24,25-double bond or a furan ring, it would appear that the sequence of steps from a tirucallene to an azadirene should progress through initial elaboration of the elemi acid side chain (fig. 23), allylic oxidation in ring D and finally degradation of the γ-lactone to a furan ring.

CHAPTER THREE

A DISCUSSION OF THE CHEMISTRY OF SOME URSANE DERIVATIVES

3.0 INTRODUCTION

During the large scale ozonolysis described in chapter two, several ursan-12-one derivatives were isolated. The structures of these compounds will now be discussed with particular reference to the configuration at C-13. A 13αH-12-ketone will be referred to as the less stable isomer and a 13βH-12-ketone as the more stable isomer.

Rings A, B, C, D and E of the more stable ketones will all adopt a chair conformation (258). If ring E of the less stable isomers were to adopt a chair conformation, then both the C-19 and C-20 methyl groups would be axial to the ring and there would be a cis 1,3-diaxial interaction between the 17β and 19β-methyl groups (259), whereas if ring E were to adopt a boat conformation, the C-19 and C-20 methyl groups would then both be equatorial to ring E and there would be no diaxial interaction with the 17β methyl group (260). In this work therefore ring E will be assumed to adopt a boat conformation in the less stable isomer.

3.1 THE PREPARATION OF α-AMYRIN-12-KETONES

Spring[242] and Ruzicka[243] prepared the less stable ketone (262) from α-amyrin acetate (261) with hydrogen peroxide in acetic acid or by ozonolysis, and considered this compound to be an epoxide. This "epoxide" was rearranged with hydrochloric acid in acetic acid and chloroform to the stable ketone (263)

of which the chirality at C-13 was undefined.

Similarly[242] the less stable ketone (265) was prepared from α-amyrin benzoate as above or with potassium permanganate in acetic acid, and was rearranged to the more stable ketone (266). Hydrolysis of the stable ketone (266) and acetylation of the product (267) gave the stable ketone (263), while oxidation of the alcohol (267) gave the stable diketone (268).

Spring[244] later found that the compounds which were previously considered to be epoxides were unstable ketones, as also did Fieser[245] who showed that the epoxides could in fact be isolated, provided they were crystallised directly from a reaction mixture without recourse to chromatography.

Characterisation of an ursan-12-one with the usual reagents was rendered difficult by the steric hindrance of the C-19 methyl group, but this fact was a means by which an ursane compound could be distinguished from an oleanane compound since the 12-ketone group in the latter series was not subjected to this hindrance.

3.2 THE PREPARATION OF URSOLIC ACID 12-KETONES

Ruzicka[246] prepared the unstable ketone (271) from acetyl ursolic acid (270) with hydrogen peroxide in acetic acid but its configuration at C-13 was undefined. Methylation of this acid (271) gave the unstable ketone (272) which was also prepared by ozonolysis of the ester (136).

Spring[247] similarly prepared the unstable ketone (272) which was rearranged to the more stable isomer (208) with hydrochloric acid in chloroform and acetic acid. A mixture of the two ketones (272) and (208) showed a considerable depression of melting point.

3.3 DIFFERENTIATION OF THE C-13 ISOMERS OF PENTACYCLIC TRITERPENE 12-KETONES

Both Spring[247] and Fieser[245] noted the considerable difference in optical rotation of the isomeric ketones in the α-amyrin series and from table 6 , the difference in molecular rotation between the unstable and the stable ketones can be seen to be approximately +575°. However, the difference in molecular rotation between the isomeric ketones in the ursolic acid series (table 7) is approximately -40°. This drastic difference must be due to the carbonyl group at C-17 in the ursolic acid derivatives and a similar effect is also noted from o.r.d. and c.d. measurements which very readily distinguish a 13αH-12-ketone from a 13βH-12-ketone. Djerassi[248] has determined the o.r.d. of some pentacyclic triterpene 12-ketones but recorded only one maximum for each compound and did not record any amplitudes.

The origin of the difference in the amplitudes of the o.r.d. curves of isomeric 12-ketones can be demonstrated by reference to the octant projections of the ketones (272) and (208) shown in fig. 58. An unstable ketone should have

TABLE 6

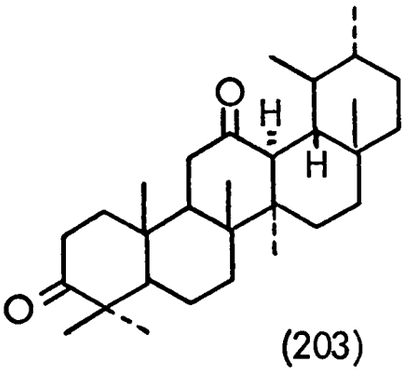
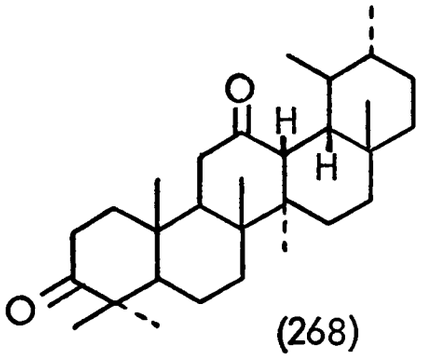
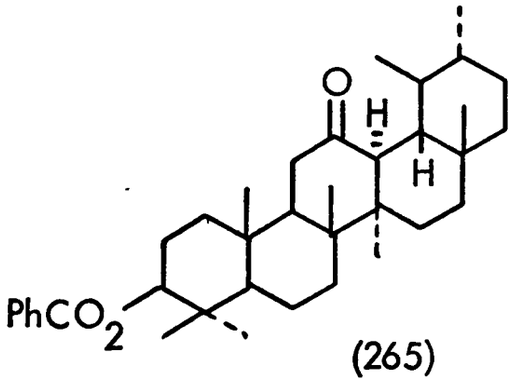
Compound	Ref.	α_D	M_D	ORD (a)
 (203)	this work	+144°	+634°	-
 (268)	242	+2°	+9°	-
 (265)	242 242	+132° +130°	+721°	

TABLE 6 (cont.)

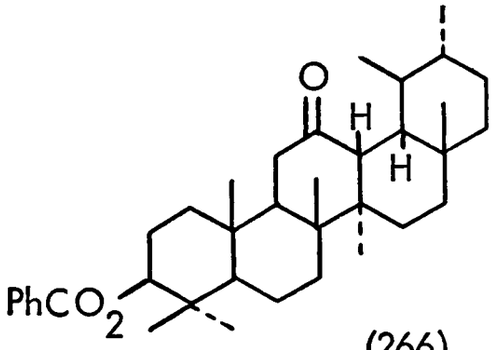
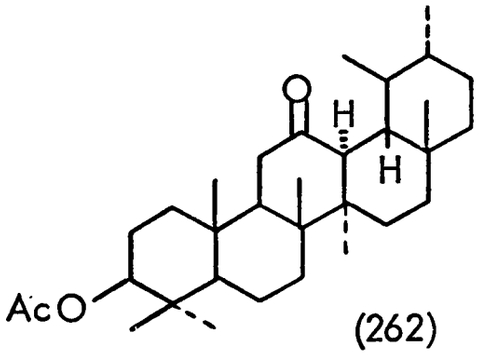
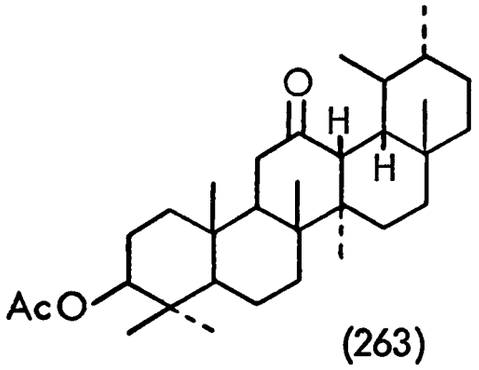
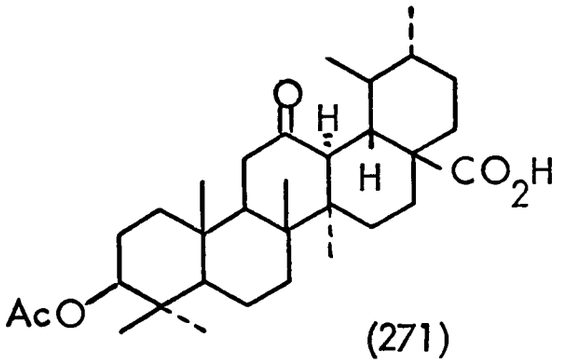
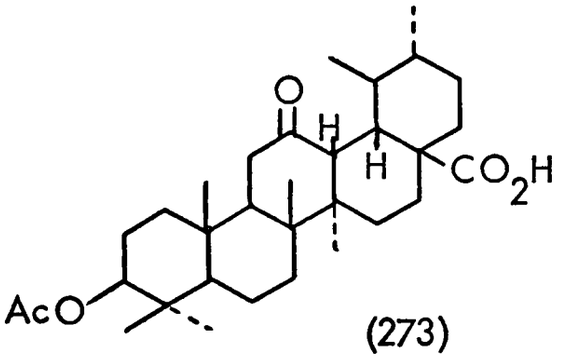
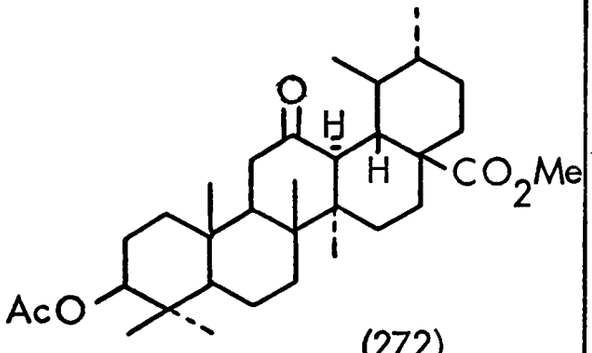
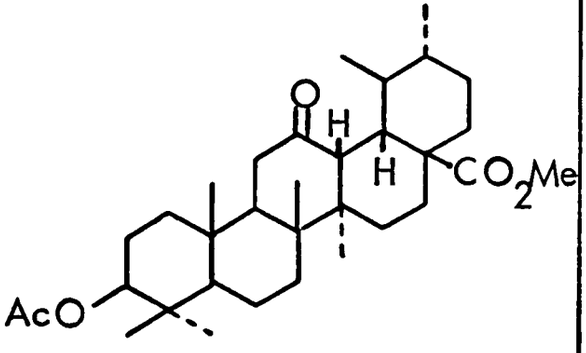
Compound	Ref.	α_D	M_D	ORD (a)
 (266)	242	+25°	+137°	-
 (262)	243 242 242 244 this work 245	+139° +114° +111° +115° +114° +124°	+557°	+61
 (263)	243 242 242 244 this work	+15° +11° +9° +12° -3°	+44°	+37 impure

TABLE 7

Compound	Ref.	α_D	M_D	ORD (a)
 (271)	246	+40°	+206°	-
 (273)	this work	+48°	+247°	+3
 (272)	246 246 247 247 this work	+35° +29° +25° +27° +31°	+132°	+109
 (208)	247 247 this work	+32° +35° +46°	+169°	+3

a large positive Cotton effect while the stable isomer should have a small positive effect. In the α-amyrin series the amplitudes should be slightly smaller than those in the ursolic acid series due to the difference in rotatory power between the carboxyl group and the methyl group at C-17.

The experimental amplitudes recorded in the present work are in agreement with these principles. The stable ketones (273) and (208) had very small amplitudes ($+3^{o}$) while the unstable isomer (272) had a large amplitude ($+109^{o}$) and the corresponding α-amyrin derivative (262) had a slightly smaller amplitude ($+61^{o}$) as expected. The ketone (263) which was not pure, had an amplitude larger than was expected for the pure compound.

3.4 THE STRUCTURE OF SOME PENTACYCLIC TRITERPENE 12-KETONES

(13αH)Ursan-3,12-dione (203) was isolated from the product from ozonolysis of a crude mixture of elemi acid methyl esters (chart I). The melting point of this diketone was very similar to that of the known diketone (268) but its optical rotation was considerably greater than that of (268) and the difference in molecular rotation between these two diketones corresponded closely with that observed between the isomeric ketones (265) and (266) and between (262) and (263). The i.r. spectrum of (203) had a strong band at 1705 cm^{-1} for a six membered ring ketone and the n.m.r. spectrum showed signals from six tertiary and two secondary methyl groups. One methyl group, thought to be the 8β-

methyl group, was strongly deshielded and it resonated at 8.74 τ. This phenomenon is characteristic of the 12-ketones.

The diketone (203) was shown to have the 13αH configuration by its conversion to the known acetate (262). Reduction of the dione with lithium tri-t-butoxy aluminium hydride gave a quantitative yield of the ketol (269), whereas use of lithium aluminium hydride would have yielded a mixture of 3,12-diols. Acetylation of the ketol (269) gave a product which had identical physical constants to those reported by Spring for the ketoacetate (262). The i.r. spectrum of (262) showed a band at 1735 cm^{-1} for the acetate group and one at 1707 cm^{-1} for the ring C carbonyl group and the 8β-methyl group had a chemical shift of 8.77 τ in the n.m.r. spectrum.

The ketone (263) isolated during the present work was not pure. It was characterised by its i.r. spectrum which showed two carbonyl bands at 1735 and 1692 cm^{-1} and by its n.m.r. spectrum. The 8β-methyl group had a chemical shift of 8.84 τ and the signal at 7.36 τ (J, 3.5 Hz) was assigned to the 13β-proton.

The corresponding ketone in the ursolic acid series (208) was also impure but was identified by the chemical shift of the 13β-proton (7.04 τ; J, 3 Hz) and of the 8β-methyl group (8.79 τ) and also by the r.d. amplitude (+3°).

The unstable ketoester (272) was isolated pure. The 12-ketone group absorbed at 1685 cm^{-1} in the i.r. spectrum, the 8β-methyl group had a chemical

shift of 8.65 τ and the r.d. amplitude was (+109°). Hydrolysis of this ester and acetylation of the product gave the stable ketoacid (273). The difference in molecular rotation between this acid (273) and the known unstable ketoacid (271) verified that isomerisation at C-13 had taken place on hydrolysis of the ester (272). The i.r. spectrum of the ketoacid (273) showed three carbonyl bands at 1750, 1731 and 1693 cm^{-1} for the acid, acetate and ketone respectively, and the acid had an r.d. amplitude of +3°.

3.5 THE MASS SPECTRA OF SOME PENTACYCLIC TRITERPENE 12-KETONES

Djerassi[249,250] has described the mass spectra of some pentacyclic triterpenes, including some 12-ketones. From the spectra of the ketones (203), (269) and (262) recorded during the present work, it has been possible to postulate further fragmentation patterns in addition to those described by Djerassi. The mass spectrum of (13αH)ursan-3,12-dione is given in appendix 4, and a table of fragments is given in appendix 5.

The ions at m/e 289 and 249 are both derived from rings A and B since they occur at m/e 291 and 251 in (269) and at m/e 333 and 293 in (262). A retro-Diels-Alder reaction (fig.59) of the enol form of ring C of the dione and loss of an electron will give rise to either the major fragment (1), m/e 234, or to fragment (5) which can also arise by homolysis of the 12,13 and 8(14) bonds followed by loss of ketene from a β-cleavage reaction (fig.60). In the spectra

of the alcohol (269) and of the acetate (262), the peak from fragment (5) is accompanied by a relatively intense peak at m/e 190, resulting from loss of water and acetic acid respectively from fragment (5). Loss of a methyl radical from the major ion (1) will generate fragment (3).

Djerassi showed that fragment (7) (fig.61) is characteristic of pentacyclic triterpenes in general and arises by transfer of a proton from C-7 to C-11 with homolysis of the 9(11)-bond and loss of an electron from the A/B fragment. It is also accompanied, in the spectra of the alcohol (269) and the acetate (262), by a peak at m/e 189, resulting from loss of water and acetic acid respectively.

The fragmentation shown in fig.62 is common to cyclic ketones and in this case gives rise to fragment (4), which together with fragment (3) will contribute to the peak at m/e 219.

Homolysis of the 11,12- and 8(14)-bonds will yield fragment (2) which may lose a methyl radical to give fragment (6) (fig.63).

Heterolysis of the 12,13-bond and homolytic cleavage of the 8(14)-bond will give rise to fragment (8) which may lose a methyl radical to give fragment (9). These latter two alkyl fragments may also arise by loss of carbon monoxide from fragments (2) and (6) respectively (fig.63), and their intensity in the spectra of (203), (269) and (262) would appear to indicate that they are particularly diagnostic of the 12-ketone group.

CHAPTER FOUR

A DISCUSSION OF THE CHEMISTRY OF SOME LUPANE DERIVATIVES

4.0 INTRODUCTION

The meliacin group of tetracyclic triterpenes is characterised by an intact ring A which is usually oxidised in the form of a 1-en-3-one or a 1α,3α-diacetate. It is debatable whether the enone is formed from, or is the precursor of the diacetate *in vivo*, but in the present work the diacetate has been synthesised from the enone. For this synthesis, reagents were used which could also be used for synthetic work with compounds which have a furan side chain. The readily available triterpene lupeol was used for this investigation and was firstly converted to lupan-3-one.

4.1 CONVERSION OF LUPEOL BENZOATE TO LUPAN-3-ONE

Pure lupeol benzoate was obtained by repeated crystallisation of the crude benzoate which had been obtained from an extraction of Gutta Jellutong.[199] Prolonged hydrolysis of the benzoate (275) gave lupeol (2) which was then acetylated to give lupeol acetate (276).

Lupeol derivatives are not very soluble in the polar solvents used for hydrogenation, and saturation of the isoprenyl group is usually carried out at elevated temperatures.[251] To overcome this, hydrogenation of lupeol acetate was carried out in purified chloroform at room temperature for 24 hr. Hydrolysis of lupanol acetate (277) then gave lupanol which yielded lupan-3-one on oxidation with Jones reagent.

4.2 THE PREPARATION OF ALICYCLIC AXIAL ALCOHOLS

Alicyclic axial alcohols are particularly difficult to prepare in satisfactory yields and methods for achieving this goal were therefore investigated. The opening of an epoxide invariably gives an axial alcohol[210] and hence reduction of an epoxide with lithium aluminium hydride[252] or with lithium in ethylamine[253] will lead to the desired alcohol. Dauben,[254] Eliel,[255] Beckett[256] and their co-workers have shown that reduction of a ketone with metal hydrides or with dissolving metals will give satisfactory yields of an axial alcohol only when the ketone is very hindered. Meerwein-Ponndorf reduction of a ketone with aluminium isopropoxide gives higher yields of axial alcohols than does reduction with metal hydrides but this method is similarly applicable only for moderately hindered ketones. As an extension of this method, Henbest[257,258] showed that chloroiridic acid will reduce unhindered ketones, exclusively to axial alcohols in excellent yields while hindered ketones do not react with this reagent.

Barton[259] has recently introduced a method for the preparation of axial acetates from a ketone hydrazone, which gives favourable yields of the desired product depending on the location of the hydrazone in an alicyclic system.

4.3 THE ATTEMPTED PREPARATION OF LUPAN-3α-OL

Lupan-3-one hydrazone (283) was prepared from lupan-3-one with hydrazine hydrate in ethanol and resort to an exchange reaction[260] was

unnecessary. The hydrazone crystallised from the reaction solution and recrystallisation was therefore unnecessary and this avoided the formation of an azine.

Reaction of the hydrazone (283) with dry lead tetra-acetate in dichloromethane gave one major product less polar than lupan-3-one, which was shown to be 5(4→3)abeolup-3-ene (γ-lupene, 284). The physical constants of this alkene indicated that it had crystallised together with some iso-γ-lupene (285). γ-Lupene was identified primarily from its characteristic n.m.r. spectrum,[261] and was further characterised by formation of the glycol (286). The reaction of γ-lupene with osmium tetroxide was particularly slow (Ruzicka[262] obtained a 90% yield after 14 days at room temperature) indicative of the steric hindrance of the double bond. Cleavage of the initially formed osmate ester with hydrogen sulphide[263] gave the diol (286). The physical constants of this diol appear to vary somewhat, for example Ruzicka[262] obtained m.p. 164-165°, $[\alpha]_D$ -14° for a hemihydrate, Baddeley[264] obtained m.p. 187-191°, $[\alpha]_D$ -6° and in the present case m.p. 171-175°, $[\alpha]_D$ -55° was obtained. This variation may be due to a difference in the proportion of 3α,4- and 3β,4-diols formed in each case. The i.r. spectrum of γ-lupene diol showed bands at 3610 and 3560 cm^{-1} ($\Delta\nu$, 50 cm^{-1}) which were indicative of hydrogen bonding between the C-3 and C-4 hydroxyl groups. In the n.m.r. spectrum of the diol (286), the C-4 methyl groups had chemical shifts of 8.72 τ and 8.75 τ (cf. 8.78 τ for t-butyl alcohol).

When the hydrazone oxidation was carried out, the mechanism of the reaction had not been defined but the result of the present work supports the mechanism proposed by Barton.[259] A hydrazone is rapidly oxidised to a diazoalkane and protonation of the diazoalkane will then yield a diazonium ion. Loss of nitrogen from this ion will result in the formation of an alkene while S_N2 displacement of nitrogen by an acetate anion will yield an alkyl acetate. Formation of a diazoalkane from lupan-3-one hydrazone is shown in fig.64.

Protonation of the diazoalkane from the α face will give the 3β-diazonium ion and loss of nitrogen from this ion will result in a retro-pinacol rearrangement which is characteristic of triterpenes having a facile leaving group at C-3.[265]

In the present work, only traces of an acetate were observed (n.m.r.) as one might expect for substitution in a neopentyl system. The C-1 atom is in a similar position to the C-3 atom and on treatment with lead tetra-acetate, a C-1 hydrazone is expected to yield an A-nor-B-homo product.

Reaction of lupan-3-one with chloroiridic acid was unsuccessful which showed that the 3-position is too hindered for this reagent to be effective.

4.4 THE PREPARATION OF LUPAN-1α,3α-DIOL DIACETATE

Reduction of an epoxide appeared to be the only satisfactory method for the preparation of the desired axial alcohol. The route investigated for the

preparation of lupan-1α,3α-diol is shown in fig.65.

Bromination of a ketone with hydrobromic acid in acetic acid is not suitable for a compound which contains a furan ring. Buchanan[112] found that cupric bromide effected bromination of a triterpene 3-ketone in high yield and similarly in the present case, bromination of lupan-3-one with cupric bromide in tetrahydrofuran gave a mixture of 2(α and β)-bromolupan-3-one in 85% yield and 2,2-dibromolupan-3-one in 9% yield. For this reaction to occur, it was found that tetrahydrofuran had to be absolutely free of peroxides which prevented bromination from taking place.

In the n.m.r. spectrum of the dibromide (280), the signal from the 1β-proton had a half-width of 2 Hz while that from the 1α-proton had a half-width of 3 Hz. This difference is due to long range coupling between the 1α proton and the protons of the 10β methyl group.[159]

Both the n.m.r. spectrum and the o.r.d. curve of 2-bromolupan-3-one showed that a mixture of C-2 isomers had been obtained. Bromination with cupric bromide is thought to be an ionic rather than a radical reaction and the mechanism appears to be complex.[266]

The formation of a mixture of isomers can be explained by consideration of the stereochemistry of a bromination reaction (fig.66).[267] If ring A of the partially enolised intermediate adopted a chair-like conformation, bromine would become attached to the axial 2β position to yield 2β-bromolupan-3-one.

In this case, the 2β position suffers 1,3-diaxial repulsion from both the 4β and 10β-methyl groups and the intermediate is more likely to adopt a boat-like conformation in which bromine will become attached to the axial 2α position to yield 2α-bromolupan-3-one. In both products ring A will adopt the conformation in which bromine has an equatorial configuration (fig.66).

The 2α-bromo isomer is therefore expected to be the major product from a kinetically controlled reaction but hydrogen bromide is liberated during bromination with cupric bromide[266] and Ourisson[268] has shown that under equilibrating conditions, 2α- and 2β-bromo-lupan-3-one are of nearly equal stability and hence both isomers were obtained in the present case.

Dehydrobromination of α-bromoketones has usually been carried out with 2,4,6-trimethylpyridine but recently several reagents have been found to be superior to this base and include lithium bromide and lithium carbonate in dimethylformamide,[269] hexamethylphosphoric triamide (HMPT, 296),[270] 1,5-diazabicyclo(4,3,0)non-5-ene (DBN, 297),[271] 1,5-diazabicyclo(5,4,0)-undec-5-ene (DBU, 298)[272] and naphthylene-1,8-(N,N,N',N'-tetramethyl)-diamine (NTMD, 299).[273]

Dehydrobromination of (300) with lithium bromide and lithium carbonate in dimethylformamide for 4.5 hr gave the enone in 77% yield.[129] Similarly, yields between 70-90% were obtained with HMPT.[270] Dehydrobromination of 2-bromolupan-3-one with NTMD in dimethylformamide for 6 hr gave lup-1-en-

3-one in 84% yield; with DBN in benzene for 50 hr, a yield of 63%; and with DBN in dimethylformamide for 14 hr, a yield of 90% was obtained.

Oxidation of the enone (287) with alkaline hydrogen peroxide gave the epoxyketone (288) in high yield. The mechanism of this reaction[274,275] (fig.67) involves attack of the peroxide anion at C-1 from the less hindered α face of the enone and subsequent intramolecular expulsion of a hydroxide ion. The stereoselectivity of this oxidation is particularly important in view of the formation of the 1α-hydroxyl group in the next stage of the synthesis. The configuration of the epoxide group in (288) was determined by o.r.d. (section 4.5).

Mangoni and Caputo[276] reduced the epoxyketone (288) with lithium aluminium hydride and obtained lupan-1α,3β-diol in 74% yield and lupan-1α,3α-diol in 29% yield. Similarly Govindachari[277] obtained lupan-1α,3β-diol in 36% yield and lupan-1α,3α-diol also in 36% yield.

A considerable improvement in the yield of the diaxial diol was obtained in the present work by way of a Wharton rearrangement (fig.68).[278] Djerassi[279] used this method to prepare C-1 oxygenated steroids and in particular obtained cholest-2-en-1α-ol from 1α,2α-epoxycholestan-3-one in 57% yield. Reduction of some entantiomeric terpene epoxides (fig.69) to the corresponding enantiomeric allylic alcohols[280] clearly demonstrated the stereospecificity of this reaction. In the present work, reduction of the epoxyketone (288) with hydrazine hydrate in t-butanol gave lup-2-en-1α-ol (289) in 53% yield, in good agreement with

that obtained in the steroid field.

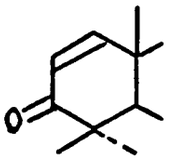
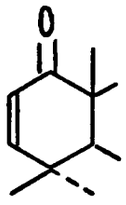
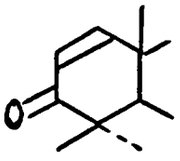
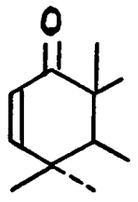
In the n.m.r. spectrum of the alcohol (289), the signals from the C-2 and C-3 protons formed an AB quartet at 4.25 τ (H-2) and 4.44 τ (H-3) [J, 10 Hz] and the two signals from the C-2 proton were both further split(J, 5 Hz) due to coupling between the 1β proton and the C-2 proton. The signal (6.35 τ) from the 1β proton was also a quartet which showed that this proton was coupled to both the C-2 proton (J, 5 Hz) and the OH proton (J, 7 Hz). Spin-spin coupling between an OH proton and a CH geminal proton is not common but it can be observed in dilute solution if the deuterochloroform is free of acidic impurities.[281]

Oxidation of allylic alcohols to unsaturated ketones is frequently effected with manganese dioxide[282] but this reagent was not able to oxidise the alcohol (289) to lup-2-en-1-one. Oxidation of the alcohol (289) with chromium trioxide in pyridine gave a quantitative yield of the enone (290). Some spectral properties of lup-1-en-3-one and of lup-2-en-1-one have been collected in Table 8 .

The outstanding feature of these data is the difference in chemical shift of the olefinic protons for the two types of enone. This difference is an excellent means by which the two enones may be differentiated and it has in fact been utilized to distinguish the isomers trichilenone (301) and isotrichilenone (302) for which the corresponding data[77] are also given in Table 8 .

Epoxidation of the allylic alcohol (289) with m-chloroperbenzoic acid

TABLE 8

Compound	(287)	(290)	(301)	(302)
Chromophore				
ν_{max} ($CHCl_3$)	1660	1675	1650	1680
λ_{max} (ϵ)	230 (9950)	226 (7500)	222 (9800)	220 (9750)
β proton (τ)	2.85 (H-1)	3.70 (H-3)	2.82 (H-1)	3.66 (H-3)
α-proton (τ)	4.17 (H-2)	4.31 (H-2)	4.18 (H-2)	4.32 (H-2)
$\Delta\sigma$ (Hz)	132	61	136	66
J (Hz)	10	10	10	10

in benzene gave 2α,3α-epoxylupan-1α-ol (291) in high yield. The stereoselectivity of this reaction in a non-polar solvent[283,284] is due to hydrogen bonding between the peracid and the hydroxyl group of the allylic alcohol (cf. 303).

The i.r. spectrum of the epoxyalcohol (291) showed a band at 3550 cm^{-1} ($\Delta\nu$, 80 cm^{-1}) indicative of strong hydrogen bonding and since the hydroxyl group was known to have an α-configuration, then the epoxide must also have an α-configuration (304).

The low field region of the n.m.r. spectrum of the epoxyalcohol (291) is shown in appendix 6 . When deuterium oxide was added to a sample of the alcohol (291), the signal from the hydroxyl group vanished and the H-1 quartet collapsed to a doublet, and these phenomena verified the assignments shown.

Henbest[253] and Brown[285] have shown that reduction of an epoxide with lithium in ethylamine is faster and is more stereoselective than reduction with lithium aluminium hydride and in the present case reduction of the epoxyalcohol (291) with lithium in ethylamine gave a quantitative yield of lupan-1α,3α-diol (292). That trans diaxial reduction had taken place was inferred from the narrow half-widths of the signals from the 1β- and 3β-protons (9 Hz) in the n.m.r. spectrum. The i.r. spectrum of this diol showed a free hydroxyl stretching band at 3630 cm^{-1} and a band at 3530 cm^{-1} ($\Delta\nu$, 100 cm^{-1}) which did not decrease in intensity upon dilution, indicative of strong intramolecular hydrogen bonding in a cyclohexan-cis-1,3-diol.[208]

The mechanism of this reduction[286] is shown in fig.70. Nucleophilic attack on the epoxide by a solvated electron gives an anion-radical of which the carbanion is sufficiently basic to abstract a proton from the solvent. The

radical then picks up an electron to yield an oxygen anion which is protonated upon addition of ethanol. In this reduction the 1α-hydroxyl group had no influence on the course of the reaction, as had been observed in several other cases.[287]

Acetylation of the diol (292) gave the diacetate (294). The narrow half-widths of the signals from the 1β and 3β-protons (7 Hz) in the n.m.r. spectrum of (294) again confirmed the axial configuration of the oxygen groups.

Several papers have been published on the n.m.r. spectra of lupane derivatives[288,289,290] and no further comments have been made in this work.

4.5 THE O.R.D. OF SOME LUPAN-3-ONE DERIVATIVES

The stereochemistry of the important intermediate 1α,2α-epoxylupan-3-one was determined essentially by o.r.d. During the work described in this chapter the o.r.d. curves of lupan-3-one, 2(α and β)-lupan-3-one and of 2,2-dibromolupan-3-one were also measured.

The octant projection diagrams of lupan-3-one (279) and of 2α-bromo-lupan-3-one (281) are shown in fig.71, that of 1α,2α-epoxylupan-3-one (288) in fig.72, and those of 2β-bromolupan-3-one (282) and 2,2-dibromolupan-3-one (280) are shown in fig.73.

From fig.71, the o.r.d. amplitude of lupan-3-one was expected to be small and positive,[291] in agreement with experiment (+36.5°). Similarly the

amplitude of 2α-bromolupan-3-one was expected to be positive but somewhat smaller than that of lupan-3-one, and this has been observed (+25°) for a bromoketone related to (281).[289]

From the inverse Cotton effect of αβ-epoxyketones,[292] the amplitude of 1α,2α-epoxylupan-3-one was expected to be large and positive, in agreement with the experimental value (+163°).

Ring A of 3β-bromolupan-3-one will adopt a boat conformation and hence a small positive amplitude was expected for this ketone. Ourisson has noted that the first extremum of a bromoketone related to (282) is positive, but was unable to measure an amplitude for this compound.[289] In the present case a mixture of 2α- and 2β-bromolupan-3-one had an amplitude of +73.5°.

From fig.73, the amplitude of 2,2-dibromolupan-3-one was expected to be large and negative and this was observed in the present work (-131°) and by Ourisson (-124°).[289]

CHAPTER FIVE

A DISCUSSION OF THE CHEMISTRY OF SOME BICYCLIC DITERPENE DERIVATIVES

5.1 THE STRUCTURE OF 12,15-EPOXYLABDA-8(17),13,14-TRIEN-16-YL ACETATE

Recently Ramm[221] isolated a new diterpene furan from the heartwood of Turraeanthus africanus for which the structure (305) has been proposed.

The i.r. spectrum showed bands at 1730 and 1220 cm^{-1} for an acetate group and at 1640 and 892 cm^{-1} for an exocyclic methylene group.

The n.m.r. spectrum showed signals from three tertiary methyl groups, an acetate group, two protons of an exocyclic methylene group, a one proton doublet at 3.64 τ from the β-proton of a furan and a one proton doublet at 2.74 τ from the α-proton of a furan. There was a two proton singlet at 5.02 τ which was assigned to the C-16 protons geminal to both the acetate group and the furan ring and a two proton multiplet at 7.20 τ which was assigned to the C-11 protons.

The base peak in the mass spectrum of the acetate (305) occurred at m/e 284 (M-60) resulting from loss of acetic acid from the molecular ion, and a further peak occurred at m/e 269 [M-(HOAc + Me)] in the high mass region. The origin of the other significant peaks in the mass spectrum, which occurred at m/e 191, 137 and 95, can be envisaged as shown in fig.74. The fragment m/e 191 arises by simple cleavage of the side chain, while that at m/e 137 occurs in the mass spectra of most bicyclic labdane diterpenes[293] and the fragment at m/e 95 is characteristic of dialkyl furans[294] but its origin in the

present case is uncertain.

Alkaline hydrolysis of (305) gave the alcohol (306). The n.m.r. spectrum of (306) was essentially identical with that of (305) except that the C-16 protons now had a chemical shift of 5.47 τ. This shift upfield of 45 Hz is that expected for a primary alcohol ($\Delta\sigma$, 46 Hz).[295] The chemical shift (5.02 τ) of the CH_2OAc protons in (305) is very similar to the shift of the same protons in furfuryl acetate (4.97 τ)[296] and similarly the chemical shift (5.47 τ) of the CH_2OH protons in (306) is very similar to the shift of the same protons in furfuryl alcohol (5.43 τ).[297] The mass spectrum of the alcohol (306) was identical with that of the acetate (305) except that the molecular ion was at m/e 302 and loss of water from this ion would give rise to the base peak, again at m/e 284.

Further evidence in support of the structure which has been assigned to the diterpene (305) is provided by a pathway along which this product might be synthesised in nature (fig.75). Cyclisation of geranylgeranyl pyrophosphate (308) would yield labda-8(17),13-dien-15-ol (309) and allylic oxidation at C-12 (310) followed by formation of a hemiketal (311) and loss of water would yield the furan (312). Oxidation at C-16 would then yield the naturally occurring furan (305). A very similar pathway must be followed during the biosynthesis of the diterpene α-levantenolide (314).[298] Oxidation of the primary alcohol (310) to a carboxylic acid and hydration of the 8(17)-double bond would yield the acid (313) which would then ketalise to the natural product (314). This ketal is the

only known diterpene in addition to (305) which is formed via the unsaturated ketol (310). Almost all other diterpene furans are formed via the intermediate (315), e.g. lambertianic acid (317)[299] of which the furan ring is formed from the terminal end of the side chain.

Unlike the triterpenes, diterpenes exist in both the normal and enantiomeric series, e.g. (306) and (307), and in order to determine the absolute stereochemistry of the furan (305) it was necessary to relate the furan (305) to a compound whose absolute stereochemistry was known. The furans (305) and (306) decomposed after a short period of time and instead of isolating further material, a partial synthesis of the natural product (305) from sclareol (4) was attempted.

5.2 THE ATTEMPTED SYNTHESIS OF 12,15-EPOXYLABDA-8(17),12,14-TRIEN-16-YL ACETATE FROM SCLAREOL

The route which was investigated for this synthesis is shown in fig.76. The key intermediate in this scheme was the aldehyde (325) and very few satisfactory methods are available for the preparation of aldehydes. The most widely used method is reduction of an acid chloride and both the Rosenmund reaction[300] and reduction with lithium tri-t-butoxy aluminium hydride[301,302] have been used for this purpose. Recently Fetizon[303] showed that very high yields of aldehydes can be obtained by oxidation of primary alcohols with silver carbonate precipitated on celite.

The neutral fraction from the oxidation of sclareol with chromic acid in acetic acid[304] contained two compounds. The less polar was norambreinolide (318), ν_{max} 1785 cm^{-1}, and the more polar compound was the acetoxyacid (319). Reduction of this acid, the melting point of which was somewhat higher than that recorded in the literature, with lithium aluminium hydride gave the diol (326), which was also obtained by reduction of norambreinolide.

Upon treatment with acid, the lactone (318) undergoes isomerisation at C-8, while after hydrolysis with potassium hydroxide in alcohol, the hydroxy acid (320) is isolated only with difficulty since it readily cyclises to norambreinolide (318).[305] Direct methanolysis of the lactone was therefore investigated.

Reaction of norambreinolide with sodium methoxide gave a 1:1 mixture of starting material and one more polar product which was assumed to be the methyl ester (321), since reduction of the mixture with lithium aluminium hydride gave the diol (326). No reaction occurred when potassium t-butoxide was added to norambreinolide.

Since a 50% yield at an early stage of a synthesis was undesirable, the alternative route to the aldehyde (325) through the diol (326) was investigated. On reflection, the acid chloride (324) was considered an unsuitable intermediate since it could undergo intramolecular cyclisation as shown in fig.77, in a similar way to that undergone by the elemi acid chlorides (chapter 2.5). At this time Carman and Deeth[306] published an account of the preparation of the acid (323)

along the route (320) → (321) → (322) and this was an additional impetus to attempt an alternative route.

Reduction of norambreinolide with lithium aluminium hydride gave a quantitative yield of the diol (326) and acetylation of this diol yielded the acetoxyalcohol (327). Dehydration of the alcohol (327) with phosphoryl chloride in pyridine gave a quantitative yield of a mixture of the alkenes (328) of which the exo isomer comprised approximately 75-80% (by n.m.r.). Retention of the chair conformation of ring B was the driving force in the production of a large proportion of the exo isomer from this reaction. The i.r. spectrum of the product (328) showed bands at 3075, 1643 and 890 cm^{-1} characteristic of an exocyclic alkene and similarly the n.m.r. spectrum showed signals at 5.15 τ and 5.43 τ from the C-17 protons.

Hydrolysis of the mixture of the acetates (328) gave a mixture of the alcohols (329). It was not possible to separate these alcohols by fractional crystallisation of either their 3,5-dinitrobenzoates or their 3-nitrophthalates.

Oxidation of the mixture of alcohols (329) with silver carbonate gave a very high yield of the mixture of aldehydes (325). The i.r. spectrum of the product showed bands at 2810, 2710 and 1730 cm^{-1} for an aldehyde group and the aldehyde proton resonated at 0.23 τ in the n.m.r. spectrum. It was not possible to separate the aldehydes (325) by fractional crystallisation of either their 2,4-dinitrophenylhydrazones or their bisulphite addition derivatives.

Reformatsky condensation[307,308] of the aldehydes (325) with ethyl α-bromoacetate and activated zinc wool[309] in ether/benzene, followed by work up with ice-cold sulphuric acid[310] gave an excellent yield of the β-hydroxy-esters (330) and addition of trimethyl borate[311] was thus unnecessary.

At this stage of the synthesis, the pure exocyclic alkene (331) was separated from the Δ^7-isomer. This was achieved by making use of the fact that a trisubstituted alkene has a greater electron density than a disubstituted alkene and the former will react with a peracid at a faster rate than will a disubstituted alkene.[312] Denny[313] has shown that the exocyclic alkene (339) can be separated from the Δ^3- and Δ^4-isomers by epoxidation of a mixture of the three isomers under carefully defined conditions.

In the present work reaction of the mixture of isomers (330) with o-monoperphthalic acid in ether gave two compounds. The less polar was a mixture of the hydroxyl epimers of the exoalkene (331) while the more polar was a similar mixture of the 7α,8α-epoxides (336).

The C-12 epimers of the alkene (331) were separated by p.l.c. and the less polar epimer was found to be the R-epimer (332) and the more polar was the S-epimer (334). The hydroxyl group in both epimers gave a broad band at 3540 cm^{-1} ($\Delta\nu$, 90 cm^{-1}) in the i.r. spectrum which is typical of a chelation hydrogen bond.

The configuration of the hydroxyl group at C-12 can be assigned from

Brewsters rules for conformational asymmetry.[314] If one considers the side chain fragment of the S-epimer (334), three gauche conformers can be formed (334,A, B,C). In order to calculate the contribution of the side chain fragment to the optical rotation of the S-epimer, Brewster has assumed that only stable conformations need to be considered and that conformer C will make a negligible contribution. In the present case, the CH_2CO_2Et group has been assumed to be equivalent to a CH_3 group and the C-9 carbon has similarly been approximated to a methyl group. From a calculation based on the above rules, conformer A will make a contribution of -21° and conformer B will make a contribution of $+59^{\circ}$ and therefore the total contribution of the side chain to the molecular rotation of the S-epimer will be $+19^{\circ}$ and for the R-epimer this will be -19°. The calculated difference in the molecular rotation of the two epimers ($\Delta M_D = 38^{\circ}$) is surprisingly close to the experimental value ($\Delta M_D = 45^{\circ}$). In the present calculation, a Newman projection along the 11,12 bond was considered, but the same values are obtained if a projection along the 12,13 bond is considered. From this calculation it may be assumed that the S-epimer will have the more positive optical rotation and on this basis, the S-configuration was assigned to the more polar compound. An identical result is obtained if only the atomic asymmetry at C-12 is considered.

A dramatic difference between the R- and S-epimers (332) and (334) is the chemical shift of one of the C-17 protons (Table 9). This difference must

TABLE 9

Compound	$[\alpha]_D$	$[M]_D$	17-H (τ)	17-H (τ)	Δσ (Hz)
R-epimer (332)	+9°	+29°	5.16	5.57	41
S-epimer (334)	+23°	+74°	5.14	5.31	17

be due to an interaction between one of the C-17 protons and the asymmetric centre at C-12. A further difference in the n.m.r. spectra of the two epimers is the shape of the signals assigned to the C-13 protons. In the spectrum of the S-epimer, this signal at 7.55 τ is complex whereas in that of the R-epimer, two singlets are seen, probably the two central signals of an AB quartet.

The mixture of epoxides (336) was also separated into the epimers (337) and (338) and by analogy with the arguments above, the most polar compound, which also had the greater positive rotation, was assigned the S-configuration at C-12. As above, both epimers showed a broad chelation band at 3540 cm^{-1} in the i.r. spectra.

In the n.m.r. spectra of the two epoxides (337) and (338) the 7β-proton had a chemical shift of 7.08 τ and the 8β-methyl group of the S-epimer resonated at 8.68 τ while the same group in the R-epimer resonated at 8.80 τ, which again demonstrated an interaction between ring B and the asymmetric centre at C-12. As above, the signals from the C-13 protons in the n.m.r. spectrum of the

R-epimer (337) appeared as two singlets while those from the C-13 protons of the S-epimer (338) were more complex and are shown in appendix 7. It can be seen that the two conformations (334 A) and (334 B) of this S-epimer will both give rise to the three coupling constants observed, J_{gem} (17 Hz), J_{trans} (9 Hz) and J_{cis} (3.5 Hz). The latter two are in agreement with those calculated from the Karplus equation ($J_{trans} \approx$ 10 Hz and $J_{cis} \approx$ 2.5 Hz).[315]

The 3,5-dinitrobenzoates (333) and (335) were prepared in the hope that they would be crystalline but this was not so. No significant information could be derived from the c.d. curves of these two compounds since the differential dichroic absorption was very small and the maxima for the two epimers occurred at different wavelengths. Again, in the n.m.r. spectra of the two epimers (333) and (335), a significant difference in the chemical shift of one of the C-17 protons was observed.

TABLE 10

Compound	17-H (τ)	17-H (τ)	Δσ (Hz)
R-epimer (333)	5.09	5.39	30
S-epimer (335)	5.04	5.08	4

Oxidation of a mixture of the alcohols (331) with bispyridine chromium oxide in dichloromethane gave the β-ketoester (340) in 78% yield. The i.r.

spectrum showed only a weak, broad band at 3430 cm^{-1} for the chelate band of the enol form and bands at 1747 and 1722 cm^{-1} for the ester and ketone carbonyl groups. The C-13 protons resonated as a singlet at 6.58 τ in the n.m.r. spectrum, while the C-17 protons, which were no longer influenced by the chirality at C-12, resonated at 5.24 τ and 5.64 τ ($\Delta\sigma$, 40 Hz). The u.v. spectrum showed a band at 250 nm (ε 620) for the enol form, corresponding to approximately 5% enolisation. On addition of base, the enolate anion was formed and a band appeared at 276.5 nm (ε 17,750).[316]

Hydrolysis of the β-ketoester (340) with potassium hydroxide in alcohol gave the methyl ketone (342) which formed a 2,4-dinitrophenylhydrazone.

The penultimate step in the synthesis of the naturally occurring diterpene was formation of the furan ring. The Feist-Benary[317,318] condensation was used for this purpose and in particular, the procedure developed by Reichstein[319,320] was investigated.

Reaction of the β-ketoester (340) in ether with 1,2-dichloroethyl ethyl ether and aqueous sodium hydroxide gave a product, the n.m.r. spectrum of which showed only traces of the desired furan (341). The chemical shifts of the observed resonance signals at 2.81 τ and 3.40 τ agreed well with the shifts calculated (2.81 τ and 3.44 τ) for the α and β-protons of the furan (341).[321]

The mass spectrum of this product showed a molecular ion at m/e 362, an intense peak at m/e 344, and a further intense peak at m/e 95, which was

mentioned earlier to be characteristic of dialkyl furans. The molecular weight of the furan (341) is 344 and hence this product may have been a mixture of the hydrated furan precursors (343) and (344).

Reaction of the β-ketoester (340) with dichloroether in boiling triethylamine gave a copius precipitate of triethylamine hydrochloride together with "two" other products, one more polar and the other less polar than the ester (340). Reduction of this mixture of products with lithium aluminium hydride however yielded a complex mixture of products which was difficult to separate.

The mechanism of this condensation[317] is shown in fig.78. In the present work only bases were used as catalysts and before this synthetic method is considered of no practical value in this particular case, acid catalysis will have to be investigated.

Elderfield and Dodd[318] have noted that the yields of furans vary considerably with the nature of the β-ketoester in this type of condensation and hence it may be necessary to adopt a completely different approach[322] to elaboration of the furan side chain.

CHAPTER SIX

EXPERIMENTAL WORK

GENERAL

Unless otherwise stated,

Melting points were determined on a Kofler block.

Optical rotations were measured for $CHCl_3$ solutions at 20° on a Perkin-Elmer P.E. 141 automatic polarimeter. Concentrations are expressed as g per 100 ml^{-1}.

Microanalyses were performed by Dr. F. B. Strauss and staff (Oxford).

Ultraviolet spectra were recorded for EtOH solutions on a Unicam S.P. 800 spectrophotometer.

Infrared spectra were recorded for CS_2 solutions on a Perkin-Elmer 237 or 257 spectrophotometer.

Nuclear magnetic resonance spectra were recorded by Mrs. E. Richards and staff on a Perkin-Elmer R14 (100 MHz) high resolution spectrometer and were determined for $CDCl_3$ solutions with tetramethylsilane as internal reference. Data are given as; chemical shift downfield from TMS, in units of parts per million (τ); number of protons; multiplicity (m = multiplet, q = quartet, t = triplet, d = doublet, s = singlet, 's' = unresolved multiplet (broad singlet); $w_{\frac{1}{2}}$ = width of signal at half its height; coupling constant (in Hz); assignment.

Mass spectra were recorded by Dr. R. T. Aplin and staff on an Atlas CH7 mass spectrometer, using a direct insertion probe.

Optical rotatory dispersion and circular dichroism curves were determined by Dr. P. M. Scopes in the laboratory of Professor W. Klyne, Westfield College,

London. Concentrations are expressed as $mg.ml^{-1}$.

Alumina refers to either, Peter Spence and Co., grade H, 100/200 mesh, deactivated by the addition of 5% or 10% w/w of a 10% solution of glacial HOAc in water, or Hopkins and Williams Ltd., "Camag" neutral alumina, 100/240 mesh, deactivated by the addition of 5% or 10% w/w of water.

Silica gel refers to Whatman Chromedia S.G. 31.

Thin layer chromatography was carried out on plates 5 x 20 cm, which were coated with a 0.25 mm layer of unbaked silica gel (Merck Kieselgel $HF_{254/366}$) and were developed in mixtures of benzene and ether (triterpenes) or petrol and acetone (diterpenes). The spots were detected by spraying the plates with a 10% solution of dodecamolybdophosphoric acid[323] in EtOH and heating at 100° for 5 min.

Preparative layer chromatography was carried out on plates 100 x 20 cm (load max. 500 mg) or 20 x 20 cm (load max. 100 mg) which were coated with a 1 mm layer of unbaked silica gel (Merck Kieselgel $PF_{254/366}$) and were prepared by Mr. R. Prior. The bands were detected by their fluorescence at either 254 nm or 366 nm.

To avoid repetition, the term "work up" has been used. This involved extraction of a neutral aqueous solution with ether. The ethereal extract was washed with dilute H_2SO_4 (1N) and/or a saturated aqueous solution of $NaHCO_3$ (whichever was appropriate) and water. The solution was then dried over anhydrous $MgSO_4$

and the solvent was evaporated under reduced pressure.

Petrol refers to the light petroleum fraction boiling between 30-40°, and ether refers to diethyl ether.

Extraction of Manila Elemi resin

A solution of elemi resin (1 kg) in ether (3 l) was extracted with NaOH solution (2%, 3 x 500 ml). The ethereal solution was washed with water (6 x 500 ml) until the washings were neutral to litmus, and dried. Evaporation of the solvent left a yellow oil, which solidified on cooling, to a crystalline mass (755 g). The aqueous extracts were combined and were washed with ether (750 ml). Of the three layers which formed during the washing, the lowest aqueous layer was separated and dilute H_2SO_4 was added to it until the pH was 10. Dilute HOAc (20% in water) was then added until the pH reached 5 and the precipitated acids were extracted into ether (5 x 750 ml). The ethereal extract was washed with brine (3 x 300 ml) and water (3 x 300 ml) and was passed through a column of alumina (350 g, 10% deactivated), which was then washed with more ether. Evaporation of the solvent from the eluate gave the crude acid mixture (140 g), which crystallised from aqueous MeOH. The first crop (45 g) had m.p. 212-218°. During a second extraction of the resin, a yield of 195 g of crude acids was obtained if the passage of the acid mixture through alimina was omitted.

Separation of the acid mixture as the methyl esters

Methylation of the crude acid mixture in ether, with an excess of ethereal diazomethane,[324] gave a yellow oil (36 g) which was adsorbed from CCl_4 onto a column of alumina (4 kg, 5% deactivated). The column was eluted with

petrol : ether mixtures.

(1) (9:1), 10 l: A colourless oil (1.5 g) from which methyl 3α-acetoxytirucalla-8,24-dien-21-oate (210 mg) was isolated by p.l.c. (four 100 cm plates, eluted 3 times with benzene : ether, 50:1) and which crystallised as needles from aqueous MeOH. M.p. 119-121°, $[\alpha]_D$: -45° (c 0.8). The i.r. and n.m.r. spectra were superimposable upon those of an authentic sample (see below).

(2) (8:1), 7.5 l: Pure methyl 3-oxotirucalla-8,24-dien-21-oate (2.37 g) which crystallised as plates from aqueous MeOH. M.p. 110-111°, $[\alpha]_D$: +23° (c 0.65), lit.[11] m.p. 109-111°, $[\alpha]_D$: +28°. ν_{max}: 1740, 1710, 1192, 1151, 1113, 833 cm^{-1}. τ: 4.91 (1H, t, J 6.5 Hz) 24H; 6.34 (3H, s) CO_2Me; 8.33, 8.43 (each 3H, s) 26H and 27H; 8.91, 8.95 (6H), 9.11, 9.22 methyls. Found: C, 79.3; H, 10.15; calc. for $C_{31}H_{48}O_3$: C, 79.4; H, 10.3%.

(3) (6:1), 5 l: A mixture (1.8 g) of α-amyrin and a small quantity of β-amyrin, which crystallised as needles from aqueous MeOH. M.p. 180-181°, $[\alpha]_D$: +81° (c 0.5); For α-amyrin, lit.[325] m.p. 185°, $[\alpha]_D^{15}$: +82°. ν_{max}: 3610, 1041, 1026, 993 cm^{-1}. Found: C, 84.2; H, 11.6; calc. for $C_{30}H_{50}O$: C, 84.4; H, 11.8%.

(4) (6:1), 5.5 l and (5:1), 11 l: A crystalline solid (8.00 g) which contained two compounds. The solid was acetylated with a mixture of Ac_2O (80 ml) and pyridine (80 ml) at room temp. for 15 hr. The mixture was poured onto ice, worked up, and the resultant oil was adsorbed from CCl_4 onto a column of silica gel (825 g).

(i) Elution with petrol : ether (20:1) 5.5 l, gave β-amyrin acetate (30 mg), which crystallised as rods from acetone. M.p. 240-241°, $[\alpha]_D$: +81° (c 1.35), lit.[326] m.p. 241-242°, $[\alpha]_D$: +82°. τ: 4.82 (1H, t, J 4 Hz) 12H; 5.48 (1H, q, $J_{ax.ax}$ 9 Hz, $J_{ax.eq}$ 7.5 Hz) 3αH; 7.96 (3H, s) OAc; 8.87, 9.03 (6H), 9.13 (12H), 9.17 methyls.

(ii) Elution with petrol : ether, 10:1, 13 l, gave methyl 3α-acetoxytirucalla-8,24-dien-21-oate (4.75 g) which crystallised as needles from aqueous MeOH. M.p. 122-123°, $[\alpha]_D$: -42° (c 0 6), lit[11] m.p. 138.5-140°, $[\alpha]_D$: -44°. ν_{max}: 1738, 1245, 1150, 1013 cm^{-1}. τ: 4.92 (1H, t, J 6.5 Hz) 24H; 5.33 (1H, 's', $w_{\frac{1}{2}}$ 6.5 Hz) 3βH; 6.34 (3H, s) CO_2Me; 7.95 (3H, s) OAc; 8.32, 8.43 (each 3H, s) 26H and 27H; 9.03, 9.09, 9.12 (6H), 9.16 methyls. Found: C, 77.4; H, 10.2; calc. for $C_{33}H_{52}O_4$: C, 77.3; H, 10.2%.

(5) (4:1), 11.5 l: A crystalline solid (5.00 g) which contained two compounds. The mixture was acetylated with Ac_2O-pyridine and the products were separated by p.l.c. (fifteen 100 cm plates, eluted twice with benzene : ether, 50:1).

(i) The less polar compound was methyl 3β-acetoxyurs-12-en-28-oate (110 mg) which crystallised as needles from aqueous MeOH. M.p. 247-248°, $[\alpha]_D$: +59° (c 0.7), lit.[327] m p. 245-247°, $[\alpha]_D$: +55°. ν_{max}: 1736, 1245, 1200, 1142, 1027 cm^{-1}. τ: 4.76 (1H, t, J 4 Hz) 12H; 5.50 (1H, q, J 9 Hz and 7.5 Hz) 3αH; 6.41 (3H, s) CO_2Me; 7.97 (3H, s) OAc; 8.93, 9.06 (6H), 9.15 (9H), 9.26 methyls.

(ii) The more polar compound was methyl 3α-acetoxytirucalla-7,24-dien-21-oate (2.10 g) which crystallised as needles from aqueous MeOH. M.p. 119-121°, $[\alpha]_D$: -51° (c 0.5). ν_{max}: 1738, 1243, 1189, 1150, 1031, 826 cm^{-1}. τ: 4.72 (1H, 's', $w_{\frac{1}{2}}$ 8 Hz) 7H; 4.90 (1H, t, J 6.5 Hz) 24H; 5.30 (1H, 's', $w_{\frac{1}{2}}$ 7 Hz) 3βH; 6.33 (3H, s) CO_2Me; 7.94 (3H, s) OAc; 8.32, 8.43 (each 3H, s) 26H and 27H; 9.03 (6H), 9.09, 9.15, 9.23 methyls. Found: C, 77.2; H, 9.9; calc. for $C_{33}H_{52}O_4$: C, 77.3; H, 10.2%.

(6) (3:1), 8.5 l and ether 2 l, a yellow oil (6.1 g).

Attempted selective hydrolysis of methyl 3α-acetoxytirucalla-8,24-dien-21-oate

LiBr (anhydrous, 260 mg) was added to a solution of methyl 3α-acetoxytirucalla-8,24-dien-21-oate (285 mg) in DMF (10 ml) and the mixture was heated under reflux for 5 hr in an atmosphere of nitrogen. After the mixture had been diluted with brine, work up left starting material, which crystallised as needles from aqueous MeOH, m.p. 121.5-122.5°.

3α-Hydroxytirucalla-8,24-dien-21-oic acid

(i) Potassium (150 mg) was added to t-butanol (5 ml) and the solution was heated under reflux in an atmosphere of nitrogen until the metal had dissolved (1.25 hr) and then left overnight. Excess t-butanol was distilled off under reduced pressure and the solid was dried at 100° under vacuum. Potassium t-butoxide (430 mg) was added to a solution of methyl 3α-acetoxytirucalla-8,24-dien-21-

oate (200 mg) in DMSO (5 ml) and the mixture was heated at 100° for 4 hr in an atmosphere of nitrogen. After the solution had been poured into ice-water (200 ml), work up left a gum, from which 3α-hydroxytirucalla-8,24-dien-21-oic acid (63 mg, 35%) was isolated by p.l.c. (one 100 cm plate, eluted once with benzene : ether, 3:2) and which crystallised as prisms from aqueous MeOH.

(ii) KOH (875 mg) was added to a solution of methyl 3α-acetoxytirucalla-8,24-dien-21-oate (2.00 g) in ethane-1,2-diol (10 ml) and the solution was heated under reflux for 5 hr in an atmosphere of nitrogen. After the solution had been diluted with water (50 ml), work up gave 3α-hydroxytirucalla-8,24-dien-21-oic acid (1.37 g, 77%) which crystallised as prisms from aqueous MeOH. M.p. 220-224°, $[\alpha]_D$: -15° (c 0.5), lit.[154] m.p. 212-222°, $[\alpha]_D$: -21.5°. ν_{max} ($CHCl_3$): 1705, 1130, 1100 cm^{-1}. τ: 4.89 (1H, t, J 6.5 Hz) 24H; 6.54 (1H, 's', $w_{\frac{1}{2}}$ 7 Hz) 3βH; 8.32, 8.40 (each 3H, s) 26H and 27H; 9.03, 9.05, 9.11, 9.14, 9.16 methyls.

3-Oxotirucalla-8,24-dien-21-oic acid

CrO_3 (0.50 g, powdered and dried over P_2O_5) was added in small portions to pyridine (5 ml) which was stirred at 0°. The yellow complex was filtered, washed with petrol and dried over P_2O_5, in a vacuum. $CrO_3 \cdot (py)_2$ (2.47 g) was added to a solution of 3α-hydroxytirucalla-8,24-dien-21-oic acid (1.08 g) in CH_2Cl_2 (80 ml) and the solution was stirred at room temp. for 1 hr. The solution was then diluted with CH_2Cl_2 (80 ml) and was filtered through celite. Evaporation of the solvent at reduced pressure left a gum, from which the major product was

isolated

by p.l.c. (two 20 cm plates, eluted once with benzene:ether, 3:2). This proved to be 3-oxotirucalla-8,24-dien-21-oic acid (175 mg, 16%), which crystallised as needles from aqueous MeOH. M.p. 215-219°, $[\alpha]_D$: +31° (c 0.6), lit.[154] m.p. 211-217°, $[\alpha]_D$: +37°. ν_{max} ($CHCl_3$): 1704, 1130, 1102 cm^{-1}. τ: 4.89 (1H, t, J 6.5 Hz) 24H; 8.29, 8.39 (each 3H, s) 26H and 27H; 8.89, 8.93, 8.95, 9.08, 9.17 methyls.

Methyl 3α-hydroxytirucalla-8,24-dien-21-oate

KOH (350 mg) was added to a solution of methyl 3α-acetoxytirucalla-8,24-dien-21-oate (1.54 g) in MeOH (10 ml) and the solution was heated under reflux for 2 hr. After the solution had been diluted with water (50 ml), work up gave 3α-hydroxytirucalla-8,24-dien-21-oate (1.17 g, 83%) which crystallised as needles from aqueous MeOH. M.p. 150-151°, $[\alpha]_D$: -12° (c 0.6), lit.[11] m.p. 149-150°, $[\alpha]_D$: -11°. ν_{max}: 3620, 1740, 1193, 1153, 1068, 1048, 980 cm^{-1}. τ: 4.92 (1H, t, J 6.5 Hz) 24H; 6.34 (3H, s) CO_2Me; 6.58 (1H, 's', $w_{\frac{1}{2}}$ 7 Hz) 3βH; 8.31, 8.42 (each 3H, s) 26H and 27H; 9.03, 9.04, 9.13 (6H), 9.20 methyls.

Methyl 3-oxotirucalla-8,24-dien-21-oate

A solution of methyl 3α-hydroxytirucalla-8,24-dien-21-oate (985 mg) in pyridine (35 ml) was added to a solution of CrO_3 (1.40 g) in pyridine (35 ml) and the mixture was stirred at room temp. for 25 hr. Excess pyridine was distilled

off under reduced pressure and the residue was poured into water. Work up gave an oil, from which methyl 3-oxotirucalla-8,24-dien-21-oate (365 mg, 37%) was isolated by p.l.c. (one 100 cm plate, eluted once with benzene:ether, 4:1) and crystallised as plates from aqueous MeOH. M.p. 108-110°, $[\alpha]_D$: +21° (c 0.3). The i.r. and n.m.r. spectra were identical to those of an authentic sample (see above).

Methyl 3β-hydroxytirucalla-8,24-dien-21-oate

A solution of methyl 3-oxotirucalla-8,24-dien-21-oate (1.50 g) in EtOH (120 ml) was added to a solution of $NaBH_4$ (200 mg) in a mixture of EtOH (10 ml) and aqueous NaOH (2M, 5 ml) and the mixture was stirred at room temp. for 24 hr. Excess EtOH (100 ml) was distilled off under reduced pressure and the residual mixture was poured into water (100 ml). Work up gave a crystalline mixture of two compounds which was separated by p.l.c. (four 100 cm plates, eluted once with benzene:ether, 4:1).

(i) The less polar compound was methyl 3α-hydroxytirucalla-8,24-dien-21-oate (190 mg, 13%) which crystallised as needles from aqueous MeOH (see above).

(ii) The more polar compound was methyl 3β-hydroxytirucalla-8,24-dien-21-oate (1.12 g, 75%) which crystallised as needles from aqueous MeOH. M.p. 119-121°, $[\alpha]_D$: -2° (c 0.6), lit.[11] m.p. 117-118°, $[\alpha]_D$: -2°. ν_{max}: 3615, 1735, 1190, 1150, 1023 cm^{-1}. τ: 4.92 (1H, t, J 7 Hz) 24H; 6.35 (3H, s) CO_2Me; 6.77 (1H, q, J 10.5 Hz, 5 Hz) 3αH; 8.31, 8.42 (each 3H, s) 26H

and 27H; 8.99, 9.06, 9.12, 9.20, 9.21 methyls.

Methyl 3β-acetoxytirucalla-8,24-dien-21-oate

Methyl 3β-hydroxytirucalla-8,24-dien-21-oate was acetylated with Ac_2O-pyridine and the product was purified by p.l.c. (one 100 cm plate, eluted once with benzene:ether, 9:1). Methyl 3β-acetoxytirucalla-8,24-dien-21-oate crystallised as plates from aqueous MeOH. M.p. 122-125°, $[\alpha]_D$: +6° (c 0.4), lit.[11] m.p. 123-124°, $[\alpha]_D$: +7°. ν_{max}: 1735, 1243, 1212, 1150, 1023 cm^{-1}. τ: 4.91 (1H, t, J 7 Hz) 24 H; 5.48 (1H, q, J 10 Hz and 6 Hz) 3αH; 6.34 (3H, s) CO_2Me; 7.96 (3H, s) OAc; 8.33, 8.43 (each 3H, s) 26H and 27H; 9.04, 9.13 (9H), 9.29 methyls.

3β-Hydroxytirucalla-8,24-dien-21-oic acid

Methyl 3β-hydroxytirucalla-8,24-dien-21-oate (5.05 g) was hydrolysed with KOH in ethane-1,2-diol as above. The solution was then poured into water (200 ml), neutralised with dilute H_2SO_4 (2N), further diluted with brine, saturated with solid NaCl, and extracted three times with EtOAc. The EtOAc extract was evaporated to dryness and the solid was taken up in ether. The ethereal solution was washed with a small volume of water and evaporation of the solvent gave 3β-hydroxytirucalla-8,24-dien-21-oic acid (4.20 g, 86%) which crystallised as needles from aqueous MeOH. M.p. 198-201°, $[\alpha]_D$: -6° (c 0.1). ν_{max} (nujol): 3370, 1690, 1020, 830 cm^{-1}. τ: 4.90 (1H, t, J 7 Hz)

24H; 6.75 (1H, q, J 10 Hz and 6 Hz) 3αH; 8.32, 8.41 (each 3H, s) 26H and 27H; 9.01, 9.08, 9.13, 9.19, 9.21 methyls. Found: C, 78.8; H, 10.35; calc. for $C_{30}H_{48}O_3$: C, 78.9; H, 10.6%.

3β-Acetoxytirucalla-8,24-dien-21-oic acid

Acetylation of 3β-hydroxytirucalla-8,24-dien-21-oic acid with Ac_2O-pyridine, gave 3β-acetoxytirucalla-8,24-dien-21-oic acid which crystallised as needles from MeOH. M.p. 233-235°, $[\alpha]_D$: +12.5° (c 1.0). ν_{max}: 1733, 1700, 1243, 1026, 982 cm^{-1}. τ: -0.65 (1H, very broad singlet) CO_2H; 4 90 (1H, t, J 6.5 Hz) 24H; 5.47 (1H, 's', $w_{\frac{1}{2}}$ 19Hz) 3αH; 7.95 (3H, s) OAc; 8.33, 8.41 (each 3H, s) 26H and 27H; 9.05, 9.12 (9H), 9.19 methyls. Found: C, 76.9; H, 10.0; calc. for $C_{32}H_{50}O_4$: C, 77.1; H, 10.1%.

3β-Acetoxy-24,25-dibromotirucall-8-en-21-oic acid

(i) A solution of bromine (1.0 ml) in $CHCl_3$ (50 ml) was added dropwise over a period of 10 min, to a stirred solution of 3β-acetoxytirucalla-8,24-dien-21-oic acid (700 mg) in $CHCl_3$ (100 ml) at 0°, and the mixture was left at room temp. for 25 hr. The solution was then evaporated to dryness under reduced pressure. The residual oil was taken up in ether and the solution was washed with brine and water, and dried. It was then filtered and evaporation of the solvent gave a yellow oil (1.8 g) which was chromatographed on plates (three 100 cm plates, eluted once with benzene : ether, 65:35). However, no single band could be discerned.

(ii) A practically identical result was obtained when ether was used as the solvent for the reaction.

(iii) When the bromination was carried out, as above, in MeOAc as solvent, a crystalline solid (1.13 g) was obtained, from which the major product 3β-acetoxy-24,25-dibromotirucall-8-en-21-oic acid (150 mg, 16%) was isolated by p.l.c. (one 100 cm plate, eluted once with benzene : ether, 65:35, followed by two 20 cm plates, eluted once with benzene : ether, 3:1). The acid crystallised as prisms from $CHCl_3$-MeOH-water. M.p. 230-232°, $[\alpha]_D$: -13° (c 0.3). ν_{max} (nujol): 1720, 1653, 1250, 1200, 1180, 1093, 1020, 947 cm^{-1}. τ: 5.51 (1H, 's', $w_{\frac{1}{2}}$ 15 Hz) 3αH; 5.82 (1H, t, J 9 Hz) 24H; 7.95 (3H, s) OAc; 8.04, 8.21 (each 3H, s) 26H and 27H; 9.04, 9.10, 9.11 (6H), 9.17 methyls. Found: C, 58.4; H, 7.4; calc. for $C_{32}H_{50}O_4Br_2$: C, 58.4; H, 7.65%.

Methyl 3α-acetoxy-24,25-dibromotirucall-8-en-21-oate

A solution of bromine (0.5 ml) in $CHCl_3$ (10 ml) was added dropwise to a stirred solution of methyl 3α-acetoxytirucalla-8,24-dien-21-oate (4.00 g) in $CHCl_3$ (200 ml) at 0° The solution was then evaporated to dryness and the crude dibromide (4.86 g, 93%) was adsorbed from CCl_4 onto a column of alumina (200 g, 5% deactivated). Elution with petrol : ether (95:5) gave pure methyl 3α-acetoxy-24,25-dibromotirucall-8-en-21-oate, which crystallised as prisms from MeOH. M.p. 163-165°, $[\alpha]_D$: -23° (c 1.0), lit.[109] m.p. 158-160°, $[\alpha]_D$: -18°. ν_{max}: 1732, 1245, 1160, 1097, 1038, 1015, 978 cm^{-1}. τ: 5.34

(1H, 's', $w_{\frac{1}{2}}$ 7 Hz) 3βH; 5.84 (1H, t, J 11 Hz) 24H; 7.95 (3H, s) OAc; 8.04 (3H, d, J 2 Hz), 8.20 (3H, s) 26H and 27H; 9.03, 9.09, 9.10, 9.12, 9.14 methyls. Found: C, 58.7; H, 7.55; Br, 24.0; calc. for $C_{33}H_{52}O_4Br_2$: C, 58.9; H, 7.8; Br, 23.8%.

Attempted hydrolysis of 3α-acetoxy-24,25-dibromotirucall-8-en-21-oate

Hydrolysis of the title compound with KOH in ethane-1,2-diol gave a gum, which was shown (t.l.c.) to be a mixture of five compounds, four of which were acids, and hence their separation was not attempted.

Attempted formation of 3β-acetoxy-24,25-dibromotirucall-8-en-21-amide

The amide of 3β-acetoxy-24,25-dibromotirucall-8-en-21-oic acid was prepared by the method outlined below. Isolation of the amide from the resultant orange-brown gum was attempted by p.l.c. (two 100 cm plates, eluted 3 times with benzene:ether, 4:1).

(i) By comparative t.l.c., the less polar compound, which increased in quantity with each elution, was shown to be 3β-acetoxy-24,25-dibromotirucall-8-en-21-oic acid.

(ii) The more polar compound, which decreased in quantity with each elution, was shown to be the required amide, but this could not be satisfactorily characterised. ν_{max} ($CHCl_3$): 3500, 3400, 1725, 1675, 1590, 1253, 1134, 1100 cm^{-1}.

3α-Acetoxy(21-24)cyclotirucalla-7,9(11),24-trien-21-one

Acetylation of a 1:1 mixture of 3α-hydroxytirucalla-7 and 8,24-dien-21-oic acids with Ac_2O-pyridine gave the acetoxy acid mixture, which crystallised as needles from aqueous MeOH. M.p. 243-246°, $[\alpha]_D$: -30° (c 0.6). $SOCl_2$ (2.5 ml) was added to a solution of the mixture of acetoxy acids (4.00 g) in benzene (300 ml) and the solution was heated under reflux for 5 hr. The solution was evaporated to dryness and the resultant oil was dissolved in more benzene. Repetition of this process gave a pale brown oil which deposited needles on standing. The acid chlorides were dissolved in benzene (250 ml) and with stirring, a stream of gaseous ammonia was blown through the solution at room temp. for 5 hr. The solution was filtered to remove precipitated NH_4Cl and the solvent was evaporated to dryness. Purification of the amide was avoided if this product was used for the photolysis. The product was taken up in benzene (150 ml), lead tetra-acetate (10.0 g) was added and the mixture was stirred in an atmosphere of nitrogen at room temp. for 30 min, without illumination. During this period, powdered iodine (6.00 g) was slowly added to the solution. The mixture was then irradiated at room temp. for 6 hr in a pyrex photochemical reactor with a 450 watt medium pressure mercury vapour arc. The solution was filtered, washed with aqueous $NaHSO_3$ solution, and water, and evaporation of the solvent gave an orange-red gum which was adsorbed from CCl_4 onto a column of alumina (400 g, 5% deactivated). Elution with petrol : ether (9:1)

5 l, gave a yellow oil. This oil contained an unsaturated compound which, by t.l.c., appeared to have been present before photolysis. The major band from p.l.c. of this oil (three 100 cm plates, eluted three times with benzene : ether, 50:1) was further purified by p.l.c. (one 20 cm plate, eluted once with benzene : ether, 85:15) and yielded 3α-acetoxy(21-24)cyclotirucalla-7,9(11),24-trien-21-one (52 mg), which crystallised as needles from MeOH. M.p. 168-173°, $[\alpha]_D$: -134° (c 0.04). ν_{max} ($CHCl_3$): 1710, 1700, 1627, 1258, 830 cm^{-1}. τ: 4.67 (2H, 's', $w_{\frac{1}{2}}$ 13 Hz) 7H and 11H; 5.28 (1H, 's', $w_{\frac{1}{2}}$ 7 Hz) 3βH; 7.75 (1H, 's', $w_{\frac{1}{2}}$ 4 Hz) 20H; 7.92 (3H, s) OAc; 8.15 (6H, s) 26H and 27H; 9.00, 9.05, 9.12, 9.14, 9.24 methyls. λ_{max}: 233 nm (log ε, 4.13); 241 (4.21); 249 (4.11); 257.5 (4.02). M/e: 478 (M^+), 403, 354, 339, 294, 279, 124 (base). Found: C, 80.2; H, 9.9; calc. for $C_{32}H_{46}O_3$: C, 80.3; H, 9.7%.

3α-Hydroxytirucall-7 and 8-en-21-oic acids

A mixture of 3α-hydroxytirucalla-7 and 8,24-dien-21-oic acids (3.0 g) in EtOH (100 ml) was hydrogenated at room temp. over Adams (PtO_2) catalyst (0.2 g). Filtration, and evaporation of the solvent gave a crystalline solid of the two isomers which were separated by p.l.c. (five 100 cm plates, eluted 10 times with benzene : ether, 9:1).

(i) The less polar compound was 3α-hydroxytirucall-8-en-21-oic acid which crystallised as needles from aqueous MeOH. M.p. 225-228°, $[\alpha]_D$: -13° (c 0.5). ν_{max} (nujol): 3625, 1718, 1650, 1413, 1276, 1213, 1185, 1043 cm^{-1}.

τ: 3.57 (2H, very broad singlet) CO_2H and OH; 6.53 (1H, 's', $w_{\frac{1}{2}}$ 6 Hz) 3βH; 9.02, 9.04, 9.07 (d, J 6 Hz), 9.10, 9.13, 9.13 (d, J 6 Hz), 9.16 methyls. Found: C, 78.3; H, 10.9; calc. for $C_{30}H_{50}O_3$: C, 78.55; H, 11.0%.

(ii) The more polar compound was 3α-hydroxytirucall-7-en-21-oic acid which crystallised as granules from aqueous MeOH M.p. 235-238°, $[\alpha]_D$: -34° (c 0.4). ν_{max} (nujol): 3350, 1695, 1115, 1091, 1068, 1040, 1021 cm^{-1}. τ: 3.70 (2H, very broad singlet) CO_2H and OH; 4.70 (1H, 's', $w_{\frac{1}{2}}$ 8 Hz) 7H; 6.50 (1H, 's', $w_{\frac{1}{2}}$ 8 Hz) 3βH; Individual methyl signals could not readily be distinguished. Found: C, 78.4; H, 11.0; calc. for $C_{30}H_{50}O_3$: C, 78.55; H, 11.0%.

3α-Acetoxytirucall-8-en-21-oic acid

Acetylation of 3α-hydroxytirucall-8-en-21-oic acid with Ac_2O-pyridine gave 3α-acetoxytirucall-8-en-21-oic acid which crystallised as needles from aqueous MeOH. M.p. 242-245°, $[\alpha]_D$: -37° (c 0.45). ν_{max} (nujol): 1731, 1710, 1645, 1250, 1183, 1120, 1040, 1022, 983, 967 cm^{-1}. τ: 5.30 (1H, 's', $w_{\frac{1}{2}}$ 5 Hz) 3βH; 7.93 (3H, s) OAc; 9.05, 9.10 (9H), 9.12 (6H), 9.15 methyls. Found: C, 76.55; H, 10.3; calc. for $C_{32}H_{52}O_4$: C, 76.75; H, 10.5%.

3α-Acetoxytirucall-8-en-21-amide

$SOCl_2$ (0.5 ml) was added to a solution of 3α-acetoxytirucall-8-en-21-oic acid (1.00 g) in benzene (75 ml) and the mixture was heated under reflux

for 4 hr. The solvent was evaporated under reduced pressure and the resultant gum was dissolved in more benzene (50 ml). Repetition of this process gave the acid chloride as colourless needles, which was not characterised. The acid chloride was taken up in benzene (75 ml) and a stream of gaseous ammonia was bubbled through the stirred solution at room temp. for 5 hr. The solution was then filtered, and evaporation of the solvent gave 3α-acetoxytirucall-8-en-21-amide (884 mg, 88%) which was precipitated pure, from ether, as a powder (microneedles). M.p. 249-252°, $[\alpha]_D$: -37° (c 0.5). ν_{max} ($CHCl_3$): 3525, 3490, 3405, 1712, 1671, 1585, 1260 cm^{-1}. τ: 3.99 (1H, 's', $w_{\frac{1}{2}}$ 16 Hz) NH; 4.45 (1H, 's', $w_{\frac{1}{2}}$ 16 Hz) NH; 5.32 (1H, 's', $w_{\frac{1}{2}}$ 6 Hz) 3βH; 7.94 (3H, s) OAc; 9.04, 9.11 (9H), 9.14 (6H), 9.17 methyls. Found: C, 76.9; H, 10.8; N, 2.7; calc. for $C_{32}H_{53}O_3N$: C, 76.9; H, 10.7; N, 2 8%.

Photolysis of 3α-acetoxytirucall-8-en-21-amide

Lead tetra-acetate (2.13 g, dried over KOH) was added to a solution of 3α-acetoxytirucall-8-en-21-amide (760 mg) in benzene (65 ml) and the solution was mixed by bubbling nitrogen through it, while iodine (1.25 g) was added slowly over a period of 30 min, without illumination. The solution was then irradiated at room temp. for 5.5 hr in a pyrex photochemical reactor with a 450 watt medium pressure mercury vapour arc. The solution was then diluted with ether, filtered, washed with dilute H_2SO_4, aqueous $NaHSO_3$, brine and water. Evaporation of the solvent gave a red oil which was chromatographed

on plates (two 100 cm plates, eluted twice with benzene : ether, 95:5). The major product (60 mg, 8%) was further purified by p.l.c. (one 20 cm plate, eluted twice with benzene : ether, 92.5:7.5) and gave 3α-acetoxytirucalla-7,9(11)-dien-21-isocyanate as a yellow gum, which failed to crystallise, and which gradually decomposed to a brown gum. ν_{max} ($CHCl_3$): 2270, 1717, 1250, 1181, 1035, 1017, 980, 966 cm^{-1}.

Ozonolysis of methyl 3α-acetoxytirucall-7 and 8-en-21-oates

A mixture of methyl 3α-hydroxytirucalla-7 and 8-24-dien-21-oates (1.23 g, approx. 1:3 by t.l.c.) was acetylated with Ac_2O-pyridine at room temp. overnight. The mixture of diesters in EtOH (50 ml) was then hydrogenated over Adams (PtO_2) catalyst (0.1 g). The crystalline mixture in EtOAc (100 ml) was ozonised at -70° for 20 min (after which a deep blue colour had developed) and then for a further 30 min. Nitrogen was then passed through the solution, to discharge excess ozone. Zinc dust (650 mg) and water (10 ml) were added and the solution was heated under reflux for 30 min. After the solution had been filtered through celite (30 ml), work up gave a pale yellow oil, which was adsorbed from CCl_4 onto a column of alumina (75 g, 5% deactivated).

(i) Elution with petrol : ether (4:1) 300 ml, gave pure methyl 3α-acetoxy-7α,8α-epoxytirucallan-21-oate (245 mg, 77% based on Δ^7 content of starting material), which crystallised as needles from aqueous MeOH. M.p. 130-132°, $[\alpha]_D$: -77° (c 0.4), lit.[109] m.p. 130-132°, $[\alpha]_D$: -78°. ν_{max}: 1737, 1244, 1191, 1159,

1026, 1013 cm^{-1}. τ: 5.32 (1H, 's', $w_{\frac{1}{2}}$ 7 Hz) 3βH; 6.35 (3H, s) CO_2Me; 7.12 (1H, 's', $w_{\frac{1}{2}}$ 4 Hz) 7βH; 7.95 (3H, s) OAc; the methyl groups are not easily distinguishable.

(ii) Elution with petrol : ether (4:1) 900 ml, gave a mixture of two unsaturated compounds which was separated by p.l.c. (two 100 cm plates, eluted twice with benzene : ether, 92.5:7.5).

(a) The less polar compound was methyl 3α-acetoxy-7,11-dioxotirucall-8-en-21-oate which crystallised as clusters of thick yellow prisms from aqueous MeOH. M.p. 148-150°, $[\alpha]_D$: -29° (c 1.0), lit.[154] m.p. 145.5-147°, $[\alpha]_D$: -33°. ν_{max}: 1735, 1673, 1240, 1214, 1160 cm^{-1}. τ: 5.26 (1H, 's', $w_{\frac{1}{2}}$ 6 Hz) 3βH; 6.28 (3H, s) CO_2Me; 7.96 (3H, s) OAc; 8.66, 8.89, 8.97 (6H), 9.09 (6H), 9.16 methyls. λ_{max}: 272.5 nm (ε, 8000). Found: C, 73.3; H, 9.1; calc. for $C_{33}H_{50}O_6$: C, 73.0; H, 9.3%.

(b) The more polar compound was methyl 3α-acetoxy-7-oxotirucall-8-en-21-oate, which crystallised as prisms from aqueous MeOH. M.p. 178-180°, $[\alpha]_D$: -42° (c 0.6), lit.[154] m.p. 189-191.5°. ν_{max}: 1735, 1660, 1240, 1212, 1155 cm^{-1}. τ: 5.28 (1H, 's', $w_{\frac{1}{2}}$ 5 Hz) 3βH; 6.33 (3H, s) CO_2Me; 7.94 (3H, s) OAc; 8.92, 9.00, 9.02, 9.12 (6H), 9.18 (3H, d, J 1 Hz), 9.19 methyls. λ_{max}: 255 nm (ε, 8900). Found: C, 75.1; H, 9.9; calc. for $C_{33}H_{52}O_5$: C, 75.0; H, 9.9%.

Methyl 3α,7α-diacetoxyapotirucall-14-en-21-oate

$BF_3.Et_2O$ (5 drops) was added to a stirred solution of methyl 3α-acetoxy-7α,8α-epoxytirucallan-21-oate (245 mg) in benzene (25 ml) and the mixture was stirred at room temp. for 30 min. Saturated aqueous $NaHCO_3$ (10 ml) was added and the mixture was stirred rapidly for a further 15 min. After the benzene layer had been separated and washed with water, evaporation of the solvent gave a gum from which methyl 3α-acetoxy-7α-hydroxyapotirucall-14-en-21-oate was isolated by p.l.c. (one 100 cm plate, eluted twice with benzene : ether (92.5:7.5), as a colourless gum which failed to crystallise. The alcohol was acetylated with Ac_2O-pyridine at room temp for 7 days. Work up gave methyl 3α,7α-diacetoxy-apotirucall-14-en-21-oate which crystallised as prisms from aqueous MeOH. M.p. 116-119°, $[\alpha]_D$: -100° (c 0.6), lit.[109] m.p. 114-116°, $[\alpha]_D$: -99°. ν_{max}: 1735, 1250, 1158, 1040, 1026, 819 cm^{-1}. τ: 4.85 (1H, 's', $w_{\frac{1}{2}}$ 6 Hz) 15H; 4.92 (1H, 's', $w_{\frac{1}{2}}$ 6 Hz) 7βH; 5.44 (1H, 's', $w_{\frac{1}{2}}$ 5 Hz) 3βH; 6.40 (3H, s) CO_2Me; 8.00 (3H, s) 3αOAc; 8.11 (3H, s) 7αOAc; 8.98, 9.01, 9.16, 9.18 (6H), 9.25, 9.32 methyls.

Ozonolysis of a methylated and brominated, crude acid fraction from Manila elemi resin

A solution of bromine (7.0 ml) in $CHCl_3$ (50 ml) was added slowly to a stirred solution of a crude mixture of elemi acid methyl esters (55 g) in $CHCl_3$ (500 ml) at 0° and then left at room temp. for 15 hr. The solution was then

washed with brine and water, and evaporation of the solvent gave a red-brown gum (74 g). The dibromide mixture, in EtOAc (1 l) was ozonised at -70° for 15 hr. Nitrogen was then passed through the solution to discharge excess ozone. Zinc dust (20 g) and water (300 ml) were added and the solution was heated under reflux for 1 hr. The solution was filtered through a pad of glass wool, and after the EtOAc layer had been separated, work up with brine, and water, gave a yellow gum, which was adsorbed from CCl_4 onto a column of alumina (3 kg, 10% deactivated). The column was eluted with mixtures of petrol and ether.

(1) (85:15), 15 l: A yellow gum (18.0 g) which crystallised as needles on standing.

(2) (4:1), 7 l: A yellow gum (11.0 g) which crystallised as large prisms on standing. The major component of this fraction was shown, by comparative t.l.c , to be methyl 3,7-dioxotirucalla-8,24-dien-21-oate (see below).

(3) (1:1), 4 l: A yellow gum (10.0 g).

(4) (1:1), 3.5 l: A yellow gum (4.5 g).

Fractions (2), (3) and (4) were not further investigated.

Fraction (1) (18.0 g) was readsorbed from CCl_4 onto a column of alumina (800 g, 10% deactivated). Elution with petrol : ether (85:15) gave;

(1/1), 1.25 l: A pale yellow viscous oil (6.10 g), which by comparative t.l.c. had the same R_F as that of an authentic sample of methyl 7α,8α-epoxy-3-oxotirucalla-24-en-21-oate (see below).

(1/2), 1.25 l: Pure methyl 3,7,11-trioxotirucalla-8,24-dien-21-oate (760 mg), which crystallised as pale yellow needles from MeOH. M.p. 164-165°, $[\alpha]_D$: +8° (c 0.8). ν_{max} ($CHCl_3$): 3030, 1726, 1706, 1678, 1670, 1182, 1166 cm^{-1}. τ: 4.89 (1H, t, J 6.5 Hz) 24H; 6.27 (3H, s) CO_2Me; 8.31, 8.42 (each 3H, s) 26H and 27H; 8.52, 8.86, 8.87, 8.90, 9.05 methyls. λ_{max}: 271 nm (ε, 9100). Found: C, 75.0; H, 8.9; calc. for $C_{31}H_{44}O_5$: C, 75.0; H, 8.9%.

(1/3), 1.00 l: Pure methyl 3,7-dioxotirucalla-8,24-dien-21-oate (285 mg) which crystallised as plates from MeOH. M.p. 214-216°, $[\alpha]_D$: -16° (c 0.6). ν_{max} ($CHCl_3$): 3030, 1725, 1706, 1652, 1586, 1162 cm^{-1}. τ: 4.88 (1H, t, J 6.5 Hz) 24H; 6.32 (3H, s) CO_2Me; 8.29, 8.39 (each 3H, s) 26H and 27H; 8.70, 8.85, 8.89, 9.00, 9.24 methyls. λ_{max}: 252.5 nm (ε, 9000). Found: C, 77.1; H, 9.4; calc. for $C_{31}H_{46}O_4$: C, 77.1; H, 9.6%.

A further compound, present in the mother liquors from fractions (1/2) and (1/3), was isolated by p.l.c. (five 100 cm plates, eluted 5 times with benzene:ether, 9:1) and was found to be methyl 7α-bromo-3,15-dioxo(14aH)apotirucalla-24-en-21-oate (84 mg) which crystallised as plates from MeOH. M.p. 82-85°, $[\alpha]_D$: -35° (c 0.2). ν_{max} ($CHCl_3$): 3035, 1725, 1700, 1197, 1174, 1161, 910 cm^{-1}. τ: 4.92 (1H, t, J 6.5 Hz) 24H; 5.18 (1H, t, J 3 Hz) 7βH; 6.27 (3H, s) CO_2Me; 7.30 (1H, s) 14aH; 8.30, 8.40 (each 3H, s) 26H and 27H; 8.82, 8.90, 8.96, 9.01, 9.03 methyls. M/e 562 (M^+), 483, 482, 369, 327,

251. CD (in appendix). Found: C, 65.2; H, 8.3; calc. for $C_{31}H_{47}O_4Br$: C, 66.0; H, 8.4%.

The isolation of (13aH)ursan-3,12-dione, after the reaction of fraction (1/1) with boron trifluoride

$BF_3.Et_2O$ (5 drops) was added to a solution of fraction (1/1) (6.00 g) in benzene (100 ml) and the solution was left at room temp. for 30 min. After the solution had been shaken with a saturated aqueous solution of $NaHCO_3$, work up gave a viscous yellow oil, which was adsorbed from CCl_4 onto a column of alumina (750 g, 5% deactivated). Elution with petrol:ether (85:15) 2 l, gave pure (13aH)ursan-3,12-dione (245 mg) which crystallised as needles from MeOH. M.p. 160-161°, $[\alpha]_D$: +144° (c 0.35). ν_{max}: 1703 cm^{-1}. τ: 8.74, 8.86, 8.88, 8.91, 8.99, 9.12 methyls, 9.09, 9.21 (each 3H, d, J 6 Hz) 19H and 20H. M/e 440 (M^+), 234, 177, 123. Found: C, 81.6; H, 10.55; calc. for $C_{30}H_{48}O_2$: C, 81.8; H, 11.0%.

3β-Hydroxy(13aH)ursan-12-one

t-Butanol (2 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (50 mg) in THF (15 ml) at 0°. After the evolution of gas had ceased, a solution of (13aH)ursan-3,12-dione (125 mg) in THF (5 ml) was then added slowly and the mixture was stirred at 0° for 2 hr, and then at room temp. for a further 2 hr. After EtOAc had been added slowly, followed by H_2SO_4 (5%), work up gave

3β-hydroxy(13αH)ursan-12-one (t.l.c. showed a quantitative yield) as a gum which was purified by p.l.c. (one 20 cm plate, eluted once with benzene:ether, 3:2) and crystallised (with some difficulty) from hexane. Sufficient was kept only for a mass spectrum. M/e 442 (M^+), 234, 177, 123.

3β-Acetoxy(13αH)ursan-12-one

Acetylation of 3β-hydroxy(13αH)ursan-12-one with Ac_2O-pyridine at room temp. gave 3β-acetoxy(13αH)ursan-12-one which crystallised as leaflets from aqueous MeOH. M.p. 205-207°, $[\alpha]_D$: +114° (c 0.7), lit.[244] m.p. 210-211°, $[\alpha]_D$: +115°. ν_{max}: 1735, 1707, 1242, 1030 cm^{-1}. τ: 5.45 (1H, q, J 7 and 9 Hz) 3αH; 7.95 (3H, s) OAc; 8.77, 8.99, 9.06, 9.09, 9.11, 9.15 methyls; 9.12, 9.24 (each 3H, d, J 6 Hz) 19H and 20H. M/e 484 (M^+), 234, 192, 177, 123. RD ($CHCl_3$, c 0.67), $[\phi]_{248}$ +2020, $[\phi]_{270}$ 0, $[\phi]_{305}$ +6080, $[\phi]_{400}$ +1730, a: +61. CD ($CHCl_3$, c 0.66), $\Delta\epsilon_{282}$ +1.54, $\Delta\epsilon_{289}$ +1 63. Found: C, 79.4; H, 10.7; calc. for $C_{32}H_{52}O_3$: C, 79 3; H, 10.8%.

Ozonolysis of an acetylated, brominated and methylated crude acid fraction from Manila elemi resin

A crude mixture of acetoxy elemi acid methyl esters (95 g) was brominated, and the product was ozonised for 35 hr. Work up as on p 117, gave a yellow-brown gum, which was adsorbed from CCl_4 onto a column of alumina (4 kg,

10% deactivated). Elution with petrol : ether (5:1) 3 l, gave a pale yellow oil (9.48 g) (see below) which, by comparative t.l.c., had a R_F very similar to that of an authentic sample of methyl 3α-acetoxy-7α,8α-epoxytirucalla-24-en-21-oate. A small portion (1 g) of this fraction was resolved by p.l.c. (two 100 cm plates, eluted twice with benzene : ether, 9:1). Only one band (the least polar) could be readily distinguished, and yielded a mixture of 3β-acetoxy(13βH)ursan-12-one and a small quantity of 3β-acetoxy(13αH)ursan-12-one (103 mg), which had a R_F identical with that of the required Δ^7-epoxide, and which crystallised as plates from $CHCl_3$-MeOH-water. M.p. 263-267°, $[\alpha]_D$: -3° (c 0.45). For the (13αH) isomer, see above. For 3β-acetoxy(13βH)-ursan-12-one, lit.[244] m.p. 280-282°, $[\alpha]_D$: +11°. ν_{max}: 1735, 1692, 1241, 1027 cm^{-1}. τ: 5.48 (1H, q, J 8 and 10 Hz) 3αH; 7.36 (1H, d, J 3.5 Hz) 13βH; 7.62 (1H, d, J 6 Hz); 7.70 (1H, d, J 7 Hz); 7.95 (3H, s) OAc; 8.84, 9.04, 9.07, 9.09, 9 12 (6H) methyls; 9.11, 9.30 (each 3H, d, J 7 Hz) 19H and 20H. M/e 484 (M^+), 469, 234, 219, 189, 123. RD ($CHCl_3$, c 1.55), $[\phi]_{240}$ -3880, $[\phi]_{260}$ -2560, $[\phi]_{307}$ +1120, a: +37. CD ($CHCl_3$, c 1.55), $\Delta\epsilon_{289}$ +0.65. Found: C, 79.0; H, 10.5; calc. for $C_{32}H_{52}O_3$: C, 79.3; H, 10.8%.

Reaction of suspected methyl 3α-acetoxy-7α,8α-epoxytirucalla-24-en-21-oate with boron trifluoride

$BF_3.Et_2O$ (5 drops) were added to a stirred solution of the yellow oil

(8.50 g, from above) in benzene (200 ml) and the solution was left at room temp. for 30 min. After the mixture had been poured into a saturated aqueous solution of $NaHCO_3$, work up gave a pale yellow oil. T.l.c. showed that no reaction had taken place.

Ozonolysis of a crude mixture of methyl 3α-acetoxy-24,25-dibromotirucalla-7 and 8-en-21-oates

A partially resolved, methylated crude acid fraction from Manila elemi resin (33 g), which was mainly methyl 3α-hydroxytirucalla-7 and 8,24-dien-21-oates, was acetylated with Ac_2O-pyridine (1:1), brominated, and the product was ozonised for 20 hr, as on p. 117. Work up gave a yellow gum (36 g) which was adsorbed from CCl_4 onto a column of alumina (1.4 kg, deactivated 5%). The column was eluted with petrol : ether mixtures.

(1) (5:1), 1 l: A colourless gum (800 mg) from which the major component was isolated by p.l.c. (two 100 cm plates, eluted twice with benzene :ether, (95:5) and which was found to be methyl 3β-acetoxy-12-oxo(13βH)ursan-28-oate (95 mg), which crystallised as microprisms from MeOH. M.p. 266-267°, $[\alpha]_D$: +46° (c 0.5), lit.[247] m.p. 253-256°, $[\alpha]_D$: +32°. ν_{max}: 1730, 1236, 1143, 1029 cm^{-1}. τ: 5.54 (1H, q, J 7 and 9 Hz) 3αH; 6.32 (3H, s) CO_2Me; 7.04 (1H, d, J 3 Hz) 13βH; 7.96 (3H, s) OAc; 8.79, 9.01, 9.12, 9.15 (6H) methyls; 9.01, 9.09 (each 3H, d, J 6 Hz) 19H and 20H; M/e 528 (M^+), 333, 278, 220, 189, 168. RD ($CHCl_3$, c 1.5), $[\phi]_{250}$ -1550, $[\phi]_{300}$ -1270, a: +3.

CD ($CHCl_3$, c 1.5), $\Delta\epsilon$ zero above 240 nm. Found: C, 75.0; H, 9.9; calc. for $C_{33}H_{52}O_5$: C, 75.0; H, 9.9%.

(2) (4:1), 2 l: A gum (5.00 g), the major component of which, by comparative t.l.c., had the same R_F as that of an authentic sample of methyl 3α-acetoxy-7α,8α-epoxytirucalla-24-en-21-oate. The epoxide was isolated from a small portion of the gum by p.l.c. (one 20 cm plate, eluted twice with benzene:ether, 95:5) and crystallised as needles from MeOH. M.p. 126-128°, $[\alpha]_D$: -79° (c 0.4), lit.[109] m.p. 127.5-129°, $[\alpha]_D$: -80°. ν_{max}: 1742, 1249, 1192, 1160 cm^{-1}. τ (CCl_4): 5.01 (1H, t, J 6.5 Hz) 24H; 5.46 (1H, t, J 3 Hz) 3βH; 6.42 (3H, s) CO_2Me; 7.31 (1H, 's', $w_{\frac{1}{2}}$ 4 Hz) 7βH; 8.00 (3H, s) OAc; 8.33, 8.44 (each 3H, s) 26H and 27H; 9.03 (9H), 9.16 (6H) methyls.

(3) (3:1), 2 l: A yellow gum (4.40 g) from which five compounds were separated by p.l.c. (ten 100 cm plates, eluted once with benzene:ether, 9:1). Each band was further purified by p.l.c. (one 20 cm plate, eluted twice with benzene:ether, 9:1).

(3/1). The least polar component was methyl 3α-acetoxy-7α-bromo-15-oxo(14αH)apotirucalla-24-en-21-oate (200 mg), which crystallised as needles from MeOH. M.p. 189-191°, $[\alpha]_D$: -99° (c 0.9). ν_{max}: 1732, 1245, 1192, 1160 cm^{-1}. τ: 4.96 (1H, t, J 6 Hz) 24H; 5.26 (1H, t, J 3 Hz) 7βH; 5.34 (1H, t, J 3 Hz) 3βH; 6.29 (3H, s) CO_2Me; 7.26 (1H, 's', $w_{\frac{1}{2}}$ 4 Hz) 14αH; 7.92 (3H, s) OAc; 8.28, 8.38 (each 3H, s) 26H and 27H; 8.85, 9.01, 9.06,

9.10, 9.15 methyls. M/e 606 (M^+), 526, 466, 451, 251, 187. RD and CD, see appendix. Found: C, 65.3; H, 8.4; Br, 13.2; calc. for $C_{33}H_{51}O_5Br$: C, 65.2; H, 8.5; Br, 13.15%.

(3/2). Methyl 3β-acetoxy-11-oxours-12-en-28-oate (302 mg) which crystallised as rods from MeOH. M.p. 245-248°, $[\alpha]_D$: +62° (c 0.9), lit.[247] m.p. 243-245°, $[\alpha]_D$: +86°. ν_{max}: 1730, 1663, 1235, 1195, 1141, 1028, 983 cm^{-1}. τ: 4.36 (1H, s) 12H; 5.44 (1H, q, J 7 Hz and 9 Hz) 3αH; 6.39 (3H, s) CO_2Me; 7.96 (3H, s) OAc; 8.70, 8.85, 9.09, 9.13 (6H) methyls. The sec. methyls are not readily distinguished. λ_{max}: 250 nm (ε, 7300). Found: C, 75.1; H, 9.65; calc. for $C_{33}H_{50}O_5$: C, 75.2; H, 9.6%.

(3/3). Methyl 3α-acetoxy-7,11-dioxotirucalla-8,24-dien-21-oate (2.86 g) as a yellow gum, which, although homogeneous by t.l.c., could not be induced to crystallise from a solvent. $[\alpha]_D$: -15° (c 0.6). ν_{max}: 1730, 1670, 1234, 1209, 1155 cm^{-1}. λ_{max}: 273 nm (ε, 8400).

(3/4). Methyl 3α-acetoxy-7-oxotirucalla-8,24-dien-21-oate (118 mg) which crystallised as needles from aqueous MeOH. M.p. 167-169°, $[\alpha]_D$: -44° (c 0 2). ν_{max}: 1735, 1660, 1240, 1212, 1150, 1030, 1011, 904 cm^{-1}. τ: 4.95 (1H, t, J 6.5 Hz) 24H; 5.32 (1H, t, J 3 Hz) 3βH; 6.33 (3H, s) CO_2Me; 7.94 (3H, s) OAc; 8.32, 8.41 (each 3H, s) 26H and 27H; 8.92, 9.00, 9.02, 9.12, 9.19 methyls. λ_{max}: 254 nm (ε, 9300). Found: C, 75.3; H, 9.45; calc. for $C_{33}H_{50}O_5$: C, 75.2; H, 9.6%.

(3/5). Methyl 3α-acetoxy-7α-hydroxy-14β,15β-epoxyapotirucalla-24-en-21-oate (53 mg) as a colourless gum which failed to crystallise. ν_{max}: 3515, 1732, 1245, 1165, 1153, 1019 cm^{-1}. τ: 4.91 (1H, t, J 6.5 Hz) 24H; 5.37 (1H, t, J 3 Hz) 3βH; 6.36 (3H, s) CO_2Me; 6.89 (1H, 's', $w_{\frac{1}{2}}$ 4 Hz) 7βH; 6.94 (1H, 's', $w_{\frac{1}{2}}$ 3 Hz) 15αH; 7.96 (3H, s) OAc; 8.32, 8.42 (each 3H, s) 26H and 27H; 8.82, 8.93, 9.01, 9.04, 9.14 methyls. M/e 544 (M^+ for $C_{33}H_{52}O_6$), 349, 319, 122. RD ($CHCl_3$, c 0.74), $[\phi]_{250}$ -4380, $[\phi]_{300}$ -2040, $[\phi]_{400}$ -1170.

Reaction of crude methyl 3α-acetoxy-7α,8α-epoxytirucalla-24-en-21-oate with boron trifluoride

$BF_3.Et_2O$ (10 drops) was added to a solution of crude methyl 3α-acetoxy-7α,8α-epoxytirucalla-24-en-21-oate (5.0 g, fraction (2) from above) in benzene (250 ml) and the solution was left at room temp. for 30 min. After the solution had been shaken with a saturated aqueous solution of $NaHCO_3$, work up gave a gum, the four components of which were separated on a column of alumina (250 g, 10% deactivated). The column was eluted with petrol : ether mixtures. (2/1) (95:5), 1 l: Methyl 3α-acetoxytirucalla-7,9(11),24-trien-21-oate (580 mg, 24% based on the Δ^7-epoxide content), which crystallised as flat prisms from $CHCl_3$-MeOH-water. M.p. 130-132°, $[\alpha]_D$: -115° (c 0.7). ν_{max}: 3040, 1735, 1243, 1185, 1152, 1032, 1012, 815 cm^{-1}. τ: 4.62, 4.79 (each 1H, 's', $w_{\frac{1}{2}}$ 9Hz) 7H and 11H; 4.88 (1H, t, J 6.5 Hz) 24H; 5.28 (1H, 's', $w_{\frac{1}{2}}$ 7 Hz)

3βH; 6.30 (3H, s) CO_2Me; 7.95 (3H, s) OAc; 8.31, 8.41 (each 3H, s) 26H and 27H; 9.00, 9.05, 9.14 (6H), 9.28 methyls. λ_{max}: 232 nm (log ε, 4.17), 240 (4.23), 248 (4.00). Found: C, 77.35; H, 9.7; calc. for $C_{33}H_{50}O_4$: C, 77.6; H, 9.9%.

(2/2) (85:15), 1 l: Methyl 3α-acetoxy-7α-bromo-15-oxo(14αH)apotirucalla-24-en-21-oate (707 mg) which crystallised as needles from MeOH. M.p. 187-189°, $[\alpha]_D$: -96° (c 0.5). The i.r. and n.m.r. spectra were superimposable upon those of the sample obtained above. Found: C, 65.6; H, 8.4; calc. for $C_{33}H_{51}O_5Br$: C, 65.2; H, 8.5%.

(2/3) (85:15), 500 ml: Methyl 3β-acetoxy-12-oxo(13αH)ursan-28-oate (444 mg) which crystallised as flat prisms from aqueous MeOH. M.p. 250-253°, $[\alpha]_D$: +31° (c 0.3), lit.[247] m.p. 250-253°, $[\alpha]_D$: +25°. ν_{max}: 1725, 1685, 1238, 1022 cm^{-1}. τ: 5.47 (1H, q, J 7 Hz and 9 Hz) 3αH; 6.26 (3H, s) CO_2Me; 7.95 (3H, s) OAc; 8.65, 9.02, 9.05, 9.10 (6H), 9.29 (3H, d, J 6Hz) 29H. M/e 528 (M^+), 333, 278, 220, 168. RD ($CHCl_3$, c 0.58), $[\phi]_{276}$ -4700, $[\phi]_{323}$ +6150, $[\phi]_{400}$ +1810, a: +109. CD($CHCl_3$, c 0.53), $\Delta\epsilon_{302}$ +2.87. Found: C, 75.4; H, 9.7; calc. for $C_{33}H_{52}O_5$: C, 75.0; H, 9.9%.

KOH (500 mg) was added to a solution of methyl 3β-acetoxy-12-oxo(13αH)ursan-28-oate (104 mg) in ethane-1,2-diol (10 ml) and the solution was heated under reflux for 6 hr. Work up gave a crystalline solid which was acetylated with Ac_2O-pyridine (1:1). Purification by p.l.c. (one 20 cm plate, eluted once with

benzene : ether, 3:2) gave 3β-acetoxy-12-oxo(13βH)ursan-28-oic acid, which crystallised as needles from aqueous MeOH. M.p. 290-295° (dec), $[\alpha]_D$: +48° (c 0.4). ν_{max}: 2660, 1750, 1731, 1693, 1243, 1214, 1025 cm^{-1}. τ: 2.47 (1H, br.s.) CO_2H; 5.48 (1H, q, J 7 Hz and 9 Hz) 3αH; 7.13 (1H, d, J 10 Hz) 11βH; 7.96 (3H, s) OAc; 8.86, 9.03, 9.09, 9.15 (6H). M/e 514 (M^+ for $C_{32}H_{50}O_5$), 499, 453, 264, 218, 203. CD ($CHCl_3$, c 0.93), $\Delta\epsilon_{254}$ +0.08, $\Delta\epsilon_{300}$ +0.04.

(2/4) (85:15), 2 l: Methyl 3α-acetoxy-7α-hydroxyapotirucalla-14,24-dien-21-oate (1.54 g, 72% based on the Δ^7-epoxide content) as a gum which failed to crystallise. ν_{max}: 3655, 3030, 1745, 1250, 1192, 1155, 1038 cm^{-1}. τ: 4.51 (1H, 's', $w_{\frac{1}{2}}$ 6 Hz) 15H; 4.88 (1H, t, J 7 Hz) 24H; 5.31 (1H, t, J 3 Hz) 3βH; 6.06 (1H, t, J 3 Hz) 7βH; 6.29 (3H, s) CO_2Me; 7.92 (3H, s) OAc; 8.31, 8.42 (each 3H, s) 26H and 27H; 8.92, 8.95, 9.10 (6H), 9.14 methyls.

Methyl 3α-acetoxy-7-oxoapotirucalla-14,24-dien-21-oate

Jones reagent (0.3 ml) was added dropwise to a stirred solution of methyl 3α-acetoxy-7α-hydroxyapotirucalla-14,24-dien-21-oate (94 mg) in acetone (50 ml) and the solution was stirred at 0° for 30 min. Work up gave methyl 3α-acetoxy-7-oxoapotirucalla-14,24-dien-21-oate (90 mg), which crystallised as needles from aqueous MeOH. M.p. 145-146°, $[\alpha]_D$: -156° (c 0.4), lit.[109] m.p. 146-148°, $[\alpha]_D$: -156°. ν_{max}: 1745, 1720, 1246, 1200, 1153, 1034,

1017 cm^{-1}. τ (CCl_4): 4.16 (1H, 's', $w_{\frac{1}{2}}$ 6 Hz) 15H; 5.02 (1H, t, J 6.5 Hz) 24H; 5.40 (1H, t, J 3 Hz) 3βH; 6.43 (3H, s) CO_2Me; 8.02 (3H, s) OAc; 8.36, 8.47 (each 3H, s) 26H and 27H; 8.78, 8.95, 9.00, 9.08, 9.17 methyls.

Methyl 3α,7α-diacetoxyapotirucalla-14,24-dien-21-oate

Acetylation of methyl 3α-acetoxy-7α-hydroxyapotirucalla-14,24-dien-21-oate with Ac_2O-pyridine (1:1) for 8 days gave the title compound which crystallised as needles from aqueous MeOH. M.p. 132-133°, $[\alpha]_D$: -105° (c 0.3), lit.[109] m.p. 133-135°, $[\alpha]_D$: -106°. ν_{max}: 1735, 1247, 1151, 1040, 1025 cm^{-1}. τ: 4.85 (3H, complex m) 7β, 15, 24H; 5.36 (1H, t, J 3 Hz) 3βH; 6.34 (3H, s) CO_2Me; 7.93 (3H, s) 3αOAc; 8.04 (3H, s) 7αOAc; 8.32, 8.43 (each 3H, s) 26H and 27H; 8.92, 8.94, 9.09, 9.12, 9.25 methyls.

3α-Acetoxy-15-oxo(14αH)apotirucalla-6,24-dien-21-oic acid

1,5-Diazabicyclo(3,4,0)non-5-ene (350 mg) was added to a solution of methyl 3α-acetoxy-7α-bromo-15-oxo(14αH)apotirucalla-24-en-21-oate (220 mg) in DMF (15 ml) and the solution was heated under reflux for 40 hr. Work up gave a red-brown gum from which the major component was isolated by p.l.c. (one 20 cm plate, eluted twice with benzene:ether, 3:1). This was shown to be 3α-acetoxy-15-oxo(14αH)apotirucalla-6,24-dien-21-oic acid (40 mg, 22%), and although solid, it could not be induced to crystallise from a solvent. $[\alpha]_D$: -64° (c 1.8). ν_{max}: 2660, 1742, 1730, 1708, 1245, 1027 cm^{-1}.

τ: 2.19 (1H, 's') CO_2H; 3.99 (1H, q, $J_{6,7}$ 10 Hz, $J_{5,6}$ 3 Hz) 6H; 4.53 (1H, d, $J_{6,7}$ 10 Hz) 7H; 4.92 (1H, t, J 6 Hz) 24H; 5.31 (1H, t, J 3 Hz) 3βH; 7.94 (3H, s) OAc; 8.32, 8.41 (each 3H, s) 26H and 27H; 8.90, 8.94, 9.11 (6H), 9.13 methyls.

Reaction of methyl 3α-acetoxy-7α-bromo-15-oxo(14αH)apotirucalla-24-en-21-oate with phosphoryl chloride

$POCl_3$ (5 drops) was added to a solution of the title compound (100 mg) in pyridine (5 ml) and the solution was left at room temp. for 25 hr. T.l.c. indicated that no reaction had taken place.

Methyl 7α-bromo-15-oxo(14αH)apotirucalla-2,24-dien-21-oate

$TsOH.H_2O$ (60 mg) was added to a solution of methyl 3α-acetoxy-7α-bromo-15-oxo(14αH)apotirucalla-24-en-21-oate (100 mg) in benzene (15 ml) and the solution was heated under reflux for 5 days. After the solution had been evaporated to dryness, the product was isolated by p.l.c. (one 20 cm plate, eluted once with benzene:ether, 4:1). This was shown to be methyl 7α-bromo-15-oxo(14αH)apotirucalla-2,24-dien-21-oate (quantitative yield), a clear gum, which could not be induced to crystallise. $[\alpha]_D$: -30° (c 3.3). ν_{max}: 1735, 1218, 1156 cm^{-1}. τ: 4.58 (2H, 'd', J 2.5 Hz) 2H and 3H; 4.95 (1H, t, J 6.5 Hz) 24H; 5.22 (1H, t, J 3 Hz) 7βH; 6.29 (3H, s) CO_2Me; 7.29 (1H, 's', $w_{\frac{1}{2}}$ 4 Hz) 14αH; 8.32, 8.42 (each 3H, s) 26H and 27H; the methyl signals could not readily be distinguished.

Attempted reduction of methyl 3α-acetoxy-7α-bromo-15-oxo(14αH)apotirucalla-24-en-21-oate

A solution of KBH_4 (20 mg) in a mixture of EtOH (1 ml) and aqueous NaOH (2M, 0.5 ml) was added to a solution of the title compound (150 mg) in EtOH (20 ml) and the mixture was stirred at room temp. for 15 hr. T.l.c. showed that no reaction had occurred and work up gave starting material which crystallised on standing.

Ozonolysis of methyl 3α-acetoxy-24,25-dibromotirucalla-7-en-21-oate

A solution of bromine (0.15 ml) in $CHCl_3$ (15 ml) was added dropwise over a period of 10 min to a stirred solution of methyl 3α-acetoxytirucalla-7,24-dien-21-oate (1.25 g) in $CHCl_3$ (50 ml) and the mixture was stirred at room temp. for a further hour. After the solution had been washed with aqueous $NaHCO_3$, and water, evaporation of the solvent gave a colourless gum. The gum, in EtOAc (100 ml) was ozonised at -70° for 1 hr. Nitrogen was then passed through the solution to discharge excess ozone. Zinc dust (650 mg) and water (10 ml) were added, and the mixture was heated under reflux for 45 min. The mixture was filtered through celite (30 g) and after the EtOAc layer had been separated, work up gave a pale orange gum which was chromatographed on a column of alumina (75 g, 5% deactivated). Elution with petrol : ether (4:1) and (3:1) gave a colourless gum (355 mg) from which the two major components were separated by p.l.c. (one 100 cm plate, eluted once with benzene : ether, 85:15).

(i) The more polar component was methyl 3α-acetoxy-7-oxotirucalla-8,24-dien-21-oate, and was identical, by m.p., $[\alpha]_D$, i.r. and n.m.r. spectra and t.l.c. behaviour, with that obtained above, p 124.

(ii) The less polar component was dissolved in benzene (25 ml) and was treated with $BF_3.Et_2O$ (4 drops). The solution was then stirred at room temp. for 1 hr. T.l.c. showed that no reaction had occurred. Saturated aqueous $NaHCO_3$ was added and the mixture was stirred rapidly for 10 min. After the benzene layer had been separated, work up gave a solid which crystallised from MeOH, m.p. 183-185°, and was identical by t.l.c., and i.r. with methyl 3α-acetoxy-7α-bromo-15-oxo(14αH)apotirucalla-24-en-21-oate obtained above.

Methyl 3α-acetoxy-24-bromotirucalla-8,24-dien-21-oate

Glacial HOAc was added to an aqueous solution of tetramethylammonium hydroxide (25%) at 0°, until the pH reached 5. Acetone was added and the solution was evaporated to dryness under reduced pressure. The acetate was recrystallised from acetone, and dried over P_2O_5, in a vacuum. Tetramethylammonium acetate (335 mg) was added to a solution of methyl 3α-acetoxy-24,25-dibromotirucalla-8-en-21-oate (995 mg) in acetone (25 ml) and the solution was heated under reflux for 70 hr. After the mixture had been poured into water, work up gave methyl 3α-acetoxy-24-bromotirucalla-8,24-dien-21-oate (705 mg, 81%) which crystallised from MeOH. A small portion was further purified by p.l.c. (one 20 cm plate, eluted once with benzene:ether,

95:5) and recrystallised as rods from MeOH. M.p. 141-144°, $[\alpha]_D$: -29° (c 0.7). ν_{max}: 1732, 1245, 1155, 1037, 1012, 978 cm^{-1}. τ: 5.28 (1H, t, J 3 Hz) 3βH; 6.30 (3H, s) CO_2Me; 7.94 (3H, s) OAc; 8.14, 8.26 (each 3H, s) 26H and 27H; 9.03, 9.08, 9.12 (6H), 9.16 methyls. Found: C, 66.6; H, 8.5; Br, 13.7; calc. for $C_{33}H_{51}O_4Br$: C, 67.0; H, 8.7; Br, 13.5%

Attempted oxidation of methyl 3α-acetoxy-24-bromotirucalla-8,24-dien-21-oate with permanganate-periodate

A solution of $KMnO_4$ (18 mg) in a mixture of acetone (5 ml) and water (5 ml) was added to a solution of the title compound (400 mg) and $NaIO_4$ (600 mg) in a mixture of acetone (85 ml) and water (30 ml) at 0°. The mixture was stirred at room temp. in an atmosphere of nitrogen for 24 hr and after the mixture had been poured into brine, work up gave only starting material (t.l.c.) as a gum.

Attempted ozonolysis of methyl 3α-acetoxy-24-bromotirucalla-8,24-dien-21-oate

The title compound (400 mg) in EtOAc (50 ml) was ozonised at -70° for 30 min. Nitrogen was passed through the solution to discharge excess ozone. Zinc dust (500 mg) and water (10 ml) were added and the solution was heated under reflux for 1 hr. After the solution had been filtered through glass wool, and diluted with brine, work up gave a pale yellow gum which contained some ten compounds and the mixture was not investigated further.

24-Bromotirucalla-8,24-dien-3α,21-diol

A solution of methyl 3α-acetoxy-24-bromotirucalla-8,24-dien-21-oate (390 mg) in ether (20 ml) was added dropwise to a solution of $LiAlH_4$ (80 mg) in ether (20 ml) and the mixture was heated under reflux for 1 hr. After the solution had cooled, EtOAc (10 ml), water (25 ml) and H_2SO_4 (5%, 50 ml) were then added. After the solution had been saturated with brine, work up gave 24-bromotirucalla-8,24-dien-3α,21-diol (quantitative yield), which crystallised as needles from aqueous acetone. M.p. 168-171°, $[\alpha]_D$: -18° (c 0.4). ν_{max}: 3615, 1056, 1039, 1020, 1009, 986, 974 cm^{-1}. τ: 6.28 (2H, 's', $w_{\frac{1}{2}}$ 8 Hz) CH_2OH; 6.56 (1H, 's', $w_{\frac{1}{2}}$ 7 Hz) 3βH; 8.14, 8.23 (each 3H, s) 26H and 27H; 9.02 (6H), 9.10, 9.13, 9.19 methyls. Found: C, 69.4; H, 9.4; calc. for $C_{30}H_{49}O_2Br$: C, 69.1; H, 9.5%.

Tirucall-8-en-3α,21-diol

24-Bromotirucalla-8,24-dien-3α,21-diol (100 mg) in EtOH (50 ml) was hydrogenated over Adams (PtO_2) catalyst. Purification of the product by p.l.c. (one 20 cm plate, eluted once with benzene:ether, 1:1) gave tirucall-8-en-3α,21-diol, which crystallised as prisms from aqueous acetone. M.p. 156-157°, $[\alpha]_D$: -20° (c 0.6). ν_{max}: 3620, 3485, 1211, 1059, 986, 977, 954, 922 cm^{-1}. τ: 6.28 (2H, 's', $w_{\frac{1}{2}}$ 6 Hz) CH_2OH; 6.55 (1H, 's', $w_{\frac{1}{2}}$ 6 Hz) 3βH; 9.01 (6H), 9.08, 9.09, 9.12, 9.15, 9.19 methyls. Found: C, 81.1; H, 11.3; calc. for $C_{30}H_{52}O_2$: C, 81.0; H, 11.8%.

Methyl 3α-acetoxy-24,25-epoxytirucall-8-en-21-oate via methyl 3α-acetoxy-25-hydroxy-24-iodotirucall-8-en-21-oate

A solution of iodine (130 mg) and potassium iodate (KIO_3, 90 mg) in a mixture of glacial HOAc (4 ml) and water (3.5 ml) was added to a solution of methyl 3α-acetoxytirucalla-8,24-dien-21-oate (1.01 g) in dioxan (10 ml) and the mixture was stirred at 50° for 13 hr. The solution was then cooled, diluted with ether, and the ethereal extract was washed with an aqueous solution of $Na_2S_2O_3$. After addition of brine, work up then gave an oil. $Ca(OH)_2$ (180 mg) was added to a solution of this oil in dioxan (20 ml) and the solution was heated under reflux for 6 hr, after which t.l.c. indicated that no reaction had taken place. KOH (235 mg) was then added to the oil in MeOH (20 ml) and the solution was heated under reflux for 17 hr. Work up gave a gum (770 mg) which was acetylated with Ac_2O-pyridine (1:2) (30 ml) for 15 hr. Work up gave a gum from which three components were separated by p.l.c. (two 100 cm plates, eluted 3 times with benzene : ether, 95:5).

(i) The least polar component was starting material, methyl 3α-acetoxytirucalla-8,24-dien-21-oate (26 mg), which crystallised as prisms from aqueous MeOH. M.p. 118.5-121.5°, $[\alpha]_D$: -44° (c 0.2).

(ii) Methyl 3α-acetoxy-24ξ,25-epoxytirucall-8-en-21-oate (70 mg, 7%), which crystallised as rods from aqueous MeOH. M.p. 112-114°, $[\alpha]_D$: -32° (c 0.4), lit.[129] m.p. 114-116°, $[\alpha]_D$: -36°. ν_{max}: 1730, 1240, 1154, 1036, 1011,

975, 962 cm^{-1}. τ (CCl_4): 5.41 (1H, t, J 3 Hz) 3βH; 6.40 (3H, s) CO_2Me; 7.5 (1H, m) 24H; 8.00 (3H, s) OAc; 8.76, 8.81 (each 3H, s) 26H and 27H; 9.04, 9.08, 9.10, 9.14, 9.17 methyls.

(iii) Methyl 3α,24§-diacetoxy-25-hydroxytirucall-8-en-21-oate, a gum (200 mg, 17%), which was further purified by p.l.c. (two 20 cm plates, eluted once with ether) and which could not be induced to crystallise from a solvent. $[\alpha]_D$: -28° (c 1.0). ν_{max}: 3585, 3440, 1730, 1240, 1212, 1154, 1036, 1014 cm^{-1}. τ: 5.21 (1H, m, $w_{\frac{1}{2}}$ 18 Hz) 24H; 5.31 (1H, t, J 3 Hz) 3βH; 6.35 (3H, s) CO_2Me; 7.90 (3H, s) 24OAc; 7.95 (3H, s) 3αOAc; 8.85 (6H, s) 26H and 27H; 9.05, 9.11, 9.14 (6H), 9.18 methyls. M/e 588 (M^+ for $C_{35}H_{56}O_7$).

KOH (100 mg) was added to a solution of methyl 3α,24§-diacetoxy-25-hydroxy-tirucall-8-en-21-oate (200 mg) in MeOH (25 ml) and the solution was heated under reflux for 15 hr. Work up from brine, and EtOAc gave a gum which contained two compounds of very similar polarity. The more polar component was isolated by p.l.c. (one 20 cm plate, eluted once with ether, and a further twice with benzene:ether, 1:1) and was methyl 3α,24§,25-trihydroxytirucall-8-en-21-oate, a gum, which could not be induced to crystallise from a solvent. $[\alpha]_D$: -29° (c 3.2). ν_{max}: 3615, 3455, 3380, 1733, 1153, 1048 cm^{-1}. τ: 6.34 (3H, s) CO_2Me; 6.56 (1H, t, J 3 Hz) 3βH; 6.70 (1H, m, $w_{\frac{1}{2}}$ 13 Hz) 24H; 8.82 (3H, d, J 1.5 Hz); 8.87 (3H, s) 26H and 27H; 9.03 (6H), 9.12, 9.14, 9.19 methyls. M/e 504 (M^+ for $C_{31}H_{52}O_5$).

Methyl 3α-acetoxy-24-oxotirucall-8-en-21-oate

Aqueous $HClO_4$ (72%, 0.05 ml) was added to a solution of methyl 3α-acetoxy-24,25-epoxytirucall-8-en-21-oate (125 mg) in butan-2-one (10 ml) and the solution was stirred at room temp. for 10 min. After the solution had been diluted with water (40 ml), work up gave a quantitative yield of methyl 3α-acetoxy-24-oxotirucall-8-en-21-oate as a gum which was purified by p.l.c. (one 20 cm plate, eluted twice with benzene:ether, 95:5) but which failed to crystallise. $[\alpha]_D$: -4° (c 1.2). ν_{max}: 1734, 1715, 1245, 1180, 1153, 1115, 1035, 1012 cm^{-1}. τ: 5.33 (1H, t, J 3 Hz) 3βH; 6.33 (3H, s) CO_2Me; 7.95 (3H, s) OAc; 8.92 (6H, d, J 7 Hz) 26H and 27H; 9.03, 9.09, 9.11, 9.13, 9.16 methyls.

Methyl 3α,7α-diacetoxy-24,25-dibromoapotirucalla-14-en-21-oate

A solution of bromine (0.15 ml, 0.44 g) in $CHCl_3$ (15 ml) was added over a period of 5 hr to a solution of methyl 3α,7α-diacetoxyapotirucalla-14,24-dien-21-oate (1.50 g) in $CHCl_3$ (50 ml) and the mixture was stirred at room temp. for a further 15 hr. The mixture was then evaporated to dryness and the residue was taken up in ether. Work up gave a yellow oil, from which the major product was isolated by p.l.c. (three 100 cm plates, eluted 5 times with benzene:ether, 99:1). The product was filtered through a small column of alumina (10 g, 10% deactivated) and elution with benzene:ether (1:1) gave methyl 3α,7α-diacetoxy-24,25-dibromoapotirucall-14-en-21-oate (725 mg, 38%) as a gum, which failed

to crystallise. $[\alpha]_D$: -188° (c 0.2). ν_{max}: 1735, 1240, 1151, 1097, 1037, 1022 cm^{-1}. τ: 4.74 (1H, 's', $w_{\frac{1}{2}}$ 7.5 Hz) 15H; 4.83 (1H, 's', $w_{\frac{1}{2}}$ 6 Hz) 7βH; 5.34 (1H, t, J 3 Hz) 3βH; 5.85 (1H, t, J 11 Hz) 24H; 6.30 (3H, s) CO_2Me; 7.92 (3H, s) 3αOAc; 8.02 (6H, s) 7αOAc and 26H; 8.21 (3H, s) 27H; 8.90 (6H), 9.08, 9.11, 9.24 methyls. M/e 728 (M^+ for $C_{35}H_{54}O_6Br_2$).

Reaction of methyl 3α,7α-diacetoxy-24,25-dibromoapotirucalla-14-en-21-oate with selenium dioxide

A solution of SeO_2 (sublimed, 160 mg) in water (2.5 ml) was added to the title compound (685 mg) in dioxan (20 ml) and the homogeneous solution was stirred at room temp. for 45 hr, after which t.l.c. showed that no reaction had taken place. The mixture was then heated under reflux for 20 hr. After the mixture had been diluted with ether, and the ethereal solution had been washed with an aqueous solution of $Na_2S_2O_3$, work up gave an orange-yellow gum from which the major product was isolated by p.l.c. (two 100 cm plates, eluted 3 times with benzene:ether, 49:1), and a further 3 times with benzene:ether, 24:1). This was shown to be starting material (71 mg, 11%) by comparative t.l.c. In addition the i.r. and n.m.r. spectra were superimposable upon those obtained above.

Methyl 3α,7α-diacetoxy-16-oxoapotirucall-14-en-21-oate

(a) A solution of NBS (recrystallised from hot water, 95 mg) and $CaCO_3$

(finely divided, 43 mg) in water (10 ml) was added to a solution of methyl 3α,7α-diacetoxyapotirucall-14-en-21-oate (100 mg) in a mixture of dioxan (10 ml) and THF (10 ml). The mixture was stirred vigorously at room temp. for 1.25 hr and was illuminated with a 60 watt tungsten light, which was placed approx. 6 inches from the reaction flask. The whole apparatus was enclosed within silver foil. After the mixture had been diluted with brine, work up gave a gum, from which the two components were separated by p.l.c. (one 20 cm plate, eluted twice with benzene:ether, 9:1).

(i) By comparative t.l.c., the less polar product was starting material (45 mg, 45%).

(ii) The more polar product was methyl 3α,7α-diacetoxy-16-oxoapotirucall-14-en-21-oate (32 mg, 31%) which crystallised as prisms from aqueous MeOH. M.p. 141-143°, $[\alpha]_D$: -131° (c 0 9), lit.[129] m.p. 142-144°, $[\alpha]_D$: -132°. ν_{max}: 1735, 1702, 1238, 1170, 1152, 1035, 1018 cm^{-1}. τ: 4.40 (1H, s) 15H, 4.86 (1H, 's', $w_{\frac{1}{2}}$ 5.5 Hz) 7βH; 5.40 (1H, 's', $w_{\frac{1}{2}}$ 7 Hz) 3βH; 6.36 (3H, s) CO_2Me; 7.99 (3H, s) 3αOAc; 8.09 (3H, s) 7αOAc; 8.78 (6H, s), 9.04, 9.09 (6H), 9.16, 9.24 methyls. λ_{max}: 238 nm (ε, 9550).

(b) CrO_3 (anhydrous, 150 mg) was added to a stirred mixture of pyridine (0.5 ml) and CH_2Cl_2 (10 ml) and the mixture was stirred at room temp. for 15 min. A solution of methyl 3α,7α-diacetoxyapotirucall-14-en-21-oate (110 mg) in CH_2Cl_2 (5 ml) was added to this solution and the mixture was then stirred at

room temp. for 40 hr. After the solution had been diluted with CH_2Cl_2, work up gave a pale yellow gum, from which the two major components were separated by p.l c. (one 20 cm plate, eluted once with benzene:ether, 4:1).

(i) By comparative t.l.c., the less polar product was starting material (44 mg, 40%).

(ii) The minor product was not isolated, but from previous work, it was assumed to be methyl 3α,7α-diacetoxy-15-oxo(14αH)apotirucallan-21-oate.

(iii) By comparative t.l.c., the more polar product was methyl 3α,7α-diacetoxy-16-oxoapotirucalla-14-en-21-oate (51 mg, 45%).

Attempted formation of methyl 3α,7α-diacetoxy-16-oxoapotirucalla-14,24-dien-21-oate

CrO_3 (anhydrous, 80 mg) was added to a mixture of pyridine (0.5 ml) and CH_2Cl_2 (5 ml) and the mixture was stirred vigorously for 10 min. A solution of methyl 3α,7α-diacetoxy-24,25-dibromoapotirucall-14-en-21-oate (50 mg) in CH_2Cl_2 (5 ml) was then added and the mixture was stirred at room temp. for 45 hr. After the solution had been diluted with CH_2Cl_2, work up gave a gum, from which methyl 3α,7α-diacetoxy-24,25-dibromo-16-oxoapotirucalla-14-en-21-oate was isolated by p.l.c. (one 20 cm plate, eluted twice with benzene:ether, 4:1). The enone was not characterised, but was dissolved in ether (10 ml), zinc dust (15 mg) was added and the suspension was heated under reflux for 1 hr. The solution was filtered through a small pad of celite and evaporation of the

solvent gave methyl 3α,7α-diacetoxy-16-oxoapotirucalla-14,24-dien-21-oate (11 mg), which was purified by p.l.c. (one 20 cm plate, eluted three times with benzene : ether, 4:1). However, the product appeared to decompose with each elution.

Havanensin triacetate

From its n.m.r. spectrum, crude havanensin triacetate[328] was found to be mostly a mixture of havanensin diacetates. This crude material was acetylated with Ac_2O-pyridine, and an ethereal solution of the triacetate was worked up, (the use of mineral acid was avoided) and was filtered through a column of alumina (100 g, 10% deactivated). Havanensin triacetate crystallised as prisms from aqueous MeOH. M.p. 185-186°, $[\alpha]_D$: -67° (c 0.6), lit.[77] m.p. 188-191°. ν_{max}: 1735, 1245, 1050, 1030, 908, 873, 785 cm^{-1}. τ: 2.65 (1H, t, J 2 Hz) furan αH; 2.91 (1H, 's', $w_{\frac{1}{2}}$ 3.5 Hz) furan α'H; 3.85 (1H, 's', $w_{\frac{1}{2}}$ 4 Hz) furan βH; 5.26 (3H, m) 1α, 3α, 7αH; 6.57 (1H, s) 15αH; 7.88 (3H, s) 7αOAc; 7.98 (6H, s) 1α, 3αOAc; 8.93, 8.98, 9.00, 9.07, 9.18 methyls.

Attempted deoxygenation of havanensin triacetate with triphenylphosphine

Ph_3P (1.00 g) was added to a solution of havanensin triacetate (2.00 g) in DMF (40 ml) and the solution was heated under reflux for 20 hr. After the solution had been poured into brine, work up left only starting material.

Deoxyhavanensin triacetate

Zn-Cu couple (prepared [329] from 150 g zinc dust) was added to a solution of havanensin triacetate (12.0 g) in EtOH (700 ml) and the solution was heated under reflux for 90 hr with stirring, after which no starting material remained. The solution was filtered through a short column of celite under reduced pressure and then excess EtOH was distilled off under reduced pressure. Deoxyhavanensin triacetate crystallised as prisms from aqueous EtOH (1st crop 4.30 g, total yield 7.90 g, 68%). M.p. 150-160°, $[\alpha]_D$: -44° (c 0.3). ν_{max}: 1735, 1250, 1051, 1029, 908 cm^{-1}. τ: 2.63 (1H, t, J 2 Hz) furan αH; 2.76 (1H, m) furan α'H; 3.72 (1H, 's', $w_{\frac{1}{2}}$ 4 Hz) furan βH; 4.63 (1H, t, J 3 Hz) 7αH; 4.80 (1H, 's', $w_{\frac{1}{2}}$ 5 Hz) 15H; 5.28 (1H, t, J 3 Hz), 5.36 (1H, t, J 3 Hz) 1α,3αH; 8.00 (9H, s) 1α,3α,7αOAc; 8.82, 9.01, 9.07, 9.18 (6H) methyls. Found: C, 70.8; H, 8.0; calc. for $C_{32}H_{44}O_7$: C, 71.1; H, 8.2%. The mother liquor consisted of an approx. 1:1 mixture of deoxyhavanensin triacetate and a compound which had a R_F very similar to that of deoxyhavanensin triacetate. Although it was not isolated, this compound is thought to be neohavanensin triacetate.

Attempted allylic oxidation of deoxyhavanensin triacetate with selenium dioxide

SeO_2 (6.0 g) was added to a solution of deoxyhavanensin triacetate (4.0 g) in a mixture of dioxan (250 ml) and water (100 ml) and the homogeneous solution was stirred at 65° for 25 hr. After the solvent had been distilled off under reduced pressure, the residue was taken up in ether and filtered through

a column of alumina (75 g, 10% deactivated). The ethereal solution was then washed with an aqueous solution of $Na_2S_2O_3$, and water, and the solvent was evaporated to leave starting material (75%).

Attempted allylic oxidation of deoxyhavanensin triacetate with anhydrous chromium trioxide

CrO_3 (anhydrous, 4.75 g) was added in small portions, to a stirred mixture of pyridine (10 ml) and CH_2Cl_2 (200 ml) and the suspension was stirred at room temp. for 5 min. A solution of deoxyhavanensin triacetate (4.20 g) in CH_2Cl_2 (75 ml) was then added and the solution was stirred at room temp. for 20 hr. After the solution had been diluted with CH_2Cl_2, filtration through a column of alumina (75 g, 10% deactivated) gave starting material. The effect of raising the temperature was not investigated.

Oxidation of deoxyhavanensin triacetate with aqueous chromic acid

Jones reagent (9 ml) was added, over a period of 10 min, to a solution of deoxyhavanensin triacetate (3.0 g) in acetone (200 ml) at 0°, with stirring. The solution was then stirred at room temp. for 20 hr. After the solution had been poured into brine, work up gave, apart from starting material, one major product, which was isolated by p.l.c. (four 100 cm plates, eluted twice with petrol : acetone, 4:1) and was found to be isophotodeoxyhavanensin triacetate (105 mg, 3%), which crystallised as needles from ether-$CHCl_3$-hexane.

M.p. 229-231°, $[\alpha]_D$: -26° (c 0.7). ν_{max} ($CHCl_3$): 3550, 3300, 1756, 1721, 1635, 1262, 955, 906 cm^{-1}. τ: 3.95 (1H, m, $w_{\frac{1}{2}}$ 12 Hz) 21H; 4.07 (1H, s) 22H; 4.57 (1H, 's', $w_{\frac{1}{2}}$ 8 Hz) 7αH; 4.78 (1H, s) 15H; 5.29 (2H, m, $w_{\frac{1}{2}}$ 9 Hz) 1α, 3αH; 7.94 (3H, s); 7.97 (6H, s) 1α, 3α,7αOAc; 8.81, 9.00, 9.06 (6H), 9.17 methyls. λ_{max}: 213 nm (ε, 11000), λ_{max} ($EtOH/NaHCO_3/H_2O$): 212 nm, 255 nm. M/e 572 (M^+). Found: C, 67.1; H, 7.5; calc. for $C_{32}H_{44}O_9$: C, 67.1; H, 7.7%.

Lup-20(29)-en-3β-yl benzoate

The crude benzoate from an extraction of Gutta Jelutong was purified by repeated crystallisation (as plates) from acetone. M.p. 268-271°, $[\alpha]_D$: +61° (c 0.7), lit.[330] m.p. 265°, $[\alpha]_D$: +60°. ν_{max}: 3065, 1720, 1640, 1275, 1115, 885, 716 cm^{-1}. τ: 1.92 (2H, m) phenyl 2H and 6H; 2.49 (3H, m) phenyl 3,4 and 5H; 5.26 (1H, m, $w_{\frac{1}{2}}$ 18 Hz) 3αH; 5.28 and 5.40 (each 1H, 's', $w_{\frac{1}{2}}$ 5.5 Hz) 29H; 8.30 (3H, s) 30H; 8.94, 8.99, 9.03, 9.07, 9.09, 9.20 methyls.

Lup-20(29)-en-3β-ol

KOH (1.50 g) was added to a solution of lup-20(29)-en-3β-yl benzoate (9.00 g) in EtOH (30 ml) and the solution was heated under reflux for 24 hr. Work up gave lup-20(29)-en-3β-ol, which crystallised as needles from aqueous acetone. M.p. 215-217°, $[\alpha]_D$: +28° (c 0.95), lit.[330] m.p. 211-212°, $[\alpha]_D$: +26°. ν_{max}: 3615, 3070, 1638, 1045, 1016, 885 cm^{-1}. τ: 5.30 and 5.44 (each 1H, d, J 2 Hz) 29H; 6.83 (1H, 's', $w_{\frac{1}{2}}$ 19 Hz) 3αH; 8.31 (3H, s) 30H; 8.96, 9.03, 9.05, 9.16, 9.21, 9.24 methyls.

Lup-20(29)-en-3β-yl acetate

Acetylation of lup-20(29)-en-3β-ol with Ac_2O-pyridine at room temp. for 25 hr gave lup-20(29)-en-3β-yl acetate, which crystallised as needles from aqueous EtOH. M.p. 219-220°, $[\alpha]_D$: +40° (c 0.5), lit.[330] m.p. 214-215°,

$[\alpha]_D$: +47°. ν_{max}: 3070, 1735, 1640, 1245, 1030, 1018, 980, 885 cm^{-1}. τ: 5.30 and 5.42 (each 1H, d, J 2 Hz) 29H; 5.51 (1H, m, $w_{\frac{1}{2}}$ 18 Hz) 3αH; 7.97 (3H, s) OAc; 8.32 (3H, s) 30H; 8.97, 9.06, 9.15, 9.16 (6H), 9.21 methyls.

Lupan-3β-yl acetate

Lup-20(29)-en-3β-yl acetate (7.10 g) in $CHCl_3$ (100 ml) was hydrogenated over Adams (PtO_2) catalyst (0.2 g) at room temp. for 25 hr. The solution was filtered and evaporation of the solvent gave lupan-3β-yl acetate which crystallised as leaflets from aqueous EtOH. M.p. 252-253°, $[\alpha]_D$: -2° (c 0.2), lit.[330] m.p. 245-246°, $[\alpha]_D$: -2°. ν_{max} ($CHCl_3$): 1720, 1255, 1030 cm^{-1}. τ: 5.52 (1H, m, $w_{\frac{1}{2}}$ 19 Hz) 3αH; 7.96 (3H, s) OAc; 8.95, 9.07, 9.13, 9.15 (6H), 9.24 methyls; 9.13, 9.20, 9.21, 9.27 isopropyl doublets.

Lupan-3β-ol

Hydrolysis of lupan-3β-yl acetate with KOH in MeOH gave lupan-3β-ol, which crystallised as needles from MeOH. M.p. 205-207°, $[\alpha]_D$: -15.5° (c 1.0), lit.[251] m.p. 205°, $[\alpha]_D$: -14°. ν_{max}: 3615, 1042, 1030, 1012, 987 cm^{-1}. τ: 6.82 (1H, m, $w_{\frac{1}{2}}$ 18 Hz) 3αH; 8.96, 9.03, 9.07, 9.15, 9.23 (6H) methyls; 9.13, 9.20, 9.21, 9.28 isopropyl doublets.

Lupan-3-one

Jones reagent was prepared by adding concentrated H_2SO_4 (3 ml) to a

stirred solution of CrO_3 (3.5 g) in water (25 ml). This reagent (7.5 ml) was added dropwise to a stirred solution of lupan-3β-ol (5.03 g) in acetone (750 ml) and the solution was left at room temp. for 30 min. The solution was evaporated to dryness and the product was taken up in ether. Work up gave lupan-3-one (4.70 g, 93%) which crystallised as plates from aqueous EtOH. M.p. 210-212°, $[\alpha]_D$: +15° (c 0.4), lit.[251] m.p 209.5-210°, $[\alpha]_D$: +16°. ν_{max}: 1705, 1112, 1080 cm^{-1}. τ: 7.55 (2H, m) 2H; 8.91 (6H), 8.96, 9.05 (6H), 9.23 methyls; 9.12, 9.19, 9.20, 9.27 isopropyl doublets. RD ($CHCl_3$, c 0.93), $[\phi]_{279}$ -1370, $[\phi]_{310}$ +2280, a: +36.5.

Lupan-3-one hydrazone

Hydrazine hydrate (100%, 0.5 ml) was added to a solution of lupan-3-one (0.50 g) in EtOH (20 ml) and the solution was heated under reflux for 5 hr. The solution was concentrated to half volume and upon cooling, lupan-3-one hydrazone (0.48 g, 93%) crystallised as needles. M.p. 275° (dec.), $[\alpha]_D$: -2° (c 0.3), lit.[330] m.p 341-342° (decomposition). ν_{max} ($CHCl_3$): 3395, 1690, 1628 cm^{-1}. τ: 5.07 (2H, 's', $w_{\frac{1}{2}}$ 13 Hz) NH_2; 8.87, 8.92, 8.98, 9.07, 9.09, 9.23 methyls; 9.12, 9.19, 9.20, 9.27 isopropyl doublets.

Lead tetra-acetate oxidation of lupan-3-one hydrazone

Lead tetra-acetate (dried over KOH, 1.45 g) was added to a solution of lupan-3-one hydrazone (720 mg) in CH_2Cl_2 (25 ml) and the solution was

stirred at 0° for 15 min. Ethane-1,2-diol (1 ml) was then added and the solution was stirred at room temp. for a further 30 min. The solution was evaporated to dryness and the solid residue was taken up in ether. Work up gave a crystalline solid from which one major and one minor component were separated by p.l.c. (two 100 cm plates, eluted once with benzene:ether, 100:1).

(i) The less polar (major) product was 5(4→3)abeolup-3-ene) (γ-lupene) (4.25 mg, 63%) which crystallised as needles from EtOAc-MeOH. M.p. 175-180°, $[\alpha]_D$: -8° (c 0.5), lit.[330] m.p. 197-199°, $[\alpha]_D$: -20°. ν_{max}: 1219, 1173, 1149, 1022, 1000 cm^{-1}. τ: 8.27, 8.42 (each 3H, s) 23H and 24H; 8.96, 9.06, 9.23, 9.38 methyls; 9.13, 9.19, 9.21, 9.27 isopropyl doublets.

(ii) The more polar (minor) product was lupan-3-one (13 mg) which was obtained as an amorphous solid from aqueous MeOH. M.p. 203-206°, $[\alpha]_D$: +12° (c 0.1). The i.r. and n.m.r. spectra were completely superimposable upon those of an authentic sample (see above).

5(4→3)Abeolupan-3ξ,4-diol

OsO_4 (100 mg) was added to a solution of γ-lupene (105 mg) in benzene (5 ml) and pyridine (5 ml) at 0° and the solution was left at room temp. for 3 days. The mixture was then diluted with benzene (25 ml), saturated with H_2S and then left at room temp. for a further 25 hr. The solution was then filtered through celite, which was washed with more ether and evaporation of the solvent left a yellow-brown gum from which 5(4→3)abeolupan-3ξ,4-diol was isolated by

p.l.c. (one 20 cm plate, eluted 5 times with benzene:ether, 4:1) and crystallised as an amorphous solid (35 mg, 31%) from aqueous MeOH. M.p. 171-175°, $[\alpha]_D$: -55.5° (c 0.3), lit.[262] m.p. 164-165°, $[\alpha]_D$: -14° (for the hemihydrate). ν_{max}: 3610, 3560, 1175, 1064, 950 cm^{-1}. τ: 8.72, 8.75 (each 3H, s) 23H and 24H; 8.98, 9.05, 9.22, 9.24 methyls; 9.13, 9.20, 9.21, 9.27 isopropyl doublets.

Attempted reduction of lupan-3-one with iridium chloride

Lupan-3-one (410 mg) was added to a solution of iridium chloride (anhydrous H_2IrCl_6, 40 mg) and trimethyl phosphite (2.0 ml) in a mixture of water (10 ml) and propan-2-ol (90 ml) and the mixture was heated under reflux for 95 hr. After the solution had been diluted with water, work up left starting material, which crystallised as plates from MeOH (identical t.l.c., m.p., n.m.r.).

Bromination of lupan-3-one with cupric bromide

$CuBr_2$ (4.00 g) was added to a solution of lupan-3-one (3.50 g) in THF (150 ml) and the solution was heated under reflux for 2 hr. The mixture was filtered and the solution was evaporated to dryness. After the solid had been taken up in ether, work up left a crystalline solid (3.88 g, 94%), a small sample of which was separated into its two components by p.l.c. (one 100 cm plate, eluted once with benzene:ether, 100:1).

(i) The less polar (minor) compound was 2,2-dibromolupan-3-one (40 mg, 10%), which crystallised as plates from $CHCl_3$-MeOH. M.p. 224-225°, $[\alpha]_D$: -9° (c 0.2), lit.[251] m.p. 223-224°, $[\alpha]_D$: -18°. ν_{max} ($CHCl_3$): 1713, 1085, 1040, 1006, 959 cm^{-1}. τ: 6.32 (1H, d, J 16 Hz, $w_{\frac{1}{2}}$ 2 Hz) 1βH; 6.84 (1H, d, J 16 Hz, $w_{\frac{1}{2}}$ 3 Hz) 1αH; 8.45, 8.76, 8.93, 9.03, 9.05, 9.23 methyls; 9.11, 9.17, 9.19, 9.25 isopropyl doublets. RD ($CHCl_3$, c 0.64), $[\phi]_{231}$ +16,200, $[\phi]_{275}$ +8560, $[\phi]_{329}$ -4510, a: -131. Found: C, 61.4; H, 8.2; calc. for $C_{30}H_{48}OBr_2$: C, 61.65; H, 8.3%.

(ii) The more polar (major) component was a mixture of 2α- and 2β-bromolupan-3-one (300 mg, 90%) which crystallised as needles from $CHCl_3$-MeOH. M.p. 229-232°, $[\alpha]_D$: -15° (c 0.5). ν_{max}: 1728, 1214, 1175, 1087, 1072, 1062, 1003, 763 cm^{-1}. τ: 4.89 (1H, m) 2H. The methyl region was complex. RD ($CHCl_3$, c 0.79), $[\phi]_{266}$ -4150, $[\phi]_{312}$ +3200, a: +73.5. Found: C, 71.0; H, 9.5; Br, 15.9; calc. for $C_{30}H_{49}OBr$: C, 71.3; H, 9.8; Br, 15.8%.

Lup-1-en-3-one

(i) Naphthylene-1,8-diamine, which was purified by crystallisation (as pale orange needles) from petrol, was permethylated with dimethyl sulphate in aqueous alkaline solution.[331] Work up gave naphthylene-1,8-(N,N,N',N'-tetramethyl)diamine, which crystallised as pale orange-red needles on standing, m.p. 46-48°. The tetramethyldiamine (80 mg) was added to a solution of 2-bromolupan-3-one (85 mg) in DMF (15 ml) and the mixture was heated under

reflux for 6 hr. After the mixture had been diluted with water, work up gave a gum from which lup-1-en-3-one (60 mg, 84%) was isolated by p.l.c. (one 20 cm plate, eluted three times with benzene : ether, 20:1) and which crystallised as needles from MeOH.

(ii) 1,5-Diazabicyclo(3,4,0)-non-5-ene (2.00 g) was added to a solution of 2-bromolupan-3-one (3.60 g) in benzene (75 ml) and the mixture was heated under reflux for 50 hr. After the solution had been diluted with brine, work up left a brown oil, from which the enone was isolated by p.l.c. (five 100 cm plates, eluted once with benzene : ether, 100:1) (1.90 g, 63%).

(iii) 1,5-Diazabicyclo-(3,4,0)-non-5-ene (4.00 g) was added to a solution of 2-bromolupan-3-one (7.5 g) in DMF (150 ml) and the mixture was heated under reflux for 14 hr. After the solution had been diluted with brine, work up gave the enone as a clear yellow gum which crystallised as needles on standing (5.65 g, 90%). M.p. 183-185°, $[\alpha]_D$: +19° (c 0.5), lit.[276] m.p. 179-180°, $[\alpha]_D$: +25°. ν_{max} ($CHCl_3$): 1660 cm^{-1}. τ: 2.85 (1H, d, J 10 Hz) 1H; 4.17 (1H, d, J 10 Hz) 2H; 8.85, 8.87, 8.91 (6H), 9.05, 9.22 methyls; 9.10, 9.17, 9.19, 9.26 isopropyl doublets. λ_{max}: 230 nm (ϵ, 9950).

1α,2α-Epoxylupan-3-one

A solution of aqueous NaOH (2M, 5 ml) and H_2O_2 (30%, 1.0 ml) was added to a solution of lup-1-en-3-one (1.70 g) in a mixture of EtOH (100 ml) and acetone (100 ml) and the solution was left at room temp. for 4 hr. After

the mixture had been diluted with brine, work up gave a crystalline solid (1.67 g, 95%), a small sample of which was purified by p.l.c. (one 20 cm plate, eluted twice with benzene : ether, 95:5) and yielded 1α,2α-epoxylupan-3-one which crystallised as needles from MeOH. M.p. 225-226°, $[\alpha]_D$: +69° (c 0.3), lit.[276] m.p. 220-221°, $[\alpha]_D$: +71°. ν_{max} ($CHCl_3$): 3030, 1695, 1034, 930, 895, 872 cm^{-1}. τ: 6.40 (1H, d, J 5 Hz) 2βH; 6.62 (1H, d, J 5 Hz) 1βH; 8.90 (6H), 9.00 (6H), 9.09, 9.22 methyls; 9.10, 9.17, 9.18, 9.25 isopropyl doublets. RD ($CHCl_3$, c 0.69), $[\phi]_{283}$ -8000, $[\phi]_{324}$ +8300, a: +163.

Lup-2-en-1α-ol

Hydrazine hydrate (100%, 5 ml) and glacial HOAc (0.5 ml) were added to a solution of 1α,2α-epoxylupan-3-one (3.82 g) in t-butanol (125 ml) and the solution was heated under reflux for 20 hr. After the mixture had been concentrated to 50 ml, work up gave a solid which was adsorbed from CCl_4 onto a column of alumina (150 g, 5% deactivated). Elution with petrol : ether (4:1) 500 ml, gave lup-2-en-1α-ol (1.94 g, 53%) which crystallised as needles from aqueous MeOH. M.p. 203-204°, $[\alpha]_D$: +64° (c 0.3). ν_{max} ($CHCl_3$): 3605, 3035, 1653, 996 cm^{-1}. τ: 4.25 (1H, q, $J_{3,2}$ 10 Hz, $J_{2,1}$ 5 Hz) 2H; 4.44 (1H, d, $J_{3,2}$ 10 Hz) 3H; 6.35 (1H, q, $J_{1,OH}$ 7 Hz, $J_{2,1}$ 5 Hz) 1βH; 8.90, 9.00, 9.02, 9.12, 9.17, 9.23 methyls; 9.13, 9.20, 9.21, 9.28 isopropyl doublets. Found: C, 84.1; H, 12.0; calc. for $C_{30}H_{50}O$: C, 84.4; H, 11.8%

Lup-2-en-1-one

(i) MnO_2 (2.0 g) was added to a solution of lup-2-en-1α-ol (94 mg) in $CHCl_3$ (20 ml) and the solution was stirred at room temp. for 15 hr. The mixture was filtered and evaporation of the solvent left the starting material as an oil, which crystallised as needles on standing.

(ii) A solution of lup-2-en-1α-ol (90 mg) in pyridine (5 ml) was added to a slurry of CrO_3 (170 mg) in pyridine (5 ml) and the mixture was stirred at room temp. for 22 hr. After the mixture had been diluted with brine, work up gave lup-2-en-1-one (t.l.c. indicated a quantitative conversion) which was purified by p.l.c. (one 20 cm plate, eluted once with benzene : ether, 100:1) and which crystallised as needles from MeOH. M.p. 191-193°, $[\alpha]_D$: +39° (c 0.35), lit.[332] m.p. 190-191°, $[\alpha]_D$: +46°. ν_{max} ($CHCl_3$): 3035, 1675 cm^{-1}. τ: 3.70 (1H, d, J 10 Hz) 3H; 4.31 (1H, d, J 10 Hz) 2H; 8.79, 8.87, 8.91, 8.94, 9.02, 9.23 methyls; 9.12, 9.19, 9 19, 9.26 isopropyl doublets. λ_{max}: 226 nm (ε, 7500).

2α,3α-Epoxylupan-1α-ol

A solution of m-chloroperbenzoic acid (855 mg) in benzene (25 ml) was added to a solution of lup-2-en-1α-ol (1.45 g) in benzene (25 ml) at 0° and the mixture was stirred at room temp. for 25 hr. After the mixture had been diluted with brine, work up gave 2α,3α-epoxylupan-1α-ol as a crystalline solid (1.41 g, 94%), a small sample of which was purified by p.l.c. (one 20 cm plate,

eluted twice with benzene:ether, 100:1) and which crystallised as clusters of rods from aqueous MeOH. M.p. 229-231°, $[\alpha]_D$: +11° (c 0.1). ν_{max} ($CHCl_3$): 3550, 1053, 978, 935, 897 cm^{-1}. τ: 6.33 (1H, q, $J_{1,2}$ 6 Hz, $J_{1,OH}$ 9 Hz) 1βH; 6.48 (1H, q, $J_{1,2}$ 6 Hz, $J_{2,3}$ 3.5 Hz) 2βH; 6.94 (1H, d, $J_{2,3}$ 3.5 Hz) 3βH; 7.71 (1H, d, $J_{1,OH}$ 9 Hz) OH; 8.91, 8.96, 9.00, 9.03, 9.21, 9.23 methyls; 9.13, 9.20, 9.21, 9.27 isopropyl doublets. Found: C, 79.8; H, 11.2; calc. for $C_{30}H_{50}O_2 \cdot \frac{1}{2}H_2O$: C, 79.8; H, 11.4%.

Lupan-1α,3α-diol

Lithium (200 mg) was added to a stirred solution of 2α,3α-epoxylupan-1α-ol (1.31 g) in $EtNH_2$ (distilled, 75 ml) at 0° and the mixture was stirred at 0° for 2 hr. EtOH (50 ml) was then added dropwise; followed by solid NH_4Cl until a clear solution was obtained. Work up afforded lupan-1α,3α-diol (t.l.c. indicated a quantitative conversion) which crystallised as needles from acetone. M.p. 254-255°, $[\alpha]_D$: -12° (c 1.0), lit.[277] m.p. 250-251°, $[\alpha]_D$: -16°. ν_{max}: 3630, 3530, 3320, 1074 cm^{-1}. τ: 6.36 (1H, 's', $w_{\frac{1}{2}}$ 10 Hz), 6.49 (1H, 's', $w_{\frac{1}{2}}$ 9 Hz) 1βH and 3βH; 8.92, 9.00 (6H), 9.15 (6H), 9.24 methyls; 9.12, 9.20, 9.21, 9.28 isopropyl doublets. Found: C, 81.15; H, 11.6; calc. for $C_{30}H_{52}O_2$: C, 81.0; H, 11.8%.

Lupan-1α,3α-diol diacetate

Acetylation of lupan-1α,3α-diol with Ac_2O-pyridine at room temp. for

8 days gave lupan-1α,3α-diol diacetate which crystallised as large needles from MeOH. M.p. 205.5-207.5°, $[C]_D$: -18° (c 1.0). ν_{max}: 1732, 1248, 1050 cm^{-1}. τ: 5.27 (1H, 's', $w_{\frac{1}{2}}$ 7 Hz), 5.29 (1H, 's', $w_{\frac{1}{2}}$ 7 Hz) 1βH and 3βH; 7.93 (3H, s) OAc; 7.95 (3H, s) OAc; 8.92, 9.00, 9.08 (9H), 9.23 methyls; 9.12, 9.19, 9.20, 9.27 isopropyl doublets. Found: C, 77.1; H, 10.4; calc. for $C_{34}H_{56}O_4$: C, 77.2; H, 10.7%.

12,15-Epoxylabda-8(17),12,14-trien-16-yl acetate

A new furanoid diterpene, which was isolated[221] from a petrol extract of the heartwood of Turraeanthus africanus by a combination of chromatography on a column of alumina, and p.l.c., was found to be 12,15-epoxylabda-8(17),12,14-trien-16-yl acetate, an oil. $[\alpha]_D$: +21° (c 0.4). ν_{max} ($CHCl_3$): 1730, 1640, 1220, 1140, 1108, 1020, 892 cm^{-1}. τ: 2.74 (1H, d, J 2 Hz) 15H; 3.64 (1H, d, J 2 Hz) 14H; 5.02 (2H, s) 16H; 5.20 and 5.40 (each 1H, 's', $w_{\frac{1}{2}}$ 4 Hz) 17H; 7.16 (1H, s) 11H; 7.23 (1H, d, J 4 Hz) 11H; 7.94 (3H, s) OAc; 9.11, 9.17, 9.22 methyls. M/e 344 (M^+ for $C_{22}H_{32}O_3$), 284, 269, 191, 137, 95.

12,15-Epoxylabda-8(17),12,14-trien-16-ol

12,15-Epoxylabda-8(17),12,14-trien-16-yl acetate (48 mg) in MeOH (10 ml) was added to a solution of KOH (400 mg) in MeOH (10 ml) and the solution was left at room temp. for 2 hr. Work up gave a gum which was adsorbed from CCl_4 onto a column of alumina (15 g, 5% deactivated). After initial elution with petrol:ether (4:1), 500 ml, 12,15-epoxylabda-8(17),12,14-trien-16-ol was eluted with petrol:ether (1:1), 200 ml, as an oil. $[\alpha]_D$: +11° (c 0.5). ν_{max} ($CHCl_3$): 3495, 3400, 3075, 1642, 1137, 1042, 990, 891 cm^{-1}. τ: 2.75 (1H, d, J 2 Hz) 15H; 3.66 (1H, d, J 2 Hz) 14H; 5.17 and 5.36 (each 1H, 's', $w_{\frac{1}{2}}$ 5 Hz) 17H; 5.47 (2H, s) 16H; 7.16 (1H, s) 11H; 7.24 (1H, d, J 4 Hz) 11H; 9.11, 9.16, 9.23 methyls. M/e 302 (M^+ for $C_{20}H_{30}O_2$), 284, 269, 191, 111, 95.

Labd-14-en-8α,13R-diol (sclareol)

Commercial sclareol[333] was recrystallised as needles from hexane. M.p. 101-102°, $[\alpha]_D$: -4° (c 0.5), lit.[304] m.p. 105-106°, $[\alpha]_D$: -3°. ν_{max}: 3595, 3400, 3080, 991, 938, 919, 908 cm^{-1}. τ: 4.07 (1H, q, J_{cis} 10 Hz, J_{trans} 17 Hz) 14H; 4.81 (1H, q, J_{gem} 2 Hz, J_{trans} 17 Hz) 15H; 5.01 (1H, q, J 2 Hz and 10 Hz) 15H; 7.29 (1H, 's', $w_{\frac{1}{2}}$ 7.5 Hz) OH; 7.90 (1H, 's', $w_{\frac{1}{2}}$ 7 Hz) OH; 8.74, 8.84 (each 3H, s) 16H and 17H; 9.14, 9.21 (6H) methyls.

Oxidation of sclareol with chromic acid in acetic acid

A solution of CrO_3 (220 g) in a mixture of water (300 ml) and glacial HOAc (2 l) was added gradually, over a period of 1 hr, to a stirred solution of sclareol (100 g) in glacial HOAc (1 l) at 0°. The addition was made at such a rate as to maintain the temperature below 20°. The solution was then stirred at room temp. for 8 hr. T.l.c. indicated that no sclareol remained after this period. Propan-2-ol (200 ml) was then added slowly, at such a rate as to maintain the temperature below 25°. The solution was evaporated to dryness under reduced pressure (4 mm and 30°) and the remaining syrup was partitioned between brine and ether. Work up gave a greenish crystalline mass, which was adsorbed from CCl_4 onto a column of alumina (1 kg, 5% deactivated). Elution with petrol : ether (95:5) gave 13,14,15,16-tetranorlabdano-12,8α-lactone (norambreinolide), (17.00 g, 21%) which crystallised as thick flakes from petrol. M.p. 125-125.5°, $[\alpha]_D$: +47.5° (c 0.7), lit.[305] m.p. 123-124°, $[\alpha]_D$: +46°. ν_{max}: 1785 cm^{-1}.

The i.r. spectrum is characterised by a large number of very sharp bands. τ: 8.67 (3H, s) 17H; 9.08, 9.11, 9.16 methyls. Elution with ether gave the remaining product, 8α-acetoxy-13,14,15,16-tetranorlabdan-12-oic acid (5.00 g, 5%), which crystallised as needles from acetone-petrol. M.p. 163-165°, $[\alpha]_D$: -22° (c 0.75), lit.[304] m.p. 157-158°. ν_{max}: 1735, 1710, 1248, 1128 cm^{-1}. τ: 1.50 (1H, 's') CO_2H; 8.13 (3H, s) OAc; 8.48 (3H, s) 17H; 9.12, 9.16, 9.20 methyls.

13,14,15,16-Tetranorlabdan-8α,12-diol

A solution of 8α-acetoxy-13,14,15,16-tetranorlabdan-12-oic acid (310 mg) in ether (10 ml) was added dropwise to a suspension of $LiAlH_4$ (50 mg) in ether (10 ml) and the solution was heated under reflux for 1.5 hr. Work up gave a gum, which was purified by p.l.c. (one 20 cm plate, eluted twice with petrol:acetone, 65:35). 13,14,15,16-Tetranorlabdan-8α,12-diol crystallised as prisms from $CHCl_3$-petrol. M.p. 130-133°, $[\alpha]_D$: -19° (c 0.3). In addition, the t.l.c. R_F was identical to that of the diol, which was prepared by reduction of norambreinolide (see below).

Attempted hydrolysis of norambreinolide

(i) A solution of norambreinolide (7.14 g) in MeOH (150 ml) was added to a solution of NaOMe (prepared from Na (1.06 g) and MeOH (100 ml)) and the mixture was heated under reflux for 2.5 hr. Work up gave a crystalline

mass, which by t.l.c., contained a 1:1 mixture of starting material and a slightly more polar product. This was assumed to be methyl 8α-hydroxy-13,14,15,16-tetranorlabdan-12-oate.

(ii) Potassium (105 mg) was added to t-butanol (30 ml) and the solution was heated under reflux for 1 hr, after which all of the potassium had dissolved. Norambreinolide (370 mg) was then added and the solution was heated under reflux for 2 hr. Work up gave a yellow oil which was purified by p.l.c. (two 20 cm plates, eluted once with petrol:acetone, 4:1, and a further once with petrol:acetone, 9:1). Crystallisation of the product from petrol gave an essentially quantitative recovery of starting material, m.p. 123-124°. The product had an identical t.l.c. R_F to that of norambreinolide and the n.m.r. spectrum was superimposable upon that obtained above.

13,14,15,16-Tetranorlabdan-8α,12-diol

A solution of norambreinolide (7.00 g) in ether (200 ml) was added to a suspension of $LiAlH_4$ (1.06 g) in ether (50 ml) and the solution was heated under reflux for 1.5 hr. Work up gave a quantitative yield of 13,14,15,16-tetranorlabdan-8α,12-diol, which crystallised as prisms from $CHCl_3$-petrol. M.p. 132-133°, $[\alpha]_D$: -16° (c 1.0), lit.[334] m.p. 131.5-132.5°, $[\alpha]_D$: -17°. ν_{max}: 3595, 3290, 1080, 1072, 1052 cm^{-1}. τ: 6.50 (4H, complex m) CH_2OH and OH; 8.82 (3H, s) 17H; 9.13, 9.21 (6H) methyls.

8α-Hydroxy-13,14,15,16-tetranorlabdan-12-yl acetate

13,14,15,16-Tetranorlabdan-8α,12-diol (15 g) was added to a mixture of Ac_2O (20 ml) and pyridine (75 ml) and the mixture was left at room temp. for 12 hr. Work up gave 8α-hydroxy-13,14,15,16-tetranorlabdan-12-yl acetate as an oil, a small portion of which was purified by p.l.c. (one 20 cm plate, eluted twice with petrol:acetone, 9:1). $[\alpha]_D$: +36° (c 0.1). ν_{max}: 3595, 3500, 1740, 1245, 1230, 1082, 1038 cm^{-1}. τ: 5.90 (2H, t, J 7.5 Hz) 12H; 7.98 (3H, s) OAc; 8.84 (3H, s) 17H; 9.12, 9.20 (6H) methyls. Found: C, 72.8; H, 10.7; calc. for $C_{18}H_{32}O_3$: C, 72.9; H, 10.9%.

Dehydration of 8α-hydroxy-13,14,15,16-tetranorlabdan-12-yl acetate with phosphoryl chloride

$POCl_3$ (5 ml) was added dropwise to a stirred solution of 8α-hydroxy-13,14,15,16-tetranorlabdan-12-yl acetate (16.0 g) in pyridine (100 ml) at 0°, and the solution was left at room temp. for 15 hr. Work up gave a quantitative yield of a reddish-yellow oil. Decolourisation of a small sample by p.l.c. (two 20 cm plates, eluted once with petrol:acetone, 95:5) gave a 1:4 mixture of 13,14,15,16-tetranorlabda-7 and 8(17)-en-12-yl acetate as an oil. $[\alpha]_D$: +43° (c 0.75). ν_{max}: 3075, 1741, 1643, 1237, 1035, 905, 890 cm^{-1}. τ (exo isomer): 5.15 and 5.43 (each 1H, 's', $w_{\frac{1}{2}}$ 4 Hz) 17H; 5.95 (2H, complex m) 12H; 7.97 (3H, s) OAc; 9.11, 9.18, 9.30 methyls. Found: C, 77.9; H, 10.7; calc. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.9%.

13,14,15,16-Tetranorlabda-7 and 8(17)-en-12-ol

KOH (3.0 g) was added to a solution of 13,14,15,16-tetranorlabda-7 and 8(17)-en-12-yl acetate (14 g) in MeOH (150 ml) and the solution was heated under reflux for 1.5 hr. Excess MeOH was distilled off under reduced pressure Work up then gave a quantitative yield of the product as a yellow viscous oil. Decolourisation of a small sample by p.l.c. (two 20 cm plates, eluted twice with petrol : acetone, 4:1) gave 13,14,15,16-tetranorlabda-7 and 8(17)-en-12-ol as an oil. $[\alpha]_D$: +25° (c 1.0). ν_{max}: 3625, 3490, 3340, 3080, 1640, 1040, 907, 890 cm^{-1}. τ (exo isomer): 5.18 and 5.47 (1H, 's', $w_{\frac{1}{2}}$ 4 Hz) 17H; 6.33 (3H, complex m) $C\underline{H}_2O\underline{H}$; 9.13, 9.20, 9.31 methyls. Found: C, 81.0; H, 11.9; calc. for $C_{16}H_{28}O$: C, 81.3; H, 11.9%.

13,14,15,16-Tetranorlabda-7 and 8(17)-en-12-al

Silver carbonate/celite (500 g, prepared[303] with $KHCO_3$) was added to a solution of 13,14,15,16-tetranorlabda-7 and 8(17)-en-12-ol (8.2 g) in benzene (2 l) and the suspension was heated under reflux with stirring for 45 hr, with the continuous removal of water in a Dean and Stark apparatus. The solution was then filtered through a sinter and evaporation of the solvent gave the product as a pale yellow oil (7.7 g, 95%). Decolourisation of a small sample by p.l.c. (one 20 cm plate, eluted twice with petrol : acetone, 95:5) gave 13,14,15,16-tetranorlabda-7 and 8(17)-en-12-al as an oil. ν_{max}: 3080, 2810, 2710, 1730, 1645, 998, 884 cm^{-1}. τ (exo isomer): 0.23 (1H, s) $C\underline{H}$=O; 5.15

and 5.36 (each 1H, s) 17H; 7.36 (5H, s) 7, 9 and 11H; 9.17, 9.24, 9.35 methyls. Found: C, 82.4; H, 11.3; calc. for $C_{16}H_{26}O$: C, 82.0; H, 11.2%.

Reformatsky condensation of 13,14,15,16-tetranorlabda-7 and 8(17)-en-12-al with ethyl α-bromoacetate, and separation of the endo alkene from the exo isomer by selective epoxidation

A solution of 13,14,15,16-tetranorlabda-7 and 8(17)-en-12-al (8.1 g) and $BrCH_2CO_2Et$ (15 ml) in a mixture of benzene (200 ml) and ether (50 ml) was added in small portions to activated zinc wool[309] (7.50 g) and the solution was heated under reflux for 1 hr, after which most of the zinc had dissolved, and then for a further 45 min. After dilution with ether, the solution was filtered through a pad of glass wool and was acidified at 0°, with an ice-cold solution of aqueous H_2SO_4 (10%, 100 ml). Work up gave the β-hydroxyester (10.5 g, 94%) as a pale yellow oil. A solution of o-monoperphthalic acid[335] (1.58 g) in ether (100 ml) was added to a solution of the β-hydroxyester in ether (500 ml) and the solution was left in the dark at 0° for 3 days. Work up gave an oil which was adsorbed from CCl_4 onto a column of alumina (400 g, 10% deactivated).

(1) Elution with petrol : ether (9:1) 2 l, gave pure ethyl 12(R and S)-hydroxy-15,16-dinorlabd-8(17)-en-14-oate as an oil.

(2) Elution with petrol : ether (1:1) 1.2 l, gave ethyl 7α,8α-epoxy-12(R and S)-hydroxy-15,16-dinorlabdan-14-oate as an oil.

Fraction (1) was separated into its hydroxyl epimers by p.l.c. (five 100 cm plates,

eluted seven times with petrol : acetone, 95:5).

(1/1) The less polar epimer was ethyl 12R-hydroxy-15,16-dinorlabd-8(17)-en-14-oate, an oil. $[\alpha]_D$: +9° (c 2.2). ν_{max}: 3540, 3075, 1730, 1640, 1180, 1090, 1055, 1027, 906, 884 cm^{-1}. τ: 5.16, 5.57 (each 1H, 's', $w_{\frac{1}{2}}$ 4 Hz) 17H; 5.83 (2H, q, J 7 Hz) $CH_3\underline{CH}_2CO_2$-; 5.94 (1H, m) 12H; 7.13 (1H, 's' $w_{\frac{1}{2}}$ 12.5 Hz) OH; 7.52 (1H, s, $w_{\frac{1}{2}}$ 1.5 Hz) 13H; 7.58 (1H, s, $w_{\frac{1}{2}}$ 3.5 Hz) 13H; 8.73 (3H, t, J 7 Hz) $\underline{CH}_3CH_2CO_2$-; 9.12, 9.19, 9.33 methyls. Found: C, 74.35; H, 10.3; calc. for $C_{20}H_{34}O_3$: C, 74 5; H, 10.6%.

(1/2) The more polar component was ethyl 12S-hydroxy-15,16-dinorlabd-8(17)-en-14-oate, an oil. $[\alpha]_D$: +23° (c 1.1). ν_{max}: 3540, 3080, 1730, 1640, 1180, 1045, 1030, 907, 894 cm^{-1}. τ: 5.14, 5.31 (each 1H, 's', $w_{\frac{1}{2}}$ 4 Hz) 17H; 5.83 (2H, q, J 7 Hz) $CH_3\underline{CH}_2CO_2$-; 5.95 (1H, m) 12H; 6.94 (1H, 's', $w_{\frac{1}{2}}$ 15 Hz) OH; 7.55 (2H, m) 13H; 8.74 (3H, t, J 7 Hz) $\underline{CH}_3CH_2CO_2$-; 9.13, 9.19, 9.31 methyls. Found: C, 74.3; H, 10.6; calc. for $C_{20}H_{34}O_3$: C, 74.5; H, 10.6%.

Fraction (2) was separated into its hydroxyl epimers by p.l.c. (one 100 cm plate, eluted five times with petrol : acetone, 9:1).

(2/1) The less polar component was ethyl 7α,8α-epoxy-12R-hydroxy-15,16-dinorlabdan-14-oate, an oil. $[\alpha]_D$: +6° (c 0.7). ν_{max}: 3540, 1730, 1183, 1165, 1046, 1029 cm^{-1}. τ: 5.89 (2H, q, J 7 Hz) $CH_3\underline{CH}_2CO_2$-; 5.96 (1H, m) 12H; 7.03 (1H, 's') OH; 7.09 (1H, 's', $w_{\frac{1}{2}}$ 6 Hz) 7βH; 7.54 (1H, s) 13H;

7.60 (1H, s) 13H; 8.80 (6H, (3H, t, J 7 Hz) and (3H, s)) $C\underline{H}_3CH_2CO_2$- and 17H; 9.21 (6H), 9.33 methyls. *M/e* 338 (M^+ for $C_{20}H_{34}O_4$).

(2/2) The more polar component was ethyl 7α,8α-epoxy-12S-hydroxy-15,16-dinorlabdan-14-oate, an oil. $[\alpha]_D$: +11° (c 0.6). ν_{max}: 3535, 1723, 1182, 1047, 1027 cm^{-1}. τ: 5.89 (2H, q, J 7 Hz) $CH_3C\underline{H}_2CO_2$-; 5.96 (1H, m) 12H; 6.73 (1H, 's', $w_{\frac{1}{2}}$ 12.5 Hz) OH; 7.08 (1H, 's', $w_{\frac{1}{2}}$ 5.5 Hz) 7βH; 7.41 (1H, q, J_{gem} 17 Hz, J_{cis} 3.5 Hz) 13H; 7.72 (1H, q, J_{gem} 17 Hz, J_{trans} 9 Hz) 13H; 8.68 (3H, s) 17H; 8.78 (3H, t, J 7 Hz) $C\underline{H}_3CH_2CO_2$-; 9.20 (6H), 9.32 methyls. *M/e* 338 (M^+ for $C_{20}H_{34}O_4$).

Ethyl 12R-(3,5-dinitrobenzoyloxy)-15,16-dinorlabd-8(17)-en-14-oate

A small excess of 3,5-dinitrobenzoyl chloride was added to a solution of ethyl 12R-hydroxy-15,16-dinorlabd-8(17)-en-14-oate in pyridine and the solution was stirred at room temp. for 20 hr. Work up gave a red oil which was purified by p.l.c. (one 20 cm plate, eluted four times with acetone : petrol, 1:9) and yielded ethyl 12R-(3,5-dinitrobenzoyloxy)-15,16-dinorlabd-8(17)-en-14-oate as an oil. $[\alpha]_D$: +32° (c 1.8). τ: 0.77 (1H, t) phenyl 4H; 0.85 (2H, 's') phenyl 2, 6H; 4.42 (1H, quintet, J 6.5 Hz) 12H; 5.09 (1H, s) 17H; 5.39 (1H, s) 17H; 5.87 (2H, q, J 7 Hz) $CH_3C\underline{H}_2CO_2$-; 7.21 (2H, m) 13H; 8.76 (3H, t, J 7 Hz) $C\underline{H}_3CH_2CO_2$-; 9.15, 9.19, 9.28 methyls. *M/e* 516 (M^+). CD (MeOH, c 0.82), $\Delta\epsilon_{333}$ -0.23. Found: N, 5.0; H, 6.6; calc. for $C_{27}H_{36}O_8N_2$: N, 5.4; H, 7.0%.

Ethyl 12S-(3,5-dinitrobenzoyloxy)-15,16-dinorlabd-8(17)-en-14-oate

Esterification of ethyl 12S-hydroxy-15,16-dinorlabd-8(17)-en-14-oate as above with 3,5-dinitrobenzoyl chloride gave ethyl 12S-(3,5-dinitrobenzoyloxy)-15,16-dinorlabd-8(17)-en-14-oate as an oil. $[\alpha]_D$: +8° (c 1.4). τ: 0.78 (1H, t) phenyl 4H; 0.85 (2H, m) phenyl 2, 6H; 4.38 (1H, quintet, J 6.5 Hz) 12H; 5.04, 5.08 (each 1H, s) 17H; 5.85 (2H, q, J 7 Hz) $CH_3\underline{CH}_2CO_2$-; 7.23 (1H, s) 13H; 7.30 (1H, s) 13H; 8.77 (3H, t, J 7 Hz) $\underline{CH}_3CH_2CO_2$-; 9.11, 9.18, 9.30 methyls. M/e 516 (M^+). CD (MeOH, c 0.88), $\Delta\epsilon_{279}$ -0.13; $\Delta\epsilon_{304}$ -0.11. Found: N, 5.1; H, 6.55; calc. for $C_{27}H_{36}O_8N_2$: N, 5.4; H, 7.0%.

Ethyl 12-oxo-15,16-dinorlabd-8(17)-en-14-oate

CrO_3 (anhydrous, 8.26 g) was added gradually to a stirred mixture of pyridine (15 ml) and CH_2Cl_2 (100 ml) at 0° and the solution was stirred at room temp. for 5 min. A solution of ethyl 12(R and S)-hydroxy-15,16-dinorlabd-8(17)-en-14-oate (4.74 g) in CH_2Cl_2 (50 ml) was then added over 5 min, and the solution was stirred at room temp. for a further 10 hr. Work up gave a red-brown oil which was filtered through a small column of alumina (50 g, 10% deactivated). Elution with ether gave the product as a pale yellow oil (3.70 g, 78%). A small sample was purified by p.l.c. (two 20 cm plates, eluted once with petrol : acetone, 4:1) and yielded ethyl 12-oxo-15,16-dinorlabd-8(17)-en-14-oate as an oil. $[\alpha]_D$ -24° (c 2.2). ν_{max}: 3430, 3075, 1747, 1722,

1640, 1155, 1030, 905, 880 cm^{-1}. τ: 5.24, 5.64 (each 1H, s) 17H; 5.81 (2H, q, J 7 Hz) $CH_3\underline{CH}_2CO_2$-; 6.58 (2H, s) 13H; 8.71 (3H, t, J 7 Hz) $\underline{CH}_3CH_2CO_2$-; 9.10, 9.18, 9.29 methyls. λ_{max}: 250 nm) ε 620), λ_{max} (EtOH/NaOH) 276.5 nm (ε, 17,750). Found: C, 75.3; H, 9.8; calc. for $C_{20}H_{32}O_3$: C, 75.0; H, 10.1%.

14,15,16-Trinorlabd-8(17)-en-12-one

A solution of KOH (1.00 g) in EtOH (10 ml) was added to a solution of ethyl 12-oxo-15,16-dinorlabd-8(17)-en-14-oate (1.73 g) in EtOH (50 ml) and the mixture was heated under reflux for 1 hr. After the mixture had been acidified at 0° with aqueous H_2SO_4 (10%), work up gave an oil, which was purified by p.l.c. (four 100 cm plates, eluted once with petrol : acetone, 95:5) and yielded 14,15,16-trinorlabd-8(17)-en-12-one (550 mg, 41%) as an oil. $[\alpha]_D$: -33° (c 1.8). ν_{max}: 3075, 1715, 1640, 1160, 903, 880 cm^{-1}. τ: 5.27, 5.66 (each 1H, s) 17H; 7.87 (3H, s) 13H; 9.10, 9.18, 9.29 methyls. M/e 248 (M^+ for $C_{17}H_{28}O$).

A solution of the ketone (200 mg), 2,4-dinitrophenylhydrazine (200 mg) and conc. H_2SO_4 (1 drop) in MeOH (75 ml) was warmed at 100° for 10 min. Work up then gave 14,15,16-trinorlabd-8(17)-en-12-one 2,4-dinitrophenylhydrazone as yellow needles from MeOH. M.p. 181-183°, $[\alpha]_D$: -72° (c 0.25). ν_{max}: 3315, 3085, 1329, 1310, 1278 cm^{-1}. τ: 0.86 (1H, d, J_m 3 Hz) phenyl 3H; 1.68 (1H, q, J_m 3 Hz, J_o 10 Hz) phenyl 5H; 2.05 (1H, d, J_o 10 Hz)

phenyl 6H; 5.17, 5.34 (each 1H, s) 17H; 7.99 (3H, s) 13H; 9.07, 9.15, 9.21 methyls. Found: C, 64.7; H, 7.6; N, 13.0; calc. for $C_{23}H_{32}O_4N_4$: C, 64.5; H, 7.5; N, 13.1%.

Attempted Feist-Benary condensation of ethyl 12-oxo-15,16-dinorlabd-8(17)-en-14-oate and dichloroether

(i) An ice-cold solution of NaOH (0.44 g) in water (10 ml) was added over a period of 30 min to an ice-cold solution of ethyl 12-oxo-15,16-dinorlabd-8(17)-en-14-oate (0.97 g) and 1,2-dichloroethyl ethyl ether (b.p. 67° at 42 mm Hg) (0.6 ml) in ether (25 ml) and the solution was stirred at 0° for a further hour. Work up gave an oil containing approximately 50% starting material (by t.l.c.) together with one more polar product, which was isolated by p l.c. (two 100 cm plates, eluted four times with petrol:acetone, 95:5). The product (an oil, 102 mg) showed only traces of the desired furan. τ: 2.81, 3.40.

(ii) A solution of the β-ketoester (250 mg) and dichloroether (0.75 ml) in triethylamine (5 ml) was stirred at 0° for 2.5 h and then at room temperature for a further 2.5 h. The solution was then heated under reflux for 15 h. T.l.c. showed the product was a mixture of two compounds, one less polar and the other more polar than the starting material. The solution was then worked up to give an oil, which was dissolved in ether (30 ml), $LiAlH_4$ (175 mg) was added and the mixture was heated under reflux for 1.5 h. Work up gave a complex mixture of compounds.

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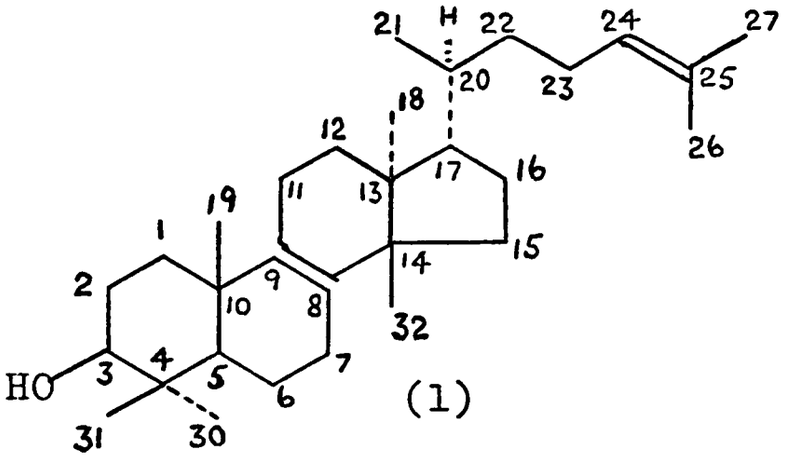
DIAGRAMS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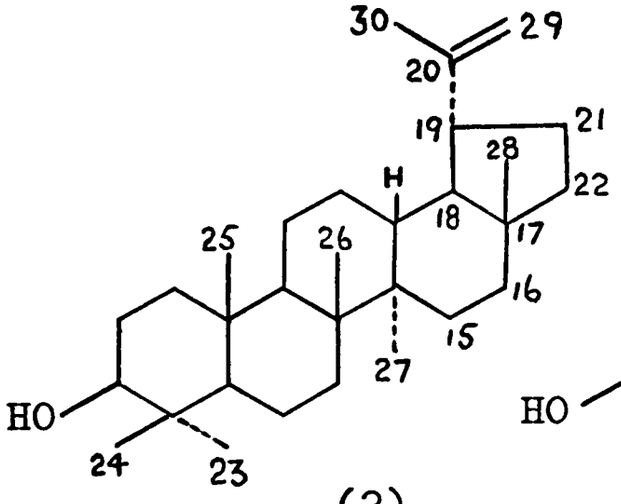
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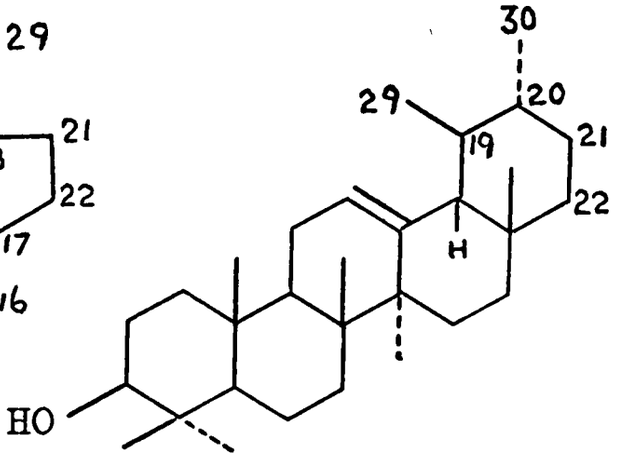
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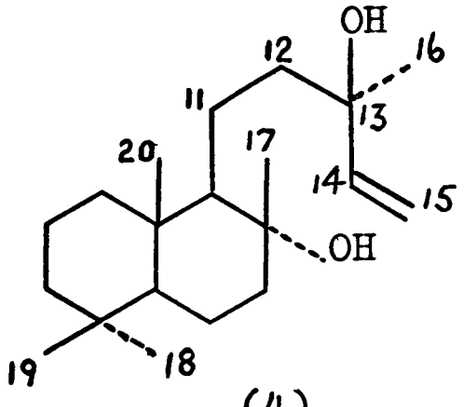
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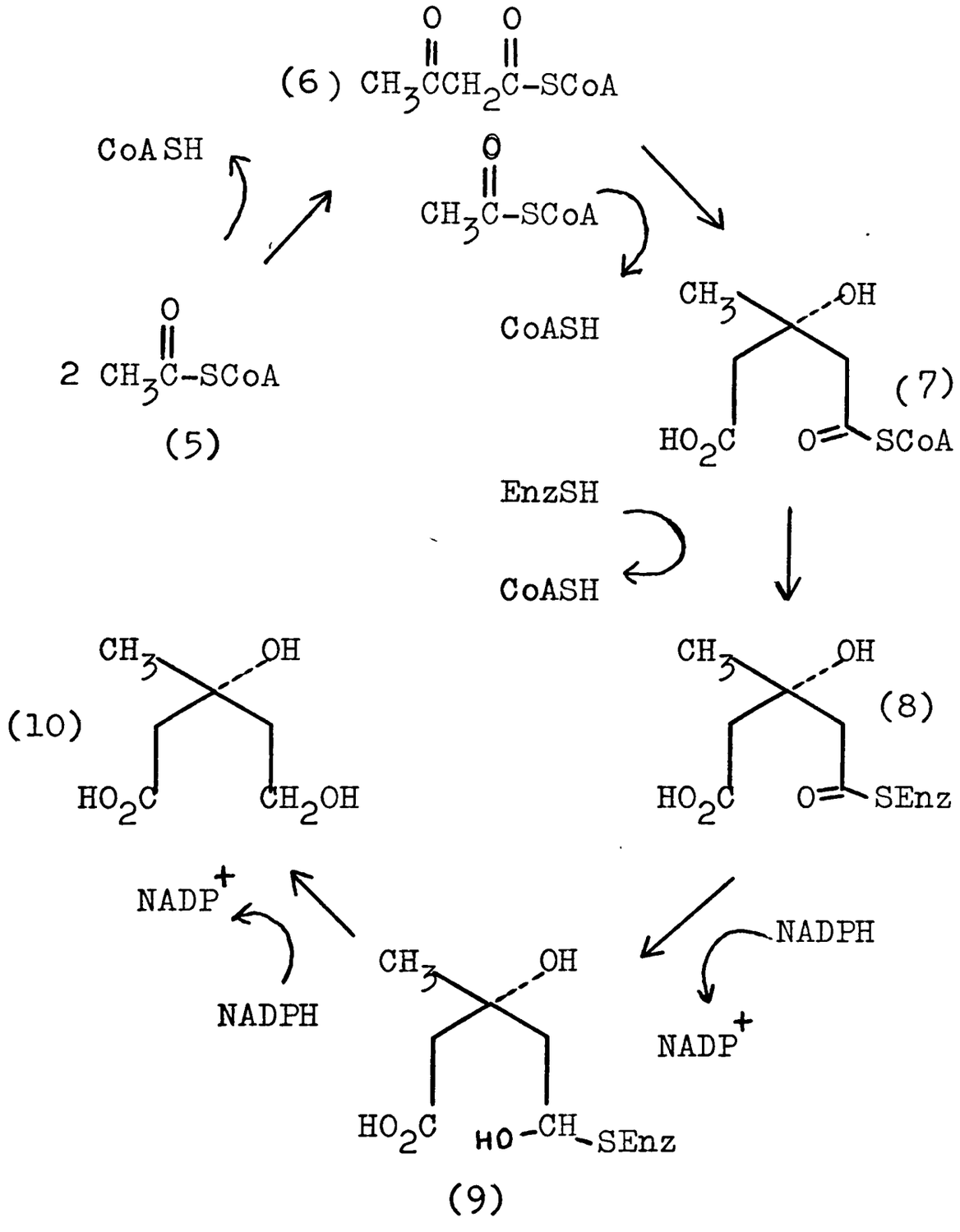
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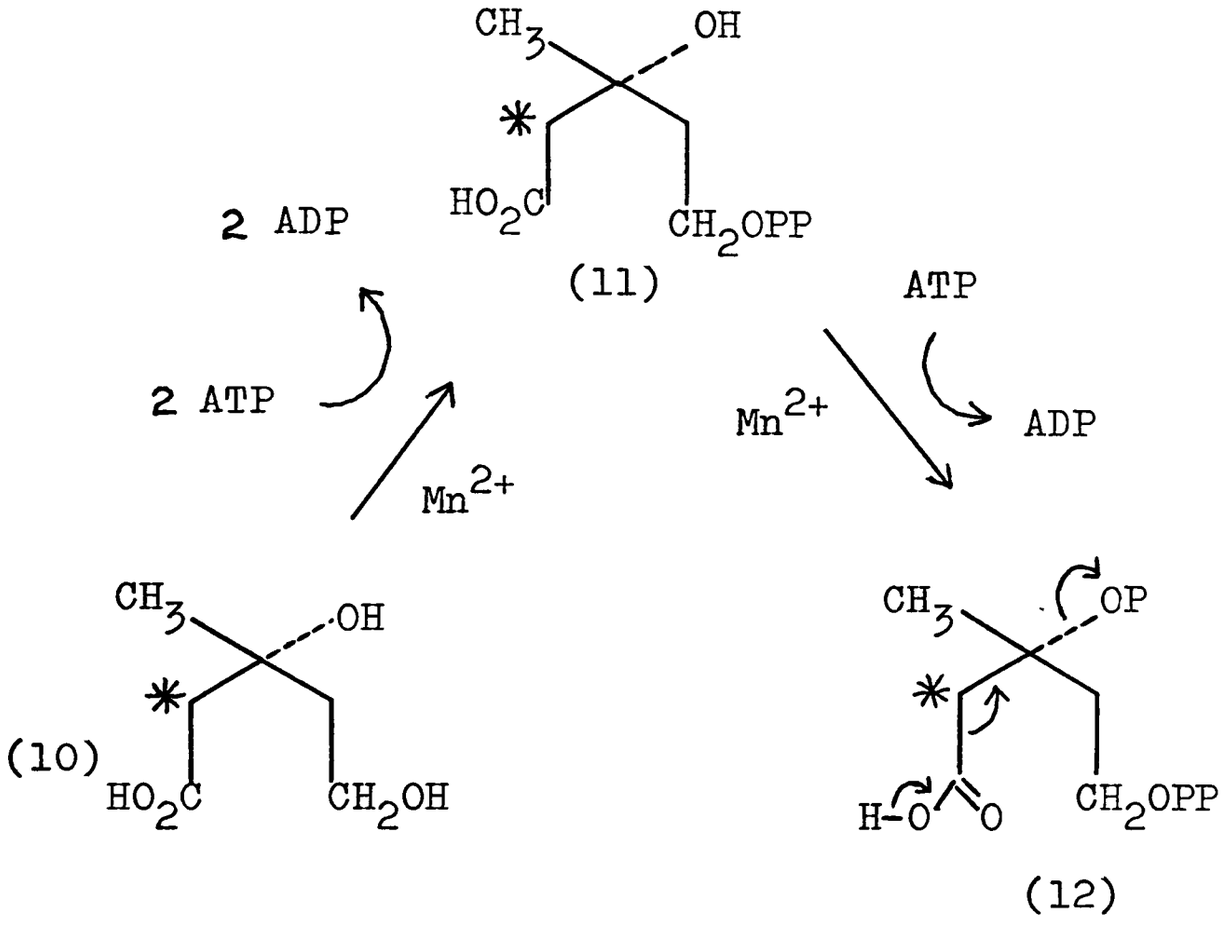
FIGURE 2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OP
H-O
O
CH2OPP
(12)

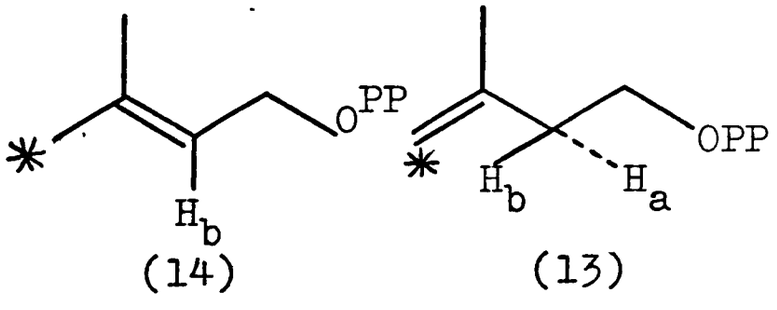

OPP
Hb
(14)
OPP
Hb
Ha
(13)

FIGURE 3

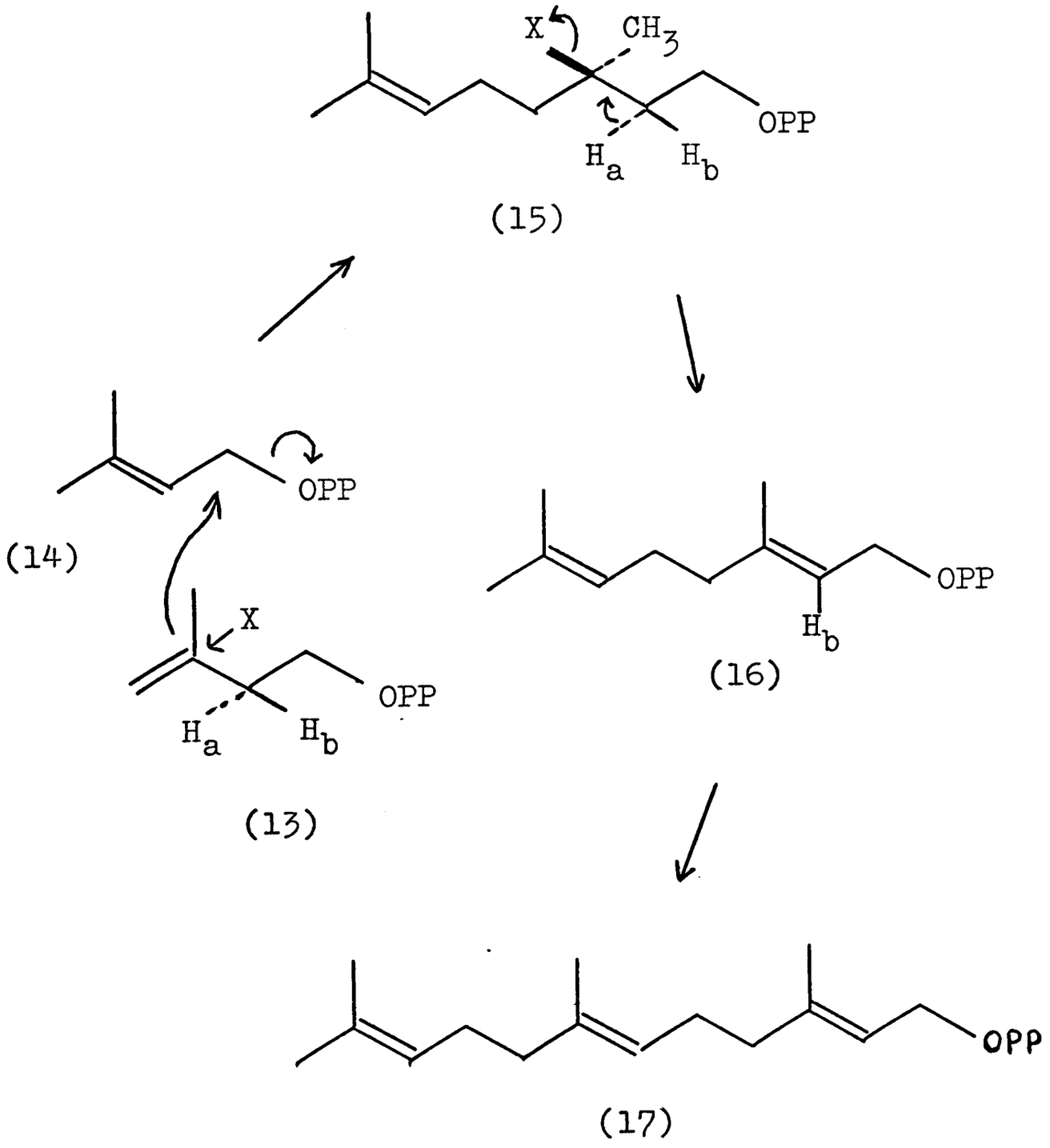


FIGURE 4

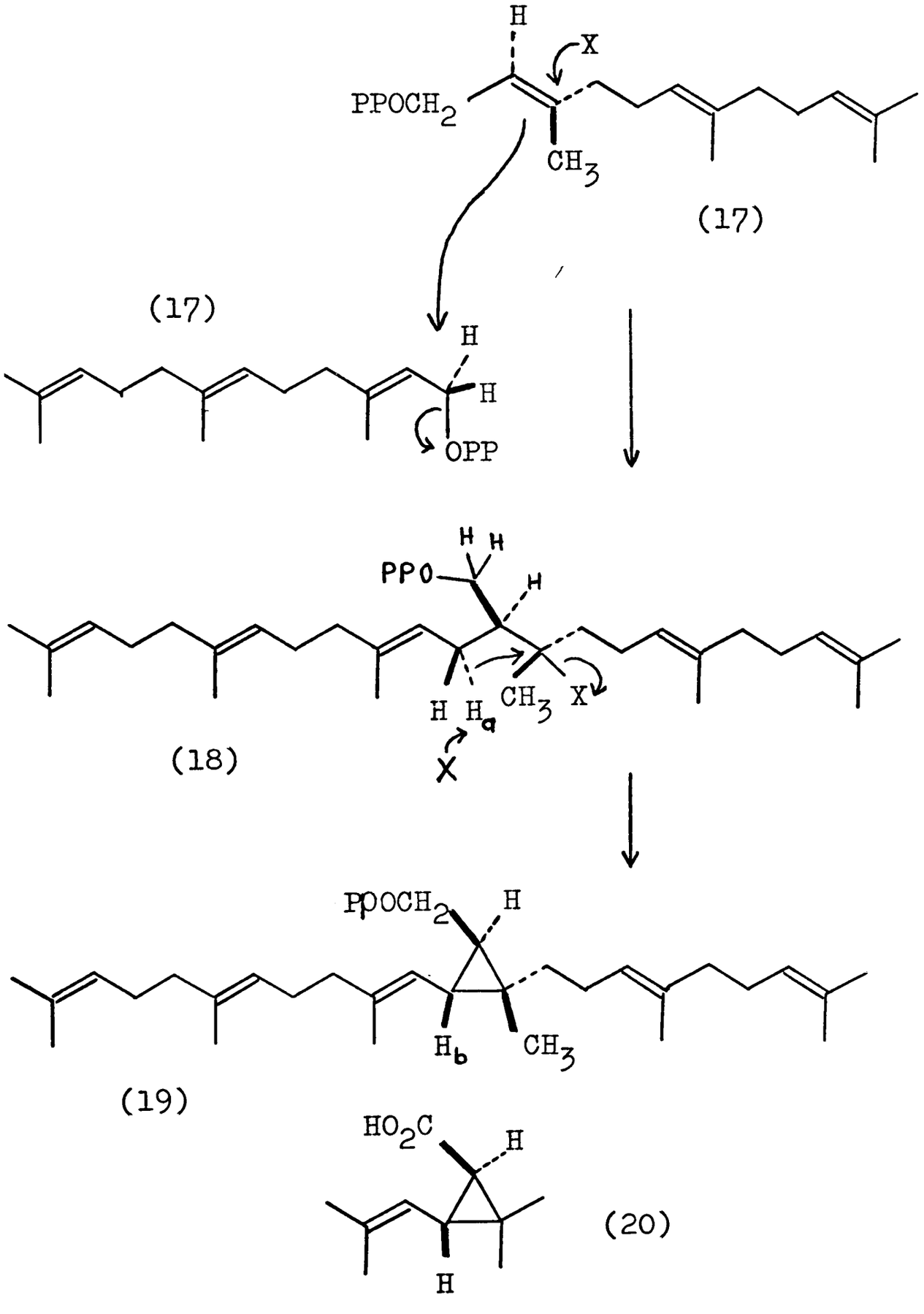

H
X
PPOCH2
CH3
(17)
(17)
H
H
OPP
H H
PPO
H
H Ha
CH3
X
X
(18)
PPOCH2
H
Hb
CH3
(19)
HO2C
H
H
(20)

FIGURE 5

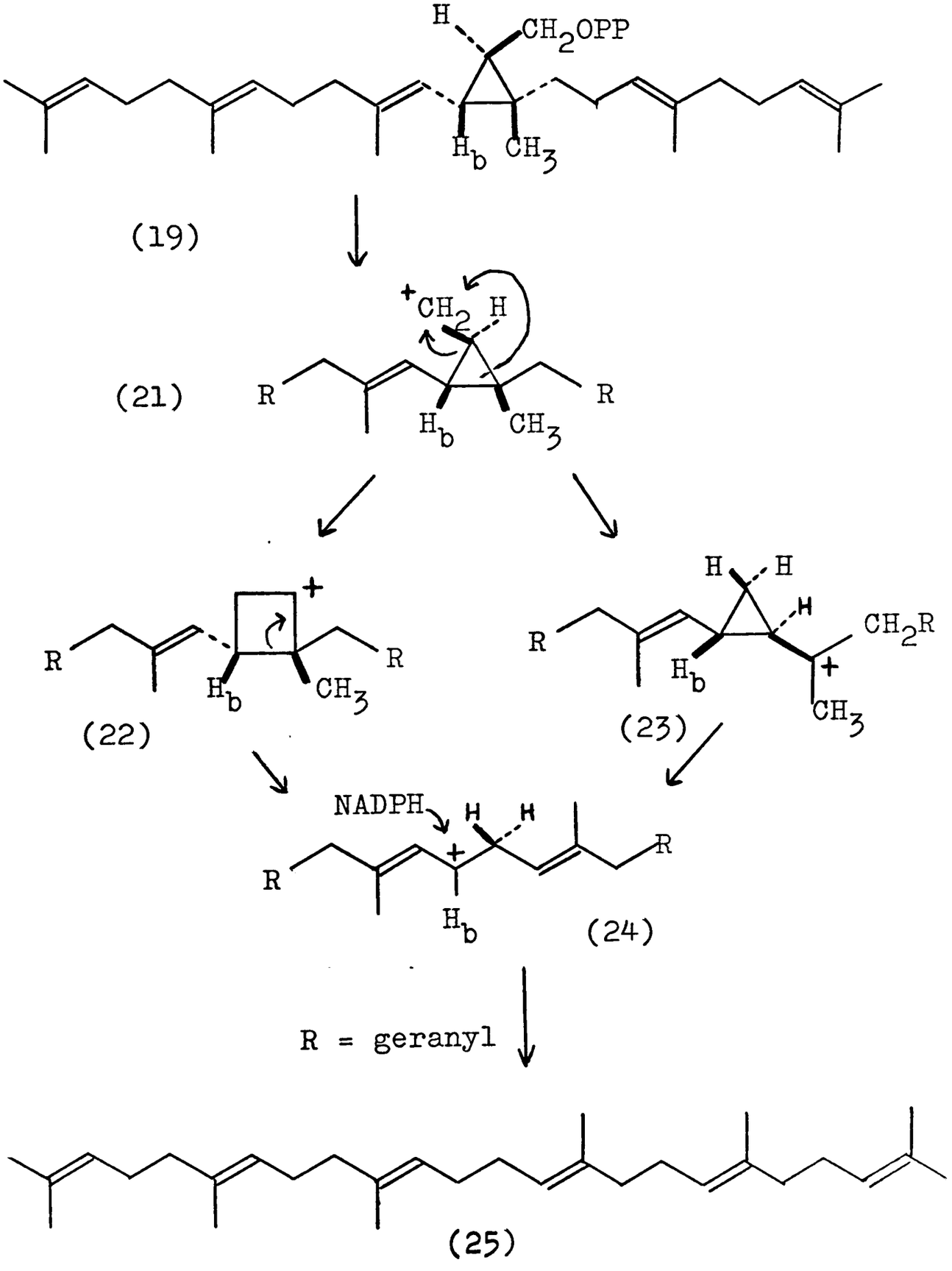
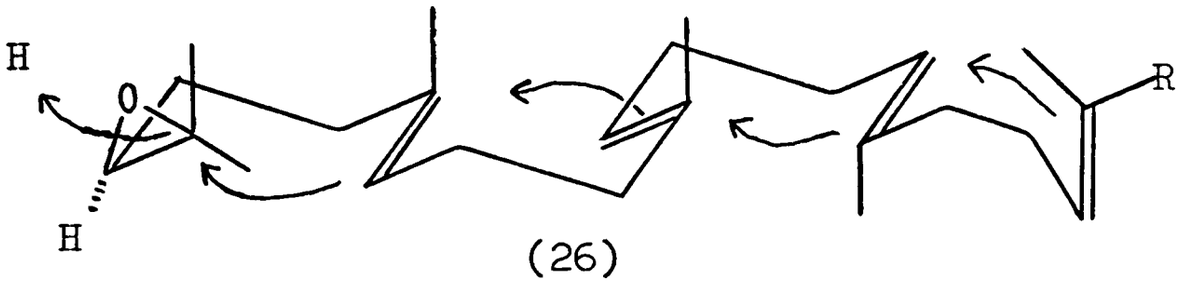
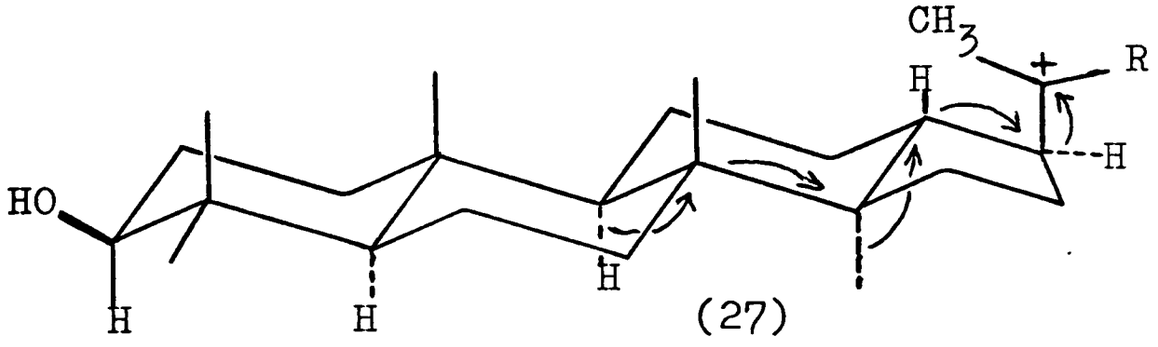

H
CH2OPP
Hb
CH3
(19)
+CH2
H
(21)
R
R
Hb
CH3
+
R
R
Hb
CH3
(22)
H
H
H
R
CH2R
Hb
+
CH3
(23)
NADPH
H
H
+
R
R
Hb
(24)
R = geranyl
(25)

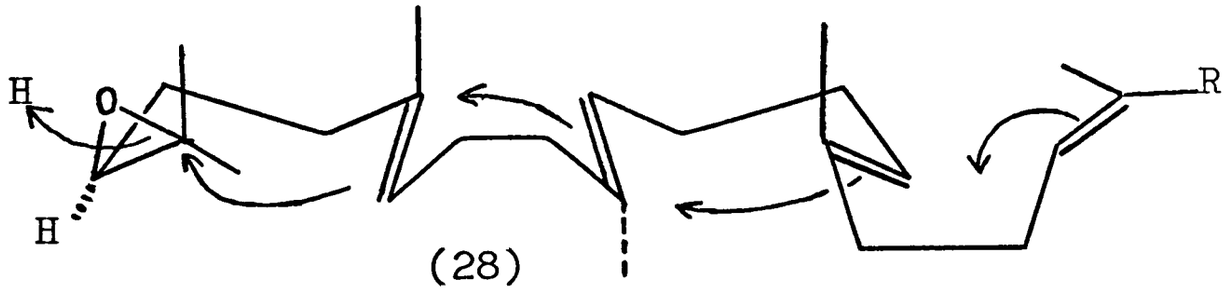
FIGURE 6



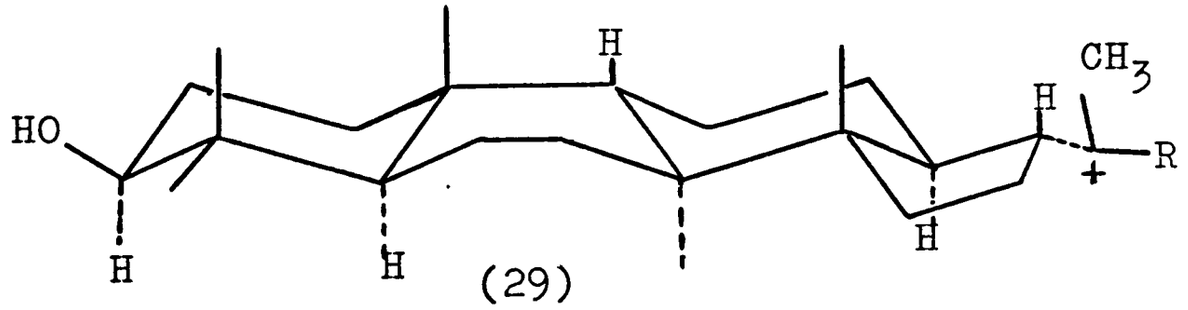
(26)



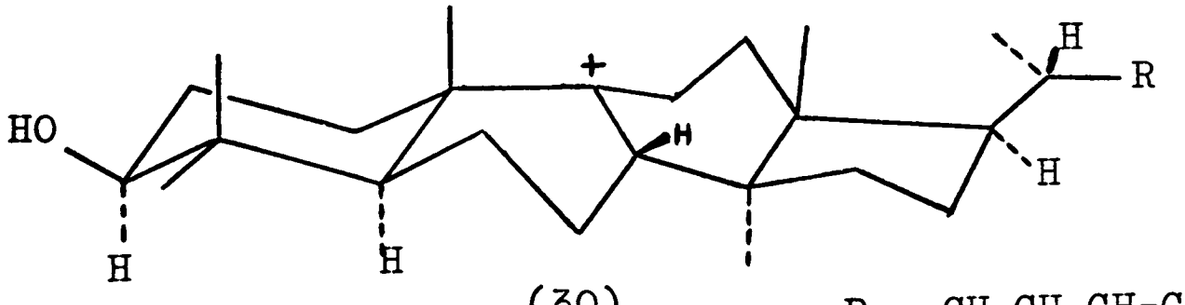
(27)



(28)

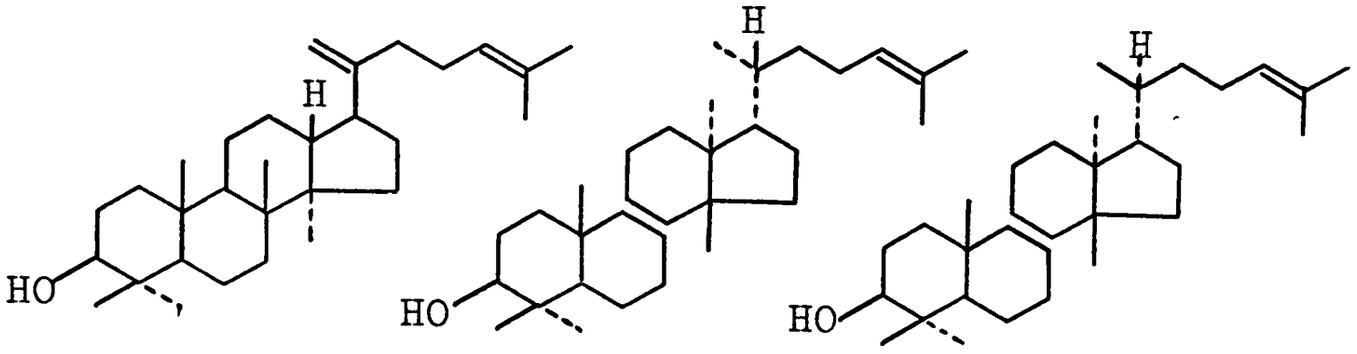


(29)

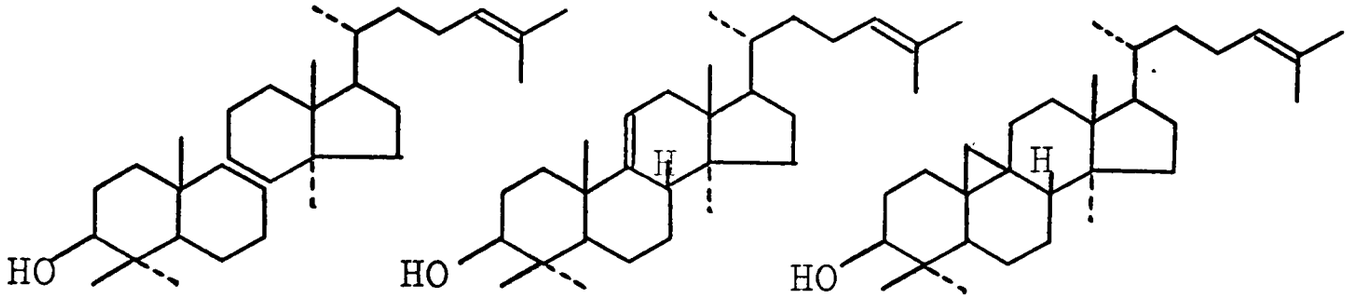


(30)

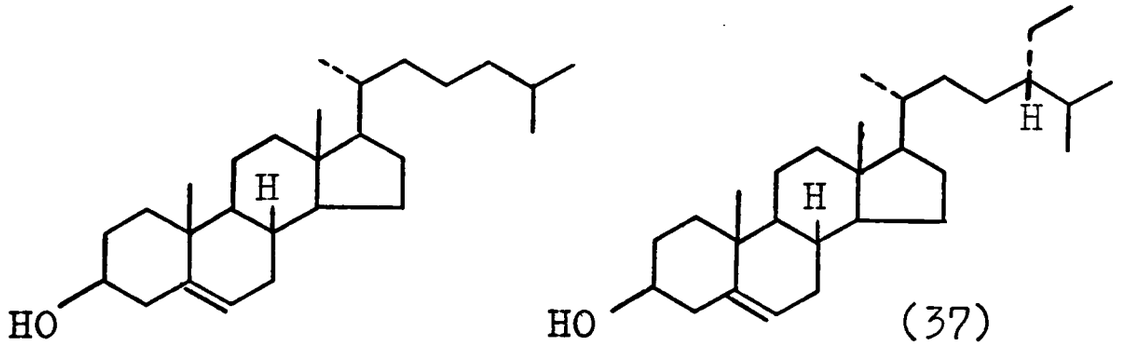
R = $CH_2CH_2CH{=}C\begin{matrix}Me\\Me\end{matrix}$



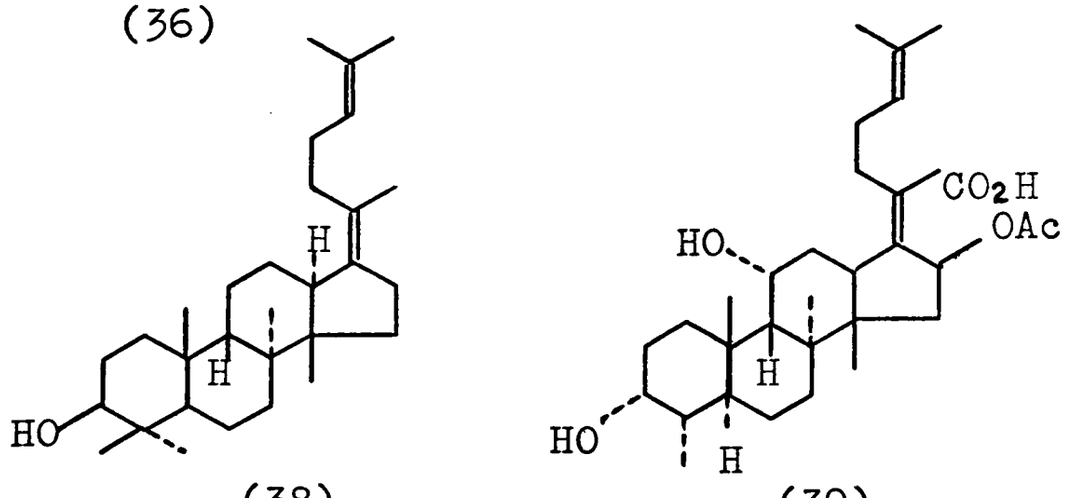
(31) (32) (1)



(33) (34) (35)

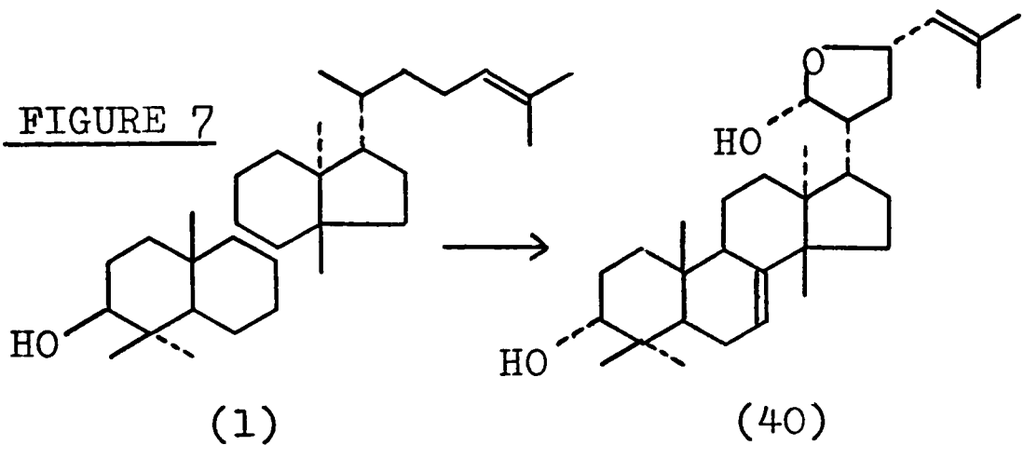


(36) (37)

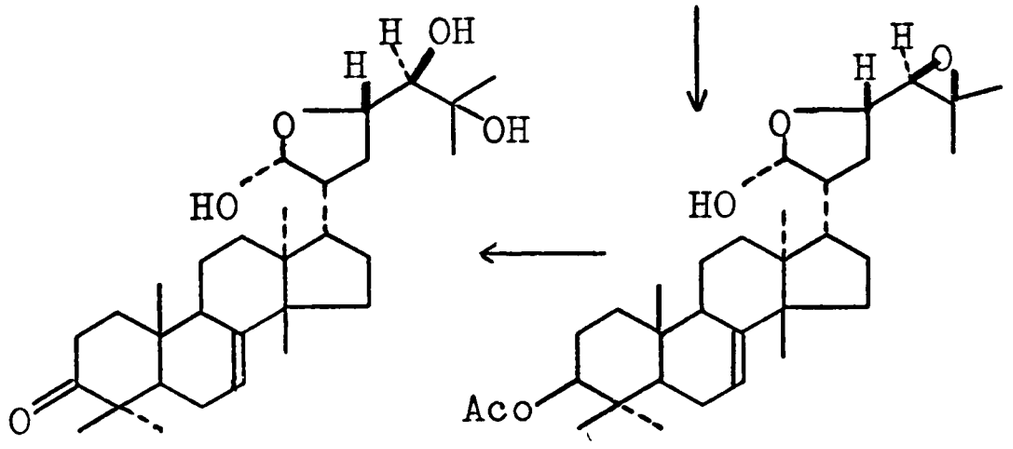


(38) (39)

FIGURE 7

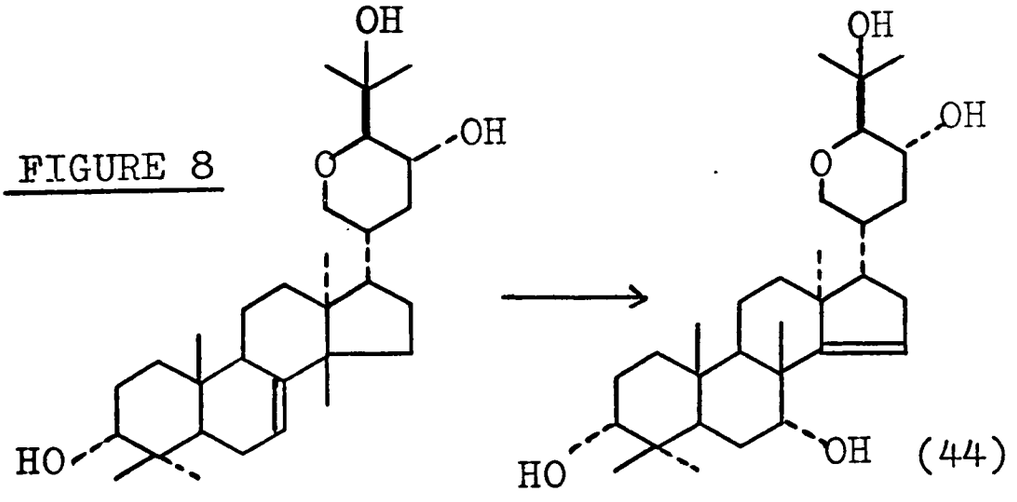


(1) (40)

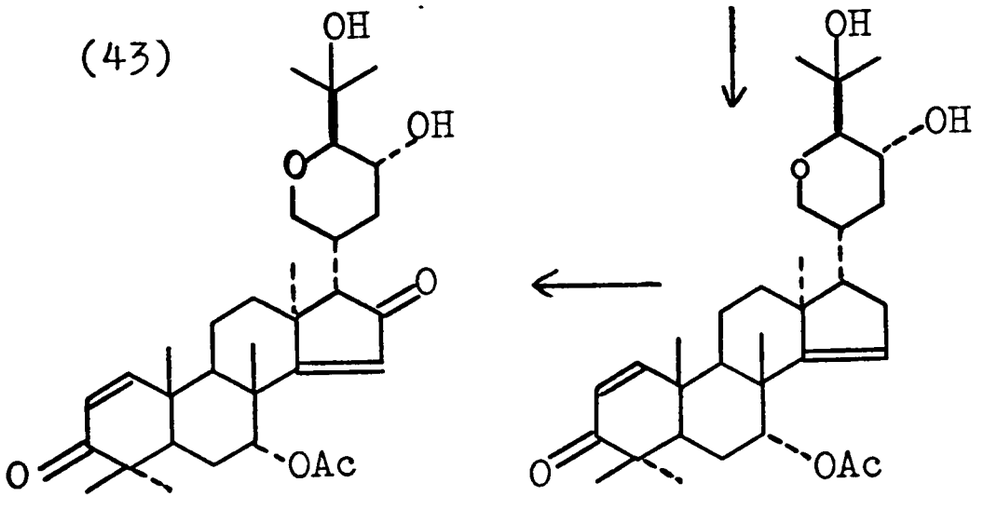


(42) (41)

FIGURE 8



(43) (44)



(46) (45)

FIGURE 9

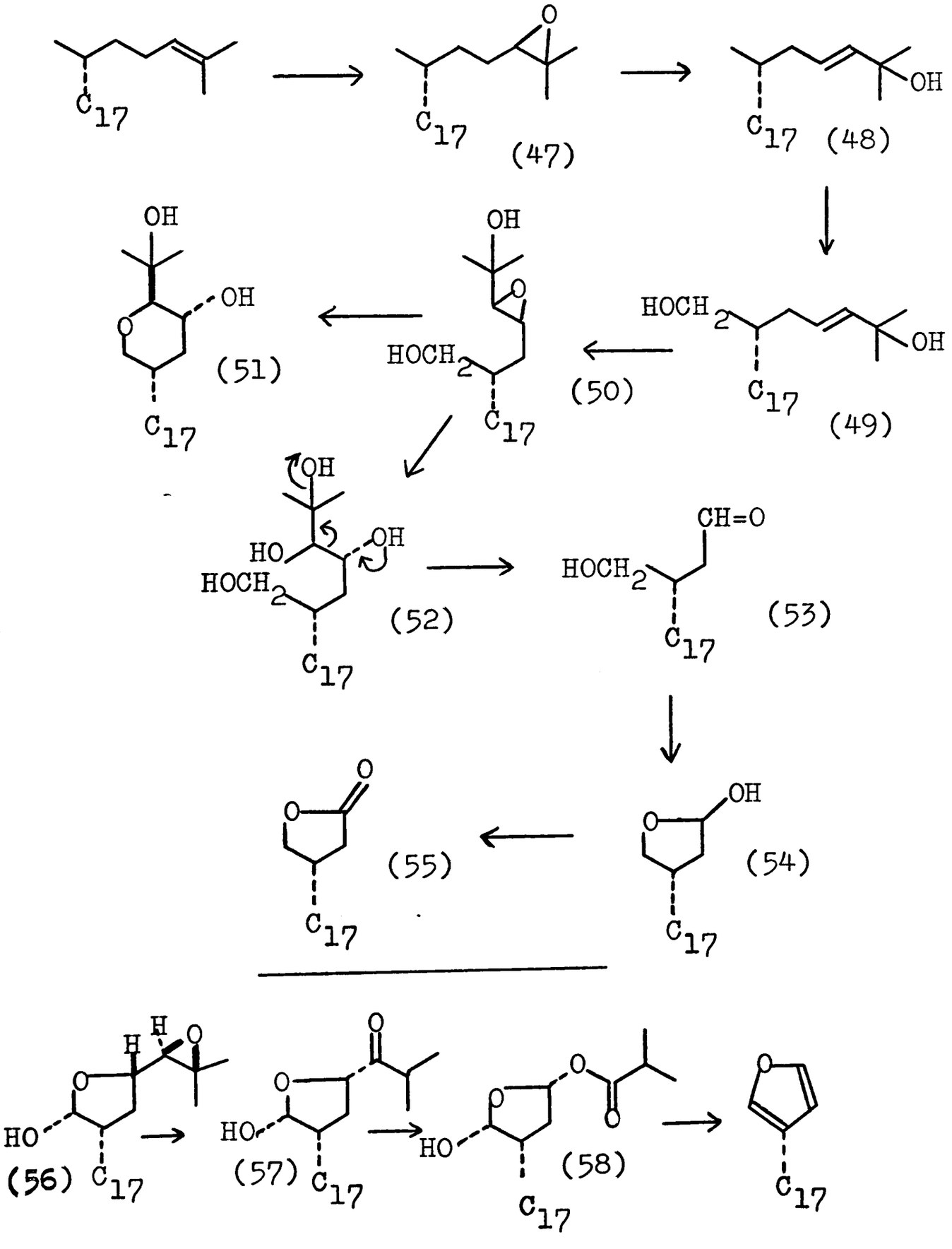


FIGURE 10

FIGURE 11

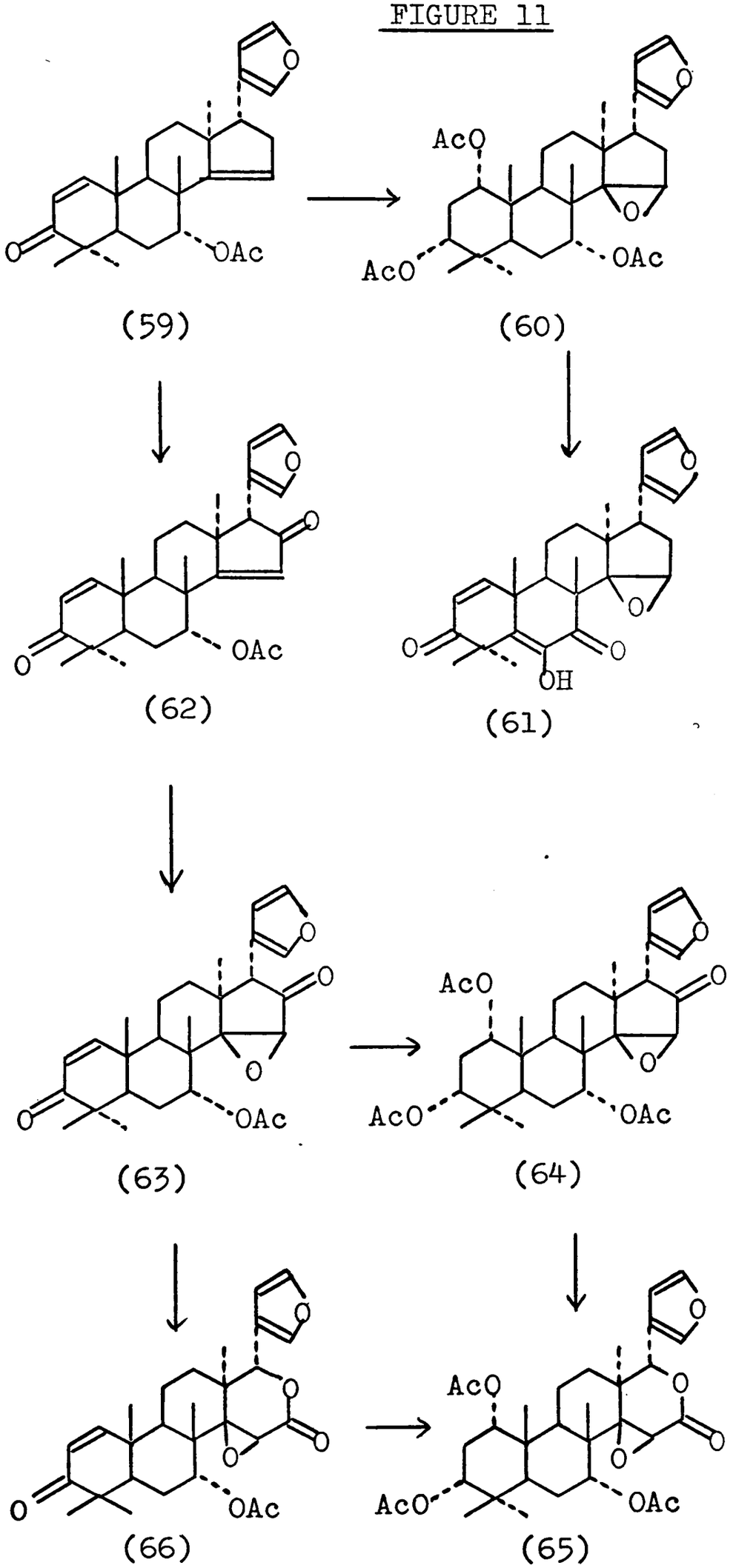
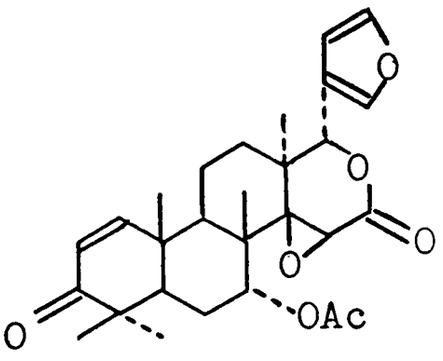
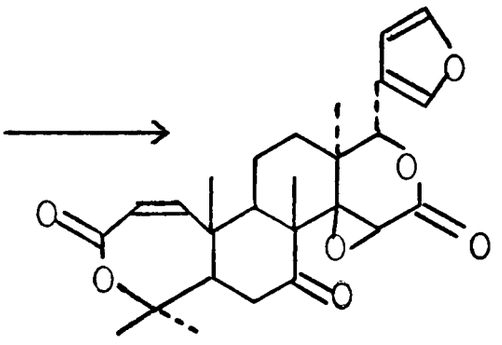

OAc
AcO
AcO
OAc
(59)
(60)
OAc
OH
(62)
(61)
AcO
AcO
OAc
(63)
(64)
OAc
AcO
AcO
OAc
(66)
(65)

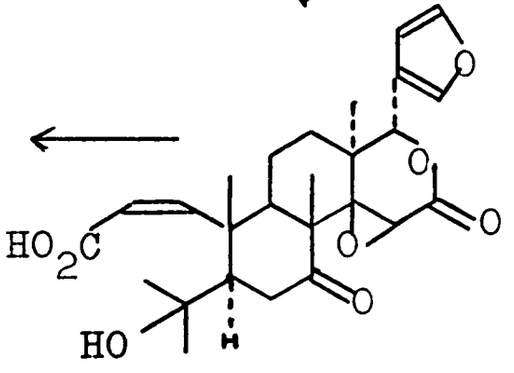
FIGURE 12



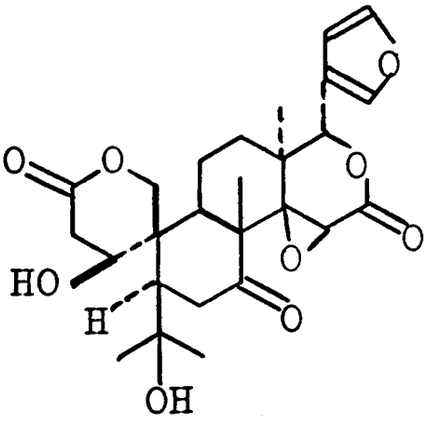
(66)



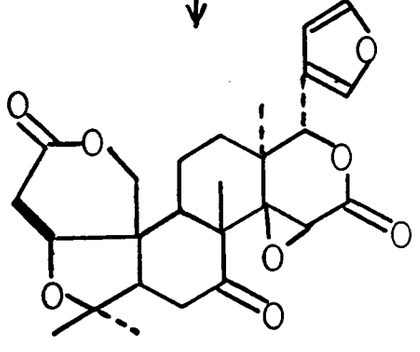
(67)



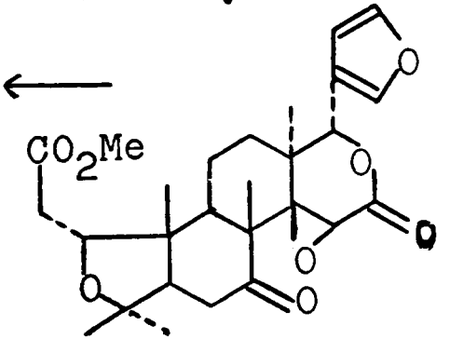
(68)



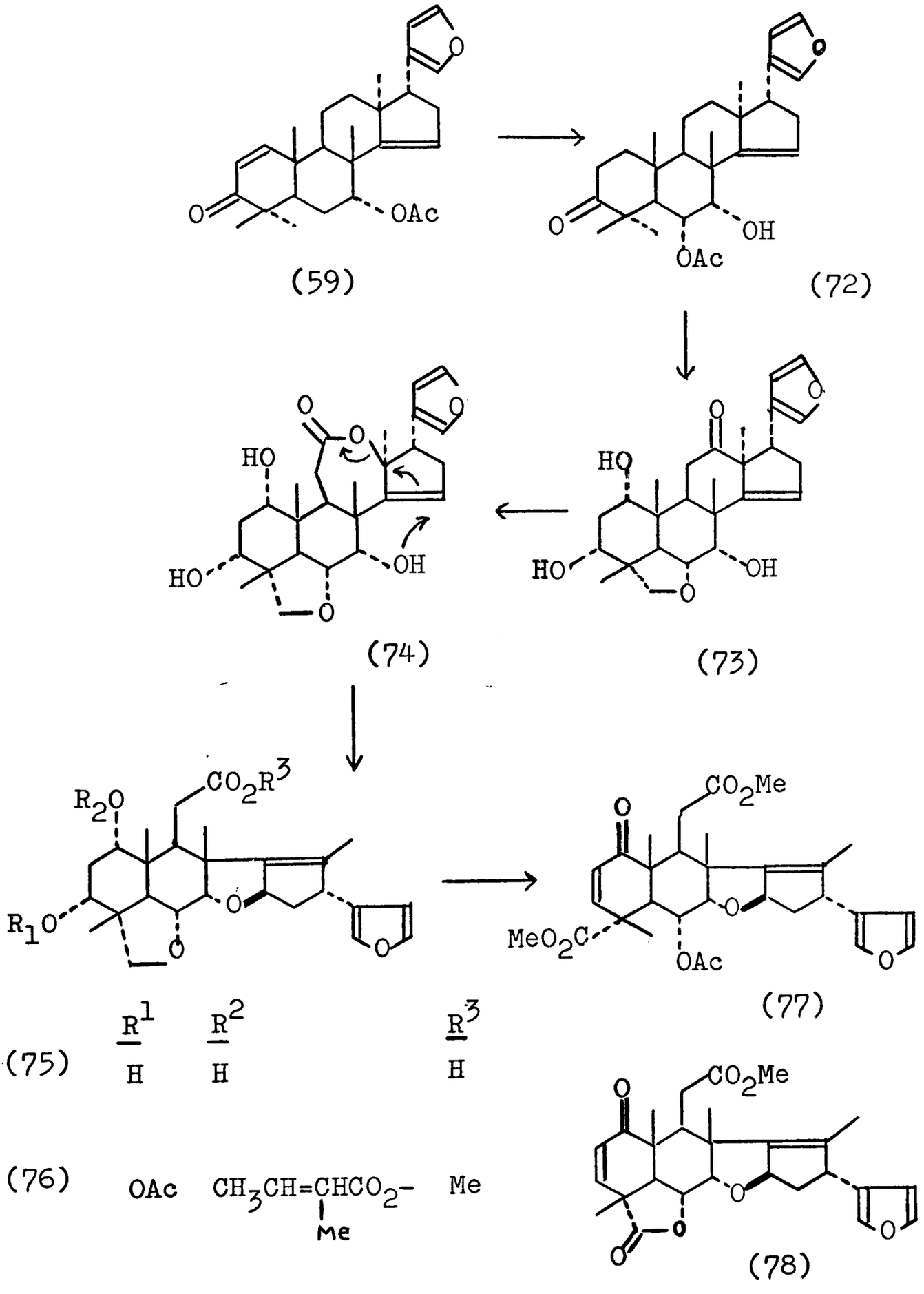
(69)



(70)

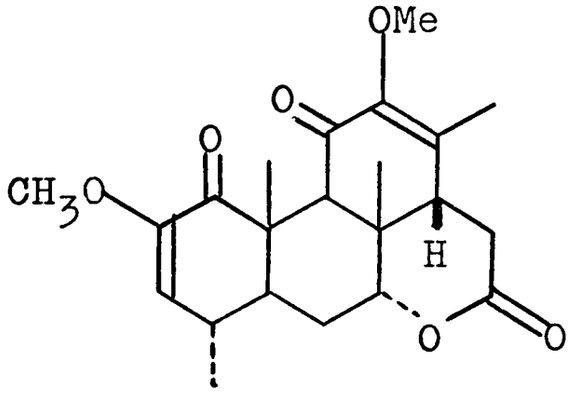


(71)

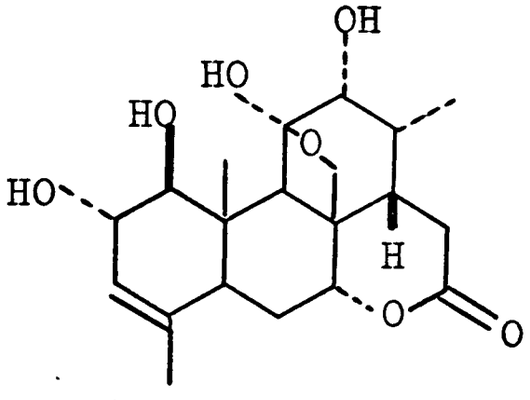


	R^1	R^2	R^3
(75)	H	H	H
(76)	OAc	$CH_3CH{=}C(Me)CO_2-$	Me

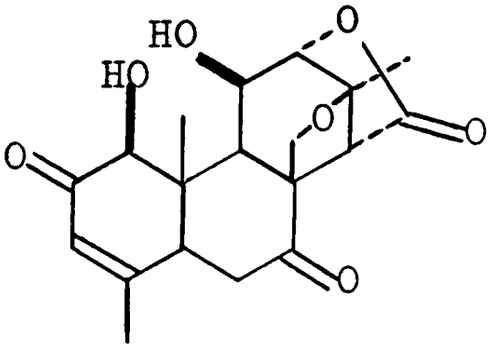
FIGURE 13



(79)



(80)



(81)

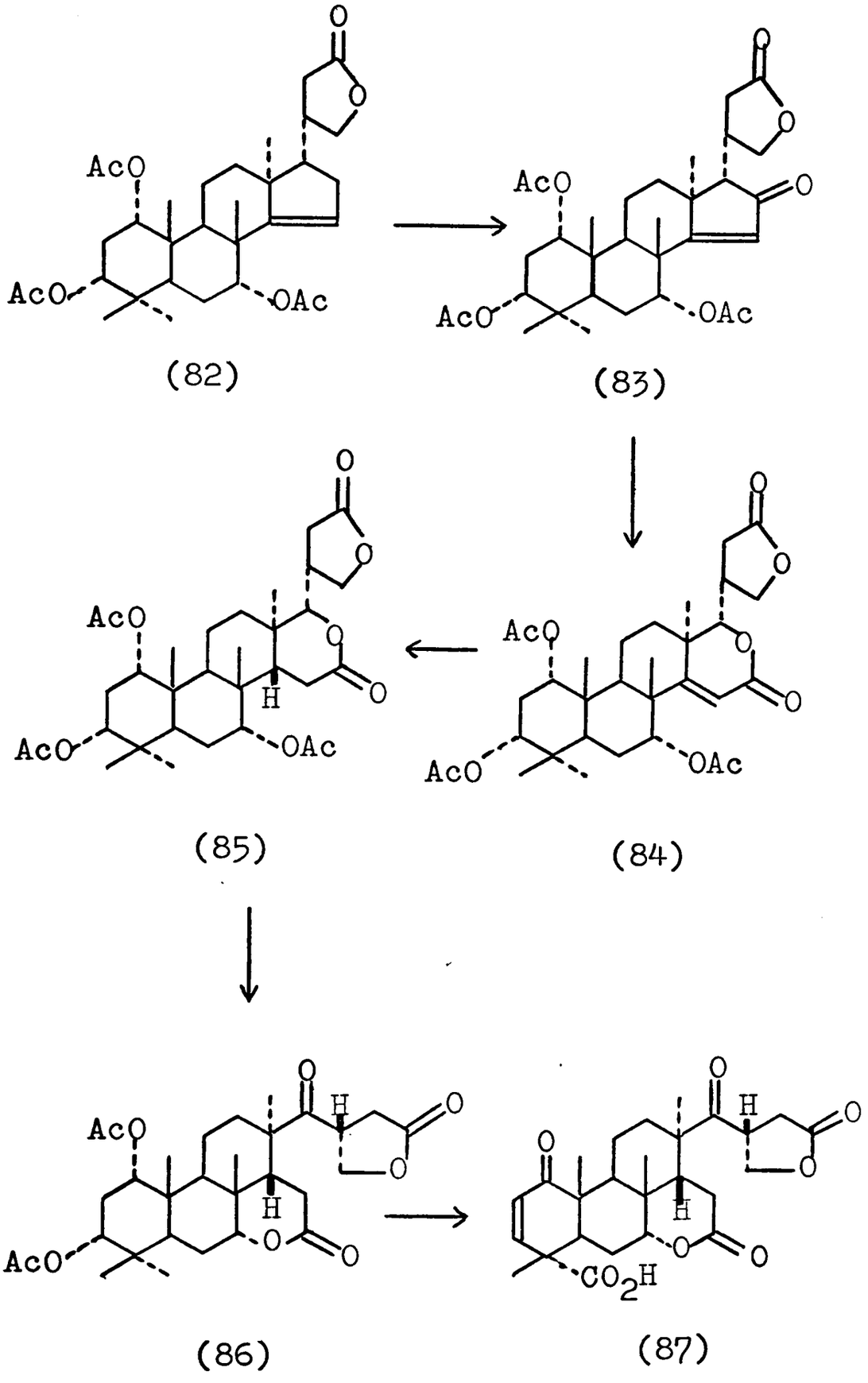
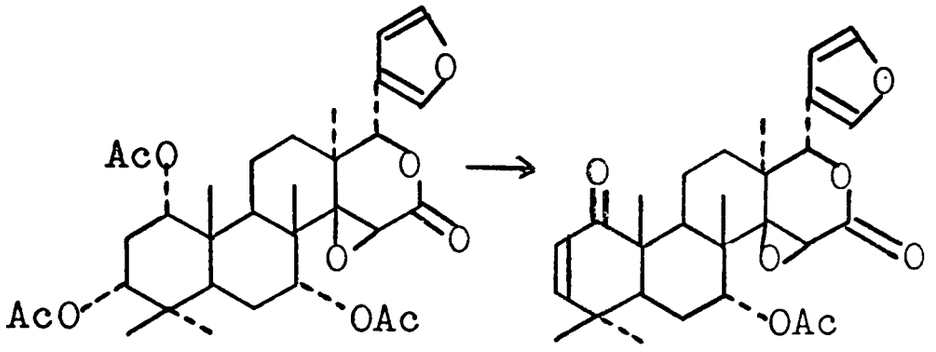
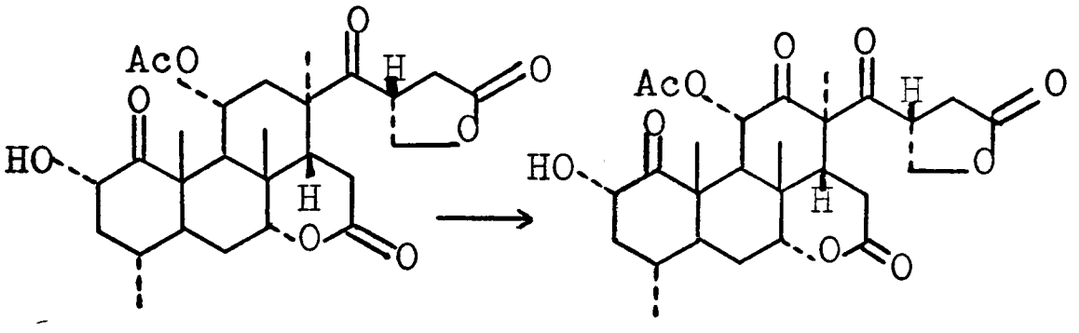


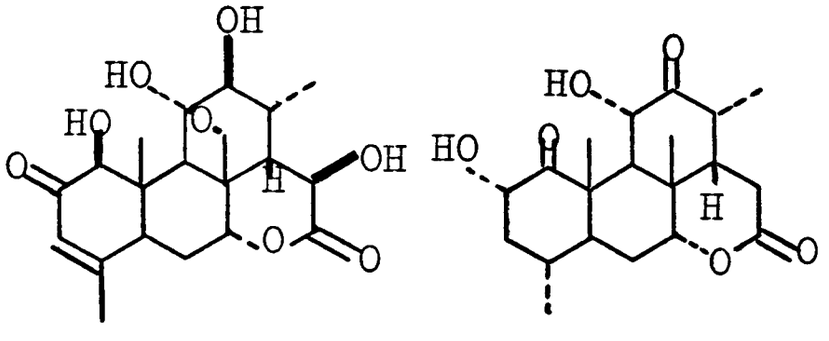
FIGURE 14



(65) (88)

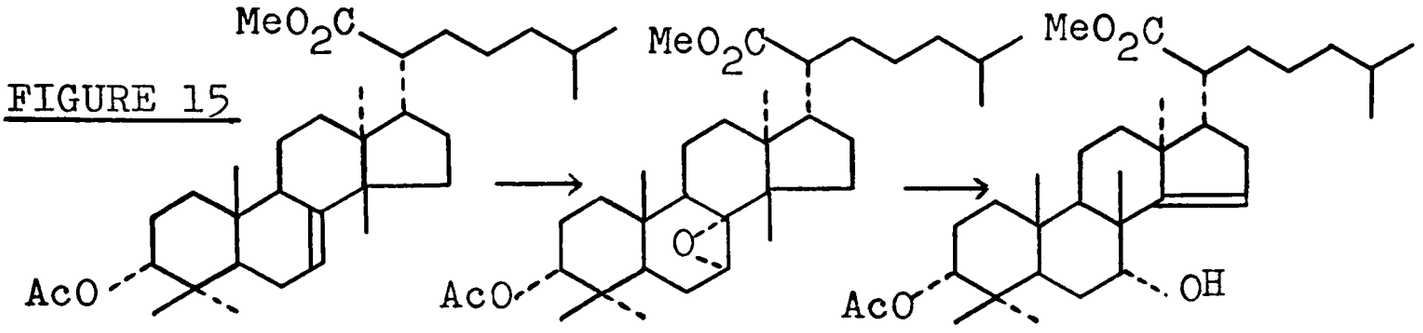


(89) (90)

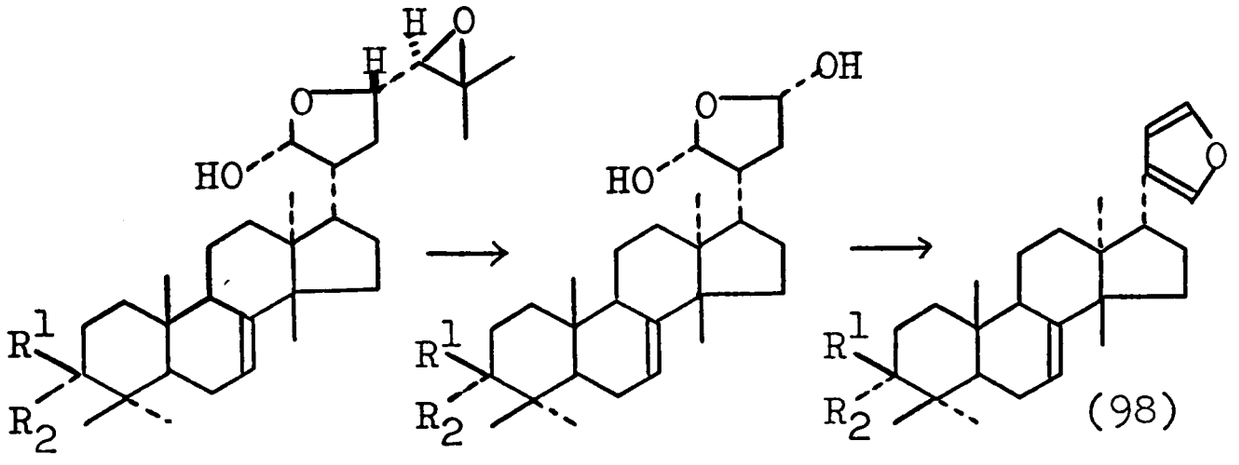


(92) (91)

FIGURE 15



(93) (94) (95)

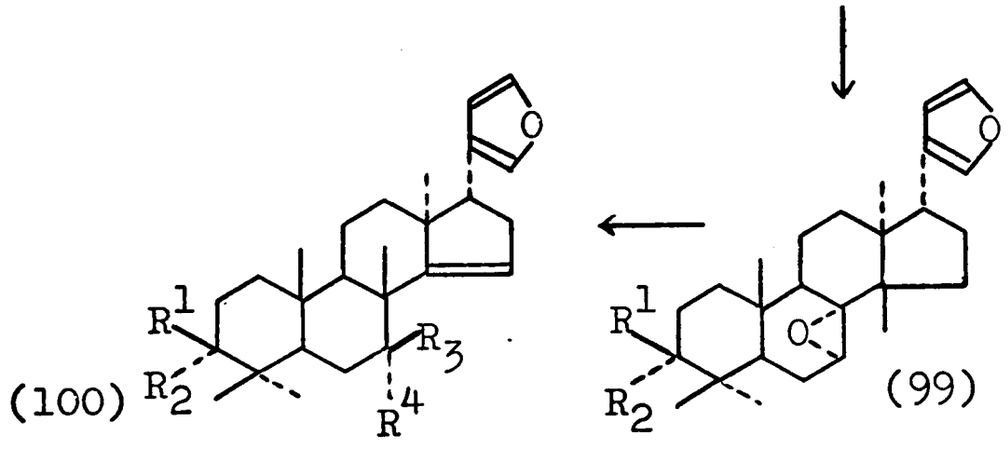


(97) (98)

(41) R_1=OAc R_2=H (a) R_1=OAc R_2=H

(96) R_1=H R_2=OAc (b) R_1=H R_2=OAc

	R_1	R_2
(a)	OAc	H
(b)	H	OAc
(c)	OH	H
(d)	H	OH
(e)	=O	



(100) (99)

	R_1	R_2	R_3	R_4
(a)	OAc	H	H	OH
(b)	H	OAc	H	OH
(c)	OH	H	H	OH
(d)	H	OH	H	OH
(e)	=O		H	OAc
(f)	=O		H	OH

	R_1	R_2
(a)	OAc	H
(b)	H	OAc
(c)	=O	

FIGURE 16

FIGURE 17

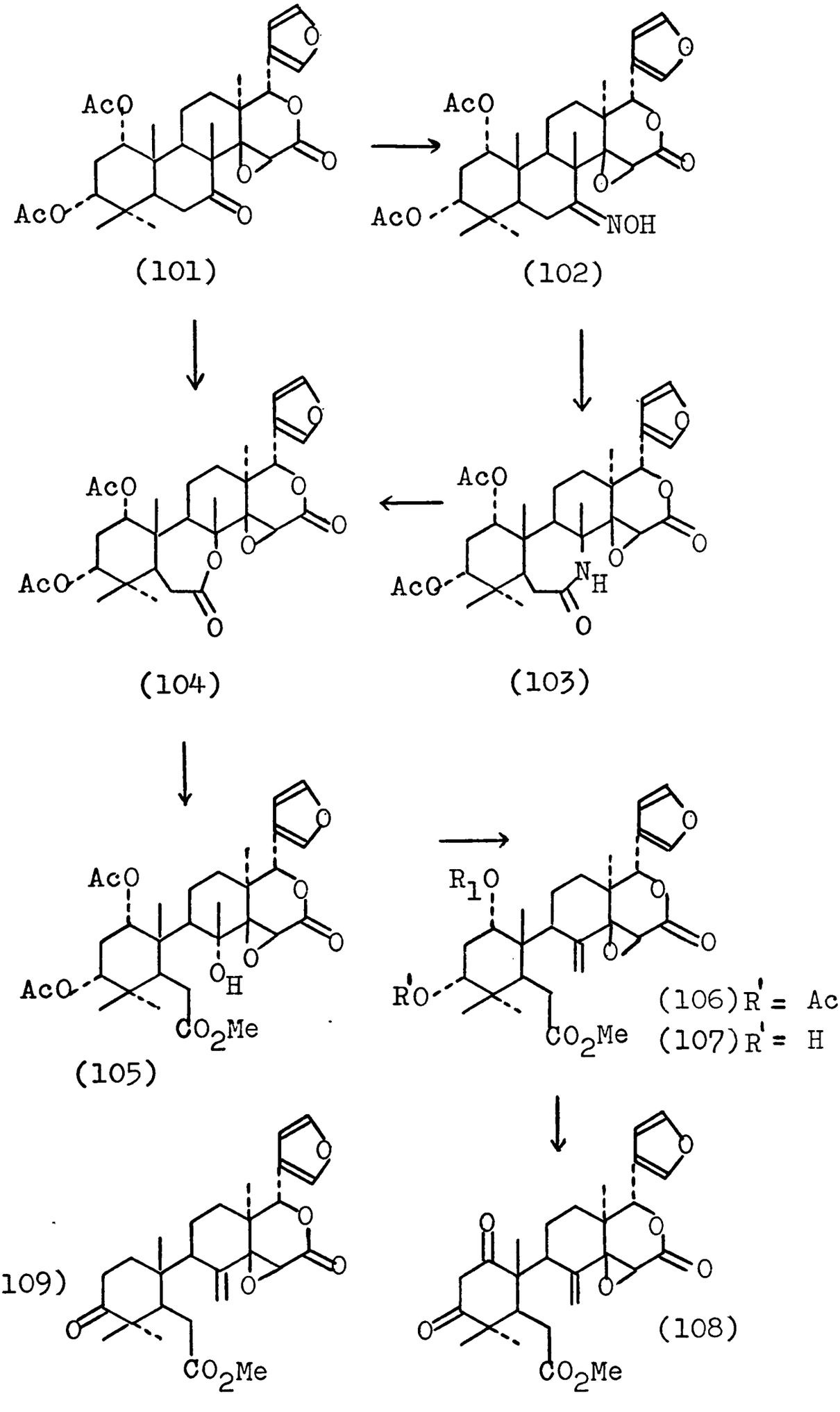
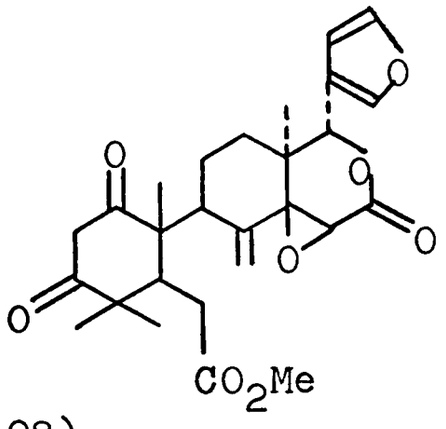
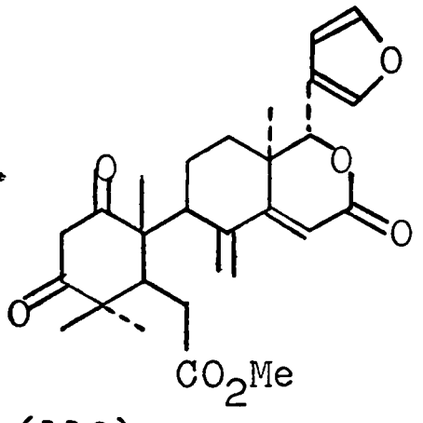

AcO
AcO
O
NOH
(101)
(102)
(103)
(104)
(105)
(106) R' = Ac
(107) R' = H
(108)
(109)
R_1O
R'O
CO_2Me
N
H

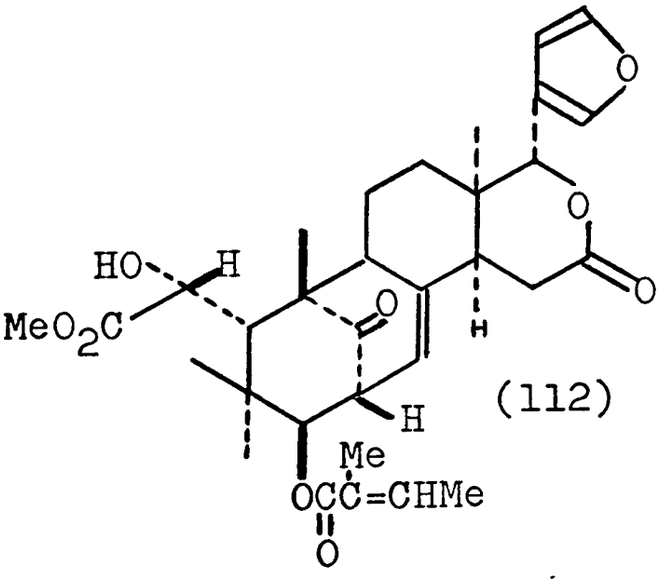
FIGURE 18



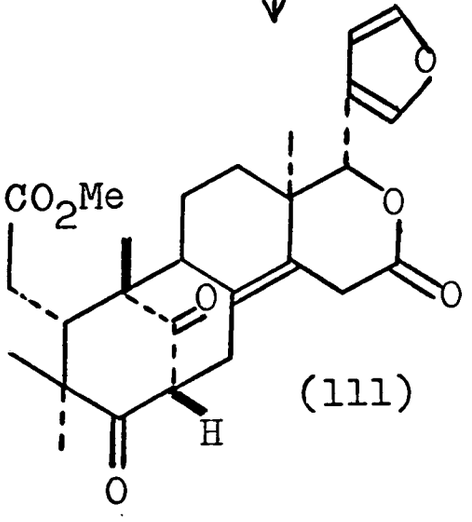
(108)



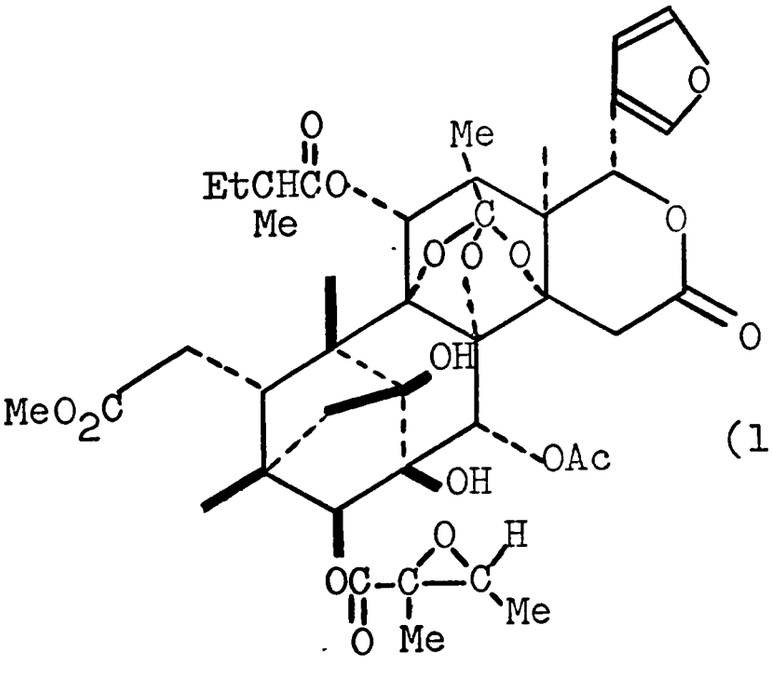
(110)



(112)

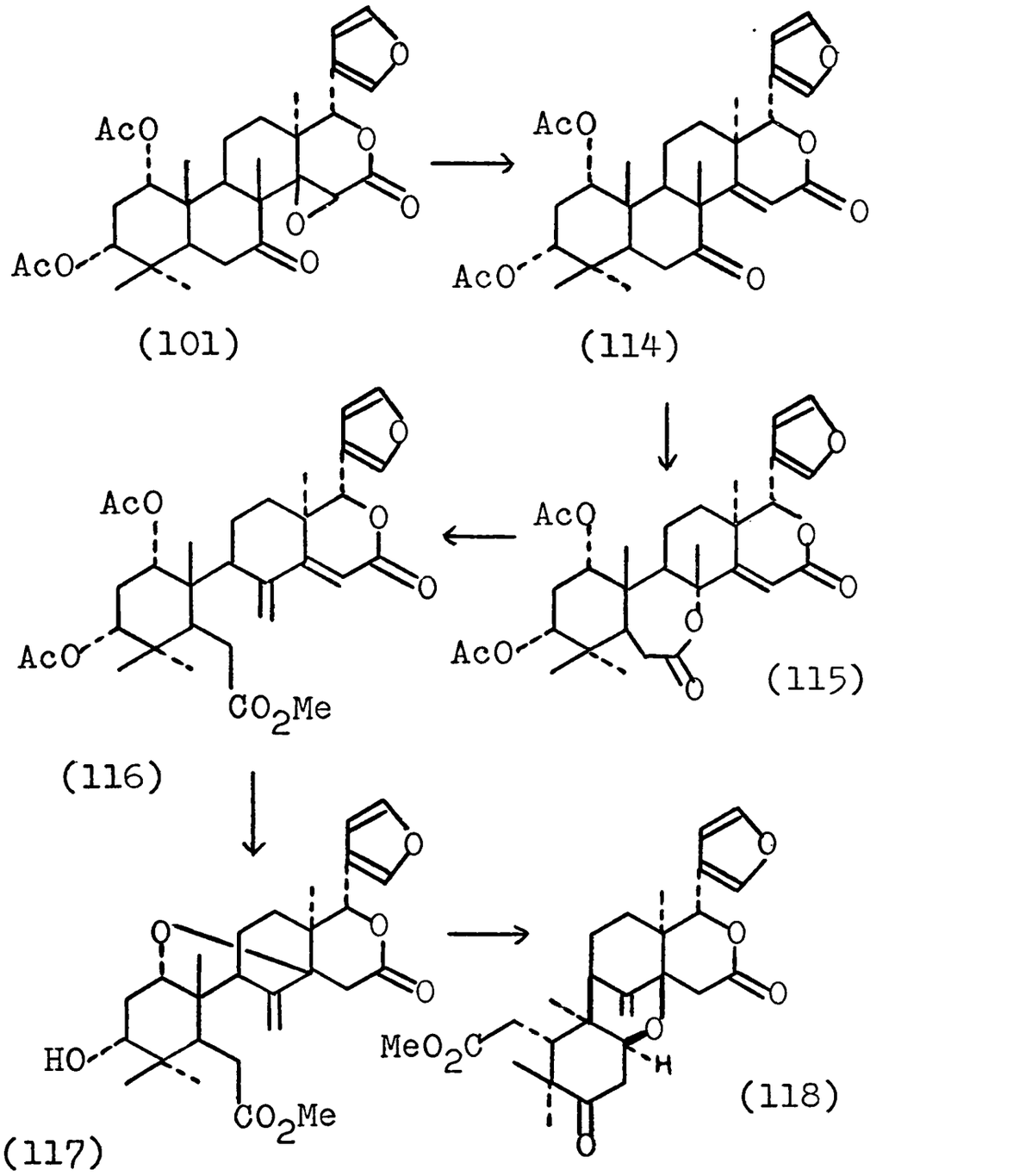


(111)



(113)

FIGURE 19



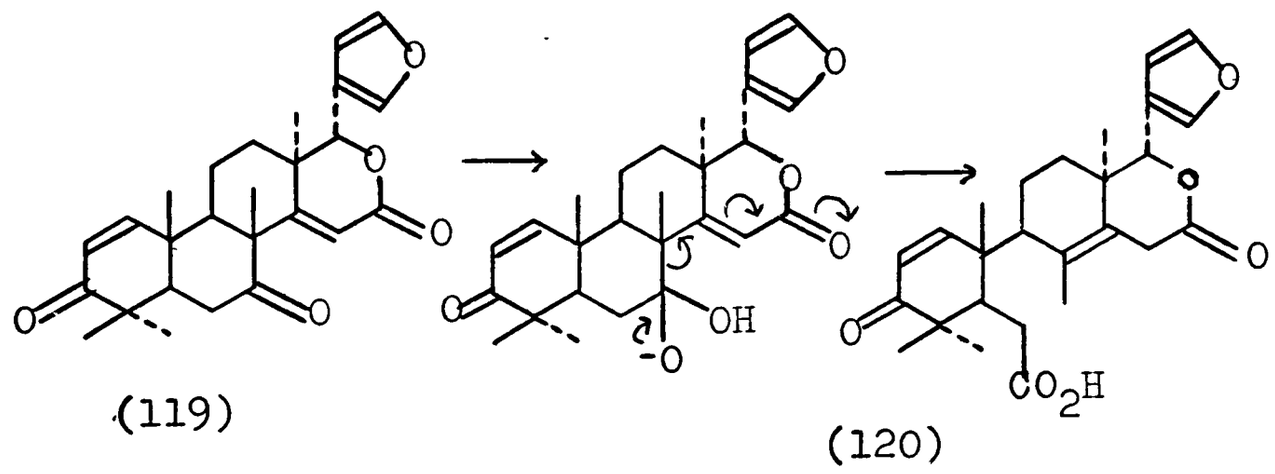
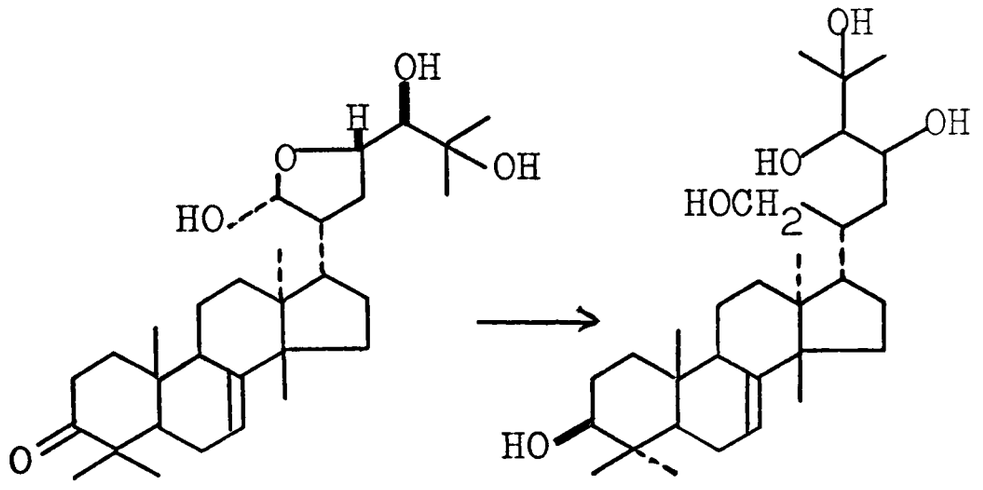
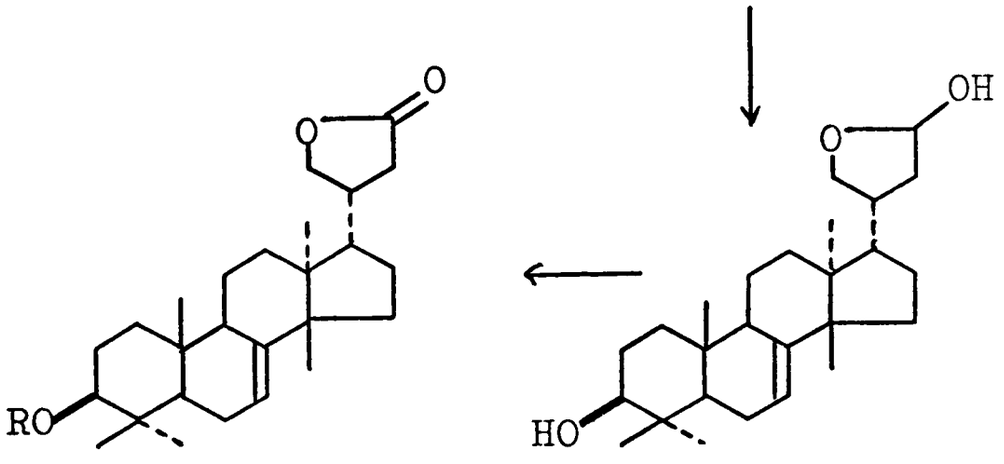


FIGURE 20

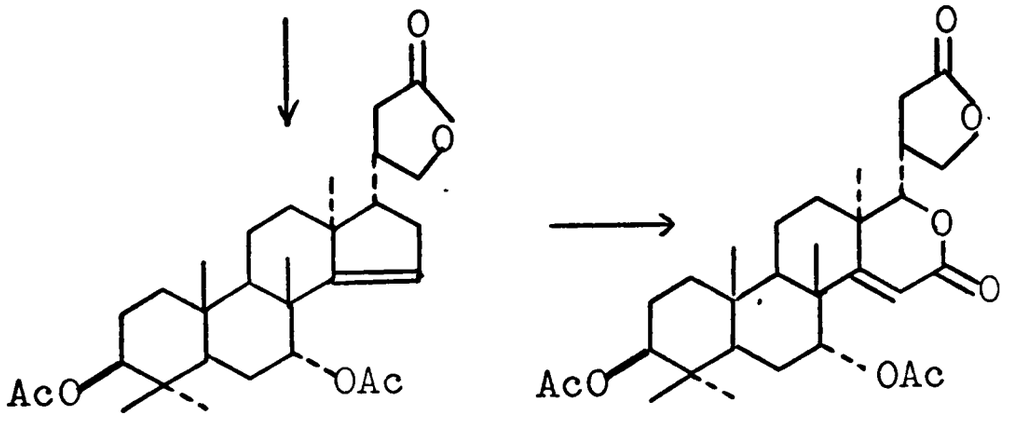


(42) (121)



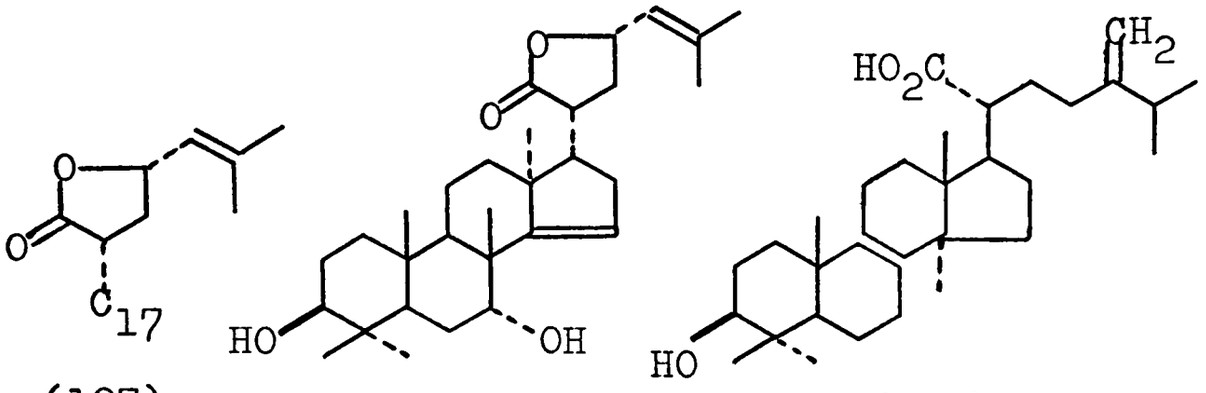
(123) R=H
(124) R=Ac

(122)



(125) (126)

FIGURE 21



(127) (128) (129)

FIGURE 22

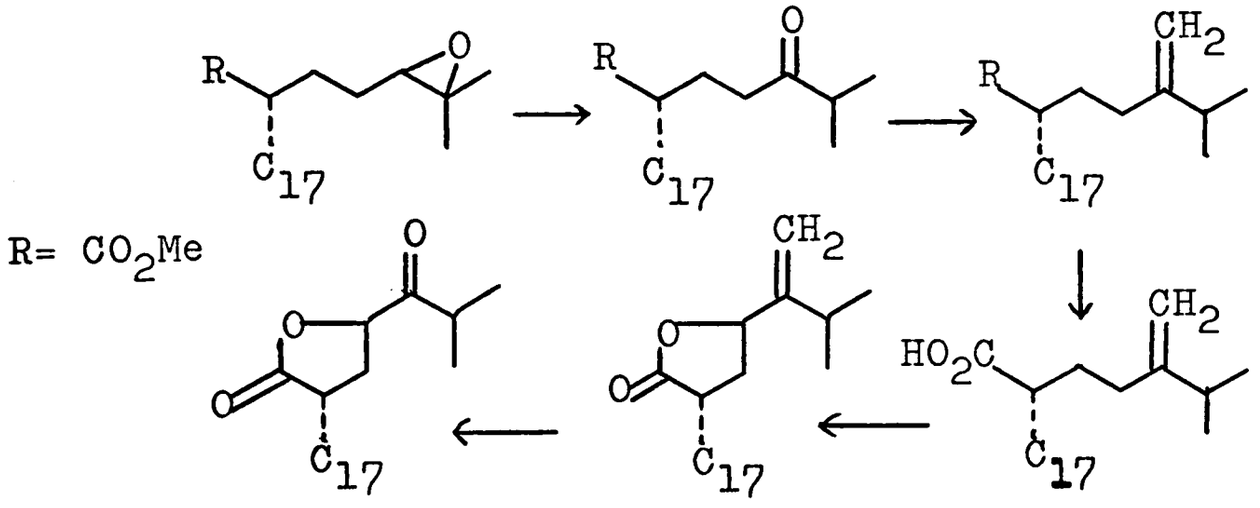
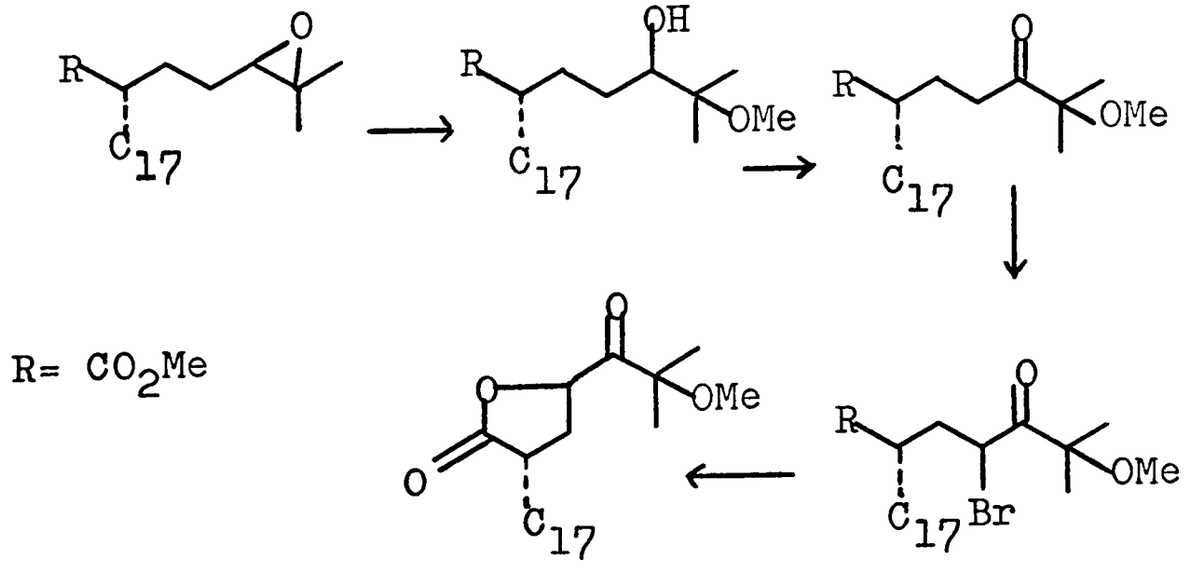
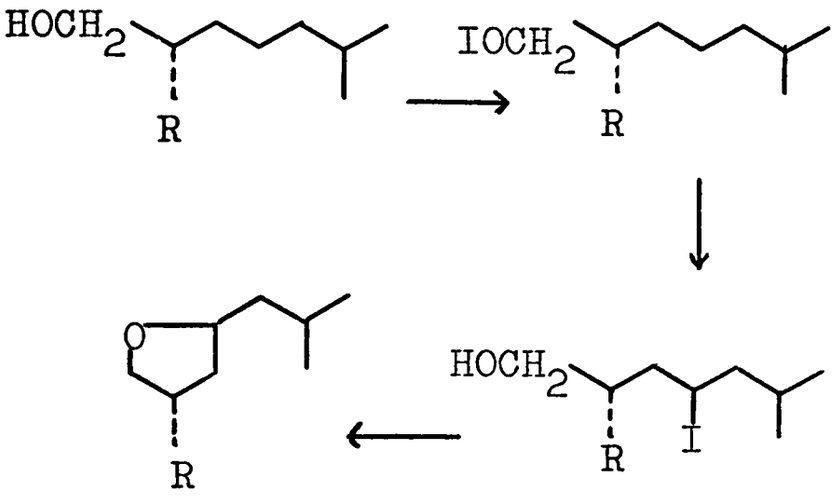


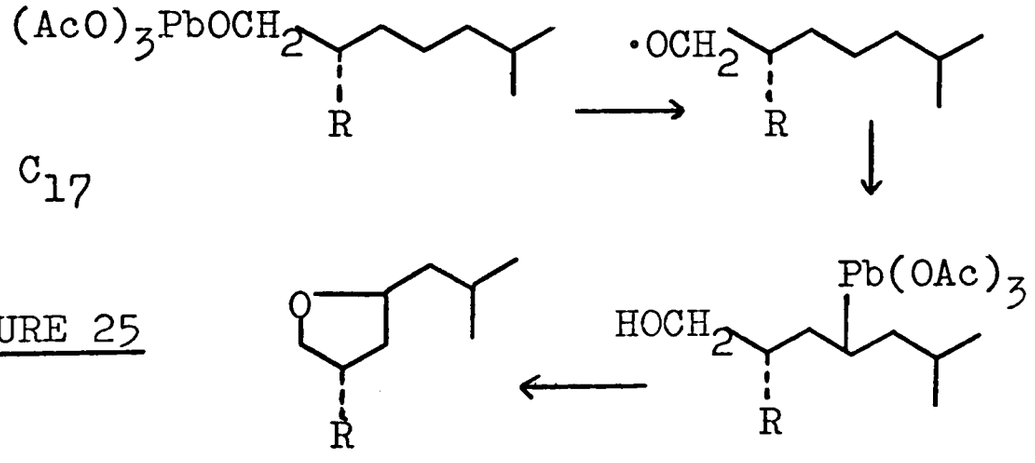
FIGURE 23





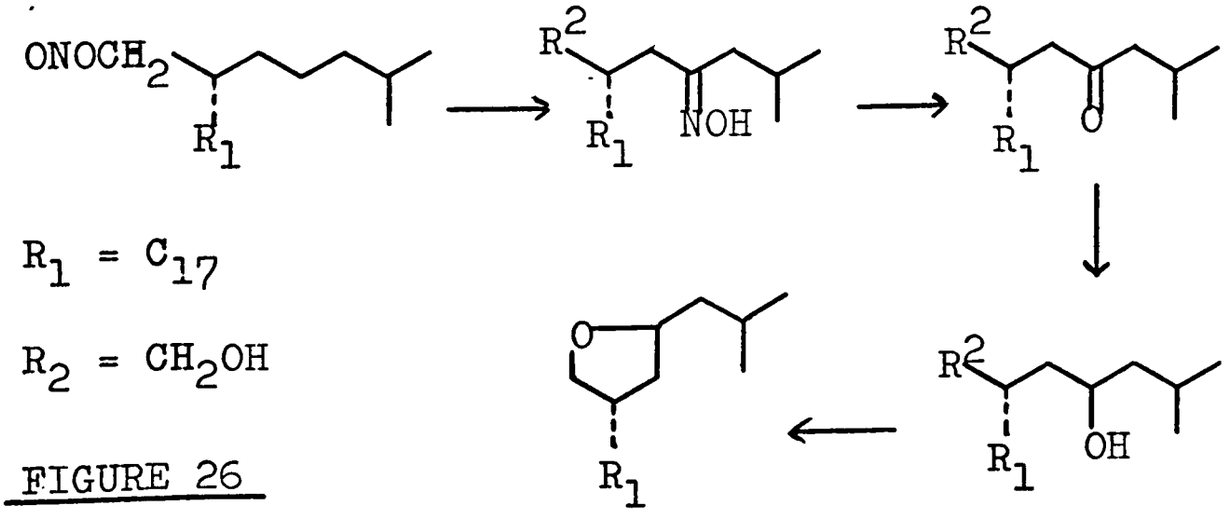
R = C_{17}

FIGURE 24



R = C_{17}

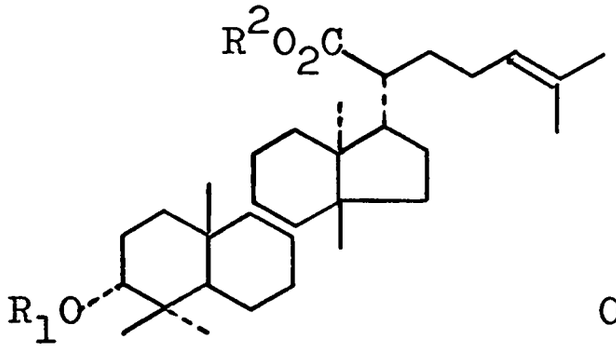
FIGURE 25



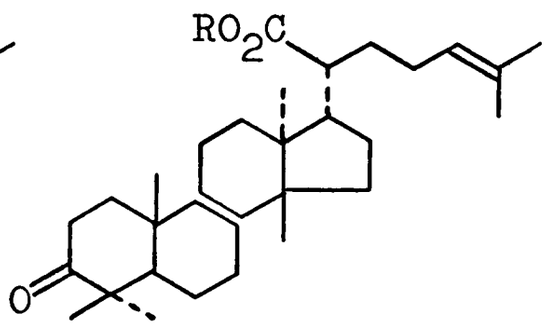
R_1 = C_{17}

R_2 = CH_2OH

FIGURE 26

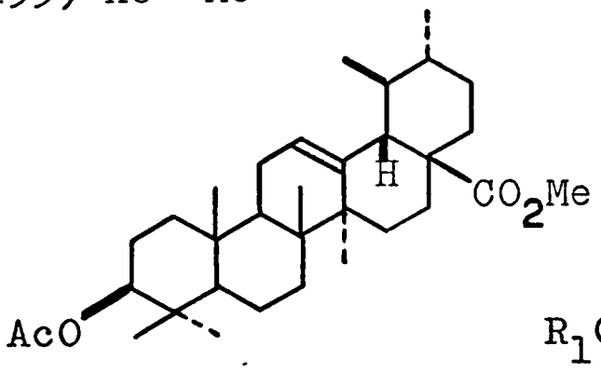


	R^1	R^2
(130)	H	H
(131)	H	Me
(132)	Ac	H
(133)	Ac	Me

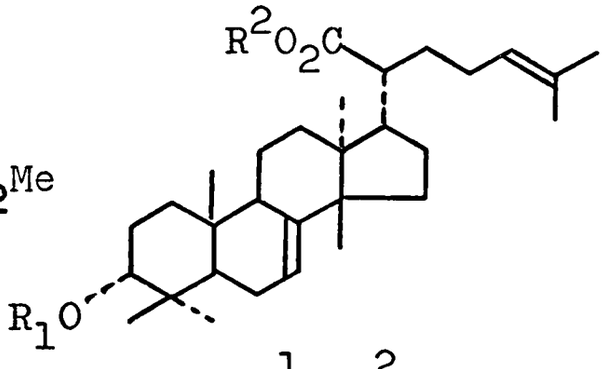


(134) R = H

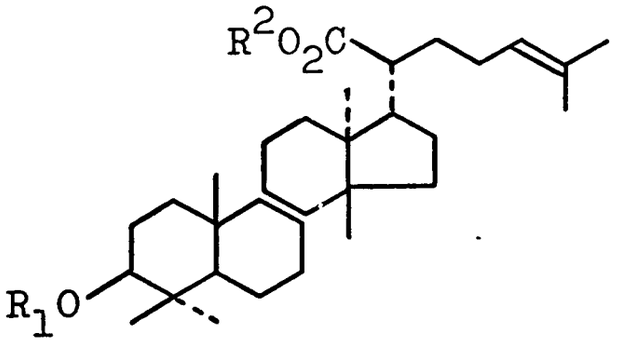
(135) R = Me



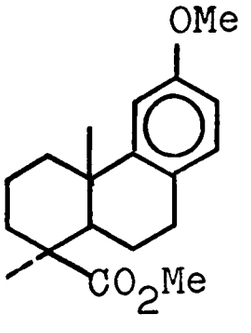
(136)



	R^1	R^2
(137)	Ac	Me
(138)	H	Me
(139)	H	H



	R^1	R^2
(141)	H	H
(142)	H	Me
(143)	Ac	H
(144)	Ac	Me



(140)

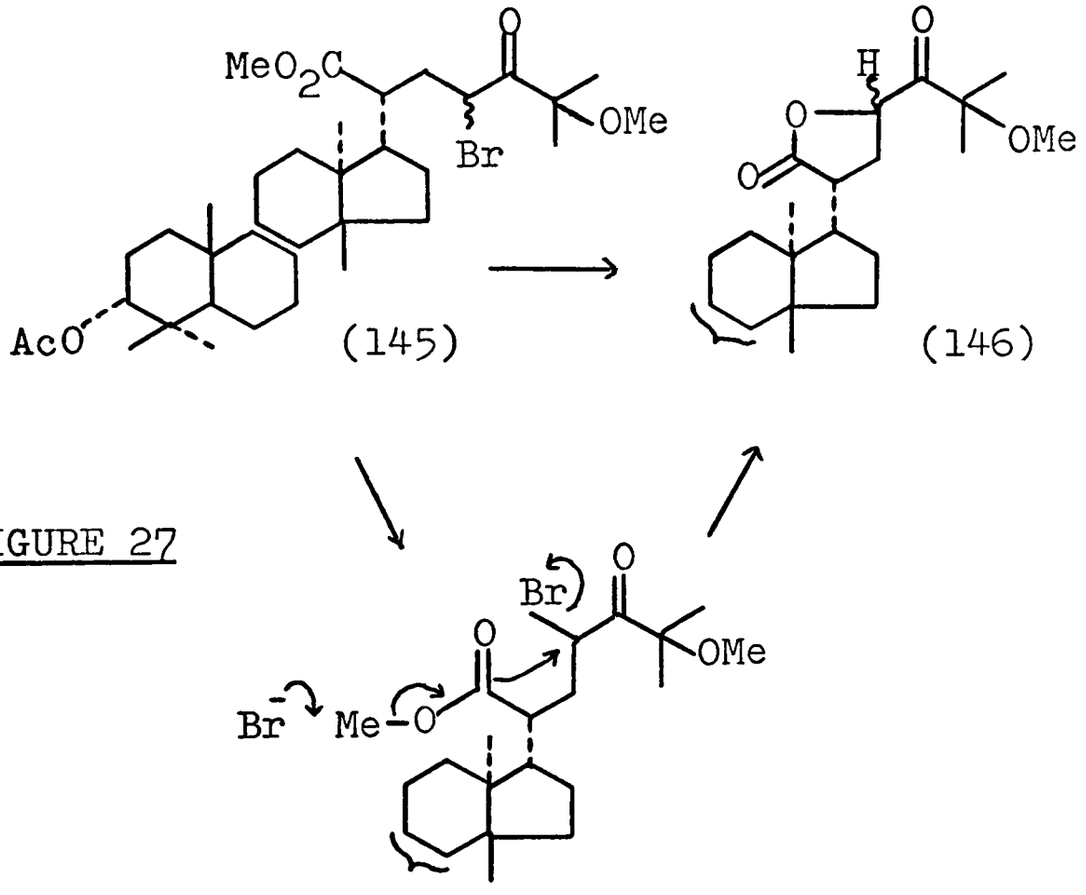
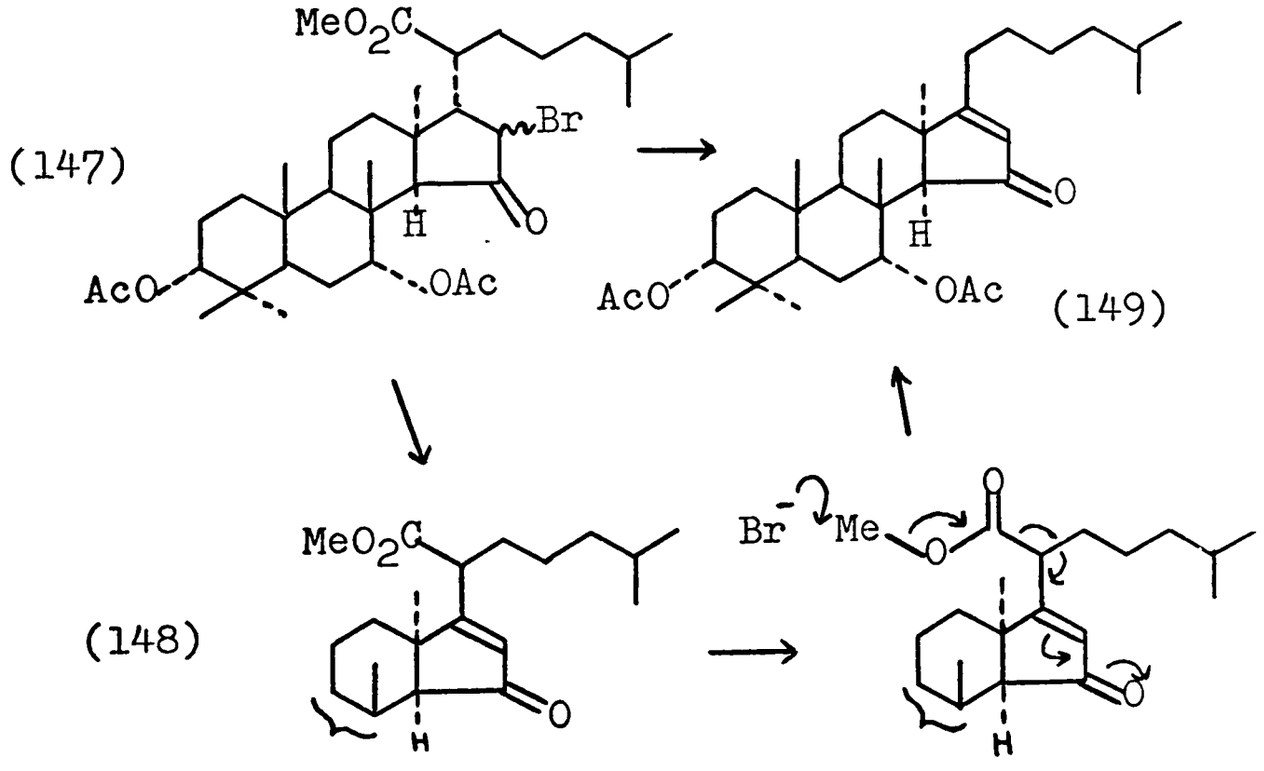


FIGURE 27

FIGURE 28



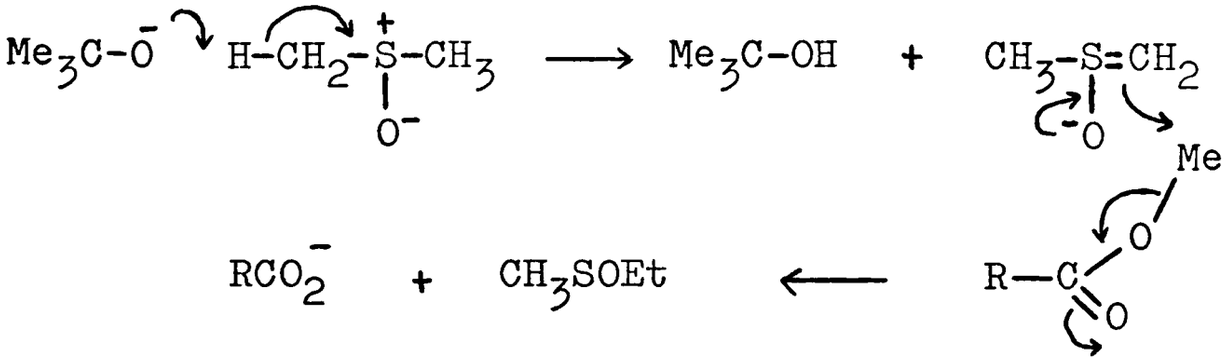


FIGURE 29

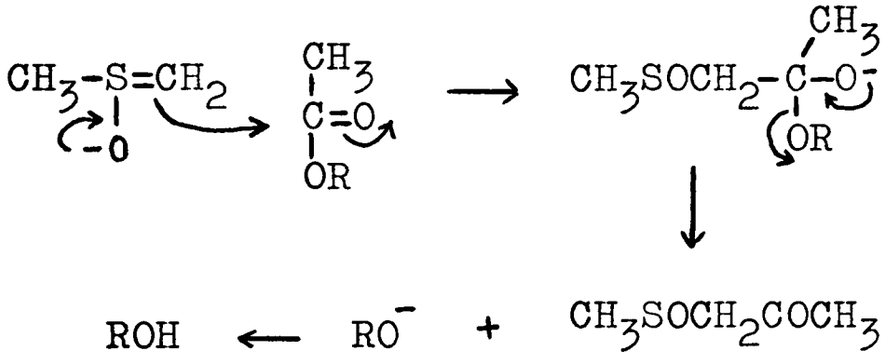
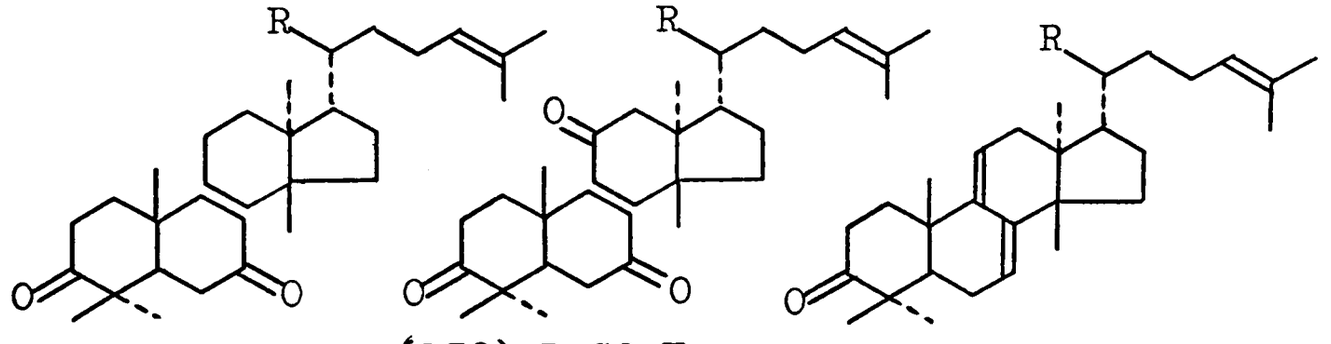


FIGURE 30



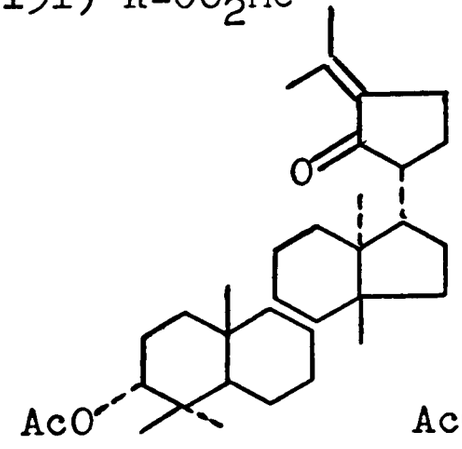
(150) R=CO_2H

(151) R=CO_2Me

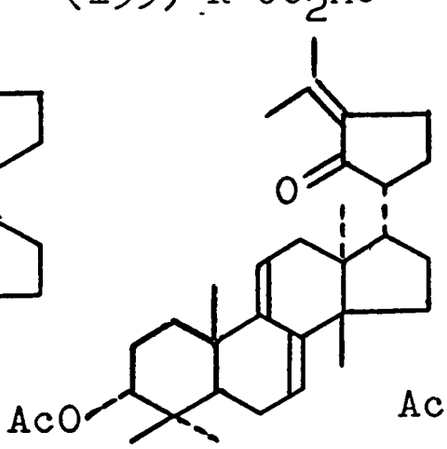
(152) R=CO_2H

(153) R=CO_2Me

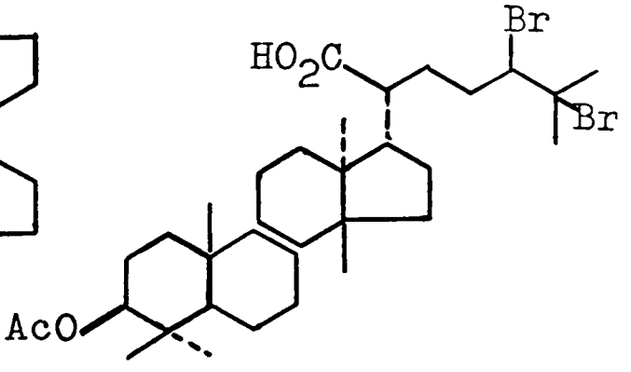
(154) R=CO_2H



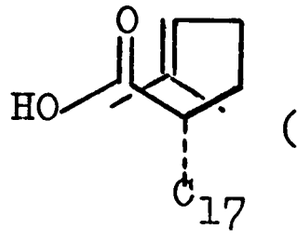
(155)



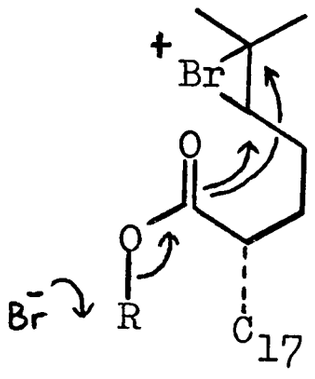
(156)



(157)

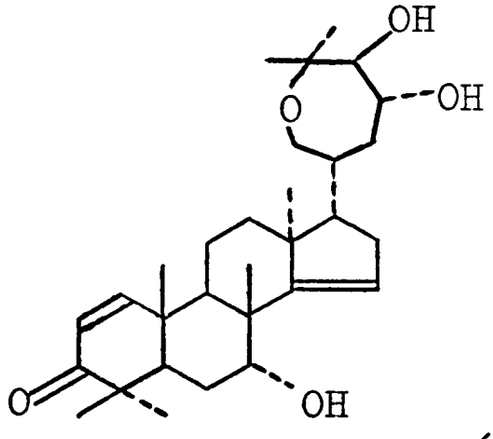


(158)

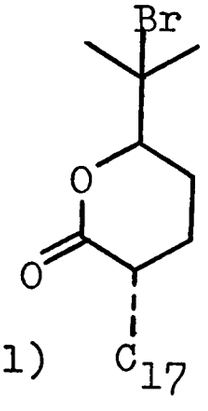


(159) R=H

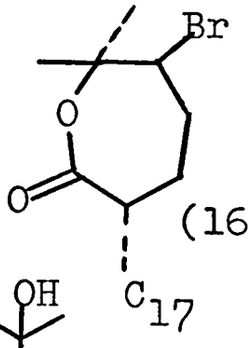
(160) R=Me



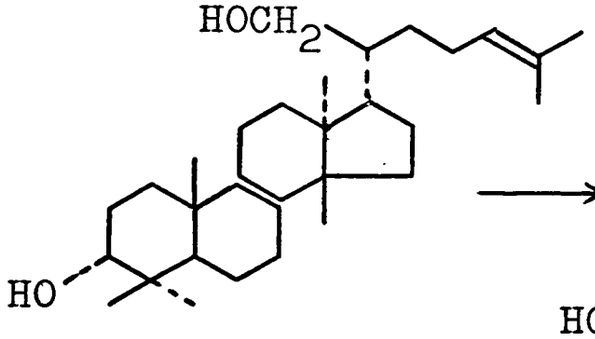
(163)



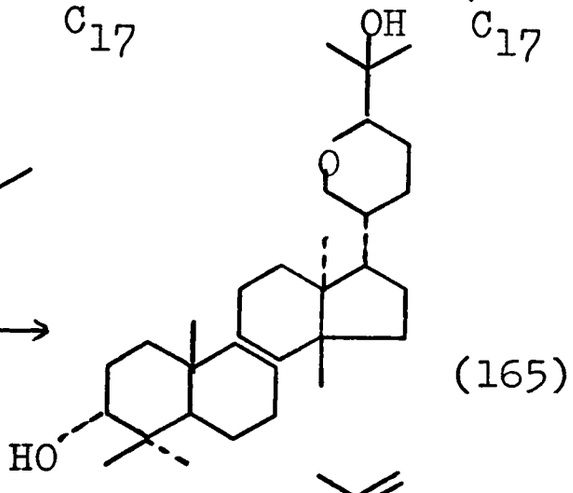
(161)



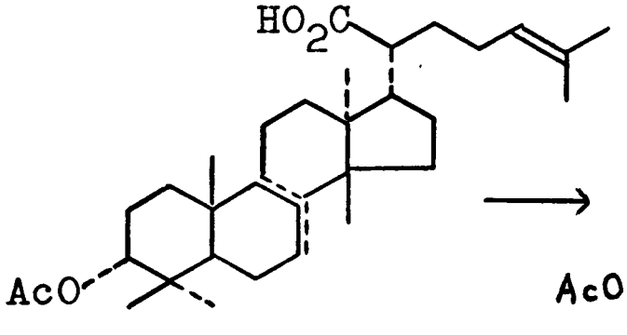
(162)



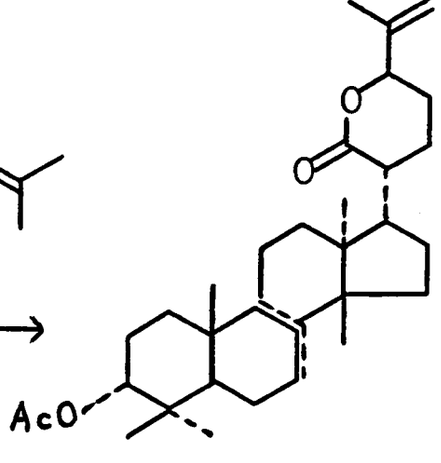
(164)



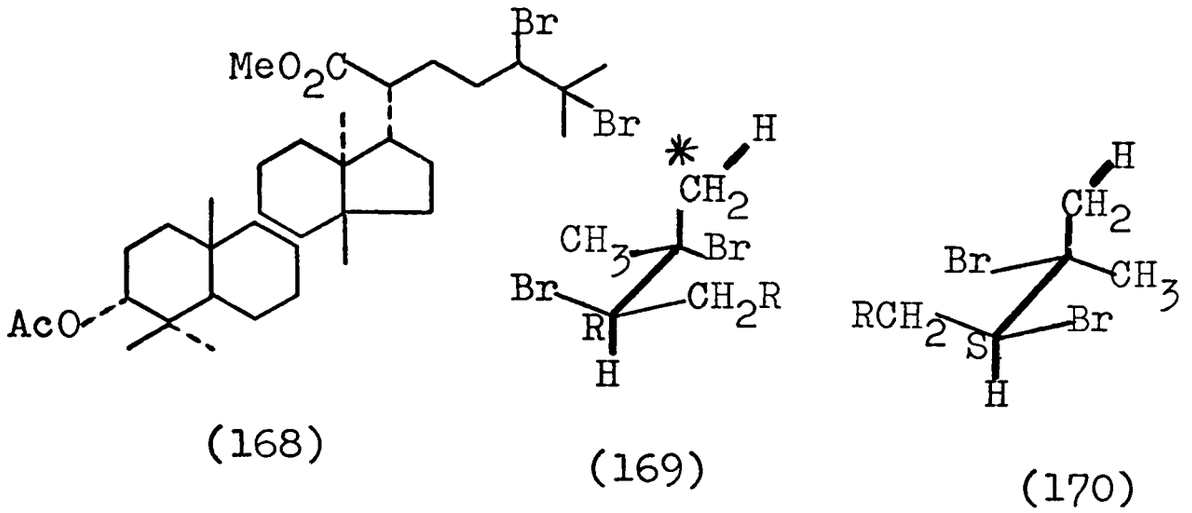
(165)



(166)



(167)



(168) (169) (170)

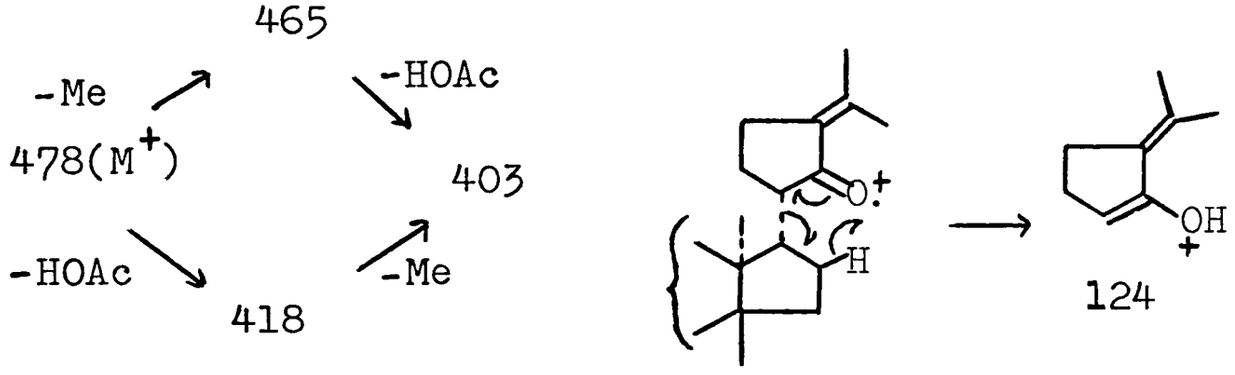
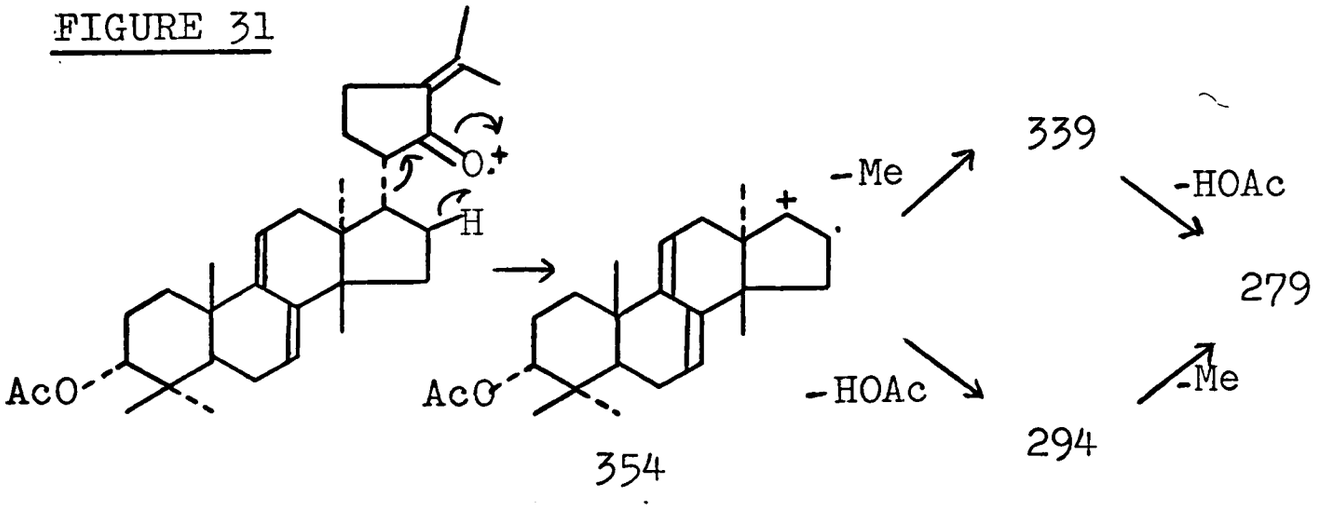


FIGURE 31



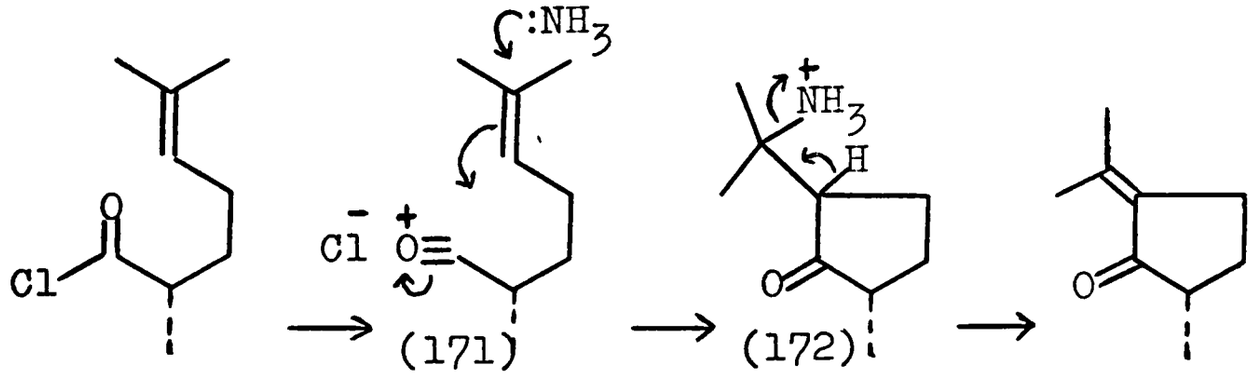
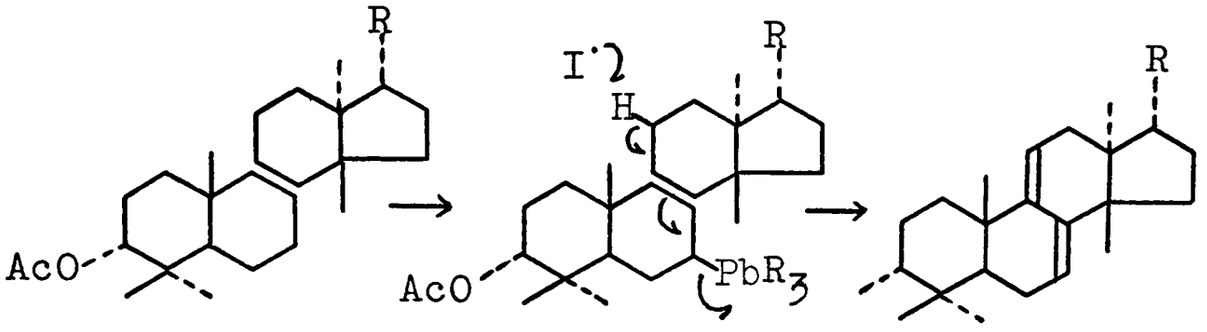
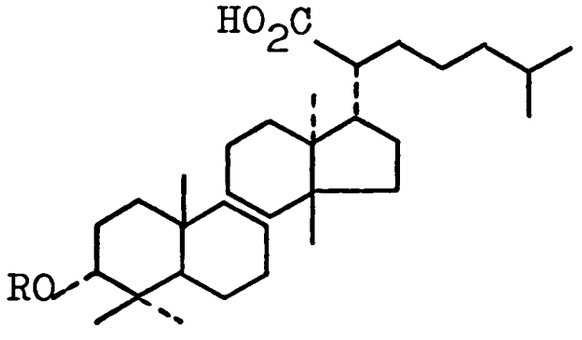


FIGURE 32

FIGURE 33

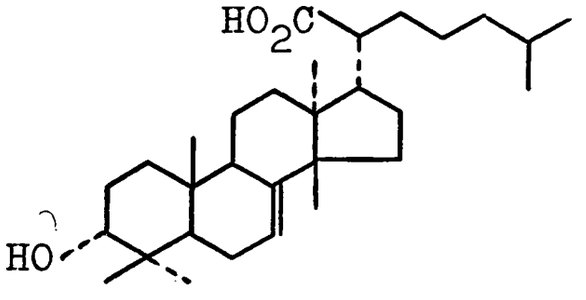


(173)

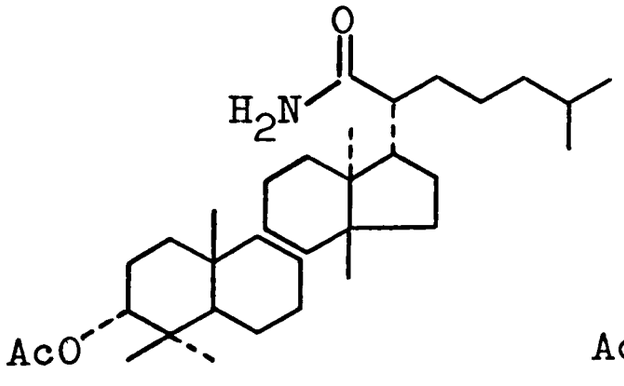


(174) R=H

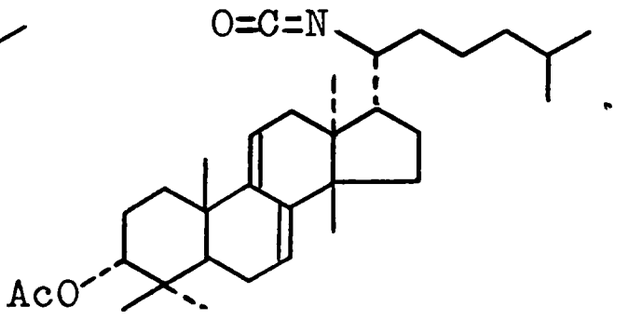
(175) R=Ac



(176)

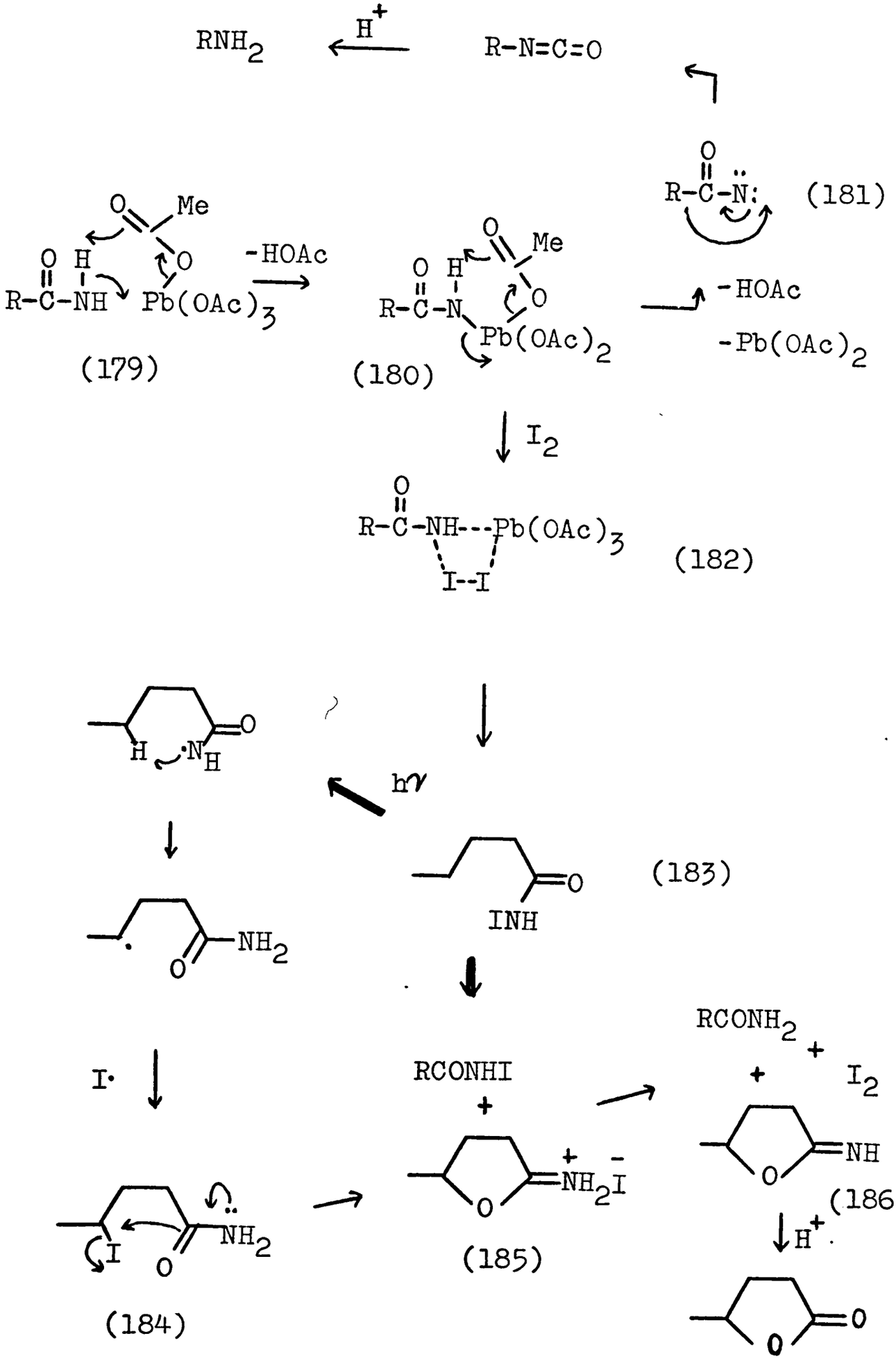


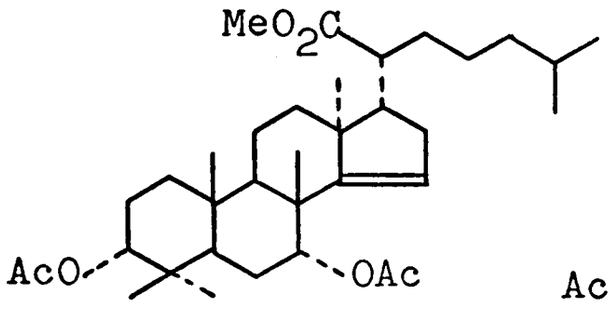
(177)



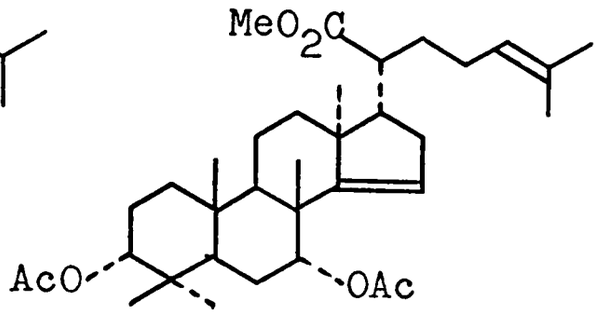
(178)

FIGURE 34


RNH2
H+
R-N=C=O
R-C-N:
(181)
-HOAc
-Pb(OAc)2
(179)
(180)
I2
(182)
hν
(183)
INH
I·
RCONHI
RCONH2
I2
NH
(186)
H+
(184)
(185)



(187)



(188)

FIGURE 35

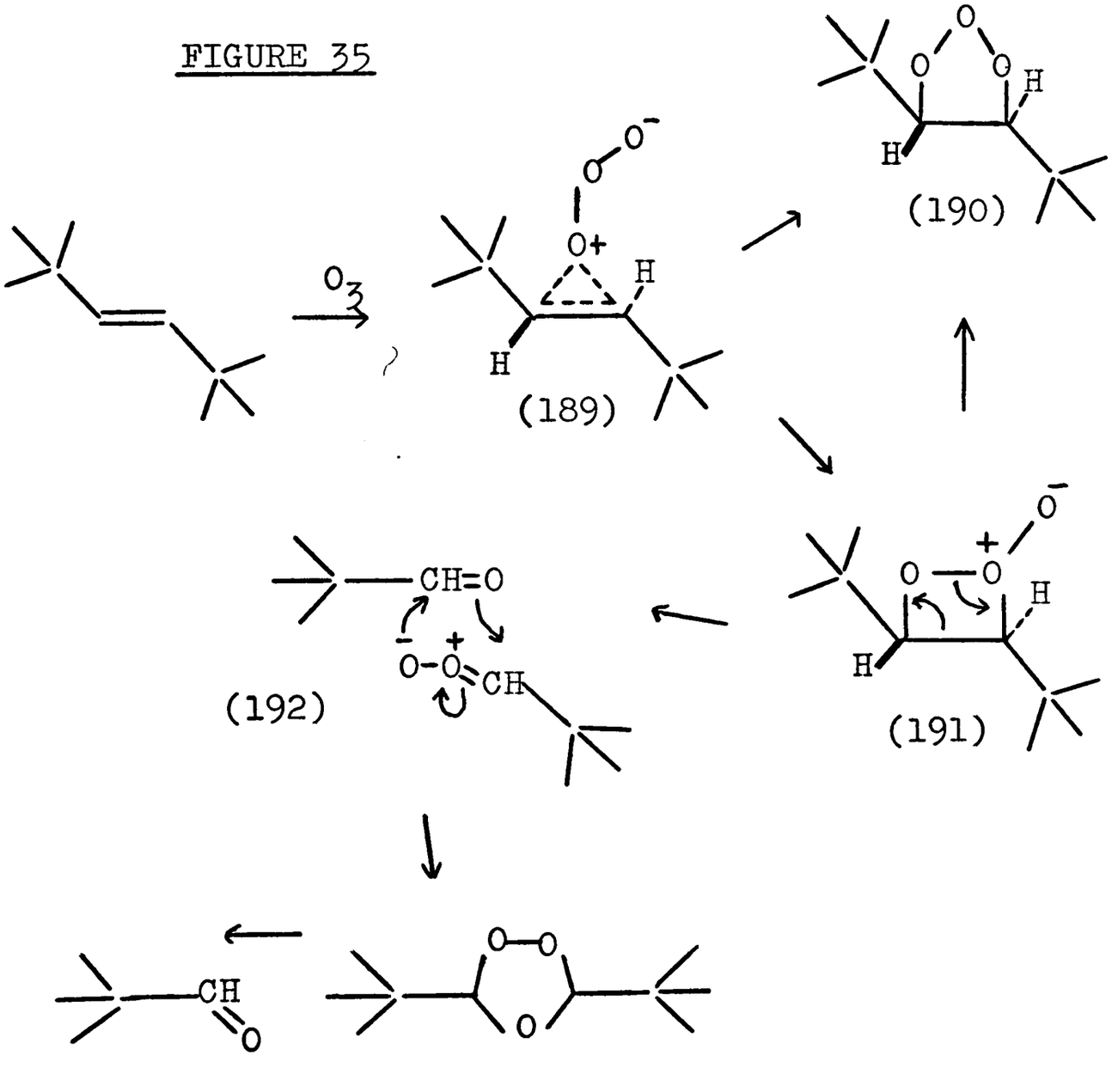
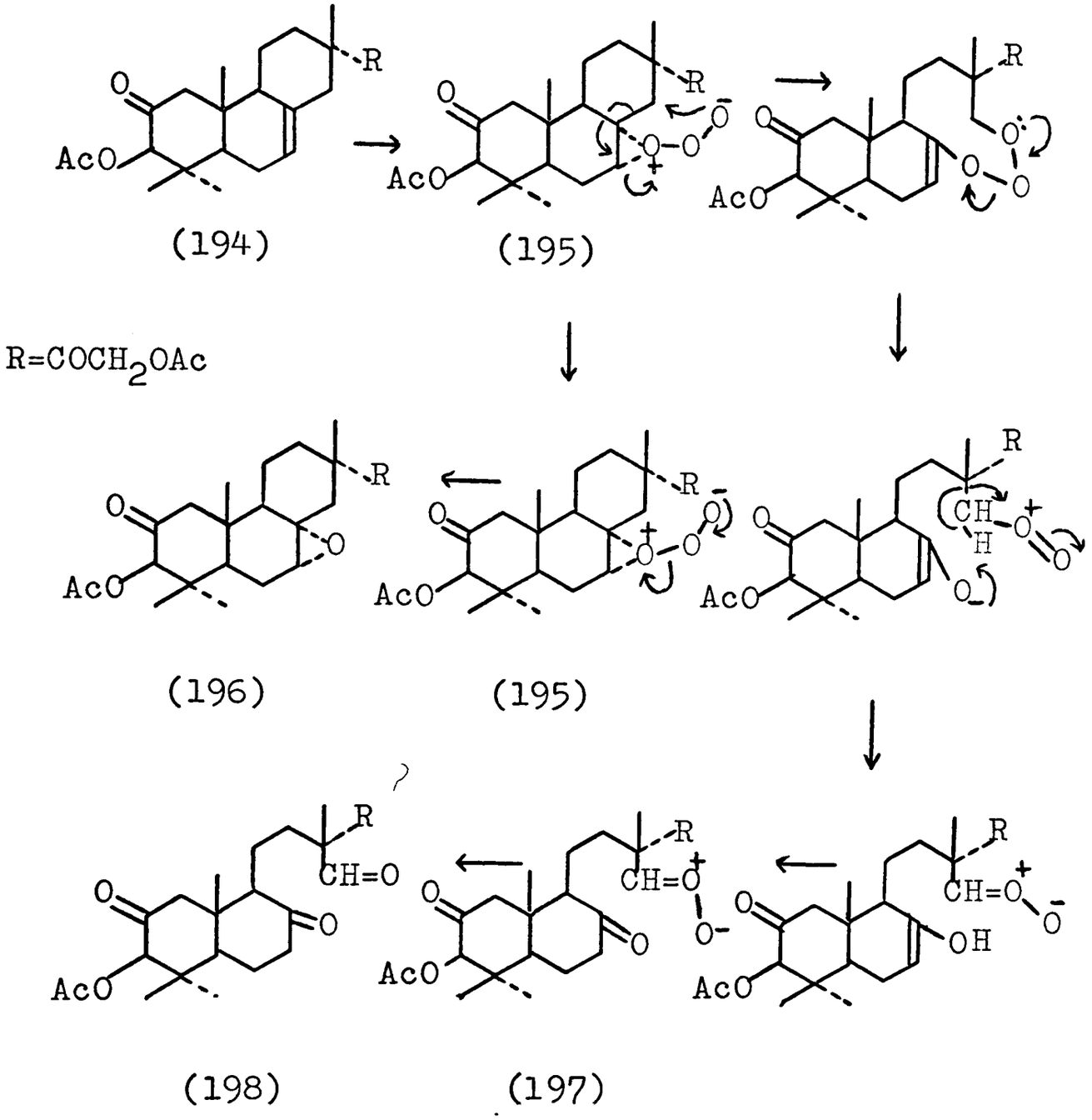


FIGURE 36



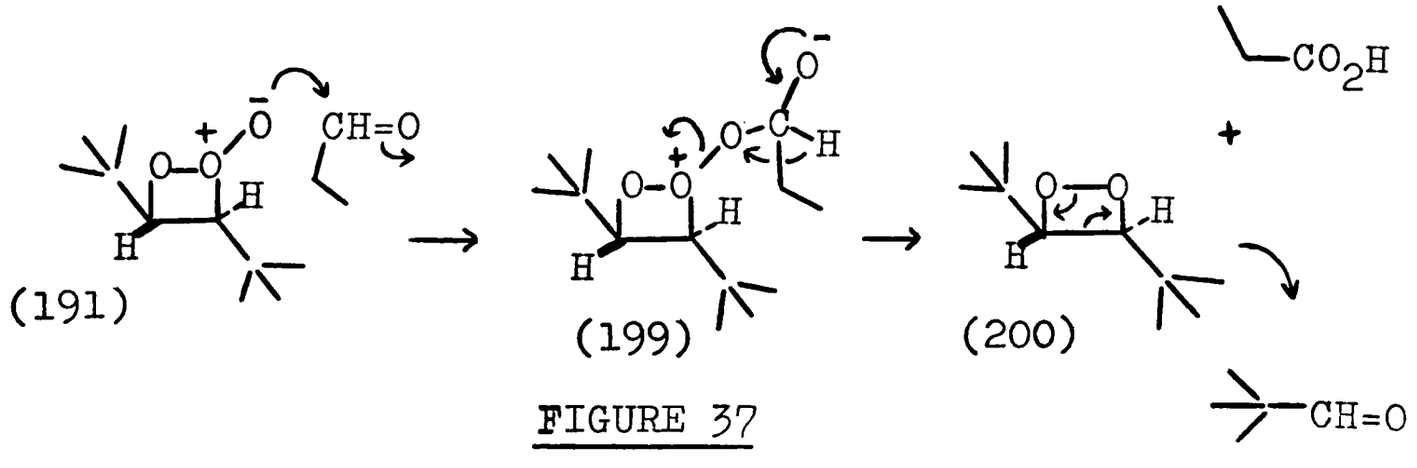


FIGURE 37

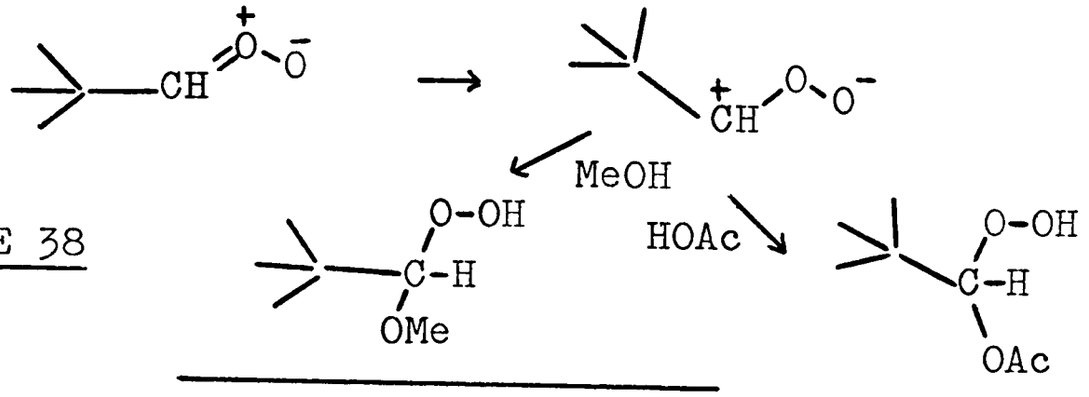


FIGURE 38

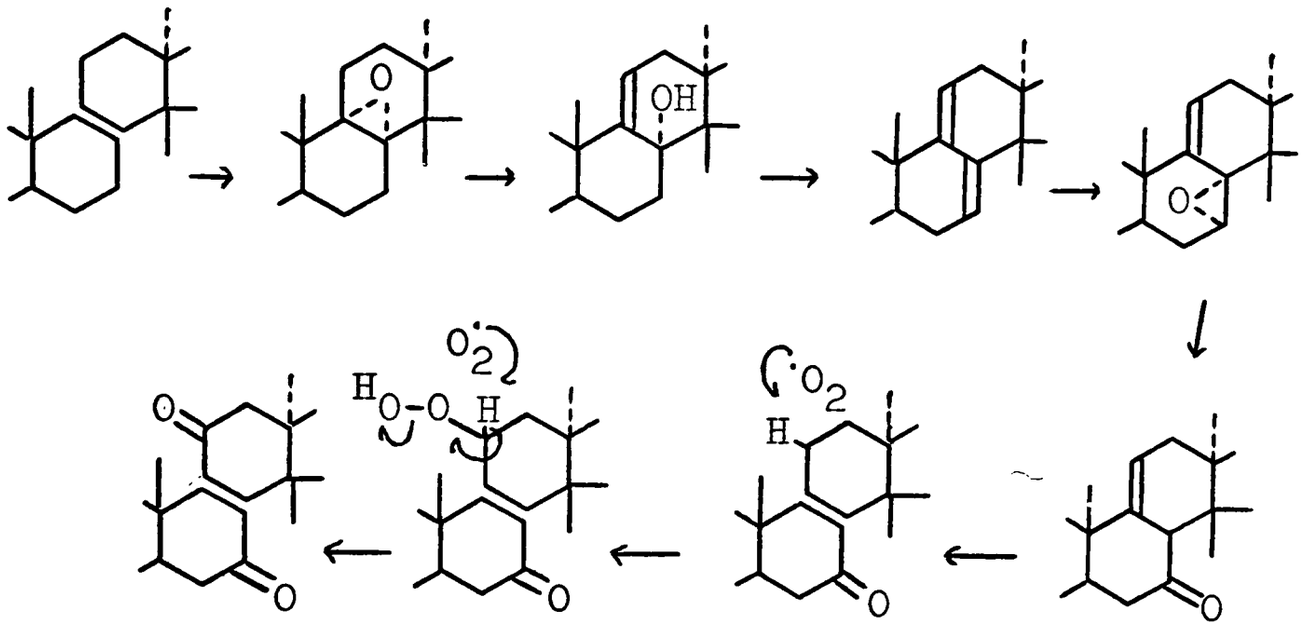


FIGURE 39

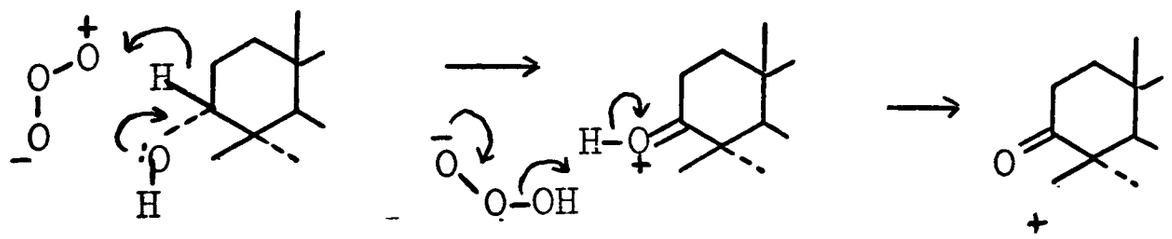
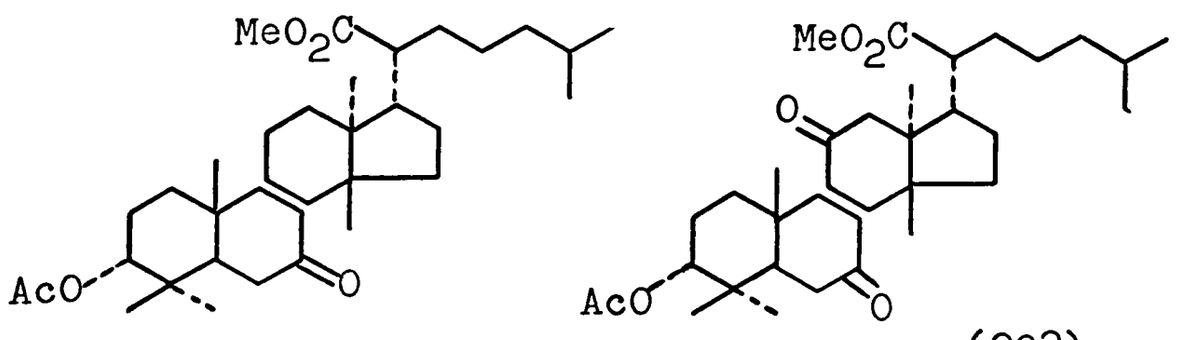


FIGURE 40



(201)

(202)

CHART 1

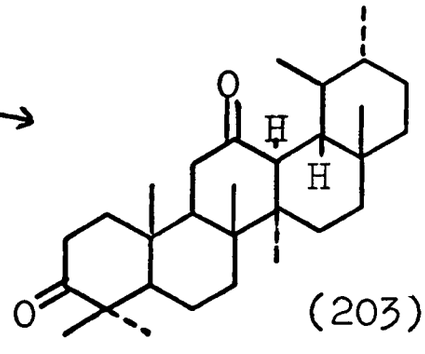
Ozonolysis product

↓

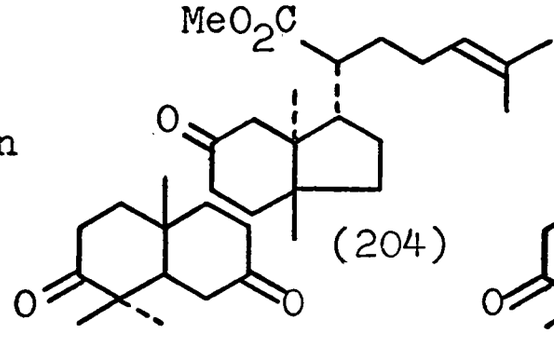
Reductive work-up

↓

Chromatography

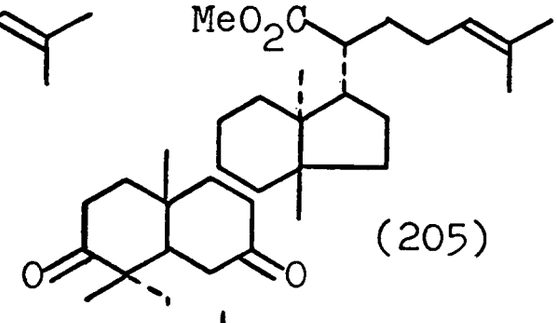
Fraction one → Rechromatography → Fraction 1/1 → Reaction with $BF_3.Et_2O$ → No reaction occurred → Chromatography → 

(203)

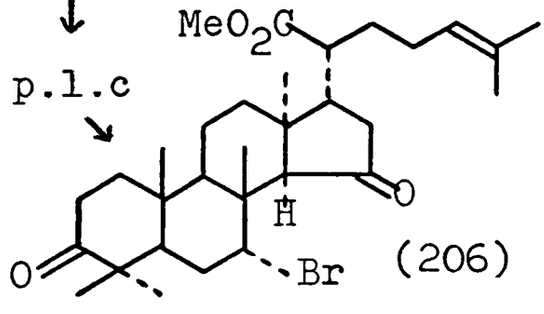
Fraction two → Fraction 1/2 → 

(204)

Fraction three → Not investigated

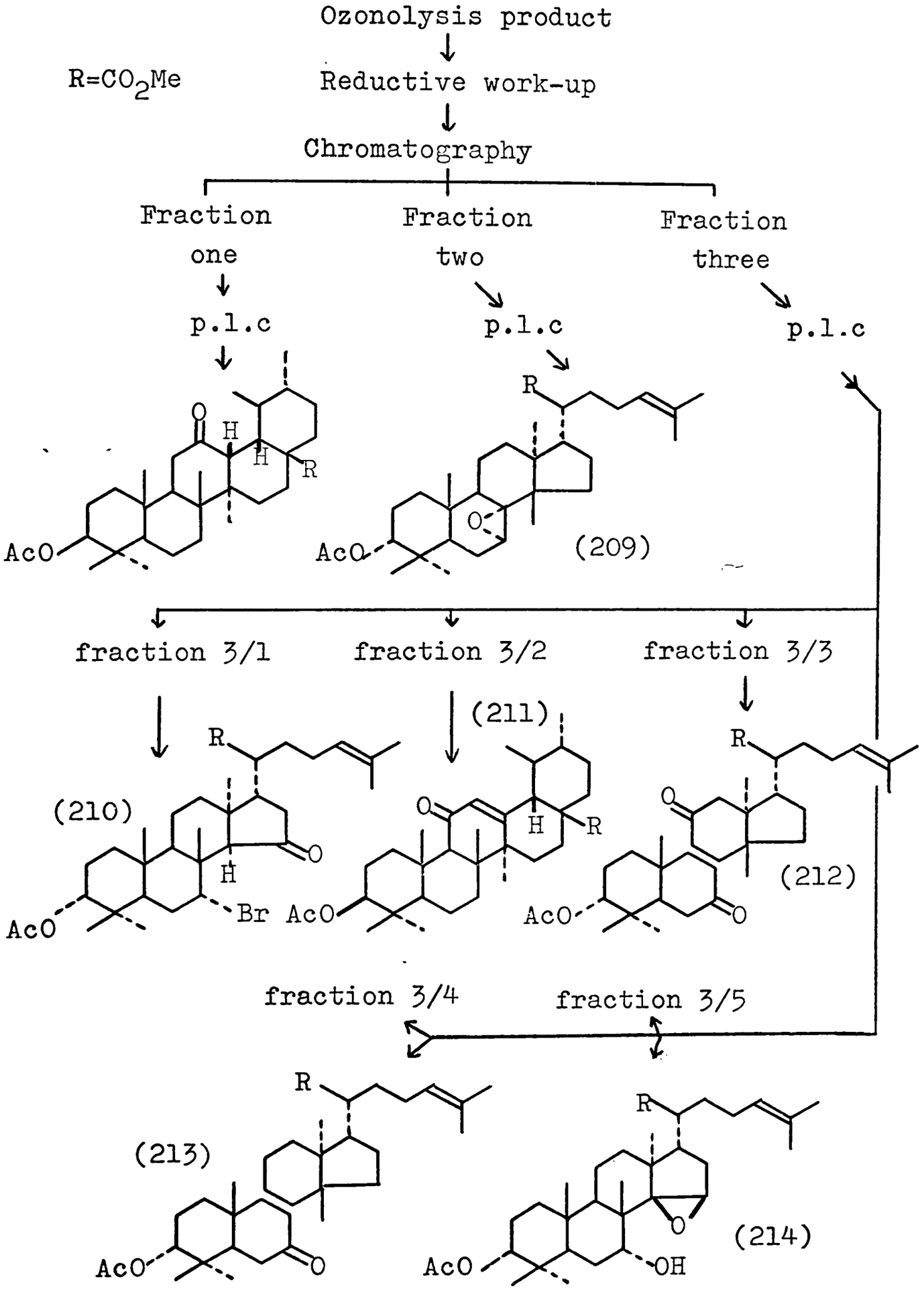
Fraction four → Fraction 1/3 → 

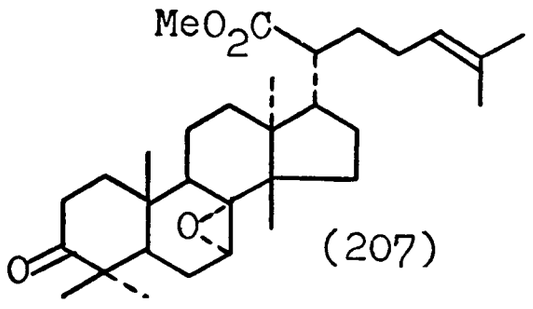
(205)

mostly by ~ t.l.c → From the mother liquors of crystallisation → p.l.c → 

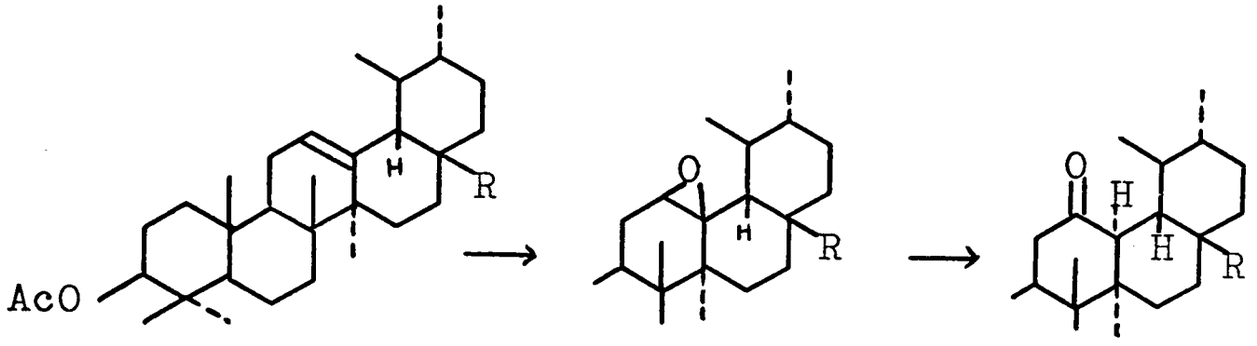
(206)

CHART 2

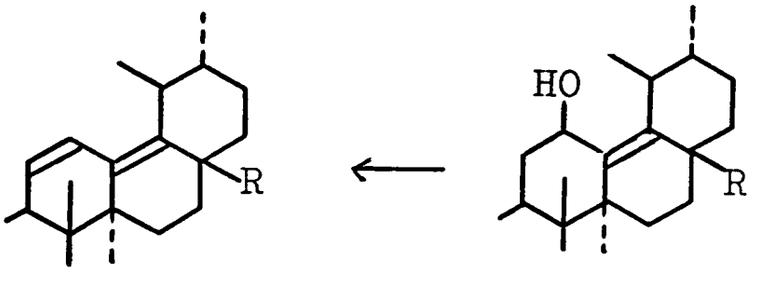

Ozonolysis product
R=CO2Me
Reductive work-up
Chromatography
Fraction one
Fraction two
Fraction three
p.l.c
p.l.c
p.l.c
AcO
(209)
fraction 3/1
fraction 3/2
fraction 3/3
(210)
(211)
(212)
Br
fraction 3/4
fraction 3/5
(213)
(214)
OH



(207)



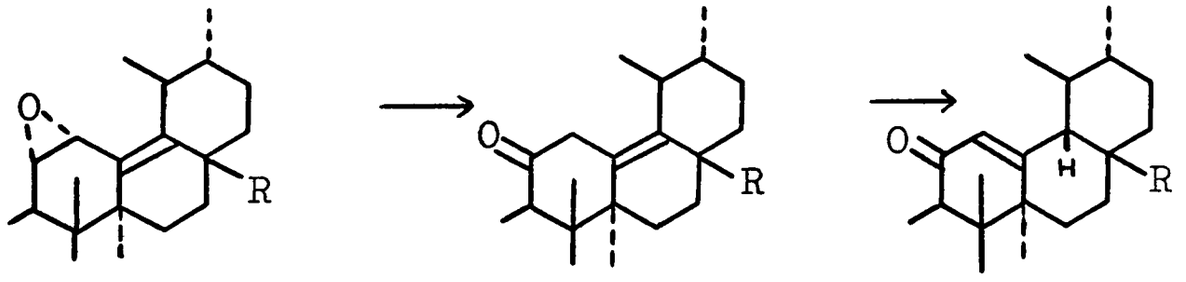
(215)



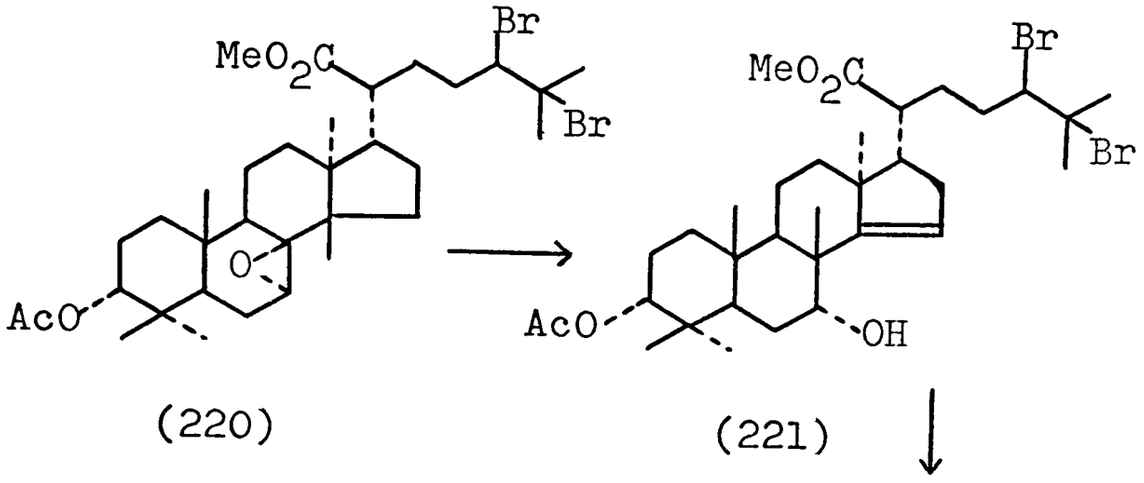
(217) (216)

$R=CO_2Me$

FIGURE 41

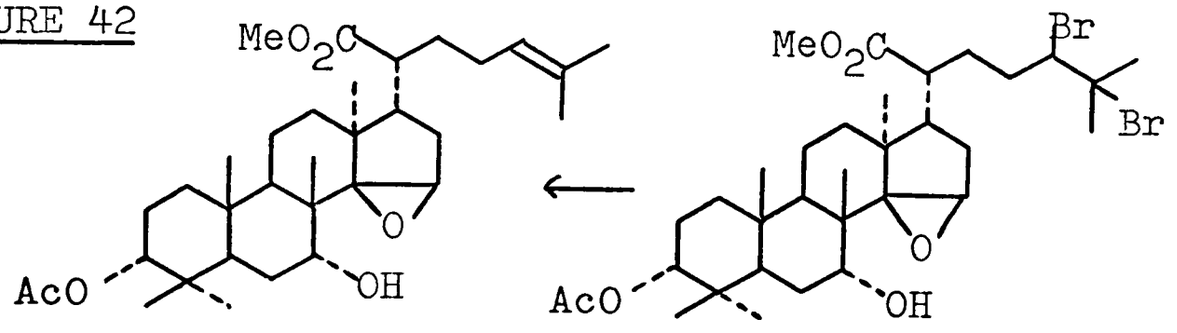


(218) (219) (211)

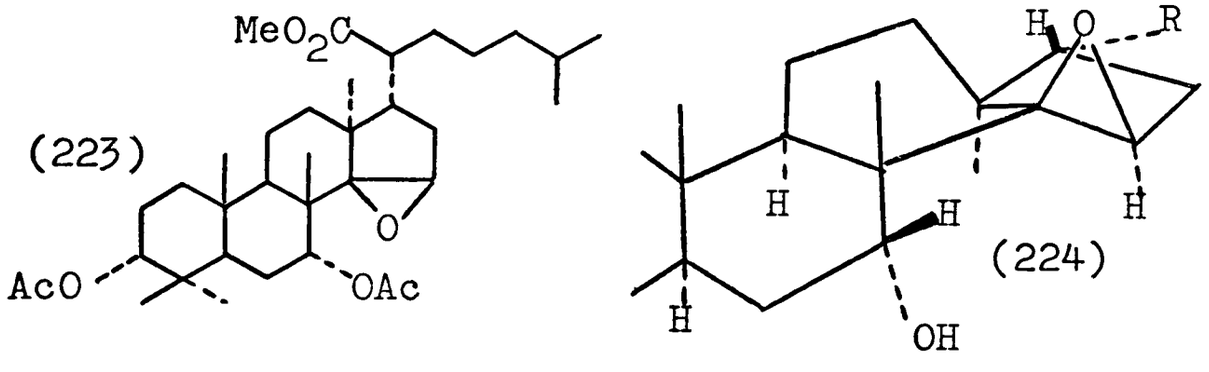


(220) (221)

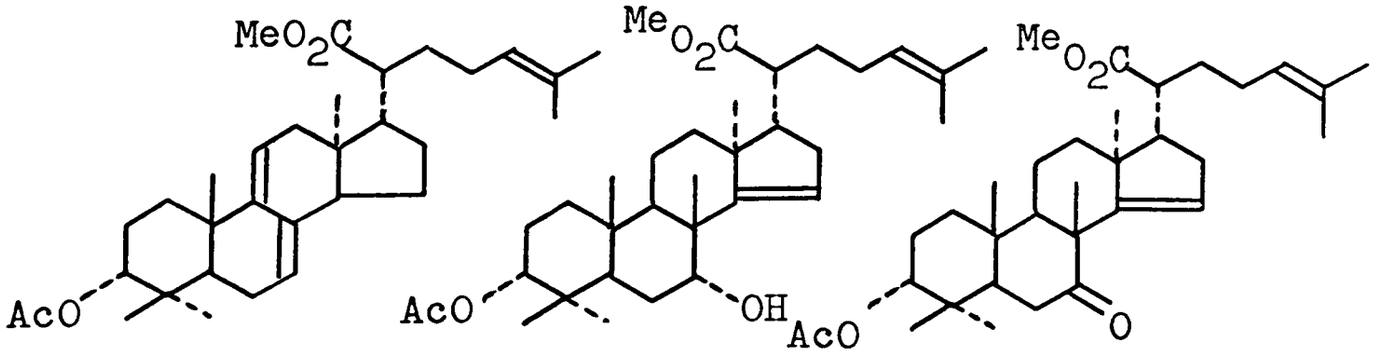
FIGURE 42



(214) (222)



(224)



(225) (226) (227)

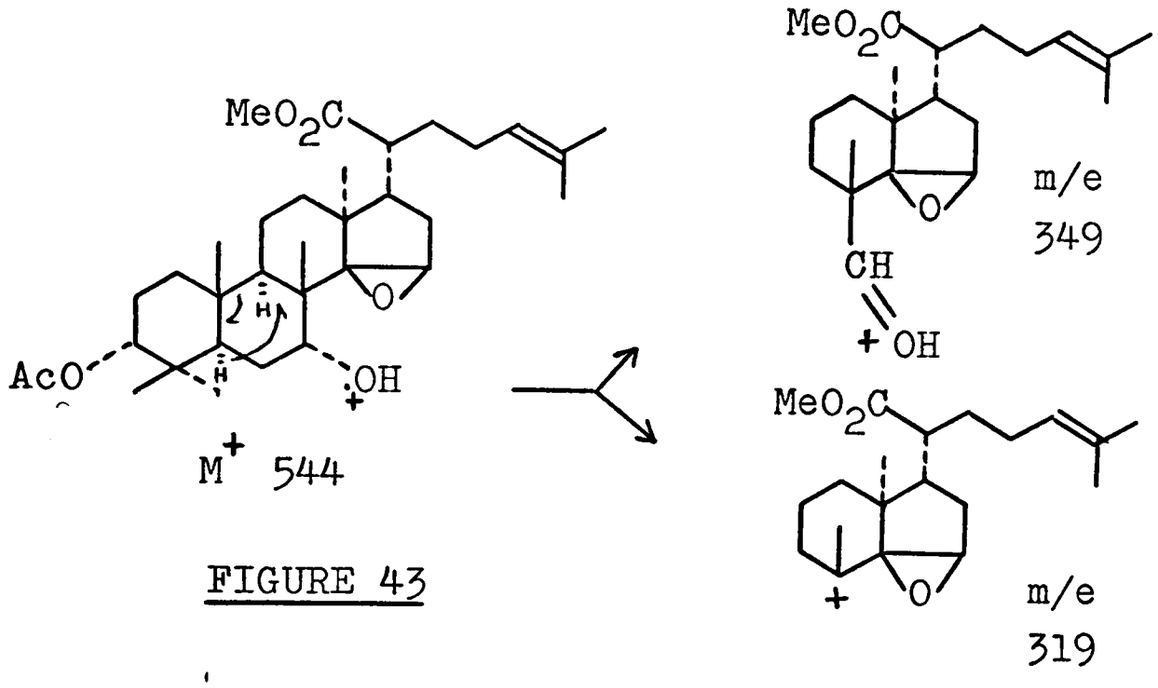
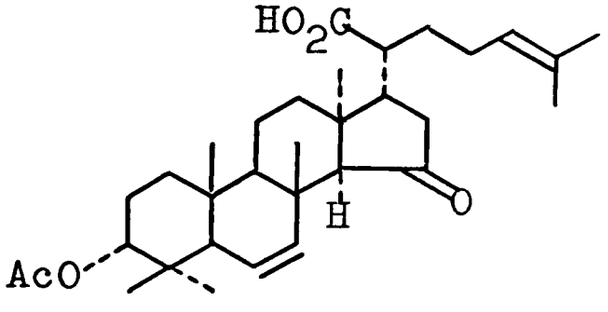
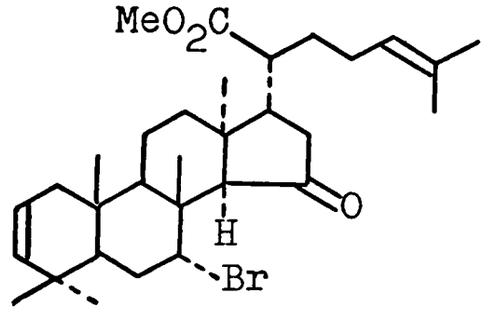


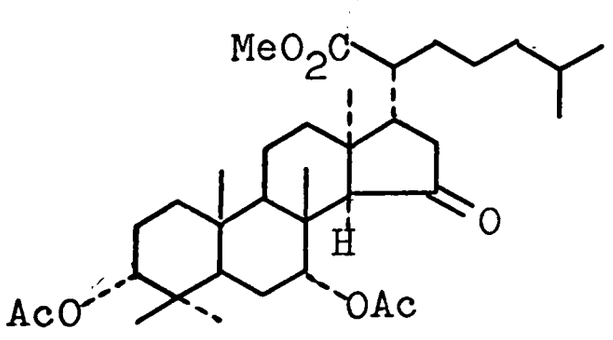
FIGURE 43



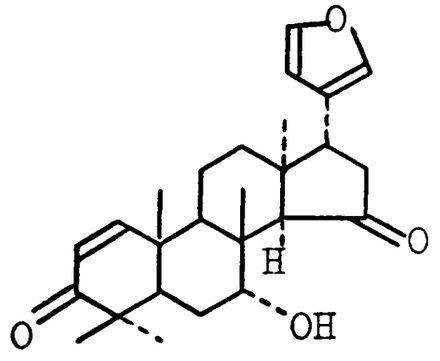
(228)



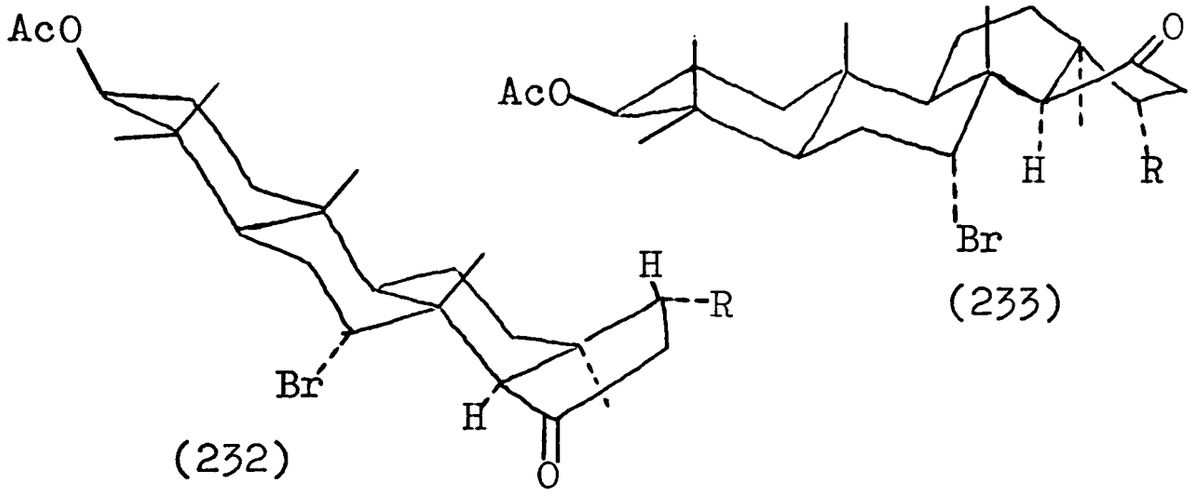
(229)



(231)



(230)



Diketone
(206)

M^+ 563 → 483 M-Br

→ 482 M-HBr

Acetate
(210)

M^+ 607 → 527 M-Br

→ 526 M-HBr

→ 467 M-(HBr + MeOC(=O))

→ 466 M-(HBr + HOAc)

→ 452 M-(HBr + MeOC(=O) + Me)

→ 451 M-(HBr + HOAc + Me)

FIGURE 44

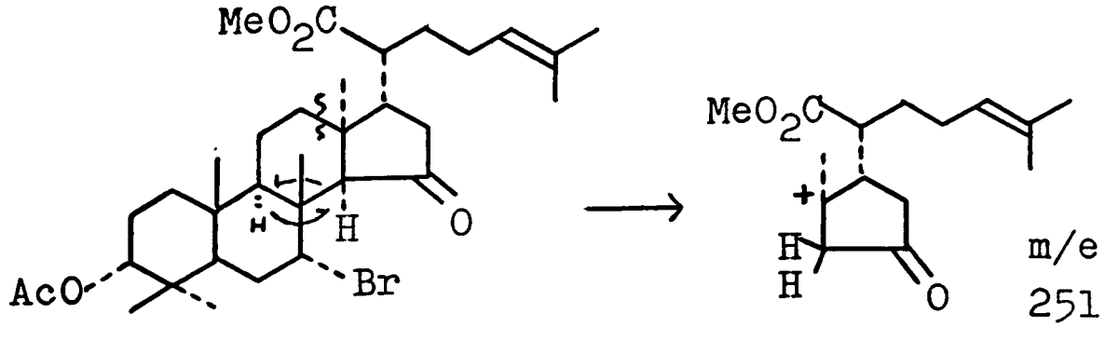


FIGURE 45

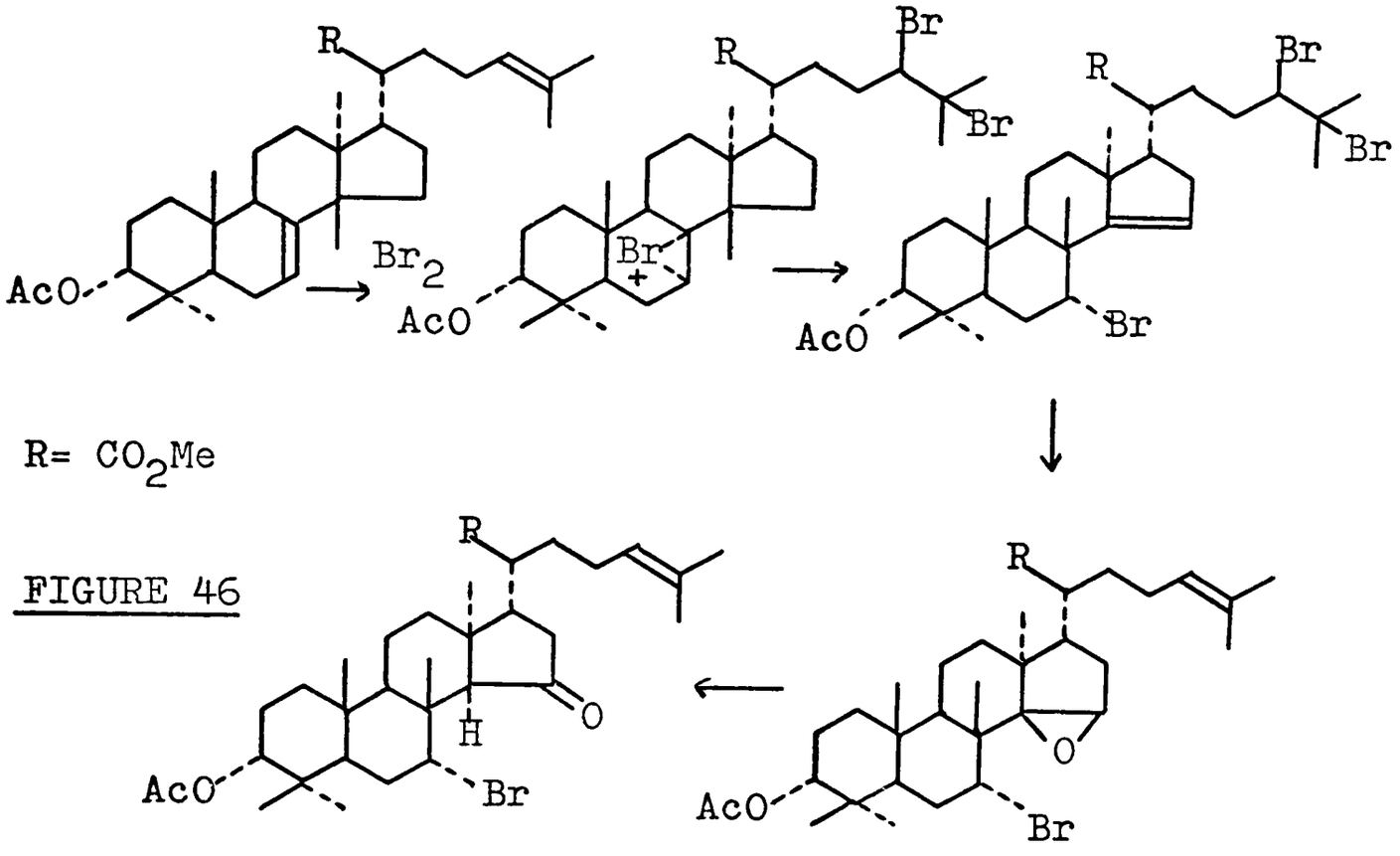


FIGURE 46

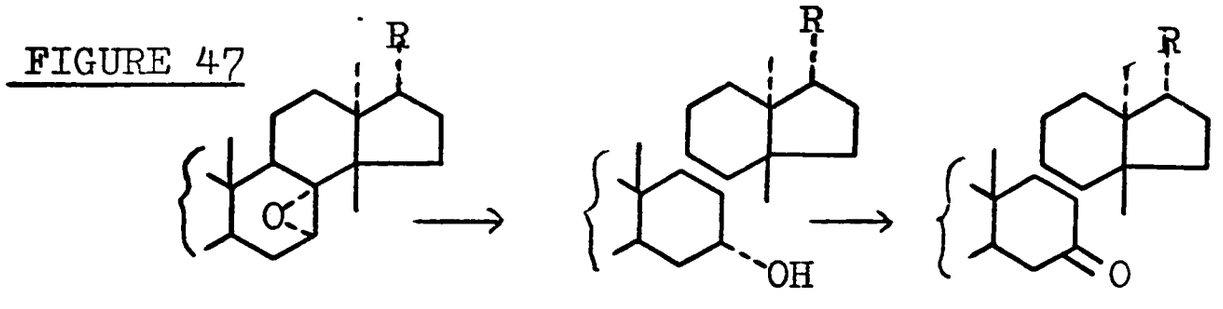
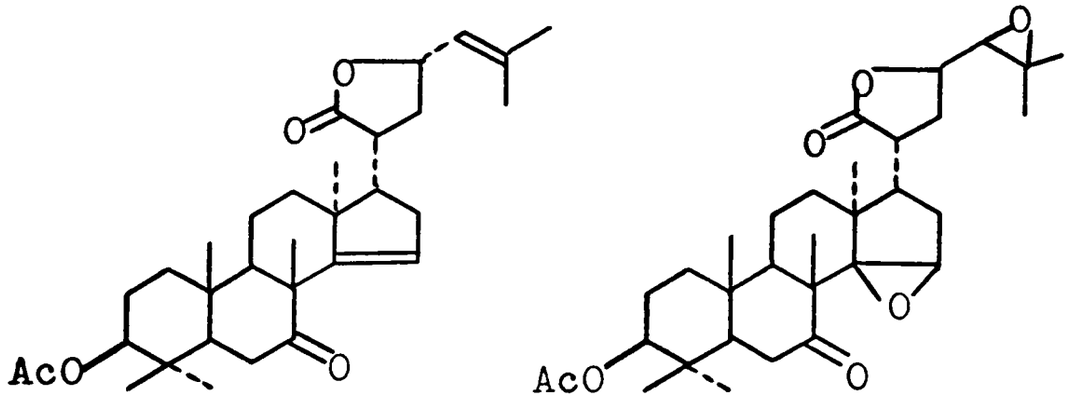
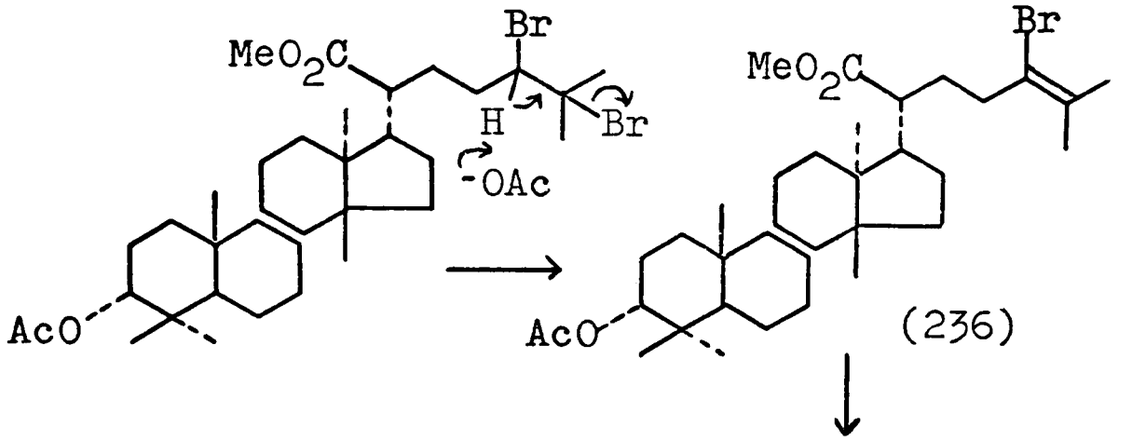


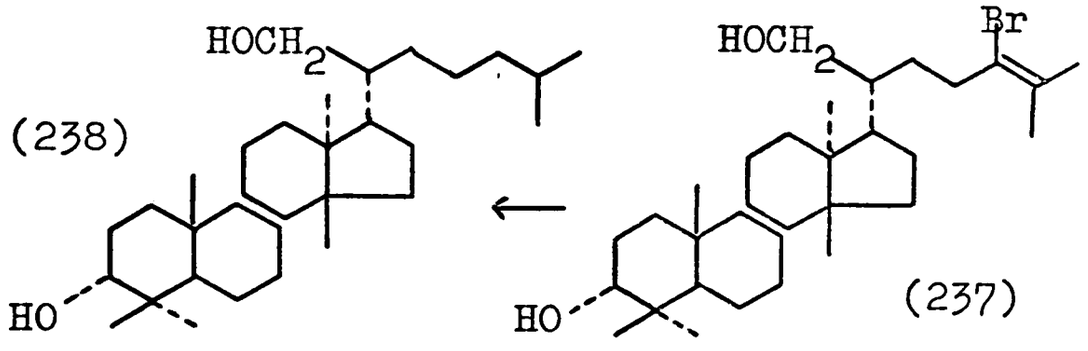
FIGURE 47



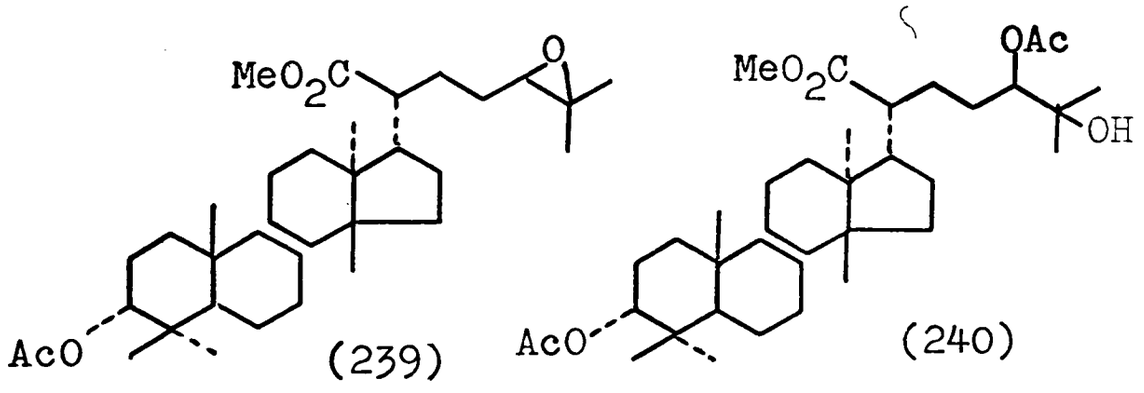
(234) (235)



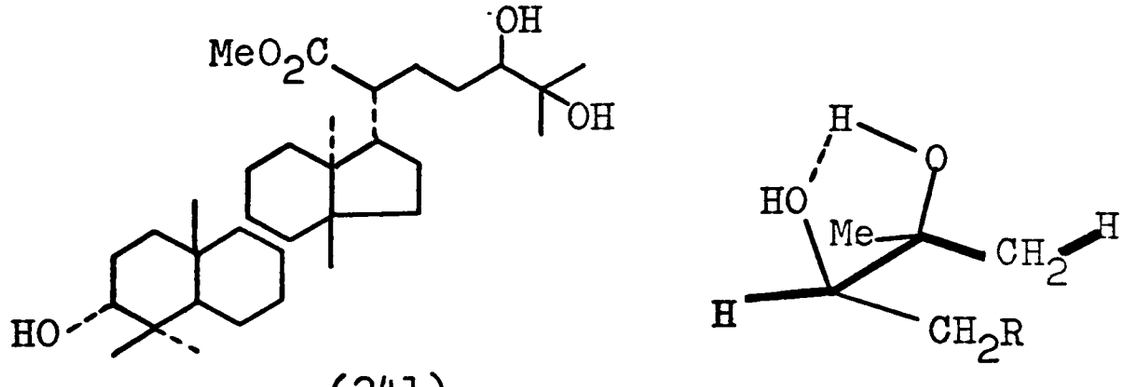
(236)



(237)

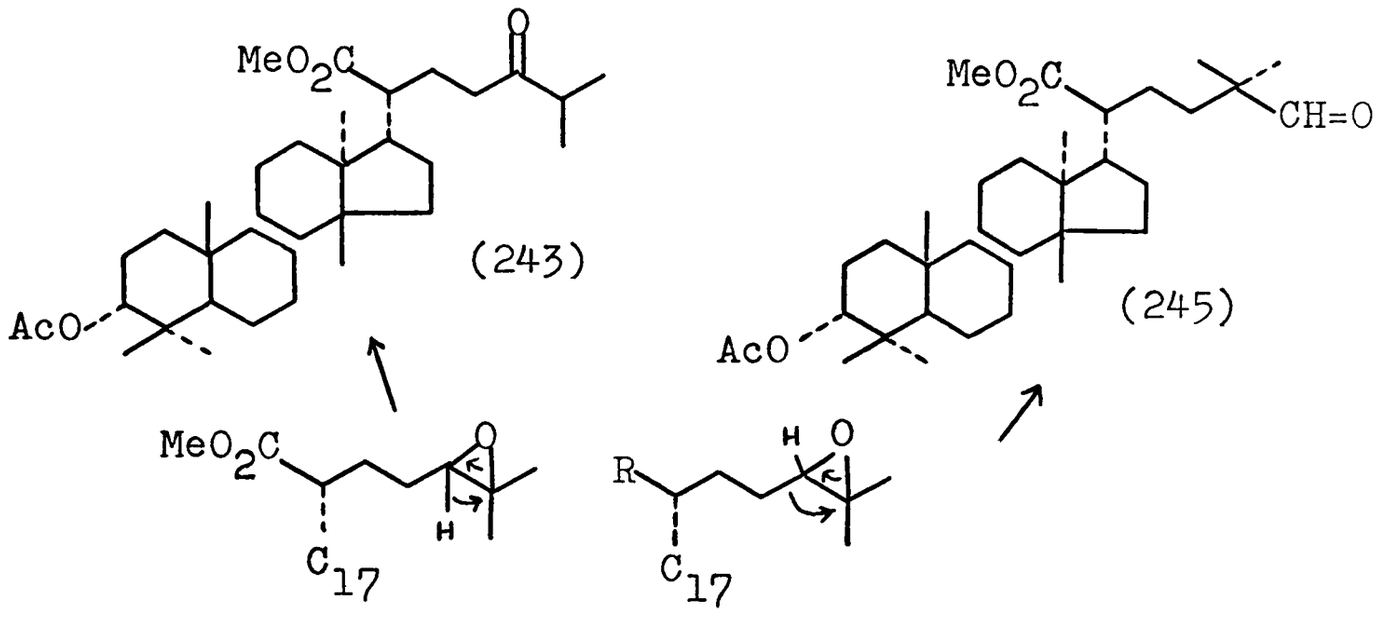


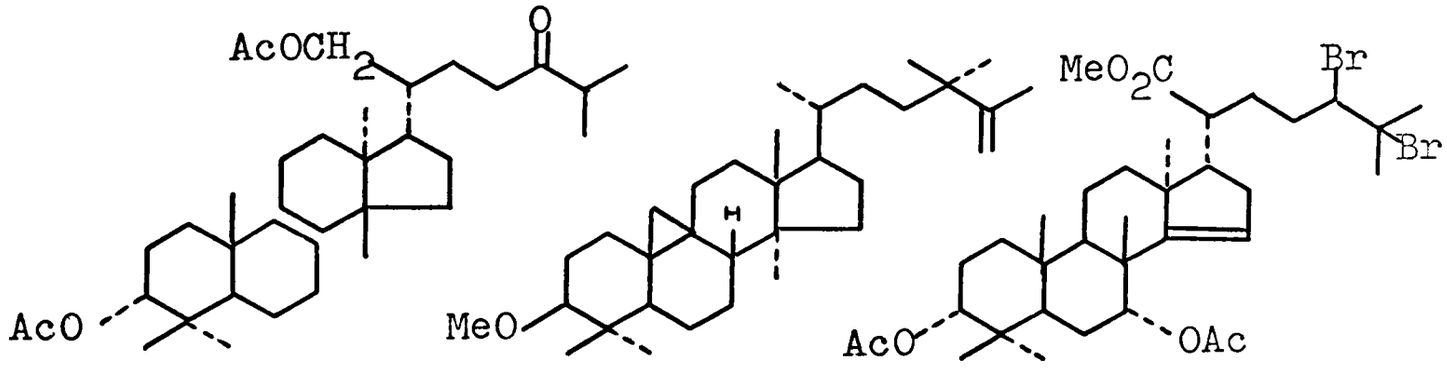
(239) (240)



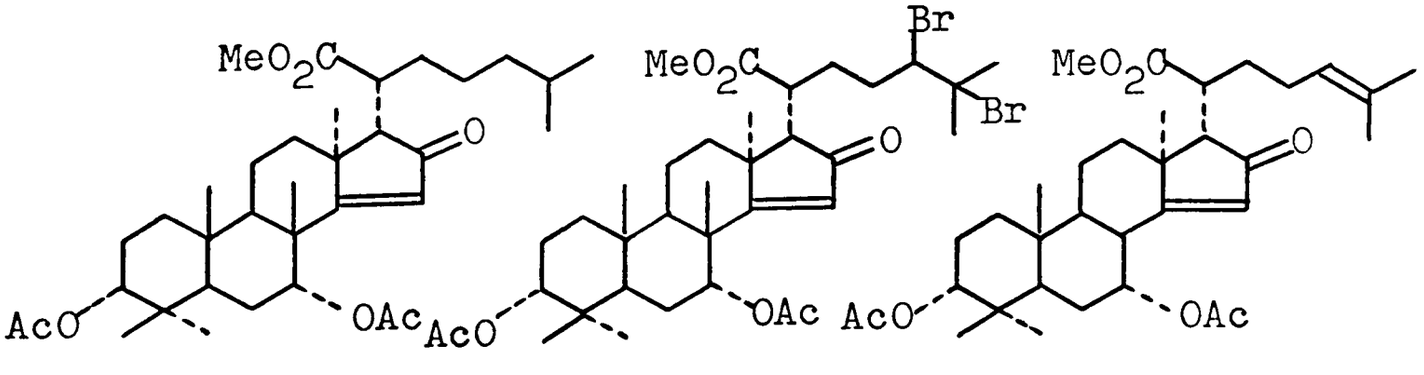
(241) (242)

FIGURE 48



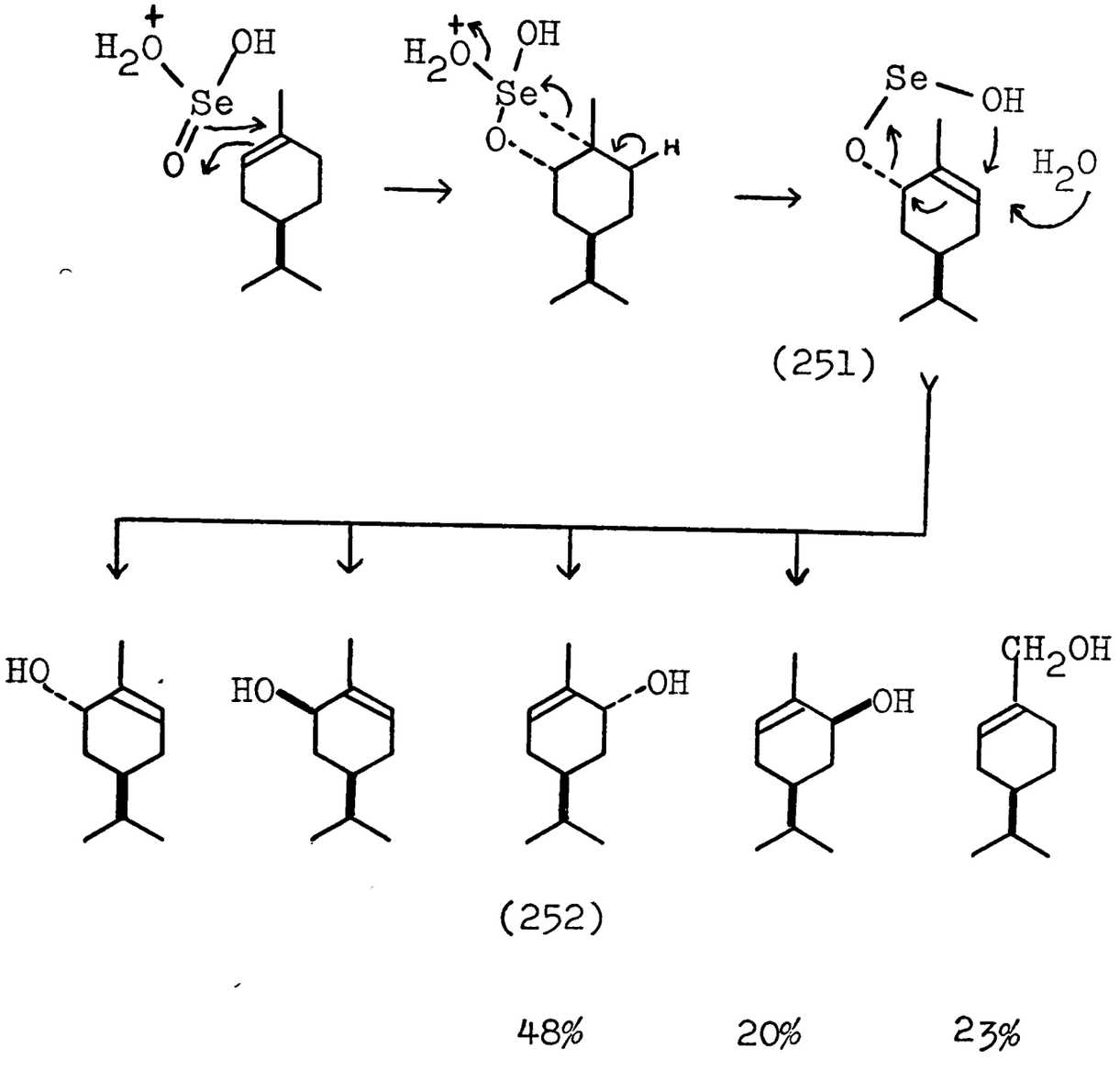


(244) (246) (247)



(248) (249) (250)

FIGURE 49



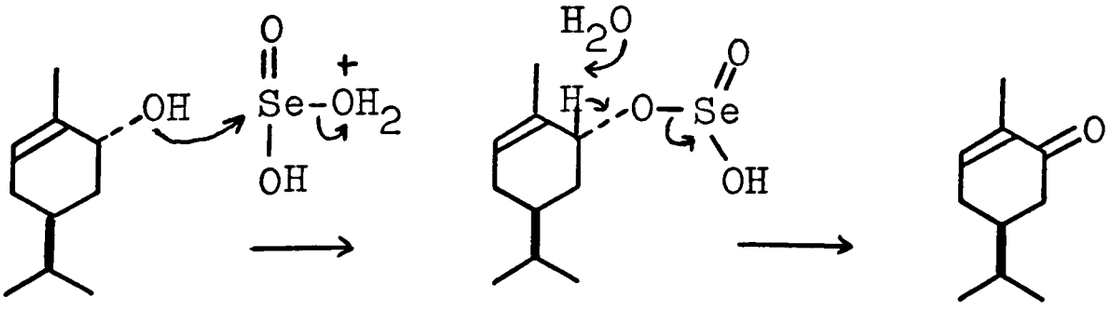
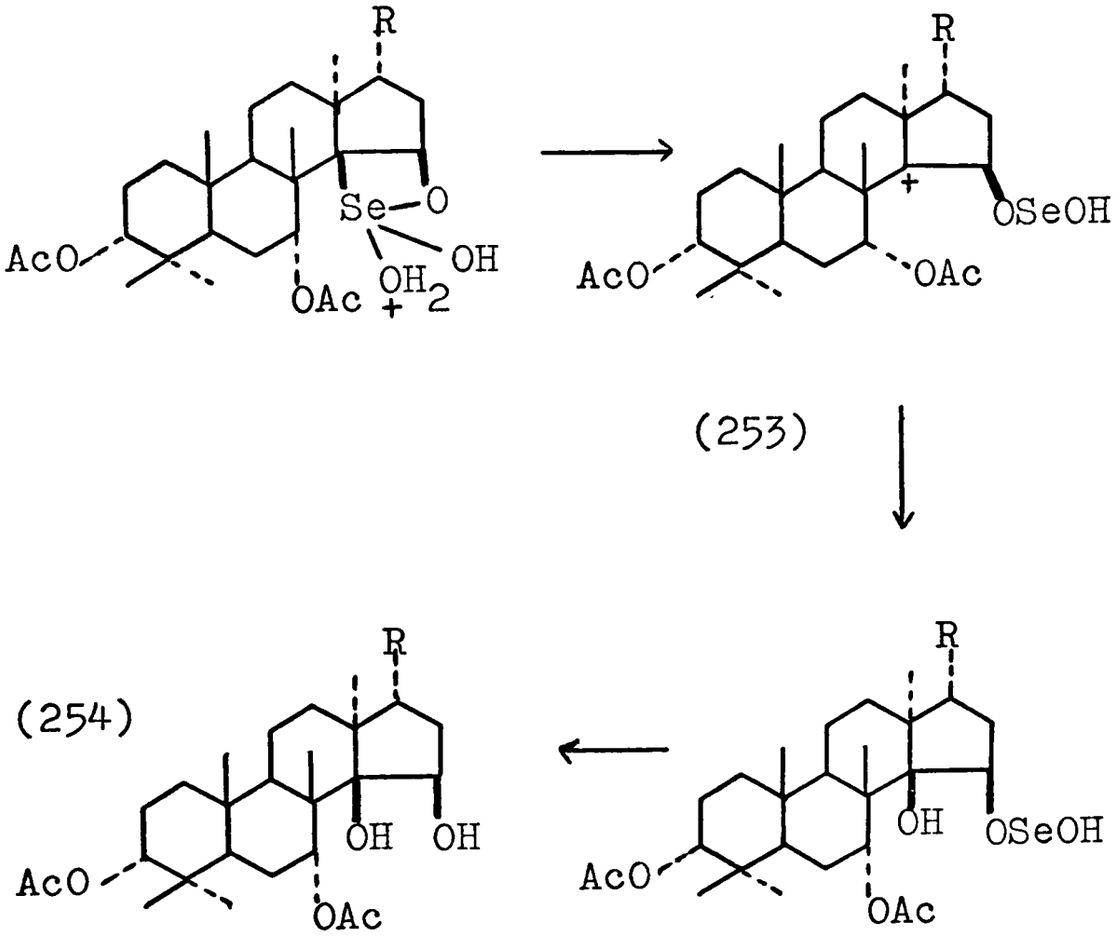


FIGURE 50

FIGURE 51


R
Se—O
AcO
OH
OAc
OH2
+
OSeOH
(253)
(254)
OH
OAc

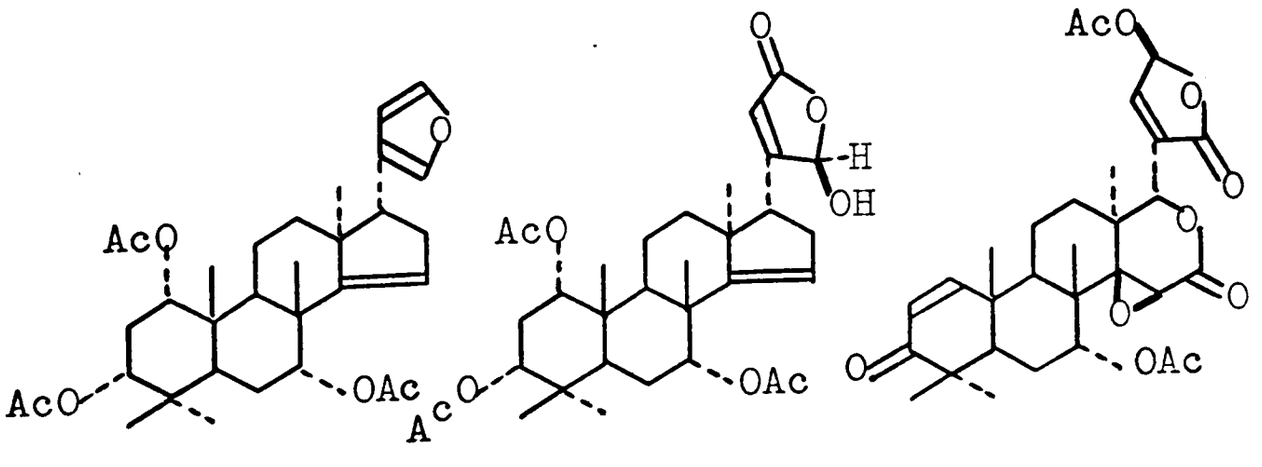
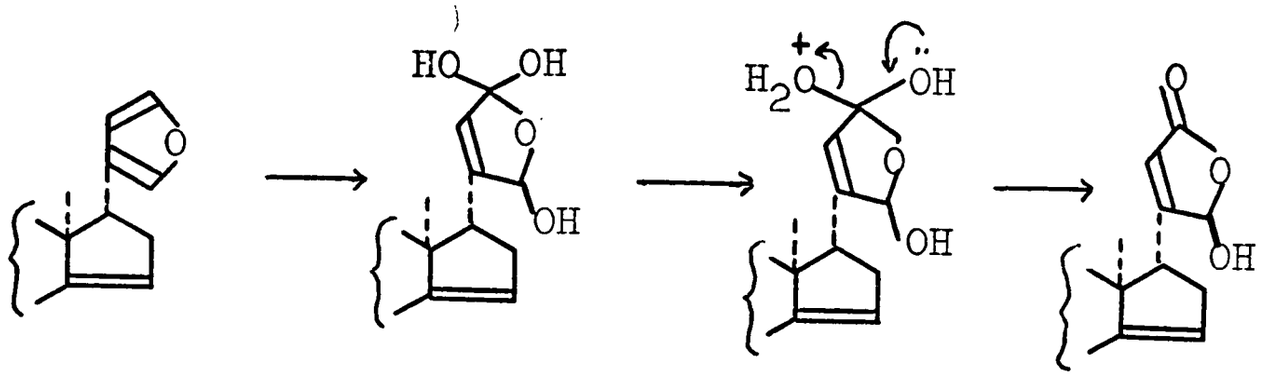

AcO
OAc
O
H
OH
(255)
(256)
(257)

FIGURE 52



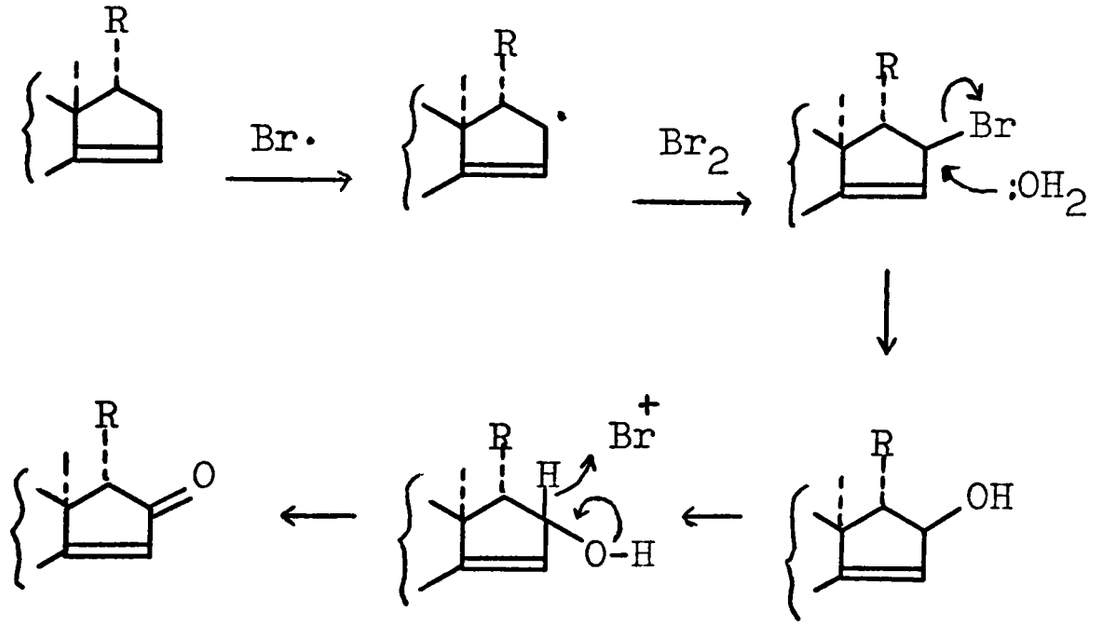


FIGURE 53

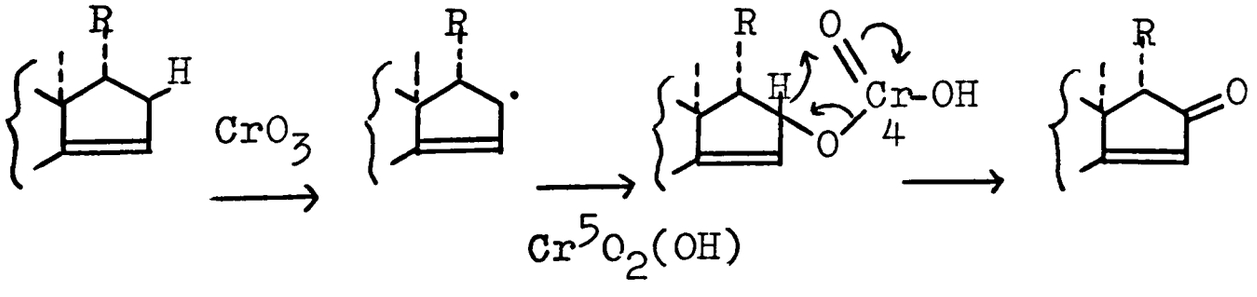


FIGURE 54

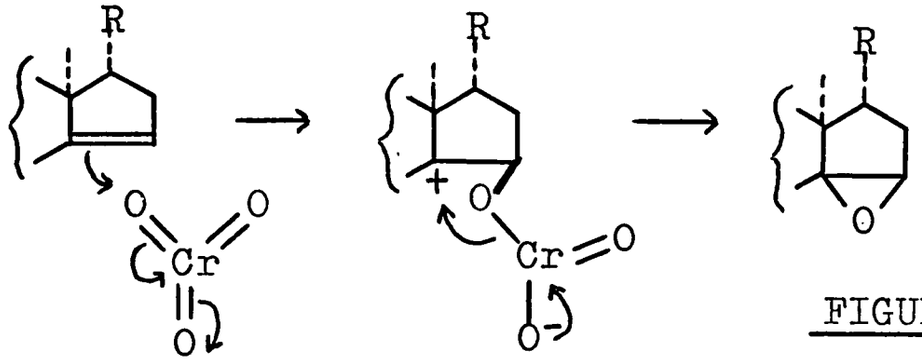
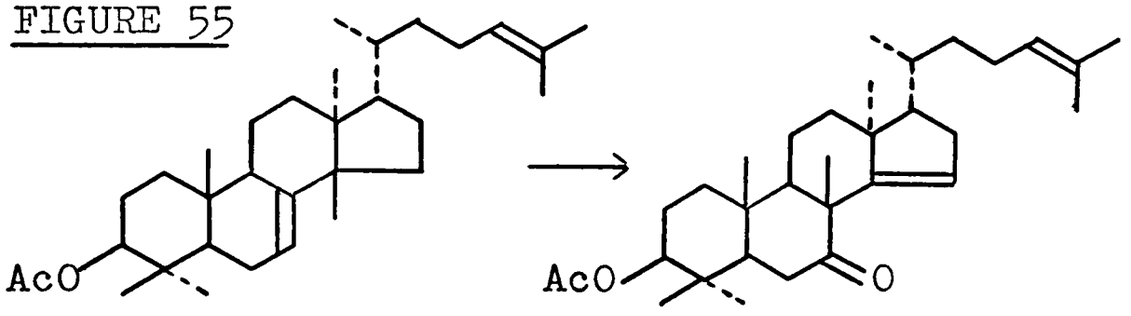
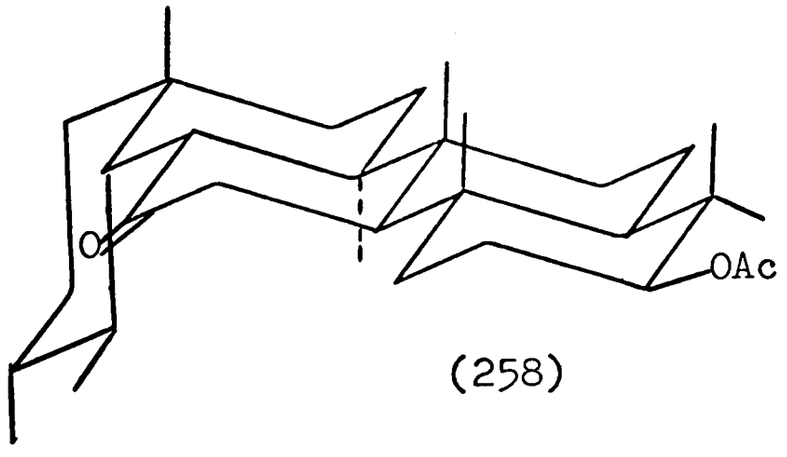


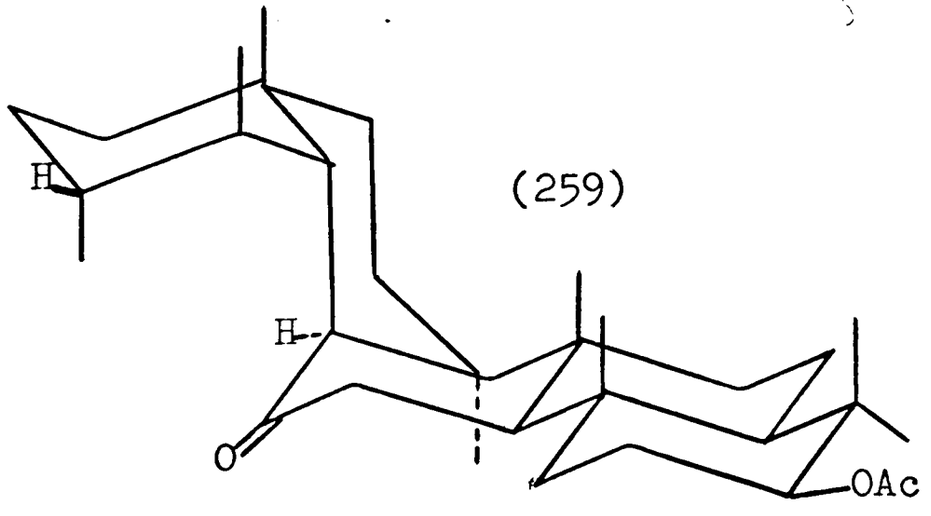
FIGURE 56

FIGURE 55

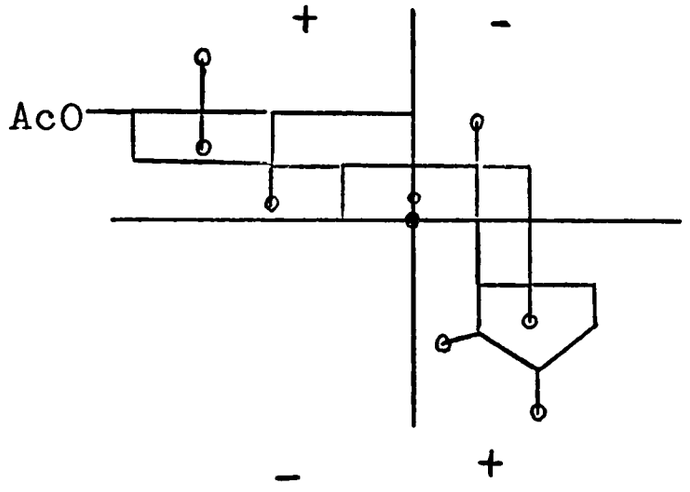




(258)

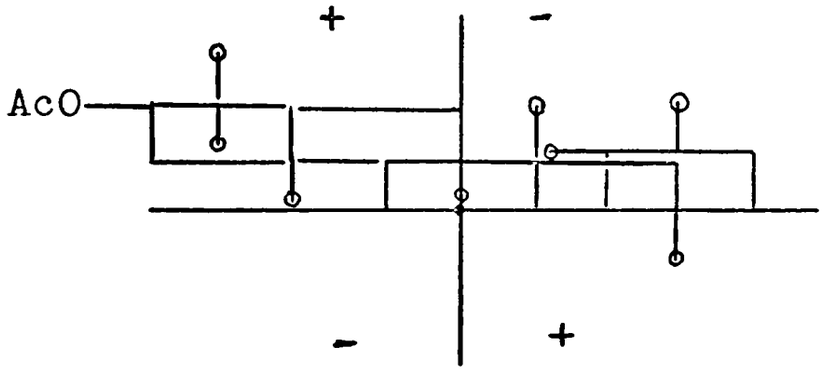


(259)

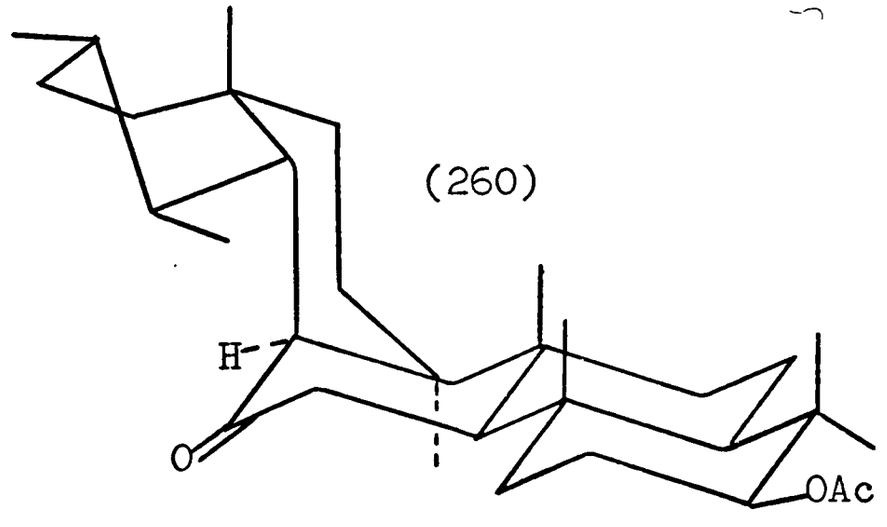


13αH-12-ketone.

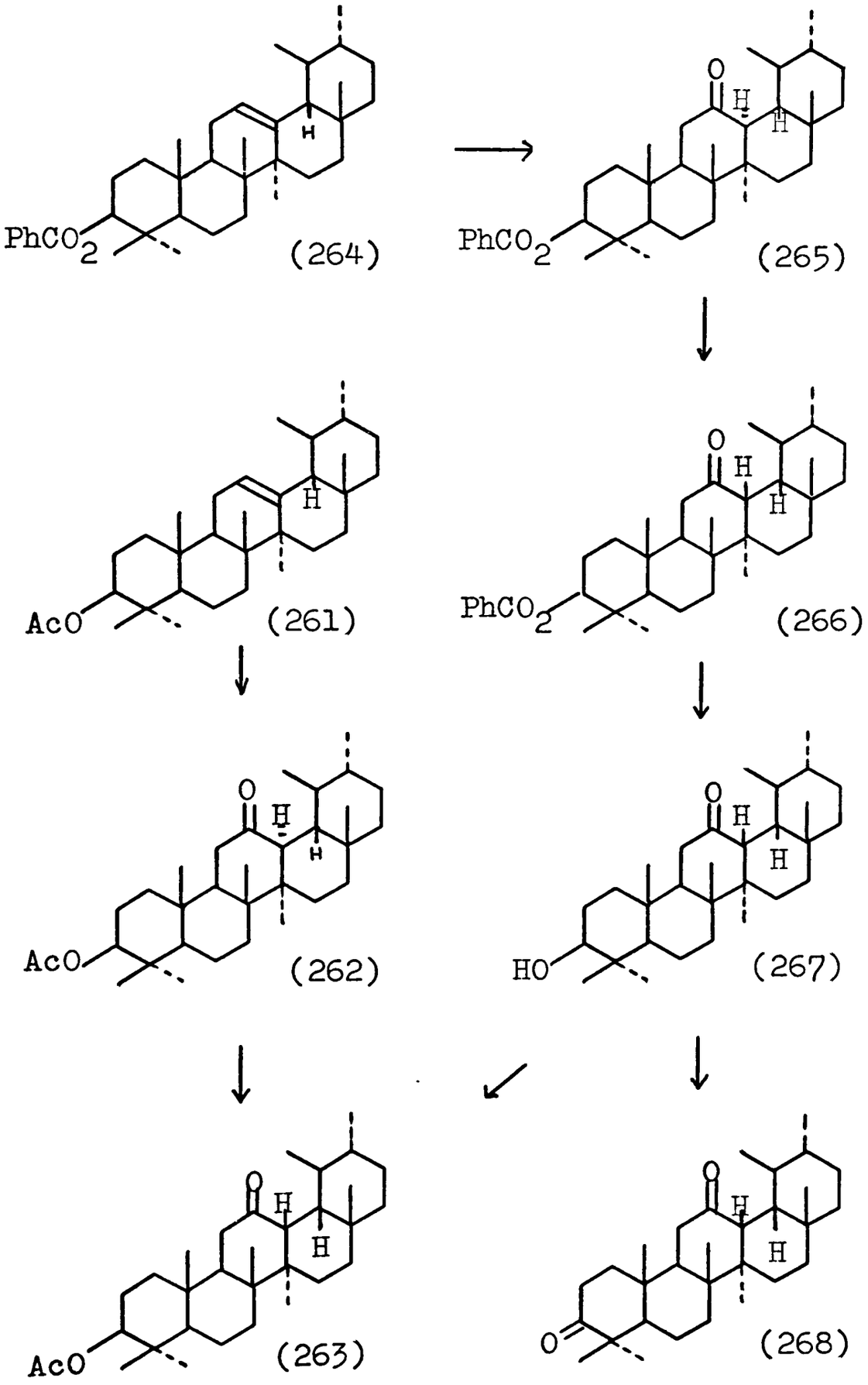
FIGURE 58

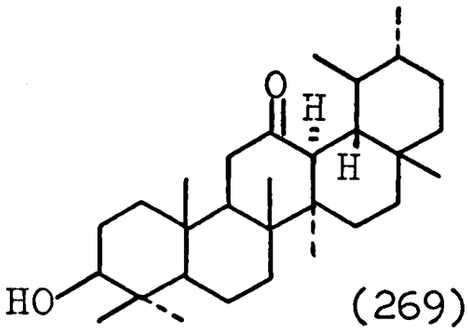


13βH-12-ketone

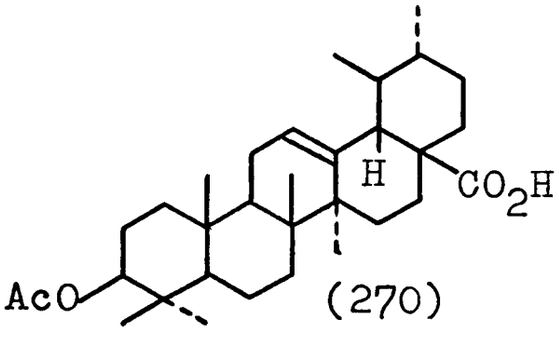


(260)

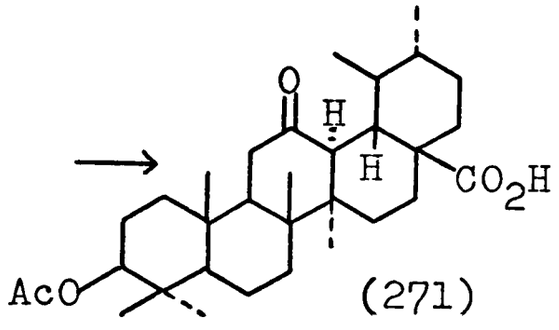

PhCO2
(264)
(265)
AcO
(261)
(266)
(262)
HO
(267)
AcO
(263)
(268)



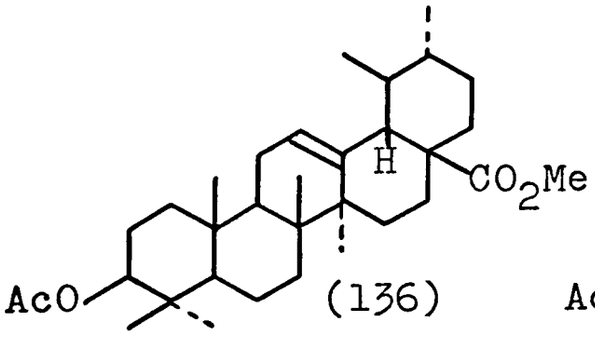
(269)



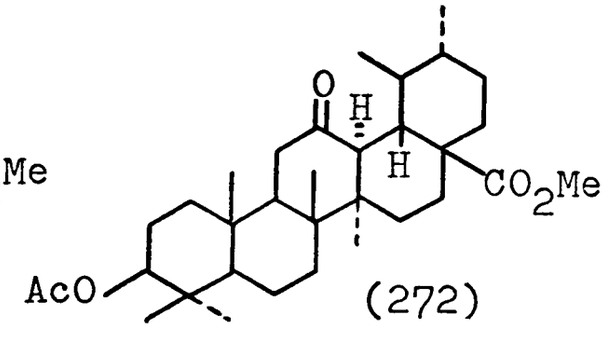
(270)



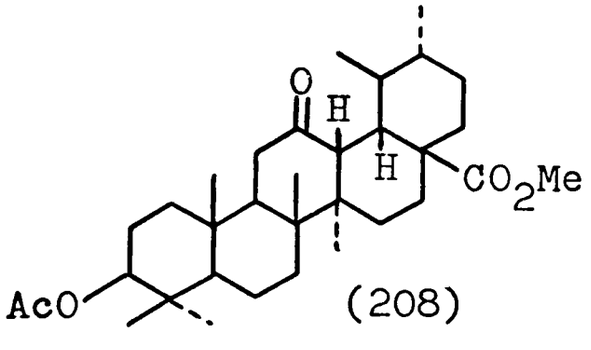
(271)



(136)



(272)



(208)

FIGURE 59

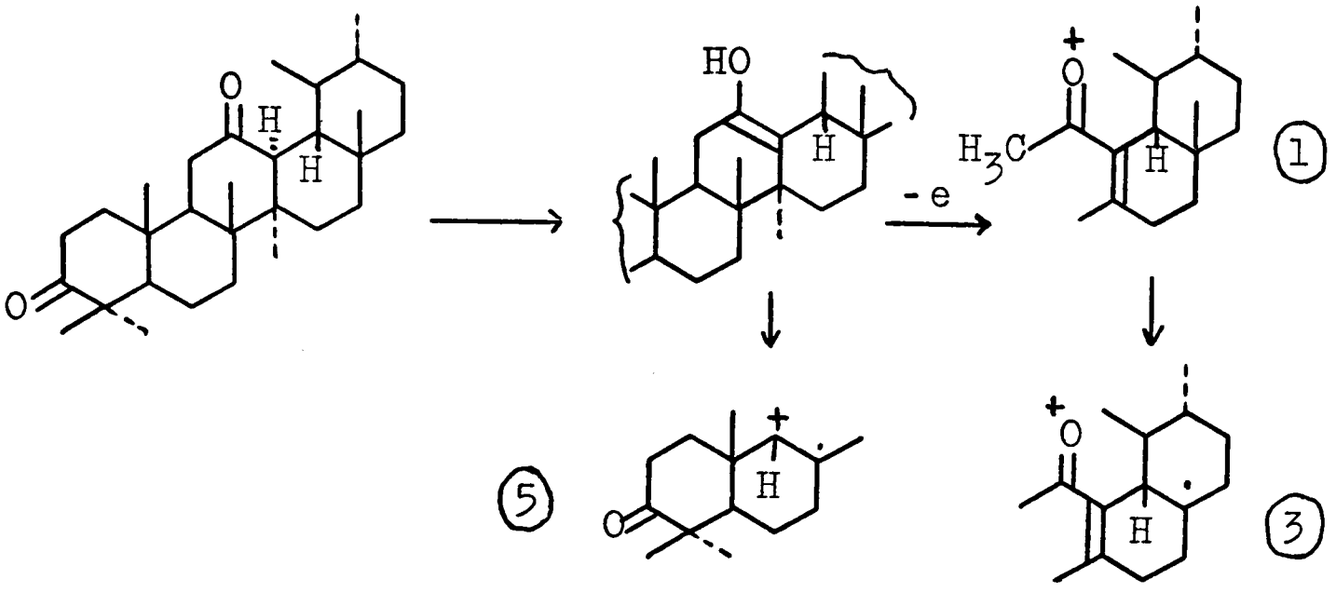


FIGURE 60

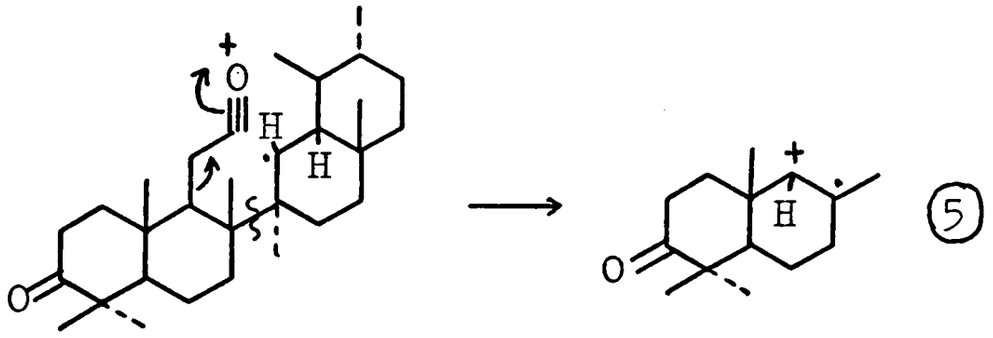


FIGURE 61

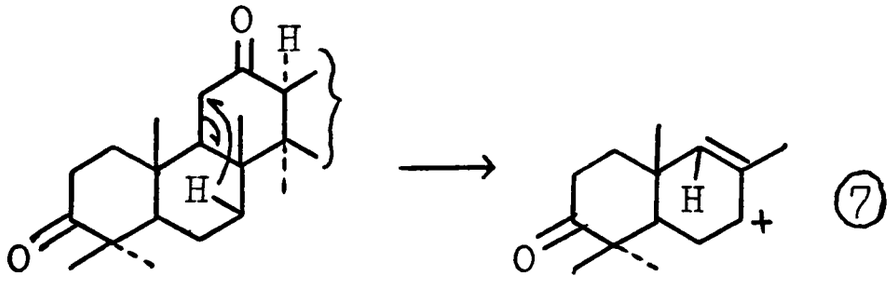


FIGURE 62

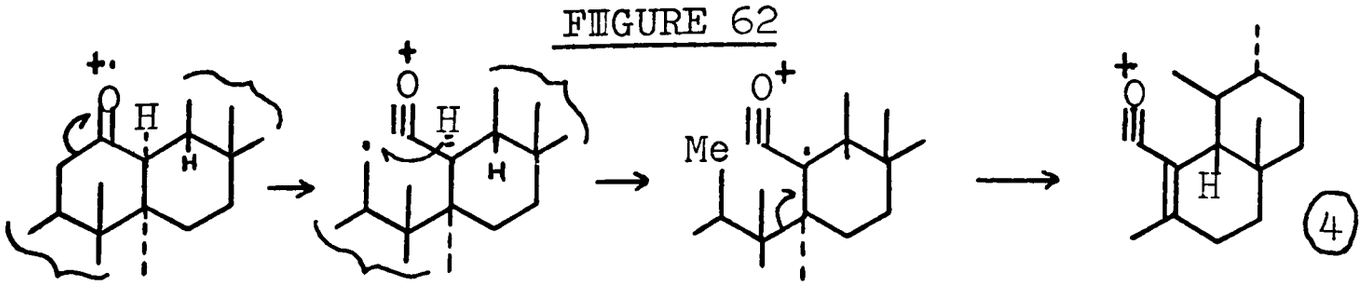
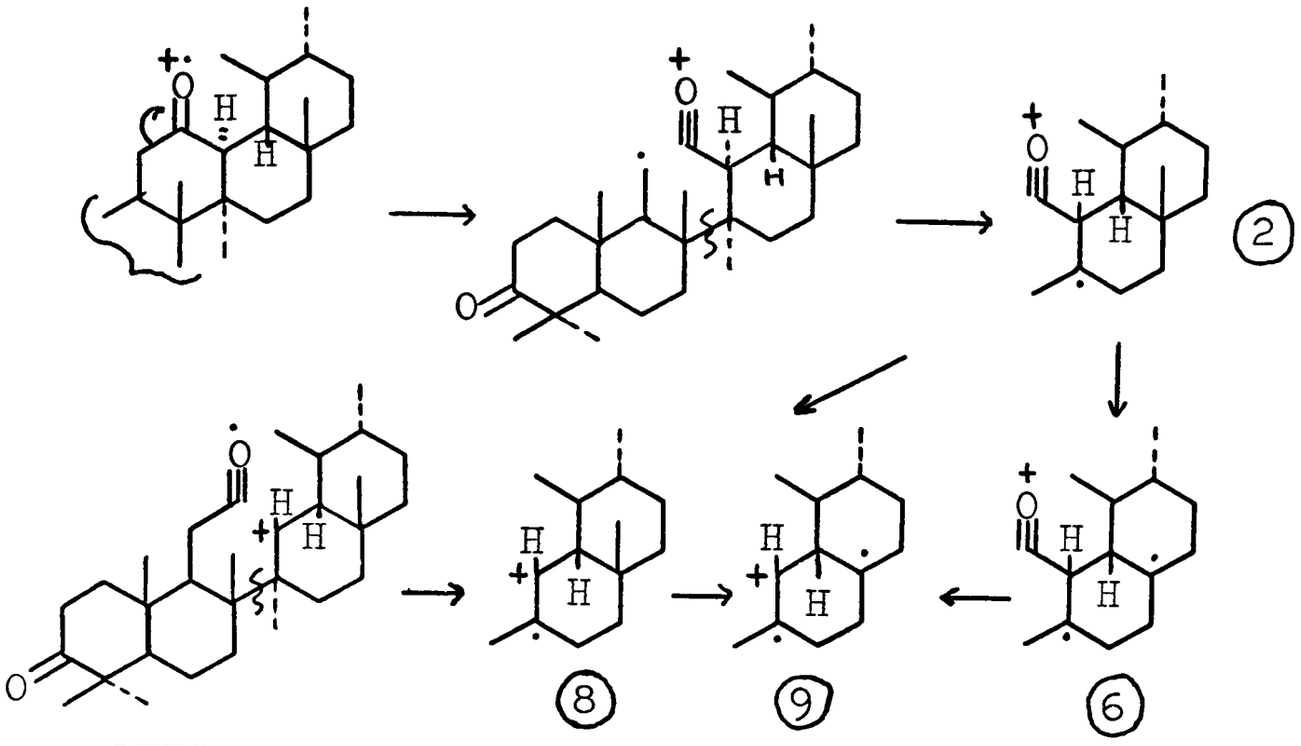
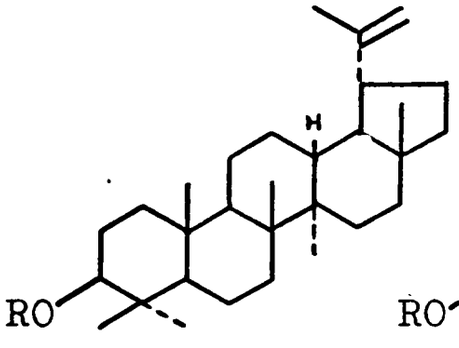
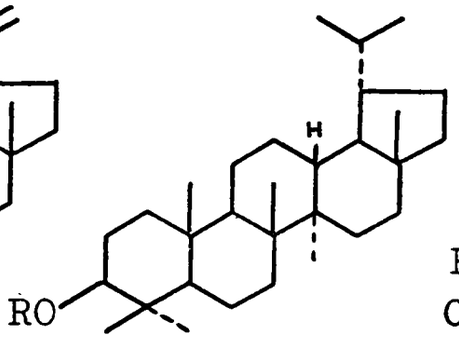


FIGURE 63

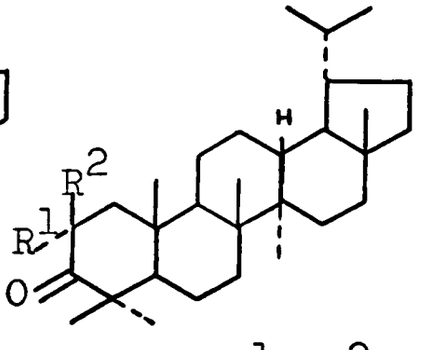




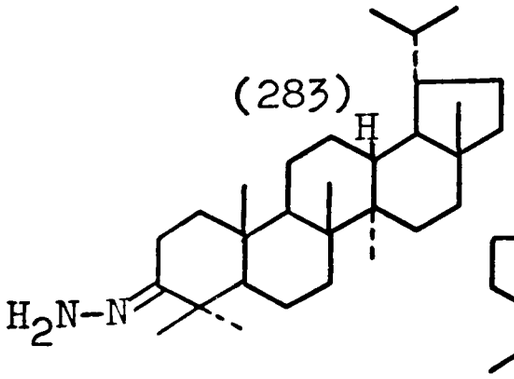
	R
(275)	PhCO
(2)	H
(276)	Ac

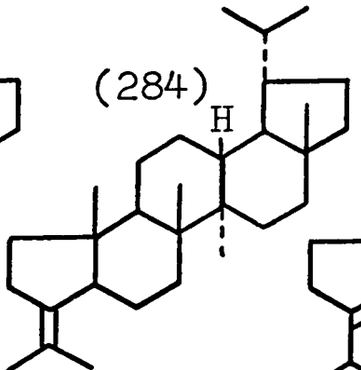


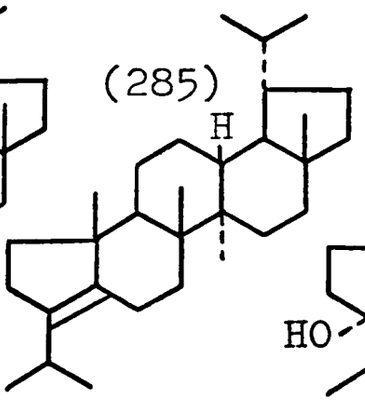
(277) R=Ac
(278) R=H

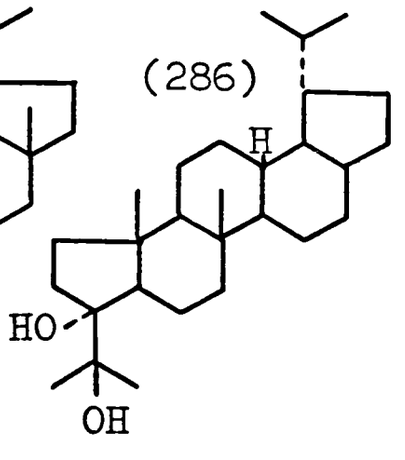


	R^1	R^2
(279)	H	H
(280)	Br	Br
(281)	Br	H
(282)	H	Br









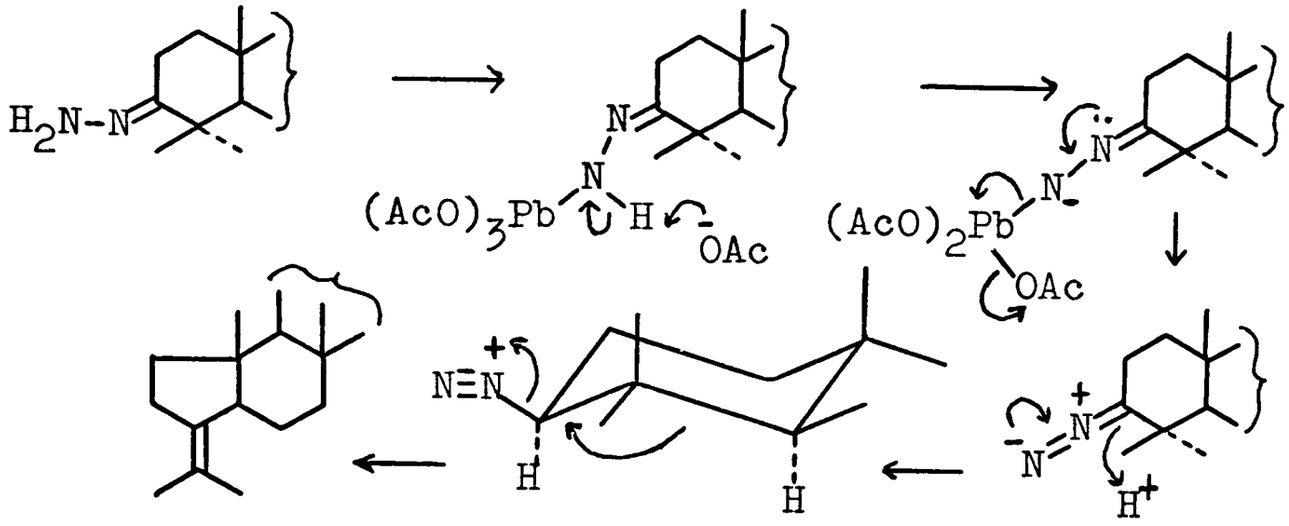
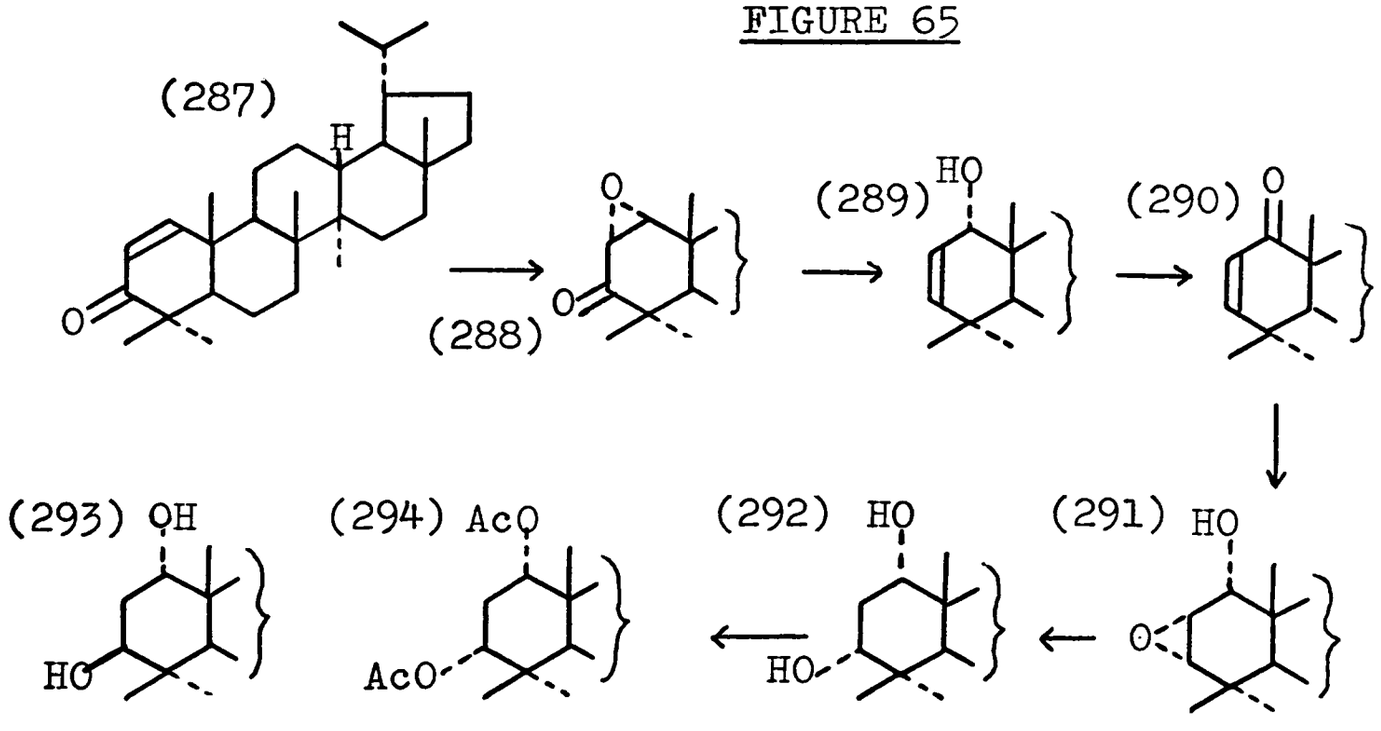


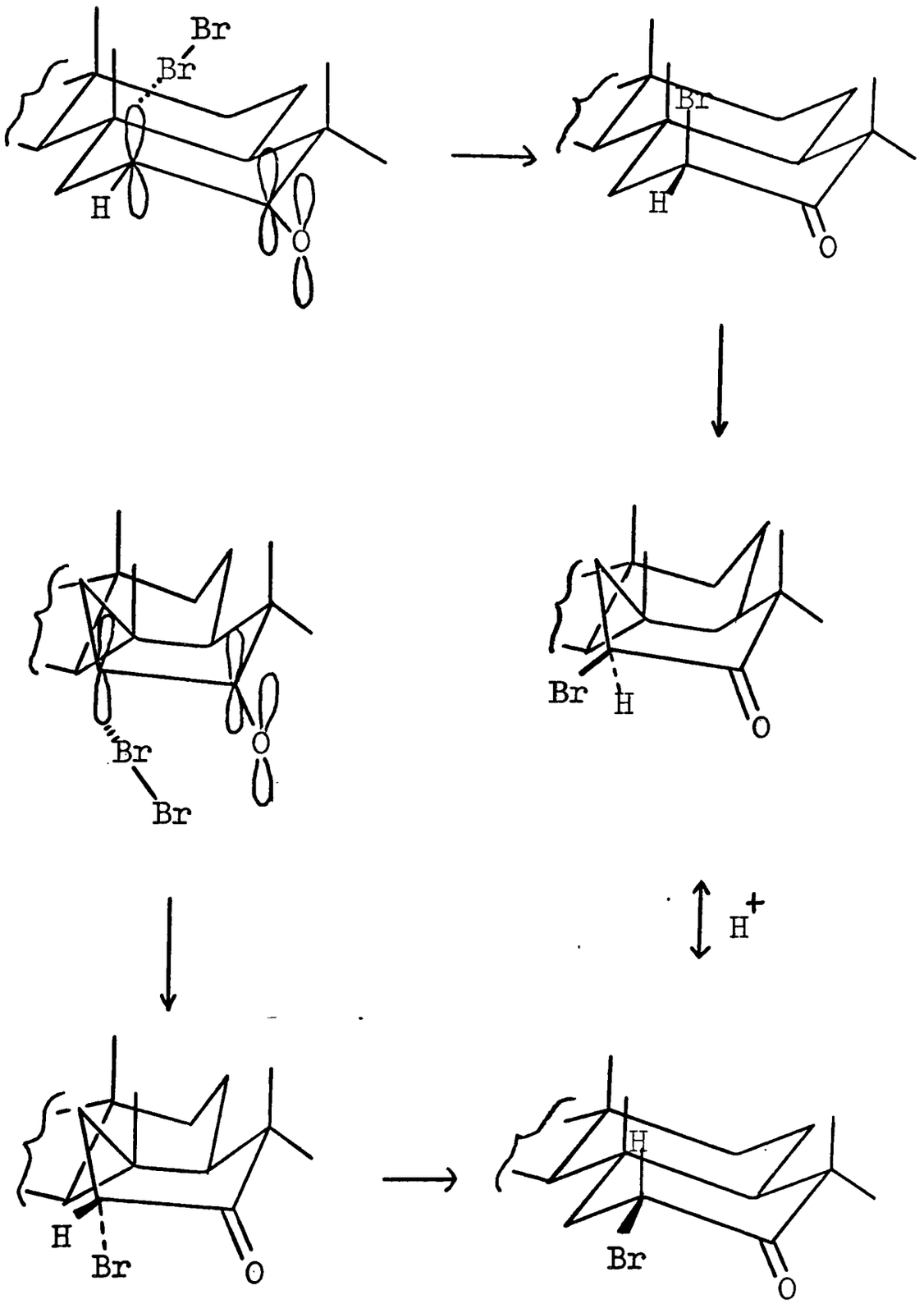
FIGURE 64

FIGURE 65



(296) (297) (298) (299)

FIGURE 66



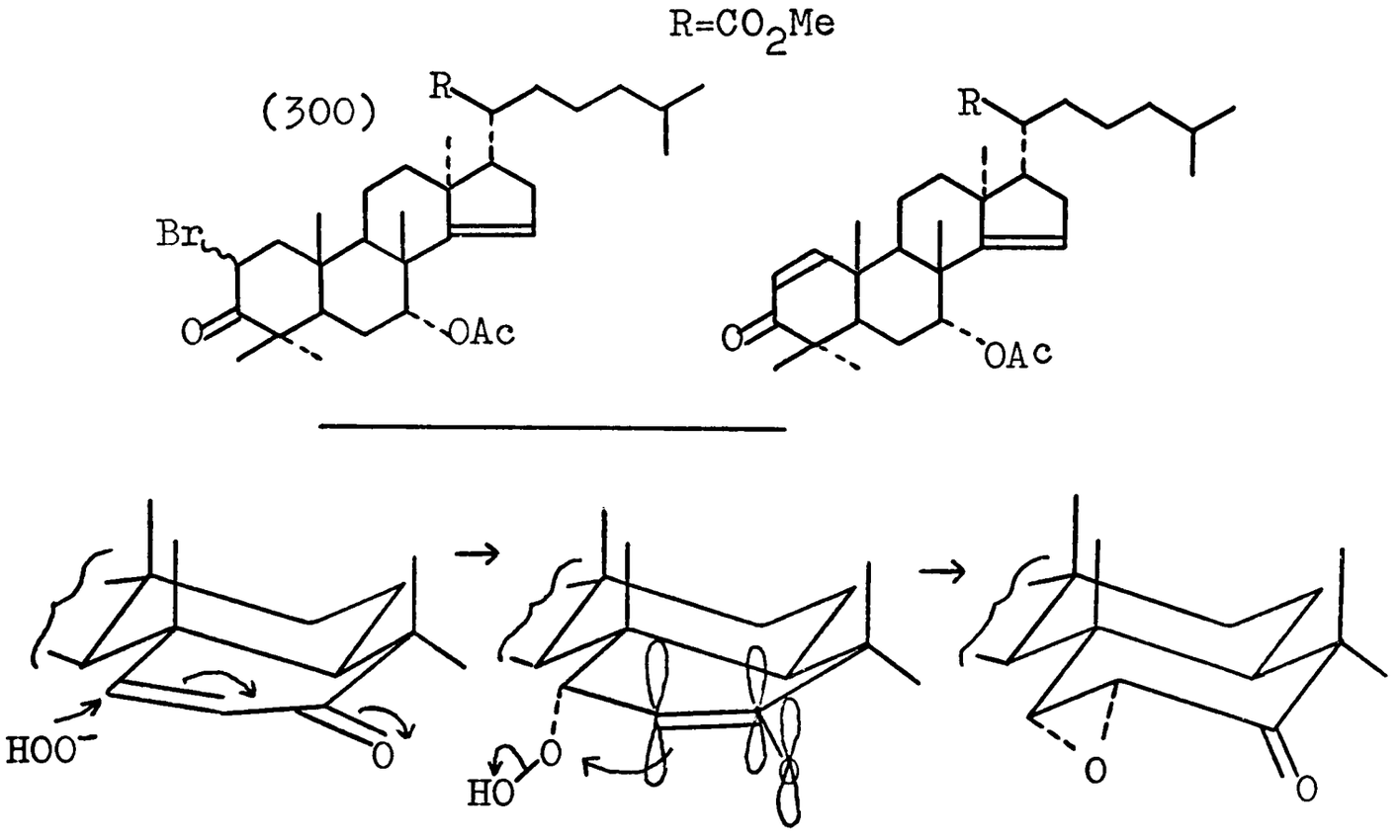


FIGURE 67

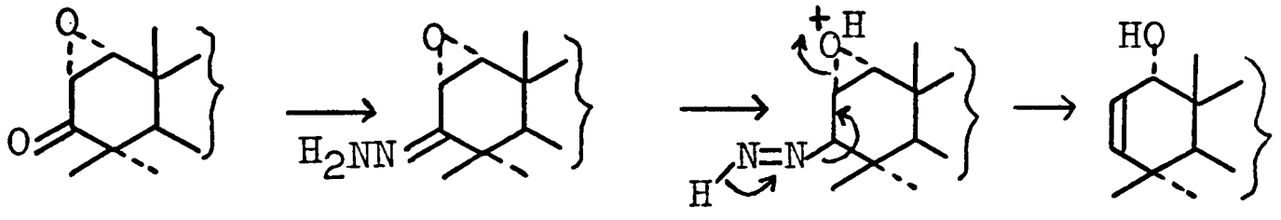


FIGURE 68

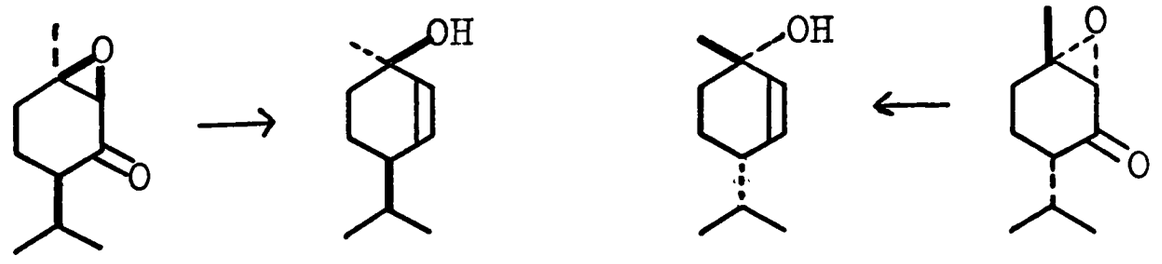
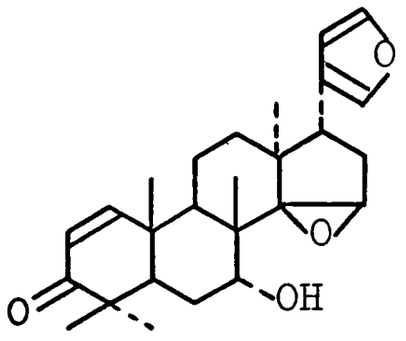
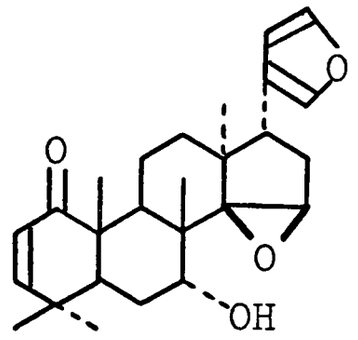


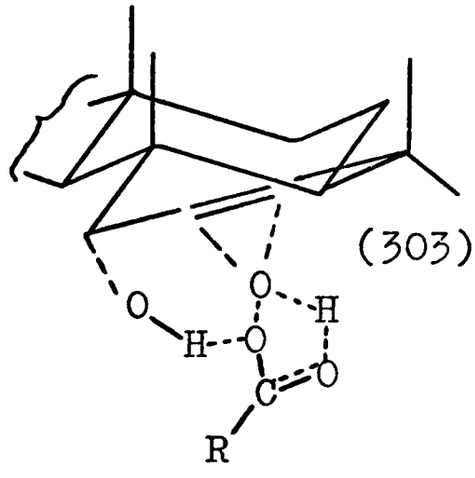
FIGURE 69



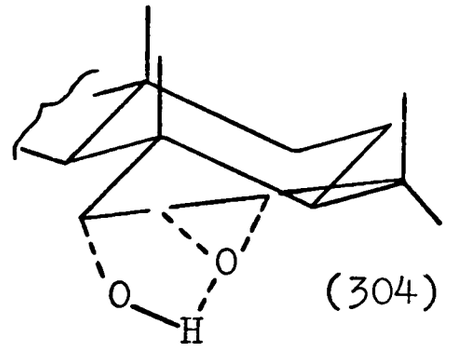
(301)



(302)



(303)



(304)

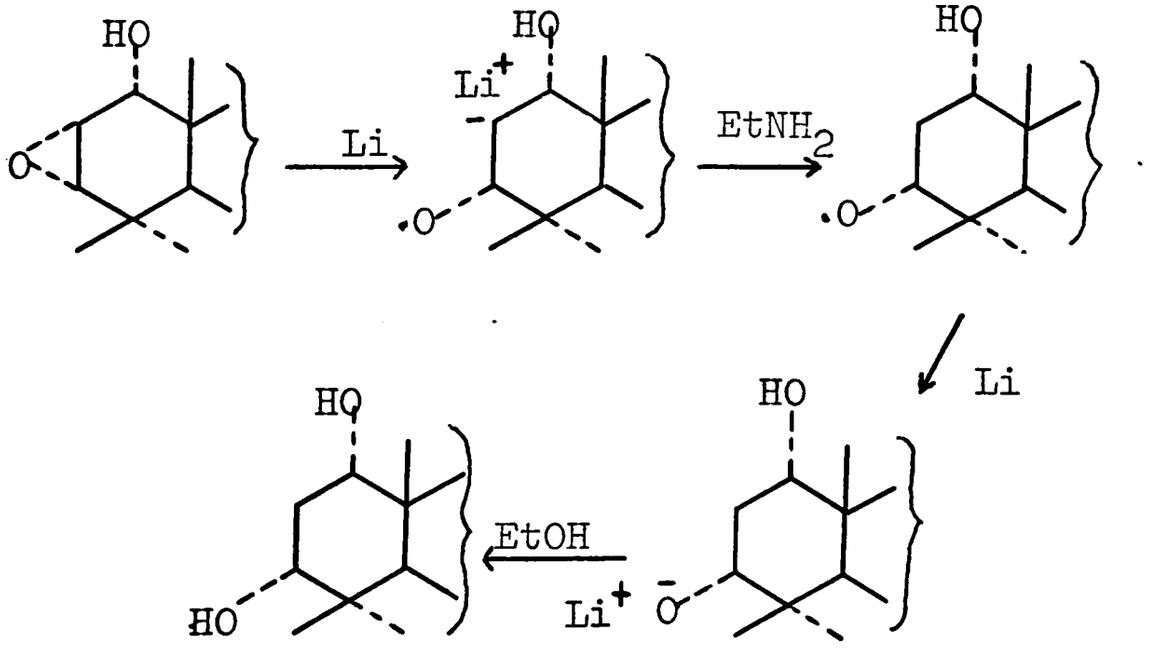


FIGURE 70

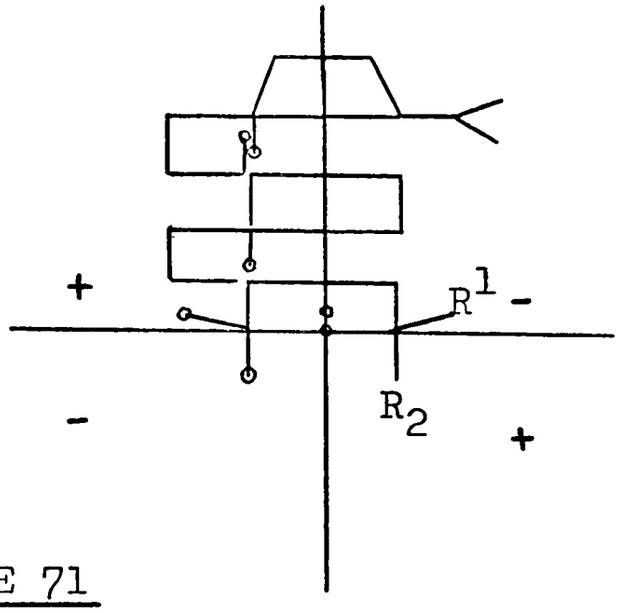
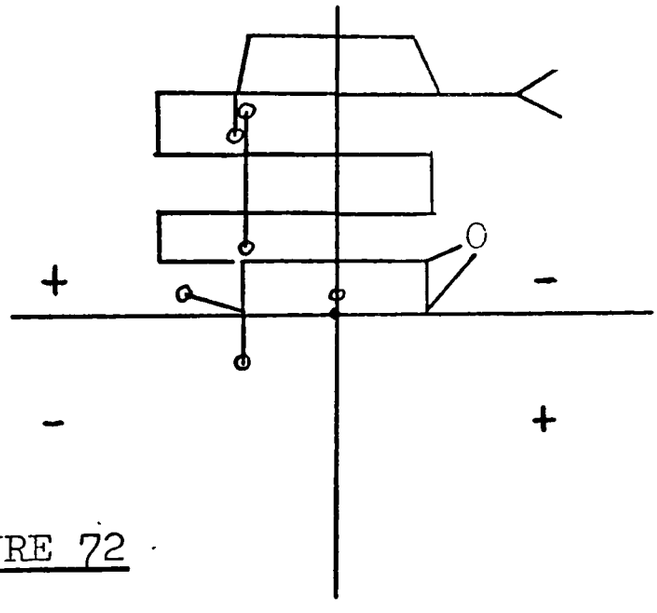


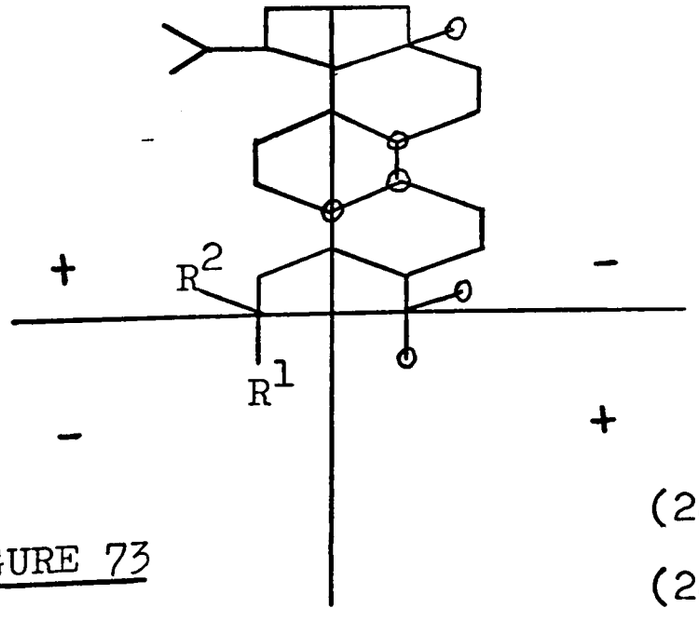
FIGURE 71

	R^1	R^2
(279)	H	H
(281)	Br	H



(288)

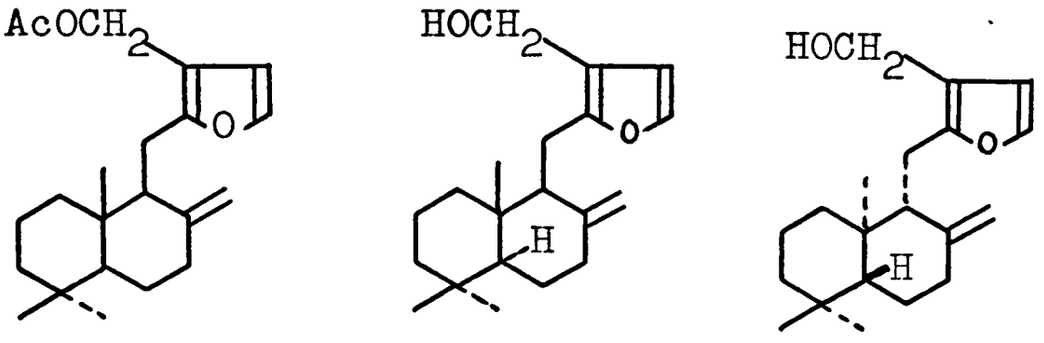
FIGURE 72

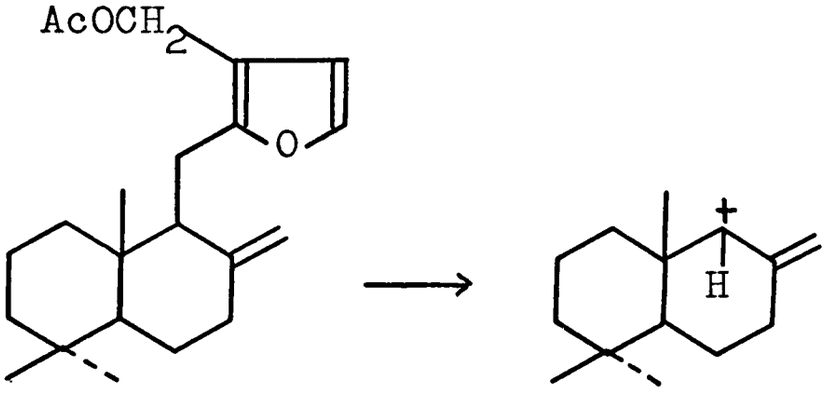


	R^1	R^2
(282)	H	Br
(280)	Br	Br

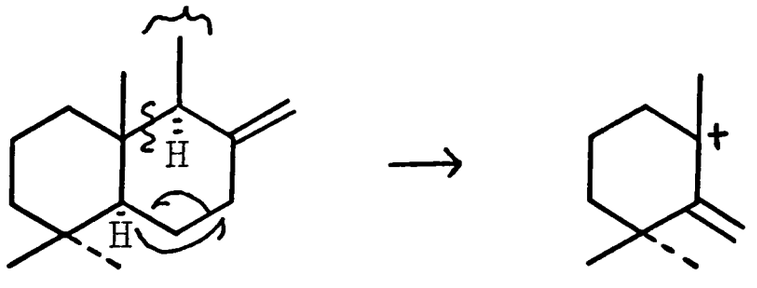
FIGURE 73

(305) (306) (307)





M^+ 344 m/e 191



m/e 137

FIGURE 74

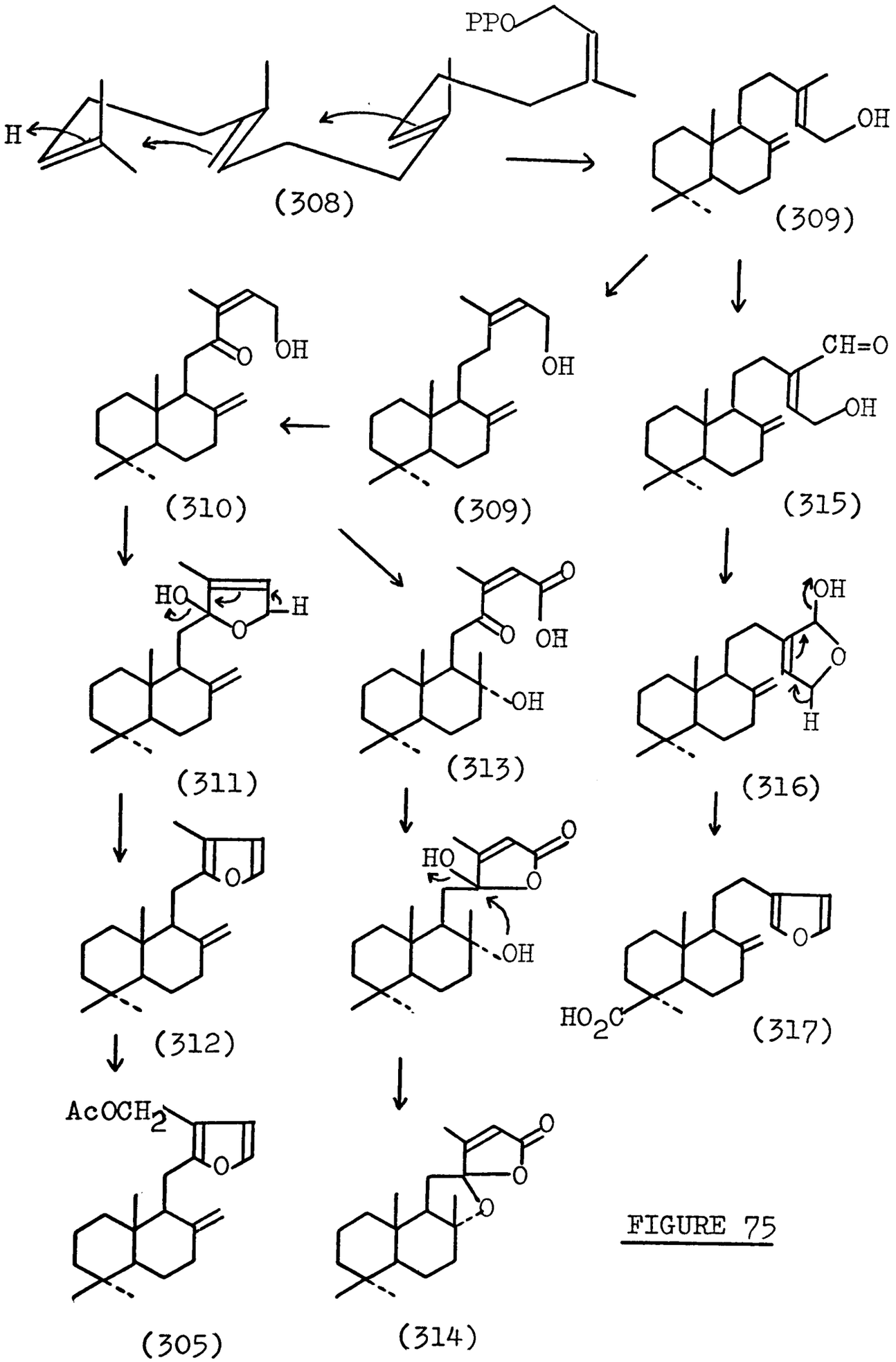

PPO
H
OH
(308)
(309)
OH
O
OH
CH=O
OH
(310)
(309)
(315)
HO
H
O
OH
OH
OH
O
H
(311)
(313)
(316)
O
HO
O
OH
O
HO2C
(312)
(317)
AcOCH2
O
O
O
O
(305)
(314)

FIGURE 75

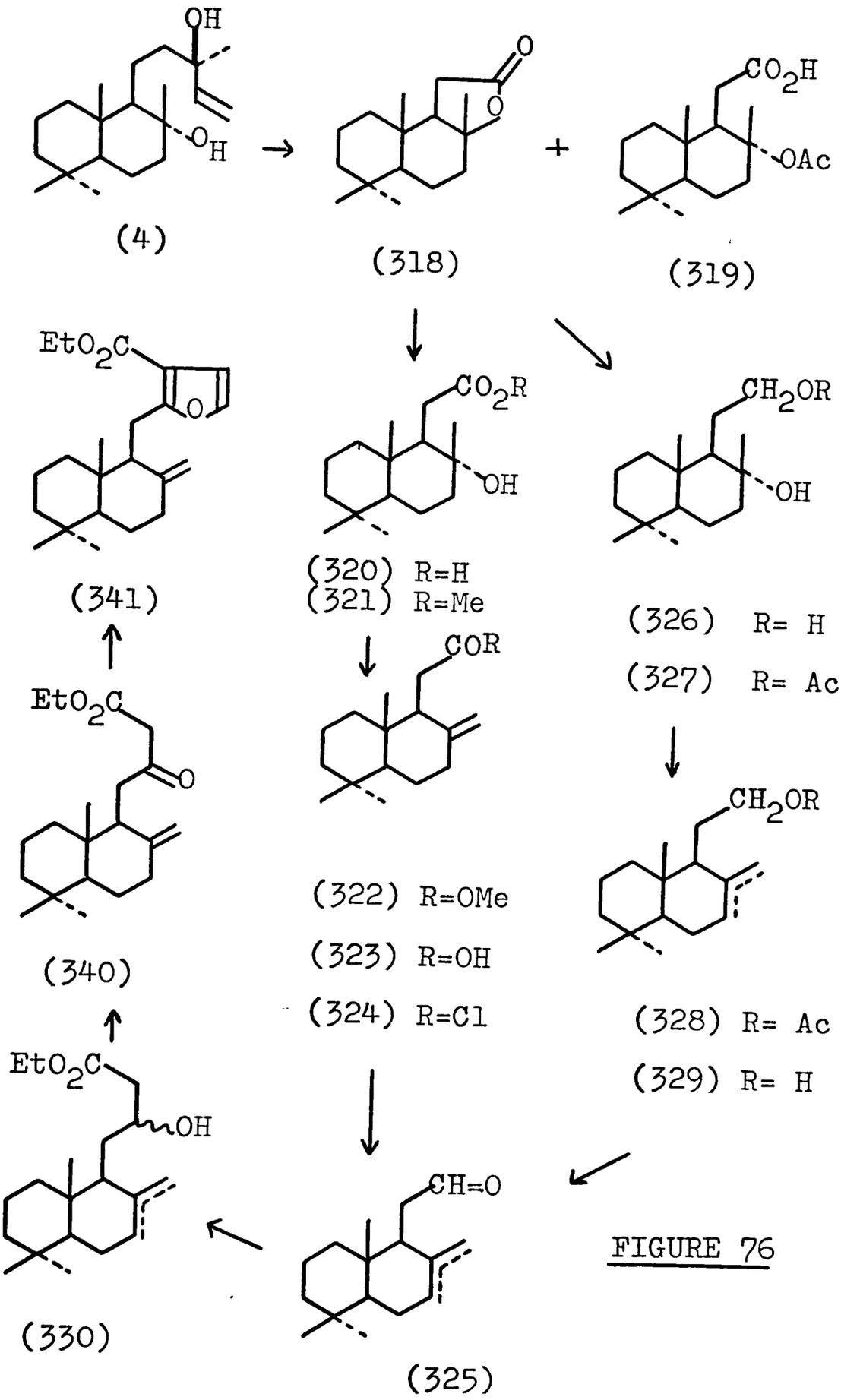
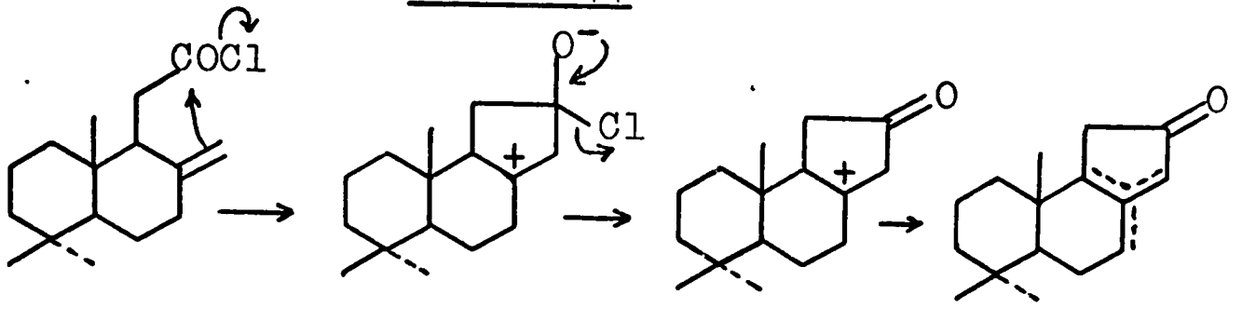
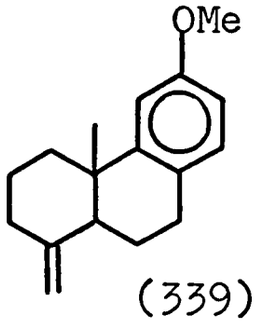

OH
OH
(4)
O
O
(318)
+
CO2H
OAc
(319)
EtO2C
O
(341)
CO2R
OH
(320) R=H
(321) R=Me
CH2OR
OH
(326) R= H
(327) R= Ac
COR
(322) R=OMe
(323) R=OH
(324) R=Cl
CH2OR
(328) R= Ac
(329) R= H
EtO2C
O
(340)
EtO2C
OH
(330)
CH=O
(325)

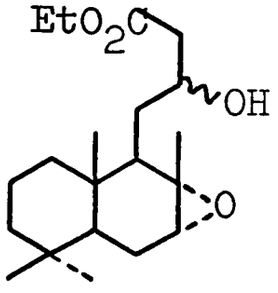
FIGURE 76

FIGURE 77

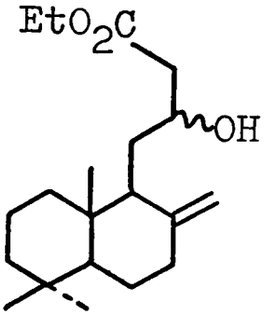




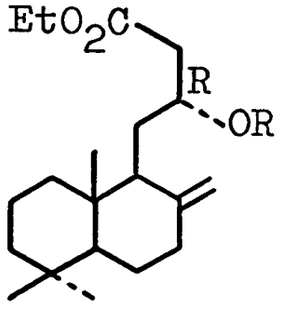
(339)



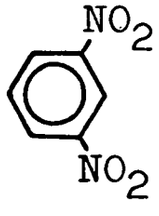
(336)

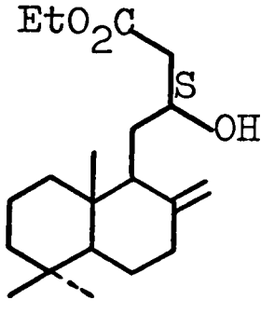


(331)

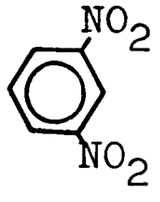


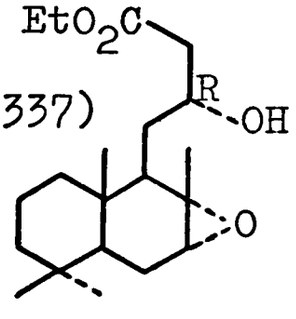
(332) R=H

(333) R= CO 

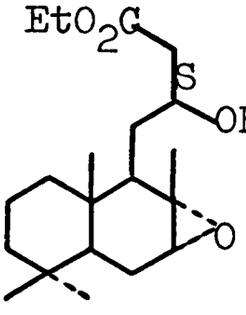


(334) R=H

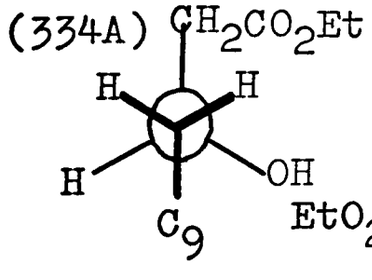
(335) R= CO 

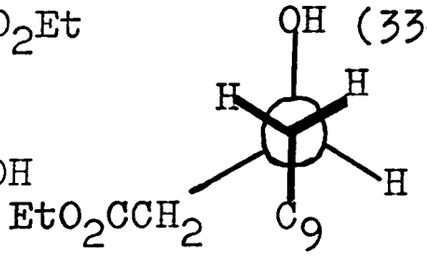


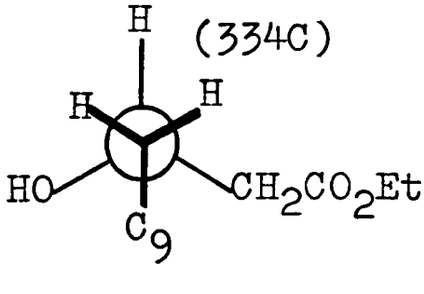
(337)

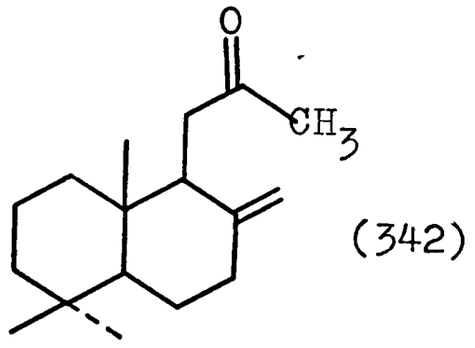


(338)









(342)

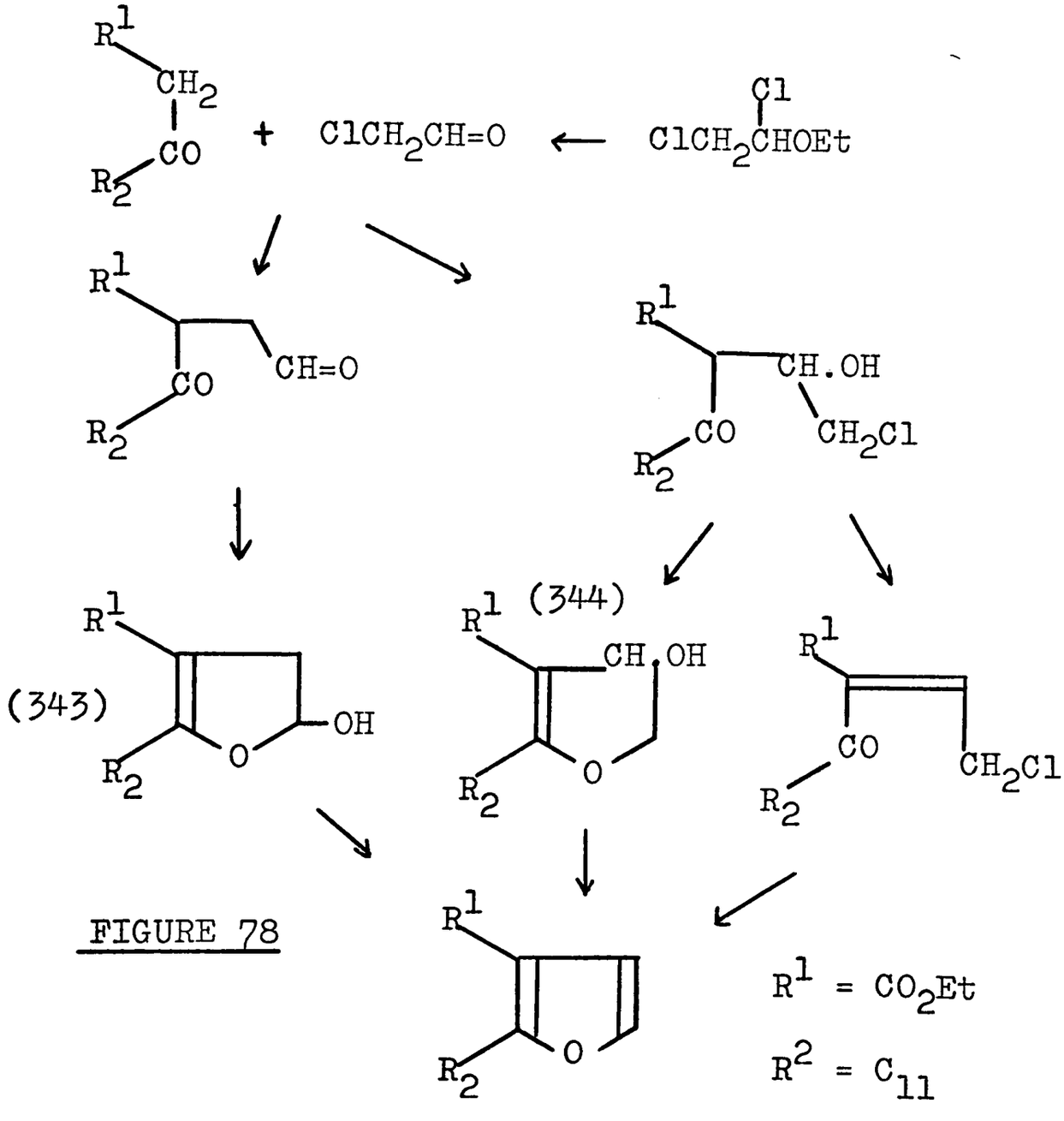
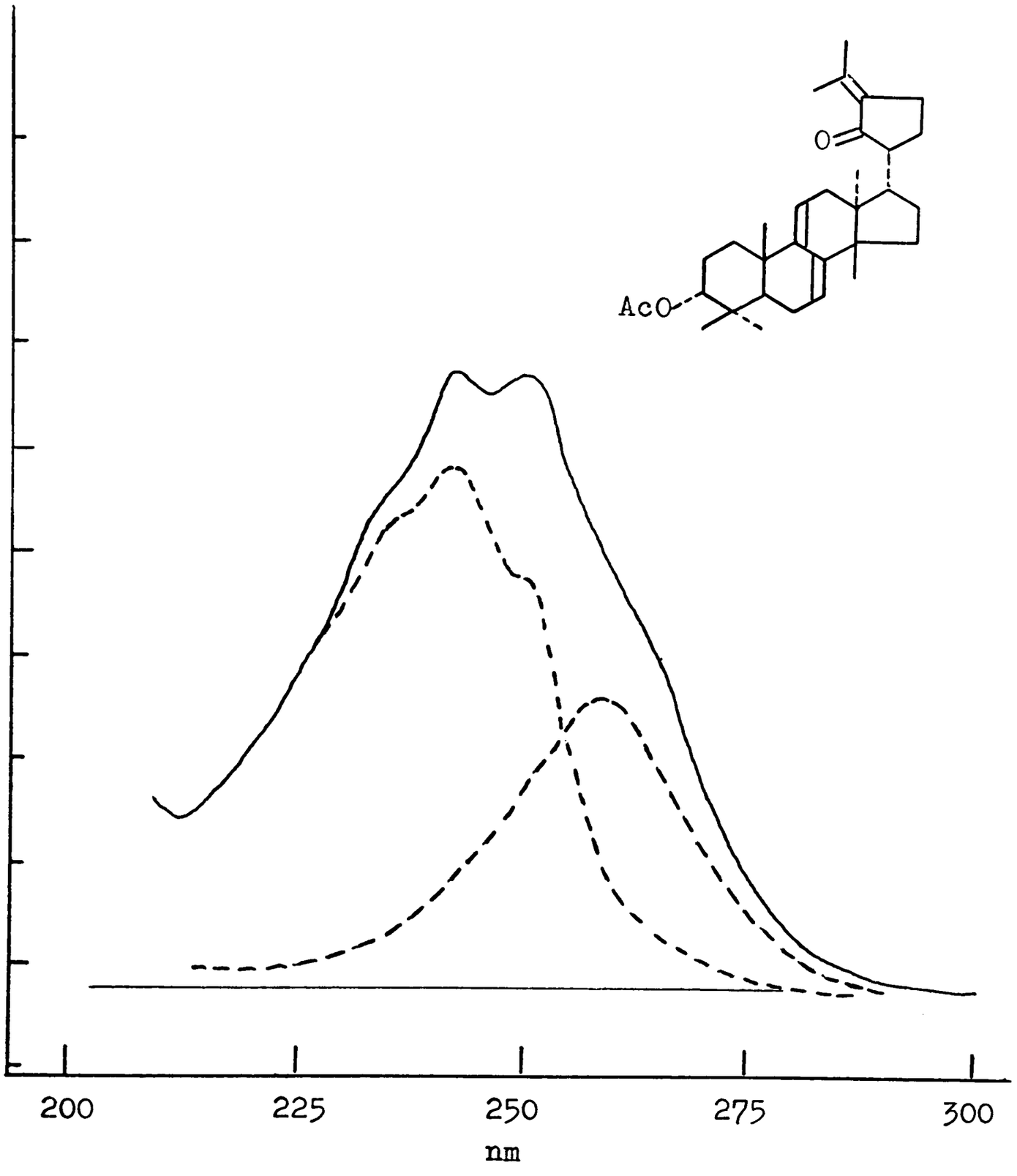
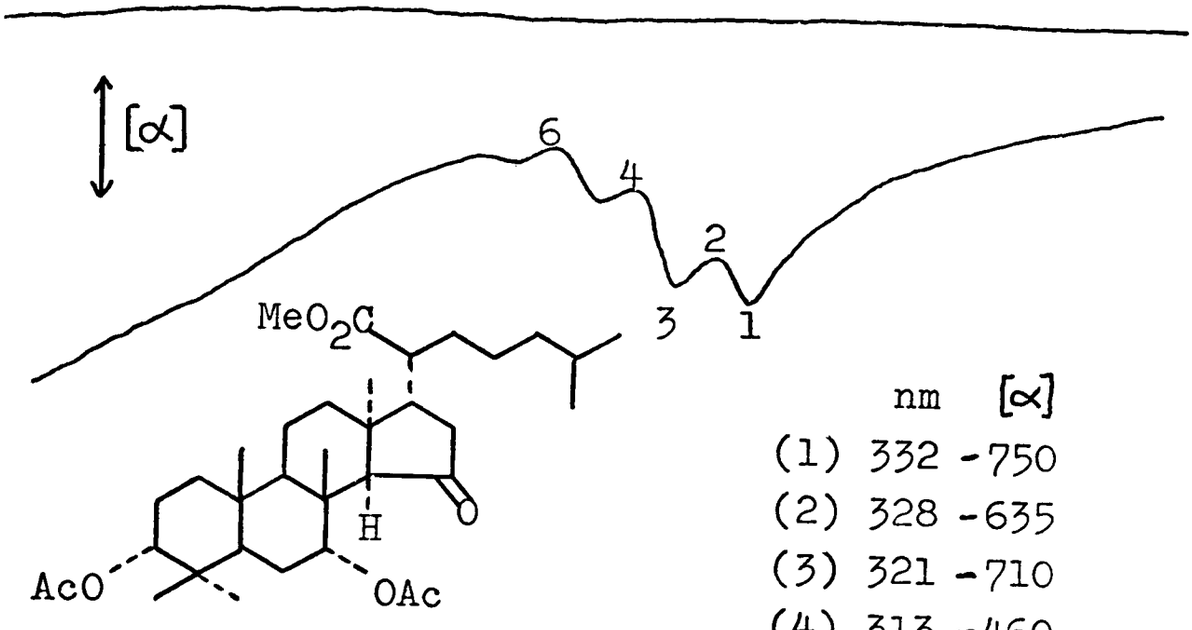


FIGURE 78

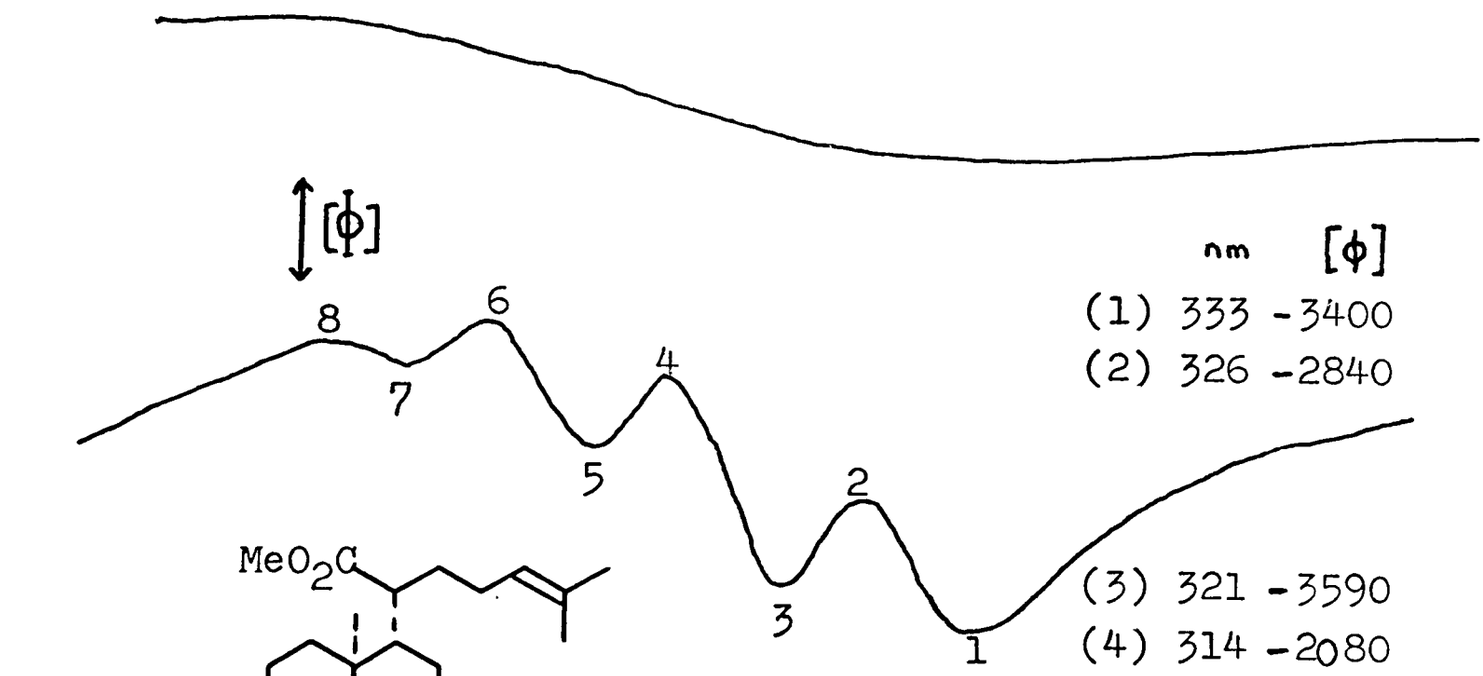


Appendix 1

Appendix 2

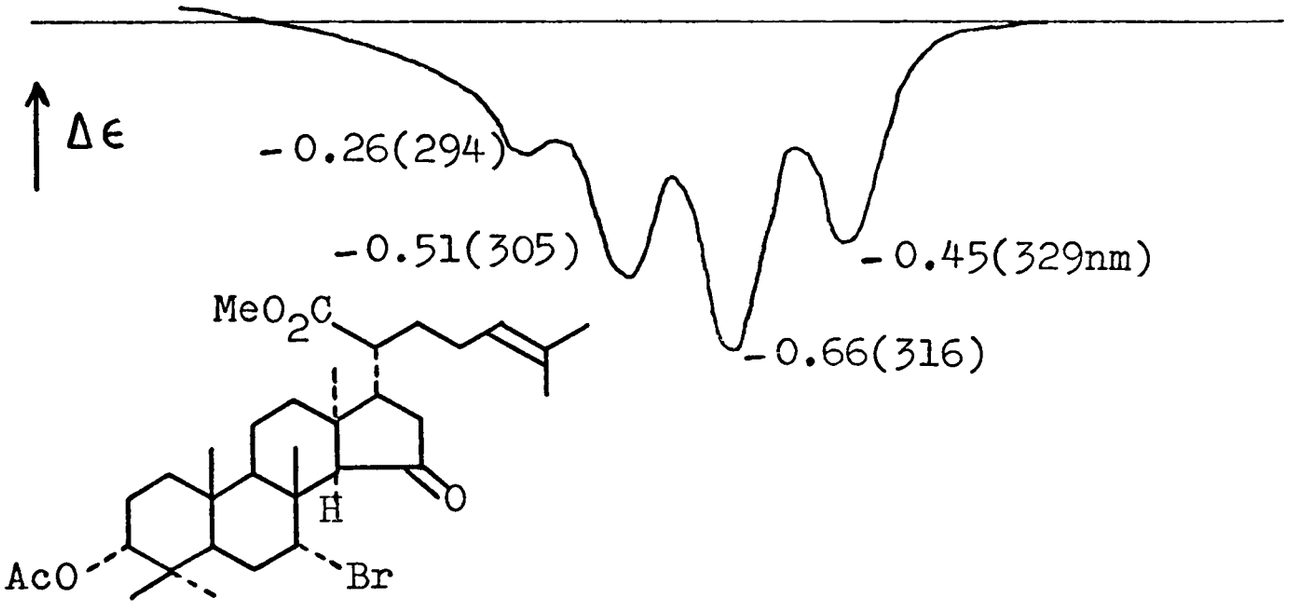


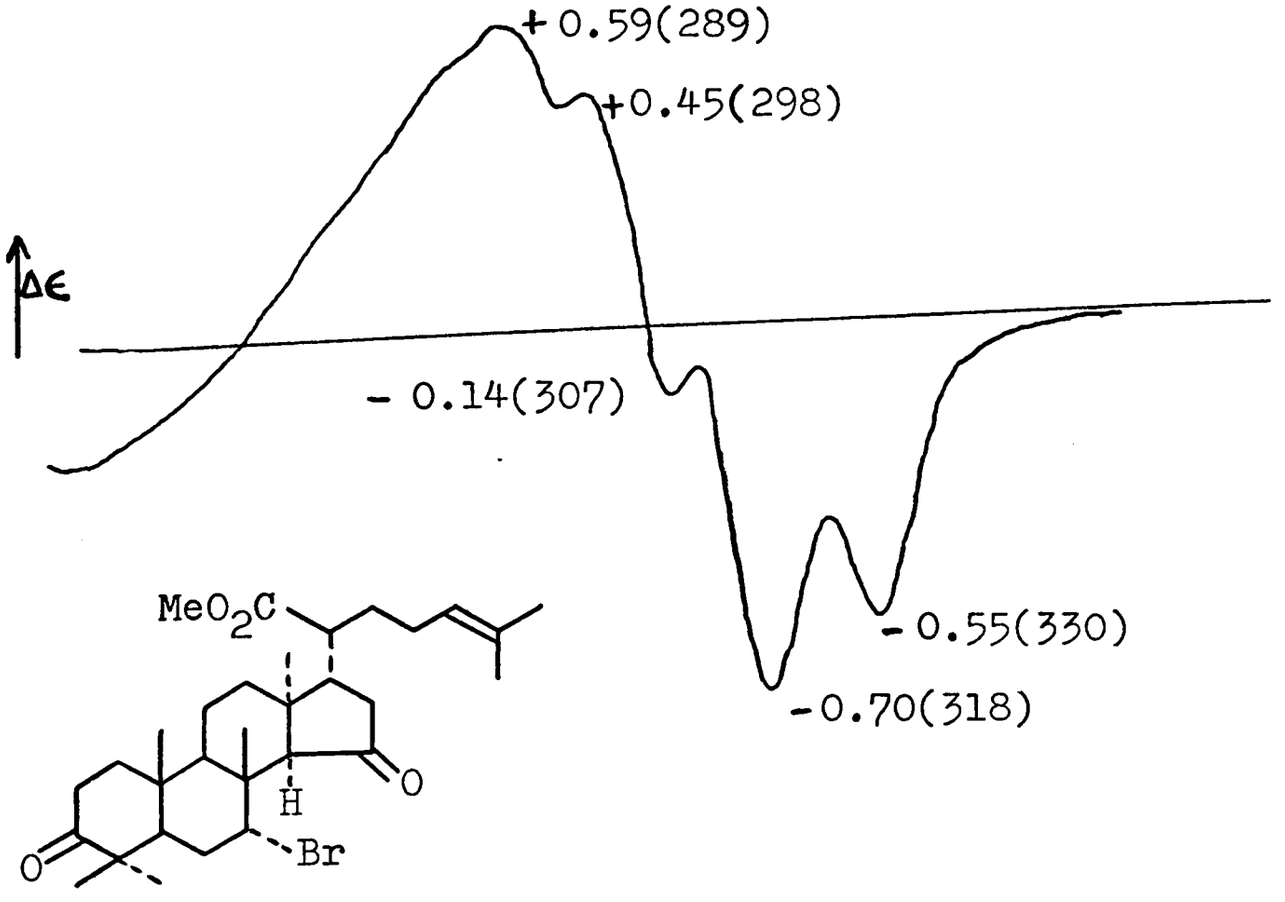
	nm	[α]
(1)	332	-750
(2)	328	-635
(3)	321	-710
(4)	313	-460
(6)	303	-330



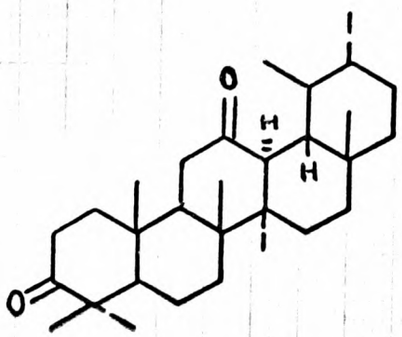
	nm	[ϕ]
(1)	333	-3400
(2)	326	-2840
(3)	321	-3590
(4)	314	-2080
(5)	309	-2930
(6)	303	-2080
(7)	298	-2550
(8)	293	-2460

Appendix 3


Δε
-0.26(294)
-0.51(305)
-0.66(316)
-0.45(329nm)
MeO2C
H
O
AcO
Br

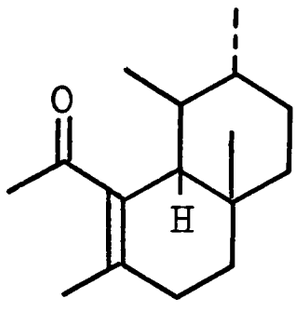
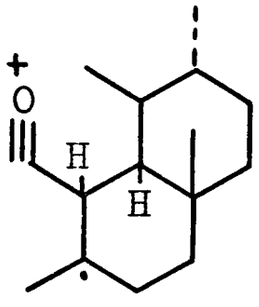
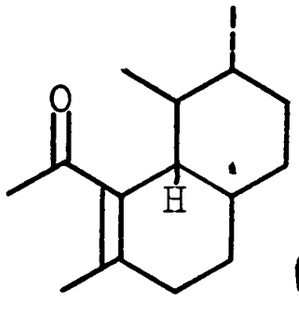
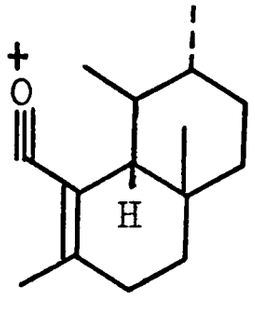
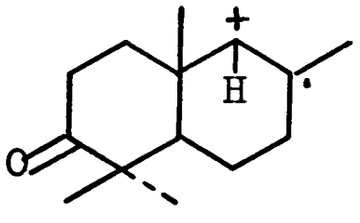

+0.59(289)
+0.45(298)
Δε
-0.14(307)
-0.55(330)
-0.70(318)
MeO2C
H
O
O
Br

Appendix 4

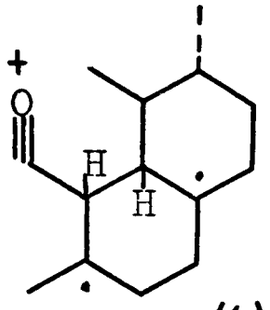
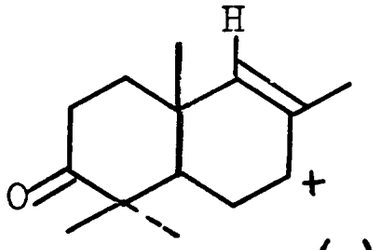
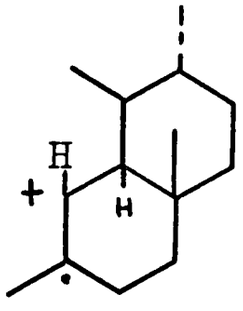
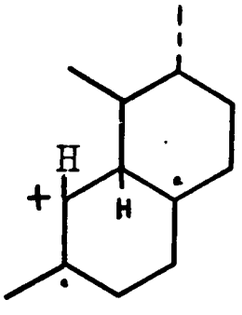

O
H
H
O

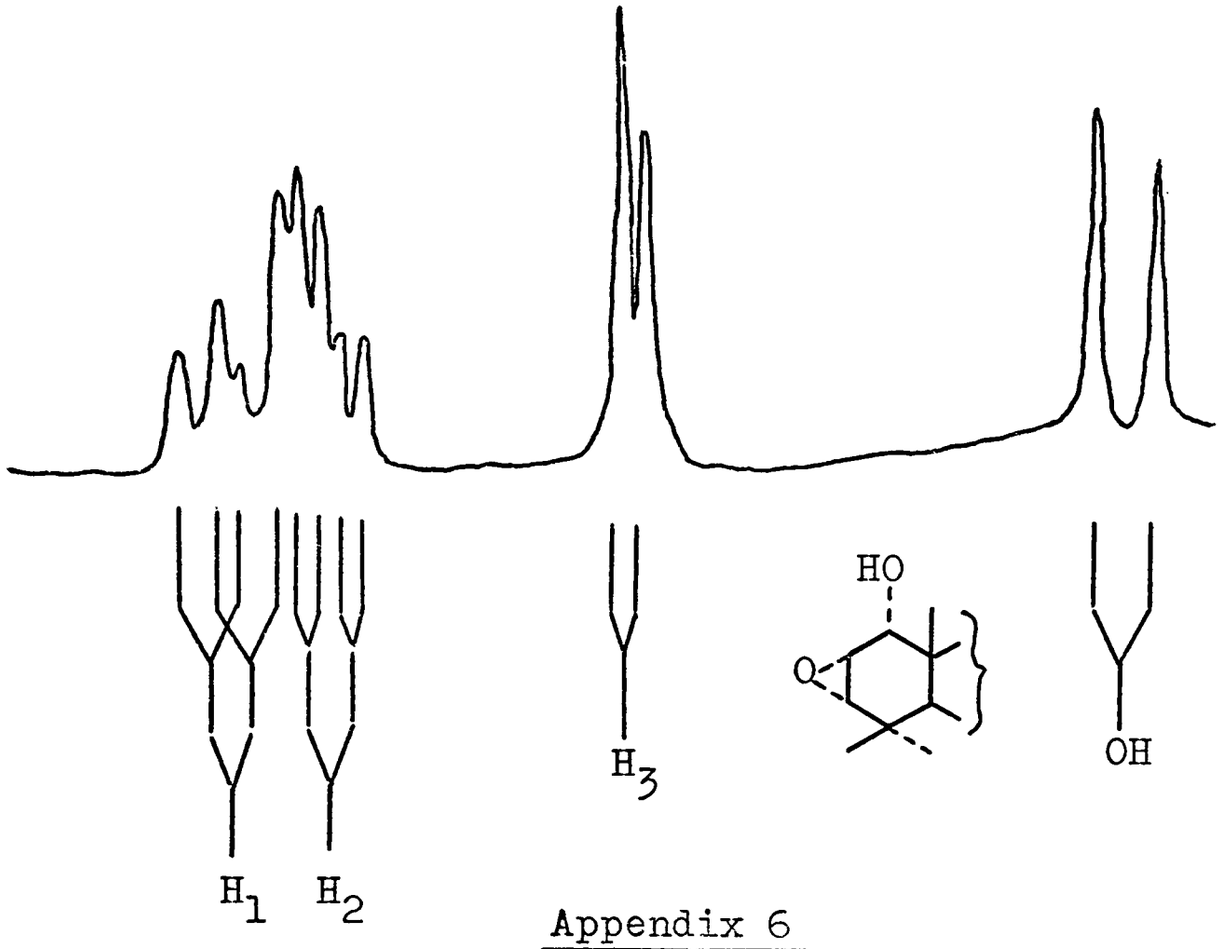
100
90
80
70
60
50
40
30
20
10
0
120
140
160
180
200
220
240
260
280
300
440

Appendix 5

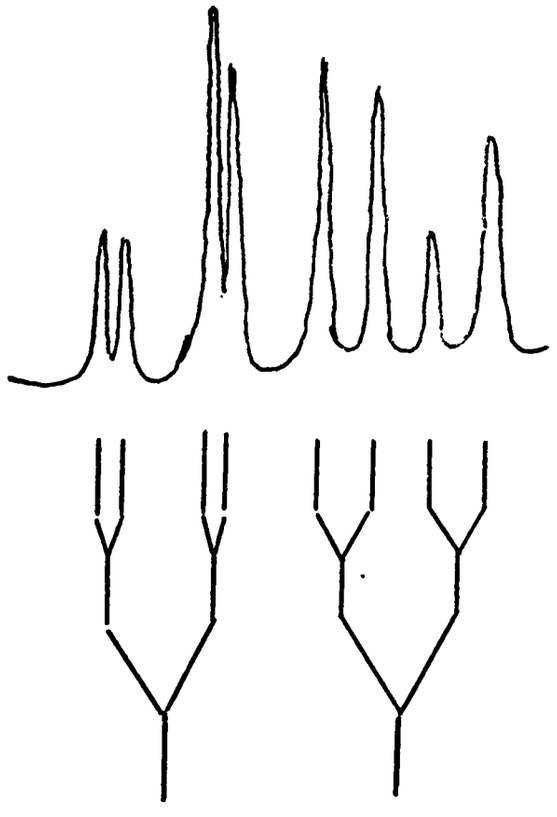
M/e	
234	 (1)
220	 (2)
219	 (3)  (4)
206	 (5)

Appendix 5 (cont.)

M/e	
205	 (6)  (7)
192	 (8)
177	 (9)



Appendix 6



Appendix 7